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Transition-Metal Free Strategies for the Construction and Functionalization of Strained Unsaturated Carbo- and Heterocyclic Systems

von

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aus

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Erklärung

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1.) "Strain-release arylations for the bis-functionalization of azetidines" Florian Trauner‡, Felix Reiners‡, Kodjo-Edmond Apaloo-Messan, Benedikt Nißl, Muhammad Shahbaz, Dongfang Jiang, Julian Aicher, Dorian Didier, *Chem. Commun.* **2022**, *58*, 2564-2567.

2.) "Stereoselective polar radical crossover for the functionalization of strained-ring systems" Florian Trauner, Rahma Ghazali, Jan Rettig, Christina M. Thiele, Dorian Didier, *Commun. Chem.* **2024**, *7*, 139.

3.) "Zweifel Olefination for *C*-Glycosylation" Florian Trauner, Bilel Boutet, Fabian Pilz, Verena Weber, Dorian Didier, accepted in *Commun. Chem.* **2024***, in press.*

4.) "Diethylzinc-Amylates – Selective Halogen-Zinc Exchange Reagents at Room-Temperature" Florian Trauner‡, Bilel Boutet‡, Flavie Rambaud, Van Nhi Ngo, Dorian Didier, **2024**, *ChemRxiv.* preprint DOI:10.26434/chemrxiv-2024-52hq3.

‡ These authors have contributed equally to the published work.

Reviews & Bookchapters:

5.) "Wie der Würfel wirkt" Florian Trauner, Muhammad Shabaz, Dorian Didier, *Nachr. Chem.* **2021**, *69*, 72-75.

6.) "Four-Membered Rings with One or More Heteroatoms" Dorian Didier, Florian Trauner, Dongfang Jiang, *Science of Synthesis Knowledge Updates*, **2024**, *in press.*

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Tetrahedron Symposium - 23rd Organic Chemistry Symposium - STRAIN-RELEASE ARYLATIONS FOR THE BIS-FUNCTIONALIZATION OF AZETIDINES - *Gotheburg, Sweden, 2023*

Abbreviations

δ	chemical shift (NMR)
9-BBN	9-borabicyclo[3.3.1]nonane
ABB	1-aza-bicyclo[1.1.0]butane
Ac_2O	acetic anhydride
acac	acetylacetonato
ACE-Cl	1-chloroethyl chloroformate
AcSH	thioacetic acid
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl substituent
ATR	attenuated total reflection
ATRA	atom transfer radical addition
B(Epin)	boronic acid 3,4-diethyl-hexane-3,4-diol ester
B(O*n*Bu)$_3$	tributyl borate
B(Pin)	boronic acid pinacol ester
$B_2(Pin)_2$	bis(pinacolato)diboron
BCB	bicyclo[1.1.0]butane
BEt_3	triethylborane
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
Bu	butyl
Bu_3SnH	tributyltin hydride
calc.	calculated
CBS	Corey–Bakshi–Shibata
CCDC	cambridge crystallographic data centre
*c*Hex	cyclohexyl
cm^{-1}	wavenumber
conc	concentrated
COVID 19	coronavirus disease 2019
Cy	cyclohexyl
$Cy_3P{\cdot}HBF_4$	tricyclohexylphosphonium tetrafluoroborate
d	doublet (NMR)
dba	dibenzylideneacetone
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEZA	$Et_2Zn{\cdot}$LiOAmyl
DEZA2	$Et_2Zn{\cdot}$2LiOAmyl
DFT	density functional theory
DIPEA	*N*,*N*-diisopropylethylamine
DLP	dilauroyl peroxide
DMF	dimethylformamide
DMG	directing metalation group
DMI	1,3-dimethyl-2-imidazolidinone
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DPPF	1,1′-bis(diphenylphosphino)ferrocene
dr.	diastereomeric ratio
DTBHN	di-*tert*-butylhyponitrite
E	entgegen (opposite), *trans*
e.g.	*exempli gratia*, for example
es.	enantiospecificity
E/*Z*	trans/ cis ratio
E^+	electrophile
ee.	enantiomeric excess
EI	electron ionization
EPR	electron paramagnetic resonance
equiv.	equivalents
er.	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
et al.	*et alumni*, and others
Et_2O	diethyl ether
EtOAc	ethyl acetate
exs.	excess
FDA	Food and Drug Administration
FG	functional group
Fmoc	Fluorenylmethoxycarbonyl

Freon-113	1,1,2-trichloro-1,2,2-trifluoroethane
GC	gas chromatography
h	hour(s)
hν	photo irradiation
Het	heteroaryl substituent
Hex	hexyl
HFIP	hexafluoroisopropanol
HMDS	hexamethyldisilazane
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	hydroxybenzotriazole
HRMS	high resolution mass spectroscopy
i	*iso*
Ipc_2BH	diisopinocampheylborane
*i*Pr	*iso*Propyl
IR	infrared
J	coupling constant (NMR)
KO*t*Bu	potassium *tert*-butoxide
KOTf	potassium trifluoromethanesulfonate
LDA	lithium di*iso*propylamide
LED	light-emitting diode
LRMS	low-resolution mass spectrometry
M	mol × L^{-1}
M	metal
m	medium (IR)
m	multiplet (NMR)
m	*meta*
M.p.	melting point
Me	methyl
MeCN	acetonitrile
MEK	mitogen-activated protein kinase kinase
MeLi	methyllithium
mg	milligrams
Mg*	Rieke magnesium
min	minutes
mmol	millimoles
mol%.	mole fraction
MOM	methoxymethyl ether
MP	melting point
mRNA	messenger ribonucleic acid
MS	mass spectroscopy
MsCl	methanesulfonyl chloride
MTHP	4-methyltetrahydropyran
n.d.	not determined
NaOTf	sodium trifluoromethanesulfonate
NBS	*N*-Bromosuccinimide
*n*BuLi	*n*butyllithium
$Ni(COD)_2$	bis(cyclooctadiene)nickel
$NiCl_2$·glyme	nickel(II) chloride ethylene glycol dimethyl ether complex
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	NOE spectroscopy
*n*Pent	*n*Pentyl
o	*ortho*
ox	oxidation
p	*para*
$P(2\text{-furyl})_3$	tri(2-furyl)phosphine
PBN	*N*-*tert*-butyl-α-Phenylnitrone
Ph	phenyl
PhLi	phenyllithium
Phth	phthalimide
pin	pinacol
PMB	*p*-methoxybenzyl
PMDTA	*N*,*N*,*N*‘,*N*‘‘,*N*‘‘‘-pentamethyldiethylenetriamine
ppm	parts per million
Pr	propyl
PRC	polar-radical crossover
psi	pounds per square inch
q	quartet (NMR)
quint	quintet (NMR)
R	undefined organic substituent
rad. [1,2]-migr.	radical [1,2]-migration
rt.	room temperature

s	*sec*
s	singulet (NMR)
s	strong (IR)
sat.	saturated
*s*Bu	*sec*Butyl
*s*BuLi	*sec*Butyllithium
SET	single electron transfer
SGLT-2	sodium-glucose linked transporter 2
SM	starting material
S_NAr	nucleophilic aromatic substitution
t	*tert*
t	triplet
TBAB	tetrabutylammonium bromide
TBME	methyl *tert*-butyl ether
TBS	*tert*Butyldimethylsilyl
*t*BuLi	*tert*Butyllithium
Tf	triflyl
Tf_2O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	Tetrahydrofuran
THP	tetrahydropyran
THX	thioxanthone
TLC	thin layer chromatography
TM	transition metal
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
TNAZ	1,3,3-trinitroazetidine
THP	tetrahydropyran
THX	thioxanthone
TP	typical procedure
TsCl	4-toluenesulfonyl chloride
UV	ultraviolet
vs, vw	very strong, very weak (IR)
Xantphos	(9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane)
Z	zusammen (together), *cis*
Zn*	Rieke zinc
χ_m	electronegativity

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A. INTRODUCTION

1. Overview

In a rapidly developing world facing the challenges of the recent COVID 19 pandemic, global conflicts, declining resources and overall continuously increasing challenges of productivity, cost and sustainability, the demand for targeted and innovative pharmaceutical drugs, agricultural agents and technical materials is higher than ever.

Synthetic organic chemistry as a scientific discipline, which since its beginnings in the 19th century made huge progress and gained drastically in relevance[1], is continually involved in the advancement and development of novel complex molecules for solving these global challenges.[2] Despite the outstanding progress made with mRNA vaccines and antibody therapies in response to the COVID-19 pandemic, the development and approval of small molecule drugs remains pivotal. The drug approvals by the FDA for 2023 revealed 31 small molecules, 24 biologics (proteins produced using recombinant DNA technologies) and 14 other therapies (including vaccines, and cell- and gene-based therapies).[3] Few key synthetic strategies dominate the synthesis of small molecules, comprising carbon-carbon bond formation as an indispensable tool. In this context, advances in organometallic chemistry and particularly advances in catalysis, are crucial in aligning synthetic objectives with the industrial demand for efficient and sustainable production.[4]

Organometallic reagents and intermediates are employed in a broad range of reactions, including 1,2-additions to aldehydes or ketones, allylations, acylations, and transition metal-catalyzed cross-coupling reactions. The importance of these advancements was highlighted by the awarding of the 2010 Nobel Prize in Chemistry to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki for their development of palladium-catalyzed cross-coupling reactions.[5] Owing to its precision, efficiency and predictability, the modern transition metal catalyzed cross-coupling has become an indispensable tool not only in pharmaceutical chemistry.[6]

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[1] a) K. C. Nicolaou, *Angew. Chem. Int. Ed.* **2013**, *52*, 131-146; b) K. C. Nicolaou, *Isr. J. Chem.* **2018**, *58*, 104-113.
[2] a) P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197-201; b) M. Yan, P. S. Baran, *Org. Process Res. Dev.* **2017**, *21*, 1091-1094; c) D. P. Rotella, *ACS Chem. Neurosci.* **2016**, *7*, 1315-1316.
[3] a) M. S. Kinch, Z. Kraft, T. Schwartz, *Drug Discov. Today* **2024**, *29*, 103966; b) B. G. de la Torre, F. Albericio, *Molecules* **2024**, *29*, 585.
[4] a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414-4435; b) K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem. Int. Ed.* **2000**, *39*, 44-122; c) L.-C. Campeau, D. E. Fogg, *Organometallics* **2019**, *38*, 1-2.
[5] a) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085; b) A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 6722-6737; c) R. F. Heck, in *Organic Reactions*, pp. 345-390; d) S. Blechert, *Nachr. Chem. Tech. Lab.* **1981**, *29*, 178-179; e) A. O. King, N. Okukado, E.-i. Negishi, *J. Chem. Soc., Chem. Commun.* **1977**, 683-684.
[6] M. J. Buskes, M.-J. Blanco, *Molecules* **2020**, *25*, 3493.

Also the field of transition metal catalyzed C-N bond formation, developed and continuously advanced by Buchwald[7] and Hartwig[8] has justified its relevance with a study of 2016 reporting, that about 10 % of papers in medicinal chemistry featured Buchwald-Hartwig Aminations.[9] The development of transition metal-catalyzed reactions continues to change the way chemists approach the construction of complex organic molecules.

In this context, photoredox catalysis has proven to be highly effective in enabling catalytic access to high-energy oxidation levels and electronically excited states of organometallic transition metal complexes.[10] From the domination of radicals generated by tin-precursors towards efficient photoinduced electron transfer (photoredox) mediated processes, the recent renaissance of radical chemistry has sparked exceptional scientific interest in harnessing these single-electron species. However, the latter being highly reactive and difficult to control, stereoselective radical reactions long remained a challenging field.[11]

Compared to the rapid developments made in other scientific areas, the integration of machine learning and predictive modeling in organic chemistry may still be considered in its infancy. Machine learning algorithms can analyze vast datasets of chemical reactions to predict outcomes, optimize reaction conditions and suggest novel synthetic pathways. Still, time- and resource-consuming trial-and-error attempts comprising large datasets continue to be required for an ingenious reaction design, limiting the impact of machine learning in synthetic organic chemistry so far.[12]

[7] A. S. Guram, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 7901-7902.
[8] F. Paul, J. Patt, J. F. Hartwig, *J. Am. Chem. Soc.* **1994**, *116*, 5969-5970.
[9] D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443-4458.
[10] J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans, D. W. C. MacMillan, *Nat. Rev. Chem.* **2017**, *1*, 0052.
[11] a) J. Großkopf, T. Kratz, T. Rigotti, T. Bach, *Chem. Rev.* **2022**, *122*, 1626-1653; b) S. Crespi, M. Fagnoni, *Chem. Rev.* **2020**, *120*, 9790-9833.
[12] S.-Q. Zhang, L.-C. Xu, S.-W. Li, J. C. A. Oliveira, X. Li, L. Ackermann, X. Hong, *Chem. Eur. J.* **2023**, *29*, e202202834.

2. Organometallic Chemistry

Organometallic compounds in general are molecules comprising at least one bond between a carbon atom of an organic residue and a metal or metalloid. A wide range of organometallic compounds is known, including alkaline, alkaline earth, transition metals and metalloids such as boron, silicon and selenium.[13]

The beginnings of organometallic chemistry may be traced back to 1757, when French pharmacist Louis-Claude Cadet de Gassicourt prepared the *liqueur fumante*, nowadays considered as the first organometallic compound. Cadet, who wasn't aware of his achievement, thermally reacted arsenious oxide with potassium acetate, forming tetramethyldiarsine colloquially known as Cacodyl.[14] Many other important discoveries followed, including the first essentially pure isolated organometallic compound trichloro(ethylene)platinate(II) monohydrate named Zeise's Salt in 1827.[15] Driven by the growing interest of preparing organic compounds from inorganic materials, Edward Frankland attempted 1848 to prepare "ethyl" by reacting ethyl iodide with zinc metal, resulting in the formation of diethyl zinc.[16] The pioneering work of Victor Grignard towards organomagnesium reagents got awarded the Nobel Prize in chemistry in 1912.[17] Nowadays the Grignard reaction is almost indispensable in organic chemistry, being involved a broad field of synthetic applications.[18] One factor that significantly influences the properties of organometallic compounds is the polarization of the carbon-metal bond, exerting a major impact on stability, reactivity and functional group (FG) tolerance. This polarization can be best characterized by the difference in electronegativity between the two participating atoms (Figure 1).[19]

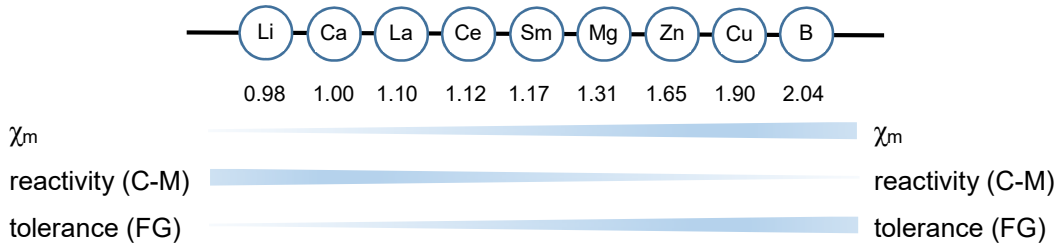
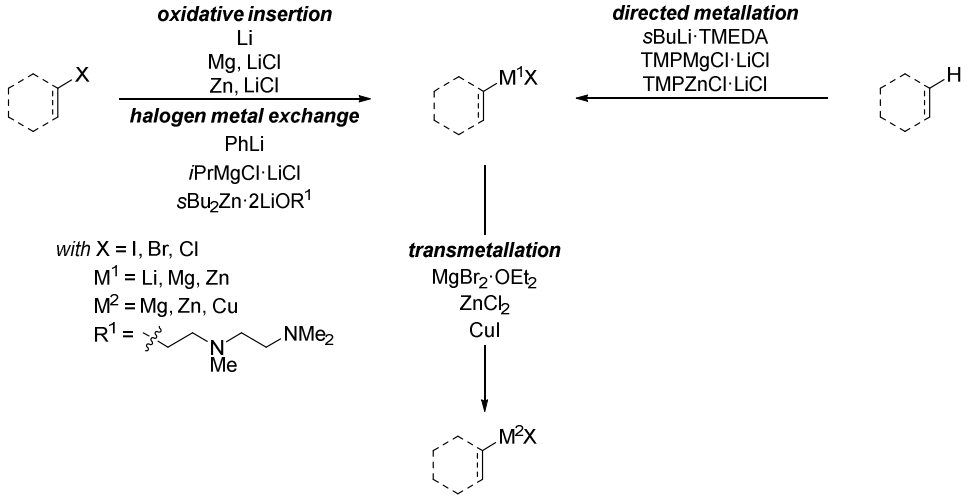


Figure 1: Eletronegativity according to Pauling scale for commonly employed metals and metalloids and the resulting effect on reactivity, stability and functional group tolerance of the respective organometallic species.

[13] a) S. D. Robertson, M. Uzelac, R. E. Mulvey, *Chem. Rev.* **2019**, *119*, 8332-8405; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489.
[14] D. Seyferth, *Organometallics* **2001**, *20*, 1488-1498.
[15] W. C. Zeise, *Ann. Phys.* **1831**, 497-541.
[16] a) E. Frankland, *Liebigs Ann. Chem.* **1848**, *71*, 171; b) E. Frankland, *J. Chem. Soc.* **1848**, *2*, 263.
[17] a) V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322–1324; b) V. Grignard, *Ann. Chim.* **1901**, *24*, 433.
[18] H. Rheinholdt, *J. Chem. Educ.* **1950**, *27*, 476.
[19] a) A. L. Allred, *J. Inorg. Nucl. Chem.* **1961**, *17*, 215-221; b) L. Pauling, *J. Am. Chem. Soc.* **1932**, *54*, 3570-3582.

As the Pauling electronegativity of carbon (2.55) exceeds all metal or metalloids, organic residues generally act as nucleophiles when bound to metals. Importantly, the reactivity of organometallics as well increases from C_{sp}-M to C_{sp}^2-M to C_{sp}^3-M species, as a result of diminished stabilization of the nucleophilic carbon atom with increasing p-orbital character.[20] Accordingly, highly ionic species like organolithium reagents provide an excellent reactivity but on the other hand are less stable and have proven to be incompatible with certain sensitive functional groups.[21] Organoboron compounds, in contrast, possess a very covalent carbon-metal bond, providing an exceptional functional group tolerance, but sometimes require further activation due to their low reactivity.[22] Depending on the polarization also different handling of the respective organometallic compounds is required. Organolithium reagents act as nucleophiles towards ethereal solvents, thus have to be stored in hydrocarbon solvents at low temperature to prevent degradation.[23] Furthermore, reactions with such highly reactive reagents require cryogenic temperatures, whereas for organometalllics with a more covalent character like organozinc compounds, harsh conditions or additives might be necessary for certain reactions due to their moderate reactivity.[24]



Scheme 1: The four major synthetic pathways towards functionalized organometallic compounds.

[20] A. Music, D. Didier, *Synlett* **2019**, *30*, 1843-1849.
[21] J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon Press, Oxford, **2002.**
[22] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483; b) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176-4211.
[23] H. Gilman, B. J. Gaj, *J. Org. Chem.* **1957**, *22*, 1165-1168.
[24] a) J. Shannon, D. Bernier, D. Rawson, S. Woodward, *Chem. Commun.* **2007**, 3945-3947; b) A. D. Dilman, V. V. Levin, *Tetrahedron Lett.* **2016**, *57*, 3986-3992.

Concerning the preparation of organometallic compounds three major pathways have been established (Scheme 1). These routes include oxidative insertion, halogen-metal exchange and directed metalation. Furthermore, transmetalation provides an additional approach towards organometallic reagents.[25]

2.1 Preparation of Organometallic Reagents

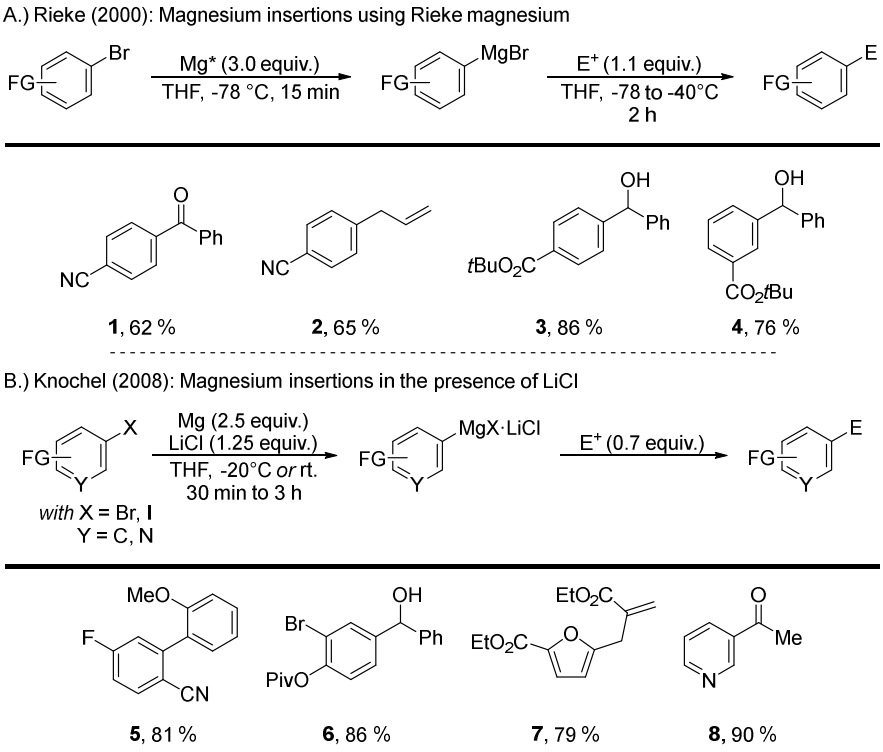
2.1.1 Oxidative Insertion

A widely used and well-studied method for synthesizing organometallic reagents is the oxidative insertion of a metal into a carbon-halogen bond. Compared to halogen/metal exchange or directed metalation, this approach offers certain advantages such as higher atom economy, low cost, and reduced toxicity of the employed metal. The first successful insertion was carried out by Grignard, who treated methyliodide with magnesium in diethyl ether.[17] However, harsh conditions were required due to the low reactivity of the zerovalent metal. Modern advancements have improved the preparation process compared to the original methods of Grignard and Frankland[16], which were limited by low functional group tolerance, long reaction times, and the need for reflux conditions (30-60°C).[26] Today, refinements, such as the addition of iodine (Gillman catalyst) or 1,2-dibromoethane, facilitate the activation of often oxidized, thus passivated magnesium metal.[27]

An important milestone was made by Rieke and coworkers, who generated magnesium powder *via in-situ* reduction of an anhydrous metal halide solution using alkali metals.[28] While early reports by Rieke *et al.* towards active magnesium described the reduction of anhydrous $MgCl_2$ or $MgBr_2$ with potassium in refluxing THF, more recent studies focused on reductions with elemental lithium, employing naphthalene as electron carrier. This highly reactive “Riecke-Magnesium” (Mg*) enables oxidative insertions at cryogenic temperatures, while at the same time sensitive functionalities like nitriles or esters are tolerated (Scheme 2, A, **1**-**4**). Remarkably, Grignard reagents from previously considered unreactive organic chlorides and fluorides can be obtained with Mg*. However, due to the hazardous handling of alkaline metals in large scale and the resulting complex experimental setup, oxidative insertions with “Riecke-magnesium” are mainly performed on laboratory scale.[27b]

[25] R. G. Jones, H. Gilman, *Chem. Rev.* **1954**, *54*, 835-890.
[26] B. J. Wakefield, *Appl. Organomet. Chem.* **2000**, *14*, 396-396.
[27] a) D. E. Pearson, D. Cowan, J. D. Beckler, *J. Org. Chem.* **1959**, *24*, 504-509; b) U. Tilstam, H. Weinmann, *Org. Process Res. Dev.* **2002**, *6*, 906-910; c) H. Gold, M. Larhed, P. Nilsson, *Synlett* **2005**, *2005*, 1596-1600; d) H. Gilman, N. B. St. John, *Recl. Trav. Chim. Pays-Bas* **1930**, *49*, 717-723; e) H. Gilman, R. H. Kirby, *Recl. Trav. Chim. Pays-Bas* **1935**, *54*, 577-583.
[28] a) T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 3674-3680; b) R. D. Rieke, *Science* **1989**, *246*, 1260-1264.

In 2008 Knochel *et al.* reported a LiCl mediated magnesium insertion.[29] The addition of LiCl may pose several advantages, firstly promoting the initial electron transfer by electrophilic activation of the aromatic ring through complexation. Secondly, the high ionic strength of LiCl solutions facilitates charge separation, and thus accelerates metal insertion. This mild method allows for oxidative insertions into (hetero)aryl bromides and chlorides at ambient temperature, combining short reaction times with a broad functional group tolerance (Scheme 2, B, **5**-**8**).

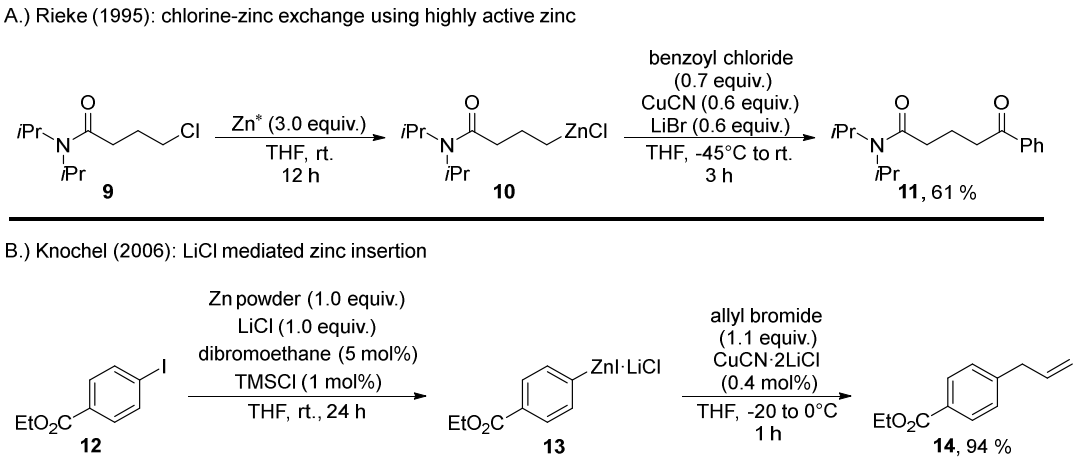


Scheme 2: Different routes towards oxidative insertion of $Mg^{(0)}$.

Analogous, functionalized organozinc reagents can be also accessed by oxidative insertion of zinc powder into carbon-halide bonds. Hereby, activation of the often passivated zinc surface has proven to be crucial to obtain complete and reproducible insertions. The combination of 1,2-dibromoethane and trimethylsilylchloride has established as a standard method to ensure full activation of the employed zinc powder. The previously mentioned approach of Rieke *et al.* presents another efficient route towards functionalized organozinc reagents, using highly active zinc ("Rieke-zinc"). Similarly, it can be accessed by *in situ* reduction of zinc salts with alkaline metals (e.g. sodium or potassium) in the presence of electron carriers like naphthalene.[30]

[29] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802-6806.
[30] R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323-4324.

When *N,N*-di*iso*propyl-3-chlorobutamide (**9**) is treated with freshly prepared “Rieke-zinc”, insertion proceeds within 12 hours. The organozinc compound (**10**) is then subjected to copper-catalysed acylation, affording compound **11** in 61 % yield.[31]



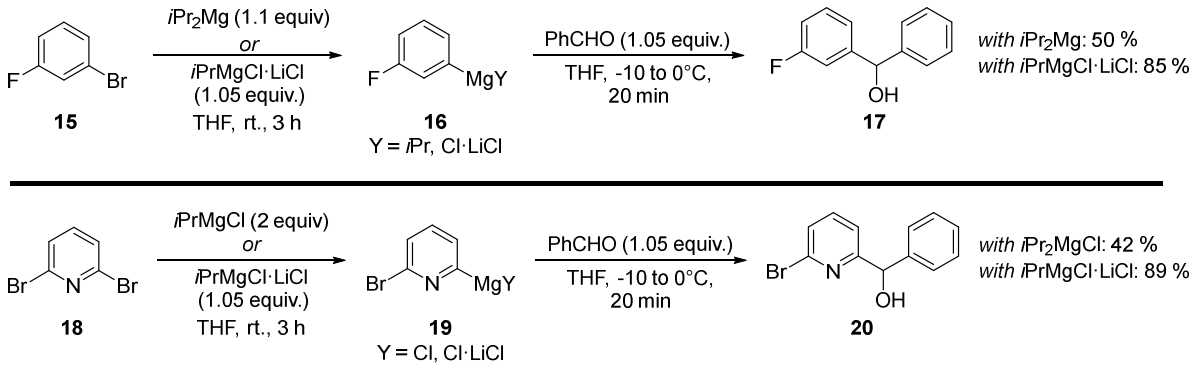
Scheme 3: Different routes towards oxidative insertion of $Zn^{(0)}$.

As shown by Knochel and coworkers, stoichiometric amounts of LiCl significantly accelerate zinc insertion by generating highly soluble RZnX·LiCl complexes, likely preventing deactivation of the Zn-metal sites. This approach enabled unprecedented insertions into (hetero)aryl iodides and bromides, as well as primary, secondary and tertiary alkyl bromides. Under these conditions, smooth insertion of zinc powder into the carbon-iodide bond of ethyl 4-iodobenzoate (**12**) is achieved within 24 hours. Copper-catalyzed allylation afforded substituted benzoate (**14**) in 94 % yield (Scheme 3, B). Notably, only less than 5 % conversion could be obtained if LiCl was omitted and the starting halide was treated with activated Zn, followed by heating to 70°C for 24 hours.[32]

[31] M. Hanson, R. D. Rieke, *Synth. Commun.* **1995**, *25*, 101-104.
[32] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040-6044.

2.1.2 Halogen-Metal Exchange

The conversion of organic halides into the corresponding organometallic compound with an exchange reagent represents a convenient and versatile pathway towards organometallic compounds.[33] Wittig and Gilman first described this route independently *via* lithium-halogen exchange in the late 1930's, reacting 1,3-dimethoxy-4,6-dibromobenzene with PhLi and *o*-bromoanisole with *n*BuLi, respectively.[34] Due to the rapid formation of the organolithium species the lithium-halogen exchange remains one of the most frequently used exchange reactions. A halogen-metal exchange reaction can basically be regarded as an equilibrium process, wherein the formation of the thermodynamically most stable species is favored by hybridization ($sp > sp^2_{vinyl} > sp^2_{aryl} > sp^3_{prim} > sp^3_{sec} > sp^3_{tert}$), compared to the exchange reagent itself. Hereby the direction of the exchange depends mainly on the organic residue, whereas the rate is determined by the electronegativity of the metal explaining the different reaction rates of lithium-halogen and magnesium-halogen exchange reactions.[35] Compared to the lithium-halogen exchange the magnesium pendant offers, due to their less ionic character, reduced reactivity and improved functional group tolerance.[33] First described by Prévost[36] in 1931 with the reaction of cinnamyl bromide and EtMgBr this route attracted great interest and was further expanded by Cahiez and Knochel.[37] Focusing on the iodine-magnesium exchange, this route was established using *i*PrMgCl and PhMgCl, while tolerating sensitive functionalities like esters and nitriles.

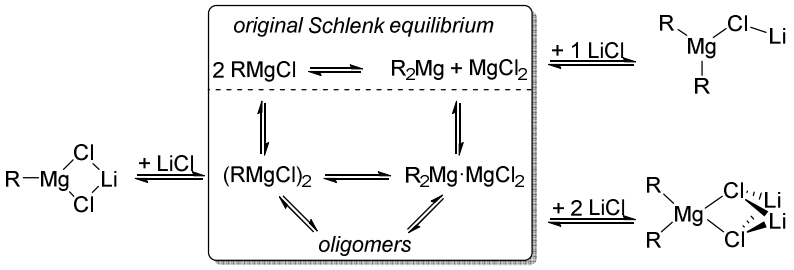


Scheme 4: Halogen-magnesium exchange employing *i*PrMgCl·LiCl and other exchange reagents.

[33] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733-738.
[34] a) G. Wittig, U. Pockels, H. Dröge, *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 1903-1912; b) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106-109.
[35] W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1-46.
[36] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, 1372.
[37] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701-1703; b) M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 7449-7453; c) G. Varchi, A. Ricci, G. Cahiez, P. Knochel, *Tetrahedron* **2000**, *56*, 2727-2731.

The commercially available “Turbo-Grignard” by Knochel and coworkers, generated by stoichiometric addition of LiCl to *i*PrMgCl, provided a combination of enhanced reactivity and solubility in comparison to its salt free predecessor. While an increase in yield and a decrease in reaction time could be observed, it was possible to apply milder reaction conditions and achieve higher functional group tolerance.

Treating 1-bromo-3-fluorobenzene (**15**) with *i*Pr_2Mg only provides the respective Grignard reagent (**16**) with moderate conversion, thus upon trapping with benzaldehyde only 50 % of alcohol (**17**) is obtained. Conducting the reaction with *i*PrMgCl·LiCl as exchange reagent affords 85 % of the desired compound (**17**). Similarly, employing salt free *i*PrMgCl provides only 42 % of compound **20**, while with *i*PrMgCl·LiCl an excellent yield of 89 % is obtained (Scheme 4).[38]



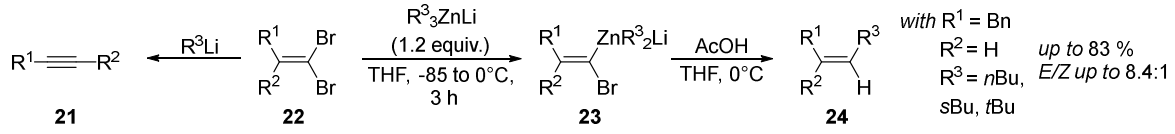
Scheme 5: Effect of LiCl on the Schlenk equilibrium of Grignard reagents.

According to the Schlenk concept for Grignard reagents, a mixture of several aggregates is present which are all connected by equilibria. The position of these equilibria may not only depend on the organic residue, but also on the applied solvent, the concentration, the temperature or the used halide. In the case of *i*PrMgCl·LiCl these equilibria are highly affected by the addition of LiCl, making the characterization of active species more complex (Scheme 5). The higher kinetic activity of this reagent is caused by the formation of magnesium-lithium ate complexes.[39] The group of Stalke demonstrated with electrical conductivity measurements, that the degree of magnesate formation and heterolytic dissociation is low for RMgCl and strongly increases upon the addition of LiCl. Compared to the salt free variant, a larger fraction of more electron-rich and, thus, putatively more nucleophilic ate complexes is present, which may explain the enhanced reactivity.[40] Still, the liquid state reactive species could not yet be clearly characterized; thus only tentative structural suggestions of the reactive species can be formulated.

[38] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333-3336.
[39] A. Hermann, R. Seymen, L. Brieger, J. Kleinheider, B. Grabe, W. Hiller, C. Strohmann, *Angew. Chem. Int. Ed.* **2023**, *62*, e202302489.
[40] C. Schnegelsberg, S. Bachmann, M. Kolter, T. Auth, M. John, D. Stalke, K. Koszinowski, *Chem. Eur. J.* **2016**, *22*, 7752-7762.

2.1.2.1 Halogen-Zinc Exchange

Alternatively, functionalized alkyl-, alkenyl and (hetero)arylzinc reagents can be accessed conveniently *via* halogen/zinc exchange, using diorganozinc reagents or zincates. As previously discussed, the more covalent character of the halogen-zinc bond kinetically disfavors the exchange. Thus, harsh conditions and polar solvents are required to drive the reaction.[41] While the iodide-zinc exchange is reported for primary alkyl iodides using excess of diethylzinc at elevated temperatures[42], zincates present a more potent class of exchange reagents to perform halogen-zinc exchanges.[43] Depending on the stoichiometry, triorganozincates (monoanion-type zincates) and tetraorganozincates (dianion-type zincates) can be accessed by treatment of the respective lewis-acidic diorganozinc with Lewis basic alkyl or alkoxide anions. Alternatively, addition of substoichiometric amounts of zinc(II) salts to organolithium reagents can be used to generate zincates of the aforementioned types.[44]
In the pioneering work by Oku *et al.* in 1988 an intramolecular alkylation of 1,1-dibromoalkenes using triorganozincates was described. Conventional treatment of these dibromoalkenes (**22**) with organolithium reagents may result in Fritsch-Buttenberg-Wiechell rearrangement, which produces the corresponding alkyne (**21**) among other side products (Scheme 6).

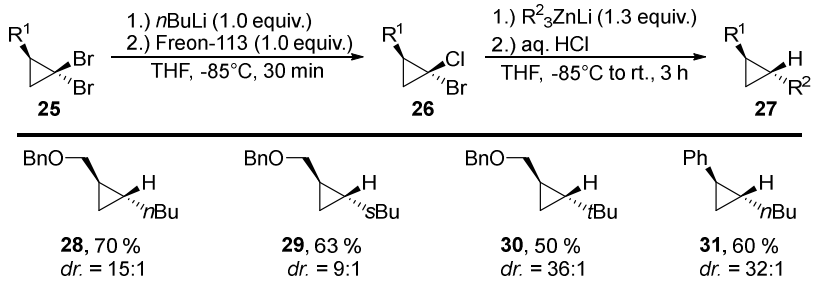


Scheme 6: First report of monoanion-type zincates by Oku and coworkers.

However, if being treated with the respective triorganozincates, 1-bromoalkenylzincates (**23**) are obtained. While being relatively stable at -85°C, these species readily undergo intramolecular alkylation towards (**24**) when being warmed to 0°C. Depending on the nature of the organozincate only moderate selectivities (*E*/*Z* = up to 8.4:1 with *t*BuLi) are obtained (Scheme 6).[45]
The same synthetic strategy was applied by Oku *et al.* to the synthesis of 1,2-disubstituted cyclopropanes (**27**). Starting from readily accessible dibromocyclobutanes (**25**), which were treated with *n*BuLi and trapped with Freon-113, gave rise to *trans*-1-bromo-1-chlorocyclopropanes of type **26**.

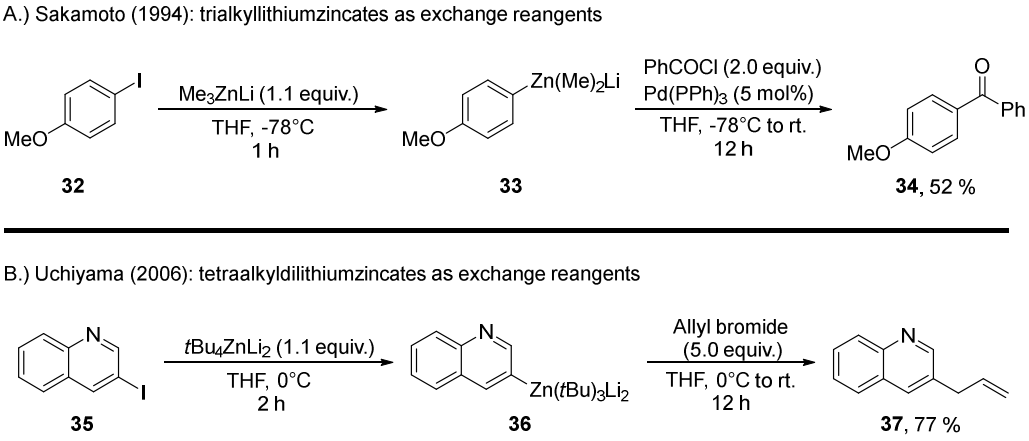
[41] S. Nakamura, C.-Y. Liu, A. Muranaka, M. Uchiyama, *Chem. Eur. J.* **2009**, *15*, 5686-5694.
[42] M. J. Rozema, A. Sidduri, P. Knochel, *J. Org. Chem.* **1992**, *57*, 1956-1958.
[43] M. Balkenhohl, P. Knochel, *Chem. Eur. J.* **2020**, *26*, 3688-3697.
[44] M. Uchiyama, Y. Kondo, *有機合成化学協会誌* **2006**, *64*, 1180-1190.
[45] T. Harada, D. Hara, K. Hattori, A. Oku, *Tetrahedron Lett.* **1988**, *29*, 3821-3824.

Upon treatment with zincates, the desired *trans*-alkylation products could be accessed. Again, depending on the steric hindrance of the employed zincate, diastereoselectivities of up to 36:1 are obtained (Scheme 7, **28**-**31**).[46]



Scheme 7: Stereoselective exchange of dihalocyclopropanes by Oku and coworkers.

Employing lithiumtrimethylzincate species, Sakamoto and coworkers disclosed the first iodide-zinc exchange of aryl iodides. Iodoarenes containing sensitive functionalities were shown to be tolerant to these conditions and treated with aldehydes, allyl halides and acyl chlorides. Iodoanisole **32** was smoothly converted to zincate **33** and trapped with benzoyl chloride under Pd-catalysis, affording benzophenone derivative **34** in 52 % yield (Scheme 8, A).[47]



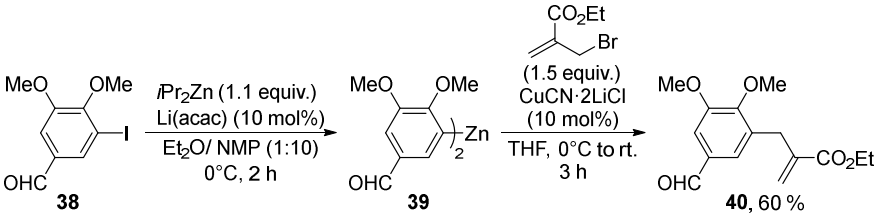
Scheme 8: Contributions by Sakamoto and Uchiyama towards halogen-zinc exchange of (hetero)aryls.

Employing the more hindered zincate $t\text{Bu}_4\text{ZnLi}_2$ allowed similar transformations at milder temperatures.[48] Readily prepared by addition of $t\text{Bu}_2\text{Zn}$ to *t*BuLi, this reagent showed excellent functional group tolerance, tolerating even free benzylic alcohols.

[46] T. Harada, K. Hattori, T. Katsuhira, A. Oku, *Tetrahedron Lett.* **1989**, *30*, 6035-6038.
[47] Y. Kondo, N. Takazawa, C. Yamazaki, T. Sakamoto, *J. Org. Chem.* **1994**, *59*, 4717-4718.
[48] M. Uchiyama, T. Furuyama, M. Kobayashi, Y. Matsumoto, K. Tanaka, *J. Am. Chem. Soc.* **2006**, *128*, 8404-8405.

Upon treatment with a slight excess of zincate the iodine-zinc exchange of 3-iodoquinoline (**35**) is completed within 2 hours at 0°C. Trapping with allyl bromide affords allylated quinoline (**37**) in 77 % yield after 12 h reaction time (Scheme 8, B).

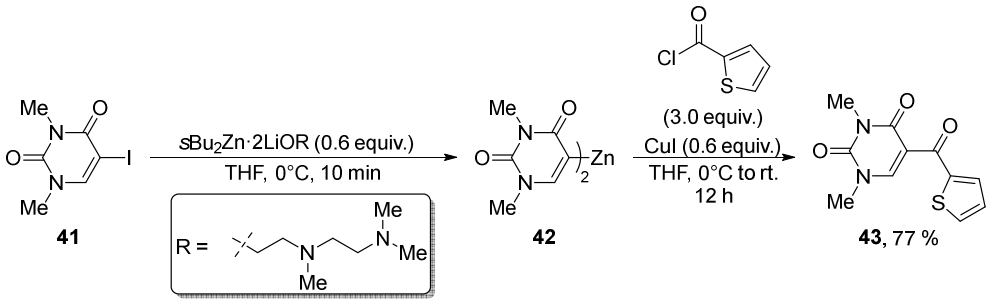
In 2004 Knochel *et al.* reported a mild strategy towards (hetero)aryl iodide-zinc exchange using either *i*Pr_2Zn or *s*Bu_2Zn. This transformation enabled the generation of functionalized bimetallic zincates at milder temperatures, compared to previous strategies. Hereby, catalytic addition of Li(acac) was found to increase the reactivity of the employed exchange reagent, by *in situ* formation of zincates.



Scheme 9: Halogen-zinc exchange of (hetero)aryl iodides with *i*Pr_2Zn/ Li(acac) system by Knochel *et al.*

Under these conditions the zincate of substituted aldehyde **38** could be smoothly obtained after 2 h at 0°C. Treatment with CuCN·2LiCl and subsequent allylation afforded the respective aldehyde **40** in 60 % yield (Scheme 9).[49]

Recently the group of Knochel reported an exchange reagent consisting of *s*Bu_2Zn complexed with two equivalents of a primary lithium alkoxide. This zincate proved to be tolerant to a wide range of functional groups, yet proved to be very reactive. Electron-rich, as well as electron deficient (hetero)aryl iodides underwent rapid exchange in under 15 min while not requiring cryogenic conditions. Notably, (hetero)aryl bromides were also tolerated, only requiring longer reaction times for the exchange. Unfortunately, the preparation of the stable bimetallic reagent requires cryogenic temperatures and switching of solvent, limiting its applicability to a certain degree.



Scheme 10: Mild halogen-zinc exchange using *s*Bu_2Zn·2LiOR reported by Knochel and coworkers.

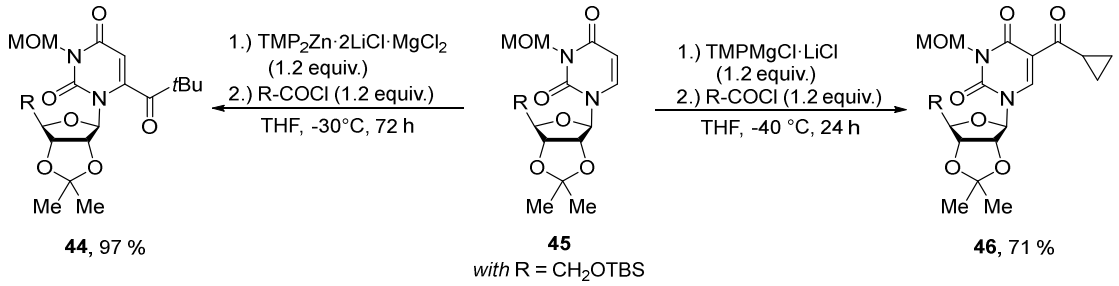
When treated with substoichiometric amounts of *s*Bu_2Zn·2LiOR the depicted 1,3-dimethyluracil (**41**) underwent iodine-zinc exchange within 10 min at 0°C. Addition of CuI and subsequent acylation afforded **43** in 77 % yield (Scheme 10).[50]

[49] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017-1021.
[50] M. Balkenhohl, D. S. Ziegler, A. Desaintjean, L. J. Bole, A. R. Kennedy, E. Hevia, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 12898-12902.

2.1.3 Directed Metalation and Transmetalation

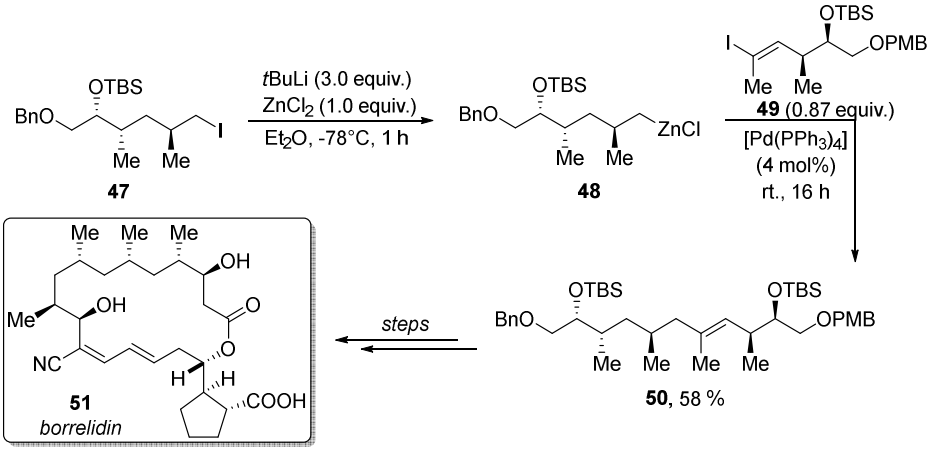
A third route towards functionalized organometallic compounds is represented by directed metalation. Hereby no organic halide precursor is required, the metalation reagent directly deprotonates an acidic carbon-hydrogen bond of the (hetero) aromatic compound or alkene, forming a carbon-metal bond.[51] The first experiments about directed metalation were carried out by Gilman and Wittig, who reported separately about the *ortho*-lithiation of anisole with *n*BuLi and PhLi, respectively.[34a, 52] Among all metalating agents, alkyl lithium bases such as *t*BuLi show the highest reactivity, though their high nucleophilicity often leads to undesired side reactions, such as halogen-lithium exchange, limiting substrate scope.[53] To address this, less nucleophilic and sterically hindered lithium amides, such as LiHMDS, LDA, or TMPLi, are often preferred.[54] However, both types of lithium bases require cryogenic temperatures and show limited functional group tolerance. Analogous to the previously discussed exchange reagents, the implementation of a more electronegative metal like magnesium led to more stable organometallics. Pioneering work from Hauser and coworkers provided the magnesium amide bases with the general formula R_2NMgX and $(R_2N)_2Mg$.[55] Several decades later Eaton and Mulzer established the sterically more hindered bases of type TMPMgX and TMP_2Mg, capable of magnesiating (hetero)arenes with sensitive functional groups like esters, carbamates, or carboxamides.[56] However, these bases still suffered from low kinetic basicity and solubility, requiring large excesses of both the reagent and electrophile to achieve high conversion. To address these challenges, Knochel and coworkers developed the highly active, LiCl-solubilized amide base TMPMgCl·LiCl. This "Turbo-Hauser" base offers excellent basicity, solubility in THF, and thermal stability.[57] Divergent regioselective magnesiations and zincations of protected uridine (**45**) can be achieved with TMPMgCl·LiCl and TMP_2Zn·2LiCl·2MgCl, respectively. Treatment with TMPMgCl·LiCl affords C(5)-magnesiated uridine derivative in excellent regioselectivity (C(5)/C(6) = 98:2) and is subjected to copper-catalyzed acylation to afford **46**. A complete switch in regioselectivity can be observed when employing TMP_2Zn·2LiCl·2MgCl (C(5)/C(6) = 3:97), providing C(6) acylated uridine (**44**) in 97 % yield (Scheme 11).[58]

[51] J. Clayden, in *The chemistry of organolithium compounds*, **2004**, pp. 495-646.
[52] R. L. B. H. Gilman, *J. Am. Chem. Soc.* **1939**, *61*, 109-112.
[53] a) P. Beak, V. Snieckus, *Acc. Chem. Res.* **1982**, *15*, 306-312; b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879-933.
[54] a) R. R. Fraser, T. S. Mansour, *J. Org. Chem.* **1984**, *49*, 3442-3443; b) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470-11487.
[55] a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295-297; b) F. C. Frostick, C. R. Hauser, *J. Am. Chem. Soc.* **1949**, *71*, 1350-1352.
[56] a) P. E. Eaton, C. H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016-8018; b) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414-8416; c) A. H. W. Schlecker, E. Ottow, J. Mulzer, *Liebigs Ann. Chem.* **1995**, 1441–1446.
[57] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958-2961; b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794-9824. [58] L. Klier, E. Aranzamendi, D. Ziegler, J. Nickel, K. Karaghiosoff, T. Carell, P. Knochel, *Org. Lett.* **2016**, *18*, 1068-1071.



Scheme 11*:* Regioselective magnesiations/ zincations of uridine derivatives with TMPMgCl·LiCl and $TMP_2Zn·2LiCl·2MgCl$.

Transmetalation provides an additional approach to functionalized organometallics. When an organometallic species is treated with the salt of a less electropositive metal, the more stable carbon metal bond and more ionic salt is generated.[59] For instance, treating a magnesium reagent with $ZnCl_2$ leads to a more covalent thus more stable organometallic species, while the more ionic salt $MgCl_2$ is produced. For the transmetalation process, the presence of a prior organometallic reagent is evident. Thus, it is often used as a followup reaction in Negishi cross-couplings or copper-catalyzed allylations and acylations.[60]



Scheme 12: Morkens approach towards the enantioselective synthesis of borrelidin.

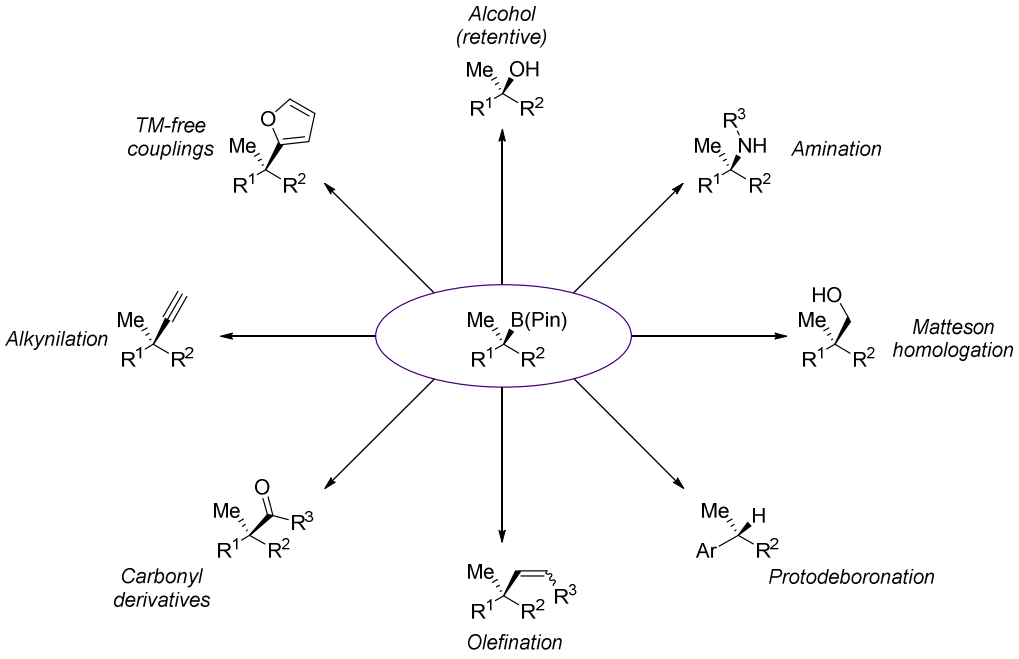
Morken and coworkers employed a modified Negishi-coupling, involving highly functionalized zinc species (**48**) in their total synthesis towards borrelidin. Halogen-metal exchange with *t*BuLi and transmetalation with $ZnCl_2$ provided chiral zinc reagent **48**, which was *in-situ* coupled with vinyl iodide (**49**) to obtain subunit **50** of borrelidin (**51**) in 58 % yield (Scheme 12).[61]

[59] a) K. Moriya, M. Simon, R. Mose, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10963-10967; b) C. Elschenbroich, *Organometallchemie*, Teubner, Wiesbaden, **2008**.
[60] a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681-7684; b) T. Bresser, G. Monzon, M. Mosrin, P. Knochel, *Org. Process Res. Dev.* **2010**, *14*, 1299-1303.
[61] M. O. Duffey, A. LeTiran, J. P. Morken, *J. Am. Chem. Soc.* **2003**, *125*, 1458-1459.

3. Organoboron Chemistry

When Frankland and Duppa prepared in 1862 triethylborane from diethylzinc and triethyl borate, they obtained upon hydrolysis ethylboronic acid, marking it the first synthesis of this class of reagents.[62] In 1909 Khotinsky und Melamed demonstrated, that the more accessible organomagnesium reagents could be employed, establishing a procedure that still remains today as a general approach towards boronic acids.[63] However, research progress in boron chemistry came slow, mainly due to the limited preparative methods for generating diborane at that period.[64] The development of sodium borohydride by Schlesinger and Brown in 1942 and lithium aluminium hydride in 1945 led to a revolutionary change towards reduction of functional groups.[65] The development of new reagents, such as $LiBH_4$ and $LiAlH(O\textit{t}Bu)_3$ allowed selective reductions of functional groups in the presence of others.[66] It wasn't until 1956, when the discovery of hydroboration by H.C. Brown and coworkers revolutionized the field of boron chemistry, as organoboranes now could be readily accessed from the corresponding alkenes or alkynes.[67] This hydroboration of olefins involves a *cis*-addition of the boron hydrogen bond; the boron being attached to the less substituted of the two olefinic carbon atoms. The assymetric version, reported in 1961 also provided the fundamentals for modern assymetric synthesis, as hydroborating agents like diisopinocampheylborane (Ipc_2BH) provided enantioselectivities (83 – 91 % *ee.*) previously only obtained through enzymatic reactions.[68] Importantly, the Brown oxidation with alkaline hydrogen peroxide occurs with complete retention of configuration providing a reliable synthetic method for the anti-Markovnikov *cis*-hydration of alkenes.[69] Many milestones in Boron chemistry followed, like the Corey–Bakshi–Shibata (CBS) reagent, allowing unprecedented asymmetric reductions.[70]
Between 1980 and 1981, Matteson not only pioneered the Matteson-homologation of boronates with (dihalo)methyllithium reagents but also extended this synthesis to produce the first peptide boronic acids.[71] Since then, numerous peptide boronic acids have been reported, exhibiting various binding modes between boron and their biological targets. The most notable of these is bortezomib marketed under the brand name Velcade, which the FDA approved as an injectable treatment for multiple myeloma in 2003.[72]

[62] E. Frankland, *J. Chem. Soc.* **1862**, *15*, 363-381.
[63] E. Khotinsky, M. Melamed, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3090-3096.
[64] H. C. Brown, Nobel Lecture, **1979**, Nobel Prize Outreach AB, NobelPrize.org, *Vol. 2024.*
[65] a) H. I. Schlesinger, H. C. Brown, H. R. Hoekstra, L. R. Rapp, *J. Am. Chem. Soc.* **1953**, *75*, 199-204; b) A. E. Finholt, A. C. Bond, Jr., H. I. Schlesinger, *J. Am. Chem. Soc.* **1947**, *69*, 1199-1203.
[66] H. C. Brown, B. C. S. Rao, *J. Am. Chem. Soc.* **1956**, *78*, 2582-2588.
[67] H. C. Brown, B. C. S. Rao, *J. Am. Chem. Soc.* **1956**, *78*, 5694-5695.
[68] H. C. Brown, G. Zweifel, *J. Am. Chem. Soc.* **1961**, *83*, 486-487.
[69] H. Brown, B. C. Rao, *J. Org. Chem.* **1957**, *22*, 1136-1137.
[70] E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.
[71] a) D. S. Matteson, *Tetrahedron* **1998**, *54*, 10555-10607; b) D. S. Matteson, *J. Org. Chem.* **2013**, *78*, 10009-10023.
[72] R. Smoum, A. Rubinstein, V. M. Dembitsky, M. Srebnik, *Chem. Rev.* **2012**, *112*, 4156-4220.



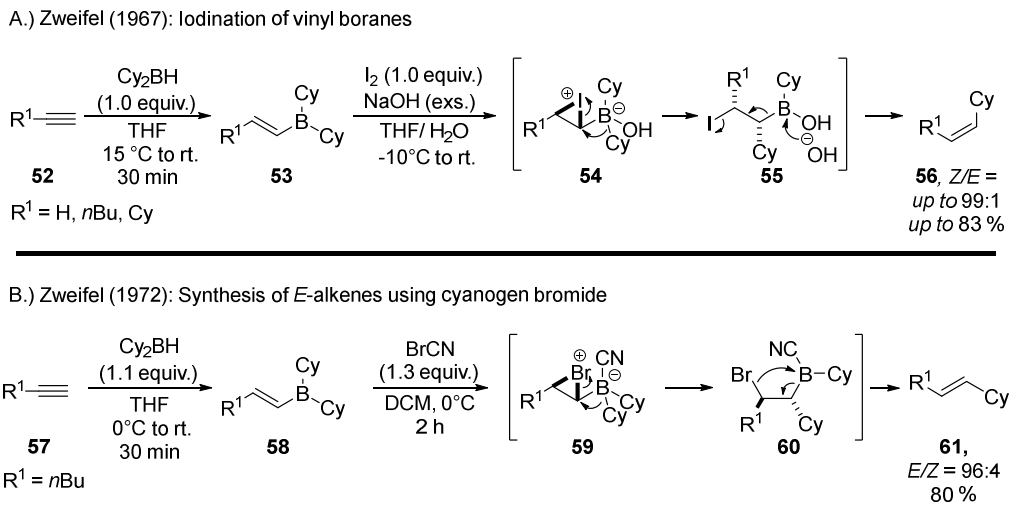
Scheme 13: Selected stereospecific transformations of secondary and tertiary boronic esters.[75]

Finally, the Nobel Prize-winning palladium-catalyzed cross-coupling of boronic acid derivatives with carbon halides, developed by Suzuki and Miyaura, significantly boosted research interest in boronic acids and their related esters.[5a, 73] Nowadays, these compounds are highly valued not only for their broad reactivity profile but also for their non-toxic nature and excellent functional group tolerance.[74] As shown in Scheme 13, numerous stereospecific transformations of boronic esters and esters thereof have been developed, establishing this class of organoboron reagents as an essential and indispensable tool in modern organic chemistry.[75]

[73] J. W. B. Fyfe, A. J. B. Watson, *Chem* **2017**, *3*, 31-55.
[74] B. S. L. Collins, C. M. Wilson, E. L. Myers, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2017**, *56*, 11700-11733.
[75] a) C. Sandford, V. K. Aggarwal, *Chem. Commun.* **2017**, *53*, 5481-5494; b) N. Xu, H. Liang, J. P. Morken, *J. Am. Chem. Soc.* **2022**, *144*, 11546-11552.

3.1 Zweifel Olefination

In 1967, G. Zweifel, a student of H.C. Brown, studied the hydroboration of alkynes. Inspired by Matteson and Liedke's earlier work on the *trans*-addition of bromine to vinylboronic esters[76], Zweifel shifted focus to the addition of iodine to vinylboranes (**53**) derived from hydroboration of **52**. However, instead of affording the corresponding vinyl iodides, he observed an alkyl-group migration from boron to the adjacent carbon. The addition of aq. NaOH further increased the remarkable (*Z*)-selectivity and efficiency of this transformation. This reaction, now famously known as the Zweifel olefination, proceeds *via* a iodinium intermediate (Scheme 14, A). The addition of sodium hydroxide leads to formation of boronate complex **54**, which after 1,2-metallate rearrangement, provides β-iodoboron species **55**. A second equivalent of hydroxide then attacks the borinic ester **55**, triggering *anti*-elimination of the boron species and iodine, to afford the respective (*Z*)-alkene (**56**).[77]



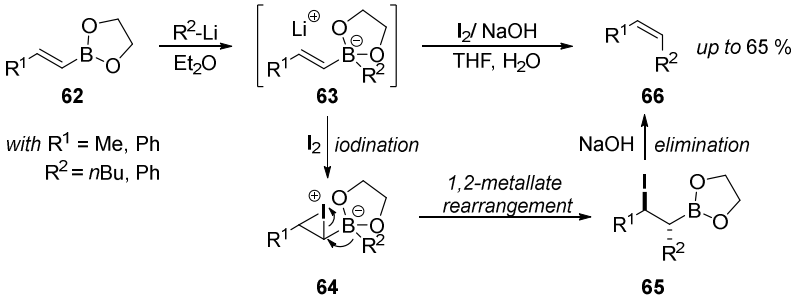
Scheme 14: Discovery of the Zweifel olefination and its variation towards the synthesis of *E*-alkenes.

At the time of Zweifel's discovery, synthetic methods were limited to the preparation of (*E*)-vinyl borane derivatives *via* alkyne hydroboration, thus only (*Z*)-alkenes were accessible by the developed protocol. Later research revealed that employing cyanogen bromide in place of a base efficiently produces the corresponding (*E*)-alkenes. After formation of the bromonium ion (**59**), a boranecarbonitrile (**60**) is formed, which undergoes *syn*-elimination to obtain the respective (*E*)-alkene (**61**) in high selectivity (Scheme 14, B).[78]

[76] D. S. Matteson, J. D. Liedtke, *J. Am. Chem. Soc.* **1965**, *87*, 1526-1531.
[77] a) G. Zweifel, H. Arzoumanian, C. C. Whitney, *J. Am. Chem. Soc.* **1967**, *89*, 3652-3653; b) K. Bojaryn, C. Hirschhäuser, *Chem. Eur. J.* **2022**, *28*, e202104125; c) R. J. Armstrong, V. K. Aggarwal, *Synthesis* **2017**, *49*, 3323-3336.
[78] G. Zweifel, R. P. Fisher, J. T. Snow, C. C. Whitney, *J. Am. Chem. Soc.* **1972**, *94*, 6560-6561.

To address the limited preparative methods and air sensitivity of borane derivatives as starting materials for the Zweifel olefination, Matteson and Evans independently introduced more stable boronic ester derivatives as substrates.

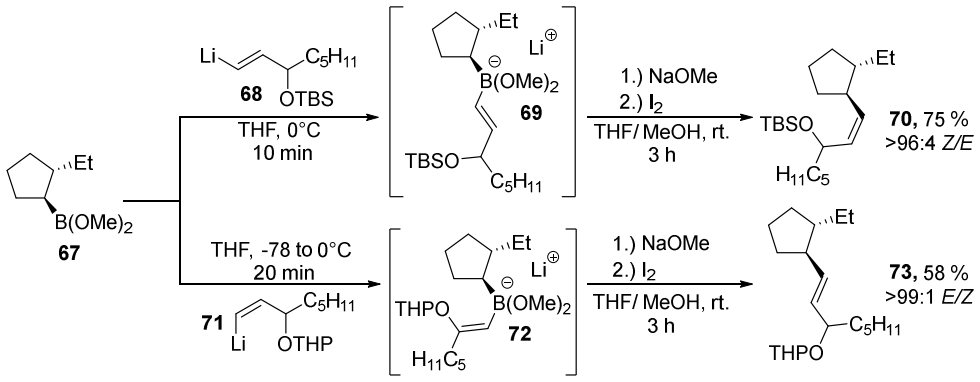
In Matteson's protocol, a vinylboronic ester derivative (**62**) is treated with an organolithium reagent to form vinyl boronate complex **63**. Then, iodine coordinates to the π-bond of the previously formed tetracoordinated boron derivative, forming the iodonium intermediate **64**. A stereospecific 1,2-metallate rearrangement is triggered, and the β-iodoboron derivative **65** is formed. In the presence of a strong base an antiperiplanar β-elimination takes place, furnishing the respective olefin (**66**). As this transformation is highly stereospecific, initial (*E*)-alkenes are transformed in (*Z*)-alkenes and *vice versa* (Scheme 15).[77c]



Scheme 15: Zweifel olefination of vinylboronic esters by Matteson and coworkers.

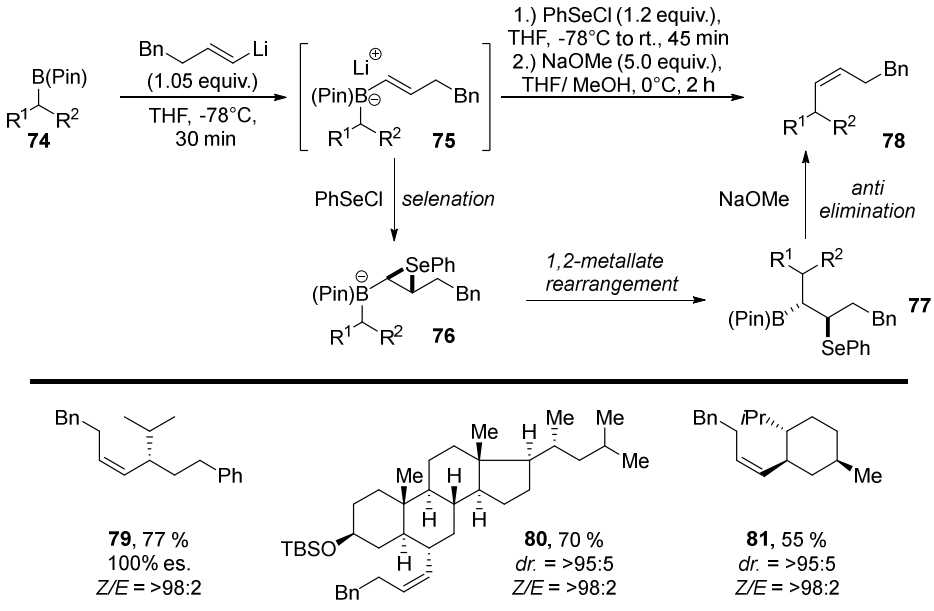
Evans and coworkers took a different approach by starting with a secondary alkyl boronic ester (**67**), which was then treated with an (*E*)-vinyl lithium species (**68**), underlining the versatility of the Zweifel olefination.[79] The intermediately formed boronate complex **69** was treated with iodine and sodium methoxide to access the respective substituted alkene **70** in high selectivity. If a (*Z*)-vinyllithium reagent (**71**) is employed, the respective alkene **73** can be accessed in excellent (*E*)-selectivity (Scheme 16). The approaches developed by Matteson and Evans remain widely applicable for Zweifel olefination, with aq. NaOH often replaced by NaOMe (in MeOH) for improved efficiency and solubility.

[79] a) D. A. Evans, T. C. Crawford, R. C. Thomas, J. A. Walker, *J. Org. Chem.* **1976**, *41*, 3947-3953; b) D. A. Evans, R. C. Thomas, J. A. Walker, *Tetrahedron Lett.* **1976**, *17*, 1427-1430.



Scheme 16: Zweifel olefination of vinyllithium species with alkylboronic esters reported by Evans *et al.*

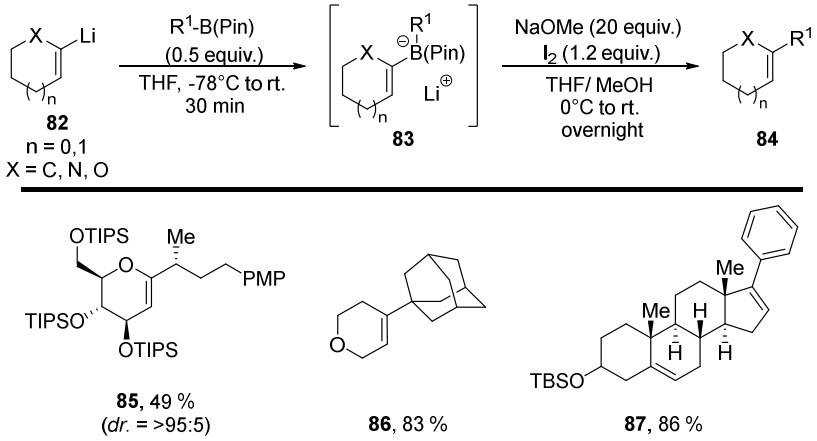
Continiously developing the field of Zweifel olefination, Aggarwal and coworkers described the possible substitution of iodine with PhSeCl to afford β-selenoboronic esters (**77**). Unlike iodine, these selenides are weaker leaving groups, resulting in exclusive *anti*-elimination and producing only the corresponding (*Z*)-isomer (**78**). Products of this transformation were obtained in good to excellent yields as single alkene isomers (Scheme 17, **79**-**81**). Notably, if the intermediately formed β-selenoboronic esters are subjected to oxidation with *m*CPBA, a complete switch of selectivity is observed and only *syn*-elimination products are obtained as single isomers.[80]



Scheme 17: Highly *Z*-selective olefination of secondary boronic esters by Aggarwal and coworkers.

[80] R. J. Armstrong, C. García-Ruiz, E. L. Myers, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2017**, *56*, 786-790.

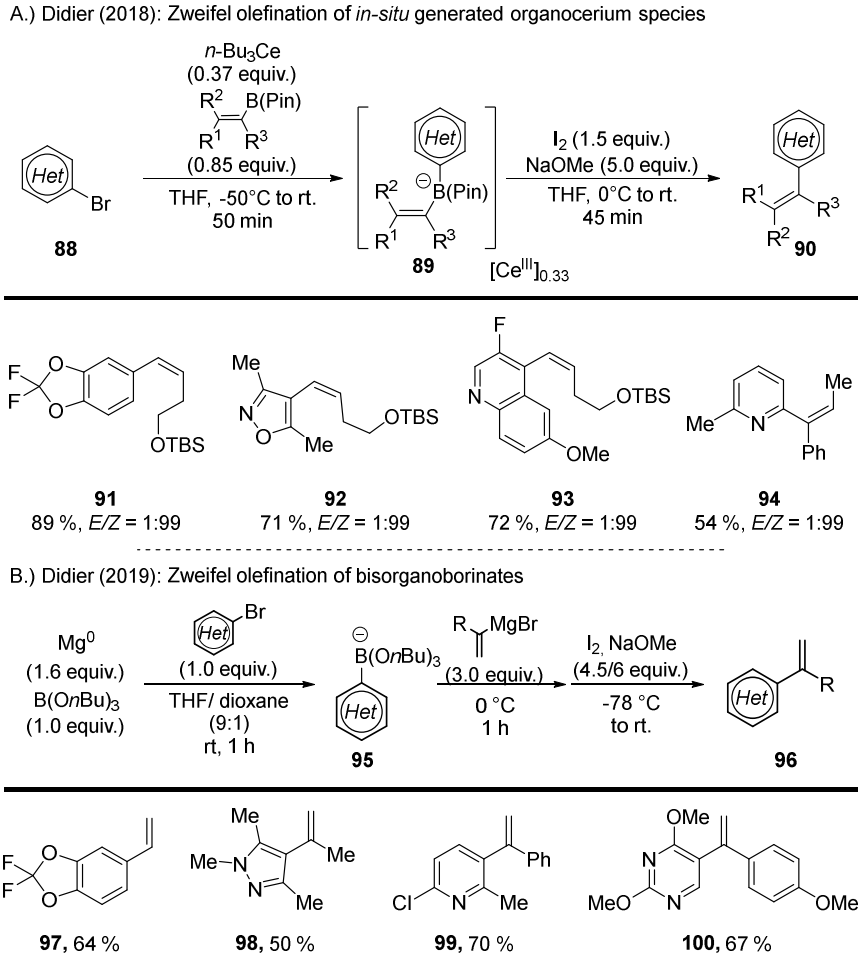
This *syn*-elimination is especially desirable in the case of five- and six-membered cyclic systems, as underlined by Aggarwal *et al.* Hereby, the intermediately formed β-iodoboronic ester cannot undergo bond rotation, making only the challenging *syn*-elimination possible. Notably, in some cases, a large excess of base (up to 20 equiv.) was required due to the slow elimination process. Various cyclic vinyllithium species (**82**) proved to be reactive under the developed conditions, providing glucal (**85**) and abiraterone derivative (**87**) amongst others (Scheme 18).[81]



Scheme 18: Zweifel olefination of cycloalkenes *via syn*-elimination.

In 2019, Didier and coworkers introduced the first application of organocerium reagents in Zweifel olefinations (Scheme 19, A). Cerium provides an optimal compromise between the highly reactive but functional group limited organolithium and less reactive organomagnesium counterparts.[20] Unique triaryl cerium species were generated by unprecedented triple exchange of (hetero)aryl halides with *n*Bu_3Ce. Notably, no excess of organocerium reagent is needed, minimizing side product formation in the often-sensitive Zweifel protocol. These triarylcerium species are converted to bisorganoborinates (**89**) and subsequent iodonium ion formation triggers a stereospecific 1,2-metallate rearrangement. Addition of sodium methoxide as base allows regeneration of the double bond (**90**) by β-elimination. Furthermore, enantioenriched secondary alkyl boron species were demonstrated to undergo stereospecific Zweifel olefination with complete retention of configuration and high yields.[82] Additionally, the group of Didier presented a one-pot Zweifel protocol relying on *in-situ* formation of (hetero)aryl boronates (**95**) from readily available boron alkoxides, thus avoiding often limited and costly boronic esters.

[81] R. J. Armstrong, W. Niwetmarin, V. K. Aggarwal, *Org. Lett.* **2017**, *19*, 2762-2765.
[82] A. Music, C. Hoarau, N. Hilgert, F. Zischka, D. Didier, *Angew. Chem. Int. Ed.* **2019**, *58*, 1188-1192.

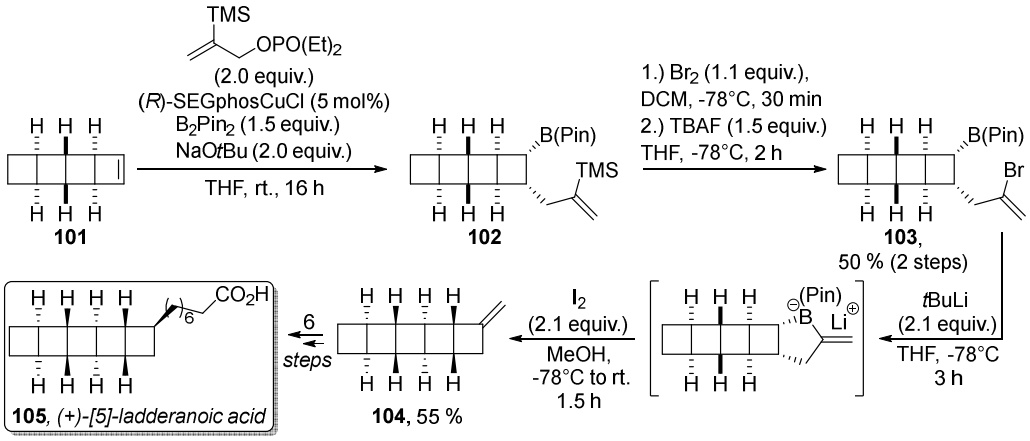


Scheme 19: Contributions by Didier *et al.* on Zweifel olefination of organocerium species and *in-situ* generated bisorganoborinates.

By premixing tributylborate with magnesium, proceeding through metal insertion and coordination these boronates (**95**) are obtained readily. Importantly, the use of dioxane as a cosolvent proved crucial to prevent formation of nondesired boron species. Upon addition of a vinylic organomagnesium species, bisorganoborinates are obtained and subjected to intramolecular alkenylation towards **96**, according to established Zweifel conditions (Scheme 19, B).[83] Due to its high efficiency, reliability and stereospecificity the Zweifel olefination has become a valuable tool in the total synthesis of natural products. The obtained olefins can be transformed into a broad series of functional groups, providing a platform for further functionalization.

Amongst many reports from Aggarwal and Morken on lithiation-borylation-Zweifel olefination towards naturally relevant targets[84], Brown and coworkers presented in 2020 a synthesis of (+)-5-ladderanoic acid, employing an allylboration/ Zweifel olefination sequence (Scheme 20).

[83] A. Music, A. N. Baumann, P. Spieß, N. Hilgert, M. Köllen, D. Didier, *Org. Lett.* **2019**, *21*, 2189-2193.
[84] a) D. Leonori, V. K. Aggarwal, *Acc. Chem. Res.* **2014**, *47*, 3174-3183; b) K. Yeung, R. C. Mykura, V. K. Aggarwal, *Nat. Synth.* **2022**, *1*, 117-126.



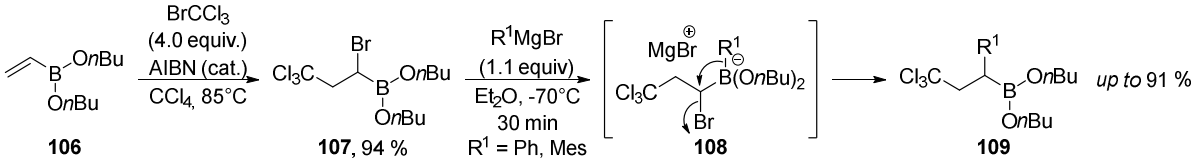
Scheme 20: Enantioselective synthesis of (+)-5-ladderanoic acid by Brown and coworkers.

The ladderane backbone **101** was assembled by photochemical [2+2] cycloadditions with cyclopentenone, diazo transfer and subsequent Wolff rearrangement. Copper catalyzed enantioselective allylboration then provided **102**. Inspired by results from Aggarwal and coworkers, an intramolecular Zweifel olefination strategy *via* a cyclic boronate complex allowed assembling the methylidenladderane moiety **104**, which provided the platform for hydroboration-oxidation and subsequent Ley oxidation towards (+)-5-ladderanoic acid **105**.[85]

[85] E. N. Hancock, E. L. Kuker, D. J. Tantillo, M. K. Brown, *Angew. Chem. Int. Ed.* **2020**, *59*, 436-441.

3.2 Polar-Radical Crossover of Boronate Complexes

The first 1,2-metallate rearrangement of a vinylboronic ester may be described by Matteson *et al.* in 1959. An AIBN initiated addition of bromotrichloromethane to a vinyl dibutylboronic ester (**106**) afforded α-haloboronic esters (**107**), which when treated with nucleophiles (Grignard reagents) resulted in displacement of the halide ions (**108**) and furnished **109** (Scheme 21).[86]



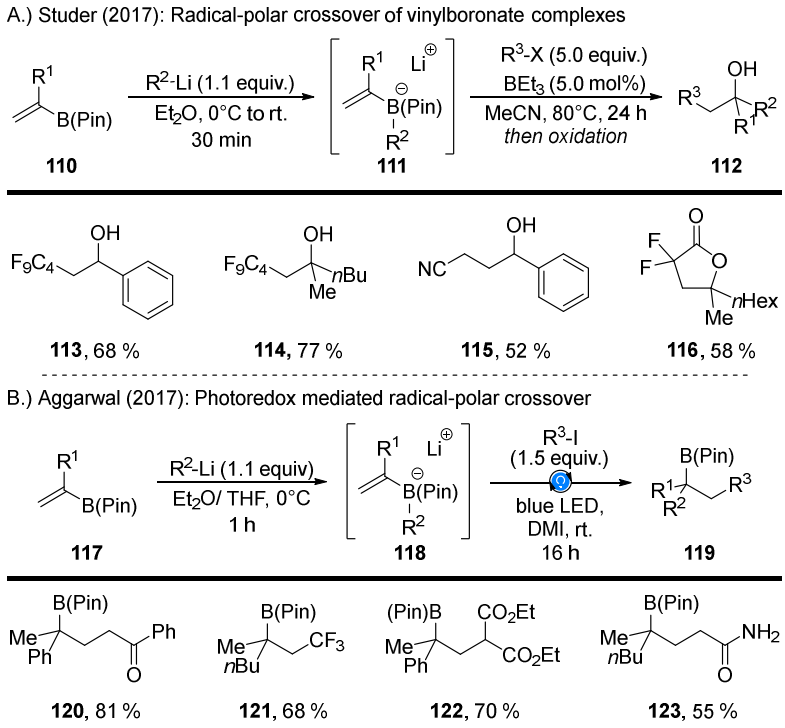
Scheme 21: Discovery of the 1,2-metallate rearrangement by Matteson and coworkers.

Interestingly, this reaction proceeded much faster than traditional S_N2-type processes, as confirmed by competition experiments with allyl bromide, suggesting a different mechanism is involved. Initial addition of the Grignard reagent forms boronate complex **108**, followed by a chemoselective 1,2-migration to the electrophilic α-carbon. After expulsion of the halide, the rearranged product **109** is obtained. This, nowadays known as the Matteson homologation, is mostly performed through an iterative two-step sequence. Firstly, formation of a α-haloboronic ester through homologation of a boronic ester with a dihalomethyllithium reagent, followed by nucleophilic displacement of the α-halide *via* ate-complex, to afford the respective one-carbon homologated boronic ester derivative.[71b, 87]

In 2017, Studer *et al.* reported a one-pot, three-component coupling involving a 1,2-metallate rearrangement of vinylboronic esters (Scheme 22, A), transforming the initial discovery of Matteson *et al.* into an *in-situ* transformation. Treating commercially available, stable vinylboronic acid pinacol esters (**110**) with organolithium reagents, the corresponding boronate complexes (**111**) can be obtained. The addition of a radical precursor, and subsequent radical initiation with triethylborane and oxygen results in radical addition to the double bond, triggering the 1,2-metallate rearrangement. In this initial protocol, perfluoroalkyl iodides (**113**, **114**) and iodoacetates were shown to be reactive as radical precursors. In order to minimize side product formation, a solvent switch from diethylether to acetonitrile was performed after formation of the boronate complex.

[86] a) D. S. Matteson, *J. Am. Chem. Soc.* **1960**, *82*, 4228-4233; b) D. S. Matteson, *J. Am. Chem. Soc.* **1959**, *81*, 5004-5005; c) D. S. Matteson, R. W. H. Mah, *J. Am. Chem. Soc.* **1963**, *85*, 2599-2603.
[87] S. P. Thomas, R. M. French, V. Jheengut, V. K. Aggarwal, *Chem. Rec.* **2009**, *9*, 24-39.

To facilitate the purification, the obtained boronates were directly subjected to Brown oxidation, affording the corresponding alcohols of type **112**. When iodoacetates were used as radical precursors, the intermediate alcohols underwent lactonization upon acidification (**116**).[88]

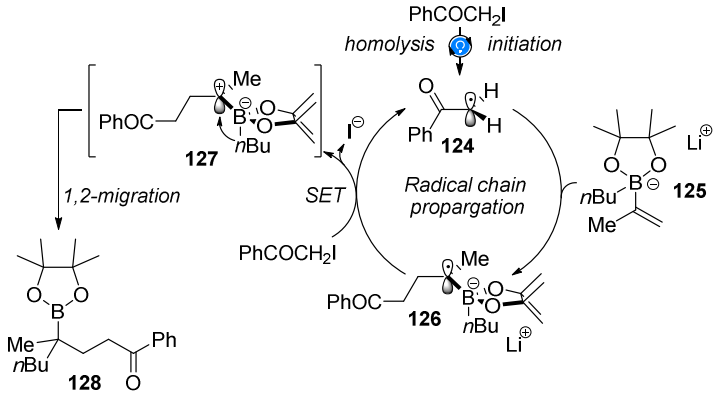


Scheme 22: First reports on polar-radical-crossover by Studer and Aggarwal.

That same year, Aggarwal *et al.* published a similar study (Scheme 22, B). Unlike Studer's approach, radicals were generated through blue light irradiation, and in some cases, a photoredox catalyst ($Ru(bpy)_3Cl_2 \cdot 6H_2O$) was employed. After formation of the boronate complex (**118**), either a solvent switch to 1,3-dimethyl-2-imidazolidinone (DMI) was performed, or the radical precursor was added as a solution in DMI. Surprisingly, steric hindrance around the boron center had little effect on radical addition, as demonstrated by the successful addition of various bulky organolithium species. In contrast to Studer's report, Aggarwal's method employed a broader range of radical precursors, including phenacyl iodides, α-iodo esters, and α-iodo nitriles, all under comparably mild conditions (**120-123**). The boronated products of type **119** of this three-component coupling were conveniently purified *via* chromatography, preserving the boron moiety for subsequent transformations. The proposed mechanism as shown in Scheme 23, describes a homolytic cleavage of the alkyl iodide by blue light, forming the electrophilic alkyl radical species **124**.

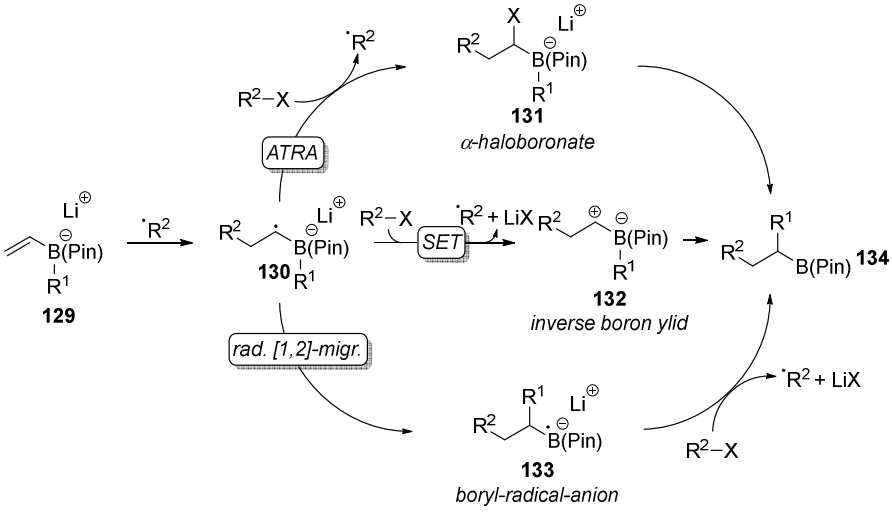
[88] M. Kischkewitz, K. Okamoto, C. Mück-Lichtenfeld, A. Studer, *Science* **2017**, *355*, 936-938.

This reacts with the boronate complex **125**, to generate the boronate radical **126**. Electron-rich radical anion then undergoes either single-electron oxidation or iodine atom transfer with another equivalent of alkyl iodide and triggers the 1,2-metallate rearrangement *via* **127**.



Scheme 23: Tentative mechanism for the PRC of vinylboronic esters as proposed by Aggarwal *et al.*

This tentative mechanism supports a continuous radical chain propagation pathway, since a new α-carbonyl radical is generated. This is consistent with the observation that photoredoxcatalysis is only necessary if the radical chain process is inefficient either by slow initiation or slow electron/ atom transfer.[89] A contribution by Renaud *et al*. focused on mechanistic insights for this rearrangement.[90] Three different mechanistic pathways were suggested in the literature (Scheme 24).

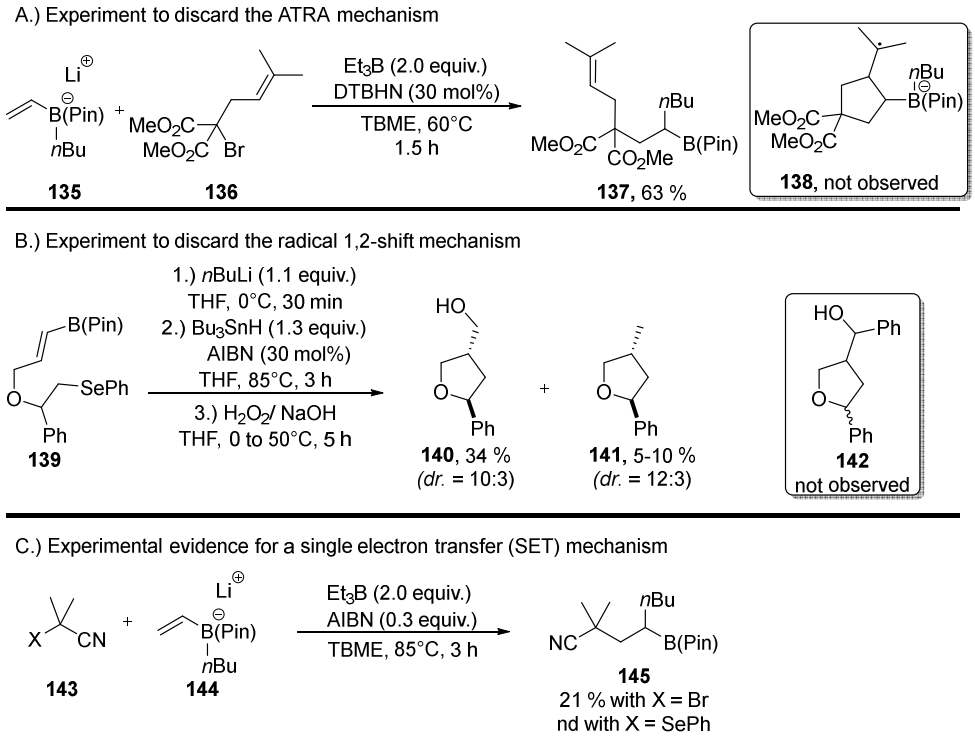


Scheme 24: Three possible mechanistic pathways for PRC of vinylboronates.

[89] M. Silvi, C. Sandford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2017**, *139*, 5736-5739.
[90] N. D. C. Tappin, M. Gnägi-Lux, P. Renaud, *Chem. Eur. J.* **2018**, *24*, 11498-11502.

Pathway 1 describes an atom transfer radical addition reaction (ATRA), furnishing an α-haloboronate **131**, which may undergo 1,2-metallate rearrangement. This tentative mechanism could be ruled out by a radical clock experiment (Scheme 25, A). Employing 3,3-(dimethylprop-2-en-1yl)malonate (**136**), an ATRA process should lead to cyclopentane derivative **138**. As the 5-*exo*-trig cyclization of intermediately formed hexenyl radical can be expected to proceed much faster than a bromine atom transfer, an ATRA process should favor formation of cyclopentane derivative **138**. However, in the experiments carried out by Renaud *et al.* only the product of 1,2-metallate rearrangement (**137**) could be detected, supporting the SET mechanism.

The second plausible mechanism may be described as a radical 1,2-migration pathway *via* a boryl radical anion **133**, which propagates the radical chain *via* a reductive single electron atom transfer (SET) process (Scheme 24). A cyclization experiment employing selenide **139** under tin hydride conditions, did not afford substituted tetrahydrofuran **142** which would result from a 1,2-shift process (Scheme 25, B). This indicates, that the respective 1,2-shift process is kinetically disfavored over the hydrogen atom transfer step by Bu_3SnH, and disagrees with the rapid 1,2-migration observed in the experiments towards the ATRA process.



Scheme 25: Mechanistic experiments towards PRC by Renaud and coworkers.

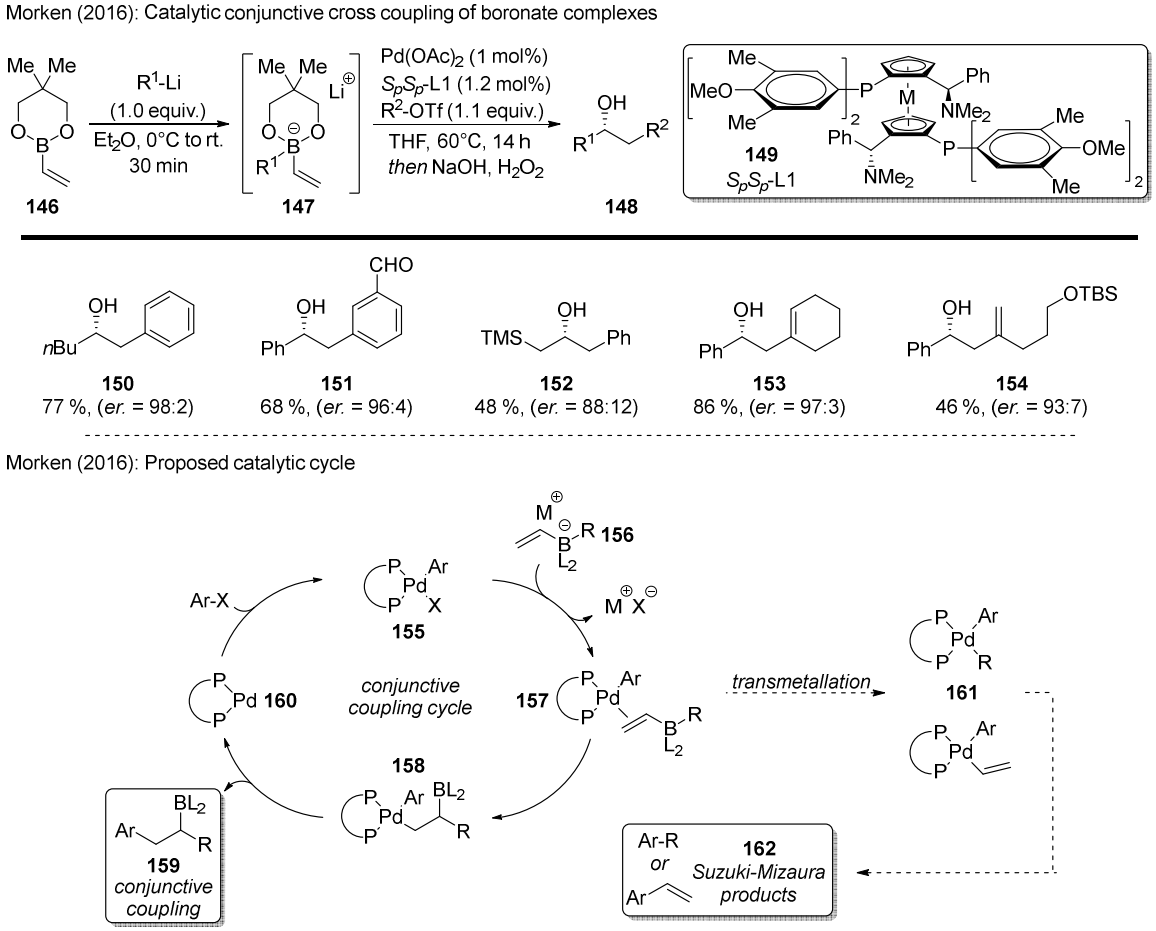
The third reaction pathway may proceed *via* radical addition to the vinylboronate complex, affording the respective radical anion. This species then reduces the radical precursor *via*

single-electron-transfer (SET), to produce the inverse ylid **132**, which may undergo rapid 1,2-metallate rearrangement (Scheme 24).

Experimental support for this route was found in comparing the reactivity of 2-bromoisobutyronitrile (**143**) and the corresponding phenylselenide (**143**) (Scheme 25, C). While the expected compound (**145**) was formed in 21 % yield employing the bromide, no trace of target compound was found for the selenide. As the reduction potentials for these two substrates vary widely, with the bromide being much easier to reduce, this experiment suggests a SET process for brominated or iodinated radical precursors. These results are supported by the work from Studer *et. al* performing a trifluoromethylation with Togni's reagent, which is known to exclusively react *via* radical pathways. When employing Umemoto's reagent Aggarwal *et al.* were able to trap the intermediately formed trifluoromethyl radical with *N-tert*-butyl-α-phenylnitrone (PBN) and provided spectroscopic evidence (EPR) of the corresponding nitroxide.

Already in 2016, Morken and coworkers demonstrated that 1,2-migrations of boronate complexes can be also triggered by palladium-aryl complexes (Scheme 26).[91] More specifically, a regioselective electrophilic aryl-palladation of the vinyl moiety induces a 1,2-alkenyl migration to provide α-arylmethyl allylboronic esters. Careful optimization of the reaction parameters found neo-pentylglycolato boronates (**146**) to form the most nucleophilic ate complexes (**147**). Upon treating these boronate complexes with aryl triflates under Pd-catalysis with Mandyphos derived ligand **149** (Scheme 26), the desired conjunctive cross-coupling products could be obtained in moderate to excellent yields, with high levels of enantiopurity (*er*. up to 99:1). A range of alkyl and aryllithium species was shown to be reactive under the described conditions. While the initial implementation did not tolerate the use of Grignard derived ate-complexes and organic halides due to the formation of "ineffective" ate complexes, further investigation found the addition of NaOTf or KOTf to largely counteract these issues.[92]

[91] L. Zhang, G. J. Lovinger, E. K. Edelstein, A. A. Szymaniak, M. P. Chierchia, J. P. Morken, *Science* **2016**, *351*, 70-74.
[92] G. J. Lovinger, M. D. Aparece, J. P. Morken, *J. Am. Chem. Soc.* **2017**, *139*, 3153-3160.

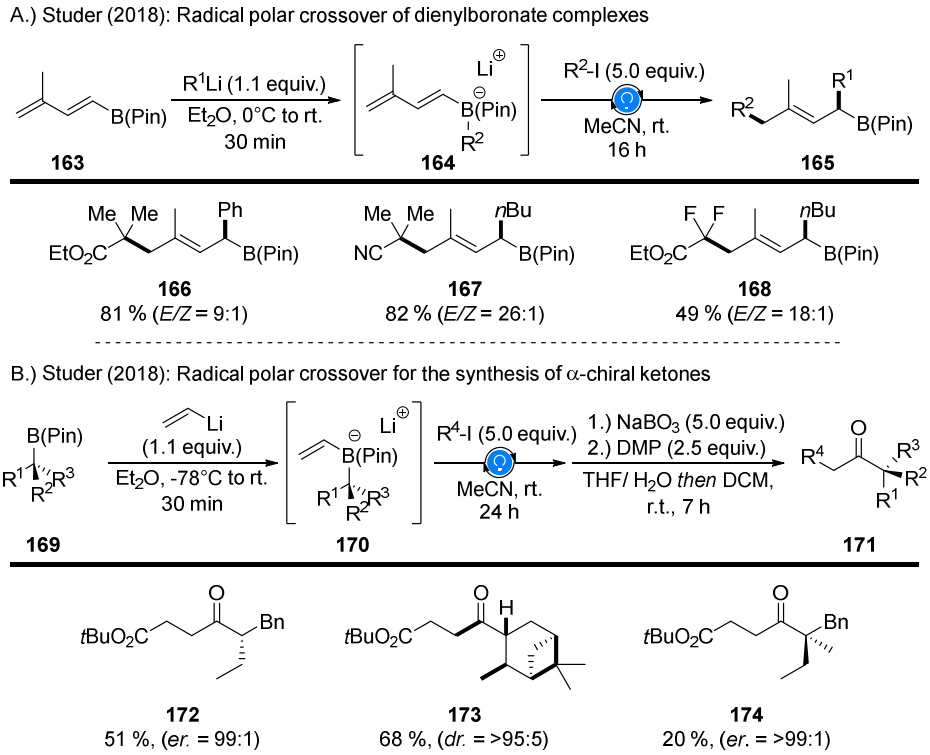


Scheme 26: Catalytic conjunctive cross-coupling of vinyl boronate complexes by Morken and coworkers.

The tentative mechanism describes, that electrophilic palladium complex **155**, generated by oxidative insertion of **160** with an organic electrophile induces 1,2-migration in a vinyl boronate complex **156** and furnishes a new C-C bond and a boron-substituted stereogenic center **158**. The following reductive elimination then establishes a new C-C bond, releases the product **159** and furnishes reduced Pd-complex **160**, which then undergoes another cycle of conjunctive cross-coupling. Importantly, reductive elimination occurs with complete retention of configuration (Scheme 26).

As demonstrated by Studer *et al.* in 2018, the 1,2-metallate strategy can be also applied to dienylboronate complexes of type **164** (Scheme 27, A).[93] A wide range of radical precursors underwent regioselective δ-addition, whilst β-addition could not be observed. Interestingly, increasing the concentration of radical precursor resulted in increased stereoselectivities, whilst increasing the concentration of the reaction mixture did not.

[93] M. Kischkewitz, C. Gerleve, A. Studer, *Org. Lett.* **2018**, *20*, 3666-3669.



Scheme 27: PRC of dienylboronate complexes and enantioenriched alkylboronic esters.

As in previous reports, alkyl and aryllithium species were tolerated. Aside from perfluoroalkyl iodides, α-iodonitriles, α-iodoesters and unprotected α-iodoamides could be employed (**166**-**168**). Notably, α-disubstituted radical precursors furnished higher stereoselectivities compared to unsubstituted ones.

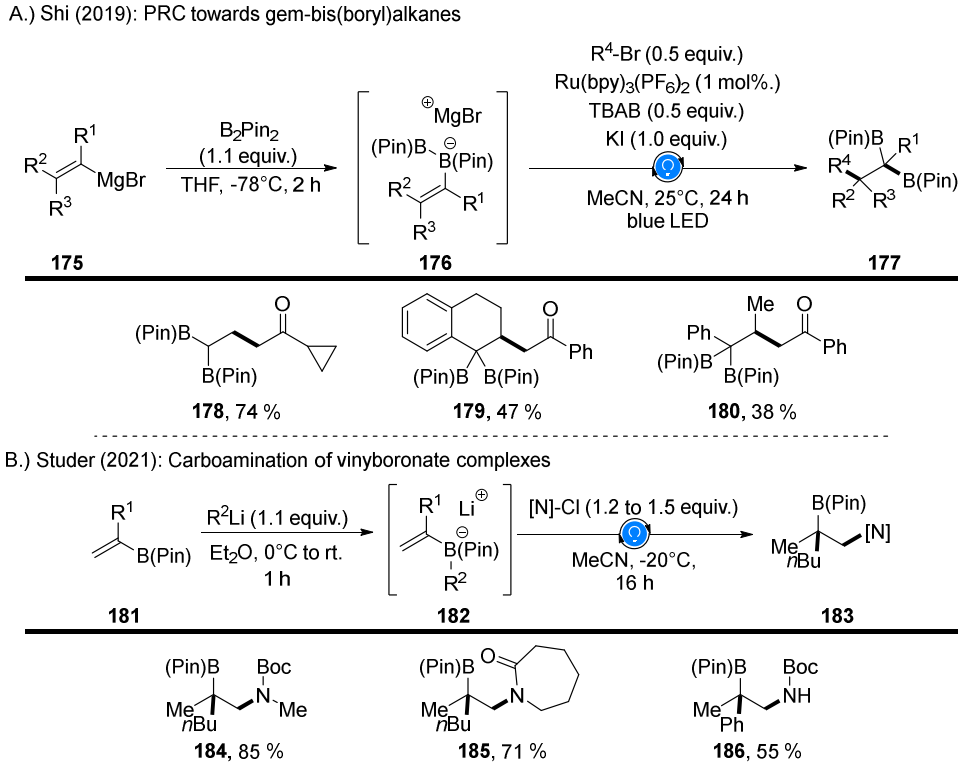
The same year the group of Studer presented the first stereospecific polar-radical crossover transformations of enantioenriched alkyl boronic esters (Scheme 27, B). Under blue-light photoredox conditions, a variety of commercially available alkyl iodides were shown be reactive as radical precursors. Interestingly, the obtained enantioenriched boronic esters were subjected to a two-step *in-situ* oxidation affording the respective ketones (**171**). Notably, the procedure allows the synthesis of ketones containing fully substituted α-quaternary centers (**174**).[94]

In 2019 Shi and coworkers demonstrated, that *in-situ* formed alkenyl diboronatecomplexes (**176**) derived from alkenyl Grignard reagents (**175**) and bis(pinacolato)diboron (B_2Pin_2), react with diverse alkylhalides mediated by a Ru-photocatalyst to give *gem*-bis-(boryl)alkanes (**177**).[95]

[94] C. Gerleve, M. Kischkewitz, A. Studer, *Angew. Chem. Int. Ed.* **2018**, *57*, 2441-2444.
[95] B. Zhao, Z. Li, Y. Wu, Y. Wang, J. Qian, Y. Yuan, Z. Shi, *Angew. Chem. Int. Ed.* **2019**, *58*, 9448-9452.

Alkyl radicals added efficiently to the alkenyldiboronate complexes, and the adduct radical anions underwent 1,2-boryl migration from boron to the α-carbon sp^2 center. Notably, the combination of KI and TBAB allows *in-situ* Finkelstein transformations of the more accessible alkyl bromides towards the corresponding iodides. Interestingly, cyclic and sterically demanding alkenylgrignard reagents showed to be less reactive, as underlined by **179** and **180** (Scheme 28, A).

While previous reports solely implemented C-based radicals, Studer *et al.* presented in 2021 a catalyst-free carboamination of vinylboronate complexes (**182**).[96] Amidyl radicals were conventiently generated under blue-light photoredoxcatalysis from the corresponding *N*-chloroamides and β-amination triggered the 1,2-metallate rearrangement, forming functionalized aminoboronic esters (**184-186**). As in previous studies, a solvent switch to MeCN was necessary to obtain high yields.



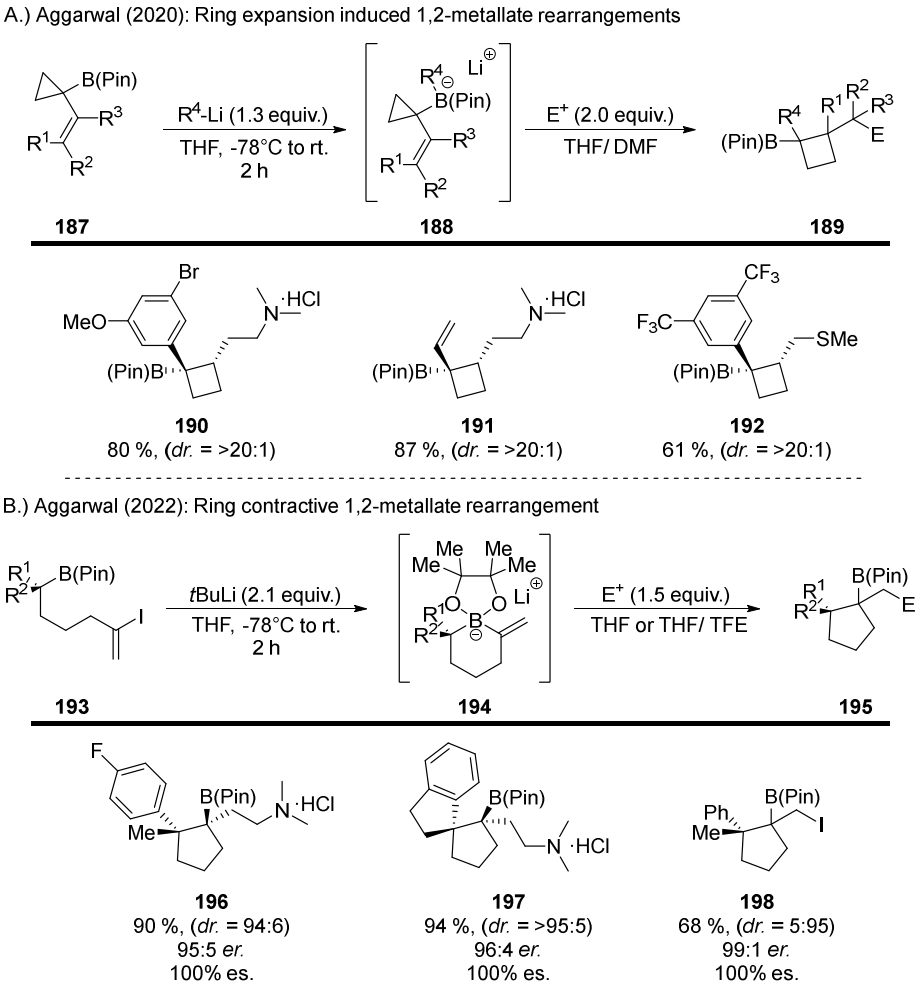
Scheme 28: Studer's contribution towards carboamination of vinylboronate complexes *via* PRC.

Primary and secondary alkyl, as well as aryllithium species were found to be compatible with the procedure, however secondary alkyllithiums only furnished the desired product in low yields, whilst tertiary only produced traces.

[96] C. You, A. Studer, *Chem. Sci.* **2021**, *12*, 15765-15769.

A wide range of conveniently accessible *N*-chloroamines was tolerated, including *N*-chloroamines derived by lactams (**185**) and *tert*-Butyl carbamate (**186**) (Scheme 28, B).

In 2020 Aggarwal and coworkers presented a novel strategy to induce 1,2-metallate rearrangements. An electrophile induced activation of vinylcyclopropyl boronate complexes (**188**) furnished cyclopropane stabilized carbocations, which triggered ring expansion and 1,2-metallate rearrangement. This route provided access to a wide range of unique 1,2-substituted cyclobutylboronic esters (**190**-**192**) with excellent diastereoselectivity. The methodology was also applied to the stereoselective synthesis of (±)-grandisol (Scheme 29, A).[97]



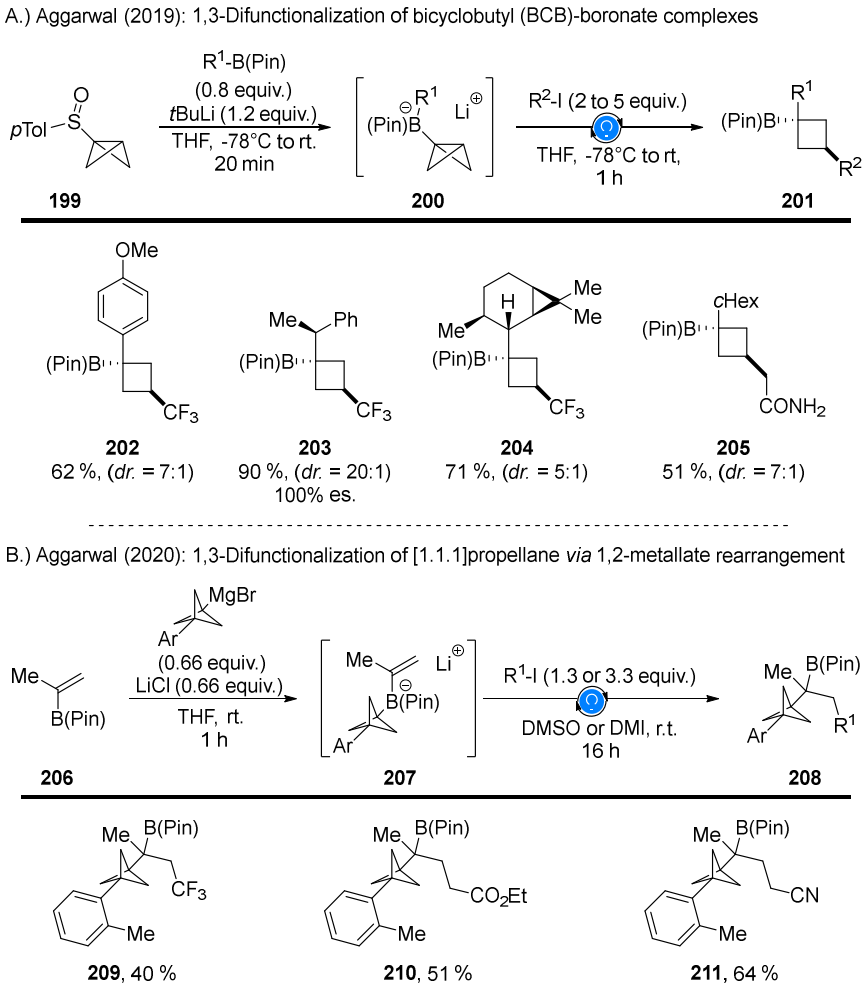
Scheme 29: Electrophile induced 1,2-metallate rearrangements towards the synthesis of cyclic alkylboronic esters by Aggarwal *et al.*

Two years later Aggarwal *et al.* applied the 1,2-metallate rearrangement to the ring contractive synthesis of boronated cyclopentanes (**195**) (Scheme 29, B).[98]

[97] D. P. Hari, J. C. Abell, V. Fasano, V. K. Aggarwal, *J. Am. Chem. Soc.* **2020**, *142*, 5515-5520.
[98] M. E. Fairchild, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205816.

Halogen-lithium exchange of enantioenriched boronated vinylic halides provided quantitative access to 6-membered cyclic alkenyl boronate complexes (**194**). When treated with Eschenmosers's salt and other electrophiles, cyclopentyl boronic esters (**196**-**198**) bearing two contiguous, fully substituted stereocenters were obtained. Notably, solvent-induced diastereodivergency was observed in the case of some carbon-based electrophiles. A photoinduced ring-contractive strategy was already used by Aggarwal and coworkers in 2020 to construct cyclobutenes with contiguous quaternary stereocenters and more strained benzofused cyclobutenes.[99]

While previous reports focused on radical additions to π-bonds of unsaturated boronate complexes, Aggarwal *et al.* presented in 2019 a strategy towards strain-release driven radical addition to the central δ-bond of bicyclobutyl (BCB)-boronate complexes **200** (Scheme 30, A).[100]



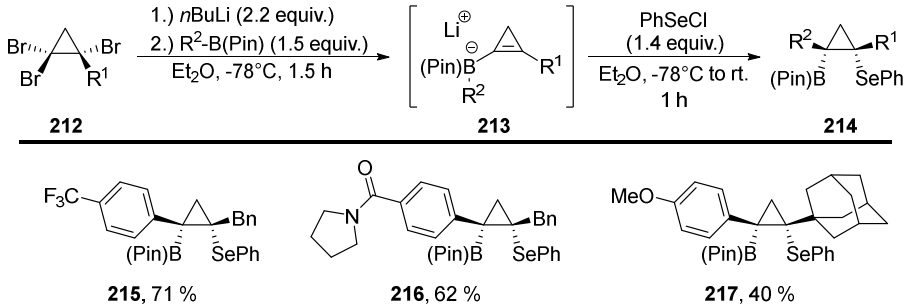
Scheme 30: 1.3-Difunctionalization of bicyclo[1.1.1]pentanes and [1.1.1]propellanes *via* PRC by Aggarwal *et al.*

[99] R. Davenport, M. Silvi, A. Noble, Z. Hosni, N. Fey, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2020**, *59*, 6525-6528.
[100] S. H. Bennett, A. Fawcett, E. H. Denton, T. Biberger, V. Fasano, N. Winter, V. K. Aggarwal, *J. Am. Chem. Soc.* **2020**, *142*, 16766-16775.

Sulfoxide lithium exchange of **199** and treatment with boronic esters provided quantitative access to strained bicyclobutyl (BCB)-boronate complexes of type **200**. Various radical precursors, including $CF_3I \cdot 2DMSO$ (Ritter complex) were shown to be reactive under visible light mediated photoredox conditions and furnished complex chiral cyclobutanes with moderate to excellent diastereoselectivity (**202**-**205**).

This methodology was also applied to the derivatization of various 1,3-difunctionalized bicyclo[1.1.1]pentanes (BCPs), considered as pharmaceutically valuable bioisosters of *para*-substituted aromatic rings. Treatment of [1.1.1]propellane with various organomagnesium reagents and subsequent trapping with boronic esters provided access to a variety of synthetically useful boronate complexes (**207**). Subsequent Zweifel olefination and four component couplings (electrophile induced or photochemical) provided access to BCP-derivatives **209**-**211** containing vicinal quaternary centers (Scheme 30, B).[101]

Although the 1,2-metallate rearrangement of vinylboronic esters has been extensively studied, the application to strained small membered cycles is only rarely described. In 2020, Sakakura and coworkers described a one-pot process towards highly substituted cyclopropenes by PhSeCl induced 1,2-metallate rearrangement of cyclopropenylboronate complexes of type **213** (Scheme 31).[102] Starting from readily available tribromocyclopropanes (**212**) and treating with *n*BuLi afforded cyclopropenyllithium lithium species, which were directly trapped with boronic esters forming the corresponding ate complexes (**213**). Phenylselenide chloride as a soft electrophile was chosen to activate the double bond, and thus induce 1,2-metallate rearrangement. Notably, all obtained compounds (**215**-**217**) were isolated as single diastereomers.



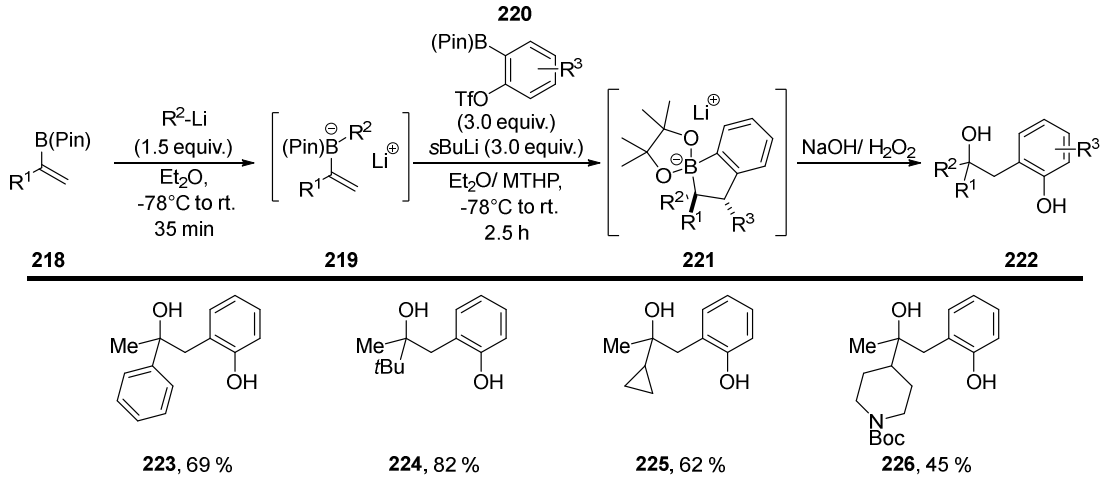
Scheme 31: PhSeCl induced 1,2-metallate rearrangements of cyclopropenylboronate complexes by Sakakura *et al*.

DFT calculations for the 1,2-metallate rearrangement step suggested that the reaction may proceed through formation of a seleniranium intermediate. The process is highly exothermic

[101] S. Yu, C. Jing, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2020**, *59*, 3917-3921.
[102] H. Mizoguchi, M. Seriu, A. Sakakura, *Chem. Commun.* **2020**, *56*, 15545-15548.

proceeding *via* a transition state with low activation barrier, probably due to the high ring strain of cyclopropene and the corresponding seleniranium species.[102]

As demonstrated by Sakakura *et al.,* 1,2-metallate rearrangements of boronate complexes can be also triggered by arynes (Scheme 32). After conventional generation of vinylboronate complexes **219**, arynes generated from Hosoya's reagent **220** led to formation of cyclic ate complex **221**, which when subjected to Brown oxidation afforded substituted hydroxyphenols **222**. Importantly, MTHP was chosen as cosolvent, as THF led to the formation of significant amounts of the THF adduct of benzyne. A variety of vinylboronic esters, arynes, and migrating groups were applicable to this reaction cascade and afforded substituted hydroxyphenols (**223**-**226**) after oxidation. Treatment with NIS instead of Brown oxidation afforded iodinated alkylboronic esters.[103]



Scheme 32: Aryne triggered 1,2-metallate rearrangements of vinylboronate complexes by Sakakura *et al.*

[103] H. Mizoguchi, H. Kamada, K. Morimoto, R. Yoshida, A. Sakakura, *Chem. Sci.* **2022**, *13*, 9580-9585.

4. Four Membered Heterocycles

4.1 Azetidines

Azetidine is a rigid four membered heterocycle featuring bond angles bent 10 – 20° respective to the plane.[104] The character of azetidines may be well delimited of its related heterocycles in context of its ring strain of approximately 25.4 kcal/mol, situated in between of the respective ring strain of commonly regarded less stable aziridines and unreactive pyrrolidines (Figure 2).[105]

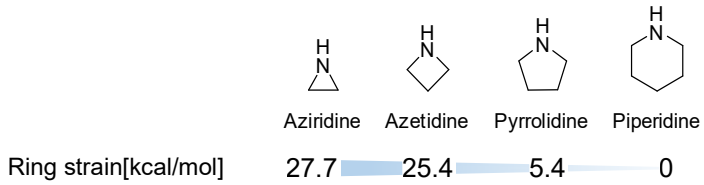


Figure 2: Comparison of the ring strain of azetidines and other related heterocycles

An analytical study of cyclic fragments in contemporary pharmaceuticals revealed that piperidine and pyrrolidine are among the top 10 most frequently used ring systems, while only 2-azetidinone (β-lactam) ranks within the top 100.[106] Accordingly, compared to their five- and six-membered *N*-heterocyclic counterparts, azetidines remain relatively underexplored, offering intriguing opportunities for nucleophilic ring-opening or ring-expansion reactions to yield larger ring systems or highly substituted acyclic amines.[107] Still, the synthetic accessibility of functionalized azetidines is in growing industrial demand due to their potential pharmaceutical and agrochemical applications.[108] Key marketed drugs such as Azelnidipine (calcium channel blocker), Delafloxacin (fluoroquinolone antibiotic), and Tebanicline (analgesic) incorporate the azetidine moiety (Figure 3).[109]

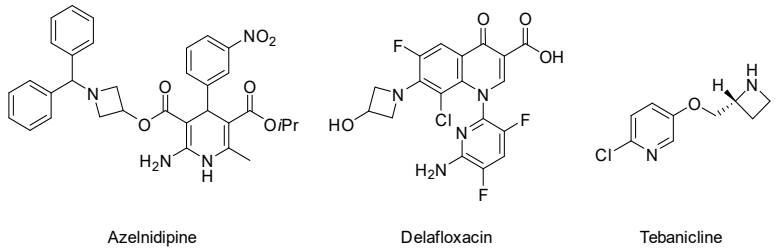
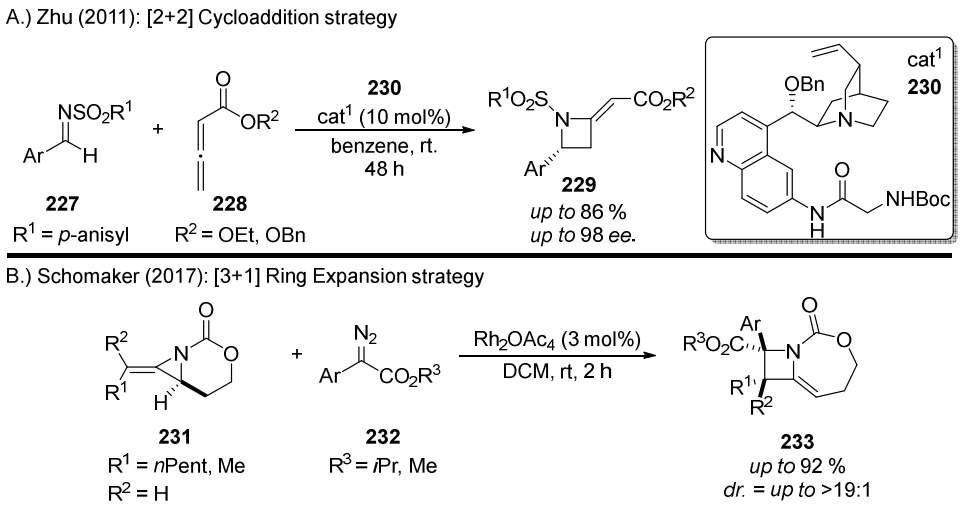


Figure 3: Selected FDA-approved drugs which incorporate azetidines.

[104] G. S. Singh, *Advances in Heterocyclic Chemistry, Vol. 130*, Elsevier, UK, **2020**.
[105] T. Dudev, C. Lim, *J. Am. Chem. Soc.* **1998**, *120*, 4450-4458.
[106] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274.
[107] A. Brandi, S. Cicchi, F. M. Cordero, *Chem. Rev.* **2008**, *108*, 3988-4035.
[108] a) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752-6756; b) T. Teng, D. M. Ridgley, A. Tsoy, G. Y. Sun, S. Askarova, J. C. Lee, *ACS Chem. Neurosci.* **2019**, *10*, 209-215.
[109] D. R. Parmar, J. Y. Soni, R. Guduru, R. H. Rayani, R. V. Kusurkar, A. G. Vala, *Arch. Pharm.* **2021**, e2100062.

The rigid three-dimensional structure of azetidines is thought to enhance critical drug design properties, including solubility, permeability, and lipophilicity, often serving as a bioisosteric replacement for phenyl groups.[110]

Numerous synthetic approaches towards construction and functionalization of this exotic motif have been developed, including cycloaddition (aza-Paterno-Büchi reactions)[111], ring contraction[107], C–H activation[112], couplings with Grignard reagents[113], and strain-release of 1-aza-bicyclo[1.1.0]butanes (ABB)[114]. Some key synthetic pathways are depicted in Scheme 33. In 2011, Zhu *et al.* reported a [2+2] cycloaddition between *N*-sulfonylimines (**227**) and alkyl 2,3-butadienoates (**228**), catalyzed by quinidine amide **230**, yielding complex azetidines of type **229** in excellent yields and enantioselectivities.[115] Schomaker *et al.* later utilized a formal [3+1] ring expansion strategy, reacting rhodium-bound carbenes with strained methylene aziridines (**231**) to produce highly substituted fused methylene azetidines (**233**) in excellent regio- and stereoselectivities.[116]

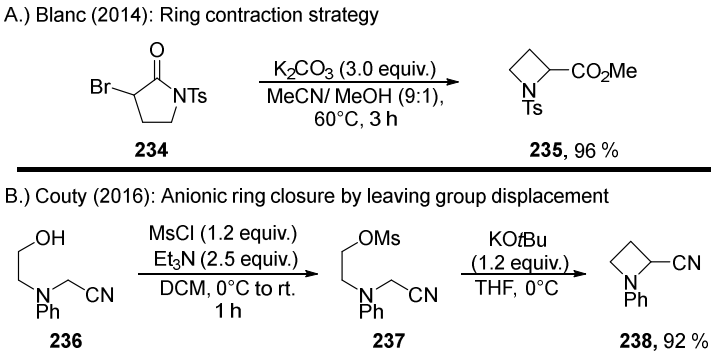


Scheme 33: Cycloaddition and ring expansion strategies towards functionalized azetidines.

