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Functionalization and Derivatization of Unsaturated 4-Membered Carbo- and Heterocycles Mediated by Organometallic Methods

von

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aus Deggendorf, Deutschland

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Erklärung

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Eidesstattliche Versicherung

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Michael Eisold

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For my family.

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1. *"Highly Diastereoselective Synthesis of Methylenecyclobutanes by Merging Boron-Homologation and Boron-Allylation Strategies"* M. Eisold, D. Didier, *Angew. Chem. Int. Ed.* **2015**, *54*, 15884.

2. *"Single-Pot Asymmetric Approach toward Enantioenriched Quaternary Stereocenter-Containing Alkylidenecyclobutanes"* M. Eisold, G. M. Kiefl, D. Didier, *Org. Lett.* **2016**, *18*, 3022.

3. *"Unsaturated Four-Membered Rings: Efficient Strategies for the Construction of Cyclobutenes and Alkylidenecyclobutanes"* M. Eisold, A. N. Baumann, G. M. Kiefl, S. T. Emmerling, D. Didier, *Chem. Eur. J.* **2017**, *23*, 1634.

4. *"Stereoselective Sequence toward Biologically Active Fused Alkylidenecyclobutanes"* A. N. Baumann, M. Eisold, D. Didier, *Org. Lett.* **2017**, *19*, 2114.

5. *"Stereoselective Access to Alkylidenecyclobutanes through γ-Selective Cross-Coupling Strategies"* M. Eisold, D. Didier, *Org. Lett.* **2017**, *19*, 4046.

6. *"Methods for the Synthesis of Substituted Azetines"* M. Eisold, A. N. Baumann, A. Music, G. Haas, Y. M. Kiw, D. Didier, *Org. Lett.* **2017**, *19*, 5681.

7. *"Regiodivergent Stereoselective Access to Fused Alkylideneazetidines"* A. Music, A. N. Baumann, M. Eisold, D. Didier, *J. Org. Chem.* **2018**, *83*, 783.

8. *„Oxidative Ring Contraction of Cyclobutenes: General Approach to Cyclopropylketones including Mechanistic Insights"* A. N. Baumann, F. Schueppel, M. Eisold, A. Kreppel, R. de Vivie-Ridle, D. Dorian, *J. Org. Chem.* **2018**, *83*, 4905.

9. *"Parallel Approaches for the Functionalization of Thietes: α-Metalation versus C-H Activation"* M. Eisold, A. Mueller-Deku, F. Reiners, D. Didier, *Org. Lett.* **2018**, *20*, 4654.

10. *"One-Pot Preparation of Stable Organoboronate Reagents for the Functionalization of Unsaturated Four- and Five-Membered Carbo- and Heterocycles"* M. Eisold, A. N. Baumann, A. Music, D. Didier, *Synthesis* **2018**, *50*, 3149.

11. *"Unsaturated Four-Membered N-Heterocycles: From Synthesis to Applications"* D. Didier, A. N. Baumann, M. Eisold, *Tetrahedron* **2018**, *59*, 3975.

Parts of this thesis have been presented at scientific conferences.

URCUP – Undergraduate Research Conference on Molecular Sciences

Single-pot Operation for the Synthesis of Alkylidenecyclobutanes (poster presentation)

Wildbad Kreuth, Germany, 2015.

BOSS XV – 15th Belgian Organic Synthesis Symposium

Single-Pot Asymmetric Approach Towards Enantiopure Quaternary Stereocenter-Containing Alkylidenecyclobutanes (poster presentation)

Antwerp, Belgium, 2016.

ESOC 20 – 20th European Symposium of Organic Chemistry

Straightforward Syntheses of Alkylidenecyclobutanes (poster presentation)

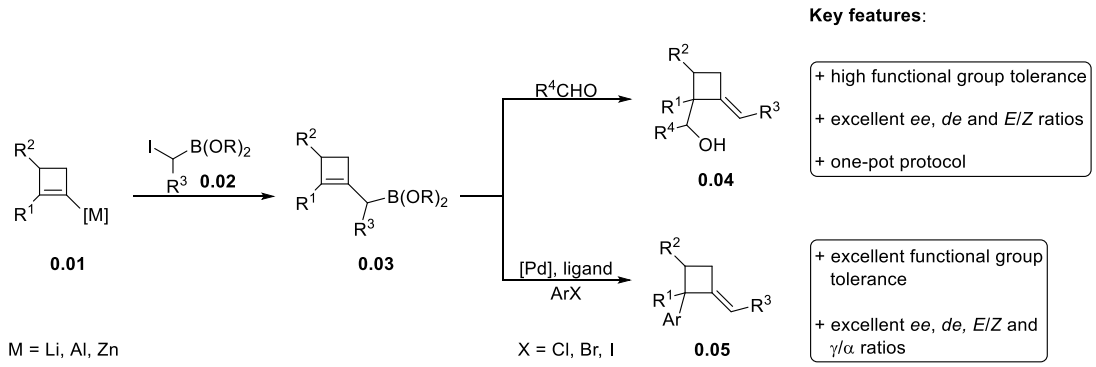
Cologne, Germany, 2017.

Abstract

This Ph.D. thesis describes the modification of simple cyclobutenes, azetines and thiete dioxides into more elaborate structures through the application of organometallic methods.

Chapter I

Cyclobutenes have been relatively little studied compared to larger unsaturated ring systems and also cyclopropenes. Substituents are usually already present in the precursors before the formation of the 4-membered carbocycle and later modifications are difficult. The first chapter of this Ph.D. thesis describes the generation of metallated cyclobutenes and unprecedented methods for their derivatisation into alkylidenecyclobutanes and use in cross-coupling reactions. The first step is based on a literature known procedure for the formation of metallated cyclobutenes **0.01**. Those species then react with iodomethyl-boronic esters **0.02**, generating an allyl-boron system through a stereospecific boron-homologation sequence. The generated allylic boronates **0.03** easily undergo addition reactions with aldehydes to furnish alkylidenecyclobutylcarbinols **0.04** or follow γ-selective Suzuki–Miyaura cross-coupling reactions to yield alkylidenecyclobutanes **0.05**.

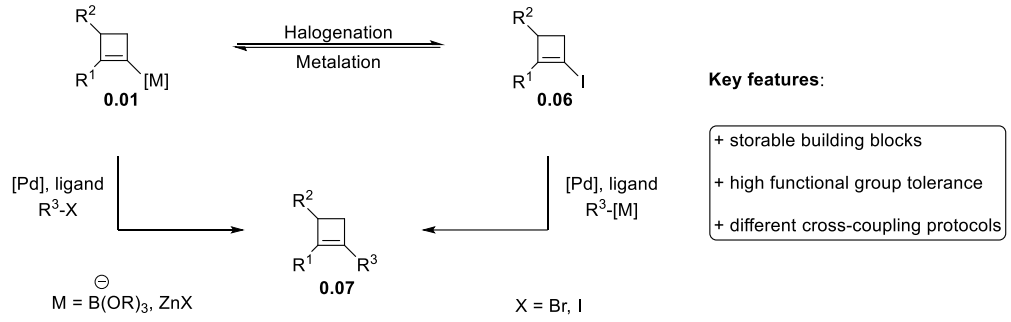


The transformation of allylic boronates to carbinols **0.04** occurred very rapidly (< 10 minutes) due to the involved strain release, with the aldehydes being of aliphatic, vinylic and aromatic nature. Up to three consecutive stereocenters could be obtained with virtually perfect diastereomeric ratios. Screening of the boronic species revealed that the allylation reaction can also take place with high *E*/*Z* ratios and very good diastereoselectivity. The reaction was also designed to be conducted in a one-pot procedure, combining the formation of metallated cyclobutene, boron-homologation and boron-allylation.

In a different method, the stable boronic esters **0.03** were subjected to Suzuki–Miyaura cross-coupling conditions whereupon selective coupling in the γ-position of the allylic boronate occurred, on account

of strain release. The reaction mostly occurred fast (< 1h), depending on the aryl species, and also showed excellent levels of diastereoselectivity and *E*/*Z* ratios. Furthermore, the first γ-selective Suzuki-Miyaura coupling furnishing a quarternary stereocenter with good enantioselectivity was performed.

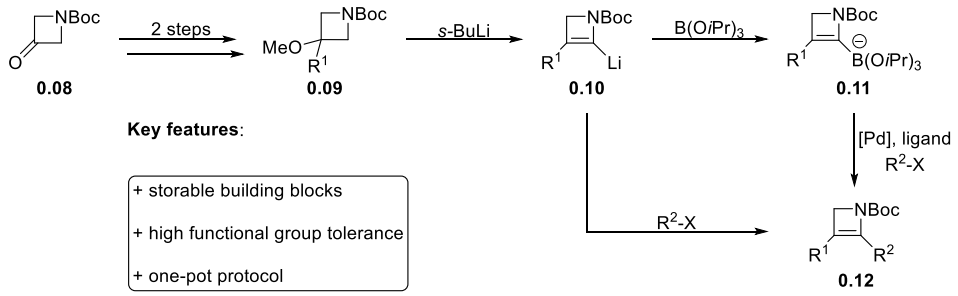
Another part of this first chapter is focused on the use of metallated or halogenated cyclobutenes as building blocks for cross-coupling reactions. The in-situ synthesized cyclobutenyl-metal species **0.01** can either be electrophilically trapped as halogenides or directly engaged in Negishi cross-coupling reactions with arylic and vinylic halides. The storable halo-cyclobutenes **0.06** can also be directly employed in Suzuki and Negishi cross-couplings or converted into air-stable organoboronates through exchange-transmetalation strategies and then engaged in further transformations.



The building blocks showed good reactivity and allowed access to more sophisticated structures with the typical high functional group tolerance for cross-coupling reactions.

Chapter II

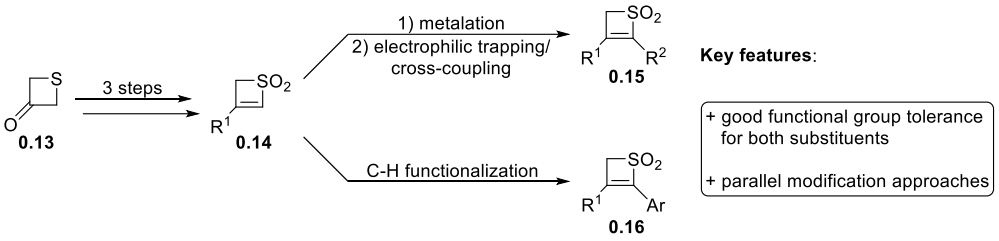
Among the 4-membered nitrogen-containing heterocycles, β-lactams have undoubtedly received the most attention. The stable 2-azetines however have only been studied to a small extent. The second chapter of this Ph.D. thesis is focused on the synthesis of disubstituted 2-azetines through simple metalation strategies. Commercially available 3-azetinone **0.08** can be converted to **0.09** by simple nucleophilic attack of a wide range of lithiated or magnesiated species and further methylation of the resulting alcohol. Following a literature procedure, the treatment with a strong base induces lithiation in α-position of the nitrogen and subsequent elimination of lithium methanolate. Another equivalent of the base allows metalation of the 2-azetine to give **0.10**, which can either be directly trapped with electrophiles or converted to the stable boronate **0.11** for following cross-coupling reactions.



Electrophilic trapping of the lithiated species **0.10** yielded the corresponding alkylated and silylated compounds – or alcohols in the case of reaction with aldehydes – in good to excellent yields. The conditions for the Suzuki–Miyaura cross-coupling showed characteristic functional group tolerance, furnishing disubstituted 2-azetines **0.12** in generally good to very good yields in a one-pot procedure starting from **0.09**.

Chapter III

The third chapter of this Ph.D. thesis aims at the derivatisation of the scarcely studied thiete dioxides. Through a known procedure of three simple steps and without intermediate purification, 3-substituted thiete dioxides **0.14** are accessible. Treatment with an organometallic base affords the metallated derivative, which can directly be trapped with electrophiles or transmetallated for further reactions such as Negishi cross-couplings. In addition, an alternative pathway has been developed, utilizing a direct C-H functionalization to introduce aryl moieties.



While the metalation-trapping strategy allowed for the synthesis of diversely disubstituted thietes in good to very good yields, the direct arylation method complemented the scope toward more base labile targets. The direct functionalization is an example of the rather uncommon C-H activation of alkenes and does not require the installation of an additional directing group to give products in overall high yield.

Glossary

°C	degree Celsius
$[\alpha]_D^{19}$	specific rotation (589 nm/19 °C)
app	apparent (NMR spectroscopy)
aq	aqueous
Ar	aryl
ATR	attenuated total reflection
B	base
Boc	*tert*-butyloxycarbonyl
br	broad (NMR spectroscopy)
br	broad (IR spectroscopy)
Bu	butyl
c	concentration
calcd	calculated
cm	centimeter
conc.	concentrated
Cp	cyclopentadienyl
Cy	cyclohexyl
Δ	heating
δ	chemical shift (NMR spectroscopy)
d	doublet (NMR spectroscopy)
DEP	direct evaporation probe
DG	directing group
d.r.	diastereomeric ratio
E	*trans*
E^+	electrophile
ee	enantiomeric excess
EI	electron ionization
ESI	electron spray ionization
eq	equivalents
e.r.	enantiomeric ratio
Et_2O	diethyl ether
EtOAc	ethyl acetate
g	gram(s)
GC	gas chromatography
gem	geminal
h	hour(s)
hν	photo irradiation
HRMS	high resolution mass spectrometry
i	*iso*
$In(tfacac)_3$	indium(III) trifluoroacetylacetonate
J	coupling constant
£	pound sterling
LA	Lewis acid
LRMS	low resolution mass spectrometry
M	molar
m	medium (IR spectroscopy)
m	meter
m	multiplet (NMR spectroscopy)
*m*CPBA	*meta*-chloroperoxybenzoic acid
MeCN	acetonitrile
MeI	methyl iodide
mg	milligrams
MHz	megahertz
mins	minutes
µL	mikroliter
mL	milliliter
mm	millimeter
mmol	millimole
mp	melting point
Ms	methanesulfonyl
MTBE	methyl *tert*-butyl ether
µW	microwave irradation
(+)-NBE-CO_2Me	norbornene methyl (1*S*,4*R*)-bicyclo[2.2.1]hept-2-ene-2-carboxylate

$\tilde{\nu}$	wave number
$NaBAr_4^F$	sodium tetrakis (pentafluorophenyl)borate
n-BuLi	butyllithium
NEt_3	triethylamine
nm	nanometer
NMR	nuclear magnetic resonance
Ns	4-nitrobenzenesulfonyl
OAc	acetate
P	*para*
PAA	*para*-Anisaldehyde stain
Piv	pivaloyl
Ph	phenyl
PLC	preparative layer chromatography
ppm	parts per million (NMR spectroscopy)
q	quartet (NMR spectroscopy)
quint	quintet (NMR spectroscopy)
R_f	retention factor
r.t.	room temperature
s	singlet (NMR spectroscopy)
s	strong (IR spectroscopy)
s-BuLi	*sec*-butyllithium
t	triplet (NMR spectroscopy)
t-Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TFP	tri(2-furyl)phospine
THF	tetrahydrofurane
TIPS	triisoproyplsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
UV	ultraviolet
vs	very strong (IR spectroscopy)
vw	very weak (IR spectroscopy)
w	weak (IR spectroscopy)
Z	*cis*

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Chapter IV – Experimental Part

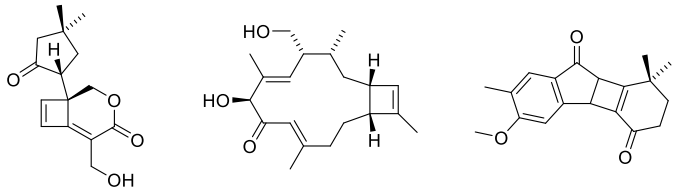
CHAPTER I

Cyclobutenes

1 Introduction

While being scarcely observed in natural compounds due to their peculiar framework, some cyclobutene and alkylidenecyclobutane containing structures have shown very interesting biological activities.

Named after the wood-rotting fungus *Fomes annosus*, fomannosin (**1.01**) represents a rare case of a sesquiterpene containing a cyclobutene moiety.[1] Fomanosin is toxic to *Pinus taeda* seedlings and some bacteria and has therefore been objective of total synthesis.[2] Bershacolone (**1.02**), a constituent of the root extract of *Maprounea africana* which has shown activity in anti-HIV screens and neofavelanone (**1.03**), which was isolated from the bark of *Cnidoscolus phyllacanthus* and has shown cytotoxicity against some leukemia cells, are other examples of natural products inheriting a cyclobutene ring.[3]



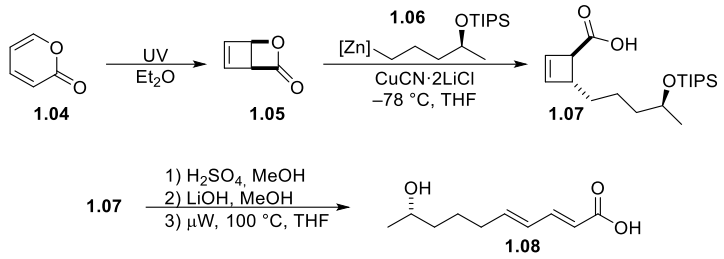
(+)-fomannosin (**1.01**) bershacolone (**1.02**) neofavelanone (**1.03**)

Figure 1: Examples of naturally occurring cyclobutenes.

1.1 Cyclobutene Syntheses

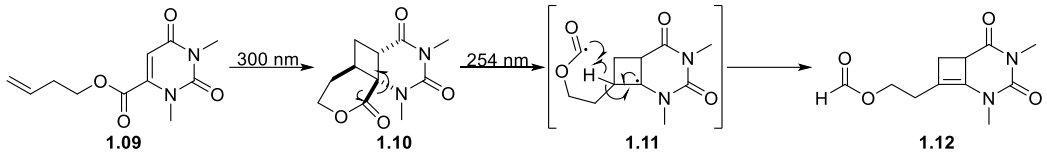
The most typical syntheses of cyclobutenes are through [2+2] cycloadditions, either photochemically or through metal catalysis. A recent example for the utilization of a photochemical cyclobutene synthesis was demonstrated by the group of Maulide.[4] Based on the photoisomerization of 2-pyrone (**1.04**) observed by Corey, the power of a nucleophilic ring opening of bicyclic lactone **1.05** to ultimately give the natural compound ieodomycin D (**1.08**) was illustrated.[5] The nucleophilic attack of zinc species **1.06**, accessed from commercial 5-iodo-pentan-2ol through silylation and zinc insertion, gives ring opened acid **1.07** as a single diastereomer. Subsequent deprotection, saponification and thermal 4π-electrocyclic ring opening afforded the product in 43% overall yield.

[1] J. A. Kepler; M. E. Wall; J. E. Mason; C. Basset; A. T. McPhail; G. A. Sim, *J. Am. Chem. Soc.* **1967**, *89*, 1260.
[2] M. F. Semmelhack; S. Tomoda; H. Nagaoka; S. D. Boettger; K. M. Hurst, *J. Am. Chem. Soc.* **1982**, *104*, 747; L. A. Paquette; X. Peng; J. Yang, *Angew. Chem. Int. Ed.* **2007**, *46*, 7817.
[3] M. W. Bernart; Y. Kashman; M. Tischler; J. H. Cardellina; M. R. Boyd, *Tetrahedron Lett.* **1993**, *34*, 4461; Y. Endo; T. Ohta; S. Nozoe, *Tetrahedron Lett.* **1992**, *33*, 353.
[4] C. Souris; A. Misale; Y. Chen; M. Luparia; N. Maulide, *Org. Lett.* **2015**, *17*, 4486.
[5] E. J. Corey; J. Streith, *J. Am. Chem. Soc.* **1964**, *86*, 950.