In 2014 *Blanc et al.* introduced a one-pot nucleophilic addition–ring contraction of easily accessible α-bromo *N*-sulfonylpyrrolidinones (**234**) to yield α-carbonylated *N*-sulfonylazetidines (**235**) (Scheme 34).

[110] F. Couty, G. Evano, *Synlett* **2009**, *2009*, 3053-3064.
[111] A. D. Richardson, M. R. Becker, C. S. Schindler, *Chem. Sci.* **2020**, *11*, 7553-7561.
[112] a) P. Jain, P. Verma, G. Xia, J.-Q. Yu, *Nat. Chem.* **2017**, *9*, 140-144; b) M. H. Shaw, V. W. Shurtleff, J. A. Terrett, J. D. Cuthbertson, D. W. C. MacMillan, *Science* **2016**, *352*, 1304-1308.
[113] G. S. Singh, in *Adv. Heterocycl. Chem., Vol. 130* (Eds.: E. F. V. Scriven, C. A. Ramsden), Academic Press, **2020**, pp. 1-74.
[114] J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C.-M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, R. Oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 3209-3226.
[115] J.-B. Denis, G. Masson, P. Retailleau, J. Zhu, *Angew. Chem. Int. Ed.* **2011**, *50*, 5356-5360.
[116] S. C. Schmid, I. A. Guzei, J. M. Schomaker, *Angew. Chem. Int. Ed.* **2017**, *56*, 12229-12233

In the presence of potassium carbonate, various nucleophiles, such as alcohols, phenols or anilines, were demonstrated to be reactive and efficiently transformed in the corresponding azetidines.[117]



Scheme 34: Selected examples of key synthetic routes towards functionalized azetidines.

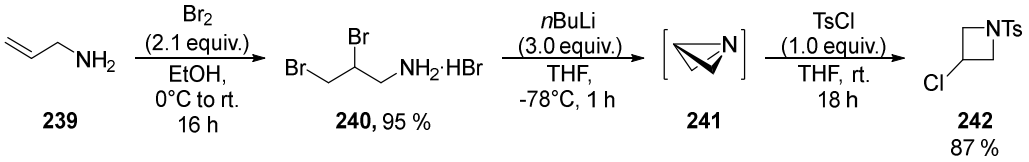
An efficient synthesis towards diversely substituted *N*-aryl-2-cyanoazetidines (**238**) based on anionic ring-closure by leaving group displacement was described by Couty and coworkers in 2016. Notably, the compounds can be prepared from β-amino alcohols in enantiomerically pure form through a three-step sequence involving copper-catalyzed *N*-arylation, *N*-cyanomethylation of the secondary aniline, and one-pot mesylation followed by base-induced ring closure (Scheme 34).[118]

[117] N. Kern, A.-S. Felten, J.-M. Weibel, P. Pale, A. Blanc, *Org. Lett.* **2014**, *16*, 6104-6107.
[118] P. Quinodoz, B. Drouillat, K. Wright, J. Marrot, F. Couty, *J. Org. Chem.* **2016**, *81*, 2899-2910.

4.2 1-Aza-bicyclo[1.1.0]butane and Strain-Release-Amination

The first route towards the 1-aza-bicyclo[1.1.0]butane motif was reported by Funke *et al.* in 1969. Analogous to a Gabriel aziridine synthesis, 1,3-dibromopropan-2-amine hydrobromide was treated with NaOH or KOH-glycol, affording 1-aza-bicyclo[1.1.0]butane in only 7 % yield.[119] However, due to the low yield and expensive starting material, this unusual ring system initially attracted only minor scientific attention.

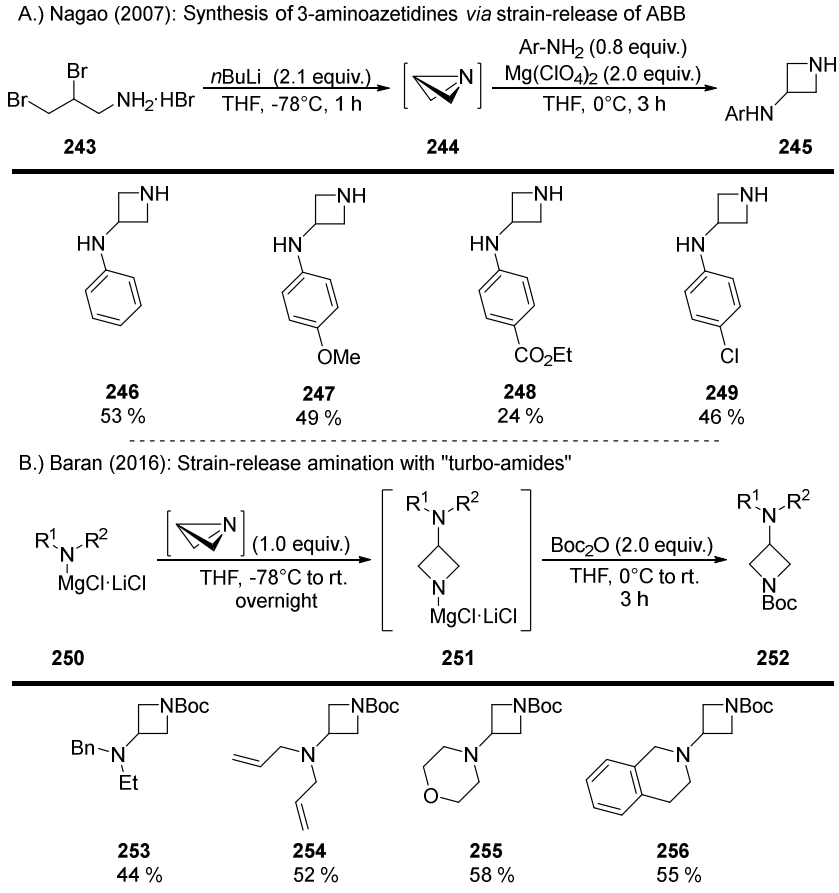
In 1999, Nagao *et al.* developed an improved synthesis of the 1-aza-bicyclo[1.1.0]butane scaffold (Scheme 35). Bromination of allylamine (**239**) afforded 2,3-dibromopropylamine hydrobromide (**240**), which was treated with *n*butyllithium to afford the strained 1-aza-bicyclo[1.1.0]butane intermediate (**241**). Subsequent trapping with TsCl, HBr or AcSH afforded substituted azetidines in moderate to good yields.[120] Driven by the convenient preparation and availability of the starting material, this route towards 1-aza-bicyclo[1.1.0]butane (ABB) has become an efficient tool in the synthesis of functionalized azetidines.



Scheme 35: Synthesis of 1,3-difunctionalized azetidines *via* 1-aza-bicyclo[1.1.0]butane intermediate by Nagao *et al.*

Later, Nagao and coworkers extended this strain-release of ABB towards nucleophilic addition of various anilines (Scheme 36, A). However, the reaction required two equivalents of $Mg(ClO_4)_2$ and only furnished the desired 3-aminoazetidines in low to moderate yields (**246-249**).[121] Further contributions from Heimgartner *et al.* described additions of morpholines and anilines to 3-phenylazabicyclo[1.1.0]butane by activation with dicyanofumarates.[122] Bott and coworkers reported about the addition of a variety of electrophiles (N_2O_4, $ClCO_2Et$, Tf_2O, and Ms_2O) to the strained cycle and a novel strategy towards the explosive 1,3,3-trinitroazetidine (TNAZ).[123]

[119] W. Funke, *Angew. Chem. Int. Ed.* **1969**, *8*, 70-71.
[120] K. Hayashi, C. Sato, S. Hiki, T. Kumagai, S. Tamai, T. Abe, Y. Nagao, *Tetrahedron Lett.* **1999**, *40*, 3761-3764.
[121] Y. Ikee, K. Hashimoto, M. Nakashima, K. Hayashi, S. Sano, M. Shiro, Y. Nagao, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 942-945.
[122] G. Mlostoń, H. Heimgartner, *Helv. Chim. Acta* **2006**, *89*, 442-449.
[123] a) A. P. Marchand, D. Rajagopal, S. G. Bott, T. G. Archibald, *J. Org. Chem.* **1994**, *59*, 1608-1612; b) A. P. Marchand, D. Rajagopal, S. G. Bott, T. G. Archibald, *J. Org. Chem.* **1995**, *60*, 4943-4946.

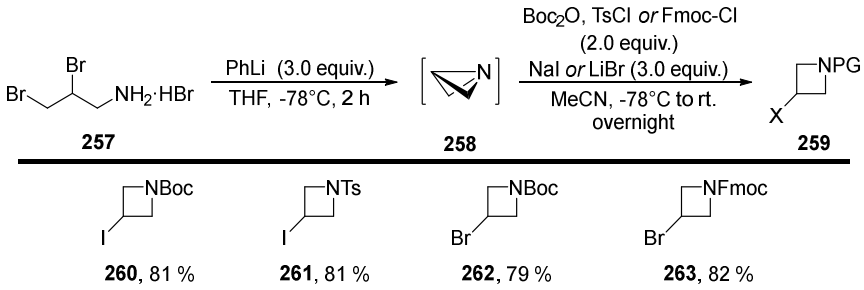


Scheme 36: Strain-release amination by Nagao and Baran.

In 2016, Baran *et al.* focused on improving the addition of amines as nucleophiles *via* strain release (Scheme 36, B).[114] Pursuing a different strategy than the aforementioned of Nagao[121] or Heimgartner[122], Baran and coworkers showcased reacting a large variety of “turbo-amides” of type **250** with ABB, followed by subsequent electrophilic trapping. The substrate scope represented both cyclic and acyclic amines, bearing functional groups like olefins and ethers, mostly isolated in moderate to good yields (**253**-**256**). The route further provided access to three late-stage modified pharmaceuticals.

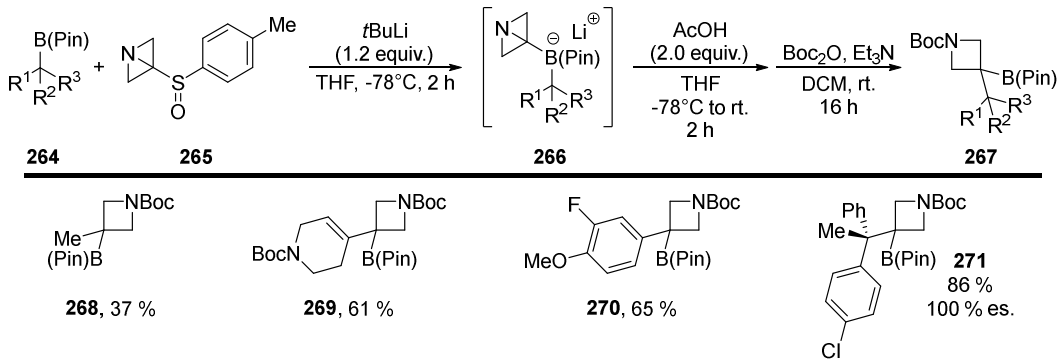
A convenient route towards 3-haloazetidines *via* ABB was reported by Lopchuk *et al.* in 2018. The *in-situ* generated ABB (**258**) was treated with both nucleophile and electrophile simultaneously furnishing the 1,3-disubstituted haloazetidines (**260**-**263**). Its assumed that ABB engages first with the electrophile as a nucleophile, forming the carbocation species, which is finally trapped by the halide. Outgoing from the protected 3-haloazetidines further functionalization included azetidine-3-carboxylic acid derivatives, 3-hydroxyazetidines and 3-cyanoazetidines (Scheme 37).[124]

[124] Y. Ji, L. Wojtas, J. M. Lopchuk, *ARKIVOC* **2018**, *2018*, 195-214.



Scheme 37: Synthesis of 3-haloazetidines by strain-release-amination of ABB.

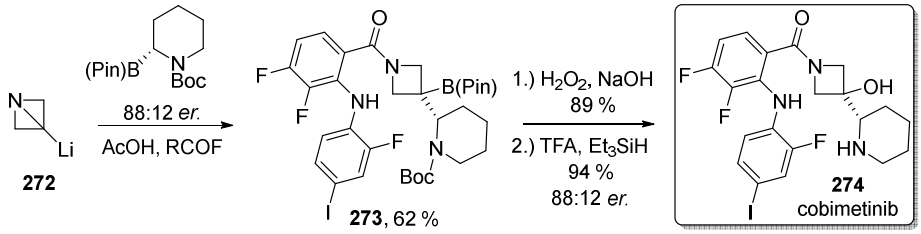
In 2019, Aggarwal *et al*. reported a route towards versatile borylated azetidines by strain-release-homologation of boronic esters with azabicyclo[1.1.0]butyl lithium (Scheme 38).[125] Following the route of Nagao, 2,3-dibromopropylamine hydrobromide was treated with phenyllithium at -78°C and subsequently lithiated with *s*BuLi/ TMEDA at -78°C forming the azabicyclo[1.1.0]butyl lithium species. Electrophilic trapping with 4-methylbenzenesulfinate afforded a bench-stable, solid reagent which could be conveniently engaged in further transformations *via* sulfoxide-lithium exchange. Upon optimization of reaction conditions a wide range of boronic esters (**264**) were reacted with azabicyclo[1.1.0]butyl sulfoxide analogue (**265**) and *t*BuLi, proceeding *via* the azabicyclo[1.1.0]butyl lithium intermediate which is then treated with boronic esters to obtain the respective boronate complexes (**266**). Subsequent trapping with AcOH and Boc_2O furnished Boc protected 3,3-disubstituted azetidines (**268**-**271**).



Scheme 38: Aggarwal's route towards azetidines by homologation of boronic esters with ABB.

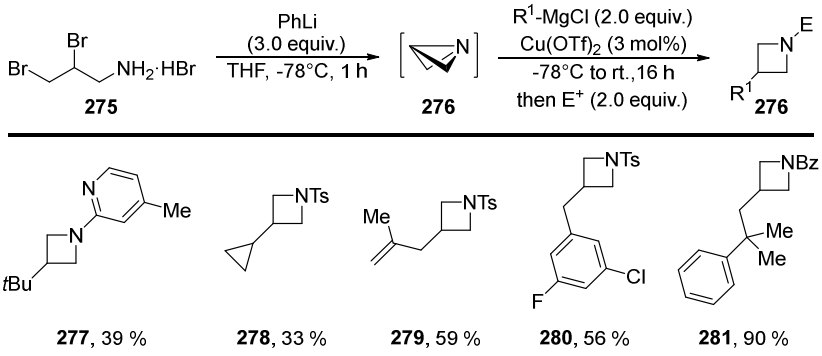
To showcase the applicability of the developed route, cobimetinib (**274**) a MEK inhibitor for treatment of melanoma was synthesized. This pathway *via* asymmetric synthesis offers a short and highly modulable approach to the pharmaceutical product (Scheme 39).

[125] A. Fawcett, A. Murtaza, C. H. U. Gregson, V. K. Aggarwal, *J. Am. Chem. Soc.* **2019**, *141*, 4573-4578.



Scheme 39: Aggarwal's modular synthesis of cobimetinib.

The same year, Gianatassio *et al.* described a route towards alkylation of ABB involving organometallic compounds.[126] Catalytic amounts of $Cu(OTf)_2$ facilitated addition of the alkylmagnesium species to ABB, forming the 3-substituted azetidinium species. Subsequent electrophilic trapping with TsCl, FmocCl and Boc_2O afforded the 1,3-disubstituted azetidines in moderate to good yields (**277**-**281**). Hereby, a wide range of Grignard reagents was shown to be reactive under the optimized conditions, comprising primary, secondary and tertiary alkyl groups, as well as vinylic, allylic and benzylic Grignards. Sterically hindered tertiary and secondary species led to diminished yields as underlined by **278** and **277**. Futhermore, other metal species like *i*PrMgCl·LiCl and zinc-species were successfully employed in the procedure. Interestingly, no aryl Grignard reagents were shown to be compatible with the reaction conditions (Scheme 40).

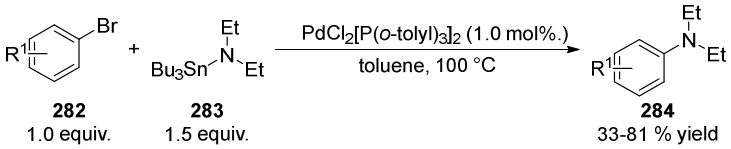


Scheme 40: Giantassio's strain-release towards alkyl-substituted azetidines.

[126] R. Gianatassio, D. Kadish, *Org. Lett.* **2019**, *21*, 2060-2063.

4.3 Buchwald-Hartwig Amination and Application to Azetidines

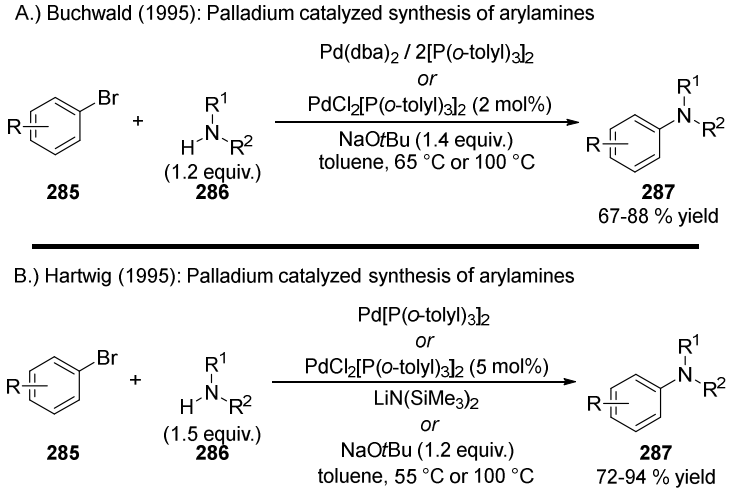
Aryl amines play a crucial role as intermediates, building blocks, and drugs in the pharmaceutical industry.[106] Introducing nitrogen atoms is a key strategy in drug design to modulate lipophilicity and essential properties like solubility, permeability, and pharmacokinetic profile.[127] Until the 1980s, only a few methods for C(sp^2)-N bond formation were available, each with distinct advantages and limitations. In 1903, Ullmann extended copper-mediated couplings to *N*-arylamines and aryl halides. Despite ongoing use, this Ullmann-type coupling requires near-stoichiometric amounts of copper and lacks the substrate tolerance, speed, and efficiency of modern transition metal-catalyzed transformations.[128] Another approach for *N*-arylation, the Nucleophilic Aromatic Substitution (S_NAr) requires highly activated substrates in order to provide efficiency and reactivity.[129] The breakthrough came in 1993 when Migita and coworkers pioneered palladium-mediated cross-couplings of stannyl amides (**283**) with aryl bromides (**282**), establishing a foundation for efficient C-N bond formation (Scheme 41).[130]



Scheme 41: Palladium catalyzed coupling of aminostannanes and aryl bromides by Migita *et al*.

It was Stephen L. Buchwald and John F. Hartwig who focused on improving the latter method and 1995 presented independently the tin-free Palladium catalyzed cross-coupling of aryl-bromides and amines, nowadays famously known as the Buchwald-Hartwig amination.[7-8]
This reaction has since become the dominant method for C-N cross-coupling, with approximately 75 % of such reactions conducted under palladium catalysis.[131] The first protocols of Buchwald and Hartwig afforded tertiary arylamines (**287**) in good to excellent yields by coupling aryl bromides (**285**) with secondary amines (**286**) under influence of a Pd^0/ P(*o*-tolyl)$_3$ Pd source, a sterically hindered base (NaO*t*Bu or LiHMDS) and toluene/ THF as solvent (Scheme 42).[132]

[127] L. D. Pennington, D. T. Moustakas, *J. Med. Chem.* **2017**, *60*, 3552-3579.
[128] F. Ullmann, J. Bielecki, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174-2185.
[129] F. Diness, D. P. Fairlie, *Angew. Chem. Int. Ed.* **2012**, *51*, 8012-8016.
[130] a) K. Masanori, K. Masayuki, M. Toshihiko, **1983**, *12*, 927-928; b) M. K. M. Kosugi, H. Sano, T. Migita, *Nippon Kagaku Kaishi* **1985**, 547 –551.
[131] M. Fitzner, G. Wuitschik, R. J. Koller, J.-M. Adam, T. Schindler, J.-L. Reymond, *Chem. Sci.* **2020**, *11*, 13085-13093.
[132] J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609-3612.



Scheme 42: First independent reports towards Pd-mediated cross-coupling of aryl bromides with secondary amines by Buchwald and Hartwig.

Due to competitive β-hydride elimination, primary amines remained challenging coupling partners until the use of aromatic bisphosphine ligands like BINAP or DPPF evolved. These Catalyst-Ligand combinations kinetically favor reductive elimination over β-hydride elimination.[133] The growing mechanistic insight led to the development of many highly specific types of ligands and palladium catalysts, tolerating a broader range of substrates and providing a higher general reactivity. Two main classes of ligands have since emerged: sterically hindered monophosphine ligands, such as BrettPhos and RuPhos, and chelating bisphosphine ligands like BINAP (Figure 4).[134]

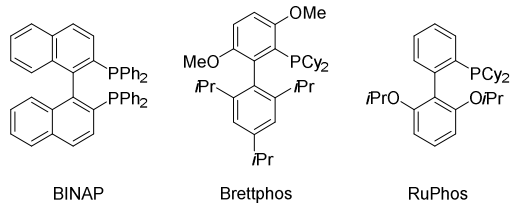
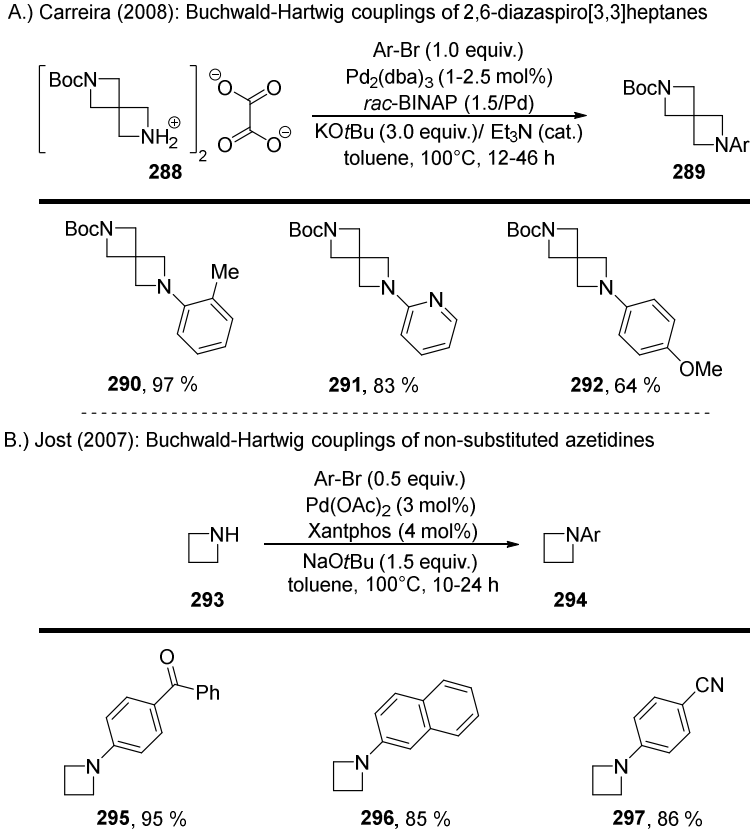


Figure 4: Structures of bisphosphine ligand BINAP and monophosphine ligands BrettPhos and RuPhos.

The literature reports only few applications of four-membered *N*-heterocyclic motifs in Buchwald-Hartwig couplings. In 2008 Carreira *et al.* reported the preparation of monoprotected 2,6-diazaspiro[3,3]heptane derivatives (**288**) and performed Pd-mediated *N*-arylations with a variety of differently functionalized substrates in moderate to excellent yields.[135]

[133] a) M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1995**, *117*, 4708-4709; b) J. F. Hartwig, S. Richards, D. Barañano, F. Paul, *J. Am. Chem. Soc.* **1996**, *118*, 3626-3633; c) M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 8232-8245.
[134] a) D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 57-68; b) J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1144-1157.
[135] J. Burkhard, E. M. Carreira, *Org. Lett.* **2008**, *10*, 3525-3526.

Hereby the spirocyclic compound was conveniently precipitated as an oxalate salt (**288**) and coupled using $Pd_2(dba)_3$ as catalyst, *rac*-BINAP as ligand and KO*t*Bu or $CsCO_3$ as base (Scheme 43, A). Remarkably, efficient coupling was only accomplished with the addition of NEt_3. Substrates with alkyl (**290**) and fluorine substituents showed the best results, though heterocyclic substrates like **291** were not extensively explored.



Scheme 43: Buchwald-Hartwig couplings of azetidines and derivates thereof.

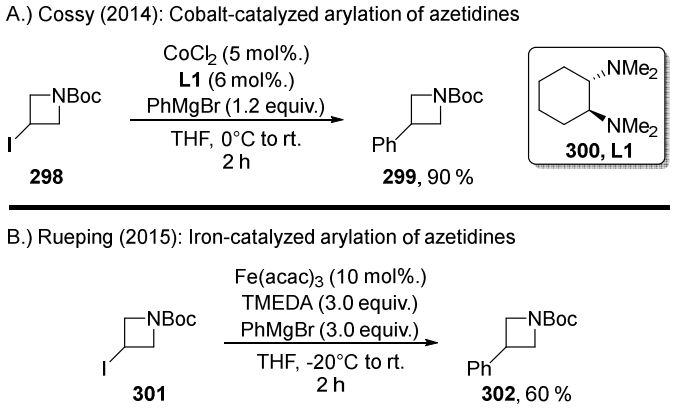
A different approach to Pd-mediated cross-couplings of azetidines and aziridines was reported in 2007 by Jost and coworkers (Scheme 43, B). Hereby the combination of $Pd(OAc)_2$, Xantphos and NaO*t*Bu proved to be suitable to couple free *NH*-azetidine (**293**) with aryl bromides in mostly good to excellent yields (**295**-**297**).[136] However, as in the method by Carreira, almost no coupling of heterocyclic substrates was showcased.

[136] B. Witulski, S. Senft, J. Bonet, O. Jost, *Synthesis* **2007**, *2007*, 243-250.

5. Objectives

5.1 Inspirational Literature – Strain Release

Among the various methods for the synthesis of 3-arylated azetidines, most rely on cross-couplings with commercially available 3-haloazetidines. However, their step-intensive preparation renders them quite expensive, especially on industrial scale. Among contributions from Kelly *et al.* on Ni-catalyzed Suzuki-Miyaura-type cross-couplings[137], most literature procedures describe Kumada-type couplings with Grignard reagents. In 2014, Cossy and coworkers described a Co-mediated coupling of 3-iodoazetidines (**298**) with organomagnesium reagents. Notably, optimization of the reaction parameters found ligand **300** (Scheme 44, A) to outperform bidentate ligand TMEDA, and was chosen for further transformations.[138]



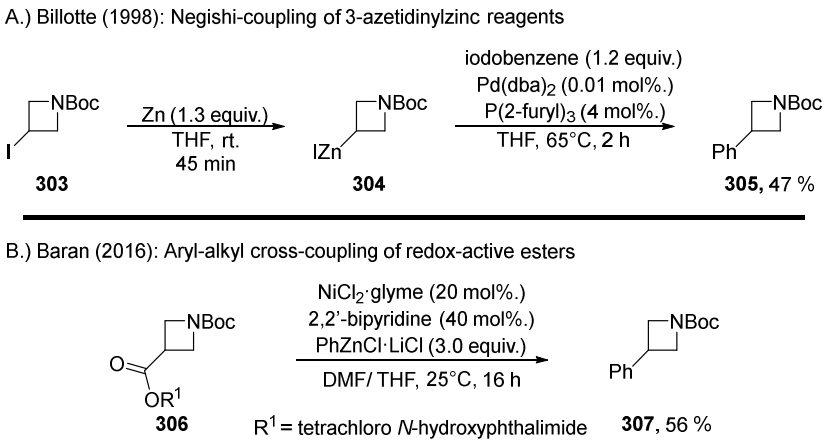
Scheme 44: Kumada-type synthesis of 3-arylated azetidines.

A similar report from Rueping *et al.* described $Fe(acac)_3$ catalyzed transformations with 3-iodoazetidines (**301**) and aryl Grignard reagents (Scheme 44, B). Compared to the $CoCl_2$ mediated coupling, a higher catalyst, ligand loading and excess of organomagnesium reagent were required to achieve sufficient conversion to **302**. Importantly, the aryl Grignard reagent needs to be added dropwise over 2 h, limiting the scalability of the transformation.[139]

An early report from Billotte *et al.* in 1998 described Negishi-couplings of 3-azetidinylzinc reagents of type **304**. Rapid Zn-insertion in 3-iodoazetidine derivatives (**303**) allowed *in-situ* cross-coupling with (hetero)aryl halides, catalyzed by a $Pd(dba)_2$/ $P(2\text{-furyl})_3$ system. Furthermore, this protocol enabled coupling with pyridine derivatives, which allowed precipitation of the corresponding HCl-salts, upon treatment with HCl/ EtOAc.[140]

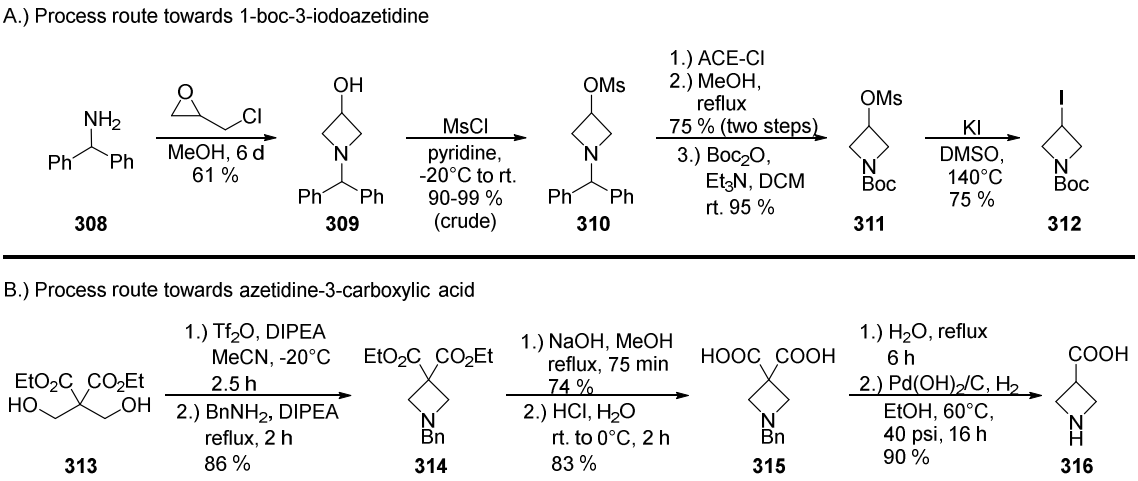
[137] M. A. J. Duncton, M. A. Estiarte, D. Tan, C. Kaub, D. J. R. O'Mahony, R. J. Johnson, M. Cox, W. T. Edwards, M. Wan, J. Kincaid, M. G. Kelly, *Org. Lett.* **2008**, *10*, 3259-3262.
[138] B. Barré, L. Gonnard, R. Campagne, S. Reymond, J. Marin, P. Ciapetti, M. Brellier, A. Guérinot, J. Cossy, *Org. Lett.* **2014**, *16*, 6160-6163.
[139] D. Parmar, L. Henkel, J. Dib, M. Rueping, *Chem. Commun.* **2015**, *51*, 2111-2113.
[140] S. Billotte, *Synlett* **1998**, *1998*, 379-380.

More recent contributions include Ni-mediated transformations of redox-active esters by Baran and coworkers.[141] Employing the catalytic system $NiCl_2$·glyme and 2,2'-bipyridine allowed coupling of secondary redox-active esters (**306**) with arylzinc reagents in moderate to excellent yields (Scheme 45, B).



Scheme 45: Other routes towards 3-arylazetidines.

Intensive optimization found *N*-hydroxyphthalimide esters and its more electron deficient tetrachloro derivative to be superior over HOAt, HOBt and Barton esters. However, in the case of azetidine derivative **307** (Scheme 45, B) no atom- or step-economic advantage is present over the previously mentioned couplings with 3-haloazetidines. To underline the extraordinary synthetic effort towards these building blocks, their industrially applied synthesis is depicted in Scheme 46.



Scheme 46: Industrially applied routes towards *N*-Boc-3-iodoazetidine and azetidine-3-carboxylic acid.

[141] J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C.-M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 2174-2177.

N-Boc-3-iodoazetidine requires a 6 step synthesis, with solely ring formation towards **309** taking 6 days of reaction time.[124, 142] The process route towards azetidine-3-carboxylic acid, as developed by researchers at Merck, requires 6 steps as well, including challenging pH-controlled decarboxylation and catalytic hydrogenation towards **316**.[143]

5.2 Experimental Objectives – Strain Release

As all the previously mentioned transformations rely on 3-substituted azetidine derivatives as modular platform for following transformations, a streamlined approach *via* azabicyclo[1.1.0]butanes (ABB) and it's subsequent nucleophilic ring opening with aryl Grignard reagents could provide a modular and step-economic alternative to the previously described strategies. Electrophilic trapping of the *in-situ* formed magnesium amides would allow introducing a variety of protecting groups. Finally, 1,3-bisarylated structures could be accessed *via* S_NAr or Buchwald-Hartwig couplings, optimally in a one-pot fashion.

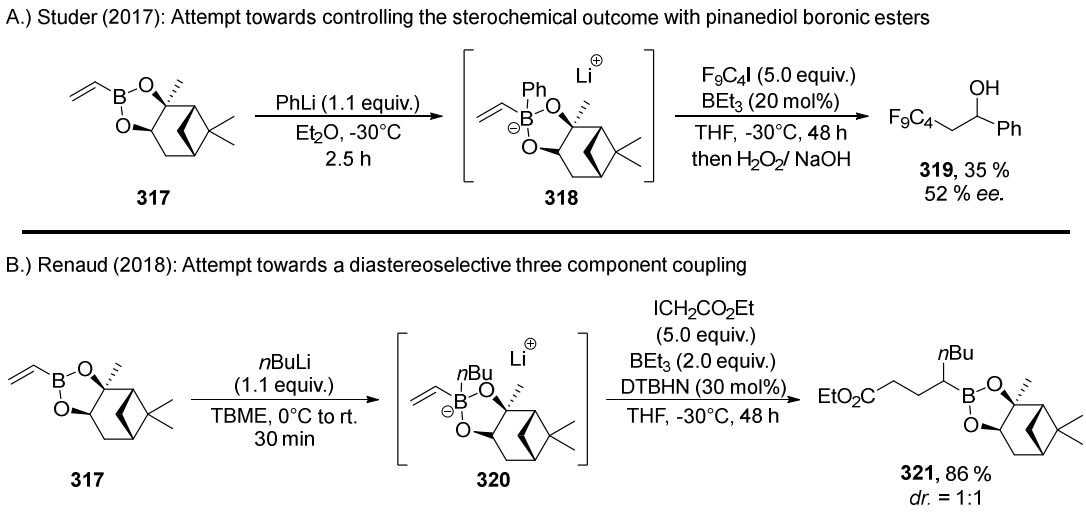
The *N*-arylation *via* S_NAr can be considered a cornerstone in organic chemistry, offering a reliable synthetic route, particularly in medicinal chemistry.[144] However, there are certain requirements on substrates participating in S_NAr. Firstly, an electron-withdrawing group on the aryl ring is essential to stabilize the negatively charged intermediate. Secondly, a strong polarization of the Carbon-Halide Bond is required, favoring the rate of reaction X = F > Cl >> Br.[145] Despite its utility, this substrate-dependancy limits efficiency and cost-effectiveness compared to modern transition metal-catalyzed transformations. Therefore, Buchwald-Hartwig cross-couplings of 3-substituted azetidines could allow overcoming the limitations of S_NAr. One-pot strain-release transformations towards 1,3-bisarylated azetidines, either via S_NAr or transition metal-catalyzed transformations, would significantly contribute to the accessability of these promising and underexplored motifs.

[142] A. G. Anderson, Jr., R. Lok, *J. Org. Chem.* **1972**, *37*, 3953-3955.
[143] R. A. Miller, F. Lang, B. Marcune, D. Zewge, Z. J. Song, S. Karady, *Synth. Commun.* **2003**, *33*, 3347-3353.
[144] A. d. Meijere. F. Diederich, *Metal-catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **2004**.
[145] H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119-2183.

5.3 Inspirational Literature – Polar-Radical Crossover

While a strain-release protocol would allow the construction of disubstituted azetidines, polar-radical crossover (PRC) could allow taking a step further towards a step-economic and stereoselective trifunctionalization of unsaturated small-membered ring systems such as azetines, cyclobutenes and cyclopentenes.

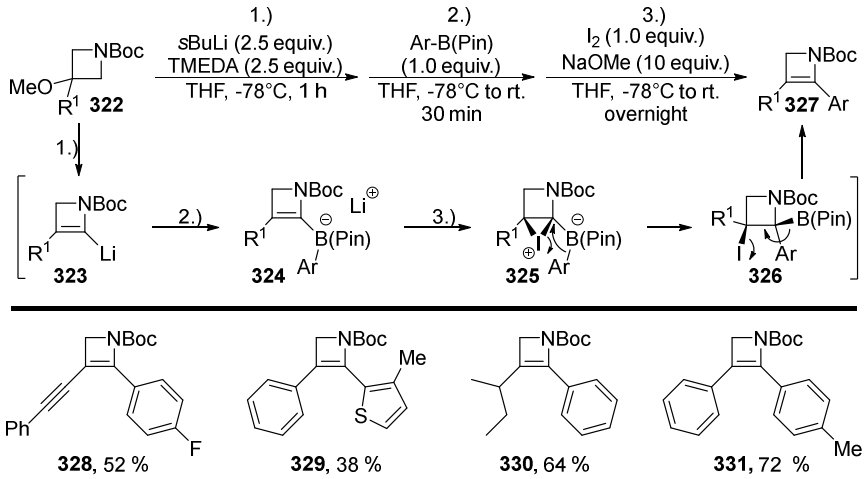
Initial attempts by the groups of Studer[88] and Renaud[90] to harness the stereochemical outcome of the 1,2-migration in PRC relied on employing pinanediol derived vinylboronic esters **317** as chiral auxiliaries (Scheme 47). However, this strategy furnished the desired coupling products **319** and **321** only with no to moderate sterocontrol. Still, the result from Studer *et al.* supports a possible enantioselective version of the cascade reaction, providing alcohol **319** with 52 % *ee.* (Scheme 47, A).



Scheme 47: Attempts towards stereoselective PRC by Studer and Renaud.

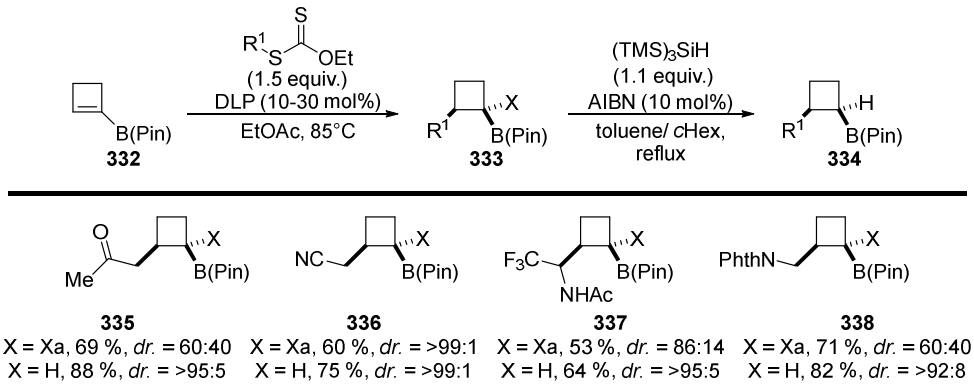
Preliminary results from Didier *et al.* demonstrated that azetinyllithium species (**323**), generated from the corresponding 3-methoxyazetidines (**322**) could be engaged in Zweifel olefinations and provided access to 3,4-disubstituted azetines (**328-331**) in reasonable yields (up to 72 %).[146] Proceeding *via* α-lithitation, β-elimination and a second α-metalation, the addition of boronic acid pinacol esters furnished the corresponding boronate complexes (**324**) (Scheme 48). As these are the platform for PRC, it was envisioned, whether they could be employed in a polar-radical crossover cascade to yield the corresponding trisubstituted azetidines.

[146] A. N. Baumann, M. Eisold, A. Music, G. Haas, Y. M. Kiw, D. Didier, *Org. Lett.* **2017**, *19*, 5681-5684.



Scheme 48: Zweifel olefination of azetinyllithium species as demonstrated by Didier *et al.*

Further encouraging work was presented from Zard and coworkers towards diasteroselective radical additions of xanthates to cyclobutylboronic esters of type **332** (Scheme 49).[147] Subsequent reductive removal of the xanthate moiety gave rise to diverse 1,2-disubstituted cyclobutylboronic esters (**335**-**338**).



Scheme 49: Diastereoselective radical additions to cyclobutenylboronic esters by Zard and coworkers.

A broad range of (α-boryl)cyclobutyl xanthates could be accessed *via* this methodology, generally with moderate diastereoselectivities. Notably, higher selectivities were only obtained with **336** and **337**, reflecting a possible interaction between nitrogen and boron in the adduct radical, and underlining a possible stereocontrol.

[147] J. Michalland, N. Casaretto, S. Z. Zard, *Angew. Chem. Int. Ed.* **2022**, *61*, e202113333.

5.4 Experimental Objectives – Polar-Radical Crossover

Except for the work of Aggarwal and coworkers on the polar-radical crossover (PRC) of bicyclobutylboronates[100] and Sakakura[102] on cyclopropenylboronates, no cyclic systems have yet been engaged in these three component couplings, most likely because of low stereocontrol. Inspired by advances in PRC from Studer[88, 94, 96], Aggarwal[89, 91, 101], Morken[92, 148] and others, this methodology could provide an entry towards unprecedented substitution patterns, once applied to small-membered (hetero)cycles like azetidines, cyclobutanes and other strained ring systems. Due to the cyclic nature of these substrates, a locked configuration of the intermediately formed vinylic boronate complexes could allow controlling the stereochemical outcome. As proven in the experiment of Studer (Scheme 47, A) and contributions by Morken and coworkers towards boron ligand design promoted diastereoselecive and enantioselective conjunctive couplings, the nature of the boronic ester exerts an influence over the stereoselectivity.[148] As there is a wide variety of boronic esters known in the literature, the influence of the diol ligand on the stereochemical outcome should be studied as well. Considering the versatility of the obtained boronated cyclic systems, a variety of stereospecific transformations would then provide a platform for further functionalization.

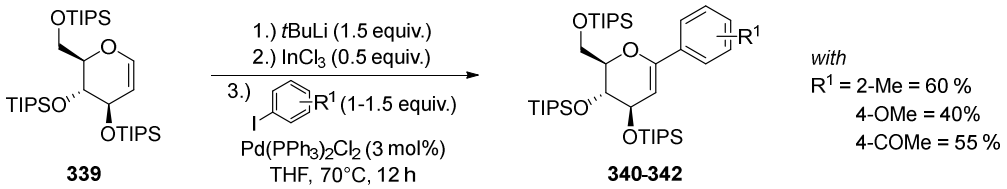
[148] J. A. Myhill, C. A. Wilhelmsen, L. Zhang, J. P. Morken, *J. Am. Chem. Soc.* **2018**, *140*, 15181-15185.

5.5 Inspirational Literature – Zweifel Olefination of Glycal Derivatives

Among promising unsaturated ring systems for PRC, glycal derivatives could represent another interesting yet challenging class of substrates. Even if no successful implementation of the corresponding glycal boronate complexes in the PRC cascade is possible, they could prove highly valuable, since an application in Zweifel olefinations may be feasible. This could enable a straightforward and transition-metal free access to arylated motifs, which often suffer from quite fastidious preparations, as underlined in the following.

Most literature procedures for C(1)-arylation of glycals rely on transition-metal catalyzed transformations, such as Suzuki-Miyaura couplings.[149] Typically, C(1)-glycalboronic esters or C(1)-haloglycals are accessed through lithiation (e.g. *t*BuLi) followed by electrophilic trapping.[150] However, these intermediates each possess certain major drawbacks: C(1)-glycalboronic acids show low stability and need to be engaged directly in further transformations, while the respective boronic esters cannot be purified by standard chromatographical techniques.[151] Similarly, C(1)-haloglycals suffer from weak stability and thus have to be stored at low temperature and light exclusion to prevent degradation.

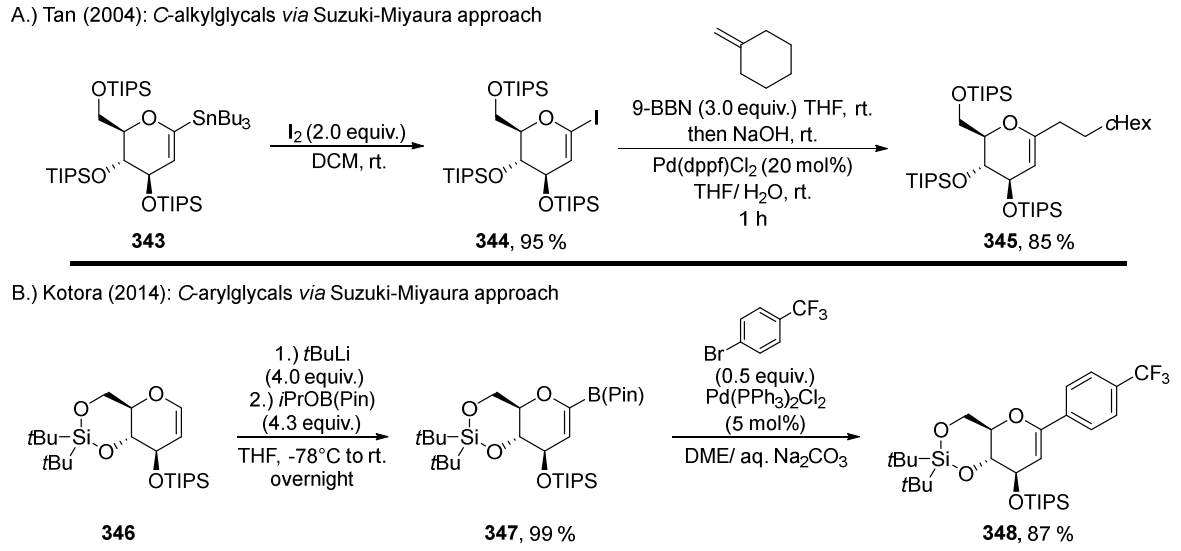
While early reports on *C*-glycosylation of glycal derivatives mostly relied on Stille couplings[152], Mineham *et al.* demonstrated in 2003 that *in-situ* generated glycalindium (III) species readily undergo palladium-catalyzed cross-couplings as a greener alternative to tin-dependent Stille transformations.[153] Appling previously optimized conditions, directed metalation of silyl protected D-glucal **339** afforded the respective α-lithiated glycal, which was then treated with $InCl_3$ to obtain stable glycalindium (III) species. Upon reaction with a slight excess of aryliodide under Pd(II) catalysis, C(1)-arylated glycal derivatives **340-342** were obtained in mostly moderate yields (Scheme 50).



Scheme 50: C(1)-Arylation of glycals *via* Pd-mediated cross-coupling of indium (III) species.

[149] Y. Yang, B. Yu, *Chem. Rev.* **2017**, *117*, 12281-12356.
[150] a) D. C. Koester, M. Leibeling, R. Neufeld, D. B. Werz, *Org. Lett.* **2010**, *12*, 3934-3937; b) X. Xue, W. Li, Z. Yin, X. Meng, Z. Li, *Tetrahedron Lett.* **2015**, *56*, 5228-5230; c) M. Liu, Y. Niu, Y.-F. Wu, X.-S. Ye, *Org. Lett.* **2016**, *18*, 1836-1839.
[151] K. Parkan, R. Pohl, M. Kotora, *Chem. Eur. J.* **2014**, *20*, 4414-4419.
[152] a) J. Hartung, B. J. D. Wright, S. J. Danishefsky, *Chem. Eur. J.* **2014**, *20*, 8731-8736; b) H. R. Khatri, H. Nguyen, J. K. Dunaway, J. Zhu, *Chem. Eur. J.* **2015**, *21*, 13553-13557; c) B. Koo, F. E. McDonald, *Org. Lett.* **2005**, *7*, 3621-3624.
[153] U. Lehmann, S. Awasthi, T. Minehan, *Org. Lett.* **2003**, *5*, 2405-2408.

In 2004, Tan and coworkers developed a method for C(1)-alkylation of glycals using an early Suzuki-Miyaura cross-coupling approach (Scheme 51, A).[154] α-Lithiation of D-glucal derivatives, followed by trapping with tributyltin chloride, yielded stable and purifiable tin intermediate **343**, which was subsequently converted to the respective iodoglucal **344**. Primary alkylboranes, conveniently obtained *via* hydroboration, were efficiently coupled under $Pd(dppf)Cl_2$ catalysis using NaOH as base. Notably, preincubation of the hydroboration products with aq. NaOH significantly reduced the undesired reduction of C(1)-iodoglucal (**344**) back to the starting glucal.

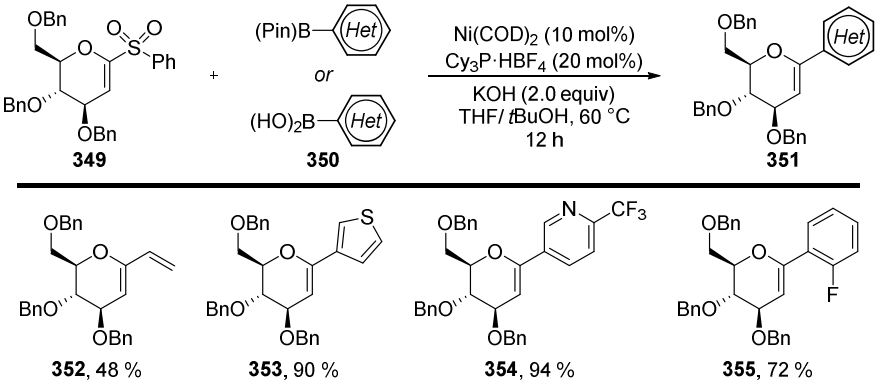


Scheme 51: Suzuki-Miyaura strategies towards C(1)-functionalized glycals.

An approach by Kotora and coworkers described arylations *via* Suyuki-Miyaura cross-couplings of boronated glycals.[151] Metalation of **346** with a large excess of *t*BuLi provided α-lithiated glycal derivatives, which were trapped with *i*PrOB(Pin) to afford the respective boronated glycal derivatives **347**. These were engaged directly in further transformations without additional purification. Importantly, using KOAc instead of K_2CO_3 minimized homocoupling. Employing a two-fold excess of boronated glycal resulted in efficient C(1)-arylated glycal formation (**348**) with excellent functional group tolerance (Scheme 51, B).

In order to overcome the issues assorted with the preparation and handling of boronated glycals, a recent report by Niu *et al.* demonstrated the *C*-glycosylation of α-oxo-vinylsulfone substituted glycals **349** in a Nickel-catalysed Suzuki-Miyaura coupling (Scheme 52).[155]

[154] J. S. Potuzak, D. S. Tan, *Tetrahedron Lett.* **2004**, *45*, 1797-1801.
[155] L. Gong, H.-B. Sun, L.-F. Deng, X. Zhang, J. Liu, S. Yang, D. Niu, *J. Am. Chem. Soc.* **2019**, *141*, 7680-7686.



Scheme 52: Suzuki-Miyaura coupling of sulfonyl glycals by Niu *et al.*

Employing KOH as base and the catalytic system $Ni(COD)_2$ and $Cy_3P{\cdot}HBF_4$, a broad variety of (hetero)aryl, vinyl and allyl boronic acid derivatives was shown to be reactive under the developed conditions. Importantly, these 1-sulfonyl glycals can be readily accessed in large scale from glycosyl sulfones by β-oxo elimination, and show excellent stability.

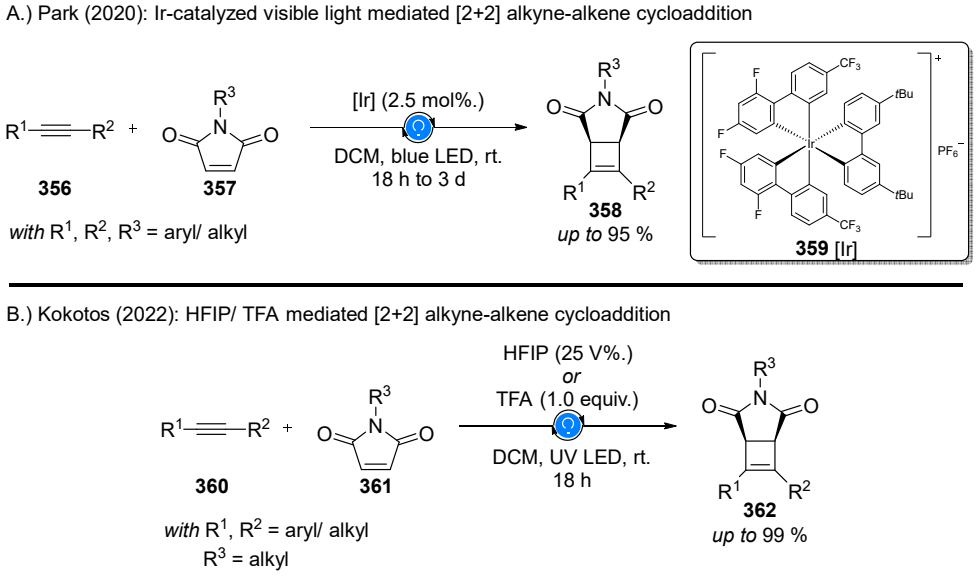
5.6 Experimental Objectives – Zweifel Olefination of Glycal Derivatives

Given that most of the aforementioned intermediates yet need to be accessed *via* α-lithiation and electrophilic trapping, a single-pot strategy using Zweifel olefination conditions could provide a streamlined approach to a variety of C(1)-arylated glycals, avoiding fastidious intermediate purifications. As described in Chapter 3.1, the corresponding boronates can be accessed either by treatment of the glycalboronic ester with an organometallic reagent or equally by reacting a glycal derived organometallic with the respective boronic ester.[77c] Concerning both routes, an efficient deprotonation at C(1) is inevitable, thus reagents and conditions need to be carefully optimized. As in the nature of this transition metal-free transformation, diversly substituted aryl- or alkylboronic esters are tolerated, which would significantly simplify fastidious multistep procedures. Further stereospecific transformations of these unsaturated sugars could include hydroboration-oxidation sequences to regenerate the parent carbohydrates entity, as well as epoxidations and cyclopropanations.

5.7 Inspirational Literature – [2+2] Cycloaddition and Zinc-Exchange

When focusing back on the effective generation of four membered ring systems, one reaction which may be directly associated with the synthesis of cyclobutanes is the [2+2] cycloaddition (Paternò–Büchi reaction). While the UV-activated alkene–alkene [2 + 2] cycloaddition is known to be an important tool to access functionalized cyclobutanes, reports about alkyne-alkene transformations relying on visible-light photocatalysis remain scarce.[156]

In 2019, Glorius and coworkers reported about a blue light mediated intermolecular [2+2] alkyne-alkene cycloaddition between carvone-derivatives and symmetrical alkynes, catalyzed by $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$.[157] Interestingly, this unexpected discovery was mainly attributed to high-troughput screening for luminescence quenchers. The same year, Maestri *et al.* reported about an intramolecular variant, the tetracyclization of linear dienynes through a radical cation cascade, mediated by visible light and Ir(III) catalysis.[158]



Scheme 53: Recent advances in alkyne-alkene [2+2] cycloadditions.

In 2020, Park and coworkers presented their blue-light mediated cycloaddition of substituted maleimide derivatives (**357**) and alkynes (**356**) (Scheme 53, A).[159] Alkyl- and aryl- substituted maleimide derivatives were shown to be reactive with non symmetrical alkyl and aryl substituted alkynes under $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$ (**359**) catalysis.

[156] a) Y. Xu, M. L. Conner, M. K. Brown, *Angew. Chem. Int. Ed.* **2015**, *54*, 11918-11928; b) S. Poplata, A. Tröster, Y.-Q. Zou, T. Bach, *Chem. Rev.* **2016**, *116*, 9748-9815.
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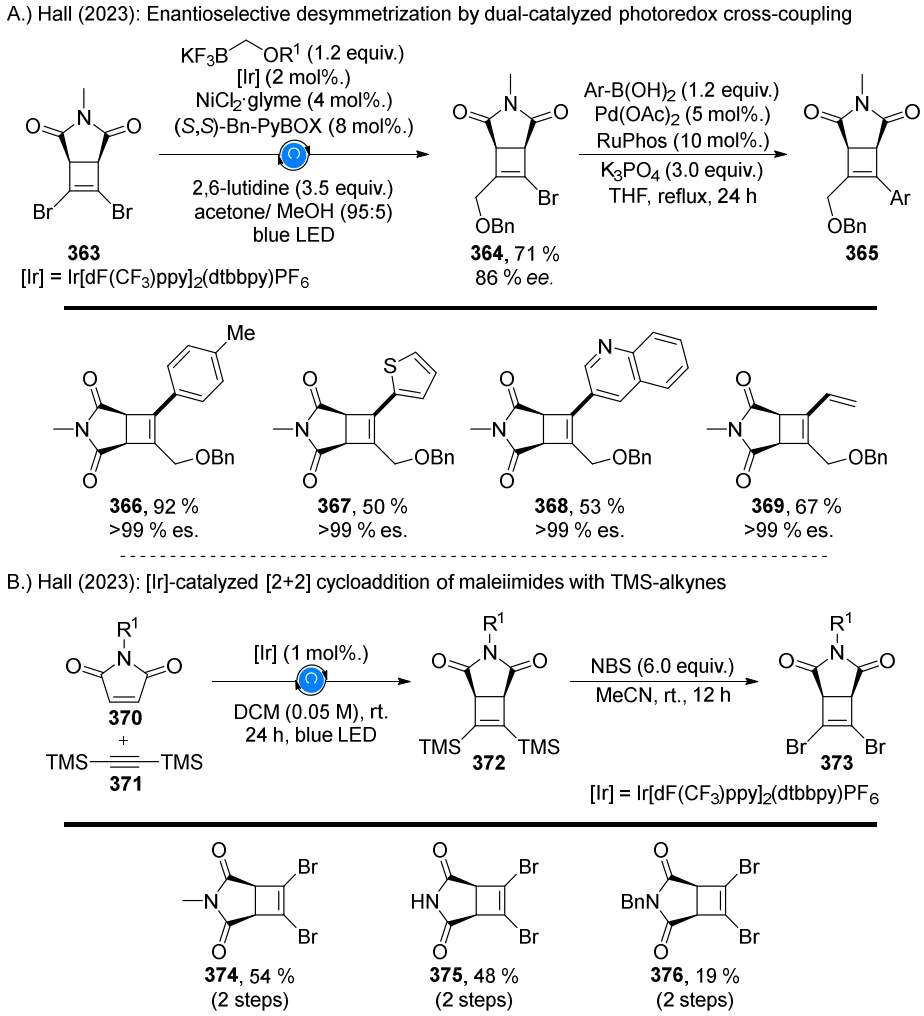
[159] S. Ha, Y. Lee, Y. Kwak, A. Mishra, E. Yu, B. Ryou, C.-M. Park, *Nat. Commun.* **2020**, *11*, 2509.



Scheme 54: Desymmetrization of dihalocyclobutenes by Hall and coworkers.

However, long reaction times (up to 3 d), strong dilution (0.05 M) and the necessity for resource-limited and high-priced iridium catalyst (≈ 1200 €/g) limit the applicability, especially in consideration of results from Kokotos *et al.* from 2022 (Scheme 53, B).[160] Similarly to the previous contribution, *N*-alkylmaleimides (**361**) underwent [2+2] cycloadditions with mono and disubstituted aryl- and alkylalkynes (**360**), under irradiation with a 43 W UV-LED (370 nm) and TFA or HFIP as an additive/ cosolvent. Reaction times were limited to 18 h, and the procedure was also applicable to *N*-aryl maleimides if thioxanthone (THX) was employed as the energy transfer photocatalyst, along with blue LED irradiation and HFIP as cosolvent.

Inspired by the aforementioned results, Hall and coworkers modified the initial procedure for [2+2] cycloaddition from Park towards employing bis(trimethylsilyl)acetylene (**371**) and diversly *N*-substituted maleimides (**370**) (Scheme 54, B).

[160] I. Triandafillidi, N. F. Nikitas, P. L. Gkizis, N. Spiliopoulou, C. G. Kokotos, *ChemSusChem* **2022**, *15*, e202102441.

The intermediately obtained bis(trimethylsilyl)cyclobutenes of type **372** were then subjected to double electrophilic bromodesilylation by treatment with excess NBS, to afford the respective dibromocyclobutenes (**374**-**376**) in mostly good yields. With the strategy of developing a divergent synthesis from single versatile intermediates these dibrominated cyclobutenes **363** were employed in mono-selective nickel/iridium dual-catalyzed photoredox $C(sp^2)$-$C(sp^3)$ coupling, developed by Molander and coworkers[161] (Scheme 54, A). Optimum conditions were found with a Pybox derived ligand, $NiCl_2$·glyme and Iridium photocatalyst, under blue LED irradiation. Further enantiospecific diversification of platform motif **364** included Suzuki-Miyaura couplings with arylboronic acids and more transformations towards saturated and unsaturated 4-membered carbocycles (**366**-**369**).[162] While these transformations allow to construct cyclobutenes bearing a wide variety of different possible substitutions, they are limited by the range of alkyltrifluoroborates which were shown to be compatible with the nickel/iridium dual-catalyzed photoredox cross-coupling.

5.8 Experimental Objectives – [2+2] Cycloaddition and Zinc-Exchange

Combining principles of photochemical and organometallic chemistry could allow overcoming the previously mentioned challenges and provide a simplified route towards diversly substituted cyclobutenes. Following the strategy of Kokotos *et al.* and employing mono-(trimethylsilyl) substituted aryl- or alkylalkynes with *N*-alkylmaleimides under UV-photochemical conditions would allow a transition-metal free construction of diverse trisubstituted TMS-cyclobutenes. Combined with the halodesilylation strategy from Hall and coworkers, trisubstituted halocyclobutenes could be accessed readily. With the broad range of available organometallic exchange reagents available, trapping with a plethora of different electrophiles and constructing complex tetra-substituted cyclobutenes in a one-pot fashion could be feasible without the need for expensive and toxic transition-metal photocatalysts. Depending on the nature of the organometallic exchange reagent (Li, Mg or Zn), following allylation, acylation or Negishi cross-coupling reactions would allow overcoming the limitations of the procedure by Hall and coworkers, and to take a step further towards rarely reported complex tri- and tetrasubstituted cyclobutenes. Owing to the imide moiety and olefin subunit, these scaffolds could serve as highly advantageous intermediates and enable great synthetic freedom for subsequent diversifications.

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[162] D. J. Konowalchuk, D. G. Hall, *Angew. Chem. Int. Ed.* **2023**, *62*, e202313503.

B. RESULTS AND DISCUSSION

1. Strain-Release Arylations for the bis-Functionalization of Azetidines

1.1 Relevance

Nitrogen-containing heterocycles are present in over 75 % of FDA-approved and currently marketed drugs, according to a 2020 study.[163] Compared to their larger sized analogues, azetidines remain relatively unexplored, largely due to challenges in their efficient and selective synthesis.[107, 164] Notably, compounds as straightforward as 1,3-bisarylated azetidines are rarely documented in the literature, likely for this reason. Despite significant advances from Nagao[120-121, 165], Baran[166], Lopchuk[124], and Gianatassio[126], the arylation of the 3-position in aza-bicyclobutanes *via* strain-release strategy remains unaddressed. While literature procedures towards these bisarylated compounds usually involve fastidious multistep approaches *via* costly halogenated azetidines, this chapter presents a straightforward strain-release transformation from a readily prepared and bench-stable ABB precursor. The *in-situ* generated azabicyclobutanes are treated with nucleophilic organometallic reagents to obtain 3-arylated azetidine intermediates, which then can be subjected to single-pot strategies for *N*-arylation, either *via* S_NAr reactions or Buchwald–Hartwig couplings.

1.2 Preamble

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The project was conducted in equal contribution with F. Reiners.

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Strain-release arylations for the bis-functionalization of azetidines†

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The addition of nucleophilic organometallic species onto *in situ* generated azabicyclobutanes enables the selective formation of 3-arylated azetidine intermediates through strain-release. Single pot strategies were further developed for the *N*-arylation of resulting azetidines, employing either S_NAr reactions or Buchwald–Hartwig couplings.

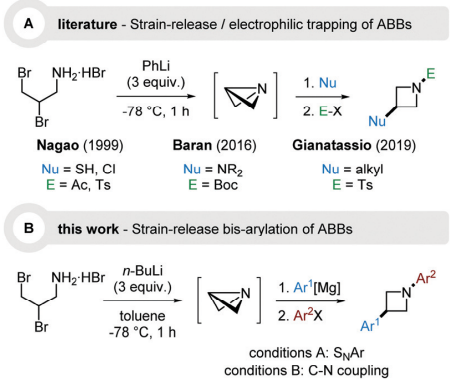
Strained sp^3-rich heterocycles have emerged as important scaffolds in medicinal chemistry over recent years, as they can help tune pharmacokinetic properties.[1] Among those, azetidines have received particular attention. They have been used in numerous occasions as phenyl isosteres or to rigidify amine structures.[2]

Diverse strategies allow for the synthesis of substituted azetidines, including [2+2]-cycloadditions,[3] ring expansions,[4] ring contractions[5] and ring closures.[6] In addition, we recently contributed to this field through manipulation of unsaturated analogs – 2*H*-azetines – *via* Diels–Alder cycloadditions or hydrogenation reactions.[7]

Due to their ring strain, easily-accessible 1-aza-bicyclo[1.1.0]-butanes (ABB) possess an interesting reactivity towards nucleophiles, representing therefore an interesting platform for further functionalizations. Given the high strain in C–N–C dihedral angles, aza-bicyclobutanes are strong nucleophiles and should readily react with electrophilic species. Following the pioneering work of Funke,[8] the group of Nagao exploited the concept of strain-release with nucleophiles such as halogens and thiols, in the presence of *N*-trapping reagents like acyl- and tosyl chlorides (Scheme 1A).[9] In 2016, Baran developed an efficient strain-release amination protocol based on the use of primary and secondary turbo-amides as nucleophiles, for the late-stage diversification of drug-like molecules.[10] More recently, Gianatassio and co-workers exemplified the nucleophilic addition of Grignard reagents in the formation of the corresponding 3-alkylazetidines when using Boc_2O, TsCl or acyl chlorides as electrophiles.[11] 1,2-Boronate rearrangements also proved efficient for the substitution of azetidines at position 3.[12]

Surprisingly, molecules as simple as 1,3-bisarylated azetidines are scarcely found in the literature, which certainly stems from the difficulty to access their structure efficiently and selectively. Despite efforts mentioned above, the introduction of aryl moieties at position 3 of aza-bicyclobutanes through strain-release remains undisclosed. With a general interest in 4-membered carbo- and heterocycles and their implication in drug discovery,[13] we set out to establish a reliable method for the construction of such functionalized azetidine architectures.

Our investigations started with the examination of the ring-opening reactions with *ex situ* generated aryl-Grignard reagents. In previous reports, AAB were generated in THF by double cyclization, employing an excess of phenyl lithium as base for deprotonation. First experiments were performed following these conditions (PhLi, THF), revealing however the formation of several by-products. The expected product **3**,



Scheme 1 Synthetic access to 1,3-bisfunctionalized azetidines.

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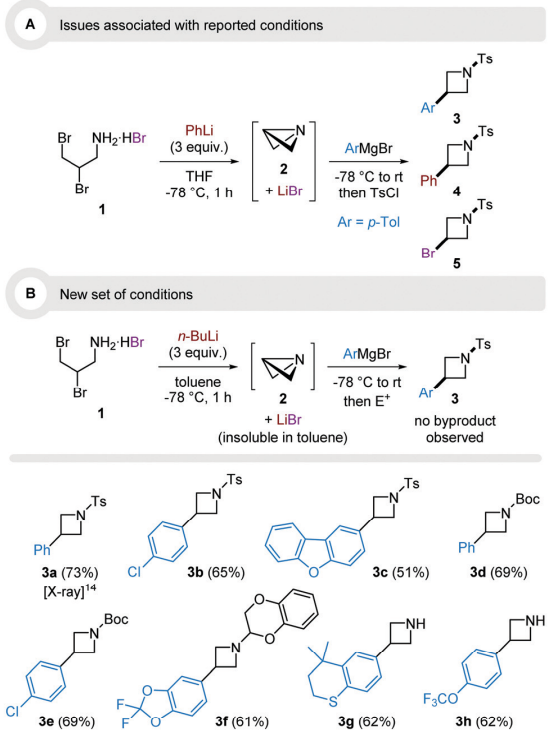
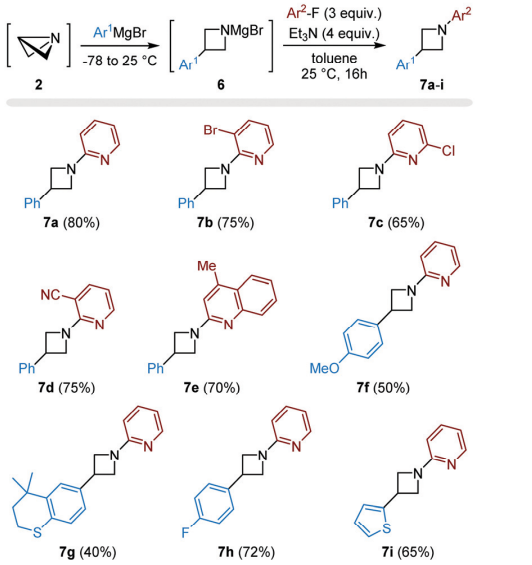
† Electronic supplementary information (ESI) available. CCDC 2128822. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc07053c
‡ These authors contributed equally.



Scheme 2 Establishment of conditions for the strain-release reaction with aryl-magnesium reagents.



Scheme 3 3-Arylazetidines in nucleophilic aromatic substitutions (S_NAr).

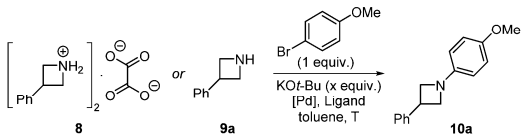
obtained *via* nucleophilic addition of *p*-TolMgBr was only produced in low yields and could not be isolated from **4** and **5**, generated by the nucleophilic additions of residual PhLi and THF-soluble LiBr, respectively (Scheme 2).

We envisioned that PhLi could be replaced by *n*-BuLi, avoiding therefore the formation of inseparable molecule **4**, *n*-BuLi being more basic, yet less nucleophilic than PhLi. Preventing the formation of **5** was achieved by switching to toluene as solvent to precipitate LiBr formed during the cyclization process, therefore inhibiting its undesired reactivity with **2**. With a new set of conditions in hands, products **3a–h** were isolated without byproducts in 51–73% yields,[14] upon addition of electrophiles like TsCl and Boc_2O or through simple hydrolysis. The unprecedented nucleophilic addition of aryl-Grignard reagents onto aza-bicyclobutanes proved efficient, with a smooth introduction of aryl moieties at position 3. We envisioned that the intermediate magnesium amide **6** resulting from a ring opening reaction could be used *in situ* in a further nucleophilic aromatic substitution onto electron-deficient aromatics, providing a first approach to bis-arylated structures. 2-Fluorinated pyridines were chosen as appropriate substrates for this transformation, given that their electron-deficient nature allow for the stabilization of the intermediate Meisenheimer complex. After successful generation of the *N*-azetidinylmagnesium species **6a** *in situ* – with PhMgBr – further S_NAr was performed in the presence of triethylamine and an excess of the electrophilic 2-fluoropyridine to give **7a** in 80% yield. Varying the substitution pattern of 2-fluoropyridines yielded halogenated compounds **7b** and **7c**, nitrile derivative **7d**, and 2-fluoroquinoline gave **7e** in 70% yield. Electron-rich (*p*-OMe, *p*-SR) and electron-poor (*p*-F) aryl-Grignard reagents were also proven efficient in this transformation, furnishing **7f–h** in 40 to 72% yield. The introduction of heteroaromatic was also exemplified with 2-thiophenylmagnesium reagents, providing **7i** (65%) (Scheme 3).

Although this strategy proved efficient, it only allows for the substitution of fluorides on pyridine-like electrophiles. Other electron-deficient aryls possessing cyano, nitro or ester groups failed to generate the desired *N*-arylated azetidines, consequently limiting the scope of the reaction. Therefore, we looked for an alternative that would broaden the possibilities for C–N bond formation and oriented ourselves towards Pd-catalyzed transformations. Buchwald–Hartwig coupling reactions have witnessed tremendous improvements since the pioneering studies of those who gave their names to the transformation.[15] Many examples from drug discovery programs have been reported on the coupling of secondary amines,[16] even including some azetidines.[12,17]

Two starting materials were tested for reaction optimizations (Table 1), azetidinium-oxalate salt (**8**), following Carreira's procedure on spiro compounds,[17] and free azetidine (**9**), isolated through basic workup, using *p*-bromoanisole as coupling partner. While catalytic systems such as $Pd_2(dba)_3$/BINAP or $Pd(OAc)_2$/Xantphos (entries 1–3) only yielded coupling product **10** in 4 to 17% from the oxalate salt **8** (with either KO*t*-Bu or NaO*t*-Bu as the base), it was isolated in 22 to 24% yield when switching to xPhosPdG3/Brettphos and RuPhosPdG3/RuPhos (entries 4 and 5), respectively. Although full consumption of the

Table 1 Optimizations on Buchwald–Hartwig couplings of azetidines



8 9a 10a

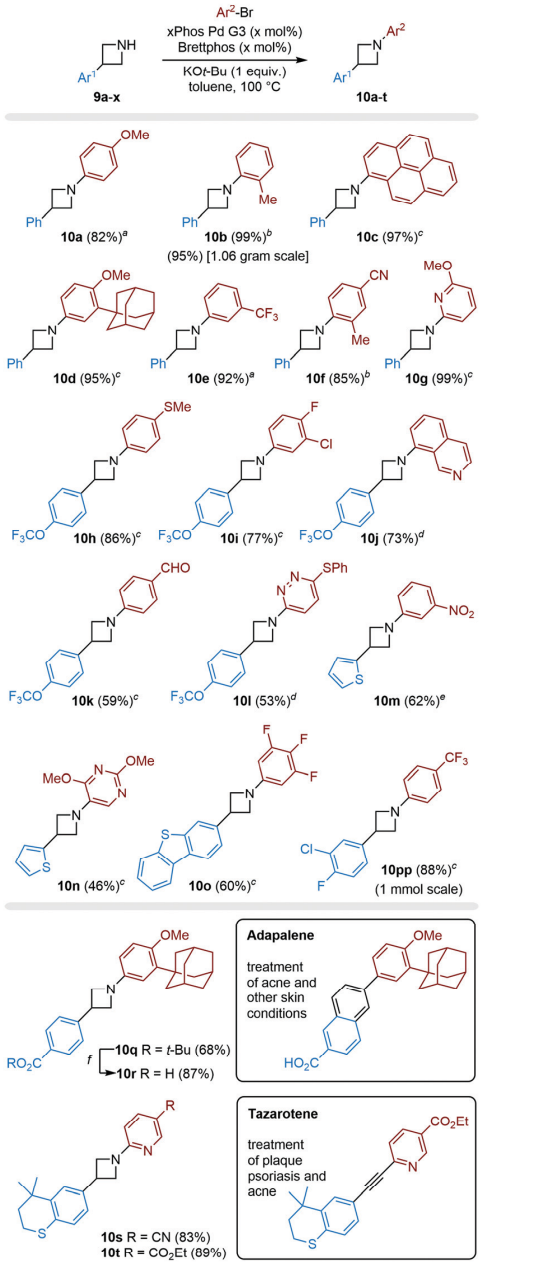
Entry	Substrate	[Pd]/ligand	T (°C)	Yield (%)
1	**8**	$Pd_2(dba)_3$/BINAP[a]	100	17
2	**8**	$Pd_2(dba)_3$/BINAP[a]	100	16[b]
3	**8**	$Pd(OAc)_2$/Xantphos[a]	100	4
4	**8**	xPhosPdG3/Brettphos[c]	100	24
5	**8**	RuPhosPdG3/RuPhos[c]	100	22
6	**9**	xPhosPdG3/Brettphos[c]	100	82
7	**9**	xPhosPdG3/Brettphos[c]	80	73
8	**9**	RuPhosPdG3/RuPhos[c]	100	71

[a] Reactions performed with 3 mol% [Pd], [Pd]/ligand = 1.5 : 1, 3.0 equiv. KO*t*-Bu. [b] NaO*t*-Bu instead of KO*t*-Bu. [c] Reactions performed with 1 mol% [Pd], [Pd]/ligand = 1 : 1, 1.4 equiv. KO*t*-Bu.

coupling partner was observed in most cases, and despite further optimization efforts using **8**, no better yield than 24% could be obtained, probably because of undesired ring-opening side-reactions. However, when employing the free azetidine **9** (entries 6–8), yields were increased to 82% in the presence of xPhosPdG3/Brettphos as the catalytic system. If lower temperatures resulted in lower yields, decreasing the catalyst loading to 1% did not show any negative influence on the efficiency of the coupling.

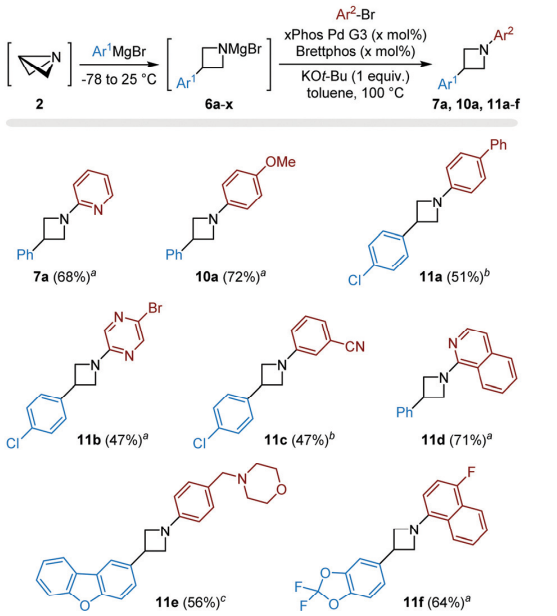
With optimal conditions in hands, the scope of Buchwald–Hartwig coupling on *ex situ* generated 3-arylazetidines was evaluated in the presence of diversely substituted aryl and heteroaryl bromides. 3-Phenylazetidines performed equally well with electron-rich and electron-poor aryl bromides, providing 1,3-bis-arylated azetidines **10a–g** in excellent yields (82 to 99%). Worthy of note, a better yield was obtained through Buchwald–Hartwig coupling on 2-bromopyridines (**10g**, 99%) than under S_NAr conditions (**7a–i**, 40 to 80%). The introduction of a donor group (OCF_3) at the *para*-position similarly led to compounds **10h–l** in moderate to good yields (up to 86%). The reaction also proved highly functional group tolerant, as witnessed in the case of **10k** containing an aldehyde (59%), and selective for bromides over chlorides (**10i**, 77%). Heterocyclic Grignard reagents such as 2-thiophenylmagnesium and 3-dibenzothiophenylmagnesium bromides were also engaged in bis-arylations (**10m–o**, 46 to 62%). The addition of an electron-poor Grignard reagent provided **10q** in 68% yield. Analogs of drug compounds were finally synthesized following this rational design, to demonstrate the applicability of such method. Azetidine-analogs (**10q–t**) of Adapalene and Tazarotene were obtained in a minimum of steps in very good yields through Buchwald–Hartwig couplings, in which the azetidine-moiety was employed to serve as isostere of either aryl- or alkynyl-groups (Scheme 4).

As the process for azetidine bis-arylation through coupling strategies led to a library of widely functionalized molecules, we next aimed at increasing step-economy by withdrawing the



Scheme 4 Buchwald–Hartwig coupling of 3-arylazetidines. [a] x = 1 mol%, [b] x = 2 mol%, [c] x = 3 mol%, [d] x = 4 mol%, [e] x = 5 mol%, [f] $ZnBr_2$, DCM, rt, 14 h.

intermediate purification of the free azetidine. A one-pot sequence was therefore developed to enable the bis-arylation of azetidines directly from **1**, given that both steps of strain-release and Buchwald–Hartwig coupling are performed in the same solvent system. *In situ* generation of aza-bicyclobutane **2** was followed by ring opening with aryl magnesium species, and



Scheme 5 One-pot ring-opening/Buchwald–Hartwig coupling sequence. [a] x = 3 mol%, [b] x = 4 mol%, [c] x = 5 mol%.

finally engaged in the coupling reaction under Pd-catalysed conditions described above without purification (Scheme 5). Compounds **7a** and **10a** were isolated in slightly lower yields than in the two-step procedure. Varying the nature of aryl Grignard reagents led to functionalized scaffolds **11a–f** in moderate to good yields after Buchwald–Hartwig C–N coupling with aryl bromides, including substituted phenyl, pyrazine and quinoline moieties.

In summary, we have developed a very efficient procedure for the 1,3-bis-arylation of azetidines, taking advantage of *in situ* generated reactive strained aza-bicyclobutanes. Unprecedented arylation at position 3 was performed with aryl-magnesium reagents, adapting the solvent system to avoid undesired products, and demonstrating the high tolerance of the method for functional groups. Simple and versatile C–N bond formation strategies were applied in a single-pot sequence, allowing the design of a vast library of building blocks, including analogs of drug compounds, taking a step further towards the challenging implementation of rigid sp^3-rich scaffolds in drug-discovery programs.

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Conflicts of interest

There are no conflicts of interest to declare.

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2. Stereoselective Polar Radical Crossover for the Functionalization of Strained-Ring Systems

2.1 Relevance

Polar-radical crossover (PRC), as a synergy between organometallic and photochemical methods, offers a powerful approach for cyclic systems, enabling the formation of three new bonds and two stereogenic centers.[167] Though this substitution pattern is rare, it does occur in nature[168], as seen in cyclobutane-based natural product grandisol[169], an agrochemical of interest (Figure 5).[170] Except for contributions on PRC by Aggarwal[100-101] and Sakakura[102], most reports describe these cascade reactions on acyclic platforms. This chapter presents an extension of the PRC strategy to unsaturated (small-membered) strained-ring systems. Outgoing from vinylboronates or unsaturated cycles themself, stereodefined trisubstituted azetidines, cyclobutanes, cyclopentanes, THFs and pyrrolidines are accessed in single-pot strategies. Carefull optimization of the reaction parameters reveal a correlation between the stereochemical outcome and diol ligand of the boronic ester. Subsequent stereospecific transformations of the boron moiety enable diversification into unique substitution patterns

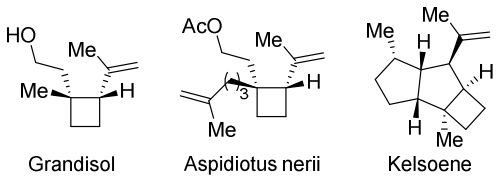

Figure 5: Natural products featuring trisubtituted cyclobutanes.

2.2 Preamble

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Stereoselective polar radical crossover for the functionalization of strained-ring systems

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Florian Trauner[1,2], Rahma Ghazali[1], Jan Rettig[1], Christina M. Thiele[1] & Dorian Didier[1,2]

Radical-polar crossover of organoborates is a poweful tool that enables the creation of two C-C bonds simultaneously. Small ring systems have become essential motifs in drug discovery and medicinal chemistry. However, step-economic methods for their selective functionalization remains scarce. Here we present a one-pot strategy that merges a simple preparation of strained organoboron species with the recently popularized polar radical crossover of borate derivatives to stereoselectively access tri-substituted azetidines, cyclobutanes and five-membered carbo- and heterocycles.

Strained carbo- and heterocycles have been brought to the forefront of medicinal chemistry and drug discovery programs in recent years as modulable sp^3-rich 3D-isosters of diverse aromatic systems[1–4]. Besides exalting greater metabolic stability, it has been shown that small molecular scaffolds can help improve lipophilicity as well as pharmacokinetics[5–9]. The puckered conformation adopted by four-membered rings renders them ideal cores for drug discovery as they can balance both rigidity (observed in constraints systems such as propellanes[10–13] or cubanes[14,15]) and flexibility (conformers in larger cyclic scaffolds). Azetidines and cyclobutanes can, therefore, be used towards the three-dimensionalization of pyridyl and phenyl moieties, their substitution pattern following defined exit vectors (Fig. 1).

Recent step-economic strategies towards substituted azetidines include the work of Baran and Gianatassio on strain-release amination[16] and alkylation[17] of 1-azabicyclo[1.1.0]butanes (ABB) that provide an elegant route to 3-substituted structures, as well as our contribution on 1,3-bisarylations[18]. The group of Aggarwal reported the strain-release of ABB through boron-homologations for the synthesis of 3,3-bis functionalized azetidines[19–22]. Cyclobutanes were similarly obtained from metallated bicyclo[1.1.0]butanes[23–27]. Aside from strain-releasing strategies, substituted azetidines and cyclobutanes are traditionally approached through [2 + 2]-cycloadditions as recently illustrated by Schindler[28–31], Bach[32–35], Glorius[36–38] and Brown[39–43] as well as cyclizations and ring contraction and expansion reactions[44–50], which imply a pre-organization of the substituents around the structure of starting materials.

Aiming at the development of a synthetic toolbox that would allow diversely and selectively access functionalized four-membered building blocks, we set out to combine our expertise on the metalation of small heterocycles[51–58] and 1,2-boronate rearrangements[59–64] to design a simple one-pot sequence towards tri-substituted architectures. We envisioned that the inspiring work on polar radical crossover (PRC) pioneered by the groups of Studer[65,66], Aggarwal[67,68], Morken[69] and Renaud[70] could reveal fantastic opportunities to introduce three substituents at once on azetidines, cyclobutanes and other heterocycles, starting from corresponding cyclic alkenyl-metal intermediates. To the best of our knowledge, control over the stereochemical outcome of this transformation remained moderate, as the radical process was only exemplified on acyclic alkenylboronates. However, for this strategy to take a consequent step further and enable a broad scope of applications, one would have to gain control over the spatial arrangement of vicinal substituents. We predicted that the diastereoselectivity of the 1,2-metalate rearrangement would be controlled thanks to the cyclic nature of our substrates, due to a locked configuration of reactive intermediates.

Results and discussion

Optimizations of reaction conditions

The first test was performed on azetinyllithium **1** (generated in situ), providing the bisorganoborinate **2** after the addition of *n*-BuBpin in THF. Generation of a radical species from nonafluorobutyl iodide under UV irradiation at −40 °C—as assumed from literature precedent[71]— provided the expected trisubstituted structure **3** in 44% with a moderate dr of 4:1 (Fig. 2, entry 1, table 1). We started optimizing the reaction parameters by assessing the importance of the stoichiometry of perfluorinated butyl-iodide on the yield. Under similar conditions, azetidine **3** was obtained with increased yields up to 78% with 1.5 equivalents of C_4F_9I (entry 2), and comparable yield could be observed under blue light irradiation at −20 °C, keeping the same levels of diastereoselectivity. Solvent effects were examined next. While 1,3-dimethyl-2-imidazolidinone (DMI), dichloromethane and dichloroethane did not improve selectivity (entries 5–7), a diastereomeric ratio of 5:1 was measured in 2-methyl-THF (mTHF, entry 8).

It is interesting to note that the reaction performed in the absence of dodecane ($C_{12}H_{26}$) as standard only resulted in product formation with poor diastereoselectivity (entry 9, dr = 2:1).

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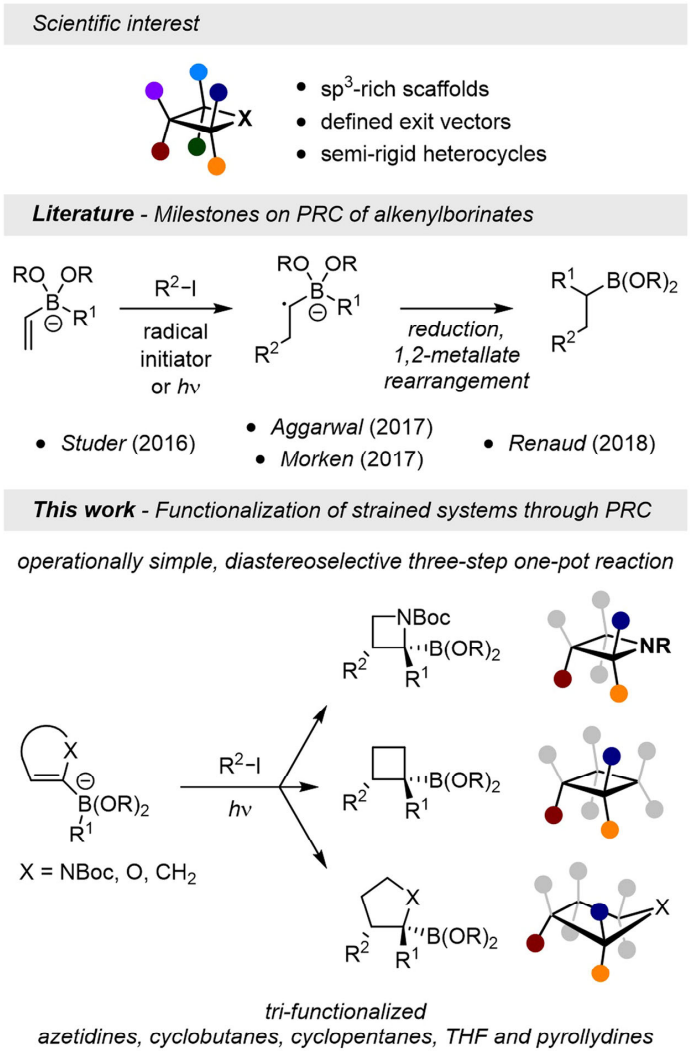

Fig. 1 | Previous work and present contribution on radical-polar crossover reactions. Achievements reached in the diastereoselective radical-polar crossover of cyclic systems such as 4- and 5-membered carbo- and heterocycles, in contrast with previous work by Studer, Aggarwal, Morken and Renaud on acyclic systems.

With these encouraging results in hands, the influence of steric effects was evaluated by changing the ligand structure on the boron atom. The process was reiterated employing organoboron species ***A***–***H*** under the conditions displayed in entry 8. While reagents ***A***, ***B*** and ***C*** gave similarly high yields (63–93%), the groups present on the pinacol scaffold allowed for a broad modulation of dr values, a maximum being reached for reagent ***A*** (*n*-BuB^{F}pin, dr = 8:1). Only traces of products were observed with 1,3-propyldiols (***E*** and ***F***) and the isopropyl-pinacol structure ***D***. Surprisingly low dr were obtained using phenyl-pinacol derivative ***G*** or "Bmac" ***H***[72], products being additionally isolated only in moderate yields.

With a fair adequation between conversion and diastereoselectivity, ethyl-pinacol (^{E}pin) ligands ***A*** were further employed to explore the scope of the reaction. In addition to positively influencing the dr, products obtained with ligand ***A*** showed high stability on silica (avoids protodenoronation) when compared to classical pinacols.

From azetines to trisubstituted azetidines

The scope of the transformation was first assessed on azetinyllithium species **1**, in situ generated from 3-methoxyazetidines.[15f] Coordination to an organoboron derivative R^{1}-B^{E}pin primarily gives borinate **2**, which was then engaged in PRC after the solvent switch to mTHF and addition of the radical precursor R^{2}-I under blue light irradiation (Fig. 3). Products **3a**–**e** were synthesized in moderate to good yields from alkylboron reagents and perfluorinated radical precursors with good dr values (8:1–20:1), except for methylboronic ester (**3e**, dr = 1:1), which might come from a lack of steric effects (vide infra).

Excellent dr (>20:1) was observed when employing ethyl 2,2-difluoro-2-iodoacetate (**3f**, **g**), and we noticed a general trend for the iodoacetates to give increased dr (**3k**–**m**, dr > 20:1) in comparison with other radical precursors (**3h**–**j**, up to 7:1 dr). The lack of sterical hindrance in the case of methyl boronic ester (**3n**, dr = 2:1). Arylboronic ester also tended to decrease the selectivity (**3i** and **3o**, 2:1 to 5:1 dr). In all cases, the 1,2-metallate rearrangement proceeded in a trans-selective fashion (R^{1} vs. R^{2}), as supported by thorough analytic measurements and experimental data (vide infra). Furthermore, substituted azetidines proved to be stable under basic conditions, and we were able to hydrolyze the ester moiety into the corresponding carboxylic acid **3l'** in good yield (76%), keeping the dr value above 20:1.

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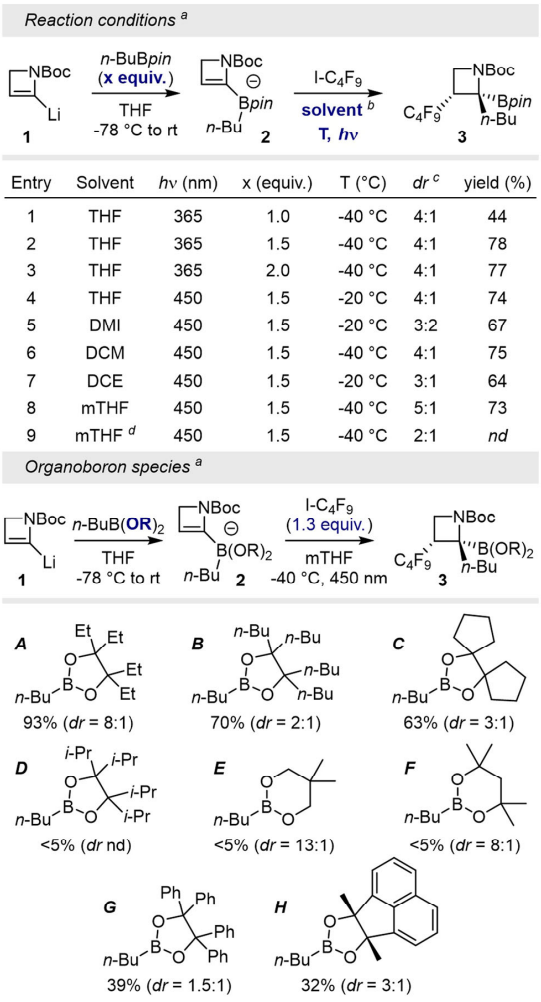

Entry	Solvent	hν (nm)	x (equiv.)	T (°C)	dr c	yield (%)
1	THF	365	1.0	-40 °C	4:1	44
2	THF	365	1.5	-40 °C	4:1	78
3	THF	365	2.0	-40 °C	4:1	77
4	THF	450	1.5	-20 °C	4:1	74
5	DMI	450	1.5	-20 °C	3:2	67
6	DCM	450	1.5	-40 °C	4:1	75
7	DCE	450	1.5	-20 °C	3:1	64
8	mTHF	450	1.5	-40 °C	5:1	73
9	mTHF d	450	1.5	-40 °C	2:1	*nd*

Fig. 2 | Optimizations of the polar radical crossover on in situ generated azetinyllithium species. a Indicated yields have been assessed by GC-analysis of the crude mixture; $C_{12}H_{26}$ (1 vol%, 30 mL) was used as standard. b for reactions performed in other solvents than THF, a solvent switch was performed after the removal of THF for the crude mixture. c indicated dr were measured on the crude mixture by 19F-NMR. d The reaction was performed in the absence of C12 standard.

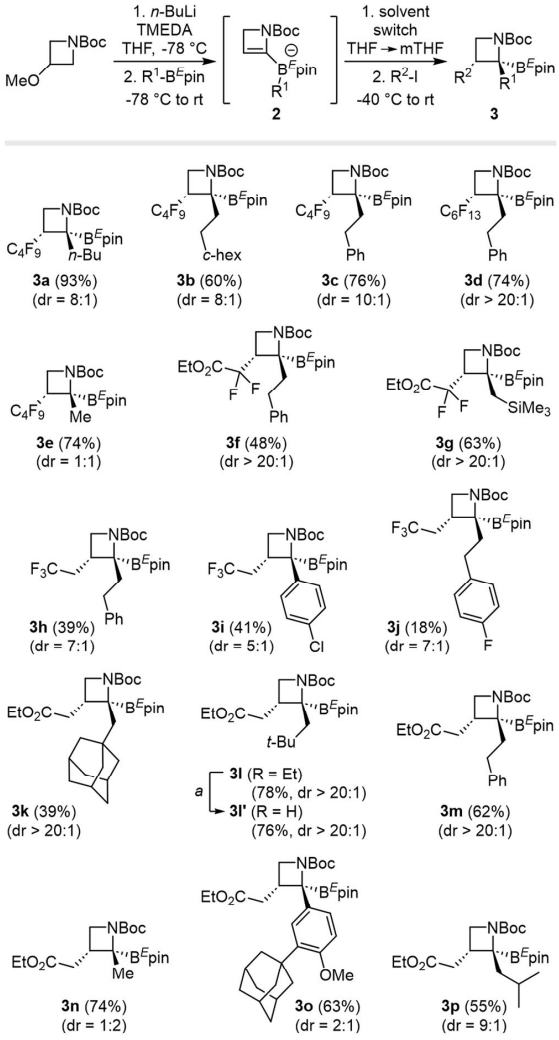

Fig. 3 | Evaluation of the PRC sequence scope for the synthesis of trisubstituted azetidines from azetinyllithium species. Azetinyllithium **1** is generated in situ by α-lithiation/elimination/α-lithiation, starting from commercially available 3-methoxyazetidines. The first steps are conducted in THF, but the best diastereoselectivities are achieved by performing the last rearrangement step in Me-THF.

From cyclobutenes to trisubstituted cyclobutanes

The stereoselective synthesis of cyclobutanes through PRC was envisioned next from readily available starting cyclobutenylboronic esters **4** (Fig. 4), applying previously optimized conditions (Fig. 2). The scope of the transformation was explored by varying both radical precursors (perfluorinated alkyl iodides and iodoacetates) and nature of the organolithium species (alkyl- and aryl-lithium). A range of functionalized cyclobutanes (**6a**–**f**) was isolated in good yields and excellent dr (up to 20:1) with the exception of cyclopropylboronic ester (**6c**, dr = 6:1). Interestingly, an iodomethylketone proved to be an efficient radical precursor for this reaction (**6e**, dr = 18:1), as well as unprotected iodoacetamide (**6f**), although with slightly decreased diastereoselectivity (dr = 7:1). It is important to note that the diastereoselectivity of the metallate rearrangement step on cyclobutyl-intermediates is generally superior to the one on azetidinyl-species.

Given the high levels of diastereoselectivity observed in cyclobutenylboron species, two derivatives possessing the thiophene sub-unit typically found in Canagliflozin (a drug used in the treatment of type 2 diabetes)[73] were synthesized, employing iodoacetate (**6g**) and trifluoromethyliodide (**6h**).

Scope of the transformation on cyclopentenes

Larger carbocyclic systems were explored next, starting from stable, storable cyclopentenylboronic ester **7a** (Fig. 5). Coordination of an organolithium reagent (R^1-Li) to **7** promotes the formation of the bisorganoborinate **8**. Radical crossover was further initiated under blue light irradiation at −40 °C after the solvent switch and addition of iodoacetates as radical precursors. Trisubstituted cyclopentanes **9a**–**e** were obtained with high yields and stereochemical ratio (up to 20:1 dr), except for the addition of aryllithium species (**9d**, dr = 2:1), as previously observed. While switching the radical precursor for a *tert*-butyl ester gave similar results, both in efficiency and

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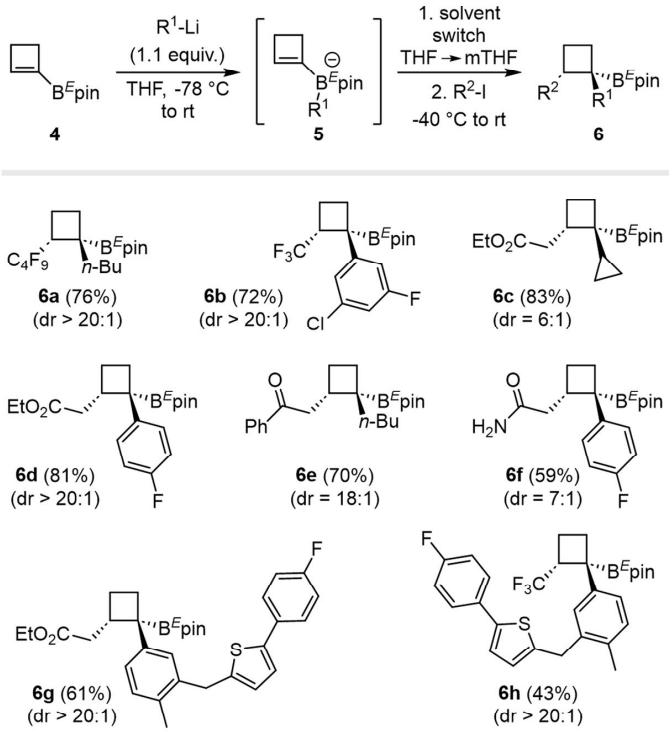

Fig. 4 | Application of the PRC sequence to the tris-functionalization of cyclobutanes from isolated cyclobutenylboronic ester derivatives 4. The scope of the reaction (R^1) is evaluated for both aryl and alkyl substituents, showing a generally higher trend in diastereoselectivities than for azetidines.

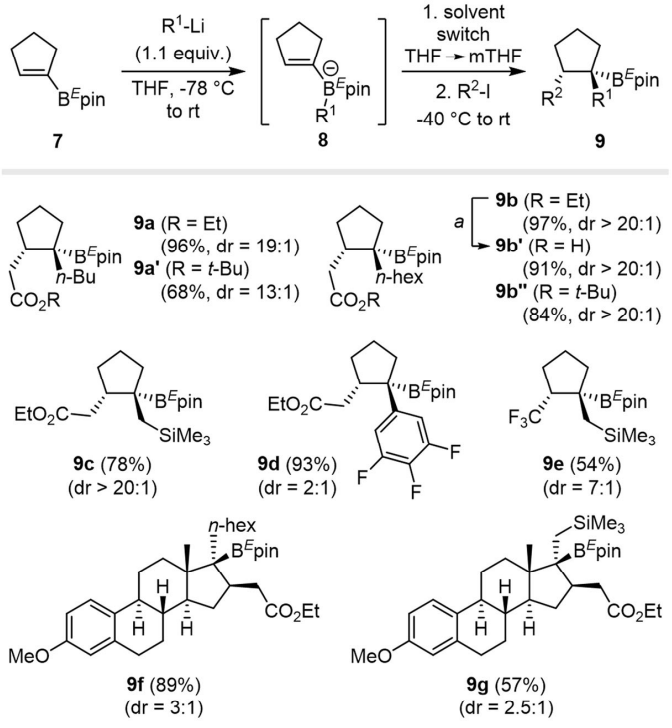

Fig. 5 | Generalization of the PRC sequence to larger rings. Evaluation of the scope for the diastereoselective formation of tris-functionalized cyclopentanes from preformed cyclopentenylboronic esters 7. Steroide-derivatives are also described, although with a lower diastereomeric ratio.

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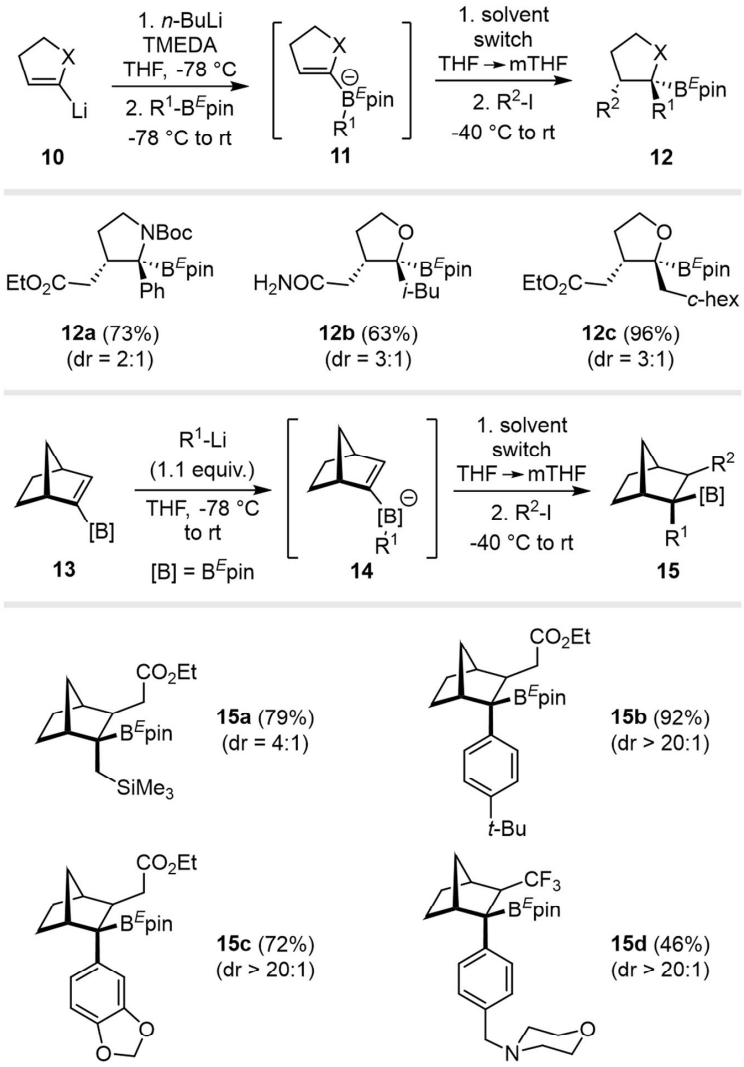

Fig. 6 | Stereoselective functionalization of pyrrolidines, THF (top) and norbornanes (bottom) via PRC. Evaluation of the reaction scope using readily accessible lithiated dihydropyrroles and dihydrofuranes **10**, as well as norbornenylboronic esters **13**.

diastereoselectivity (**9a'** and **9b"**), trifluoromethyl iodide furnished product **9e** with slightly lower levels of selectivity (7:1 dr).

These compounds also proved stable under basic conditions, product **9b** being hydrolyzed into **9b'** in excellent yield (91%). Interestingly, we demonstrated the applicability of this stereoselective method to the functionalization of estron scaffolds. The stable alkenylboronic ester substrate **7b** was first accessed in few steps from (+)-estrone 3-methyl ether and further engaged in PRC, leading to products **9f** and **9g** in high yields, although the diastereoselectivity could only reach 3:1. It is, however, important to note that addition of the in situ generated radical species occurred on the least hindered face of the cyclopentenylboronates (*cis* to the methyl substituent).

Scope of the transformation on heterocycles and norbornenes

Although heterocyclic five-membered rings were efficiently engaged in PRC to provide trisubstituted pyrrolidine **12a** and THF **12b, c** (up to 96% yield), the diastereomeric ratio could only reach up to 3:1 (Fig. 6).

Norbornenylboronic ester **13** was readily prepared in a few steps from commercially available norbornene and proved to be a suitable building block for PRC. It efficiently provided substituted structures **15a**–**c** in both high yields (72–92%) and stereoselectivities (dr > 20:1). The formation of the major diastereoisomer can be explained by the addition of the radical species on the least hindered bridged side of the norbornenyl-substrate, followed by an antiperiplanar 1,2-metallate rearrangement.

Determination of the relative configuration

Stereochemical relationships between newly introduced substituents were studied first by NOE and HOE on compounds **3e**, **3d** and **3a** (Fig. 7, see supporting information). The poor diastereomeric ratio (ca. 1:1) obtained for **3e** allowed us to separate both diastereoisomers ($\mathbf{3e_{syn}}$ and $\mathbf{3e_{anti}}$) in sufficient quantities for NMR experiments. In the case of $\mathbf{3e_{anti}}$, while a strong NOE was observed between the H-atom at position 3 and the methyl group at position 2, we could not detect any significant HOE (^1H–^{19}F), supporting the anti-configuration of R^1 and R^2 groups. Inversed observations were made for compound $\mathbf{3e_{syn}}$, for which a very weak NOE was detected, but with a strong HOE (^1H–^{19}F) between the perfluorinated chain at position 3 and the methyl group at position 2. Analogy was then made for compound **3d**, isolated with a higher dr (>20:1), for which we assigned the anti-configuration through both detections of a strong H–CH_3 NOE and the

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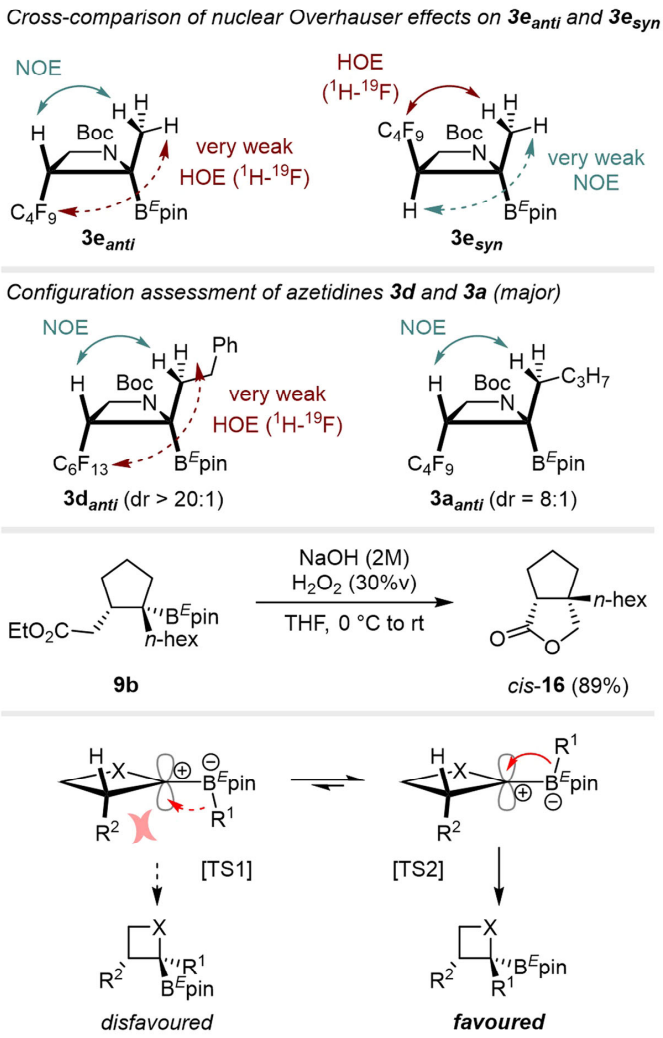

Fig. 7 | Nuclear Overhauser effect (NOE) and heteronuclear Overhauser effect (HOE) on synthesized azetidines to support the assigned relative configuration of the three substituents (top). Experimental assessment of the relative configuration through oxidative C–B bond cleavage followed by lactonization (middle). Proposed model for the stereoselectivity and elements of support for the observed relative configuration (bottom).

absence of significant HOE (^{1}H-^{19}F). Similarly, strong NOE on compound **3a** (dr = 8:1) allowed us to assign its anti-configuration.

Brown oxidation (NaOH, H_2O_2) on **9b** led to the bicyclic compound *cis*-**16** by subsequent lactonization, which brought additional support to the assigned stereochemistry. We propose that the R^2-chain introduced from the radical precursor shields one of the two diastereotopic faces of the cyclic intermediate, disfavoring the 1,2-metallate rearrangement of R^1 from the same face [TS1], to favor an antiperiplanar addition [TS2].

Further applications

Finally, we evaluated the robustness and the configurational stability of our cyclic organoboron systems under different conditions (Fig. 8). Switching the Boc protecting group on the nitrogen atom (**3a**) for a benzyl group in a two-step sequence led to *N*-benzyl product **17a**, which was isolated in 67% yield with retained diastereomeric ratio (8:1). **17b** was obtained through the same reaction sequence from its NBoc derivative parent in 56%, without the need for intermediate purification. Ligand exchange on **17b** also proceeded with stereorentention towards the potassium trifluoroborate salt **19** in good yields (75%). Using a modified Brown oxidation sequence in which the B^Epin group was transiently transformed into the more reactive BCl_2 derivative, the bicyclic azetidine-based aminoacetal **20** was isolated in 84% with retention of the stereochemistry (dr = 9:1). A similar procedure than on the azetidines was used to stereoretentively transform the cyclopentyl-compound **9c** into the corresponding trifluoroborate salt **21** with high efficiency (85%). Surprisingly, when compound **9a'** was treated with BCl_3, bicyclic oxaborinanone **22** was obtained upon the addition of water and concentration in vacuo, supporting once again the relative stereochemistry observed for polar radical crossover on cyclic systems.

Conclusion

We have developed a robust, efficient and highly diastereoselective sequence based on polar radical crossover that allows to access stereodefined trisubstituted azetidines, cyclobutanes, cyclopentanes, THFs and pyrrolidines. Fine tuning of reaction conditions revealed the importance of diol ligands on the boron to maximize the stereoselectivity, opening thereof new opportunities in boron-based synthetic methodologies.

Methods

See Supplementary methods.

See Supplementary Data 1.

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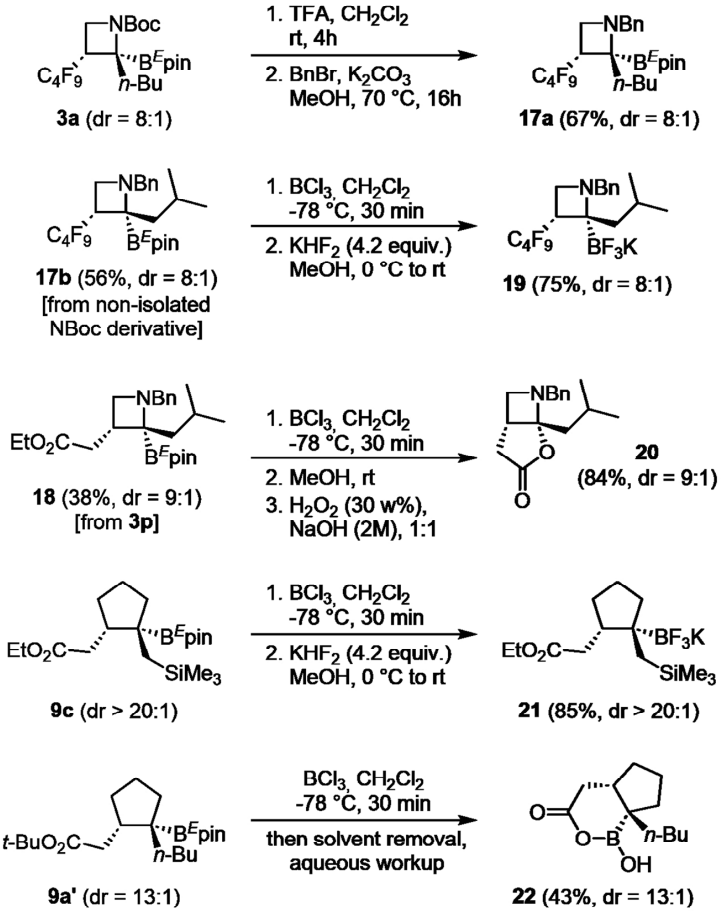

Fig. 8 | Post-functionalization of cyclic boronic esters. Including manipulation of N-protecting groups, ligand exchanges on the boron atom and oxidation / lactonization on azetidines, ligand exchange and oxidative formation of oxaborinanone on borylated cyclopentanes.

Data availability

Data for this manuscript has been deposited in figshare: https://doi.org/10.6084/m9.figshare.25907506. "Supplementary Methods" contains detailed protocols for the preparation of substrates, reaction optimizations, scope evaluation and description of analytical data (^{1}H and ^{13}C NMR, HRMS). "Supplementary Data 1" contains all ^{1}H and ^{13}C NMR spectra.

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Author contributions

Conceptualization and supervision: D.D. Experimental investigation: F.T., R.G. Structure analysis: J.R., C.M.T. Writing: D.D., C.M.T. Supporting information: F.T., R.G., J.R. Proofreading: D.D., C.M.T., F.T., R.G., and J.R.

Competing interests

The authors declare no competing interests.

Additional information

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3. Zweifel Olefination for *C*-Glycosylation

3.1 Relevance

C(1)-arylated sugars are a prominent motif not only in natural products like Vitexin (Figure 6).[171] Originally designed as a selective treatment for diabetes mellitus, SGLT-2 inhibitors like Empagliflocin and Dapaglifolcin rely on a C(1)-arylated glucose subunit to selectively inhibit the sodium-glucose-cotransporter.[172] Additionally, recent studies showed their efficacy in the treatment of cardiovascular disfunctions and chronic kidney diseases, as approved by the FDA.[173] Unlike the numerous strategies for *N*- or *O*-glycosylation[174], methods for *C*-glycosylation[149] are limited, often relying on transition-metal-catalyzed transformations like Suzuki-Miyaura couplings. This chapter presents a transition-metal free single-pot Zweifel olefination strategy towards C(1)-arylated glycal derivatives. Outgoing from various readily accessible glycal derivatives, deprotonation at C(1) and treatment with the respective boronic esters affords boronate complexes, which are subjected to Zweifel-olefination conditions. Hydroboration-oxidation sequences allow regeneration of the carbohydrate framework, as efficiently demonstrated with the synthesis of various SGLT-2 inhibitor derivatives in a simplified, one-pot process.

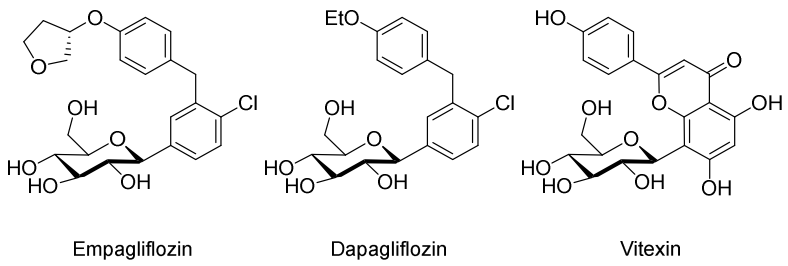

Figure 6: SGLT-2 Inhibitors Empagliflozin and Dapagliflozin and natural occurring *C*-glycoside Vitexin.

3.2 Preamble

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Zweifel Olefination for *C*-Glycosylation

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Abstract:

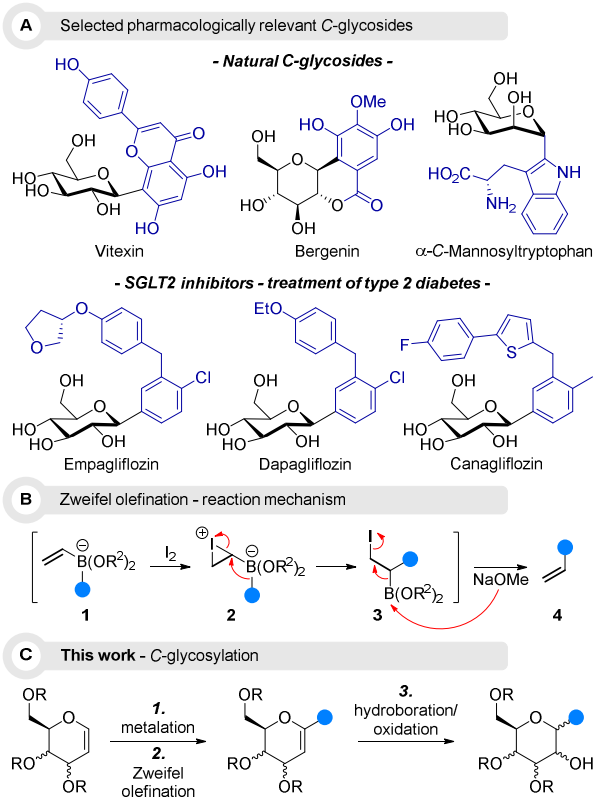
C-glycosides are significant in medicinal chemistry due to their resistance to enzymatic hydrolysis, making them more stable and bioavailable compared to *O*-glycosides. Their unique structure also offers potential for developing drugs with improved therapeutic properties, particularly in treating diseases like diabetes and cancer. The main challenge in synthesizing *C*-glycosides lies in forming the carbon-carbon bond between the sugar and aglycone efficiently, while controlling the stereochemistry and minimizing side reactions. Starting from glycal derivatives, the Zweifel olefination presents an elegant opportunity to access *C*-glycosides in a selective manner. α-Lithiation of D-glucal, L-rhamnal, D-xylal and L-arabinal scaffolds was employed as a starting point in the synthesis of corresponding unsaturated aryl-, heteroaryl- and alkenyl-*C*-glycosides. This provides a straightforward strategy towards pharmacorelevant gliflozins and other unreported rhamnal- and xylal-analogs.

I. Introduction:

Carbohydrates play a pivotal role in drug discovery and in the pharmaceutical industry, being omnipresent in bioactive compounds and natural derivatives.[1] They constitute the base of genetic material and are essential building blocks in epigenetic studies.[2]

Naturally occurring *C*-glycosides include Vitexin,[3] an apigenin (flavone) derivative found in different flowers and leaves, Bergenin,[4] isolated from *Bergenia* flowering plants and α-*C*-Mannosyltryptophan,[5] a product of post-translational modification by *C*-mannosyltransferases (figure 1A). Among synthetic pharmaceuticals of interest, gliflozins – compounds that we later access through our method - are a class of SGLT2 inhibitors used in the treatment of type 2 diabetes, as they exert effects on the sodium glucose cotransporter.[6] These *C*-glycosides are based on the glucose scaffolds, arylated at position 2, and include Empagliflozin, Dapagliflozin and Canagliflozin. More importantly, the FDA has recently approved Empagliflozin in the treatment of cardiovascular disfunctions and chronic kidney diseases.[7]

When compared with *O*- and *N*-glycosylations, methods for *C*-glycosylation[8] remain limited and mostly rely on either nucleophilic attack at the anomeric position or radical reactions.[9]



A. Selected examples of pharmacologically relevant *C*-glycosides; **B**. General mechanism of the Zweifel olefination; **C**. Our strategic design to stereoselectively access *C*-glycosides via a sequence of Zweifel olefination/Brown oxidation.

Figure 1 - Our conceptual approach to *C*-glycosides in the context of current research interests.

We envisioned that *C*-glycosides could easily be accessed from their parent unsaturated structures, strategically placing a double bond between C1 and C2. Such C=C bond can be regarded as polarized alkoxy-alkenes, prone to deprotonation at the α-position (C1) in the presence of appropriate bases, which provides a regioselective anchor for further functionalization. The carbohydrate integrity can then be restored through classical double bond manipulation such as the hydroboration/oxidation sequence (figure 1C).[10]

Among the various elegant methods available for double bond manipulation, Zweifel olefination is most appealing because of its high efficiency, good versatility and stereocontrol. Pioneered by Zweifel in 1967,[11] it has received increasing attention over the last decade as an indispensable tool in total synthesis, especially by the group of Aggarwal.[12] In this reaction, a 1,2-metallate rearrangement is triggered upon addition of iodide onto a bis-organoborinate species **1** (figure 1B). The creation of an electrophilic site at the position α to the boron atoms via the intermediate iodonium species **2** promotes the key 1,2-rearrangement, transferring the organyl moiety in an intramolecular substitution reaction that leads to an α,β-iodoboronic ester intermediate **3**. An elimination then proceeds in the presence of a base, usually sodium methanolate, providing the formal coupling product between the organyl group and the former double bond.

Our recent interest on Zweifel olefination stems from the ability to perform C(sp^2)-C(sp^2) bond formation without the use of precious, often toxic transition metals. Aiming at improving its efficiency and applicability, we have established different methods that rely on the in situ formation of bisorganoborinate intermediates[13] or the use of organocerium species, generated through halogen-cerium exchange.[14] Moreover, thorough investigations of reaction mechanism and de novo design of organoborate species led us to develop one-electron electro- and photocoupling processes based on an oxidative pseudo-1,2-metallate rearrangement.[15]

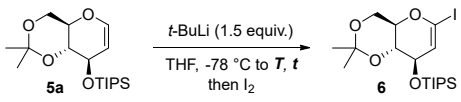
II. Results and discussion

1. Optimizations of reaction conditions

Metalation conditions were optimized first on a benchmark substrate, a protected D-glucal derivative (**5a**, figure 2A). In contrast with classical vinyl-ethers that can be easily metalated at the position α to the heteroatom, the metalation of protected glucal **5a** proved more difficult, with no conversion observed between -78 °C and -60 °C, using either *n*-BuLi, *s*-BuLi or even *t*-BuLi (entries 1 and 2, figure 2A). The first iodolysis product **6** was isolated in 51%

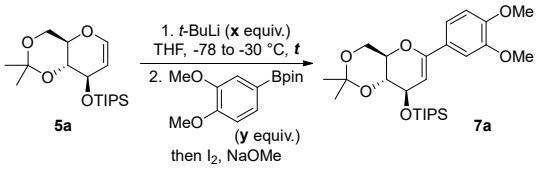
yield when conducting the reaction for 15 min at -50 °C (entry 3). Warming the temperature up to -30 °C allowed the metalation to reach its maximum conversion, allowing for the isolation of **6** in 73% after 30 min (entry 7), while both lower and higher temperatures show any improvements (entries 5,6 and 8-10).
These first optimized conditions were then applied to the Zweifel olefination of compound **5a**, adding a boron pinacol ester as the organoboron partner (figure 2B). The reaction conducted in the presence of substoichiometric amount of boron species (0.9 equiv., entry 1, figure 2B) only yielded low amounts of desired products. However, employing a slight excess of ArBpin (entry 2) furnished **7a** in 67% yield. No significant improvement was noticed when further increasing the amount of organoboron species (entries 3 and 4). However, lowering the amount of base used in the initial α-metalation step to 1.15 equiv. provided **7a** in 71% (entry 5), value that was further increased to 74% under prolonged metalation time (60 min, entry 6).

A Optimization of the α-metalation step



entry	T (°C)	t (min)	yield (%)
1	-78	15	0
2	-60	15	0
3	-50	15	51
4	-40	15	55
5	-40	30	65
6	-30	15	70
7	-30	30	73
8	-20	15	71
9	-10	15	60
10	0	15	40

B Optimization of the one-pot Zweifel olefination



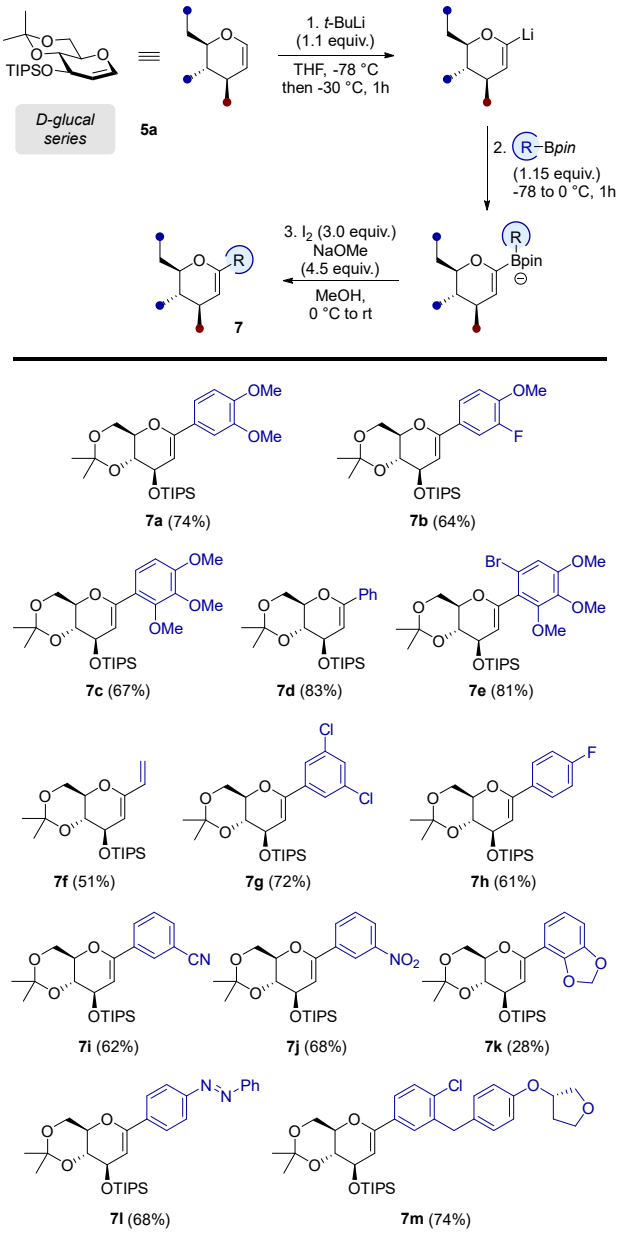
entry	x	t (min)	y	yield (%)
1	1.3	45	0.9	< 50
2	1.3	45	1.15	67
3	1.3	45	1.3	69
4	1.3	60	1.5	54
5	1.1	45	1.15	71
6	1.1	60	1.15	74

A. Condition optimizations for the a-*O*-metalation step, controlled by iodolysis; **B**. Optimization of the Zweifel olefination step using a *m*,*p*-dimethoxyarylboronic ester as benchmark reagent.