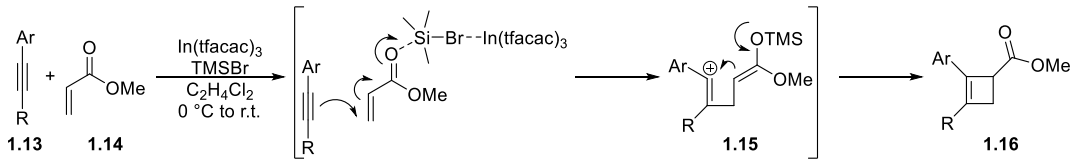
Scheme 1: Total synthesis of ieodomycin D (**1.08**).

In 2016 Bach presented an intramolecular photocycloaddition of oroates to cyclobutene annulated pyrimidine-diones.[6] Following irradiation at 300 nm, a fused 6/4/6-ring system is created with a lactone and the pyrimidine-dione annulated to a cyclobutane (**1.10**). Further irradiation at 254 nm triggers a homolytic decomposition of the lactone in a Norrish type I fashion and, after intramolecular hydrogen abstraction and radical recombination, cyclobutene **1.12** is obtained.[7]



Scheme 2: Photochemical rearrangement of oroate **1.09** to cyclobutene-pyrimidine-dione **1.12**.

An example for an intermolecular [2+2] synthesis of cyclobutenes can be found in a report by Loh.[8] Employing an indium (III) catalyst with TMSBr to enhance the Lewis acidity, aryl alkynes and acrylates could be cyclized with perfect regioselectivity. A possible mechanism includes a 1,4-addition of the alkyne to the activated acrylate. The resulting benzylic cation **1.15** then gets attacked by the silyl enol giving the cyclobutene in two steps.



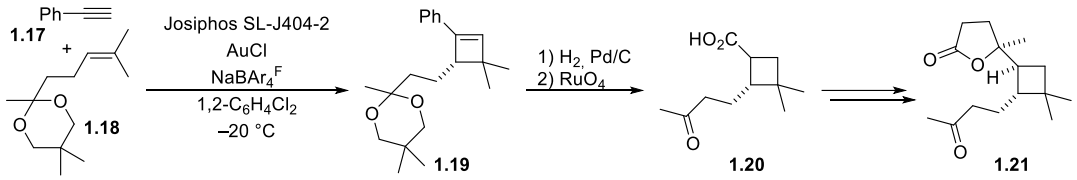
Scheme 3: Indium catalyzed [2+2] cycloaddition to cyclobutenes.

[6] A. Hölzl; T. Bach, *Journal of Photochemistry and Photobiology A: Chemistry* **2016**, *331*, 60.

[7] J. N. Pitts; R. Simonaitis; J. M. Vernon, *Tetrahedron Lett.* **1965**, *6*, 3209; L. K. Sydnes; D. Van Ha, *Aust. J. Chem.* **2009**, *62*, 101; R. G. W. Norrish; F. W. Kirkbride, *J. Chem. Soc.* **1932**, 1518.

[8] L. Shen; K. Zhao; K. Doitomi; R. Ganguly; Y.-X. Li; Z.-L. Shen; H. Hirao; T.-P. Loh, *J. Am. Chem. Soc.* **2017**, *139*, 13570.

The synthesis of rumphellaone (**1.21**) by the group of Echavarren depicts a case where a cyclobutene gets constructed through metal catalyzed cyclization of an alkyne and an alkene.[9] Utilizing a chiral Josiphos digold(I) complex, cyclobutene **1.19** could be accessed in high yield and good enantioselectivity. After reduction of the cyclobutene and oxidative cleavage, cyclobutane carboxylic acid **1.20** was obtained. Six more steps were necessary to convert the latter into rumphellaone **1.21**.[10]



Scheme 4: Enantioselective synthesis of rumphellaone (**1.21**).[11]

1.2 Alkylidenecyclobutanes

The alkylidenecyclobutane moiety can be found embedded in a number of protoilludene sesquiterpenes, which consist of an annulated 5/6/4-ring system.[12] Isolated from *Lactarius repraesentaneus*, Repraesentin A (**1.22**) is a mono-oxidized version of 6-protoilludene and has been found to act as a plant growth promoter.[13] Pasteurestin A (**1.23**), which was isolated from *Agrocybe aegeritta* and exhibited strong activity against a pathogen for bovine respiratory disease, depicts a further member of the protoilludene family.[14] Another alkylidenecyclobutane incorporating natural compound is the highly oxidized providencin (**1.24**) isolated from *Pseudopterogorgia kallos*.[15] The diterpene exhibited activity against several human cancer cell lines and has therefore been object of some total syntheses.[16]

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[9] C. García-Morales; B. Ranieri; I. Escofet; L. López-Suarez; C. Obradors; A. I. Konovalov; A. M. Echavarren, *J. Am. Chem. Soc.* **2017**, *139*, 13628.

[10] B. Ranieri; C. Obradors; M. Mato; A. M. Echavarren, *Org. Lett.* **2016**, *18*, 1614.

[11] Josiphos SL-J404-2: (*S*)-1-{(R_p)-2-[Di(1-naphthyl)phosphino]ferrocenyl}ethyldi(3,5-xylyl)phosphine.

[12] P. Siengalewicz; J. Mulzer; U. Rinner, *Eur. J. Org. Chem.* **2011**, *2011*, 7041.

[13] M. Hirota; Y. Shimizu; T. Kamo; H. Makabe; H. Shibata, *Bioscience, Biotechnology, and Biochemistry* **2003**, *67*, 1597.

[14] M. Kögl; L. Brecker; R. Warrass; J. Mulzer, *Angew. Chem. Int. Ed.* **2007**, *46*, 9320.

[15] J. Marrero; A. D. Rodríguez; P. Baran; R. G. Raptis, *Org. Lett.* **2003**, *5*, 2551.

[16] Selected articles: E. Schweizer; T. Gaich; L. Brecker; J. Mulzer, *Synthesis* **2007**, *2007*, 3807; T. Gaich; H. Weinstabl; J. Mulzer, *Synlett* **2009**, *2009*, 1357; J. D. White; S. Jana, *Org. Lett.* **2009**, *11*, 1433; S. J. Stevens; A. Bérubé; J. L. Wood, *Tetrahedron* **2011**, *67*, 6479.

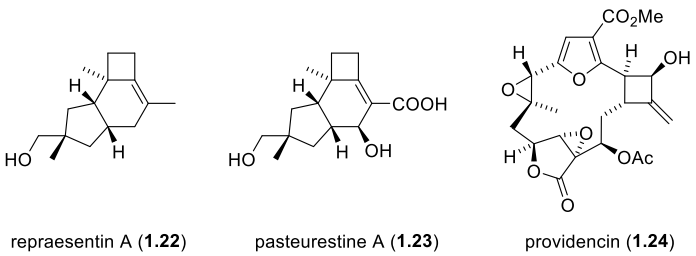
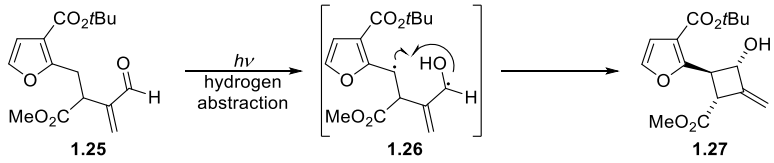
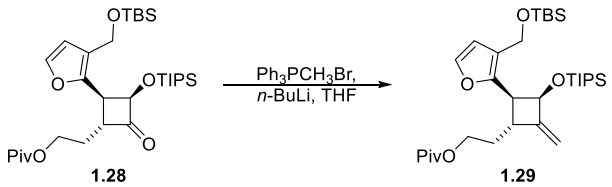


Figure 2: Natural products containing an alkylidenecyclobutane moiety.

One account on its synthesis describes a Norrish type II reaction to form the methylenecyclobutane fragment, unfortunately a wrong diastereomer (**1.27**) is formed.[17] A successful attempt for the formation of this moiety was found in the transformation of the corresponding cyclobutanone **1.28** through Wittig reaction.[18]



Scheme 5: Synthesis of the methylenecyclobutane moiety through Norrish type II reaction.



Scheme 6: Synthesis of the methylenecyclobutane moiety through Wittig reaction.

The amount of reports about the synthesis of providencine that are focused on the construction of the cyclobutyl entity is a clear indicator for the lack of methods for accessing this structural moiety.

1.3 Synthesis of Iodo-cyclobutenes

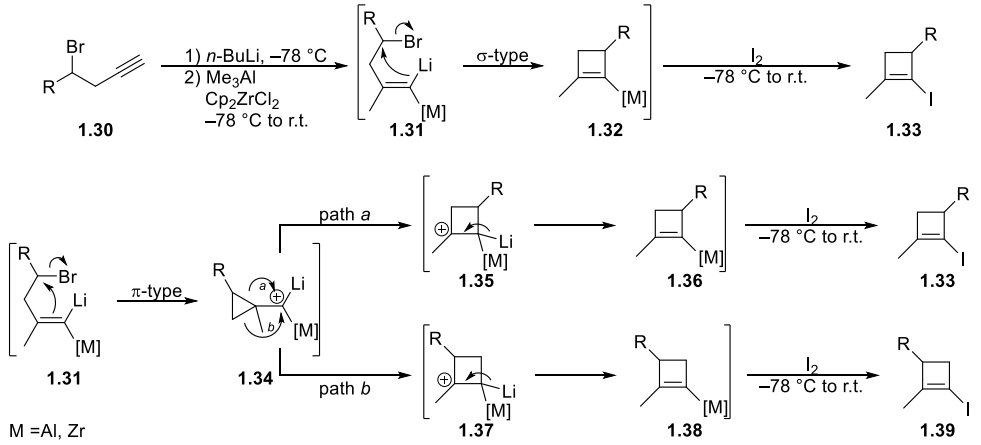
To overcome this methodological gap, it was devised to functionalize simple cyclobutenes through organometallic modifications. The easiest access to metallated cyclobutenes is through metalation of iodo-cyclobutenes. While there are some reports on the synthesis of iodo-cyclobutenes, only very few can be considered, as most give either non-innocent substrates that are prone to different reactions under metallating conditions or consist of many steps, making the substrate synthesis rather

[17] C. D. Bray; G. Pattenden, *Tetrahedron Lett.* **2006**, *47*, 3937.
[18] J. D. White; S. Jana, *J. Org. Chem.* **2014**, *79*, 700.

uncomely.[19] To overcome these restrictions, further studies were based on a cyclization of 4-halobut-1-ynes described by Negishi as early as 1983.[20] The high yielding and short synthesis of iodo-cyclobutenes devised from those findings was therefore the entry point toward the further functionalization of cyclobutenes through organometallic methods.[21]

As proposed by Negishi, the cyclization of 4-halobut-1-ynes can follow two possible mechanisms, the σ- or the π-type cyclization, ultimately giving rise to two different regioisomers of cyclobutenes. The first step consists of the alkyne deprotonation with *n*-BuLi, which is followed by a carbometalation with a mixture of trimethylaluminium and zirconocene dichloride to give the *gem*-bismetallated intermediate **1.31**. When following the σ-type mechanism, the carbon-lithium σ-bond attacks the carbon atom bearing the halogen in a S_N2 reaction, releasing lithium bromide and giving metallated cyclobutene **1.32**. This can then be converted to the iodo-cyclobutene **1.33** by reacting it with elemental iodine.

In the π-type mechanism, the electrons of the double bond perform the S_N2 reaction, leading to the bismetallated cyclopropane **1.34**. In order to obtain the cyclobutyl moiety, two possible Wagner–Meerwein rearrangements can occur, giving intermediates **1.35** and **1.37** which after releasing the lithium cation and trapping with iodine produce the possible regioisomers **1.33** and **1.39**.



Scheme 7: Possible mechanisms for the cyclization of 4-haloalk-1-ynes to iodo-cyclobutenes.

[19] A. Fürstner; A. Schlecker; C. W. Lehmann, *Chem. Commun.* **2007**, 4277; A. Allen; K. Villeneuve; N. Cockburn; E. Fatila; N. Riddell; W. Tam, *Eur. J. Org. Chem.* **2008**, *2008*, 4178; A. B. Koldobskii; N. P. Tsvetkov; P. V. Verteletskii; I. A. Godovikov; V. N. Kalinin, *Russ. Chem. Bull.* **2009**, *58*, 1431; Y. Li; X. Liu; H. Jiang; B. Liu; Z. Chen; P. Zhou, *Angew. Chem. Int. Ed.* **2011**, *50*, 6341; Y.-P. Wang; R. L. Danheiser, *Tetrahedron Lett.* **2011**, *52*, 2111; J. Ciesielski; D. Lebœuf; H. A. Stern; A. J. Frontier, *Adv. Synth. Catal.* **2013**, *355*, 2077; J. He; M. L. Snapper, *Tetrahedron* **2013**, *69*, 7831; B. Alcaide; P. Almendros; C. Lázaro-Milla, *Adv. Synth. Catal.* **2017**, *359*, 2630; D. Kossler; F. G. Perrin; A. A. Suleymanov; G. Kiefer; R. Scopelliti; K. Severin; N. Cramer, *Angew. Chem. Int. Ed.* **2017**, *56*, 11490.

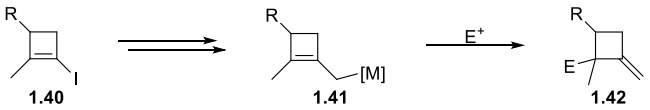
[20] E. Negishi; L. D. Boardman; J. M. Tour; H. Sawada; C. L. Rand, *J. Am. Chem. Soc.* **1983**, *105*, 6344.

[21] L. D. Boardman; V. Bagheri; H. Sawada; E. Negishi, *J. Am. Chem. Soc.* **1984**, *106*, 6105; E.-i. Negishi; F. Liu; D. Choueiry; Mohamud; A. Silveira; M. Reeves, *J. Org. Chem.* **1996**, *61*, 8325; F. Liu; E.-i. Negishi, *Tetrahedron Lett.* **1997**, *38*, 1149.

Negishi has shown in studies on 4-iodoalkynes that both mechanisms are active and the product outcome could be manipulated by transmetallating from lithium to aluminium with dimethylaluminium chloride before carbometalation. Changing the substituent R from position four to position three of the alkyne also has a strong impact on the product ratio. However, when applying the conditions to substituted 4-bromoalkynes **1.30**, we only ever observed products of type **1.39**, indicating that path *b* of the π-type cyclization mechanism was strongly preferred.

1.4 Boron-Allylation

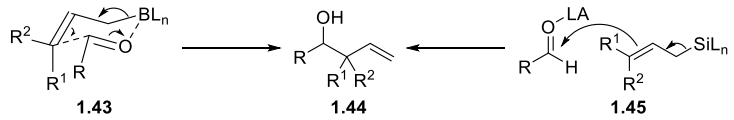
With a short and reliable iodo-cyclobutene synthesis in hand, the research focus shifted toward the possibility of transforming the cyclobutene moiety into an alkylidenecyclobutane. Through the installation of a methylenemetallic species (**1.41**), an allylic system would be generated, allowing for an allylic substitution and therefore creation of an alkylidenecyclobutane (**1.42**) containing a desirable quaternary stereocenter.



Scheme 8: Transformation of an iodo-cyclobutene to an alkylidenecyclobutane.

Allylation reactions with carbonyl or related compounds are mostly performed employing boron, silicon or tin reagents.[22] While boron and silicon are superior to tin due to ecological reasons, boron also has the advantage of reacting through a chair-like transition state, as shown by Hoffmann, and therefore providing diastereoselectivity in the reaction.[23] In the shown Zimmerman–Traxler-like transition state (**1.43**), the boron atom gets activated by the oxygen of an aldehyde. Furthermore, the reaction can be facilitated by employing Lewis acids or changing the ligands of the boron center. Allylations with silicon (Hosomi–Sakurai reaction) on the contrary proceed through an open transition state and require activation with additional reagents. Lewis acids can coordinate to the electrophile, thus activating it, whereas the use of hypervalent or strained silanes accomplishes activation through the nucleophile.[24]

[22] S. E. Denmark; E. J. Weber, *Helv. Chim. Acta* **1983**, *66*, 1655.
[23] R. W. Hoffmann; H.-J. Zeiss, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 306; R. W. Hoffmann; H. J. Zeiss, *J. Org. Chem.* **1981**, *46*, 1309.
[24] For a short review see: J. W. J. Kennedy; D. G. Hall, *Angew. Chem. Int. Ed.* **2003**, *42*, 4732.



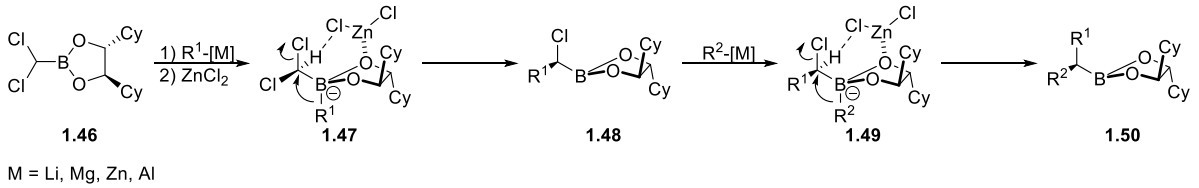
Scheme 9: Zimmerman–Traxler like transition state for boron-allylation and open transition state for silicon-allylation.

The use of boron for the transformation of cyclobutenes to alkylidenecyclobutanes holds another huge advantage:

1.5 Boron-Homologation

By reacting an organometallic species with an α-haloboronic ester, a boron-homologation can be triggered, creating the desired allylic system with a potentially huge variety of substituents in its α-position.[25] When starting from dihaloboronic esters, one can consecutively introduce the desired substituents through reaction with different organometallic species. The use of a chiral ligand on the boron atom even allows for the erection of allylic boronic esters with virtually perfect control over the newly formed stereocenter.

As shown in extensive studies by Matteson, a metallic carbon nucleophile attacks the boronic ester **1.46** at the boron atom, creating a boronate. The boronate undergoes a 1,2-metallate rearrangement, substituting a chloride in a S_N2-type fashion. In the presence of zinc chloride, the substitution occurs stereoselectively, due to coordination of the less hindered oxygen of the diol-ligand to the zinc and hydrogen-halogen bonding of the α-hydrogen to a chloride ion. Additionally, the zinc chloride locks the conformation of the carbon-boron bond due to steric repulsion of an α-chloride and the zinc salt (see **1.47**). In the following stereospecific homologation the same effects take place, leading to the α-chiral boronic ester **1.50**.[26]



Scheme 10: Double boron-homologation.

[25] D. S. Matteson; R. W. H. Mah, *J. Am. Chem. Soc.* **1963**, *85*, 2599; D. S. Matteson; D. Majumdar, *J. Organomet. Chem.* **1980**, *184*, C41; D. S. Matteson; D. Majumdar, *J. Am. Chem. Soc.* **1980**, *102*, 7588; D. S. Matteson; R. Ray, *J. Am. Chem. Soc.* **1980**, *102*, 7590.

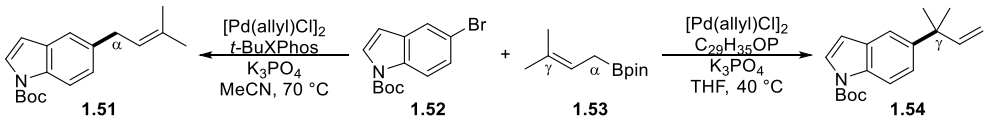
[26] D. S. Matteson; K. M. Sadhu, *J. Am. Chem. Soc.* **1983**, *105*, 2077; E. J. Corey; D. Barnes-Seeman; T. W. Lee, *Tetrahedron: Asymmetry* **1997**, *8*, 3711; S. P. Thomas; R. M. French; V. Jheengut; V. K. Aggarwal, *Chem. Rec.* **2009**, *9*, 24; D. S. Matteson, *J. Org. Chem.* **2013**, *78*, 10009.

By introducing a metallic species, which contains a leaving group in its α-position, to a boronic ester of type **1.50**, one can enter a repetitive cycle of homologation reactions. The group of Aggarwal has proven this idea with the synthesis of natural products containing several consecutive stereocenters.[27]

Apart from allylations, we have employed this concept for the synthesis of various allylic boronic esters in the construction of alkylidenecyclobutanes through γ-selective Suzuki–Miyaura cross-coupling reactions.

1.6 γ-Selective Suzuki–Miyaura Cross-Coupling Reactions

Combining an organic halide with an organo-boron compound under transition metal catalysis, the Suzuki–Miyaura cross-coupling is a well-established and extensively used method for forming a new carbon-carbon bond.[28] When the boron moiety of the substrate is embedded in an allylic system however, an interesting feature presents itself.[29] The cross-coupling can either occur α to the boron or in the equally nucleophilic γ-position, depending on the catalytic system used.[30] The group of Buchwald used this concept to install prenyl residues in a regioselective fashion.



Scheme 11: Prenylation of protected indole **1.52** through α- and γ-selective Suzuki–Miyaura cross-coupling reaction.[31]

[27] S. Balieu; G. E. Hallett; M. Burns; T. Bootwicha; J. Studley; V. K. Aggarwal, *J. Am. Chem. Soc.* **2015**, *137*, 4398; A. Noble; S. Roesner; V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2016**, *55*, 15920; T. Bootwicha; J. M. Feilner; E. L. Myers; V. K. Aggarwal, *Nature Chem.* **2017**, *9*, 896.

[28] *Metal-Catalyzed Cross-Coupling Reactions,* 2nd ed.; A. de Meijere; F. Diederich; Wiley-VCH: Weinheim, Germany, 2004; *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials,* 2nd ed.; D. G. Hall; Wiley-VCH: Weinheim, Germany, 2011.

29 S. Sebelius; V. J. Olsson; O. A. Wallner; K. J. Szabó, J. Am. Chem. Soc. 2006, 128, 8150.

30 Y. Yang; S. L. Buchwald, J. Am. Chem. Soc. 2013, 135, 10642.

31 $C_{29}H_{35}OP$: 2'-Dicyclohexylphosphino-2-methoxy-1-phenylnaphthalene.

2 Results

2.1 Highly Diastereoselective Synthesis of Methylenecyclobutanes by Merging Boron-Homologation and Boron-Allylation Strategies

Angewandte Communications

Synthetic Methods

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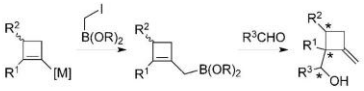
Highly Diastereoselective Synthesis of Methylenecyclobutanes by Merging Boron-Homologation and Boron-Allylation Strategies

*Michael Eisold and Dorian Didier**

Dedicated to Professor Paul Knochel on the occasion of his 60th birthday

Abstract: *A highly diastereoselective synthesis of methylenecyclobutanes possessing a quaternary stereocenter is reported, in which boron homologation of an easily-generated cyclobutenylmetal species is performed, followed by an allylation reaction. Combining three steps in a one-pot process further optimized the method, which afforded the expected adducts in excellent yields and stereoselectivity, starting from commercially available 4-bromobutyne.*

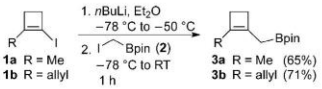
Possessing a unique geometry, alkylidenecyclobutanes (ACBs) are fascinating motifs that are encountered in natural compounds[1] and found as key intermediates in their syntheses.[2] Moreover, ACBs can undergo valuable ring-expansion reactions towards the synthesis of substituted cyclopentanones, cyclopentenes, or eight-membered-ring derivatives.[3] Despite several reports reviewing stereoselective access to substituted cyclobutanes,[4] the chemistry of alkylidenecyclobutanes remains a relatively unexplored and challenging domain among strained systems.[5] Commonly generated through gold(I)-catalyzed [2+2] cycloadditions between an allene and an unsaturated system,[6] ACBs have recently been accessed by other transition-metal-mediated processes.[7] On the other hand, if one could access a cyclobutenylmetal species, boron homologation could lead to in situ formation of the desired methylenecyclobutane (MCB) through a simple allylation reaction (Scheme 1). Following pioneering work by Matteson et al.,[8] Aggarwal et al. showed the high synthetic potential of such a method for the construction of elaborated structures[9] by applying a reagent-controlled asymmetric homologation using Hoppe's carbamates.[10]



Scheme 1. Unprecedented approach to MCBs containing quaternary stereocenters.

We report herein the results of our successful investigation of unprecedented boron allylation reactions based on cyclobutenylmethylboronic esters for the sequential one-pot diastereoselective synthesis of MCBs possessing a quaternary stereocenter.

Cyclobutenylmethylboron derivatives (**3a** and **3b**; Scheme 2) were identified as key units of this study. Since they would directly undergo an allylation reaction in the presence of an electrophile, their synthesis was undertaken first. Performing an iodine–lithium exchange on **1a**[11a] or **1b**[11b] at −50 °C, followed by introduction of the boronic ester **2** led to formation of the desired cyclobutenylmethylboronic esters **3a** and **3b** (65 % and 71 % respectively).



Scheme 2. Synthesis of cyclobutenylmethylboronic esters **3a** and **3b**.

Next, we investigated the allylation reaction of benzaldehyde in the presence of **3a**. The reaction was carried out at room temperature in dichloromethane and completion was reached in less than five minutes. Surprisingly, low-temperature conditions were not required to achieve high levels of diastereoselectivity, and the alkylidenecyclobutane **4a** was isolated in good yield and stereoselectivity (84 %, d.r. > 97:3, Table 1). Aromatic aldehydes possessing an electron-donating group (*o*-OMe, *m*-OMe, *p*-NMe_2) or an electron-withdrawing group (*p*-NO_2) also led to the desired products (**4c**–**4f**) with comparable levels of stereoselectivity. Halogenated aromatic aldehydes also underwent boron allylation to form MCBs **4g** and **4h** in moderate to good yields (58–73 %). Interestingly, heteroaromatic aldehydes also reacted quickly with **3a**, leading to the synthesis of MCBs with greater functionalization. Oxygen-, nitrogen-, and sulfur-containing heterocycles were introduced in the same way, furnishing MCBs **5a**–**5f** in good yields and excellent diastereoselectivity (d.r. > 97:3). To further extend the reaction scope, we employed aliphatic aldehydes: dihydrocinnamal, isovaleraldehyde, and 11-hexadecenal gave products **6a**–**6c** to good yields and excellent diastereoselectivity. However, even using reported methods for the enhancement of allylation reactions, ketones and imines did not lead to the expected products.[12]

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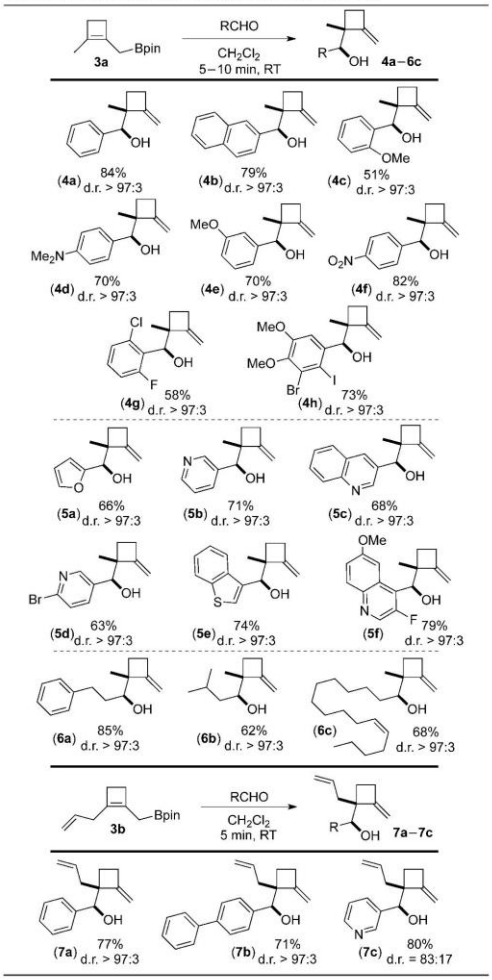
Supporting information (experimental procedures and spectroscopic characterization (IR, HRMS, and ^1H and ^{13}C NMR data) of all new compounds) and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201507444.

Table 1: Diastereoselective synthesis of MCBs from **3a**.

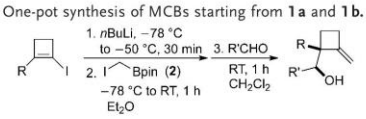


Promising results obtained with **3a** encouraged us to explore the potential and versatility of **3b** in allylation reactions towards the synthesis of more diverse MCBs. Gratifyingly, the reaction with benzaldehyde was complete within five minutes and **7a** was isolated in 77% yield with a high diastereoisomeric ratio (d.r. > 97:3). 4-Biphenylcarboxaldehyde led to similar results (**7b**, 71% yield, d.r. > 97:3). 3-Pyridine-carboxaldehyde afforded the MCB **7c** with a lower diastereoisomeric ratio (d.r. = 83:17).

The relative configuration of MCBs was assigned by analogy with **4f**, which could be crystallized as a single diastereoisomer (d.r. > 99:1 by GC) and analyzed by X-ray diffraction (see the Supporting Information).[13]

We additionally investigated the possibility of merging the different steps of the sequence into a one-pot process to facilitate the production of MCBs from commercially available materials. Cyclobutene iodides **1a** and **1b** were evaluated first. After carrying out lithium–iodine exchange, iodomethylboronic ester **2** was subsequently introduced to perform the boron homologation. Dichloromethane was added to the reaction mixture along with the electrophile (Table 2) to

Table 2: One-pot synthesis of MCBs starting from **1a** and **1b**.



Entry	Substrate	Product	Yield[a]	d.r.[b]
1	**1a**	**4a**	68%	> 97:3
2	**1a**	**5b**	55%	> 97:3
3	**1b**	**7a**	56%	> 97:3

[a] Yield of isolated product. [b] Determined by ^{13}C NMR.

allow the allylation reaction to proceed directly on the in situ generated allylboron intermediate. In these cases, completion of the reaction was only observed after one hour, thus indicating a possible competitive interaction of the coordinative solvent (diethyl ether) with the substrate. Similar results were obtained in terms of diastereoselectivity (d.r. > 97:3), but the yields of isolated product were lower compared to the two-step procedure (Table 1). Addition of benzaldehyde led to **4a** and **7a** (61% and 56%, respectively), and 3-pyridine-carboxaldehyde furnished **5b** in 55% yield.

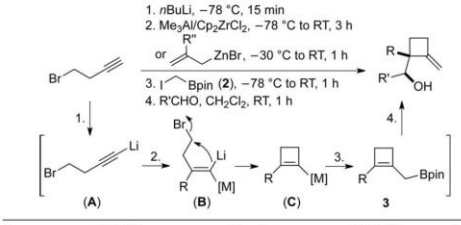
Having successfully performed the two-step, one-pot procedure, we took on the challenge of forming the metalated cyclobutene in situ, starting the sequence directly from commercially available 4-bromobutyne (Table 3).

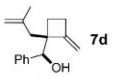
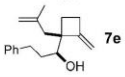
Deprotonation of the alkyne with *n*-butyllithium is followed by a carbometallation reaction (Me_3Al/Cp_2ZrCl_2 or allylzinc bromide), which leads to the formation of *gem*-bimetallic intermediate **B**.[14] Nucleophilic substitution of the bromide takes place at 20°C, giving the desired metalated cyclobutene species of Al or Zn (**C**). The homologation is performed by adding **2** to the reaction mixture to furnish the intermediate **3**. After diluting the solution with dichloromethane, the allylation reaction proceeds after the addition of aldehydes to give the product with high diastereoselectivity (d.r. > 97:3) and in good yields (78 to 85%), which demonstrates the efficiency of this four-step, one-pot sequence. Different allylzinc species were also used to promote the formation of a wider range of compounds (**7a**, **7d** and **7e**) with the same stereoselectivity and in good yields (52 to 72%).

More elaborate chiral substrate were further studied. Iodocyclobutene **8** was synthesized according to Negishi's procedure,[11] from which the chiral cyclobutenylmethylboronic ester **9** (Table 4) was generated in situ through the procedure described above (Table 2).

The addition of aldehydes to achieve the formation of MCBs possessing three consecutive stereocenters, with one

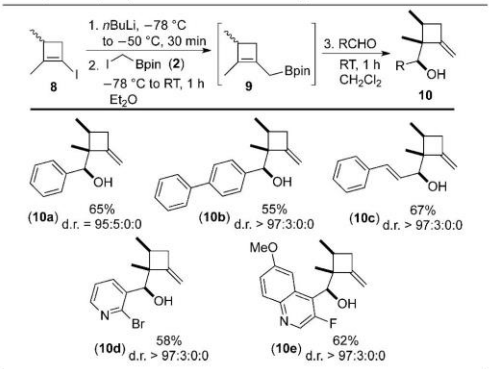
Table 3: One-pot synthesis of MCBs starting from 4-bromo-1-butyne.



Entry	R-[M][a]	Product	Yield[b]	d.r.[c]
1	Me_3Al/[Zr]	**4a**	85%	>97:3
2	Me_3Al/[Zr]	**5b**	78%	>97:3
3	Me_3Al/[Zr]	**6a**	84%	>97:3
4	Allyl-ZnBr	**7a**	52%	>97:3
5		 **7d**	72%	>97:3
6		 **7e**	66%	>97:3

[a] See the Supporting Information. [b] Yield of isolated product. [c] Determined by ^{13}C NMR.

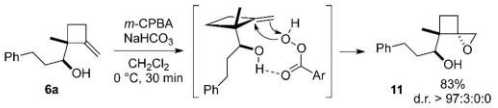
Table 4: One-pot synthesis of MCBs starting from **8**.



being quaternary, was then pursued with the crude mixture after changing the solvent system to dichloromethane. A selection of aldehydes was used, leading to the formation of **10a**–**10e** with high diastereoselectivity and 55–67% yield.

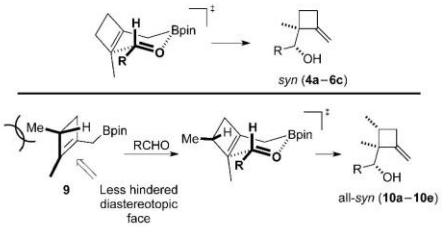
Since allylation reactions could be performed within short periods of time, the specific cyclobutane geometry plays an incontestable role. In fact, only a few boron allylation processes have been described in which tetrasubstituted olefins were used. Up to 24 h and/or the presence of a catalyst were needed to achieve good yields.[15] The particularly good reactivity of our cyclobutenylmethyl boron system could be attributed to strain release when going from cyclobutene to an ACB.[16]

To highlight the synthetic utility of the method, we considered the transformation of **6a** into a substituted 1-oxaspiro[2.3]hexane. The epoxidation of **6a** was performed in the presence of *m*-CPBA to furnish **11**, which possesses three stereocenters, two of which are quaternary, in high yield and diastereoisomeric ratio (Scheme 3).



Scheme 3. Further transformation of MCB into chiral 1-oxaspiro-[2.3]hexane.

A Zimmermann–Traxler transition state is proposed to explain the stereochemical outcome of the allylation reaction (Scheme 4).[17] The chain of the aldehyde preferentially adopts the pseudo-equatorial position, thereby minimizing the energy of the system. In the cases of achiral substrates **3a** and **3b**, the proposed model furnishes a *syn* relative configuration, which correlates with the configuration observed by X-ray diffraction. Concerning the chiral substrate **9**, the attack from one or the other diastereotopic faces has to be considered. We assume that the methyl group shields one of the two faces, thereby orienting the approach of the aldehyde from the opposite face, which leads to formation of the "all-*syn*" MCB based on a Zimmermann–Traxler transition state.



Scheme 4. Zimmerman–Traxler models explain the *syn*-diastereoselectivity in MCBs.

In conclusion, we have reported an unprecedented and straightforward way of approaching methylenecyclobutanes possessing up to three adjacent stereocenters through multistep one-pot sequences, starting from either easily synthesized or commercially available starting materials. Perfect diastereocontrol of the allylation process is achieved under mild conditions, in short periods of time, and without the addition of a catalyst.

Acknowledgments

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Keywords: allylboration · boron homologation · diastereoselectivity · methylenecyclobutanes · one-pot reactions

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2.2 Single-Pot Asymmetric Approach toward Enantioenriched Quaternary Stereocenter-Containing Alkylidenecyclobutanes

Organic LETTERS

Letter

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Single-Pot Asymmetric Approach toward Enantioenriched Quaternary Stereocenter-Containing Alkylidenecyclobutanes

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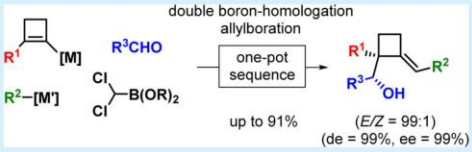
Supporting Information

ABSTRACT: Enantioenriched alkylidenecyclobutanes possessing a quaternary stereogenic center, usually difficult to access, have been synthesized by combining a double boron-homologation and an allylboration through a highly efficient and diastereoselective one-pot process. Starting from commercially available substrates, this protocol represents a simple way of accessing chiral unsaturated four-membered ring systems with excellent stereoisomeric ratios.



Small, unsaturated ring systems have received great interest in organic chemistry due to their fascinating and blossoming panel of reactivity.[1−6] Among them, alkylidenecyclobutanes (ACBs) are important synthons and core patterns that can be found in various natural architectures.[2] Only a few reports relate their accessibility via cycloadditions,[3] rearrangements,[4] or other transition-metal-assisted processes.[5] However, their synthesis is often limited by the lack of efficient and selective methodologies. Possessing a relatively higher ring strain than alkylidenes of larger cycloalkanes, ACBs have been studied for their exceptional reactivity toward the synthesis of substituted cyclopentenes, cyclopentanones, or eight-membered-ring derivatives.[6]

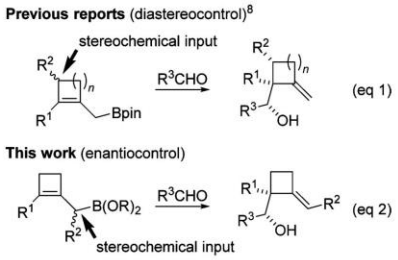
We recently reported a highly diastereoselective sequence to allow for accessing methylenecyclopropanes[7] and -butanes[8] in their racemic forms (Scheme 1), starting from simple substrates or commercially available materials. We wish to report herein efficient one-pot diastereo- and enantioselective sequences for the construction of unsaturated four-membered ring systems containing a quaternary stereocenter (Scheme 1, eq 1).

We based our study on the interesting work of Matteson about boron-homologation and establishments he made on the asymmetric formation of α-chiral boronic esters.[9] While enantiomerically pure diols as ligands for allylboron species usually lead to an incomplete transfer of chirality for allylboration reactions,[10] boron-homologations have proven to furnish α-chiral boronic esters with a perfect control of the new stereocenter.[11] We envisioned combining asymmetric homologations with allylborations to synthesize chiral alkylidenecyclobutanes.

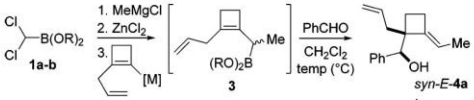
The stereochemical information would then be relayed by the newly generated stereocenter (Schemes 1, eq 2), α to the boronic ester moiety, to the allylic position when preforming the final allylation reaction, controlled by the transition state.

First, we optimized the conditions for the synthesis of racemic alkylidenecyclobutanes, starting from α,α-dichloromethylboronic esters (Scheme 2). One equivalent of nucleophile (MeMgCl) was added to perform the first boron-homologation, in the presence of zinc chloride, followed by the addition of a preformed cyclobutenyl metal species, to allow for the formation of **3**, through a second, in situ, boron homologation. After the solvent was switched to dichloromethane, benzaldehyde was added to allow the allylboration to proceed.