Figure 2 - Stepwise optimization of reaction conditions.

2. Scope of the reaction on D-Glucal derivatives

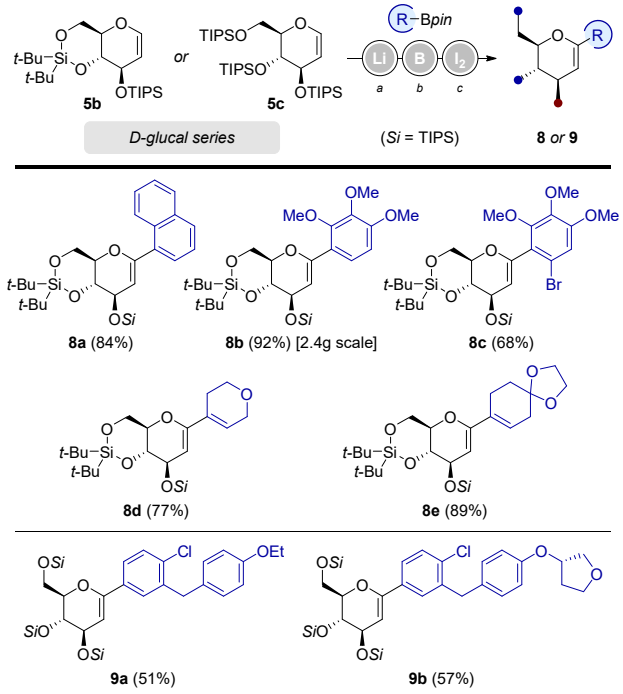
With optimized conditions in hands, we further evaluated the scope of the transformation on protected D-glucal **5a** (figure 3). Neutral phenylboronic pinacol ester gave **7d** in 83%, and electron-poor aryl boronic esters gave similarly high yields than electron-rich ones (**7b-c**, **7e** and **7g-j**, 61-81%). Drops in yields were however observed with acetal-protected reagent (**7k**, 28%), which could be attributed to sensitivity issues during the purification process, as we ruled out the question of sterical hindrance with examples **7c** and **7e** (67 and 81%, respectively). Interestingly, the addition of vinylboronic ester enabled the formation of diene **7f** in 51%. The procedure proved quite robust for the introduction of a diazobenzene moiety at glycosidic position (**7l**, 68%). The aryl substituent typically found in Empagliflozin was also introduced via its corresponding boronic ester to provide **7m** - a dehydrated Empaglilfozin precursor - in 74%.



The scope of the reaction with D-glucal was evaluated through the introduction of aryl and heteroaryl moieties, displaying both electron-donating and -withdrawing functional groups.

Figure 3 - Zweifel olefination's scope on D-Glucal substrates.

Other protecting groups on D-glucal substrates were successfully applied to the Zweifel olefination (figure 4). Arylated glucals **8a** and **8b** were obtained in good yields from silylacetal **5b**. The use of alkenylboronic esters as partners in the Zweifel olefination provided embedded diene systems **8d** and **8e** in 77 and 89% yield, respectively. The reaction proved less efficient when employing tris-TIPS protected D-glucal **5c**, furnishing dehydrated precursors of Dapagliflozin and Empagliflozin **9a** and **9b** in up to 57%.

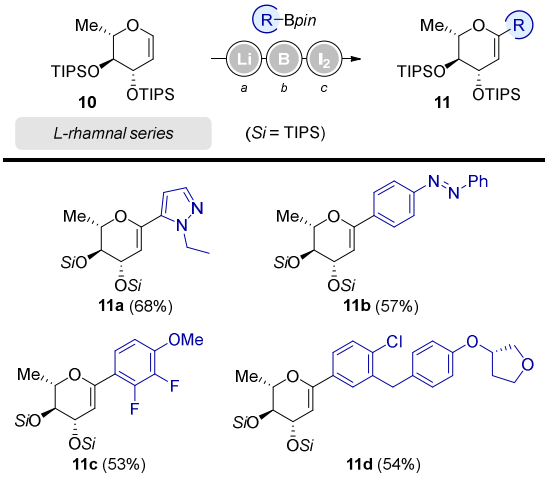


[a] *t*-BuLi (1.3 equiv.), THF, -78 to -30 °C, 30 min. [b] RBpin (1.15 equiv.), -78 to 0 °C, 1h. [c] I_2 (3.0 equiv.), NaOMe (4.5 equiv.), MeOH, 0 °C to rt.

Figure 4 - Variation of protecting groups on D-Glucal substrates.

3. Scope of the reaction on other Glycal derivatives

The L-rhamnal series (6-desoxy-L-glucal) was examined next (figure 5), starting from bis-TIPS protected structure **10**. The same reaction sequence than for the D-glucal series was employed, providing a range of dehydrated *C*-rhamnosides **11**. Electron-rich pyrazol-containing boronic ester gave the heteroaryl derivative **11a** in 68%.

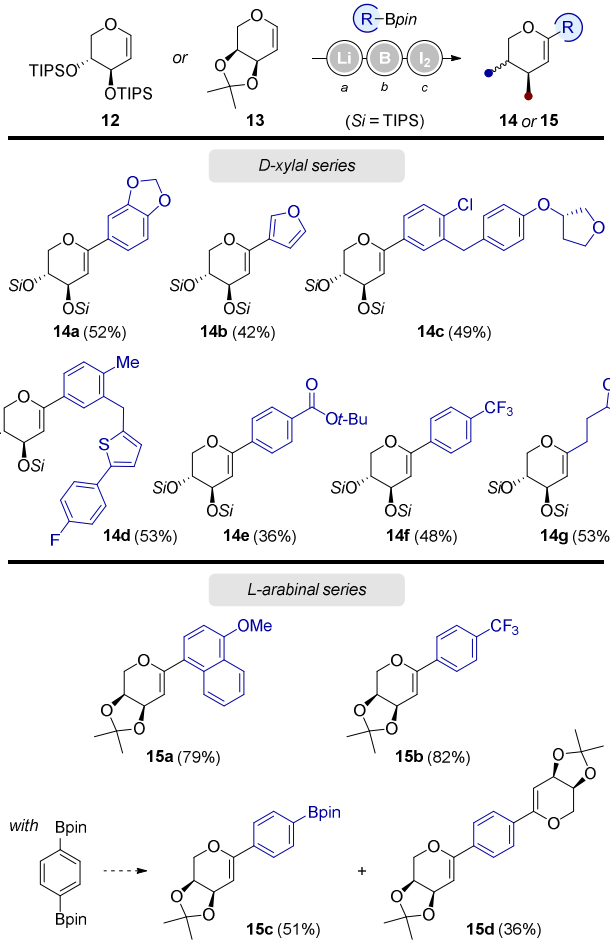


[a] *t*-BuLi (1.3 equiv.), THF, -78 to -30 °C, 30 min. [b] RBpin (1.15 equiv.), -78 to 0 °C, 1h. [c] I_2 (3.0 equiv.), NaOMe (4.5 equiv.), MeOH, 0 °C to rt.

Figure 5 - Scope of Zweifel's olefination on L-Rhamnal substrates.

Lower yields were obtained for the introduction of diazobenzene (**11b**) and bisfluorinated anisole (**11c**). The rhamnose-analog precursor of Empagliflozin (**11d**) was isolated in 54% yield.

The variation of the carbohydrate core drove us to challenge unsaturated pentopyranoses **12** and **13** (D-xylal and L-arabinal series, respectively). Applying the optimized conditions described above provided dehydrated *C*-xylosides **14** and *C*-arabinosides **15** (figure 6). Yields in the D-xylal series (from *trans*-bis-TIPS protected D-xylal **12**) were generally lower than the ones obtained in the D-glucal and L-rhamnal series, independently from the nature of the boronic ester used in the transformation. Both electron-donating and electron-withdrawing partners provided olefination products **14a-f** with moderate yields (36-53%). The nature of the boronic ester was also evaluated via the introduction of alkyl substituents. Product **14g** was isolated in 53%.



[a] *t*-BuLi (1.1 equiv.), THF, -78 to -30 °C, 30 min. [b] RBpin (1.15 equiv.), -78 to 0 °C, 1h for the D-Xylal series, 30 min for the L-arabinal series. [c] I_2 (3.0 equiv.), NaOMe (4.5 equiv.), MeOH, 0 °C to rt.

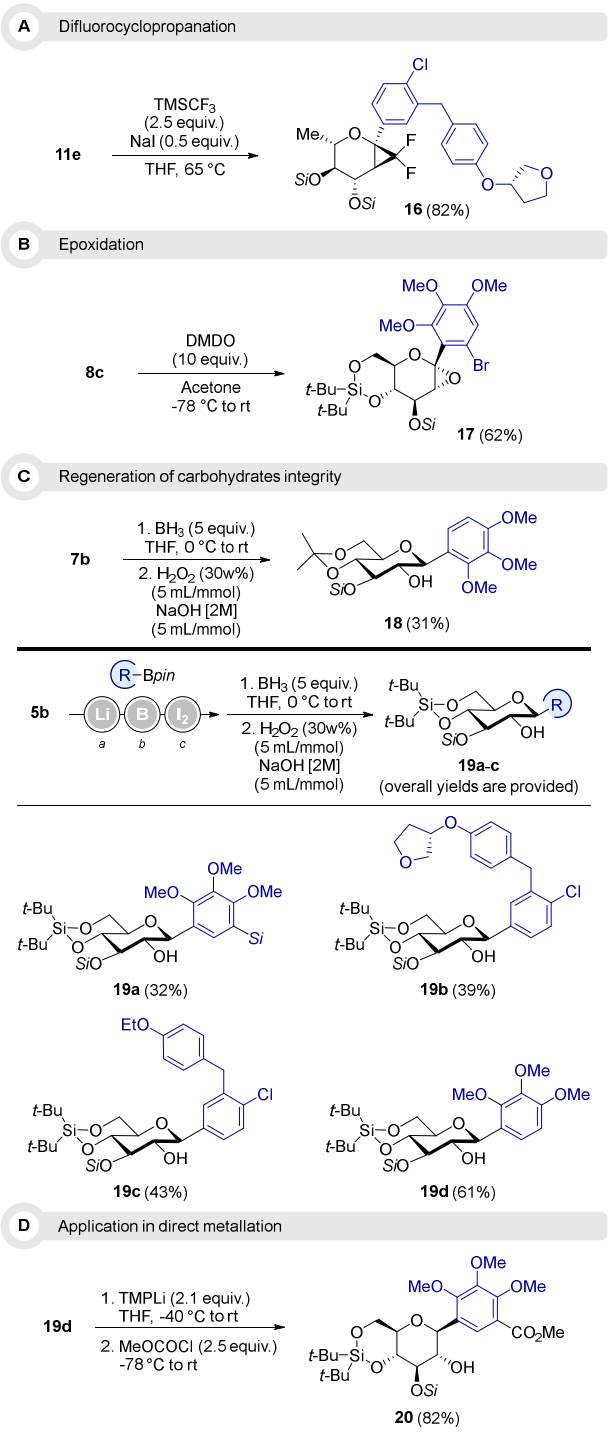
Figure 6 - Scope of Zweifel's olefination on D-Xylal and L-Arabinal substrates.

Despite lower yields in the D-xylal series, it is worth noting that two new D-xylal precursors of Empagliflozin (**14c**, 49%) and Canagliflozin (**14d**, 53%) were obtained.

Cis-acetal-protected L-arabinal substrates led to the corresponding arylated L-arabinal series in similarly high yields up to 82% (**15a**-**b**), whatever the electronic nature of the boronic ester partner. Interestingly, when a bis-boronic ester was engaged in Zweifel olefination, both products of mono- and bis-olefination (**15c** and **15d**) were isolated, in 51 and 36% (overall yield of 87%).

4. Further applications

To demonstrate the applicability of this procedure, selected examples were engaged in further useful transformations. Given the paramount significance of fluorinated substituents as well as cyclopropyl-rings in drug discovery, gem-difluorocyclopropanes are anticipated to offer sophisticated frameworks for enhancing therapeutic attributes.[16] Therefore, L-rhamnal derivative **11e** was subjected to difluorocyclopropanation conditions recently described, providing stereoselectively the bicyclic compound **16** in 82% (figure 7A). The diastereoselectivity of electrophilic additions onto the double bond of glycal derivatives was demostrated in previous reports and seem to be dependent on the orientation of the silyl-ether substituent at position 3. Epoxidation of D-glucal **8c** was performed in the presence of DMDO, furnishing stereoselectively D-oxyglucal compound **17** in 62% (figure 7B). The regeneration of the carbohydrate entity was demonstrated on D-glucal **7a** through a first step of hydroboration followed by Brown's oxidation (figure 7C). Protected C-glucoside **18** was obtained stereoselectively (anti-Markovnikov product) in moderate yield (31% over two steps). With a clean and straightforward Zweifel olefination procedure, we showed that the application of Brown's oxidation did not necessitate purification of intermediates to yield C-glucosides **19a**-**c** in 32 to 43% (over 3 steps). This method offers a straightforward and highly stereoselective route towards protected Empagliflozin **19b** and Dapagliflozin **19c**. **19d** was also accessed in 61% from **5b** (figure 7C) and used in further metalation chemistry using TMPLi (figure 7D).[17] This strategy proceeds regioselectively ortho to one of the methoxy groups on the aryl scaffold, allowing the introduction of an ester upon addition of methylchloroformate as electrophile. **20** was isolated in 82% as a single regioisomer.



Glycal derivatives obtained via Zweifel olefinations were engaged in further selective transformations: **A**. Difluorocyclopropanation; **B**. Epoxidation; **C**. Regioselective Brown oxidation towards the regeneration of the carbohydrate integrity; **D**. Directed metalation.

Figure 7 - Further applications of glycal-based *C*-glycosides

III. Conclusions

The simplicity of metal olefination was applied to the synthesis of *C*-glycosides, providing an efficient and selective alternative to oftentimes fastidious carbohydrate chemistry. A single-pot sequence based on a transition-metal free 1,2-boronate rearrangement allowed us to access functionalized D-glucals, L-rhamnals, D-xylals and L-arabinals in moderate to high yields, compounds that were further engaged in the regeneration and sophistication of sugar-based drug-like molecules and natural scaffolds. Given the importance of *C*-glycosides such as gliflozins in drug

discovery, the efficiency and simplicity of this strategy could easily be applied in high-throughput screening methodology.

Methods:

Optimization of reaction conditions:

See Supplementary Methods, section 2 p.4-8.

Synthetic procedures:

See supplementary Methods, section 4 p.10-14.

Analytical data:

See supplementary Methods, section 4 p.15-84.

NMR spectra:

See Supplementary Data 1.

Acknowledgements

The authors would like to thank the Technical University of Darmstadt and the state of Hessen for PhD scholarships (Landestelle) and the Ludwig-Maximilians-Universität for financial support. DD is grateful to the Deutsche Forschungsgemeinschaft for research funding through the Heisenberg-Program (DI 2227/4-1). Hans-Joachim Luedekke, Dr. Med., is kindly acknowledged for his useful advice and information he provided on the use of gliflozins in modern medicine.

Data Availability:

Data for this manuscript has been deposited in figshare:
https://doi.org/10.6084/m9.figshare.27233724.v1

"Supplementary Methods" contains detailed protocols for the preparation of substrates, reaction optimizations, scope evaluation and description of analytical data (^{1}H and ^{13}C NMR, HRMS).

"Supplementary Data 1" contains all ^{1}H and ^{13}C NMR spectra.

Author Contributions

Conceptualization and supervision: D.D.

Experimental investigation: F.T., B.B., F.P., V.W.

Writing: D.D.

Supporting information: F.T., B.B., F.P.

Proof reading: D.D., F.T., B.B.

Competing interests

There are no competing interests to declare.

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Figure titles:

Figure 1 - Our conceptual approach to *C*-glycosides in the context of current research interests
Figure 2 - Stepwise optimization of reaction conditions
Figure 3 - Zweifel olefination's scope on D-Glucal substrates
Figure 4 - Variation of protecting groups on D-Glucal substrates
Figure 5 - Scope of Zweifel's olefination on L-Rhamnal substrates
Figure 6 - Scope of Zweifel's olefination on D-Xylal and L-Arabinal substrates
Figure 7 - Further applications of glycal-based *C*-glycosides

Figure footnotes:

Figure 1 - **A**. Selected examples of pharmacologically relevant *C*-glycosides; **B**. General mechanism of the Zweifel olefination; **C**. Our strategic design to stereoselectively access *C*-glycosides via a sequence of Zweifel olefination/Brown oxidation.

Figure 2 - **A**. Condition optimizations for the α-*O*-metalation step, controlled by iodolysis; **B**. Optimization of the Zweifel olefination step using a *m*,*p*-dimethoxyarylboronic ester as benchmark reagent.

Figure 3 – The scope of the reaction with D-glucal was evaluated through the introduction of aryl and heteroaryl moieties, displaying both electron-donating and -withdrawing functional groups.

Figure 4 - [a] *t*-BuLi (1.3 equiv.), THF, -78 to -30 °C, 30 min. [b] RBpin (1.15 equiv.), -78 to 0 °C, 1h. [c] I_2 (3.0 equiv.), NaOMe (4.5 equiv.), MeOH, 0 °C to rt.

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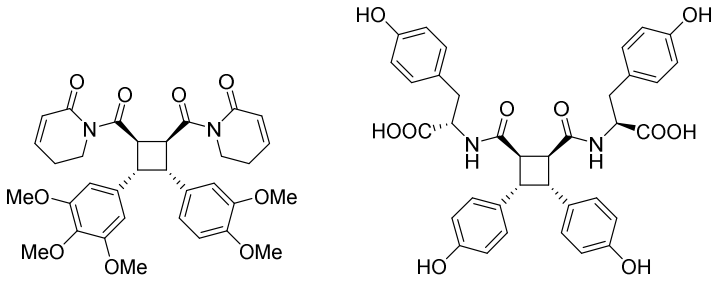
Figure 6 - [a] *t*-BuLi (1.1 equiv.), THF, -78 to -30 °C, 30 min. [b] RBpin (1.15 equiv.), -78 to 0 °C, 1h for the D-Xylal series, 30 min for the L-arabinal series. [c] I_2 (3.0 equiv.), NaOMe (4.5 equiv.), MeOH, 0 °C to rt.

Figure 7 – Glycal derivatives obtained via Zweifel olefinations were engaged in further selective transformations: **A**. Difluorocyclopropanation; **B**. Epoxidation; **C**. Regioselective Brown oxidation towards the regeneration of the carbohydrate integrity; **D**. Directed metalation.

4. Diethylzinc-Amylates – Selective Halogen-Zinc Exchange Reagents at Room-Temperature

4.1 Relevance

Cyclobutanes and cyclobutenes are key structural motifs in many biologically active molecules and serve as versatile intermediates in chemical synthesis due to their reactivity in ring expansion, contraction, and fragmentation processes.[156a] Among various synthetic approaches towards these unique scaffolds, [2+2] cycloadditions stand out as conceptually simple, atom-economical, and step-efficient, while offering high regio- and stereoselectivity.[156b, 175] Drug discovery efforts have highlighted cyclobutane-containing molecules as promising therapeutic agents (Figure 7).[176] This may be associated with their structural rigidity and sp^3-rich nature, which provides a defined spatial arrangement of substituents - an attribute often advantageous in drug design.[177]



Piperaborenine D Abrusamide A

Figure 7: Naturally occurring tetrasubstituted cyclobutanes.

The photochemical [2+2] cycloaddition towards cyclobutanes [alkene+alkene] is a well-established method, extensively advanced by the groups of Bach[178], Yoon[179] and many others. However, the corresponding alkyne variant [alkene+alkyne] remains comparatively underexplored.[180]

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In this chapter, functionalized halogenated cyclobutenes are accessed *via* transition-metal free [2+2]-cycloadditions and subjected to halogen-zinc exchange at ambient temperature, employing the newly developed zincate reagent Et_2Zn·LiOAmyl (DEZA). While this reagent is readily available from stoichiometric addition of LiOAmyl to Et_2Zn, and allows the exchange of vinylic iodides, its analogue containing two equivalents of LiOAmyl (DEZA2) enables selective iodide-zinc exchange in aromatic systems.

4.2 Preamble

The project was conducted in equal contribution with B. Boutet.

Diethylzinc-Amylates – Selective Halogen-Zinc Exchange Reagents at Room-Temperature

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† Equal contribution

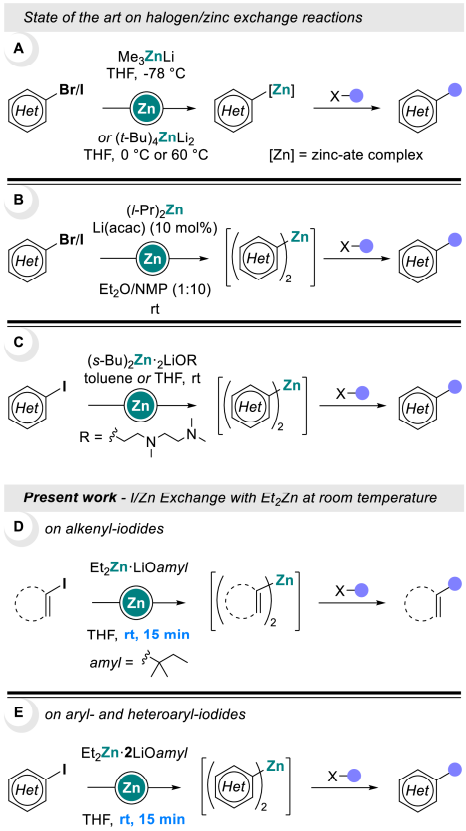
Abstract

The cheapest available organozinc species (diethylzinc) – yet rarely employed in halogen-Zn exchanges – is used in a combination with amylate salts to generate new overtime stable reagents that allow smooth iodide-zinc exchange at room temperature, preventing therefore the need for fastidious and time-consuming preparation of complex mixtures. The scope of the reaction has been explored on polyfunctionalized alkenes (including sensitive cyclobutenes, steroids and glycals), aryls and heteroaryls.

When compared to halogen-metal exchange reactions using nowadays classical organolithium or organomagnesium species, halogen-zinc exchanges are scarcer throughout the literature.[1] The lower reactivity of C-Zn bonds (lower polarization) stemming from a smaller difference in electronegativity (χ_C-χ_{Zn} = 0.9) in contrast with that of C-Li ($\Delta\chi$ = 1.57) or C-Mg ($\Delta\chi$ = 1.24) makes them milder and more functional group tolerant. While *n*-BuLi and *i*-PrMgCl are usually reactive enough for halogen-metal exchanges,[2] polycoordinated zincates have to be used to promote those reactions. However, the higher reactivity of generated organolithium and organomagnesium species prevents them for being applied on molecules that contain sensitive functional groups such as aldehydes, nitriles or esters. As organozinc reagents are known to tolerate these functionalities even at room temperature and higher, a general interest has emerged towards the direct generation of C-Zn bonds through exchanges or directed metalation,[3] as opposed to classical transmetalation strategies.

The first example of iodide-zinc exchange (1968) can certainly be attributed to Furukawa[4] for their work on improving the Simmons-Smith reaction[5] using Et_2Zn on diiodomethane. A few years later, Oku introduced the use of trialkylzincates (R_3ZnLi) on similar dihaloalkanes,[6] but it was only in 1994 that Sakamoto showed the first example of I/Zn exchange on aryl derivatives (Scheme 1A).[7] Similar exchanges were later reported by Uchiyama employing tetraalkylzincates (R_4ZnLi_2).[8]

While diisopropylzinc species were also reported, they imply the inconvenient use of NMP in the solvent mixture (Scheme 1B),[9] and Et_2Zn was only described in halogen-iodide exchanges on alkyliodides in NMP at 50 °C.[10] The group of Knochel recently reported that the formation of dialkylzinc alcoholates (*s*-Bu)$_2$Zn and 2-((2-(dimethylamino)ethyl)(methyl)amino)ethanol (Scheme 1C) could perform such exchange reactions in THF or toluene.[11] Despite higher reactivity – also in apolar solvents – these reagents suffer from their overdelicately demanding preparation method, including cryogenic conditions. With the goal of developing broadly applicable and selective species for halogen-metal exchanges, we set out to create new reagents from available and inexpensive sources through a straightforward and non-fastidious procedure, by simple mixing at room temperature.



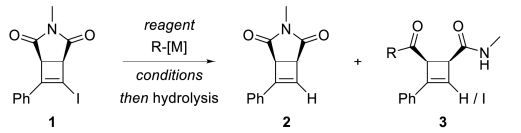
Scheme 1. Overview on halogen-zinc exchange reactions and our work based on diethyl-zinc amylates (DEZA).

We were originally looking for a method to generate cyclobutenylmetal species [**A**] from halocyclobutenes **1**, as part of our program on four-membered ring functionalization. It is worth mentioning that the desymmetrization of similar cyclobutenes was recently exemplified by Hall and coworkers,[12] which inspired us to gain access to new halocyclobutenes such as **1**. However, the presence of a maleimide rendered it unfit for organolithium (*t*-BuLi or *n*-BuLi, entries 1 and 2, Table 1) and organomagnesium reagents (*i*-PrMgCl, entry 3), even at low temperatures.

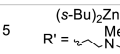
We then turned to organozinc reagents for their increased functional group tolerance, starting with the evaluation of tetrabutylzincate species (entry 4) that unfortunately remained unsuccessful. Next, *s*-Bu_2Zn was tested in the presence of an alcoholate ligand (entry 5), as it has recently shown improved efficiency for I/Zn exchanges in both THF and toluene.[10] Although the hydrolysis product **2** was observed for the first time (in ca. 20%), it was accompanied by undesired addition of the alcoholate onto the maleimide moiety (**3**, major product). With promising results in hands, we decided to optimize both the structure of the ligand and the nature of the organozinc reagent. As a matter of facts, *s*-Bu_2Zn is not commercially available, and its preparation method is quite fastidious. Therefore, we opted for Et_2Zn, which extensive industrial use renders it inexpensive and largely available. Despite the great challenge it represents due to the less reactive primary nature of its alkyl substituents, we envisioned that a successful procedure could unlock a broader use of halogen-metal exchange reactions for the general preparation of organozinc species. The sterical hindrance on the alcoholate was increased to prevent the undesired nucleophilic addition of the ligand onto the maleimide moiety. To our delight, while potassium tertbutoxide did not provide any metalated cyclobutene, no degradation product of

nucleophilic addition was observed (entry 6). We attributed this lack of reactivity towards halogen-metal exchange to the low solubility of the reagent in heptane (a cloudy solution was obtained). Lithium amylate was finally engaged to improve solubility (clear solution of the reagent mixture), which showed no degradation and full conversion into the desired cyclobutenylzinc species (as attested by hydrolysis product **2**).

Table 1. Optimization of the halogen-metal exchange on cyclobutenyliodide **1**



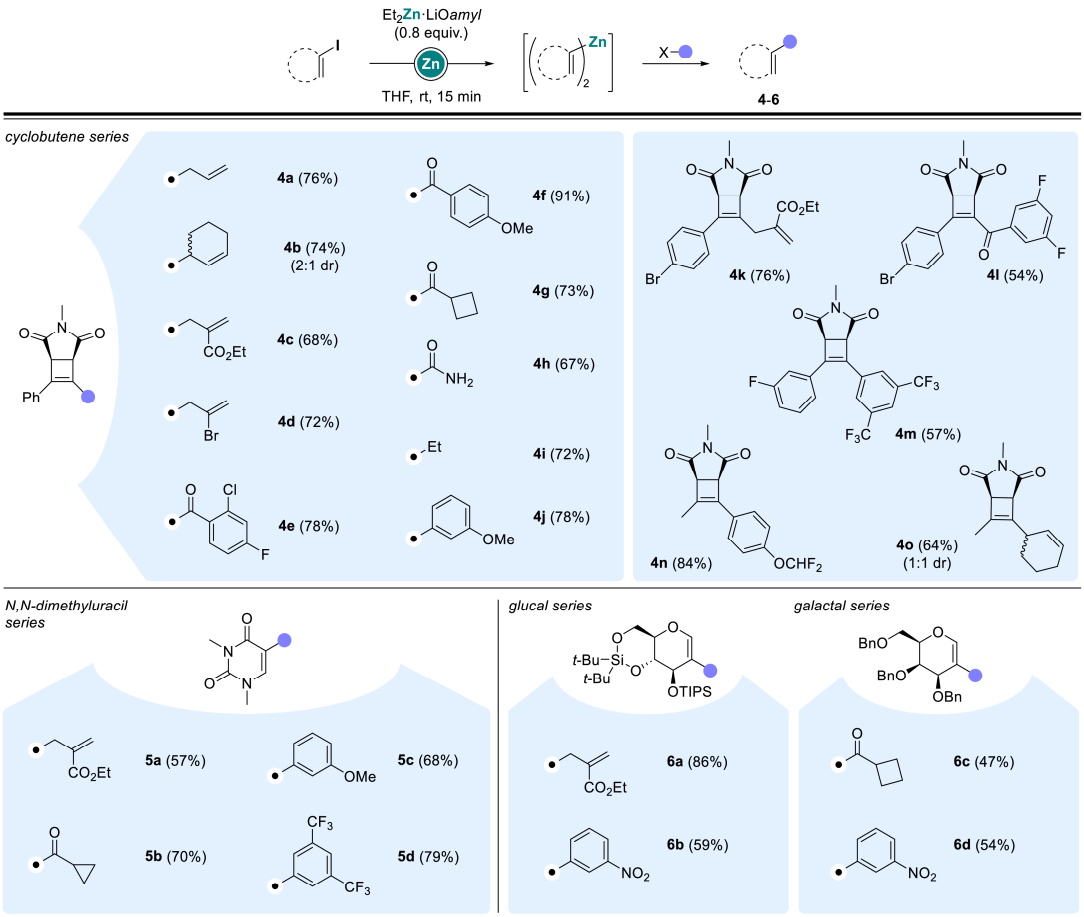
1 **2** **3**

entry	R-[M]	equiv.	conditions	observation
1	*t*-BuLi	1.3	THF, -78 °C	**3** (R = *n*-Bu)[a] + degradation[b]
2	*n*-BuLi	1.3	THF, -78 °C	**3** (R = *n*-Bu)[a] + degradation[b]
3	*i*-PrMgCl	1.3	THF, -40 °C	**3** (R = *n*-Bu)[a] + degradation[b]
4	$(n\text{-Bu})_4ZnLi_2$	1.2	THF, -40 °C *or* -78 °C	**3** (R = *n*-Bu)[a] + degradation[b]
5	$(s\text{-Bu})_2Zn\cdot 2LiOR'$ R' = 	0.7	THF, 20 °C *or* toluene, 20 °C	**2** (18%)[c] + **3** (R = OR')[a]
6	$Et_2Zn\cdot KO\textit{t}\text{-Bu}$	0.8	THF / heptane 20 °C	no conversion but no degradation
7	$Et_2Zn\cdot LiO\textit{amyl}$	0.8	THF / heptane 20 °C	**2** (> 95%)[c]

[a] Addition products **3** observed by GC-MS. [b] unidentified degradation products observed by GC-MC. [c] Hydrolysis product **2** observed by GC-MS.

With optimized conditions in hands for substrate **1**, we started exploring the scope of further electrophilic trapping reactions. Allylations were performed using substoichiometric amounts of CuI, providing the corresponding products in fair yields (**4a**-**d**, 68 to 76%, Scheme 2). Acylations proceeded similarly towards conjugated products **4e**-**g**, isolated in yields up to 91%. We were also able to install a free amide (**4h**) in 67% yield using trichloroacetyl isocyanate as electrophile. Interestingly, the residual ethyliodide, generated in situ via I/Zn exchange was able to undergo coupling reaction in the presence of a palladium catalyst, towards the formation of ethyl-substituted structure **4i** (72%). However, in the presence of another more adequate partner in the reaction, its coupling is favored, giving **4j** in 78% yield. Differently substituted cyclobutenes – including 4-bromo-, 3-fluoroarylated and methylated – readily underwent I/Zn exchange reaction and were further engaged in allylations, acylations and cross-coupling reactions, providing compounds **4k**-**o** in yields up to 84%. It is important to highlight that the exchange reaction is significantly more efficient with alkenyl-iodides compared to aryl-bromides, as demonstrated by the high yields of products **4k** and **4l**, which preserved their bromine atom.

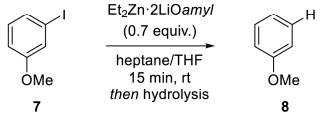
For our next targets, we challenged the metalation of bio-relevant building blocks such as methylated uracil and protected glycals, as they represent valuable intermediates in drug design. The metalation of uracil derivatives proceeded fairly well with isolated yields for allylations (**5a**), acylations (**5b**) and Negishi coupling reactions (**5c**-**d**) reaching up to 79%. 3-Iodoglucal protected with silylether moieties went through fast I/Zn exchange, leading to the formation of functionalized structures **6a**-**b** in 59 to 86% yield. Perbenzylated galactal proceeded similarly to furnish **6c**-**d** in up to 54% yield.



Scheme 2. Scope of the iodide-zinc exchange / electrophilic trapping sequence on alkene derivatives with DEZA (Et_2Zn·LiO*amyl*).

After having successfully demonstrated the usefulness of our new reagent, especially for its functional group tolerance and general efficiency, we directed our focus towards the metalation of aryl derivatives. Unfortunately, similar conditions than the ones described for alkenyl-iodides using Et_2Zn·LiOamyl only led to 60% conversion of 3-iodoanisole **7** towards its corresponding hydrolysis product **8** (table 2, entry 2). We anticipated that enhancing the electron density around the zinc atom would boost the reactivity of our reagent. This was confirmed by adding a second equivalent of LiOamyl, which resulted in the hydrolysis product **8** being obtained in a 96% yield (entry 1). It seems that THF as cosolvent is essential to the success of the exchange, as the reaction solely performed in heptane only showed traces of desired product (entry 6). Switching THF for other cosolvents such as 2-MeTHF, toluene or Et_2O notably decreased the efficiency of the exchange process (entries 3-5).

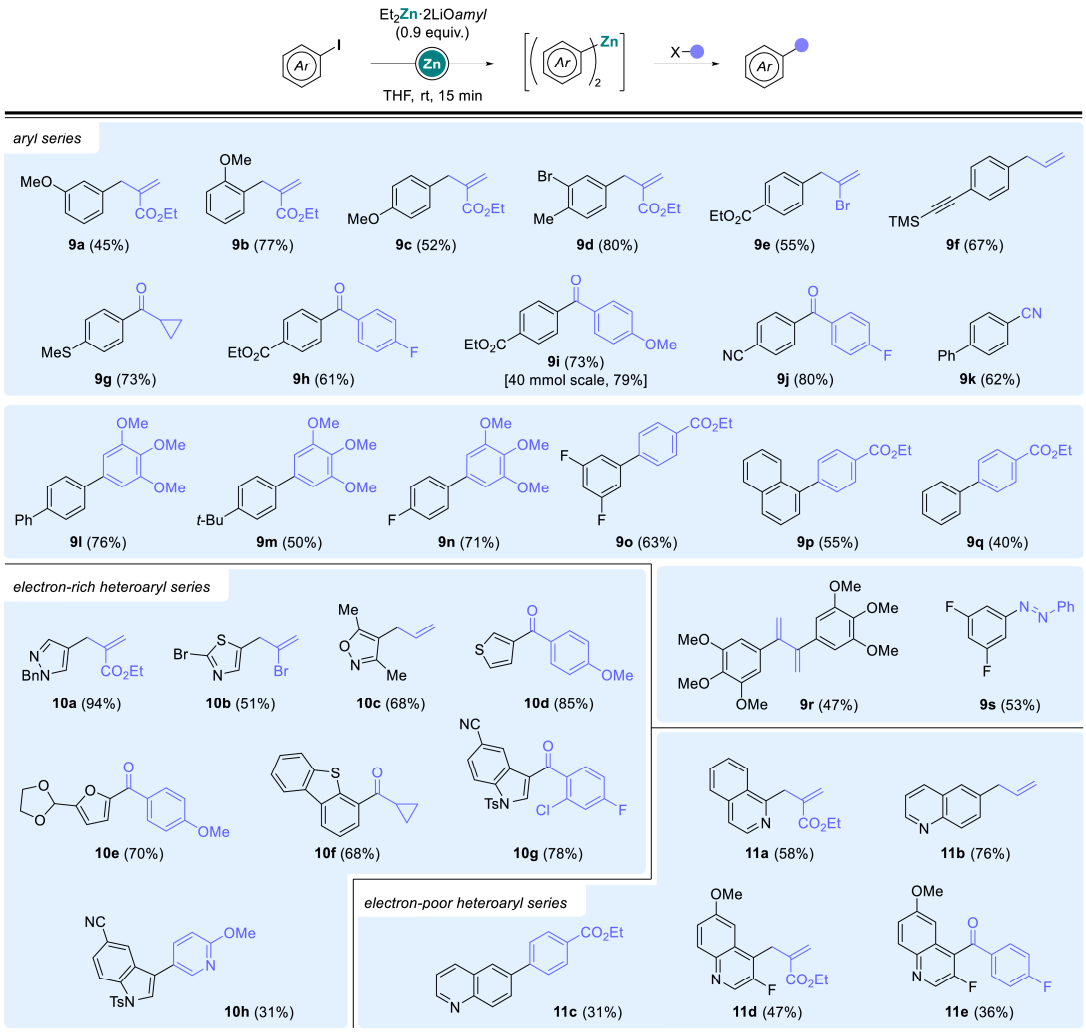
Table 2. Optimization of the halogen-metal exchange on 3-iodoanisole **7**



entry	deviation from initial conditions	yield (**8**)
1	none	96%
2	$Et_2Zn{\cdot}LiOamyl$ instead of $Et_2Zn{\cdot}2LiOamyl$	60%
3	2-MeTHF instead of THF	19%
4	toluene instead of THF	traces
5	Et_2O instead of THF	traces
6	no THF added, only heptane	traces

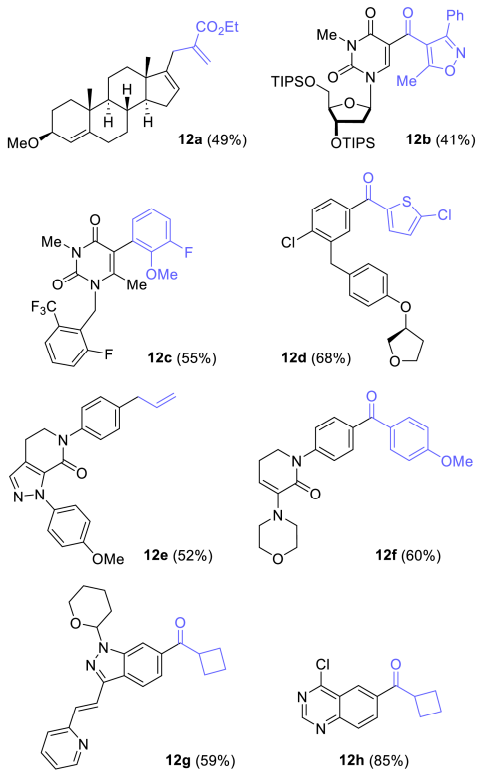
With suitable metalation conditions in hands, we assessed the electrophilic trapping of newly generated arylzinc species. The influence of the regiochemistry of a methoxy substituent was evaluated first. While ortho-substituted species led to the allylation product **9b** in 77%, meta- and para-substituted derivatives only provided **9a** and **9c** in moderate yields (Scheme 3). The metalation strategy also showed great functional group tolerance towards esters (**9e** and **9h**-**i**, up to 73%), alkynes (**9f**, 67%), nitriles (**9j**, 80%) and thioethers (**9g**, 73%). More importantly, the exchange was entirely chemoselective towards iodide in the presence of a bromide atom (**9e**, 80%). Those conditions showed similarly good reactivity through the introduction of allyl, acyl and cyano moieties (**9k**, 62%) as electrophiles. The scope of the transformation was explored further by engaging Negishi cross-coupling reactions. Worthy of note, the addition of zinc chloride (1 equivalent) proved essential to minimize homocoupling reactions.[13][14] Robustness of the cross-coupling was attested with yields ranging from 40 to 76% (**9l**-**q**). Heteroaryls were evaluated next, starting with electron-rich substrates. Iodinated pyrazoles (**10a**), isoxazoles (**10c**), thiophenes (**10d**), furan (**10e**), dibenzothiophenes (**10f**) and indoles (**10g**-**h**) were successfully engaged in I/Zn exchanges, providing electrophilic trapping and cross-coupling products in generally high yields (above 68%), apart from thiazole, which allylated product **10b** was only isolated in 51% yield and indole coupling product **10h** (31%).

Electron-poor substrates showed a different trend in reactivity. While the metalation of pyridine derivatives remained unsuccessful, quinolines and isoquinolines iodinated at various positions only led to moderate yields after electrophilic trapping of the corresponding organozinc species (**11a**-**e**, 31 to 76% yield).



Scheme 3. Scope of the iodide-zinc exchange / electrophilic trapping sequence on aryl derivatives with DEZA$_2$ (Et_2Zn·2LiO*amyl*).

Lastly, we took the halogen-zinc exchange to pharmacologically relevant motifs in order to demonstrate the broad application potential of our method. The allylation of a steroid scaffold provided structure **12a** in 49% yields, while the acylation of a nucleoside by metalation of Idoxuridine,[15] or a Negishi coupling performed on a nucleobase subunit of Elagolix[16] gave the respective functionalized products **12b**-**c** in 41 to 55% yield. Metalation of the aglycone moiety of Empaglyflozin[17] and subsequent acyclation resulted in compound **12d**, isolated in 68%. Pyrazole-containing building block in the synthesis of Apixaban[18] and its monocyclic lactam precursors were also efficiently engaged in the exchange reaction, giving the allylation and acylation products **12e**-**f** in 52 and 60% yield, respectively. The indazole contained in compound **12g** is a motif present in Axitinib, a tyrosine kinase inhibitor.[19] It was successfully metalated, allowing for its acylation in 59% yield. Quinazoline possessing a chloride atom at position 4 is a building block in the synthesis of Lapatinib.[20] A sequence of halogen-metal exchange/acylation provided **12h** in 85% yield.



Scheme 4. Application of our new reagents to the synthesis of pharmacologically relevant intermediates.

In summary, we have developed two new reagents from readily available and affordable chemicals that enable selective halogen-zinc exchanges at room temperature. The organozinc species generated in situ exhibit high tolerance for various functional groups, allowing us to apply this method across a wide range of substrates, including seldom-studied cyclobutenes, uracils, glycals, aryl, and heteroaryl derivatives. This approach yields a diverse library of novel functionalized building blocks. The simplicity in preparing these new reagent classes is likely to expand their applications in synthesis.

Acknowledgements

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[14] See Supporting Information.

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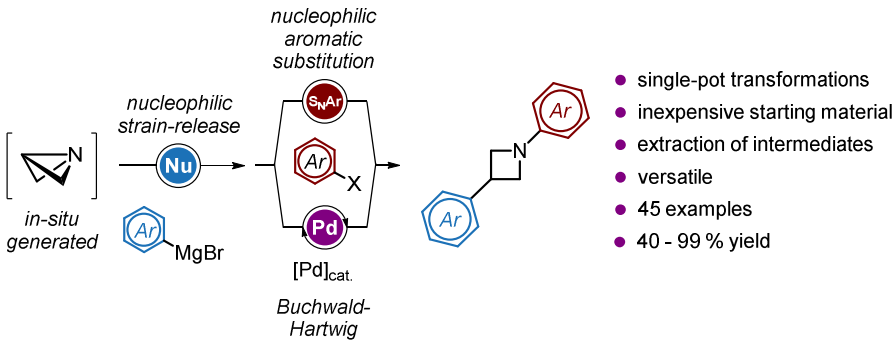
5. Conclusions

5.1 Summary

This work has presented transition-metal free strategies towards the synthesis and functionalization of strained (unsaturated) ring systems. The primary focus was on the efficient generation and functionalization of four-membered (hetero)cycles like azetidines and cyclobutanes, as well as their unsaturated analogs, using principles of organometallic and photoredox chemistry.

Strain-release arylation of *in-situ* generated 1-aza-bicyclo[1.1.0]-butanes with aryl-Grignard reagents enabled access to versatile intermediate 3-arylated magnesium amides, which were then subjected to various *N*-arylation strategies or electrophilic trapping. Fine-tuning of the conditions revealed the superiority of the combination toluene - *n*BuLi over THF - PhLi, leading to reduced side-product formation. Notably, the non-protected 3-aryl azetidines can be accessed conveniently *via* extraction and employed effectively in Pd-mediated Buchwald-Hartwig couplings.

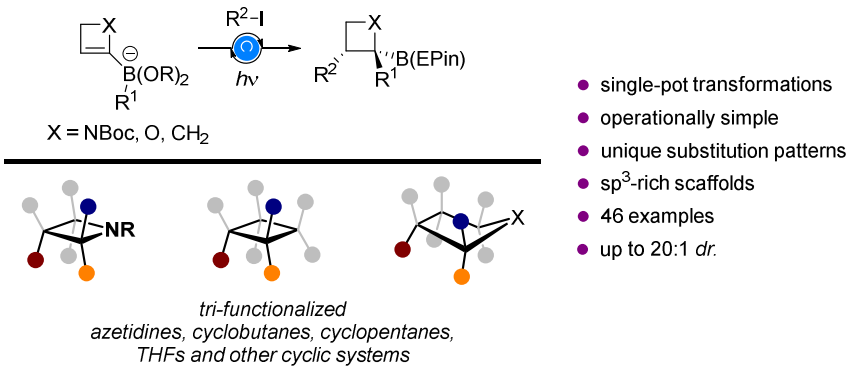


Scheme 55: 1,3-bisarylated azetidines *via* strain-release of ABB.

Alternatively, one-pot S_NAr or Buchwald-Hartwig strategies eliminate the necessity for intermediate purifications. Following the recent trend of increased three-dimensionalization by incorporation of sp^3-rich scaffolds in drug design, analogs of FDA-marketed drugs highlight the potential of the transformation (Scheme 55).

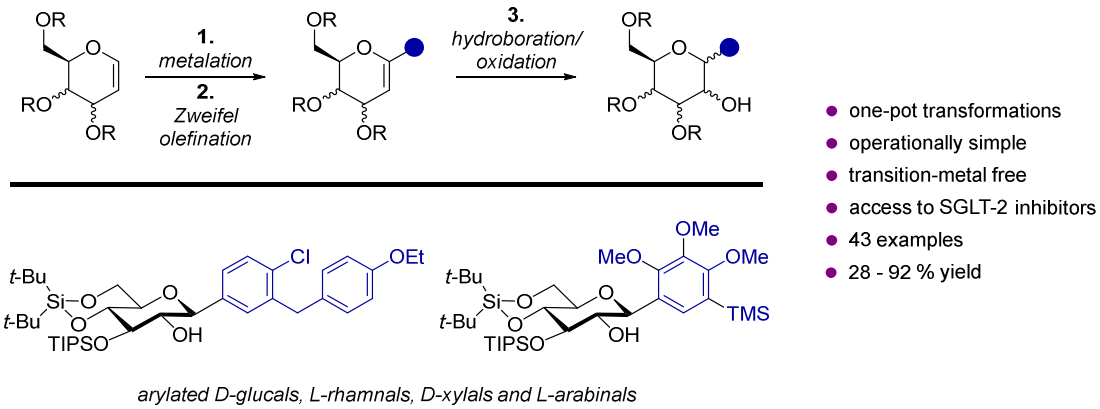
Taking advantage of expertise in the Didier-group towards the synthesis of strained unsaturated (hetero)cycles like azetines, cyclobutenes or cylopentenes, a protocol based on polar-radical crossover was developed. *In-situ* generated cyclic vinylboronate complexes were shown to undergo diastereoselective 1,2-migration in the presence of radicals. Careful optimization revealed the importance of diol ligand, solvent system and crucial additives. Radicals were conveniently generated under photocatalyst-free conditions by blue-light irradiation of iodinated precursors and added efficiently to the unsaturated cycles. Unique

trisubstituted azetidines, cyclobutanes, cyclopentanes, THFs, pyrrolidines and norbornanes were synthesized and further employed in stereospecific transformations of the boron moiety (Scheme 56).



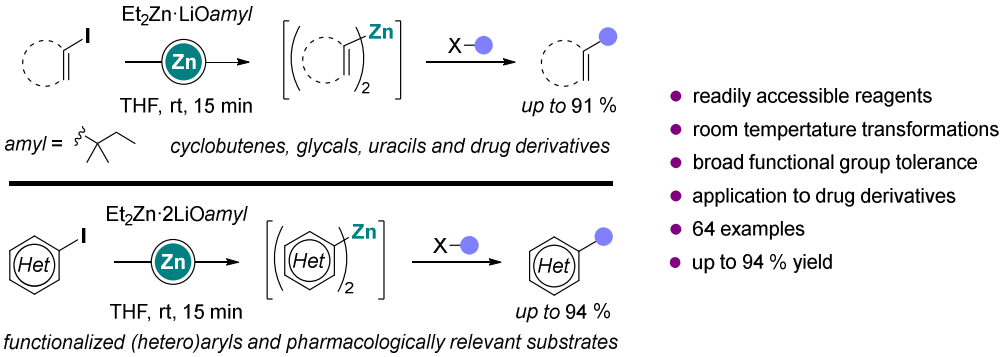
Scheme 56: Steroselective PRC of cyclic vinylboronate complexes.

While glycal derivatives could not be employed efficiently in the PRC protocol, the corresponding boronate complexes proved to be reactive under Zweifel olefination conditions towards C(1)-arylation. Careful fine-tuning of stoichiometry and temperature for metalation proved crucial to avoid side-product formation in the often-sensitive Zweifel protocol. A wide range of variously protected D-glucals, L-rhamnals, D-xylals and L-arabinals were employed in the transition-metal free sequence towards the corresponding *C*-glycosides. Cyclopropanation, epoxidation and hydroboration-oxidation strategies were developed to further diversify the unsaturated motifs. A single-pot Zweifel olefination hydroboration-oxidation sequence was developed and demonstrated to be effective to synthesize prominent SGLT-2 inhibitors (Scheme 57).



Scheme 57: *C*-Glycosylation *via* Zweifel olefination.

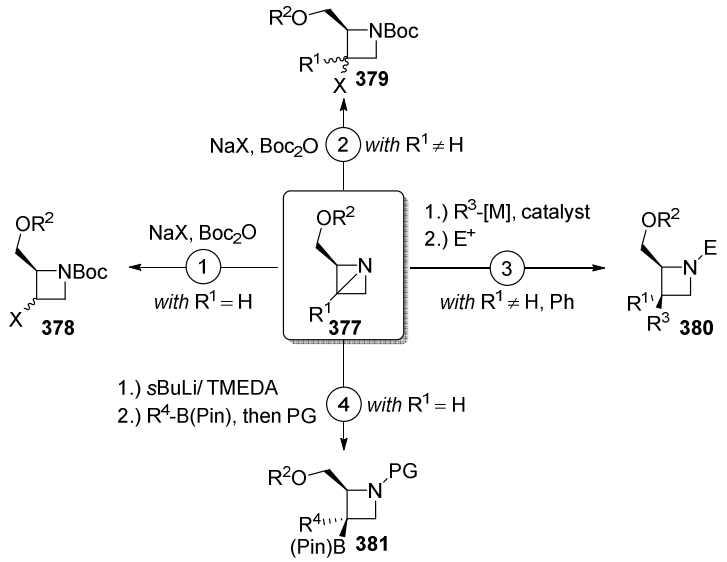
The idea of generating cyclobutenylmetal species from halogenated cyclobutenes obtained through [2+2]-cycloadditions led to the development of previously unknown exchange reagents $Et_2Zn{\cdot}LiOamyl$ (DEZA) and $Et_2Zn{\cdot}2LiOamyl$ (DEZA2). Simple room-temperature mixing of inexpensive Et_2Zn and LiOamyl provides stable and reactive Zn-exchange reagents in hydrocarbon solvents. Polyfunctionalized alkenes could be rapidly diversified using $Et_2Zn{\cdot}LiOamyl$, while $Et_2Zn{\cdot}2LiOamyl$ proved to be reactive towards (hetero)aryl iodides. Post-functionalization of drug derivatives and pharmacologically relevant motifs further underline the potential of the developed reagents (Scheme 58).



Scheme 58: Room-temperature iodine-zinc exchange with diethylzinc amylates.

5.2 Outlook

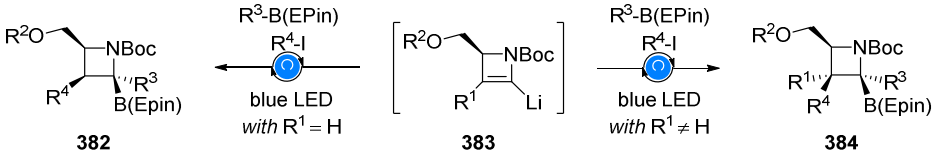
A recent contribution by Baran and coworkers demonstrated the synthesis of enantiopure 2-substituted ABBs of type **377** (Scheme 59).[181] These versatile new building blocks could open new pathways towards unprecedented substitution patterns. Following the strategy of Lopchuk[124] (Pathways 1 and 2) would allow to synthesize 3-halogenated azetidine derivatives **378** and **379**, bearing substituents at position 2 and 3, respectively. Elimination and lithiation of the intermediate azetine derivative then would provide access to a multifunctional building block, as previously demonstrated by Didier and coworkers.[146] A diastereoselective nucleophilic ring opening of **377** (Pathway 3) with organometallic reagents and subsequent electrophilic trapping would eventually lead to unique trisubstituted azetidine derivatives of type **380**. Finally, directed metalation and homologation of **377** (Pathway 4), similar to Aggarwal's procedure[125], would lead to boronated trisubstituted azetidine derivatives of type **381**. A hydroboration-methylation-elimination sequence could subsequently produce unique (2,3,4)-trisubstituted azetines.



Scheme 59: 2-Substituted enantioenriched ABB's as platform building blocks.

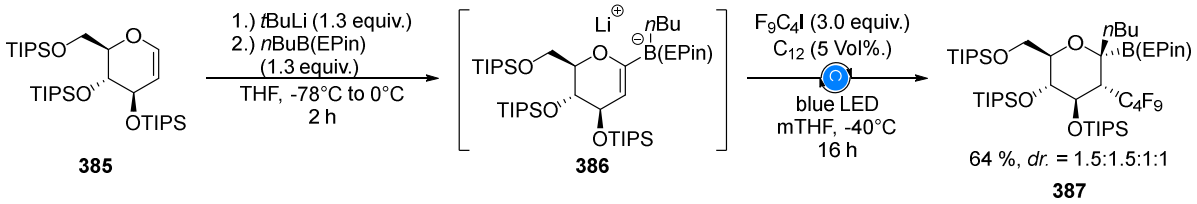
These versatile lithiated azetines **383** could serve as a platform for polar-radical crossover. Depending on the substitution at position 3, tetra- or pentasubstituted boronated azetidines with up to two quarternary stereocenters **382** and **384** could be obtained (Scheme 60).

[181] M. Bielecki, M. Nassir, H. Sharma, N. Truax, N. Raheja, T. Thompson, T. Ewing, B. Melillo, B. Cravatt, P. Baran, **2024**, *ChemRxiv*. preprint DOI:10.26434/chemrxiv-2024-cmvd4.



Scheme 60: Application of the PRC strategy to employ pre-functionalized lithiated azetines.

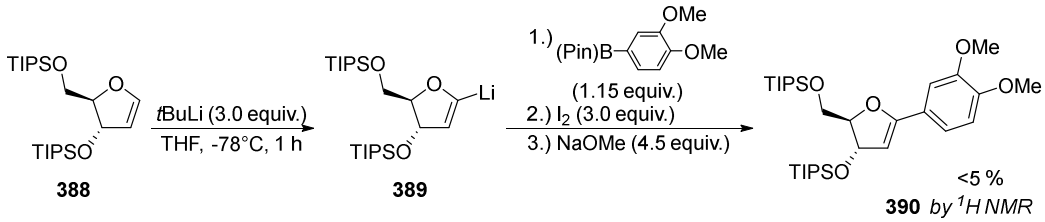
Preliminary results demonstrated that glycal derivatives can be subjected to the PRC protocol. Deprotonation of **385** with *t*BuLi and treatment with an alkylboronic ester afforded boronate complex **386**, which was treated with a radical precursor and subjected to the developed PRC protocol. Boronated glucal derivative **387** was obtained in 64 % yield, albeit in poor diastereomeric ratio.



Scheme 61: Glycal derived boronate complexes and application to PRC.

Further optimization of the reaction conditions is required to optimize the stereochemical outcome. Potentially also the electrophile-induced PRC strategy pioneered by Aggarwal[100-101] and Sakakura[102] could lead to stereodefined carbohydrate derivatives.

Regarding the Zweifel olefination of glycal derivatives, a major limitation was encountered with the five-membered D-ribal **388**, which could not be effectively lithiated under the developed procedure due to degradation of the lithium species at elevated temperatures (-30°C). An alternative approach involved metalation under reported conditions[182] using a large excess of *t*BuLi (3.0 equiv.). However, this method proved incompatible with the Zweifel protocol, yielding only trace amounts of the desired coupling product **390**, as detected by ^{1}H NMR analysis of the crude mixture (Scheme 62).

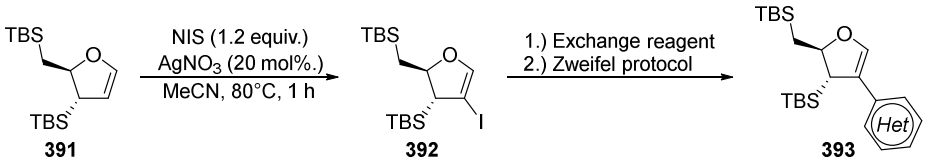


Scheme 62: Unsuccessful implementation of protected D-ribal in the Zweifel protocol.

[182] J. M. Wurst, A. L. Verano, D. S. Tan, *Org. Lett.* **2012**, *14*, 4442-4445.

Access to C(1)-arylated derivatives of D-ribal remains of significant scientific interest, as highlighted by the large number of nucleoside-based marketed drugs.[183] Potentially, variation of the protecting group pattern or the use of a different base could be the key to an efficient metalation and arylation of the D-ribal scaffold.

Similarly, the implementation of C(2)-iodinated glycal derivatives could provide a straightforward approach for C(2)-diversification of various glycal derivatives *via* Zweifel olefination. Notably, this procedure is expected to tolerate a broader range of protected glycals (e.g. OBn or OTMS), as the iodine-lithium exchange is likely to proceed rapidly and selectively, even at lower temperatures.



Scheme 63: Preparation of C(2)-iodinated TBS-protected D-ribal and possible Zweifel olefination.

As illustrated in Scheme 63, selective C(2)-iodination of TBS-protected D-ribal (**391**) proceeds smoothly, according to reported conditions from Cossy *et al.* with **392** being isolated in 60 % yield.[184] Upon treatment with the appropriate exchange reagent and application of the developed Zweifel protocol, C(2)-arylated glycal derivatives of type **393** could be accessed in a straightforward manner.

Concerning the results towards iodine-zinc exchange using the newly developed reagents $Et_2Zn{\cdot}LiOAmyl$ and $Et_2Zn{\cdot}2LiOAmyl$, the high selectivity for iodine over bromine is advantageous but also limits the procedure's versatility. Incorporating brominated precursors, which are more affordable, readily available, and stable, would significantly enhance the scope of halogen-zinc exchange with zincate reagents of the aforementioned types. This in turn could potentially be accomplished by adjusting the stoichiometry of the respective alkoxide towards reagents of the general formula $EtZn(OR){\cdot}2LiOR$. According to the results from Knochel[50] and Uchiyama[48], sterically hindered diorganozinc reagents could further increase the reactivity of the respective zincate. However, their limited commercial availability necessitates an *in-situ* preparation *via* transmetalation from the corresponding Grignard reagent with $ZnCl_2$, ultimately leading to quite fastidious preparations. Extending this approach to sterically hindered zinc bases, such as TMP_2Zn, also appears promising, as demonstrated in recent studies by Hevia *et al.*[185]

[183] a) E. D. Clercq, A. Holý, *Nat. Rev. Drug Discov.* **2005**, *4*, 928-940; b) N. Borbone, G. Piccialli, G. N. Roviello, G. Oliviero, *Molecules* **2021**, *26*, 986.
[184] P. Polák, J. Cossy, *Chem. Eur. J.* **2022**, *28*, e202104311.
[185] N. R. Judge, E. Hevia, *Chem. Sci.* **2024**, *15*, 14757-14765.

C. EXPERIMENTAL PART

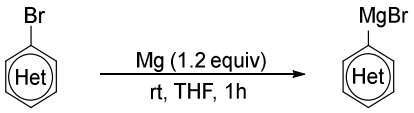
1. Strain-Release Arylations for the bis-Functionalization of Azetidines

1.1 General Considerations

All reactions were carried out under N_2 atmosphere in flame-dried glassware unless otherwise stated. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with nitrogen three times prior to use. THF was purchased in 99.5 % purity from Acros Organics. Toluene was purchased in 99.85 % purity from Acros Organics. *t*BuOH was purchased 99.5 % purity from Acros Organics. Chromatography purifications were performed using silica gel (SiO_2, 0.040-0.063 mm, 230- 400 mesh ASTM) from Merck. The spots were visualized under UV (254 nm) or by staining the TLC plate with either $KMnO_4$ solution (K_2CO_3, 10 g – $KMnO_4$, 1.5 g – H_2O, 150 mL – NaOH 10 % in H_2O, 1.25 mL) or *p*-anisaldehyde solution (conc. H_2SO_4, 10 mL – EtOH, 200 mL – AcOH, 3 mL – *p*-anisaldehyde, 4 mL). Yields refer to isolated yields of compounds estimated to be >95 % pure as determined by ^{1}H NMR and GC-analysis. The ^{13}C and ^{1}H NMR spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ values in ppm relative to the residual solvent peak (^{1}H-NMR, ^{13}C-NMR) in deuterated chloroform ($CDCl_3$: δ 7.26 ppm for ^{1}H-NMR and δ 77.16 ppm for ^{13}C-NMR). Abbreviations for signal coupling are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet) and br (broad). Reaction endpoints were determined by GC monitoring of the reactions with *n*-undecane as an internal standard. Gas chromatography was performed with machines of Agilent Technologies 7890, using a column of type HP 5 (Agilent 5 % phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm) or Hewlett-Packard 6890 or 5890 series II, using a column of type HP 5 (Hewlett-Packard, 5 % phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm). High resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were recorded on Finnigan MAT 95Q, Finnigan MAT 90 instrument or JEOL JMS-700. Infrared spectra were recorded on a Perkin 281 IR spectrometer and samples were measured neat (ATR, Smiths Detection DuraSample IR II Diamond ATR). The absorption bands were reported in wave numbers (cm^{-1}) and abbreviations for intensity are as follows: vs (very strong; maximum intensity), s (strong; above 75 % of max. intensity), m (medium; from 50 % to 75 % of max. intensity), w (weak; below 50 % of max. intensity) and br (broad). Melting points were determined on a Büchi B-540 apparatus and are uncorrected. *n*BuLi solution in hexane was purchased from Rockwood Lithium and the concentration was determined by titration using 1,10-phenanthroline in THF with *i*PrOH. Phenylmagnesiumchloride solution in THF was purchased from Rockwood Lithium and the concentration was determined by titration using iodine in THF. Aryl Grignard reagents were titrated using iodine in THF at 0 °C.

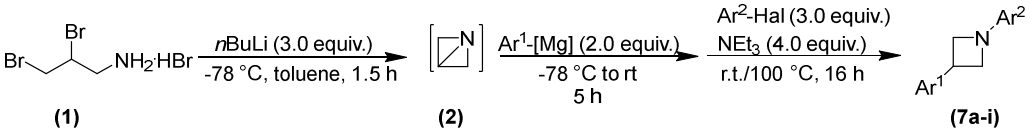
2. General Procedures

General Procedure I: Synthesis of Aryl Grignard Reagents



A Schlenk flask was charged with magnesium turnings (583 mg, 24 mmol, 1.2 equiv.) and dried *in vacuo* using a heat gun (600°C, 2 x 5 min). After addition of THF (2.0 mL) and iodine (1 pellet), the mixture was heated to reflux with a heat gun to activate the magnesium. The corresponding aryl bromide (20 mmol, 1.0 equiv.) was dissolved in THF (18.0 mL for approximately 1 M solution or 38 mL for 0.5 M solution) and added to the activated magnesium suspension dropwise, while keeping the THF refluxing. After completion of the addition, the mixture was stirred for 0.5 h at room temperature to yield a THF-solution of the arylmagnesium reagents. The concentration was determined by titrating set aliquots against iodine.

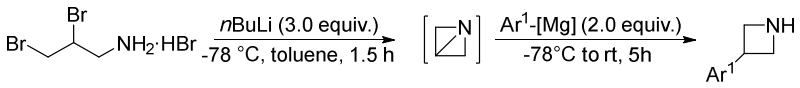
General Procedure J: One-Pot Synthesis of Fuctionalized Azetidines via 1-Azabiclo[1.1.0]butane and Nucleophilic Aromatic Substitution



(1) **(2)** **(7a-i)**

A flame-dried flask was charged with 2,3-dibromopropan-1-amine hydrobromide **(1)** (60 mg, 0.2 mmol, 1.0 equiv.) and suspended in toluene (2 mL). The suspension was cooled to -78 °C using a dry ice acetone bath, and *n*BuLi (0.6 mmol, 3.0 equiv.) was added. Following the addition, the mixture was stirred for 1.5 h. Then, the desired organomagnesium compound (0.4 mmol, 2.0 equiv.) was added. After 1 h the dry ice acetone bath was removed, and the reaction was stirred for an additional 4 h. In a separate flask, the desired arylchloride or arylfluoride (0.6 mmol, 3.0 equiv.) was dissolved in toluene (2 mL) and NEt_3 (0.11 mL, 0.8 mmol, 4.0 equiv.) was added. This mixture was then added to the previously prepared reaction. The mixture was then stirred overnight at 100 °C or room temperature. After completion, the reaction was quenched with saturated aqueous NH_4Cl and extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography over silica gel to give pure 1,3-disubstituted azetidines **(7a-7i)**.

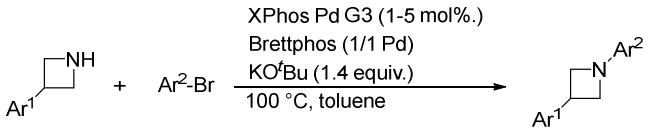
General Procedure K: Synthesis of 3-substituted Azetidines as Intermediates for Buchwald-Hartwig Cross-Coupling.



(1) **(2)** **(8a-8g)**

A flame-dried flask equipped with a magnetic stirring bar was charged with starting salt 2,3-dibromopropan-1-amine hydrobromide **(1)** (2.24 g, 8.00 mmol, 1.00 equiv.) and suspended in toluene (40 mL). The suspension was cooled to -78 °C using a dry ice acetone bath, and *n*BuLi (24 mmol, 3.0 equiv.) was added. Following the addition, the mixture was stirred for 1.5 h. Then, the respective organomagnesium compound (16 mmol, 2.0 equiv.) was added. After 1 h the dry ice acetone bath was removed, and the reaction was stirred for an additional 4 h. The reaction was quenched with saturated aqueous NH_4Cl and acidified to pH 1 with 2 M HCl (typically 10 mL). The mixture was thoroughly shaken, and the organic layer was separated and discarded. Then, the aqueous layer was basified to pH 9 with 2 M NaOH and extracted with dichloromethane (5 × 30 mL). In case of no phase separation centrifugation was used. The combined organic phases were dried over $MgSO_4$ and the solvents were removed *in vacuo* to afford pure 1-substituted azetidines **(8a-8g)**. 3-Substituted azetidines except **8b** and **8d** were directly engaged without any further purification.

General Procedure L: Synthesis of 1,3-disubstituted Azetidines *via* Buchwald-Hartwig Cross-Coupling of 3-substituted Azetidines.

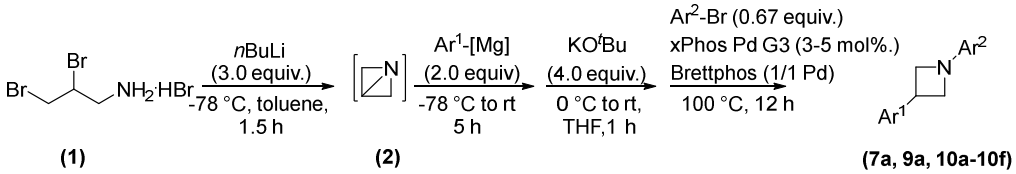


1.4 equiv. 1.0 equiv.

(8a-8g) **(9a-9t)**

In a flame-dried pressure tube equipped with magnetic stirring bar was added in the following order solvent (2 mL), 3-substituted azetidine (0.28 mmol, 1.4 equiv.), aryl halogenide (0.2 mmol, 1.0 equiv.), xPhos Pd G3 (1-5 mol%.), Brettphos (1/1 Pd), and base (1.4 equiv.) under nitrogen atmosphere. The septum was changed to a screw-cap and the pressure tube was heated to 100 °C for the respective amount of time. The reaction was monitored by TLC and GC-analysis. Once no further reaction progress or full consumption of the aryl halide was observed the brownish mixture was cooled to rt and filtered over celite 545. The filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography over silica gel to yield pure 1,3-disubstituted azetidines **(9a-9t)**.

General Procedure M: One-Pot Synthesis of Functionalized Azetidines via 1-Azabiclo[1.1.0]butane and following Buchwald-Hartwig Amination

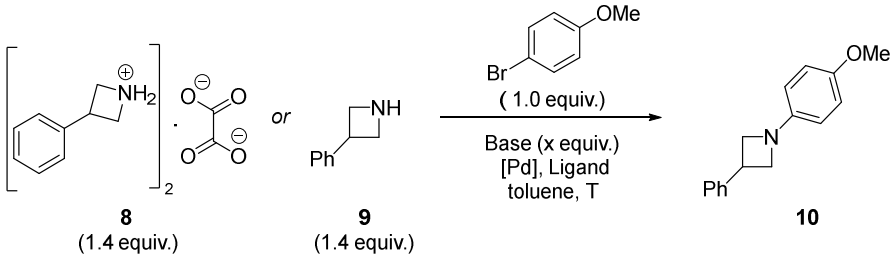


(1) **(2)** **(7a, 9a, 10a-10f)**

A flame-dried flask was charged with 2,3-dibromopropan-1-amine hydrobromide **(1)** (89 mg, 0.3 mmol, 1.0 equiv.) and suspended in toluene (2 mL). The suspension was cooled to -78 °C using a dry ice acetone bath, and *n*BuLi (0.9 mmol, 3.0 equiv.) was added. Following the addition, the mixture was stirred for 1.5 h. Then, the desired organomagnesium compound (0.6 mmol, 2.0 equiv.) was added. After 1 h the dry ice acetone bath was removed, and the reaction was stirred for an additional 4 h. After this, KO*t*Bu (134 mg, 4.0 equiv.) was suspended in THF (1 mL) and added dropwise to the mixture at 0°C. After 0.5 h at 0°C and 0.5 h warming to rt., the suspension was cannulated to a flame-dried pressure tube containing: aryl-bromide (0.2 mmol, 0.67 equiv.), xPhos Pd G3 (3-5 mol%.), Brettphos (1/1 Pd). The reaction was then stirred overnight (12 h) at 100 °C. After set time, the reaction was either checked by GC-analysis or it was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography over silica gel to give pure 1,3-disubstituted azetidines **(7a, 9a, 10a-10f)**.

3. Optimizations on Buchwald-Hartwig coupling

General Procedure for Screening of Catalyst-Ligand Combinations for Buchwald-Hartwig Coupling of Azetidines



8 (1.4 equiv.) **9** (1.4 equiv.) **10**

Table 1: Optimization on Buchwald-Hartwig coupling of 3-substituted azetidines.

Entry	Substrate	Catalyst	Ligand	Base	T (°C)	Yield (%)
1	8	$Pd_2(dba)_3$	*rac*-BINAP	KO^{t}Bu	100	17[a]
2	8	$Pd_2(dba)_3$	*rac*-BINAP	NaO^{t}Bu	100	16[a]
3	8	$Pd(OAc)_2$	Xantphos	KO^{t}Bu	100	4[a]
4	8	$Pd(OAc)_2$	Xantphos	NaO^{t}Bu	100	4[a]
5	8	xPhos Pd G3	Brettphos	KO^{t}Bu	100	24[b,c]
6	8	Ruphos Pd G3	RuPhos	KO^{t}Bu	100	22[b,c]
7	9	xPhos Pd G3	Brettphos	KO^{t}Bu	100	82[b,c]
8	9	xPhos Pd G3	Brettphos	KO^{t}Bu	80	73[b,c]
9	9	Ruphos Pd G3	Ruphos	KO^{t}Bu	100	71[b,c]
10	9	RuPhos Pd G3	Ruphos	KO^{t}Bu	80	68[b,c]

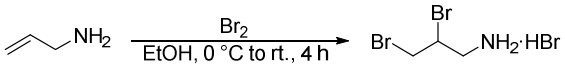
[a] Reactions performed with 3 mol% [Pd], [Pd]/ligand = 1.5:1 and 3 equiv. of Base, [b] Reactions performed with 1 mol% [Pd], [Pd]/ligand = 1:1 and 1.4 equiv. of Base,[c] Yields refer to isolated compounds.

In a flame-dried pressure tube equipped with magnetic stirring bar was added in the following order: toluene (2 mL), 3-phenylazetidin-1-ium oxalate (100 mg, 0.28 mmol, 1.4 equiv.) or 3-phenylazetidine (37 mg, 0.28 mmol, 1.4 equiv.), 4-bromoanisole (25 µL, 0.2 mmol, 1.0 equiv.), catalyst (3 mol% for reactions involving substrate **8,** 1 mol% for reactions involving substrate **9**), ligand ([Pd]/ligand = 1.5:1 for reactions involving substrate **8**, [Pd]/ligand = 1:1 for reactions involving substrate **9**) , and base (3 mol% for reactions involving substrate **8**, 1.4 mol% for reactions involving substrate **9**) under nitrogen atmosphere. The septum was changed to a

screw-cap and the pressure tube was stirred overnight (14 h) at the indicated temperature. After set time, the reaction was either checked by GC-analysis or it was filtered through a plug of Celite 545. The filtrate was concentrated *in vacuo* and the crude mixture was purified by flash column chromatography over silica gel (*i*-hexane/EtOAc; 98:2) to give pure 1-(4-methoxyphenyl)-3-phenylazetidine.

4. Experimental Section

2,3-Dibromopropan-1-amine hydrobromide (1)

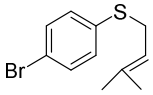


(1)

The compound was prepared according to a modified literature procedure.[186] Bromine (10.75 mL, 210 mmol, 2.10 equiv.) was added dropwise to 40 mL EtOH in a round necked flask at 0 °C. Allylamine (7.48 mL, 100 mmol, 1.00 eq.) was added dropwise to the dark solution. The icebath was removed and the solution was allowed to warm to room temperature. After 4 h the precipitate was filtered off and the crude product was washed with cold Et_2O (3 × 15 mL). The colorless solid was recrystallized two times from methanol (30 mL) to obtain colorless crystals of the title compound (17.6 g, 58.9 mmol, 59 % overall yield).

^{1}H NMR (400 MHz, CD_3OD): δ (ppm) = 4.49 (dddd, J = 9.4, 8.0, 4.6, 3.2 Hz, 1H), 4.00 (dd, J = 11.0, 4.6 Hz, 1H), 3.85 (dd, J = 11, 8.7 Hz, 1H), 3.69 (dd, J = 14.0, 3.2 Hz, 1H), 3.39 – 3.31 (m, 1H). **^{13}C NMR (100 MHz, CD_3OD):** δ (ppm) = 47.95, 45.54, 33.90.

(4-Bromophenyl)(3-methylbut-2-en-1-yl)sulfane



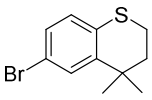
The compound was prepared according to a modified literature procedure.[187] 4-bromobenzenethiol (3.03 g, 16.0 mmol, 1.00 equiv.) was charged in a flame dried flask under nitrogen atmosphere and dissolved in dry acetone (120 mL). 1-Bromo-3-methylbut-2-ene (3.7 mL, 32 mmol, 2.0 equiv.) was added to the solution under continuous stirring. Then NEt_3 (3.05 mL, 21.8 mmol, 1.36 equiv.) was added dropwise at 0 °C upon which immediately a colorless precipitate was formed. The mixture was then allowed to warm to rt and was stirred overnight at this temperature. After 24 h the precipitate was filtered off and washed thoroughly with acetone (around 50 mL). Then the filtrate was diluted with water (40 mL) and extracted with EtOAc (3 × 40 mL).

[186] J. L. Tyler, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2021**, *60*, 11824-11829.
[187] I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12774-12777.

Combined organic layers were washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane) to afford the title compound as a yellowish oil (3.1 g, 12 mmol, 75 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.49 – 7.28 (m, 4H), 7.22 – 7.15 (m, 2H), 5.27 (tt, J = 7.7, 1.3 Hz, 1H), 3.51 (d, J = 7.7 Hz, 2H), 1.71 (s, 3H), 1.59 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 136.95, 136.16, 132.35, 131.84, 131.34, 129.50, 119.95, 119.06, 32.38, 25.80, 17.87.

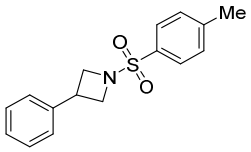
6-Bromo-4,4-dimethylthiochromane



The compound was prepared according to a modified literature procedure.[187] Polyphosphoric acid (2.7 g, 27 mmol, 3.5 eq.) was charged into a pressure tube and flushed with nitrogen. (4-Bromophenyl)(3-methylbut-2-en-1-yl)sulfane (2.0 g, 7.7 mmol, 1.0 equiv.) was dissolved in toluene (5 mL) and added. The brownish mixture was heated to 100 °C for 48 h and the mixture including the solid residues were transferred to a separatory funnel by washing with EtOAc (3 × 10 mL) and water (2 × 10 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL), the combined organic phases were washed with saturated aq. $NaHCO_3$ (20 mL), water (30 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane), and recrystallized from *i*hexane to obtain the title compound as colorless needles (1.7 g, 6.6 mmol, 86 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.45 (d, J = 2.2 Hz, 1H), 7.13 (dd, J = 8.4, 2.2 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 3.04 – 2.99 (m, 2H), 1.95 – 1.91 (m, 2H), 1.31 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 144.07, 131.05, 129.43, 128.99, 128.03, 117.31, 77.35, 77.03, 76.72, 37.10, 33.24, 30.02, 23.00.

3-Phenyl-1-tosylazetidine (3a)

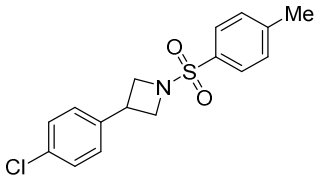


Cyclization was carried out using phenylmagnesium chloride (0.4 mmol, 2.0 equiv.) according to general procedure J, deviating from this, tosylchloride (76 mg, 0.4 mmol, 2.0 equiv.) in THF (1 mL) was added at 0 °C as the electrophile. After warming to room temperature the reaction was stirred for 3 h. After completion, the reaction was quenched with saturated aqueous NH_4Cl and extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column

chromatography over silica gel to give pure 3-phenyl-1-tosylazetidine (42 mg, 0.15 mmol, 73 %) as a colorless solid (hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.83 – 7.76 (m, 2H), 7.46 – 7.38 (m, 2H), 7.28 – 7.16 (m, 3H), 7.03 – 6.94 (m, 2H), 4.16 (t, J = 8.5 Hz, 2H), 3.81 (dd, J = 8.1, 7.0 Hz, 2H), 3.68 – 3.56 (m, 1H), 2.50 ppm (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 144.3, 140.7, 131.6, 130.0, 128.9, 128.7, 127.5, 127.0, 58.0, 33.4, 21.8 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 155 (24), 103 (100), 92 (20), 78 (58). **HRMS** (ESI) m/z: $[M]^+$ calcd for $C_{16}H_{17}NO_2S^+$: 287.0980; found: 288.0987. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2971 (w), 1595 (m), 1494 (m), 1492 (m), 1454 (m), 1338 (s), 1325 (m), 1308 (m), 1292 (m), 1161 (s), 1152 (s), 1121 (m), 1105 (m), 1087 (m), 1072 (m), 1056 (s), 1019 (m), 999 (m), 960 (m), 956 (m), 872 (m), 870 (m), 816 (s), 800 (m), 766 (s), 763 (s), 723 (s), 708 (s), 705 (s), 671 (vs), 667 (vs), 664 (s), 660 (s), 658 (s), 655 (s), 652 cm^{-1} (m). **Melting point**: mp = 134 °C.

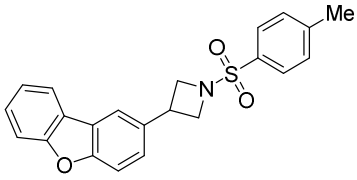
3-(4-Chlorophenyl)-1-tosylazetidine (3b)



Cyclization was carried out using (4-chlorophenyl)magnesium bromide (0.4 mmol, 2.0 equiv.) according to general procedure J, deviating from this, tosylchloride (76 mg, 0.4 mmol, 2.0 equiv.) in THF (1 mL) was added at 0 °C as the electrophile. After warming to room temperature the reaction was stirred for 3 h. After completion, the reaction was quenched with saturated aqueous NH_4Cl and extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography over silica gel to give pure 3-(4-chlorophenyl)-1-tosylazetidine (42 mg, 0.13 mmol, 65 %) as a colorless solid (hexane/EtOAc 8.5:1.5).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.78 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 4.14 (t, J = 8.4 Hz, 2H), 3.79 – 3.71 (m, 2H), 3.63 – 3.52 (m, 1H), 2.50 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 144.35, 139.12, 133.15, 131.23, 129.90, 128.88, 128.58, 128.23, 77.36, 77.05, 76.73, 57.76, 32.63, 21.67. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 140 (33), 138 (100), 103 (25). **HRMS** (ESI) m/z: $[M]^+$ calcd for: $C_9H_9ClN^+$:166.0424 found: 166.0416. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2966 (w), 2950 (w), 2921 (w), 2884 (w), 1729 (vw), 1598 (w), 1493 (m), 1475 (w), 1453 (w), 1414 (w), 1401 (w), 1377 (vw), 1339 (vs), 1306 (m), 1297 (m), 1240 (w), 1225 (vw), 1208 (vw), 1174 (m), 1151 (vs), 1114 (m), 1093 (s), 1056 (m), 1038 (w), 1023 (m), 1013 (s), 980 (w), 960 (m), 864 (m), 836 (w), 814 (s), 766 (w), 711 (m). **Melting point**: mp = 123 °C.

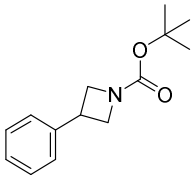
3-(Dibenzo[b,d]furan-2-yl)-1-tosylazetidine (3c)



Cyclization was carried out using dibenzo[b,d]furan-2-ylmagnesium bromide lithium chloride (0.4 mmol, 2.0 equiv.) according to general procedure J, deviating from this, tosylchloride (76 mg, 0.4 mmol, 2.0 equiv.) in THF (1 mL) was added at 0 °C as the electrophile. After warming to room temperature the reaction was stirred for 3 h. After completion, the reaction was quenched with saturated aqueous NH_4Cl and extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography over silica gel to give pure 3-(dibenzo[b,d]furan-2-yl)-1-tosylazetidine (39 mg, 0.10 mmol, 51 %) as a yellow solid (hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.84 (dd, J = 7.6, 3.4 Hz, 3H), 7.55 (d, J = 8.7 Hz, 2H), 7.46 (dd, J = 7.6, 5.4 Hz, 3H), 7.41 (d, J = 8.7 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.07 (dd, J = 8.7, 1.8 Hz, 1H), 4.25 (t, J = 8.3 Hz, 2H), 3.93 – 3.87 (m, 1H), 3.79 (p, J = 8.3 Hz, 1H), 2.54 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 156.58, 155.34, 144.26, 135.23, 131.39, 129.95, 128.73, 127.51, 126.16, 124.62, 123.75, 122.82, 120.54, 118.66, 111.82, 111.72, 77.35, 77.03, 76.71, 58.54, 33.29, 21.72. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 195 (15), 194 (100), 165 (18). **HRMS** (ESI) m/z: $[M]^+$ calcd for $C_{15}H_{12}NO^+$: 222.0919; found: 222.0914. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2950 (w), 2919 (w), 2888 (w), 2359 (vw), 1931 (vw), 1898 (vw), 1731 (vw), 1651 (vw), 1594 (w), 1480 (m), 1447 (m), 1430 (w), 1397 (w), 1382 (w), 1371 (w), 1343 (s), 1319 (m), 1305 (m), 1292 (w), 1260 (w), 1244 (w), 1230 (w), 1200 (m), 1186 (w), 1174 (m), 1156 (vs), 1143 (s), 1123 (m), 1111 (w), 1102 (m), 1088 (s), 1073 (s), 1058 (m), 1020 (m), 1007 (w), 989 (w), 957 (m), 941 (w), 887 (w), 875 (w), 851 (w), 841 (m), 823 (s), 802 (m), 782 (w), 770 (m), 758 (s), 733 (w), 713 (s). **Melting point**: mp = 144 °C

***tert*-Butyl 3-phenylazetidine-1-carboxylate (3d)**

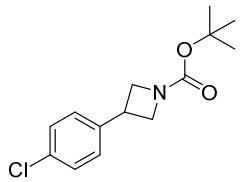


Cyclization was carried out using phenylmagnesium chloride (0.4 mmol, 2.0 equiv.) according to general procedure J, deviating from this, Boc_2O (87 mg, 0.4 mmol, 2.0 equiv.) in THF (1 mL) was added at 0 °C as the electrophile. After warming to room temperature the reaction was stirred for 3 h. After completion, the reaction was quenched with saturated aqueous NH_4Cl and extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and

the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography over silica gel to give pure tert-butyl 3-phenylazetidine-1-carboxylate (32 mg, 0.14 mmol, 69 %) as a colorless oil (hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.38 – 7.30 (m, 4H), 7.29 – 7.27 (m, 1H), 4.33 (t, J = 8.7 Hz, 2H), 3.98 (t, J = 8.7 Hz, 2H), 3.73 (tt, J = 8.7, 6.1 Hz, 1H), 1.47 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 156.55, 142.41, 128.86, 127.10, 126.91, 79.65, 77.48, 77.16, 76.84, 33.63, 28.57. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 104 (100), 103 (22), 91 (17), 78 (29). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{10}H_{10}NO_2^+$: 176.0712; found: 176.0705. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2884 (w), 1699 (vs), 1605 (vw), 1495 (w), 1480 (w), 1455 (w), 1391 (s), 1365 (s), 1354 (m), 1296 (w), 1283 (vw), 1254 (w), 1161 (m), 1127 (s), 1085 (w), 1031 (vw), 965 (w), 908 (w), 860 (w), 774 (w), 756 (m).

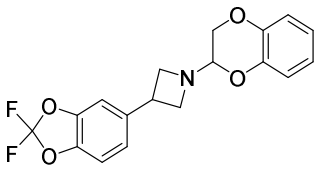
tert-Butyl 3-(4-chlorophenyl)azetidine-1-carboxylate (3e)



Cyclization was carried out using (4-chlorophenyl)magnesium bromide (0.4 mmol, 2.0 equiv.) according to general procedure J, deviating from this, Boc_2O (87 mg, 0.4 mmol, 2.0 equiv.) in THF (1 mL) was added at 0 °C as the electrophile. After warming to room temperature the reaction was stirred for 3 h. After completion, the reaction was quenched with saturated aqueous NH_4Cl and extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography over silica gel to give pure *tert*-butyl 3-phenylazetidine-1-carboxylate (37 mg, 0.14 mmol, 69 %) as a colorless oil (hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.32 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 4.32 (t, J = 8.7 Hz, 1H), 3.92 (dd, J = 8.7, 6.0 Hz, 2H), 3.69 (tt, J = 8.7, 6.0 Hz, 1H), 1.46 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 156.36, 140.78, 132.74, 128.86, 128.18, 79.69, 77.35, 77.04, 76.72, 32.98, 28.42. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 140 (17), 138 (61), 125 (17), 57 (100), 41 (14). **HRMS** (ESI) m/z: $[M]^+$ calcd for $C_{14}H_{18}ClNO_2$: 267.1026; found: 267.1036. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2885 (w), 2362 (vw), 1699 (vs), 1598 (vw), 1494 (m), 1478 (w), 1457 (w), 1417 (m), 1391 (s), 1366 (m), 1338 (w), 1297 (w), 1254 (w), 1160 (m), 1132 (s), 1094 (m), 1014 (w), 967 (w), 908 (w), 859 (w), 822 (m), 774 (w), 762 (w), 715 (vw).

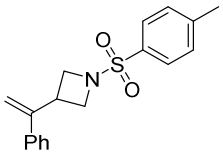
3-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-2-yl)azetidine (3f)



Cyclization was carried out using (2,2-difluorobenzo[d][1,3]dioxol-5-yl)magnesium bromide (0.4 mmol, 2.0 equiv.) according to general procedure J, deviating from this, 2-bromo-2,3-dihydrobenzo[b][1,4]dioxine (86 mg, 0.4 mmol, 2.0 equiv.) in THF (1 mL) was added at 0°C as the electrophile. After warming to room temperature the reaction was stirred for 3 h. After completion, the reaction was quenched with saturated aqueous NH_4Cl and extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography over silica gel (hexane/EtOAc 8:2) to obtain the title compound as a colorless oil (43 mg, 0.12 mmol, 61 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.16 (d, *J* = 1.6 Hz, 1H), 7.06 – 6.97 (m, 2H), 6.79 – 6.75 (m, 1H), 6.08 – 6.01 (m, 2H), 4.29 – 4.18 (m, 6H), 3.87 – 3.79 (m, 1H), 3.74 (t, *J* = 6.2 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 147.12, 144.14, 143.96, 142.52, 139.14, 136.21, 122.17, 117.57, 109.22, 108.29, 105.25, 100.82, 77.35, 77.03, 76.71, 64.78, 64.22, 60.03, 35.03. **^{19}F NMR (377 MHz, $CDCl_3$):** δ (ppm) = -50.07. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 347 (21), 163 (100), 107 (19), 79 (10), 43 (10). **HRMS (EI):** for: $C_{18}H_{15}F_2NO_4$ calc. [M^+]: 347.0969; found: 347.0967. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2850 (w), 1622 (w), 1587 (w), 1503 (s), 1481 (m), 1460 (w), 1384 (vw), 1344 (vw), 1306 (m), 1277 (m), 1235 (s), 1217 (vs), 1184 (m), 1146 (s), 1125 (s), 1067 (s), 1035 (m), 971 (w), 925 (m), 904 (w), 888 (m), 864 (w), 830 (m), 795 (m), 746 (m), 719 (w), 702 (m).

3-(1-Phenylvinyl)-1-tosylazetidine (3i)

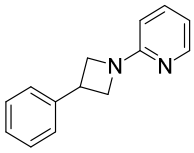


Cyclization was carried out using (1-phenylvinyl) magnesium bromide (0.4 mmol, 2.0 equiv.) according to general procedure J, deviating from this tosylchloride (76 mg, 0.4 mmol, 2.0 equiv.) in THF (1 mL) was added at 0 °C as the electrophile. After warming to room temperature the reaction was stirred for 3 h. After completion, the reaction was quenched with saturated aqueous NH_4Cl and extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture

was purified by flash column chromatography over silica gel (hexane/EtOAc 9:1) to obtain the title compound as a yellow oil (27 mg, 0.09 mmol, 43 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.72 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.31 – 7.27 (m, 3H), 7.16 (dd, J = 7.6, 1.9 Hz, 2H), 5.36 (s, 1H), 4.89 (s, 1H), 4.10 – 3.95 (m, 2H), 3.73 – 3.64 (m, 3H), 2.46 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 146.71, 144.21, 139.24, 131.61, 129.87, 128.69, 128.57, 128.14, 125.86, 112.44, 77.48, 77.16, 76.84, 55.69, 32.25, 21.78. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 313 (11), 206 (34), 104 (19), 103 (100). **HRMS (EI):** for: $C_{18}H_{19}NO_2S$ calc. [M$^+$]: 313.1136; found: 313.1131. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2958 (vw), 2924 (vw), 2875 (vw), 1629 (vw), 1597 (w), 1574 (vw), 1495 (w), 1474 (vw), 1446 (w), 1400 (vw), 1342 (s), 1304 (m), 1291 (w), 1262 (vw), 1185 (w), 1156 (vs), 1119 (m), 1092 (s), 1064 (m), 1029 (m), 1019 (w), 905 (m), 816 (m), 777 (m), 722 (m), 707 (m), 673 (s).

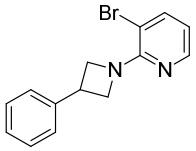
2-(3-Phenylazetidin-1-yl)pyridine (7a)



Using phenylmagnesium chloride (0.4 mmol, 2.0 equiv.) and 2-fluoropyridine (58 mg, 0.6 mmol, 3.0 equiv.) according to general procedure J, yielded **7a** (34 mg, 0.16 mmol, 80 %) as colorless oil (hexane/EtOAc 9:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 8.19 (ddd, J = 5.1, 2.0, 0.9 Hz, 1H), 7.47 (ddd, J = 8.7, 7.2, 1.9 Hz, 1H), 7.41 – 7.32 (m, 4H), 7.29 – 7.23 (m, 1H), 6.63 (ddd, J = 7.2, 5.1, 1.1 Hz, 1H), 6.35 (dd, J = 8.4, 1.1 Hz, 1H), 4.45 (t, J = 8.1 Hz, 2H), 4.07 (dd, J = 7.8, 6.0 Hz, 2H), 3.95 ppm (ddd, J = 14.4, 8.4, 6.0 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 160.9, 148.3, 142.8, 137.2, 128.8, 127.1, 127.0, 113.1, 106.1, 58.1, 35.0 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 210.1 (37), 181.1 (14), 104.1 (100), 79.0 (65). **HRMS** (EI) m/z: [M]$^+$ calcd for $C_{14}H_{14}N_2$: 210.1157; found: 210.1148. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3061 (w), 3026 (w), 3008 (w), 2951 (w), 2862 (w), 1756 (w), 1589 (s), 1557 (m), 1490 (s), 1472 (vs), 1454 (m), 1436 (vs), 1374 (m), 1351 (m), 1301 (m), 1294 (m), 1273 (m), 1147 (s), 1081 (m), 1062 (w), 1025 (m), 977 (m), 947 (w), 907 (w), 880 (w), 846 (w), 772 (s), 756 (s), 735 (s), 723 (m), 715 (m), 697 (vs), 675 (m), 673 (m), 669 (m), 667 (m), 661 (m), 657 (m), 655 cm^{-1} (w).

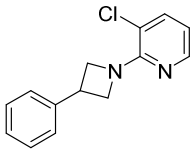
3-Bromo-2-(3-phenylazetidin-1-yl)pyridine (7b)



Using phenylmagnesium chloride (0.4 mmol, 2.0 equiv.) and 3-bromo-2-fluoropyridine (106 mg, 0.6 mmol, 3.0 equiv.) according to general procedure J, yielded **7b** (43 mg, 0.15 mmol, 75 %) as yellow solid (hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.15 (dd, J = 4.8, 1.6 Hz, 1H), 7.65 (dd, J = 7.7, 1.5 Hz, 1H), 7.42 – 7.32 (m, 4H), 7.30 – 7.21 (m, 1H), 6.58 (dd, J = 7.6, 4.8 Hz, 1H), 4.69 (t, J = 8.5 Hz, 2H), 4.30 (dd, J = 8.4, 6.4 Hz, 2H), 3.87 ppm (tt, J = 8.6, 6.4 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 157.45, 146.5, 142.7, 141.8, 128.8, 127.1, 126.9, 115.4, 104.7, 60.1, 34.6 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 288.0 (9), 156.9 (25), 104.1 (100). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{14}H_{13}BrN_2$: 288.0262; found: 288.0259. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3058 (w), 3026 (w), 2955 (w), 2928 (w), 2870 (w), 1580 (s), 1540 (w), 1455 (s), 1443 (vs), 1434 (s), 1337 (m), 1290 (m), 1247 (m), 1153 (w), 1077 (m), 1024 (m), 1007 (m), 957 (m), 777 (m), 747 (s), 698 cm^{-1} (s).

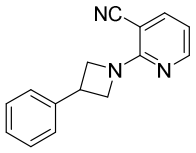
3-Chloro-2-(3-phenylazetidin-1-yl)pyridine (7c)



Using phenylmagnesium chloride (0.4 mmol, 2.0 equiv.) and 3-chloro-2-fluoropyridine (79 mg, 0.6 mmol, 3.0 equiv.) according to general procedure J, yielded **7c** (31 mg, 0.13 mmol, 65 %) as yellow solid (hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.43 – 7.31 (m, 5H), 7.31 – 7.22 (m, 1H), 6.62 (d, J = 7.5 Hz, 1H), 6.19 (d, J = 8.1 Hz, 1H), 4.46 (t, J = 8.3 Hz, 2H), 4.08 (dd, J = 8.1, 6.0 Hz, 2H), 3.94 ppm (tt, J = 8.5, 5.9 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 160.7, 150.2, 142.5, 139.4, 128.9, 127.1, 127.0, 112.1, 103.9, 58.2, 34.8 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 244.0 (7), 104.1 (100). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{14}H_{13}ClN_2$: 244.0767; found: 244.0760. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3080 (vw), 3056 (w), 3022 (w), 2957 (w), 2924 (w), 2871 (w), 2852 (m), 1584 (s), 1544 (m), 1484 (s), 1463 (vs), 1449 (vs), 1436 (s), 1413 (s), 1409 (s), 1400 (s), 1375 (s), 1352 (m), 1293 (s), 1282 (m), 1277 (m), 1254 (m), 1177 (m), 1148 (s), 1112 (s), 1091 (m), 1072 (m), 1062 (m), 1043 (m), 1030 (m), 973 (s), 949 (m), 912 (m), 894 (w), 771 (vs), 762 (vs), 725 (s), 704 (vs), 652 cm^{-1} (m). **Melting point**: mp = 66 °C.

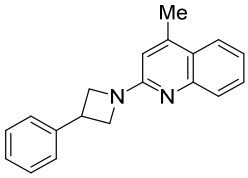
2-(3-Phenylazetidin-1-yl)nicotinonitrile (7d)



Using phenylmagnesium chloride (0.4 mmol, 2.0 equiv.) and 2-fluoronicotinonitrile (73 mg, 0.6 mmol, 3.0 equiv.) according to general procedure J, yielded **7d** (35 mg, 0.16 mmol, 75 %) as yellow solid (hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.30 (dd, J = 4.9, 1.9 Hz, 1H), 7.68 (dd, J = 7.7, 1.9 Hz, 1H), 7.37 (d, J = 5.0 Hz, 4H), 7.33 – 7.24 (m, 1H), 6.64 (dd, J = 7.7, 4.9 Hz, 1H), 4.76 (t, J = 8.8 Hz, 2H), 4.38 (dd, J = 8.9, 6.2 Hz, 2H), 3.98 ppm (tt, J = 8.8, 6.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 159.7, 152.7, 143.1, 142.0, 128.9, 127.2, 126.9, 117.9, 112.5, 90.2, 59.2, 34.7 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 235.1 (5), 104.1 (100), 78.0 (27). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{15}H_{13}N_3$: 235.1109; found: 235.1100. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3061 (vw), 3028 (w), 2956 (w), 2876 (w), 2213 (m), 1582 (vs), 1553 (vs), 1489 (s), 1462 (vs), 1445 (vs), 1354 (w), 1294 (m), 1278 (w), 1256 (m), 1243 (s), 1184 (w), 1155 (w), 1087 (w), 1048 (w), 1025 (w), 953 (w), 907 (w), 788 (m), 756 (vs), 698 (s), 652 cm^{-1} (w). **Melting point**: mp = 126 °C.

4-Methyl-2-(3-phenylazetidin-1-yl)quinoline (7e)

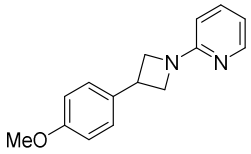


Phenylmagnesium chloride (0.4 mmol, 2.0 equiv.) and 2-chloro-4-methylquinoline (106 mg, 0.6 mmol, 3.0 equiv.) were used according to general procedure J. After addition of the electrophile this reaction was stirred overnight at 100 °C, yielded **7e** (38 mg, 0.14 mmol, 70 %) as yellow solid (hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.82 – 7.74 (m, 2H), 7.58 – 7.52 (m, 1H), 7.42 – 7.38 (m, 2H), 7.38 – 7.33 (m, 2H), 7.29 – 7.23 (m, 2H), 6.49 (d, J = 1.3 Hz, 1H), 4.60 (t, J = 8.3 Hz, 2H), 4.23 (t, J = 8.0, 6.0 Hz, 2H), 3.98 (ddd, J = 14.5, 8.5, 6.0 Hz, 1H), 2.61 ppm (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 158.8, 148.1, 145.2, 142.8, 129.6, 129.5, 128.8, 127.1, 127.0, 123.8, 123.7, 122.2, 109.1, 58.0, 34.8, 19.1 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 274.1 (25), 170.1 (25), 143.1 (100), 115.1 (12). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{19}H_{18}N_2$: 274.1470; found: 274.1477. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3050 (w), 2957 (w), 2924 (m), 2859 (m), 1612 (s), 1552 (s), 1503 (s), 1493 (s), 1479 (s), 1468 (s), 1447 (m), 1424 (s), 1412 (s), 1378 (m), 1356 (m), 1341 (m), 1299 (m), 1278 (m), 1260 (m), 1225 (m), 1182 (m), 1154 (m),

1091 (m), 1075 (m), 1030 (m), 1025 (m), 946 (w), 918 (w), 849 (s), 761 (s), 751 (vs), 708 (m), 702 (vs), 690 cm^{-1} (s). **Melting point**: mp = 126 °C.

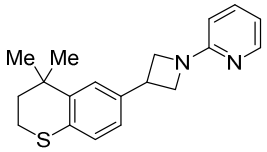
2-(3-(4-Methoxyphenyl)azetidin-1-yl)pyridine (7f)



Using (4-methoxyphenyl)magnesium bromide (0.4 mmol, 2.0 equiv.) and 2-fluoropyridine (58 mg, 0.6 mmol, 3.0 equiv.) according to general procedure J, yielded **7f** (25 mg, 0.10 mmol, 50 %) as light yellow solid (hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.18 (ddd, J = 5.1, 1.9, 0.9 Hz, 1H), 7.47 (ddd, J = 8.7, 7.1, 1.9 Hz, 1H), 7.34 – 7.24 (m, 2H), 6.93 – 6.85 (m, 2H), 6.62 (ddd, J = 7.2, 5.0, 1.0 Hz, 1H), 6.34 (dd, J = 8.3, 1.1 Hz, 1H), 4.43 (t, J = 8.1 Hz, 2H), 4.02 (dd, J = 7.7, 6.0 Hz, 2H), 3.90 (tt, J = 8.4, 5.9 Hz, 1H), 3.80 ppm (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 160.8, 158.6, 148.2, 137.3, 134.9, 128.1, 114.2, 113.0, 106.2, 58.4, 55.5, 34.3 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 240.1 (5), 134.1 (100), 119.0 (20). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{14}H_{14}N_2O$: 240.1263; found: 240.1251. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3032 (vw), 3003 (w), 2951 (w), 2862 (w), 2833 (w), 1590 (s), 1557 (m), 1513 (s), 1490 (s), 1471 (vs), 1435 (vs), 1372 (m), 1301 (m), 1295 (m), 1273 (m), 1244 (vs), 1177 (s), 1147 (s), 1114 (m), 1081 (m), 1034 (s), 1028 (s), 1011 (m), 977 (m), 953 (w), 885 (w), 826 (s), 804 (m), 802 (m), 772 (s), 736 (s), 722 (m), 720 (m), 719 (m), 712 cm^{-1} (m). **Melting point**: mp = 57 °C.

2-(3-(4,4-Dimethylthiochroman-6-yl)azetidin-1-yl)pyridine (7g)

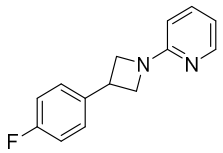


Using (4,4-dimethylthiochroman-6-yl)magnesium bromide (0.4 mmol, 2.0 equiv.) and 2-fluoropyridine (58 mg, 0.6 mmol, 3.0 equiv.) according to general procedure J, yielded **7g** (25 mg, 0.08 mmol, 40 %) as colorless solid (hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.18 (ddd, J = 5.0, 2.0, 0.9 Hz, 1H), 7.47 (ddd, J = 8.8, 7.1, 1.9 Hz, 1H), 7.30 (d, J = 1.8 Hz, 1H), 7.12 – 7.05 (m, 2H), 6.63 (ddd, J = 7.2, 5.1, 1.0 Hz, 1H), 6.34 (d, J = 8.4 Hz, 1H), 4.42 (t, J = 8.1 Hz, 2H), 4.02 (dd, J = 7.8, 6.1 Hz, 2H), 3.87 (tt, J = 8.5, 6.1 Hz, 1H), 3.07 – 2.96 (m, 2H), 2.01 – 1.92 (m, 2H), 1.33 ppm (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 160.8, 148.2, 142.2, 138.4, 137.3, 130.3, 127.1, 125.5, 124.6, 113.0, 106.2, 58.2, 37.9, 34.9, 33.2, 30.4, 23.2 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 310.1 (1), 204.1 (100), 189.1 (39), 156.1 (15). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{19}H_{22}N_2S$: 310.1504; found:

310.1501. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2957 (m), 2931 (m), 2856 (w), 1592 (s), 1558 (m), 1490 (s), 1471 (vs), 1435 (vs), 1362 (m), 1301 (m), 1287 (m), 1272 (m), 1251 (m), 1213 (m), 1146 (s), 1115 (m), 1057 (s), 980 (m), 884 (m), 815 (m), 772 (s), 734 (s), 710 (m).

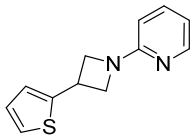
2-(3-(4-Fluorophenyl)azetidin-1-yl)pyridine (7h)



Using (4-fluorophenyl)magnesium bromide (0.4 mmol, 2.0 equiv.) and 2-fluoropyridine (58 mg, 0.6 mmol, 3.0 equiv.) according to general procedure J, yielded **7h** (33 mg, 0.14 mmol, 72 %) as light yellow oil (hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.18 (ddd, J = 5.1, 1.9, 0.9 Hz, 1H), 7.47 (ddd, J = 8.4, 7.2, 1.9 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.08 – 6.98 (m, 2H), 6.63 (ddd, J = 7.2, 5.1, 1.0 Hz, 1H), 6.34 (dt, J = 8.3, 1.0 Hz, 1H), 4.44 (t, J = 8.1 Hz, 2H), 4.01 (dd, J = 7.6, 5.9 Hz, 2H), 3.91 ppm (tt, J = 8.4, 6.0 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 161.9 (d, J = 245.1 Hz), 160.9, 148.4, 138.6 (d, J = 3.2 Hz), 137.2, 128.6 (d, J = 8.0 Hz), 115.6 (d, J = 21.4 Hz), 113.2, 106.1, 58.3 (d, J = 1.0 Hz), 34.4 ppm. **^{19}F NMR (377 MHz, $CDCl_3$):** δ (ppm) = -115.99 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 228.1 (18), 122.0 (100), 79.0 (40). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{14}H_{13}FN_2$: 228.1063; found: 228.1053. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3069 (vw), 3046 (vw), 3011 (vw), 2956 (w), 2863 (w), 1756 (w), 1599 (s), 1592 (s), 1558 (m), 1511 (s), 1491 (s), 1473 (vs), 1437 (vs), 1371 (m), 1299 (m), 1273 (w), 1222 (s), 1159 (m), 1148 (m), 1103 (w), 1082 (w), 1053 (w), 1030 (w), 978 (w), 955 (w), 831 (s), 817 (m), 774 (s), 737 (m), 718 cm^{-1} (w).

2-(3-(Thiophen-2-yl)azetidin-1-yl)pyridine (7i)

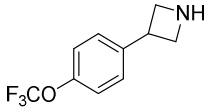


Using thiophen-2-ylmagnesium bromide (0.4 mmol, 2.0 equiv.) and 2-Fluoropyridine (58 mg, 0.6 mmol, 3.0 equiv.) according to general procedure J, yielded **7i** (28 mg, 0.13 mmol, 65 %) as light yellow solid (hexane/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.18 (ddd, J = 5.1, 2.0, 1.0 Hz, 1H), 7.48 (ddd, J = 8.3, 7.1, 1.9 Hz, 1H), 7.23 – 7.20 (m, 1H), 6.97 (d, J = 3.4 Hz, 2H), 6.64 (ddd, J = 7.1, 5.1, 1.0 Hz, 1H), 6.34 (d, J = 8.3 Hz, 1H), 4.47 (t, J = 7.9 Hz, 2H), 4.22 (tt, J = 8.1, 6.2 Hz, 1H), 4.07 ppm (dd, J = 7.6, 6.2 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 160.8, 148.2, 146.2, 137.3, 127.2, 124.4, 124.2, 113.3, 106.3, 59.3, 30.8 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 216.0 (12), 110.0 (100). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{12}H_{12}N_2S$: 216.0721; found: 216.0714. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2955 (w), 2923 (w), 2855 (w), 1598 (s), 1589 (s), 1559 (m), 1489

(s), 1471 (vs), 1435 (vs), 1377 (m), 1360 (m), 1301 (m), 1147 (s), 1079 (m), 1049 (m), 1024 (m), 976 (m), 843 (m), 823 (m), 772 (vs), 735 (s), 696 (s), 694 cm^{-1} (s).

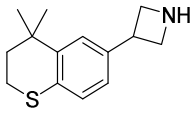
3-(4-(Trifluoromethoxy)phenyl)azetidine (9b/3h)



According to general procedure K, 2,3-dibromopropan-1-amine hydrobromide **1** (2.24 g, 8.00 mmol, 1.00 equiv.) was suspended in toluene (40 mL). *n*BuLi (24 mmol, 3.0 equiv.) was added dropwise at -78 °C and the mixture was stirred for 1.5 h. Then (4-(trifluoromethoxy)phenyl)magnesium bromide (16 mmol, 2.0 equiv.) was added. After 1 h the dry ice acetone bath was removed, and the reaction was stirred for an additional 4 h. Extraction and evaporation of the solvent *in vacuo* afforded the title compound as a brown oil (1.34 g, 4.9 mmol, 62 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.41 – 7.37 (m, 2H), 7.23 – 7.18 (m, 2H), 4.14 (t, J = 7.1 Hz, 2H), 3.99 (t, J = 7.1 Hz, 2H), 3.73 (tt, J = 7.1, 3.9 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 148.28, 139.57, 128.33, 121.35, 53.70, 37.73.#

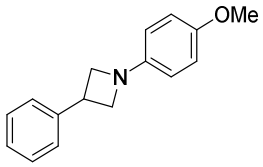
3-(4,4-Dimethylthiochroman-6-yl)azetidine (9d/3g)



According to general procedure K, 2,3-dibromopropan-1-amine hydrobromide **1** (0.48 g, 1.6 mmol, 1.00 equiv.) was suspended in toluene (40 mL). *n*BuLi (4.8 mmol, 3.0 equiv.) was added dropwise at -78 °C and the mixture was stirred for 1.5 h. Then (4,4-dimethylthiochroman-6-yl)magnesium bromide (3.2 mmol, 2.0 equiv.) was added. After 1 h the dry ice acetone bath was removed, and the reaction was stirred for an additional 4 h. Extraction and evaporation of the solvent *in vacuo* afforded the title compound as a brown oil (0.23 g, 1.0 mmol, 62 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.24 (d, J = 1.5 Hz, 1H), 7.06 – 7.04 (m, 2H), 3.93 (t, J = 5.9 Hz, 2H), 3.83 (t, J = 5.9 Hz, 2H), 3.74 (ddd, J = 6.6, 4.2, 2.5 Hz, 1H), 3.04 – 2.99 (m, 2H), 1.95 (ddd, J = 6.1, 4.0, 2.9 Hz, 2H), 1.33 (s, 4H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 142.13, 129.17, 128.36, 126.88, 125.26, 124.56, 77.48, 77.16, 76.84, 68.12, 54.76, 39.66, 37.89, 33.20, 30.38, 25.75, 23.19.

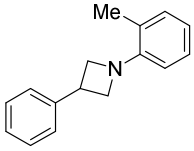
1-(4-Methoxyphenyl)-3-phenylazetidine (10a)



According to general procedure L, 3-phenylazetidine **9a** (37 mg, 0.28 mmol, 1.4 equiv.), 4-bromoanisole (25 µL, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (1.7 mg, 1 mol%), Brettphos (1.1 mg, 1 mol%), and KO*t*Bu (31 mg, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 18 h. The now brownish mixture was cooled to rt and filtered over celite 545. After the filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo.* The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 98:2) to obtain the title compound as a colorless solid (39 mg, 0.16 mmol, 82 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.40 – 7.31 (m, 4H), 7.25 – 7.22 (m, 1H), 6.88 – 6.81 (m, 2H), 6.53 – 6.46 (m, 2H), 4.26 (t, J = 6.5 Hz, 2H), 3.97 – 3.88 (m, 1H), 3.83 (t, J = 6.5 Hz, 2H), 3.77 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 152.47, 146.87, 142.76, 128.72, 127.21, 126.85, 114.82, 113.00, 77.48, 77.16, 76.84, 60.17, 55.96, 35.41. **LRMS** (DEP/EI-Orbitrap): m/z (%): 135 (96), 120 (100), 92 (10). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{16}H_{17}NO$: 239.1310; found: 239.1302. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2921 (vs), 2852 (s), 2721 (vw), 2675 (vw), 2353 (vw), 1730 (w), 1698 (vw), 1692 (vw), 1681 (vw), 1619 (vw), 1604 (vw), 1579 (vw), 1511 (m), 1492 (w), 1478 (w), 1461 (m), 1454 (m), 1441 (w), 1377 (w), 1366 (w), 1333 (w), 1288 (w), 1258 (m), 1237 (m), 1210 (w), 1181 (w), 1175 (w), 1163 (w), 1119 (m), 1087 (m), 1073 (m), 1051 (m), 1035 (m), 1029 (m), 1004 (w), 950 (w), 919 (w), 873 (vw), 822 (m), 799 (w), 789 (w), 762 (m), 749 (w), 741 (w), 722 (w), 709 (m). **Melting point**: mp = 87 °C.

3-Phenyl-1-(*o*-tolyl)azetidine (10b)

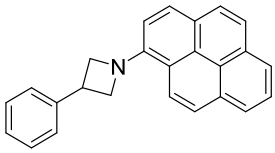


According to general procedure L, 3-phenylazetidine **9a** (37 mg, 0.28 mmol, 1.4 equiv.), 2-bromotoluene (24 µL, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (3.4 mg, 2 mol%), Brettphos (2.1 mg, 2 mol%), and KO*t*Bu (31 mg, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 0.5 h. The now brownish mixture was cooled to rt and filtered over celite 545. After the filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo* the crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 99:1) to obtain the title compound as a colorless oil (44 mg, 0.198 mmol, 99 %). Gram-scale synthesis was performed with 3-phenylazetidine **9a** (0.93 g, 7 mmol, 1.4 equiv.), 2-bromotoluene (0.86 g, 5 mmol, 1.0 equiv.), xPhos Pd G3 (85 mg, 2 mol%), Brettphos (54 mg,

2 mol%) and KO^{t}Bu (0.79 g, 7 mmol, 1.4 equiv.), to afford the title compound as a colorless oil (1.06 g, 4.8 mmol, 95 %).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.42 – 7.31 (m, 4H), 7.28 – 7.22 (m, 1H), 7.13 (td, 7.4, 1.0 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 6.80 (td, J = 7.4, 1.0 Hz, 1H), 6.57 (m, 1H), 4.36 (t, J = 7.2 Hz, 2H), 3.97 – 3.84 (m, 3H), 2.26 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm) = 163.94, 160.22, 142.96, 139.78, 128.79, 127.11, 126.93, 97.46, 97.29, 77.48, 77.16, 76.84, 58.21, 53.32, 35.03. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 120 (23), 119 (100), 78 (11). **HRMS (EI):** for $C_{16}H_{17}N$: calc. [M$^+$]: 223.1361; found: 223.1351. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 3062 (w), 3028 (w), 2954 (m), 2923 (m), 2852 (m), 2726 (vw), 2606 (vw), 2358 (vw), 2340 (vw), 2331 (vw), 2199 (vw), 1940 (vw), 1764 (vw), 1725 (s), 1693 (vw), 1681 (vw), 1673 (vw), 1600 (m), 1579 (w), 1510 (w), 1493 (s), 1477 (m), 1463 (m), 1454 (m), 1438 (m), 1413 (vw), 1401 (vw), 1378 (w), 1366 (w), 1310 (m), 1286 (s), 1272 (s), 1261 (s), 1208 (w), 1133 (m), 1121 (m), 1072 (s), 1051 (m), 1032 (m), 1018 (m), 987 (m), 955 (w), 947 (w), 923 (w), 907 (w), 889 (w), 884 (w), 878 (w), 872 (w), 796 (m), 749 (vs), 715 (m), 698 (s).

3-Phenyl-1-(pyren-1-yl)azetidine (10c)

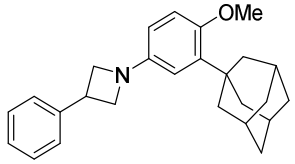


According to general procedure L, 3-phenylazetidine **9a** (37 mg, 0.28 mmol, 1.4 equiv.), 1-bromopyrene (56 mg, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (5.1 mg, 3 mol%), Brettphos (3.2 mg, 3 mol%), and KO^{t}Bu (31 mg, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 1.5 h. The now brownish mixture was cooled to rt and filtered over celite 545. After the filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo* the crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 99:1) to obtain the title compound as a colorless solid (65 mg, 0.195 mmol, 97 %).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 8.19 (d, J = 9.3 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.03 (dd, J = 7.4, 4.6 Hz, 2H), 7.96 – 7.88 (m, 3H), 7.83 (d, J = 8.4 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 4.82 (t, J = 7.8 Hz, 2H), 4.39 (t, J = 7.8 Hz, 2H), 4.14 – 4.05 (m, 1H). **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm) = 128.90, 127.67, 127.20, 127.12, 126.12, 125.81, 123.55, 122.96, 77.48, 77.16, 76.84, 62.90, 35.70. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 333 (27), 230 (15), 229 (82), 228 (100), 201 (42), 200 (28). **HRMS (EI):** for $C_{25}H_{19}N$: calc. [M$^+$]: 333.1517; found: 333.1510. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 3023 (w), 2952 (w), 2921 (w), 2865 (w), 2848 (m), 1887 (w), 1872 (w), 1726 (w), 1620 (w), 1600 (s), 1540 (w), 1511 (s), 1494 (m), 1478 (s), 1464 (m), 1452 (m), 1436 (s), 1410 (m), 1380 (s), 1359 (m), 1354 (m), 1348 (m), 1302 (s), 1294 (s), 1267 (m), 1238 (m), 1209 (m), 1195 (m), 1176 (m), 1147 (m), 1134 (s), 1086 (m), 1065 (m), 1052 (w), 1032 (w),

1016 (w), 998 (w), 976 (w), 957 (w), 943 (w), 936 (w), 906 (w), 882 (w), 837 (m), 824 (vs), 786 (m), 756 (s), 749 (vs), 710 (s), 696 (vs). **Melting point**: mp = 133 °C.

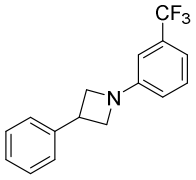
1-(3-(Adamantan-1-yl)-4-methoxyphenyl)-3-phenylazetidine (10d)



According to general procedure L, 3-phenylazetidine **9a** (37 mg, 0.28 mmol, 1.4 equiv.), 1-(5-bromo-2-methoxyphenyl)adamantane (64 mg, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (5.1 mg, 3 mol%), Brettphos (3.2 mg, 3 mol%), and KO^{t}Bu (31 mg, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 1 h. The now brownish mixture was cooled to rt and filtered over celite 545. After the filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo* the crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 99:1) to obtain the title compound as a colorless solid (71 mg, 0.19 mmol, 95 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.40 – 7.31 (m, 4H), 7.26 – 7.21 (m, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.45 (d, J = 2.8 Hz, 1H), 6.36 (dd, J = 8.6, 2.8 Hz, 1H), 4.26 (t, J = 7.1 Hz, 2H), 3.96 – 3.87 (m, 1H), 3.84 (t, J = 7.1 Hz, 2H), 3.78 (s, 3H), 2.09 (d, J = 2.6 Hz, 6H), 2.05 (s, 3H), 1.76 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 151.88, 146.47, 142.91, 139.67, 128.68, 127.23, 126.77, 113.31, 111.11, 109.50, 77.48, 77.16, 76.84, 60.06, 55.95, 40.72, 37.27, 37.20, 35.38, 29.26, 1.17. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 373 (10), 270 (20), 269 (100), 184 (19), 175 (13). **LRMS (EI):** for $C_{26}H_{31}NO$: calc. [M$^+$]: 373.2406; found: 373.2398. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2914 (m), 2900 (m), 2885 (m), 2849 (s), 2829 (w), 1728 (w), 1610 (w), 1605 (w), 1575 (m), 1491 (s), 1477 (m), 1460 (m), 1453 (m), 1446 (m), 1439 (m), 1414 (m), 1384 (w), 1377 (w), 1366 (w), 1357 (w), 1334 (m), 1316 (w), 1296 (m), 1287 (m), 1255 (m), 1225 (vs), 1210 (m), 1187 (m), 1179 (w), 1174 (w), 1150 (m), 1129 (m), 1099 (m), 1087 (w), 1061 (m), 1038 (m), 1034 (m), 1024 (m), 1000 (w), 979 (w), 976 (w), 964 (w), 907 (w), 856 (m), 816 (m), 801 (s), 792 (m), 769 (w), 763 (w), 755 (vs), 730 (w). **Melting point**: mp = 131 °C.

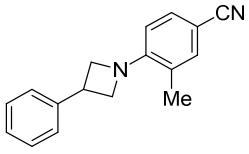
3-Phenyl-1-(3-(trifluoromethyl)phenyl)azetidine (10e):



According to general procedure L, 3-phenylazetidine **9a** (37 mg, 0.28 mmol, 1.4 equiv.), 1-bromo-3-(trifluoromethyl)benzene (28 µL, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (1.7 mg, 1 mol%), Brettphos (1.1 mg, 1 mol%), and KO^{t}Bu (31 mg, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 13 h. The now brownish mixture was cooled to rt and filtered over celite 545. After the filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo.* The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 98:2) to obtain the title compound as a colorless oil (51 mg, 0.18 mmol, 92 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.46 (d, J = 8.4 Hz, 2H), 7.39 – 7.33 (m, 4H), 7.30 – 7.24 (m, 1H), 6.50 (d, J = 8.4 Hz, 2H), 4.43 – 4.26 (m, 2H), 4.05 – 3.90 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 128.90, 127.17, 127.06, 126.47, 126.43, 110.77, 77.48, 77.16, 76.84, 59.30, 35.06. **^{19}F NMR (377 MHz, $CDCl_3$):** δ (ppm) = -60.94. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 173 (100), 172 (69), 145 (29), 104 (26), 78 (12). **HRMS (EI):** for $C_{16}H_{14}F_3N$: calc. [M^+]: 277.1078; found: 277.1070. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 3030 (vw), 2923 (w), 2918 (w), 2863 (w), 2847 (w), 2639 (vw), 2357 (vw), 1893 (vw), 1726 (w), 1638 (vw), 1609 (s), 1602 (m), 1581 (w), 1569 (w), 1528 (m), 1493 (w), 1477 (m), 1461 (w), 1454 (w), 1430 (vw), 1381 (m), 1353 (w), 1313 (vs), 1295 (s), 1260 (m), 1216 (w), 1179 (m), 1164 (s), 1150 (m), 1124 (s), 1105 (vs), 1062 (vs), 1047 (s), 1016 (m), 1003 (m), 998 (m), 977 (w), 955 (w), 949 (w), 939 (w), 916 (w), 880 (vw), 872 (vw), 855 (w), 824 (s), 811 (m), 772 (vw), 764 (s), 730 (w), 705 (s), 690 (m).

3-Methyl-4-(3-phenylazetidin-1-yl)benzonitrile (10f)

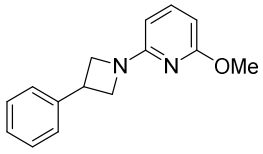


According to general procedure L, 3-phenylazetidine **9a** (37 mg, 0.28 mmol, 1.4 equiv.), 4-bromo-3-methylbenzonitrile (39 mg, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (3.4 mg, 2 mol%), Brettphos (2.1 mg, 2 mol%), and KO^{t}Bu (31 mg, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 1 h. The now brownish mixture was cooled to rt and filtered over celite 545. The filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo.* The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 95:5) to obtain the title compound as a colorless solid (42 mg, 0.17 mmol, 85 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.41 – 7.34 (m, 5H), 7.33 – 7.26 (m, 2H), 6.43 (d, J = 8.4 Hz, 1H), 4.49 (t, J = 8.0 Hz, 2H), 4.08 (t, J = 8.0 Hz, 2H), 3.91 (tt, J = 8.0, 6.0 Hz, 1H), 2.27 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 153.24, 142.06, 135.09, 131.29, 128.92, 127.25, 126.98, 124.53, 120.48, 112.53, 100.72, 77.48, 77.16, 76.84, 60.98, 34.93, 19.63.

LRMS (DEP/EI-Orbitrap): *m/z* (%): 144 (37), 143 (100), 116 (17), 104 (22). **HRMS (EI):** for $C_{17}H_{16}N_2$: calc. [M$^+$]: 248.1313; found: 248.1305. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2957 (w), 2923 (w), 2866 (w), 2852 (w), 2616 (vw), 2215 (s), 2165 (vw), 2161 (vw), 1736 (vw), 1723 (vw), 1599 (vs), 1561 (w), 1530 (vw), 1502 (vs), 1473 (s), 1453 (m), 1412 (m), 1374 (m), 1342 (s), 1334 (s), 1300 (m), 1289 (m), 1264 (w), 1223 (s), 1163 (m), 1156 (m), 1140 (m), 1116 (w), 1093 (m), 1082 (m), 1057 (m), 1033 (w), 1017 (m), 998 (m), 954 (w), 944 (w), 918 (w), 888 (w), 881 (m), 859 (vw), 817 (s), 757 (s), 724 (w), 698 (s). **Melting point**: mp = 79 °C.