Scheme 1. Access to ACBs via One-Pot Sequences



Scheme 2. Optimization of the One-Pot Sequence



-B(OR)$_2$		substrate	temp (°C)	E/Z
-Bpin	(-Bpin)	**1a**	25	33:67
-Bneo	(-Bneo)	**1b**	25	89:11
			0	97:3

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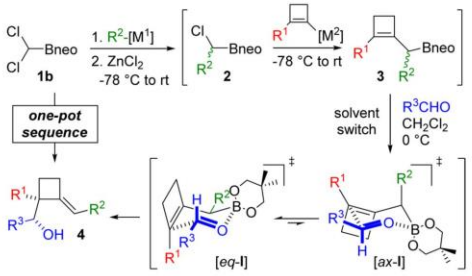
When pinacol was used as a ligand, a mixture of ACBs *syn*-*E*-**4a** and *syn*-*Z*-**4a** (33:67, respectively) was obtained. This ratio was further improved to 89:11 (with *syn*-*E*-**4a** as the major isomer) by employing neopentyl glycol as a ligand. As a matter of fact, it has been previously shown that the *E*/*Z* ratio can easily be changed by modifying the composition of the allylboronate.[12] Lowering the temperature to 0 °C gave the best results in terms of *E*/*Z* ratio (>97:3).

Such a difference in the stereoselectivity can be explained by steric effects of methyl groups in the case of pinacol ligands, hindering the pseudoequatorial position and forcing the R^2 chain to adopt the pseudoaxial position. Less hindered diols (**1b**) (Scheme 3) do not shield the pseudoequatorial position,

Scheme 3. Diastereoselective Approach to ACBs



balancing the equilibrium toward *eq*-**I**, leading to the exclusive formation of (*E*)-**4** derivatives. This same transition state also allows us to explain the diastereoselectivity observed in the allylation reaction for the relative *syn* configuration of the two new stereocenters following the model proposed by Hoffmann,[13] giving *syn*-(*E*)-**4** as the major product.

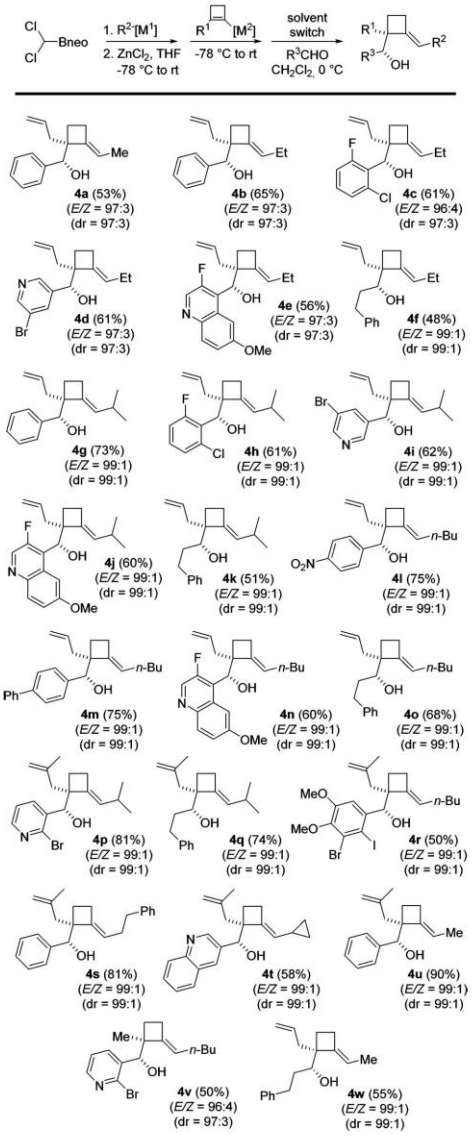
On the strength of this successful experiment, different racemic α-chiral cyclobutenylmethylboronic esters made of neopentyl glycol were generated in situ to explore the synthetic scope of such a methodology for the formation of alkylidenecyclobutanes containing a quaternary stereocenter. The scope of the double-homologation/allylation sequence is depicted in Scheme 4.

Employing various organometallic nucleophiles (R^2-[M^1]) for the first homologation could furnish α-chloro boronic esters **2**, to which was subsequently added the ex situ generated cyclobutenylmetal species, leading to the formation of **3**.

The first boron-homologation was performed by introduction of MeMgCl (**4a**,**u**,**w**), EtMgCl (**4b**−**f**), *i*-PrMgCl (**4g**−**k** and **4p**−**q**), *n*-BuLi (**4l**−**o**,**r**,**v**), $PhCH_2CH_2MgBr$ (**4s**) or *c*-PrMgBr (**4t**), affording the respective α-chloroboronic ester. In parallel, cyclobutenylmetal species were generated ex situ by addition of allylzinc bromide (**4a**−**o**), (2-methylallyl)zinc bromide (**4p**−**u**), or Me_3Al/Cp_2ZrCl_2 (**4v**) to the commercially available 4-bromobutyne after deprotonation and were subsequently added to **2**, leading to a large panel of chiral cyclobutenylmethylboronic esters **3**. Allylation reactions were then performed, furnishing alkylidene cyclobutanes **4a**−**v** in exceptionally high levels of diastereoselectivity (dr up to 99:1, *E*/*Z* ratio up to 99:1) (Table 1) and in good to high yields (up to 90%).

In the case of **4u** (90%), the solvent was not switched to dichloromethane and allylation was performed in THF, leading

Scheme 4. Scope of the Method[a]



[a]dr (*syn*/*anti*) and *E*/*Z* ratios were determined by GC and ^{13}C NMR.

to similar results in terms of diastereoselectivity and 83% yield. However, the reaction reached its completion only after 18 h at room temperature, when 30 min was usually necessary for allylation in dichloromethane at 0 °C. We attributed this difference of reactivity to a possible competition of the solvent with the aldehyde in the coordination to the boron atom.

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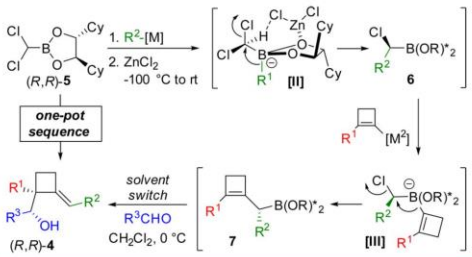
Table 1. Access to ACBs in Their Enantiopure Form

-B(OR)$_2$	product	yield (%)[a]	de (%)[b]	E/Z[b]	ee (%)[c]
 (R,R)	(+)-**4l**	58	99	99:1	99
	(-)-**4r**	62	99	99:1	99
	(+)-**4q**	58	99	99:1	99
	(-)-**4p**	91	99	99:1	97
 (S,S)	(-)-**4l**	47	99	99:1	99
	(+)-**4r**	55	99	99:1	99
	(-)-**4q**	79	99	99:1	99
	(+)-**4p**	88	99	99:1	97

[a]Isolated yields. [b]Determined by GC. [c]Determined by HPLC utilizing a chiral stationary phase.

To push the method further, we envisioned that a chiral ligand for the formation of the organoboronic ester would ultimately lead to the formation of enantiomerically enriched ACBs. Pioneered by Matteson, the introduction of 1,2-dicyclohexylethanediols (Cy = cyclohexyl) has proven to efficiently promote a transfer of chirality to the α-position when performing a boron-homologation of an organoboron derivative **5** by addition of a nucleophile R^2-[M] (Scheme 5).[11] (*R*,*R*)-**5** was then submitted to homologation, furnishing the boronate species **II**.

Scheme 5. Substrate-Controlled Synthesis of Enantiopure ACBs

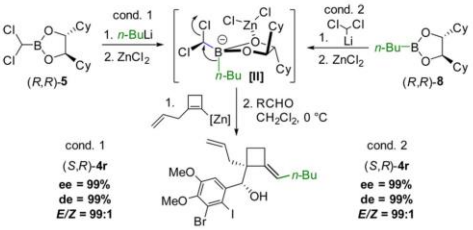


According to the literature, the presence of $ZnCl_2$ is necessary for the stereoselectivity to be maximal. In the proposed model, coordination of $ZnCl_2$ by an oxygen atom of the diol helps the positioning of the dichloromethyl side chain, with one of the diastereotopic chlorides being antiperiplanar to R^1 and the other one away from the salt **II**. Moreover, a H-bonding between a chloride atom ($ZnCl_2$) and the residual H of the dicholoromethyl chain reinforces the diastereoselectivity of the 1,2-metalate rearrangement. A diastereoselective intramolecular substitution takes place, leading to the formation of **6**. A cyclobutenylmetal species was subsequently added, giving stereospecifically the α-chiral allylboronic ester **7**, through the intermediate **III**, in which the substitution occurs antiperiplanary. Finally, allylborations were performed after the solvent was switched to dichloromethane and the appropriate electrophile was added.

As previously proposed, a Zimmermann−Traxler model could explain the diastereoselective formation of ACBs **4**, obtained as their pure enantiomeric forms (ee up to 99%).[14] The results are described in Table 1. Through this highly diastereoselective one-pot process, organoboron derivatives, cyclobutenylmetal species, and aldehydes of different natures could furnish ACBs with excellent diastereo- and enantiomeric ratios (up to >99:1) and good to excellent yields. Ultimately, both enantiomers (*R*,*R*)-**5** and (*S*,*S*)-**5** were used to obtain isomers of **4l**, **4p**, **4q**, and **4r** of opposite absolute configurations.

Importantly, we finally show that starting from either (*R*,*R*)-**5**, possessing the dichloromethyl moiety, or from (*R*,*R*)-**8**, having the *n*-butyl chain preinstalled, followed by addition of dichloromethyllithium led to obtaining (*S*,*R*)-**4r** (after subsequent introduction of the appropriate aldehyde) in comparably high levels of enantio- and diastereoselectivities (ee = 99%, de = 99%). This observation supports the involvement of the intermediate boron−ate complex **II** (Scheme 6) in the diastereoselective 1,2-metalate rearrangement.

Scheme 6. Comparison between (*R*,*R*)-5 and (*R*,*R*)-8 as Substrates for the Sequence Leading to (*S*,*R*)-4r



In conclusion, we have assembled an efficient route for the preparation of ACBs through highly diastereoselective one-pot sequences involving boron-homologation and allylboration strategies. Moreover, a powerful tool involving chiral auxiliaries for rapidly accessing enantiomerically pure ACBs was developed using commercially available starting material.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01432.

Experimental procedures and spectroscopic characterization (IR, HRMS, and ^{1}H and ^{13}C NMR data) of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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2.3 Unsaturated Four-Membered Rings: Efficient Strategies for the Construction of Cyclobutenes and Alkylidenecyclobutanes

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Cyclobutenes

Unsaturated Four-Membered Rings: Efficient Strategies for the Construction of Cyclobutenes and Alkylidenecyclobutanes

Michael Eisold[+], Andreas N. Baumann[+], Gabriel M. Kiefl, Sebastian T. Emmerling, and Dorian Didier*[a]

Abstract: Our recent studies of the diastereo- and enantioselective formation of strained alkylidenecycloalkanes drove us to more-thoroughly investigate the formation of four-membered rings for which only few efficient methods are described. We first developed a strategy to diversify the saturated part of the four-membered ring and applied it to a highly diastereoselective synthesis of more-elaborate alkylidenecyclobutanes, which completed our precedent studies. In parallel, cyclobutene structures were built employing simple organometallic methods and further functionalized to give a diverse range of new substitution patterns, which consequently enriched the pool of cyclobutene-based building blocks.

Introduction

Cyclobutenes (CBs) and alkylidenecyclobutanes (ACBs) are interesting structural motifs and drive continuous interest among the organic chemistry community.

CBs are rarely observed in natural architectures,[1] whereas ACBs are found in the cores of a number of natural products (Figure 1).[2] Besides their natural occurrences, CBs and ACBs have enticed curiosity for their ability to undergo transformations such as ring expansions[3] and rearrangements.[4] However, and despite growing interest, four membered-ring systems have been scarcely studied, mainly due to the difficulty in accessing their core structure. Generally obtained via [2+2] cycloaddition reactions[5] or metal-catalyzed processes,[6] the synthesis of CBs and ACBs remains a challenge in the area of organic chemistry. The development of simple and straightforward strategies to generate these strained building blocks[7] undoubtedly warrants further exploration,
because the limitation of the scope is a consequence of the lack of diverse and available methodologies.

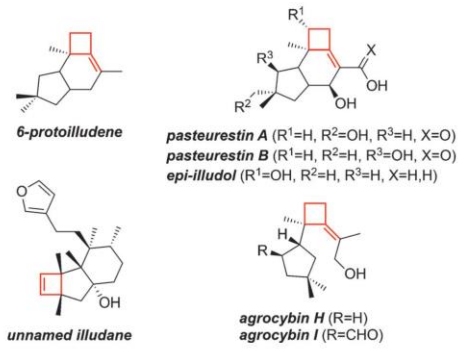


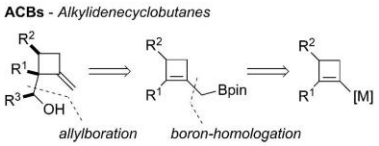
Figure 1. Naturally occurring CB- and ACB-containing substances.

Results and Discussion

Synthetic routes towards ACBs

We recently reported an efficient method for the diastereo- and enantioselective preparation of alkylidenecyclopropanes[8] and ACBs.[9] Our general approach is based on a one-pot boron-homologation/allylboration sequences. A boron homologation reaction, based on the useful and pioneering work of Matteson,[10] installs the allylic boron moiety onto a preformed cyclobutenyl metal species then simple aldehyde allylboration forms the ACB (Scheme 1).

A representative example is shown in Scheme 2. Addition of dihydrocinnamaldehyde to cyclobutenylmethylboronate **1**



Scheme 1. Retrosynthetic approach to ACBs.

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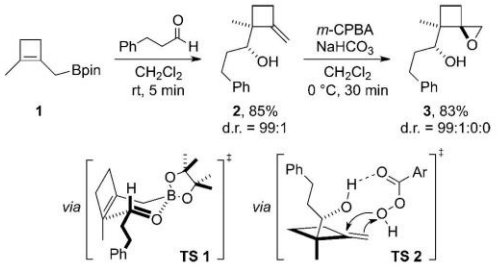


Scheme 2. ACB formation, and application of the method to the synthesis of oxaspirohexane **3**. Bpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

afforded methylenecyclobutane **2** in 85% yield with perfect diastereocontrol control (diastereomeric ratio (d.r.) = 99:1) in a remarkably short time at ambient temperature. Subsequent oxidation furnished diastereomerically pure oxaspirohexane **3** in 83% yield. The high d.r. observed for the formation of **2** can be explained by a Zimmermann–Traxler transition state, in which the lateral chain of the aldehyde adopts the pseudo-equatorial position, which was initially postulated by Hoffmann for allylboration reactions (**TS 1**).[11] We also propose that, in the absence of a protic solvent, epoxidation of the alkylidene moiety takes place on the same face as the secondary alcohol by hydrogen bonding with *m*-chloroperbenzoic acid (*m*-CPBA) (**TS 2**).

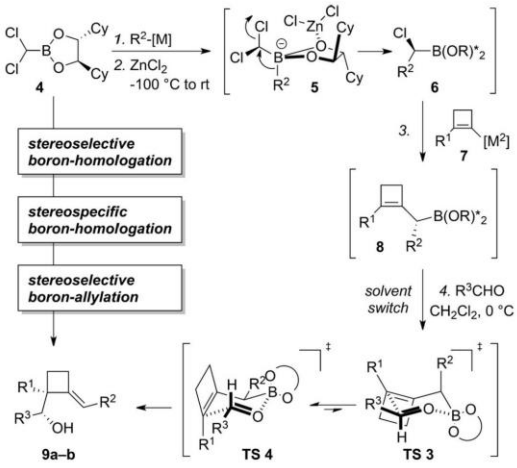
This new method to easily generate ACBs proved to be quite general; a wide range of aromatic, heteroaromatic, and aliphatic aldehydes were used to generate chiral adducts with good diastereoselectivity.

Next, we developed an asymmetric version of the one-pot sequence by using chiral diols as boron ligands, which allowed enantiomerically enriched ACBs to be prepared (Scheme 3).[9b]

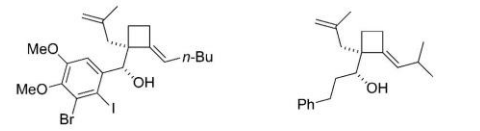
In this one-pot sequence, dichloromethylboronic ester **4** reacted with an organometallic nucleophile, which promoted stereoselective formation of a α-chiral chloromethylboronic ester **6** via a 1,2-metalate rearrangement. The rearrangement was controlled by the chiral diol ligand, and the selectivity was relayed through the intermediate boronate **5** by the presence of zinc chloride.[12] A second stereospecific boron homologation occurred upon addition of cyclobutenyl metal species **7** and gave α-chiral cyclobutenylmethylboronic ester **8**. Finally, an allylation reaction occurred upon addition of an aldehyde. A Zimmerman–Traxler transition state, in which both the R^2 and R^3 groups adopted pseudo-equatorial positions (**TS 4**), controlled the diastereoselectivity of the reaction.

A wide variety of novel ACBs **9a** (R^3 = aromatic) and **9b** (R^3 = aliphatic) were generated by using this diastereo- and enantioselective procedure. Figure 2 shows representative examples of the ACBs obtained in 55–79% yield with excellent diastereo- and enantiocontrol over the one-pot sequence.

Alternatively, we envisioned that the diastereoselectivity could come from the cyclobutene ring itself. In this case, propargyl bromides had to be adequately prepared to install the lateral chain R^2 (Scheme 4). To avoid the use of expensive propargylation reagents,[13] we employed readily available alde-



Scheme 3. One-pot stereoselective synthesis of ACBs **9a** and **9b** (Cy = cyclohexyl).



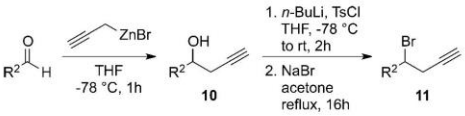
9a, 62%
syn/anti = 99:1
ee = 99% (-)

***ent*-9a**, 55%
syn/anti = 99:1
ee = 99% (+)

9b, 58%
syn/anti = 99:1
ee = 99% (+)

***ent*-9b**, 79%
syn/anti = 99:1
ee = 99% (-)

Figure 2. Representative examples of enantiomerically enriched ACBs.



Scheme 4. Synthesis of homopropargylic bromides **11** (Ts = tosyl).

hydes and a pre-prepared storable propargylzinc reagent to form the substituted homopropargylic alcohol precursors **10**. The temperature was maintained at −78 °C, which allowed selective formation of the expected alkyne that contained only traces of the competitive allenylation compound. Subsequent tosylation of the secondary alcohols **10** followed by nucleophilic substitution afforded the corresponding homopropargylic bromides **11**. Notably, only traces of the required substituted propargyl bromides were obtained if PBr_3 or Appel's conditions were employed for direct synthesis from the corresponding alcohols; instead, the major product resulted from an elimination reaction.

The boron homologation and allylboration reactions were merged in a one-pot sequence, and ACBs **12a–l** were obtained with excellent diastereoselectivity (in all cases d.r. > 99:1:0:0).