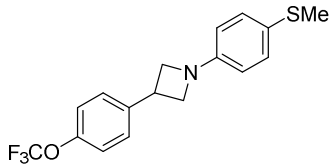
2-Methoxy-6-(3-phenylazetidin-1-yl)pyridine (10g):



According to general procedure L, 3-phenylazetidine **9a** (37 mg, 0.28 mmol, 1.4 equiv.), 2-bromo-6-methoxypyridine (25 µL, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (5.1 mg, 3 mol%), Brettphos (3.2 mg, 3 mol%), and KO^{t}Bu (31 mg, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 0.5 h. The now brownish mixture was cooled to rt and filtered over celite 545. After the filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo* the crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 99:1) to obtain the title compound as a colorless solid (47 mg, 0.197 mmol, 99 %).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.43 – 7.32 (m, 5H), 7.29 – 7.21 (m, 1H), 6.07 (d, *J* = 7.9 Hz, 1H), 5.90 (d, *J* = 7.9 Hz, 1H), 4.41 (t, *J* = 8.2 Hz, 2H), 4.03 (t, *J* = 8.2 Hz, 2H), 3.96 – 3.89 (m, 1H), 3.87 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm) = 163.93, 160.22, 142.96, 139.78, 128.78, 127.10, 126.93, 97.46, 97.29, 77.48, 77.16, 76.84, 58.21, 53.31, 35.03. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 240 (13), 136 (62), 135 (26), 109 (100), 80 (11). **HRMS (EI):** for $C_{15}H_{16}N_2O$: calc. [M$^+$]: 240.1263; found: 240.1255. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 3010 (vw), 2963 (w), 2928 (w), 2859 (w), 1727 (w), 1643 (vw), 1589 (s), 1574 (s), 1512 (w), 1486 (m), 1472 (s), 1455 (s), 1449 (s), 1411 (s), 1379 (m), 1350 (w), 1292 (m), 1281 (w), 1261 (s), 1250 (s), 1218 (m), 1204 (w), 1178 (w), 1138 (s), 1090 (w), 1080 (m), 1070 (w), 1021 (s), 978 (w), 960 (w), 916 (w), 839 (vw), 829 (vw), 782 (vs), 758 (s), 734 (m), 702 (vs), 679 (w). **Melting point**: mp = 99 °C.

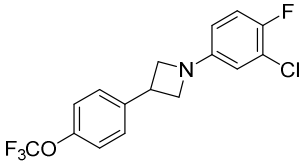
1-(4-(Methylthio)phenyl)-3-(4-(trifluoromethoxy)phenyl)azetidine (10h)



According to general procedure L, 3-(4-(trifluoromethoxy)phenyl)azetidine **9b** (61 mg, 0.28 mmol, 1.4 equiv.), (4-bromophenyl)(methyl)sulfane (41 mg, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (51 mg, 3 mol%), Brettphos (32 mg, 3 mol%), and KO*t*Bu (31 mg, 0.28 mmol, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 2 h. The now brownish mixture was cooled to rt and filtered over celite 545. The filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 97:3) to obtain the title compound as a colorless solid (58 mg, 0.17 mmol, 86 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.40 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 6.58 (s, 2H), 4.35 (t, J = 6.7 Hz, 2H), 4.02 – 3.95 (m, 1H), 3.92 (t, J = 6.7 Hz, 2H), 2.44 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 148.26, 130.76, 128.51, 121.44, 60.00, 34.52, 18.75. **^{19}F NMR (377 MHz, $CDCl_3$):** δ (ppm) = -57.92. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 339 (31), 151 (100), 136 (35). **HRMS (EI):** for: $C_{17}H_{16}F_3NOS$ calc. [M^+]: 339.0905; found: 339.0901. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2921 (w), 2853 (w), 1597 (w), 1508 (w), 1495 (m), 1479 (m), 1436 (w), 1345 (w), 1330 (m), 1322 (m), 1257 (vs), 1218 (s), 1188 (s), 1153 (s), 1129 (s), 1106 (s), 1095 (s), 1082 (s), 1062 (s), 1012 (s), 968 (w), 953 (w), 919 (w), 848 (m), 806 (vs), 739 (w), 712 (w), 703 (w). **Melting point**: mp = 109 °C.

1-(3-Chloro-4-fluorophenyl)-3-(4-(trifluoromethoxy)phenyl)azetidine (10i)

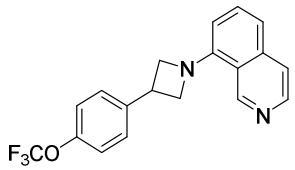


According to general procedure L, 3-(4-(trifluoromethoxy)phenyl)azetidine **9b** (61 mg, 0.28 mmol, 1.4 equiv.), 4-bromo-2-chloro-1-fluorobenzene (24 µL, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (5.1 mg, 3 mol%), Brettphos (3.2 mg, 3 mol%), and KO*t*Bu (31 mg, 0.28 mmol, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 3 h. The now brownish mixture was cooled to rt and filtered over celite 545. The filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 98:2) to obtain the title compound as a colorless solid (53 mg, 0.15 mmol, 77 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.39 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 7.01 (t, J = 8.9 Hz, 1H), 6.50 (dd, J = 6.1, 2.8 Hz, 1H), 6.33 (dt, J = 8.9, 2.8 Hz, 1H), 4.28 (t, J = 7.4

Hz, 2H), 3.92 (dt, J = 13.7, 7.4 Hz, 1H), 3.84 (t, J = 7.4 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 152.81, 150.44, 148.65, 148.26, 141.09, 128.47, 121.88, 121.42, 121.19, 119.33, 117.00, 116.78, 113.37, 111.16, 111.09, 59.93, 34.46. **^{19}F NMR (377 MHz, $CDCl_3$):** δ (ppm) = -57.92, -130.54. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 345 (12), 188 (68), 159 (28), 158 (15), 157 (100), 156 (25), 128 (11), 119 (10), 91 (11). **HRMS (EI):** for: $C_{16}H_{12}ClF_4NO$ calc. [M^+]: 345.0544; found: 345.0536. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2853 (w), 1607 (w), 1582 (w), 1501 (vs), 1479 (s), 1339 (w), 1253 (vs), 1221 (vs), 1199 (vs), 1154 (vs), 1109 (s), 1070 (m), 1052 (m), 1018 (m), 958 (w), 921 (w), 899 (vw), 835 (m), 803 (s), 713 (m), 686 (w). **Melting point**: mp = 92 °C.

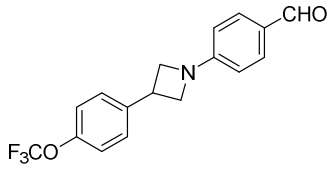
8-(3-(4-(Trifluoromethoxy)phenyl)azetidin-1-yl)isoquinoline (10j)



According to general procedure L, 3-(4-(trifluoromethoxy)phenyl)azetidine **9b** (61 mg, 0.28 mmol, 1.4 equiv.), 8-bromoisoquinoline (42 mg, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (68 mg, 4 mol%), Brettphos (42 mg, 4 mol%), and KO^{t}Bu (31 mg, 0.28 mmol, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 6 h. The now brownish mixture was cooled to rt and filtered over celite 545. The filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 7:3) to obtain the title compound as a colorless solid (50 mg, 0.15 mmol, 73 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.41 (s, 1H), 8.40 (d, J = 5.7 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 7.9 Hz, 1H), 7.23 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 7.9 Hz, 1H), 4.74 (t, J = 8.0 Hz, 2H), 4.29 (t, J = 8.0 Hz, 2H), 4.12 – 4.03 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 149.28, 148.37, 147.25, 140.79, 139.89, 138.03, 132.44, 128.45, 121.88, 121.55, 116.87, 109.28, 62.62, 35.08. **^{19}F NMR (377 MHz, $CDCl_3$):** δ (ppm) = -57.92. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 344 (30), 207 (17), 188 (18), 157 (12), 156 (100), 155 (78), 129 (71), 128 (28), 101 (14), 91 (12), 61 (14), 45 (12), 44 (24), 43 (84). **HRMS (EI):** for: $C_{19}H_{15}F_3N_2O$ calc. [M^+]: 344.1136; found: 344.1131. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2929 (vw), 2855 (w), 1613 (m), 1594 (vw), 1562 (s), 1509 (m), 1482 (w), 1445 (s), 1407 (s), 1369 (w), 1332 (m), 1311 (m), 1251 (s), 1219 (s), 1199 (s), 1150 (vs), 1108 (s), 1066 (m), 1052 (m), 1018 (m), 995 (w), 965 (w), 945 (w), 920 (w), 888 (vw), 847 (m), 824 (s), 806 (m), 795 (m), 739 (m), 671 (w). **Melting point**: mp = 107 °C.

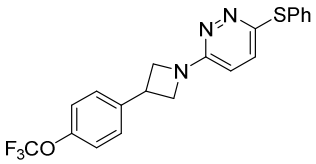
4-(3-(4-(Trifluoromethoxy)phenyl)azetidin-1-yl)benzaldehyde (10k)



According to general procedure L, 3-(4-(trifluoromethoxy)phenyl)azetidine **9b** (61 mg, 0.28 mmol, 1.4 equiv.), 4-bromobenzaldehyde (37 mg, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (51 mg, 3 mol%), Brettphos (32 mg, 3 mol%), and K_2CO_3 (39 mg, 0.28 mmol, 1.4 equiv.) in *t*BuOH (2 mL) were heated to 100 °C for 14 h. The now brownish mixture was cooled to rt and filtered over celite 545. The filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 8:2) to obtain the title compound as a colorless solid (38 mg, 0.12 mmol, 59 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.77 (s, 1H), 7.75 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 6.49 (d, J = 7.9 Hz, 2H), 4.45 (t, J = 7.7 Hz, 2H), 4.05 – 3.95 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 190.63, 154.91, 140.92, 132.10, 128.41, 126.60, 121.55, 110.44, 58.87, 34.25. **^{19}F NMR (377 MHz, $CDCl_3$):** δ (ppm) = -57.93. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 321 (19), 189 (10), 188 (97), 134 (10), 133 (100), 132 (67), 119 (13), 91 (16), 77 (18). **HRMS (EI):** for: $C_{17}H_{14}F_3NO_2$ calc. [M^+]: 321.0977; found: 321.0971. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2928 (w), 2862 (w), 2734 (w), 2646 (w), 1679 (m), 1592 (s), 1554 (m), 1527 (m), 1509 (m), 1474 (m), 1437 (w), 1392 (m), 1343 (w), 1326 (w), 1250 (s), 1217 (s), 1198 (s), 1145 (vs), 1108 (s), 1017 (m), 997 (m), 948 (w), 921 (w), 846 (m), 816 (s), 701 (w), 683 (m), 671 (m). **Melting point**: mp = 112 °C.

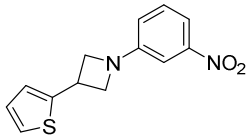
3-(Phenylthio)-6-(3-(4-(trifluoromethoxy)phenyl)azetidin-1-yl)pyridazine (10l)



According to general procedure L, 3-(4-(trifluoromethoxy)phenyl)azetidine **9b** (61 mg, 0.28 mmol, 1.4 equiv.), 3-bromo-6-(phenylthio)pyridazine (61 mg, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (68 mg, 4 mol%), Brettphos (42 mg, 4 mol%), and KO*t*Bu (31 mg, 0.28 mmol, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 5 h. The now brownish mixture was cooled to rt and filtered over celite 545. The filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 7:3) to obtain the title compound as a colorless solid (35 mg, 0.11 mmol, 53 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.53 – 7.50 (m, 2H), 7.42 – 7.31 (m, 5H), 7.21 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 9.2 Hz, 1H), 6.49 (d, J = 9.2 Hz, 1H), 4.54 (t, J = 8.4 Hz, 2H), 4.13 (t, J = 8.4 Hz, 2H), 4.05 – 3.96 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 159.02, 153.25, 148.21, 140.83, 133.11, 132.58, 129.42, 129.04, 128.29, 128.26, 121.39, 112.52, 77.35, 77.03, 76.71, 58.17, 34.74. **^{19}F NMR (377 MHz, $CDCl_3$):** δ (ppm) = -57.91. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 403 (21), 402 (19), 215 (19), 214 (100), 188 (15). **HRMS (EI):** for: $C_{20}H_{16}F_3N_3OS$ calc. [M^+]: 403.0966; found: 403.0958. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2920 (w), 2875 (w), 1585 (m), 1527 (w), 1508 (m), 1468 (s), 1440 (m), 1273 (s), 1234 (s), 1201 (s), 1154 (vs), 1104 (m), 1079 (m), 1069 (m), 1018 (m), 997 (w), 967 (w), 945 (w), 921 (w), 888 (w), 872 (w), 849 (s), 806 (m), 756 (w), 735 (s), 688 (m). **Melting point**: mp = 128 °C.

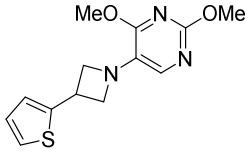
1-(3-Nitrophenyl)-3-(thiophen-2-yl)azetidine (10m)



According to general procedure L, 3-(thiophen-2-yl)azetidine **9c** (39 mg, 0.28 mmol, 1.4 equiv.), 1-bromo-3-nitrobenzene (40 mg, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (8.5 mg, 5 mol%), Brettphos (5.4 mg, 5 mol%), and $CsCO_3$ (91 mg, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 5 h. The now brownish mixture was cooled to rt and filtered over celite 545. After the filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 97:3) to obtain the title compound as a yellow crystalline solid (32 mg, 0.12 mmol, 62 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.59 (ddd, J = 8.1, 2.2, 0.7 Hz, 1H), 7.35 (t, J = 8.1 Hz, 1H), 7.28 (t, J = 2.2 Hz, 1H), 7.23 (dd, J = 4.6, 1.7 Hz, 1H), 7.00 – 6.95 (m, 2H), 6.75 (ddd, J = 8.1, 2.2, 0.7 Hz, 1H), 4.45 – 4.37 (m, 2H), 4.32 – 4.20 (m, 1H), 3.97 (t, J = 7.2 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 152.08, 149.33, 145.52, 129.78, 127.24, 124.55, 124.43, 117.44, 112.48, 106.03, 77.48, 77.16, 76.84, 60.67, 30.96. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 110 (100). **HRMS (EI):** for $C_{13}H_{12}N_2O_2S$: calc. [M^+]: 260.0619; found: 260.0615. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 3079 (vw), 3069 (vw), 2949 (w), 2922 (w), 2854 (w), 1737 (w), 1613 (m), 1572 (w), 1518 (vs), 1486 (m), 1474 (m), 1461 (m), 1442 (w), 1433 (w), 1396 (vw), 1380 (w), 1342 (s), 1325 (m), 1295 (m), 1287 (m), 1277 (m), 1260 (m), 1243 (m), 1223 (m), 1205 (w), 1160 (m), 1130 (m), 1117 (m), 1092 (w), 1078 (m), 1071 (m), 1039 (m), 1028 (m), 989 (m), 968 (w), 946 (w), 910 (vw), 883 (vw), 877 (w), 861 (m), 853 (m), 845 (m), 828 (m), 786 (m), 746 (w), 741 (vw), 730 (s), 720 (vs), 715 (vs), 671 (s). **Melting point**: mp = 97 °C.

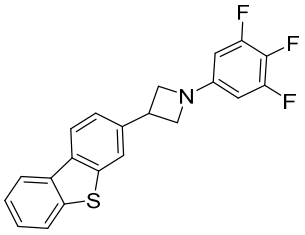
2,4-Dimethoxy-5-(3-(thiophen-2-yl)azetidin-1-yl)pyrimidine (10n)



According to general procedure L, 3-(thiophen-2-yl)azetidine **9c** (39 mg, 0.28 mmol, 1.4 equiv.), 5-bromo-2,4-dimethoxypyrimidine (44 mg, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (5.1 mg, 3 mol%), Brettphos (3.2 mg, 3 mol%), and KO^{t}Bu (31 mg, 0.28 mmol, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 6 h. The now brownish mixture was cooled to rt and filtered over celite 545. After the filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 97:3) to obtain the title compound as a colorless solid (26 mg, 0.09 mmol, 46 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.45 (s, 1H), 7.20 (dd, J = 5.0, 1.2 Hz, 1H), 7.00 – 6.90 (m, 2H), 4.31 (t, J = 7.7 Hz, 2H), 4.22 – 4.11 (m, 1H), 3.99 (s, 3H), 3.94 (s, 3H), 3.82 (t, J = 7.7 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 162.41, 159.33, 145.63, 139.44, 129.12, 127.15, 124.38, 124.17, 77.48, 77.16, 76.84, 62.09, 54.72, 54.01, 32.39. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 167 (100), 166 (68), 152 (16), 138 (52), 137 (19), 110 (22). **HRMS (EI):** for $C_{13}H_{15}N_3O_2S$: calc. [M^+]: 277.0885; found: 277.0881. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2853 (w), 1736 (vw), 1725 (vw), 1597 (w), 1564 (s), 1479 (m), 1463 (s), 1455 (s), 1407 (s), 1374 (vs), 1297 (s), 1259 (m), 1239 (s), 1187 (m), 1130 (w), 1075 (s), 1014 (s), 1002 (m), 961 (w), 938 (w), 919 (w), 901 (w), 845 (w), 823 (w), 802 (w), 781 (m), 759 (w). **Melting point**: mp = 92 °C.

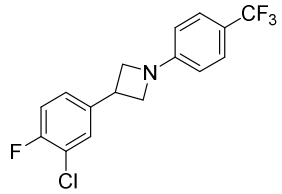
3-(Dibenzo[b,d]thiophen-3-yl)-1-(3,4,5-trifluorophenyl)azetidine (10o)



According to general procedure L, 3-(dibenzo[b,d]thiophen-3-yl)azetidine **9e** (67 mg, 0.28 mmol, 1.4 equiv.), 5-bromo-1,2,3-trifluorobenzene (24 µL, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (51 mg, 3 mol%), Brettphos (32 mg, 3 mol%), and KO^{t}Bu (31 mg, 0.28 mmol, 1.4 equiv.) in toluene (2 mL) were heated to 100 °C for 4 h. The now brownish mixture was cooled to rt and filtered over celite 545. The filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 97:3) to obtain the title compound as a colorless solid (44 mg, 0.12 mmol, 60 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.22 – 8.14 (m, 1H), 8.12 (d, J = 1.7 Hz, 1H), 7.91 – 7.81 (m, 2H), 7.54 – 7.42 (m, 3H), 6.08 (dd, J = 9.8, 5.6 Hz, 2H), 4.34 (t, J = 7.5 Hz, 2H), 4.10 (ddd, J = 14.0, 7.5, 5.9 Hz, 1H), 3.95 (t, J = 7.5 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 139.93, 138.43, 138.17, 135.94, 135.19, 126.95, 125.71, 124.44, 123.16, 122.95, 121.62, 119.81, 95.53, 95.28, 77.34, 77.03, 76.71, 59.86, 34.72. **^{19}F NMR (377 MHz, $CDCl_3$):** δ (ppm) = -122.48, -122.50, -134.52, -134.54, -134.57, -134.60, -175.71, -175.72, -175.74, -175.77, -175.78, -175.80, -175.82, -175.84, -175.85. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 211 (13), 210 (100). **HRMS (EI):** for: $C_{21}H_{14}F_3NS$ calc. [M^+]: 369.0799; found: 369.0806. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2919 (w), 2851 (m), 1641 (m), 1628 (m), 1592 (m), 1574 (m), 1526 (s), 1509 (s), 1471 (s), 1444 (m), 1431 (m), 1392 (w), 1368 (m), 1298 (m), 1259 (m), 1239 (vs), 1209 (s), 1188 (w), 1156 (m), 1136 (m), 1106 (m), 1083 (w), 1069 (w), 1024 (s), 924 (w), 879 (m), 823 (s), 808 (s), 776 (w), 762 (s), 732 (s), 718 (w). **Melting point**: mp = 113 °C.

3-(3-Chloro-4-fluorophenyl)-1-(4-(trifluoromethyl)phenyl)azetidine (10p)

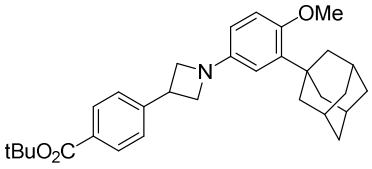


According to general procedure L, 3-(3-chloro-4-fluorophenyl)azetidine **9f** (0.40 g, 1.4 mmol, 1.4 equiv.), 1-bromo-4-(trifluoromethyl)benzene (0.14 mL, 1.0 mmol, 1.0 equiv.), xPhos Pd G3 (25 mg, 3 mol%), Brettphos (16 mg, 3 mol%), and KO^{t}Bu (0.16 g, 0.28 mmol, 1.4 equiv.) in toluene (10 mL) were heated to 100 °C for 7 h. The now brownish mixture was cooled to rt and filtered over celite 545. The filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 98:2) to obtain the title compound as a colorless solid (0.29 g, 0.88 mmol, 88 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.47 (d, J = 8.4 Hz, 2H), 7.43 (dd, J = 6.9, 2.2 Hz, 1H), 7.24 (ddd, J = 8.6, 4.6, 2.2 Hz, 1H), 7.12 (t, J = 8.6 Hz, 1H), 6.50 (d, J = 8.4 Hz, 2H), 4.38 – 4.31 (m, 2H), 3.94 – 3.84 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 158.51, 156.04, 153.39, 139.58, 139.54, 129.25, 126.82, 126.75, 126.55, 126.51, 126.47, 126.44, 123.75, 121.45, 121.27, 119.66, 119.34, 119.01, 117.04, 116.84, 110.92, 77.48, 77.16, 76.84, 59.23, 34.28. **^{19}F NMR (377 MHz, $CDCl_3$):** δ (ppm) = -61.02, -117.80, -117.81, -117.82, -117.82, -117.83, -117.84, -117.84, -117.86. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 329 (11), 174 (10), 173 (100), 172 (36), 158 (17), 156 (53), 145 (29), 121 (10), 42 (31). **HRMS (EI):** for: $C_{16}H_{12}ClF_4N$ calc. [M^+]: 329.0594; found: 329.0590. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2858 (w), 2359 (w), 1611 (m), 1573 (w), 1526 (w), 1500 (s), 1482 (m), 1417 (w), 1365 (m), 1326 (m), 1315 (m), 1298 (m), 1265 (w), 1249 (m), 1207 (m), 1181 (w), 1151 (m), 1124 (m), 1100 (vs), 1062 (s),

1002 (w), 961 (w), 940 (w), 875 (w), 854 (w), 821 (s), 727 (w), 708 (w). **Melting point**: mp = 92 °C.

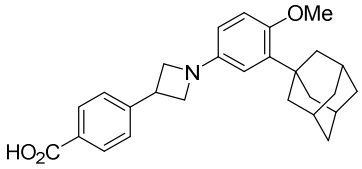
tert-Butyl 4-(1-(3-(adamantan-1-yl)-4-methoxyphenyl)azetidin-3-yl)benzoate (10q)



According to general procedure L, *tert*-butyl 4-(azetidin-3-yl)benzoate **9g** (65 mg, 0.28 mmol, 1.4 equiv.), 1-(5-bromo-2-methoxyphenyl)adamantane (64 mg, 0.2 mmol, 1.0 equiv.), xPhos Pd G3 (8.5 mg, 5 mol%), Brettphos (5.4 mg, 5 mol%), and K_2CO_3 (39 mg, 0.28 mmol, 1.4 equiv.) in DME (2 mL) were heated to 100 °C for 48 h. The now brownish mixture was cooled to rt and filtered over celite 545. The filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 95:5) to obtain the title compound as a brown solid (65 mg, 0.14 mmol, 68 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.95 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 6.82 (d, J = 8.6 Hz, 1H), 6.45 (d, J = 2.8 Hz, 1H), 6.36 (dd, J = 8.6, 2.8 Hz, 1H), 4.27 (t, J = 7.3 Hz, 2H), 3.93 (dt, J = 13.8, 7.3 Hz, 1H), 3.84 (t, J = 7.3 Hz, 2H), 3.78 (s, 3H), 2.07 (d, J = 13.1 Hz, 9H), 1.76 (s, 6H), 1.59 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 165.68, 151.87, 147.59, 146.09, 139.60, 130.44, 129.74, 126.92, 113.17, 110.96, 109.38, 80.95, 77.35, 77.03, 76.71, 59.64, 55.81, 40.57, 37.13, 37.08, 35.17, 29.12, 28.23. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 473 (32), 270 (20), 269 (100), 197 (12), 131 (10). **HRMS (EI):** for: $C_{31}H_{39}NO_3$ calc. [M^+]: 473.2930; found: 473.2926. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2823 (m), 2290 (m), 1645 (s), 1587 (m), 1571 (m), 1481 (s), 1466 (s), 1423 (m), 1412 (s), 1330 (w), 1319 (m), 1286 (vs), 1229 (s), 1199 (w), 1179 (m), 1055 (m), 1019 (w), 860 (m), 803 (m), 791 (m). **Melting point**: mp = 143 °C.

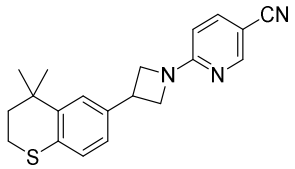
4-(1-(3-(Adamantan-1-yl)-4-methoxyphenyl)azetidin-3-yl)benzoic acid (10r)



tert-Butyl 4-(1-(3-(adamantan-1-yl)-4-methoxyphenyl)azetidin-3-yl)benzoate **10q** (47 mg, 0.1 mmol, 1.0 equiv.) was suspended in DCM (1 mL) and treated with $ZnBr_2$ (0.11 g, 0.5 mmol, 5.0 equiv.). After stirring for 14 h, the solvent was removed *in vacuo,* and the crude mixture was purified by flash column chromatography (silica gel, DCM/MeOH = 9.5:0.5) to obtain the title compound as a brown solid (36 mg, 0.09 mmol, 87 %).

^{1}H NMR (400 MHz, DMSO-D$_6$): δ (ppm) = 12.89 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 6.89 – 6.79 (m, 1H), 6.37 – 6.28 (m, 2H), 4.19 (t, J = 7.4 Hz, 2H), 4.02 – 3.92 (m, 1H), 3.72 (d, J = 6.6 Hz, 5H), 2.02 (s, 9H), 1.72 (s, 6H). **^{13}C NMR (100 MHz, DMSO-D$_6$):** δ (ppm) = 167.22, 151.23, 147.93, 146.15, 138.31, 129.62, 129.09, 127.17, 113.43, 110.23, 109.50, 59.10, 55.77, 40.20, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 36.58, 36.43, 34.23, 28.41. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 417 (32), 270 (20), 269 (100), 184 (26), 184 (13), 148 (14), 134 (11), 131 (10). **HRMS (ESI):** for: $C_{27}H_{30}NO_3$ calc. [M$^+$]: 417.2304; found: 417.2309. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2850 (m), 2363 (m), 1675 (vs), 1608 (s), 1574 (m), 1496 (s), 1478 (m), 1448 (m), 1432 (s), 1418 (s), 1332 (m), 1319 (m), 1294 (s), 1229 (vs), 1193 (m), 1179 (m), 1037 (m), 1019 (m), 860 (m), 803 (m), 791 (m). **Melting point**: mp = 130 °C.

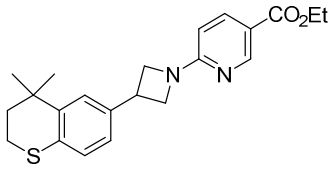
6-(3-(4,4-Dimethylthiochroman-6-yl)azetidin-1-yl)nicotinonitrile (10s)



According to general procedure L, 3-(4,4-dimethylthiochroman-6-yl)azetidine **9d** (54 mg, 0.28 mmol, 1.4 equiv.), 2-bromo-5-cyanopyridine (37 mg, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (8.5 mg, 5 mol%), Brettphos (5.4 mg, 5 mol%), and KO*t*Bu (31 mg, 0.28 mmol, 1.4 equiv.) in *t*BuOH (2 mL) were heated to 100 °C for 1 h. The now brownish mixture was cooled to rt and filtered over celite 545. After that, the filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 4:1) to obtain the title compound as a colorless solid (56 mg, 0.17 mmol, 83 %).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) = 8.42 (dd, J = 2.2, 0.8 Hz, 1H), 7.60 (dd, J = 8.8, 2.2 Hz, 1H), 7.27 (d, J = 1.9 Hz, 1H), 7.12 – 7.04 (m, 2H), 6.27 (dd, J = 8.7, 0.9 Hz, 1H), 4.50 (t, J = 8.7 Hz, 2H), 4.11 (dd, J = 8.7, 6.0 Hz, 2H), 3.92 (tt, J = 8.6, 6.0 Hz, 1H), 3.06 – 2.98 (m, 2H), 2.00 – 1.92 (m, 2H), 1.33 (s, 6H). **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm) = 153.37, 142.44, 139.37, 137.44, 127.29, 125.37, 124.33, 105.10, 77.48, 77.16, 76.84, 57.76, 37.72, 34.49, 33.23, 30.34, 23.19, 1.17. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 205 (15), 204 (100), 189 (36), 156 (18). **HRMS (EI):** for $C_{20}H_{21}N_3S$: calc. [M$^+$]: 335.1456; found: 335.1450. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2935 (w), 2880 (w), 2217 (m), 1598 (vs), 1543 (m), 1502 (s), 1469 (s), 1418 (s), 1401 (s), 1364 (m), 1347 (w), 1302 (m), 1279 (m), 1249 (m), 1207 (m), 1188 (w), 1173 (w), 1159 (w), 1141 (m), 1108 (m), 1072 (w), 1056 (m), 1022 (w), 1007 (m), 989 (w), 967 (w), 942 (w), 891 (w), 826 (m), 814 (s), 782 (w), 750 (w). **Melting point**: mp = 131 °C.

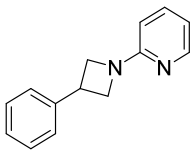
Ethyl 6-(3-(4,4-dimethylthiochroman-6-yl)azetidin-1-yl)nicotinate (10t)



According to general procedure L, 3-(4,4-dimethylthiochroman-6-yl)azetidine **9d** (54 mg, 0.28 mmol, 1.4 equiv.), ethyl 6-bromonicotinate (46 mg, 0.20 mmol, 1.0 equiv.), xPhos Pd G3 (8.5 mg, 5 mol%), Brettphos (5.4 mg, 5 mol%), and K_2CO_3 (39 mg, 0.28 mmol, 1.4 equiv.) in *t*BuOH (2 mL) were heated to 100 °C for 3 days. The now brownish mixture was cooled to rt and filtered over celite 545. After that, the filter cake was washed with ethyl acetate (3 × 10 mL) and the filtrate was concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 9:1) to obtain the title compound as a light brown solid (68 mg, 0.18 mmol, 89 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.82 – 8.81 (m, 1H), 8.02 (dd, J = 8.8, 2.2 Hz, 1H), 7.28 (s, 1H), 7.08 (d, J = 1.5 Hz, 2H), 6.26 (d, J = 9.3 Hz, 1H), 4.50 (t, J = 8.6 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 4.11 (dd, J = 8.4, 6.1 Hz, 2H), 3.90 (ddd, J = 14.5, 8.7, 6.0 Hz, 1H), 3.05 – 3.00 (m, 2H), 1.99 – 1.91 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H), 1.33 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 166.31, 166.21, 161.54, 151.64, 151.59, 142.34, 138.25, 138.10, 137.87, 130.70, 127.20, 125.39, 124.46, 115.15, 104.54, 104.44, 77.48, 77.16, 76.84, 60.67, 60.59, 57.89, 37.76, 34.75, 34.59, 34.55, 33.22, 30.35, 29.85, 23.18, 14.54. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 205 (17), 204 (100), 189 (34), 156 (13), 97 (11), 83 (11), 71 (12), 69 (14), 57 (15), 55 (17), 43 (12), 42 (12), 39 (12). **HRMS (EI):):** for $C_{22}H_{26}N_2O_2S$: calc. [M^+]: 382.1715; found: 382.1704. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2920 (m), 2872 (w), 2854 (m), 2710 (vw), 2550 (vw), 2360 (vw), 1701 (s), 1599 (s), 1555 (m), 1523 (s), 1473 (m), 1461 (m), 1436 (s), 1411 (m), 1386 (w), 1365 (m), 1297 (m), 1267 (vs), 1172 (m), 1153 (m), 1107 (vs), 1054 (m), 1038 (m), 1017 (m), 1003 (m), 961 (w), 922 (w), 886 (w), 868 (w), 832 (m), 816 (w), 779 (s), 733 (w), 721 (w). **Melting point**: mp = 126 °C.

2-(3-Phenylazetidin-1-yl)pyridine (7a)

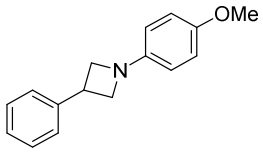


Following general procedure K, with phenylmagnesiumchloride (0.6 mmol, 2.0 equiv.). After quenching with KO^{t}Bu (134 mg, 4.0 equiv.) the mixture was transferred to a pressure tube containing 2-bromopyridine (24 µL, 0.20 mmol, 0.67 equiv.), xPhos Pd G3 (5.1 mg, 3 mol%), Brettphos (3.2 mg, 3 mol%). After heating to 100 °C for 14 h, the grey suspension was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 15 mL). The combined

organic phases were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 9:1) over silica gel to give 1-(4-methoxyphenyl)-3-phenylazetidine as a colorless oil (29 mg, 0.14 mmol, 68 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.19 (ddd, J = 5.1, 2.0, 0.9 Hz, 1H), 7.47 (ddd, J = 8.7, 7.2, 1.9 Hz, 1H), 7.41 – 7.32 (m, 4H), 7.29 – 7.23 (m, 1H), 6.63 (ddd, J = 7.2, 5.1, 1.1 Hz, 1H), 6.35 (dd, J = 8.4, 1.1 Hz, 1H), 4.45 (t, J = 8.1 Hz, 2H), 4.07 (dd, J = 7.8, 6.0 Hz, 2H), 3.95 ppm (ddd, J = 14.4, 8.4, 6.0 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 160.9, 148.3, 142.8, 137.2, 128.8, 127.1, 127.0, 113.1, 106.1, 58.1, 35.0 ppm. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 210.1 (37), 181.1 (14), 104.1 (100), 79.0 (65). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{14}H_{14}N_2$: 210.1157; found: 210.1148. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3061 (w), 3026 (w), 3008 (w), 2951 (w), 2862 (w), 1756 (w), 1589 (s), 1557 (m), 1490 (s), 1472 (vs), 1454 (m), 1436 (vs), 1374 (m), 1351 (m), 1301 (m), 1294 (m), 1273 (m), 1147 (s), 1081 (m), 1062 (w), 1025 (m), 977 (m), 947 (w), 907 (w), 880 (w), 846 (w), 772 (s), 756 (s), 735 (s), 723 (m), 715 (m), 697 (vs), 675 (m), 673 (m), 669 (m), 667 (m), 661 (m), 657 (m), 655 cm^{-1} (w).

1-(4-Methoxyphenyl)-3-phenylazetidine (10a)

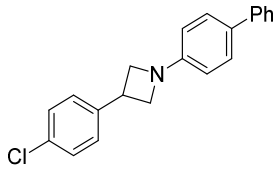


Following general procedure K, with phenylmagnesiumchloride (0.6 mmol, 2.0 equiv.). After quenching with KO^{t}Bu (134 mg, 4.0 equiv.) the mixture was transferred to a pressure tube containing 4-bromoanisole (25 µL, 0.20 mmol, 0.67 equiv.), xPhos Pd G3 (5.1 mg, 3 mol%), Brettphos (3.2 mg, 3 mol%). After heating to 100 °C for 14 h, the grey suspension was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 98:2) over silica gel to give 1-(4-methoxyphenyl)-3-phenylazetidine as a colorless solid (35 mg, 0.14 mmol, 72 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.40 – 7.31 (m, 4H), 7.25 – 7.22 (m, 1H), 6.88 – 6.81 (m, 2H), 6.53 – 6.46 (m, 2H), 4.26 (t, *J* = 6.5 Hz, 2H), 3.97 – 3.88 (m, 1H), 3.83 (t, *J* = 6.5 Hz, 2H), 3.77 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 152.47, 146.87, 142.76, 128.72, 127.21, 126.85, 114.82, 113.00, 77.48, 77.16, 76.84, 60.17, 55.96, 35.41. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 135 (96), 120 (100), 92 (10). **HRMS (EI):** for $C_{16}H_{17}NO$: calc. $[M^+]$: 239.1310; found: 239.1302. **IR (Diamond-ATR, neat):** $\tilde{\nu}$/ cm^{-1} = 2921 (vs), 2852 (s), 2721 (vw), 2675 (vw), 2353 (vw), 1730 (w), 1698 (vw), 1692 (vw), 1681 (vw), 1619 (vw), 1604 (vw), 1579 (vw), 1511 (m), 1492 (w), 1478 (w), 1461 (m), 1454 (m), 1441 (w), 1377 (w), 1366 (w), 1333 (w),

1288 (w), 1258 (m), 1237 (m), 1210 (w), 1181 (w), 1175 (w), 1163 (w), 1119 (m), 1087 (m), 1073 (m), 1051 (m), 1035 (m), 1029 (m), 1004 (w), 950 (w), 919 (w), 873 (vw), 822 (m), 799 (w), 789 (w), 762 (m), 749 (w), 741 (w), 722 (w), 709 (m). **Melting point**: mp = 87 °C.

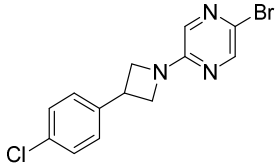
1-([1,1'-Biphenyl]-4-yl)-3-(4-chlorophenyl)azetidine (11a)



Following general procedure K, with (4-chlorophenyl)magnesium bromide (0.6 mmol, 2.0 equiv.). After quenching with KO*t*Bu (134 mg, 4.0 equiv.) the mixture was transferred to a pressure tube containing 4-bromobiphenyl (47 mg, 0.20 mmol, 0.67 equiv.), xPhos Pd G3 (6.8 mg, 4 mol%), Brettphos (4.3 mg, 4 mol%). After heating to 100 °C for 14 h, the grey suspension was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 99:1) to give 1-([1,1'-biphenyl]-4-yl)-3-(4-chlorophenyl)azetidine as a colorless solid (33 mg, 0.10 mmol, 51 %).

^{1}H NMR (400 MHz, CD_3CN): δ (ppm) = 7.60 – 7.56 (m, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.44 – 7.35 (m, 6H), 7.27 (t, J = 7.5 Hz, 1H), 6.60 (d, J = 8.6 Hz, 2H), 4.30 (t, J = 7.5 Hz, 1H), 3.99 – 3.91 (m, 1H), 3.86 (t, J = 7.5 Hz, 2H). **^{13}C NMR (100 MHz, CD_3CN):** δ (ppm) = 152.53, 142.99, 142.00, 132.77, 130.85, 129.76, 129.72, 129.50, 128.37, 127.17, 127.01, 112.94, 60.02, 35.25. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 319 (14), 182 (12), 181 (100), 153 (14), 152 (14). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{21}H_{18}ClN$: 319.1128; found: 319.1127. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3032 (w), 2924 (w), 2860 (w), 2842 (w), 1607 (m), 1596 (m), 1526 (m), 1488 (s), 1416 (w), 1398 (w), 1363 (m), 1331 (m), 1279 (w), 1254 (w), 1219 (w), 1205 (m), 1181 (w), 1158 (w), 1138 (m), 1123 (w), 1107 (w), 1090 (m), 1078 (m), 1042 (w), 1013 (m), 991 (w), 942 (w), 889 (w), 835 (w), 817 (vs), 759 (vs), 735 (w), 714 (m). **Melting point**: mp = 145 °C.

2-Bromo-5-(3-(4-chlorophenyl)azetidin-1-yl)pyrazine (11b)

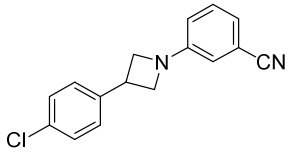


Following general procedure K, with (4-chlorophenyl)magnesium bromide (0.6 mmol, 2.0 equiv.). After quenching with KO*t*Bu (134 mg, 4.0 equiv.) the mixture was transferred to a pressure tube containing 2,5-dibromopyrazine (48 mg, 0.20 mmol, 0.67 equiv.), xPhos Pd G3 (5.1 mg, 3 mol%), Brettphos (3.2 mg, 3 mol%). After heating to 100 °C for 14 h, the grey

suspension was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 9:1) to give 2-bromo-5-(3-(4-chlorophenyl)azetidin-1-yl)pyrazine as a yellow solid (31 mg, 0.09 mmol, 47 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.13 (d, J = 1.3 Hz, 1H), 7.60 (d, J = 1.3 Hz, 1H), 7.40 – 7.28 (m, 4H), 4.50 (t, J = 8.4 Hz, 2H), 4.11 – 4.06 (m, 2H), 4.05 – 3.94 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 154.15, 143.51, 140.10, 133.11, 129.93, 129.03, 128.20, 126.34, 77.35, 77.03, 76.72, 58.24, 34.73. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 140 (33), 138 (100), 103 (29). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{13}H_{11}BrClN_3$: 322.9825; found: 322.9817. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2869 (w), 1564 (s), 1512 (m), 1493 (m), 1472 (vs), 1394 (w), 1292 (w), 1192 (w), 1167 (w), 1114 (m), 1094 (m), 1014 (w), 1002 (w), 822 (m). **Melting point**: mp = 138 °C.

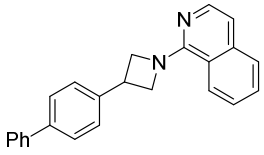
3-(3-(4-Chlorophenyl)azetidin-1-yl)benzonitrile (11c)



Following general procedure K, with (4-chlorophenyl)magnesium bromide (0.6 mmol, 2.0 equiv.). After quenching with KO^{t}Bu (134 mg, 4.0 equiv.) the mixture was transferred to a pressure tube containing 3-bromobenzonitrile (36 mg, 0.20 mmol, 0.67 equiv.), xPhos Pd G3 (6.8 mg, 4 mol%), Brettphos (4.3 mg, 4 mol%). After heating to 100 °C for 14 h, the grey suspension was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 98:2) to give 3-(3-(4-chlorophenyl)azetidin-1-yl)benzonitrile as a colorless oil (25 mg, 0.09 mmol, 47 %).

^{1}H NMR (400 MHz, CD_3CN): δ (ppm) = 7.41 – 7.30 (m, 5H), 7.03 (dt, J = 7.6, 1.2 Hz, 1H), 6.81 – 6.73 (m, 2H), 4.29 (t, J = 7.8 Hz, 2H), 4.00 – 3.91 (m, 1H), 3.85 (t, J = 7.8 Hz, 2H). **^{13}C NMR (100 MHz, CD_3CN):** δ (ppm) = 152.89, 142.62, 132.89, 130.80, 129.66, 129.53, 121.46, 120.21, 116.87, 115.22, 113.24, 59.82, 35.07. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 140 (27), 138 (100), 130 (12), 103 (16), 102 (11). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{16}H_{13}ClN_2$: 268.0767; found: 268.0766. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2925 (m), 2855 (m), 2225 (m), 1735 (w), 1598 (vs), 1573 (s), 1526 (w), 1491 (s), 1474 (s), 1438 (s), 1416 (m), 1365 (s), 1341 (m), 1323 (m), 1292 (m), 1259 (m), 1206 (m), 1173 (m), 1149 (m), 1123 (m), 1107 (m), 1091 (m), 1043 (w), 1013 (m), 985 (w), 962 (w), 883 (w), 860 (m), 844 (w), 820 (vs), 778 (s), 761 (m), 715 (w), 681 (s).

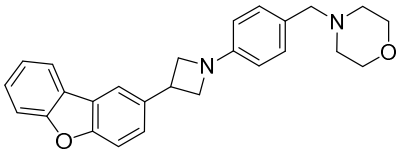
1-(3-([1,1'-Biphenyl]-4-yl)azetidin-1-yl)isoquinoline (11d)



Following general procedure K, with [1,1'-biphenyl]-4-ylmagnesium bromide (0.6 mmol, 2.0 equiv.). After quenching with KO*t*Bu (134 mg, 4.0 equiv.) the mixture was transferred to a pressure tube containing 1-bromoisoquinoline (42 mg, 0.20 mmol, 0.67 equiv.), xPhos Pd G3 (5.1 mg, 3 mol%), Brettphos (3.2 mg, 3 mol%). After heating to 100 °C for 14 h, the grey suspension was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 8:2) to give 1-(3-([1,1'-biphenyl]-4-yl)azetidin-1-yl)isoquinoline as a yellow solid (48 mg, 0.14 mmol, 71 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.09 (d, J = 5.8 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.63 – 7.56 (m, 5H), 7.51 (d, J = 8.4 Hz, 2H), 7.47 – 7.40 (m, 3H), 7.35 (t, J = 7.3 Hz, 1H), 7.05 (d, J = 5.8 Hz, 1H), 4.88 (t, J = 8.5 Hz, 2H), 4.55 – 4.49 (m, 2H), 4.06 (ddd, J = 14.7, 8.5, 6.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 158.83, 141.82, 141.24, 140.79, 139.90, 138.00, 129.64, 128.81, 127.46, 127.44, 127.29, 127.07, 126.99, 125.30, 124.77, 119.22, 112.33, 77.35, 77.03, 76.72, 60.99, 35.20. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 181 (14), 180 (100), 129 (15). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{24}H_{20}N_2$: 336.1626; found: 336.1622. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3030 (w), 2922 (m), 2857 (m), 1614 (w), 1583 (m), 1549 (s), 1504 (s), 1485 (m), 1453 (s), 1435 (vs), 1422 (vs), 1357 (s), 1314 (w), 1291 (s), 1268 (m), 1254 (m), 1218 (m), 1174 (w), 1157 (m), 1134 (m), 1120 (m), 1076 (w), 1052 (w), 1040 (w), 1021 (w), 1006 (m), 950 (w), 890 (w), 874 (m), 827 (m), 805 (s), 794 (m), 761 (vs), 750 (s), 722 (s), 690 (s). **Melting point**: mp = 106 °C.

4-(4-(3-(Dibenzo[b,d]furan-2-yl)azetidin-1-yl)benzyl)morpholine (11e)

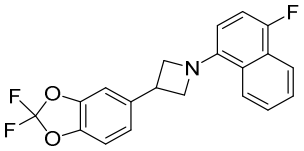


Following general procedure K, with dibenzo[b,d]furan-2-ylmagnesium bromide (0.6 mmol, 2.0 equiv.). After quenching with KO*t*Bu (134 mg, 4.0 equiv.) the mixture was transferred to a pressure tube containing 4-(4-bromobenzyl)morpholine (59 mg, 0.20 mmol, 0.67 equiv.), xPhos Pd G3 (8.5 mg, 5 mol%), Brettphos (5.4 mg, 5 mol%). After heating to 100 °C for 14 h, the grey suspension was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by

flash column chromatography (silica gel, *i*hexane/EtOAc = 1:1) to give 4-(4-(3-(dibenzo[b,d]furan-2-yl)azetidin-1-yl)benzyl)morpholine as a colorless solid (44 mg, 0.11 mmol, 56 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.99 (d, J = 1.6 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.55 (dd, J = 14.6, 8.3 Hz, 2H), 7.46 (ddd, J = 8.3, 6.1, 1.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 8.3 Hz, 2H), 6.53 (d, J = 8.3 Hz, 2H), 4.38 (t, J = 7.3 Hz, 2H), 4.08 (dt, J = 13.9, 7.3 Hz, 1H), 3.97 (t, J = 7.3 Hz, 2H), 3.71 (t, J = 4.6 Hz, 4H), 3.44 (s, 2H), 2.44 (s, 4H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 156.59, 155.20, 151.12, 137.39, 130.21, 127.26, 126.35, 124.54, 124.07, 122.75, 120.69, 118.86, 111.74, 111.61, 111.45, 77.35, 77.03, 76.71, 67.06, 63.16, 60.13, 53.53, 35.31. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 398 (29), 313 (26), 312 (100), 204 (33), 195 (10), 194 (63), 181 (20), 165 (16), 119 (16), 118 (100), 86 (12). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{26}H_{26}N_2O_2$: 398.1994; found: 398.1991. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2959 (w), 2948 (w), 2919 (w), 2894 (w), 2853 (m), 2801 (w), 2760 (w), 2688 (vw), 2359 (vw), 1746 (vw), 1609 (m), 1571 (vw), 1517 (s), 1477 (m), 1449 (m), 1432 (w), 1391 (w), 1369 (m), 1343 (s), 1331 (m), 1318 (m), 1297 (w), 1285 (w), 1262 (m), 1198 (s), 1172 (w), 1148 (m), 1113 (vs), 1072 (m), 1034 (w), 1023 (w), 1005 (m), 952 (w), 930 (w), 911 (w), 862 (s), 831 (m), 818 (s), 793 (m), 765 (w), 743 (vs), 728 (m). **Melting point**: mp = 126 °C.

3-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-fluoronaphthalen-1-yl)azetidine (11f)



Following general procedure K, with (2,2-difluorobenzo[d][1,3]dioxol-5-yl)magnesium bromide (0.6 mmol, 2.0 equiv.). After quenching with KO*t*Bu (134 mg, 4.0 equiv.) the mixture was transferred to a pressure tube containing 1-bromo-4-fluoronaphthalene (45 mg, 0.20 mmol, 0.67 equiv.), xPhos Pd G3 (5.1 mg, 3 mol%), Brettphos (3.2 mg, 3 mol%). After heating to 100 °C for 14 h, the grey suspension was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, *i*hexane/EtOAc = 95:5) to give 3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-fluoronaphthalen-1-yl)azetidine as a colorless oil (46 mg, 0.13 mmol, 64 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.09 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.57 – 7.45 (m, 2H), 7.26 (s, 1H), 7.14 – 7.01 (m, 3H), 6.53 (dd, J = 8.1, 4.4 Hz, 1H), 4.51 (t, J = 7.6 Hz, 2H), 4.03 (t, J = 7.6 Hz, 2H), 3.97 – 3.87 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 154.77, 152.35, 144.53, 144.50, 144.19, 142.62, 139.00, 134.22, 131.69, 129.15, 126.17, 126.13, 126.11, 125.51, 124.65, 124.47, 123.61, 123.58, 122.22, 121.11, 121.06, 109.33,

109.08, 108.87, 108.31, 107.53, 107.45, 77.36, 77.04, 76.72, 61.99, 35.56. **LRMS** (DEP/EI-Orbitrap): *m/z* (%): 357 (33), 174 (12), 173 (100), 172 (72), 146 (11), 145 (20), 83 (11). **HRMS** (EI) m/z: $[M]^+$ calcd for $C_{20}H_{14}F_3NO_2$: 357.0977; found: 357.0970. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2854 (vw), 1632 (vw), 1600 (w), 1582 (w), 1503 (m), 1463 (m), 1449 (w), 1430 (w), 1400 (m), 1341 (vw), 1292 (w), 1233 (vs), 1148 (s), 1102 (w), 1037 (m), 949 (w), 937 (vw), 900 (vw), 863 (vw), 810 (m), 789 (vw), 774 (w), 759 (m).

6. Single Crystal X-Ray Diffraction Studies

Single crystals of compound **3a**, suitable for X-ray diffraction, were obtained by slow evaporation of a CH_2Cl_2/ MeOH mixture in a NMR Tube. The X-ray intensity data of **3a** were measured on a Bruker D8 Venture TXS system equipped with a multilayer mirror monochromator and a Mo Kα rotating anode X-ray tube (λ = 0.71073 Å). The frames were integrated with the Bruker SAINT software package.[188] Data were corrected for absorption effects using the Multi-Scan method (SADABS).[189] The structure was solved and refined using the Bruker SHELXTL Software Package.[190] All hydrogen atoms have been calculated in ideal geometry riding on their parent atoms. The figures have been drawn at the 25 % ellipsoid probability level.[191]

[188] Bruker, **2012**. SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.
[189] G. M. Sheldrick, *SADABS*. **1996**, University of Göttingen, Germany.
[190] G. M. Sheldrick, *Acta Cryst.* **2015,** *71*, 3-8.
[191] L. J. Farrugia, *J. Appl. Cryst.* **2012,** *45*, 849-854.

Table 2: Details for X-ray data collection and structure refinement for compound **3a**.

	3a
Net formula	$C_{16}H_{17}NO_2S$
M_r/g mol^{-1}	287.36
Crystal size/mm	0.120 × 0.090 × 0.030
T/K	173.(2)
Radiation	MoKα
Diffractometer	'Bruker D8 Venture TXS
Crystal system	monoclinic
Space group	'P 1 21/c 1'
a/Å	15.2425(6)
b/Å	8.2235(3)
c/Å	11.6263(5)
α/°	90
β/°	100.9660(10)
γ/°	90
V/Å^3	1430.71(10)
Z	4
Calc. density/g cm^{-3}	1.334
μ/mm^{-1}	0.227
Absorption correction	Multi-Scan
Transmission factor range	0.95–0.99
Refls. measured	24576
R_{int}	0.0373
Mean $\sigma(I)/I$	0.0222
θ range	3.053–27.485
Observed refls.	2849
x, *y* (weighting scheme)	0.0484, 0.7417
Hydrogen refinement	constr
Flack parameter	?
Refls in refinement	3266
Parameters	182
Restraints	0
$R(F_{obs})$	0.0403
$R_w(F^2)$	0.1083
S	1.063
Shift/error$_{max}$	0.001
Max electron density/e Å^{-3}	0.257
Min electron density/e Å^{-3}	−0.455

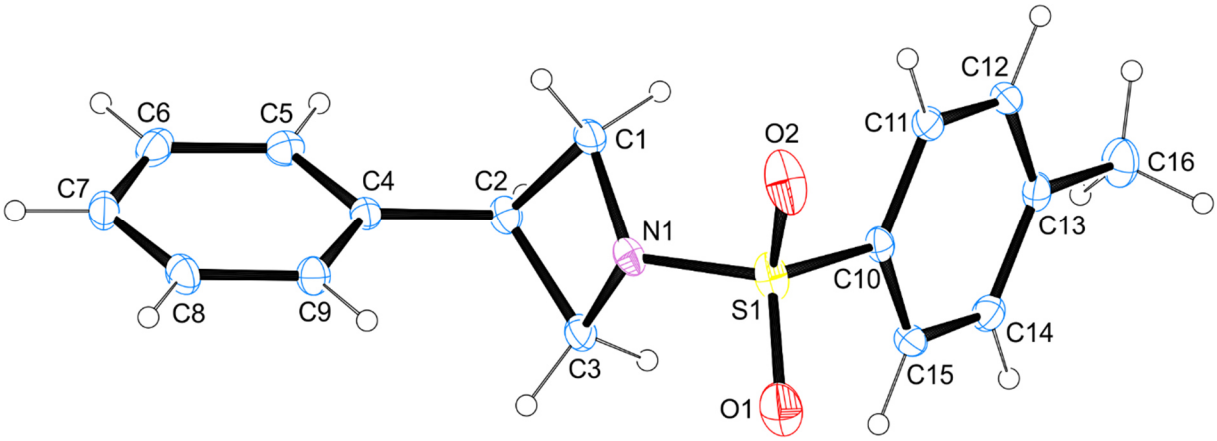


Figure 8: Molecular Structure of compound **3a** in the crystal. DIAMOND[192] representation; thermal ellipsoids are drawn at 25 % probability level.

Table 3: Selected bond lengths (Å) of compound **3a**.

S1-O1	1.4298(15)	C13-C14	1.394(2)
S1-O2	1.4332(14)	C13-C16	1.505(2)
S1-N1	1.6330(15)	C14-C15	1.380(2)
S1-C10	1.7582(15)	C1-H1AB	0.9900
N1-C1	1.488(2)	C1-H1A	0.9900
N1-C3	1.488(2)	C2-H2	1.0000
C1-C2	1.547(2)	C3-H3AB	0.9900
C2-C3	1.543(2)	C3-H3A	0.9900
C2-C4	1.506(2)	C5-H5	0.9500
C4-C5	1.389(2)	C6-H6	0.9500
C4-C9	1.392(2)	C7-H7	0.9500
C5-C6	1.391(2)	C8-H8	0.9500
C6-C7	1.377(2)	C9-H9	0.9500
C7-C8	1.383(3)	C11-H11	0.9500
C8-C9	1.392(2)	C12-H12	0.9500
C10-C11	1.390(2)	C14-H14	0.9500
C10-C15	1.391(2)	C15-H15	0.9500
C11-C12	1.382(2)	C16-H16A	0.9800
C12-C13	1.389(2)	C16-H16B	0.9800

[192] DIAMOND, Crystal Impact GbR., Version 3.2i

Table 4: Selected bond angles (°) of compound **3a**.

O1-S1-O2	120.65(10)	C12-C13-C16	120.95(14)
O1 -S1-N1	106.02(8)	C14-C13-C16	120.52(15)
O1 -S1-C10	107.92(8)	C13-C14-C15	120.84(15)
O2 -S1-N1	105.58(8)	C10-C15-C14	119.63(14)
O2-S1-C10	108.56(8)	N1-C1-H1AB	114.00
N1-S1-C10	107.45(7)	N1-C1-H1A	114.00
S1 -N1-C1	122.13(11)	C2-C1-H1AB	114.00
S1-N1-C3	122.26(11)	C2-C1-H1A	114.00
C1-N1-C3	91.33(12)	H1AB-C1-H1A	111.00
N1-C1-C2	88.65(12)	C1-C2-H2	112.00
C1-C2-C3	87.06(12)	C3-C2-H2	112.00
C1-C2-C4	115.91(12)	C4-C2-H2	112.00
C3-C2-C4	116.90(13)	N1-C3-H3AB	114.00
N1-C3-C2	88.77(12)	N1-C3-H3A	114.00
C2-C4-C5	119.34(14)	C2-C3-H3AB	114.00
C2-C4-C9	122.44(14)	C2-C3-H3A	114.00
C5-C4-C9	118.22(14)	H3AB-C3-H3A	111.00
C4-C5-C6	121.12(15)	C4-C5-H5	119.00
C5-C6-C7	120.04(16)	C6-C5-H5	119.00
C6-C7-C8	119.75(16)	C5-C6-H6	120.00
C7-C8-C9	120.18(16)	C7-C6-H6	120.00
C4-C9-C8	120.68(15)	C6-C7-H7	120.00
S1-C10-C11	120.07(12)	C8-C7-H7	120.00
S1-C10-C15	119.38(11)	C7-C8-H8	120.00
C11-C10-C15	120.43(14)	C9-C8-H8	120.00
C10-C11-C12	119.07(14)	C4-C9-H9	120.00
C11-C12-C13	121.49(14)	C8-C9-H9	120.00
C12-C13-C14	118.54(15)	C10-C11-H11	120.00

Table 5: Selected torsion angles (°) of compound **3a**.

O1-S1-N1-C1	-170.10(12)	C3-C2-C4-C9	28.8(2)
O1-S1-N1-C3	-54.71(14)	C1-C2-C4-C9	-71.67(19)
O2-S1-N1-C1	60.81(14)	C1-C2-C3-N1	15.12(11)
O2-S1-N1-C3	176.20(13)	C2-C4-C5-C6	178.17(15)
C10-S1-N1-C1	-54.91(13)	C9-C4-C5-C6	-1.6(2)
C10-S1-N1-C3	60.49(14)	C2-C4-C9-C8	-178.75(15)
O1-S1-C10-C11	-154.46(13)	C5-C4-C9-C8	1.0(2)
O1-S1-C10-C15	29.50(15)	C4-C5-C6-C7	0.9(3)
O2-S1-C10-C11	-22.11(15)	C5-C6-C7-C8	0.4(3)
O2-S1-C10-C15	161.85(13)	C6-C7-C8-C9	-1.0(3)
N1-S1-C10-C11	91.62(13)	C7-C8-C9-C4	0.3(2)
N1-S1-C10-C15	-84.43(13)	S1-C10-C11-C12	-175.64(12)
S1-N1-C1-C2	145.86(11)	C15-C10-C11-C12	0.4(2)
C3-N1-C1-C2	15.69(11)	S1-C10-C15-C14	175.20(12)
S1-N1-C3-C2	-145.81(11)	C11-C10-C15-C14	-0.8(2)
C1-N1-C3-C2	-15.73(11)	C10-C11-C12-C13	0.6(2)
N1-C1-C2-C3	-15.13(11)	C11-C12-C13-C14	-1.1(2)
N1-C1-C2-C4	103.46(14)	C11-C12-C13-C16	178.74(15)
C4-C2-C3-N1	-102.55(14)	C12-C13-C14-C15	0.6(2)
C1-C2-C4-C5	108.60(16)	C16-C13-C14-C15	-179.21(15)
C3-C2-C4-C5	-150.90(14)	C13-C14-C15-C10	0.4(2)

7. Representative NMR-Spectra

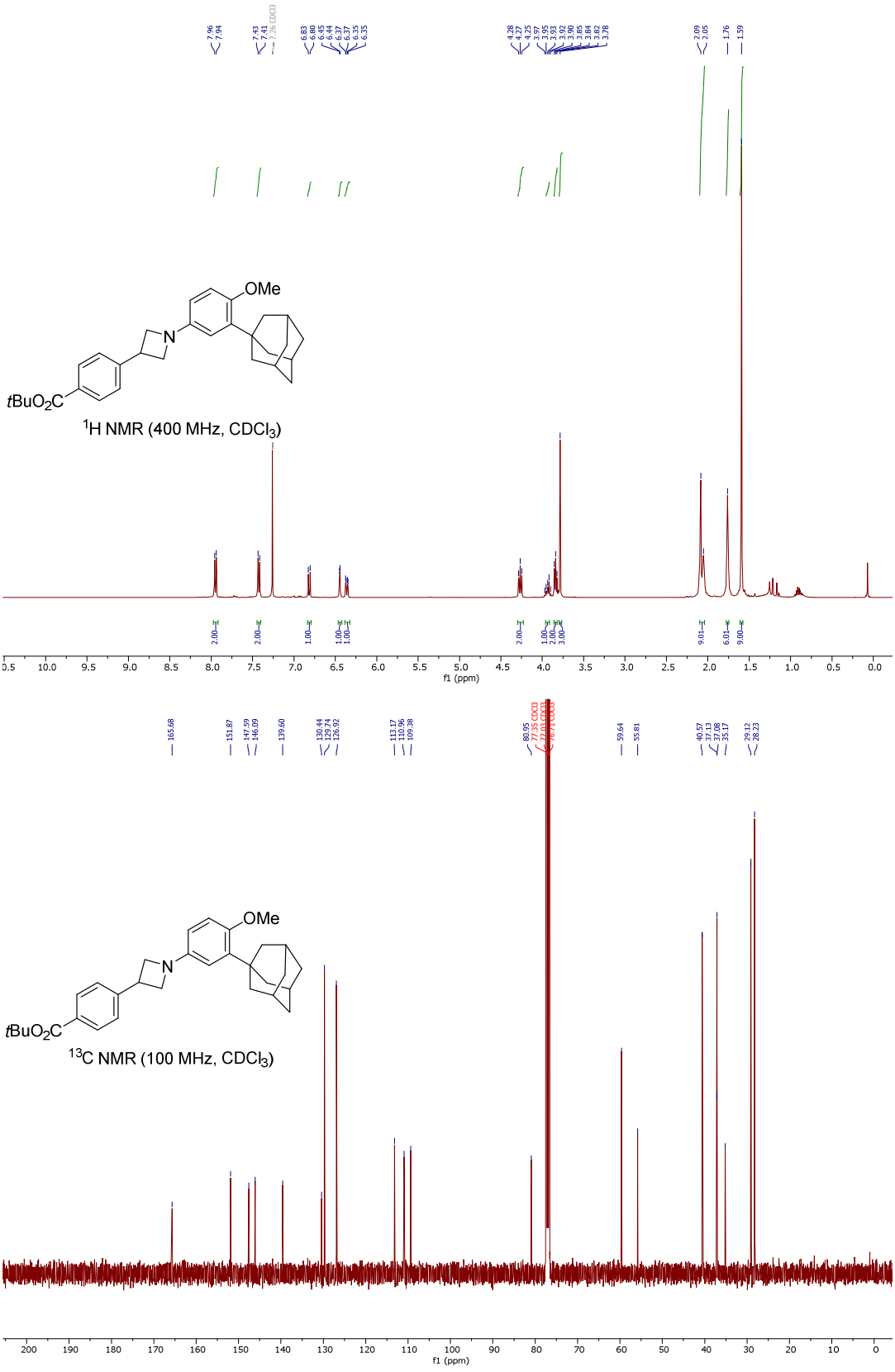


Figure 9: ^{1}H NMR and ^{13}C NMR of *tert*-Butyl 4-(1-(3-(adamantan-1-yl)-4-methoxyphenyl)azetidin-3-yl)benzoate (10q).

2. Stereoselective Polar Radical Crossover for the Functionalization of Strained-Ring Systems

Florian Trauner,[a,b] Rahma Ghazali,[a,b] Jan Rettig,[a] Christina M. Thiele,[a] and Dorian Didier[a,b]

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1. General Considerations

All reactions were carried out under dry N_2 atmosphere in flame-dried glassware unless otherwise stated. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with nitrogen three times prior to use. THF (stabilized) was purchased in 99.5 % purity from Acros Organics. Inhibitor-free THF was purchased by Sigma-Aldrich in 99.7 % purity. 2-Methyltetrafuran (inhibitor-free) was purchased in >99 % purity from Sigma-Aldrich. Organolithiums (*n*BuLi, *s*BuLi, *t*BuLi,) were purchased from Rockwood Lithium and the concentration was determined by titration against *i*PrOH using 1,10-phenantroline as indicator. Gringard reagents were prepared in THF, the used magnesium was activated by addition of 1,2-dibromoethane and subsequent heating to reflux. Titration of Gringard reagents was performed with benzoic acid and 4-phenylazodiphenylamin as indicator. Chromatographic purifications were performed using silica gel (SiO_2, 0.040-0.063 mm, 230- 400 mesh ASTM) from Merck or Alumina (Al_2O_3, 32-63 µm) from MP EcoChrom™. The spots were visualized under UV (254 nm) or by staining the TLC plate with either $KMnO_4$ solution (K_2CO_3, 10 g – $KMnO_4$, 1.5 g – H_2O, 150 mL – NaOH 10 % in H_2O, 1.25 mL) or Curcumin solution (Curcumin, 0.4 g – EtOH, 400 mL – 2 M HCl, 20 mL). Yields refer to isolated yields of compounds estimated to be >95 % pure as determined by ^{1}H NMR and GC-analysis. The ^{13}C and ^{1}H NMR spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ values in ppm relative to the residual solvent peak (^{1}H-NMR, ^{13}C-NMR) in deuterated chloroform ($CDCl_3$: δ 7.26 ppm for ^{1}H-NMR and δ 77.16 ppm for ^{13}C-NMR) and deuterated acetone (Acetone-D_6: δ 2.05 ppm for ^{1}H-NMR and δ 29.84 ppm for ^{13}C-NMR). Abbreviations for signal coupling are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet) and br (broad). Reaction endpoints were determined by GC monitoring of the reactions with *n*dodecane as an internal standard. Gas chromatography was performed with machines of Agilent Technologies 7890, using a column of type HP 5 (Agilent 5 % phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm) or Hewlett-Packard 6890 or 5890 series II, using a column of type HP 5 (Hewlett-Packard, 5 % phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm). High resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were recorded on Finnigan MAT 95Q, Finnigan MAT 90 instrument or JEOL JMS-700. Infrared spectra were recorded on a Perkin 281 IR spectrometer and samples were measured neat (ATR, Smiths Detection DuraSample IR II Diamond ATR). The absorption bands were reported in wave numbers (cm^{-1}) and abbreviations for intensity are as follows: vs (very strong; maximum intensity), s (strong; above 75 % of max. intensity), m (medium; from 50 % to 75 % of max. intensity), w (weak; below 50 % of max. intensity) and br (broad). Melting points were determined on a Büchi B-540 apparatus and are uncorrected.

1.1 Photochemical Setup

Photochemical Reactions at ambient temperature were performed using the EvoluChem PhotoRedOx Box Setup by Hepatochem. *Via* built in cooling fan the temperature could be adjusted to 15°C. The employed LED's were 365 nm (18 W, 60 °, EvoluChem 365PF) and/or 450 nm (18 W, 25 °, EvoluChem 450PF). Reactions at or below 0°C were performed using a Huber TC-100e immersion cooler to chill a dewar filled with EtOH (cutoff wavelength 210 nm).

Figure 10: Photochemical Setup for low-temperature Reactions

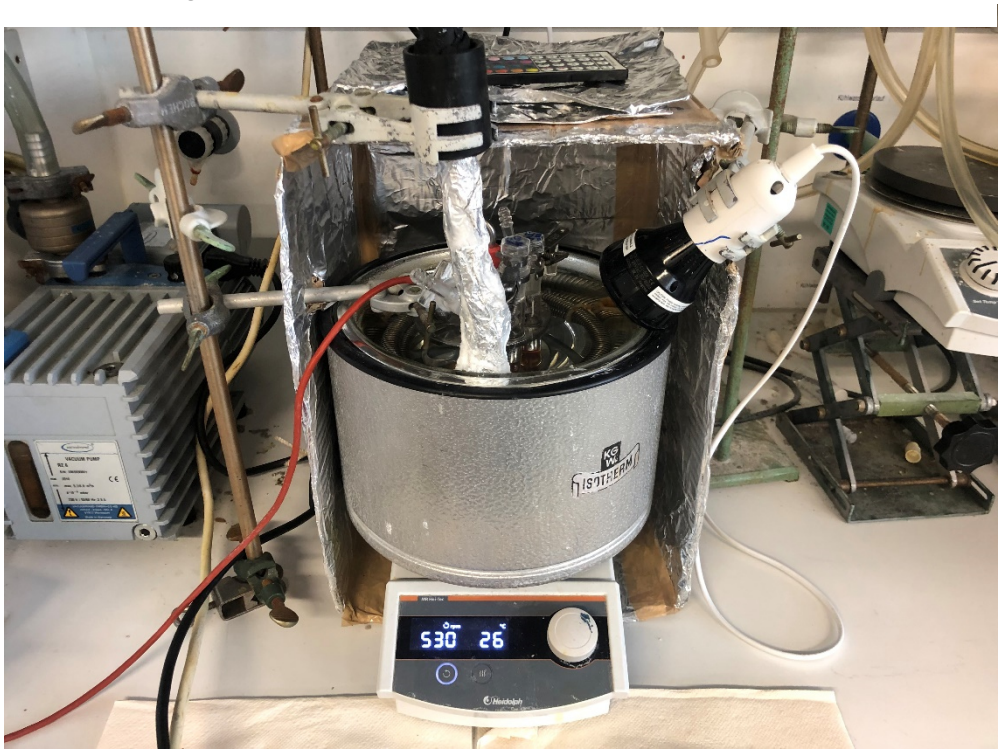
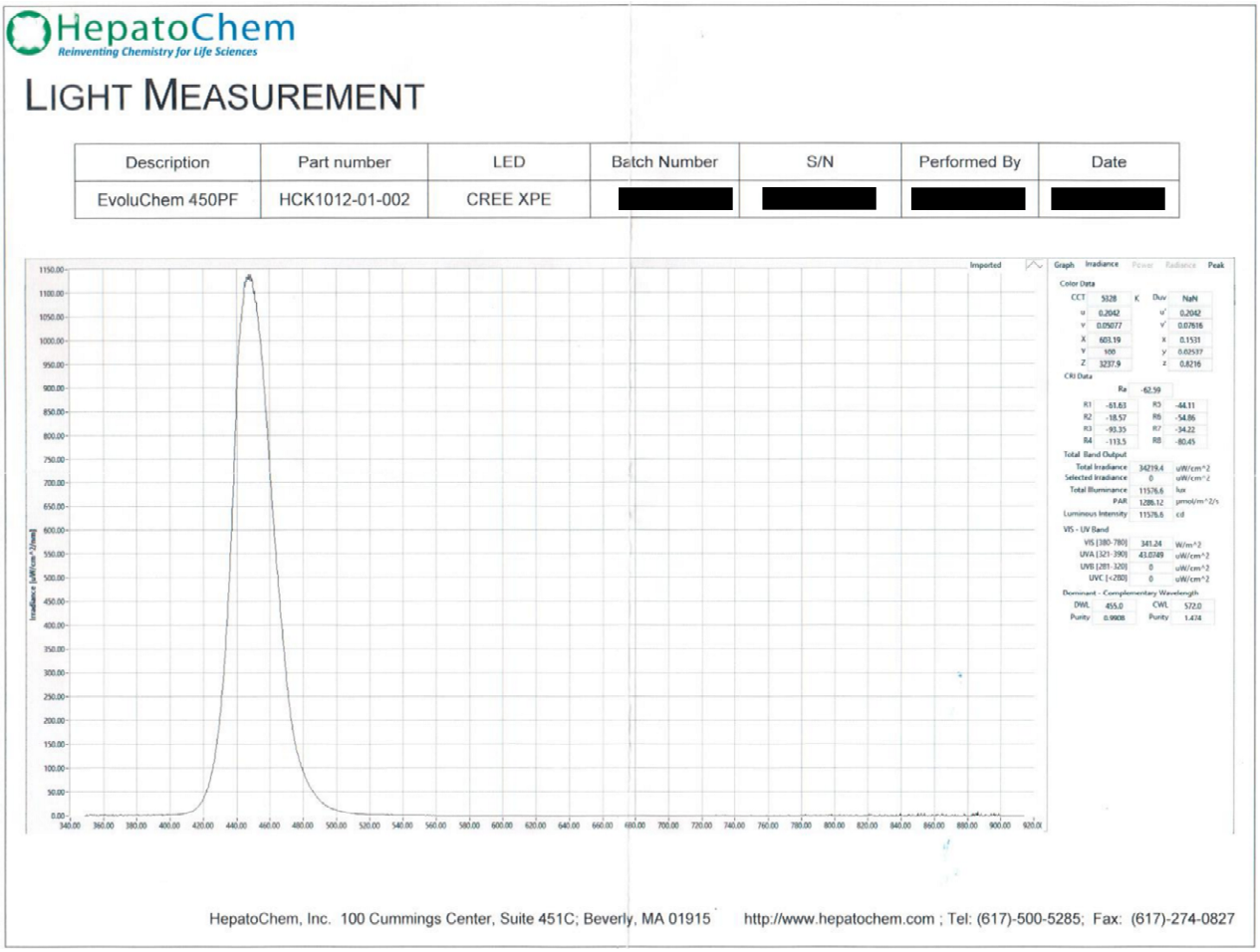


Figure 11 *:* UV-Vis emission spectrum of employed EvoluChem 450PF LED*.*



2. Optimization of Reaction Parameters

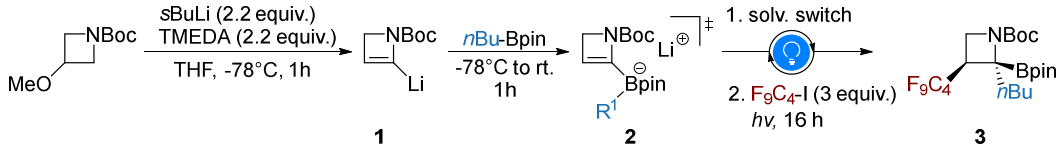


Table 6: Reaction parameter optimization.

Solvent	Hv [nm]	Eq. Bpin	Photocatalyst	*T* [°C]	*dr.* [A]	Yield[A,B]
MeCN	365	1	-----	15	2:1	51 (45)
MeCN	365	1	-----	Rt.	1:1	47 (41)
Et_2O	365	1	-----	15	2:1	40 (34)
THF	365	1	$Ru(bpy)_3(PF_6)_2$	Rt.	3:1	50
THF	365+450	1	$Ru(bpy)_3(PF_6)_2$	-20	3:1	42 (39)
THF	365+450	1	$Ru(bpy)_3(PF_6)_2$	-40	4:1	55 (53)
THF	365+450	1	-----	-40	4:1	44
THF	365	2	-----	15	3:1	68 (66)
THF	365+450	2	-----	-40	4:1	77 (75)
THF	365+450	1.5	-----	-40	4:1	78 (77)
THF	450	1.5	-----	-20	4:1	74
THF	450	1.5	$Ru(bpy)_3(PF_6)_2$	-20	4:1	66 (64)
THF	450	1.3	-----	-20	4:1	62 (59)
DMI	450	1.5	-----	-20	1.5:1	67
EtCN	450	1.5	-----	-40	1:1	49
DCM	450	1.5	-----	-40	4:1	75 (74)
m-THF	450	1.5	-----	-40	5:1	73 (71)
m-THF	450	1.3	-----	-40	5:1	74 (71)
DCE	450	1.5	-----	-20	3:1	64
Dioxane/ THF (1:1)	450	1.5	-----	Rt.	4:1	nd
DME	450	1.5	-----	-20	2:1	41
BTF	450	1.5	-----	-20	3:1	51
m-THF	-----	1.3	-----	-40	5:1	nd

[A] The *dr.* was determined by ^{19}F NMR analysis of the crude reaction mixture before chromatographical purification. Yields were determined by GC-analysis using Dodecane as internal standard.[B] Yields in parentheses refer to isolated yields after FCC.

Concentration Optimization

Table 7: Concentration optimization.

Concentration A [M][A]	Concentration B [M][B]	*dr.*	Yield [D]
0.15	0.1	5:1	74
0.3	0.1	5:1	67
0.3	0.3	4:1	66
0.15	0.05	5:1	69

[A] referring to the respective molarity in the lithiation-elimination step. [B] referring to the respective molarity after the solvent switch.[C] The *dr.* was determined by ^{19}F NMR analysis of the crude reaction mixture before chromatographical purification. [D] isolated yields.

Boron Source Optimization

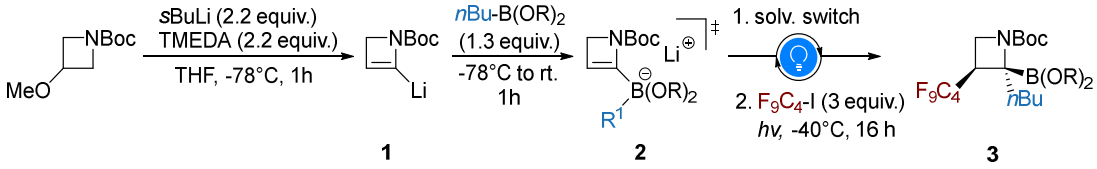
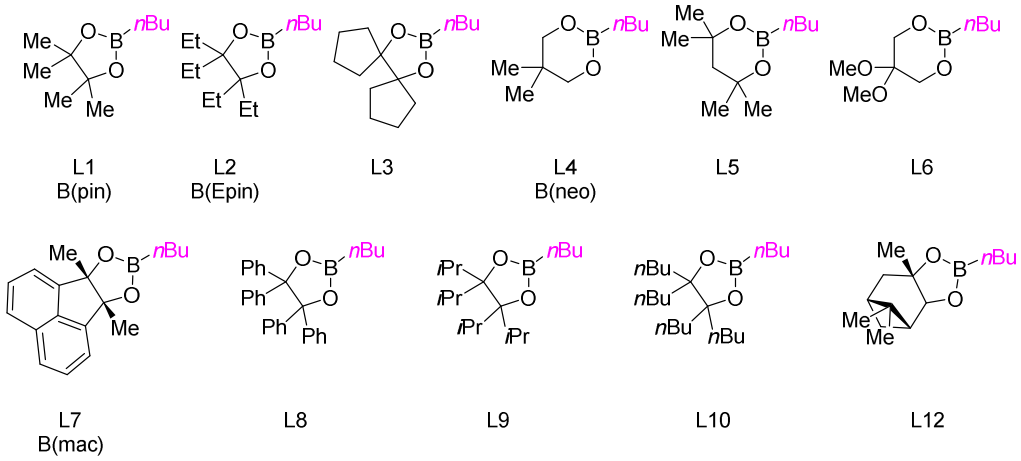


Table 8: Boron source optimization.

Boron Source	*T* [°C]	*dr.* [A]	Yield [%][A,B]
L1 = B(pin)	-40	5:1	73 (71)
L2 = B(Epin)	-40	7:1	92 (92)
L3	-40	3:1	63
L4 = B(neo)	-40	13:1	<5
L4 = B(neo)	-20	>20:1	<5
L4 = B(neo)	15	>20:1	<5
L5	-40	8:1	<5
L6	-40	5:1	<5
L7 = B(mac)	-40	3:1	32
L7 = B(mac)	-60	3:1	37
L8	-40	1.5:1	39
L9	-40	nd	<5
L10	-40	2:1	70
L11	-40	nd	nd
L12	-40	2:1	44

[A] The *dr.* was determined by ^{19}F NMR analysis of the crude reaction mixture before chromatographical purification. Yields were determined by GC-analysis using Dodecane as internal standard.[B] Yields in parentheses refer to isolated yields after FCC.



Observations:

- Partial protodeboronation of obtained azetidines on silica gel was observed when using L1 (Bpin). Hereby protodeboronation was especially dominant with aromatic residues as R^1.
- More sterically demanding ligands suppressed protodeboronation.

Additives/ Cosolvents

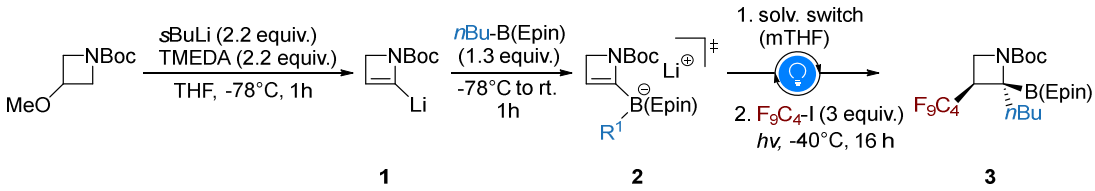


Table 9: Additives/ Cosolvents

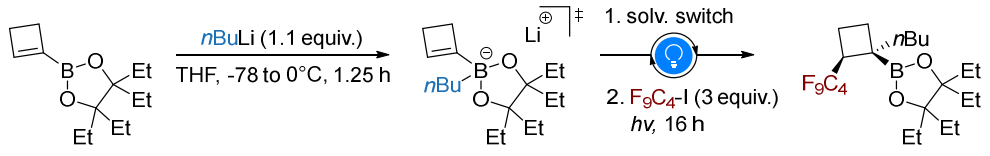
Additive/ Cosolvent	T [°C]	*dr.* [crude][A]	Yield [%][A,B]
None	-40	6:1	93
Dodecane 1Vol%	-40	7:1	92
Dodecane 5Vol%	-40	8:1	94 (93)
Dodecane 10Vol%	-40	8:1	88 (89)
$ZnCl_2$ (1 equiv.)	-40	4:1	67
BTF (2 equiv.)	-40	5:1	nd
18-crown-6	-40	4:1	nd

[A] The *dr.* was determined by ^{19}F NMR analysis of the crude reaction mixture before chromatographical purification. Yields were determined by GC-analysis using Dodecane as internal standard.[B] Yields in parentheses refer to isolated yields after FCC.

Observations:

- when dodecane (1 Vol%.) was omitted the *dr* decreased to 6:1
- increasing the amount of dodecane to 5 Vol%. the *dr* rose to 8:1. 10 Vol%. dodecane led to a decreased yield, while not affecting anymore the *dr*.

Addition temperature for Cyclobutanes



4 **5** **6a**

Table 10: Optimization of addition temperature for cyclobutanes.

Addition Temperature[A]	Warming to[B]	*dr.* [crude][C]	Yield [%][D]
0°C	25°C	>20:1	31
-20°C	0°C	>20:1	63
-40°C	0°C	>20:1	77
-78°C	0°C	>20:1	82

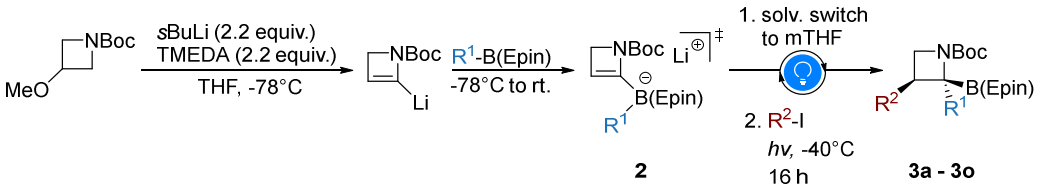
[A] referring to the reaction temperature when adding *n*BuLi. [B] referring to the reaction temperature to which the reaction is allowed to warm 30 min after addition of *n*BuLi. [C] The *dr.* was determined by ^{19}F NMR analysis of the crude reaction mixture before chromatographical purification. [C] isolated yields.

Observations:

- Addition of the lithium species at 0°C and stirring at this temperature for 30 min, followed by warming to rt. leads to a visible (brown) degradation/ insufficient formation of the boronate complex.
- The optimum addition temperature was found to be -78°C with stirring at that temperature for 30 min, followed by warming to 0°C for 45 min.
- For azetidines, warming to rt. is essential as only minor ate complex formation is observed at 0°C.

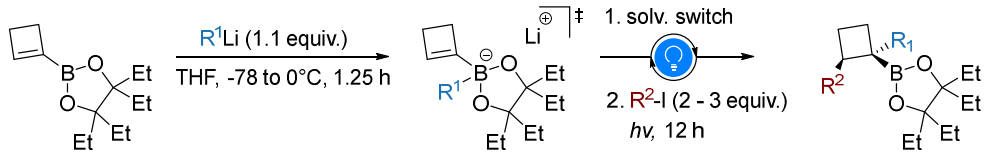
3. General Procedures

General Procedure A: Synthesis of trisubstituted azetidines



A flame-dried Schlenk flask was charged with *tert*-butyl 3-methoxyazetidine-1-carboxylate (56 mg, 0.3 mmol, 1.0 equiv.) followed by the addition of THF (2 mL). The solution was cooled to -78°C and TMEDA (99 µL, 0.66 mmol, 2.2 equiv.) was added. *s*BuLi (0.66 mmol, 2.2 equiv.) was added dropwise over a period of 4 minutes (0.12 mL/ min) and the pale-red solution was allowed to stir for 1h at -78°C. Subsequently, the respective boronate ester (0.39 mmol, 1.3 equiv.) was dissolved in THF (0.5 mL) and added dropwise to the solution. Following this, the mixture was stirred at -78°C for 30 minutes, and was then allowed to warm to ambient temperature. After stirring at this temperature for a further 30 minutes, the solvents were carefully removed *in vacuo*. The residual oil was dissolved in 2-methyltetrahydrofuran (2.5 mL), dry dodecane (0.15 mL, 5 Vol%.) was added and the flask was transferred to the photoreactor precooled to -40 °C. The respective radical precursor (0.9 mmol, 3.0 equiv. or 0.6 mmol, 2.0 equiv.) was dissolved in 2-methyltetrahydrofuran (0.5 mL) and added dropwise to the solution under irradiation with a blue LED (450 nm, 18 W). The yellow solution was stirred at the indicated temperature under LED irradiation for 16 h. The crude mixture was pushed through a Silica-Plug (4 cm), eluting with Et_2O (50 mL) and was concentrated *in vacuo*. Flash column chromatography (SiO_2 or Al_2O_3; pentane – EtOAc) afforded the respective Azetidines (**3a - 3o**). **Note:** TMEDA was distilled from CaH_2 and stored under inert atmosphere prior to use. *s*BuLi was filtered *via* Syringe filter prior to use.

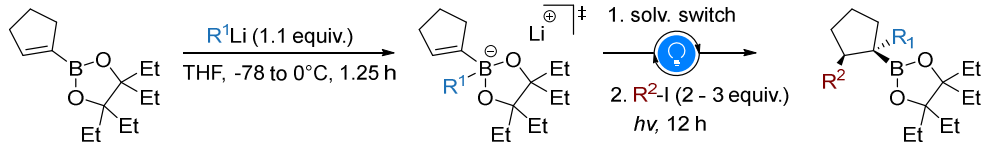
General Procedure B: Synthesis of trisubstituted Cyclobutanes



A flame-dried Schlenk flask was charged with the respective Aryl/ Alkyl halide for Halogen-Lithium exchange (0.22 mmol, 1.1 equiv.), THF (1 mL) was added and the solution was cooled to -78°C. *t*BuLi/ *n*BuLi (0.22 mmol, 1.1 equiv.) was slowly added dropwise and the mixture was stirred for the indicated time at -78°C, then warming to rt. 2-(Cyclobut-1-en-1-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (**4**) (47 mg, 0.2 mmol, 1.0 equiv.) was dissolved in THF (0.3 mL) and added slowly dropwise to the mixture at -78°C. Commercially available lithium species (1.1 equiv.) were also added at -78°C. Stirring was continued at this temperature for 30 min,

before the mixture was allowed to warm to 0°C for 45 min. Following this, the solvents were carefully removed *in vacuo*. The residue was dissolved in 2-methyltetrahydrofuran (1.5 mL), dry dodecane (0.1 mL, 5 Vol%.) was added and the flask was transferred to the photoreactor precooled to -40 °C. The respective radical precursor (0.6 mmol, 3.0 equiv. or 0.4 mmol, 2.0 equiv.) was dissolved in 0.5 mL 2-methyltetrahydrofuran and added dropwise to the solution under irradiation with a blue LED (450 nm, 18 W). The colorless solution was stirred at the indicated temperature under LED irradiation for 12 h. The crude mixture was pushed through a Silica-Plug (4 cm), eluting with Et_2O (50 mL) and was concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane – EtOAc) afforded the respective Cyclobutanes (**6a – 6h**).

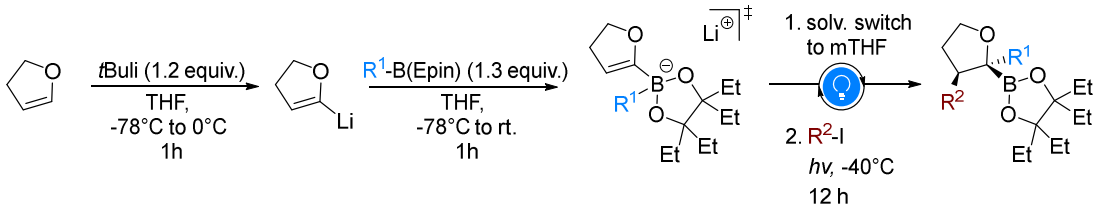
General Procedure C: Synthesis of trisubstituted Cyclopentanes



7 **8** **9a - 9h**

A flame-dried Schlenk flask was charged with the respective Aryl/ Alkyl halide for Halogen-Lithium exchange (0.22 mmol, 1.1 equiv.), THF (1 mL) was added and the solution was cooled to -78°C. *t*BuLi/ *n*BuLi (0.22 mmol, 1.1 equiv.) was slowly added dropwise and the mixture was stirred for the indicated time at -78°C, then warming to rt. Commercially available lithium species (1.1 equiv.) were also added at -78°C. 2-(Cyclopent-1-en-1-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (**7**) (50 mg, 0.2 mmol, 1.0 equiv.) was dissolved in THF (0.3 mL) and added slowly dropwise to the mixture at -78°C. Stirring was continued at this temperature for 30 min, before the mixture was allowed to warm to 0°C for 45 min. Following this, the solvents were carefully removed *in vacuo*. The residue was dissolved in 2-methyltetrahydrofuran (1.5 mL), dry dodecane (0.1 mL, 5 Vol%.) was added and the flask was transferred to the photoreactor precooled to -40 °C. The respective radical precursor (0.6 mmol, 3.0 equiv. or 0.4 mmol, 2.0 equiv.) was dissolved in 0.5 mL 2-methyltetrahydrofuran and added dropwise to the solution under irradiation with a blue LED (450 nm, 18 W). The colorless solution was stirred at the indicated temperature under LED irradiation for 12 h. The crude mixture was pushed through a Silica-Plug (4 cm), eluting with Et_2O (50 mL) and was concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane – EtOAc) afforded the respective Cyclopentanes (**9a - 9h**).

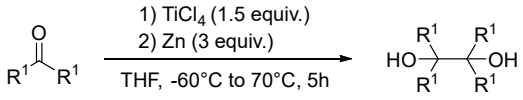
General Procedure D: Synthesis of trisubstituted Tetrahydrofuranes



10 **11** **12b; 12c**

A flame-dried Schlenk flask was charged with 2,3-dihydrofuran (15 µL, 0.2 mmol, 1.0 equiv.) followed by the addition of THF (1 mL). The solution was cooled to -78°C and *t*BuLi (0.24 mmol, 1.2 equiv.) was added dropwise over a period of 3 minutes. The reaction mixture stirred at that temperature for a further 10 min. and was then allowed to warm to 0°C for 45 min. Subsequently the mixture was recooled to -78°C and the respective Boronate ester (0.26 mmol, 1.3 equiv.) was added in 0.5 mL THF. The mixture was allowed to stir at -78°C for 30 min before warming to rt. for a further 30 min. Following this, the solvents were carefully removed *in vacuo*. The residue was dissolved in 2-methyltetrahydrofuran (1.5 mL), dry dodecane (0.1 mL, 5 Vol%.) was added and the flask was transferred to the photoreactor precooled to -40 °C. The respective radical precursor (0.6 mmol, 3.0 equiv. or 0.4 mmol, 2.0 equiv.) was dissolved in 2-methyltetrahydrofuran (0.5 mL) and added dropwise to the solution under irradiation with a blue LED (450 nm, 18 W). The colorless solution was stirred at the indicated temperature under LED irradiation for 12 h. The crude mixture was pushed through a Silica-Plug (4 cm), eluting with Et_2O (50 mL) and was concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane – EtOAc) afforded the respective tetrahydrofuranes (**12b; 12c**).

General Procedure E: Synthesis of symmetric Diols by Pinacol Coupling using $TiCl_4$ and Zn

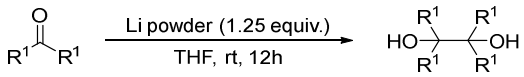


In analogy to a literature procedure [193], a flame-dried three-necked flask was charged with anhydrous THF (100 mL) and the respective ketone (40 mmol, 1.0 equiv.) was added. The solution was cooled to -60°C and $TiCl_4$ (6.6 mL, 60 mmol, 1.5 equiv.) was added dropwise over a period of 30 minutes *via* a dropping funnel. The yellow suspension was stirred for a further 30 minutes at the aforementioned temperature and was then allowed to warm to ambient temperature. Zn dust (7.86 g, 120 mmol, 3 equiv.) was added in one portion and the green suspension was heated to 70°C for 3 h.

[193] R. Rubio-Presa, S. Suárez-Pantiga, M. R. Pedrosa, R. Sanz, *Adv. Synth. Catal.* **2018**, *360*, 2216-2220.

Then, the mixture was cooled to 0°C and a saturated aqueous solution of K_2CO_3 was added carefully, upon which stirring was continued for a further 30 minutes. The suspension was filtered through a plug of Celite, and the solid residues were washed with EtOAc (120 mL). Following this, the organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). All organic fractions were combined, washed with Brine and dried over anhydrous magnesium sulfate. Evaporation of the solvents *in vacuo* and flash column chromatography (*i*hexane/ EtOAc) afforded the respective diols. Note: When filtering the dark suspension over Celite, only the organic phase should be decanted.

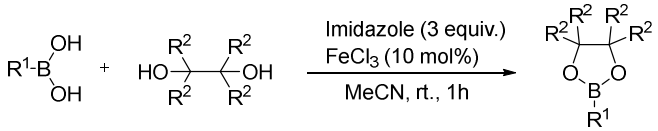
General Procedure F: Synthesis of symmetric Diols by Pinacol Coupling using Lithium powder



A pre-weighted and flame-dried Schlenk-flask was charged with Lithium powder (Suspension in Heptane) and the solvent was removed *in vacuo*. After determining the amount of Lithium (usually around 0.5 g, 70 mmol, 1.0 equiv.) anhydrous THF (200 mL) was added. The respective Ketone (56 mmol, 0.8 equiv.) was added dropwise and the grey suspension was allowed to stir overnight. Then, the reaction mixture was poured into ice-water (150 mL) and the aqueous phase was extracted with EtOAc (4 × 100 mL). The combined organic fractions were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Flash column chromatography (SiO_2, *i*hexane; EtOAc) afforded the desired diols.

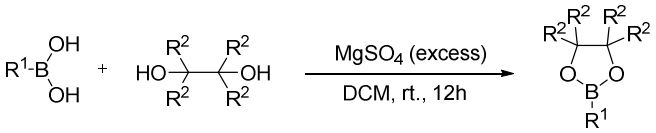
General Procedure G: Synthesis of Boronic Esters

Method A – $FeCl_3$ mediated esterification



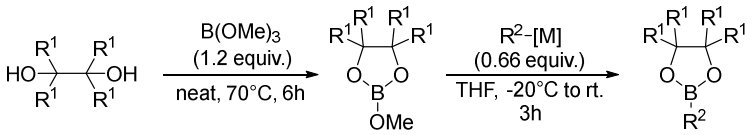
According to a modified literature procedure [194]: to an Erlenmeyer flask equipped with a stirring bar was added in the following order: MeCN (20 mL), Boronic acid (4 mmol, 1.0 equiv.), the respective diol (4 mmol, 1.0 equiv.), Imidazole (0.81 g, 3.0 equiv.), and $FeCl_3$ (32 mg, 0.2 mmol, 5 mol%.) The mixture was stirred at ambient temperature for 1h, then filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (SiO_2 plug, *i*hexane/ EtOAc) to yield the desired Boronate esters. Note: Method selected for insensitive substrates

Method B – classical esterification



A flame-dried flask was charged with the respective Boronic acid (4 mmol, 1.0 equiv.), the respective Diol (4 mmol, 1.0 equiv.) and anhydrous magnesium sulfate (1 g). Anhydrous DCM (15 mL) was added and the suspension was allowed to stir overnight. After filtration and concentration *in vacuo*, the crude boronic acid esters were purified by flash-column chromatography (SiO_2, *i*hexane; EtOAc). Note: This method is typically selected for base sensitive substrates.

Method C – *via* respective methoxyboronic ester

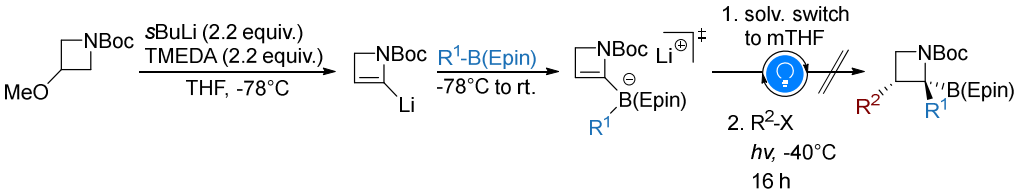


A flame-dried flask equipped with a Dean-Stark apparatus was charged with the respective diol (20 mmol, 1.0 equiv.) and $B(OMe)_3$ (2.2 mL, 20 mmol, 1.2 equiv.) was added *via* syringe and the mixture was heated to 70 °C for 6 h. Residual $B(OMe)_3$ was removed under high-vacuum to afford the respective crude methoxy boronic esters, which were employed in the next step without further purification. Hereby, the respective methoxy boronic ester (2 mmol, 1.5 equiv.) was dissolved in dry THF (10 mL) and the reaction mixture was cooled to -20°C. The respective Grignard or Lithium species (1.3 mmol, 1.0 equiv.) was added dropwise and the solution was allowed to stir for 1h at the aforementioned temperature. After warming to rt. and stirring at that temperature for a further 2h, the reaction was quenched by addition of HCl (1M, 2 mL). The solution was extracted with Et_2O (3 × 15 mL), the combined organic fractions were washed with Brine, dried over anhyd. $MgSO_4$ and concentrated *in vacuo.* Flash column chromatography (SiO_2; pentane – EtOAc) afforded the desired Boronic esters. Note: This method is preferentially selected for Boronic esters containing bulky diol ligands. Method A or B only afford insufficient yields for these substrates.

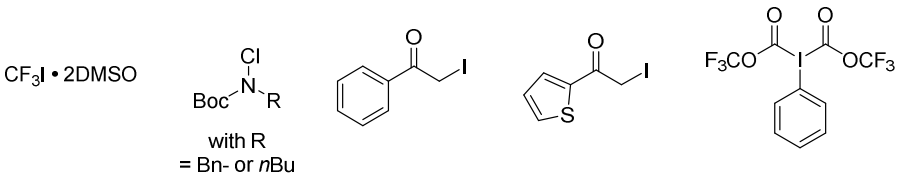
[194] J. L. Wood, L. D. Marciasini, M. Vaultier, M. Pucheault, *Synlett* **2014**, *25*, 551-555.

4. Limitations

For Azetidines:

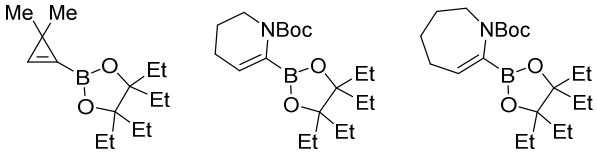


incompatible with R^2-X =



incompatible with R^1-B(Epin) =

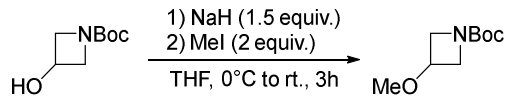
- Radical precursors Ritter trifluoroiodomethane, *N*-chlorocarbamates and α-Iodoketones shown above did not furnish the desired products.
- Alkynes as R^1 proved incompatible; tertiary alkyl moieties as well.



- Ate complex formation observed for depicted cyclopropene, *N*-Boc-tetrahydropyridine and *N*-Boc-tetrahydroazepine but no desired product detected on GC-MS.

5. Experimental Data

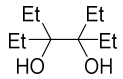
tert-Butyl 3-methoxyazetidine-1-carboxylate (Si-1)



In analogy to a modified literature procedure [195], a flame-dried Schlenk-Flask was charged with *tert*-butyl 3-hydroxyazetidine-1-carboxylate (5.2 g, 30 mmol, 1.0 equiv.) and dry THF (50 mL). The solution was cooled to 0°C and NaH in mineral oil (1.8 g, 45 mmol, 1.5 equiv.) was added portionwise. The ice-bath was removed after 10 min and the suspension was allowed to warm to rt. and stir for 50 min. Once again the mixture was cooled to 0°C and MeI (60 mmol, 2.0 equiv.) was added dropwise. The ice-bath was removed and the mixture stirred for 3 hours before it was carefully quenched by addition of MeOH (20 mL). The solvents were removed *in vacuo*, and the mixture was redissolved in Et_2O and filtered. After removal of residual solvents *in vacuo*, and flash-column chromatography (SiO_2; pentane – EtOAc: 85:15) the title compound was obtained as a colorless oil (5.3 g, 28 mmol, 94 %). If a yellowish oil was obtained, the product was pushed through a short plug of activated charcoal eluting with Et_2O.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.10 – 4.02 (m, 1H), 4.01 – 3.97 (m, 2H), 3.78 – 3.72 (m, 2H), 3.21 (s, 3H), 1.37 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 156.48, 79.63, 69.15, 56.12, 28.48.

3,4-Diethylhexane-3,4-diol – Epin (L-2)

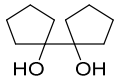


According to GP-E, using 3-pentanone (38.4 mL, 350 mmol, 1.00 equiv.) in THF (900 mL) and $TiCl_4$ (57.6 mL, 0.525 mol, 1.50 equiv.), as well as Zn powder (68.7 g, 1.05 mol, 3.00 equiv.). Final flash-column chromatography (SiO_2; pentane – EtOAc: 9:1 to 85:15) afforded the title compound as a slightly yellow oil, which was eluted through a plug of activated charcoal, to obtain 3,4-diethylhexane-3,4-diol as a colorless oil (24 g, 0.14 mol, 79 %). Note: Running the synthesis on this scale requires slow and portionwise addition of the Zn powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.99 (s, 2H), 1.61 (qd, J = 7.5, 2.7 Hz, 8H), 0.94 (t, J = 7.5 Hz, 12H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 78.96, 27.43, 9.17.

[195] D. M. Hodgson, C. I. Pearson, M. Kazmi, *Org. Lett.* **2014**, *16*, 856-859.

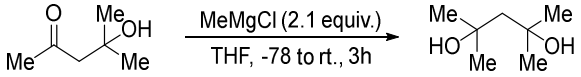
[1,1'-Bi(cyclopentane)]-1,1'-diol (L-3)



According to GP-E, using cyclopentanone (3.5 mL, 40 mmol, 1.0 equiv.) and final flash-column chromatography (SiO_2; pentane – EtOAc: 89:11) afforded the title compound as a colorless solid (2.3 g, 13 mmol, 67 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.94 (s, 2H), 1.90 – 1.78 (m, 4H), 1.79 – 1.67 (m, 4H), 1.67 – 1.57 (m, 8H). **^{13}C NMR (100 MHz, $CDCl_3$):** 87.30, 36.54, 24.98.

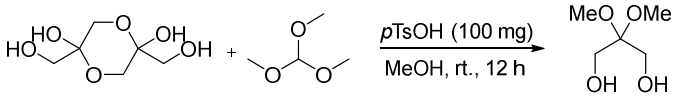
2,4-Dimethylpentane-2,4-diol (L-5)



A flame-dried flask was charged with 4-hydroxy-4-methylpentan-2-one (20 mmol, 1.0 equiv.) and dissolved in anhydrous THF (50 mL). A solution of MeMgCl in THF (42 mmol, 2.1 equiv.) was added dropwise *via* syringe-pump at -78°C and the solution was allowed to stir at that temperature for 1 h before warming to rt. After stirring at that temperature for another 2 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL). The organic phase was separated and the aqueous fraction was extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with Brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane – EtOAc: 87:13) afforded the title compound as a colorless oil (1.7 g, 13 mmol, 63 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.75 (s, 2H), 1.34 (s, 12H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 72.36, 52.31, 32.19.

2,2-Dimethoxypropane-1,3-diol (L-6)

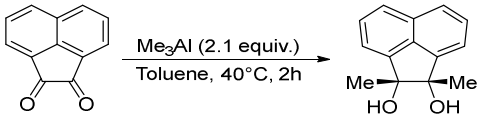


According to a literature procedure[196], 2,5-dihydroxydioxane-2,5-dimethanol (25 g, 0.14 mol, 1.0 equiv.), *p*-toluenesulfonic acid (100 mg), and trimethyl orthoformate (30 mL, 0.27 mol, 1.3 equiv.) were suspended in MeOH (300 mL) and stirred at ambient temperature overnight. Following this, Na_2CO_3 (300 mg) was added and the solvent was removed *in vacuo*. The solid residue was purified *via* flash column chromatography (SiO_2; DCM – MeOH: 93:7) to yield the title compound as a light yellow solid (13.8 g, 101 mmol, 73 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.69 (d, J = 6.1 Hz, 4H), 3.30 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 100.11, 61.88, 48.89.

[196] E. Cesarotti, P. Antognazza, M. Pallavicini, L. Villa, *Helv. Chim. Acta* **1993**, *76*, 2344-2349.

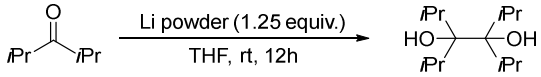
syn-1,2-Dimethyl-1,2-dihydroacenaphthylene-1,2-diol – Mac (L-7)



According to a literature procedure [148], a flame-dried 1 L three-necked flask was charged with Acenaphthoquinone (18.2 g, 100 mmol, 1.00 equiv.). Dry toluene was added and the resulting yellow suspension was heated to 40 ºC. A 2 M solution of Trimethylaluminum in hexane (105 mL, 210 mmol, 2.10 equiv.) was added dropwise *via* syringe pump. Upon completion of addition, the reaction was allowed to stir for 1 hour at 40 ºC, cooled to 0 ºC and quenched carefully by addition of H_2O (50 mL) and 2 M HCl (30 mL). EtOAc (200 mL) was added and the mixture was filtered over a plug of Celite, washing with EtOAc (50 mL). The filtrate was transferred in a separatory funnel and washed with water (200 mL). The aqueous fraction was extracted with EtOAc (3 × 150 mL) and the combined organic layers were washed with B rine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was obtained in a *syn*/*anti* ratio of 3.9:1 as determined by crude NMR. Recrystallization from EtOAc (500 mL) afforded pure *syn*-1,2-dimethyl-1,2-dihydroacenaphthylene-1,2-diol as off-white crystals (10.3 g, 48.3 mmol, 48 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.75 (d, J = 8.2 Hz, 2H), 7.60 – 7.53 (m, 2H), 7.48 (d, J = 6.9 Hz, 2H), 3.01 (s, 2H), 1.62 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 146.27, 134.42, 131.25, 128.61, 125.00, 119.26, 82.29, 23.45.

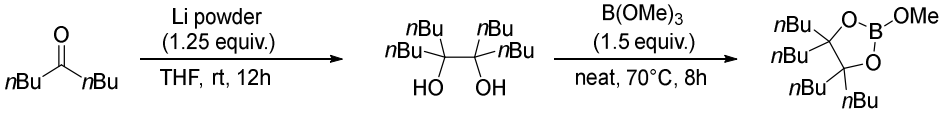
3,4-Diisopropyl-2,5-dimethylhexane-3,4-diol (L-9)



Following GP-F, with freshly distilled 2,4-dimethylpentan-3-on (7.5 mL, 53 mmol, 0.8 equiv.) and Lithium powder (0.46 g, 66 mmol, 1.0 equiv.) in dry THF (200 mL). Flash column chromatography (SiO_2; pentane – EtOAc: 9:1) afforded the title compound as a colorless solid (2.6 g, 11 mmol, 43 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.43 – 2.28 (m, 4H), 1.04 (s, 24H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 83.03, 20.59.

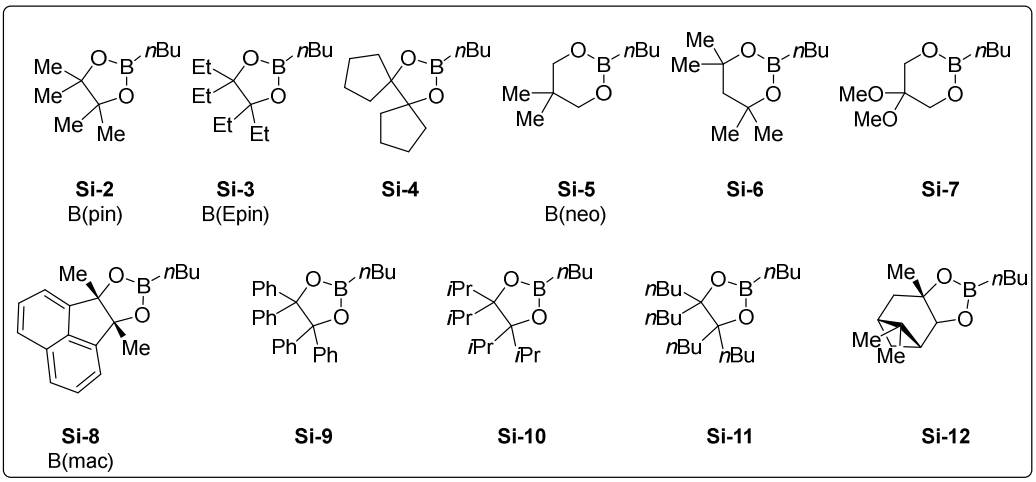
5,6-Dibutyldecane-5,6-diol (L-10) and 4,4,5,5-tetrabutyl-2-methoxy-1,3,2-dioxaborolane



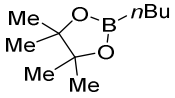
Following GP-F with 5-nonanone (8.4 mL, 49 mmol, 0.8 equiv.) and lithium powder (0.43 g, 61 mmol, 1.0 equiv.) in dry THF (200 mL). Flash column chromatography (SiO_2; pentane – EtOAc; 95:5 to 9:1) afforded the title compound as a colorless solid (2.17 g, 7.6 mmol, 31 %).

The full amount of the title compound was directly employed to obtain 4,4,5,5-tetrabutyl-2-methoxy-1,3,2-dioxaborolane as follows: A dry 25 mL flask equipped with reflux condenser was charged with diol (2.17 g, 7.6 mmol, 1.0 equiv.) and $B(OMe)_3$ (1.3 mL, 11 mmol, 1.5 equiv.) and the reaction mixture was heated to 70°C for 8 h according to TLC. The resulting viscous oil was dried under high-vacuum and directly used to prepare 2,4,4,5,5-Pentabutyl-1,3,2-dioxaborolane without further purification. Note: with increasing steric hindrance of the diol ligands Method C of General Procedure C is preferred over Method A or B.

Overview: Boronic Esters employed for Optimization



2-Butyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Si-2)

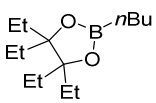


According to GP-G (Method A), using *n*butylboronic acid (0.41 g, 4.0 mmol, 1.0 equiv.) and pinacol (0.47 g, 4 mmol, 1.0 equiv.). Final flash column chromatography (SiO_2; pentane – EtOAc; 97:3) afforded the title compound as a colorless oil (0.47 g, 2.6 mmol, 65 %).

Note: *n*butylboronic acid was prepared by treating $B(OiPr)_3$ (1.5 equiv.) in THF (0.15 M) with *n*BuLi (1.0 equiv.) at -20°C and final recrystallization from water.

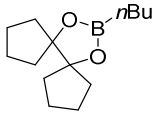
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.42 – 1.26 (m, 4H), 1.23 (s, 12H), 0.87 (t, J = 7.5 Hz, 3H), 0.76 (t, J = 7.5 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 82.96, 26.35, 25.56, 24.95, 14.04.

2-Butyl-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (Si-3)



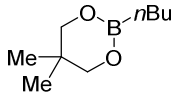
According to GP-G (Method A), using *n*butylboronic acid (0.70 g, 6.9 mmol, 1.0 equiv.) and 3,4-diethylhexane-3,4-diol (**L-2**) (0.99 g, 6.9 mmol, 1.0 equiv.). Final flash column chromatography (SiO_2; pentane – EtOAc; 98:2) afforded the title compound as a colorless oil (1.22 g, 5.1 mmol, 74 %). Note: *n*butylboronic acid was prepared by treating $B(OiPr)_3$ (1.5 equiv.) in THF (0.15 M) with *n*BuLi (1.0 equiv.) at -20°C and final recrystallization from water.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.65 (qd, *J* = 7.5, 5.8 Hz, 8H), 1.43 – 1.23 (m, 4H), 0.95 – 0.85 (m, 15H), 0.77 (t, *J* = 7.7 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 87.97, 26.58, 26.49, 25.62, 14.35, 14.07, 8.95.

12-Butyl-11,13-dioxa-12-boradispiro[4.0.46.35]tridecane (Si-4)



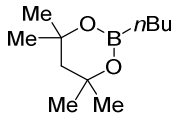
According to GP-G (Method A), using *n*butylboronic acid (0.41 g, 4.0 mmol, 1.0 equiv.) and [1,1'-bi(cyclopentane)]-1,1'-diol (**L-3**) (0.68 g, 4.0 mmol, 1.0 equiv.). Final flash column chromatography (SiO_2; pentane – EtOAc; 98:2) afforded the title compound as a colorless oil (0.44 g, 1.9 mmol, 48 %). Note: *n*butylboronic acid was prepared by treating $B(OiPr)_3$ (1.5 equiv.) in THF (0.15 M) with *n*BuLi (1.0 equiv.) at -20°C and final recrystallization from water.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.92 – 1.78 (m, 4H), 1.76 – 1.54 (m, 12H), 1.44 – 1.23 (m, 4H), 0.87 (t, J = 7.5 Hz, 3H), 0.76 (t, J = 7.5 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 92.97, 35.83, 26.49, 25.55, 23.16, 14.08.

2-Butyl-5,5-dimethyl-1,3,2-dioxaborinane (SI-5)



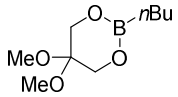
According to GP-G (Method A), using *n*butylboronic acid (0.41 g, 4.0 mmol, 1.0 equiv.) and neopentyl glycol (0.42 g, 4.0 mmol, 1.0 equiv.). Final flash column chromatography (SiO_2; pentane – EtOAc; 98:2) afforded the title compound as a colorless oil (0.45 g, 2.6 mmol, 66 %). Note: *n*butylboronic acid was prepared by treating $B(OiPr)_3$ (1.5 equiv.) in THF (0.15 M) with *n*BuLi (1.0 equiv.) at -20°C and final recrystallization from water.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.58 (s, 4H), 1.39 – 1.18 (m, 4H), 0.94 (s, 6H), 0.87 (t, J = 7.1 Hz, 3H), 0.70 (t, J = 7.1 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 72.10, 35.01, 31.74, 26.51, 25.65, 21.96, 14.11.

2-Butyl-4,4,6,6-tetramethyl-1,3,2-dioxaborinane (Si-6)



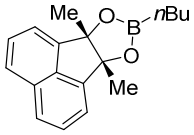
According to GP-G (Method A), using *n*butylboronic acid (0.41 g, 4.0 mmol, 1.0 equiv.) and 2,4-dimethylpentane-2,4-diol (**L-5**) (0.53 g, 4.0 mmol, 1.0 equiv.). Final flash column chromatography (SiO_2; pentane – EtOAc; 95:5) afforded the title compound as a colorless oil (0.48 g, 2.4 mmol, 59 %). Note: *n*butylboronic acid was prepared by treating $B(OiPr)_3$ (1.5 equiv.) in THF (0.15 M) with *n*BuLi (1.0 equiv.) at -20°C and final recrystallization from water.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.78 (s, 2H), 1.32 (s, 12H), 1.30 – 1.23 (m, 4H), 0.86 (t, J = 7.1 Hz, 3H), 0.64 (t, J = 7.6 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 70.22, 48.94, 31.96, 26.77, 25.61, 14.19.

2-Butyl-5,5-dimethoxy-1,3,2-dioxaborinane (Si-7)



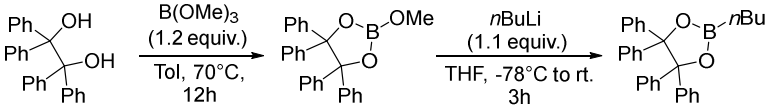
According to GP-G (Method B), using *n*butylboronic acid (0.41 g, 4.0 mmol, 1.0 equiv.) and 2,2-dimethoxypropane-1,3-diol (**L-6**) (0.54 g, 4.0 mmol, 1.0 equiv.). Final flash column chromatography (SiO_2; pentane – EtOAc; 97:3) afforded the title compound as a colorless oil (0.36 g, 1.8 mmol, 45 %). Note: *n*butylboronic acid was prepared by treating $B(OiPr)_3$ (1.5 equiv.) in THF (0.15 M) with *n*BuLi (1.0 equiv.) at -20°C and final recrystallization from water.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.87 (s, 4H), 3.28 (s, 6H), 1.39 – 1.22 (m, 4H), 0.87 (t, J = 7.1 Hz, 3H), 0.71 (t, J = 7.1 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 95.61, 64.60, 48.79, 26.42, 25.48, 14.10.

(6bR,9aS)-8-butyl-6b,9a-dimethyl-6b,9a-dihydroacenaphtho[1,2-d][1,3,2]dioxaborole (Si-8)



According to GP-G (Method A), using *n*butylboronic acid (0.41 g, 4.0 mmol, 1.0 equiv.) and *syn*-1,2-dimethyl-1,2-dihydroacenaphthylene-1,2-diol (**L-7**) (0.86 g, 4.0 mmol, 1.0 equiv.). Final flash column chromatography (SiO_2; pentane – EtOAc; 98:2) afforded the title compound as a colorless solid (0.71 g, 2.5 mmol, 63 %). Note: *n*butylboronic acid was prepared by treating $B(OiPr)_3$ (1.5 equiv.) in THF (0.15 M) with *n*BuLi (1.0 equiv.) at -20°C and final recrystallization from water.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.79 (d, J = 8.6 Hz, 2H), 7.65 – 7.48 (m, 4H), 1.77 (s, 6H), 1.37 – 1.27 (m, 2H), 1.27 – 1.15 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H), 0.72 (d, J = 7.9 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 145.02, 134.77, 131.47, 128.61, 125.35, 119.54, 91.71, 26.22, 25.49, 22.28, 13.95.

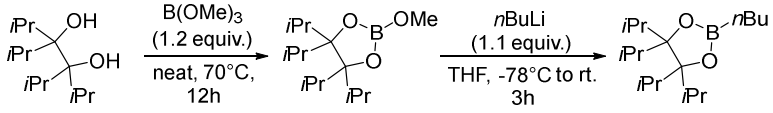
2-Butyl-4,4,5,5-tetraphenyl-1,3,2-dioxaborolane (Si-9)



According to GP-G (Method C), using benzopinacol (1.83 g, 5.0 mmol, 1.0 equiv.) and $B(OMe)_3$ (0.67 mL, 6 mmol, 1.2 equiv.) in toluene (10 mL). After removal of excess $B(OMe)_3$ and toluene *in vacuo*, the crude methoxyester was dissolved in THF (30 mL) and cooled to -78°C. A solution of *n*BuLi in hexane (5.5 mmol, 1.1 equiv.) was added dropwise and the mixture was allowed to stir for 1h at that temperature. After warming to rt. for a further 2h, the reaction was quenched and extracted. Flash column chromatography (SiO_2; pentane – EtOAc; 95:5) afforded the title compound as a colorless viscous oil (1.4 g, 3.3 mmol, 65 %).

^{1}H NMR (400 MHz, $CDCl_2$): δ (ppm) = 7.19 – 7.12 (m, 8H), 7.10 – 7.05 (m, 12H), 1.70 – 1.62 (m, 2H), 1.51 – 1.45 (m, 2H), 1.27 – 1.23 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_2$):** δ (ppm) = 143.28, 129.03, 127.72, 127.38, 96.18, 26.76, 26.08, 14.30.

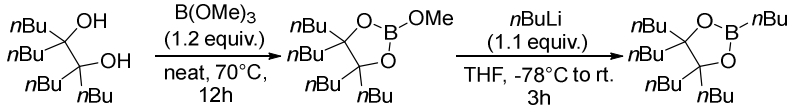
2-Butyl-4,4,5,5-tetraisopropyl-1,3,2-dioxaborolane (Si-10)



According to GP-G (Method C), using 3,4-diisopropyl-2,5-dimethylhexane-3,4-diol (L-9) (1.2 g, 5.0 mmol, 1.0 equiv.) and $B(OMe)_3$ (0.67 mL, 6 mmol, 1.2 equiv.) in toluene (10 mL). After removal of excess $B(OMe)_3$ and toluene *in vacuo*, the crude methoxyester was dissolved in THF (30 mL) and cooled to -78°C. A solution of *n*BuLi in hexane (5.5 mmol, 1.1 equiv.) was added dropwise and the mixture was allowed to stir for 1h at that temperature. After warming to rt. for a further 2h, the reaction was quenched and extracted. Flash column chromatography (SiO_2; pentane – EtOAc; 97:3) afforded the title compound as a colorless oil (0.5 g, 1.7 mmol, 34 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.19 (hept, J = 7.0 Hz, 4H), 1.41 – 1.24 (m, 4H), 1.01 – 0.87 (m, 24H), 0.83 (t, J = 7.1 Hz, 3H), 0.78 (t, J = 7.6 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 93.10, 31.73, 26.84, 25.63, 20.52, 19.56, 14.15.

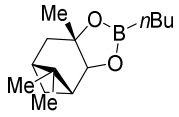
2,4,4,5,5-Pentabutyl-1,3,2-dioxaborolane (Si-11)



According to GP-G (Method C), using 5,6-dibutyldecane-5,6-diol (L-10) (0.9 g, 3.1 mmol, 1.0 equiv.) and $B(OMe)_3$ (0.41 mL, 3.7 mmol, 1.2 equiv.) in toluene (5 mL). After removal of excess $B(OMe)_3$ and toluene *in vacuo*, the crude methoxyester was dissolved in THF (30 mL)

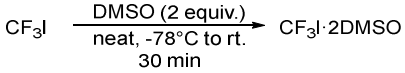
and cooled to -78°C. A solution of *n*BuLi in hexane (3.4 mmol, 1.1 equiv.) was added dropwise and the mixture was allowed to stir for 1h at that temperature. After warming to rt. for a further 2h, the reaction was quenched and extracted. Flash column chromatography (SiO_2; pentane – EtOAc; 99:1) afforded the title compound as a colorless oil (0.6 g, 1.6 mmol, 51 %).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.61 – 1.52 (m, 8H), 1.42 – 1.19 (m, 20H), 0.95 – 0.85 (m, 15H), 0.76 (t, J = 7.6 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 87.68, 34.50, 26.58, 25.58, 23.58, 14.19.

(4*R*,6*R*,7a*S*)-2-Butyl-5,5,7a-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (Si-12)



According to GP-G (Method A), using *n*butylboronic acid (0.2 g, 2 mmol, 1.0 equiv.) and (1*R*,2*R*,3*S*,5*R*)-(−)-Pinanediol (0.34 g, 2 mmol, 1.0 equiv.). Final flash column chromatography (SiO_2; pentane/ EtOAc – 96:4) afforded the title compound as a colorless oil (0.32 g, 1.3 mmol, 67 %). Note: *n*butylboronic acid was prepared by treating $B(OiPr)_3$ (1.5 equiv.) in THF (0.15 M) with *n*BuLi (1.0 equiv.) at -20°C and final recrystallization from water.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.24 (dd, J = 8.6, 1.8 Hz, 1H), 2.37 – 2.29 (m, 1H), 2.24 – 2.16 (m, 1H), 2.04 (t, J = 5.6 Hz, 1H), 1.93 – 1.80 (m, 2H), 1.43 – 1.26 (m, 10H), 1.11 (d, J = 10.9 Hz, 1H), 0.91 – 0.77 (m, 8H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 85.40, 51.40, 39.66, 38.25, 35.71, 28.84, 27.22, 26.51, 25.61, 24.15, 14.06.

Ritter's trifluoroiodomethane-DMSO complex (Si-13)

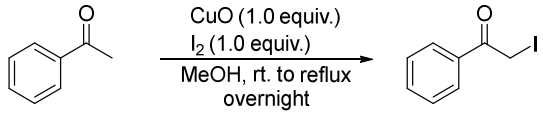


According to a literature procedure[197], Trifluoromethyl iodide was condensed in a pre-weighted and dry Schlenk-flask at -78°C. After determining the amount of CF_3I, dry DMSO (3.3 mL, 46 mmol, 2.0 equiv.) was added dropwise at -78°C. The reaction mixture was allowed to warm to rt. and the flask was sealed, wrapped with aluminum foil and stored at -18°C.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.50 (s, 12H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 40.74. **^{19}F NMR (400 MHz, $CDCl_3$):** δ (ppm) = -5.68.

[197] F. Sladojevich, E. McNeill, J. Börgel, S.-L. Zheng, T. Ritter, *Angew. Chem. Int. Ed.* **2015**, *54*, 3712-3716.

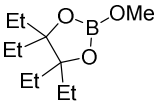
2-Iodo-1-phenylethan-1-one (Si-14)



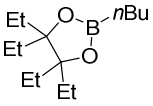
According to a literature procedure [198], Acetophenone (2.3 mL, 20 mmol, 1.0 equiv.) was dissolved in dry MeOH (50 mL) followed by addition of CuO (1.6 g, 20 mmol, 1.0 equiv.) and I_2 (5.1 g, 20 mmol, 1.0 equiv.). After stirring for 5 min, the solution was heated to reflux overnight. The next day, the solvent was removed *in vacuo*, and sat. aq. $Na_2S_2O_3$ (100 mL) was added. The suspension was extracted with EtOAc (3 × 100 mL), the combined organic fractions were washed with Brine and concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane – EtOAc; 9:1) afforded the title compound as red crystals (4.3, 18 mmol, 88 %). **^{1}H NMR (400 MHz, $CDCl_3$):** δ (ppm) = 8.01 – 7.97 (m, 2H), 7.63 – 7.58 (m, 1H), 7.52 – 7.46 (m, 2H), 4.36 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 192.96, 133.96, 129.16, 128.96, 1.85.

[198] G. Yin, M. Gao, N. She, S. Hu, A. Wu, Y. Pan, *Synthesis* **2007**, *2007*, 3113-3116.