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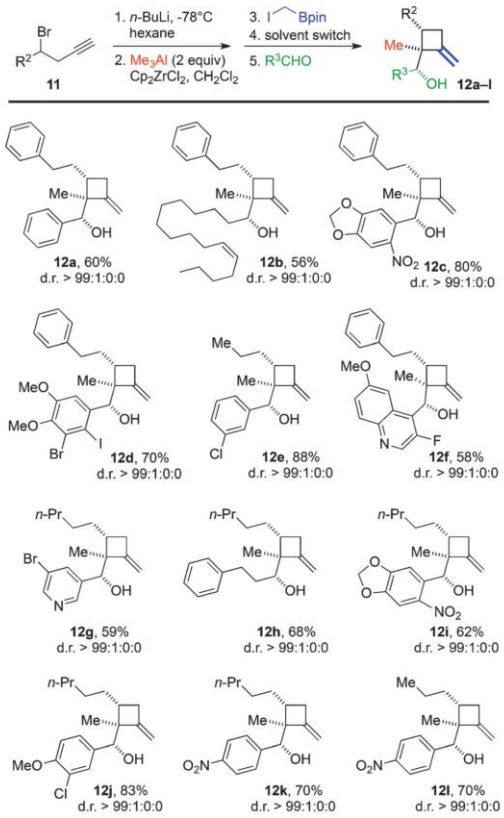
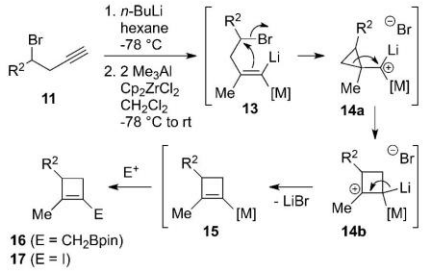
Simple propargyl bromides **11** and aromatic, heteroaromatic, and aliphatic aldehydes were employed, and the reaction furnished the expected compounds **12** with three consecutive stereocenters (one quaternary) in good yields up to 88% (Scheme 5).



Scheme 5. One-pot diastereoselective synthesis of ACBs containing a side chain.

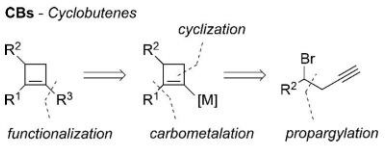
The reaction was initiated by alkyne deprotonation with *n*-butyllithium, and the remainder of the sequence was realized by a carboalumination reaction upon addition of a mixture of dichlorozirconocene and trimethylaluminium in dichloromethane (**13**). Following the mechanism proposed by Negishi,[14] a π cyclization took place to furnish *gem*-bismetalated cyclopropyl methylium intermediate **14a**. Subsequent C–C bond cleavage and migration of the methylene group gave cyclobutenylium **14b** then lithium bromide elimination gave cyclobutenyl metal species **15**. The regiochemistry of the overall cyclization process was clarified by NMR spectroscopy.[15] Finally, introduction of the appropriate electrophile gave either the cyclobutenylmethylboronic ester **16** (Scheme 6), used for the allylation sequence with an aldehyde, or the iodocyclobutene **17**, which is useful for CB functionalization.



Scheme 6. Proposed mechanism for the formation of cyclobutene derivatives.

Synthetic routes towards CBs

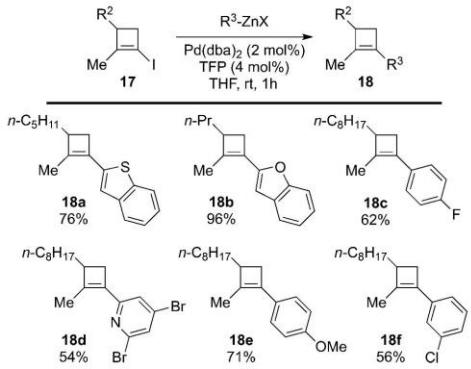
We envisioned that CBs could be functionalized later in the sequence by employing the previously generated cyclobutenyl metal species with a preinstalled R^2 moiety by following the aforementioned cyclization strategies (see above). Consequently, derivatization of the unsaturated CB was undertaken via a cyclobutenyl metal intermediate (Scheme 7).



Scheme 7. Retrosynthetic approach to CBs.

With a range of propargyl bromides **11** in hand, cyclobutene iodides **17** were simply synthesized by the addition of iodine to cyclobutenyl metal species **15**, which was generated in situ.

A first derivatization was undertaken by cross-coupling **17** with different zinc species in the presence of bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) and tri-2-furylphosphane (TFP). The results are depicted in Scheme 8. Aromatic and hetero



Scheme 8. Derivatization of CBs via Negishi cross-coupling.

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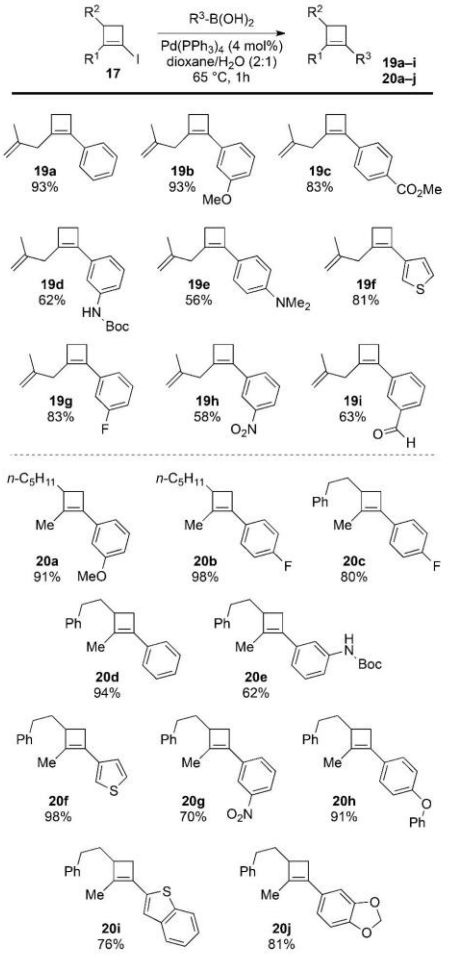
aromatic substrates were easily introduced, and substituted CBs **18a–f** were obtained in good-to-excellent yield.

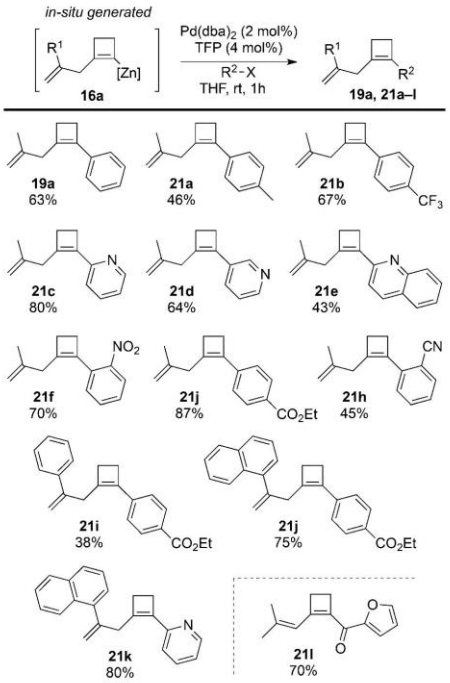
On the strength of these successful initial results, we took a step further and envisaged boronic acids as cross-coupling partners. A wide range of commercially available boronic acids were used in the Suzuki cross-coupling of cyclobutene iodides **17** in the presence of tetrakis(triphenylphosphine)palladium (4 mol%) (Scheme 9).[16] Halogen-, ether-, and nitro- substituted



Scheme 9. Derivatization of CBs via Suzuki cross-coupling

aromatic groups were introduced very efficiently, as well as *tert*-butoxycarbonyl (Boc) protected aromatic amines (**19d** and **20e**) and the even more challenging *m*-formyl phenyl group (**19i**). Functionalized four-membered rings were obtained in very good yields (up to 98%), and the system had high tolerance for a wide range of functional groups in the cross-coupling reaction (**19a–i** and **20a–j**). Unfortunately, only the starting cyclobutene iodides **17** were recovered when Suzuki cross-couplings with alkylboronic acids were attempted, and no alkyl-substituted product was obtained.

Alternatively, cyclobutenyl metal species can be generated and used in situ by employing allylzinc species. Simple insertion of zinc into the carbon–halogen bond (Scheme 10) proceeded when the condition described by Villiéras et al. were used[17].



Scheme 10. Derivatization of cyclobutenylzinc species generated in situ.

Allylzinc reagents were added to 4-bromobutyne, which initiated a carbometalation–cyclization sequence to form a new cyclobutenylzinc species in situ. First, aromatic and heteroaromatic iodides added in the presence of $Pd(dba)_2$ and TFP underwent the cross-coupling reaction and furnished substituted CBs **19a** and **21a–k** in good yields (up to 87%). Second, furoyl chloride was used in the reaction to give the conjugated cyclobutenylketone **21l**. Surprisingly, isomerization of the allylic double bond was observed, and the more-stable six-π-electron conjugated system was the sole product of the reaction.

Taking into account the propensity of 1,3-enyne systems to undergo further interesting transformations,[18] we envisaged that alkynylcyclobutenes could be highly valuable substrates

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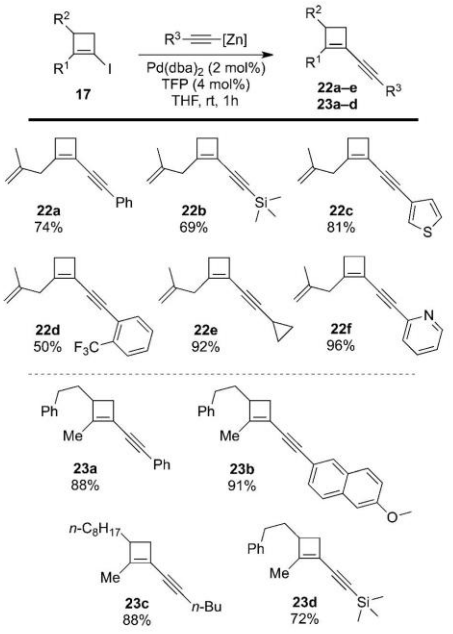
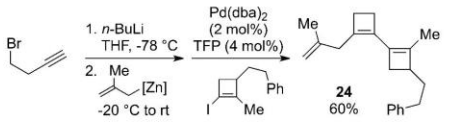


Scheme 11. Cross-coupling reactions of allylcyclobutene iodides.

for further studies. Alkynylzinc reagents—prepared by deprotonation of the corresponding terminal alkyne and subsequent transmetalation with $ZnCl_2$—underwent rapid cross-coupling reactions with a variety of allylcyclobutene iodides **17** to obtain conjugated cyclobutenyl acetylenes **22a–f** and **23a–d** in good yields (50–96%; Scheme 11), which showed the potential of this methodology to diversify the pool of previously described CBs. The Sonogashira-type cross-coupling of a cyclobutene iodide was previously described by Okamura et al.[19] The resulting cyclobutenyl acetylene was applied to a concise synthesis of (+)-sterpurene.

Finally, we applied this straightforward methodology to the synthesis of bicyclobutene **24**. A similar one-pot sequence was employed to generate the allylcyclobutenyl metal species, followed by a cross-coupling reaction that involved a cyclobutene iodide. Compound **24** was obtained in 60% yield (Scheme 12).



Scheme 12. Synthetic approach to bicyclobutene **24**.

Conclusion

We used simple organometallic chemistry to thoroughly assemble efficient routes to access substituted four-membered rings. On one hand, an unprecedented highly diastereo selective one-pot sequence produced ACBs that possessed three consecutive stereocenters, including one quaternary center. On the other hand, an efficient preparation of cyclobutenyl derivatives merged with a cross-coupling reaction generated valuable aryl-, alkynyl-, and acyl-CBs. The easily accessible routes to unsaturated four-membered-ring architectures described warrants further investigations because these structures are usually difficult to access.

Experimental Section

General procedure A: Preparation of propargyl alcohols 10

A few drops of 1,2-dibromoethane were added to a suspension of zinc dust (3.8 equiv) and lithium chloride (2.0 equiv) to activate the zinc. The reaction was kept slightly above rt (about 30–40 °C), and a solution of propargyl bromide (1.0 equiv) in THF (2.0 M) was slowly added. Upon complete addition, the mixture was stirred for 90 min at rt. The suspension was cooled to −78 °C and the appropriate aldehyde was slowly added. The mixture was allowed to react for 30 min at −78 °C then quenched by adding conc. hydrochloric acid (2.0 equiv). The mixture was allowed to reach rt overnight, and then was extracted with diethyl ether (3×50 mL). The combined organic phases were washed with a saturated aqueous solution of sodium hydrogen carbonate (50 mL) and brine (50 mL) then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure (Caution! some products **10** are quite volatile). The crude alcohol was purified by flash column chromatography on silica gel (eluent: ethyl acetate/hexanes). See the Supporting Information for the characterization data for alcohols **10a–d**.

General procedure B: Synthesis of propargyl bromides 11 via tosylates 25

A solution of *n*BuLi (1.0 equiv) in hexanes (2.86 M) was added dropwise to a solution of alcohol **10** (1.0 equiv) in THF (0.5 M) at −78 °C. The solution was stirred for 30 mins at −78 °C then warmed to rt. A solution of 4-methylbenzene-1-sulfonyl chloride (1.1 equiv) in THF (1.0 M) was added. The reaction mixture was stirred at rt for 30 min. The mixture was poured into water (50 mL) and extracted with diethyl ether (3×50 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude tosylate **25** was used without further purification. For data analysis, a sample of crude **25** was purified by flash column chromatography on silica gel (eluent: ethyl acetate/hexanes).

The crude tosylate **25** was dissolved in acetone (0.3 M) and lithium bromide (5.0 equiv) was added. The reaction mixture was stirred at reflux temperature for 10 h, after which time full consumption of **25** was observed (alternatively, the reaction can be performed in a pressure vessel at 65 °C for 10 h). The reaction mixture was cooled to rt then poured into water (50 mL) and extracted with hexanes (3×50 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure (*Caution!* some

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products **11** are quite volatile). The crude bromide was purified by flash column chromatography on silica gel (eluent: hexanes).

Compound 25a: Compound **25a** (4.21 g, quantitative) was obtained from alcohol **10a** as a colorless oil by following general procedure B. R_f = 0.35 (9:1 hexanes/EtOAc, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 7.7 Hz, 2H), 4.63–4.50 (m, 1H), 2.55–2.50 (m, 2H), 2.45 (s, 3H), 1.96 (t, J = 2.7 Hz, 1H), 1.70 (td, J = 8.1, 6.4 Hz, 2H), 1.39–1.13 (m, 2H), 0.83 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.9, 134.1, 129.9, 128.0, 80.2, 78.6, 71.3, 35.5, 24.8, 21.8, 18.0, 13.7 ppm; IR: $\tilde{\nu}$ = 3289 (w), 2962 (w), 2936 (w), 2876 (vw), 1599 (w), 1496 (vw), 1460 (w), 1356 (m), 1308 (w), 1292 (w), 1188 (m), 1174 (vs), 1097 cm^{-1} (m); HRMS (EI): m/z calcd for $C_{14}H_{18}O_3S^+$: 266.0977; found: 266.0980.

Compounds 25b–d: See the Supporting Information.

Compound 11a: Compound **11a** (1.10 g, 40%) was obtained from tosylate **25a** as a colorless oil by following general procedure B. R_f = 0.41 (hexanes, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (dtd, J = 8.8, 6.3, 4.5 Hz, 1H), 2.87–2.72 (m, 2H), 2.12 (t, J = 2.6 Hz, 1H), 2.01–1.78 (m, 2H), 1.69–1.50 (m, 1H), 1.44 (dddd, J = 13.4, 9.6, 7.4, 6.3 Hz, 1H), 0.95 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 80.7, 71.1, 52.3, 39.9, 29.4, 20.8, 13.5 ppm; HRMS (EI): m/z calcd for $C_7H_{11}{}^{79}Br^+$: 174.0044; found: 174.0101.

Compounds 11b–d: See the Supporting Information.

General procedure C: Synthesis of cyclobutyl iodides 17a–d

A solution of *n*BuLi (1.0 equiv) in hexanes (2.86 M) was added dropwise to a solution of 4-bromobutyne **11** (1.0 equiv) in hexanes (0.5 M) at −78 °C, and the mixture was stirred for 30 min. A second flask was charged with Cp_2ZrCl_2 (1.0 equiv) in CH_2Cl_2 (0.5 M) and a solution of trimethylaluminium (2.0 equiv) in hexanes (2.00 M) was added at rt. The mixture was stirred for 30 min. The second solution was transferred to the first at −78 °C via cannula. The resulting mixture was the allowed to stir at RT for 2 h, to form the metalated cyclobutenyl derivative **16**. The suspension was cooled to 0 °C, and a solution of iodine in THF (1.5 equiv) was added slowly via cannula. The mixture was stirred for 30 min at 0 °C then slowly poured into ice-cold hydrochloric acid (10 equiv, ≈0.5 M) with continued vigorous stirring. The aqueous phase was extracted with hexanes (3×50 mL). The combined organic phases were washed with a saturated aqueous solution of sodium hydrogen carbonate (50 mL) and brine (50 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure (*Caution!* some products **17** are quite volatile). The crude cyclobutyl iodide **17** was purified by flash column chromatography on silica gel (eluent: hexanes).

Compound 17a: Compound **17a** (260 mg, 59%) was obtained as a colorless oil from **11a** by following general procedure C. R_f = 0.87 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.97–2.81 (m, 2H), 2.38–2.29 (m, 1H), 1.58 (td, J = 2.3, 1.1 Hz, 4H), 1.41–1.22 (m, 3H), 0.90 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.3, 83.0, 48.6, 43.4, 35.0, 20.7, 14.9, 14.3 ppm; IR: $\tilde{\nu}$ = 2958 (vs), 2931 (s), 2872 (s), 1710 (vs), 1462 (s), 1379 (s), 1211 (s), 1166 (s), 1088 cm^{-1} (s); HRMS (EI): m/z calcd for $C_8H_{13}I^+$: 236.0062; found: 236.0059.

Compounds 17b–d: See the Supporting Information.

Compound 17e

A solution of *n*BuLi (1 equiv) in hexanes (2.86 M) was added dropwise to a stirred solution of 4-bromobut-1-yne (1 equiv) in THF (0.2 M) at −78 °C. After 15 min the cooling bath was exchanged for a −30 °C bath. The temperature was held −30 °C for 5 min then (2-methylallyl)zinc bromide (1 equiv) was added dropwise. After 10 min the cooling bath was removed and the colorless solution was slowly warmed to rt over 1 h, during which time the color changed to pale yellow. The reaction mixture was treated with iodine (1 equiv) followed by a small amount (2 mL/mmol) of water. The crude mixture was extracted with diethyl ether (3×5.0 mL/mmol), and the combined organic phases were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure at 0 °C. The crude product was purified by column chromatography on silica gel (eluent: hexanes) in the dark to obtain **17e** (945 mg, 40%) as a colorless oil. R_f = 0.9 (hexanes, UV, $KMnO_4$, *p*-anisaldehyde (PAA)); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.80–4.77 (m, 1H), 4.75–4.72 (m, 1H), 2.78–2.74 (m, 2H), 2.73–2.70 (m, 2H), 2.69–2.66 (m, 2H), 1.72 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.5, 141.5, 112.3, 84.5, 39.5, 36.4, 34.7, 22.7 ppm; HRMS (EI): m/z calcd for $C_8H_{11}I^+$: 233.9905; found: 233.9906.

Compound 17f

Following the procedure described above for the preparation of **17e**, *N*-bromosuccinimide (1 equiv) was employed as the electrophile and **17f** (299 mg, 32%) was obtained as a colorless oil. R_f = 0.79 (hexanes, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.80–4.77 (m, 1H), 4.75–4.73 (m, 1H), 2.77–2.74 (m, 2H), 2.74–2.71 (m, 2H), 2.49 (ddd, J = 4.1, 2.2, 1.0 Hz, 2H), 1.73 ppm (t, J = 1.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.5, 141.6, 112.2, 109.8, 37.5, 35.2, 31.0, 22.7 ppm; IR: $\tilde{\nu}$ = 2963 (s), 2948 (s), 2930 (vs), 2854 (m), 2362 (m), 2334 (m), 1735 (m), 1700 (m), 1653 (s), 1456 (m), 1438 (m), 1375 (m), 1261 (m), 1094 (s), 1031 (s), 1021 cm^{-1} (s); MS (EI): m/z (%): 188.0 (11) $[M]^+$, 186.0 (11) $[M]^+$, 171.0 (6), 107.1 (35), 91.1 (100), 79.1 (61), 65.1 (34), 51.0 (22); HRMS (EI): m/z calcd for $C_8H_{11}{}^{79}Br^+$: 186.0044; found: 188.0034.

General procedure D: Synthesis of alkylidenecyclobutylcarbinols 12

A solution of *n*BuLi (1.0 equiv) in hexanes (2.86 M) was added dropwise to a solution of 4-bromobutyne **11** (1.0 equiv) in hexanes (0.5 M) at −78 °C, and the mixture was stirred for 30 min. A second flask was charged with Cp_2ZrCl_2 (1.0 equiv) in CH_2Cl_2 (0.5 M) and a solution of trimethylaluminium (2.0 equiv) in hexanes (2.00 mL) was added at rt. The mixture was stirred for 30 min then transferred to the first flask at −78 °C via cannula. The resulting mixture was stirred at rt for 2 h, during which time the metalated cyclobutenyl derivative **15** formed. The reaction mixture was cooled to −78 °C and 2-(iodomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.0 equiv) in THF (0.5 M) was added. The solution was warmed to rt over 2 h. Excess organometallic species were quenched by the careful addition of water. The boronic ester **16** was extracted with diethyl ether (3×20 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (0.5 M), and the solution was cooled to 0 °C. The required aldehyde (0.5 equiv) was added neat (liquid) or as a solution in CH_2Cl_2 (solid). Upon complete consumption of the boronate intermediate **16** a saturated aqueous solution of ammonium chloride (4.0 mL/mmol) and diethyl ether (4.0 mL/mmol) were added, and the mixture was stirred vigorously. The aqueous phase was extracted with diethyl ether (3×20 mL), and the combined organic phases were washed with an aqueous solution of sodium metabisulfite (20 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude alcohol was purified by flash column

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chromatography on silica gel (eluent: ethyl acetate/hexanes or diethyl ether/hexanes) to afford the pure alkylidenecyclobutylcarbinol **12**.

Compound 12a

Following general procedure D, **12a** (88 mg, 60%, d.r. = 99:1:0:0) was obtained as a colorless oil from bromide **11d** and benzaldehyde. R_f = 0.24 (95:5 hexanes/EtOAc, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.21 (m, 7H), 7.19–7.11 (m, 1H), 7.08–7.03 (m, 2H), 5.02 (t, J = 2.6 Hz, 1H), 4.84 (t, J = 2.1 Hz, 1H), 4.67 (d, J = 2.9 Hz, 1H), 2.79–2.69 (m, 1H), 2.48 (ddd, J = 14.3, 9.4, 5.3 Hz, 1H), 2.35–2.18 (m, 3H), 2.11 (d, J = 2.9 Hz, 1H, OH), 1.54–1.31 (m, 2H), 1.00 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.6, 142.4, 141.0, 128.5, 128.4, 127.9, 127.5, 127.2, 125.8, 106.0, 79.2, 54.1, 36.3, 33.8, 33.8, 32.3, 14.3 ppm; IR: $\tilde{\nu}$ = 3568 (vw), 3454 (vw), 3084 (vw), 3062 (vw), 3027 (w), 2963 (w), 2932 (w), 2856 (w), 1668 (w), 1603 (w), 1494 (w), 1452 (m), 1371 (w), 1296 (w), 1188 (w), 1155 (w), 1081 (w), 1034 (m), 1022 cm^{-1} (m); HRMS (EI): m/z calcd for $C_{14}H_{18}^+$: 186.1403 [$M-C_7H_7O$]$^+$; found: 186.1397.

Compound 12b

Following general procedure D, **12b** (120 mg, 56%, d.r. = 99:1:0:0) was obtained as a colorless oil from bromide **11d** and (*Z*)-hexadec-11-enal. R_f = 0.16 (98:2 hexanes/EtOAc, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2H), 7.20–7.16 (m, 3H), 5.41–5.30 (m, 2H), 4.89 (t, J = 2.7 Hz, 1H), 4.81 (t, J = 2.1 Hz, 1H), 3.49–3.42 (m, 1H), 2.80 (ddt, J = 16.0, 9.0, 2.5 Hz, 1H), 2.55 (dddd, J = 40.8, 13.7, 10.1, 5.8 Hz, 2H), 2.22 (ddt, J = 15.9, 5.0, 2.4 Hz, 1H), 2.07–1.96 (m, 5H), 1.85–1.75 (m, 1H), 1.72–1.69 (m, 1H), 1.68–1.59 (m, 1H), 1.59–1.52 (m, 1H), 1.32–1.26 (m, 19H), 1.01 (s, 3H), 0.91–0.88 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.1, 142.5, 130.0, 130.0, 125.9, 105.7, 77.0, 54.1, 36.8, 34.2, 33.8, 33.0, 32.1, 31.3, 29.9, 29.9, 29.8, 29.8, 29.7, 29.5, 27.4, 27.3, 27.1, 22.5, 14.2, 13.4 ppm; IR: $\tilde{\nu}$ = 2924 (vs), 2854 (s), 1774 (w), 1668 (w), 1604 (w), 1496 (w), 1454 (m), 1375 (w), 1058 (w), 1030 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{30}H_{46}O^+$: 424.3705; found: 424.3690.

Compounds 12c–l: See the Supporting Information.

Compound 18a

A freshly titrated solution of 2,2,6,6-tetramethyl piperidine lithium chloride (TMPMgCl·LiCl; 1.1 equiv) in THF (1.1 M) was added dropwise to a solution of benzo[*b*]thiophene (1.0 equiv) in THF (0.25 M) at rt. The mixture was stirred at rt for 2 h until iodolysis of an aliquot of the reaction mixture indicated that completed metalation had occurred. A solution of zinc chloride (1.1 equiv) in THF (1.0 M) was added dropwise to the reaction mixture, which was then stirred for 30 min at rt to allow full transmetalation. In a second reaction vessel, $Pd(dba)_2$ (2 mol%) and TFP (4 mol%) were dissolved in THF, and the mixture was stirred for 5 min to allow ligand exchange. Iodide **17b** (1.0 equiv) in THF (0.3 M) was added and the reaction mixture was stirred for 5 min. The zinc species (1.5 equiv) in the first flask was added immediately. The reaction mixture was stirred at rt for 2 h, and then quenched by addition of a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic phases were washed with brine and dried over anhydrous magnesium sulfate. The organic phase was filtered and concentrated under reduced pressure then flash column chromatography on silica gel (eluent: hexanes) gave **18a** as a colorless oil (61 mg, 76%). R_f = 0.67 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.30 (7.33–7.24, m, 2H), 7.04 (s, 1H), 2.84 (ddt, J = 11.4, 4.3, 2.2 Hz, 1H), 2.77–2.65 (m, 1H), 2.28 (dquin, J = 11.9, 2.1 Hz, 1H), 1.98 (q, J = 2.0 Hz, 3H), 1.79–1.62 (m, 1H), 1.46–1.24 (m, 7H), 0.92 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.8, 139.8, 139.6, 139.2, 130.9, 124.4, 124.0, 123.3, 122.3, 119.0, 42.8, 33.8, 33.0, 32.3, 27.4, 22.8, 14.3, 14.3 ppm; IR: $\tilde{\nu}$ = 3057 (vw), 2955 (m), 2920 (m), 2853 (m), 1713 (w), 1695 (w), 1667 (w), 1593 (vw), 1562 (vw), 1516 (w), 1456 (m), 1435 (m), 1372 (m), 1354 (w), 1330 (w), 1302 (m), 1250 (w), 1227 (w), 1182 (w), 1155 (m), 1130 (w), 1066 (w), 1016 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{18}H_{22}S^+$: 270.1442; found: 270.1446.

Compound 18b

Compound **18b** was obtained as a colorless oil (48 mg, 96%) from iodide **17a** by using the procedure described above for **18a**. The metalation of benzofuran with TMPMgCl·LiCl was incomplete after 3 h at rt, therefore the concentration of the metalated benzofuran was determined by iodolysis followed by GC analysis. Excess zinc chloride in THF was used to promote complete transmetalation of the metalated benzofuran. R_f = 0.71 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (dd, J = 7.5, 1.7 Hz, 1H), 7.45–7.40 (m, 1H), 7.28–7.14 (m, 2H), 6.46 (s, 1H), 2.83–2.70 (m, 2H), 2.23 (dq, J = 11.7, 2.0 Hz, 1H), 2.05 (q, J = 2.0 Hz, 3H), 1.76–1.65 (m, 1H), 1.48–1.30 (m, 3H), 0.99–0.91 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.7, 153.6, 146.5, 128.9, 126.7, 123.9, 122.7, 120.7, 111.0, 101.6, 43.2, 35.2, 32.2, 20.9, 14.7, 14.5 ppm; IR: $\tilde{\nu}$ = 2957 (w), 2920 (m), 2871 (w), 2844 (w), 2359 (vw), 2337 (vw), 1713 (w), 1708 (w), 1699 (w), 1683 (m), 1614 (w), 1559 (w), 1464 (w), 1451 (s), 1374 (w), 1356 (w), 1301 (m), 1256 (m), 1184 (m), 1156 (m), 1140 (m), 1108 (w), 1086 (w), 1025 (w), 1005 cm^{-1} (m).

Compound 18c

A solution of *n*BuLi (1.0 equiv) in hexanes (2.86 M) was added dropwise to a solution of 1-fluoro-4-iodobenzene (1.0 equiv) in THF (0.5 M) at −78 °C. The solution was stirred for 30 min at rt to allow complete halogen–metal exchange. A solution of zinc chloride (1.1 equiv) in THF (1.0 M) was added dropwise, and the solution was warmed to rt then stirred for 30 min. The amount of metalated species was determined by iodolysis and GC analysis. In a second reaction vessel, $Pd(dba)_2$ (2 mol%) and TFP (4 mol%) were dissolved in THF and the mixture was stirred for 5 min to allow ligand exchange. Iodide **17c** (1.0 equiv) in THF (0.3 M) was added. The reaction mixture was stirred for 5 min then the previously prepared zinc species (1.5 equiv) was added immediately. The reaction mixture was stirred at rt for 2 h then quenched by addition of a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic phases were washed with brine and dried over anhydrous magnesium sulfate. The organic phase was filtered and concentrated under reduced pressure. Flash column chromatography on silica gel (eluent: hexanes) gave **18c** as a colorless oil (51 mg, 62%). R_f = 0.85 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 2H), 7.06–6.99 (m, 2H), 2.75 (ddq, J = 12.0, 4.3, 2.1 Hz, 1H), 2.62 (dd, J = 8.7, 4.8 Hz, 1H), 2.17 (dquin, J = 12.1, 2.2 Hz, 1H), 1.96 (q, J = 2.0 Hz, 3H), 1.73–1.65 (m, 1H), 1.44–1.22 (m, 13H), 0.94–0.86 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.5 (d, J = 245.6 Hz), 142.3 (d, J = 2.2 Hz), 134.8, 132.8 (d, J = 3.2 Hz), 127.1 (d, J = 7.8 Hz), 115.3 (d, J = 21.4 Hz), 41.9, 33.1, 32.9, 32.1, 30.1, 29.8, 29.5, 27.7, 22.9, 14.3, 14.2 ppm; IR: $\tilde{\nu}$ = 2956 (m), 2923 (s), 2853 (m), 1716 (vw), 1690 (w), 1655 (vw), 1601 (w), 1508 (vs), 1466 (w), 1410 (w), 1376 (w), 1354 (w), 1324 (w), 1294 (w), 1230 (s), 1155 (m), 1104 (w), 1070 (vw), 1013 cm^{-1} (vw).

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Compound 18 d

Compound **18 d** (67 mg, 54%) was obtained as a slightly yellow oil from iodide **17 c** by using the procedure described above for **18 a**. Complete metalation of 2,4-dibromopyridine was achieved at −25 °C after 3 h. R_f = 0.33 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 1H), 7.17 (d, J = 1.4 Hz, 1H), 2.83–2.70 (m, 1H), 2.70–2.59 (m, 1H), 2.24–2.14 (m, 1H), 2.11 (q, J = 1.9 Hz, 3H), 1.74–1.61 (m, 1H), 1.44–1.16 (m, 13H), 0.88 ppm (t, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.2, 154.1, 141.9, 133.6, 133.6, 127.1, 121.8, 42.6, 32.5, 32.4, 31.9, 29.9, 29.6, 29.3, 27.5, 22.7, 14.6, 14.2 ppm; IR: $\tilde{\nu}$ = 3098 (vw), 2954 (w), 2921 (m), 2852 (m), 1654 (m), 1554 (vs), 1520 (s), 1465 (w), 1430 (w), 1380 (w), 1368 (m), 1352 (m), 1300 (w), 1240 (vw), 1184 (w), 1151 (s), 1122 (w), 1081 cm^{-1} (m); HRMS (EI): m/z calcd for $C_{18}H_{25}{}^{79}Br_2N^+$: 413.0345; found: 413.0345.

Compound 18 e

A solution of zinc chloride (1.0 equiv) in THF (1.0 M) was added to a freshly titrated solution of (4-methoxyphenyl)magnesium bromide (1.0 equiv) in THF (0.55 M), and the mixture was stirred for 30 min at rt. In a second reaction vessel, $Pd(dba)_2$ (2 mol%) and TFP (4 mol%) were dissolved in THF (1.0 mL), and the mixture was stirred for 5 min to allow ligand exchange. Iodide **17 c** (1.0 equiv) in THF (0.3 M) was added, and the reaction mixture was stirred for 5 min then the previously prepared zinc species (1.5 equiv) was added immediately. The reaction mixture was stirred at rt for 2 h then quenched by addition of a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic phases were washed with brine and dried over anhydrous magnesium sulfate. The organic phase was filtered and concentrated under reduced pressure. Flash column chromatography on silica gel (eluent: hexanes) gave **18 e** (61 mg, 71%) was obtained as a colorless oil. R_f = 0.1 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.24 (m, 2H), 6.90–6.85 (m, 2 h), 3.81 (s, 3H), 2.73 (m, 1H), 2.62–2.55 (m, 1H), 2.15 (dt, J = 12.1, 2.1 Hz, 1H), 1.95–1.92 (m, 3H), 1.74–1.62 (m, 1H), 1.44–1.22 (m, 13H), 0.90 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.3, 140.4, 135.2, 129.7, 126.8, 113.9, 55.4, 41.8, 33.2, 32.9, 32.1, 30.2, 29.8, 29.5, 27.8, 22.9, 14.3, 14.2 ppm; IR: $\tilde{\nu}$ = 2955 (w), 2922 (s), 2852 (m), 1606 (m), 1673 (w), 1510 (s), 1464 (m), 1442 (w), 1418 (w) 1375 (w), 1330 (w), 1301 (w), 1391 (m), 1344 (vs), 1172 (m), 1114 (w), 1072 (w), 1038 cm^{-1} (m); HRMS (EI): m/z calcd for $C_{20}H_{30}O^+$: 286.2297; found: 286.2304.

Compound 18 f

Compound **18 f** (56 mg, 56%) was obtained as a colorless oil from 1-chloro-3-iodobenzene by using the procedure described above for **18 c**. R_f = 0.95 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.14 (m, 4H), 2.75 (ddq, J = 12.1, 4.4, 2.2 Hz, 1H), 2.67–2.58 (m, 1H), 2.18 (dq, J = 12.1, 2.2 Hz, 1H), 1.98 (q, J = 2.0 Hz, 3H), 1.74–1.64 (m, 1H), 1.44–1.21 (m, 13H), 0.94–0.86 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.0, 138.2, 134.7, 134.4, 129.7, 126.4, 125.6, 123.7, 42.0, 32.9, 32.8, 32.1, 30.1, 29.8, 29.5, 27.7, 22.9, 14.4, 14.3 ppm; IR: $\tilde{\nu}$ = 2956 (m), 2924 (vs), 2853 (m), 2361 (vw), 2339 (vw), 1716 (vw), 1693 (w), 1652 (w), 1593 (m), 1562 (w), 1468 (w), 1425 (w), 1374 (w), 1325 (w), 1260 (vw), 1233 (vw), 1182 (vw), 1110 (vw), 1080 cm^{-1} (w).

General procedure E: Synthesis of aryl-CB derivatives by Suzuki cross-coupling (19/20)

Arylboronic acid (1.33 equiv) and K_2CO_3 (2.7 equiv) were added to a stirred solution of cyclobutene iodide **17** (1 equiv) in 2:1 dioxane/H_2O (0.05 M) at rt. The reaction mixture was stirred for 10 min then $Pd(PPh_3)_4$ (4 mol%) was added. The reaction mixture was stirred at 50 °C for 1 h, during which time a color change to red or black indicated a complete reaction. Water (5.0 mL) was added and the aqueous solution was extracted with diethyl ether (3×20 mL). The combined organic phases were dried over anhydrous magnesium sulfate, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel or preparative TLC to afford the aryl-CB derivative **19/20**.

Compound 19 a: Compound **19 a** (43 mg, 93%) was obtained as pale-yellow oil from **17 e** and phenylboronic acid by following general procedure E. R_f = 0.8 (hexanes, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 4H), 7.24–7.18 (m, 1H), 4.83–4.79 (m, 2H), 3.11–3.07 (m, 2H), 2.69–2.63 (m, 2H), 2.47–2.43 (m, 2H), 1.79 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.7, 140.4, 139.3, 136.1, 128.5, 126.8, 125.7, 111.6, 39.1, 28.4, 26.1, 23.1 ppm; IR: $\tilde{\nu}$ = 3079 (w), 3061 (w), 3027 (w), 2914 (m), 2836 (w), 1720 (w), 1714 (w), 1688 (s), 1656 (w), 1650 (m), 1644 (w), 1598 (m), 1493 (m), 1448 (m), 1426 (w), 1414 (w), 1374 (m), 1358 (w), 1335 (w), 1323 (m), 1301 (w), 1263 (m), 1245 (m), 1221 (w), 1212 (m), 1179 (w), 1107 (w), 1082 (w), 1066 (m), 1052 (w), 1020 (m), 1002 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{14}H_{16}{}^+$: 184.1252; found: 184.1247.

Compound 19 b: Compound **19 b** (50 mg, 93%) was obtained as a colorless oil from **17 e** and (3-methoxyphenyl)boronic acid by following general procedure E. R_f = 0.4 (9:1 hexanes/EtOAc, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (t, J = 7.9 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 6.86–6.84 (m, 1H), 6.75 (dd, J = 8.2, 1.8 Hz, 1H), 4.82–4.77 (m, 2H), 3.79 (s, 3H), 3.08–3.05 (m, 2H), 2.65–2.61 (m, 2H), 2.44–2.40 (m, 2H), 1.76 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.7, 142.7, 140.8, 139.2, 137.4, 129.4, 118.4, 112.4, 111.7, 111.2, 55.3, 39.1, 28.4, 26.2, 23.0 ppm; IR: $\tilde{\nu}$ = 3075 (w), 2939 (m), 2913 (m), 2833 (w), 1689 (w), 1650 (w), 1598 (m), 1576 (s), 1486 (m), 1482 (m), 1464 (m), 1452 (m), 1428 (m), 1374 (w), 1334 (m), 1285 (m), 1262 (s), 1220 (s), 1195 (m), 1175 (m), 1166 (s), 1092 (w), 1043 cm^{-1} (s); HRMS (EI): m/z calcd for $C_{15}H_{18}O^+$: 214.1358; found: 214.1350.

Compound 19 c–i: See the Supporting Information.