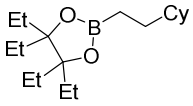
Boronic Esters:



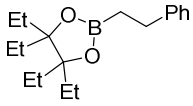
Si-15



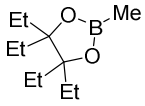
Si-3



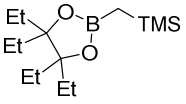
Si-16



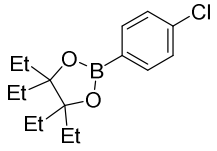
Si-17



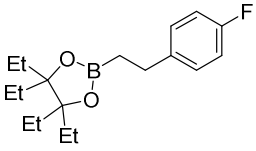
Si-18



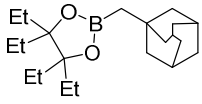
Si-19



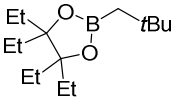
Si-20



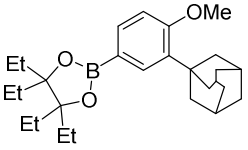
Si-21



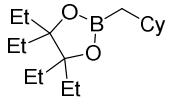
Si-22



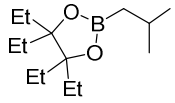
Si-23



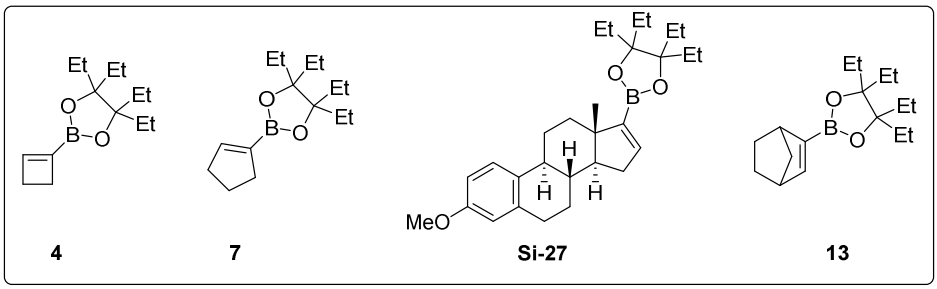
Si-24



Si-25

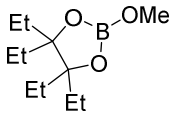


Si-26



4 **7** **Si-27** **13**

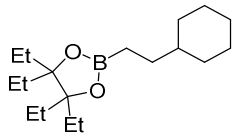
4,4,5,5-Tetraethyl-2-methoxy-1,3,2-dioxaborolane (MeO-B(Epin)) (<u>Si-15</u>)



According to GP-G (Method C) 3,4-diethylhexane-3,4-diol (8.7 g, 50 mmol, 1.0 equiv.) was reacted with $B(OMe)_3$ (6.7 mL, 60 mmol, 1.2 equiv.). Distillation of the crude mixture afforded the title compound as a colorless oil (10.3 g, 48 mmol, 96 %). Boiling Point (74°C | 4 × 10^{-1} mbar).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.60 (s, 3H), 1.77 – 1.57 (m, 8H), 0.91 (t, *J* = 7.5 Hz, 12H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 87.87, 52.76, 26.38, 8.82.

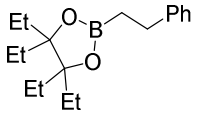
2-(2-Cyclohexylethyl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (Si-16)



According to GP-G (Method A), using (2-cyclohexylethyl)boronic acid (0.62 g, 4.0 mmol, 1.0 equiv.) and subsequent flash column chromatography (pentane/ EtOAc – 97:3) afforded the title compound as a colorless oil (0.95 g, 3.2 mmol, 81 %). **Note:** (2-cyclohexylethyl)boronic acid was prepared by treating $B(OiPr)_3$ (1.5 equiv.) 0.15 M in THF with freshly prepared (2-cyclohexylethyl)magnesium bromide with at -20°C and final recrystallization from water.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.74 – 1.59 (m, 13H), 1.31 – 1.26 (m, 2H), 1.22 – 1.09 (m, 4H), 0.90 (t, J = 7.5 Hz, 12H), 0.83 (td, J = 12.0, 3.2 Hz, 2H), 0.78 – 0.74 (m, 2H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 87.97, 40.09, 33.17, 31.76, 26.94, 26.63, 26.47, 8.96.

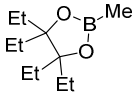
4,4,5,5-Tetraethyl-2-phenethyl-1,3,2-dioxaborolane (Si-17)



According to GP-G (Method A), using phenethylboronic acid (0.75 g, 5.0 mmol, 1.0 equiv.) and subsequent flash column chromatography (pentane/ EtOAc – 96:4) afforded the title compound as a colorless oil (0.98 g, 3.4 mmol, 68 %). **Note**: phenethylboronic acid was prepared by treating freshly prepared phenethyl magnesium bromide with $B(OMe)_3$ (1.5 equiv.) in THF (0.15 M) at -20°C.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = δ 7.26 – 7.23 (m, 2H), 7.23 – 7.20 (m, 2H), 7.16 – 7.13 (m, 1H), 2.77 – 2.73 (m, 2H), 1.63 (qd, J = 7.4, 4.5 Hz, 8H), 1.17 – 1.13 (m, 2H), 0.88 (t, J = 7.5 Hz, 12H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 144.68, 128.27, 125.55, 88.25, 30.21, 26.44, 8.93.

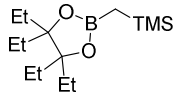
4,4,5,5-Tetraethyl-2-methyl-1,3,2-dioxaborolane (Si-18)



According to GP-G (Method A), using commercially available methylboronic acid (0.24 g, 4.0 mmol, 1.0 equiv.) and subsequent flash column chromatography (pentane/ EtOAc – 98:2) afforded the title compound as a colorless oil (0.98 g, 3.4 mmol, 54 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.65 (qd, J = 7.5, 5.9 Hz, 8H), 0.91 (t, J = 7.5 Hz, 12H), 0.25 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 88.19, 26.56, 8.95.

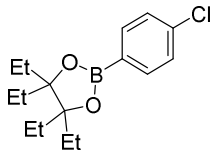
Trimethyl((4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)methyl)silane (Si-19)



According to GP-G (Method C), by quenching commercially available (trimethylsilyl)methyl magnesium chloride (3 mmol, 1.0 equiv.) in THF with MeO-B(Epin) (0.96 g, 4.5 mmol, 1.5 equiv.). Subsequent flash column chromatography (SiO_2; pentane/ EtOAc – 98:2) afforded the title compound as a colorless oil (0.65 g, 2.5 mmol, 82 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.64 (qd, J = 7.4, 3.1 Hz, 8H), 0.90 (t, J = 7.5 Hz, 21H), 0.08 (s, 2H), 0.04 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 87.92, 32.02, 29.73, 26.41, 8.96.

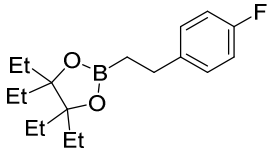
2-(4-chlorophenyl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (Si-20)



According to GP-G (Method A), using commercially available (4-chlorophenyl)boronic acid (0.63 g, 4.0 mmol, 1.0 equiv.) and subsequent flash column chromatography (pentane/ EtOAc – 96:4) afforded the title compound as a colorless solid (0.99 g, 3.4 mmol, 84 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.77 – 7.72 (m, 2H), 7.37 – 7.31 (m, 2H), 1.84 – 1.66 (m, 8H), 0.96 (t, J = 7.5 Hz, 12H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 137.48, 136.31, 128.11, 89.14, 26.56, 8.98.

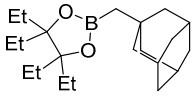
4,4,5,5-Tetraethyl-2-(4-fluorophenethyl)-1,3,2-dioxaborolane (Si-21)



According to GP-G (Method A), using (4-fluorophenethyl)boronic acid (0.67 g, 4.0 mmol, 1.0 equiv.) and subsequent flash column chromatography (pentane/ EtOAc – 98:2) afforded the title compound as a colorless oil (0.53 g, 1.7 mmol, 43 %). **Note:** (4-fluorophenethyl)boronic acid was prepared by treating freshly prepared (4-fluorophenethyl) magnesium bromide with $B(OMe)_3$ (1.5 equiv.) in THF (0.15 M) at -20°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.20 – 7.12 (m, 2H), 6.98 – 6.88 (m, 2H), 2.72 (t, J = 8.1 Hz, 2H), 1.68 – 1.56 (m, 8H), 1.15 – 1.10 (m, 2H), 0.88 (t, J = 7.5 Hz, 12H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 129.46, 129.39, 115.00, 114.79, 88.32, 29.43, 26.47, 8.92.

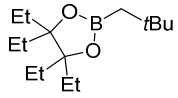
2-(Adamantan-1-yl)methyl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (Si-22)



According to GP-G (Method C), by quenching (adamantan-1-yl)methyl)magnesium chloride (3 mmol, 1.0 equiv.) in THF with MeO-B(Epin) (0.96 g, 4.5 mmol, 1.5 equiv.). Subsequent flash column chromatography (pentane/ EtOAc – 98:2) afforded the title compound as a colorless solid (0.70 g, 2.1 mmol, 71 %). **Note:** (adamantan-1-yl)methyl)magnesium chloride was prepared in THF (2 M) at 60°C. Activation of Mg-turnings with 1,2-dibromoethane.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.94 – 1.87 (m, 3H), 1.72 – 1.61 (m, 12H), 1.57 (d, *J* = 2.9 Hz, 6H), 0.91 (t, *J* = 7.5 Hz, 12H), 0.65 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 87.91, 44.82, 37.14, 31.79, 29.21, 26.37, 8.99.

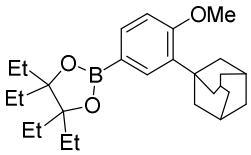
4,4,5,5-Tetraethyl-2-neopentyl-1,3,2-dioxaborolane (Si-23)



According to GP-G (Method C), by quenching neopentylmagnesium bromide (3 mmol, 1.0 equiv.) in THF with MeO-B(Epin) (0.96 g, 4.5 mmol, 1.5 equiv.). Subsequent flash column chromatography (SiO_2; pentane/ EtOAc – 99:1) afforded the title compound as a colorless oil (0.67 g, 2.6 mmol, 88 %). **Note:** neopentylmagnesium bromide was prepared in THF (1 M) at 25°C. Activation of Mg-turnings with 1,2-dibromoethane.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.65 (qd, J = 7.5, 5.9 Hz, 8H), 0.98 (s, 9H), 0.91 (t, J = 7.5 Hz, 12H), 0.81 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 87.92, 32.02, 29.73, 26.41, 8.96.

2-(3-(Adamantan-1-yl)-4-methoxyphenyl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (Si-24)

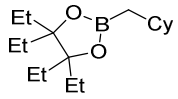


According to GP-G (Method C), by quenching (3-(adamantan-1-yl)-4-methoxyphenyl)magnesium bromide (1.9 mmol, 1.0 equiv.) in THF with MeO-B(Epin) (0.6 g, 2.9 mmol, 1.5 equiv.). Subsequent flash column chromatography (SiO_2; pentane/ EtOAc – 95:5) afforded the title compound as a colorless solid (0.77 g, 1.8 mmol, 96 %). **Note:** 3-(adamantan-1-yl)-4-methoxyphenyl)magnesium bromide was prepared in THF (1 M) at 25°C. Activation of Mg-turnings with 1,2-dibromoethane.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.70 – 7.64 (m, 2H), 6.89 – 6.84 (m, 1H), 3.85 (s, 3H), 2.17 – 2.04 (m, 10H), 1.84 – 1.68 (m, 13H), 0.97 (t, J = 7.5 Hz, 12H). **^{13}C NMR (100 MHz,**

$CDCl_3$): δ (ppm) = 137.65, 134.43, 133.15, 111.09, 88.50, 54.97, 40.60, 37.32, 29.28, 26.55, 9.05.

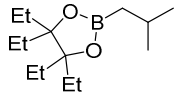
2-(Cyclohexylmethyl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (Si-25)



According to GP-G (Method C), by quenching (cyclohexylmethyl)magnesium bromide (4 mmol, 1.0 equiv.) in THF with MeO-B(Epin) (1.3 g, 6 mmol, 1.5 equiv.). Subsequent flash column chromatography (SiO_2; pentane/ EtOAc – 98:2) afforded the title compound as a colorless oil (0.63 g, 2.2 mmol, 56 %). **Note:** (cyclohexylmethyl)magnesium bromide was prepared in THF (1 M) at 25°C. Activation of Mg-turnings with 1,2-dibromoethane.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.73 – 1.58 (m, 14H), 1.52 – 1.44 (m, 1H), 1.29 – 1.05 (m, 4H), 0.90 (t, J = 7.5 Hz, 12H), 0.71 (d, J = 7.1 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 87.98, 36.03, 34.47, 33.64, 26.94, 26.75, 26.62, 26.48, 26.38, 8.95.

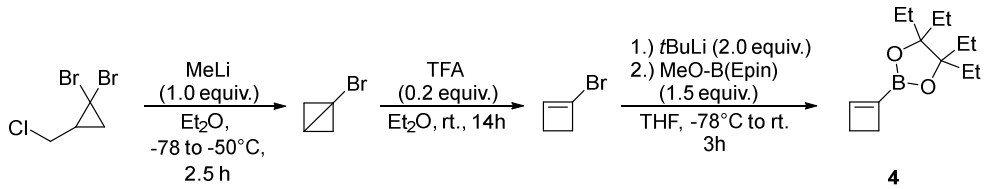
4,4,5,5-Tetraethyl-2-isobutyl-1,3,2-dioxaborolane (Si-26)



According to GP-G (Method A), using commercially available *i*butylboronic acid (0.41 g, 4.0 mmol, 1.0 equiv.) and subsequent flash column chromatography (pentane/ EtOAc – 98:2) afforded the title compound as a colorless oil (0.74 g, 3.1 mmol, 77 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.85 (dt, J = 13.5, 6.7 Hz, 1H), 1.74 – 1.57 (m, 8H), 0.98 – 0.84 (m, 18H), 0.73 (d, J = 7.1 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 87.98, 26.40, 25.36, 25.03, 8.95.

2-(Cyclobut-1-en-1-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (4)



4

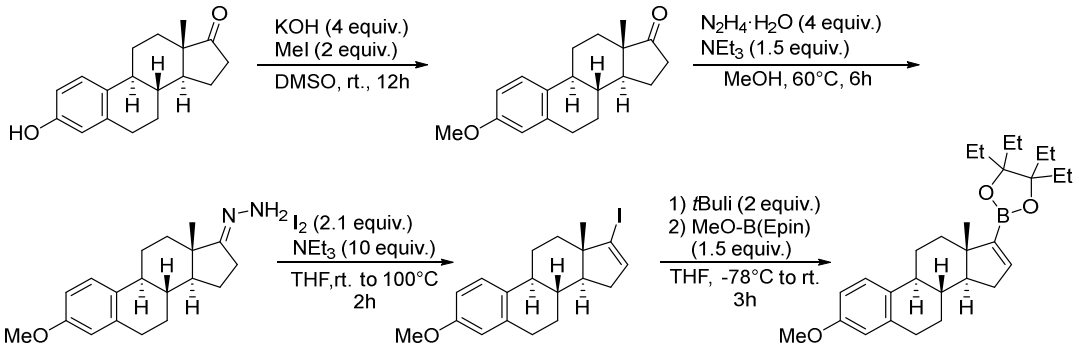
According to a literature procedure[199], a flame-dried Schlenk flask was charged with 1,1-dibromo-2-(chloromethyl)cyclopropane (4.83 g, 19.4 mmol, 1.00 equiv.) and dry Et_2O (15 mL). A solution of Methyllithium in Et_2O (19.4 mmol, 1.00 equiv.) was added dropwise at -78°C and the dark solution was allowed to stir for 30 min at that temperature.

[199] L. P. Jayathilaka, M. Deb, R. F. Standaert, *Org. Lett.* **2004**, *6*, 3659-3662.

The dry-ice acetone bath was allowed to warm to -50°C and the solvent was removed *in vacuo* using a cooling trap cooled to -78°C. To the colorless solution was added TFA (0.3 mL, 4 mmol, 0.2 equiv.) and the mixture was allowed to stir overnight under nitrogen. The next day, the organic phase was washed with sat. aq. $NaHCO_3$ (30 mL), sat. aq. $NaHSO_3$ (2 × 30 mL), Brine (50 mL) and dried over anhydrous $MgSO_4$. After concentration of the solution, the molarity was determined by NMR-titration using Mesitylene as standard. The degassed stock solution of 1-bromocyclobut-1-ene (4.9 mmol, 1.0 equiv.) was transferred in a flame-dried flask and dry THF (30 mL) was added. After cooling the solution to -78°C, *t*BuLi in pentane (9.8 mmol, 2.0 equiv.) was added dropwise *via* syringe-pump (0.3 mL/min) and the mixture was allowed to stir at that temperature for 1h. Subsequently 4,4,5,5-tetraethyl-2-methoxy-1,3,2-dioxaborolane (2.1 g, 9.8 mmol, 2.0 equiv.) was added dropwise and the solution was allowed to stir at -78°C for 1h before warming to rt. After hydrolysis with 2 M HCl (5 mL) the mixture was extracted with EtOAc (3 × 30 mL) and the combined organic fractions were washed with Brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* and subsequent flash column chromatography (pentane/ EtOAc – 99:1 to 97: 3 afforded the title compound as a colorless oil (0.83 g, 3.5 mmol, 72 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.81 (t, J = 1.0 Hz, 1H), 2.65 – 2.59 (m, 4H), 1.76 – 1.58 (m, 8H), 0.91 (t, J = 7.5 Hz, 12H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 153.28, 88.33, 32.19, 31.39, 26.48, 8.97.

4,4,5,5-Tetraethyl-2-((8*S*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-17-yl)-1,3,2-dioxaborolane (Si-27)



Estrone (2.0 g, 7.4 mmol, 1.0 equiv.) was charged to a solution of KOH (1.7 g, 30 mmol, 4 equiv.) in DMSO (20 mL). MeI (0.92 mL,15 mmol, 2.0 equiv.) was added at room temperature and the reaction mixture was stirred overnight. The colorless precipitate was collected by filtration, washed with water (50 mL) and dried *in vacuo,* to afford (8*R*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[a]phenanthren-17-one as a colorless solid (1.7 g, 6.1 mmol, 83 %).[200]

[200] H. E. Montenegro, P. Ramírez-López, M. C. de la Torre, M. Asenjo, M. A. Sierra, *Chem. Eur. J.* **2010**, *16*, 3798-3814.

The full amount of the obtained compound was directly employed in further synthesis. Hydrazine monohydrate (1.2 mL, 24 mmol, 4.0 equiv.) was added to a solution of the methylated steroid in MeOH (30 mL), followed by triethylamine (1.3 mL, 9.2 mmol, 1.5 equiv.). The reaction mixture was heated to reflux for 6h, cooled to rt. and the volatiles were removed *in vacuo* in a well ventilated hood. Crude (*E*)-((8*R*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[a]phenanthren-17-ylidene)hydrazine was obtained as a light yellow solid (1.78 g, 6.0 mmol, 98 %).[200]

The full amount of the crude hydrazone was dissolved in THF (60 mL) and NEt_3 (8.4 mL, 60 mmol, 10 equiv.) was added, followed by dropwise addition of a solution of I_2 (3.3 g, 13 mmol, 2.1 equiv.) in THF (30 mL). Subsequently, the solvent was removed *in vacuo* and Pyridine (25 mL) was added. The reaction mixture was refluxed for 1h, the cooled to rt. and dissolved in EtOAc (100 mL). The organic fraction was washed with HCl (2 M, 50 mL), Na_2SO_3 (50 mL), Water, Brine and was dried over anhydrous $MgSO_4$. After removal of the solvents *in vacuo* the residue was purified via flash column chromatography (SiO_2; Pentane – EtOAc: 99/1 to 97/3). (8*R*,9*S*,13*S*,14*S*)-17-Iodo-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6*H*-cyclopenta[a]phenanthrene was obtained as colorless crystals (1.3 g, 3.2 mmol, 54 %).[201]

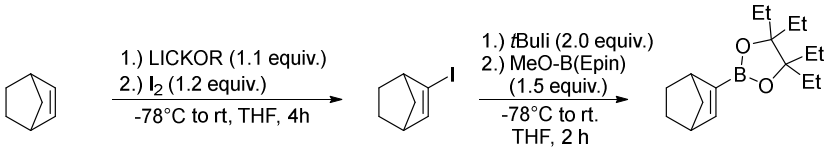
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.20 (dd, J = 8.7, 1.1 Hz, 1H), 6.72 (dd, J = 8.7, 2.8 Hz, 1H), 6.65 (t, J = 1.8 Hz, 1H), 6.17 (dd, J = 3.3, 1.7 Hz, 1H), 3.78 (s, 3H), 2.97 – 2.83 (m, 2H), 2.45 – 2.36 (m, 1H), 2.32 – 2.21 (m, 2H), 2.11 – 1.98 (m, 1H), 1.98 – 1.89 (m, 1H), 1.80 – 1.37 (m, 6H), 0.77 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 157.62, 137.94, 137.54, 132.59, 126.20, 113.94, 112.83, 111.57, 55.35, 54.15, 50.42, 44.28, 37.93, 36.40, 33.59, 29.81, 27.59, 26.52, 15.42.

The vinyl iodide (0.78 g, 2.0 mmol, 1.0 equiv.) was dissolved in dry THF (40 mL) and cooled to -78°C. *t*BuLi in pentane (4.0 mmol, 2.0 equiv.) was added dropwise over 15 min and the reaction mixture was allowed to stir at that temperature for 45 min. MeO-B(Epin) (0.64 g, 3.0 mmol, 1.5 equiv.) was added dropwise to the solution and stirring at -78°C was continued for 1h before warming to rt. The reaction was quenched by addition of HCl (1 M, 2 mL) and stirred for 30 min. before being extracted with EtOAc (3 × 40 mL). The combined organic fractions were washed with Brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Flash-column chromatography (SiO_2; Pentane – EtOAc: 99/1 to 97/3; long column) afforded the title compound as a light yellow oil (0.65 g, 1.4 mmol, 72 %)

[201] B. Schweder, E. Uhlig, *J. Prakt. Chem.* **1991**, *333*, 223-228.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.24 – 7.18 (m, 1H), 6.72 (dt, J = 8.6, 2.6 Hz, 1H), 6.64 (t, J = 3.0 Hz, 1H), 6.53 (dd, J = 3.1, 1.6 Hz, 1H), 3.78 (d, J = 0.9 Hz, 3H), 2.99 – 2.80 (m, 2H), 2.43 – 2.18 (m, 4H), 2.11 – 2.01 (m, 2H), 1.98 – 1.88 (m, 1H), 1.78 – 1.38 (m, 12H), 1.00 – 0.89 (m, 8H), 0.85 – 0.74 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 157.45, 145.72, 144.11, 138.16, 137.94, 137.54, 133.43, 133.24, 132.58, 129.41, 126.23, 113.90, 112.83, 111.47, 87.84, 60.55, 56.03, 55.33, 54.16, 50.42, 48.18, 45.92, 44.60, 44.29, 37.94, 37.71, 37.47, 36.41, 36.07, 33.44, 29.97, 28.41, 28.12, 27.59, 26.92, 26.49, 21.22, 17.22, 17.04, 15.42, 14.35, 9.00.

2-(bicyclo[2.2.1]hept-2-en-2-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (13)



According to a modified literature procedure[202], a flame-dried flask was charged with norbornene (1.9 g, 20 mmol, 1.0 equiv.), KO*t*Bu (2.5 g, 1.1 equiv.) and dry THF (20 mL) was added. After cooling to -78°C, *n*BuLi (22 mmol, 1.1 equiv.) was added *via* syringe-pump (0.3 mL/min). The reaction mixture was allowed to stir at the aforementioned temperature for 1h and was then allowed to warm to -50°C for 30 min. After cooling back to -78°C, a solution of I_2 (6.1 g, 24 mmol, 1.2 equiv.) in THF (10 mL) was added via syringe-pump (0.9 mL/min). After warming to rt. for 1h, the reaction was quenched with sat. aq. NH_4Cl (10 mL). EtOAc (50 mL) was added and the organic phase was seperated and washed with sat. aq. $Na_2S_2O_3$ (2 × 50 mL). Organic extracts were washed with Brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane) afforded 2-iodobicyclo[2.2.1]hept-2-ene as a colorless oil (1.9 g, 8.6 mmol, 43 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.36 (d, J = 3.2 Hz, 1H), 2.96 – 2.93 (m, 1H), 2.81 – 2.77 (m, 1H), 1.64 – 1.52 (m, 3H), 1.14 – 1.04 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 144.28, 96.78, 53.54, 48.24, 44.90, 25.86, 24.30.

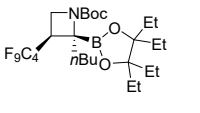
A flame-dried schlenk flask was charged with 2-iodobicyclo[2.2.1]hept-2-ene (0.65 g, 2.9 mmol, 1.0 equiv.) and dry THF (30 mL) was added. The solution was cooled to -78°C and *t*BuLi (5.8 mmol, 2.0 equiv.) was added dropwise. The yellow reaction mixture was allowed to stir for 30min at -78°C before MeO-B(Epin) (0.93 g, 4.4 mmol, 1.5 equiv.) was added dropwise.

[202] P. Mayo, W. Tam, *Tetrahedron* **2002**, *58*, 9527-9540.

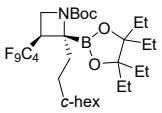
After stirring for a further 30min at -78°C the now colorless solution was allowed to warm to rt. for 1h before quenching with sat. aq. NH_4Cl (5 mL). The organic phase was seperated and the aqeous fraction extracted with EtOAc (3 × 30 mL). The combined organic fractions were washed with Brine, dried over $MgSO_4$ and concentrated *in vacuo*. Final flash column chromatography (SiO_2; pentane – EtOAc: 98:2) afforded the title compound as a colorless oil. (0.64 g, 2.3 mmol, 79 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.77 (d, J = 2.9 Hz, 1H), 3.07 – 3.04 (m, 1H), 2.90 – 2.87 (m, 1H), 1.72 – 1.60 (m, 11H), 0.93 – 0.89 (m, 15H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = δ 151.24, 88.01, 48.54, 43.48, 27.33, 26.57, 26.47, 24.75, 24.22, 9.06, 8.94.

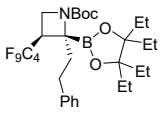
Overview: trisubstituted Azetidines:



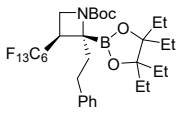
3a (NOESY)
dr = 8:1



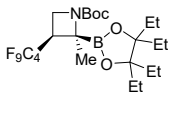
3b
dr = 8:1



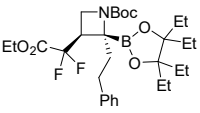
3c
dr = 10:1



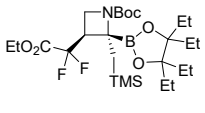
3d
dr = >20:1



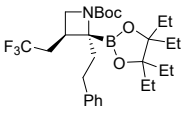
3e
dr = 1,5:1



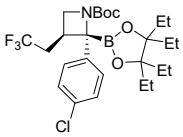
3f
dr = >20:1



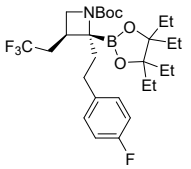
3g
dr = >20:1



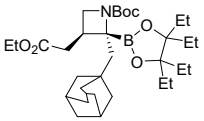
3h
dr = 7:1



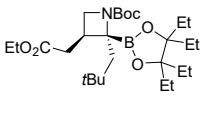
3i
dr = 4:1



3j
dr = 7:1



3k
dr = >20:1



3l
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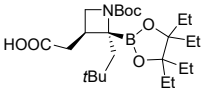

3l'
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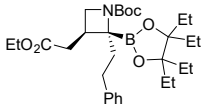
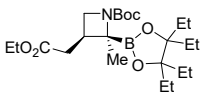
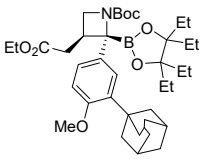


3m
dr = >20:1

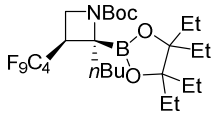


3n
dr = 2:1



3o
dr = 2:1

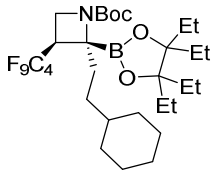
***tert*-Butyl (2*R*,3*S*)-2-butyl-3-(perfluorobutyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (3a)**



According to GP-A, using 2-butyl-4,4,5,5-tetraethyl-1,3,2-dioxaborolane **Si-3** (94 mg, 0.39 mmol, 1.3 equiv.) and nonafluoro-1-iodobutane (0.15 mL, 0.9 mmol, 3.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 99:1 to 98:2) yielded the title compound as a colorless oil (0.17 g, 0.28 mmol, 93 %). ^{19}F NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 8:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^{1}H NMR.

^{1}H NMR (600 MHz, Acetone-D$_6$): δ (ppm) = 3.97 – 3.89 (m, 1H), 3.85 (d, J = 8.6 Hz, 1H), 3.40 – 3.27 (m, 1H), 1.92 – 1.84 (m, 2H), 1.82 – 1.68 (m, 8H), 1.67 – 1.55 (m, 2H), 1.43 (d, J = 6.0 Hz, 9H), 1.39 – 1.33 (m, 2H), 0.97 – 0.87 (m, 15H). **^{13}C NMR (150 MHz, Acetone-D$_6$):** δ (ppm) = 155.51, 154.75, 118.31, 117.04, 116.40, 89.56, 89.50, 78.88, 78.65, 46.43, 46.40, 46.37, 44.95, 44.91, 44.88, 38.04, 37.67, 37.51, 37.36, 37.33, 37.17, 37.02, 36.90, 27.76, 27.72, 27.63, 25.68, 25.67, 25.35, 25.25, 25.14, 25.00, 22.89, 22.88, 13.51, 13.47, 8.44, 8.24, 7.89, 7.63. **^{19}F NMR (400 MHz, Acetone-D$_6$):** δ (ppm) = -81.88, -81.89, -81.91, -81.93, -81.94, -81.95, -81.96, -81.97, -112.98, -113.16, -113.70, -113.89, -115.77, -115.80, -115.84, -115.88, -115.91, -115.96, -116.46, -116.49, -116.53, -116.56, -116.60, -116.64, -117.22, -117.25, -117.29, -117.32, -117.35, -123.25, -123.56, -124.04, -124.31, -124.33, -124.34, -124.35, -124.37, -124.38, -124.72. **HRMS** (ESI) m/z: $[H]^+$ calcd for $C_{26}H_{41}BF_9NO_4H^+$: 614.3065 found: 614.3072. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2934 (m), 2900 (w), 1732 (w), 1702 (s), 1458 (m), 1388 (s), 1362 (s), 1314 (m), 1290 (m), 1232 (vs), 1158 (s), 1134 (vs), 1112 (s), 1094 (m), 1066 (m), 1052 (m), 1026 (m), 966 (w), 922 (s), 890 (w), 854 (m), 800 (w), 776 (w), 744 (w), 726 (m), 680 (vw).

***tert*-Butyl (2*R*,3*S*)-2-(2-cyclohexylethyl)-3-(perfluorobutyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (3b)**

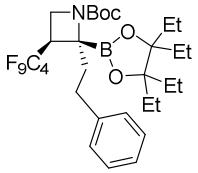


According to GP-A, using 2-(2-cyclohexylethyl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane **Si-16** (115 mg, 0.39 mmol, 1.3 equiv.) and nonafluoro-1-iodobutane (0.15 mL, 0.9 mmol, 3.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 99:1 to 97:3) yielded the title compound as a colorless oil (0.12 g, 0.18 mmol, 60 %). ^{19}F NMR analysis of the crude

reaction mixture indicated a diastereomeric ratio of 8:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^{1}H NMR.

^{1}H NMR (600 MHz, Acetone-D$_6$): δ (ppm) = 3.93 (dd, J = 17.6, 8.7 Hz, 1H), 3.85 (d, J = 8.7 Hz, 1H), 3.40 – 3.21 (m, 1H), 1.95 – 1.83 (m, 2H), 1.80 – 1.67 (m, 12H), 1.66 – 1.61 (m, 1H), 1.43 (d, J = 8.3 Hz, 9H), 1.31 – 1.13 (m, 6H), 0.97 – 0.87 (m, 14H). **^{13}C NMR (150 MHz, Acetone-D$_6$):** δ (ppm) = 155.45, 154.79, 118.31, 116.40, 89.58, 89.48, 87.53, 78.90, 78.64, 46.44, 44.89, 38.09, 37.63, 37.47, 37.32, 37.15, 36.99, 35.66, 34.64, 33.39, 33.37, 33.31, 33.16, 32.91, 30.85, 30.60, 27.78, 27.72, 26.46, 26.44, 26.12, 25.71, 25.35, 25.16, 24.99, 8.46, 8.25, 7.93, 7.66. **^{19}F NMR (400 MHz, Acetone-D$_6$):** δ (ppm) = -81.87, -81.88, -81.90, -81.92, -81.95, -81.96, -112.80, -113.17, -113.52, -113.90, -115.81, -116.40, -117.17, -123.23, -123.59, -124.02, -124.36, -124.69, -124.95, -125.48, -125.76, -126.72, -126.76, -126.79, -126.82, -126.86, -126.87. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{30}H_{47}BF_9NO_4Na^+$: 690.3351; found: 690.3365. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2926 (m), 2854 (w), 1704 (m), 1478 (w), 1456 (w), 1388 (m), 1362 (m), 1316 (m), 1292 (w), 1232 (vs), 1202 (s), 1182 (s), 1160 (s), 1132 (vs), 1068 (w), 1028 (w), 958 (w), 922 (m), 876 (w), 854 (w), 810 (w), 794 (w), 772 (w), 744 (m), 726 (m).

tert-Butyl (2*R*,3*S*)-3-(perfluorobutyl)-2-phenethyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (3c)

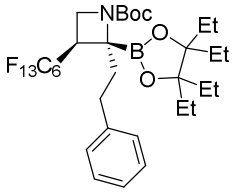


According to GP-A, using 4,4,5,5-tetraethyl-2-phenethyl-1,3,2-dioxaborolane **Si-17** (112 mg, 0.39 mmol, 1.3 equiv.) and nonafluoro-1-iodobutane (0.15 mL, 0.9 mmol, 3.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 98:2) yielded the title compound as a colorless oil (0.15 g, 0.23 mmol, 76 %). ^{19}F NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 10:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^{1}H NMR.

^{1}H NMR (600 MHz, Acetone-D$_6$): δ (ppm) = 7.32 – 7.23 (m, 4H), 7.20 – 7.15 (m, 1H), 3.99 (dt, J = 22.1, 8.2 Hz, 1H), 3.92 (d, J = 8.2 Hz, 1H), 3.62 – 3.41 (m, 1H), 3.03 – 2.93 (m, 1H), 2.74 – 2.65 (m, 1H), 2.23 – 2.12 (m, 2H), 1.87 – 1.69 (m, 8H), 1.45 (d, J = 9.0 Hz, 9H), 0.97 – 0.89 (m, 12H). **^{13}C NMR (150 MHz, Acetone-D$_6$):** δ (ppm) = 155.64, 154.81, 142.61, 142.29, 128.45, 128.34, 128.26, 128.25, 125.81, 125.64, 110.00, 89.78, 89.72, 79.16, 78.88, 41.13, 39.75, 37.92, 37.75, 37.60, 37.35, 37.20, 37.04, 30.41, 29.79, 27.81, 27.71, 25.75, 25.35, 25.22, 25.01, 8.47, 8.24, 7.99, 7.69. **^{19}F NMR (400 MHz, Acetone-D$_6$):** δ (ppm) = -81.85, -81.86, -81.88, -81.89, -81.90, -81.91, -81.92, -81.94, -81.95, -112.90, -113.01, -113.64, -113.75, -115.87, -116.26, -116.60, -117.00, -123.18, -123.49, -123.98, -124.27, -124.64, -

124.88, -125.43, -125.69, -125.98, -126.75, -126.77, -126.79, -126.81, -126.82, -126.84. **HRMS** (ESI) m/z: $[H]^+$ calcd for $C_{30}H_{41}BF_9NO_4H^+$: 661.3065; found: 661.3075. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2890 (w), 1704 (s), 1496 (vw), 1478 (w), 1456 (w), 1388 (m), 1362 (s), 1342 (m), 1292 (w), 1232 (vs), 1184 (s), 1162 (s), 1132 (vs), 1070 (m), 1028 (m), 990 (w), 956 (w), 922 (m), 898 (w), 870 (w), 854 (m), 794 (m), 770 (w), 744 (m), 726 (m).

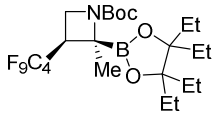
***tert*-Butyl (2*R*,3*S*)-3-(perfluorohexyl)-2-phenethyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (3d)**



According to GP-A, using 4,4,5,5-tetraethyl-2-phenethyl-1,3,2-dioxaborolane **Si-17** (112 mg, 0.39 mmol, 1.3 equiv.) and perfluorohexyl iodide (0.19 mL, 0.9 mmol, 3.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 99:1 to 98:2) yielded the title compound as a colorless oil (0.17 g, 0.22 mmol, 74 %). ^{19}F NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^1H NMR.

^1H NMR (600 MHz, Acetone-D_6): δ (ppm) = 7.32 – 7.22 (m, 4H), 7.21 – 7.15 (m, 1H), 4.02 – 3.90 (m, 2H), 3.62 – 3.42 (m, 1H), 3.04 – 2.92 (m, 1H), 2.75 – 2.64 (m, 1H), 2.24 – 2.12 (m, 2H), 1.86 – 1.71 (m, 8H), 1.46 (d, J = 9.1 Hz, 9H), 0.98 – 0.89 (m, 12H). **^{13}C NMR (150 MHz, Acetone-D_6):** δ (ppm) = 156.52, 155.70, 143.51, 143.18, 129.23, 129.14, 126.69, 126.53, 90.67, 90.61, 80.05, 79.77, 42.01, 40.63, 31.30, 28.70, 28.60, 26.64, 26.24, 25.91, 9.36, 9.12, 8.88, 8.58. **^{19}F NMR (400 MHz, Acetone-D_6):** δ (ppm) = -81.64, -81.67, -81.69, -112.55, -112.71, -113.28, -113.43, -115.68, -116.04, -116.39, -116.77, -122.29, -122.56, -123.07, -123.39, -123.75, -124.34, -124.59, -126.71. **HRMS** (ESI) m/z: $[H]^+$ calcd for $C_{32}H_{41}BF_{13}NO_4H^+$:762.3001; found: 762.3019. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2956 (w), 2894 (vw), 1704 (m), 1690 (m), 1496 (vw), 1476 (w), 1456 (w), 1416 (m), 1390 (m), 1362 (m), 1316 (w), 1296 (w), 1274 (w), 1230 (s), 1206 (s), 1168 (s), 1142 (vs), 1124 (s), 1068 (w), 1028 (w), 978 (w), 968 (w), 914 (m), 882 (w), 846 (vw), 792 (w), 770 (w), 746 (w), 716 (m).

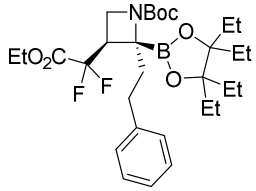
***tert*-butyl (2*R*,3*S*)-2-methyl-3-(perfluorobutyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (3e)**



According to GP-A, using 4,4,5,5-tetraethyl-2-methyl-1,3,2-dioxaborolane **Si-18** (77 mg, 0.39 mmol, 1.3 equiv.) and nonafluoro-1-iodobutane (0.15 mL, 0.9 mmol, 3.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 99:1 to 98:2) yielded the title compound as a colorless oil (0.13 g, 0.23 mmol, 78 %). ^{19}F NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 1:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^{1}H NMR.

^{1}H NMR (600 MHz, Acetone-D_6): δ (ppm) = 4.18 – 3.83 (m, 2H), 3.48 – 3.15 (m, 1H), 1.84 – 1.66 (m, 8H), 1.60 – 1.51 (m, 3H), 1.43 (d, J = 3.2 Hz, 9H), 0.99 – 0.86 (m, 12H). **^{13}C NMR (150 MHz, Acetone-D_6):** δ (ppm) = 155.90, 155.71, 154.82, 89.68, 79.18, 78.81, 27.76, 27.72, 27.66, 25.86, 25.75, 25.70, 25.38, 25.13, 25.02, 24.95, 24.81, 8.41, 8.24, 8.20, 8.08, 7.88, 7.65. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{23}H_{35}BF_9NO_4Na^+$: 594.2413; found: 594.2418. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2890 (w), 1704 (m), 1460 (w), 1384 (m), 1362 (m), 1316 (w), 1290 (w), 1236 (s), 1198 (s), 1162 (s), 1142 (vs), 1058 (m), 1026 (w), 972 (w), 956 (vw), 924 (m), 888 (w), 874 (w), 860 (w), 800 (w), 776 (w), 734 (w).

***tert*-Butyl (2*R*,3*S*)-3-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-phenethyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (3f)**

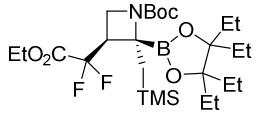


According to GP-A, using 4,4,5,5-tetraethyl-2-phenethyl-1,3,2-dioxaborolane **Si-17** (112 mg, 0.39 mmol, 1.3 equiv.) and ethyl iododifluoroacetate (145 mg, 0.6 mmol, 2.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 93:7) yielded the title compound as a colorless oil (82 mg, 0.14 mmol, 48 %). ^{19}F NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^{1}H NMR.

^{1}H NMR (600 MHz, Acetone-D_6): δ (ppm) = 7.32 – 7.14 (m, 5H), 4.41 – 4.28 (m, 2H), 3.93 – 3.82 (m, 2H), 3.49 – 3.39 (m, 1H), 2.97 (tdd, J = 13.4, 10.5, 6.0 Hz, 1H), 2.72 – 2.65 (m, 1H), 2.20 – 2.08 (m, 2H), 1.85 – 1.67 (m, 8H), 1.45 (d, J = 10.9 Hz, 9H), 1.37 – 1.33 (m, 3H), 0.95 – 0.88 (m, 12H). **^{13}C NMR (150 MHz, Acetone-D_6):** δ (ppm) = 156.19, 155.73, 143.71, 143.36, 129.33, 129.20, 129.15, 126.64, 126.46, 90.57, 90.37, 79.46, 79.26, 63.87, 41.46, 40.16, 31.28, 30.72, 28.70, 28.64, 26.72, 26.28, 26.07, 25.65, 14.15, 9.57, 9.19, 8.89, 8.41. **^{19}F NMR (400 MHz, Acetone-D_6):** δ (ppm) = -105.26, -105.30, -105.98, -106.03, -106.59, -106.64, -107.30, -107.35, -108.41, -108.45, -109.12, -109.16, -110.27, -110.32, -111.00, -111.05. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{30}H_{46}BF_2NO_6Na^+$: 588.3284; found: 588.3295. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (m), 2888 (w), 1772 (m), 1698 (s), 1604 (vw), 1496 (w), 1476 (w), 1456

(m), 1410 (m), 1388 (s), 1362 (s), 1342 (m), 1306 (s), 1258 (m), 1240 (m), 1220 (m), 1156 (s), 1100 (vs), 1072 (m), 1044 (m), 1018 (m), 982 (w), 950 (w), 920 (m), 864 (w), 826 (w), 768 (m), 752 (m).

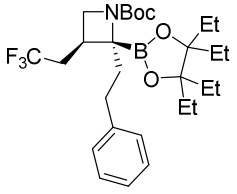
***tert*-Butyl (2*S*,3*S*)-3-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-2-((trimethylsilyl)methyl)azetidine-1-carboxylate (3g)**



According to GP-A, using trimethyl((4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)methyl)silane **Si-19** (0.11 g, 0.39 mmol, 1.3 equiv.) and ethyl iododifluoroacetate (145 mg, 0.6 mmol, 2.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 92:8) yielded the title compound as a colorless oil (103 mg, 0.19 mmol, 63 %). ^{19}F NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^{1}H NMR.

^{1}H NMR (400 MHz, Acetone-D_6): δ (ppm) = δ 4.43 – 4.27 (m, 2H), 3.95 – 3.74 (m, 2H), 3.35 – 3.10 (m, 1H), 1.86 – 1.63 (m, 8H), 1.43 (d, J = 8.6 Hz, 9H), 1.40 – 1.31 (m, 4H), 1.28 – 1.19 (m, 1H), 0.97 – 0.85 (m, 12H), 0.13 (d, J = 21.6 Hz, 9H). **^{13}C NMR (100 MHz, Acetone-D_6):** δ (ppm) = 156.26, 155.96, 90.59, 90.39, 79.36, 79.18, 66.11, 63.86, 47.17, 45.20, 43.89, 43.65, 42.29, 42.06, 41.82, 28.73, 28.70, 28.00, 26.74, 26.21, 26.15, 25.64, 15.61, 14.18, 9.67, 9.14, 8.30, 0.91, 0.68, 0.44. **^{19}F NMR** (**400 MHz, Acetone-D_6**): δ (ppm) = -104.58, -104.62, -105.31, -105.35, -106.75, -106.81, -107.46, -107.52, -108.68, -108.71, -109.39, -109.43, -110.71, -110.77, -111.45, -111.50. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{26}H_{48}BF_2NO_6SiNa^+$: 570.3201; found: 570.3207. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2952 (m), 2888 (w), 1774 (m), 1762 (m), 1702 (s), 1478 (w), 1458 (m), 1390 (s), 1364 (s), 1334 (m), 1306 (s), 1244 (s), 1160 (s), 1092 (vs), 1066 (m), 1028 (m), 994 (w), 924 (m), 912 (m), 856 (vs), 836 (vs), 790 (w), 768 (m), 726 (w).

***tert*-Butyl (2*R*,3*S*)-2-phenethyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-3-(2,2,2-trifluoroethyl)azetidine-1-carboxylate (3h)**

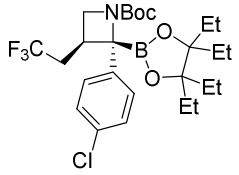


According to GP-A, using 4,4,5,5-tetraethyl-2-phenethyl-1,3,2-dioxaborolane **Si-17** (112 mg, 0.39 mmol, 1.3 equiv.) and 1,1,1-trifluoro-2-iodoethane (89 µL, 0.9 mmol, 3.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 98:2 to 95:5) yielded the title compound as a colorless oil (62 mg, 0.12 mmol, 39 %). ^{19}F NMR analysis of the crude

reaction mixture indicated a diastereomeric ratio of 7:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^{1}H NMR.

^{1}H NMR (600 MHz, Acetone-D$_6$): δ (ppm) = 7.31 – 7.21 (m, 4H), 7.20 – 7.12 (m, 1H), 4.01 – 3.86 (m, 1H), 3.75 – 3.62 (m, 1H), 2.93 – 2.65 (m, 3H), 2.63 – 2.48 (m, 2H), 2.19 – 2.07 (m, 2H), 1.90 – 1.68 (m, 8H), 1.44 (s, 9H), 1.03 – 0.89 (m, 12H). **^{13}C NMR (150 MHz, Acetone-D$_6$):** δ (ppm) = 143.99, 143.69, 129.15, 126.41, 90.52, 90.09, 79.36, 53.33, 51.86, 41.58, 40.06, 36.30, 36.02, 35.75, 35.47, 32.22, 31.47, 28.73, 28.66, 26.58, 26.37, 14.36, 13.93, 9.27, 9.02. **^{19}F NMR (400 MHz, Acetone-D$_6$):** -65.83, -65.86, -65.89, -65.92, -65.98, -66.00, -66.03, -66.06. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{28}H_{43}BF_3NO_4Na^+$: 548.3129; found: 548.3141. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (m), 2886 (w), 1696 (s), 1604 (vw), 1496 (w), 1478 (w), 1456 (m), 1390 (s), 1362 (s), 1330 (m), 1272 (m), 1254 (s), 1232 (m), 1140 (vs), 1110 (m), 1050 (m), 1028 (w), 1004 (m), 980 (w), 954 (w), 920 (m), 854 (w), 836 (w), 782 (w), 752 (w).

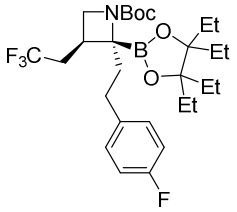
tert-Butyl (2*S*,3*S*)-2-(4-chlorophenyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-3-(2,2,2-trifluoroethyl)azetidine-1-carboxylate (3i)



According to GP-A, using 2-(4-chlorophenyl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane **Si-20** (0.12 g, 0.39 mmol, 1.3 equiv.) and 1,1,1-trifluoro-2-iodoethane (89 µL, 0.9 mmol, 3.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 97/3) yielded the title compound as a colorless oil (65 mg, 0.12 mmol, 41 %).^{19}F NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 4:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 0,75:1, as indicated by ^{1}H NMR.

^{1}H NMR (800 MHz, Acetone-D$_6$): δ (ppm) = 7.51 – 7.26 (m, 4H), 4.40 – 4.20 (m, 1H), 3.81 – 3.63 (m, 1H), 3.10 – 2.99 (m, 1H), 1.87 – 1.74 (m, 10H), 1.50 (d, J = 7.4 Hz, 9H), 0.97 – 0.90 (m, 12H). **^{13}C NMR (200 MHz, Acetone-D$_6$):** δ (ppm) = 129.31, 128.52, 91.15, 90.72, 90.30, 80.00, 78.88, 54.96, 53.60, 52.04, 28.61, 28.50, 27.87, 27.83, 26.56, 26.52, 9.45, 9.23, 8.98, 8.91. **^{19}F NMR (400 MHz, Acetone-D$_6$):** δ (ppm) = -65.23, -65.25, -65.28, -65.85, -65.88, -65.91. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{26}H_{38}BClF_3NO_4^+$: 554.2433; found: 554.2428. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2946 (w), 2888 (w), 1700 (vs), 1490 (w), 1458 (w), 1436 (w), 1388 (s), 1362 (s), 1340 (s), 1292 (m), 1274 (m), 1246 (vs), 1144 (vs), 1092 (s), 1030 (m), 1014 (m), 998 (m), 968 (m), 922 (m), 906 (m), 852 (w), 826 (w), 782 (m), 722 (vw), 704 (vw).

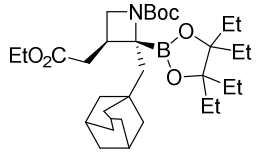
***tert*-Butyl (2*R*,3*S*)-2-(4-fluorophenethyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-3-(2,2,2-trifluoroethyl)azetidine-1-carboxylate (3j)**



According to GP-A, using 4,4,5,5-tetraethyl-2-(4-fluorophenethyl)-1,3,2-dioxaborolane **Si-21** (0.12 g, 0.39 mmol, 1.3 equiv.) and 1,1,1-trifluoro-2-iodoethane (89 µL, 0.9 mmol, 3.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 96:4) yielded the title compound as a colorless oil (29 mg, 0.05 mmol, 18 %). ^{19}F NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 7:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^{1}H NMR.

^{1}H NMR (400 MHz, Acetone-D_6): δ (ppm) = 7.30 – 7.20 (m, 2H), 7.08 – 6.97 (m, 2H), 3.99 – 3.86 (m, 1H), 3.73 – 3.65 (m, 1H), 2.88 – 2.64 (m, 4H), 2.61 – 2.51 (m, 2H), 2.11 – 2.07 (m, 1H), 1.86 – 1.70 (m, 8H), 1.42 (d, J = 4.3 Hz, 9H), 0.99 – 0.89 (m, 12H). **^{13}C NMR (100 MHz, Acetone-D_6):** δ (ppm) = 129.84, 129.76, 128.33, 125.58, 114.67, 112.00, 89.64, 89.64, 79.25, 78.47, 52.39, 50.93, 40.67, 39.14, 35.38, 35.10, 34.83, 34.55, 27.73, 27.49, 27.47, 25.65, 25.45, 19.88, 13.57, 8.34, 8.14, 8.08. **^{19}F NMR (400 MHz, Acetone-D_6):** δ (ppm) = -65.77, -65.80, -65.83, -65.87, -65.90, -65.92, -65.98, -66.01, -66.04, -66.07, -119.41, -119.42, -119.43, -119.44, -119.47, -119.62, -119.63, -119.64, -119.66, -119.67, -119.68, -119.69. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{28}H_{42}BF_4NO_4^+$: 566.3041; found: 566.3046. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2886 (w), 1740 (w), 1696 (s), 1602 (vw), 1510 (m), 1478 (w), 1456 (w), 1390 (s), 1362 (s), 1330 (m), 1274 (m), 1254 (s), 1224 (m), 1142 (vs), 1112 (m), 1100 (m), 1054 (m), 1026 (m), 1006 (m), 982 (w), 956 (w), 922 (m), 854 (w), 832 (m), 776 (m).

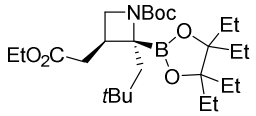
***tert*-Butyl (2*R*,3*S*)-2-(adamantan-1-ylmethyl)-3-(2-ethoxy-2-oxoethyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (3k)**



According to GP-A, using 2-(adamantan-1-yl)methyl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane **Si- 22** (0.13 g, 0.39 mmol, 1.3 equiv.) and ethyl iodoacetate (71 µL, 0.6 mmol, 2.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 91:9) yielded the title compound as a colorless oil (0.11 g, 0.2 mmol, 66 %). ^{1}H NMR and GC analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 0.75:1, as indicated by ^{1}H NMR.

^{1}H NMR (800 MHz, Acetone-D$_6$): δ (ppm) = 4.12 – 4.04 (m, 2H), 3.89 (dt, J = 57.9, 8.5 Hz, 1H), 3.53 (dt, J = 57.9, 8.5 Hz, 1H), 2.69 – 2.59 (m, 2H), 2.09 – 2.06 (m, 2H), 1.96 – 1.88 (m, 3H), 1.82 – 1.67 (m, 22H), 1.42 (d, J = 23.4 Hz, 9H), 1.24 – 1.20 (m, 2H), 0.97 – 0.90 (m, 12H). **^{13}C NMR (200 MHz, Acetone-D$_6$):** δ (ppm) = 172.18, 156.82, 156.11, 90.19, 79.03, 78.64, 60.79, 53.82, 52.20, 51.81, 49.61, 44.82, 44.30, 37.77, 36.95, 36.82, 35.86, 34.83, 34.59, 34.54, 28.80, 28.75, 26.77, 26.42, 26.34, 14.55, 9.27, 9.21, 9.07, 8.88. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{33}H_{56}BNO_6Na^+$: 596.4098; found: 596.4092. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2900 (s), 2844 (m), 1734 (s), 1692 (s), 1454 (m), 1416 (m), 1386 (s), 1354 (s), 1320 (s), 1308 (s), 1232 (m), 1214 (m), 1176 (s), 1152 (vs), 1110 (s), 1094 (s), 1050 (m), 1026 (s), 994 (w), 976 (w), 958 (w), 920 (s), 892 (w), 862 (m), 820 (w), 800 (w), 778 (m), 746 (w), 706 (w), 672 (w).

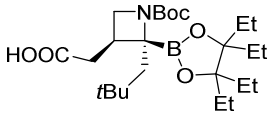
***tert*-Butyl (2*R*,3*S*)-3-(2-ethoxy-2-oxoethyl)-2-neopentyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (<u>3l</u>)**



According to GP-A, using 4,4,5,5-tetraethyl-2-neopentyl-1,3,2-dioxaborolane **<u>Si-23</u>** (0.10 g, 0.39 mmol, 1.3 equiv.) and ethyl iodoacetate (71 µL, 0.6 mmol, 2.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 91:9) yielded the title compound as a colorless oil (0.12 g, 0.23 mmol, 78 %). ^{1}H NMR and GC analysis of the crude reaction mixture indicated a diastereomeric ratio of ><u>20:1</u>. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^{1}H NMR.

^{1}H NMR (600 MHz, Acetone-D$_6$): δ (ppm) = 4.08 (q, J = 7.2 Hz, 2H), 3.96 – 3.78 (m, 1H), 3.62 – 3.43 (m, 1H), 3.21 – 2.89 (m, 1H), 2.68 – 2.54 (m, 2H), 1.96 – 1.86 (m, 2H), 1.84 – 1.67 (m, 8H), 1.42 (d, J = 9.5 Hz, 9H), 1.22 (t, J = 7.1 Hz, 3H), 1.06 (d, J = 11.3 Hz, 9H), 0.99 – 0.88 (m, 12H). **^{13}C NMR (150 MHz, Acetone-D$_6$):** δ (ppm) = 172.15, 157.10, 156.32, 90.34, 90.28, 79.12, 78.72, 60.82, 53.72, 52.16, 51.71, 49.69, 47.91, 37.01, 36.85, 35.12, 33.88, 32.35, 32.28, 32.02, 31.73, 28.79, 26.87, 26.48, 26.43, 26.29, 9.32, 9.19, 9.08, 8.80. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{27}H_{50}BNO_6^+$: 518.3629; found: 518.3623. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2948 (m), 2884 (w), 1728 (m), 1694 (s), 1478 (w), 1458 (m), 1422 (m), 1384 (s), 1364 (s), 1350 (s), 1320 (s), 1304 (m), 1250 (m), 1222 (m), 1180 (s), 1156 (vs), 1112 (m), 1092 (s), 1062 (m), 1026 (m), 1000 (w), 966 (w), 950 (w), 916 (s), 876 (w), 856 (w), 814 (w), 782 (m), 760 (w), 712 (w), 674 (w).

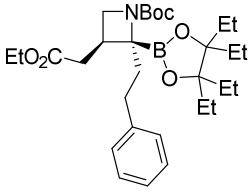
2-((2*R*,3*S*)-1-(*tert*-Butoxycarbonyl)-2-neopentyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidin-3-yl)acetic acid (3l')



tert-Butyl (2*S*,3*S*)-3-(2-ethoxy-2-oxoethyl)-2-neopentyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (49 mg, 0.1 mmol, 1.0 equiv.) was dissolved in a mixture of H_2O (0.5 mL), THF (1 mL) and MeOH (1 mL) and treated with LiOH (0.06 g, 2.5 mmol, 25 equiv.). After stirring at rt. overnight, the solvents were removed *in vacuo*, and the residue was dissolved in Et_2O (10 mL) and filtered. Further concentration *in vacuo* and flash column chromatography (SiO_2; DCM – MeOH: 99:1) afforded the title compound as a viscous colorless oil (35 mg, 0.08 mmol, 76 %). ^{1}H NMR and GC analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1.

^{1}H NMR (600 MHz, Acetone-D_6): δ (ppm) = 3.35 – 3.28 (m, 1H), 3.15 – 3.05 (m, 1H), 2.61 (dd, J = 17.0, 7.8 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.27 (dd, J = 17.0, 8.5 Hz, 1H), 1.94 (d, J = 14.5 Hz, 1H), 1.86 – 1.71 (m, 8H), 1.64 (d, J = 14.5 Hz, 1H), 1.40 (s, 9H), 1.00 (s, 9H), 0.93 (td, J = 7.5, 3.4 Hz, 12H). **^{13}C NMR (150 MHz, Acetone-D_6):** δ (ppm) = 176.27, 156.62, 91.32, 78.94, 51.68, 49.26, 42.03, 33.41, 31.89, 31.28, 28.55, 26.26, 26.17, 8.88, 8.83. **HRMS** (ESI) m/z: $[H]^+$ calcd for $C_{25}H_{45}O_6BN^+$: 466.3340; found: 466.3348.

***tert*-Butyl (2*R*,3*S*)-3-(2-ethoxy-2-oxoethyl)-2-phenethyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (3m)**

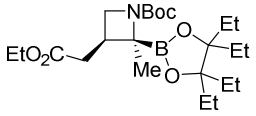


According to GP-A, using 4,4,5,5-tetraethyl-2-phenethyl-1,3,2-dioxaborolane **Si-17** (112 mg, 0.39 mmol, 1.3 equiv.) and Ethyl iodoacetate (71 µL, 0.6 mmol, 2.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 92:8) yielded the title compound as a colorless oil (0.99 g, 0.19 mmol, 62 %). ^{1}H NMR and GC analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^{1}H NMR.

^{1}H NMR (600 MHz, Acetone-D_6): δ (ppm) = δ 7.32 – 7.23 (m, 4H), 7.20 – 7.14 (m, 1H), 4.13 – 4.05 (m, 2H), 3.94 (dt, J = 55.1, 8.4 Hz, 1H), 3.58 (dt, J = 55.1, 8.4 Hz, 1H), 2.94 – 2.85 (m, 1H), 2.79 – 2.63 (m, 3H), 2.17 – 2.07 (m, 2H), 1.89 – 1.71 (m, 8H), 1.45 (d, J = 12.4 Hz, 9H), 1.26 – 1.21 (m, 3H), 1.01 – 0.91 (m, 12H). **^{13}C NMR (150 MHz, Acetone-D_6):** δ (ppm) = 172.21, 172.10, 157.45, 156.07, 144.35, 144.07, 129.23, 129.16, 129.12, 126.43, 126.28, 90.29, 90.20, 79.13, 78.94, 66.11, 60.82, 53.62, 52.02, 41.59, 40.11, 36.92, 36.85, 34.45, 33.60, 31.64,

31.09, 28.78, 28.69, 26.77, 26.53, 26.43, 26.40, 15.61, 14.54, 9.27, 9.20, 9.06, 8.95. **HRMS** (ESI) m/z: $[H]^+$ calcd for $C_{30}H_{48}BNO_6H^+$:530.3655; found: 530.3661. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (m), 2940 (m), 2884 (w), 1734 (s), 1694 (vs), 1604 (vw), 1496 (w), 1476 (w), 1456 (m), 1388 (s), 1362 (s), 1310 (m), 1288 (m), 1254 (m), 1178 (s), 1154 (vs), 1110 (s), 1064 (m), 1028 (m), 970 (w), 952 (w), 922 (m), 866 (w), 782 (w), 752 (m), 700 (s).

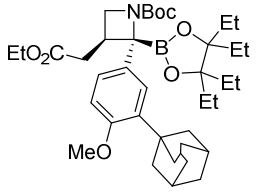
***tert*-Butyl (2*R*,3*S*)-3-(2-ethoxy-2-oxoethyl)-2-methyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (3n)**



According to GP-A, using 4,4,5,5-tetraethyl-2-methyl-1,3,2-dioxaborolane **Si-18** (77 mg, 0.39 mmol, 1.3 equiv.) and ethyl iodoacetate (71 µL, 0.6 mmol, 2.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 9:1) yielded the title compound as a colorless oil (76 mg, 0.17 mmol, 58 %). ^{1}H NMR and GC analysis of the crude reaction mixture indicated a diastereomeric ratio of 2:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^{1}H NMR.

^{1}H NMR (600 MHz, Acetone-D$_6$): δ (ppm) = 4.12 – 4.07 (m, 2H), 3.57 – 3.44 (m, 1H), 2.84 (s, 3H), 2.70 – 2.58 (m, 2H), 1.84 – 1.67 (m, 10H), 1.45 – 1.40 (m, 9H), 1.25 – 1.20 (m, 3H), 1.00 – 0.87 (m, 12H). **^{13}C NMR (150 MHz, Acetone-D$_6$):** δ (ppm) = 172.51, 172.43, 172.19, 172.09, 157.38, 157.23, 156.31, 155.99, 90.17, 90.09, 89.75, 78.85, 60.78, 60.76, 60.67, 53.92, 53.18, 52.33, 51.56, 37.74, 37.41, 36.66, 36.50, 34.64, 34.54, 31.61, 31.50, 28.71, 28.69, 27.87, 26.85, 26.71, 26.65, 26.51, 26.44, 26.37, 24.97, 24.69, 17.28, 17.07, 14.51, 9.45, 9.20, 9.13, 9.04, 9.00, 8.96, 8.94. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{23}H_{42}BNO_6Na^+$: 462.2997; found: 462.2997. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2942 (m), 2884 (w), 1736 (s), 1694 (vs), 1458 (m), 1388 (s), 1362 (s), 1310 (s), 1250 (m), 1178 (s), 1154 (vs), 1110 (s), 1054 (m), 1026 (s), 970 (w), 924 (s), 886 (w), 862 (w), 776 (m).

***tert*-Butyl (2*S*,3*S*)-2-(3-(adamantan-1-yl)-4-methoxyphenyl)-3-(2-ethoxy-2-oxoethyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (3o)**

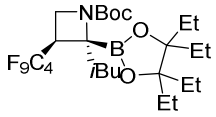


According to GP-A, using 2-(3-(adamantan-1-yl)-4-methoxyphenyl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane **Si-24** (0.17 g, 0.39 mmol, 1.3 equiv.) and ethyl iodoacetate (71 µL, 0.6 mmol, 2.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 92/8)

yielded the title compound as a colorless oil (0.13 g, 0.19 mmol, 63 %). ^{1}H NMR and GC analysis of the crude reaction mixture indicated a diastereomeric ratio of 2:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 1:1, as indicated by ^{1}H NMR.

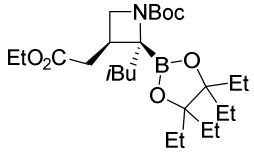
^{1}H NMR (600 MHz, Acetone-D$_6$): δ (ppm) = 7.32 – 7.07 (m, 2H), 6.94 – 6.82 (m, 1H), 4.26 – 4.17 (m, 1H), 4.15 – 4.08 (m, 1H), 4.02 – 3.94 (m, 2H), 3.83 (d, J = 4.6 Hz, 3H), 3.13 – 3.02 (m, 1H), 2.13 (s, 6H), 1.84 – 1.73 (m, 15H), 1.47 (d, J = 4.6 Hz, 5H), 1.37 – 1.31 (m, 5H), 1.25 – 1.18 (m, 1H), 1.13 (t, J = 7.1 Hz, 2H), 1.00 – 0.87 (m, 15H). **^{13}C NMR (150 MHz, Acetone-D$_6$):** δ (ppm) = 172.21, 158.04, 137.50, 90.55, 90.12, 79.18, 60.91, 60.67, 55.32, 41.59, 37.92, 37.72, 36.44, 28.71, 28.69, 26.57, 26.30, 14.53, 14.44, 9.31, 9.18. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{39}H_{60}BNO_7Na^+$: 688.4361; found: 688.4351. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2904 (s), 2850 (m), 1734 (s), 1698 (s), 1606 (vw), 1496 (m), 1456 (m), 1386 (s), 1364 (s), 1312 (m), 1288 (m), 1258 (m), 1234 (vs), 1154 (vs), 1028 (s), 994 (m), 974 (w), 912 (s), 808 (m), 776 (m), 700 (vw).

***tert*-Butyl (2*R*,3*S*)-2-isobutyl-3-(perfluorobutyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate**



According to GP-A on a 2 mmol scale, using 4,4,5,5-tetraethyl-2-isobutyl-1,3,2-dioxaborolane **Si-26** (0.58 g, 2.6 mmol, 1.3 equiv.) and nonafluoro-1-iodobutane (1.0 mL, 6.0 mmol, 3.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 99/1 -> 97:3) yielded the title compound as a colorless oil (1.0 g, 1.7 mmol, 84 %). GC analysis of the crude reaction mixture indicated a diastereomeric ratio of 8:1. The title compound was directly employed in a deprotection – reprotection sequence towards compound **17b**. No additional analytics were determined.

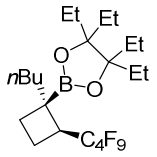
***tert*-Butyl (2*R*,3S)-3-(2-ethoxy-2-oxoethyl)-2-isobutyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate (3p)**



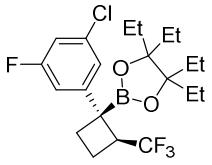
According to GP-A on a 2 mmol scale, using 4,4,5,5-tetraethyl-2-isobutyl-1,3,2-dioxaborolane **Si-26** (0.58 g, 2.6 mmol, 1.3 equiv.) and ethyl iodoacetate (0.47 mL, 4 mmol, 2.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 9/1) yielded the title compound as a colorless oil (0.53 g, 1.1 mmol, 55 %). GC analysis of the crude reaction

mixture indicated a diastereomeric ratio of 9:1. The title compound was directly employed in a deprotection – reprotection sequence towards compound **18**. No additional analytics were determined.

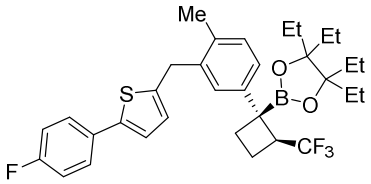
Overview: trisubstituted Cyclobutanes



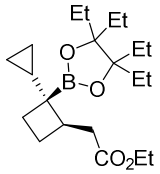
6a
dr = >20:1



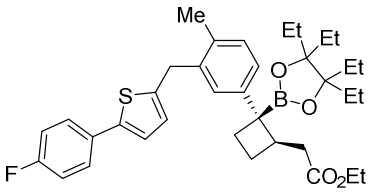
6b
dr = >20:1



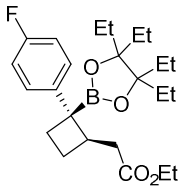
6c
dr = >20:1



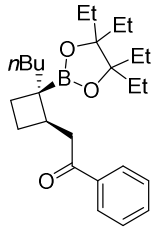
6d
dr = 6:1



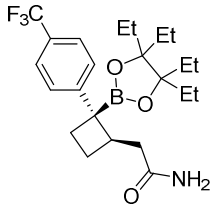
6e
dr = >20:1



6f
dr = >20:1

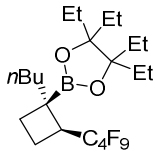


6g
dr = 18:1



6h
dr = 7:1

2-((1*S*,2*S*)-1-Butyl-2-(perfluorobutyl)cyclobutyl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (6a)

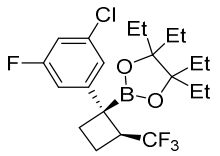


According to GP-B, using *n*BuLi (0.22 mmol, 1.1 equiv.) and nonafluoro-1-iodobutane (0.1 mL, 0.6 mmol, 3.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 99,5:0,5 to 98:2) yielded the title compound as a colorless oil (84 mg, 0.16 mmol, 82 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1.

^{1}H NMR (800 MHz, $CDCl_3$): δ (ppm) = 2.67 (dq, J = 26.6, 8.8, 8.0 Hz, 1H), 2.18 – 2.11 (m, 2H), 1.89 (q, J = 9.5 Hz, 1H), 1.83 (td, J = 12.3, 4.4 Hz, 1H), 1.76 – 1.62 (m, 8H), 1.55 – 1.52 (m, 1H), 1.34 – 1.25 (m, 3H), 1.20 – 1.15 (m, 1H), 1.11 – 1.06 (m, 1H), 0.91 – 0.86 (m, 15H). **^{13}C NMR (200 MHz, $CDCl_3$):** δ (ppm) = 88.81, 45.62, 45.50, 45.38, 40.99, 30.46, 28.11, 27.79,

25.71, 25.65, 23.39, 19.28, 19.24, 14.22, 8.75, 8.71. **^{19}F NMR (400 MHz, $CDCl_3$):** δ (ppm) = -81.04, -81.05, -81.06, -81.07, -81.08, -81.10, -81.11, -114.42, -115.13, -116.57, -116.60, -117.30, -117.34, -122.77, -122.80, -122.82, -123.56, -123.58, -123.61, -123.75, -123.77, -123.79, -124.54, -124.56, -124.58, -126.19, -126.23, -126.26, -126.29. **HRMS (EI-orbitrap):** *m/z*: [M] calc. for [$C_{20}H_{29}BO_2F_9$]: 483.2117; found: 483.2110. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2960 (w), 2936 (w), 2886 (w), 1460 (w), 1410 (w), 1388 (m), 1352 (m), 1304 (w), 1288 (w), 1224 (vs), 1158 (m), 1132 (s), 1114 (s), 1084 (w), 1068 (w), 1024 (m), 988 (w), 968 (w), 924 (s), 868 (w), 850 (w), 830 (w), 810 (w), 774 (w), 732 (m), 694 (vw).

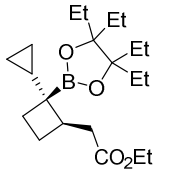
2-((1S,2S)-1-(3-Chloro-5-fluorophenyl)-2-(trifluoromethyl)cyclobutyl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (<u>6b</u>)



According to GP-B, using 1-bromo-3-chloro-5-fluorobenzene (27 µL, 0.22 mmol, 1.1 equiv.) and *n*BuLi (0.22 mmol, 1.1 equiv.) for Halogen-Lithium exchange at -78°C for 30min. Radical precursor Ritter-trifluoromethyl iodide (0.28 g, 0.8 mmol, 4.0 equiv.) was finally added to the reaction mixture in methyl-THF (0.5 mL). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 99.05:0.5 to 99:1) yielded the title compound as a colorless oil (63 mg, 0.14 mmol, 72 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of <u>≥20:1</u>.

^{1}H NMR (800 MHz, DCM-D_2): δ (ppm) = 6.92 (t, J = 1.7 Hz, 1H), 6.89 (dt, J = 8.5, 2.1 Hz, 1H), 6.79 (ddd, J = 9.9, 2.1, 1.7 Hz, 1H), 3.16 (h, J = 9.4 Hz, 1H), 2.65 – 2.62 (m, 1H), 2.27 (p, J = 9.8 Hz, 1H), 2.14 – 2.05 (m, 2H), 1.68 – 1.55 (m, 8H), 0.85 (t, J = 7.5 Hz, 6H), 0.76 (t, J = 7.5 Hz, 6H). **^{13}C NMR (200 MHz, DCM-D_2):** δ (ppm) = 163.79, 162.55, 152.45, 135.05, 134.99, 129.12, 127.75, 126.37, 124.99, 122.31, 113.49, 113.37, 111.89, 111.78, 90.15, 47.34, 47.19, 47.04, 46.89, 28.52, 26.94, 26.27, 25.94, 19.10, 9.01, 8.59. **^{19}F NMR (400 MHz, DCM-D_2):** δ (ppm) = -69.34, -69.36, -112.19, -112.21, -112.23. **HRMS (EI-orbitrap):** *m/z*: [M] calc. for [$C_{21}H_{28}BO_2ClF_4$]: 434.1807; found: 434.1797. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2948 (w), 2886 (w), 1606 (w), 1584 (w), 1458 (w), 1432 (w), 1412 (w), 1384 (m), 1356 (m), 1340 (m), 1312 (w), 1292 (w), 1272 (m), 1248 (w), 1224 (vw), 1200 (vw), 1160 (m), 1134 (m), 1110 (m), 1088 (m), 1046 (w), 1026 (w), 968 (w), 908 (s), 870 (m), 848 (w), 804 (w), 796 (w), 732 (vs).

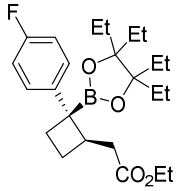
Ethyl 2-((1*R*,2*R*)-2-cyclopropyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)acetate (6c)



According to GP-B, using bromocyclopropane (18 µL, 0.22 mmol, 1.1 equiv.) and *t*BuLi (0.22 mmol, 1.1 equiv.) for Halogen-Lithium exchange at -78°C for 1h. Radical precursor ethyl iodoacetate (47 µL, 0.4 mmol, 2.0 equiv.) was finally added to the reaction mixture in methyl-THF (0.5 mL). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 97/3) yielded the title compound as a colorless oil (69 mg, 0.17 mmol, 83 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 6:1.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 4.17 – 4.06 (m, 2H), 2.60 – 2.51 (m, 1H), 2.46 – 2.39 (m, 1H), 1.98 – 1.89 (m, 1H), 1.81 – 1.60 (m, 10H), 1.37 (td, J = 10.0, 8.8 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H), 0.99 – 0.87 (m, 14H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 173.48, 88.28, 88.09, 60.12, 39.42, 39.40, 26.46, 26.40, 26.23, 26.17, 24.88, 23.33, 16.77, 14.42, 9.04, 8.98, 8.92, 8.83, 1.31, 1.12, 0.78. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{21}H_{37}BO_4Na^+$: 387.2683; found: 387.2679. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974 (m), 2942 (m), 2884 (w), 1734 (vs), 1460 (m), 1412 (m), 1386 (s), 1366 (m), 1344 (s), 1294 (s), 1240 (m), 1162 (s), 1102 (s), 1032 (s), 970 (w), 956 (w), 922 (vs), 848 (w), 820 (w), 772 (w), 706 (vw), 686 (w).

Ethyl 2-((1*R*,2*S*)-2-(4-fluorophenyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)acetate (6d)

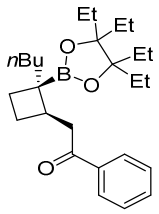


According to GP-B, using 4-bromofluorobenzene (24 µL, 0.22 mmol, 1.1 equiv.) and *n*BuLi (0.22 mmol, 1.1 equiv.) for Halogen-Lithium exchange at -78°C for 30 min. Radical precursor ethyl iodoacetate (47 µL, 0.4 mmol, 2.0 equiv.) was finally added dropwise to the reaction mixture in methyl-THF (0.5 mL). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 96:4) yielded the title compound as a colorless oil (66 mg, 0.16 mmol, 81 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.07 – 7.03 (m, 2H), 6.94 – 6.89 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 2.88 – 2.82 (m, 2H), 2.68 – 2.60 (m, 1H), 2.50 – 2.45 (m, 1H), 2.15 – 2.02 (m, 2H), 1.85 – 1.78 (m, 1H), 1.70 – 1.53 (m, 10H), 1.24 (t, J = 7.2 Hz, 3H), 0.97 – 0.90 (m, 2H),

0.89 – 0.78 (m, 12H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 173.12, 161.41, 159.80, 144.85, 126.97, 114.72, 114.58, 88.77, 60.33, 42.22, 40.25, 29.27, 26.32, 26.02, 14.41, 8.94, 8.66. **^{19}F NMR (400 MHz, $CDCl_3$):** δ (ppm) = -118.98, -119.00, -119.00, -119.02, -119.03, -119.04, -119.06, -119.31, -119.33, -119.33, -119.34, -119.35, -119.36, -119.36, -119.37, -119.39. **HRMS** (ESI) m/z: $[K]^+$ calcd for $C_{24}H_{36}BFO_4K^+$: 457.2322; found: 457.2330. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2942 (m), 2884 (w), 1734 (vs), 1602 (vw), 1508 (s), 1460 (m), 1366 (s), 1346 (s), 1296 (s), 1224 (s), 1160 (s), 1102 (vs), 1030 (s), 968 (w), 952 (w), 922 (vs), 858 (m), 832 (m), 810 (m), 772 (w), 736 (w), 680 (vw).

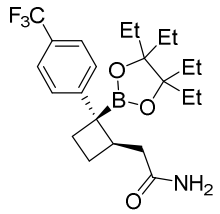
2-((1*R*,2*S*)-2-Butyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)-1-phenylethan-1-one (<u>6e</u>)



According to GP-B, using *n*BuLi (0.22 mmol, 1.1 equiv.) and 2-iodo-1-phenylethan-1-one (98 mg, 0.4 mmol, 2.0 equiv.). The radical precursor was added dropwise dissolved in 2-methylTHF (0.5 mL). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 96:4) yielded the title compound as a colorless oil (58 mg, 0.14 mmol, 70 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of <u>18:1</u>.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 7.94 – 7.92 (m, 2H), 7.55 – 7.52 (m, 1H), 7.47 – 7.42 (m, 2H), 3.23 – 3.10 (m, 2H), 2.59 – 2.46 (m, 1H), 2.08 – 1.99 (m, 2H), 1.74 – 1.60 (m, 10H), 1.53 – 1.45 (m, 1H), 1.30 – 1.21 (m, 3H), 1.21 – 1.12 (m, 2H), 0.95 – 0.84 (m, 15H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 200.35, 137.57, 132.81, 128.58, 128.18, 88.25, 43.88, 40.92, 40.66, 29.03, 28.61, 26.32, 26.13, 25.71, 23.60, 14.31, 8.99, 8.87. **HRMS** (ESI) m/z: $[K]^+$ calcd for $C_{26}H_{41}BO_3K^+$: 451.2780; found: 451.2788. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3366 (vw), 3086 (vw), 2966 (s), 2954 (s), 2930 (s), 2884 (m), 2860 (m), 1686 (s), 1598 (w), 1582 (w), 1512 (vw), 1454 (s), 1408 (m), 1388 (s), 1352 (s), 1284 (s), 1238 (m), 1216 (m), 1182 (m), 1144 (m), 1112 (s), 1076 (w), 1060 (w), 1044 (w), 1026 (w), 1000 (m), 988 (m), 956 (w), 924 (vs), 888 (w), 862 (w), 796 (vw), 750 (s).

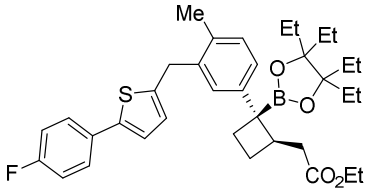
2-((1*R*,2*S*)-2-(4,4,5,5-Tetraethyl-1,3,2-dioxaborolan-2-yl)-2-(4-(trifluoromethyl)-phenyl)cyclobutyl)acetamide (6f)



According to GP-B, using 4-bromobenzotrifluoride (31 µL, 0.22 mmol, 1.1 equiv.) and *n*BuLi (0.22 mmol, 1.1 equiv.) for Halogen-Lithium exchange at -78°C for 30 min. Radical precursor iodoacetamide (74 mg, 0.4 mmol, 2.0 equiv.) was finally added to the reaction mixture in one portion under nitrogen flow. Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 55:45) yielded the title compound as a colorless oil (52 mg, 0.12 mmol, 59 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 7:1.

^{1}H NMR (600 MHz, Acetone-D$_6$): δ (ppm) = 7.56 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 6.76 (s, 1H), 6.12 (s, 1H), 3.02 – 2.92 (m, 1H), 2.84 – 2.75 (m, 1H), 2.60 – 2.50 (m, 2H), 2.16 – 2.07 (m, 2H), 1.97 – 1.86 (m, 1H), 1.73 – 1.58 (m, 8H), 0.91 – 0.79 (m, 12H). **^{13}C NMR (150 MHz, Acetone-D$_6$):** δ (ppm) = 173.95, 155.57, 128.53, 127.08, 127.03, 125.53, 125.49, 125.41, 89.70, 43.74, 42.25, 42.22, 26.84, 26.78, 26.62, 8.87. **^{19}F NMR (100 MHz, Acetone-D$_6$):** δ (ppm) = -62.52, -62.53. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{23}H_{33}BF_3NO_3Na^+$: 462.2403; found: 462.2399. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3192 (vw), 2976 (w), 2942 (w), 2886 (w), 1740 (w), 1666 (m), 1616 (m), 1460 (w), 1444 (w), 1386 (m), 1366 (m), 1350 (m), 1324 (vs), 1288 (m), 1244 (m), 1190 (w), 1162 (m), 1112 (s), 1068 (s), 1046 (m), 1016 (m), 968 (vw), 954 (vw), 922 (m), 858 (w), 836 (w), 784 (vw), 768 (vw), 756 (vw).

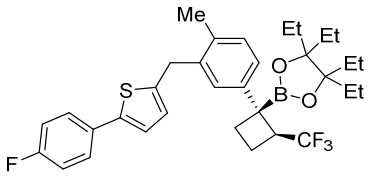
Ethyl 2-((1*R*,2*S*)-2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)acetate (6g)



According to GP-B, using 2-(4-fluorophenyl)-5-(5-iodo-2-methylbenzyl)thiophene (99 mg, 0.22 mmol, 1.1 equiv.) and *n*BuLi (0.22 mmol, 1.1 equiv.) for Halogen-Lithium exchange at -78°C for 30min. Radical precursor ethyl iodoacetate (47 µL, 0.4 mmol, 2.0 equiv.) was finally added to the reaction mixture in methyl-THF (0.5 mL). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 96:4) yielded the title compound as a colorless oil (74 mg, 0.12 mmol, 61 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of ≥20:1.

^{1}H NMR (800 MHz, DCM-D$_2$): δ (ppm) = 7.51 – 7.48 (m, 2H), 7.07 – 7.02 (m, 4H), 6.95 (d, J = 2.0 Hz, 1H), 6.92 (dd, J = 7.7, 2.1 Hz, 1H), 6.67 (dt, J = 3.7, 1.2 Hz, 1H), 4.10 – 4.05 (m, 4H), 2.87 – 2.79 (m, 2H), 2.64 (dd, J = 15.2, 10.7 Hz, 1H), 2.46 – 2.41 (m, 1H), 2.26 (s, 3H), 2.11 – 2.04 (m, 2H), 1.86 – 1.80 (m, 1H), 1.67 – 1.57 (m, 8H), 1.21 (t, J = 7.1 Hz, 3H), 0.86 – 0.81 (m, 12H). **^{13}C NMR (200 MHz, DCM-D$_2$):** δ (ppm) = 173.20, 163.18, 161.96, 147.79, 144.82, 141.67, 138.24, 133.00, 131.62, 130.50, 127.58, 126.37, 124.42, 123.21, 116.18, 116.08, 89.20, 60.56, 42.82, 40.49, 34.70, 29.67, 26.65, 26.52, 19.24, 14.63, 9.13, 9.01. **^{19}F NMR (400 MHz, DCM-D$_2$):** δ (ppm) = -116.11, -116.13, -116.14, -116.15, -116.16, -116.17, -116.17, -116.18, -116.19, -116.20. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{36}H_{46}BFO_4SNa^+$:627.3092; found: 627.3084. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2940 (m), 2884 (w), 1732 (vs), 1606 (w), 1548 (vw), 1508 (s), 1460 (m), 1444 (m), 1410 (w), 1366 (s), 1344 (s), 1296 (s), 1258 (s), 1230 (vs), 1172 (s), 1160 (s), 1100 (s), 1030 (m), 970 (w), 954 (w), 922 (s), 894 (w), 858 (vw), 834 (s), 800 (s), 770 (w), 728 (w).

4,4,5,5-Tetraethyl-2-((1*S*,2*S*)-1-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-2-(trifluoromethyl)cyclobutyl)-1,3,2-dioxaborolane (<u>6h</u>)

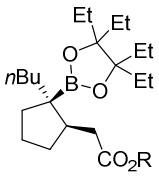


According to GP-B, using 2-(4-fluorophenyl)-5-(5-iodo-2-methylbenzyl)thiophene (99 mg, 0.22 mmol, 1.1 equiv.) and *n*BuLi (0.22 mmol, 1.1 equiv.) for Halogen-Lithium exchange at -78°C for 30min. Radical precursor Ritter-trifluoromethyl iodide (0.28 g, 0.8 mmol, 4.0 equiv.) was finally added to the reaction mixture in methyl-THF (0.5 mL). Purification *via* column chromatography (SiO_2; Pentane – EtOAc: 99.05:0.5 to 99:1; long column) yielded the title compound as a colorless oil (50 mg, 0.86 mmol, 43 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of <u>>20:1</u>.

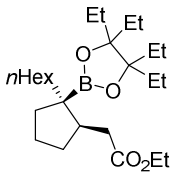
^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) = 7.48 – 7.44 (m, 2H), 7.08 (d, J = 7.7 Hz, 1H), 7.04 – 6.97 (m, 5H), 6.63 (dd, J = 3.6, 1.1 Hz, 1H), 4.08 (s, 2H), 3.14 (h, J = 9.6 Hz, 1H), 2.65 (td, J = 9.6, 2.4 Hz, 1H), 2.27 (s, 3H), 2.22 (q, J = 9.9 Hz, 1H), 2.13 (q, J = 9.6 Hz, 1H), 2.05 (dtd, J = 11.0, 8.8, 2.4 Hz, 1H), 1.65 – 1.46 (m, 8H), 0.81 (t, J = 7.5 Hz, 6H), 0.72 (t, J = 7.5 Hz, 6H). **^{13}C NMR (150 MHz, CDCl$_3$):** δ (ppm) = 162.96, 161.33, 145.70, 144.07, 144.06, 141.40, 137.82, 133.08, 131.13, 131.11, 130.37, 127.86, 127.21, 127.15, 126.02, 125.82, 124.15, 122.69, 122.68, 115.87, 115.72, 110.15, 89.07, 47.31, 47.12, 46.92, 46.72, 34.40, 32.08, 29.86, 29.52, 29.48, 28.11, 25.80, 25.66, 22.85, 19.13, 18.86, 18.83, 14.29, 8.76, 8.60, 1.17. **^{19}F NMR (400 MHz, CDCl$_3$):** δ (ppm) = -69.17, -69.19, -115.36, -115.38, -115.39, -115.39, -

115.40, -115.41, -115.41, -115.42, -115.44. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{33}H_{39}BF_4O_2SNa^+$: 609.2598; found: 609.2596.

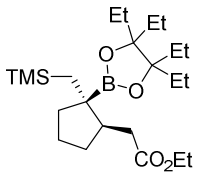
Five Membered Rings: Overview



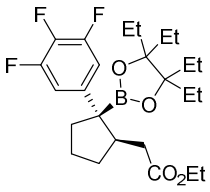
9a (R = Et)
dr = 19:1
9a' (R = *t*Bu)
dr = 13:1



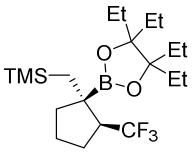
9b (R = Et)
dr = >20:1
9b' (R = H)
dr = >20:1
9b'' (R = *t*Bu)
dr = >20:1



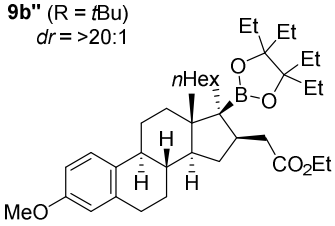
9c
dr = >20:1



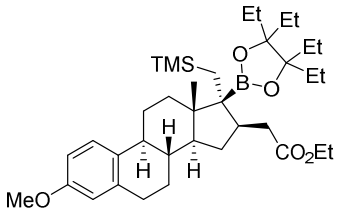
9d
dr = 2:1



9e
dr = 7:1

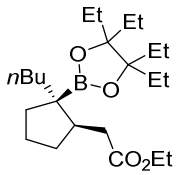


9f
dr = 3:1



9g
dr = 2,5:1

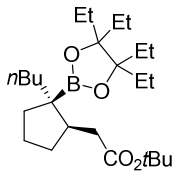
Ethyl 2-((1*R*,2*S*)-2-butyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)acetate (9a)



According to GP-C, using *n*BuLi (0.22 mmol, 1.1 equiv.) and ethyl iodoacetate (47 µL, 0.4 mmol, 2.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 97:3) yielded the title compound as a colorless oil (76 mg, 0.19 mmol, 96 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 19:1.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 4.11 (q, J = 7.1 Hz, 2H), 2.60 (dd, J = 15.0, 3.5 Hz, 1H), 2.19 (dd, J = 15.0, 11.3 Hz, 1H), 1.97 – 1.85 (m, 2H), 1.84 – 1.78 (m, 1H), 1.72 – 1.53 (m, 11H), 1.31 – 1.14 (m, 9H), 1.04 (td, J = 12.3, 4.1 Hz, 1H), 0.92 – 0.84 (m, 15H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 174.47, 88.18, 60.14, 46.87, 38.22, 37.76, 35.03, 32.04, 29.82, 26.37, 25.77, 23.96, 22.53, 14.45, 14.27, 9.07, 8.62. **HRMS (EI-orbitrap):** *m/z*: [M] calc. for $[C_{21}H_{38}BO_4]$: 365.2863; found: 365.2841. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2934 (m), 2882 (m), 1736 (vs), 1458 (m), 1410 (m), 1388 (s), 1348 (m), 1288 (s), 1258 (s), 1222 (m), 1184 (s), 1152 (s), 1112 (s), 1030 (m), 994 (w), 956 (w), 922 (s), 856 (w), 796 (w), 774 (w), 728 (vw), 692 (w).

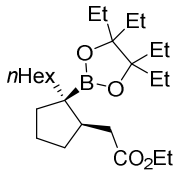
***tert*-Butyl 2-((1*R*,2*S*)-2-butyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)acetate (9a')**

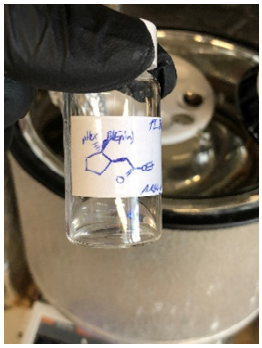


According to GP-C, using 2-(cyclopent-1-en-1-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (0.8 g, 3.2 mmol, 1.0 equiv.) in THF (16 mL). *n*Butylllithium (3.5 mmol, 1.1 equiv.) was added over 30 min at -78°C and after 30 min at the same temperature the mixture was allowed to warm to 0°C for 1h. After solvent switch to methylTHF (33 mL) and addition of dodecane (1.5 mL, 5 Vol%.) *tert*-butyl iodoacetate (1.6 g, 6.4 mmol, 2.0 equiv.) was added dropwise to the mixture under irradiation at -40°C. Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 98:2) yielded the title compound as a colorless oil (0.92 g, 2.2 mmol, 68 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 13:1.

^{1}H NMR (600 MHz, CD_2Cl_2): δ (ppm) = 2.47 (dd, J = 14.6, 3.6 Hz, 1H), 2.42 – 2.36 (m, 1H), 2.05 (dd, J = 14.6, 11.2 Hz, 1H), 1.97 – 1.72 (m, 3H), 1.69 – 1.60 (m, 10H), 1.42 (s, 9H), 1.31 – 1.14 (m, 6H), 1.07 – 0.98 (m, 1H), 0.93 – 0.86 (m, 15H). **^{13}C NMR (150 MHz, CD_2Cl_2):** δ (ppm) = 173.24, 88.09, 79.35, 54.00, 47.05, 38.84, 38.17, 34.78, 31.69, 29.72, 27.81, 27.33, 26.32, 26.17, 25.58, 23.87, 22.31, 13.90, 8.70, 8.59, 8.26. **HRMS (EI-orbitrap):** *m/z*: [M] calc. for [$C_{21}H_{38}BO_4$]: 365.2863; found: 365.2868.

Ethyl 2-((1*R*,2*S*)-2-hexyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)acetate (9b)





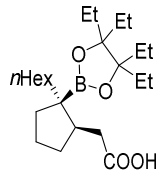
0.2 mmol Scale: According to GP-C, using hexyllithium (0.22 mmol, 1.1 equiv.) and ethyl iodoacetate (47 µL, 0.4 mmol, 2.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 96:4) yielded the title compound as a colorless oil (82 mg, 0.19 mmol, 97 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of ≥20:1.

3.0 mmol Scale: According to GP-C, using 2-(cyclopent-1-en-1-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (**7**) (0.75 g, 3.0 mmol, 1.0 equiv.) in THF (15 mL). Hexyllithium (3.3 mmol, 1.1 equiv.) was added over 30 min at -78°C and after 30 min at the same temperature the mixture was allowed to warm to 0°C for 1h. After solvent switch to methylTHF (30 mL) and addition of dodecane (1.5 mL, 5 Vol%.) ethyl iodoacetate (0.71 mL, 6.0 mmol, 2.0 equiv.) was

added dropwise to the mixture under irradiation at -40°C. Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 95:5) yielded the title compound as a colorless oil (1.2 g, 2.8 mmol, 95 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 4.11 (q, J = 7.1 Hz, 2H), 2.59 (dd, J = 15.0, 3.5 Hz, 1H), 2.19 (dd, J = 15.0, 11.2 Hz, 1H), 1.98 – 1.85 (m, 2H), 1.84 – 1.77 (m, 1H), 1.72 – 1.53 (m, 11H), 1.32 – 1.13 (m, 13H), 1.04 (td, J = 12.8, 12.3, 4.0 Hz, 1H), 0.92 – 0.83 (m, 14H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 174.47, 88.18, 60.14, 46.90, 38.55, 37.76, 35.03, 32.03, 32.00, 30.58, 27.52, 26.37, 25.79, 22.79, 22.52, 14.44, 14.27, 9.06, 8.64. **HRMS (EI-orbitrap):** *m/z*: [M] calc. for [$C_{23}H_{43}BO_4$]: 394.3254; found: 394.3205. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2928 (s), 2884 (m), 2856 (m), 1736 (vs), 1458 (m), 1388 (s), 1348 (m), 1290 (s), 1258 (s), 1180 (s), 1150 (s), 1112 (s), 1032 (m), 976 (w), 956 (w), 922 (vs), 856 (w), 796 (w), 772 (w), 724 (w), 692 (w).

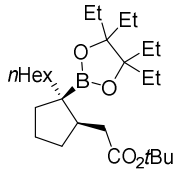
2-((1*R*,2*S*)-2-Hexyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)acetic acid (9b')



Ethyl 2-((1*R*,2*S*)-2-hexyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)acetate **9b** (85 mg, 0.2 mmol, 1.0 equiv.) was dissolved in a mixture of H_2O (1 mL), THF (2 mL) and MeOH (2 mL) and treated with LiOH (0.12 g, 5 mmol, 25 equiv.). After stirring at rt. overnight, the solvents were removed *in vacuo*, and the residue was dissolved in Et_2O (10 mL) and filtered. Further concentration *in vacuo* and flash column chromatography (SiO_2; DCM – MeOH: 98:2) afforded the title compound as a colorless oil (56 mg, 0.18 mmol, 91 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.65 (dd, J = 15.3, 3.7 Hz, 1H), 2.28 (dd, J = 15.3, 10.9 Hz, 1H), 1.99 – 1.93 (m, 2H), 1.84 – 1.80 (m, 1H), 1.65 (s, 11H), 1.30 – 1.19 (m, 10H), 1.09 – 1.03 (m, 1H), 0.91 – 0.86 (m, 15H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 179.38, 88.36, 46.54, 38.52, 35.09, 32.18, 31.99, 30.55, 27.51, 26.39, 25.81, 22.79, 22.49, 14.26, 9.05, 8.64. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{23}H_{42}O_4B^+$: 393.3174; found: 393.3184. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (m), 2924 (m), 2882 (m), 2858 (m), 2680 (w), 1700 (vs), 1454 (m), 1394 (m), 1364 (w), 1348 (m), 1320 (m), 1296 (s), 1250 (m), 1226 (w), 1210 (m), 1184 (w), 1158 (m), 1142 (w), 1112 (m), 1086 (w), 1058 (vw), 1028 (w), 974 (m), 954 (m), 922 (s), 854 (w), 818 (vw), 796 (vw), 774 (w), 724 (vw).

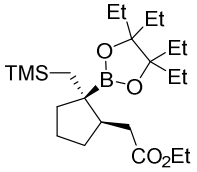
tert-Butyl 2-((1*R*,2S)-2-hexyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)acetate (9b'')



According to GP-C, using 2-(cyclopent-1-en-1-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (**7**) (0.52 g, 2.1 mmol, 1.0 equiv.) in THF (11 mL). Hexyllithium (2.3 mmol, 1.1 equiv.) was added over 30 min at -78°C and after 30 min at the same temperature the mixture was allowed to warm to 0°C for 1h. After solvent switch to methylTHF (20 mL) and addition of dodecane (1 mL, 5 Vol%.) *tert*-butyl iodoacetate (1.0 g, 4.2 mmol, 2.0 equiv.) was added dropwise to the mixture under irradiation at -40°C. Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 97:3) yielded the title compound as a colorless oil (0.8 g, 1.8 mmol, 84 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1.

^{1}H NMR (600 MHz, CD_2Cl_2): δ (ppm) = 2.39 (dd, J = 14.5, 3.7 Hz, 1H), 2.34 – 2.28 (m, 1H), 1.97 (dd, J = 14.6, 11.2 Hz, 1H), 1.87 – 1.65 (m, 3H), 1.62 – 1.52 (m, 10H), 1.34 (s, 9H), 1.22 – 1.15 (m, 8H), 1.12 – 1.04 (m, 2H), 0.97 – 0.90 (m, 1H), 0.86 – 0.76 (m, 15H). **^{13}C NMR (150 MHz, CD_2Cl_2):** δ (ppm) = 173.24, 88.09, 79.34, 47.07, 38.84, 38.50, 34.79, 31.87, 31.69, 30.47, 27.82, 27.42, 26.32, 26.17, 25.60, 22.65, 22.31, 13.90, 8.70, 8.59, 8.28. **HRMS (EI-orbitrap):** *m/z*: [M] calc. for [$C_{23}H_{42}BO_4$]: 393.3176; found: 393.3168.

Ethyl 2-((1*R*,2*S*)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-2-((trimethylsilyl)methyl)cyclopentyl)acetate (9c)

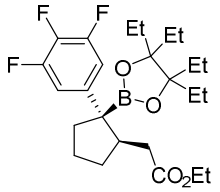


According to GP-C, using (trimethylsilyl)methyllithium (0.22 mmol, 1.1 equiv.) and ethyl iodoacetate (47 µL, 0.4 mmol, 2.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 96:4) yielded the title compound as a colorless oil (66 mg, 0.16 mmol, 78 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1.

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 4.11 (qd, J = 7.1, 1.1 Hz, 2H), 2.59 (dd, J = 14.8, 3.3 Hz, 1H), 2.17 (dd, J = 14.8, 11.4 Hz, 1H), 1.97 – 1.92 (m, 1H), 1.89 – 1.83 (m, 1H), 1.76 – 1.56 (m, 13H), 1.29 – 1.20 (m, 5H), 0.92 – 0.85 (m, 12H), 0.01 (s, 9H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 174.56, 88.30, 60.15, 51.36, 37.07, 36.78, 30.96, 26.38, 26.07, 25.17, 22.32, 14.45, 8.86, 0.94. **HRMS (EI-orbitrap):** *m/z*: [M] calc. for [$C_{21}H_{40}BO_4Si$]: 395.2789; found: 395.2769.

IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2950 (m), 2884 (w), 1736 (s), 1458 (w), 1410 (w), 1384 (m), 1348 (m), 1290 (m), 1246 (s), 1202 (w), 1172 (m), 1140 (m), 1112 (m), 1074 (w), 1030 (m), 990 (w), 958 (vw), 920 (m), 856 (s), 836 (vs), 798 (m), 762 (w).

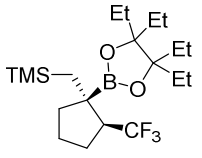
Ethyl 2-((1*R*,2*S*)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-2-(3,4,5-trifluorophenyl)cyclopentyl)acetate (9d)



According to GP-C, using 5-bromo-1,2,3-trifluorobenzene (26 µL, 0.22 mmol, 1.1 equiv.) and *n*BuLi (0.22 mmol, 1.1 equiv.) for Halogen-Lithium exchange at -78°C for 30min. Radical precursor ethyl iodoacetate (47 µL, 0.4 mmol, 2.0 equiv.) was finally added to the reaction mixture in methyl-THF (0.5 mL). Purification *via* column chromatography (SiO_2; Pentane – EtOAc: 96:4) yielded the title compound as a colorless oil (88 mg, 0.19 mmol, 93 %). ^{1}H NMR and GC analysis of the crude reaction mixture indicated a diastereomeric ratio of 2:1. Separation of Diastereomers is possible *via* column chromatography.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.97 – 6.91 (m, 2H), 4.13 (q, J = 7.2 Hz, 2H), 2.44 – 2.40 (m, 1H), 2.25 – 2.17 (m, 1H), 2.04 – 1.93 (m, 1H), 1.77 – 1.54 (m, 12H), 1.49 – 1.41 (m, 1H), 1.26 (t, J = 7.1 Hz, 4H), 0.92 – 0.82 (m, 12H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm) = 173.63, 111.34, 111.12, 89.18, 60.45, 45.27, 37.60, 36.87, 31.34, 26.15, 25.88, 22.25, 14.40, 8.68. **^{19}F NMR (400 MHz, $CDCl_3$)**: δ (ppm) = -135.47, -135.49, -135.52, -135.55, -135.62, -135.64, -135.67, -135.70, -165.20, -165.22, -165.23, -165.25, -165.27, -165.30, -165.31, -165.33, -165.35, -165.37, -165.39, -165.41, -165.42, -165.44. **HRMS** (ESI) m/z: $[HCO_2]^+$ calcd for $C_{25}H_{36}BF_3O_4HCO_2^+$: 513.2635; found: 513.2644. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2948 (m), 2884 (w), 1734 (s), 1614 (m), 1590 (vw), 1528 (vs), 1458 (m), 1430 (m), 1368 (m), 1338 (s), 1300 (s), 1266 (s), 1240 (s), 1186 (s), 1152 (s), 1112 (m), 1036 (vs), 1000 (w), 954 (w), 916 (s), 852 (m), 802 (vw), 772 (w), 706 (w).

Trimethyl(((1*S*,2*S*)-1-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)cyclopentyl)methyl)silane (9e)

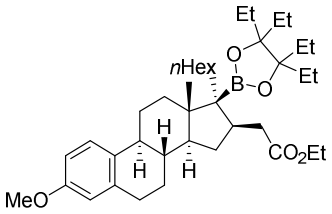


According to GP-C, using (trimethylsilyl)methyllithium (0.22 mmol, 1.1 equiv.) and Ritter trifluoroiodomethane (0.28 g, 0.8 mmol, 4.0 equiv.). Purification *via* flash-column chromatography (SiO_2; Pentane – EtOAc: 99:1; long column) yielded the title compound as a

colorless oil (44 mg, 0.11 mmol, 54 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 7:1.

^{1}H NMR (600 MHz, CD_2Cl_2): δ (ppm) = 2.26 – 2.15 (m, 1H), 2.01 – 1.80 (m, 4H), 1.74 – 1.61 (m, 8H), 1.42 – 1.26 (m, 3H), 0.88 (dt, J = 8.6, 7.5 Hz, 12H), 0.57 (d, J = 14.5 Hz, 1H), 0.03 (s, 9H). **^{13}C NMR (150 MHz, CD_2Cl_2):** δ (ppm) = 89.19, 38.51, 27.32, 26.40, 25.65, 22.77, 9.42, 8.64, 1.23. **^{19}F NMR (400 MHz, CD_2Cl_2):** δ (ppm) = -66.19, -66.22. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{20}H_{38}BF_3O_2SiNa^+$: 429.2584; found: 429.2592.

Ethyl 2-((8*S*,9*S*,13*S*,14*S*,16*R*,17*R*)-17-hexyl-3-methoxy-13-methyl-17-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-16-yl)acetate (9f)

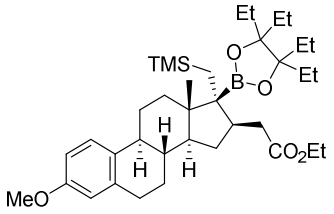


A flame-dried Schlenk flask was charged with 4,4,5,5-tetraethyl-2-((8*S*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-17-yl)-1,3,2-dioxaborolane (**Si-27**) (45 mg, 0.1 mmol, 1.0 equiv.) and THF (0.5 mL) was added. The solution was cooled to -78°C and (trimethylsilyl)methyllithium in pentane (0.11 mmol, 1.1 equiv.) was added dropwise. Stirring was continued at this temperature for 30 min, before the mixture was allowed to warm to 0°C for 1 h. Following this, the solvents were carefully removed *in vacuo*. The residue was dissolved in 2-methyltetrahydrofuran (1 mL), dodecane (50 µL, 5 Vol%.) was added and the flask was transferred to the photoreactor precooled to -40 °C. Ethyl iodoacetate (0.71 mL, 6.0 mmol, 2.0 equiv.) was added dropwise to the mixture under irradiation at -40°C). The colorless solution was stirred at the indicated temperature under LED irradiation for 14 h. Purification *via* column chromatography (SiO_2; Pentane – EtOAc: 98:2 to 96:4) yielded the title compound as a colorless oil (48 mg, 0.09 mmol, 89 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 3:1.

^{1}H NMR (800 MHz, CD_2Cl_2): δ (ppm) = 7.19 – 7.15 (m, 1H), 6.65 (dd, J = 8.6, 2.8 Hz, 1H), 6.59 (d, J = 2.8 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.12 – 4.06 (m, 2H), 3.73 (s, 3H), 3.69 (s, 2H), 2.86 – 2.77 (m, 2H), 2.23 – 2.12 (m, 2H), 1.81 – 1.60 (m, 11H), 1.49 – 1.23 (m, 20H), 0.93 – 0.86 (m, 16H). **^{13}C NMR (200 MHz, CD_2Cl_2):** δ (ppm) = 174.60, 169.22, 157.93, 138.73, 138.69, 133.68, 133.66, 126.62, 114.10, 111.71, 88.89, 88.67, 88.47, 62.64, 60.42, 55.61, 50.78, 49.31, 47.73, 46.93, 44.38, 44.26, 43.95, 40.36, 39.88, 39.66, 39.24, 38.91, 37.05, 36.04, 33.81, 33.60, 32.45, 32.41, 32.15, 31.73, 31.57, 30.63, 30.49, 30.44, 29.53, 28.89, 28.67, 28.36, 27.12, 27.01, 26.42, 26.10, 25.92, 23.31, 23.26, 18.99, 14.69, 14.47, 14.21, 9.43, 9.17, 8.92, 8.83. **HRMS (EI-orbitrap):** *m/z*: [M] calc. for $[C_{39}H_{63}BO_5]$: 622.4769; found:

622.4790. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2930 (m), 1734 (s), 1610 (w), 1576 (vw), 1500 (m), 1458 (m), 1418 (w), 1384 (m), 1368 (m), 1348 (m), 1254 (vs), 1176 (s), 1158 (m), 1140 (m), 1112 (s), 1032 (s), 980 (w), 958 (w), 922 (s), 858 (w), 816 (w), 786 (w), 724 (vw).

Ethyl 2-((8*S*,9*S*,13*S*,14*S*,16*R*,17*R*)-3-methoxy-13-methyl-17-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-17-((trimethylsilyl)methyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-16-yl)acetate (9g)

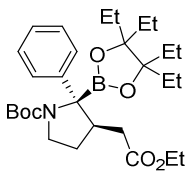


A flame-dried Schlenk flask was charged with 4,4,5,5-Tetraethyl-2-((8*S*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-17-yl)-1,3,2-dioxaborolane (**Si-27**) (45 mg, 0.1 mmol, 1.0 equiv.) and THF (0.5 mL) was added. The solution was cooled to -78°C and (trimethylsilyl)methyllithium in pentane (0.11 mmol, 1.1 equiv.) was added dropwise. Stirring was continued at this temperature for 30 min, before the mixture was allowed to warm to 0°C for 1 h. Following this, the solvents were carefully removed *in vacuo*. The residue was dissolved in 2-methyltetrahydrofuran (1 mL), dodecane (50 µL, 5 Vol%.) was added and the flask was transferred to the photoreactor precooled to -40 °C. Ethyl iodoacetate (0.71 mL, 6.0 mmol, 2.0 equiv.) was added dropwise to the mixture under irradiation at -40°C). The colorless solution was stirred at the indicated temperature under LED irradiation for 14 h. Purification *via* column chromatography (SiO_2; Pentane – EtOAc: 98:2 to 95:5) yielded the title compound as a colorless oil that solidified in the freezer (36 mg, 0.06 mmol, 57 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 2,5:1.

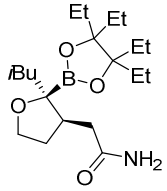
^{1}H NMR (600 MHz, CD_2Cl_2): δ (ppm) = 7.18 – 7.16 (m, 1H), 6.67 (td, J = 8.1, 2.7 Hz, 1H), 6.61 (dd, J = 6.8, 2.7 Hz, 1H), 3.74 (d, J = 1.5 Hz, 3H), 2.91 – 2.86 (m, 2H), 2.29 – 2.25 (m, 4H), 2.08 – 2.03 (m, 2H), 1.95 – 1.91 (m, 2H), 1.71 – 1.59 (m, 13H), 1.45 – 1.42 (m, 2H), 1.41 (s, 3H), 1.26 (t, J = 3.5 Hz, 1H), 0.95 – 0.87 (m, 15H), 0.78 (d, J = 24.5 Hz, 9H), 0.08 (s, 2H). **^{13}C NMR (150 MHz, CD_2Cl_2):** δ (ppm) = 158.09, 157.94, 145.97, 144.50, 138.59, 138.44, 138.18, 133.82, 133.68, 133.06, 129.77, 126.51, 126.45, 125.96, 114.19, 113.16, 111.81, 111.73, 111.72, 88.25, 56.57, 55.99, 55.62, 50.81, 48.58, 46.31, 45.15, 44.71, 38.44, 38.25, 38.00, 36.92, 33.94, 33.79, 32.26, 30.63, 30.34, 30.19, 28.83, 28.55, 27.99, 27.40, 27.22, 26.92, 26.74, 17.42, 17.26, 15.66, 9.24, 9.14, 1.32, 0.52. **HRMS (EI-orbitrap):** *m/z*: [M] calc. for [$C_{37}H_{61}BO_5Si$]: 624.4381; found: 624.4396. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2922 (s), 2880 (m), 2850 (m), 2812 (w), 1736 (w), 1608 (m), 1578 (w), 1500 (s), 1452 (m), 1406 (w), 1370 (m), 1358 (m), 1312 (m), 1284 (s), 1246 (vs), 1236 (vs), 1198 (m), 1176 (m), 1158 (m), 1130 (m),

1112 (m), 1094 (s), 1068 (m), 1042 (vs), 1032 (vs), 992 (m), 976 (m), 954 (m), 926 (m), 902 (m), 878 (w), 856 (s), 842 (m), 822 (s), 788 (m), 706 (m), 694 (m).

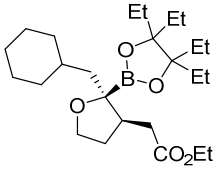
Others:



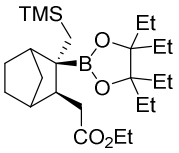
12a
dr = 2:1



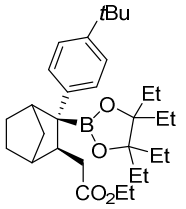
12b
dr = 3:1



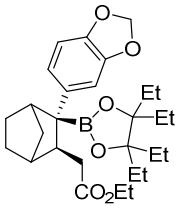
12c
dr = 3:1



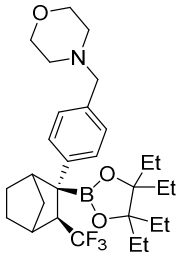
15a
dr = 4:1



15b
dr = >20:1

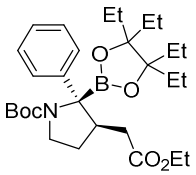


15c
dr = >20:1



15d
dr = >20:1

***tert*-Butyl (2*S*,3*R*)-3-(2-ethoxy-2-oxoethyl)-2-phenyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)pyrrolidine-1-carboxylate (12a)**

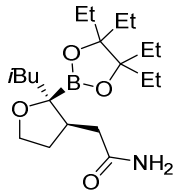


A flame-dried Schlenk flask was charged with *tert*-butyl 5-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-pyrrole-1-carboxylate (70 mg, 0.2 mmol, 1.0 equiv.) and THF (0.5 mL) was added. The solution was cooled to -78°C and phenyllithium (0.22 mmol, 1.1 equiv.) was added dropwise. Stirring was continued at this temperature for 30 min, before the mixture was allowed to warm to 0°C for 45 min. Following this, the solvents were carefully removed *in vacuo*. The residue was dissolved in 2-methyltetrahydrofuran (1.5 mL), dodecane (0.1 mL, 5 Vol%.) was added and the flask was transferred to the photoreactor precooled to -40 °C. Ethyl iodoacetate (47 µL, 0.4 mmol, 2.0 equiv.) was dissolved in 2-methylTHF (0.5 mL) and added dropwise to the mixture under irradiation at -40°C. The colorless solution was stirred at the indicated temperature under LED irradiation for 12 h. The crude mixture was pushed through a Silica-Plug (4 cm), eluting with Et_2O (50 mL) and was concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane – EtOAc: 93:7) afforded the title compound as a viscous colorless oil (75 mg, 0.15 mmol, 73 %). ^{1}H NMR and GC analysis of the crude reaction

mixture indicated a diastereomeric ratio of 2:1. The title compound was obtained in a mixture of *N*-Boc Rotamers in a ratio of 3:1, as indicated by ^{1}H NMR.

^{1}H NMR (800 MHz, Acetone-D$_6$): δ (ppm) = 7.37 – 7.34 (m, 2H), 7.33 – 7.30 (m, 1H), 7.28 – 7.26 (m, 2H), 4.13 – 4.01 (m, 2H), 3.83 – 3.49 (m, 2H), 2.91 (dd, J = 16.1, 5.5 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.36 (ddd, J = 26.4, 15.7, 10.3 Hz, 1H), 1.90 – 1.73 (m, 10H), 1.47 (d, J = 24.5 Hz, 9H), 1.22 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.4 Hz, 6H), 0.87 (t, J = 7.5 Hz, 6H). **^{13}C NMR (200 MHz, Acetone-D$_6$):** δ (ppm) = 172.99, 172.37, 172.08, 155.58, 155.02, 154.26, 147.74, 146.84, 128.59, 128.43, 128.29, 128.06, 126.74, 126.59, 126.49, 126.25, 90.31, 89.90, 89.75, 79.62, 79.21, 60.84, 60.77, 60.72, 52.57, 49.20, 47.73, 47.15, 46.37, 43.74, 36.71, 36.54, 35.57, 31.20, 30.52, 28.79, 28.36, 28.26, 26.66, 26.54, 26.40, 26.15, 25.88, 14.50, 14.43, 9.35, 9.21, 9.17, 9.05. **HRMS** (ESI) m/z: [Na]$^+$ calcd for $C_{29}H_{46}BNO_6Na^+$: 538.3316; found: 538.3323. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (m), 2942 (m), 2884 (w), 1734 (s), 1686 (vs), 1602 (vw), 1492 (w), 1478 (w), 1456 (m), 1394 (vs), 1364 (s), 1332 (m), 1296 (m), 1268 (m), 1244 (s), 1164 (vs), 1114 (s), 1084 (m), 1060 (w), 1030 (m), 976 (m), 958 (w), 922 (s), 856 (w), 776 (m), 766 (m), 740 (m).

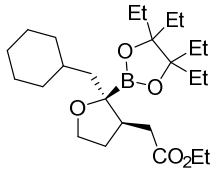
2-((2*R*,3*R*)-2-Isobutyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)tetrahydrofuran-3-yl)acetamide (12b)



According to GP-D, using 4,4,5,5-tetraethyl-2-isobutyl-1,3,2-dioxaborolane (**Si-26**) (62 mg, 0.26 mmol, 1.3 equiv.) and iodoacetamide (74 mg, 0.4 mmol, 2.0 equiv.). Flash column chromatography (SiO_2; pentane – EtOAc: 1:1; 3 % TEA) afforded the title compound as a light orange oil (46 mg, 0.13 mmol, 63 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 3:1.

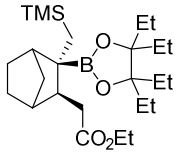
^{1}H NMR (800 MHz, CD$_2$Cl$_2$): δ (ppm) = 5.50 (t, 1H), 3.88 – 3.73 (m, 2H), 2.43 – 2.37 (m, 1H), 2.21 – 2.14 (m, 1H), 2.14 – 2.10 (m, 1H), 2.03 – 1.98 (m, 1H), 1.79 – 1.55 (m, 11H), 1.31 – 1.25 (m, 2H), 0.95 – 0.86 (m, 18H). **^{13}C NMR (200 MHz, CD$_2$Cl$_2$):** δ (ppm) = 174.83, 89.92, 89.57, 66.29, 65.77, 46.46, 46.29, 43.20, 40.04, 38.60, 36.19, 33.03, 31.72, 27.06, 26.73, 26.51, 26.28, 26.01, 24.85, 24.20, 24.02, 23.98, 9.26, 9.03, 8.76. **HRMS** (ESI) m/z: [Na]$^+$ calcd for $C_{20}H_{38}BNO_4Na^+$: 390.2792; found: 390.2792. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3198 (w), 2972 (m), 2950 (m), 2884 (m), 1740 (w), 1670 (vs), 1620 (m), 1456 (m), 1432 (m), 1396 (s), 1352 (s), 1306 (m), 1288 (m), 1240 (m), 1182 (w), 1146 (m), 1110 (s), 1040 (s), 988 (w), 958 (w), 916 (vs), 854 (w), 792 (w), 770 (w).

Ethyl 2-((2*R*,3*R*)-2-(cyclohexylmethyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)tetrahydrofuran-3-yl)acetate (12c)



According to GP-D, using 4,4,5,5-tetraethyl-2-isobutyl-1,3,2-dioxaborolane (**Si-25**) (62 mg, 0.26 mmol, 1.3 equiv.) and ethyl iodoacetate (47 µL, 0.4 mmol, 2.0 equiv.). Flash column chromatography (SiO_2; pentane – EtOAc: 98:2 to 93:7) afforded the title compound as a colorless oil (84 mg, 0.19 mmol, 96 %). ^{1}H NMR and GC analysis of the crude reaction mixture indicated a diastereomeric ratio of 3:1. The two diastereomers were conveniently separated *via* column chromatography. Analytics are reported for the depicted major diastereomer.
^{1}H NMR (800 MHz, $CDCl_3$): δ (ppm) = 4.12 (q, J = 7.1 Hz, 2H), 3.88 – 3.81 (m, 2H), 2.66 (dd, J = 15.2, 3.2 Hz, 1H), 2.46 – 2.41 (m, 1H), 2.16 – 2.09 (m, 2H), 1.87 – 1.82 (m, 1H), 1.74 – 1.61 (m, 13H), 1.40 – 1.35 (m, 1H), 1.25 (t, J = 7.1 Hz, 4H), 1.22 – 1.18 (m, 2H), 1.12 (dd, J = 13.5, 6.0 Hz, 1H), 0.91 – 0.88 (m, 15H). **^{13}C NMR (200 MHz, $CDCl_3$):** δ (ppm) = 173.34, 89.20, 66.09, 60.39, 42.47, 34.81, 34.69, 34.34, 31.18, 26.61, 25.92, 25.82, 14.37, 8.85, 8.78. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{25}H_{45}BO_5Na^+$: 459.3258; found: 459.3261. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2922 (s), 2850 (m), 1736 (vs), 1450 (m), 1396 (m), 1368 (m), 1352 (m), 1302 (s), 1288 (s), 1252 (m), 1208 (m), 1170 (s), 1144 (s), 1110 (s), 1030 (s), 994 (w), 970 (w), 956 (w), 922 (s), 892 (m), 854 (w), 792 (w), 770 (w), 698 (w).

Ethyl 2-((2*S*,3*S*)-3-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-3-((trimethylsilyl)methyl)bicyclo[2.2.1]heptan-2-yl)acetate (15a)

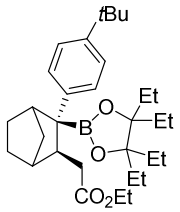


A flame-dried Schlenk flask was charged with 2-(bicyclo[2.2.1]hept-2-en-2-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (**13**) (55 mg, 0.2 mmol, 1.0 equiv.) and THF (1 mL) was added. The solution was cooled to -78°C and (trimethylsilyl)methyllithium (0.22 mmol, 1.1 equiv.) was added dropwise. Stirring was continued at this temperature for 30 min, before the mixture was allowed to warm to 0°C for 45 min. Following this, the solvents were carefully removed *in vacuo*. The residue was dissolved in 2-methyltetrahydrofuran (1.5 mL), dodecane (0.1 mL, 5 Vol%.) was added and the flask was transferred to the photoreactor precooled to -40 °C. Ethyl iodoacetate (47 µL, 0.4 mmol, 2.0 equiv.) was dissolved in 2-methylTHF (0.5 mL) and added dropwise to the mixture under irradiation at -40°C. The colorless solution was stirred at the indicated temperature under LED irradiation for 12 h. The crude mixture was pushed

through a Silica-Plug (4 cm), eluting with Et_2O (50 mL) and was concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane – EtOAc: 97:3) afforded the title compound as a viscous colorless oil (71 mg, 0.16 mmol, 79 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 4:1.

^{1}H NMR (600 MHz, CD_2Cl_2): δ (ppm) = 4.13 – 4.01 (m, 2H), 2.32 – 2.03 (m, 4H), 1.91 – 1.78 (m, 2H), 1.73 – 1.58 (m, 10H), 1.42 – 1.29 (m, 2H), 1.22 (t, J = 7.1 Hz, 2H), 1.03 – 0.95 (m, 1H), 0.93 – 0.84 (m, 15H), 0.09 – 0.01 (m, 9H). **^{13}C NMR (150 MHz, CD_2Cl_2):** δ (ppm) = 174.54, 88.55, 88.23, 60.63, 60.39, 47.94, 46.06, 43.27, 36.89, 35.16, 30.65, 27.46, 27.23, 26.71, 26.40, 26.21, 20.54, 14.61, 9.20, 9.13, 9.07, 9.03, 1.18, 0.51. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{25}H_{47}BO_4SiNa^+$: 473.3234; found: 473.3241.**IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2948 (m), 2884 (w), 1736 (m), 1458 (w), 1382 (m), 1366 (m), 1346 (m), 1284 (m), 1246 (m), 1224 (w), 1170 (m), 1142 (m), 1112 (m), 1030 (m), 990 (w), 958 (vw), 922 (m), 856 (s), 836 (vs), 798 (w), 770 (w), 752 (w), 688 (w).

Ethyl 2-((2*S*,3*S*)-3-(4-(*tert*-butyl)phenyl)-3-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)bicyclo[2.2.1]heptan-2-yl)acetate (15b)

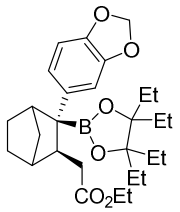


A flame-dried Schlenk flask was charged with 1-*tert*-butyl-4-iodobenzene (39 µL, 0.22 mmol, 1.0 equiv.) and THF (1 mL) was added. After cooling to -78°C, *n*BuLi (0.22 mmol, 1.1 equiv.) was added dropwise and the mixture was allowed to stir for 30min. 2-(Bicyclo[2.2.1]hept-2-en-2-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (**13**) (55 mg, 0.2 mmol, 1.0 equiv.) was dissolved in THF (0.2 mL) and added dropwise. Stirring was continued at this temperature for 30min, before the mixture was allowed to warm to 0°C for 45 min. Following this, the solvents were carefully removed *in vacuo*. The residue was dissolved in 2-methyltetrahydrofuran (1.5 mL), dodecane (0.1 mL, 5 Vol%.) was added and the flask was transferred to the photoreactor precooled to -40 °C. Ethyl iodoacetate (47 µL, 0.4 mmol, 2.0 equiv.) was dissolved in 2-methylTHF (0.5 mL) and added dropwise to the mixture under irradiation at -40°C. The colorless solution was stirred at the indicated temperature under LED irradiation for 12 h. The crude mixture was pushed through a Silica-Plug (4 cm), eluting with Et_2O (50 mL) and was concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane – EtOAc: 96:4) afforded the title compound as a viscous colorless oil (91 mg, 0.18 mmol, 92 %). ^{1}H NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of >20:1

^{1}H NMR (400 MHz, DCM-D_2): δ (ppm) = 7.29 – 7.24 (m, 2H), 7.13 – 7.08 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.43 (q, J = 7.0 Hz, 1H), 2.99 (dd, J = 15.2, 3.2 Hz, 1H), 2.92 – 2.89 (m, 1H), 2.33

– 2.28 (m, 1H), 2.16 (dd, J = 15.2, 12.3 Hz, 1H), 2.00 – 1.97 (m, 1H), 1.63 – 1.57 (m, 1H), 1.56 – 1.49 (m, 3H), 1.47 – 1.40 (m, 3H), 1.36 – 1.23 (m, 17H), 1.09 – 1.02 (m, 1H), 0.79 (t, J = 7.6 Hz, 6H), 0.63 (t, J = 7.6 Hz, 6H). **^{13}C NMR (100 MHz, DCM-D_2):** δ (ppm) = 174.10, 147.87, 143.06, 128.08, 125.18, 88.86, 66.22, 60.56, 48.56, 43.91, 42.90, 40.80, 37.47, 34.61, 31.68, 30.92, 26.51, 25.63, 24.39, 15.65, 14.68, 9.32, 8.34. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{31}H_{49}BO_4Na^+$: 519.3622 found: 519.3630. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2962 (s), 2872 (m), 1734 (vs), 1512 (w), 1458 (m), 1412 (w), 1362 (s), 1348 (m), 1326 (s), 1280 (vs), 1250 (s), 1206 (m), 1160 (s), 1144 (s), 1114 (s), 1032 (s), 998 (w), 956 (w), 924 (vs), 890 (w), 856 (w), 830 (m), 798 (w), 774 (w), 744 (vw), 722 (vw).