Compound 20 a: Compound **20 a** (49 mg, 91%) was obtained as a colorless oil from **17 b** and (3-methoxyphenyl)boronic acid by following general procedure E. R_f = 0.62 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 7.9 Hz, 1H), 6.94 (ddd, J = 7.5, 1.2, 1.2 Hz, 1H), 6.85 (dd, J = 2.6, 1.5 Hz, 1H), 6.75 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 3.82 (s, 3H), 2.74 (ddt, J = 12.0, 4.3, 2.1 Hz, 1H), 2.65–2.56 (m, 1H), 2.17 (dt, J = 12.1, 2.1 Hz, 1H), 1.96 (q, J = 2.0 Hz, 3H), 1.73–1.62 (m, 1H), 1.44–1.23 (m, 7H), 0.95–0.86 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.7, 143.6, 137.9, 135.7, 129.4, 118.3, 112.0, 111.1, 55.3, 41.9, 33.0, 32.9, 32.3, 27.4, 22.9, 14.3, 14.3 ppm; IR: $\tilde{\nu}$ = 2955 (m), 2922 (vs), 2870 (m), 2854 (m), 1653 (w), 1604 (s), 1599 (s), 1577 (s), 1487 (m), 1465 (m), 1454 (m), 1432 (m), 1376 (w), 1372 (w), 1332 (m), 1323 (m), 1285 (s), 1250 (s), 1230 (w), 1212 (m), 1176 (m), 1167 (m), 1047 cm^{-1} (s); HRMS (EI): m/z calcd for $C_{17}H_{24}O^+$: 244.1827; found: 244.1816.

Compound 20 b: Compound **20 b** (51 mg, 98%) was obtained as a colorless oil from **17 b** and (4-fluorophenyl)boronic acid by following general procedure E. R_f = 0.88 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 2H), 7.07–6.98 (m, 2H), 2.75 (ddq, J = 12.0, 4.4, 2.1 Hz, 1H), 2.65–2.57 (m, 1H), 2.17 (dquin, J = 12.1, 2.2 Hz, 1H), 1.96 (q, J = 2.0 Hz, 3H), 1.75–1.65 (m, 1H),

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1.45–1.27 (m, 7H), 0.92 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.5 (d, J = 245.5 Hz), 142.3 (d, J = 2.3 Hz), 134.8, 132.8 (d, J = 3.2 Hz), 127.1 (d, J = 7.8 Hz), 115.3 (d, J = 21.4 Hz), 41.9, 33.0, 32.9, 32.3, 27.4, 22.9, 14.3, 14.2. ppm; IR: $\tilde{\nu}$ = 2957 (m), 2923 (m), 2855 (m), 1655 (vw), 1601 (w), 1507 (vs), 1467 (w), 1408 (vw), 1376 (w), 1324 (w), 1294 (w), 1230 (s), 1182 (vw), 1155 (m), 1104 (w), 1069 (vw), 1012 cm^{-1} (vw); HRMS (EI): m/z calcd for $C_{16}H_{21}F^+$: 232.1627; found: 232.1624.

Compounds 20 c–j: See the Supporting Information.

General procedure F: Synthesis of CB derivatives 21 and 24 by in-situ Negishi cross-coupling

*n*BuLi (1 equiv) in hexanes (2.86 M) was added dropwise to a stirred solution of 4-bromobut-1-yne (1 equiv) in THF (0.2 M) at −78 °C. After 15 min the cooling bath was exchanged for a −30 °C bath. The temperature was held at −30 °C for 5 min then the allylzinc species (1 equiv) was added dropwise. After 10 min the cooling bath was removed and the colorless solution was warmed to rt over 1 h (a color change to pale yellow was observed). During this time, in a second vessel, $Pd(dba)_2$ (4 mol%) and TFP (8 mol%) were dissolved in THF. After stirring for 10–20 min the red solution turned yellow. Aryl iodide (0.95 equiv) in THF (0.15 M) was added to the yellow catalyst solution, and the mixture was stirred for 10 min. Finally, the cyclobutenylzinc species **15** was quickly added to the flask that contained the aryl iodide, and the mixture was stirred for 1 h then quenched with water. The crude mixture was extracted diethyl ether (3×mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel or preparative TLC to obtain the CB derivative **21**/**24**.

Compound 21 a: Compound **21 a** (56 mg, 46%) was obtained as pale-yellow oil from (2-methylallyl)zinc bromide and 1-iodo-4-methylbenzene by following general procedure F. R_f = 0.8 (hexanes, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 2H), 7.17–7.12 (m, 2H), 4.83–4.79 (m, 2H), 3.10–3.07 (m, 2H), 2.68–2.63 (m, 2H), 2.47–2.42 (m, 2H), 2.35 (s, 3H), 1.79 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.8, 139.2, 139.1, 136.5, 133.4, 129.1, 125.7, 111.5, 39.1, 28.3, 26.2, 23.1, 21.4 ppm; IR: $\tilde{\nu}$ = 3077 (w), 3024 (w), 2969 (m), 2939 (s), 2914 (vs), 2872 (m), 2836 (m), 2361 (w), 2331 (vw), 1652 (m), 1511 (s), 1443 (m), 1374 (m), 1328 (w), 1112 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{15}H_{18}^+$: 198.1409; found: 198.1410.

Compound 21 b: Compound **21 b** (100 mg, 67%) was obtained as a yellowish oil from (2-methylallyl)zinc bromide and 1-iodo-4-(trifluoromethyl)benzene by following general procedure F. R_f = 0.8 (9:1 hexanes/EtOAc, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 4.86–4.78 (m, 2H), 3.12–3.08 (m, 2H), 2.70–2.67 (m, 2H), 2.51–2.48 (m, 2H), 1.79 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.7, 142.1, 139.2 (q, J = 2.0 Hz), 138.2, 128.44 (q, J = 32.3 Hz), 125.8, 125.43 (q, J = 3.9 Hz), 124.4 (q, J = 272.7 Hz), 112.0, 39.1, 28.7, 26.1, 23.1 ppm; IR: $\tilde{\nu}$ = 3079 (vw), 2918 (w), 2840 (vw), 1650 (vw), 1616 (w), 1411 (w), 1325 (vs), 1165 (m), 1124 (m), 1112 (m), 1070 (m), 1015 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{15}H_{15}F_3^+$: 252.1126; found: 252.1112.

Compounds 21 c–k: See the Supporting Information.

Compound 21 l: Compound **21 l** (40 mg, 68%) was obtained as colorless oil from (2-methylallyl)zinc bromide and furan-2-carbonyl chloride by following general procedure F. R_f = 0.3 (9:1 hexanes/EtOAc, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (dd, J = 1.7, 0.8 Hz, 1H), 7.15 (dd, J = 3.5, 0.8 Hz, 1H), 6.90 (d, J = 1.4 Hz, 1H), 6.52 (dd, J = 3.6, 1.7 Hz, 1H), 3.01–2.98 (m, 2H), 2.93–2.89 (m, 2H), 1.93 (s, 3H), 1.91 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.0, 157.9, 153.8, 147.8, 146.2, 133.1, 120.9, 117.1, 112.1, 31.6, 29.3, 27.7, 20.1 ppm; IR: $\tilde{\nu}$ = 3145 (w), 3100 (w), 2966 (m), 2917 (m), 2853 (w), 1654 (m), 1635 (s), 1610 (s), 1569 (vs), 1560 (s), 1541 (m), 1507 (m), 1463 (vs), 1448 (m), 1437 (m), 1394 (m), 1377 (m), 1370 (m), 1343 (m), 1288 (m), 1276 (m), 1188 (m), 1151 (m), 1040 (m), 1014 cm^{-1} (m); HRMS (EI): m/z calcd for $C_{13}H_{14}O_2^+$: 202.0994; found: 202.0986.

Compound 24: Compound **24** (45 mg, 60%) was obtained as a colorless oil from (2-methylallyl)zinc bromide and (2-(3-iodo-2-methylcyclobut-2-en-1-yl)ethyl)-benzene (instead of an aryl iodide) by following general procedure F. R_f = 0.51 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (tt, J = 7.1, 2.4 Hz, 2H), 7.28–7.20 (m, 3H), 4.82–4.79 (m, 1H), 4.78 (q, J = 1.5 Hz, 1H), 2.89 (s, 1H), 2.75–2.66 (m, 4H), 2.60–2.56 (m, 2H), 2.47–2.43 (m, 2H), 2.19–2.13 (m, 1H), 2.04–1.96 (m, 1H), 1.81–1.77 (m, 6H), 1.72–1.61 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.5, 142.9, 142.6, 139.6, 136.0, 132.8, 128.5, 128.4, 125.7, 111.3, 43.2, 38.8, 35.2, 34.1, 33.8, 29.8, 27.2, 22.8, 13.7 ppm; IR: $\tilde{\nu}$ = 3026 (w), 2912 (m), 2855 (w), 1712 (w), 1694 (w), 1651 (w), 1604 (w), 1496 (w), 1453 (m), 1440 (m), 1374 (m), 1355 (w), 1261 (w), 1198 (w), 1177 (w), 1065 (w), 1030 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{21}H_{26}^+$: 278.2035; found: 278.2042.

General procedure G: Synthesis of alkynyl-CB derivatives 22 and 23 by Negishi cross-coupling

*n*BuLi (1 equiv) in hexanes (2.86 M) was added dropwise to a stirred solution of alkyne (1 equiv) in THF (0.15 M) at −78 °C. After 30 min zinc chloride (1.33 equiv) in THF (1 M) was added dropwise to the reaction mixture at −78 °C. The reaction mixture was stirred for 30 min at −78 °C. The cooling bath was removed and the system was allowed to reach rt. During this time, $Pd(dba)_2$ (4 mol%) and TFP (8 mol%) was dissolved in THF (1.0 mL) in a second flask. After 10–20 min the red solution turned yellow. Iodide **17** (0.95 equiv) in THF (0.15 M) was added to the yellow catalytic solution, which was then stirred for 10 min. Finally, the alkenylzinc species was quickly added to the second flask that contained **17**. The reaction mixture was stirred for 1 h then quenched with water. The crude mixture was extracted with diethyl ether (3×20 mL) and the combined organic phases were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel or preparative TLC to obtain the alkynyl-CB derivative **22**/**23**.

Compound 22 a: Compound **22 a** (45 mg, 74%) was obtained as pale-yellow oil from **17 e** and ethynylbenzene by following general procedure G. R_f = 0.7 (hexanes, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 2H), 7.34–7.27 (m, 3H), 4.82–4.76 (m, 2H), 2.96–2.91 (m, 2H), 2.63–2.59 (m, 2H), 2.43–2.39 (m, 2H), 1.78 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.6, 142.5, 131.6, 128.4, 128.1, 123.6, 121.3, 112.2, 91.1, 84.5, 39.8, 30.1, 29.8, 22.9 ppm; IR: $\tilde{\nu}$ = 3078 (w), 2959 (w), 2916 (w), 2870 (w), 2842 (w), 1650 (w), 1594 (w), 1488 (m), 1443 (m), 1374 (w), 1322 (w), 1260 (w), 1224 (w), 1202 (w), 1178 (w), 1069 (w), 1027 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{16}H_{16}^+$: 208.1252; found: 208.1253.

Compound 22 b: Compound **22 b** (41 mg, 69%) was obtained as a pale-yellow oil from **17 e** and ethynyltrimethylsilane by following general procedure G. R_f = 0.6 (hexanes, UV, $KMnO_4$, PAA); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79–4.72 (m, 2H), 2.90–2.85 (m, 2H), 2.55–2.49 (m, 2H), 2.37–2.31 (m, 2H), 1.74 (s, 3H), 0.19 ppm (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.9, 142.3, 121.4, 112.2, 99.8, 96.4, 39.8, 30.0, 29.6, 22.8, 0.2 ppm; IR: $\tilde{\nu}$ = 2962 (w), 2929 (w), 2254 (vw), 2140 (vw), 1722 (w), 1713 (w), 1698 (w), 1679 (w), 1631 (w), 1620 (w), 1613 (w), 1422 (w), 1410 (w), 1392 (w), 1378 (w), 1366 (w), 1360 (w), 1252 (m), 1174 (w), 1112 cm^{-1} (w); HRMS (EI): m/z calcd for $C_{13}H_{20}Si^+$: 204.1334; found: 204.1330.

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Compounds 22 c–f: See the Supporting Information.

Compound 23 a: Compound **23 a** (83 mg, 88%) was obtained as a colorless oil from **17 d** and ethynylbenzene by following general procedure G. R_f = 0.33 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.41 (m, 2H), 7.33–7.26 (m, 5H), 7.22–7.15 (m, 3H), 2.77–2.70 (m, 1H), 2.70–2.63 (m, 3H), 2.25–2.18 (m, 1H), 2.02–1.91 (m, 1H), 1.83 (q, J = 2.0 Hz, 3H), 1.72–1.60 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.3, 142.5, 133.2, 131.6, 128.5, 128.5, 128.1, 125.9, 123.6, 119.0, 91.4, 84.4, 43.1, 36.5, 34.6, 34.0, 14.7 ppm; IR: $\tilde{\nu}$ = 3413 (w), 3062 (w), 3028 (w), 2936 (w), 2863 (w), 2366 (w), 2335 (vw), 2201 (m), 1754 (m), 1710 (s), 1703 (vs), 1672 (s), 1644 (m), 1620 (w), 1599 (m), 1582 (w), 1493 (m), 1452 (m), 1436 (w), 1434 (m), 1416 (m), 1358 (m), 1315 (m), 1266 (s), 1175 (m), 1160 (m), 1142 (m), 1100 (m), 1071 (m), 1029 (m), 1000 cm^{-1} (m); HRMS (EI): m/z calcd for $C_{21}H_{20}^+$: 272.1565; found: 272.1598.

Compound 23 b: Compound **23 b** (107 mg, 91%) was obtained as a colorless oil from **17 d** and 2-ethynyl-6-methoxynaphthalene by following general procedure G. R_f = 0.20 (hexanes, UV, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (t, J = 1.1 Hz, 1H), 7.67 (t, J = 8.7 Hz, 2H), 7.46 (dd, J = 8.4, 1.7 Hz, 1H), 7.30 (ddd, J = 7.6, 6.4, 1.9 Hz, 2H), 7.22–7.18 (m, 3H), 7.14 (dd, J = 8.9, 2.5 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 3.92 (s, 3H), 2.76 (ddd, J = 12.0, 4.5, 2.2 Hz, 1H), 2.72–2.64 (m, 3H), 2.23 (dt, J = 11.9, 2.1 Hz, 1H), 2.06–1.93 (m, 1H), 1.86 (d, J = 2.0 Hz, 3H), 1.74–1.61 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.3, 156.0, 142.6, 134.1, 131.2, 129.4, 129.2, 128.6, 128.6, 128.5, 126.9, 125.9, 119.5, 119.1, 118.5, 105.9, 92.0, 84.1, 55.5, 43.2, 36.5, 34.6, 34.1, 14.8 ppm; IR: $\tilde{\nu}$ = 3060 (w), 3026 (w), 2920 (m), 2843 (w), 2363 (w), 2340 (vw), 1717 (m), 1706 (w), 1700 (m), 1684 (w), 1653 (m), 1646 (m), 1625 (s), 1600 (vs), 1559 (m), 1540 (w), 1506 (m), 1498 (s), 1482 (s), 1456 (s), 1438 (m), 1419 (w), 1411 (m), 1391 (s), 1368 (w), 1364 (w), 1336 (w), 1266 (vs), 1250 (s), 1226 (m), 1207 (vs), 1164 (s), 1135 (m), 1069 (w), 1031 cm^{-1} (s); HRMS (EI): m/z calcd for $C_{26}H_{24}O^+$: 352.1827; found: 352.1822.

Compounds 23 c–d: See the Supporting Information.

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2.4 Stereoselective Access to Alkylidenecyclobutanes through γ-Selective Cross-Coupling Strategies

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Stereoselective Access to Alkylidenecyclobutanes through γ-Selective Cross-Coupling Strategies

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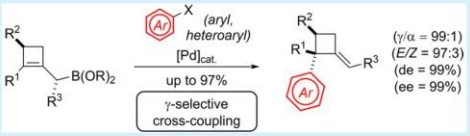
Supporting Information

ABSTRACT: Alkylidenecyclobutanes (ACBs) containing all-carbon quaternary stereocenters were simply and efficiently synthesized by combining boron-homologation and γ-selective cross-coupling strategies. This unique sequence led to excellent regio- and diastereoselectivities in the generation of targeted four-membered rings with up to 99% enantiomeric excess using chiral substrates. In addition to the original synthesis of ACBs, the first asymmetric catalytic formation of quaternary stereocenters based on γ-selective cross-coupling reactions is finally shown.



While the Suzuki–Miyaura cross-coupling is already a well-established method in pharmaceutical sciences,[1] the use of allylic boronic esters therein still remains scarcely described. Pioneering studies by Szabó and Miyaura[2] demonstrated that the reaction of allylboronic ester at the γ-position can be triggered by employing an appropriate palladium precatalyst. Since then, however, this interesting transformation was only examined by a few groups.

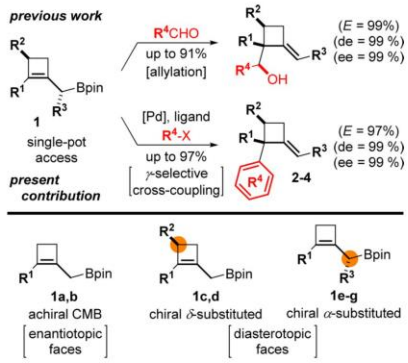
Recently, the groups of Morken, Buchwald, and Organ independently illustrated highly regioselective γ-cross-coupling reactions,[3] while Aggarwal and Crudden described very good stereoselectivities of these transformations when employing substituted allyl- and propargylboronic esters.[4]

We envisioned that combining such a powerful tool with an in situ generation of cyclobutenylmethylboronic esters (CMBs) would result in a straightforward formation of alkylidenecyclobutanes (ACBs). These small architectures have a rather limited accessibility but are encountered in many natural products and biologically active substances.[5] Moreover, the relatively strained nature of ACBs allows for a variety of further transformations.[6] Recently, merging boron homologation of cyclobutenyl metal species and allylboration strategies in a one-pot sequence, we have described a very efficient approach toward stereodefined ACBs.[7]

In this communication, we present a unique combination of boron homologation with a highly γ-selective Suzuki–Miyaura cross-coupling for the diastereo- and enantioselective construction of ACBs containing a quaternary stereocenter (Scheme 1) starting from achiral CMBs (**1a,b**) and chiral α- or δ-substituted CMBs (**1c–g**).

Negishi π-cyclization[8] of readily available 4-bromobutynes followed by a Matteson homologation led to CMBs **1**. Morken's conditions were initially employed for optimizing our reaction conditions when 4-iodotoluene was used as the cross-coupling partner.[3d] After a short screening, reactions performed in THF with KOH introduced from a stock solution proved to give the best results (Table 1, entry 3) in only 1 h.

Scheme 1. Approach to ACBs Containing a Quaternary Stereocenter through γ-Selective Cross-Coupling



Similar conversions were observed when replacing THF by MTBE or ethyl acetate (Table 1, entries 8 and 9), nonetheless requiring 14 h to reach completion. Attempts to replace potassium hydroxide as the base only resulted in decreasing either conversion or regioselectivity levels (Table 1, entries 4 and 5).

With optimal conditions in hand, a set of various aryl halides were engaged in the presence of **1a,b** (Scheme 2). With an exception for aldehydes (that would lead to a fast allylboration) and alcohols, a wide range of functional groups were tolerated.