Ethyl 2-((2*S*,3*S*)-3-(benzo[d][1,3]dioxol-5-yl)-3-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)bicyclo[2.2.1]heptan-2-yl)acetate (<u>15c</u>)

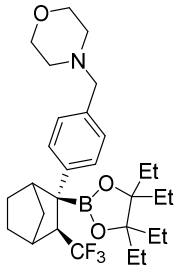


A flame-dried Schlenk flask was charged with 4-bromo-1,2-(methylenedioxy)benzene (26 µL, 0.22 mmol, 1.0 equiv.) and THF (1 mL) was added. After cooling to -78°C, *n*BuLi (0.22 mmol, 1.1 equiv.) was added dropwise and the mixture was allowed to stir for 20min. 2-(Bicyclo[2.2.1]hept-2-en-2-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (**<u>13</u>**) (55 mg, 0.2 mmol, 1.0 equiv.) was dissolved in THF (0.2 mL) and added dropwise. Stirring was continued at this temperature for 30min, before the mixture was allowed to warm to 0°C for 45 min. Following this, the solvents were carefully removed *in vacuo*. The residue was dissolved in 2-methyltetrahydrofuran (1.5 mL), dodecane (0.1 mL, 5 Vol%.) was added and the flask was transferred to the photoreactor precooled to -40 °C. Ethyl iodoacetate (47 µL, 0.4 mmol, 2.0 equiv.) was dissolved in 2-methylTHF (0.5 mL) and added dropwise to the mixture under irradiation at -40°C. The colorless solution was stirred at the indicated temperature under LED irradiation for 12 h. The crude mixture was pushed through a Silica-Plug (4 cm), eluting with Et_2O (50 mL) and was concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane – EtOAc: 95:5) afforded the title compound as a viscous colorless oil (70 mg, 0.14 mmol, 72 %). ^{1}H NMR of the crude reaction mixture indicated a diastereomeric ratio of <u>>20:1.</u>

^{1}H NMR (400 MHz, DCM-D_2): δ (ppm) = 6.73 – 6.69 (m, 2H), 6.64 (dd, J = 8.2, 1.8 Hz, 1H), 5.89 (q, J = 1.4 Hz, 2H), 4.20 – 4.09 (m, 2H), 2.96 (dd, J = 13.9, 1.8 Hz, 1H), 2.84 (dd, J = 3.9, 1.6 Hz, 1H), 2.27 – 2.10 (m, 2H), 1.97 (dd, J = 3.9, 1.6 Hz, 1H), 1.61 – 1.35 (m, 11H), 1.33 – 1.23 (m, 5H), 1.11 – 1.01 (m, 1H), 0.82 (t, J = 7.5 Hz, 6H), 0.70 (t, J = 7.5 Hz, 6H). **^{13}C NMR (100 MHz, DCM-D_2):** δ (ppm) = 174.01, 147.79, 145.17, 140.39, 121.31, 109.21, 108.02, 101.30, 88.94, 62.63, 60.58, 48.94, 44.35, 43.00, 40.72, 37.44, 30.93, 26.40, 25.80, 24.24,

14.67, 14.20, 9.22, 8.54. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{28}H_{41}BO_6Na^+$: 507.2894; found: 507.2901.

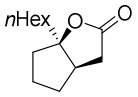
4-(4-((2S,3S)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)bicyclo[2.2.1]heptan-2-yl)benzyl)morpholine (<u>15d</u>)



A flame-dried Schlenk flask was charged with 4-(4-bromobenzyl)morpholine (56 mg, 0.22 mmol, 1.0 equiv.) and THF (1 mL) was added. After cooling to -78°C, *n*BuLi (0.22 mmol, 1.1 equiv.) was added dropwise and the mixture was allowed to stir for 30min. 2-(Bicyclo[2.2.1]hept-2-en-2-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (**<u>13</u>**) (55 mg, 0.2 mmol, 1.0 equiv.) was dissolved in THF (0.2 mL) and added dropwise. Stirring was continued at this temperature for 30min, before the mixture was allowed to warm to 0°C for 45 min. Following this, the solvents were carefully removed *in vacuo*. The residue was dissolved in 2-methyltetrahydrofuran (1.5 mL), dodecane (0.1 mL, 5 Vol%.) was added and the flask was transferred to the photoreactor precooled to -40 °C. Ritter trifluoroiodomethane (0.28 g, 0.8 mmol, 4.0 equiv.) was dissolved in 2-methylTHF (0.5 mL) and added dropwise to the mixture under irradiation at -40°C. The colorless solution was stirred at the indicated temperature under LED irradiation for 12 h. The crude mixture was pushed through a Silica-Plug (4 cm), eluting with Et_2O (50 mL) and was concentrated *in vacuo*. Flash column chromatography (SiO_2 deactivated with TEA; pentane – EtOAc: 9:1; 1 % TEA) afforded the title compound as a viscous colorless oil (48 mg, 0.09 mmol, 46 %). ^{1}H NMR of the crude reaction mixture indicated a diastereomeric ratio of <u>>20:1.</u>

^{1}H NMR (400 MHz, DCM-D_2): δ (ppm) = 7.24 – 7.20 (m, 2H), 7.15 – 7.11 (m, 2H), 3.64 (q, J = 4.7, 4.2 Hz, 4H), 3.43 (d, J = 1.7 Hz, 2H), 3.04 (dd, J = 4.2, 2.2 Hz, 1H), 2.39 (q, J = 5.5, 4.9 Hz, 4H), 1.89 (d, J = 10.2 Hz, 1H), 1.81 – 1.70 (m, 1H), 1.58 – 1.49 (m, 5H), 1.45 – 1.36 (m, 5H), 1.26 – 1.20 (m, 2H), 1.12 – 1.03 (m, 1H), 0.95 (t, J = 7.5 Hz, 2H), 0.79 (t, J = 7.6 Hz, 6H), 0.60 (t, J = 7.6 Hz, 6H). **^{13}C NMR (100 MHz, DCM-D_2):** δ (ppm) = 144.09, 135.29, 129.49, 128.98, 128.15, 89.06, 67.48, 63.46, 44.35, 39.58, 38.33, 31.00, 26.92, 26.07, 25.40, 24.27, 9.16, 8.32. **^{19}F NMR (400 MHz, DCM-D_2):** δ (ppm) = -64.92, -64.95. **HRMS** (ESI) m/z: $[Na]^+$ calcd for $C_{29}H_{43}BF_3NO_3Na^+$: 544.3186; found: 544.3182.

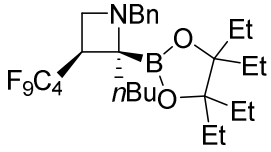
(6aR)-6a-hexylhexahydro-2H-cyclopenta[b]furan-2-one (16)



Ethyl 2-((1*R*,2*S*)-2-hexyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)acetate **9b** (47 mg, 0.1 mmol, 1.0 equiv.) was dissolved in THF (3 mL) and cooled to 0°C. NaOH (2 M, 2 mL) was added, followed by dropwise addition of aq. H_2O_2 (30w%., 1 mL). The reaction mixture was allowed to warm to rt. under vigorous stirring. After 7h sat. aq. $Na_2S_2O_3$ (3 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic fractions were washed with Brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (SiO_2; Pentane – EtOAc: 95:5) afforded the title compound as a colorless oil (19 mg, 0.09 mmol, 89 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.85 (dd, J = 18.5, 10.2 Hz, 1H), 2.50 (ddt, J = 10.2, 8.9, 3.1 Hz, 1H), 2.29 (dd, J = 18.5, 3.1 Hz, 1H), 2.07 – 2.02 (m, 1H), 1.93 – 1.86 (m, 1H), 1.76 – 1.64 (m, 4H), 1.62 – 1.57 (m, 1H), 1.56 – 1.50 (m, 1H), 1.42 – 1.35 (m, 2H), 1.34 – 1.24 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 177.65, 98.40, 42.22, 39.50, 38.22, 37.22, 34.56, 31.82, 29.65, 24.34, 24.09, 22.70, 14.20. **HRMS (EI-orbitrap):** *m/z*: [M] calc. for [$C_{12}H_{22}O_2$]: 210.1620; found: 210.1613. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2930 (m), 2860 (w), 1764 (vs), 1456 (w), 1420 (w), 1378 (vw), 1328 (w), 1304 (w), 1270 (w), 1252 (w), 1218 (m), 1188 (s), 1150 (m), 1120 (w), 1104 (w), 1090 (w), 1050 (w), 960 (m), 918 (m), 888 (vw), 846 (vw), 816 (vw), 726 (w), 708 (vw).

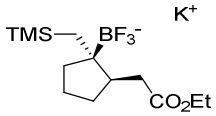
(2*R*,3*S*)-1-benzyl-2-butyl-3-(perfluorobutyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine (17a)



tert-Butyl (2*S*,3*S*)-2-butyl-3-(perfluorobutyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine-1-carboxylate **3a** (61 mg, 0.1 mmol, 1.0 equiv.) was dissolved in DCM (1 mL) and treated with TFA (0.5 mL). After stirring at rt. for 4h, the solvents were removed *in vacuo* and the residue was transferred in a pressure tube containing BnBr (36 µL, 0.3 mmol, 3.0 equiv.), K_2CO_3 (41 mg, 0.3 mmol, 3.0 equiv.) in MeOH (3 mL). The reaction mixture was then heated to 70°C overnight. After removing the solvents *in vacuo*, water (5 mL) was added and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic fractions were washed with Brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane – EtOAc; 99:1) afforded the title compound as a colorless oil (40 mg, 0.067 mmol, 67 %). ^{19}F NMR analysis of the crude reaction mixture indicated a diastereomeric ratio of 8:1.

^{1}H NMR (600 MHz, Acetone-D$_6$): δ (ppm) = 7.36 – 7.27 (m, 4H), 7.24 – 7.19 (m, 1H), 4.00 – 3.79 (m, 2H), 3.34 – 3.09 (m, 2H), 3.11 – 2.96 (m, 1H), 1.84 – 1.75 (m, 8H), 1.54 – 1.44 (m, 1H), 1.40 – 1.27 (m, 3H), 0.97 (td, J = 7.5, 1.8 Hz, 12H), 0.93 – 0.86 (m, 5H). **^{13}C NMR (150 MHz, Acetone-D$_6$):** δ (ppm) = 140.58, 129.20, 128.99, 127.62, 90.10, 60.17, 51.26, 42.64, 42.28, 42.05, 27.75, 27.08, 26.37, 24.11, 14.33, 14.20, 9.10, 9.06. **^{19}F NMR (400 MHz, Acetone-D$_6$):** δ (ppm) = -81.92, -81.93, -81.94, -81.95, -81.96, -81.98, -81.99, -113.46, -113.49, -113.58, -113.62, -123.45, -124.23, -124.77, -125.54, -126.76, -126.79, -126.83. **HRMS** (ESI) m/z: $[H]^+$ calcd for $C_{28}H_{40}BF_9NO_2^+$: 604.3003; found: 604.3021. **IR** (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2936 (w), 2886 (w), 2860 (w), 1494 (vw), 1458 (w), 1386 (w), 1352 (m), 1306 (w), 1288 (w), 1232 (vs), 1168 (m), 1134 (vs), 1112 (s), 1074 (m), 1026 (m), 968 (w), 922 (m), 888 (w), 854 (w), 834 (w), 800 (w), 778 (w), 742 (m), 728 (m).

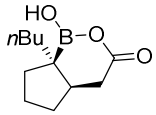
Ethyl 2-((1*R*,2*S*)-2-(trifluoro-l4-boraneyl)-2-((trimethylsilyl)methyl)cyclopentyl)acetate, potassium salt (<u>17b</u>)



A flame-dried flask was charged with ethyl 2-((1*R*,2*S*)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-2-((trimethylsilyl)methyl)cyclopentyl)acetate (<u>**9c**</u>) (42 mg, 0.1 mmol, 1.0 equiv.), dry DCM (3 mL) was added and the mixture was cooled to -78°C. A solution of BCl_3 in Heptane (1 mmol, 10 equiv.) was added dropwise to the mixture and stirring was continued at the aforementioned temperature for 30 min. Next, the dry-ice bath was removed and the red solution was allowed to warm to rt, stirring at this temperature for a further 4 h. Dry MeOH (2 mL) was added dropwise at 0°C and the mixture was allowed to warm to rt. for 1 h. After that, the solvents were removed *in vacuo* and the residue was dissolved in MeOH (1 mL). Saturated aqueous KHF_2 (0.42 mmol, 4.2 equiv.) was added dropwise and the mixture was allowed to stir overnight at ambient temperature. After addition of MeOH (2 mL) the solvents were removed *in vacuo* and the residual solid was washed and sonicated with pentane (3 × 2 mL) to obtain the title compound as an off-white solid (30 mg, 0.09 mmol, 85 %).

^{1}H NMR (400 MHz, CD$_3$OD): δ (ppm) = 3.61 (s, 2H), 2.61 (d, J = 14.7 Hz, 1H), 2.28 (t, J = 12.9 Hz, 1H), 1.97 – 1.35 (m, 7H), 1.18 – 0.78 (m, 3H), 0.33 – 0.13 (m, 2H), -0.02 (s, 9H). **^{13}C NMR (100 MHz, CD$_3$OD):** δ (ppm) = 178.70, 51.84, 51.60, 38.70, 38.17, 32.51, 29.08, 24.08, 1.32. **^{11}B NMR (128 MHz, CDCl$_3$):** δ (ppm) = 5.55. **^{19}F NMR (400 MHz, CD$_3$OD):** δ (ppm) = -142.96, -154.89, -155.65, -155.74, -156.38. **HRMS** (ESI) m/z: $[H]^+$ calcd for $C_{12}H_{23}BF_3O_2Si^+$: 295.1517; found: 295.1516.

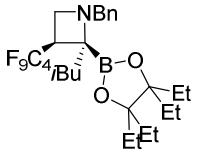
(4a*R*,7a*S*)-7a-Butyl-1-hydroxyhexahydrocyclopenta[c][1,2]oxaborinin-3(1H)-one (<u>17c</u>)



According to a modified literature procedure, a flame-dried flask was charged with *tert*-Butyl 2-((1*R*,2*S*)-2-butyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclopentyl)acetate (**<u>9a'</u>**) (85 mg, 0.2 mmol, 1.0 equiv.) and dry DCM (5 mL). The mixture was cooled to -78°C and a solution of BCl_3 in Heptane (2 mmol, 10 equiv.) was added dropwise. After 30 min, the yellow solution was allowed to warm to rt. and stirred at this temperature overnight. The next day, the solvents were removed *in vacuo* and the residue was dissolved in Et_2O (10 mL). After washing with water (10 mL), the aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic fractions were washed with Brine, dried over anhydr. $MgSO_4$ and concentrated *in vacuo.* The residual solid was carefully washed with ice-cold pentane (10 mL) to afford the title compound as a colorless solid (18 mg, 0.086 mmol, 43 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.19 (dd, J = 14.2, 8.1 Hz, 1H), 2.32 (d, J = 14.2 Hz, 1H), 2.06 – 1.92 (m, 2H), 1.68 – 1.43 (m, 5H), 1.36 – 1.05 (m, 5H), 0.92 – 0.82 (m, 3H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 186.82, 43.14, 40.18, 37.67, 35.48, 32.55, 29.05, 25.26, 24.11, 14.52. **^{11}B NMR (128 MHz, $CDCl_3$):** δ (ppm) = 34.46. **HRMS** (ESI) m/z: $[H]^+$ calcd for $C_{11}H_{18}BO_3^+$: 209.1349; found: 209.1354.

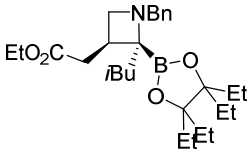
(2*R*,3*S*)-1-Benzyl-2-isobutyl-3-(perfluorobutyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidine (<u>17b</u>)



The *N*-Boc protected azetidine (1.0 g, 1.7 mmol, 1.0 equiv.) was charged to a flame-dried flask and dissolved in dry DCM (8 mL). TFA (1.5 mL, 20 mmol, 12 equiv.) was added dropwise and the reaction mixture was allowed to stir for 3 h at ambient temperature. After that, the volatiles were removed *in vacuo*, and the dark red mixture was dissolved in EtOAc (50 mL) and washed with sat. aq. Na_2CO_3 (2 × 30 mL) and Brine (30 mL). The solvent was removed *in vacuo*, and the deprotected azetidine was transferred to an Ace pressure vial containing benzyl bromide (0.5 mL, 4 mmol, 2.3 equiv.), DIPEA (1.7 mL, 10 mmol, 6 equiv.) and MeCN (3 mL). The vial was closed and the mixture was allowed to stir at 100 °C overnight. The next day, all volatiles were removed *in vacuo*, and the crude product was purified by flash column chromatography ((silica; pentane – EtOAc; 99:1 to 96:4) to obtain the title compound as a yellow oil (0.58 g, 1 mmol, 56 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.34 – 7.28 (m, 4H), 7.24 – 7.20 (m, 1H), 4.01 (d, J = 13.2 Hz, 1H), 3.77 (d, J = 13.2 Hz, 1H), 3.23 (t, J = 7.1 Hz, 1H), 3.11 (dd, J = 10.0, 6.2 Hz, 1H), 3.04 – 2.90 (m, 1H), 1.90 – 1.62 (m, 11H), 1.02 (d, J = 6.6 Hz, 3H), 0.99 – 0.91 (m, 15H). **^{13}C NMR (126 MHz, $CDCl_3$):** δ (ppm) = 139.65, 128.65, 128.43, 126.97, 89.40, 59.23, 50.80, 42.68, 42.50, 42.32, 25.99, 25.49, 25.19, 24.86, 24.76, 9.09, 8.63. **^{19}F NMR (471 MHz, $CDCl_3$)** δ (ppm) = -81.07, -81.08, -81.09, -81.10, -81.10, -81.12, -81.12, -113.44, -113.48, -113.51, -123.14, -123.77, -124.43, -125.06, -126.14, -126.17, -126.20. **HRMS** (ESI) m/z: $[H]^+$ calcd for $C_{28}H_{40}BF_9NO_2^+$: 604.3010; found: 604.3013.

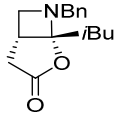
Ethyl 2-((2*R*,3*S*)-1-benzyl-2-isobutyl-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)azetidin-3-yl)acetate (<u>18</u>)



Compound **<u>3p</u>** (0.5 g, 1 mmol, 1.0 equiv.) was charged to a flame-dried flask and dissolved in dry DCM (6 mL). TFA (1.7 mL, 20 mmol, 20 equiv.) was added dropwise and the reaction mixture was allowed to stir for 3 h at ambient temperature. After that, the volatiles were removed *in vacuo*, and the dark red mixture was dissolved in EtOAc (50 mL) and washed with sat. aq. Na_2CO_3 (2 × 30 mL) and Brine (30 mL). The solvent was removed *in vacuo*, and the deprotected azetidine was transferred to an Ace pressure vial containing benzyl bromide (0.2 mL, 1.5 mmol, 1.5 equiv.), DIPEA (0.96 mL, 1.5 mmol, 1.5 equiv.) and MeCN (1 mL). The vial was closed and the mixture was allowed to stir at 100 °C overnight. The next day, all volatiles were removed *in vacuo*, and the crude product was purified by flash column chromatography ((SiO_2; pentane – EtOAc; 8:2 to 7:3) to obtain the title compound as a colorless oil (0.2 g, 0.4 mmol, 38 %).

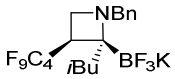
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.33 – 7.27 (m, 5H), 4.58 (d, *J* = 14.8 Hz, 1H), 4.47 (d, *J* = 14.9 Hz, 1H), 4.11 – 4.04 (m, 2H), 3.26 (dd, *J* = 11.7, 5.2 Hz, 1H), 2.87 (t, *J* = 10.8 Hz, 1H), 2.54 – 2.48 (m, 1H), 2.42 (dq, *J* = 9.0, 5.6 Hz, 1H), 2.23 (dd, *J* = 16.2, 10.4 Hz, 1H), 1.92 (dt, *J* = 13.3, 6.7 Hz, 1H), 1.66 – 1.59 (m, 10H), 1.19 – 1.16 (m, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 12H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ (ppm) = 171.75, 154.23, 137.02, 128.64, 128.38, 127.58, 90.34, 60.90, 52.68, 48.55, 44.18, 36.25, 34.06, 26.02, 25.89, 24.84, 24.54, 24.27, 14.24, 8.81, 8.71. **HRMS** (ESI) m/z: $[H]^+$ calcd for $C_{28}H_{47}BNO_4^+$: 472.3600; found: 472.3606.

(1*R*,5*R*)-7-Benzyl-1-isobutyl-2-oxa-7-azabicyclo[3.2.0]heptan-3-one (20)



Compound **18** (24 mg, 0.05 mmol, 1.0 equiv.) was charged to a flame-dried flask and dissolved in dry DCM (1 mL) and cooled to -78°C. A solution of BCl_3 in heptane (0.5 mmol, 10 equiv.) was added dropwise, and the reaction mixture was allowed to stir at the aforementioned temperature for 1 h. After that, the pale yellow solution was allowed to warm to rt., stirring at this temperature for 1 h. Dry MeOH (0.5 mL) was added dropwise and stirring was continued for 30 min. Following this, the solvents were removed by high-vacuum, and residue was dissolved in THF (1 mL). A 1:1 mixture of 2 M NaOH (0.5 mL) and H_2O_2 (30 %, 0.5 mL) was added dropwise to the mixture at 0°C, and the reaction was allowed to warm to rt. After 1 h stirring at rt. sat. aq. NH_4Cl (2 mL) was added. H_2O (3 mL) was added and the aq. fraction was extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with Brine (5 mL), dried over anhydr. $MgSO_4$ and the solvents were removed *in vacuo.* The crude compound was purified by flash column chromatograophy (SiO_2, pentane – EtOAc: 9:1 to 3:7) to obtain the title compound as a colorless oil (11 mg, 0.04 mmol, 84 %)**^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm) = 7.37 – 7.27 (m, 3H), 7.25 – 7.20 (m, 2H), 4.52 (d, *J* = 14.7 Hz, 1H), 4.38 (d, *J* = 14.7 Hz, 1H), 3.45 (dd, *J* = 9.7, 6.4 Hz, 1H), 3.36 (t, *J* = 9.1 Hz, 1H), 3.26 (q, *J* = 8.0 Hz, 1H), 2.66 (d, *J* = 8.5 Hz, 2H), 2.31 (d, *J* = 2.2 Hz, 1H), 2.29 (d, *J* = 1.2 Hz, 1H), 2.14 (dt, *J* = 13.4, 6.7 Hz, 1H), 0.88 (dd, *J* = 6.6, 3.9 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$):** δ (ppm) = 208.07, 172.33, 136.10, 128.92, 128.31, 127.89, 50.60, 47.41, 46.75, 43.00, 33.42, 24.36, 22.64. **HRMS** (ESI) m/z: $[H]^+$ calcd for $C_{16}H_{22}NO_2^+$: 260.1652; found: 260.1644.

(2*R*,3*S*)-1-Benzyl-2-isobutyl-3-(perfluorobutyl)-2-(trifluoro-l4-boraneyl)azetidine, potassium salt (19)



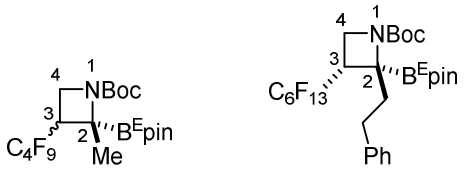
Compound **17b** (60 mg, 0.1 mmol, 1.0 equiv.) was charged to a flame-dried flask and dissolved in dry DCM (1 mL) and cooled to -78°C. A solution of BCl_3 in heptane (1 mmol, 10 equiv.) was added dropwise, and the reaction mixture was allowed to stir at the aforementioned temperature for 1 h. After that, the red solution was allowed to warm to rt., stirring at this temperature for 2 h. Dry MeOH (0.5 mL) was added dropwise and stirring was continued for 30 min. Following this, the solvents were removed by high-vacuum, and residue was dissolved in MeOH (1 mL). A 4.2 M aq. solution of KHF_2 (0.4 mmol, 4 equiv.) was added, and the mixture was allowed to stir at rt. for 30 min. The solvents were removed *in vacuo*, and dry acetone (2 mL) was added. After sonication, the acetone was carefully decanted and removed *in vacuo*. The solid residue was dissolved in MeOH (0.1 mL) and dropped in hexane.

The colorless solid was collected by filtration to obtain the title compound as a colorless amorphous solid (40 mg, 0.08 mmol, 75 %). **^{1}H NMR (500 MHz, CD_3OD):** δ (ppm) = 7.45 (s, 5H), 4.48 – 4.39 (m, 2H), 4.14 (ddd, *J* = 10.9, 8.8, 1.5 Hz, 1H), 3.56 (t, *J* = 8.7 Hz, 1H), 3.23 – 3.11 (m, 1H), 2.12 (dt, *J* = 12.6, 6.3 Hz, 1H), 1.99 (dd, *J* = 13.9, 5.7 Hz, 1H), 1.75 (dd, *J* = 13.9, 5.3 Hz, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR (126 MHz, CD_3OD):** δ (ppm) = 132.18, 131.50, 130.78, 130.39, 56.11, 49.77, 42.38, 42.17, 41.97, 25.04, 25.02, 24.96, 24.70. **^{19}F NMR (471 MHz, CD_3OD)**: δ (ppm) = -82.63, -82.63, -82.65, -82.66, -82.66, -82.68, -82.68, -114.23, -114.25, -114.26, -114.27, -114.28, -114.29, -114.30, -114.33, -114.83, -114.85, -114.86, -114.87, -114.88, -114.89, -114.90, -114.91, -114.93, -119.82, -119.88, -120.46, -123.60, -123.62, -123.64, -123.65, -123.67, -123.69, -123.71, -123.73, -124.23, -124.25, -124.27, -124.29, -124.30, -124.32, -124.34, -124.34, -124.36, -125.35, -125.36, -125.38, -125.40, -125.42, -125.44, -125.46, -125.98, -126.00, -126.01, -126.03, -126.05, -126.07, -126.09, -126.45, -126.47, -126.49, -126.51, -126.53, -127.08, -127.09, -127.11, -127.13, -127.14, -127.15, -127.25, -127.26, -127.27, -127.28, -127.30, -127.31, -127.32, -127.33, -127.35, -127.36, -127.37, -127.39, -127.87, -127.89, -127.90, -127.91, -127.92, -127.93, -127.95, -141.16. **HRMS** (ESI) m/z: $[H]^+$ calcd for $C_{18}H_{19}BF_{12}N^+$: 489.1558; found: 489.1563.

6. NMR-Spectroscopic Determination of the Relative Configuration

General strategy and nomenclature

The determination of the respective relative configurations was done using a combination of the (^{1}H-^{1}H) nuclear Overhauser effect (NOE) and the (^{1}H-^{19}F) heteronuclear Overhauser effect (HOE). The structures of the compounds **3d** and **3e** investigated in detail are shown in Figure 12.



3e (74%)
(dr = 1:1)

3d (74%)
(dr > 20:1)

Figure 12: Structures of the investigated compounds **3e** and **3d** including the numbering used for the combined NOE/HOE analysis. For both compounds the anti (referring to the relation of the perfluorinated and the alkylic side chain) configuration is depicted for consistency with the main text (despite the fact that the determination of the configuration is the subject of this chapter).

Compound **3e** is formed in a diastereomeric ratio of ca. 1:1, which allows the investigation and comparison of the relative configuration of both diastereomers **3e$_{syn}$** and **3e$_{anti}$**, with *syn* meaning that the methyl group at position 2 and the perfluorinated side chain at position 3 are located on the same side of the four-membered heterocycle, whereas *anti* refers to both being on opposite sides. For the *anti* diastereoisomer we would expect to see a strong ^{1}H,^{1}H-NOE

between the methyl group at position 2 and proton 3 accompanied by a weak $^{1}H,^{19}F$-HOE between the methyl group and the perfluorinated side chain at position 3. For the *syn* diastereomer we would expect to see the opposite behavior of a weak NOE and a strong HOE (see scheme 6 in the main text). Compound **3d** was synthesized with such a high diastereomeric purity (*dr.* = 20:1) that no minor diastereomer could be observed *via* NMR spectroscopy. For the assignment we use the fact that (only) one of the patterns described above can be observed for the *major* (sole) diastereomer, allowing to unambiguously assign its relative configuration to be *anti*. It should be noted that both compounds exhibit two signal sets as they exist as ca. 1:1 mixtures of Boc-rotamers in slow chemical exchange. This can be seen in the 2D NOESYs (figures 15 (**3e**) and figure 21 (**3d**)), where exchange peaks of the same sign as the diagonal peaks can be observed close to the diagonal. In figure 20 the appearance of chemical exchange in NOE spectra is explained in more detail, using one-dimensional spectra.

Experimental details

NMR spectra were recorded on a 400 MHz (^{1}H resonance frequency, Bruker AVANCE III HD, BBFO probe) and a 700 MHz (^{1}H resonance frequency, Bruker AVANCE III HD, QCI cryo $^{1}H/^{19}F$-$^{31}P/^{13}C/^{15}N$-^{2}H probe) spectrometer. Acquisition and analysis of all spectra was accomplished using the software TopSpin (versions 3.6.2 and 3.5.7) from Bruker. The samples were prepared in standard 5 mm NMR tubes using acetone-d_6 (Sigma Aldrich ampoule, 99.9 atom % D) as solvent. Compounds **3e** (8.32 mg) and **3d** (8.25 mg) were each weighed into an NMR tube directly, acetone-d_6 was added and the tubes were flame-sealed under atmosphere resulting in samples with a concentration of 33.7 µmol/L for **3e** (377.39 mg acetone-d_6) and 28.8 µmol/L for **3d** (327.59 mg acetone-d_6). All measurements were carried out at 300 K. For assignment of resonances ^{1}H, ^{13}C, ^{19}F, $^{1}H,^{13}C$-HSQC, $^{1}H,^{13}C$-HMBC, $^{1}H,^{1}H$-COSY, ^{1}H-^{1}H-TOCSY and $^{1}H,^{1}H$-NOESY spectra were acquired at 700 MHz using standard Bruker pulse sequences. 1D selective $^{1}H,^{1}H$-NOE spectra were recorded at 700 MHz using a standard Bruker pulse sequence (*selnogpzs.2*[203]). Spectra were acquired with 64k points using 8 dummy scans (DS) and 32 or 64 scans (NS), zero-filled to 128k points and processed using an exponential apodization with a line broadening factor of 2 Hz. For the selective refocusing *RSnob* shaped pulses (for durations and bandwidths see table 11) were used which were calibrated according to the Bruker *Shapetool*.

[203] a) K. Stott, J. Keeler, Q. N. Van, A. J. Shaka, *J. Magn. Reson.* **1997**, *125*, 302-324; b) M. J. Thrippleton, J. Keeler, *Angew. Chem. Int. Ed.* **2003**, *42*, 3938-3941.

Table 11: Durations, offsets and bandwidths of selective RSnob pulses used for this 1D NOE analysis.

compound	proton	diastereomer		rotamer			offset /	duration /	bandwidth
		anti	syn	1	2	1+2	ppm	ms	/ Hz
3d	H3	x		x			3.47	58	40
3d	H3	x			x		3.58	58	40
3d	H3	x				x	3.53	19	120
3e	H3		x			x	3.41	39	60
3e	H3	x				x	3.25	31	75

The sufficient selectivity of the shaped pulses was checked by acquisition of 1D selective spin echo spectra (Bruker pulse sequence *selgpse*) before the NOE measurements. NOE mixing time series with mixing times (D8) of 50, 100, 150, 200, 250, 300, 350, 400 and 500 ms were acquired. To ensure quantifiability of all spectra the relaxation delay D1 was set to at least five times the longest T_1 (D1 = 23 s). Longitudinal relaxation times were determined *via* the inversion recovery method (Bruker pulse sequence *t1ir*).

2D ^{1}H,^{1}H-NOESY spectra (Bruker pulse sequence *noesygpphzs* [203b, 204]) were recorded at 400 MHz with 2k points (DS = 32, NS = 4 or 8, D1 = 2 s) in the direct dimension F2, spectral widths (SW) of 5 ppm (**3e**) and 8 ppm (**3d**) and offsets of 2.5 ppm (**3e**) and 4.2 ppm (**3d**). In the indirect dimension F1 256 (**3e**) or 512 (**3d**) points were acquired. The raw data was processed to 4k points in F2 and 1k (**3e**) or 2k (**3d**) points in F1 using a sine-bell apodization (SSB = 2) in both dimensions. The mixing time D8 was set to 400 (**3e**) or 500 (**3d**) ms.

2D ^{1}H,^{19}F-HOESY spectra (Bruker pulse sequence *hoesygpph*[205]) were recorded at 400 MHz with 2k points (DS = 32, NS = 32, D1 = 2 s) in the direct proton dimension F2, spectral widths (SW2) of 5 ppm (offset (O2P) 2.5 ppm, **3e**) and 8 ppm (offset (O2P) 4.2 ppm, **3d**). In the indirect fluorine dimension F1 128 points with spectral widths (SW1) of 20 ppm and an offset (O1P) of -121 ppm were acquired. The raw data was processed to 4k points in F2 and 1k points in F1 using a sine-bell apodization (SSB = 2) in both dimensions. The mixing time D8 was set to 500 ms.

Investigations of compound 3e

The ^{1}H NMR spectrum of **3e** shows baseline separated signals for the protons 3_{syn} and $3_{anti,}$ allowing for selective refocusing of the resonances and therefore a straightforward NOE analysis *via* 1D NOE spectra. Every diastereomer is represented by two signal sets due to the mixture of Boc rotamers.

[204] R. Wagner, S. Berger, *J. Magn. Reson., A* **1996**, *123*, 119-121.
[205] C. Yu, G. C. Levy, *J. Am. Chem. Soc.* **1984**, *106*, 6533-6537.

Therefore, both rotamer signals of one diastereomer are refocused simultaneously by one selective pulse (see table 11). An assignment of all ^{1}H resonances relevant to this NOE analysis is given in figure 13.

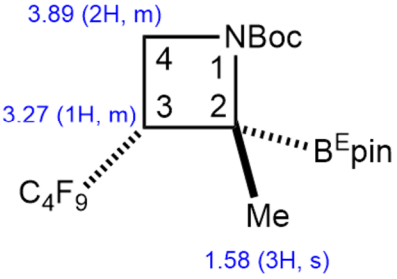
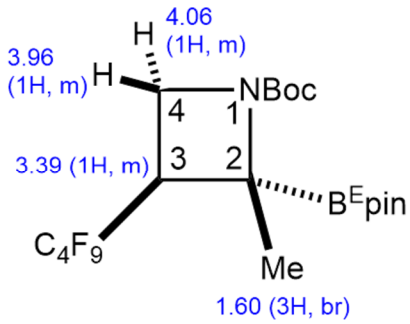
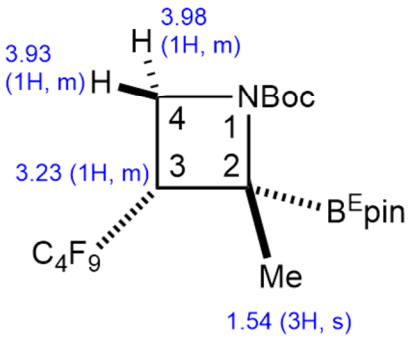
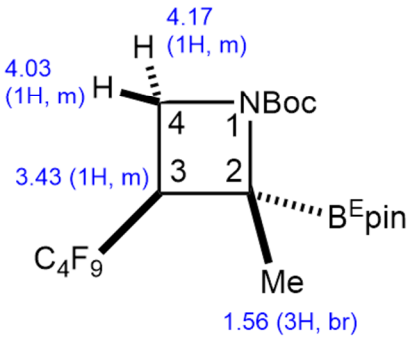
^{1}H chemical shifts (ppm) 700 MHz, 300K, acetone-d_6	diastereomer 1 **3e$_{anti}$**	diastereomer 2 **3e$_{syn}$**
rotamer 1		
rotamer 2		

Figure 13: Assignment of ^{1}H resonances to the different diastereomers and rotamers. Only the chemical shifts (blue) relevant to this analysis are visualized.

.

Interestingly, already in the normal ^{1}H NMR spectra (see figure 14) the methyl groups of the two diastereomers show a completely different signal shape with the *anti* methyl groups being sharp singlets and the *syn* methyl groups being substantially more broadened, indicating significantly different rotamer inversion barriers. This is also seen to a lesser extent in the respective signals of H3.

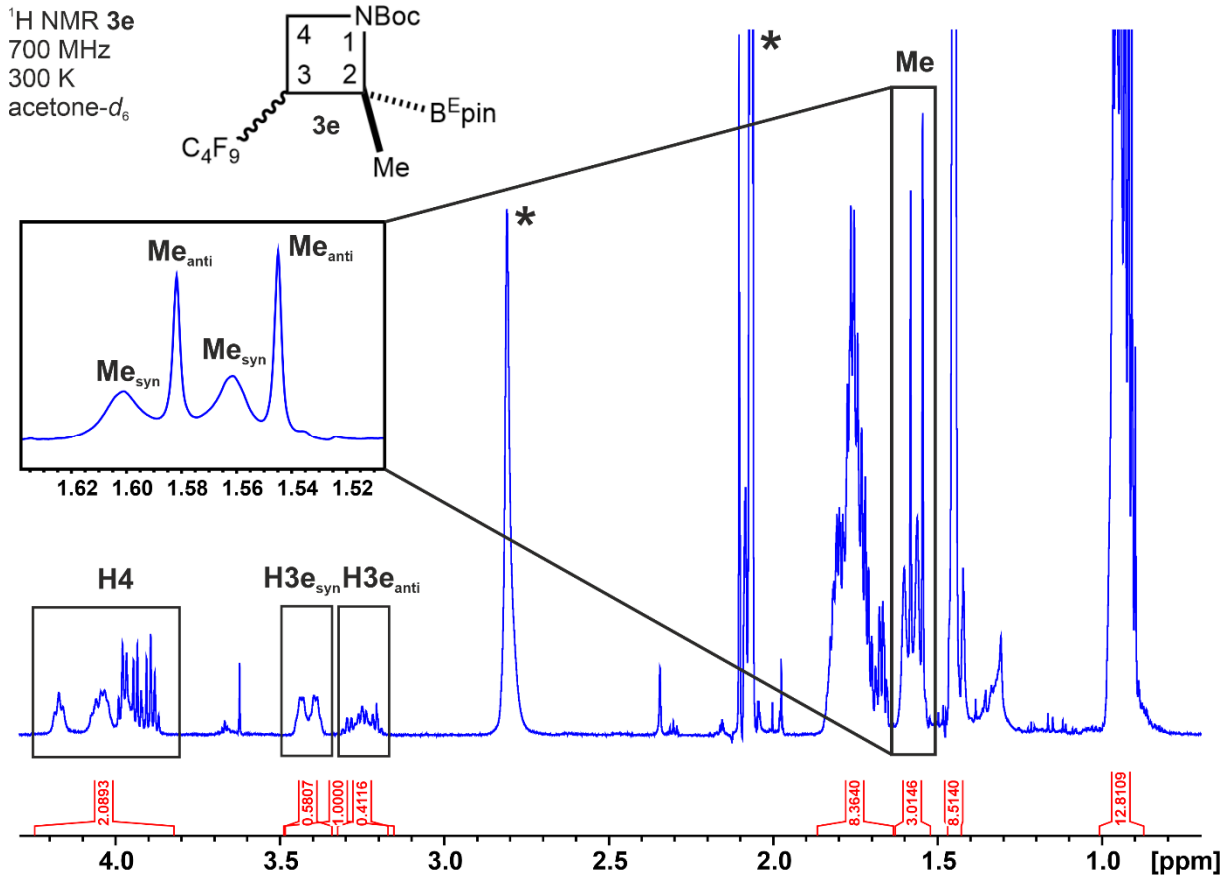


Figure 14: ^{1}H NMR spectrum (relevant part shown) of compound **3e** in acetone-d_6 at 700 MHz and 300 K. Water and acetone are marked with an asterisk.

A 2D NOESY spectrum (figure 15) was acquired to gain insights into the stereochemical relation of the protons $H3_{syn}$/$H3_{anti}$ and the methyl groups.

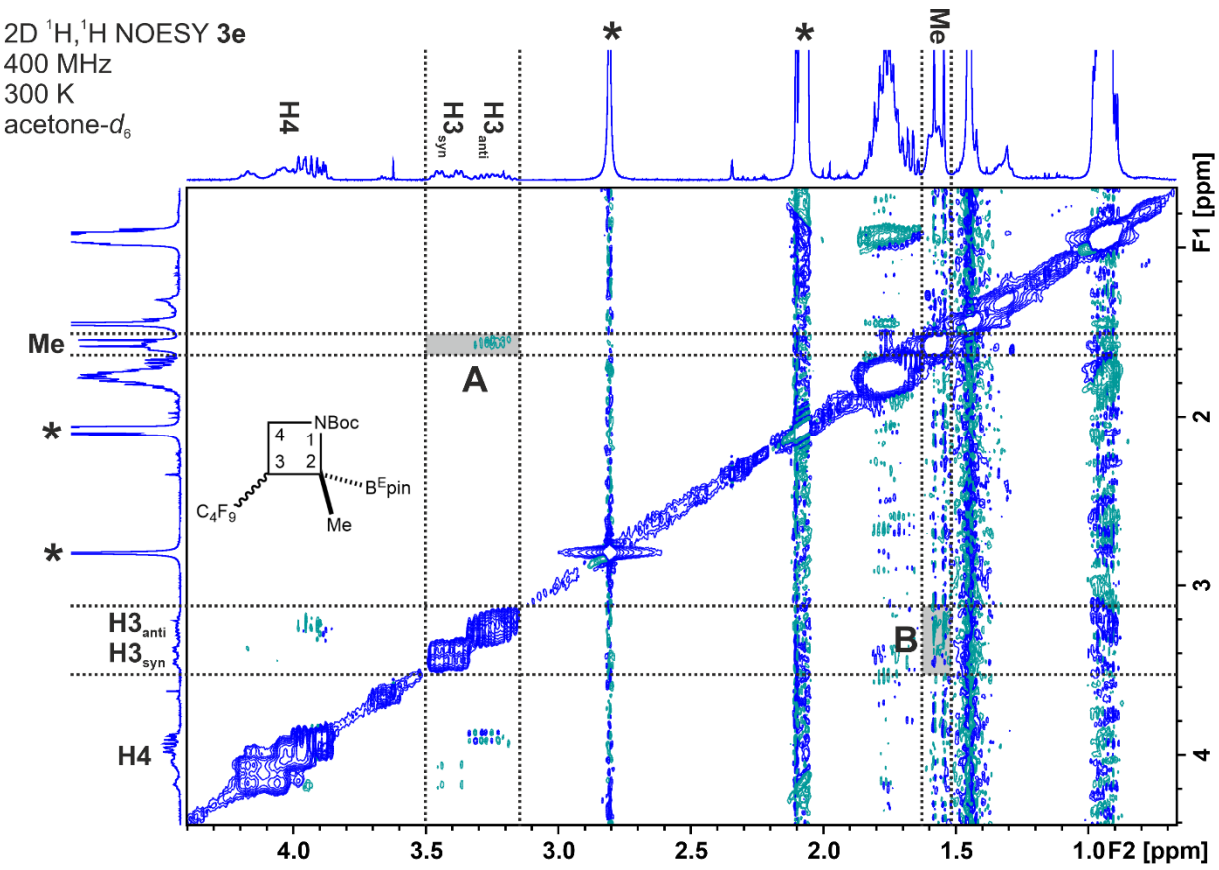


Figure 15: 2D NOESY of compound **3e** in acetone-d_6 at 400 MHz and 300 K. The regions A and B where NOE cross peaks between H3$_{anti}$ and the methyl groups are observed (and not observed for H3$_{syn}$ and the methyl groups) are highlighted with grey boxes. Water and acetone are marked with asterisks.

The 2D NOESY in figure 15 shows NOE cross peaks between H3$_{anti}$ and the methyl groups and no NOE cross peak between H3$_{syn}$ and the methyl groups. The four methyl groups are poorly separated in F1 because of their similar chemical shifts and the limited resolution in the indirect dimension (see region A in figure 15). Additionally, spectrometer instability (also known as t1 noise), reduces spectral quality in region B drastically. Because of these findings, 1D NOE spectra (figure 16) were acquired, avoiding both drawbacks mentioned. These were recorded by selectively refocusing H3$_{syn}$ (red spectrum, in the middle) and H3$_{anti}$ (black spectrum, at the bottom) respectively. The ^{1}H NMR spectrum (blue, at the top) is also shown in figure 16 for easier understanding.

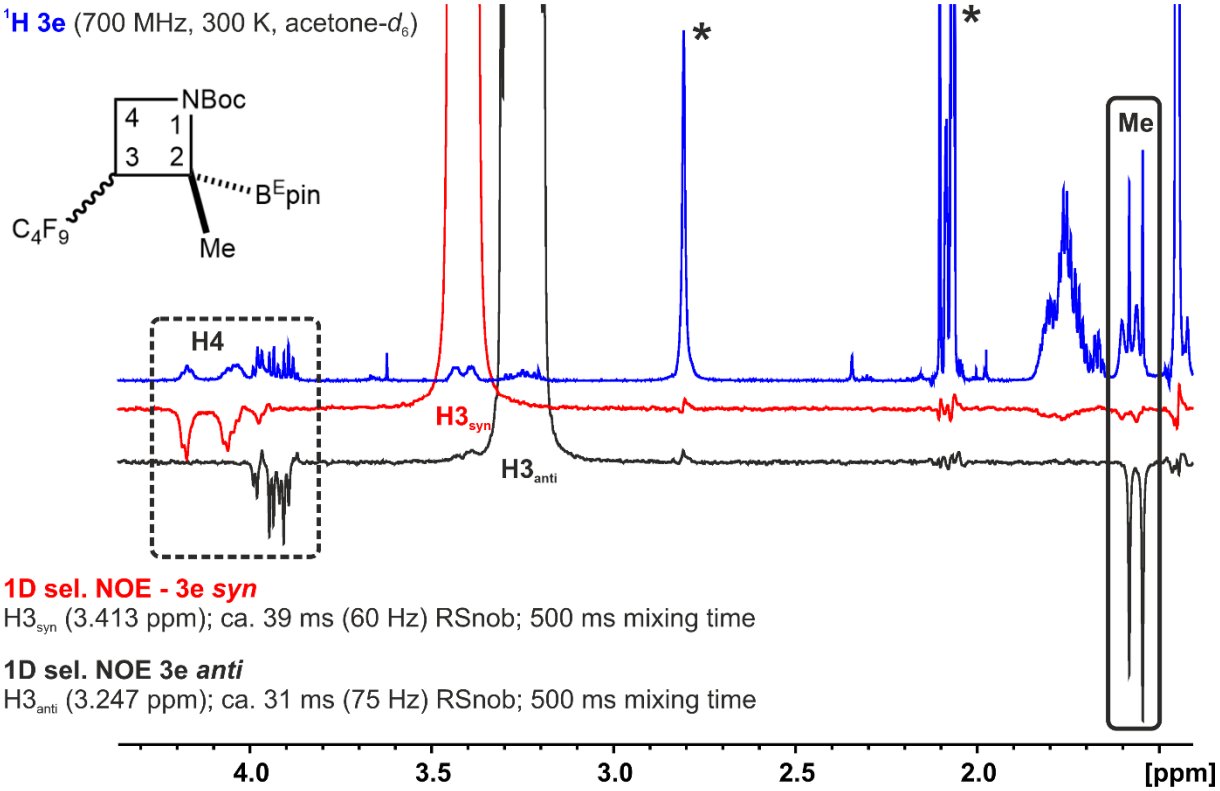


Figure 16: Selective 1D NOE spectra and ^{1}H spectrum (blue, spectrum at the top) of compound **3e** in acetone-d_6 at 700 MHz and 300 K. $H3_{syn}$ (red, spectrum in the middle) and $H3_{anti}$ (black, spectrum at the bottom) were selectively refocused using RSnob pulses (see also table 11) of ca. 39 ms (60 Hz bandwidth, $H3_{syn}$) and ca. 31 ms (75 Hz bandwidth, $H3_{anti}$). The mixing time was set to 500 ms in both NOE experiments. Water and acetone are marked with asterisks.

For the *anti* diastereomer (black spectrum at the bottom) an intense NOE signal between $H3_{anti}$ and the sharp methyl groups Me_{anti} can be observed (black box with solid lines), whereas only a very weak NOE signal between $H3_{syn}$ and the broad methyl groups Me_{syn} can be observed. This indicates that in the *anti* diastereomer $H3_{anti}$ and the methyl group are on the same side of the heterocycle. Therefore, the methyl group and the perfluorinated side chain have to be on opposite sides (and *vice versa* for the *syn* diastereomer). As expected, for both the *syn* and the *anti* diastereomer intense NOEs can be observed between H3 and the neighboring protons H4 (black box with dotted line), which allows assignment of the diastereotopic protons. To further support this interpretation a 2D ^{1}H,^{19}F-HOESY spectrum (figure 17) was acquired to determine the stereochemical relation of the perfluorinated side chain with respect to the methyl group.

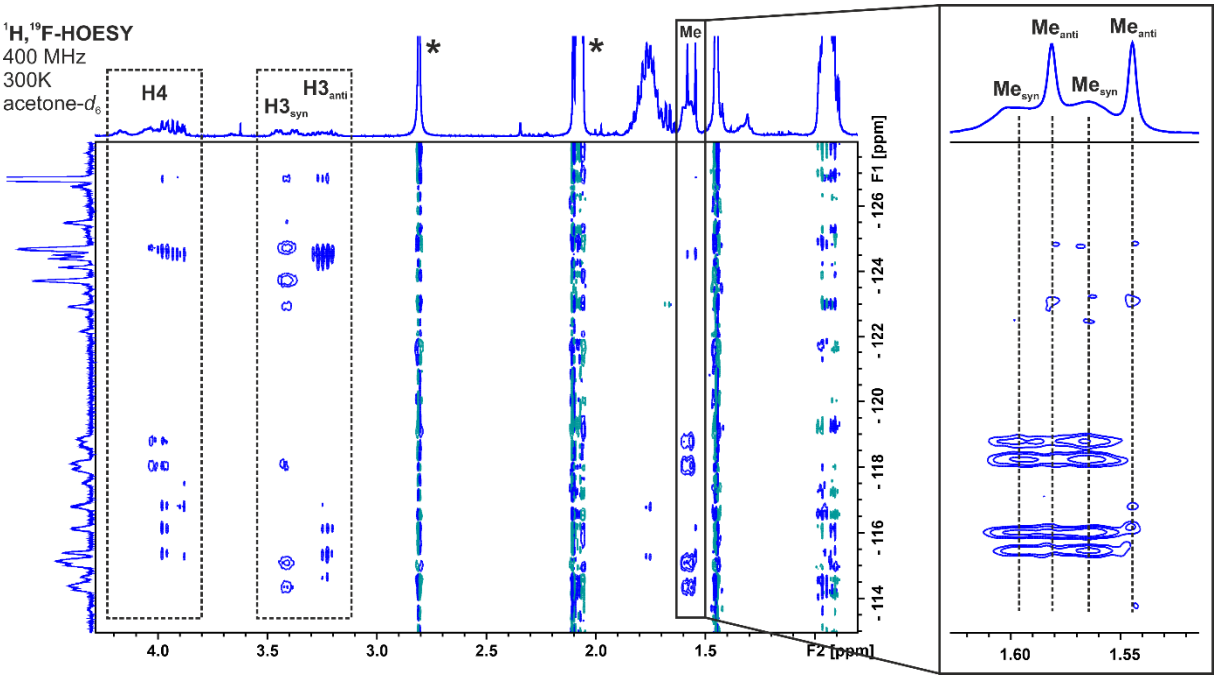


Figure 17: 2D ^{1}H,^{19}F HOESY of compound **3e** in acetone-d_6 at 400 MHz and 300 K. The region where HOEs between the methyl groups and the perfluorinated side chains can be observed is highlighted (black box with solid line) and shown in more detail.

Intense HOEs are observed between the broad methyl groups Me_{syn} and the perfluorinated side chain, whereas no significant HOEs are observed between the sharp methyl groups Me_{anti} and the perfluorinated side chain (black box with solid lines and detailed view). Both findings match the expectations and results of the NOE analysis, allowing for an unambiguous assignment of the relative configuration by a combined analysis of NOESY and HOESY spectra. Additionally, the HOESY shows intense HOEs between the perfluorinated side chain and the protons H4 of both diastereomers, $H3_{anti}$ and $H3_{syn}$ (black boxes with dashed lines), which matches the expectation because of their close proximities in both diastereomers.

Investigations of compound 3d

No minor component is observed *via* ^{1}H NMR spectroscopy (figure 19) because of the excellent diastereoselectivity of the reaction. As for compound **3e**, two signal sets are visible because of the two Boc rotamers in slow exchange with each other. An example of the chemical exchange is demonstrated in figure 20 using selective 1D sel. NOE and 1D selective spin echo spectra. An assignment of all ^{1}H resonances that are relevant for the NOE analysis is shown in figure 18.

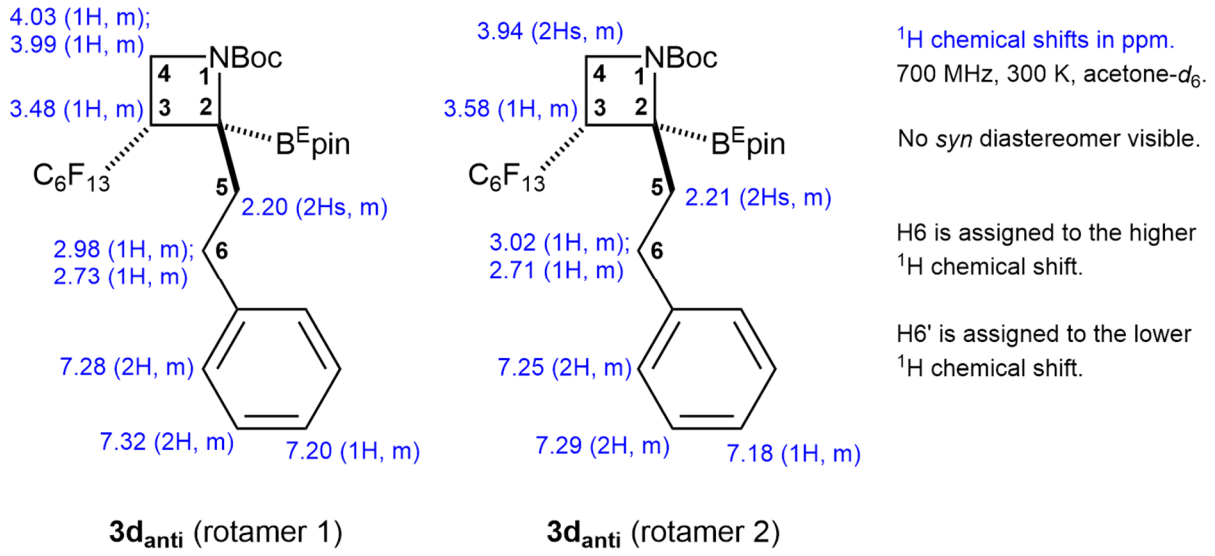


Figure 18: Assignment of ^{1}H chemical shifts (acetone-d$_6$, 700 MHz, 300 K) to the two Boc rotamers present in compound **3d$_{anti}$**.

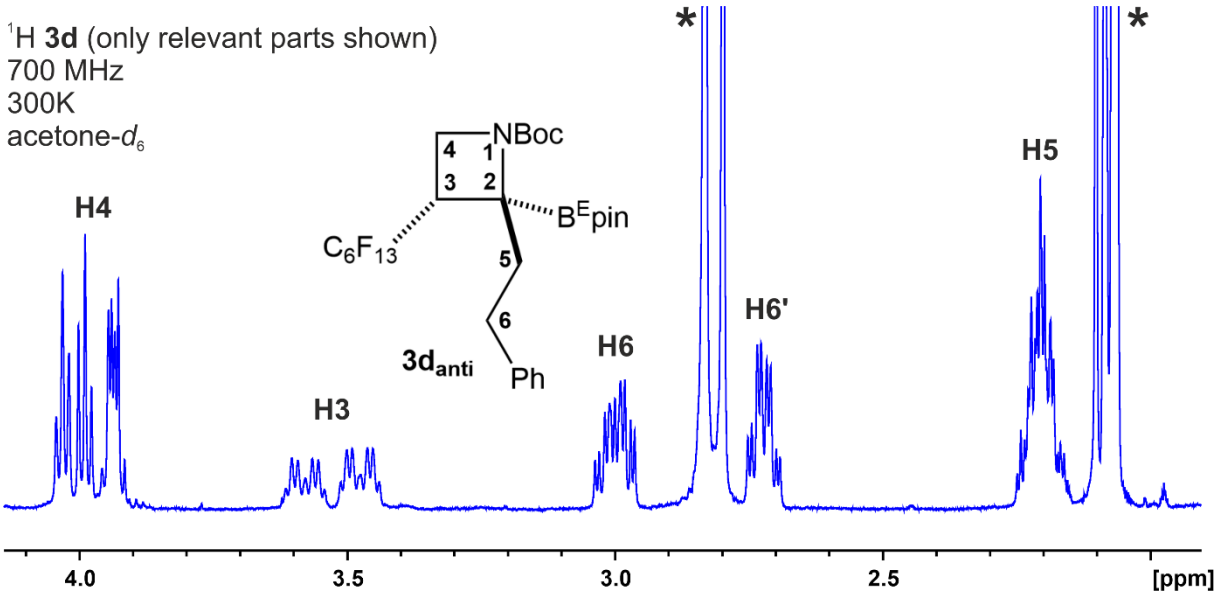


Figure 19: ^{1}H NMR spectrum (acetone-d$_6$, 700 MHz, 300 K) of compound **3d**. Only the part relevant to this analysis is shown.

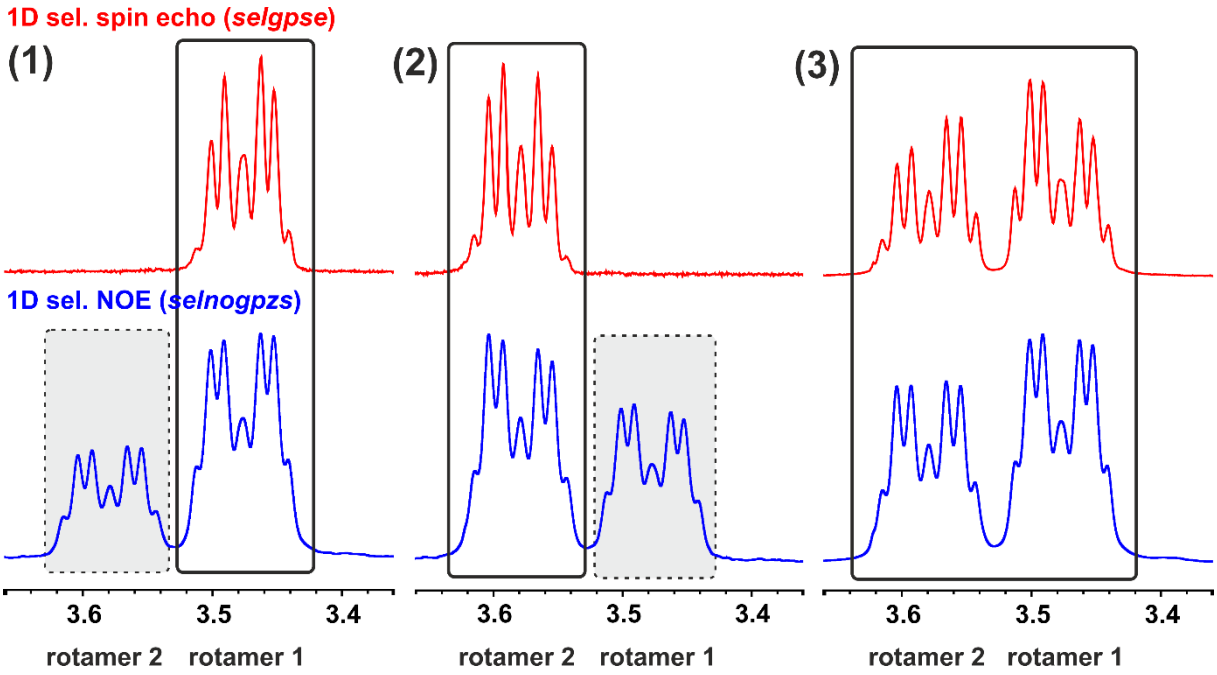


Figure 20: 1D sel. NOE (blue, bottom) and 1D sel. spin echo (red, top) spectra of the two different H3s of compound **3d** (700 MHz, 300 K, acetone-d_6). The boxes with black solid lines show which proton (or combination of protons) is selectively refocused. The grey boxes symbolize signals caused by chemical exchange. In (1) $H3_{anti}$ of rotamer 1 and in (2) $H3_{anti}$ of rotamer 2 is refocused. In (3) $H3_{anti}$ of both rotamers are refocused simultaneously. Durations, bandwidths and offsets of the shaped pulses (RSnob) are given in table 11.

The comparison of the 1D sel. spin echo (red) and 1D sel. NOE spectra (blue) in figure 20 allows to clearly identify the two signals for H3 as caused by chemical exchange: The 1D sel. spin echo spectra show a clean selective refocusing of both different signals in (1) and (2). In the respective 1D sel. NOE spectra, where the same selective pulses were used, the non-refocused signals are visible as signals with the same sign as the refocused one, proofing that the existence of the second signal set is caused by chemical exchange. If the non-refocused signal would originate from a NOE contact, it would have the opposite phase/sign as the refocused signal.[206]

To determine the relative configuration of **3d** a 2D NOESY and a 2D HOESY are acquired. The NOESY is shown in figure 21.

[206] D. X. Hu, P. Grice, S. V. Ley, *J. Org. Chem.* **2012**, *77*, 5198-5202.

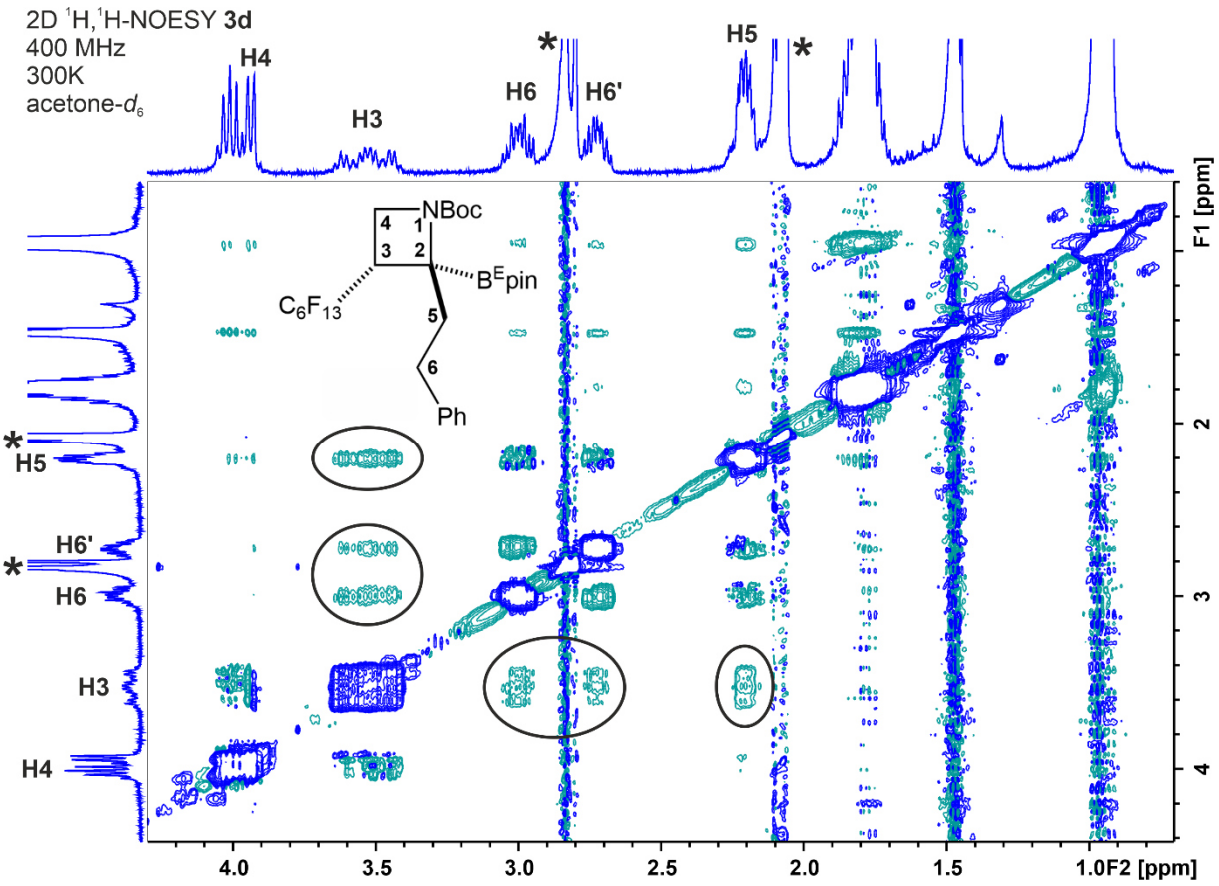


Figure 21: 2D NOESY spectrum of compound **3d** in acetone-d_6 at 400 MHz and 300 K. The NOE cross peaks between H3 and the phenethyl side chain (H5, H6, H6') are marked with black ellipses.

The NOESY spectrum (figure 21) shows strong NOEs between H3 and the protons H5, H6 and H6' of the phenethyl side chain indicating that H3 and the phenethyl side chain are located on the same side of the heterocycle. This implies that the phenethyl side chain and the perfluorinated side chain have to be on opposite sides, resulting in the *anti* diastereomer being the sole product of the reaction. This can be further supported by acquisition of a 2D ^{1}H,^{19}F-HOESY spectrum which is shown in figure 22.

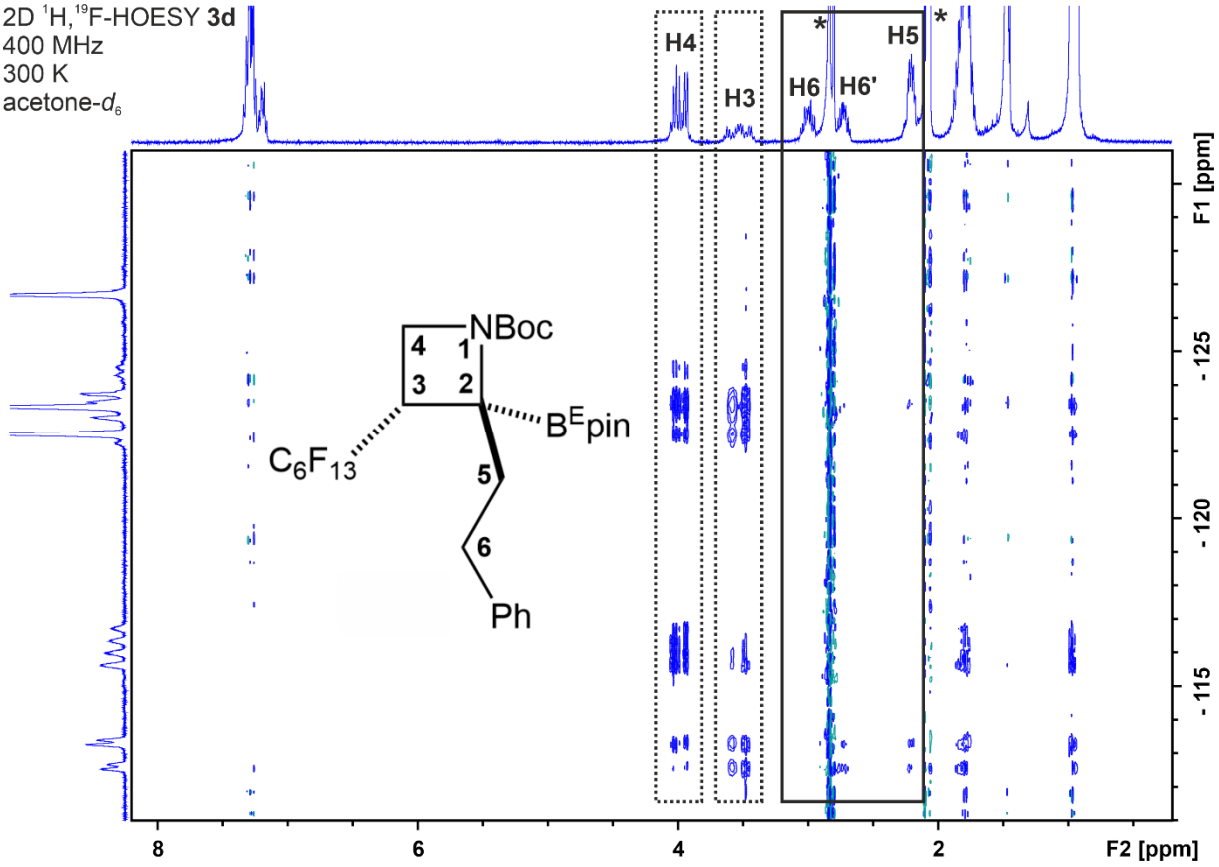


Figure 22: 2D HOESY spectrum of compound **3d** in acetone-d_6 at 400 MHz and 300 K.

No significant HOE is observed between the perfluorinated side chain and the protons H5, H6 and H6' in the phenethyl side chain, allowing the unequivocal assignment of the relative configuration to be *anti* (phenethyl to perfluorinated side chain). This diastereomer is the sole/major diastereomer formed during the reaction.

Additionally, intense HOEs can be observed between the perfluorinated side chain and the protons H3 and H4 (black box with dashed line) which are located in close proximity.

7. Representative NMR-Spectra

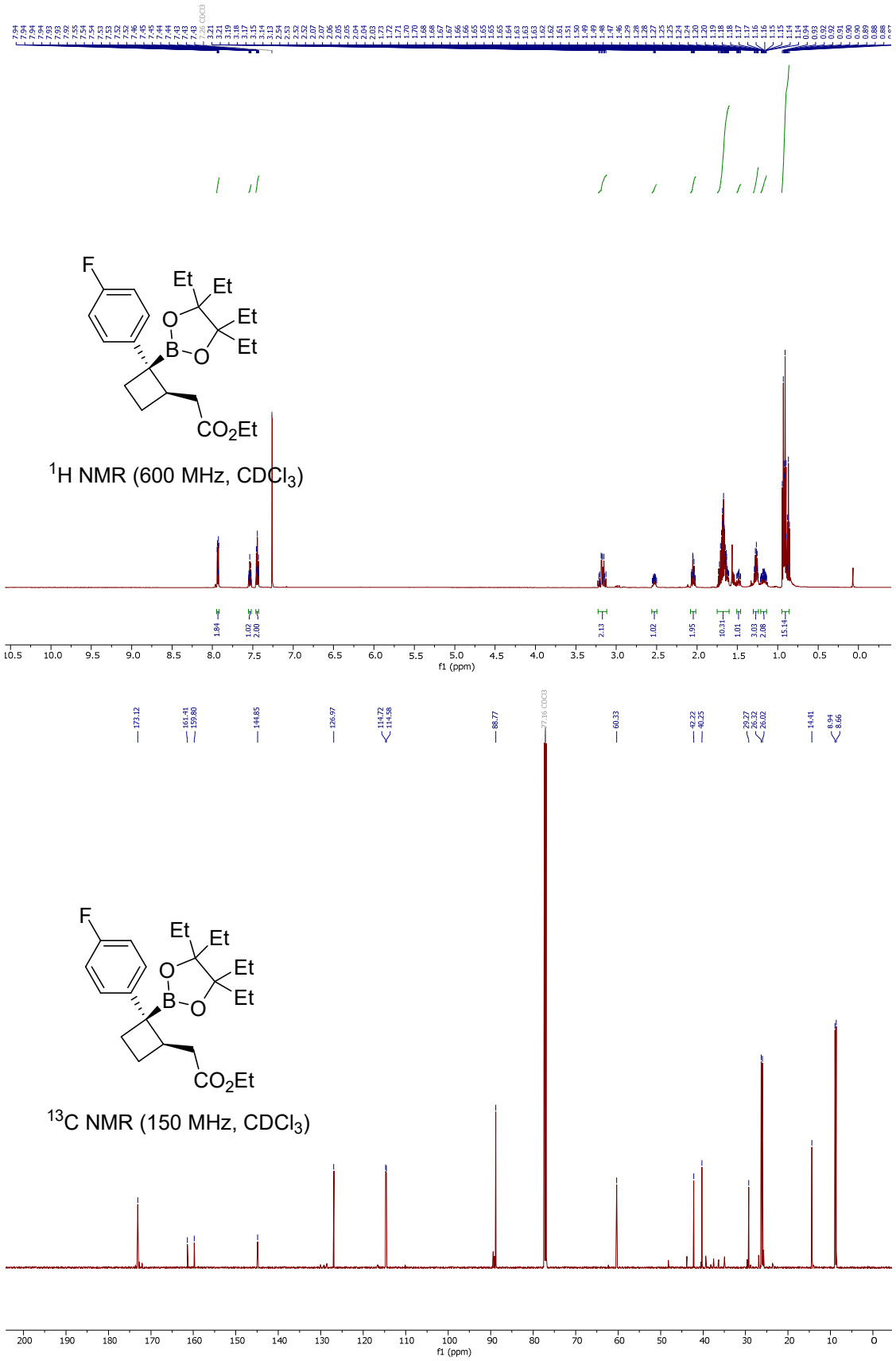


Figure 23: ^{1}H NMR and ^{13}C NMR of Ethyl 2-((1*R*,2*S*)-2-(4-fluorophenyl)-2-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)acetate (6d)

3. Zweifel Olefination for *C*-Glycosylation

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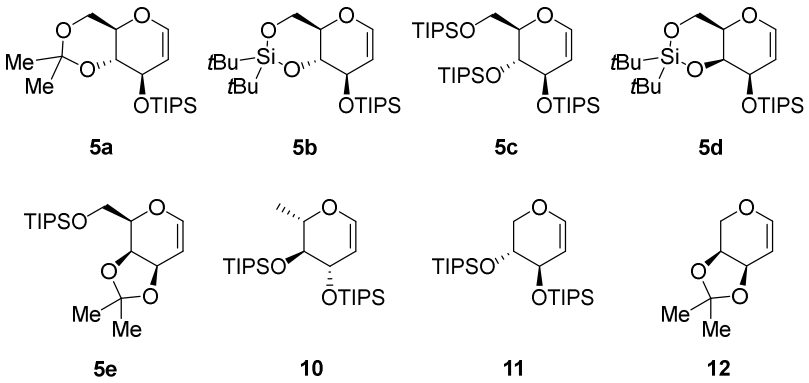
1. General Considerations

All reactions were carried out under dry N_2 / Ar atmosphere in flame-dried glassware unless otherwise stated. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with nitrogen or argon three times prior to use. THF (stabilized) was purchased in 99.5 % purity from Acros Organics. Organolithiums (*n*BuLi, *s*BuLi, *t*BuLi,) were purchased from Rockwood Lithium and the concentration was determined by titration against *i*PrOH using 1,10-phenantroline as indicator. Gringard reagents were prepared in THF, the used magnesium was activated by addition of 1,2-dibromoethane and subsequent heating to reflux. Titration of Gringard reagents was performed with benzoic acid and 4-phenylazodiphenylamin as indicator. Chromatographic purifications were performed using silica gel (SiO_2, 0.040-0.063 mm, 230- 400 mesh ASTM) from Merck or Alumina (Al_2O_3, 32-63 µm) from MP EcoChrom™. The spots were visualized under UV (254 nm) or by staining the TLC plate with either $KMnO_4$ solution (K_2CO_3, 10 g – $KMnO_4$, 1.5 g – H_2O, 150 mL – NaOH 10 % in H_2O, 1.25 mL) or Curcumin solution (Curcumin, 0.4 g – EtOH, 400 mL – 2 M HCl, 20 mL). Yields refer to isolated yields of compounds estimated to be >95 % pure as determined by ^{1}H-NMR and GC-analysis. The ^{13}C and ^{1}H-NMR spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ values in ppm relative to the residual solvent peak (^{1}H-NMR, ^{13}C-NMR) in deuterated chloroform ($CDCl_3$: δ 7.26 ppm for ^{1}H-NMR and δ 77.16 ppm for ^{13}C-NMR). Abbreviations for signal coupling are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet) and br (broad). Reaction endpoints were determined by GC monitoring of the reactions with *n*dodecane as an internal standard. Gas chromatography was performed with machines of Agilent Technologies 7890, using a column of type HP 5 (Agilent 5 % phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm) or Hewlett-Packard 6890 or 5890 series II, using a column of type HP 5 (Hewlett-Packard, 5 % phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm). High resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were recorded on Finnigan MAT 95Q, Finnigan MAT 90 instrument or JEOL JMS-700. Infrared spectra were recorded on a Perkin 281 IR spectrometer and samples were measured neat (ATR, Smiths Detection DuraSample IR II Diamond ATR). The absorption bands were reported in wave numbers (cm^{-1}) and abbreviations for intensity are as follows: vs (very strong; maximum intensity), s (strong; above 75 % of max. intensity), m (medium; from 50 % to 75 % of max. intensity), w (weak; below 50 % of max. intensity) and br (broad). Melting points were determined on a Büchi B-540 apparatus and are uncorrected

1.1 Investigated Glycals



2. Optimization

2.1 Initial Optimization:

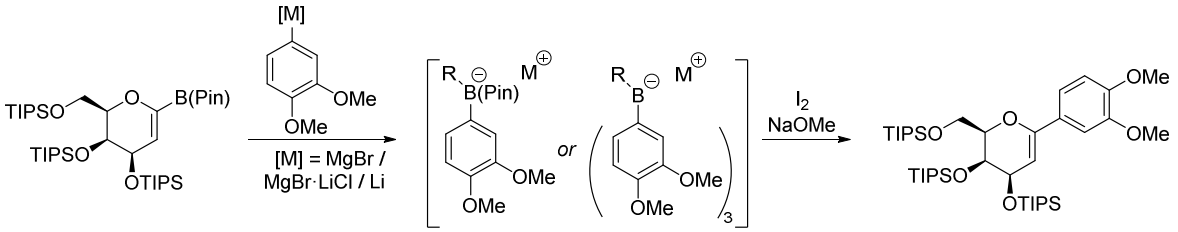


Table 12: Initial optimization

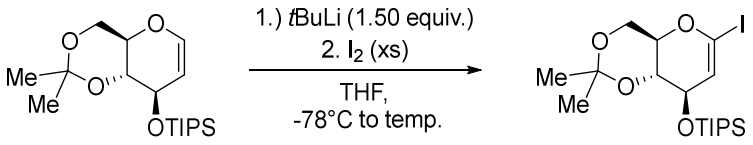
Entry[a]	Organometallic species [M]	Equiv.	Yield [%]
1[b]	MgBr	1.0	-
2[b]	MgBr	2.0	-
3[c]	MgBr · LiCl	2.0	-
4[d]	Li	1.0	Trace
5[d]	Li	1.5	38

[a] Experiments were performed according to GP-B. [b] According to GP-B, but as the first step Aryl-MgBr (0.84M in THF) was added to a solution of the respective glucal at -78 °C. [c] Aryl-MgBr · LiCl was generated from 4-bromo-1,2-dimethoxybenze (2 equiv.), Mg (3.2 equiv.) and LiCl (2.2 equiv.). [d] Aryllithium was generated from 4-bromo-1,2-dimethoxybenze (1 equiv. or 1.5 equiv., respectively) and *n*BuLi (1.1 equiv. or 1.6 equiv., respectively).

- No desired product could be detected *via* ^{11}B-NMR for entries 1 – 3 using Grignard and turbo Grignard reagents respectively.
- Using 1 equiv. of aryllithium species, traces of the desired zweifel coupling could be detected, 1.5 equiv. furnished the desired compound in 38 %.

- Due to the moderate reaction outcome (38 %, entry 5) the “inverse” pathway (metalation of the respective glycal, followed by treatment with boronic ester) was chosen for further investigations.

2.2 Optimization of Lithiation – Temperature dependence



5a **6**

Table 13: Optimization of lithiation – temperature dependence

Entry [a]	Temperature [°C] [b]	Rct. time [min]	Yield [%] [c]
1	-78	15	0
2	-60	15	0
3	-50	15	51
4	-40	15	55
5	-40	30	65
6	-30	15	70
7	-30	30	73
8	-20	15	71
9	-10	15	60
10	0	15	40
11	0	45	0

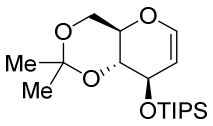
[a] The reaction was carried out on a 0.30 mmol scale in THF (2.0 mL) with *t*BuLi (1.50 equiv.) and undecane (1.00 equiv.). Addition of *t*BuLi at -78°C followed by stirring for 10 min at this temperature and warming to the indicated temperature for the indicated time. Subsequent quench of an aliquot of the mixture with iodine (xs) afforded the substituted glycal. [b] Temperatures were adjusted using a dry ice/acetone bath. [c] The yields of these reactions were determined by GC using undecane as internal standard.

Table 14: Temperature dependance

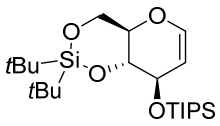
Entry	Temperature [°C] [b]	Rct. Time [min]	Yield [%] [c]
1	-30	30	69
2	-30	60	80
3	-30	90	63

[a] The reaction was carried out on a 0.20 mmol scale in THF (1.0 mL) with undecane (1.00 equiv.) as internal standard. Subsequent quench of an aliquot with iodine (xs). [b] Temperatures were adjusted using a dry ice/acetone bath. [c] The yields of the reactions were determined by GC using undecane as internal standard.

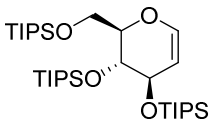
2.3 Deuterolysis Experiments



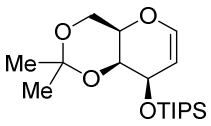
5a



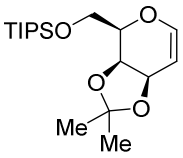
5b



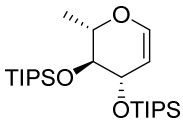
5c



5d



5e



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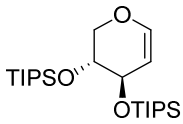

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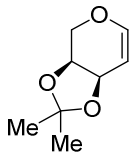
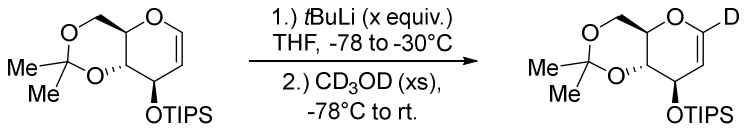


12

Table 15: Lithiation-deuterolysis of glycal sources.

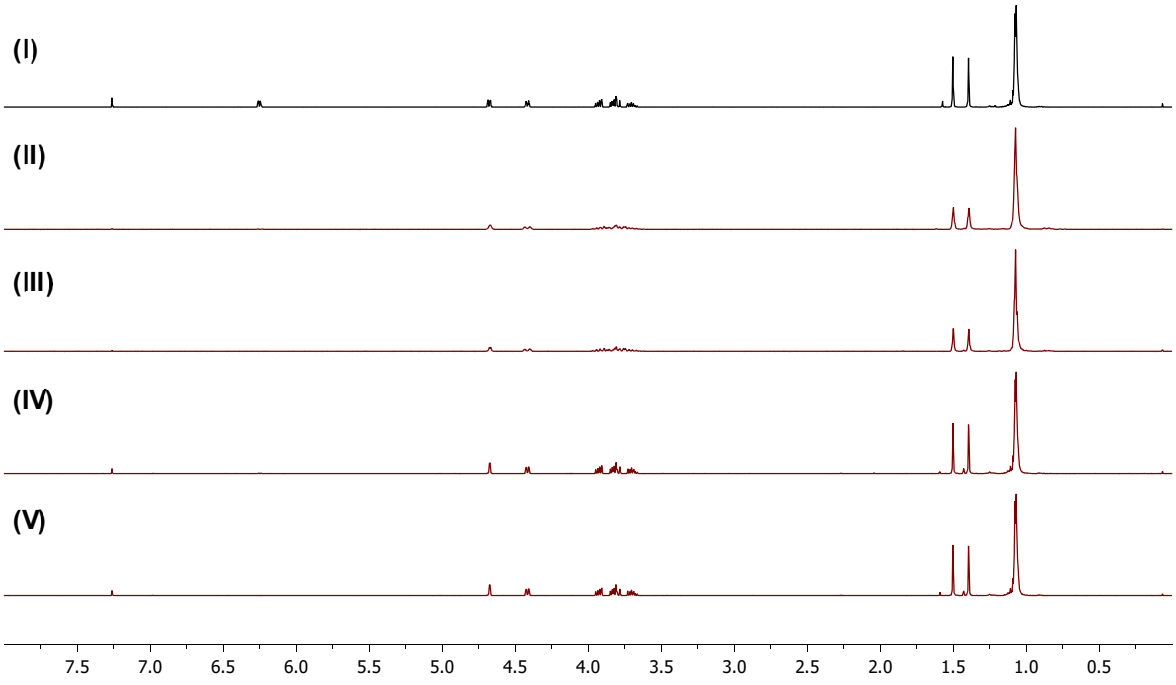


5a **6**

Entry	Glycal	Equiv. of *t*BuLi	Time [min]	D incorporation at C1 [%][a]
1	**5a**	1.1	15	89
2	**5a**	1.1	30	92
3	**5a**	1.1	45	92
4	**5a**	1.1	60	98
5	**5a**	1.3	15	97
6	**5a**	1.3	30	99
7	**5a**	1.3	85	99
8	**5b**	1.1	60	100
9	**5b**	1.3	30	100
10	**5c**	1.1	60	85
11	**5c**	1.3	30	79
12	**5d**	1.1	60	-
13[b]	**5d**	1.3	30	-
14	**5e**	1.1	60	-
15	**5e**	1.3	30	-
16	**10**	1.1	60	83
17	**10**	1.3	30	88
18	**11**	1.3	30	77
19	**11**	1.3	60	84
20	**12**	1.1	30	92
21	**12**	1.3	30	96

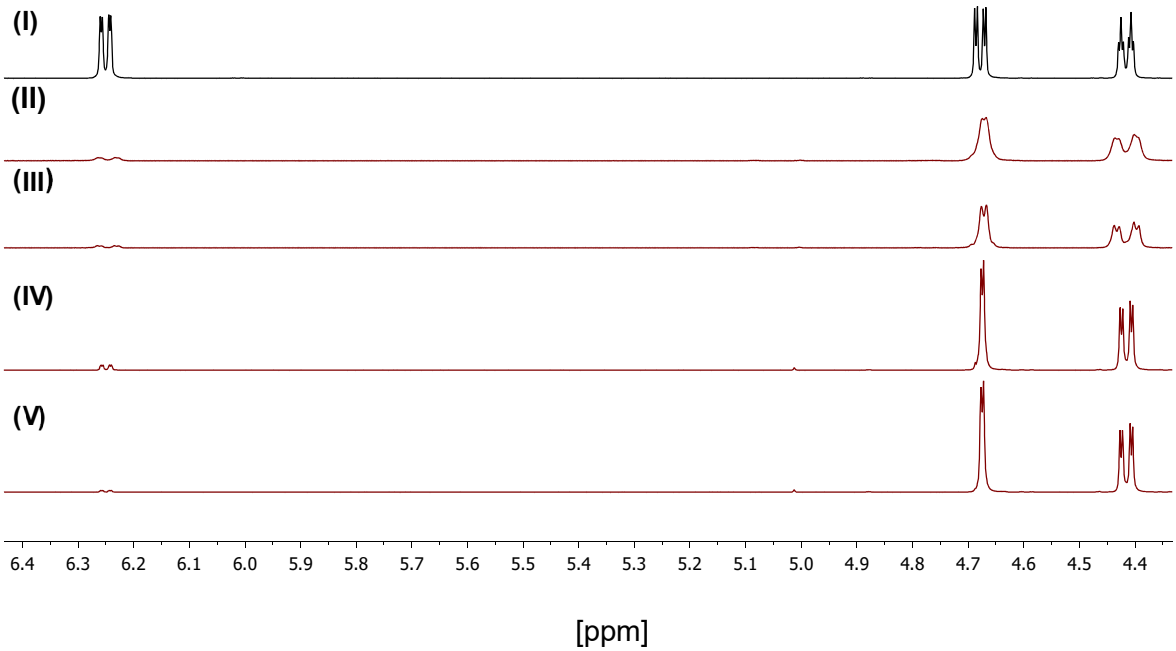
[a] Experiments were performed according to general procedure **A**. Equivalents of *t*BuLi and reaction time at -30°C were adjusted as listed in the table. [b] Reaction was performed according to general procedure **A**, but on a 0.10 mmol scale.

Figure 24: ^{1}H NMR Spectra of lithiation-deuterolysis of entries 1-4.



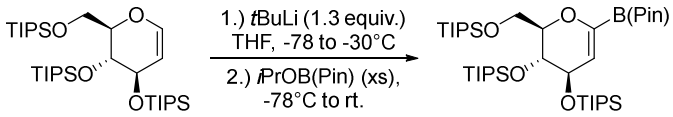
^{1}H-NMR spectra of (**I**) 1 and entries (**II**) 1, (**III**) 2, (**IV**) 3 and (**V**) 4.

Figure 25: Zoom in of ^{1}H NMR Spectra of lithiation-deuterolysis of entries 1-4.

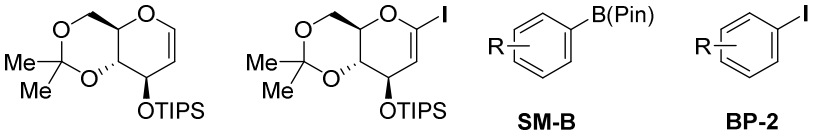


Zoom in on the ^{1}H-NMR spectra of (**I**) 1 and entries (**II**) 1, (**III**) 2, (**IV**) 3 and (**V**) 4.

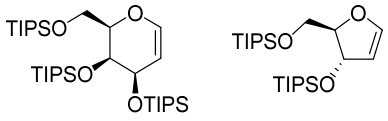
3. Observations



- Can be obtained with reasonable purity (90 %)
- Chromatographic separation from byproducts was not possible (Silica-Gel, Alumina and Florisil)
- B(Epin) derivative could also not be further purified.



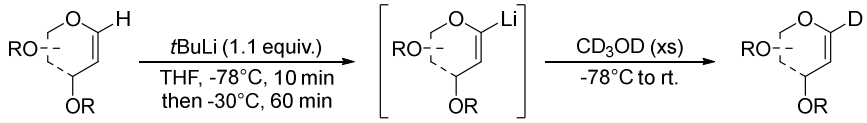
- Possible byproducts of the Zweifel-protocol include iodinated glycal (**BP-1**) and the iodo-(hetero)aryl derived by the respective boronic ester (**BP-2**).
- If after the Zweifel-protocol residual boronic acid pinacol ester is detected (TLC), a 4.2 M aq. solution of KHF_2 is added to the reaction mixture in MeOH. After 30 min of stirring at ambient temperature, the solvent is removed *in vacuo* and the residue is washed and decanted with Et_2O (3×20 mL). This facilitates chromatographic separation and avoids streaking of the residual boronic ester.
- Some electron-rich Zweifel-coupling products show rapid degradation at ambient temperature and should be stored at -30°C.
- TIPS protected glycals generally lead to less clean Li-incorporation.



- Metalation and deuterolysis of **NW-1** (TIPS-galactal) and **NW-2** (TIPS-ribal) resulted in unsatisfactory D-incorporation, and required up to 3 equiv. of *t*BuLi, which resulted in major side product formation during the Zweifel-protocol.

4. General Procedures

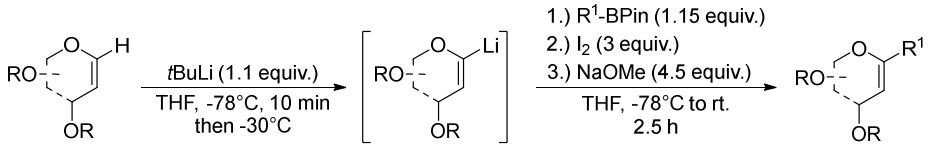
General procedure A: Lithiation/Deuterization of Glycals



(5a-5e, 10-12)

A solution of the appropriate glycal (0.2 mmol, 1.0 equiv.) in THF (1.0 mL) at -78°C was treated dropwise with *t*BuLi (1.1 equiv.) and the solution stirred for 10 min, then stirred at -30°C for 60 min. The reaction mixture was cooled to -78°C, quenched with excess CD_3OD and allowed to warm to ambient temperature. After stirring at this temperature for approximately 30 min, the solution was filtered (Et_2O with a drop of methanol) through a glass pipette with $MgSO_4$ and concentrated. The crude deuterated reaction products were filtered (*i*Hexane/Et_2O) through a plug of silica gel and the solvents were removed *in vacuo*. ^{1}H-NMR integration allowed to determine the D-incorporation ratio.

General procedure B: Coupling of Glycals with Boronic acid pinacol esters

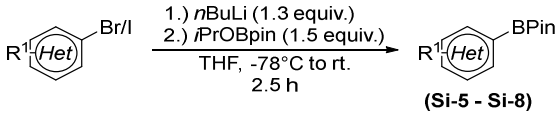


(5a-5e, 10-12)

(7a-7m, 8a-8e, 9a,9b, 11a-11d, 14a-14f, 15a-15d, 19a-19d)

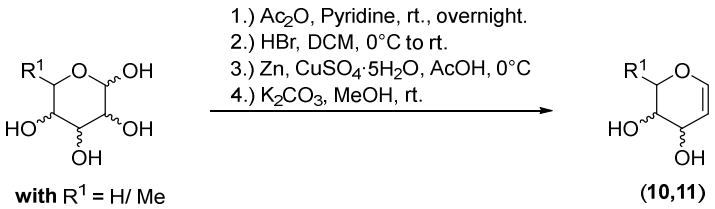
A stirred solution of the respective protected glycal (0.2 mmol, 1.0 equiv.) in THF (1.0 mL) was cooled to -78°C and *t*BuLi (0.22 mmol, 1.10 equiv. or 0.26 mmol, 1.3 equiv.) was added dropwise. The resulting solution stirred at -78°C for 10 min and then warmed to -30°C and stirred for further 60 min (or as indicated) at this temperature. After this time, the solution was cooled back to -78°C and a solution of the respective boronic acid pinacol ester (0.23 mmol, 1.15 equiv.) in THF (0.5 mL) was added dropwise. The reaction mixture was allowed to stir at -78°C for 15 min and then warmed to 0°C and stirred for a further 45 min. After this time, the solution was cooled to -78°C and a solution of iodine (152 mg, 0.60 mmol, 3.00 equiv.) in THF (0.5 mL) was added dropwise over 5 min. The resulting dark red reaction mixture was stirred for 15 min at the aforementioned temperature, then warmed to 0°C and stirred for 30 min. After this time, a solution of sodium methoxide (0.5 M in MeOH, 1.80 mL, 0.90 mmol, 4.50 equiv.) was added dropwise. The resulting mixture stirred at 0°C for 30 min and was then allowed to reach ambient temperature. After reaching rt., the reaction is completed. The reaction was then quenched by addition of sat. aq. $Na_2S_2O_3$ (2 mL), followed by water (20 mL) and Et_2O (20 mL). The organic layer was separated and the aqueous layer was extracted twice with Et_2O (2×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (SiO_2).

General Procedure C: Preparation of Boronic Acid Pinacol Esters *via* Lithium-Halogen exchange (SI-5 – SI-8)



The desired (hetero)aryl bromide/ iodide (5 mmol, 1.0 equiv.) was charged to a flame-dried flask and dissolved in dry THF (20 mL). *n*BuLi (6.5 mmol, 1.3 equiv.) was added dropwise to the mixture at -78°C and the mixture was stirred at this temperature for 30 min. *i*PrOBPin (7.5 mmol, 1.5 equiv.) was added dropwise to the mixture at -78°C and the solution was allowed to stir for 1 h at this temperature. After this period the reaction mixture was allowed to warm to rt. and stirred at this temperature for a further 60 min. The reaction was quenched by addition of sat. aq. NH_4Cl (5 mL), and water (50 mL) was added. The aq. phase was extracted with EtOAc (3 × 50 mL), the combined org. fractions were washed with Brine (50 mL), and all volatiles were removed *in vacuo*. Purification of the crude mixture *via* Flash column chromatography (SiO_2) furnished the desired hetero(aryl) boronic acid pinacol esters. **Note**: Curcumin stain helps visualizing the respective boronic esters on TLC.

General Procedure D: Preparation of Glycals (10, 11)

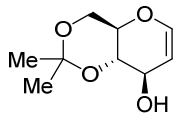


Peracetylation:

The respective sugar (20 mmol, 1.0 equiv.) was charged to a dry flask under argon atmosphere and dissolved in dry pyridine (50 mL). Acetic anhydride (23 mL, 0.24 mmol, 12 equiv.) was added dropwise to the mixture and the solution was allowed to stir overnight at rt. The next day the reaction mixture was transferred to a separatory funnel and EtOAc (100 mL) and H_2O (100 mL) was added. The organic fraction was separated and washed with sat. $NaHCO_3$ (100 mL) and Brine (50 mL). After drying over anhydr. $MgSO_4$ and concentration *in vacuo* the obtained crude Ac-sugar was directly employed in the next step. **Bromination:** The peracetylated sugar was charged to a 250 mL flask and dissolved in DCM (100 mL). After cooling the mixture to 0°C, a solution of HBr in AcOH (33 wt%, 5.0 equiv.) was added dropwise *via* dropping funnel and the mixture was allowed to warm to rt. After TLC control showed full consumption of the starting material, DCM (100 mL) was added and the mixture was transferred to a separatory funnel. The organic phase was separated and washed three times with sat. aq. $NaHCO_3$ (150 mL) and Brine (100 mL). After drying over anhydr. $MgSO_4$ the solvent was removed *in vacuo.* **Elimination:** The crude product from the previous step was

dissolved in AcOH (100 mL) and $CuSO_4$ pentahydrate (5 mmol, 0.25 equiv.) was added. The reaction mixture was cooled to 0°C and Zn Powder (0.4 mol, 20 equiv.) was added in portions. After full consumption of starting material judged by TLC control, DCM (150 mL) was added and the reaction mixture was transferred to a separatory funnel. H_2O (100 mL) was added and the organic phase was separated and washed three times with sat. aq. $NaHCO_3$ (100 mL) and Brine (100 mL). Drying over anhydr. $MgSO_4$ and removal of the solvent *in vacuo* afforded the crude Ac-Glycal, which was purified by Flash Colum Chromatography (SiO_2, pentane/ EtOAc). **Deprotection:** The respective Ac-Glycal was dissolved in MeOH (50 mL) and K_2CO_3 (0.1 equiv) was added in one portion. After stirring overnight at rt., the reaction mixture was filtered over Celite and the solvent was removed *in vacuo*. The free anhydrosugar was directly used in further synthesis without additional purification.

4,6-*O*-isopropylidene-D-glucal (SI-1)

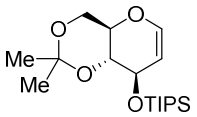


According to a modified literature procedure [207], 2,2-dimethoxypropane (21.2 mL, 171 mmol, 5.00 equiv.) was dissolved in DMF (52 mL) and the solution was acidified to p*H* 3 with *p*-TsOH monohydrate. D-Glucal (5.0 g, 34 mmol, 1.0 equiv.) was added at once and the reaction mixture was stirred at rt. for 45 min, then quenched with sat. $NaHCO_3$ solution and extracted with chloroform (3×150 mL). The combined organic layers were washed with Brine (150 mL) and dried over $MgSO_4$. All volatiles were removed *in vacuo*. Purification by flash column chromatography (SiO_2, *i*H/EtOAc 9:1 to 1:1) afforded the title compound **SI-1** as a colorless oil (2.16 g, 11.6 mmol, 34 %).

^{1}H-NMR ($CDCl_3$, 400MHz, 300K) δ = = 6.24 (dd, *J* = 6.2, 1.8 Hz, 1H), 4.68 (dd, *J* = 6.1, 1.9 Hz, 1H), 4.35 – 4.23 (m, 1H), 3.89 (dd, *J* = 10.9, 5.5 Hz, 1H), 3.80 – 3.62 (m, 3H), 1.48 (s, 3H), 1.38 (s, 3H). **^{13C}-NMR** ($CDCl_3$, 101MHz, 300K) δ = 144.1, 103.8, 99.9, 73.5, 69.3, 67.2, 61.6, 29.0, 19.1. **LR-MS (70eV):** m/z [%] = 186.0 (9). 171.0 (14), 110.0 (34), 97.0 (25), 81.0 (38), 71.0 (68), 59.0 (100). **IR (FT-ATR)** $\tilde{\nu}$ [cm^{-1}]: 3437 (w), 2994 (w), 2944 (w), 2893 (w), 1641 (m), 1479 (w), 1462 (w), 1436 (w), 1375 (m), 1301 (w), 1268 (m), 1228 (s), 1198 (s), 1166 (s), 1114 (s), 1088 (vs), 1062 (s), 1032 (s), 1002 (s), 965 (m), 941 (s), 918 (w), 866 (vs), 816 (w), 753 (s), 706 (w), 681 (w), 658 (w). Spectral characteristics were in agreement with previously reported data.[207]

[207] B. Fraser-Reid, D. L. Walker, S. Y.-K. Tam, N. L. Holder, *Can. J. Chem.* **1973**, *51*, 3950-3954.

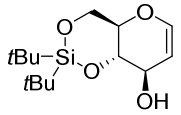
1,5-Anhydro-4,6-*O*-(isopropylidene)-3-(*O*-triisopropylsilyl)-2-*deoxy*-D*arabino*-hex-1-enitol (5a)



According to a modified literature procedure [208], the alcohol **SI-1** (2.16 g, 11.6 mmol, 1.00 equiv.) was dissolved in DMF (11 mL) and imidazole (1.58 g, 23.2 mmol, 2.00 equiv.) and TIPSCl (3.72 mL, 17.4 mmol, 1.50 equiv.) were added. The reaction mixture was stirred at 80°C overnight. After cooling to ambient temperature, H_2O (100 mL) was added and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were washed with Brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, *i*H/EtOAc, 9:1 with 5 % NEt_3) to afford **5a** as a colorless oil (3.31 g, 9.64 mmol, 83 %).

^{1}**H-NMR** ($CDCl_3$, 400MHz, 300K) δ = 6.25 (dd, *J* = 6.2, 1.6 Hz, 1H), 4.68 (dd, *J* = 6.2, 1.9 Hz, 1H), 4.42 (ddd, *J* = 7.2, 1.8, 1.8 Hz, 1H), 3.93 (dd, *J* = 11.0, 5.6 Hz, 1H), 3.83 (dd, *J* = 10.3, 7.2 Hz, 1H), 3.81 (dd, *J* = 10.8 Hz, 1H), 3.70 (ddd, *J* = 10.3, 5.5 Hz, 1H), 1.50 (s, 3H), 1.40 (s, 3H), 1.17 – 1.01 (m, 21H). **^{13}C-NMR** ($CDCl_3$, 101MHz, 300K) δ = 143.3, 105.9, 99.7, 73.5, 69.8, 67.9, 61.9, 29.1, 19.0, 18.1, 18.0, 12.4. **LR-MS (70eV):** m/z [%] = 299.1 (41), 241.0 (39), 213.0 (19), 197.0 (11), 185.0 (45), 169.0 (15), 155.0 (7), 143.0 (9), 131.0 (22), 115.0 (45), 103.0 (41), 87.0 (13), 75.0 (100), 61.0 (60). **IR (FT-ATR)** $\tilde{\nu}$ [cm^{-1}]: 2995 (w), 2943 (m), 2894 (w), 2867 (m), 1638 (m), 1464 (w), 1382 (m), 1372 (m), 1268 (m), 1261 (w), 1232 (s), 1218 (m), 1200 (m), 1168 (m), 1119 (s), 1100 (vs), 1076 (s), 1066 (s), 1056 (s), 1010 (s), 998 (m), 974 (w), 943 (m), 922 (m), 874 (vs), 846 (m), 794 (s), 754 (m), 729 (m), 678 (s), 658 (m). Spectral characteristics were in agreement with previously reported data.[208]

4,6-*O*-Di(*tert*-butyl)silanediyl-D-glucal (SI-2)



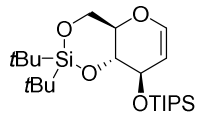
According to a literature procedure[208], D-glucal (754 mg, 5.16 mmol, 1.00 equiv.) was dissolved in DMF (7 mL). Then 2,6-lutidine (1.80 mL, 15.5 mmol, 3.0 equiv.) was added and the solution was cooled to -15 °C using an acetone/ice bath. Di(*tert*-butyl)silyl ditriflate (1.84 mL, 5.68 mmol, 1.1 equiv.) was added dropwise and the mixture was warmed to rt. and stirred for 1.5 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with Et_2O (3×20 mL). The combined organic extracts were washed with Brine (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford a light-yellow oil.

[208] S. E. Denmark, T. Kobayashi, C. S. Regens, *Tetrahedron* **2010**, *66*, 4745-4759.

The crude reside was purified *via* flash column chromatography (SiO_2, *i*H/EtOAc, 15:1), which afforded **SI-2** as a colorless solid (956 mg, 3.35 mmol, 65 %).

^{1}**H-NMR** ($CDCl_3$, 400MHz, 300K) δ = 6.26 (dd, *J* = 6.1, 1.9 Hz, 1H), 4.75 (dd, *J* = 6.1, 1.9 Hz, 1H), 4.34 – 4.26 (m, 1H), 4.17 (dd, *J* = 10.2, 4.9 Hz, 1H), 4.01 – 3.88 (m, 2H), 3.83 (td, *J* = 10.2, 4.9 Hz, 1H), 2.50 (d, *J* = 2.9 Hz, 1H), 1.06 (s, 9H). **^{13}C-NMR** ($CDCl_3$, 101MHz, 300K) δ = 143.8, 103.1, 77.5, 77.2, 76.8, 72.4, 70.3, 65.8, 27.6, 27.0, 22.9, 20.0. **LR-MS (70eV):** m/z [%] = 286.0 (6), 268.1 (1), 229.0 (100), 211.0 (6), 199.0 (15), 187.0 (68), 168.9 (7), 157.0 (65), 143.0 (9), 131.0 (20), 115.0 (48), 103.0 (29), 91.0 (23), 77.0 (85), 57.0 (50), 41.0 (47). **IR (FT-ATR)** $\tilde{\nu}$ [cm^{-1}]: 3606 (vw), 3459 (w), 3363 (vw), 2964 (w), 2934 (m), 2890 (m), 2859 (m), 1646 (m), 1470 (m), 1393 (w), 1364 (w), 1313 (vw), 1274 (w), 1233 (m), 1214 (w), 1186 (w), 1157 (m), 1140 (w), 1119 (s), 1093 (s), 1078 (s), 1057 (m), 1029 (m), 1012 (m), 989 (s), 953 (m), 938 (w), 905 (w), 867 (vs), 824 (vs), 780 (m), 763 (vs), 720 (w), 690 (w), 686 (w), 652 (s). Spectral characteristics were in agreement with previously reported data.[208]

1,5-Anhydro-2-*deoxy*-4,6-*O*-bis(*tert*-butylsilylidene)-3-*O*-triisopropylsilylD-*arabino*-hex-1-enitol (5b)



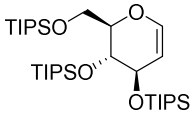
According to a literature procedure [209], to a solution of **SI-2** (936 mg, 3.27 mmol, 1.00 equiv.) in DMF (20 mL) was added imidazole (556 mg, 8.17 mmol, 2.50 equiv.) and TIPSCl (0.90 mL, 4.25 mmol, 1.30 equiv.). The reaction mixture was stirred at 60°C overnight, then cooled to rt. and quenched with H_2O (25 mL) and extracted with Et_2O (3×50 mL). The combined organic fractions were washed with H_2O (5×50 mL) and Brine (50 mL) and then dried over $MgSO_4$. After removal of the solvents *in vacuo*, the crude reside was purified by flash column chromatography (SiO_2, *i*H/EtOAc 19:1) to give **5b** as colorless crystals (1.38 g, 3.11 mmol, 95 %).

^{1}**H-NMR** ($CDCl_3$, 400MHz, 300K) δ = 6.23 (dd, *J* = 6.1, 1.6 Hz, 1H), 4.67 (dd, *J* = 6.1, 1.9 Hz, 1H), 4.42 (dd, *J* = 6.9, 1.9 Hz, 1H), 4.15 (dd, *J* = 10.3, 5.0, 1H), 4.05 – 3.96 (m, 1H), 4.02 – 3.91 (m, 1H), 3.80 (td, *J* = 10.3, 5.0 Hz, 1H), 1.23 – 1.06 (m, 21H), 1.06 (s, 9H), 0.99 (s, 9H). **^{13}C-NMR** ($CDCl_3$, 101MHz, 300K) δ = 142.9, 105.5, 77.7, 72.9, 70.9, 66.2, 27.6, 27.1, 22.9, 20.0, 18.3, 12.6. **LR-MS (70eV):** m/z [%] = 399.2 (2), 369.2 (1), 343.1 (1), 317.1 (7), 261.1 (1), 244.9 (1), 229.1 (1), 206.9 (3), 185.0 (6), 157.0 (3), 134.9 (4), 115.0 (8), 81.0 (100), 57.1 (11). **IR (FT-ATR)** $\tilde{\nu}$ [cm^{-1}]: 2959 (m), 2943 (m), 2889 (m), 2861 (m), 1647 (m), 1470 (m), 1391 (w), 1381 (w), 1364 (w), 1282 (w), 1258 (w), 1238 (m), 1215 (w), 1185 (w), 1160 (s), 1142 (m), 1124 (s), 1105 (vs), 1080 (s), 1058 (s), 1012 (m), 998 (s), 968 (m), 917 (w), 875 (vs), 827 (vs), 773 (s), 762 (vs), 734 (s), 678 (s), 652 (vs).

[209] K. A. Parker, A. T. Georges, *Org. Lett.* **2000**, *2*, 497-499.

Spectral characteristics were in agreement with previously reported data.[209]

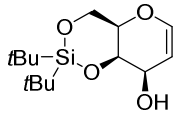
1,5-Anhydro-2-deoxy-3,4,6-tri-*O*-triisopropylsilyl-D-arabino-hex-1-enitol (5c)



According to a modified literature procedure [210], D-glucal (4.00 g, 27.4 mmol, 1.00 equiv.) was dissolved in DMF (30 mL), and was cooled to 0°C. To the solution was added imidazole (14.9 g, 219 mmol, 8.00 equiv.) and TIPSCl (23.4 mL, 109 mmol, 4.00 equiv.). After being stirred at 80°C for 72 h, the reaction mixture was poured into cold sat. aq. $NaHCO_3$ (100 mL). The resultant mixture was filtered thought a paper filter. The aqueous layer was separated and extracted with Et_2O (2×50 mL). The combined organic extracts were washed with water (2×100 mL), Brine (50 mL), and then dried over $MgSO_4$. After removal of the solvents *in vacuo*, flash column chromatography (SiO_2, *i*Hexane/DCM 19:1 to 4:1) furnished the title compound **5c** as a colorless oil (11.2 g, 18.2 mmol, 66 %).

^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ = 6.36 (d, *J* = 6.3 Hz, 1H), 4.80 (ddd, *J* = 6.7, 5.2, 1.8 Hz, 1H), 4.23 (ddt, *J* = 7.7, 3.7, 1.8 Hz, 1H), 4.11 – 4.02 (m, 2H), 3.94 (dt, *J* = 5.2, 2.1 Hz, 1H), 3.82 (dd, *J* = 11.3, 3.7 Hz, 1H), 1.06 (d, *J* = 3.9 Hz, 63H). **^{13}C-NMR** ($CDCl_3$, 101MHz, 300K) δ = 143.0, 100.5, 80.9, 70.4, 65.1, 62.2, 18.3, 18.2, 18.2, 18.1, 18.1, 12.7, 12.6, 12.4, 12.1. **LR-MS (70eV):** m/z [%] = 571.5 (15), 385.3 (80), 359.3 (19), 335.0 (7), 308.9 (17), 253.2 (43), 213.2 (29), 185.1 (29), 157.2 (80), 115.1 (100), 87.1 (66), 59.0 (85). Spectral characteristics were in agreement with previously reported data.[210]

1,5-Anhydro-4,6-*O*-(di-*tert*-butyl)silanediyl-2-*deoxy*-D-lyxo-hex-1-enitol (SI-3)

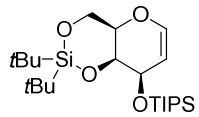


According to a literature procedure [211], D-galactal (121 mg, 830 µmol, 1.00 equiv.)was dissolved in DMF (3 mL) and was cooled to -45°C and $(t\text{Bu})_2\text{Si}(\text{OTf})_2$ (300 µL, 913 µmol, 1.10 equiv.) was added dropwise over 5 min. The reaction mixture was left stirring at -40°C for 30 min after which pyridine (80 µL, 996 µmol, 1.20 equiv.) was added and the solution was allowed to warm to 0°C. After 30 min at 0°C the reaction was diluted with Et_2O (20 mL) and quenched with sat. aq. $NaHCO_3$ solution (5 mL). The organic layer was washed with Brine (4×20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, *i*H/EtOAc = 4:1) to afford **SI-3** as a colorless solid (153 mg, 535 µmol, 64 %).

[210] R. W. Friesen, C. F. Sturino, A. K. Daljeet, A. Kolaczewska, *J. Org. Chem.* **1991**, *56*, 1944-1947.

[1]**H-NMR** ($CDCl_3$, 400MHz, 300K) δ = 6.31 (dd, *J* = 6.4, 1.8 Hz, 1H), 4.71 (dt, *J* = 6.4, 1.8 Hz, 1H), 4.40 (dt, *J* = 5.1, 1.4 Hz, 1H), 4.37 – 4.31 (m, 1H), 4.28 (dd, *J* = 12.5, 1.8 Hz, 1H), 4.23 (dd, *J* = 12.5, 1.8 Hz, 1H), 3.88 (td, *J* = 1.8, 1.0 Hz, 1H), 2.74 (d, J = 11.4 Hz, 1H), 1.08 (s, 9H), 1.02 (s, 9H). **[13]C-NMR** ($CDCl_3$, 101MHz, 300K) δ = 144.1, 103.4, 73.4, 68.8, 67.5, 63.9, 27.8, 27.1, 23.5, 21.1. **LR-MS (70eV):** m/z [%] = 253.0 (1), 229.0 (47), 211.0 (9), 199.0 (11), 185.0 (3), 173.0 (80), 161.0 (46), 143.0 (15), 131.0 (12), 115.0 (55), 103.0 (31), 87.0 (8), 77.0 (100), 66.9 (2), 57.1 (45). Spectral characteristics were in agreement with previously reported data.[211]

(4a*R*,8*R*,8a*S*)-2,2-Di-*tert*-butyl-8-((triisopropylsilyl)oxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (<u>5d</u>)

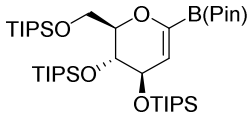


According to a literature procedure [212], to a stirred mixture of **<u>SI-3</u>** (139 mg, 486 µmol, 1.00 equiv.) and imidazole (66.2 mg, 972 µmol, 2.00 equiv.) in DMF (5 mL) was added TIPSCl (217 µL, 1.02 mmol, 2.10 equiv.) dropwise. The solution was heated to 60°C and stirred overnight. The next day, the reaction was quenched with H_2O (10 mL) and the aq. phase was extracted with Et_2O (3×20 mL). The combined organic fractions were dried over $MgSO_4$ and the solvents were removed *in vacuo.* Flash column chromatography (SiO_2, *i*H/EtOAc 19:1 to 9:1) furnished the title compound **<u>5d</u>** as colorless crystals. (194 mg, 438 µmol, 90 %).

[1]**H-NMR** ($CDCl_3$, 400MHz, 300K) δ = 6.24 (dd, *J* = 6.4, 1.9 Hz, 1H), 4.63 (dt, *J* = 6.4, 1.9 Hz, 1H), 4.61 – 4.56 (m, 1H), 4.39 – 4.35 (m, 1H), 4.26 (dd, *J* = 12.4, 1.9 Hz, 1H), 4.22 (dd, *J* = 12.4, 1.9 Hz, 1H), 3.84 (t, *J* = 1.6 Hz, 1H), 1.11 – 1.08 (m, 18H), 1.08 – 1.07 (m, 3H), 1.06 (s, 9H), 1.02 (s, 9H). **[13]C-NMR** ($CDCl_3$, 101MHz, 300K) δ = 143.0, 104.0, 73.7, 69.6, 67.7, 66.0, 27.8, 27.2, 23.6, 21.0, 18.2, 18.2, 12.6. **LR-MS (70eV):** m/z [%] = 427.2 (1), 399.8 (27), 385.3 (100), 367.2 (1), 343.2 (5), 317.2 (8), 289.1 (1), 269.1 (2), 247.2 (5), 229.2 (28), 211.1 (37), 185.1 (12), 157.1 (23), 135.0 (17), 115.1 (55), 81.1 (62), 57.1 (16). **IR (FT-ATR)** $\tilde{\nu}$ [cm^{-1}]: 2940 (m), 2890 (m), 2864 (m), 1740 (vw), 1652 (w), 1474 (m), 1465 (m), 1396 (w), 1388 (w), 1365 (w), 1342 (w), 1274 (w), 1234 (m), 1214 (w), 1178 (s), 1137 (m), 1109 (s), 1081 (vs), 1028 (m), 1013 (m), 996 (m), 988 (m), 933 (s), 924 (s), 908 (s), 881 (s), 860 (s), 825 (s), 788 (m), 758 (s), 739 (m), 717 (m), 680 (s), 664 (s). Spectral characteristics were in agreement with previously reported data.[212]

[211] G. Gabrielli, F. Melani, S. Bernasconi, C. Lunghi, B. Richichi, P. Rollin, C. Venturi, C. Nativi, *J. Carbohydr. Chem.* **2009**, *28*, 124-141.
[212] Y. Kobayashi, S. Masakado, Y. Takemoto, *Angew. Chem. Int. Ed.* **2018**, *57*, 693-697.

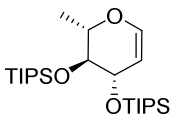
(1,5-Anhydro-2-*deoxy*-3,4,6-tris-*O*-triisopropylsilyl-D-*arabino*-hex-1enitolyl)boronic acid pinacol ester (SI-4)



According to a modified literature procedure [151], to a solution of **5c** (2.50 g, 4.06 mmol, 1.00 equiv.) in THF (27 mL) was added *t*BuLi (16.7 mmol, 4.10 equiv.) at -78°C dropwise over 15 min. The dark yellow solution was stirred at -78°C for 15 min, then was allowed to warm to 0°C and stirred at that temperature for 45 min. Following this, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.5 mL, 17.1 mmol, 4.20 equiv.) was added dropwise at -78°C over 15 min. The reaction mixture was stirred at that temperature for 15 min, then allowed to reach rt. and stirred overnight. The mixture was poured into a separatory funnel containing Et_2O (100 mL) and H_2O (75 mL). The organic layer was washed with H_2O (3×75 mL), Brine (75 mL), dried over $MgSO_4$ and the solvents were removed *in vacuo*. The title compound **SI-4** was obtained as colorless oil, which was used in further reactions without additional purification. The title compound was determined to be of 90 % purity by ^{1}H spectroscopy (2.70 g, 3.60 mmol, 90 %). **Note:** Any attempts to further purify the title compound by chromatographic separation (SiO_2, Alumina, Florisil) were unsuccessful.

^{1}**H-NMR** ($CDCl_3$, 400MHz, 300K) δ = 5.58 (dd, *J* = 5.3, 1.8 Hz, 1H), 4.31 (ddt, *J* = 7.4, 5.6, 1.8 Hz, 1H), 4.14 (q, *J* = 1.9 Hz, 1H), 3.99 – 3.91 (m, 2H), 3.87 (dd, *J* = 10.7, 5.6 Hz, 1H), 1.28, 1.26 (2 × s, 12H), 1.11 - 0.98 (m, 63H). **^{13}C-NMR** ($CDCl_3$, 101MHz, 300K) δ = 114.0, 84.1, 79.7, 69.8, 65.1, 61.7, 25.0, 24.4, 18.4, 18.3, 18.3, 18.2, 12.7, 12.5, 12.1. **LR-MS (70eV):** m/z [%] = 697.5 (21), 641.4 (1), 597.3 (1), 523.3 (51), 498.0 (15), 385.3 (100), 355.2 (8), 311.1 (11), 245.1 (5), 213.1 (77), 157.1 (55), 115.0 (71), 73.0 (47). **IR (FT-ATR)** $\tilde{\nu}$ [cm^{-1}]: 2943 (m), 2893 (m), 2866 (m), 1644 (vw), 1464 (m), 1429 (w), 1407 (w), 1379 (m), 1371 (m), 1334 (m), 1283 (w), 1271 (w), 1250 (w), 1215 (w), 1146 (m), 1102 (s), 1061 (s), 1013 (m), 996 (m), 965 (w), 952 (w), 919 (w), 882 (vs), 864 (m), 848 (m), 830 (w), 811 (w), 761 (m), 741 (w), 716 (w), 679 (vs), 656 (s). Spectral characteristics were in agreement with previously reported data.[151]

(((2*S*,3*S*,4*S*)-2-Methyl-3,4-dihydro-2*H*-pyran-3,4- diyl)bis(oxy))bis (triisopropylsilane) (10)

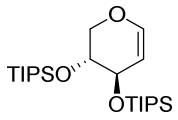


According to GP-D, starting from α-L-Rhamnose (3.3 g, 20 mmol, 1.0 equiv.) to obtain the intermediate (2*S*,3*S*,4*S*)-2-methyl-3,4-dihydro-2*H*-pyran-3,4-diyl diacetate as a colorless oil (1.7 g, 8 mmol, 39 % overall) after column chromatography (SiO_2; pentane – EtOAc | 8:2 to 1:1). This was directly employed in a deprotection-TIPS protection sequence. The peracetylated glycal (1.7 g, 8 mmol, 1.0 equiv.) was dissolved in MeOH (50 mL) and treated with NaOMe (30w%, 10 mol%) and the reaction mixture was allowed to stir at ambient

temperature overnight. After TLC control, the solvents were removed and the crude glycal was dissolved in dry DMF (40 mL) and imidazole (2.1 g, 31 mmol, 4.0 equiv.) was added. TIPSCl (3.7 mL, 17 mmol, 2.2 equiv.) was added dropwise at 0°C, and the mixture was allowed to stir overnight at rt. The next day, H_2O (100 mL) was added and the aq. phase was extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with water (100 mL) Brine (50 mL), and dried over anhydr. $MgSO_4$. After concentration *in vacuo*, flash column chromatography (SiO_2; pentane – EtOAc | 97:3) afforded the title compound as a colorless oil (5.8 g, 13 mmol, 66 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 6.31 – 6.20 (m, 1H), 4.71 (ddd, *J* = 6.2, 2.5, 0.7 Hz, 1H), 4.30 (dt, *J* = 6.6, 2.0 Hz, 1H), 3.95 (dq, *J* = 8.6, 6.6 Hz, 1H), 3.52 (ddd, *J* = 8.5, 6.2, 4.1 Hz, 1H), 2.19 (d, *J* = 4.1 Hz, 1H), 1.39 (dd, *J* = 6.6, 0.7 Hz, 3H), 1.18 – 0.98 (m, 42H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 143.60, 103.46, 75.24, 74.41, 70.27, 18.21, 17.85, 12.59, 12.42. Spectral characteristics were in agreement with previously reported data.[213]

(((3*R*,4*R*)-3,4-Dihydro-2*H*-pyran-3,4-diyl)bis(oxy))bis(triisopropylsilane) (11)

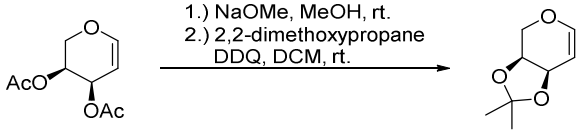


According to GP-D, starting from α-D-Xylose (4.5 g, 30 mmol, 1.0 equiv.) to obtain the intermediate (3*R*,4*R*)-3,4-dihydro-2*H*-pyran-3,4-diyl diacetate as a colorless oil (2.5 g, 13 mmol, 42 % overall) after column chromatography (SiO_2; pentane – Acetone | 7:3 to 1:1). This was directly employed in a deprotection-TIPS protection sequence. The peracetylated glycal (2 g, 10 mmol, 1.0 equiv.) was dissolved in MeOH (50 mL) and treated with NaOMe (30w%, 10 mol%) and the reaction mixture was allowed to stir at ambient temperature for 3 h. After TLC control, the solvents were removed and the crude glycal was dissolved in dry DMF (60 mL) and imidazole (2.7 g, 40 mmol, 4.0 equiv.) was added. TIPSCl (4.7 mL, 22 mmol, 2.2 equiv.) was added dropwise at 0°C, and the mixture was allowed to stir overnight at rt. The next day, H_2O (100 mL) was added and the aq. phase was extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with water (50 mL), Brine (50 mL), and dried over anhydr. $MgSO_4$. After concentration *in vacuo*, flash column chromatography (SiO_2; pentane – EtOAc | 99:1 to 96:4) afforded the title compound as a colorless oil (2.7 g, 6.3 mmol, 48 %).

[213] T. Shinozuka, *ACS Omega* **2020**, *5*, 33196-33205.

^{1}H-NMR ($CDCl_3$, 500MHz, 300K) δ = 6.43 (d, *J* = 6.2 Hz, 1H), 4.83 (ddd, *J* = 6.2, 5.3, 1.7 Hz, 1H), 3.99 (t, *J* = 1.7 Hz, 2H), 3.95 – 3.89 (m, 1H), 3.85 (p, *J* = 2.1 Hz, 1H), 1.08 – 1.04 (m, 42H). **^{13}C-NMR** ($CDCl_3$, 126MHz, 300K) δ = 145.44, 101.28, 69.64, 65.96, 64.28, 18.27, 18.21, 18.17, 18.13, 12.61, 12.57. **HR-MS** (ESI): m/z calcd. for ($[C_{23}H_{49}O_3Si_2]^+$, $[M^+]$): 429.3222, found: 429.3216.

(3a*S*,7a*R*)-2,2-dimethyl-3a,7a-dihydro-4*H*-[1,3]dioxolo[4,5-c]pyran (12)

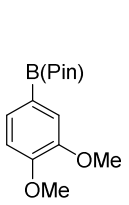


(3*S*,4*R*)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (4 g, 20 mmol, 1.0 equiv.) was suspended in MeOH (50 mL) and treated with NaOMe (30w%, 10 mol%). After stirring for 2 h at ambient temperature the solvent was removed *in vacuo*. According to a modified literature procedure [214], the now deprotected (3*S*,4*R*)-3,4-dihydro-2H-pyran- 3,4-diol (L-Arabinal) (10 mmol, 1.0 equiv.) was charged to a flame-dried flask and dissolved in dry DCM (120 mL). 2,2-Dimethoxypropane (4.9 mL, 40 mmol, 2.0 equiv.) and DDQ (0.45 g, 2 mmol, 10 mol%) was added, and the reaction mixture was allowed to stir at ambient temperature for 12 h. The next day, the solvents were removed *in vacuo* and the dark residue was purified by flash column chromatography (SiO_2; pentane – Et_2O |99:1 to 6:4) to obtain the title compound as a colorless oil (0.56 g, 3.6 mmol, 36 %). **Caution:** the title compound is quite volatile.

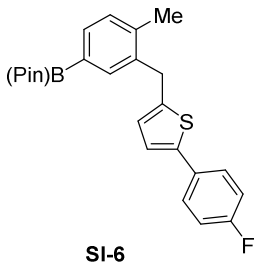
^{1}H-NMR ($CDCl_3$, 400MHz, 300K) δ = 6.54 (d, J = 6.1 Hz, 1H), 5.04 – 4.98 (m, 1H), 4.48 (t, J = 5.0 Hz, 1H), 4.19 (ddd, J = 8.0, 5.7, 4.1 Hz, 1H), 4.02 (dd, J = 11.1, 4.1 Hz, 1H), 3.63 (dd, J = 11.1, 8.0 Hz, 1H), 1.48 (s, 3H), 1.39 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 101MHz, 300K) δ = 148.23, 109.51, 100.59, 71.08, 67.73, 65.63, 28.98, 26.70. Spectral characteristics were in agreement with previously reported data.[214]

[214] O. N. Kjølberg, Klaus, *Acta Chem. Scand.* **1993**, *47*, 843-845.

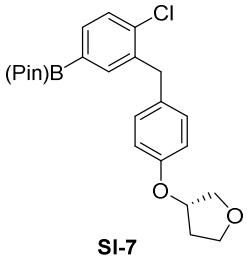
Boronic esters



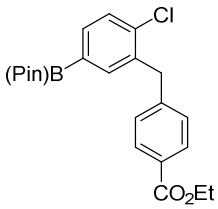
SI-5



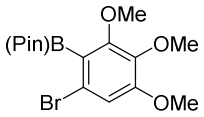
SI-6



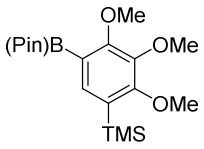
SI-7



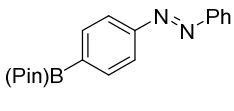
SI-8



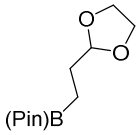
SI-9



SI-10



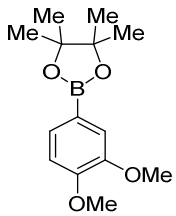
SI-11



SI-12

- All other boronic acid pinacol esters were obtained from commercial sources.

3,4-Dimethoxyphenylboronic acid pinacol ester (<u>SI-5</u>)

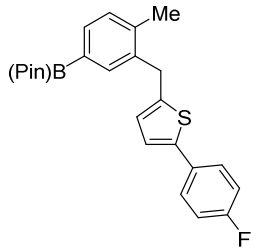


According to GP-C on a 10 mmol scale, with 4-bromoveratrole (1.3 mL, 10 mmol, 1.0 equiv.) in THF (12 mL) and *n*BuLi (11 mmol, 1.1 equiv.). Flash column chromatography (SiO_2, *i*H/EtOAc 9:1 to 3:1) furnished **<u>SI-5</u>** as colorless crystals (1.6 g, 6 mmol, 60 %).

^{1}**H-NMR** ($CDCl_3$, 400MHz, 300K) δ = 7.42 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.28 (d, *J* = 1.5 Hz), 6.88 (d, *J* = 8.0 Hz), 3.92 (s, 3H), 3.90 (s, 3H), 1.34 (s, 12H). ^{13}**C-NMR** ($CDCl_3$, 101MHz, 300K) δ =

151.7, 148.4, 128.7, 116.6, 110.6, 83.8, 56.0, 55.9, 25.0. Spectral characteristics were in agreement with previously reported data.[215]

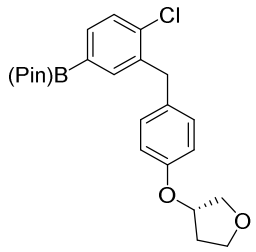
2-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (SI-6)



2-(4-Fluorophenyl)-5-[(5-iodo-2-methylphenyl)methyl]thiophene (6.1 g, 15 mmol, 1.0 equiv.) was dissolved in dry THF (70 mL) and cooled to -78°C. A solution of *n*BuLi in hexanes (19.5 mmol, 1.3 equiv.) was added dropwise to the mixture over 30 min *via* syringe pump. After stirring at the aforementioned temperature for a further 30 min, 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.7 mL, 22.5 mmol, 1.5 equiv.) was added dropwise. After 1 h at -78°C, the reaction mixture was allowed to warm to rt. stirring at this temperature for 1 h. The reaction was quenched by addition of sat. aq. NH_4Cl (10 mL) and H_2O (30 mL) was added. The aq. phase was extracted with EtOAc (3 × 100 mL), the combined org. fractions were washed with Brine (50 mL) and dried over anhydr. $MgSO_4$. After concentration *in vacuo,* flash-column chromatography (SiO_2, pentane – EtOAc: 97:3 -> 85:5) afforded the title compound as a colorless viscous oil (4.9 g, 12 mmol, 82 %).
^{1}H-NMR: ($CDCl_3$, 400 MHz, 300 K) δ = 7.75 (d, *J* = 1.3 Hz, 1H), 7.70 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.51 (ddd, *J* = 8.7, 3.7, 3.2 Hz, 1H), 7.49 (ddd, *J* = 8.7, 3.7, 3.2 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.11 – 6.98 (m, 3H), 6.66 (dd, *J* = 3.7, 0.8 Hz, 1H), 4.18 (s, 2H), 2.37 (s, 3H), 1.39 (s, 12H). **^{13}C-NMR:** ($CDCl_3$, 101 MHz, 300 K) δ = 162.05, 143.8, 141.3, 140.1, 137.5, 136.2, 133.7, 131.0, 130.9, 130.2, 127.0, 125.7, 122.6, 115.8, 83.7, 34.3, 24.9, 19.8. Spectral characteristics were in agreement with previously reported data.[216]

[215] L. Pan, M. M. Deckert, M. V. Cooke, A. R. Bleeke, S. Laulhé, *Org. Lett.* **2022**, *24*, 6466-6471.
[216] S. Jin, H. T. Dang, G. C. Haug, R. He, V. D. Nguyen, V. T. Nguyen, H. D. Arman, K. S. Schanze, O. V. Larionov, *J. Am. Chem. Soc.* **2020**, *142*, 1603-1613.

(*S*)-2-(4-Chloro-3-(4-((tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (SI-7)

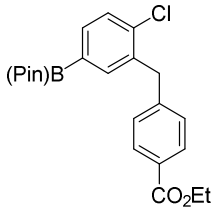


(*S*)-3-(4-(5-Bromo-2-chlorobenzyl)phenoxy)tetrahydrofuran (3.7 g, 10 mmol, 1.0 equiv.) was dissolved in dry THF (50 mL) and cooled to -78°C. A solution of *n*BuLi in hexanes (13 mmol, 1.3 equiv.) was added dropwise to the mixture over 30 min *via* syringe pump. After stirring at the aforementioned temperature for a further 30 min, 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.5 mL, 15 mmol, 1.5 equiv.) was added dropwise. After 1 h at -78°C, the reaction mixture was allowed to warm to rt. stirring at this temperature for 1 h. The reaction was quenched by addition of sat. aq. NH_4Cl (8 mL) and H_2O (20 mL) was added. The aq. phase was extracted with EtOAc (3 × 75 mL), the combined org. fractions were washed with Brine (40 mL) and dried over anhydr. $MgSO_4$. After concentration *in vacuo,* flash-column chromatography (SiO_2, pentane – EtOAc: 97:3 -> 9:1) afforded the title compound as a colorless oil, that solidified in the fridge (3.2 g, 7.6 mmol, 76 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 1.6 Hz, 1H), 7.60 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.13 – 7.07 (m, 2H), 6.79 – 6.74 (m, 2H), 4.88 (tt, *J* = 5.2, 2.7 Hz, 1H), 4.05 (s, 2H), 4.02 – 3.85 (m, 4H), 2.20 – 2.11 (m, 2H), 1.33 (s, 12H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 155.86, 138.21, 137.79, 134.26, 132.32, 129.86, 129.29, 115.38, 84.13, 77.39, 73.28, 67.33, 38.46, 33.14, 25.00. Spectral characteristics were in agreement with previously reported data.[217]

[217] S. Pan, Q. Xie, X. Wang, Q. Wang, C. Ni, J. Hu, *Chem. Commun.* **2022**, *58*, 5156-5159.

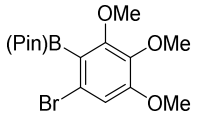
Ethyl 4-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzoate (SI-8)



Ethyl 4-(5-bromo-2-chlorobenzyl)benzoate (1.8 g, 5 mmol, 1.0 equiv.) was dissolved in dry THF (30 mL) and cooled to -78°C. A solution of *n*BuLi in hexanes (6.5 mmol, 1.3 equiv.) was added dropwise to the mixture over 30 min *via* syringe pump. After stirring at the aforementioned temperature for a further 30 min, 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 mL, 7.5 mmol, 1.5 equiv.) was added dropwise. After 1 h at -78°C, the reaction mixture was allowed to warm to rt. stirring at this temperature for 1 h. The reaction was quenched by addition of sat. aq. NH_4Cl (5 mL) and H_2O (15 mL) was added. The aq. phase was extracted with EtOAc (3 × 50 mL), the combined org. fractions were washed with Brine (50 mL) and dried over anhydr. $MgSO_4$. After concentration *in vacuo,* flash-column chromatography (SiO_2, pentane – EtOAc: 92:8) afforded the title compound as a colorless solid (1.7 g, 4.3 mmol, 86 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.70 (d, J = 1.6 Hz, 1H), 7.60 (dd, J = 7.9, 1.6 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.13 – 7.06 (m, 2H), 6.84 – 6.77 (m, 2H), 4.06 (s, 2H), 3.99 (q, J = 7.0 Hz, 2H), 1.39 (t, J = 7.0 Hz, 3H), 1.34 (s, 12H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ = 157.41, 138.36, 137.79, 134.19, 131.82, 129.75, 129.27, 114.47, 84.11, 63.48, 38.48, 25.00. **HR-MS (ESI)**: m/z calcd. for ($[C_{22}H_{27}BClO_4]^+$, $[M]^+$): 401.7140, found: 401.7144.

2-(6-Bromo-2,3,4-trimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (SI-9)

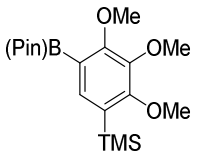


5-Bromo-1,2,3-trimethoxybenzene (3.3 g, 13 mmol, 1.0 equiv.) was dissolved in anhydr. Et_2O (10 mL) and was added in one portion to a freshly prepared solution of TMPLi (42 mmol, 3.2 equiv.) in Et_2O (90 mL) and THF (30 mL) at -100 °C (MeOH/ liquid N_2). After stirring for 1 min at the aforementioned temperature, 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.5 mL, 40 mmol, 3.0 equiv.) dissolved in Et_2O (20 mL) was added rapidly to the solution. The cooling bath was removed, and the mixture was allowed to reach ambient temperature. After that the reaction was quenched by addition of sat. aq. NH_4Cl (10 mL) and was transferred to a seperatory funnel. H_2O (50 mL) was added, and the aq. fraction was extracted with Et_2O (3 × 100 mL). The combined organic fractions were washed with Brine (50 mL) and dried over anhydr. $MgSO_4$. After removal of the solvents *in vacuo* and flash column chromatography

(SiO_2; pentane/ EtOAc 97:3 -> 88:12), the title compound was obtained as a colorless oil, which solidified in the fridge (2.4 g, 6.4 mmol, 48 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 6.79 (s, 1H), 3.86 (s, 3H), 3.81 (d, *J* = 3.7 Hz, 6H), 1.39 (s, 12H). **^{13}C-NMR:** ($CDCl_3$, 101 MHz, 300 K) δ = 157.01, 155.24, 141.06, 119.32, 112.16, 84.52, 24.86. **HR-MS (ESI)**: m/z calcd. for ($[C_{15}H_{23}BBrO_5]^+$, $[M]^+$): 374.0580, found: 374.0574.

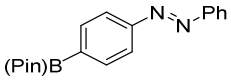
Trimethyl(2,3,4-trimethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)silane (<u>SI-10</u>)



1,2,3-Trimethoxybenzene (0.84 g, 5 mmol, 1.0 equiv.) was added suspended in dry Et_2O (20 mL) and cooled to -20°C. Dry TMEDA (0.9 mL, 6 mmol, 1.2 equiv.) was added in one portion, followed by dropwise addition of *s*BuLi (6 mmol, 1.2 equiv.). After stirring at this temperature for 30 min, TMSCl (0.69 mL, 5.5 mmol, 1.1 equiv.) was added dropwise, and the mixture was allowed to warm to rt., stirring at this temperature for 2 h. The reaction was quenched by addition of sat. aq. NH_4Cl (5 mL), H_2O (20 mL) was added and the aq. fraction was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with Brine, dried over anhydr. $MgSO_4$ and the solvents were removed *in vacuo*. The crude trimethyl(2,3,4-trimethoxyphenyl)silane was dried under high-vacuum, before being dissolved in Et_2O (20 mL) and cooling to -20°C. Dry TMEDA (0.9 mL, 6 mmol, 1.2 equiv.) was added in one portion, followed by dropwise addition of *s*BuLi (6 mmol, 1.2 equiv.). After stirring at this temperature for 30 min, 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.98 mL, 6 mmol, 1.2 equiv.) was added dropwise and the mixture was allowed to warm to rt. stirring at this temperature overnight. The reaction was quenched by addition of sat. aq. NH_4Cl (5 mL), H_2O (20 mL) was added and the aq. fraction was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with Brine, dried over anhydr. $MgSO_4$ and the solvents were removed *in vacuo*. The crude product was purified *via* flash column chromatography (SiO_2; pentane/ EtOAc: 99:1 to 92:8) to obtain the title compound as a colorless solid (0.73 g, 3.1 mmol, 61 %)

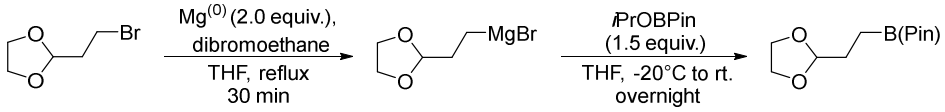
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.41 (s, 1H), 3.93 (s, 3H), 3.87 (d, J = 1.5 Hz, 6H), 1.34 (s, 12H), 0.26 (s, 9H). **^{13}C-NMR:** ($CDCl_3$, 101 MHz, 300 K) δ = 145.13, 136.70, 129.37, 128.26, 83.51, 61.96, 60.84, 24.95, -0.41.

(*E*)-1-phenyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)diazene (<u>SI-11</u>)



According to a modified literature procedure[218], (*E*)-1-(4-iodophenyl)-2-phenyldiazene (0.71 g, 2.3 mmol, 1.0 equiv.) was charged to an Ace pressure tube, containing dry KOAc (0.5 g, 5.1 mmol, 2.2 equiv.), bis(pinacolato)diboron (0.8 g, 3.2 mmol, 1.4 equiv.) and $PdCl_2(dppf)_2$ (220 mg, 0.3 mmol, 13 mol%). The pressure tube was evacuated and backfilled with Ar for three times, and dry dioxane (20 mL) was added. The vial was closed and the reaction mixture was heated to 90°C overnight. The next day, the reaction mixture was diluted with Et_2O and passed through a plug of silica, eluting with Et_2O (150 mL). After removing the solvents *in vacuo*, the crude product was purified by flash column chromatography (SiO_2; pentane/ EtOAc: 99:1 to 95:5) to obtain the title compound as an amorphous red solid (0.41 g, 1.3 mmol, 58 %). **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 7.99 – 7.89 (m, 6H), 7.55 – 7.46 (m, 3H), 1.38 (s, 12H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ = 154.50, 152.85, 135.79, 131.31, 129.24, 123.09, 122.11, 84.21, 25.05. Spectral characteristics were in agreement with previously reported data.[218]

2-(2-(1,3-Dioxolan-2-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Sl-12)



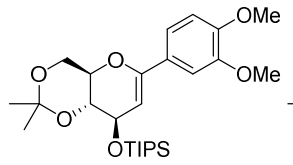
In a flame-dried Schlenk flask, magnesium turnings (1.49 g, 60 mmol, 2.0 equiv.) were suspended in dry THF (10 mL) and dibromoethane (5 drops) was added. The magnesium was activated by heating to reflux with a heat-gun twice. In a separate flask, 2-(2-bromoethyl)-1,3-dioxolane (3.5 mL, 30 mmol, 1.0 equiv.) was dissolved in THF (20 mL) and then added dropwise to the activated magnesium. Iodometric titration gave a concentration of 0.93 M.

A fraction of this grignard solution (10 mmol, 1.0 equiv.) was then added dropwise to a solution of *i*PrOBPin (3.1 mL, 15 mmol, 1.5 equiv.) in THF (20 mL) at -20°C. After 1 h at this temperature, the cooling bath was removed and the reaction mixture was allowed to stir at rt. overnight. The next day, sat. aq. NH_4Cl (5 mL), followed by water (30 mL) was added. The mixture was transferred to a separatory funnel and the aq. fraction was extracted with EtOAc (3 × 50 mL). The combined org. phases were washed with Brine (50 mL), dried over anhydr. $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane/ EtOac = 95:5 to 9:1) gave the title compound as a viscous oil (1.9 g, 8.4 mmol, 84 %).

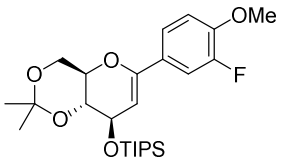
^{1}H-NMR (500 MHz, $CDCl_3$) δ = 4.85 (t, J = 4.4 Hz, 1H), 3.93 – 3.87 (m, 2H), 3.82 – 3.76 (m, 2H), 1.75 (td, J = 7.8, 4.4 Hz, 2H), 1.20 (s, 12H), 0.80 (t, J = 7.8 Hz, 2H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ = 105.30, 83.04, 65.01, 28.35, 24.87.

[218] G. Das, T. Prakasam, M. A. Addicoat, S. K. Sharma, F. Ravaux, R. Mathew, M. Baias, R. Jagannathan, M. A. Olson, A. Trabolsi, *J. Am. Chem. Soc.* **2019**, *141*, 19078-19087.

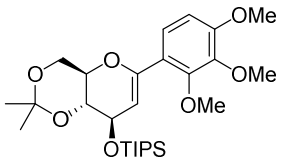
D-Glucal Series



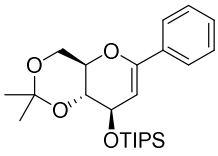
7a (74%)



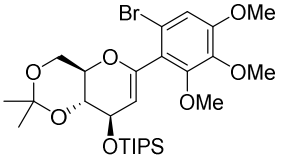
7b (64%)



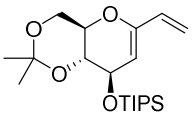
7c (67%)



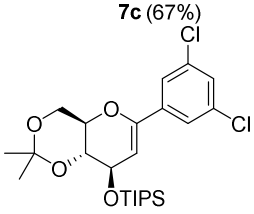
7d (83%)



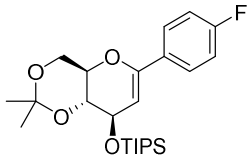
7e (81%)



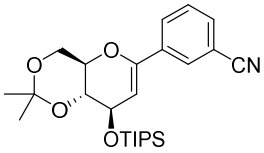
7f (51%)



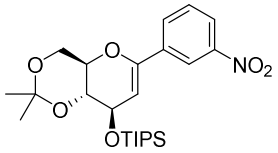
7g (72%)



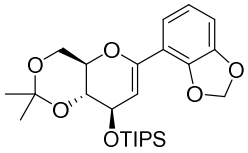
7h (61%)



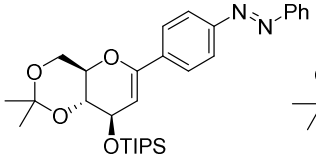
7i (62%)



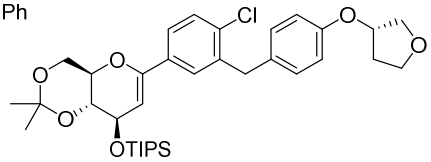
7j (68%)



7k (28%)

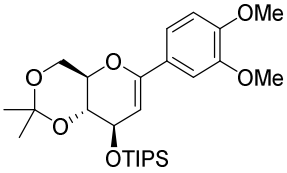


7l (68%)



7m (74%)

(((4a*R*,8*R*,8a*R*)-6-(3,4-Dimethoxyphenyl)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl)oxy)triisopropylsilane (7a)

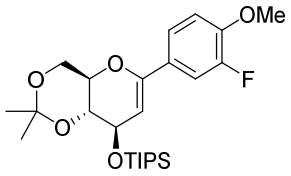


According to GP-B, using *t*BuLi (0.22 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing 2-(3,4-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (61 mg, 0.23 mmol, 1.3 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 199:1 to 99:1) furnished the title compound as a colorless oil (71 mg, 0.15 mmol, 74 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.11 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.11 (d, *J* = 2.3 Hz, 1H), 4.57 (dd, *J* = 7.0, 2.3 Hz, 1H), 4.08 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.99 – 3.92 (m, 1H), 3.91 – 3.86 (m, 10H), 3.48 (q, *J* = 7.0 Hz, 1H), 1.53 (s, 3H), 1.43 (s, 3H), 1.23 – 1.19 (m, 3H), 1.14 – 1.08 (m, 18H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 151.51, 149.62, 148.67, 127.38, 118.20, 110.79, 108.52, 100.54, 99.65, 73.48, 69.93, 68.78, 66.01, 62.12, 56.03, 29.13, 19.08, 18.18, 18.10, 12.47. **HR-MS** (EI pos): m/z calcd. for ([C26H42O6Si]+, [M]+): 478.2751, found: 478.2740. **IR** (FT-ATR) ν̃ [cm^{-1}]: 2993 (w), 2940 (m),

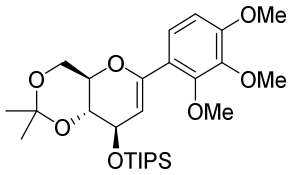
2866 (m), 1645 (w), 1606 (w), 1584 (w), 1515 (s), 1463 (m), 1417 (w), 1382 (m), 1370 (m), 1346 (w), 1325 (w), 1288 (w), 1260 (s), 1244 (m), 1211 (m), 1201 (m), 1172 (s), 1141 (m), 1114 (s), 1100 (vs), 1056 (s), 1030 (s), 1013 (m), 998 (m), 944 (m), 920 (m), 909 (m), 882 (m), 867 (s), 843 (m), 825 (w), 802 (s), 765 (s), 724 (w), 677 (s), 659 (m).

(((4a*R*,8*R*,8a*R*)-6-(3-Fluoro-4-methoxyphenyl)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl)oxy)triisopropylsilane (7b)



According to GP-B, using *t*BuLi (0.22 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing 2-(3-fluoro-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (50 mg, 0.20 mmol, 1.0 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 199:1 to 32:1) furnished the title compound as a colorless oil (60 mg, 0.13 mmol, 64 %). **^{1}H-NMR:** ($CDCl_3$, 400 MHz, 300 K) δ = 7.26 – 7.22 (m, 2H), 6.89 (t, *J* = 8.5 Hz, 1H), 5.11 (d, *J* = 2.3 Hz, 1H), 4.55 (dd, *J* = 6.9, 2.3 Hz, 1H), 4.06 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.96 – 3.90 (m, 1H), 3.88 (s, 3H), 3.87 – 3.80 (m, 2H), 1.52 (s, 3H), 1.42 (s, 3H), 1.09 (td, *J* = 3.6, 1.7 Hz, 21H). **^{13}C-NMR:** ($CDCl_3$, 101 MHz, 300 K) δ = 153.31, 150.88, 150.31 (d, *J* = 2.3 Hz), 148.03 (d, *J* = 11.0 Hz), 127.61 (d, *J* = 6.7 Hz), 121.13 (d, *J* = 3.5 Hz), 113.14 (d, *J* = 20.0 Hz), 112.83 (d, *J* = 2.1 Hz), 100.97, 99.68, 73.36, 69.92, 68.68, 62.03, 56.33, 29.85, 29.11, 19.05, 18.18, 18.10, 12.44. **^{19}F-NMR**: ($CDCl_3$, 377 MHz, 300 K) δ = -135.39, -135.40, -135.42, -135.42, -135.43, -135.45, -135.46. **HR-MS (EI pos)**: m/z calcd. for ($[C_{25}H_{39}FO_5Si]]^+$, $[M]^+$): 466.2551, found: 466.2550. **IR (FT-ATR)** ṽ [cm^{-1}]: 2994 (w), 2942 (m), 2866 (m), 1646 (w), 1620 (w), 1581 (w), 1517 (s), 1464 (m), 1436 (m), 1424 (w), 1383 (m), 1370 (m), 1343 (m), 1313 (w), 1280 (m), 1259 (m), 1234 (m), 1218 (m), 1202 (m), 1192 (m), 1172 (m), 1134 (s), 1112 (s), 1099 (vs), 1056 (s), 1032 (s), 1010 (m), 998 (m), 967 (w), 945 (w), 927 (m), 914 (m), 882 (s), 869 (s), 847 (m), 803 (s), 762 (s), 718 (w), 679 (s), 658 (m).

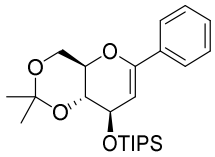
(((4a*R*,8*R*,8a*R*)-2,2-Dimethyl-6-(2,3,4-trimethoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl)oxy)triisopropylsilane (7c)



According to GP-B, using *t*BuLi (0.22 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing 4,4,5,5-tetramethyl-2-(2,3,4-trimethoxyphenyl)-1,3,2-dioxaborolane (68 mg, 0.23 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 99:1

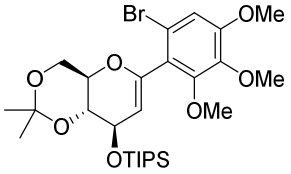
to 9:1) furnished the title compound as a colorless oil (68 mg, 0.13 mmol, 67 %). The title compound was employed in the Hydroboration-oxidation procedure to furnish compound **18**.
^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.15 (d, *J* = 8.8 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 5.33 (d, *J* = 2.2 Hz, 1H), 4.57 (dd, *J* = 7.1, 2.2 Hz, 1H), 4.02 (dd, *J* = 10.3, 5.0 Hz, 1H), 3.95 – 3.90 (m, 2H), 3.90 – 3.88 (m, 1H), 3.86 – 3.85 (m, 9H), 1.54 (s, 3H), 1.42 (s, 3H), 1.15 – 1.05 (m, 21H). **Note**: ^{1}H-NMR shows trace of aromatic impurity. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ = 154.18, 152.18, 148.93, 142.88, 142.72, 132.73, 123.47, 121.91, 109.93, 107.02, 105.10, 99.62, 73.52, 69.90, 68.93, 63.00, 62.13, 61.04, 60.95, 56.12, 29.18, 19.14, 18.17, 18.08, 12.46. **HR-MS** (ESI): m/z calcd. for ($[C_{27}H_{44}O_7Si]^+$, $[H^+]$): 509.2936, found: 509.293.

(((4a*R*,8*R*,8a*R*)-2,2-Dimethyl-6-phenyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl)oxy)triisopropylsilane (7d)



According to GP-B, using *t*BuLi (0.22 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (47 mg, 0.23 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 299:1 to 99:1) furnished the title compound as a colorless oil (70 mg, 0.17 mmol, 83 %).
^{1}H-NMR: ($CDCl_3$, 400 MHz, 300 K) δ = 7.56 – 7.52 (m, 2H), 7.36 – 7.31 (m, 3H), 5.25 (d, *J* = 2.3 Hz, 1H), 4.60 (dd, *J* = 6.9, 2.3 Hz, 1H), 4.09 (dd, *J* = 10.4, 5.0 Hz, 1H), 4.00 – 3.88 (m, 3H), 1.55 (s, 3H), 1.44 (s, 3H), 1.13 (dq, *J* = 5.9, 3.2 Hz, 21H). **^{13}C-NMR:** ($CDCl_3$, 101 MHz, 300 K) δ = 151.57, 134.38, 128.79, 128.33, 125.19, 101.71, 99.66, 73.43, 69.94, 68.78, 62.11, 29.14, 19.08, 18.20, 18.12, 12.47. **LR-MS (70 eV):** m/z [%] = 375.1 (46), 343.1 (5), 317.1 (25), 289.0 (9), 261.1 (15), 235.0 (8), 211.0 (4), 175.0 (8), 157.0 (17), 131.0 (16), 105.0 (100), 75.0 (27), 59.0 (15). **HR-MS (EI pos):** m/z calcd. for ($[C_{24}H_{38}O_4Si]^+$, $[M^+]$): 418.2539, found: 418.2543. **IR (FT-ATR)** $\tilde{\nu}$ [cm^{-1}]: 2994 (w), 2942 (m), 2866 (m), 1647 (w), 1496 (w), 1463 (w), 1448 (w), 1382 (m), 1370 (m), 1338 (w), 1282 (w), 1270 (w), 1258 (m), 1218 (w), 1200 (m), 1170 (m), 1116 (s), 1100 (vs), 1056 (s), 1031 (s), 1014 (m), 998 (m), 943 (m), 921 (w), 885 (s), 860 (m), 808 (s), 780 (m), 754 (s), 712 (w), 687 (s), 679 (s), 656 (m).

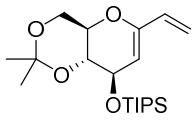
(((4a*R*,8*R*,8a*R*)-6-(6-Bromo-2,3,4-trimethoxyphenyl)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl)oxy)triisopropylsilane (7e)



According to GP-B on a 0.5 mmol scale, using *t*BuLi (0.55 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing 2-(6-bromo-2,3,4-trimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (215 mg, 0.58 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 97:3 to 7:3) furnished the title compound as a colorless oil (0.24 g, 0.41 mmol, 81 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 6.86 (s, 1H), 4.93 (d, *J* = 10.3 Hz, 1H), 4.36 (dd, *J* = 10.3, 8.5 Hz, 1H), 4.15 (s, 3H), 3.93 (dd, *J* = 10.3, 5.2 Hz, 1H), 3.82 (s, 3H), 3.81 – 3.73 (m, 2H), 3.71 (s, 3H), 3.57 (td, *J* = 10.3, 5.2 Hz, 1H), 1.49 (s, 3H), 1.38 (s, 3H), 1.27 (m, 3H), 1.15 (t, *J* = 7.3 Hz, 18H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 153.31, 151.99, 139.32, 126.17, 115.74, 114.60, 99.55, 85.35, 82.65, 77.41, 77.36, 77.16, 76.90, 75.13, 74.14, 70.42, 62.63, 62.14, 60.58, 56.31, 36.99, 29.29, 28.09, 25.85, 25.64, 18.89, 18.79, 18.61, 13.66. **HR-MS** (ESI): m/z calcd. for ($[C_{27}H_{43}BrO_7Si]^+$, $[M^+]$): 587.2041, found: 587.204.

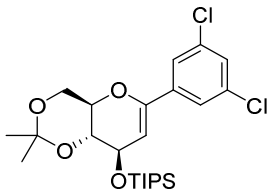
(((4a*R*,8*R*,8a*R*)-2,2-Dimethyl-6-vinyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl)oxy)triisopropylsilane (7f)



According to GP-B on a 0.2 mmol scale, using *t*BuLi (0.22 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (58 mg, 0.23 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 99.6:0.4 to 99:1) furnished the title compound as a colorless oil (38 mg, 0.1 mmol, 51 %). The title compound was obtained as a 3:1 mixture with the respective 6-iodoglucal. The yield was determined by GC-analysis.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.04 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.53 – 5.42 (m, 1H), 5.11 (dd, *J* = 10.9, 1.6 Hz, 1H), 4.72 (d, *J* = 2.3 Hz, 1H), 4.48 (dd, *J* = 7.2, 2.3 Hz, 1H), 3.95 – 3.79 (m, 4H), 1.50 (d, *J* = 2.6 Hz, 3H), 1.40 (s, 3H), 1.08 (qd, *J* = 2.9, 1.7 Hz, 21H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 150.46, 131.23, 114.95, 106.68, 99.62, 73.41, 69.55, 68.70, 62.07, 29.11, 19.04, 18.15, 18.06, 12.42. **HR-MS (EI pos)**: m/z calcd. for ($[C_{17}H_{29}O_4Si]^+$, $[M\text{-}i\text{Pr}]^+$): 325.1835, found: 325.1830. **LR-MS (70 eV):** m/z [%] = 325.1 (98), 293.1 (9), 267.1 (50), 239.0 (13), 225.0 (10), 211.1 (100), 185.0 (25), 169.0 (10), 154.9 (9), 141.0 (10), 124.9 (21), 107.0 (38), 91.0 (10), 75.0 (62), 55.0 (60). **IR (FT-ATR)** $\tilde{\nu}$ [cm^{-1}]: 2994 (w), 2943 (m), 2893 (w), 2866 (m), 1651 (vw), 1618 (w), 1599 (w), 1464 (w), 1409 (vw), 1382 (m), 1370 (m), 1349 (w), 1328 (vw), 1292 (w), 1266 (m), 1258 (m), 1233 (w), 1218 (w), 1202 (m), 1188 (m), 1169 (m), 1143 (w), 1093 (vs), 1056 (s), 1030 (m), 1014 (m), 997 (m), 980 (m), 944 (w), 917 (m), 903 (m), 879 (s), 863 (m), 813 (s), 781 (m), 762 (m), 731 (w), 718 (w), 678 (s), 656 (m).

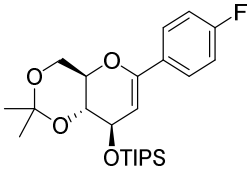
(((4a*R*,8*R*,8a*R*)-6-(3,5-Dichlorophenyl)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl)oxy)triisopropylsilane (7g)



According to GP-B, using *t*BuLi (0.22 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing 2-(3,5-dichlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (63 mg, 0.23 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 39:1 to 7:3) furnished the title compound as a colorless oil (70 mg, 0.14 mmol, 72 %).

^{1}H-NMR: ($CDCl_3$, 400 MHz, 300 K) δ = 7.39 (d, *J* = 1.9 Hz, 2H), 7.29 (t, *J* = 1.9 Hz, 1H), 5.24 (d, *J* = 2.3 Hz, 1H), 4.59 – 4.55 (m, 1H), 4.11 – 4.05 (m, 1H), 3.97 – 3.83 (m, 3H), 1.53 (s, 3H), 1.43 (s, 3H), 1.11 (dq, *J* = 5.8, 3.4 Hz, 21H). **^{13}C-NMR:** ($CDCl_3$, 101 MHz, 300 K) δ = 149.15, 137.28, 135.02, 128.56, 123.64, 103.79, 99.79, 73.10, 70.19, 68.57, 61.91, 29.09, 19.03, 18.21, 18.13, 12.46. **LR-MS (70 eV):** m/z [%] = 443.1 (78), 411.1 (7), 385.0 (55), 329.0 (58), 303.0 (8), 284.9 (7), 260.9 (11), 242.9 (18), 224.9 (26), 198.9 (5), 172.9 (100), 145.0 (28), 127.0 (13), 103.0 (50), 75.0 (85), 55.0 (11). **HR-MS (EI pos):** m/z: calcd. for ($[C_{21}H_{29}Cl_2O_4Si]^+$, $[M\text{-}Me]^+$): 471.1525, found: 471.1549. **IR (FT-ATR)** $\tilde{\nu}$ [cm^{-1}]: 2994 (w), 2942 (m), 2925 (m), 2866 (m), 1987 (w), 1644 (w), 1588 (w), 1562 (m), 1463 (m), 1440 (w), 1416 (m), 1383 (m), 1370 (m), 1333 (m), 1288 (w), 1270 (m), 1260 (m), 1243 (w), 1218 (m), 1200 (m), 1169 (m), 1125 (s), 1117 (s), 1100 (vs), 1057 (s), 1032 (m), 1015 (m), 996 (m), 944 (m), 922 (w), 902 (m), 882 (s), 859 (s), 815 (s), 801 (s), 787 (m), 762 (m), 744 (w), 680 (s), 652 (s).

(((4a*R*,8*R*,8a*R*)-6-(4-Fluorophenyl)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl)oxy)triisopropylsilane (7h)

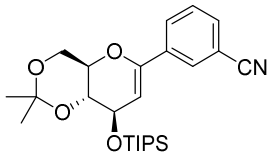


According to GP-B, using *t*BuLi (0.22 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing 4-fluorophenylboronic acid pinacol ester (51 mg, 0.23 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 39:1) furnished the title compound as a colorless oil (54 mg, 0.12 mmol, 61 %).

^{1}H-NMR: ($CDCl_3$, 400 MHz, 300 K) δ = 7.54 – 7.48 (m, 2H), 7.06 – 6.95 (m, 2H), 5.16 (d, *J* = 2.3 Hz, 1H), 4.57 (dd, *J* = 6.9, 2.3 Hz, 1H), 4.07 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.94 (t, *J* = 9.8 Hz, 1H), 3.92 – 3.81 (m, 2H), 1.54 (s, 3H), 1.43 (s, 3H), 1.18 – 1.05 (m, 21H). **^{13}C-NMR:** δ = ($CDCl_3$, 101 MHz, 300 K) δ = 163.2 (d, *J* = 248.1 Hz), 150.8, 130.6 (d, *J* = 3.2 Hz), 127.1 (d, *J* = 8.2

Hz), 115.3 (d, *J* = 21.7 Hz), 101.5 (d, J = 1.6 Hz), 99.7, 73.4, 70.0, 68.7, 62.1, 29.1, 19.1, 18.2, 18.1, 12.5. 101.51. **^{19}F-NMR**: ($CDCl_3$, 376 MHz, 300 K) δ = -113.0. **LR-MS (70 eV):** m/z [%] = 393.1 (55), 361.0 (6), 335.1 (29), 307.0 (9), 279.1 (18), 253.0 (7), 211.0 (4), 192.9 (9), 174.9 (15), 146.0 (8), 123.0 (100), 102.9 (17), 75.0 (29), 59.0 (11). **HR-MS (EI pos):** m/z calcd. for ($[C_{24}H_{37}FO_4Si]^+$, $[M^+]$): 436.2445, found: 436.2460. **IR (FT-ATR)** ṽ [cm^{-1}]: 2994 (w), 2942 (m), 2894 (w), 2866 (m), 1647 (w), 1606 (w), 1510 (s), 1464 (m), 1411 (w), 1383 (m), 1370 (m), 1337 (m), 1297 (w), 1280 (m), 1270 (m), 1258 (m), 1234 (m), 1218 (m), 1200 (m), 1170 (m), 1159 (m), 1099 (vs), 1057 (s), 1032 (m), 1014 (m), 997 (m), 970 (w), 943 (m), 921 (w), 888 (s), 861 (m), 840 (s), 818 (m), 800 (s), 767 (s), 731 (w), 718 (w), 679 (s), 658 (m).

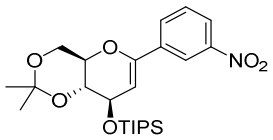
3-((4a*R*,8*R*,8a*R*)-2,2-Dimethyl-8-((triisopropylsilyl)oxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-6-yl)benzonitrile (7i)



According to GP-B, using *t*BuLi (0.22 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing 3-cyanophenylboronic acid pinacol ester (53 mg, 0.23 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 99:1 to 97:3) furnished the title compound as a colorless oil (55 mg, 0.12 mmol, 62 %).

^{1}H-NMR: ($CDCl_3$, 400 MHz, 300 K) δ = 7.82 (t, *J* = 1.7 Hz, 1H), 7.75 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.58 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 5.30 (d, *J* = 2.3 Hz, 1H), 4.61 – 4.57 (m, 1H), 4.11 – 4.07 (m, 1H), 3.99 – 3.87 (m, 3H), 1.54 (s, 3H), 1.43 (s, 3H), 1.16 – 1.06 (m, 21H). **^{13}C-NMR:** δ = ($CDCl_3$, 101 MHz, 300 K) δ = 149.48, 135.56, 132.03, 129.26, 128.82, 118.84, 112.65, 103.60, 99.82, 73.13, 70.19, 68.55, 61.92, 29.09, 19.04, 18.20, 18.11, 12.45. **LR-MS (70 eV):** m/z [%] = 400.2 (100), 368.1 (8), 342.1 (75), 314.1 (13), 286.1 (68), 270.0 (10), 242.0 (7), 225.9 (5), 207.0 (49), 182.0 (30), 153.0 (6), 130.0 (100), 103.0 (56), 75.0 (91), 59.0 (45). **HR-MS (EI pos):** m/z calcd. for ($[C_{24}H_{34}NO_4Si]^+$, $[M\text{-}Me^+]$): 428.2257, found: 428.2268. **IR (FT-ATR)** ṽ [cm^{-1}]: 2993 (w), 2943 (m), 2892 (w), 2866 (m), 2232 (w), 1646 (w), 1480 (w), 1464 (w), 1431 (w), 1418 (w), 1383 (m), 1370 (m), 1339 (w), 1295 (w), 1272 (w), 1259 (m), 1218 (m), 1201 (m), 1171 (m), 1151 (w), 1115 (s), 1101 (vs), 1057 (s), 1032 (m), 1011 (m), 997 (m), 944 (m), 921 (w), 902 (s), 882 (s), 864 (s), 825 (s), 796 (s), 764 (s), 737 (w), 681 (s), 656 (m).

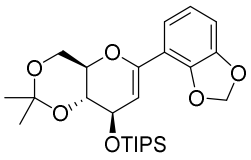
(((4a*R*,8*R*,8a*R*)-2,2-Dimethyl-6-(3-nitrophenyl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl)oxy)triisopropylsilane (7j)



According to GP-B, using *t*BuLi (0.26 mmol, 1.3 equiv.) and stirring for 30 min at -30°C for lithiation and employing 3-nitrophenylboronic acid pinacol ester (57 mg, 0.23 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 99:1 to 19:1) furnished the title compound as a yellow oil (65 mg, 0.14 mmol, 68 %).

^{1}H-NMR: ($CDCl_3$, 400 MHz, 300 K) δ = 8.37 (t, *J* = 2.0 Hz, 1H), 8.15 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 7.84 (dt, *J* = 8.0, 1.4 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 5.36 (d, *J* = 2.3 Hz, 1H), 4.61 (dt, *J* = 5.9, 2.1 Hz, 1H), 4.15 – 4.08 (m, 1H), 4.00 – 3.89 (m, 3H), 1.55 (s, 3H), 1.44 (s, 3H), 1.17 – 1.09 (m, 21H). **^{13}C-NMR:** (101 MHz, $CDCl_3$) δ = 149.38, 148.47, 136.08, 130.86, 129.30, 123.40, 120.13, 103.94, 99.82, 73.11, 70.26, 68.57, 61.93, 29.08, 22.76, 19.03, 18.20, 18.11, 12.46. **LR-MS (70 eV):** m/z [%] = 421.2 (26), 420.2 (100), 363.1 (21), 362.1 (80), 306.1 (35), 150.0 (11). **HR-MS** (EI pos): m/z: calcd. for ($[C_{23}H_{34}NO_6Si]^+$, [M-*i*Pr]$^+$): 448.2155, found: 448.2147. **IR (FT-ATR)** $\tilde{\nu}$ [cm^{-1}]: 2993 (w), 2942 (m), 2924 (m), 2866 (m), 1646 (w), 1532 (s), 1464 (m), 1440 (w), 1383 (m), 1370 (m), 1349 (s), 1312 (w), 1294 (w), 1260 (m), 1241 (w), 1218 (m), 1200 (m), 1169 (m), 1105 (vs), 1090 (s), 1057 (s), 1031 (m), 1014 (m), 998 (m), 945 (m), 924 (w), 905 (s), 882 (s), 868 (s), 853 (m), 805 (s), 774 (s), 761 (m), 741 (s), 714 (w), 679 (vs), 659 (m).

(((4a*R*,8*R*,8a*R*)-6-(Benzo[*d*][1,3]dioxol-4-yl)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl)oxy)triisopropylsilane (7k)

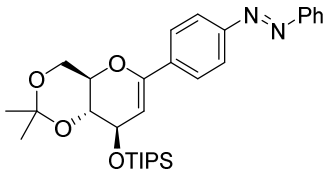


According to GP-B, using *t*BuLi (0.26 mmol, 1.3 equiv.) and stirring for 30 min at -30°C for lithiation and employing 2,3-methylenedioxyphenylboronic acid pinacol ester (57 mg, 0.23 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 99:1 to 19:1) furnished the title compound as a colorless oil (26 mg, 0.06 mmol, 28 %).

^{1}H-NMR: ($CDCl_3$, 400 MHz, 300 K) δ = 7.06 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.00 (d, *J* = 1.7 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 5.96 (q, *J* = 1.4 Hz, 2H), 5.09 (d, *J* = 2.2 Hz, 1H), 4.56 (dd, *J* = 7.0, 2.2 Hz, 1H), 4.06 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.95 – 3.83 (m, 3H), 1.53 (s, 3H), 1.43 (s, 3H), 1.14 – 1.08 (m, 21H). **^{13}C-NMR:** ($CDCl_3$, 101 MHz, 300 K) δ = 151.28, 148.11, 147.73, 128.74, 119.33, 108.12, 105.89, 101.33, 100.68, 99.67, 73.45, 69.94, 68.79, 62.10, 29.15, 19.10, 18.20, 18.12, 12.49. **HR-MS (EI pos):** m/z calcd. for ($[C_{25}H_{38}O_6Si]^+$, [M]$^+$): 462.2438, found:

462.2432. **IR (FT-ATR)** $\tilde{\nu}$ [cm^{-1}]: 2994 (w), 2941 (m), 2926 (m), 2892 (m), 2866 (m), 1649 (w), 1643 (w), 1611 (w), 1607 (w), 1504 (m), 1491 (m), 1462 (m), 1445 (m), 1413 (w), 1383 (m), 1370 (m), 1359 (m), 1322 (m), 1289 (m), 1274 (m), 1249 (s), 1215 (s), 1200 (m), 1170 (m), 1140 (m), 1103 (vs), 1087 (s), 1056 (s), 1040 (s), 1032 (s), 1015 (m), 996 (m), 941 (s), 924 (m), 908 (s), 882 (s), 870 (vs), 852 (m), 804 (s), 766 (s), 739 (w), 722 (w), 704 (w), 678 (s), 664 (m), 659 (m).

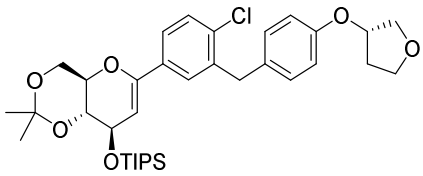
(*E*)-1-(4-((4a*R*,8*R*,8a*R*)-2,2-Dimethyl-8-((triisopropylsilyl)oxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-6-yl)phenyl)-2-phenyldiazene (7l)



According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.11 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing (*E*)-1-phenyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)diazene (35.4 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 99:1 to 95:5) furnished the title compound as a red oil (36 mg, 0.07 mmol, 68 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.94 – 7.88 (m, 4H), 7.72 – 7.67 (m, 2H), 7.55 – 7.47 (m, 3H), 5.37 (d, *J* = 2.3 Hz, 1H), 4.62 (dd, *J* = 6.9, 2.3 Hz, 1H), 4.11 (dd, *J* = 10.6, 5.0 Hz, 1H), 4.02 – 3.90 (m, 3H), 1.56 (s, 3H), 1.45 (s, 3H), 1.17 – 1.10 (m, 21H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 175.28, 174.58, 164.44, 162.45, 148.20, 132.34, 129.11 (d, *J* = 8.5 Hz), 128.05 (d, *J* = 3.5 Hz), 127.69 (d, *J* = 8.5 Hz), 126.28 (d, *J* = 2.7 Hz), 115.96 (d, *J* = 22.2 Hz), 62.87, 60.52, 55.54, 51.60, 49.58, 47.35, 43.71, 25.00, 21.16. **HR-MS** (ESI): m/z calcd. for ([$C_{30}H_{42}N_2O_4Si$]$^+$, [H^+]): 523.2994, found: 523.299.

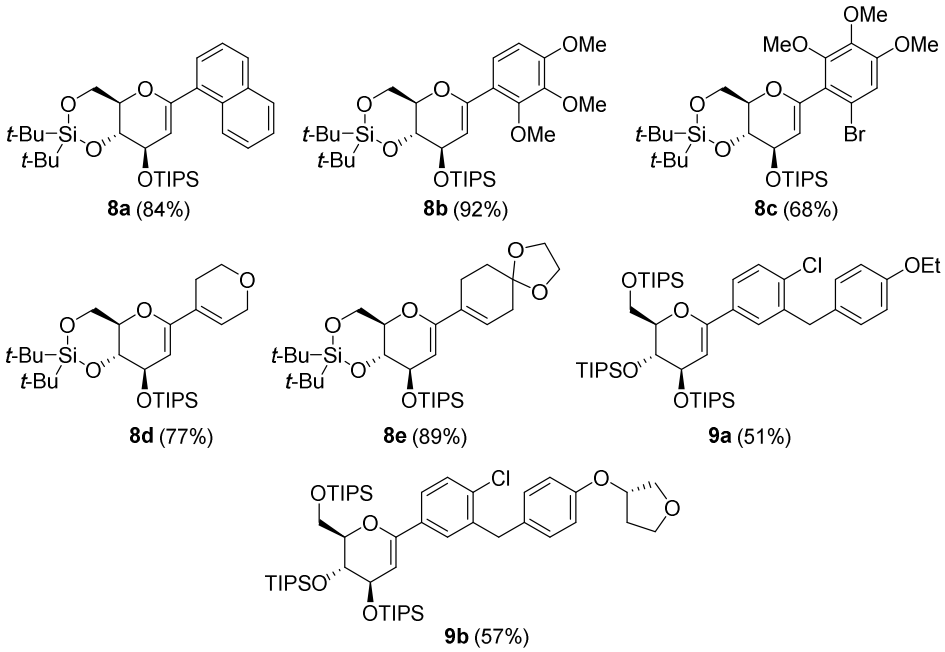
(((4a*R*,8*R*,8a*R*)-6-(4-Chloro-3-(4-(((S)-tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-8-yl)oxy)triisopropylsilane (7m)



According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.11 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing (*S*)-2-(4-chloro-3-(4-((tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (48 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 99:1 to 9:1) furnished the title compound as a colorless oil (47 mg, 0.07 mmol, 74 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.32 (s, 3H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.81 – 6.76 (m, 2H), 5.14 (d, *J* = 2.3 Hz, 1H), 4.91 – 4.86 (m, 1H), 4.55 (dd, *J* = 6.9, 2.3 Hz, 1H), 4.07 – 3.81 (m, 10H), 2.20 – 2.13 (m, 2H), 1.53 (s, 3H), 1.43 (s, 3H), 1.17 – 1.06 (m, 21H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 156.04, 150.68, 138.80, 134.59, 133.14, 131.73, 130.03, 129.48, 127.64, 124.43, 115.46, 102.09, 99.70, 77.38, 73.27, 70.01, 68.68, 67.33, 62.01, 38.51, 33.16, 29.10, 19.07, 18.17, 18.09, 12.45. **HR-MS** (ESI): m/z calcd. for ($[C_{35}H_{49}ClO_6Si]^+$, $[H^+]$): 629.3060, found: 629.306.

D-Glucal Series

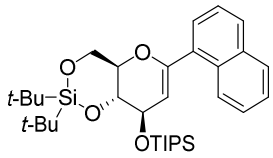


8a (84%) **8b** (92%) **8c** (68%)

8d (77%) **8e** (89%) **9a** (51%)

9b (57%)

(4a*R*,8*R*,8a*R*)-8-((l1-silyl)oxy)-2,2-Di-tert-butyl-6-(naphthalen-1-yl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (8a)

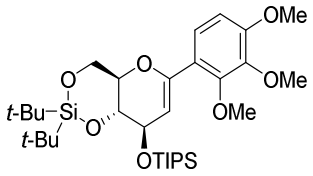


According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 30 min at -30°C for lithiation and employing 4,4,5,5-tetramethyl-2-(naphthalen-1-yl)-1,3,2-dioxaborolane (29 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 999:1 to 98:2) furnished the title compound as a colorless oil, which solidified (48 mg, 0.08 mmol, 84 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 8.15 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.86 – 7.82 (m, 2H), 7.55 – 7.41 (m, 4H), 5.05 (d, *J* = 2.1 Hz, 1H), 4.66 (dd, *J* = 6.8, 2.1 Hz, 1H), 4.30 – 4.23 (m, 2H), 4.19 – 4.11 (m, 2H), 1.16 – 1.11 (m, 30H), 1.06 (s, 9H). **Note**: ^{1}H-NMR shows trace of EtOAc. **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 152.15, 133.81, 133.12, 131.30, 129.53, 128.43, 127.07, 126.43,

126.04, 125.78, 125.23, 106.51, 77.86, 73.58, 71.96, 66.31, 27.67, 27.17, 22.97, 20.07, 18.33, 14.36, 12.64. **HR-MS** (ESI): m/z calcd. for ($[C_{33}H_{52}O_4Si_2]^+$, $[M^+]$): 569.3484, found: 569.348.

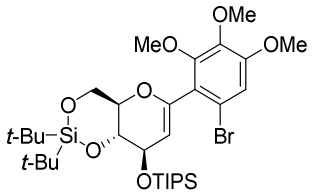
(4a*R*,8*R*,8a*R*)-8-((l1-Silyl)oxy)-2,2-di-*tert*-butyl-6-(2,3,4-trimethoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (8b)



According to GP-B on a 4.3 mmol scale, using *t*BuLi (5.6 mmol, 1.3 equiv.) and stirring for 45 min at -30°C for lithiation and employing 4,4,5,5-tetramethyl-2-(2,3,4-trimethoxyphenyl)-1,3,2-dioxaborolane (1.45 g, 4.95 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 98:2 to 88:12) furnished the title compound as a colorless oil (2.4 g, 3.9 mmol, 92 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.13 (d, *J* = 8.7 Hz, 1H), 6.63 (d, *J* = 8.7 Hz, 1H), 5.31 (s, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 4.26 (dd, *J* = 10.4, 4.7 Hz, 1H), 4.13 – 4.04 (m, 2H), 4.01 – 3.96 (m, 1H), 3.86 (s, 9H), 1.17 – 1.10 (m, 21H), 1.08 (s, 9H), 1.01 (s, 9H). **Note**: ^{1}H-NMR shows trace of aromatic impurity. **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 154.20, 152.19, 148.65, 142.70, 123.54, 121.85, 107.03, 104.80, 77.74, 73.11, 72.10, 66.29, 61.05, 61.02, 56.12, 27.63, 27.12, 22.92, 20.03, 18.33, 12.63. **HR-MS** (ESI): m/z calcd. for ($[C_{32}H_{56}O_7Si_2]^+$, $[H^+]$): 609.3645, found: 609.364.

(4a*R*,8*R*,8a*R*)-6-(6-Bromo-2,3,4-trimethoxyphenyl)-2,2-di-*tert*-butyl-8-((triisopropylsilyl)oxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (8c)

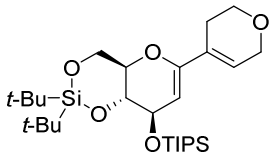


According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 30 min at -30°C for lithiation and employing 2-(6-bromo-2,3,4-trimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (43 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 98:2 to 91:9) furnished the title compound as a colorless oil (47 mg, 0.07 mmol, 68 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 6.85 (s, 1H), 4.90 (d, *J* = 10.1 Hz, 1H), 4.30 (t, *J* = 9.3 Hz, 1H), 4.19 (dd, *J* = 10.4, 5.3 Hz, 1H), 4.15 (s, 3H), 4.01 – 3.94 (m, 2H), 3.82 (s, 3H), 3.72 (s, 3H), 3.68 (dd, *J* = 9.9, 5.1 Hz, 1H), 1.34 – 1.31 (m, 3H), 1.19 (d, *J* = 7.5 Hz, 18H), 1.08 (s, 9H), 1.01 (s, 9H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ = 153.28, 152.18, 139.33, 126.33, 115.61, 114.73,

78.71, 73.07, 66.74, 62.40, 60.53, 56.31, 37.30, 27.93, 27.15, 23.27, 20.17, 19.12, 18.82, 14.30. **HR-MS** (ESI): m/z calcd. for ($[C_{32}H_{56}BrO_7Si_2]^+$, $[H^+]$): 687.2750, found: 687.275.

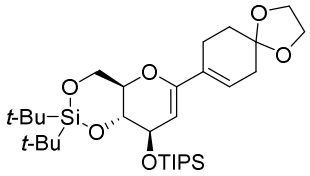
(4a*R*,8*R*,8a*R*)-8-((l1-Silyl)oxy)-2,2-di-*tert*-butyl-6-(3,6-dihydro-2*H*-pyran-4-yl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (8d)



According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 30 min at -30°C for lithiation and employing 2-(3,6-dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (24.1 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 96:4) furnished the title compound as a colorless oil (40 mg, 0.08 mmol, 77 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 6.11 (d, *J* = 3.1 Hz, 1H), 4.74 (d, *J* = 2.4 Hz, 1H), 4.50 (dd, *J* = 7.0, 2.4 Hz, 1H), 4.25 – 4.20 (m, 3H), 4.06 – 3.98 (m, 2H), 3.87 – 3.74 (m, 3H), 1.30 (d, *J* = 7.5 Hz, 2H), 1.14 – 1.09 (m, 21H), 1.06 (s, 9H), 0.99 (s, 9H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 150.33, 127.94, 123.62, 101.13, 77.72, 72.76, 71.87, 66.25, 65.63, 64.18, 27.64, 27.59, 27.08, 25.40, 25.21, 24.69, 22.90, 20.01, 18.31, 18.28, 12.61. **HR-MS** (ESI): m/z calcd. for ($[C_{28}H_{52}O_5Si_2]^+$, $[H^+]$): 525.3433, found: 525.342.

(4a*R*,8*R*,8a*R*)-8-((l1-Silyl)oxy)-2,2-di-*tert*-butyl-6-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (8e)

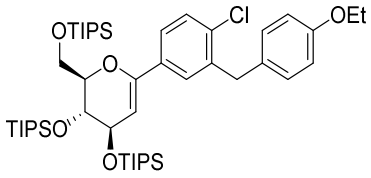


According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 30 min at -30°C for lithiation and employing 4,4,5,5-tetramethyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (31 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 93:7) furnished the title compound as a colorless oil (52 mg, 0.09 mmol, 89 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 6.09 – 6.06 (m, 1H), 4.77 (d, *J* = 2.4 Hz, 1H), 4.47 (dd, *J* = 7.0, 2.4 Hz, 1H), 4.20 (dd, *J* = 10.3, 5.0 Hz, 1H), 4.03 – 3.95 (m, 6H), 3.80 (td, *J* = 10.3, 5.0 Hz, 1H), 2.36 (d, *J* = 4.6 Hz, 4H), 1.30 – 1.24 (m, 2H), 1.14 – 1.08 (m, 21H), 1.05 (s, 9H), 0.98 (s, 9H). **Note**: ^{1}H-NMR shows trace of EtOAc. **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 150.82, 129.67, 122.80, 107.88, 101.11, 77.71, 72.69, 71.99, 66.29, 64.60, 35.75, 31.09, 27.59, 27.08, 24.15,

22.89, 20.00, 18.31, 18.28, 12.60. **HR-MS** (ESI): m/z calcd. for ($[C_{31}H_{56}O_6Si_2]^+$, $[H^+]$): 581.3695, found: 581.370.

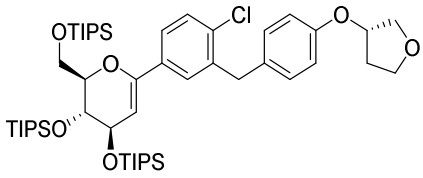
(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-6-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-8-((triisopropylsilyl)oxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (9a)



According to GP-B on a 0.5 mmol scale, using *t*BuLi (0.65 mmol, 1.3 equiv.,) and stirring for 60 min at -30°C for lithiation and employing 2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (214 mg, 0.575 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 999:1 to 93:7) furnished the title compound as a colorless oil (0.22 g, 0.26 mmol, 51 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.45 – 7.40 (m, 2H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.11 – 7.07 (m, 2H), 6.82 – 6.79 (m, 2H), 5.26 (dd, *J* = 5.3, 1.5 Hz, 1H), 4.43 (ddt, *J* = 7.9, 3.9, 1.9 Hz, 1H), 4.14 – 4.07 (m, 3H), 4.03 – 3.98 (m, 4H), 3.84 (dd, *J* = 11.3, 3.9 Hz, 1H), 1.40 (t, *J* = 7.0 Hz, 3H), 1.12 – 0.98 (m, 63H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 157.52, 149.48, 138.61, 135.12, 134.11, 131.48, 129.96, 129.22, 127.99, 124.65, 114.52, 97.17, 81.54, 70.11, 66.73, 63.47, 62.07, 38.66, 18.33, 18.26, 18.20, 18.14, 18.11, 15.04, 12.68, 12.56, 12.15. **HR-MS** (ESI): m/z calcd. for ($[C_{48}H_{83}ClO_5Si_3]^+$, $[H^+]$): 859.5317, found: 859.532.

(((2*R*,3*R*,4*R*)-2-(((l1-Silyl)oxy)methyl)-6-(4-chloro-3-(4-(((*S*)-tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-3,4-dihydro-2*H*-pyran-3,4-diyl)bis(oxy))bis(l1-silane) (9b)

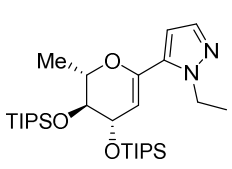


According to GP-B on a 0.5 mmol scale, using *t*BuLi (0.65 mmol, 1.3 equiv.,) and stirring for 60 min at -30°C for lithiation and employing (*S*)-2-(4-chloro-3-(4-((tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (238 mg, 0.575 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 92:8) furnished the title compound as a colorless oil (0.26 g, 0.29 mmol, 57 %).

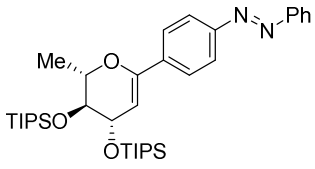
^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.47 (d, *J* = 2.2 Hz, 1H), 7.42 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.12 – 7.08 (m, 2H), 6.79 – 6.75 (m, 2H), 5.27 (dd, *J* = 5.4, 1.5 Hz, 1H), 4.88 (tt, *J* = 4.9, 2.2 Hz, 1H), 4.44 (ddt, *J* = 7.8, 3.9, 1.9 Hz, 1H), 4.16 – 4.11 (m, 2H), 4.11 – 4.07 (m, 2H), 4.03 (d, *J* = 4.9 Hz, 2H), 4.00 – 3.95 (m, 3H), 3.91 – 3.87 (m, 1H), 3.84 (dd, *J* = 11.3, 3.9 Hz, 1H), 2.20 – 2.12 (m, 2H), 1.08 – 0.99 (m, 63H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ =

155.96, 149.44, 138.43, 135.17, 134.11, 132.04, 130.04, 129.26, 128.04, 124.72, 115.40, 97.20, 81.56, 77.39, 73.32, 70.11, 67.34, 66.71, 62.06, 38.64, 33.18, 18.33, 18.27, 18.25, 18.20, 18.14, 18.11, 12.68, 12.55, 12.15. **HR-MS** (ESI): m/z calcd. for ($[C_{50}H_{85}ClO_6Si_3]^+$, $[H^+]$): 901.5422, found: 901.543.

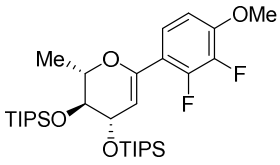
L-Rhamnal Series



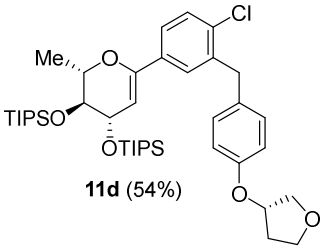
11a (68%)



11b (57%)

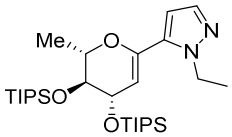


11c (53%)



11d (54%)

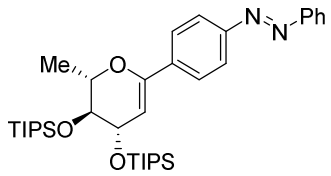
1-Ethyl-5-((2*S*,3*S*,4*S*)-2-methyl-3,4-bis((triisopropylsilyl)oxy)-3,4-dihydro-2*H*-pyran-6-yl)-1*H*-pyrazole (11a)



According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 30 min at -30°C for lithiation and employing 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (26 mg, 0.115 mmol, 1.15 equiv.). Preparative TLC purification (SiO_2 – hexane/ EtOAc 99:1 -> 97:3) afforded the title compound as a pale yellow oil (36 mg, 0.07 mmol, 68 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.40 (d, *J* = 1.9 Hz, 1H), 6.25 (d, *J* = 1.9 Hz, 1H), 5.19 (dd, *J* = 5.2, 1.5 Hz, 1H), 4.48 (qt, *J* = 7.0, 2.0 Hz, 1H), 4.35 – 4.23 (m, 2H), 4.18 (dt, *J* = 5.2, 2.0 Hz, 1H), 3.98 (q, *J* = 2.0 Hz, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.09 – 1.05 (m, 42H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 142.77, 138.11, 106.04, 101.69, 75.79, 72.69, 66.76, 46.00, 18.29, 18.24, 18.23, 18.19, 16.17, 15.96, 12.61, 12.59. **HR-MS** (ESI): m/z calcd. for ($[C_{29}H_{56}N_2O_3Si_2]^+$, $[H^+]$): 537.3909, found: 537.3909.

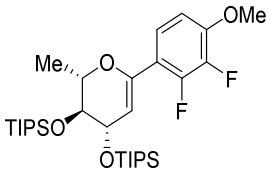
(*E*)-1-(4-((2*S*,3*S*,4*S*)-2-Methyl-3,4-bis((triisopropylsilyl)oxy)-3,4-dihydro-2*H*-pyran-6-yl)phenyl)-2-phenyldiazene (11b)



According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 30 min at -30°C for lithiation and employing (*E*)-1-phenyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)diazene (36 mg, 0.115 mmol, 1.15 equiv.). Preparative TLC purification (SiO_2 – hexane/ EtOAc 99:1) afforded the title compound as a pale red oil (35 mg, 0.06 mmol, 57 %).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.92 (td, *J* = 6.3, 1.8 Hz, 4H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.56 – 7.47 (m, 3H), 5.50 (d, *J* = 5.1 Hz, 1H), 4.53 (d, *J* = 7.3 Hz, 1H), 4.27 (d, *J* = 5.2 Hz, 1H), 4.05 – 3.99 (m, 1H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.14 – 1.05 (m, 42H). **Note**: ^{1}H-NMR shows trace of EtOAc. **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 152.92, 152.51, 149.14, 139.09, 131.05, 129.21, 125.99, 123.00, 122.86, 98.61, 75.49, 73.35, 67.61, 31.41, 18.36, 18.30, 18.28, 18.22, 16.19, 12.75, 12.71. **HR-MS** (ESI): m/z calcd. for ($[C_{36}H_{58}N_2O_3Si_2]^+$, $[H^+]$): 623.4066, found: 623.406.

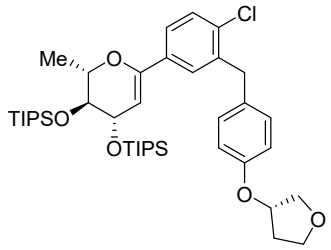
(((2*S*,3*S*,4*S*)-6-(2,3-Difluoro-4-methoxyphenyl)-2-methyl-3,4-dihydro-2*H*-pyran-3,4-diyl)bis(oxy))bis(triisopropylsilane) (11c)



According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 30 min at -30°C for lithiation and employing 2-(2,3-difluoro-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (31 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – hexane/ EtOAc 99:1 -> 93:7) afforded the title compound as a colorless oil (31 mg, 0.05 mmol, 53 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.29 – 7.26 (m, 1H), 6.71 (ddd, *J* = 9.2, 7.5, 1.9 Hz, 1H), 5.40 (d, *J* = 5.1 Hz, 1H), 4.45 (qt, *J* = 7.1, 2.1 Hz, 1H), 4.21 (dt, *J* = 4.9, 2.1 Hz, 1H), 3.99 – 3.96 (m, 1H), 3.90 (s, 3H), 1.45 (d, *J* = 7.1 Hz, 3H), 1.07 (dd, *J* = 9.1, 5.0 Hz, 42H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 144.32 (t, J = 3.1 Hz), 142.50, 122.29 (t, J = 4.0 Hz), 118.95 (d, J = 9.3 Hz), 107.66 (d, *J* = 3.4 Hz), 101.59 (d, *J* = 9.2 Hz), 100.52, 75.55, 73.24, 67.32, 56.75, 18.26 (t, *J* = 7.0 Hz), 16.08, 12.73, 12.63. **^{19}F-NMR:** (471 MHz, $CDCl_3$) δ = -138.46, -138.50, -160.26, -160.30. **HR-MS** (ESI): m/z calcd. for ($[C_{31}H_{54}F_2O_4Si_2]^+$, $[H^+]$): 585.3609, found: 585.3608.

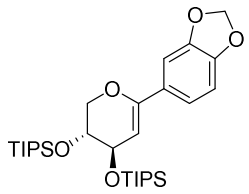
(((2*S*,3*S*,4*S*)-6-(4-chloro-3-(4-(((*S*)-tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-2-methyl-3,4-dihydro-2*H*-pyran-3,4-diyl)bis(oxy))bis(triisopropylsilane) (<u>11d</u>)



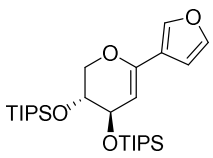
According to GP-B on a 1 mmol scale, using *t*BuLi (1.3 mmol, 1.3 equiv.) and stirring for 45 min at -30°C for lithiation and employing (*S*)-2-(4-chloro-3-(4-((tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.477 g, 1.15 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – hexane/ EtOAc 99:1 -> 9:1) afforded the title compound as a colorless oil (0.39 g, 0.54 mmol, 54 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.41 – 7.37 (m, 2H), 7.33 – 7.29 (m, 1H), 7.13 – 7.09 (m, 2H), 6.81 – 6.76 (m, 2H), 5.27 (dd, *J* = 5.2, 1.4 Hz, 1H), 4.89 (ddt, *J* = 6.6, 4.8, 2.3 Hz, 1H), 4.45 (qt, *J* = 7.0, 2.0 Hz, 1H), 4.20 (dt, *J* = 5.2, 2.1 Hz, 1H), 4.04 (d, *J* = 3.2 Hz, 2H), 4.01 – 3.94 (m, 4H), 3.89 (td, *J* = 8.2, 4.5 Hz, 1H), 2.20 – 2.12 (m, 2H), 1.41 (d, *J* = 7.1 Hz, 3H), 1.09 – 1.03 (m, 42H). **Note**: ^{1}H-NMR shows trace of EtOAc. **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 156.00, 148.91, 138.56, 135.38, 134.06, 131.99, 130.10, 129.36, 127.77, 124.57, 115.45, 97.46, 75.42, 73.31, 67.55, 67.35, 38.62, 33.17, 18.33, 18.27, 18.20, 16.19, 12.73, 12.68. **HR-MS** (ESI): m/z calcd. for ($[C_{41}H_{65}ClO_5Si_2]^+$, $[H^+]$): 729.4139, found: 729.413.

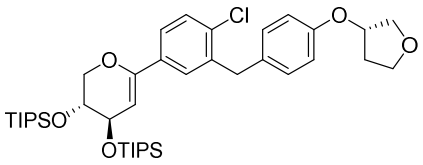
D-Xylal Series



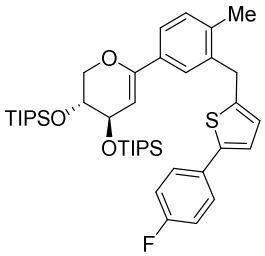
14a (52%)



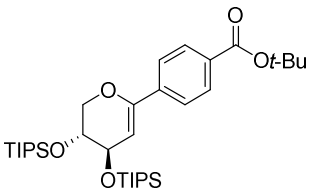
14b (42%)



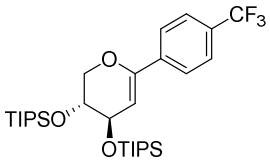
14c (49%)



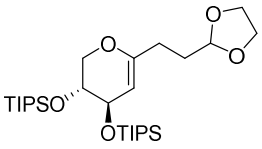
14d (53%)



14e (36%)

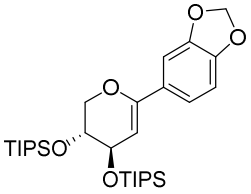


14f (48%)



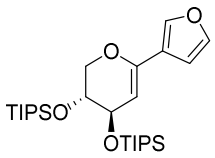
14g (53%)

(((3*R*,4*R*)-6-(Benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-2*H*-pyran-3,4-diyl)bis(oxy))bis(triisopropylsilane) (<u>14a</u>)



According to GP-B, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 60 min at -30°C for lithiation and employing 2-(benzo[*d*][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (29 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 999:1 to 98:2) furnished the title compound as a colorless oil (28 mg, 0.05 mmol, 52 %).
^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.10 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.05 (d, *J* = 1.8 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.95 (s, 2H), 5.22 (dd, *J* = 5.5, 1.5 Hz, 1H), 4.21 – 4.09 (m, 3H), 3.94 – 3.87 (m, 1H), 1.11 – 1.01 (m, 42H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 152.59, 147.79, 147.61, 130.65, 119.22, 108.06, 106.04, 101.19, 96.52, 69.34, 66.65, 65.80, 18.33, 18.26, 18.19, 18.14, 12.71, 12.60. **HR-MS** (ESI): m/z calcd. for ($[C_{30}H_{52}O_5Si_2]^+$, $[H^+]$): 549.3433, found: 549.342.

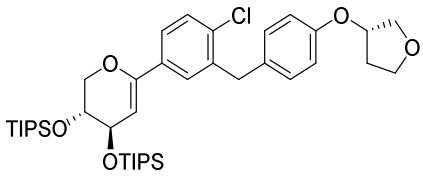
(((3*R*,4*R*)-6-(Furan-3-yl)-3,4-dihydro-2*H*-pyran-3,4-diyl)bis(oxy))bis(triisopropylsilane) (14b)



According to GP-B, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 60 min at -30°C for lithiation and employing 2-(furan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (22 mg, 0.115 mmol, 1.15 equiv.). Preparative TLC purification (SiO_2 – pentane/ EtOAc 99:1 -> 98:2) furnished the title compound as a colorless oil (21 mg, 0.04 mmol, 42 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 1.5 Hz, 1H), 7.34 (t, *J* = 1.8 Hz, 1H), 6.47 (d, *J* = 1.8 Hz, 1H), 5.10 (dd, *J* = 5.6, 1.5 Hz, 1H), 4.12 (q, *J* = 1.7 Hz, 1H), 4.09 (dd, *J* = 5.0, 2.5 Hz, 1H), 3.98 (d, *J* = 1.7 Hz, 1H), 3.90 (td, *J* = 2.5, 1.4 Hz, 1H), 1.05 (td, *J* = 8.3, 4.4 Hz, 42H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 143.01, 140.02, 107.76, 101.28, 97.05, 69.49, 66.33, 65.43, 18.31, 18.24, 18.17, 18.13, 12.68, 12.61. **HR-MS** (ESI): m/z calcd. for ($[C_{27}H_{50}O_4Si_2]^+$, $[H^+]$): 495.3328, found: 495.332.

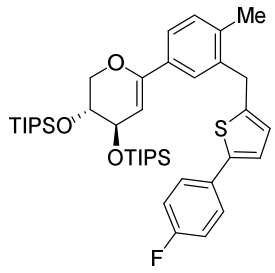
(((3*R*,4*R*)-6-(4-Chloro-3-(4-(((*S*)-tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-3,4-dihydro-2*H*-pyran-3,4-diyl)bis(oxy))bis(triisopropylsilane) (14c)



According to GP-B, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 60 min at -30°C for lithiation and employing (*S*)-2-(4-chloro-3-(4-((tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (48 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 93:7) furnished the title compound as a colorless oil (35 mg, 0.05 mmol, 49 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.41 – 7.35 (m, 2H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.81 – 6.76 (m, 2H), 5.28 (dd, *J* = 5.5, 1.5 Hz, 1H), 4.88 (dp, *J* = 6.7, 2.3 Hz, 1H), 4.19 – 4.09 (m, 3H), 4.03 (s, 2H), 4.00 – 3.95 (m, 3H), 3.92 – 3.88 (m, 2H), 2.19 – 2.12 (m, 2H), 1.08 – 1.03 (m, 42H). **Note**: ^{1}H-NMR shows trace of EtOAc. **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 155.99, 151.96, 138.62, 134.90, 134.11, 131.98, 130.10, 129.37, 127.71, 124.43, 115.45, 97.79, 73.30, 69.17, 67.34, 66.61, 65.55, 38.59, 33.17, 18.30, 18.22, 18.16, 18.11, 12.66, 12.58. **HR-MS** (ESI): m/z calcd. for ($[C_{40}H_{63}ClO_5Si_2]^+$, $[H^+]$): 715.3983, found: 715.398.

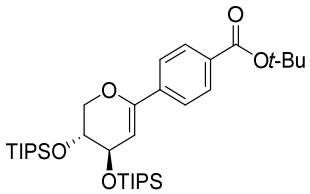
(((3*R*,4*R*)-6-(4-Chloro-3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)phenyl)-3,4-dihydro-2*H*-pyran-3,4-diyl)bis(oxy))bis(triisopropylsilane) (<u>14d</u>)



According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 60 min at -30°C for lithiation and employing 2-(4-chloro-3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (49 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 999:1 -> 95:5) furnished the title compound as a colorless oil (39 mg, 0.05 mmol, 53 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.51 – 7.45 (m, 3H), 7.41 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.05 – 6.99 (m, 3H), 6.67 (d, *J* = 3.5 Hz, 1H), 5.32 (dd, *J* = 5.5, 1.4 Hz, 1H), 4.20 – 4.12 (m, 5H), 3.96 – 3.91 (m, 1H), 2.31 (s, 3H), 1.10 – 1.04 (m, 42H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 163.18, 161.22, 152.77, 143.55, 141.60, 137.91, 136.65, 134.25, 131.07 (d, *J* = 3.3 Hz), 130.38, 127.23 (d, *J* = 7.8 Hz), 126.41, 126.10, 123.80, 122.78, 115.81 (d, *J* = 21.7 Hz), 96.96, 69.39, 66.60, 65.81, 34.37, 19.43, 18.33, 18.25, 18.20, 18.15, 12.70, 12.62. **^{19}F-NMR**: (471 MHz, $CDCl_3$) δ = -115.99. **HR-MS** (ESI): m/z calcd. for ($[C_{41}H_{61}FO_3SSi_2]^+$, $[H^+]$): 709.3944, found: 709.394.

***tert*-butyl 4-((3*R*,4*R*)-3,4-bis((triisopropylsilyl)oxy)-3,4-dihydro-2*H*-pyran-6-yl)benzoate (14e)**

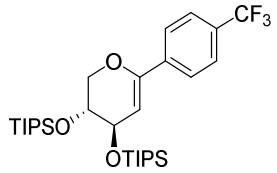


According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 60 min at -30°C for lithiation and employing *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (37 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 99:1 -> 93:7) furnished the title compound as a colorless oil (22 mg, 0.04 mmol, 36 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.97 – 7.92 (m, 2H), 7.67 – 7.58 (m, 2H), 5.47 (dd, *J* = 5.5, 1.5 Hz, 1H), 4.26 – 4.20 (m, 1H), 4.19 – 4.13 (m, 2H), 3.95 – 3.93 (m, 1H), 1.59 (s, 9H), 1.10 – 1.02 (m, 42H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 165.75, 152.08, 139.89, 131.72, 129.41,

124.86, 99.09, 81.06, 69.18, 66.65, 65.52, 28.36, 18.31, 18.23, 18.16, 18.11, 12.68, 12.59. **HR-MS** (ESI): m/z calcd. for ($[C_{34}H_{60}O_5Si_2]^+$, $[H^+]$): 605.4059, found: 605.405.

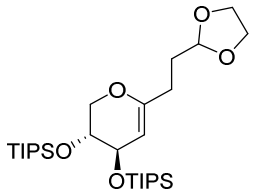
(((3*R*,4*R*)-6-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-pyran-3,4-diyl)bis(oxy))bis(triisopropylsilane) (14f)



According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 60 min at -30°C for lithiation and employing 4,4,5,5-tetramethyl-2-(4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (33 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 999:1 -> 98:2) furnished the title compound as a colorless oil (27 mg, 0.05 mmol, 48 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 5.46 (dd, *J* = 5.6, 1.5 Hz, 1H), 4.26 – 4.22 (m, 1H), 4.20 – 4.13 (m, 2H), 3.96 – 3.93 (m, 1H), 1.10 – 1.03 (m, 42H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 151.66, 139.49 (d, J = 1.1 Hz), 130.21 (q, J = 32.1 Hz), 125.40, 125.23 (q, *J* = 3.8 Hz), 99.18, 69.13, 66.71, 65.40, 18.30, 18.23, 18.16, 18.11, 12.67, 12.57. **^{19}F NMR:** (471 MHz, $CDCl_3$) δ = -62.57. **HR-MS** (ESI): m/z calcd. for ($[C_{30}H_{51}F_3O_3Si_2]^+$, $[H^+]$): 573.3409, found: 573.348.

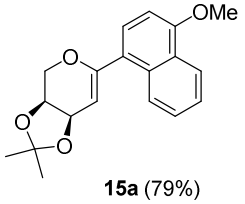
(((3*R*,4*R*)-6-(2-(1,3-Dioxolan-2-yl)ethyl)-3,4-dihydro-2H-pyran-3,4-diyl)bis(oxy))bis(triisopropylsilane) (14g)



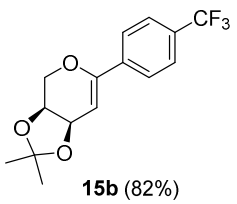
According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 60 min at -30°C for lithiation and employing 2-(2-(1,3-dioxolan-2-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **SI-12** (27 mg, 0.12 mmol, 1.2 equiv.). Purification of the crude mixture by preparative TLC (SiO_2 – hexane/ EtOAc 98:2) furnished the title compound as a colorless oil (28 mg, 0.05 mmol, 53 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 5.96 (dd, J = 9.9, 1.6 Hz, 1H), 5.82 (dd, J = 9.9, 2.7 Hz, 1H), 4.89 (t, J = 4.9 Hz, 1H), 4.62 (t, J = 7.4 Hz, 1H), 4.51 – 4.46 (m, 1H), 4.14 (dd, J = 9.9, 4.9 Hz, 1H), 3.99 – 3.96 (m, 2H), 3.86 – 3.84 (m, 2H), 3.71 – 3.60 (m, 2H), 2.57 – 2.49 (m, 2H), 1.08 – 1.05 (m, 42H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 149.68, 129.81, 124.40, 104.00, 103.42, 70.31, 65.12, 65.10, 63.70, 29.93, 18.11, 17.85, 12.44, 12.39. **HR-MS** (ESI): m/z calcd. for ($[C_{28}H_{56}O_5Si_2]^+$, $[H^+]$): 529.3746, found: 529.3744.

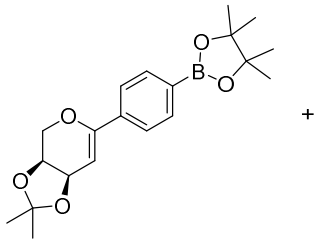
L-Arabinal Series



15a (79%)

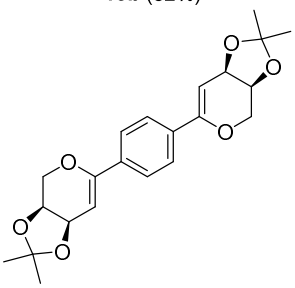


15b (82%)



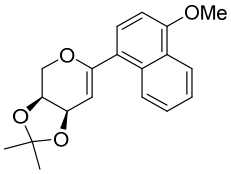
15c (51%)

+



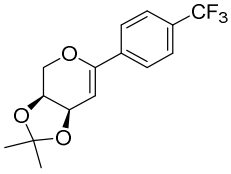
15d (36%)

(3a*S*,7a*R*)-6-(4-Methoxynaphthalen-1-yl)-2,2-dimethyl-3a,7a-dihydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran (15a)



According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 30 min at -30°C for lithiation and employing 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (33 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 8:2) furnished the title compound as a colorless oil (25 mg, 0.05 mmol, 79 %). **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 8.3 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.54 – 7.43 (m, 3H), 6.77 (d, *J* = 7.9 Hz, 1H), 5.32 (dd, *J* = 4.1, 1.7 Hz, 1H), 4.76 (t, *J* = 5.0 Hz, 1H), 4.41 – 4.35 (m, 1H), 4.28 (dd, *J* = 11.0, 4.1 Hz, 1H), 4.01 (s, 3H), 4.00 – 3.94 (m, 1H), 1.58 (s, 3H), 1.47 (s, 3H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 157.62, 156.51, 132.24, 127.43, 126.97, 126.23, 125.71, 125.57, 125.40, 122.31, 109.17, 102.99, 100.11, 70.68, 69.04, 66.10, 55.71, 28.70, 26.33. **HR-MS** (ESI): m/z calcd. for ($[C_{19}H_{20}O_4]^+$, $[H^+]$): 313.1442, found: 313.143.

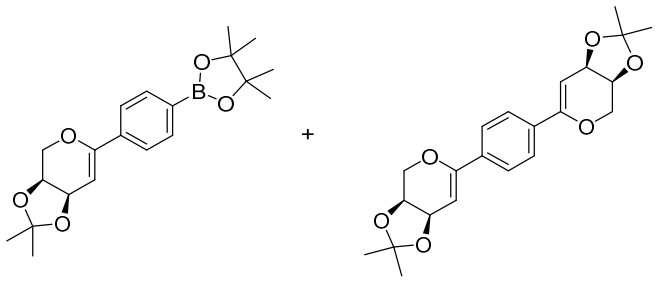
(3a*S*,7a*R*)-2,2-Dimethyl-6-(4-(trifluoromethyl)phenyl)-3a,7a-dihydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran (15b)



According to GP-B on a 0.1 mmol scale, using *t*BuLi (0.13 mmol, 1.3 equiv.) and stirring for 30 min at -30°C for lithiation and employing 4,4,5,5-tetramethyl-2-(4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (33 mg, 0.115 mmol, 1.15 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 8:2) furnished the title compound as a colorless oil (25 mg, 0.08 mmol, 82 %). **^{1}H-NMR:** (500 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 5.67 (d, *J* = 4.3 Hz, 1H), 4.72 (dd, *J* = 5.9, 4.3 Hz, 1H), 4.32 (ddd, *J* = 7.7, 5.9, 3.9 Hz, 1H), 4.23 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.90 (dd, *J* = 11.1, 7.7 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H). **Note**: ^{1}H-NMR shows trace of residual glycal. **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 154.19, 137.87 (q, *J* = 1.4 Hz), 125.59, 125.40 (q, *J* = 3.8 Hz, 109.49, 97.90, 70.64, 68.72, 66.25, 28.49, 26.27. **HR-MS** (ESI): m/z calcd. for ($[C_{15}H_{15}F_3O_3]^+$, $[H^+]$): 301.1053, found: 301.104.

2-(4-((3a*S*,7a*R*)-2,2-Dimethyl-3a,7a-dihydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (<u>15c</u>)

1,4-bis((3a*S*,7a*R*)-2,2-Dimethyl-3a,7a-dihydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)benzene (<u>15d</u>)

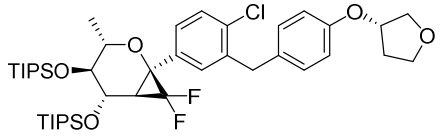


A B

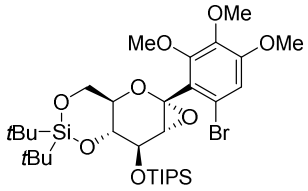
According to GP-B, using *t*BuLi (0.26 mmol, 1.3 equiv.) and stirring for 30 min at -30°C for lithiation and employing 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (33 mg, 0.10 mmol, 0.5 equiv.). Flash column chromatography (SiO_2 – pentane/ EtOAc 99:1 to 88:12) furnished the title compounds as colorless oils (**<u>15c</u>** = 18 mg, 0.05 mmol, 50 % | **<u>15d</u>** = 14 mg, 0.04 mmol, 36 %).

^{1}H NMR: <u>15c</u> (500 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 7.7 Hz, 2H), 7.60 (d, *J* = 7.7 Hz, 2H), 5.64 (d, *J* = 4.3 Hz, 1H), 4.70 (t, *J* = 5.1 Hz, 1H), 4.30 (dt, *J* = 9.4, 5.1 Hz, 1H), 4.22 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.84 (dd, *J* = 11.0, 8.2 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.34 (s, 12H). **^{13}C-NMR: <u>15c</u>** (126 MHz, $CDCl_3$) δ = 155.59, 136.97, 134.84, 124.53, 109.23, 96.58, 84.02, 70.68, 68.98, 66.17, 28.52, 26.27, 25.01. **^{1}H NMR: <u>15d</u>** (500 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 1.6 Hz, 4H), 5.61 (d, *J* = 4.2 Hz, 2H), 4.70 (t, *J* = 5.2 Hz, 2H), 4.33 – 4.27 (m, 2H), 4.22 (dd, *J* = 10.9, 4.0 Hz, 2H), 3.84 (dd, *J* = 10.9, 8.1 Hz, 2H), 1.48 (s, 6H), 1.43 (s, 6H). **^{13}C NMR: <u>15d</u>** (126 MHz, $CDCl_3$) δ = 155.16, 134.97, 125.22, 109.25, 96.29, 70.67, 68.95, 66.18, 28.52, 26.26. **HR-MS** (ESI): **<u>15c</u>** m/z calcd. for ($[C_{20}H_{28}BO_5]^+$, $[M^+]$): 359.2032, found: 359.203. **HR-MS** (ESI): **<u>15d</u>** m/z calcd. for ($[C_{22}H_{27}O_6]^+$, $[M^+]$): 387.1809, found: 387.181.

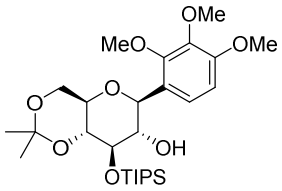
Derivatizations



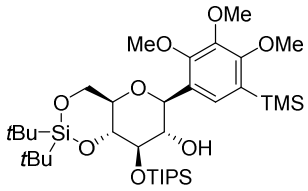
16 (82%)



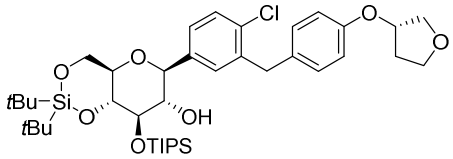
17 (62%)



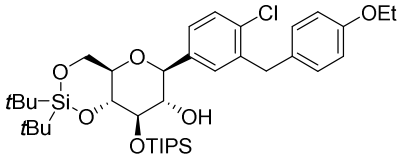
18 (31%)



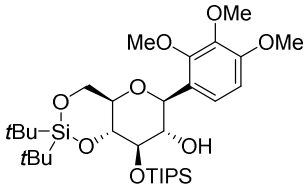
19a (32%)



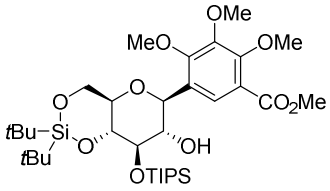
19b (39%)



19c (43%)

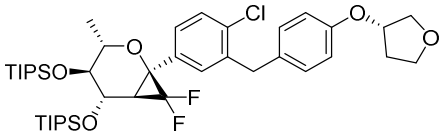


19d (61%)



19e (82%)

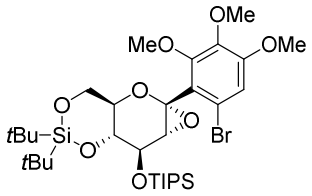
(((3*S*,4*S*,5*R*,6*R*)-1-(4-Chloro-3-(4-(((*S*)-tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-7,7-difluoro-3-methyl-2-oxabicyclo[4.1.0]heptane-4,5-diyl)bis(oxy))bis(triisopropylsilane) (<u>16</u>)



(((2*S*,3*S*,4*R*)-6-(4-Chloro-3-(4-(((*S*)-tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-2-methyl-3,4-dihydro-2H-pyran-3,4-diyl)bis(oxy))bis(triisopropylsilane) **<u>11d</u>** (73 mg, 0.1 mmol, 1.0 equiv.) was charged to an Ace pressure tube containing NaI (8 mg, 0.05 mmol, 0.5 equiv.) and dry THF (2 mL) was added. $TMSCF_3$ (37 µL, 0.25 mmol, 2.5 equiv.) was added in one portion and the vial was sealed. The reaction mixture was heated to 65 °C for 6 h, the solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; pentane/ EtOAc: 999:1 to 92:8) to obtain the title compound as a colorless oil (64 mg, 0.08 mmol, 82 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.34 (d, *J* = 8.3 Hz, 1H), 7.26 (m, 1H), 7.21 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.10 – 7.07 (m, 2H), 6.79 – 6.76 (m, 2H), 4.89 (ddt, *J* = 6.4, 4.6, 2.3 Hz, 1H), 4.29 (s, 1H), 4.10 (q, *J* = 7.2 Hz, 1H), 4.04 (s, 2H), 4.01 – 3.94 (m, 3H), 3.92 – 3.86 (m, 1H), 3.62 (t, *J* = 1.8 Hz, 1H), 2.22 – 2.10 (m, 3H), 1.15 – 1.01 (m, 45H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 155.87, 138.56, 135.70 (d, J = 1.8 Hz), 133.29, 131.72, 129.91, 129.25, 128.73, 125.21, 73.83 (d, J = 2.4 Hz), 73.17, 72.75 (d, J = 1.7 Hz), 67.21, 64.96, 38.53, 33.03, 18.13, 18.03, 16.67, 12.58, 12.28. **^{19}F NMR**: (471 MHz, $CDCl_3$) δ = -132.80, -133.13, -144.02, -144.35. **HR-MS** (ESI): m/z calcd. for ($[C_{42}H_{65}ClF_2O_5Si_2]^+$, $[H^+]$): 779.4107, found: 779.411.

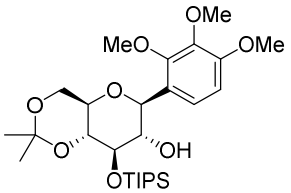
(4a*R*,5a*S*,6a*R*,7*R*,7a*R*)-5a-(6-Bromo-2,3,4-trimethoxyphenyl)-2,2-di-*tert*-butyl-7-((triisopropylsilyl)oxy)hexahydrooxireno[2',3':5,6]pyrano[3,2-*d*][1,3,2]dioxasiline (<u>17</u>)



Compound **<u>8c</u>** (0.2 mmol, 1.0 equiv.) was dissolved in dry DCM (5 mL), and the solution was cooled to -78°C. A freshly prepared solution of DMDO in acetone (2 mmol, 10 equiv.) was added dropwise and the reaction was allowed to stir for 1h at the aforementioned temperature. The cooling bath was removed and the reaction mixture was allowed to warm to rt. for 1h. After that, the solvents were removed *in vacuo*, and the crude product was purified *via* flash column chromatography (SiO_2; pentane/ EtOAc: 98:2 -> 85:15) to obtain the title compound as a colorless oil, which solidified in the fridge (88 mg, 0.12 mmol, 62 %)

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 6.89 (s, 1H), 4.79 (d, *J* = 2.2 Hz, 1H), 4.58 (dd, *J* = 6.8, 2.2 Hz, 1H), 4.21 – 4.10 (m, 2H), 4.05 – 4.00 (m, 2H), 3.88 – 3.83 (m, 9H), 1.13 – 1.07 (m, 30H), 1.02 (s, 9H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 154.42, 153.30, 147.91, 141.95, 124.36, 118.04, 112.02, 107.70, 77.92, 73.54, 71.90, 66.16, 62.08, 61.04, 56.41, 27.65, 27.15, 22.92, 20.03, 18.30, 12.61. **HR-MS** (ESI): m/z calcd. for ($[C_{32}H_{56}BrO_8Si_2]^+$, $[H^+]$): 703.2699, found: 703.269.

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Dimethyl-8-((triisopropylsilyl)oxy)-6-(2,3,4-trimethoxyphenyl)hexahydropyrano[3,2-*d*][1,3]dioxin-7-ol (<u>18</u>)

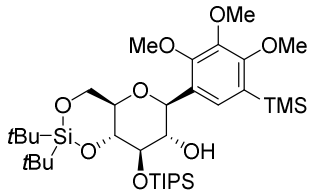


Compound **<u>7c</u>** (0.35 g, 0.66 mmol, 1.0 equiv.) was suspended in dry THF (10 mL) and cooled to 0°C. Borane THF complex (6.6 mmol, 10 equiv.) was added dropwise at 0°C and the reaction mixture was allowed to stir for 22 h at rt. Following this, the reaction mixture was

cooled to 0°C and a 1:1 mixture of H_2O_2 (30 %, 5 mL) and 2 M NaOH (5 mL) was added carefully dropwise and the ice-bath was removed. After stirring at ambient temperature for 4 h, sat. aq. NH_4Cl (20 mL) was added and the reaction mixture was transferred to a separatory funnel. H_2O (40 mL) was added and the aq. fraction was extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with Brine, dried over anhydr. $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane/ EtOAc: 9:1 -> 8:2) yielded the title compound as a colorless amorphous solid (0.11 g, 0.2 mmol, 31 %).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.10 (d, *J* = 8.6 Hz, 1H), 6.73 (d, *J* = 8.6 Hz, 1H), 4.67 (d, *J* = 9.7 Hz, 1H), 3.93 – 3.84 (m, 11H), 3.74 (t, *J* = 10.5 Hz, 1H), 3.70 – 3.66 (m, 1H), 3.63 (t, *J* = 9.3 Hz, 1H), 3.47 – 3.42 (m, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.21 – 1.14 (m, 3H), 1.09 (t, *J* = 7.5 Hz, 18H). **Note**: ^{1}H-NMR shows trace of DCM. **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 153.92, 152.61, 142.31, 124.75, 122.31, 108.09, 99.42, 77.71, 76.49, 76.17, 74.35, 72.48, 62.57, 61.80, 60.93, 56.18, 29.19, 18.99, 18.41, 18.34, 12.73. **HR-MS** (ESI): m/z calcd. for ($[C_{27}H_{46}O_8Si]^+$, $[Na^+]$): 549.2859, found: 549.286.

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-8-((triisopropylsilyl)oxy)-6-(2,3,4-trimethoxy-5-(trimethylsilyl)phenyl)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (<u>19a</u>)

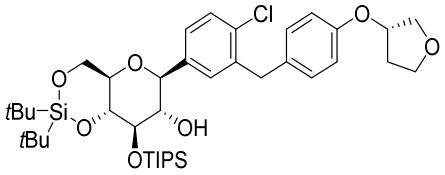


According to GP-B on a 0.9 mmol scale, using *t*BuLi (0.99 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing trimethyl(2,3,4-trimethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)silane (0.38 g, 1.0 mmol, 1.15 equiv.). After extraction, the crude glycal was dried under high vacuum and directly submitted to hydroboration - oxidation. Dry THF (10 mL) was added, and borane THF complex (5 mmol, 5 equiv.) was added dropwise at 0°C and the reaction mixture was allowed to stir at rt. for 24 h. Following this, the reaction mixture was cooled to 0°C and a 1:1 mixture of H_2O_2 (30 %, 5 mL) and 2 M NaOH (5 mL) was added carefully dropwise and the ice-bath was removed. After stirring at ambient temperature for 2 h, sat. aq. NH_4Cl (30 mL) was added and the reaction mixture was transferred to a seperatory funnel. H_2O (50 mL) was added and the aq. fraction was extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with Brine, dried over anhydr. $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane/ EtOAc: 98:2 -> 9:1) yielded the title compound as a colorless oil (0.2 g, 0.29 mmol, 32 % overall yield).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.04 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 4.61 (d, *J* = 9.7 Hz, 1H), 4.17 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.91 (s, 3H), 3.89 – 3.85 (m, 8H), 3.65 (t, *J* = 9.0 Hz, 1H), 3.56 (td, *J* = 9.7, 4.9 Hz, 1H), 1.29 – 1.23 (m, 3H), 1.13 (t, *J* = 6.9 Hz, 18H), 1.08 (s,

9H), 1.03 (s, 9H), 0.26 (s, 9H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 158.79, 155.32, 154.16, 145.27, 129.37, 128.87, 127.77, 126.77, 107.36, 80.40, 78.30, 75.72, 75.70, 66.83, 61.73, 60.72, 60.63, 60.56, 60.46, 56.08, 27.70, 27.19, 22.93, 20.14, 18.67, 18.55, 13.14, -0.34, -0.36. **HR-MS** (ESI): m/z calcd. for ($[C_{35}H_{66}O_8Si_3]^+$, $[H^+]$): 699.4145, found: 699.414.

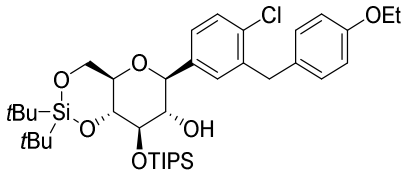
(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-(4-chloro-3-(4-(((*S*)-tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-8-((triisopropylsilyl)oxy)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (<u>19b</u>)



According to GP-B on a 0.2 mmol scale, using *t*BuLi (0.22 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing (*S*)-2-(4-chloro-3-(4-((tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (95 mg, 0.23 mmol, 1.15 equiv.). After extraction, the crude glycal was dried under high vacuum and directly submitted to hydroboration - oxidation. Dry THF (2 mL) was added, and borane THF complex (1 mmol, 5 equiv.) was added dropwise at 0°C and the reaction mixture was allowed to stir at rt. for 24 h. Following this, the reaction mixture was cooled to 0°C and a 1:1 mixture of H_2O_2 (30 %, 1 mL) and 2 M NaOH (1 mL) was added carefully dropwise and the ice-bath was removed. After stirring at ambient temperature for 1 h, sat. aq. NH_4Cl (10 mL) was added and the reaction mixture was transferred to a seperatory funnel. H_2O (20 mL) was added and the aq. fraction was extracted with EtOAc (3 × 20 mL). The combined organic fractions were washed with Brine, dried over anhydr. $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane/ EtOAc: 9:1 -> 8:2) yielded the title compound as a colorless amorphous solid (58 mg, 0.08 mmol, 39 % overall yield).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.37 (d, *J* = 8.1 Hz, 1H), 7.22 – 7.18 (m, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.88 (dp, *J* = 6.6, 2.2 Hz, 1H), 4.20 – 4.14 (m, 2H), 4.11 – 4.06 (m, 1H), 4.01 – 3.94 (m, 4H), 3.91 – 3.80 (m, 4H), 3.53 (td, *J* = 9.7, 4.9 Hz, 1H), 3.43 (t, *J* = 8.8 Hz, 1H), 2.21 – 2.10 (m, 2H), 1.26 – 1.21 (m, 3H), 1.12 (t, *J* = 7.4 Hz, 18H), 1.08 (s, 9H), 1.01 (s, 9H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 155.99, 139.05, 137.58, 134.36, 131.87, 130.36, 130.08, 129.85, 126.49, 115.49, 81.52, 79.92, 78.13, 76.62, 75.45, 73.26, 67.32, 66.67, 38.54, 33.14, 27.63, 27.13, 22.91, 20.10, 18.62, 18.50, 13.13. **HR-MS** (ESI): m/z calcd. for ($[C_{40}H_{63}ClO_7Si_2]^+$, $[H^+]$): 747.3881, found: 747.389.

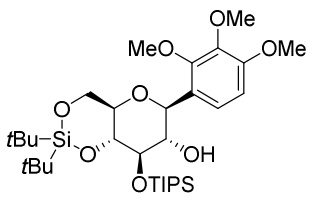
(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-8-((triisopropylsilyl)oxy)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (19c)



According to GP-B on a 0.2 mmol scale, using *t*BuLi (0.22 mmol, 1.1 equiv.) and stirring for 60 min at -30°C for lithiation and employing 2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (86 mg, 0.23 mmol, 1.15 equiv.). After extraction, the crude glycal was dried under high vacuum and directly submitted to hydroboration - oxidation. Dry THF (2 mL) was added, and borane THF complex (1 mmol, 5 equiv.) was added dropwise at 0°C and the reaction mixture was allowed to stir for 16 h at rt. Following this, the reaction mixture was cooled to 0°C and a 1:1 mixture of H_2O_2 (30 %, 1 mL) and 2 M NaOH (1 mL) was added carefully dropwise and the ice-bath was removed. After stirring at ambient temperature for 1 h, sat. aq. NH_4Cl (10 mL) was added and the reaction mixture was transferred to a seperatory funnel. H_2O (20 mL) was added and the aq. fraction was extracted with EtOAc (3 × 20 mL). The combined organic fractions were washed with Brine, dried over anhydr. $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane/ EtOAc: 96:4 -> 88:12) yielded the title compound as a colorless amorphous solid (61 mg, 0.09 mmol, 43 % overall yield).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 8.0 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 4.16 (dd, *J* = 9.7, 6.8 Hz, 2H), 4.08 (d, *J* = 15.4 Hz, 1H), 4.03 – 3.96 (m, 3H), 3.91 – 3.79 (m, 3H), 3.52 (td, *J* = 9.7, 4.8 Hz, 1H), 3.46 – 3.39 (m, 1H), 1.40 (t, *J* = 7.0 Hz, 3H), 1.23 (dt, *J* = 15.0, 7.8 Hz, 3H), 1.12 (t, *J* = 7.4 Hz, 18H), 1.07 (s, 9H), 1.01 (s, 9H). **^{13}C-NMR:** (126 MHz, $CDCl_3$) δ = 157.56, 139.24, 137.51, 134.39, 131.36, 130.37, 130.00, 129.83, 126.42, 114.60, 81.55, 79.94, 78.14, 76.60, 75.46, 66.68, 63.54, 38.56, 27.64, 27.14, 22.92, 20.12, 18.63, 18.50, 15.02, 13.13. **HR-MS** (ESI): m/z calcd. for ($[C_{38}H_{61}ClO_6Si_2]^+$, $[H^+]$): 705.3775, found: 705.377.

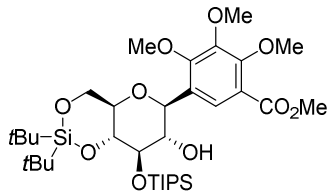
(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-8-((triisopropylsilyl)oxy)-6-(2,3,4-trimethoxyphenyl)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (19d)



Zweifel Protocol according to GP-B on a 1.6 mmol scale, using *t*BuLi (2.1 mmol, 1.3 equiv.) and stirring for 60 min at -30°C for lithiation and employing 4,4,5,5-tetramethyl-2-(2,3,4-trimethoxyphenyl)-1,3,2-dioxaborolane (0.54 g, 1.8 mmol, 1.15 equiv.). After extraction, the crude glycal was dried under high vacuum and directly submitted to hydroboration - oxidation. Dry THF (15 mL) was added, and borane THF complex (8 mmol, 5 equiv.) was added dropwise at 0°C and the reaction mixture was allowed to stir at ambient temperature for 24 h. Following this, the reaction mixture was cooled to 0°C and a 1:1 mixture of H_2O_2 (30 %, 5 mL) and 2 M NaOH (5 mL) was added carefully dropwise and the ice-bath was removed. After stirring at ambient temperature for 5 h, sat. aq. NH_4Cl (30 mL) was added and the reaction mixture was transferred to a seperatory funnel. H_2O (50 mL) was added and the aq. fraction was extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with Brine, dried over anhydr. $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (SiO_2; pentane/ EtOAc: 95:5 -> 8:2) yielded the title compound as a colorless amorphous solid (0.61 g, 0.98 mmol, 61 % overall yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.07 (d, *J* = 8.7 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 4.63 (d, *J* = 9.7 Hz, 1H), 4.16 (dd, *J* = 10.1, 5.0 Hz, 1H), 3.92 (s, 3H), 3.86 (d, *J* = 10.1 Hz, 9H), 3.64 – 3.53 (m, 2H), 1.24 (p, *J* = 7.4 Hz, 3H), 1.12 (t, *J* = 6.8 Hz, 18H), 1.07 (s, 9H), 1.02 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 153.92, 152.58, 142.28, 124.73, 122.25, 108.15, 80.36, 78.37, 76.03, 75.70, 75.57, 66.84, 61.85, 60.93, 56.18, 27.67, 27.19, 22.95, 20.13, 18.66, 18.53, 13.15. **HR-MS** (ESI): m/z calcd. for ($[C_{32}H_{59}O_8Si_2]^+$, $[H^+]$): 627.3750, found: 627.375.

Methyl 5-((4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-di-*tert*-butyl-7-hydroxy-8-((triisopropylsilyl)oxy)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-6-yl)-2,3,4-trimethoxybenzoate (19e)



Compound **19d** (0.53 g, 0.85 mmol, 1.0 equiv.) was charged to a flame dried flask and dissolved in dry THF (8 mL). A freshly prepared solution of TMPLi (1.8 mmol, 2.1 equiv.) in THF (2 mL) was added dropwise to the mixture at -40 °C, and the solution was allowed to stir at that temperature for 1h. Methyl chloroformate (0.2 mL, 2.5 mmol, 3.0 equiv.) was added dropwise and the mixture stirred at -78°C for 1h, before warming to ambient temperature and stirring at this temperature for 30 min. The reaction was quenched by addition of sat. aq. NH_4Cl (3 mL) and the mixture was transferred to a seperatory funnel. Water (50 mL) and EtOAc (50 mL) was added and the mixture was extracted twice more with EtOAc (50 mL). The combined organic fractions were washed with Brine (50 mL), dried over anhydr. $MgSO_4$ and

concentrated. Flash column chromatography (SiO_2; pentane – EtOAc | 95:5 -> 8:2) afforded the title compound as a bright yellow solid (0.47 g, 0.69 mmol, 82 %).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.10 (d, *J* = 8.7 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 1H), 4.88 (t, *J* = 9.4 Hz, 1H), 4.71 (d, *J* = 10.0 Hz, 1H), 4.17 (dd, *J* = 10.0, 4.9 Hz, 1H), 4.01 (t, *J* = 8.6 Hz, 1H), 3.93 (d, *J* = 9.0 Hz, 1H), 3.88 (s, 3H), 3.83 (d, *J* = 6.6 Hz, 6H), 3.55 (td, *J* = 10.0, 4.9 Hz, 1H), 3.51 (s, 3H), 1.18 – 1.13 (m, 3H), 1.12 – 1.06 (m, 27H), 1.02 (s, 9H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ = 154.75, 153.99, 152.58, 141.84, 123.41, 122.76, 107.70, 79.31, 78.65, 75.52, 66.68, 61.72, 60.81, 56.05, 54.71, 27.65, 27.16, 22.96, 20.13, 18.54, 18.41, 13.34. **HR-MS** (ESI): m/z calcd. for ($[C_{34}H_{61}O_{10}Si_2]^+$, $[H^+]$): 685.3805, found: 685.381.

5. Representative NMR-Spectra

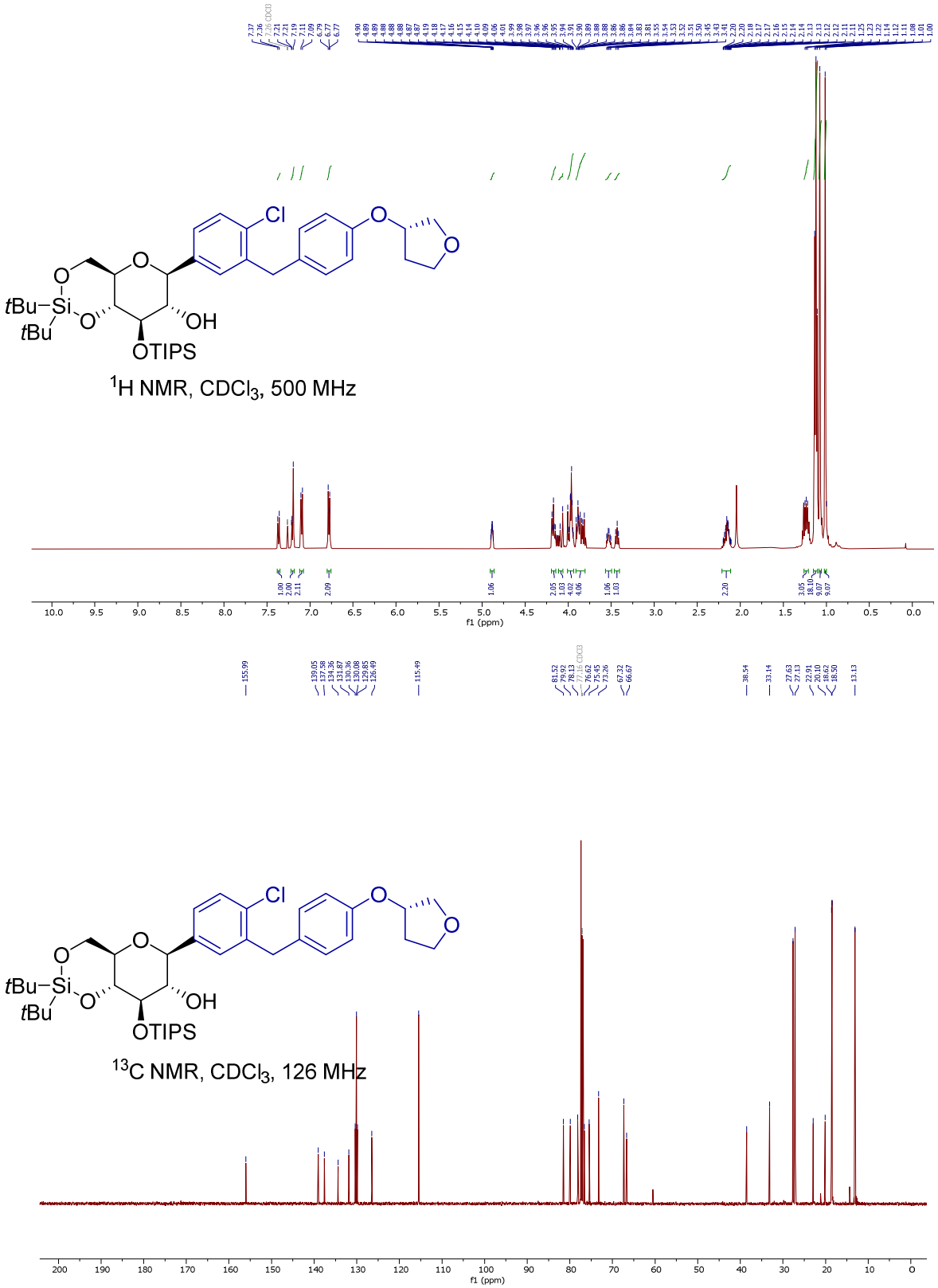


Figure 26: ^{1}H NMR and ^{13}C NMR for (4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-6-(4-chloro-3-(4-(((*S*)-tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-8-((triisopropylsilyl)oxy)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (19b)

4. Diethylzinc-Amylates – Selective Halogen-Zinc Exchange reagents at Room-Temperature

Florian Trauner, Bilel Boutet, Flavie Rambaud, Van Nhi Ngo and Dorian Didier

1. General Information

All reactions were carried out under dry argon or nitrogen atmosphere with anhydrous solvents in flame-dried glassware, unless otherwise stated. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with nitrogen or argon three times prior to use. THF (stabilized) was purchased in 99.5 % purity from Acros Organics. Lithium amylate and diethylzinc (both as solution in heptanes) were obtained from Sigma-Aldrich. Grignard reagents were prepared in THF, the magnesium was activated by addition of 1,2-dibromoethane and subsequent heating to reflux. Zinc insertion was performed in THF, zinc powder was activated with 1,2-dibromoethane and TMSCl and subsequent heating to reflux. Organolithiums (*n*BuLi, *s*BuLi, *t*BuLi,) were purchased from Sigma-Aldrich and the concentration was determined by titration against *i*PrOH using 1,10-phenantroline as indicator. Titration of Grignard reagents was performed with benzoic acid in THF at 0°C, using 4-phenylazodiphenylamin as indicator. Zinc–species were titrated against iodine in THF at 0°C.

Reaction endpoints were determined by GC monitoring of the reactions with *n*-dodecane/ *n*-decane as internal standard.

Gas chromatography was performed with machines of Agilent Technologies 7890, using a column of type HP 5 (Agilent 5 % phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm) or Hewlett-Packard 6890 or 5890 series II, using a column of type HP 5 (Hewlett-Packard, 5 % phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm).

Chromatographic purifications were performed using silica gel (SiO_2, 0.040-0.063 mm, 230-400 mesh ASTM) from Merck. The spots were visualized under UV (254 nm) or by staining the TLC plate with $KMnO_4$ solution (K_2CO_3, 10 g – $KMnO_4$, 1.5 g – H_2O, 150 mL – NaOH 10 % in H_2O, 1.25 mL). Yields refer to isolated yields of compounds estimated to be >95 % pure as determined by ^{1}H-NMR and GC-analysis.

The ^{13}C and ^{1}H-NMR spectra were recorded on Bruker DRX 500, ARX 300 and AC 300 spectrometer. Chemical shifts are reported as δ values in ppm relative to the residual solvent peak (^{1}H-NMR, ^{13}C-NMR) in deuterated chloroform ($CDCl_3$: δ 7.26 ppm for ^{1}H-NMR and δ 77.16 ppm for ^{13}C-NMR) or deuterated DMSO (DMSO-d_6: δ 2.50 ppm for ^{1}H-NMR and δ 39.52 ppm for ^{13}C-NMR). Abbreviations for signal coupling are as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintuplet), m (multiplet) and br (broad).

High resolution mass spectra (HRMS) were recorded on a Bruker Impact II (ESI) or GC Orbitrap Exploris (Thermo Fisher, EI/CI). Reagents, whose preparation is not described were obtained from commercial sources.

2. Optimization Experiments:

2.1 Selection of Exchange Reagent

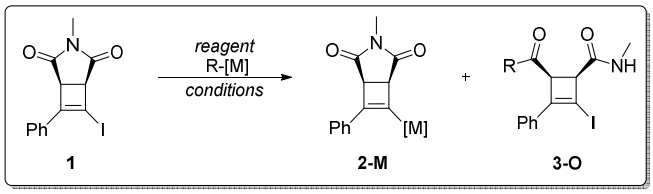
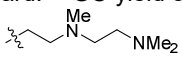


Table 16: Selection of exchange reagent

Entry	Exchange reagent	Equiv.	T [°C]	Solvent	Yield [%][a]
1	*n*BuLi	1.3	-78°C	THF	-
2	*t*BuLi	1.3	-78°C	THF	-
3	*i*PrMgCl·LiCl	1.3	-20°C	THF	Trace
4	*i*PrMgCl·LiCl	1.3	-50°C	THF	Trace
5[48]	nBu_4ZnLi_2	1.2	-40°C	THF	-
6[48]	nBu_4ZnLi_2	1.2	-78°C	THF	-
7[50]	$sBu_2Zn{\cdot}2LiOR^1$ [e]	0.7	0°C	toluene	97[b]|64[c]|44[d]
8[50]	$sBu_2Zn{\cdot}2LiOR^1$ [e]	0.7	0°C	THF	98[b]|53[c]|37[d]
9[50]	$sBu_2Zn{\cdot}2LiOR^1$ [e]	0.7	0°C	DMF	94[b]|67[c]|45[d]
10	$Et_2Zn{\cdot}LiOAmyl$	0.8	rt	toluene	13[b]|16[c]|25[d]|64%[f]
11	$Et_2Zn{\cdot}LiOAmyl$	0.8	rt	THF	97% |95%[f]

[a] Yields were determined by GC-Analysis of NH_4Cl (aq.) quenched aliquots with *n*-dodecane as internal standard. [b] GC-yield of **2-M** after 5 min. [c] GC-yield of **2-M** after 10 min. [d] GC-yield of **2-M** after 15 min. [e] R^1 =  [f] GC-yield of **2-M** after 14 h (sealed Schlenk-flask).

- Using $sBu_2Zn{\cdot}2LiOR^1$ (0.7 equiv.) full consumption of **1** is observed.[50] Interestingly, the zinc-species usually precipitates after 10-15 min. This corresponds with GC-analyses, showing rapid degradation of the organozinc derivative (Entry 7: over 50 % degradation after 15 min.). Lower temperatures and variation of solvent did not solve this issue (Entry 8 and 9).
- Employing more sterically hindered LiOAmyl (lithium *tert*-amoxide), with easily accessible Et_2Zn, no significant degradation of **2-M** is observed, even after 14 h at ambient temperature (Entry 11).

#

2.1 Selection of Exchange Reagent – Electrophile trapping

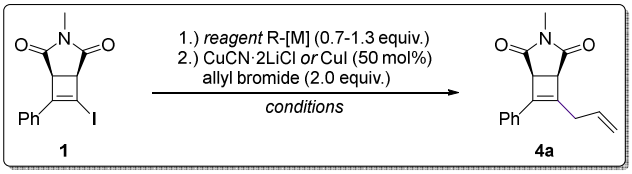
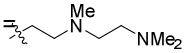


Table 17: Electrophile trapping

Entry	Reagent R-[M]/ $M^{(0)}$	Equiv.	Met. Time [min]	T [°C]	Yield [%]
1	*n*BuLi	1.3	30	-78°C	-
2	*t*BuLi	1.3	30	-78°C	-
3	*i*PrMgCl · LiCl	1.3	30	-20°C	trace [d]
4	*i*PrMgCl · LiCl	1.3	30	-50°C	trace [d]
5[a]	$Zn^{(0)}$	1.5	overnight		<5 % [e]
6[219]	$Zn^{(0)}$ $Fe(acac)_3$ NMP Et_2Zn		overnight		-
7[48][b]	nBu_4ZnLi_2	1.2	30		-
8[50]	$sBu_2Zn{\cdot}2LiOR^1$ [c]	0.7	15	rt	18 %[e]
9	Et_2Zn ·2LiOAmyl	0.8	15	rt	19 %[e]
10	Et_2Zn · LiOAmyl	0.8	15	rt	71 %[e]

[a] Zn dust (1.5 equiv.), LiCl (1.0 equiv.), dibromoethane (3 mol%), TMSCl (2 mol%), THF, 60°C, overnight. [b] *n*BuLi (4.0 equiv.) $ZnCl_2$ (1.0 equiv.), THF, -78°C to rt., 2 h. [c] R^1 =  [d] Yields were determined by GC-Analysis of NH_4Cl (aq.) quenched aliquots with *n*-dodecane as internal standard. [e] Yields refer to isolated compounds after flash column chromatography.

- Employing 0.7 equiv of $sBu_2Zn \cdot 2LiOR^1$ as exchange reagent, full consumption of SM is observed. Typically, after around 10-15 min, precipitation of the zinc species is observed and a maximum yield of 18 % of allylation product **4a** was obtained (Entry 8).
- Employing $Et_2Zn \cdot$ LiOAmyl, full consumption of **1** was also observed, and the yield has been increased to 71 % of the allylated product **4a** (Entry 10).

[219] A. S. Sunagatullina, F. H. Lutter, K. Karaghiosoff, P. Knochel *Adv. Synth. Catal.* **2022**, *364*, 4049 – 4053

2.2 Deviation from Standard Conditions: $Et_2Zn{\cdot}2LiOAmyl$

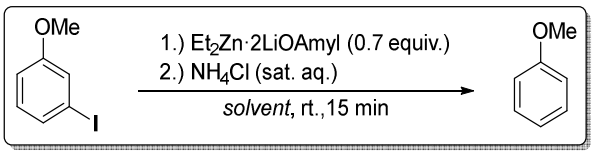


Table 18: Deviation of standard conditions: $Et_2Zn{\cdot}LiOAmyl$.

Entry	Deviation	Conc. [M]	GC yield [%][a]
1	none	0.2	96 %
2	$Et_2Zn{\cdot}LiOAmyl$ (0.7 equiv.)	0.2	60 %
3	2-methylTHF instead of THF	0.2	19 %
4	toluene instead of THF	0.2	-
5	Et_2O instead of THF	0.2	-
6	neat	≈ 0.55	-
7[b]	Base premixed with 2 equiv. THF then neat	≈ 0.5	35 %
8[b]	Base premixed with 4 equiv. THF then neat	≈ 0.45	80 %

[a] Yields were determined by GC-Analysis of NH_4Cl (aq.) quenched aliquots with *n*-decane as internal standard. [b] Premixing of the exchange reagent with THF leads to reduced storage stability.

2.3 Negishi Cross-coupling $Et_2Zn{\cdot}LiOAmyl$

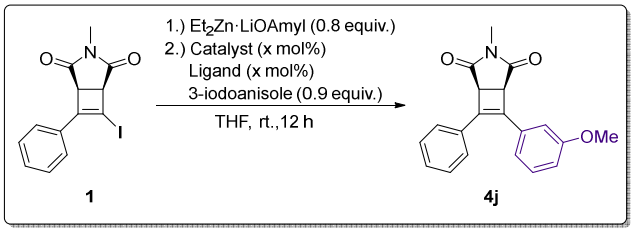


Table 19: Negishi coupling $Et_2Zn{\cdot}LiOAmyl$.

Entry	Catalyst	Ligand	Yield [%][a]
1	$Pd(dppf)Cl_2$ 2 mol%	-	62
2	Peppsi-*i*pent 2 mol%	-	57
3	$Pd(OAc)_2$ 1 mol%	SPhos 2 mol%	78

[a] Yields refer to isolated compounds after flash column chromatography.

2.4 Deviation from Standard Conditions - Negishi Cross-coupling $Et_2Zn \cdot 2LiOAmyl$

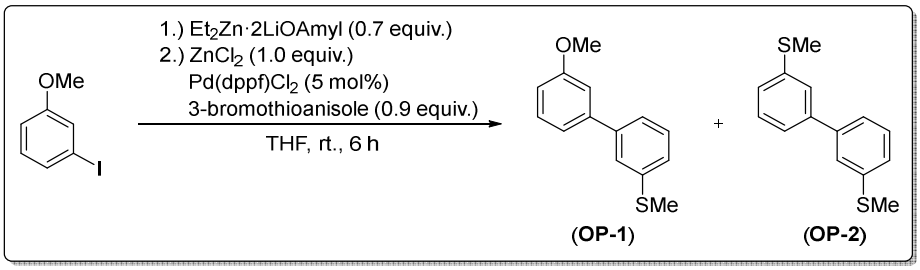


Table 20: Deviation from standard conditions – Negishi coupling $Et_2Zn \cdot 2LiOAmyl$

Entry[a]	Deviation	OP-1 [%]	OP-2 [%]
1	none	71	5
2	$Pd(OAc)_2$ (2 mol%), SPhos (5 mol%)[b]	9	0
3	$MgBr_2$ instead of $ZnCl_2$	54	8
4	no additive	47	4
5	1:1 toluene THF	12	3

[a] Yields were determined by GC-Analysis of NH_4Cl (aq.) quenched aliquots with *n*-dodecane as internal standard. [b] $Pd(OAc)_2$ and SPhos were used instead of $Pd(dppf)Cl_2$ and $ZnCl_2$.

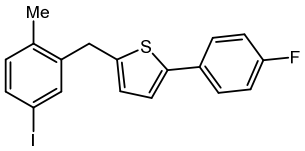
Observations:

As extensively studied by Salas *et al*. and Organ and coworkers[220], many different factors need to be considered in order to increase the yield of the Negishi cross-coupling reaction. Indeed, the formation of homocoupling products such as **OP-2** can result from a kinetic competition between reductive elimination and aryl exchange reaction on the finale intermediate. To avoid this, the choice of catalyst, ligand and solvent are important. Organ *et al.* have also investigated the role of additive salt such as $ZnCl_2$ in the Negishi reaction to enhance the reactivity by breaking down the aggregates.[220c]

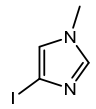
[220] a) J. del Pozo, G. Salas, R. Álvarez, J. A. Casares, P. Espinet, *Organometallics* **2016**, *35*, 3604-3611; b) J. A. Casares, P. Espinet, B. Fuentes, G. Salas, *J. Am. Chem. Soc.* **2007**, *129*, 3508-3509; c) L. C. McCann, M. G. Organ, *Angew. Chem. Int. Ed.* **2014**, *53*, 4386-4389.

3. Limitations

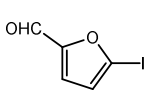
Degradation of substrate



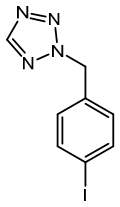
Degradation



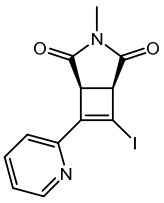
Degradation



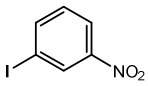
Degradation



Degradation

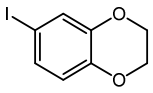


Degradation

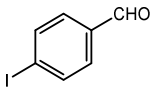


Degradation

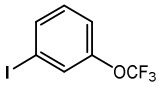
Partial/ no exchange



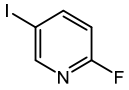
Partial exchange observed



no exchange observed



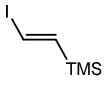
no exchange observed



no exchange observed

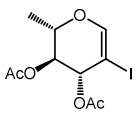
no exchange observed

no exchange observed

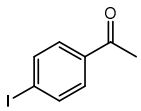


no exchange observed

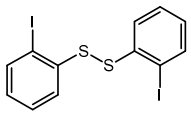
Mixed



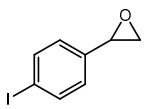
OAc deprotection by alkoxide



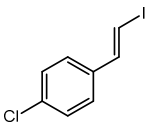
reaction with enolate



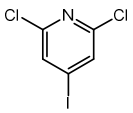
partial disulfide cleavage



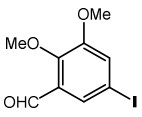
Ring opening of epoxide



full exchange, but no reactivity towards electrophiles



full exchange, but no reactivity towards electrophiles



full exchange, but partial attack of Et_2Zn on the aldehyde

4. General Procedures

Preparation of $Et_2Zn \cdot LiOAmyl$

A multiple times flame-dried Schlenk-flask equipped with stirring bar was charged with lithium *tert*-amylate in heptanes (10 mmol, 1.0 equiv.). A carefully titrated solution of Et_2Zn in heptanes (10 mmol, 1.0 equiv.) was added dropwise at ambient temperature and the reaction mixture was allowed to stir for 2 h at rt. Iodometric titration of the base gave concentrations ranging from 0.71 to 0.725 M, corresponding to yields of 95 to 97 % of $Et_2Zn \cdot LiOAmyl$.

Preparation of $Et_2Zn \cdot 2LiOAmyl$

A multiple times flame-dried Schlenk-flask equipped with stirring bar was charged with lithium *tert*-amylate in heptanes (20 mmol, 2.0 equiv.). A carefully titrated solution of Et_2Zn in heptanes (10 mmol, 1.0 equiv.) was added dropwise at ambient temperature and the reaction mixture was allowed to stir for 2 h at rt. Iodometric titration of the base gave concentrations ranging from 0.56 to 0.58 M, corresponding to yields of 93 to 97 % of $Et_2Zn \cdot 2LiOAmyl$.

Iodometric titration:

A flame dried flask was charged with iodine (typically around 100 mg) and THF (1 mL) was added. The zinc reagent (1 mL) was added dropwise, until the solution became colorless. The concentration was calculated according to equation 1.

$$\mathrm{C\ [M]} = \left(\frac{mg\ (I_2)}{253.81 \frac{g}{mol}} \div (amount\ of\ zinc\ reagent\ [mL]) \right) \div 2$$

General Procedure A: Iodine-Zinc exchange of functionalized vinyl iodides (Acylation/ Allylation)

A flame-dried Schlenk flask was charged with the respective vinyl iodide (0.2 mmol, 1.0 equiv.) and dry THF (2 mL) was added. $Et_2Zn \cdot LiOAmyl$ (0.16 mmol, 0.8 equiv.) was added dropwise to the solution at ambient temperature, and the reaction mixture was allowed to stir at this temperature for 15 min. Solid copper(I) iodide (0.1 mmol, 50 mol%) was added in one portion to the mixture, and the solution was allowed to stir for 30 min at rt. The respective electrophile (0.4 mmol, 2.0 equiv. or as specified) was added to the mixture and the Schlenk flask was sealed and the mixture stirred overnight at ambient temperature. The next day, sat. aq. NH_4Cl (2 mL) was added, followed by water (5 mL) and the mixture was transferred to a seperatory funnel. The aq. fraction was extracted with EtOAc (3 × 15 mL), the combined org. phases were washed with Brine (20 mL) and dried over anhydr. $MgSO_4$. Concentration *in vacuo*, and

purification by flash column chromatography (SiO_2; petroleum ether/ EtOAc) furnished the desired functionalized vinylic substrates.

General Procedure B: Iodine-Zinc exchange of vinyl iodides (Negishi Cross-coupling)

A flame-dried Schlenk flask was charged with the respective vinyl iodide (0.2 mmol, 1.0 equiv.) and dry THF (2 mL) was added. $Et_2Zn \cdot LiOAmyl$ (0.16 mmol, 0.8 equiv.) was added dropwise to the solution at ambient temperature, and the reaction mixture was allowed to stir at this temperature for 15 min. $Pd(OAc)_2$ (0.5 mg, 1 mol%) and SPhos (1.6 mg, 2 mol%.) were added as a solution in THF (0.2 mL), followed by the electrophile (0.18 mmol, 0.9 equiv.). The Schlenk flask was sealed and the mixture stirred overnight at ambient temperature. The next day, Sat. aq. NH_4Cl (2 mL) was added, followed by water (5 mL) and the mixture was transferred to a seperatory funnel. The aq. fraction was extracted with EtOAc (3 × 15 mL), the combined org. phases were washed with Brine (20 mL) and dried over anhydr. $MgSO_4$. Concentration *in vacuo*, and purification by flash column chromatography (SiO_2; petroleum ether/ EtOAc) furnished the desired functionalized vinylic substrates.

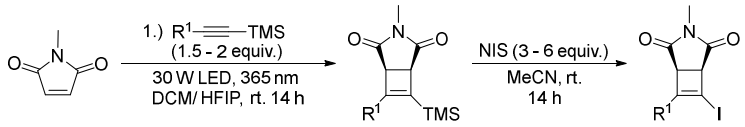
General Procedure C: Iodine-Zinc exchange of functionalized Aromatics (Acylation/ Allylation)

A flame-dried Schlenk flask was charged with the respective (hetero)aryl iodide (0.2 mmol, 1.0 equiv.) and dry THF (1 mL) was added. $Et_2Zn{\cdot}2LiOAmyl$ (0.16 mmol, 0.7 equiv. or as specified) was added dropwise to the solution at ambient temperature, and the reaction mixture was allowed to stir at this temperature for 15 min. Solid copper(I) iodide (0.1 mmol, 50 mol%) was added in one portion to the mixture, and the solution was allowed to stir for 30 min at rt. The respective electrophile (0.4 mmol, 2.0 equiv. or as specified) was added to the mixture stirred at ambient temperature for the indicated amount of time. Upon completion of the reaction judged by TLC or GC/MS following, sat. aq. NH_4Cl (2 mL) was added, followed by water (5 mL). The mixture was transferred to a seperatory funnel and the aq. fraction was extracted with EtOAc (3 × 15 mL), the combined org. phases were washed with Brine (20 mL) and dried over anhydr. $MgSO_4$. Concentration *in vacuo*, and purification by flash column chromatography (SiO_2; petroleum ether/ EtOAc) furnished the desired functionalized (hetero)aromatics.

General Procedure D: Iodine-Zinc exchange of functionalized Aromatics (Negishi Cross-coupling)

A flame-dried Schlenk flask was charged with the respective (hetero)aryl iodide (0.2 mmol, 1.0 equiv.) and dry THF (1 mL) was added. $Et_2Zn \cdot 2LiOAmyl$ (0.16 mmol, 0.7 equiv. or as specified) was added dropwise to the solution at ambient temperature, and the reaction mixture was allowed to stir at this temperature for 15 min. $ZnCl_2$ (0.2 mmol, 1.0 equiv., 1 M solution in THF) and $Pd(dppf)Cl_2$ (0.5 mg, 1 mol%) were added in the reaction mixture, followed by the electrophile (0.18 mmol, 0.9 equiv.). The Schlenk flask was sealed and the mixture stirred overnight at ambient temperature. The next day, sat. aq. NH_4Cl (2 mL) was added, followed by water (5 mL) and the mixture was transferred to a seperatory funnel. The aq. fraction was extracted with EtOAc (3 × 15 mL), the combined org. phases were washed with Brine (20 mL) and dried over anhydr. $MgSO_4$. Concentration *in vacuo*, and purification by flash column chromatography (SiO_2; petroleum ether/ EtOAc) furnished the desired functionalized (hetero)aromatics.

General Procedure E: [2+2] Cycloaddition of TMS protected alkynes with *N*-methylmaleimide.



According to a modified literature procedure[160], the respective TMS-protected alkyne (7.5 mmol, 1.5 equiv.) was charged to a flame-dried Schlenk-flask and dry DCM (30 mL) and HFIP (10 mL) was added. Finally, solid *N*-methylmaleimide (0.56 g, 5 mmol, 1.0 equiv.) was added in one portion and the Schlenk-flask was sealed. The reaction mixture was then irradiated with a 30 W LED (365 nm) for 14 h. The next day, all volatiles were removed *in vacuo* and the crude TMS-cyclobutene was purified by flash column chromatography (Silica Plug, SiO_2; pentane: EtOAc). The obtained TMS-cyclobutene was then directly engaged, and charged to a flame-dried flask and dissolved in MeCN (0.2 M). Solid NIS (3 - 6 equiv. as specified) was added portion wise to the mixture and stirring was continued at rt. overnight. Then, sat. aq. $Na_2S_2O_3$ (50 mL) was added and the reaction mixture was transferred to a separatory funnel. Water (50 mL) was added and the aq. fraction was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with Brine (50 mL) and dried over anhydr. $MgSO_4$. Concentration *in vacuo* and subsequent flash column chromatography (SiO_2; pentane: EtOAc) afforded the respective iodinated cyclobutene. **Note:** No significant degradation of the iodinated cyclobutenes could be observed at ambient temperature over the course of one week. Still, storage at -20°C under light exclusion is recommended.

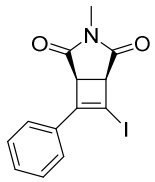
$Et_2Zn{\cdot}LiOAmyl$ and $Et_2Zn{\cdot}2LiOAmyl$ – crystallization for single crystal X-Ray diffraction

A 50 mL Schlenk-flask (3 × flame-dried) was charged with Et_2Zn (in heptane, 10 mmol, 1.0 equiv.). Lithium *tert*-amylate in heptane (10 mmol, 1.0 equiv. *or* 20 mmol, 2.0 equiv., respectively) was added dropwise to the mixture, and the reaction mixture was allowed to stir for 2 h at rt. Then, the reaction mixture was concentrated *via* Schlenk-line, until the reaction mixture became milky (slight precipitation observed, typically concentration to half the initial volume). The Schlenk-flask was backfilled with Argon, sealed with a glass-stopper and warmed until full dissolution of the precipitate (max. 50°C). Crystallization was induced upon cooling to ambient temperature overnight. If no crystals were obtained, the reaction mixture was cooled to 0°C overnight.

5. Experimental Data

5.1 Preparation of Iodinated Substrates

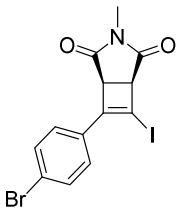
(1*S*,5*S*)-6-Iodo-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (1)



According to general procedure E on a 10 mmol scale, using 1-phenyl-2-trimethylsilylacetylene (1.97 mL, 13.0 mmol, 1.30 equiv.). and *N*-methylmaleimide (1.1 g, 10 mmol, 1.0 equiv.) in DCM (60 mL) and HFIP (20 mL). After irradiation for 24 hours, flash column chromatography (CombiFlash EZ Prep, SiO_2 (120 g); petroleum ether/ EtOAc; 100 % to 8:2) furnished the title compound as a colorless solid (2.7 g, 9.4 mmol, 94 %). The TMS-cyclobutene (2.7 g, 9.4 mmol, 1.0 equiv.) was directly employed in the next step and charged to a flame-dried flask. Dry MeCN (70 mL) was added, followed by NIS (8.5 g, 38 mmol, 4.0 equiv.), which was added portionwise to the mixture. The flask was covered with aluminium foil, and the reaction mixture was allowed to stir at rt. for 18 h. After extraction, flash column chromatography (CombiFlash EZ Prep, SiO_2 (120 g); petroleum ether/ EtOAc; 100 % to 6:4) furnished the title compound as a colorless solid (2.4 g, 7.1 mmol, 76 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.96 – 7.89 (m, 2H), 7.46 – 7.40 (m, 3H), 4.29 (d, J = 3.5 Hz, 1H), 3.97 (d, J = 3.5 Hz, 1H), 2.98 (s, 3H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ = 173.16, 153.11, 131.15, 130.40, 128.72, 126.50, 125.64, 81.76, 50.11, 50.10, 25.10. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{13}H_{10}INO_2H^+$: 339.98290 found: 339.98347.

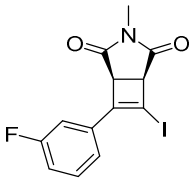
(1*S*,5*S*)-6-(4-Bromophenyl)-7-iodo-3-methyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (SI-1)



According to general procedure E on a 3.9 mmol scale, using ((4-bromophenyl)ethynyl)trimethylsilane (1 g, 3.9 mmol, 1.1 equiv.) and *N*-methylmaleimide (0.39 g, 3.6 mmol, 1.0 equiv.) in DCM (30 mL) and HFIP (10 mL). After irradiation for 18 hours, flash column chromatography (CombiFlash EZ Prep, SiO_2 (80 g); petroleum ether/ EtOAc; 100 % to 6:4) furnished the title compound as a colorless solid (1.1 g, 3 mmol, 85 %). The TMS-cyclobutene (1.1 g, 3 mmol, 1.0 equiv.) was directly employed in the next step and charged to a flame-dried flask. Dry MeCN (40 mL) was added, followed by NIS (2.7 g, 12 mmol, 4.0 equiv.), which was added portionwise to the mixture. The flask was covered with aluminium foil, and the reaction mixture was allowed to stir at rt. for 16 h. After extraction, flash column chromatography (CombiFlash EZ Prep, SiO_2 (80 g); petroleum ether/ EtOAc; 100 % to 1:1) furnished the title compound as a colorless solid (0.65 g, 1.6 mmol, 52 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.82 – 7.77 (m, 2H), 7.58 – 7.55 (m, 2H), 4.27 (d, J = 3.5 Hz, 1H), 3.97 (d, J = 3.5 Hz, 1H), 2.98 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 172.87, 172.64, 152.07, 131.88, 129.89, 127.79, 126.94, 124.53, 82.81, 50.07, 49.91, 25.02. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{13}H_9BrINO_2H^+$: 417.8941 found: 417.8932.

(1*S*,5*S*)-6-(3-Fluorophenyl)-7-iodo-3-methyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (SI-2)

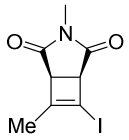


According to general procedure E on a 6.9 mmol scale, using ((3-fluorophenyl)ethynyl)trimethylsilane (1.7 g, 9.0 mmol, 1.3 equiv.) and *N*-methylmaleimide (0.77 g, 6.9 mmol, 1.0 equiv.) in DCM (60 mL) and HFIP (20 mL). After irradiation for 16 hours, flash column chromatography (CombiFlash EZ Prep, SiO_2 (80 g); petroleum ether/ EtOAc; 100 % to 6:4) furnished the title compound as a colorless solid (1.89 g, 6.23 mmol, 92 %). The TMS-cyclobutene (1.89 g, 6.23 mmol, 1.0 equiv.) was directly employed in the next step and charged to a flame-dried flask. Dry MeCN (80 mL) was added, followed by NIS (5.6 g, 25 mmol, 4.0 equiv.), which was added portionwise to the mixture. The flask was covered with aluminium foil, and the reaction mixture was allowed to stir at rt. for 14 h. After extraction, flash

column chromatography (CombiFlash EZ Prep, SiO_2 (80 g); petroleum ether/ EtOAc; 100 % to 1:1) furnished the title compound as a colorless solid (1.0 g, 2.8 mmol, 45 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.70 – 7.62 (m, 2H), 7.43 – 7.36 (m, 1H), 7.15 – 7.08 (m, 1H), 4.26 (d, J = 3.5 Hz, 1H), 3.98 (d, J = 3.5 Hz, 1H), 2.97 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 172.77 (d, J = 15.7 Hz), 163.64, 161.67, 152.05 (d, J = 3.3 Hz), 133.06 (d, J = 8.1 Hz), 130.44 (d, J = 8.1 Hz), 121.58 (d, J = 3.3 Hz), 117.33 (d, J = 21.5 Hz), 112.18 (d, J = 22.9 Hz), 83.95, 50.16, 50.12, 25.11. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{13}H_9FINO_2H^+$: 357.9742 found: 357.9736.

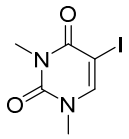
(1*S*,5*S*)-6-Iodo-3,7-dimethyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (SI-3)



According to general procedure E on a 20 mmol scale, using trimethyl(prop-1-yn-1-yl)silane (2.3 mL, 26 mmol, 1.3 equiv.) and *N*-methylmaleimide (2.2 g, 20 mmol, 1.0 equiv.) in DCM (120 mL) and HFIP (40 mL). After irradiation for 16 hours, flash column chromatography (CombiFlash EZ Prep, SiO_2 (80 g); petroleum ether/ EtOAc; 100 % to 7:3) furnished the title compound as a pale yellow liquid (3.3 g, 15 mmol, 74 %). The TMS-cyclobutene (3.3 g, 15 mmol, 1.0 equiv.) was directly employed in the next step and charged to a flame-dried flask. Dry MeCN (160 mL) was added, followed by NIS (27 g, 120 mmol, 6 equiv.), which was added portionwise to the mixture. The flask was covered with aluminium foil, and the reaction mixture was allowed to stir at rt. for 16 h. After extraction, flash column chromatography (CombiFlash EZ Prep, SiO_2 (120 g); petroleum ether/ EtOAc; 100 % to 1:1) furnished the title compound as a yellow solid (2.54 g, 9.2 mmol, 62 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.88 – 3.83 (m, 2H), 2.96 (s, 3H), 1.80 – 1.78 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 173.35, 173.08, 156.98, 87.01, 51.94, 50.34, 24.98, 15.41. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_8H_8INO_2H^+$: 277.96725 found: 277.96776.

5-Iodo-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (SI-4)

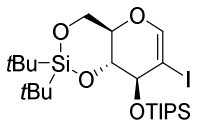


According to a modified literature procedure[221], 1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (1.69 g, 12.1 mmol, 1.00 equiv.) was charged to a flame-dried flask and I_2 (3.4 g, 13 mmol, 1.1 equiv.), dry DMF (50 mL) and *m*-CPBA (2.7 g, 16 mmol, 1.3 equiv.) were added successively. The reaction mixture was allowed to stir for 30 min. Then, all volatiles were removed *in vacuo*, and the resulting solid was triturated with Et_2O. The remaining solid was

then washed with cold Et_2O followed by recrystallization from EtOH, to obtain the title compound as a brown solid (3.2 g, 9.0 mmol, 75 %).

^{1}H NMR (500 MHz, DMSO-D_6) δ = 8.24 (s, 1H), 3.30 (s, 3H), 3.21 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-D_6) δ = 160.27, 151.12, 148.96, 66.21, 36.40, 28.74. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_6H_7IN_2O_2H^+$: 266.96250 found: 266.96286. Spectral characteristics were in agreement with previously reported data.[221]

(4a*R*,8*S*,8a*R*)-2,2-Di-*tert*-butyl-7-iodo-8-((triisopropylsilyl)oxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (SI-5)

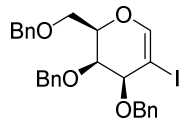


According to a modified literature procedure[222], (4a*R*,8*R*,8aR)-2,2-di-*tert*-butyl-8-((triisopropylsilyl)oxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (1 g, 2.4 mmol, 1.0 equiv.) was charged to a flame-dried Ace pressure vial, followed by $AgNO_3$ (84 mg, 0.48 mmol, 20 mol%.), NIS (0.67 g, 2.95 mmol, 1.2 equiv.) and dry MeCN (10 mL). The vial was closed, and the reaction mixture was heated to 80°C overnight. EtOAc (50 mL) was added, the mixture was filtered through a pad of silica and the filtrate was concentrated *in vacuo*. Then EtOAc (100 mL) was added and the org. fraction was washed with sat. aq. $Na_2S_2O_3$ (50 mL) and Brine (50 mL). After removal of the solvents *in vacuo*, flash column chromatography (SiO_2; pentane: EtOAc: 9:1) furnished the title compound as a colorless solid (0.71 g, 1.3 mmol, 52 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.61 (d, J = 1.4 Hz, 1H), 4.38 (dd, J = 6.8, 1.4 Hz, 1H), 4.15 – 4.08 (m, 2H), 3.98 – 3.89 (m, 2H), 1.35 (p, J = 7.5 Hz, 3H), 1.19 – 1.14 (m, 18H), 1.06 (s, 12H), 0.99 (s, 12H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ = 147.57, 78.57, 77.85, 75.53, 73.73, 65.39, 27.40, 27.10, 18.90, 18.69, 13.86. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{23}H_{45}IO_4Si_2H^+$: 569.1981 found: 569.1974.

[221] C. H. Hwang, J. S. Park, J. H. Won, J. N. Kim, E. K. Ryu, *Arch. Pharmacal Res.* **1992**, *15*, 69-72.
[222] S. Dharuman, Y. D. Vankar, *Org. Lett.* **2014**, *16*, 1172-1175.

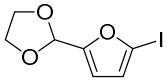
(2*R*,3*S*,4*S*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-iodo-3,4-dihydro-2*H*-pyran (SI-6)



According to a literature procedure [222], (2*R*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran (1 g, 2.4 mmol, 1.0 equiv.) was charged to a flame-dried Ace pressure vial, followed by $AgNO_3$ (82 mg, 0.48 mmol, 20 mol%.), NIS (0.65 g, 2.88 mmol, 1.2 equiv.) and dry MeCN (20 mL). The vial was closed, and the reaction mixture was heated to 80°C for 1 h. EtOAc (50 mL) was added, the mixture was filtered through a pad of silica and the filtrate was concentrated *in vacuo*. Then EtOAc (100 mL) was added and the org. fraction was washed with sat. aq. $Na_2S_2O_3$ (50 mL) and Brine (50 mL). After removal of the solvents *in vacuo*, flash column chromatography (SiO_2; pentane: EtOAc: 9:1) furnished the title compound as a colorless solid (1.1 g, 2.0 mmol, 83 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44 (d, J = 6.9 Hz, 2H), 7.40 – 7.28 (m, 13H), 6.66 (s, 1H), 4.85 – 4.75 (m, 3H), 4.62 (d, J = 11.8 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 4.44 (d, J = 11.8 Hz, 1H), 4.39 (dt, J = 7.5, 3.7 Hz, 1H), 4.14 (d, J = 3.7 Hz, 1H), 4.08 (t, J = 3.7 Hz, 1H), 3.85 (dd, J = 10.7, 7.5 Hz, 1H), 3.74 (dd, J = 10.7, 4.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 147.66, 138.11, 138.03, 137.93, 128.55, 128.50, 128.44, 128.14, 128.05, 127.99, 127.86, 127.84, 76.00, 75.89, 74.03, 73.54, 73.27, 73.14, 67.95. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{27}H_{27}IO_4H^+$: 543.1027 found: 543.1026. Spectral characteristics were in agreement with previously reported data.[222]

2-(5-Iodofuran-2-yl)-1,3-dioxolane (SI-7)

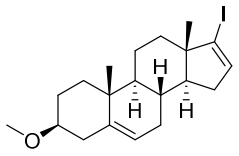


5-Iodo furan-2-carbaldehyde (2.5 g, 11.3 mmol, 1.0 equiv.) was charged to a flask containing ethylene glycol (1.9 mL, 34 mmol, 3.0 equiv.), PTSA monohydrate (65 mg, 3 mol%). Toluene (15 mL) was added and a dean-stark apparatus was attached. The reaction mixture was heated to 110°C for 5 h. After full consumption of the starting material, the solution was transferred to a separatory funnel containing water (50 mL). The aq. fraction was extracted twice with EtOAc (2 × 100 mL), the combined org. phases were washed with Brine (100 mL) and dried over anhydr. $MgSO_4$. After concentration *in vacuo*, flash column chromatography (SiO_2; pentane: EtOAc; 99:1 to 6:4) yielded the title compound as a colorless oil (1.3 g, 4.9 mmol, 43 %)

Note: Compound is instable and degrades rapidly at ambient temperature. Storage in the freezer at -20°C is recommended. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.50 (d, J = 3.3 Hz, 1H), 6.35 (d, J = 3.3 Hz, 1H), 5.89 (s, 1H), 4.15 – 4.08 (m, 2H), 4.04 – 3.96 (m, 2H). **^{13}C NMR** (126

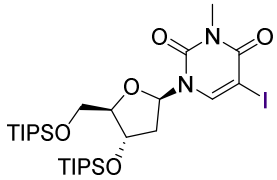
MHz, $CDCl_3$) δ = 156.76, 120.86, 111.64, 97.35, 89.13, 65.30. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_7H_7IO_3H^+$: 266.95127 found: 266.95116.

(3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-17-Iodo-3-methoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthrene (SI-8)



To a solution of 17-iodoandrosta-5,16-diene-3β-ol (600 mg, 1.5 mmol, 1.0 equiv.) in 8 mL of THF at 0 °C, NaH (78 mg, 1.95 mmol, 1.3 equiv., 60 % dispersion in mineral oil) was added portionwise and reaction mixture was stirred at this temperature for 1 h before addition of methyliodide (0.12 mL, 1.95 mmol, 1.3 equiv.). The mixture was stirred at 0 °C for 1 h and at ambient temperature for 24 h and was then quenched with H_2O (15 mL). The mixture was transferred to a seperatory funnel and the aq. fraction was extracted with EtOAc (3 × 15 mL), the combined org. phases were washed with brine (20 mL) and dried over anhydr. $MgSO_4$. Concentration *in vacuo*, and purification by flash column chromatography (SiO_2; pentane/ EtOAc 95:5) furnished the title compound as a colorless powder (460 mg, 1.12 mmol, 75 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.14 (dd, J = 3.3, 1.7 Hz, 1H), 5.39 – 5.34 (m, 1H), 3.36 (s, 3H), 3.06 (tt, J = 11.3, 4.5 Hz, 1H), 2.41 (ddd, J = 13.1, 4.7, 2.4 Hz, 1H), 2.22 – 2.12 (m, 2H), 2.06 – 1.90 (m, 3H), 1.86 (dt, J = 13.5, 3.6 Hz, 1H), 1.72 – 1.59 (m, 3H), 1.54 – 1.34 (m, 3H), 1.31 – 1.18 (m, 1H), 1.09 – 0.96 (m, 5H), 0.86 (dt, J = 19.1, 6.9 Hz, 1H), 0.76 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 141.49, 137.64, 121.16, 112.85, 80.39, 55.78, 54.98, 50.71, 50.10, 38.83, 37.28, 37.24, 36.33, 33.90, 31.40, 31.17, 28.11, 20.95, 19.43, 15.26. **HRMS (EI)** m/z: [H] + calcd for $C_{20}H_{29}IO^+$: 412.1258 found: 412.1264.

5-Iodo-3-methyl-1-((2*R*,4*S*,5*R*)-4-((triisopropylsilyl)oxy)-5-(((triisopropylsilyl)oxy)methyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (SI-9)

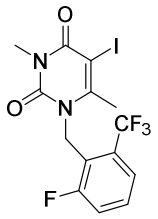


3-Methyl-1-((2*R*,4*S*,5*R*)-4-((triisopropylsilyl)oxy)-5-(((triisopropylsilyl)oxy)methyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (2.5 g, 3.7 mmol, 1.0 equiv.) was charged to a flame-dried flask and dry K_2CO_3 (0.62 g, 4.5 mmol, 1.2 equiv.), dry MeCN (13 mL) and MeI (0.4 mL, 5.6 mmol, 1.5 equiv.) were added successively. The reaction mixture was allowed to stir at rt. overnight under argon atmosphere. The next day, all the solvents were removed *in vacuo* and the product was purified *via* flash

column chromatography (SiO_2; hexane/ EtOAc; 95:5 to 9:1) to obtain the title compound as a yellow oil (1.9 g, 2.8 mmol, 76 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.08 – 8.04 (m, 1H), 6.34 – 6.27 (m, 1H), 4.62 – 4.58 (m, 1H), 4.08 – 4.04 (m, 1H), 3.98 – 3.93 (m, 1H), 3.90 – 3.84 (m, 1H), 3.40 (d, J = 2.7 Hz, 3H), 2.99 – 2.95 (m, 1H), 2.91 – 2.87 (m, 1H), 2.39 (ddt, J = 12.9, 4.8, 2.1 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.25 – 1.16 (m, 3H), 1.12 – 1.04 (m, 39H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 160.07, 150.76, 142.26, 89.07, 86.71, 73.20, 68.12, 63.76, 42.66, 29.41, 18.10, 18.07, 12.17, 12.04. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{28}H_{53}IN_2O_5Si_2H^+$: 681.26105 found: 681.26150.

1-(2-Fluoro-6-(trifluoromethyl)benzyl)-5-iodo-3,6-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (SI-10)

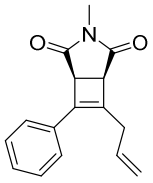


1-(2-Fluoro-6-(trifluoromethyl)benzyl)-3,6-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (0.96 g, 2.2 mmol, 1.0 equiv.) was charged to a flame-dried flask and dry K_2CO_3 (0.37 g, 2.7 mmol, 1.2 equiv.), dry MeCN (10 mL) and MeI (0.21 mL, 3.4 mmol, 1.5 equiv.) were added successively. The reaction mixture was allowed to stir at rt. overnight under argon atmosphere. The next day, all volatiles were removed *in vacuo*, and the crude product was purified by flash column chromatography (SiO_2; pentane/ EtOAc: 8:2) to obtain the title compound as a yellow solid (0.82 g, 1.9 mmol, 83 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55 (d, J = 7.8 Hz, 1H), 7.42 (td, J = 7.8, 5.0 Hz, 1H), 7.26 – 7.21 (m, 1H), 5.52 (s, 2H), 3.43 (s, 3H), 2.57 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 162.36, 160.61 – 151.77 (m), 129.72 (d, J = 10.0 Hz), 122.82 (tq, J = 6.2, 3.2 Hz), 121.87 (d, J = 11.4 Hz), 121.16 (d, J = 23.8 Hz), 75.43, 44.40 (q, J = 3.6 Hz), 30.19, 25.75. **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -59.72, -116.47. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{14}H_{11}F_4IN_2O_2H^+$: 442.98741 found: 442.98784.

5.2 Scope of the Cyclobutene Series

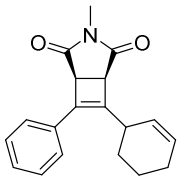
(1*S*,5*R*)-6-Allyl-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**4a**)



According to GP-A, using 6-iodo-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**1**) (68 mg, 0.2 mmol, 1.0 equiv.). After treatment with CuI (19 mg, 0.1 mmol, 50 mol%.) and stirring for 30 min at ambient temperature, allyl bromide (34 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, flash column chromatography (SiO_2; petroleum ether/ EtOAc; 9:1 to 6:4) furnished the title compound as a colorless oil (39 mg, 0.15 mmol, 76 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.58 – 7.54 (m, 2H), 7.41 – 7.36 (m, 2H), 7.33 – 7.28 (m, 1H), 5.93 (ddt, *J* = 16.7, 10.0, 6.4 Hz, 1H), 5.24 – 5.15 (m, 2H), 4.01 (dt, *J* = 2.8, 1.3 Hz, 1H), 3.75 (d, *J* = 3.4 Hz, 1H), 3.38 – 3.19 (m, 2H), 2.95 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 175.46, 175.17, 141.36, 140.55, 132.74, 132.18, 128.87, 128.74, 126.74, 117.69, 45.58, 45.00, 33.65, 24.88. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{16}H_{15}NO_2H^+$: 254.11756 found: 254.11720.

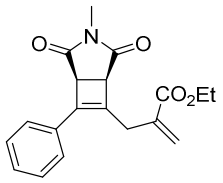
(1*S*,5*R*)-6-(Cyclohex-2-en-1-yl)-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (4b)



According to GP-A, using 6-iodo-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**1**) (68 mg, 0.2 mmol, 1.0 equiv.). After treatment with CuI (19 mg, 0.1 mmol, 50 mol%.) and stirring for 30 min at ambient temperature, 3-bromocyclohexene (46 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, flash column chromatography (SiO_2; petroleum ether/ EtOAc; 95:5 to 7:3) furnished the title compound as a colorless oil (43 mg, 0.15 mmol, 74 %) as a mixture of diastereomers (*dr.* = 2:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.61 – 7.56 (m, 2H), 7.41 – 7.35 (m, 2H), 7.32 – 7.27 (m, 1H), 5.95 – 5.85 (m, 1H), 5.58 (dp, J = 10.4, 2.5 Hz, 1H), 3.97 (dd, J = 9.1, 3.4 Hz, 1H), 3.76 (dd, J = 3.6, 1.3 Hz, 1H), 3.60 – 3.52 (m, 1H), 2.95 (d, J = 6.6 Hz, 3H), 2.18 – 2.04 (m, 1H), 1.97 – 1.85 (m, 1H), 1.79 – 1.70 (m, 1H), 1.62 – 1.55 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 175.61 (Dia1, major), 175.49 (Dia1, major), 175.41 (Dia2, minor), 175.32 (Dia2, minor), 146.51 (Dia1, major), 146.50 (Dia2, minor), 139.94 (Dia1, major), 139.92 (Dia2, minor), 132.88 (Dia1, major), 132.80 (Dia2, minor), 130.18 (Dia1, major), 129.81 (Dia2, minor), 128.82 (Dia2, minor), 128.80 (Dia1, major), 128.56, 127.14 (Dia1, major), 127.10 (Dia2, minor), 126.62 (Dia1, major), 126.22 (Dia2, minor), 44.92 (Dia2, minor), 44.62 (Dia1, major), 44.50 (Dia2, minor), 44.47 (Dia1, major), 37.07 (Dia1, major), 36.82 (Dia2, minor), 27.09 (Dia2, minor), 26.61 (Dia1, major), 24.96 (Dia1, major), 24.92 (Dia2, minor), 24.82 (Dia1, major), 24.77 (Dia2, minor), 21.66 (Dia1, major), 21.54 (Dia2, minor). **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{19}H_{19}NO_2H^+$: 294.14886 found: 294.14881.

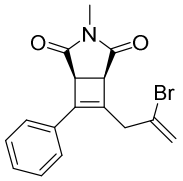
Ethyl 2-(((1*S*,5*R*)-3-methyl-2,4-dioxo-7-phenyl-3-azabicyclo[3.2.0]hept-6-en-6-yl)methyl)acrylate (4c)



According to GP-A, using 6-iodo-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**1**) (68 mg, 0.2 mmol, 1.0 equiv.). After treatment with CuI (19 mg, 0.1 mmol, 50 mol%.) and stirring for 30 min at ambient temperature, ethyl-2-(brommethyl)acrylat (56 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 1:1) furnished the title compound as a colorless oil (44 mg, 0.14 mmol, 68 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.63 (t, J = 1.3 Hz, 2H), 7.40 – 7.36 (m, 2H), 7.33 – 7.29 (m, 1H), 6.37 – 6.35 (m, 1H), 5.75 (q, J = 1.3 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.00 (dt, J = 2.5, 1.4 Hz, 1H), 3.72 (d, J = 3.4 Hz, 1H), 3.67 (d, J = 16.2 Hz, 1H), 3.39 (d, J = 16.2 Hz, 1H), 2.95 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 175.40, 174.93, 166.53, 142.39, 139.39, 135.50, 132.59, 128.86, 127.58, 126.86, 61.25, 45.49, 44.95, 31.91, 24.87, 14.31. **HRMS (EI)** m/z: calcd for $C_{19}H_{19}NO_4$: 325.1314 found: 325.1308.

(1*S*,5*R*)-6-(2-Bromoallyl)-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (4d)

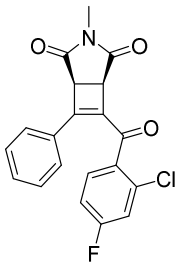


According to GP-A, using 6-iodo-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**1**) (68 mg, 0.2 mmol, 1.0 equiv.). After treatment with CuI (19 mg, 0.1 mmol, 50 mol%.) and stirring for 30 min at ambient temperature, 2,3-dibrompropene (38 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, flash column chromatography (SiO_2; petroleum ether/ EtOAc; 99:1 to 6:4) furnished the title compound as a colorless oil (48 mg, 0.14 mmol, 72 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.64 – 7.59 (m, 2H), 7.40 (dd, J = 8.4, 6.9 Hz, 2H), 7.36 – 7.31 (m, 1H), 5.83 (q, J = 1.5 Hz, 1H), 5.62 (d, J = 2.0 Hz, 1H), 4.04 (dd, J = 3.6, 1.5 Hz, 1H), 3.83 (d, J = 3.4 Hz, 1H), 3.73 (d, J = 16.1 Hz, 1H), 3.60 (dd, J = 16.2, 1.7 Hz, 1H), 2.96 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 175.08, 174.72, 144.05, 137.59, 132.25, 129.26, 128.94, 128.85, 127.52, 126.93, 126.49, 119.72, 45.48, 45.23, 41.09, 24.89. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{16}H_{14}BrNO_2H^+$: 332.02807 found: 332.02802.

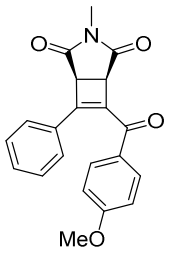
(1*S*,5*R*)-6-(2-Chloro-4-fluorobenzoyl)-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (4e)



According to GP-A, using 6-iodo-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**1**) (68 mg, 0.2 mmol, 1.0 equiv.). After treatment with CuI (19 mg, 0.1 mmol, 50 mol%.) and stirring for 30 min at ambient temperature, 2-chloro-4-fluorobenzoyl chloride (53 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 3:7) furnished the title compound as a colorless oil (58 mg, 0.16 mmol, 78 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.18 – 8.14 (m, 2H), 7.52 – 7.48 (m, 2H), 7.45 (dd, J = 8.3, 6.5 Hz, 2H), 7.19 (dd, J = 8.4, 2.4 Hz, 1H), 7.13 (td, J = 8.2, 2.4 Hz, 1H), 4.22 (d, J = 3.6 Hz, 1H), 4.10 (d, J = 3.6 Hz, 1H), 2.93 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 188.28, 173.34, 172.79, 162.78, 155.75, 134.23, 132.59, 131.12, 131.04, 130.78, 129.87, 128.82, 117.79, 117.59, 115.03, 114.86, 77.28, 77.02, 76.77, 45.28, 44.15, 25.10. **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -106.11. **HRMS (EI)** m/z: calcd for $C_{20}H_{13}ClFNO_3$: 369.0568 found: 369.0564.

(1*S*,5*R*)-6-(4-Methoxybenzoyl)-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (4f)

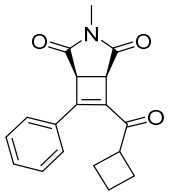


According to GP-A, using 6-iodo-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**1**) (68 mg, 0.2 mmol, 1.0 equiv.). After treatment with CuI (19 mg, 0.1 mmol, 50 mol%.) and stirring for 30 min at ambient temperature, 4-methoxybenzoylchloride (68 mg, 0.4 mmol, 2.0 equiv.) dissolved in THF (0.2 mL) was added, and the reaction mixture was allowed to stir overnight. After workup, flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 1:1) furnished the title compound as a colorless oil (63 mg, 0.18 mmol, 91 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.00 – 7.95 (m, 2H), 7.86 – 7.82 (m, 2H), 7.41 – 7.34 (m, 3H), 6.94 – 6.91 (m, 2H), 4.29 (d, J = 3.6 Hz, 1H), 4.22 (d, J = 3.6 Hz, 1H), 3.87 (s, 3H), 3.00 (s,

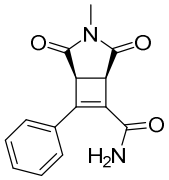
3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 187.58, 173.80, 173.67, 164.19, 151.47, 135.31, 131.86, 131.39, 131.01, 129.50, 129.46, 128.76, 114.21, 55.68, 45.39, 45.30, 25.25. **HRMS (EI)** m/z: calcd for $C_{21}H_{17}NO_4$: 347.1158 found: 347.1150.

(1*S*,5*R*)-6-(Cyclobutanecarbonyl)-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (4g)



According to GP-A, using 6-iodo-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**1**) (68 mg, 0.2 mmol, 1.0 equiv.). After treatment with CuI (19 mg, 0.1 mmol, 50 mol%.) and stirring for 30 min at ambient temperature, cyclobutanecarbonyl chloride (45 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 4:6) furnished the title compound as a colorless oil (43 mg, 0.15 mmol, 73 %).
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.41 – 8.35 (m, 2H), 7.49 – 7.44 (m, 3H), 4.15 (d, J = 3.6 Hz, 1H), 3.94 (d, J = 3.6 Hz, 1H), 3.93 – 3.87 (m, 1H), 2.97 (s, 3H), 2.48 – 2.39 (m, 2H), 2.26 – 2.19 (m, 1H), 2.18 – 2.06 (m, 1H), 1.94 – 1.86 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 197.37, 174.27, 173.24, 154.82, 134.27, 132.33, 131.06, 130.09, 128.80, 126.48, 45.22, 44.15, 43.77, 25.78, 25.19, 22.86, 17.87. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{18}H_{17}NO_3H^+$: 296.12812 found: 296.12830.

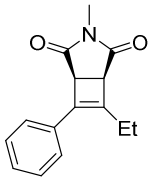
(1*S*,5*R*)-3-Methyl-2,4-dioxo-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-6-carboxamide (4h)



According to GP-A, using 6-iodo-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**1**) (68 mg, 0.2 mmol, 1.0 equiv.). After stirring 15 min at ambient temperature, trichloroacetyl isocyanate (31 µL, 0.26 mmol, 1.3 equiv.) was added and the reaction mixture was allowed to stir for 6 h. K_2CO_3 (41 mg, 0.3 mmol, 1.5 equiv.) was added in one portion, followed by dry MeOH (1 mL). The Schlenk flask was sealed and the suspension was allowed to stir overnight at rt. After workup, flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 2:8) furnished the title compound as a colorless solid (34 mg, 0.13 mmol, 67 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.36 – 8.33 (m, 2H), 7.46 – 7.43 (m, 3H), 4.17 (d, J = 3.5 Hz, 1H), 3.95 (d, J = 3.5 Hz, 1H), 3.01 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 175.77, 173.48, 163.33, 153.31, 131.69, 130.84, 130.08, 129.96, 128.80, 44.91, 43.99, 25.29. **Note:** ^{1}H and ^{13}C NMR show the presence of an impurity (^{1}H: 6.6 ppm and 5.6 ppm, ca. 10 %), which could not be separated *via* FCC or preparative TLC. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{14}H_{12}N_2O_3H^+$: 257.09207 found: 257.09134.

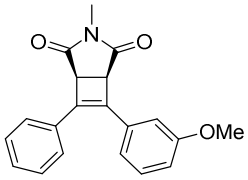
(1*S*,5*R*)-6-Ethyl-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (4i)



According to a modified GP-B, using 6-iodo-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**1**) (68 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, $Pd(OAc)_2$ (2.2 mg, 5 mol%) and PCy_3 (5.6 mg, 10 mol%.) were added as a solution in THF (0.2 mL) and the Schlenk-flask was sealed and the reaction mixture stirred overnight at rt. (EtI (1.0 equiv.) is generated *in-situ* by the exchange). After workup, flash column chromatography (SiO_2; pentane/ EtOAc; 100 % to 6:4) furnished the title compound as a colorless solid (35 mg, 1.4 mmol, 72 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55 (d, J = 6.9 Hz, 2H), 7.38 (t, J = 7.7 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 3.97 (dt, J = 3.1, 1.6 Hz, 1H), 3.76 (dt, J = 3.1, 1.3 Hz, 1H), 2.95 (s, 3H), 2.64 – 2.47 (m, 2H), 1.23 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 175.62, 145.10, 139.56, 133.05, 128.85, 128.45, 126.65, 45.25, 44.58, 24.89, 22.68, 11.55. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{15}H_{15}NO_2H^+$: 242.1183 found: 242.1177.

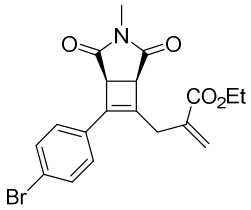
(1*S*,5*R*)-6-(3-Methoxyphenyl)-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (4j)



According to GP-B, using 6-iodo-3-methyl-7-phenyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**1**) (68 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, $Pd(OAc)_2$ (0.5 mg, 1 mol%) and SPhos (1.6 mg, 2 mol%.) were added as a solution in THF (0.2 mL). 3-Iodoanisole (21 µL, 0.18 mmol, 0.9 equiv.) was added, and the schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 1:1) furnished the title compound as a colorless solid (45 mg, 0.14 mmol, 78 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.77 (dd, J = 7.3, 1.7 Hz, 2H), 7.41 – 7.29 (m, 6H), 6.91 – 6.87 (m, 1H), 4.11 – 4.07 (m, 2H), 3.80 (s, 3H), 2.98 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 175.14, 159.82, 139.64, 139.27, 134.26, 132.94, 129.89, 129.40, 128.83, 128.78, 127.12, 125.63, 119.53, 115.67, 111.88, 55.43, 45.24, 45.12, 25.00. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{20}H_{17}NO_3H^+$: 320.12812 found: 320.12849.

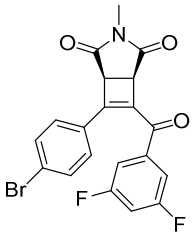
Ethyl 2-(((1*S*,5*R*)-7-(4-bromophenyl)-3-methyl-2,4-dioxo-3-azabicyclo[3.2.0]hept-6-en-6-yl)methyl)acrylate (4k)



According to GP-A, using (1*S*,5*S*)-6-(4-bromophenyl)-7-iodo-3-methyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**SI-1**) (84 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added and stirring was continued for 30 min at ambient temperature. Then, ethyl-2-(bromomethyl)acrylate (56 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 1:1) furnished the title compound as a colorless solid (61 mg, 0.15 mmol, 76 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.51 (s, 4H), 6.36 (s, 1H), 5.77 (q, J = 1.3 Hz, 1H), 4.21 (qd, J = 7.1, 0.9 Hz, 2H), 3.96 (dt, J = 3.6, 1.3 Hz, 1H), 3.71 (dd, J = 2.9, 1.7 Hz, 1H), 3.63 (d, J = 16.0 Hz, 1H), 3.35 (d, J = 16.0 Hz, 1H), 2.95 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 175.24, 174.59, 166.42, 141.24, 140.36, 135.28, 132.07, 131.45, 128.43, 127.87, 123.08, 61.31, 45.58, 44.86, 32.07, 24.90, 14.32. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{19}H_{18}BrNO_4H^+$: 242.1183 found: 242.1177.

(1*R*,5*S*)-6-(4-Bromophenyl)-7-(3,5-difluorobenzoyl)-3-methyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (4l)

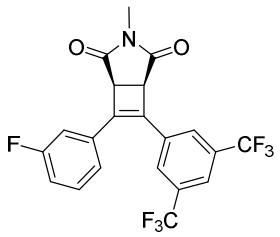


According to GP-A, using (1*S*,5*S*)-6-(4-bromophenyl)-7-iodo-3-methyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**SI-1**) (84 mg, 0.2 mmol, 1.0 equiv.). After addition of

$Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added and stirring was continued for 30 min at ambient temperature. Then, 3,5-difluorobenzoyl chloride (47 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 4:6) furnished the title compound as a colorless solid (47 mg, 0.11 mmol, 54 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.01 – 7.97 (m, 2H), 7.60 – 7.53 (m, 4H), 7.05 (tt, J = 8.4, 2.3 Hz, 1H), 4.29 (d, J = 3.7 Hz, 1H), 4.24 (d, J = 3.7 Hz, 1H), 2.99 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 185.83, 172.85 (d, J = 88.7 Hz), 163.04 (dd, J = 251.8, 11.9 Hz), 155.29, 139.82 (t, J = 7.9 Hz), 133.75, 132.14, 131.39, 128.46 (d, J = 236.0 Hz), 112.28 – 111.67 (m), 108.60 (t, J = 25.3 Hz), 45.58, 44.97, 25.25. **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -107.22. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{20}H_{12}BrF_2NO_3H^+$: 432.0049 found: 432.00418.

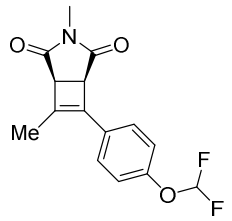
6-(3,5-Bis(trifluoromethyl)phenyl)-7-(3-fluorophenyl)-3-methyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (4m)



According to GP-B, using 6-(3-fluorophenyl)-7-iodo-3-methyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**SI-2**) (71 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, $Pd(OAc)_2$ (0.5 mg, 1 mol%) and SPhos (1.6 mg, 2 mol%.) were added as a solution in THF (0.2 mL). 1-Iodo-3,5-bis(trifluoromethyl)benzene (32 µL, 0.18 mmol, 0.9 equiv.) was added, and the Schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 6:4) furnished the title compound as a colorless viscous oil (51 mg, 0.11 mmol, 57 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.17 (d, J = 1.7 Hz, 2H), 7.85 (s, 1H), 7.47 (dt, J = 7.7, 1.3 Hz, 1H), 7.40 (ddd, J = 11.2, 5.8, 3.4 Hz, 2H), 7.12 (tdd, J = 8.3, 2.7, 1.0 Hz, 1H), 4.17 (d, J = 1.3 Hz, 2H), 3.01 (s, 3H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ = 174.00 (d, J = 23.4 Hz), 164.09, 162.11, 142.26 (d, J = 2.6 Hz), 137.32, 134.48, 133.84 (d, J = 7.7 Hz), 132.55 (q, J = 33.7 Hz), 130.93 (d, J = 8.2 Hz), 126.99 (d, J = 3.9 Hz), 124.18, 122.93 – 122.84 (m), 122.77 (d, J = 3.2 Hz), 122.01, 117.58 (d, J = 21.2 Hz), 114.01 (d, J = 22.8 Hz), 45.60, 45.16, 25.23. **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -63.13, -110.98. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{21}H_{12}F_7NO_2H^+$: 444.08290 found: 444.08308.

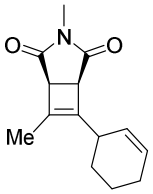
6-(4-(Difluoromethoxy)phenyl)-3,7-dimethyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (4n)



According to GP-B, using 6-iodo-3,7-dimethyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**SI-3**) (55 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, $Pd(OAc)_2$ (0.5 mg, 1 mol%) and SPhos (1.6 mg, 2 mol%.) were added as a solution in THF (0.2 mL). 1-(Difluoromethoxy)-4-iodobenzene (26 µL, 0.18 mmol, 0.9 equiv.) was added, and the Schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 1:1) furnished the title compound as a colorless solid (49 mg, 0.17 mmol, 84 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.51 (t, J = 73.7 Hz, 1H), 3.96 (dq, J = 3.8, 2.0 Hz, 1H), 3.70 – 3.65 (m, 1H), 2.95 (s, 3H), 2.14 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 175.33 (d, J = 62.4 Hz), 150.94 (t, J = 2.9 Hz), 139.56 (d, J = 19.8 Hz), 130.59 (d, J = 37.6 Hz), 128.05, 119.89, 115.82 (t, J = 260.6 Hz), 49.63, 47.01, 45.02, 44.12, 24.86, 15.78, 15.09. **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -81.05 (d, J = 3.5 Hz). **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{15}H_{13}F_2NO_3H^+$: 294.09363 found: 294.09344.

(1*S*,5*R*)-6-(cyclohex-2-en-1-yl)-3,7-dimethyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (4o)



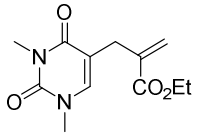
According to GP-A, using 6-iodo-3,7-dimethyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (**SI-3**) (55 mg, 0.2 mmol, 1.0 equiv.). After treatment with CuI (19 mg, 0.1 mmol, 50 mol%.) and stirring for 30 min at ambient temperature, 3-bromocyclohexene (46 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, flash column chromatography (SiO_2; petroleum ether/ EtOAc; 100 % to 7:3) furnished the title compound as a colorless solid (30 mg, 0.13 mmol, 64 %) in a mixture of diastereomers (*dr* ≈ 1:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.82 – 5.76 (m, 1H), 5.63 – 5.58 (m, 1H), 3.60 – 3.55 (m, 1H), 3.46 (dd, J = 2.9, 1.5 Hz, 1H), 3.06 – 2.97 (m, 1H), 2.93 (d, J = 2.1 Hz, 3H), 2.03 – 1.99 (m, 1H), 1.83 (s, 3H), 1.81 – 1.75 (m, 1H), 1.71 – 1.56 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 176.20, 175.91 (Dia1, major), 175.85 (Dia2, minor), 146.63 (Dia1, major), 146.54 (Dia2, minor),

140.05 (Dia1, major), 139.65 (Dia2, minor), 129.27 (Dia1, major), 128.98 (Dia2, minor), 126.91 (Dia2, minor), 126.88 (Dia1, major), 46.69 (Dia1, major), 46.67 (Dia2, minor), 45.59 (Dia2, minor), 45.00 (Dia1, major), 36.47 (Dia2, minor), 35.96 (Dia1, major), 27.19 (Dia2, minor), 27.04 (Dia1, major), 24.99 (Dia1, major), 24.90 (Dia2, minor), 24.76, 21.01 (Dia2, minor), 20.89 (Dia1, major), 13.69 (Dia2, minor), 13.66 (Dia1, major). **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{14}H_{17}NO_2H^+$: 232.13321 found: 232.13302.

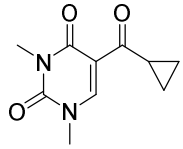
5.3 Scope of the *N,N*-dimethyluracil Series

Ethyl 2-((1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)acrylate (5a)



According to GP-A, using 5-iodo-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**SI-4**) (53 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 30 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added at rt. and stirring was continued for 30 min at this temperature. Then, ethyl-2-(bromomethyl)acrylate (41 µL, 0.3 mmol, 1.5 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, purification of the crude mixture by flash column chromatography (SiO_2; hexane/ EtOAc; 8:2) furnished the title compound as a colorless solid (29 mg, 0.11 mmol, 57 %).
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.12 (s, 1H), 6.25 (d, J = 1.4 Hz, 1H), 5.79 (q, J = 1.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.36 (s, 3H), 3.34 – 3.31 (m, 5H), 1.28 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 166.80, 163.46, 151.84, 141.08, 137.13, 127.71, 110.66, 60.95, 37.02, 29.66, 28.07, 14.30. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{12}H_{16}N_2O_4H^+$: 253.1183 found: 253.1183. Spectral characteristics were in agreement with previously reported data.[223]

5-(Cyclopropanecarbonyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (5b)

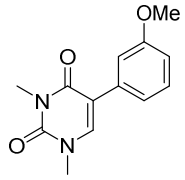


According to GP-A, using 5-iodo-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**SI-4**) (53 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 30 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added at rt. and stirring was continued for 30 min at this temperature. Then, cyclopropanecarbonyl chloride (27 µL, 0.3 mmol, 1.5 equiv.) was added and the reaction mixture was allowed to stir overnight.

[223] T. M. Stevenson, A. S. B. Prasad, J. R. Citineni, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 8375-8378.

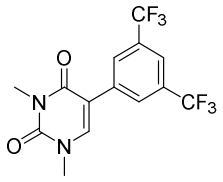
After workup, purification of the crude mixture by flash column chromatography (SiO_2; hexane/ EtOAc; 8:2) furnished the title compound as a colorless solid (29 mg, 0.14 mmol, 70 %).
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.13 (s, 1H), 3.49 (s, 3H), 3.39 (s, 3H), 3.34 (tt, J = 7.9, 4.6 Hz, 1H), 1.16 (p, J = 3.6 Hz, 2H), 1.01 (dq, J = 7.3, 3.6 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 197.43, 161.60, 151.24, 149.01, 111.96, 37.93, 28.35, 19.52, 12.94. **HRMS (ESI)** m/z: calcd for $C_{10}H_{12}N_2O_3$: 208.0848 found: 208.0845. Spectral characteristics were in agreement with previously reported data.[58]

5-(4-Methoxyphenyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (5c)



According to GP-B, using 5-iodo-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**SI-4**) (53 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, $Pd(OAc)_2$ (0.5 mg, 1 mol%) and SPhos (1.6 mg, 2 mol%.) were added as a solution in THF (0.2 mL). 3-Iodoanisole (21 µL, 0.18 mmol, 0.9 equiv.) was added, and the Schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; hexane/ EtOAc; 8:2) furnished the title compound as a colorless solid (33 mg, 0.14 mmol, 68 %).
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.34 – 7.29 (m, 2H), 7.13 – 7.08 (m, 1H), 7.07 – 7.02 (m, 1H), 6.89 – 6.86 (m, 1H), 3.83 (s, 3H), 3.47 (s, 3H), 3.43 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 162.38, 159.74, 151.59, 140.66, 138.35, 134.38, 129.57, 120.67, 114.14, 113.76, 77.41, 77.16, 76.91, 55.46, 37.25, 28.41. **Note:** ^{1}H NMR indicates trace of aromatic impurity. **HRMS (EI)** m/z: calcd for $C_{13}H_{14}N_2O_3$: 246.1104 found: 246.0998.

5-(3,5-Bis(trifluoromethyl)phenyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (5d)



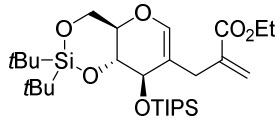
According to GP-B, using 5-iodo-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**SI-4**) (53 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, $Pd(OAc)_2$ (0.5 mg, 1 mol%) and SPhos (1.6 mg, 2 mol%.) were added as a solution in THF (0.2 mL). 1-Iodo-3,5-bis(trifluoromethyl)benzene (32 µL, 0.18 mmol, 0.9 equiv.) was added, and the Schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, purification of the crude mixture by flash column

chromatography (SiO_2; hexane/ EtOAc; 9:1) furnished the title compound as a colorless solid (56 mg, 0.16 mmol, 79 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.00 (d, J = 1.7 Hz, 2H), 7.83 (s, 1H), 7.46 (s, 1H), 3.54 (s, 3H), 3.44 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 161.84, 151.26, 141.76, 135.21, 131.96 (q, J = 33.4 Hz), 128.38 (d, J = 3.8 Hz), 124.45, 122.28, 121.59 (p, J = 4.1 Hz), 111.75, 37.56, 28.52. **HRMS (ESI)** m/z: calcd for $C_{14}H_{10}F_6N_2O_2$: 352.0646 found: 352.0635. Spectral characteristics were in agreement with previously reported data.[224]

5.4 Scope of the Glucal and Galactal Series

Ethyl 2-(((4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-8-((triisopropylsilyl)oxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-yl)methyl)acrylate (6a)

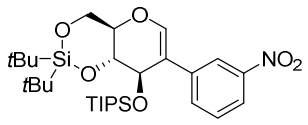


According to GP-A, using (4a*R*,8*S*,8a*R*)-2,2-di-*tert*-butyl-7-iodo-8-((triisopropylsilyl)oxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (**SI-5**) (110 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added and stirring was continued for 30 min at ambient temperature. Then, ethyl-2-(bromomethyl)acrylate (56 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 100 % to 9:1) furnished the title compound as a colorless oil, that solidified in the fridge. (95 mg, 0.17 mmol, 86 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.23 (s, 1H), 6.05 (s, 1H), 5.59 (q, J = 1.6 Hz, 1H), 4.42 (d, J = 6.9 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.12 (dd, J = 10.4, 4.9 Hz, 1H), 4.05 (dd, J = 10.4, 6.9 Hz, 1H), 3.95 (t, J = 10.4 Hz, 1H), 3.75 (td, J = 10.4, 4.9 Hz, 1H), 3.20 (d, J = 16.8 Hz, 1H), 2.89 (d, J = 16.8 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.26 – 1.20 (m, 3H), 1.10 (dd, J = 7.5, 4.7 Hz, 18H), 1.06 (s, 9H), 0.99 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 167.19, 141.35, 139.34, 125.51, 113.60, 78.82, 73.59, 73.38, 65.77, 60.81, 29.51, 27.43, 27.15, 22.89, 20.04, 18.75, 18.57, 14.37, 13.64. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{29}H_{54}O_6Si_2H^+$: 555.3509 found: 555.3506.

[224] R. Kumar, A. Sharma, A. Sharma, *ACS Sustain. Chem. Eng.* **2024**, *12*, 12808-12818.

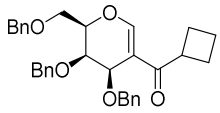
(4a*R*,8*R*,8a*R*)-2,2-di-*tert*-butyl-7-(3-nitrophenyl)-8-((triisopropylsilyl)oxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (6b)



According to GP-B, using (4a*R*,8*S*,8a*R*)-2,2-di-*tert*-butyl-7-iodo-8-((triisopropylsilyl)oxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (**SI-5**) (110 mg, 0.2 mmol, 1.0 equiv After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, $Pd(OAc)_2$ (0.5 mg, 1 mol%) and SPhos (1.6 mg, 2 mol%.) were added as a solution in THF (0.2 mL). 1-Iodo-3-nitrobenzene (45 mg, 0.18 mmol, 0.9 equiv.) was added, and the Schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, purification of the crude mixture by preparative TLC (SiO_2; hexane/ EtOAc; 9:1) furnished the title compound as a colorless solid (67 mg, 0.12 mmol, 59 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.14 (t, J = 2.0 Hz, 1H), 8.09 (dd, J = 8.2, 2.0 Hz, 1H), 7.59 (dt, J = 7.7, 1.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 6.47 (s, 1H), 4.94 (d, J = 6.7 Hz, 1H), 4.20 (ddd, J = 10.4, 7.7, 5.7 Hz, 2H), 4.03 (t, J = 10.4 Hz, 1H), 3.94 (td, J = 10.4, 4.7 Hz, 1H), 1.08 (s, 9H), 1.04 (s, 9H), 1.02 – 0.98 (m, 3H), 0.94 (d, J = 7.3 Hz, 9H), 0.88 (d, J = 7.3 Hz, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 148.17, 143.11, 139.02, 134.59, 129.08, 123.49, 121.69, 118.09, 78.47, 73.66, 73.46, 65.59, 27.38, 27.21, 22.92, 20.11, 18.52, 18.24, 13.56. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{29}H_{49}NO_6Si_2H^+$: 564.3178 found: 564.3183.

((2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)(cyclobutyl)methanone (6c)

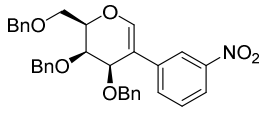


According to GP-A, using (2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-iodo-3,4-dihydro-2*H*-pyran (**SI-6**) (108 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.18 mmol, 0.9 equiv.) and stirring for 15 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added at 0°C and stirring was continued for 30 min at this temperature. Then, cyclobutanecarbonyl chloride (46 µL, 0.4 mmol, 2.0 equiv.) was added, the ice bath was removed and the reaction mixture was allowed to stir overnight. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 8:2) furnished the title compound as a colorless oil. (47 mg, 0.09 mmol, 47 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.45 – 7.21 (m, 16H), 4.81 (d, J = 11.2 Hz, 1H), 4.75 (d, J = 11.3 Hz, 1H), 4.73 – 4.67 (m, 2H), 4.67 – 4.61 (m, 1H), 4.62 – 4.56 (m, 2H), 4.50 (d, J = 11.9 Hz, 1H), 4.06 – 3.95 (m, 2H), 3.82 (dd, J = 5.7, 3.5 Hz, 1H), 3.50 (p, J = 8.5 Hz, 1H), 2.49 – 2.24 (m, 2H), 2.20 – 2.07 (m, 2H), 2.06 – 1.94 (m, 1H), 1.90 – 1.77 (m, 1H). **^{13}C NMR** (126

MHz, $CDCl_3$) δ = 199.01, 155.99, 139.25, 138.18, 137.70, 128.60, 128.46, 128.20, 128.02, 127.98, 127.73, 127.63, 127.32, 115.28, 77.06, 74.21, 74.02, 73.43, 71.48, 68.55, 66.13, 41.20, 25.72, 24.94, 18.27. **HRMS (ESI)** m/z: [H] + calcd for $C_{32}H_{34}O_5^+$: 499.2479 found: 499.2485.

(2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-(3-nitrophenyl)-3,4-dihydro-2*H*-pyran (6d)

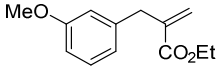


According to GP-B, using (2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-iodo-3,4-dihydro-2H-pyran (**SI-6**) (108 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, $Pd(OAc)_2$ (0.5 mg, 1 mol%) and SPhos (1.6 mg, 2 mol%.) were added as a solution in THF (0.2 mL). 1-bromo-3-nitrobenzene (36 mg, 0.18 mmol, 0.9 equiv.) was added, and the Schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 9:1) furnished the title compound as a red oil. (52 mg, 0.10 mmol, 54 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.08 (t, J = 2.1 Hz, 1H), 8.03 (dd, J = 8.1, 2.3 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.42 – 7.30 (m, 11H), 7.28 – 7.24 (m, 3H), 7.22 – 7.11 (m, 2H), 6.75 (s, 1H), 4.87 (d, J = 11.2 Hz, 1H), 4.83 (d, J = 11.8 Hz, 1H), 4.74 (d, J = 11.8 Hz, 1H), 4.62 (dd, J = 11.6, 7.1 Hz, 2H), 4.58 – 4.54 (m, 2H), 4.52 (d, J = 12.0 Hz, 1H), 4.18 (t, J = 3.9 Hz, 1H), 4.04 (dd, J = 11.0, 8.0 Hz, 1H), 3.92 (dd, J = 11.1, 3.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 148.44, 143.85, 139.21, 138.13, 137.86, 137.80, 131.89, 129.17, 128.64, 128.51, 128.46, 128.42, 128.26, 128.23, 128.10, 128.02, 127.88, 127.83, 121.04, 120.87, 112.61, 75.81, 73.91, 73.78, 73.54, 72.90, 71.11, 67.99. **HRMS (ESI)** m/z: [H] + calcd for $C_{33}H_{31}NO_6^+$: 538.2224 found: 538.2912. Note: product has degraded during MS analysis.

5.5 Scope of the Aryl Series

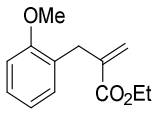
Ethyl 2-(3-methoxybenzyl)acrylate (9a)



According to GP-C, with 1-iodo-3-methoxybenzene (26 μL, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for stirring for 15 min at ambient temperature CuI (19 mg, 0.1 mmol, 50 mol%.) was added at rt. and stirring was continued for 30 min. Then, ethyl 2-(bromomethyl)acrylate (56 µL, 0.4 mmol, 2 equiv.) was added and the reaction mixture was allowed to stir overnight at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 100 % to 9:1) furnished the title compound as a white solid (20 mg, 0.09 mmol, 45 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.24 – 7.17 (m, 1H), 6.84 – 6.78 (m, 1H), 6.78 – 6.71 (m, 2H), 6.25 – 6.21 (m, 1H), 5.49 – 5.43 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 3.61 (s, 2H), 1.27 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 166.93, 159.68, 140.42, 140.21, 129.35, 126.06, 121.47, 114.77, 111.70, 60.76, 55.15, 38.07, 14.16. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{13}H_{16}O^+$: 221.1172 found: 221.1173. Spectral characteristics were in agreement with previously reported data.[225]

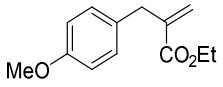
Ethyl 2-(2-methoxybenzyl)acrylate (9b)



According to GP-C, with 1-iodo-2-methoxybenzene (26 μL, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for stirring for 15 min at ambient temperature CuI (19 mg, 0.1 mmol, 50 mol%.) was added at rt. and stirring was continued for 30 min. Then, ethyl 2-(bromomethyl)acrylate (56 µL, 0.4 mmol, 2 equiv.) was added and the reaction mixture was allowed to stir overnight at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 100 % to 9:1) furnished the title compound as a white solid (34 mg, 0.15 mmol, 77 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.25 – 7.18 (m, 1H), 7.16 – 7.11 (m, 1H), 6.94 – 6.88 (m, 1H), 6.88 – 6.83 (m, 1H), 6.19 (q, J = 1.3 Hz, 1H), 5.33 (q, J = 1.3 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.80 (s, 3H), 3.63 (s, 2H), 1.29 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 167.27, 157.58, 139.55, 130.67, 127.71, 127.23, 125.43, 120.44, 110.48, 60.65, 55.33, 31.99, 14.20. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{13}H_{16}O^+$: 221.1172 found: 221.1173.

Ethyl 2-(4-methoxybenzyl)acrylate (9c)

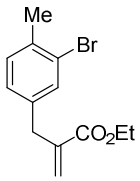


According to GP-C, with 1-iodo-4-methoxybenzene (46 mL, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for stirring for 15 min at ambient temperature CuI (19 mg, 0.1 mmol, 50 mol%.) was added at rt. and stirring was continued for 30 min. Then, ethyl 2-(bromomethyl)acrylate (56 µL, 0.4 mmol, 2 equiv.) was added and the reaction mixture was allowed to stir overnight at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 100 % to 9:1) furnished the title compound as a white solid (23 mg, 0.10 mmol, 52 %).

[225] M. L. N. Rao, S. Giri, *Eur. J. Org. Chem.* **2012**, *2012*, 4580-4589.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.11 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.20 (d, J = 1.3 Hz, 1H), 5.43 (d, J = 1.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.57 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 167.02, 158.15, 140.82, 130.83, 130.05, 125.61, 113.83, 60.71, 55.25, 37.24, 14.16. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{13}H_{16}O^+$: 221.1172 found: 221.1172. Spectral characteristics were in agreement with previously reported data.[226]

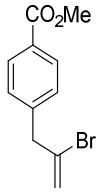
Ethyl 2-(3-bromo-4-methylbenzyl)acrylate (9d)



According to GP-C, using 2-bromo-4-iodo-1-methylbenzene (29 µL, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added and stirring was continued for 30 min at ambient temperature. Then, ethyl-2-(bromomethyl)acrylate (56 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 99:1 to 9:1) furnished the title compound as a colorless oil (45 mg, 0.16 mmol, 80 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.37 (d, J = 1.8 Hz, 1H), 7.14 (d, J = 7.7 Hz, 1H), 7.04 (dd, J = 7.7, 1.8 Hz, 1H), 6.24 (d, J = 1.3 Hz, 1H), 5.48 (q, J = 1.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.56 (s, 2H), 2.36 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 166.82, 140.03, 138.42, 135.86, 132.86, 130.83, 128.12, 126.43, 124.93, 60.97, 37.41, 22.58, 14.28. **HRMS (EI)** m/z: calcd for $C_{13}H_{15}BrO_2$: 282.0255 found: 282.0253.

Methyl 4-(2-bromoallyl)benzoate (9e)

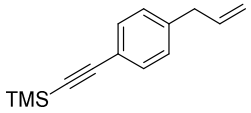


According to GP-C, using methyl 4-iodobenzoate (52 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added at 0°C and stirring was continued for 30 min at this temperature. Then, 2,3-dibrompropene (38 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight warming to rt.

[226] J. Xu, Z. He, J. Zhang, J. Chen, Y. Huang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202211408.

After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 100 % to 8:2) furnished the title compound as a colorless oil (28 mg, 0.11 mmol, 55 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.01 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 5.61 (d, J = 1.5 Hz, 1H), 5.54 (d, J = 1.5 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 167.05, 142.53, 131.68, 130.02, 129.19, 129.14, 118.91, 52.22, 47.73. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{11}H_{11}BrO_2H^+$: 255.00152 found: 255.00156.

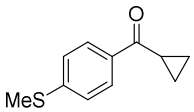
((4-Allylphenyl)ethynyl)trimethylsilane (9f)



According to GP-C, using ((4-iodophenyl)ethynyl)trimethylsilane (60 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added and stirring was continued for 30 min at ambient temperature. Then, allyl bromide (34 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane) furnished the title compound as a colorless oil (29 mg, 0.13 mmol, 67 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 5.94 (ddt, J = 16.9, 10.3, 6.6 Hz, 1H), 5.10 – 5.04 (m, 2H), 3.37 (d, J = 6.6 Hz, 2H), 0.25 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 140.79, 136.97, 132.18, 128.65, 120.98, 116.35, 105.37, 93.71, 40.21, 0.16. **HRMS (EI)** m/z: calcd for $C_{14}H_{18}Si$: 214.1178 found: 214.1182. Spectral characteristics were in agreement with previously reported data.[48]

Cyclopropyl(4-(methylthio)phenyl)methanone (9g)

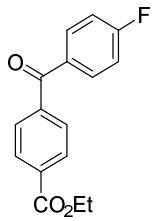


According to GP-C, with (4-iodophenyl)(methyl)sulfane (50 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for stirring for 15 min at ambient temperature CuI (19 mg, 0.1 mmol, 50 mol%.) was added at 0°C and stirring was continued for 30 min at this temperature. Then, cyclopropanecarbonyl chloride (27 µL, 0.3 mmol, 1.5 equiv.) was added and the reaction mixture was allowed to for 5 h at rt. After workup, purification of the crude mixture by flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 7:3) furnished the title compound as a colorless solid (28 mg, 0.15 mmol, 73 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.96 – 7.91 (m, 2H), 7.31 – 7.27 (m, 2H), 2.65 – 2.60 (m, 1H), 2.53 (s, 3H), 1.23 – 1.21 (m, 2H), 1.04 – 1.00 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 199.65,

145.48, 134.47, 128.59, 125.18, 16.98, 15.00, 11.62. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{11}H_{12}OSH^+$: 193.06816 found: 193.06798. Spectral characteristics were in agreement with previously reported data.[227]

Ethyl 4-(4-fluorobenzoyl)benzoate (9h)

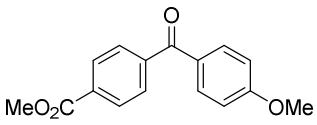


According to GP-C, with ethyl 4-iodobenzoate (34 µL, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature CuI (8 mg, 0.04 mmol, 20 mol%.) was added at ambient temperature and stirring was continued for 30 min at this temperature. Then, 4-fluorobenzoyl chloride (47 µL, 0.40 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir 1 h at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 95:5) furnished the title compound as a white solid (33 mg, 0.12 mmol, 61 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.15 (d, J = 8.4 Hz, 2H), 7.84 (dd, J = 8.6, 5.5 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.17 (t, J = 8.6 Hz, 2H), 4.42 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 194.71, 165.89, 165.80 (d, J = 255.1 Hz), 141.24, 133.38 (d, J = 2.9 Hz), 133.37, 132.89 (d, J = 9.4 Hz), 129.70, 129.67, 115.82 (d, J = 22.0 Hz), 61.61, 14.43. **HRMS (ESI)** m/z: [H] + calcd for $C_{16}H_{13}FO_3^+$: 273.0922 found: 273.0921. Spectral characteristics were in agreement with previously reported data.[228]

[227] C. Chen, H. Wang, T. Li, D. Lu, J. Li, X. Zhang, X. Hong, Z. Lu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205619.
[228] A. D. Benischke, M. Leroux, I. Knoll, P. Knochel, *Org. Lett.* **2016**, *18*, 3626-3629.

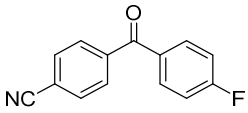
Methyl 4-(4-methoxybenzoyl)benzoate (9i)



According to GP-C on a 40 mmol and 0.2 mmol scale, respectively. Methyl 4-iodobenzoate (10.5 g, 40 mmol, 1.0 equiv) in THF (50 mL). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (28 mmol, 0.7 equiv.) and stirring for 30 min at ambient temperature, CuI (3.8 g, 20 mmol, 50 mol%.) was added portionwise at 0°C and stirring was continued for 30 min at this temperature. Then, 4-methoxybenzoyl chloride (10.2 g, 60 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was allowed to stir overnight warming to rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 100 % to 3:7) furnished the title compound as a light-yellow solid (8.5 g, 32 mmol, 79 %). A comparative run on 0.2 mmol scale yielded a lower yield of a colorless solid (39 mg, 0.15 mmol, 73 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.13 (d, J = 8.4 Hz, 2H), 7.80 (dd, J = 15.9, 8.4 Hz, 4H), 7.00 – 6.93 (m, 2H), 3.96 (s, 3H), 3.89 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 194.90, 166.53, 163.77, 142.30, 132.75, 129.57, 113.89, 55.68, 52.55. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{16}H_{14}O_4H^+$: 271.09649 found: 271.09671. Spectral characteristics were in agreement with previously reported data.[229]

4-(4-Fluorobenzoyl)benzonitrile (9j)

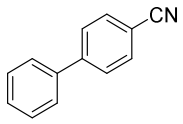


According to GP-C, with 4-iodobenzonitrile (46 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for stirring for 15 min at ambient temperature CuI (19 mg, 0.1 mmol, 50 mol%.) was added at rt. and stirring was continued for 30 min. Then, 4-fluorobenzoyl chloride (47 µL, 0.4 mmol, 2 equiv.) was added and the reaction mixture was allowed to stir for 3 h at rt. After workup, purification of the crude mixture by flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 8:2) furnished the title compound as a colorless solid (36 mg, 0.16 mmol, 80 %).

[229] Y.-T. Zhao, Y.-X. Su, X.-Y. Li, L.-L. Yang, M.-Y. Huang, S.-F. Zhu, *Angew. Chem. Int. Ed.* **2021**, *60*, 24214-24219.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.00 – 7.68 (m, 6H), 7.19 (t, J = 8.5 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 193.64, 165.99 (d, J = 256.0 Hz), 141.26, 132.88 (d, J = 9.3 Hz), 132.74 (d, J = 3.0 Hz), 132.37, 130.18, 118.03, 116.04 (d, J = 22.0 Hz), 115.89, 77.41, 77.16, 76.91. **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -104.02. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{14}H_8FNO^+$: 226.0661 found: 226.0668. Spectral characteristics were in agreement with previously reported data.[230]

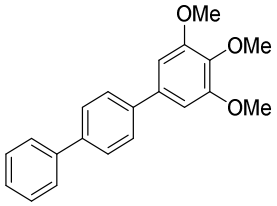
[1,1'-Biphenyl]-4-carbonitrile (9k)



According to GP-C, using 4-iodobiphenyl (56 mg, 0.1 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, *p*-toluenesulfonyl cyanide (54 mg, 0.3 mmol, 1.5 equiv.) was added and the mixture stirred overnight at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 100 % to 95:5) furnished the title compound as a colorless solid (22 mg, 0.12 mmol, 62 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.75 – 7.67 (m, 4H), 7.61 – 7.57 (m, 2H), 7.51 – 7.46 (m, 2H), 7.45 – 7.41 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 145.84, 139.34, 132.74, 129.26, 128.80, 127.88, 127.38, 119.07, 111.09. **HRMS (EI)** m/z: calcd for $C_{13}H_9N$: 179.0735 found: 179.0726. Spectral characteristics were in agreement with previously reported data.[225]

3,4,5-Trimethoxy-1,1':4',1''-terphenyl (9l)

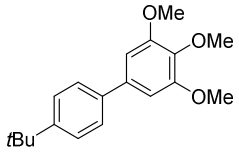


According to GP-D, using 4-iodo-1,1'-biphenyl (56 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, $ZnCl_2$ (0.2 mL, 0.2 mmol, 1.0 equiv., 1 M solution in THF) and $Pd(dppf)Cl_2$ (8 mg, 5 mol%) were added in the reaction mixture. 5-Iodo-1,2,3-trimethoxybenzene (53 mg, 0.18 mmol, 0.9 equiv.) was added, and the Schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, flash column chromatography (SiO_2; pentane/ EtOAc; 9:1) furnished the title compound as a colorless solid (43 mg, 0.13 mmol, 76 %).

[230] S. Lai, N. Takaesu, W. X. Lin, D. M. Perrin, *Tetrahedron Lett.* **2021**, *74*, 153147.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.70 – 7.63 (m, 6H), 7.47 (t, J = 7.7 Hz, 2H), 7.40 – 7.35 (m, 1H), 6.84 (s, 2H), 3.95 (s, 6H), 3.92 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 153.65, 140.77, 140.39, 140.32, 137.89, 136.83, 128.97, 127.59, 127.57, 127.52, 127.16, 104.53, 61.11, 56.36. **HRMS (EI)** m/z: calcd for $C_{21}H_{20}O_3$: 320.1412 found: 320.1404. Spectral characteristics were in agreement with previously reported data.[231]

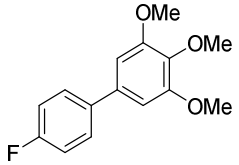
4'-(*tert*-Butyl)-3,4,5-trimethoxy-1,1'-biphenyl (9m)



According to GP-D, using 1-(*tert*-butyl)-4-iodobenzene (36 µL, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, $ZnCl_2$ (0.2 mL, 0.2 mmol, 1.0 equiv., 1 M solution in THF) and $Pd(dppf)Cl_2$ (8 mg, 5 mol%) were added in the reaction mixture. 5-Iodo-1,2,3-trimethoxybenzene (53 mg, 0.18 mmol, 0.9 equiv.) was added, and the Schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, flash column chromatography (SiO_2; pentane/ EtOAc; 9:1) furnished the title compound as a colorless solid (27 mg, 0.08 mmol, 50 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.52 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 6.80 (s, 2H), 3.94 (s, 6H), 3.92 (s, 3H), 1.39 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 153.41, 150.38, 138.54, 137.45, 137.16, 126.76, 125.68, 104.39, 60.96, 56.18, 34.55, 31.37. **HRMS (EI)** m/z: calcd for $C_{19}H_{24}O_3H^+$: 300.1725 found: 300.1715. Spectral characteristics were in agreement with previously reported data.[232]

4'-Fluoro-3,4,5-trimethoxy-1,1'-biphenyl (9n)



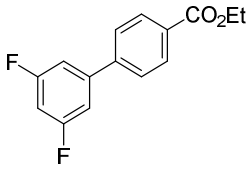
According to GP-D, using 1-fluoro-4-iodobenzene (23 µL, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, $ZnCl_2$ (0.2 mL, 0.2 mmol, 1.0 equiv., 1 M solution in THF) and $Pd(dppf)Cl_2$ (8 mg, 5 mol%) were added in the reaction mixture.

[231] X. Li, Y. Ma, Q. Hu, B. Jiang, Q. Wu, Z. Yuan, *Catal. Commun.* **2018**, *117*, 57-62.
[232] Z.-Y. Wang, B. Ma, H. Xu, X. Wang, X. Zhang, H.-X. Dai, *Org. Lett.* **2021**, *23*, 8291-8295.

5-Iodo-1,2,3-trimethoxybenzene (53 mg, 0.18 mmol, 0.9 equiv.) was added, and the Schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, flash column chromatography (SiO_2; pentane/ EtOAc; 9:1) furnished the title compound as a colorless solid (37 mg, 0.14 mmol, 71 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.53 – 7.48 (m, 2H), 7.14 – 7.08 (m, 2H), 6.72 (s, 2H), 3.92 (s, 6H), 3.89 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 163.52, 161.56, 153.63, 140.86, 137.81, 137.61 (d, J = 2.9 Hz), 136.38, 128.75 (d, J = 7.6 Hz), 115.78, 115.61, 104.56, 61.09, 56.35. **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -115.66. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{15}H_{15}FO_3H^+$: 263.10780 found: 263.10798. Spectral characteristics were in agreement with previously reported data.[233]

Ethyl 3',5'-difluoro-[1,1'-biphenyl]-4-carboxylate (9o)

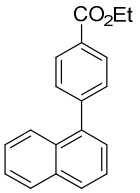


According to GP-D, using 1,3-difluoro-5-iodobenzene (24 µL, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, $ZnCl_2$ (0.2 mL, 0.2 mmol, 1.0 equiv., 1 M solution in THF) and $Pd(dppf)Cl_2$ (8 mg, 5 mol%) were added in the reaction mixture. Ethyl 4-iodobenzoate (50 mg, 0.18 mmol, 0.9 equiv.) was added, and the Schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, flash column chromatography (SiO_2; pentane/ EtOAc; 99:1 to 9:1) furnished the title compound as a colorless solid (30 mg, 0.12 mmol, 63 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.12 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.16 – 7.10 (m, 2H), 6.83 (tt, J = 9.1, 2.5 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 166.31, 164.49 (d, J = 13.3 Hz), 162.52 (d, J = 12.9 Hz), 143.51 (t, J = 9.3 Hz), 143.16 (t, J = 2.6 Hz), 130.57, 130.40, 127.09, 110.65 – 110.08 (m), 103.47 (t, J = 25.5 Hz), 61.30, 14.48. **HRMS (EI)** m/z: calcd for $C_{15}H_{12}F_2O_2$: 262.0805 found: 262.0802.

[233] A. Music, A. N. Baumann, P. Spieß, A. Plantefol, T. C. Jagau, D. Didier, *J. Am. Chem. Soc.* **2020**, *142*, 4341-4348.

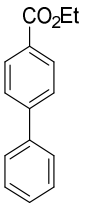
Ethyl 4-(naphthalen-1-yl)benzoate (9p)



According to GP-D, using 1-iodonaphthalene (29 µL, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, $ZnCl_2$ (0.2 mL, 0.2 mmol, 1.0 equiv., 1 M solution in THF) and $Pd(dppf)Cl_2$ (7 mg, 5 mol%) were added in the reaction mixture. Ethyl 4-iodobenzoate (30 µL, 0.18 mmol, 0.9 equiv.) was added, and the schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, flash column chromatography (SiO_2; pentane/ EtOAc; 98:2) furnished the title compound as a colorless solid (27 mg, 0.10 mmol, 55 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.18 (d, J = 7.8 Hz, 2H), 7.91 (dd, J = 13.9, 8.2 Hz, 2H), 7.84 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 7.8 Hz, 2H), 7.52 (dt, J = 14.9, 7.6 Hz, 2H), 7.44 (dd, J = 10.8, 7.2 Hz, 2H), 4.44 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 166.70, 145.59, 139.31, 133.90, 131.38, 130.20, 129.66, 129.52, 128.51, 128.37, 127.04, 126.45, 126.08, 125.75, 125.45, 61.16, 14.52. **HRMS (ESI)** m/z: [H] + calcd for $C_{19}H_{16}O_2^+$: 277.1223 found: 277.1226. Spectral characteristics were in agreement with previously reported data.[234]

Ethyl [1,1'-biphenyl]-4-carboxylate (9q)

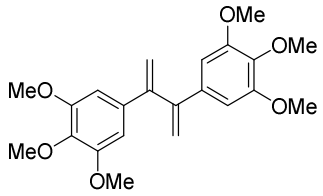


According to GP-D, using iodobenzene (22 µL, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, $ZnCl_2$ (0.2 mL, 0.2 mmol, 1.0 equiv., 1 M solution in THF) and $Pd(dppf)Cl_2$ (7 mg, 5 mol%) were added in the reaction mixture. Ethyl 4-iodobenzoate (30 µL, 0.18 mmol, 0.9 equiv.) was added, and the schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, flash column chromatography (SiO_2; pentane/ EtOAc; 98:2) furnished the title compound as a colorless oil (16 mg, 0.07 mmol, 40 %).

[234] M. O. Akram, P. S. Shinde, C. C. Chintawar, N. T. Patil, *Org. Biomol. Chem.* **2018**, *16*, 2865-2869.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.12 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 7.0 Hz, 2H), 7.47 (t, J = 7.7 Hz, 2H), 7.40 (t, J = 7.4 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 166.66, 145.67, 140.21, 130.19, 129.40, 129.04, 128.23, 127.41, 127.14, 61.10, 14.49. **HRMS (ESI)** m/z: [H] + calcd for $C_{15}H_{14}O_2^+$: 227.1067 found: 227.1070. Spectral characteristics were in agreement with previously reported data.[235]

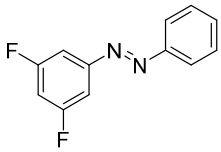
5,5'-(Buta-1,3-diene-2i,3-diyl)bis(1,2,3-trimethoxybenzene) (9r)



According to GP-C, with 5-iodo-1,2,3-trimethoxybenzene (59 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 20 min at ambient temperature. Then, 1,4-dichlorobut-2-yne (30 µL, 0.3 mmol, 1.5 equiv.) was added and the reaction mixture was allowed to stir overnight warming to rt. After workup, flash column chromatography (SiO_2; pentane/ EtOAc; 9:1) furnished the title compound as a colorless oil (34 mg, 0.08 mmol, 47 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.61 (s, 4H), 5.50 (d, J = 1.6 Hz, 2H), 5.31 (d, J = 1.6 Hz, 2H), 3.83 (s, 6H), 3.81 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 153.06, 149.86, 137.93, 136.10, 116.21, 105.03, 61.02, 56.25. **Note:** ^{1}H NMR indicates trace of aromatic impurity. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{22}H_{26}O_6H^+$: 387.18022 found: 387.18049. Spectral characteristics were in agreement with previously reported data.[236]

(*E*)-1-(3,5-Difluorophenyl)-2-phenyldiazene (9s)



According to GP-C, with 1,3-difluoro-5-iodobenzene (36 µL, 0.3 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.21 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature the mixture was cooled to -50 °C and phenyl diazonium tetrafluoroborate (21 mg, 0.1 mmol, 0.33 equiv.) was added and the reaction mixture was allowed to stir overnight warming to rt.

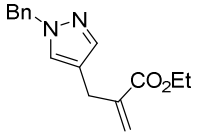
[235] J. K. Vankar, S. Tothadi, G. N. Gururaja, *Eur. J. Org. Chem.* **2024**, e202400776.
[236] H. Jiang, L. He, X. Li, H. Chen, W. Wu, W. Fu, *Chem. Commun.* **2013**, *49*, 9218-9220.

After workup, flash column chromatography (SiO_2; pentane/ EtOAc; 95:5 to 9:1) furnished the title compound as an orange solid (11 mg, 0.05 mmol, 53 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.02 – 7.85 (m, 2H), 7.59 – 7.51 (m, 3H), 7.47 (dd, J = 7.7, 2.4 Hz, 2H), 6.93 (tt, J = 8.5, 2.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 163.45 (d, J = 249.7 Hz), 163.34 (d, J = 249.6 Hz), 154.69, 152.22, 132.12, 129.38, 123.40, 106.36 - 105.73 (m, 3CH). **HRMS (EI)** m/z: calcd for $C_{12}H_8F_2N_2$: 218.0656 found: 218.0651. Spectral characteristics were in agreement with previously reported data.[237]

5.6 Scope of the Electron-rich Heteroaryl Series

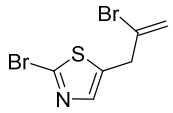
Ethyl 2-((1-benzyl-1H-pyrazol-4-yl)methyl)acrylate (10a)



According to GP-C, with 1-benzyl-4-iodo-1H-pyrazole (57 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature CuI (19 mg, 0.10 mmol, 50 mol%.) was added at ambient temperature and stirring was continued for 30 min at this temperature. Then, ethyl 2-(bromomethyl)acrylate (55 µL, 0.40 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 80:20) furnished the title compound as a colorless oil (53 mg, 0.19 mmol, 94 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36 (s, 1H), 7.34 – 7.22 (m, 3H), 7.21 – 7.10 (m, 3H), 6.13 (d, J = 1.4 Hz, 1H), 5.47 (d, J = 1.5 Hz, 1H), 5.23 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.43 (s, 2H), 1.23 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 166.97, 140.40, 139.64, 136.80, 128.86, 128.64, 128.07, 127.71, 125.19, 118.85, 60.81, 56.06, 27.11, 14.25. **HRMS (ESI)** m/z: [H] + calcd for $C_{16}H_{18}N_2O_2^+$: 271.1441 found: 271.1439.

2-Bromo-5-(2-bromoallyl)thiazole (10b)



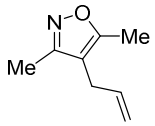
According to GP-C, with 2-bromo-5-iodothiazole (58 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature CuI (19 mg, 0.1 mmol, 50 mol%.) was added at 0°C and stirring was continued for 30 min at this temperature. Then, 2,3-dibrompropene (38 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight warming to rt.

[237] H. Song, J. Wei, Z. Wang, Y. Liu, S. Zhao, X. Cai, Y. Xiao, L. Yang, P. Bai, L. Fang, F. Yang, S. Zheng, W. Zhang, J. Pan, C. Xu, *ACS Catal.* **2024**, *14*, 12372-12384.

After workup, purification of the crude mixture by flash column chromatography (CombiFlash EZ Prep, SiO_2 (25 g); petroleum ether/ EtOAc; 100 % to 7:3) furnished the title compound as a colorless oil (29 mg, 0.1 mmol, 51 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.39 (s, 1H), 5.73 (dt, J = 2.1, 1.2 Hz, 1H), 5.56 (d, J = 2.1 Hz, 1H), 3.89 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 141.63, 138.28, 135.54, 129.73, 119.46, 39.26. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_6H_5Br_2NSH^+$: 281.8582 found: 281.8581.

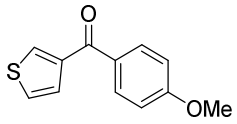
4-Allyl-3,5-dimethylisoxazole (10c)



According to GP-C, using 4-iodo-3,5-dimethylisoxazole (45 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added and stirring was continued for 30 min at ambient temperature. Then, allyl bromide (34 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight. After workup, purification of the crude mixture by flash column chromatography (SiO_2; petroleum ether/ EtOAc; 100 % to 7:3) furnished the title compound as a colorless oil (19 mg, 0.14 mmol, 68 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.80 (ddt, J = 17.0, 10.1, 5.8 Hz, 1H), 5.04 (dq, J = 10.1, 1.6 Hz, 1H), 4.96 (dq, J = 17.0, 1.8 Hz, 1H), 3.05 (dt, J = 5.8, 1.8 Hz, 2H), 2.29 (s, 3H), 2.17 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 165.33, 160.06, 134.95, 115.82, 111.03, 26.41, 11.02, 10.28. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_8H_{11}NOH^+$: 138.0913 found: 138.0914.

(4-Methoxyphenyl)(thiophen-3-yl)methanone (10d)

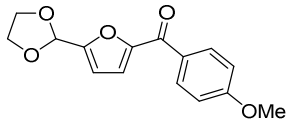


According to GP-C, with 3-iodothiophene (20 µL, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added and stirring was continued for 30 min at ambient temperature. Then, 4-methoxybenzoyl chloride (54 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir for 6 h at ambient temperature. After workup, purification of the crude mixture by flash column chromatography (SiO_2; petroleum ether/ EtOAc; 95:5 to 8:2) furnished the title compound as a colorless solid (42 mg, 0.17 mmol, 85 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.91 – 7.86 (m, 3H), 7.56 (dd, J = 5.0, 1.2 Hz, 1H), 7.37 (dd, J = 5.0, 2.9 Hz, 1H), 7.01 – 6.95 (m, 2H), 3.89 (s, 3H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ = 188.99, 163.29, 141.71, 132.86, 131.99, 131.34, 128.85, 126.12, 113.79, 55.64. **HRMS (ESI)** m/z: $[H]^+$

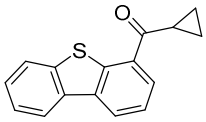
calcd for $C_{12}H_{10}O_2SH^+$: 219.04743 found: 219.04741. Spectral characteristics were in agreement with previously reported data.[238]

(5-(1,3-Dioxolan-2-yl)furan-2-yl)(4-methoxyphenyl)methanone (10e)



According to GP-C, using 2-(5-iodofuran-2-yl)-1,3-dioxolane (**SI-7**) (53 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added at 0°C and stirring was continued for 30 min at this temperature. Then, 4-methoxybenzoyl chloride (54 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight warming to rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 95:5 to 6:4) furnished the title compound as a colorless oil (38 mg, 0.14 mmol, 70 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.02 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 3.5 Hz, 1H), 6.97 (d, J = 9.0 Hz, 2H), 6.59 (d, J = 3.5 Hz, 1H), 6.02 (s, 1H), 4.17 – 4.10 (m, 2H), 4.07 – 4.01 (m, 2H), 3.87 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 181.07, 163.47, 155.74, 152.84, 131.91, 129.81, 119.87, 113.84, 110.21, 97.57, 65.46, 55.59, 27.08. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{15}H_{14}O_5H^+$: 275.09140 found: 275.09146.

Cyclopropyl(dibenzo[*b,d*]thiophen-4-yl)methanone (10f)

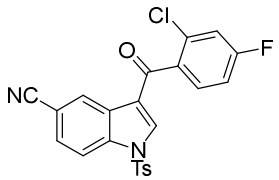


According to GP-C, with 4-iododibenzothiophene (62 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature CuI (8 mg, 0.04 mmol, 20 mol%.) was added at ambient temperature and stirring was continued for 30 min at this temperature. Then, cyclopropanecarbonyl chloride (36 µL, 0.40 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight warming to rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 95:5) furnished the title compound as a colorless oil (34 mg, 0.13 mmol, 68 %).

[238] L. Röder, A. J. Nicholls, I. R. Baxendale, *Molecules* **2019**, *24*, 1996.

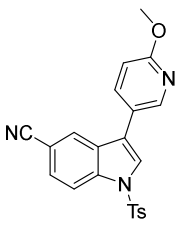
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.38 (d, J = 7.7 Hz, 1H), 8.31 (d, J = 7.5 Hz, 1H), 8.18 (dd, J = 6.7, 2.2 Hz, 1H), 7.93 (dd, J = 6.7, 2.1 Hz, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.52 – 7.41 (m, 2H), 2.87 (tt, J = 8.1, 4.5 Hz, 1H), 1.42 – 1.36 (m, 2H), 1.12 (dq, J = 7.3, 3.7 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 199.36, 142.34, 139.34, 137.39, 133.91, 131.36, 128.43, 127.23, 125.89, 124.56, 124.22, 122.85, 121.47, 16.84, 11.94. **HRMS (EI)** m/z: [H] + calcd for $C_{16}H_{12}OS^+$: 252.0603 found: 252.0602.

3-(2-Chloro-4-fluorobenzoyl)-1-tosyl-1*H*-indole-5-carbonitrile (10g)



According to GP-C, with 3-iodo-1-tosyl-1H-indole-5-carbonitrile (84 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature CuI (8 mg, 0.04 mmol, 20 mol%.) was added at ambient temperature and stirring was continued for 30 min at this temperature. Then, 2-chloro-4-fluorobenzoylchloride (53 µL, 0.40 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir 2 h at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 80:20) furnished the title compound as an orange oil (70 mg, 0.15 mmol, 78 %).
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.72 (d, J = 1.7 Hz, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.91 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.65 (dd, J = 8.7, 1.7 Hz, 1H), 7.48 (dd, J = 8.5, 5.9 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.25 (dd, J = 8.5, 2.3 Hz, 1H), 7.14 (td, J = 8.1, 2.4 Hz, 1H), 2.38 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 188.04, 163.54 (d, J = 254.9 Hz), 147.04, 136.67, 136.45, 134.78 (d, J = 3.6 Hz), 133.70, 132.70 (d, J = 10.5 Hz), 130.79 (d, J = 9.3 Hz), 130.67, 129.17, 128.16, 127.38, 120.31, 118.84, 118.26 (d, J = 24.8 Hz), 114.67 (d, J = 21.5 Hz), 114.28, 109.04, 21.79. **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -106.47. **HRMS (EI)** m/z: [H] + calcd for $C_{23}H_{14}ClFN_2O_3S^+$: 452.0392 found: 452.0392.

3-(6-methoxypyridin-3-yl)-1-tosyl-1*H*-indole-5-carbonitrile (10h)



According to GP-D, using 3-Iodo-1-tosyl-1*H*-indole-5-carbonitrile (84 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, $ZnCl_2$ (0.2 mL, 0.2 mmol, 1.0 equiv., 1 M solution in THF) and

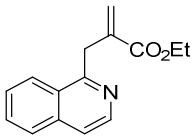
$Pd(dppf)Cl_2$ (7 mg, 5 mol%) were added in the reaction mixture. 5-Bromo-2-methoxypyridine (23 µL, 0.18 mmol, 0.9 equiv.) was added, and the schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, flash column chromatography (SiO_2; pentane/ EtOAc; 90:10) furnished the title compound as a yellow oil (22 mg, 0.06 mmol, 31 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.35 (d, J = 2.5 Hz, 1H), 8.14 (d, J = 8.7 Hz, 1H), 8.00 (d, J = 1.4 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.75 (s, 1H), 7.73 (dd, J = 8.5, 2.5 Hz, 1H), 7.62 (dd, J = 8.7, 1.5 Hz, 1H), 7.29 (d, J = 8.1 Hz, 2H), 6.88 (d, J = 8.5 Hz, 1H), 3.99 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.18, 146.12, 145.90, 138.24, 137.12, 134.78, 130.44, 129.48, 128.12, 127.12, 125.35, 124.59, 120.95, 120.42, 119.26, 114.84, 111.58, 107.53, 53.83, 21.80. **HRMS (ESI)** m/z: [H] + calcd for $C_{22}H_{17}N_3O_3S^+$: 404.1069 found: 404.1063.

5.7 Scope of the Electron-poor Heteroaryl Series

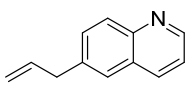
Ethyl 2-(isoquinolin-1-ylmethyl)acrylate (11a)



According to GP-C, with 1-iodoisoquinoline (51 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.18 mmol, 0.9 equiv.) and stirring for 15 min at ambient temperature CuI (8 mg, 0.04 mmol, 20 mol%.) was added at ambient temperature and stirring was continued for 30 min at this temperature. Then, ethyl 2-(bromomethyl)acrylate (55 µL, 0.40 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir 1 h at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 80:20) furnished the title compound as a colorless oil (28 mg, 0.12 mmol, 58 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.41 (d, J = 7.8 Hz, 1H), 7.73 – 7.58 (m, 1H), 7.54 – 7.41 (m, 2H), 7.18 (d, J = 7.4 Hz, 1H), 6.50 (d, J = 7.4 Hz, 1H), 6.39 (s, 1H), 5.74 (s, 1H), 4.84 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 165.92, 162.28, 137.21, 135.30, 132.41, 132.35, 128.39, 128.01, 126.98, 126.31, 126.04, 106.25, 61.23, 49.38, 14.27. **HRMS (ESI)** m/z: [H] + calcd for $C_{15}H_{15}NO_2^+$: 242.1176 found: 242.1175. Spectral characteristics were in agreement with previously reported data.[239]

6-Allylquinoline (11b)



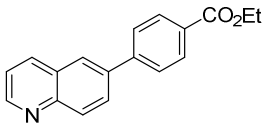
According to GP-C, with 6-iodoquinoline (51 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.18 mmol, 0.9 equiv.) and stirring for 15 min at ambient temperature CuI

[239] B. M. Trost, Z. Jiao, C.-I. Hung, *Angew. Chem. Int. Ed.* **2019**, *58*, 15154-15158.

(8 mg, 0.04 mmol, 20 mol%) was added at ambient temperature and stirring was continued for 30 min at this temperature. Then, allylbromide (35 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir 1 h at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 80:20) furnished the title compound as an orange oil (25 mg, 0.15 mmol, 76 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.87 (s, 1H), 8.07 (dd, J = 24.5, 8.4 Hz, 2H), 7.65 – 7.51 (m, 2H), 7.37 (dd, J = 8.3, 4.1 Hz, 1H), 6.10 – 5.99 (m, 1H), 5.14 (d, J = 11.6 Hz, 2H), 3.57 (d, J = 6.6 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 149.84, 147.25, 138.65, 136.86, 135.85, 131.23, 130.95, 129.43, 126.53, 121.26, 116.68, 40.20. **HRMS (ESI)** m/z: [H] + calcd for $C_{12}H_{11}N^+$: 170.0964 found: 170.0965. Spectral characteristics were in agreement with previously reported data.[240]

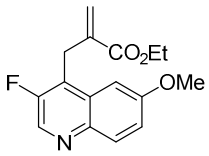
Ethyl 4-(quinolin-6-yl)benzoate (11c)



According to GP-D, using 6-iodoquinoline (51 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature, $ZnCl_2$ (0.2 mL, 0.2 mmol, 1.0 equiv., 1 M solution in THF) and $Pd(dppf)Cl_2$ (7 mg, 5 mol%) were added in the reaction mixture. Ethyl 4-iodobenzoate (30 µL, 0.18 mmol, 0.9 equiv.) was added, and the schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, flash column chromatography (SiO_2; pentane/ EtOAc; 80:20) furnished the title compound as a yellow oil (15 mg, 0.06 mmol, 31 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.00 (s, 1H), 8.34 (s, 2H), 8.18 (d, J = 6.6 Hz, 2H), 8.08 (d, J = 23.5 Hz, 2H), 7.79 (d, J = 7.5 Hz, 2H), 7.54 (s, 1H), 4.43 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 166.48, 150.55, 144.37, 138.97, 130.42, 130.06, 129.98, 129.45, 128.75, 127.60, 126.30, 122.19, 61.26, 29.82, 14.50. **HRMS (ESI)** m/z: [H] + calcd for $C_{18}H_{15}NO_2^+$: 278.1181 found: 278.1176.

Ethyl 2-((3-fluoro-6-methoxyquinolin-4-yl)methyl)acrylate (11d)



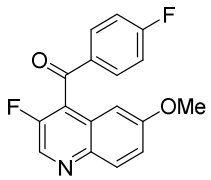
According to GP-C, with 3-fluoro-4-iodo-6-methoxyquinoline (60 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.18 mmol, 0.9 equiv.) and stirring for 15 min at ambient

[240] L. Mengozzi, A. Gualandi, P. G. Cozzi, *Eur. J. Org. Chem.* **2016**, *2016*, 3200-3207.

temperature CuI (19 mg, 0.10 mmol, 50 mol%.) was added at ambient temperature and stirring was continued for 30 min at this temperature. Then, ethyl 2-(bromomethyl)acrylate (55 µL, 0.40 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 90:10) furnished the title compound as a yellow oil (27 mg, 0.09 mmol, 47 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.64 (s, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.30 (dd, J = 9.2, 2.7 Hz, 1H), 7.12 (d, J = 2.8 Hz, 1H), 6.24 (s, 1H), 5.21 (s, 1H), 4.27 (d, J = 7.1 Hz, 2H), 4.06 (d, J = 1.6 Hz, 2H), 3.89 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 166.75, 158.98, 155.39 (d, J = 252.6 Hz), 141.52, 138.14 (d, J = 29.4 Hz), 136.90, 131.56, 129.41, 126.86 (d, J = 12.7 Hz), 126.55, 120.90 (d, J = 2.8 Hz), 102.31, 102.27, 61.37, 55.72, 26.04, 26.01, 14.29. **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -131.72. **HRMS (ESI)** m/z: [H] + calcd for $C_{16}H_{16}FNO_3^+$: 290.1187 found: 290.1189.

(3-Fluoro-6-methoxyquinolin-4-yl)(4-fluorophenyl)methanone (11e)

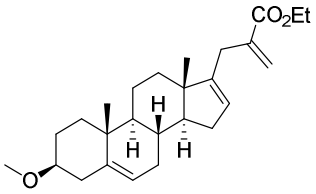


According to GP-C, with 3-fluoro-4-iodo-6-methoxyquinoline (60 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.18 mmol, 0.9 equiv.) and stirring for 15 min at ambient temperature CuI (19 mg, 0.10 mmol, 50 mol%) was added at ambient temperature and stirring was continued for 30 min at this temperature. Then, 4-fluorobenzoyl chloride (48 µL, 0.40 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 90:10) furnished the title compound as a yellow oil (21 mg, 0.07 mmol, 36 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.90 (s, 1H), 8.19 (d, J = 9.3 Hz, 1H), 8.15 (dd, J = 8.6, 5.6 Hz, 2H), 7.40 (dd, J = 9.3, 2.7 Hz, 1H), 7.15 (t, J = 8.6 Hz, 2H), 6.50 (d, J = 2.8 Hz, 1H), 3.63 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 170.01, 167.33, 165.30, 159.67, 141.49, 138.24 (d, J = 28.3 Hz), 132.90 (d, J = 9.5 Hz), 131.43, 128.59, 126.08 (d, J = 2.9 Hz), 121.94 (d, J = 2.5 Hz), 120.61 (d, J = 14.1 Hz), 115.78 (d, J = 22.1 Hz), 103.03, 102.99, 55.74. **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -104.73, -125.76. **HRMS (ESI)** m/z: [H] + calcd for $C_{17}H_{11}F_2NO_2^+$: 300.0831 found: 300.0832.

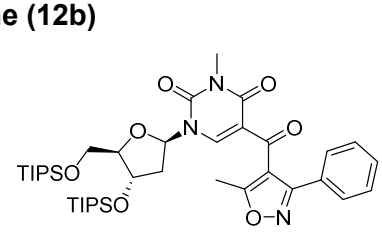
5.8 Scope of Pharmacologically Relevant Intermediates

Ethyl 2-(((3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-3-methoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)methyl)acrylate (12a)



According to GP-C, with O-methylated steroid **SI-8** (42 mg, 0.1 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.20 mmol, 2.0 equiv.) and stirring for 15 min at ambient temperature CuI (10 mg, 0.05 mmol, 50 mol%.) was added at ambient temperature and stirring was continued for 30 min at this temperature. Then, ethyl 2-(bromomethyl)acrylate (28 µL, 0.2 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 100 % to 98:2) furnished the title compound as a white solid (19 mg, 0.05 mmol, 49 %).
^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.19 (d, J = 1.8 Hz, 1H), 5.56 (d, J = 1.5 Hz, 1H), 5.40 – 5.33 (m, 1H), 5.23 (dt, J = 3.3, 1.7 Hz, 1H), 4.25 – 4.20 (m, 3H), 3.35 (s, 3H), 3.06 (tt, J = 11.4, 4.6 Hz, 1H), 2.99 (s, 1H), 2.40 (ddd, J = 13.1, 4.8, 2.4 Hz, 1H), 2.24 – 2.12 (m, 1H), 2.08 – 1.97 (m, 2H), 1.96 – 1.89 (m, 1H), 1.88 – 1.80 (m, 2H), 1.76 – 1.51 (m, 5H), 1.48 – 1.31 (m, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.03 (s, 3H), 0.95 – 0.83 (m, 2H), 0.81 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 167.40, 153.07, 141.35, 139.18, 125.99, 123.84, 121.56, 80.47, 60.72, 57.32, 55.75, 50.96, 46.79, 38.90, 37.29, 34.54, 31.77, 31.32, 30.69, 30.06, 28.17, 20.91, 19.45, 15.64, 14.34. **HRMS (ESI)** m/z: [H] + calcd for $C_{26}H_{38}O_3^+$: 399.2894 found: 399.2891.

3-Methyl-5-(5-methyl-3-phenylisoxazole-4-carbonyl)-1-((2*R*,4*S*,5*R*)-4-((triisopropylsilyl)oxy)-5-(((triisopropylsilyl)oxy)methyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (12b)

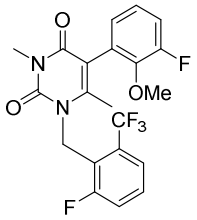


According to GP-A, using 5-Iodo-3-methyl-1-((2*R*,4*S*,5*R*)-4-((triisopropylsilyl)oxy)-5-(((triisopropylsilyl)oxy)methyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (**SI-9**) (108 mg, 0.16 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.13 mmol, 0.8 equiv.) and stirring for 30 min at ambient temperature, CuI (16 mg, 0.08 mmol, 50 mol%.) was added at rt. and stirring was continued for 30 min at this temperature. Then, 5-methyl-2-phenyloxazole-4-

carbonyl chloride (54 mg, 0.24 mmol, 1.5 equiv.) was added and the reaction mixture was allowed to stir overnight at ambient temperature. After workup, purification of the crude mixture by flash column chromatography (SiO_2; hexane/ EtOAc; 95:5 to 9:1) furnished the title compound as a yellow oil (21 mg, 0.06 mmol, 41 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.14 (s, 1H), 7.38 – 7.33 (m, 3H), 7.30 – 7.26 (m, 2H), 6.20 (dd, J = 8.6, 5.5 Hz, 1H), 4.61 (dt, J = 5.5, 1.6 Hz, 1H), 4.10 (td, J = 3.4, 1.6 Hz, 1H), 3.90 (d, J = 3.4 Hz, 2H), 2.91 (s, 3H), 2.65 (s, 3H), 2.42 (ddd, J = 12.9, 5.5, 1.6 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.19 – 1.12 (m, 3H), 1.09 – 1.04 (m, 39H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 183.49, 174.35, 162.02, 159.62, 149.97, 142.11, 129.63, 129.31, 128.90, 127.96, 116.98, 114.75, 89.18, 86.94, 73.15, 63.77, 42.50, 27.54, 18.13, 18.11, 18.10, 18.08, 13.06, 12.18, 11.96. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{39}H_{61}N_3O_7Si_2H^+$: 740.41208 found: 740.41296.

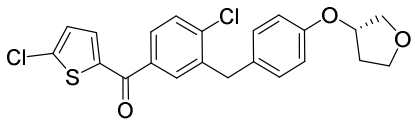
5-(3-Fluoro-2-methoxyphenyl)-1-(2-fluoro-6-(trifluoromethyl)benzyl)-3,6-dimethylpyrimidine-2,4(1*H*,3H)-dione (12c)



According to GP-B, using 1-(2-fluoro-6-(trifluoromethyl)benzyl)-5-iodo-3,6-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**SI-10**) (86 mg, 0.2 mmol, 1.0 equiv.). After addition of $Et_2Zn{\cdot}LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, $Pd(OAc)_2$ (0.5 mg, 1 mol%) and SPhos (1.6 mg, 2 mol%.) were added as a solution in THF (0.2 mL). 1-Bromo-3-fluoro-2-methoxybenzene (24 µL, 0.18 mmol, 0.9 equiv.) was added, and the Schlenk-flask was sealed and the reaction mixture stirred overnight at rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; hexane/ EtOAc; 9:1 to 1:1) furnished the title compound as a colorless solid (48 mg, 0.11 mmol, 55 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.53 (d, J = 8.0 Hz, 1H), 7.39 (td, J = 8.0, 5.0 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.09 (td, J = 8.0, 1.4 Hz, 1H), 6.96 (td, J = 8.0, 1.4 Hz, 1H), 6.81 – 6.77 (m, 1H), 5.51 – 5.41 (m, 2H), 3.87 (s, 3H), 3.39 (s, 3H), 2.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 162.46, 161.65, 160.48, 152.18, 151.38, 149.64, 149.42, 148.13 (d, J = 11.4 Hz), 129.50 (d, J = 10.0 Hz), 124.05 (d, J = 1.5 Hz), 123.96 (d, J = 4.8 Hz), 122.69 (dd, J = 5.7, 3.3 Hz), 122.53 (d, J = 13.4 Hz), 122.28 (d, J = 11.4 Hz), 121.01 (d, J = 23.8 Hz), 113.44 (d, J = 2.4 Hz), 108.28, 56.41, 42.84 (d, J = 3.8 Hz), 28.61, 17.89. **^{19}F NMR** (471 MHz, $CDCl_3$) δ = -59.72, -116.56, -135.94. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{21}H_{17}F_5N_2O_3H^+$: 441.12321 found: 441.12293.

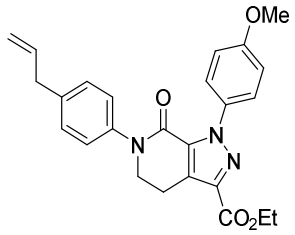
(*S*)-(4-Chloro-3-(4-((tetrahydrofuran-3-yl)oxy)benzyl)phenyl)(5-chlorothiophen-2-yl)methanone (12d)



According to GP-C, with (*S*)-3-(4-(2-chloro-5-iodobenzyl)phenoxy)tetrahydrofuran (85 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature CuI (19 mg, 0.1 mmol, 50 mol%.) was added at 0°C and stirring was continued for 30 min at this temperature. Then, 5-chlorothiophene-2-carbonyl chloride (48 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight warming to rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 100 % to 75:25) furnished the title compound as a colorless viscous oil (59 mg, 0.14 mmol, 68 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.64 – 7.59 (m, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 4.0 Hz, 1H), 7.14 – 7.09 (m, 2H), 6.95 (d, J = 4.0 Hz, 1H), 6.83 – 6.78 (m, 2H), 4.89 (ddt, J = 6.5, 4.4, 2.2 Hz, 1H), 4.10 (s, 2H), 4.01 – 3.93 (m, 3H), 3.89 (td, J = 8.3, 4.4 Hz, 1H), 2.23 – 2.09 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 186.01, 156.27, 141.99, 140.51, 139.97, 138.90, 135.97, 134.36, 131.57, 131.13, 130.19, 129.90, 128.22, 127.63, 115.69, 77.46, 73.23, 67.32, 38.41, 33.13. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{22}H_{18}Cl_2O_3SH^+$: 433.04265 found: 433.04255.

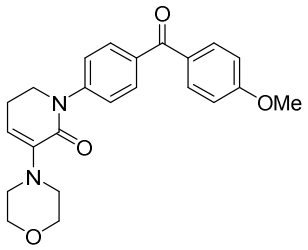
Ethyl 6-(4-allylphenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (12e)



According to GP-C, using ethyl 6-(4-iodophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (52 mg, 0.1 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added at 0°C and stirring was continued for 30 min at this temperature. Then, allyl bromide (34 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight warming to rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 100 % to 1:1, slow gradient) furnished the title compound as a colorless solid (45 mg, 0.1 mmol, 52 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.51 – 7.46 (m, 2H), 7.24 – 7.16 (m, 4H), 6.91 – 6.87 (m, 2H), 5.92 (ddt, J = 16.8, 10.1, 6.7 Hz, 1H), 5.10 – 5.03 (m, 2H), 4.09 (t, J = 6.7 Hz, 2H), 3.80 (s, 3H), 3.38 – 3.34 (m, 2H), 3.26 (t, J = 6.7 Hz, 2H), 1.97 (q, J = 7.5 Hz, 2H), 0.98 (t, J = 7.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 161.39, 159.87, 157.47, 140.38, 139.99, 138.59, 137.21, 133.07, 132.85, 129.20, 128.47, 127.05, 126.32, 125.54, 116.14, 113.67, 84.91, 55.62, 51.21, 39.84, 33.62, 25.95, 21.92, 8.55. **HRMS (ESI)** m/z: $[-C_2H_4]^+$ calcd for $C_{23}H_{21}N_3O_4H^+$: 404.1612 found: 404.1610.

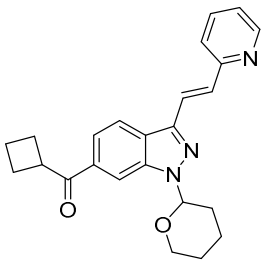
1-(4-(4-Methoxybenzoyl)phenyl)-3-morpholino-5,6-dihydropyridin-2(1*H*)-one (12f)



According to GP-C, with 1-(4-iodophenyl)-3-morpholino-5,6-dihydropyridin-2(1*H*)-one (77 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature (an orange precipitate formed), CuI (19 mg, 0.1 mmol, 50 mol%.) was added at 0°C and stirring was continued for 30 min at this temperature (clear solution again). Then, 4-methoxybenzoyl chloride (40 µL, 0.3 mmol, 1.5 equiv.) was added and the reaction mixture was allowed to stir overnight warming to rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 95:5 to 6:4) furnished the title compound as a colorless solid (47 mg, 0.12 mmol, 60 %).

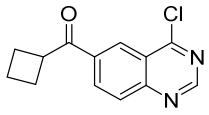
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.85 – 7.77 (m, 4H), 7.50 – 7.45 (m, 2H), 6.97 – 6.93 (m, 2H), 5.70 (t, J = 4.7 Hz, 1H), 3.90 – 3.81 (m, 9H), 2.95 – 2.88 (m, 4H), 2.53 (td, J = 6.6, 4.7 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 194.71, 163.36, 161.49, 146.11, 143.81, 135.52, 132.65, 130.55, 130.31, 124.25, 115.04, 113.71, 66.86, 55.65, 50.66, 48.54, 23.49. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{23}H_{24}N_2O_4H^+$: 393.1809 found: 393.1814.

(*E*)-Cyclobutyl(3-(2-(pyridin-2-yl)vinyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)methanone (12g)



According to GP-C, using ethyl 6-(4-iodophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-c]pyridine-3-carboxylate (52 mg, 0.1 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.16 mmol, 0.8 equiv.) and stirring for 15 min at ambient temperature, CuI (19 mg, 0.1 mmol, 50 mol%.) was added at 0°C and stirring was continued for 30 min at this temperature. Then, allyl bromide (34 µL, 0.4 mmol, 2.0 equiv.) was added and the reaction mixture was allowed to stir overnight warming to rt. After workup, purification of the crude mixture by flash column chromatography (SiO_2; pentane/ EtOAc; 100 % to 6:4, slow gradient) furnished the title compound as a light yellow solid (46 mg, 0.12 mmol, 59 %).
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.63 (dd, J = 5.2, 1.7 Hz, 1H), 8.20 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 16.5 Hz, 1H), 7.72 (ddd, J = 17.6, 8.1, 1.6 Hz, 2H), 7.62 (d, J = 16.5 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.21 – 7.17 (m, 1H), 5.82 (dd, J = 9.2, 2.8 Hz, 1H), 4.06 (ddd, J = 10.9, 4.2, 2.4 Hz, 1H), 3.83 – 3.76 (m, 1H), 2.65 – 2.57 (m, 1H), 2.51 – 2.41 (m, 2H), 2.40 – 2.31 (m, 2H), 2.21 – 2.17 (m, 1H), 2.15 – 2.06 (m, 2H), 1.99 – 1.89 (m, 1H), 1.84 – 1.74 (m, 2H), 1.73 – 1.65 (m, 1H), 1.27 – 1.14 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 201.17, 149.48, 142.58, 140.76, 137.05, 134.16, 130.44, 125.66, 123.77, 122.50, 122.11, 121.60, 121.17, 111.35, 85.69, 67.71, 42.80, 29.62, 25.43, 25.39, 25.20, 22.57, 18.30. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{24}H_{25}N_3O_2H^+$: 388.2020 found: 388.2025.

(4-Chloroquinazolin-6-yl)(cyclobutyl)methanone (12h)



According to GP-C, with 4-chloro-6-iodoquinazoline (58 mg, 0.2 mmol, 1.0 equiv). After addition of $Et_2Zn{\cdot}2LiOAmyl$ (0.14 mmol, 0.7 equiv.) and stirring for 15 min at ambient temperature CuI (19 mg, 0.1 mmol, 50 mol%.) was added at 0°C and stirring was continued for 30 min at this temperature. Then, cyclobutanecarbonyl chloride (46 µL, 0.4 mmol, 2.0 equiv.) was added, the ice bath was removed and the reaction mixture was allowed to stir 4 h at ambient temperature. After workup, purification of the crude mixture by flash column chromatography (SiO_2; petroleum ether/ EtOAc; 95:5 to 75:25) furnished the title compound as an orange oil (42 mg, 0.17 mmol, 85 %).
^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.11 (s, 1H), 8.75 (d, J = 1.9 Hz, 1H), 8.47 (dd, J = 8.8, 1.9 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 4.20 – 4.08 (m, 1H), 2.53 – 2.36 (m, 4H), 2.24 – 2.12 (m, 1H), 2.02 – 1.94 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 199.34, 164.05, 155.44, 153.04, 135.67, 133.56, 129.68, 127.19, 123.79, 42.52, 25.31, 18.34. **HRMS (ESI)** m/z: $[H]^+$ calcd for $C_{13}H_{11}ClN_2OH^+$: 247.06327 found: 247.06373.

6. Representative NMR-Spectra:

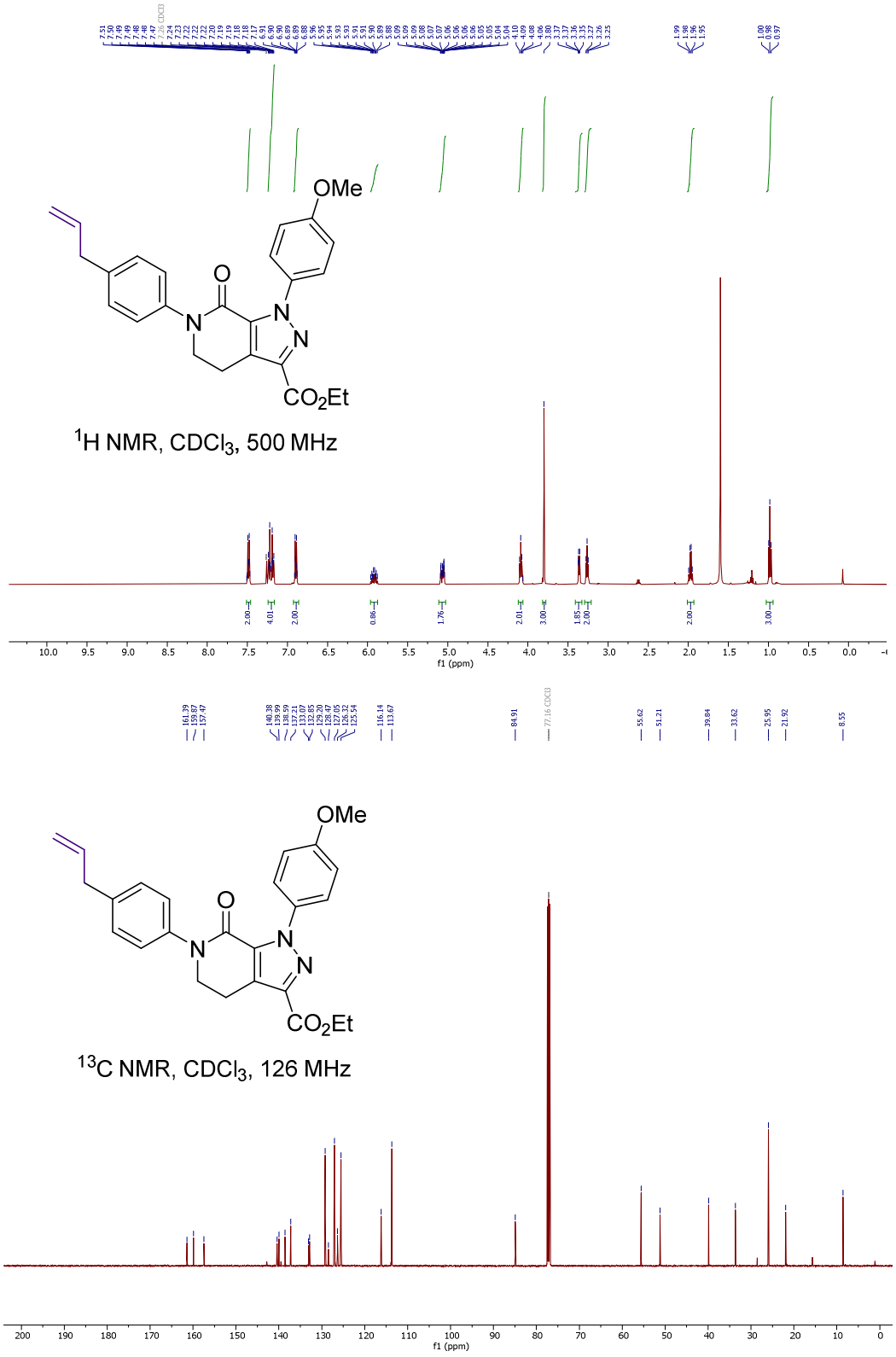


Figure 27: ^{1}H NMR and ^{13}C NMR for Ethyl 6-(4-allylphenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (12e)