Not only aryl iodides or bromides but also aryl chlorides were successfully engaged, although with lower yield (**2f**: 57% compared to 91% for the corresponding aryl bromide). The

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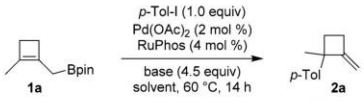
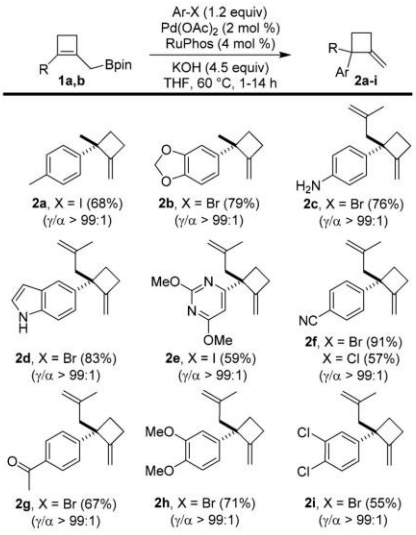
Table 1. Survey of Base and Solvent in γ-Cross-Coupling Reactions



entry	solvent	base	conv (%)[a]	γ/α[a]
1	THF	KOH	72	>99:1
2	THF/H_2O (1:1)	KOH	80	>99:1
3	**THF**	**$KOH_{(aq)}$**[b]	**>99**[c]	**>99:1**
4	THF	TBAF	74	86:14
5	THF	CsF	65	>99:1
6	dioxane	$KOH_{(aq)}$[b]	91	>99:1
7	acetonitrile	KOH	94	72:28
8	MTBE	KOH	>99	>99:1
9	ethyl acetate	KOH	>99	>99:1

[a]Determined by GC. [b]8.0 M solution. [c]After 1 h.

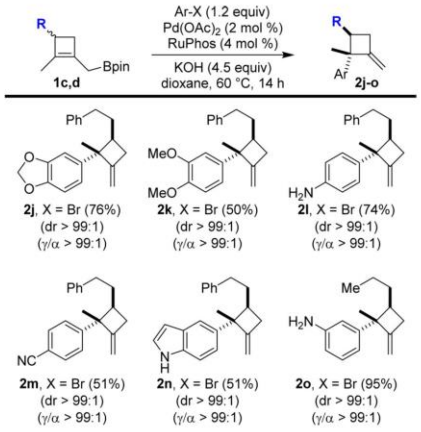
Scheme 2. Electrophilic Scope of γ-Selective Cross-Coupling



lower reaction rate of aryl chloride was exploited in the chemoselective synthesis of **2i**, accounting for only negligible side reactions. Electron-donating (**2a,b** and **2h**) as well as electron-withdrawing groups (**2f,g**) led to good yields up to 91%, while heterocyclic products were isolated in up to 83% yield (**2d** and **2e**). Interestingly, free amines led to a complete conversion of the starting material, giving the expected cross-coupled compound in 76% yield. In all cases the γ-selective cross-coupling products were exclusively detected, probably enhanced by a strain release when shifting the π-system outside of the ring structure.[9]

Having established an efficient route toward alkylidenecyclobutanes, we took a step further by employing chiral cyclobutenylmethylboronic esters (**1c,d**) (Scheme 3) possessing a lateral chain R. Performing reactions in dioxane showed slightly better diastereoselectivities in this case, and aromatic- as

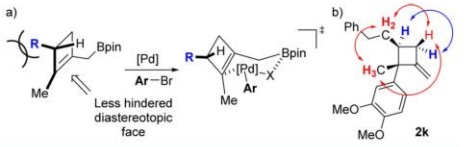
Scheme 3. γ-Selective Cross-Coupling of Chiral Substrates 1c and 1d



well as heteroaromatic-substituted methylenecyclobutanes **2j–o** were obtained with high yields up to 95% and with a full control over the diastereochemical outcome of the transformation (dr >99:1).

As postulated by Buchwald et al. (Scheme 4), we propose to explain the high diastereoselectivity by a ZT transition state in which the transmetalation step would follow a chair model.[10]

Scheme 4. (a) Proposed ZT Model and (b) Observed NOEs Supporting the Proposed Configuration



In this case, the palladium complex preferably approaches from the less hindered diastereotopic face of the double bond—opposite side of the R chain—leading selectively to the described isomer. The 2D-NMR assignments of **2k** supported the above-mentioned hypothesis, placing the aromatic moiety *anti* to the preinstalled R chain (Scheme 4).

To further expand the scope toward more elaborated structures and to open the possibility of synthesizing enantioenriched ACBs, we chose to study the reactivity of α-chiral boronic esters in γ-selective cross-coupling reactions. First experiments using previously described catalytic systems led to expected compounds but without control over *E*/*Z* ratios (50:50). Screening of diverse conditions showed the best results when PCy_3 or dppb (1,4-bis(diphenylphosphino)-butane) was employed as ligands in the presence of $Pd(OAc)_2$ or $Pd(PPh_3)_2Cl_2$, respectively (Table 2, entries 1 and 12). However, when full conversion was to be observed, other conditions only led to worse *E*/*Z* ratios. In most cases bidentate ligands gave better *E*/*Z* ratios, a trend that could be attributed to a favorable shielding of the pseudoaxial position toward the formation of the *E*-product. Presenting similar stereoselectiv-

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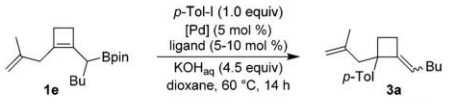
Table 2. Survey of Conditions for Synthesis of Alkylidenecyclobutanes



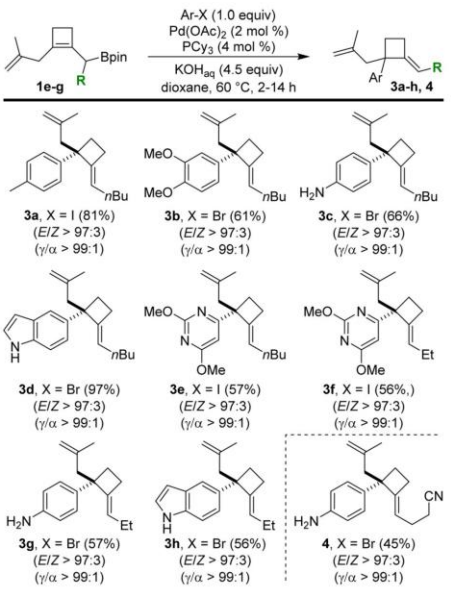
entry	Pd species	ligand[a]	E/Z[b]
1	**$Pd(OAc)_2$**	**PCy_3**	**95:5**
2	$Pd(OAc)_2$	XPhos	87:13
3	$Pd(OAc)_2$	DavePhos	66:34
4	$Pd(OAc)_2$	RuPhos	49:51
5	$Pd(OAc)_2$	Tetraphos-Li	89:11
6	$Pd(OAc)_2$	dppBz	88:12
7	$Pd(OAc)_2$	dppb	92:8
8	$Pd(OAc)_2$	dppp	92:8
9	$Pd(OAc)_2$	PPh_3	50:50
10	$Pd(PPh_3)_2Cl_2$	PCy_3	91:9
11	$Pd(PPh_3)_2Cl_2$	dppp	92:8
12	**$Pd(PPh_3)_2Cl_2$**	**dppb**	**94:6**
13	$Pd(PPh_3)_4$	PCy_3	91:9
14	$[Allyl\text{-}PdCl]_2$	PCy_3	93:7

[a]10 mol % of monodentate, 5 mol % of bidentate ligands. [b]Determined by GC.

ities, the $Pd(OAc)_2/PCy_3$ (Table 2, entry 1) system was preferentially employed for economic reasons.

$Pd(OAc)_2$ was thus chosen as precatalyst, and the transformation was exemplified with a range of coupling partners (Scheme 5). Boronic esters **1e,f** were readily prepared by a double boron homologation in order to introduce α-substituents and subsequently cross-coupled with different halides, achieving overall good to excellent yields (up to 97%). None of the reactions showed α-cross-coupling, and *E*-**3a–h** were obtained in more than 97% of stereochemical purity. In the case of **4**, a 2-cyanoethyl substituent was introduced through the double-homologation sequence, pointing out the functional group tolerance of the transformation. Worthy of note, the starting cyclobutenylmethylboronic ester bearing the 2-cyanoethyl chain was engaged in the γ-cross-coupling after simple filtration of residual salts, avoiding fastidious purification steps and furnishing **4** in 45% yield. 2D NMR experiments on **3f** supported the favored formation of *E*-isomers.

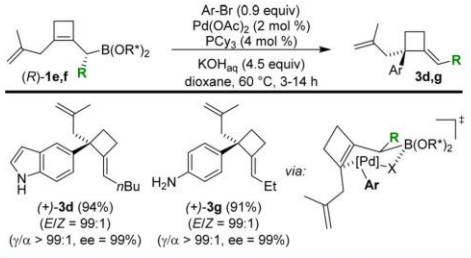
Scheme 5. Synthesis of Alkylidenecyclobutanes from 1e and 1g



Taking advantage of a substituent present at the α-position—that can easily be introduced in a stereoselective way—we took on the challenge of relaying the chiral information from the boronic ester moiety to the quaternary stereocenter.

A preinstalled enantiomerically pure ligand on the boron atom led to enantiomerically enriched cyclobutene derivatives ((*R*)-**1e** and (*R*)-**1f**) via successively diastereoselective and diastereospecific boron-homologation sequences. 5-Bromoindole and 4-bromoaniline were chosen for the γ-selective cross-coupling, and corresponding ACBs were obtained in very good yields up to 94% and with a perfect control of the stereochemistry (99% *E* and 99% ee) (Scheme 6). High stereoselectivities observed in this reaction can be attributed to a sterically favored *pseudo*-equatorial positioning of the α-substituent R in the ZT transition state.

Scheme 6. Diastereoselective Access to Enantioenriched ACBs 3d and 3g



The next step toward enantioenriched ACBs was designed through asymmetric catalysis, employing chiral palladium ligands in the presence of achiral substrates **1b**.

To the best of our knowledge, intermolecular enantioselective formation of a quaternary stereocenter through γ-selective cross-coupling remains unexplored. While TADDOL-$PNMe_2$[11] failed our expectations, the first positive results were observed when employing (*R*)-BINAP as the chiral ligand (er = 64:36) (Table 3, entry 2). Changing the ligand to the JosiPhos series (entries 3–8) could improve the enantiomeric ratio to 81:19 with **L1** at 60 °C. Performing the reaction at room temperature gave the best enantioselectivities (er = 85:15). Adjustments on the ligand structure (**L2–5**) did not lead to any amelioration on the stereoselectivity of the reaction. Finally, methylenecyclobutanes (−)-**2c** and (−)-**2g** were—for the first time—generated from corresponding allylboron species through stereoselective γ-cross-coupling in up to 77% yield and moderate enantiomeric ratios (up to 85:15 er).

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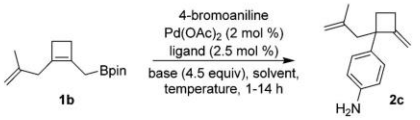
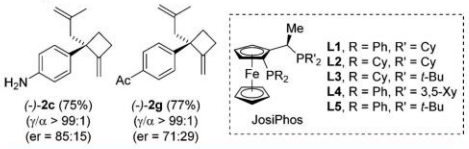
Table 3. Survey of Conditions for Enantioselective Synthesis of MCBs



entry	ligand	base	solvent	temp (°C)	er[a]
1	TADDOL-PNMe$_2$[b]	CsF[c]	THF	60	-[d]
2	(*R*)-BINAP	KOH$_{aq}$	dioxane	60	64:36
3	L1	KOH$_{aq}$	dioxane	60	81:19
4	**L1**	**KOH$_{aq}$**	**dioxane**	**rt**	**85:15**
5	L2	KOH$_{aq}$	dioxane	60	50:50
6	L3	KOH$_{aq}$	dioxane	60	-[d]
7	L4	KOH$_{aq}$	dioxane	60	74:26
8	L5	KOH$_{aq}$	dioxane	60	-[d]

[a]Determined by HPLC utilizing a chiral stationary phase. [b]7 mol %. [c]3.0 equiv. [d]No conversion.



(-)-**2c** (75%) (γ/α > 99:1) (er = 85:15)

(-)-**2g** (77%) (γ/α > 99:1) (er = 71:29)

In conclusion, we have reported a new strategy to easily synthesize alkylidenecyclobutanes containing a quaternary stereocenter in very good yields by combining boron-homologation sequences with γ-selective Suzuki−Miyaura cross-coupling reactions. Excellent regio- and diastereocontrol was established in this unique transformation, and the first—yet moderate—enantioselective intermolecular couplings of allylboronic esters were undertaken for the generation of quaternary stereocenter-containing ACBs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01803.

Contains all experimental procedures and characterization (IR, HRMS, and ^{1}H and ^{13}C NMR data) for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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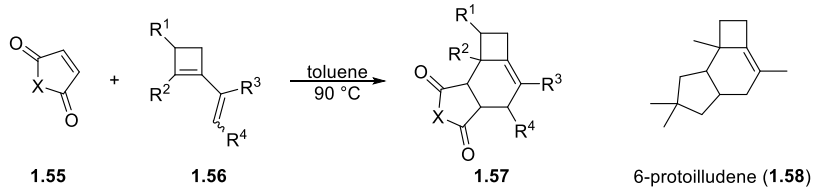
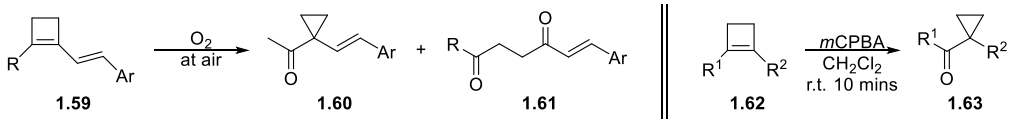
3 Outlook

The Negishi and Suzuki–Miyaura cross-coupling reactions demonstrated in 2.3 were later expanded toward the creation of conjugated dienes **1.56**. Diels–Alder reaction with maleic anhydride and maleimides yielded annulated alkylidenecyclobutanes **1.57** with the 5/6/4-ring system observed in protoilludenes. First attempts toward a total synthesis of 6-protoilludene (**1.58**) unfortunately always gave rearrangement products, destroying the desirable ring system. Some of the maleimide derivatives were tested against the leukemia cell line HL60 and showed reasonable cytotoxicity, encouraging us to further investigate toward potential pharmacological applications.[32]



Scheme 12: Diels–Alder reaction of conjugated dienes and 6-protoilludene **1.58**.

During our studies of conjugated dienes **1.59**, we observed in some cases the formation of oxidized products when substrates were left at air.[33] Computational analysis allowed us to understand the effect of O_2 on our products and prompted us to develop a methodology for the selective synthesis of cyclopropyl ketones. Several bioactive compounds containing said moiety could therefore be synthesized in a straightforward fashion.[34]



Scheme 13: Observed side reactions and optimized reaction conditions.

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CHAPTER II

2-Azetines

4 Introduction

Unlike the well-known β-lactams and azetidines, the unsaturated 2-azetines have received much less attention by the scientific society. While β-lactams are most renowned for being part of the antibiotic penicillins (**2.01**), there are many other bioactive compounds possessing this structural moiety. Aztreonam (**2.02**) and nocardicin A (**2.03**) are two examples which have shown antimicrobial activity against Gram-negative organisms like *Pseudomonas aeruginosa* and have been used in the treatment of infections caused by the latter.[35]

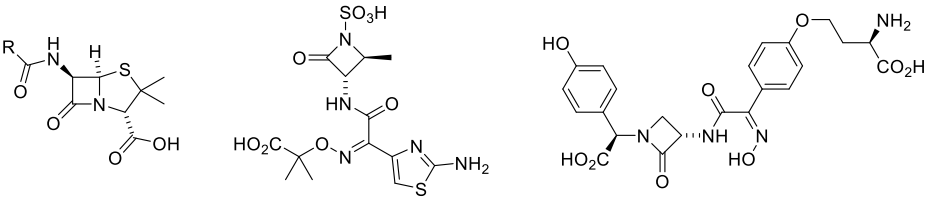

Figure 3: β-Lactam based bioactive compounds.

Azetidines are also often found in biologically active substances, owing to their interesting properties. Noteworthy examples are **2.05** and **2.06**, which were found to exhibit improved antibacterial activity against *Staphylococcus aureus* compared to some used fluoroquinolones, such as levofloxacin (**2.04**).[36]

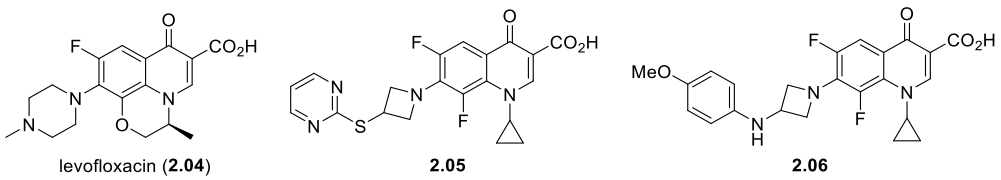

Figure 4: Levofloxacin (**2.04**) and derived azetidine containing bioactive compounds.

Only very few reports exist on the synthesis of 2-azetines. This is mostly due to the fact, that this moiety is rather unstable and is prone to an electrocyclic ring-opening reaction, affording azadienes. Ways to stabilize 2-azetines toward isolation are through the installation of an electron-withdrawing group at the nitrogen atom or a metal-carbene functionality at position 3.[37]

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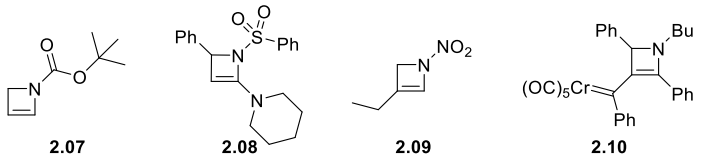
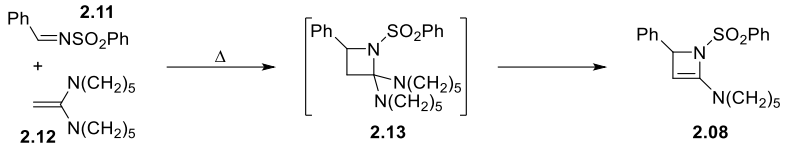


2.07 **2.08** **2.09** **2.10**

Figure 5: Examples of isolated 2-azetines.

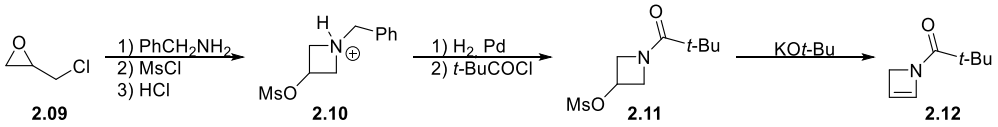
Most syntheses for 2-azetines rely on β-elimination on the easily accessible azetidines. Through intermediary formation of azetidine **2.13** by [2+2] cycloaddition, sulfonyl-protected azetine **2.08** is formed after a thermally caused elimination reaction.[38]



2.11 **2.12** **2.13** **2.08**

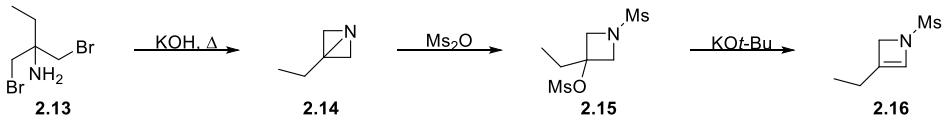
Scheme 14: [2+2] Cycloaddition and subsequent elimination to 2-azetine **2.08**.

Other procedures rely on nucleophilic substitution to first form an azetidinium **2.10** and bicyclic azetidine **2.14**, respectively. After further modifications to introduce a leaving group and protect the ring-nitrogen, elimination is induced through heating with potassium *tert*-butanolate.[39]



2.09 **2.10** **2.11** **2.12**

Scheme 15: Double nucleophilic substitution starting from chloro oxirane **2.09** to give 2-azetine **2.12** after elimination.



2.13 **2.14** **2.15** **2.16**

Scheme 16: Formation of azabicyclobutane **2.14** and subsequent elimination to afford 2-azetine **2.16**.

[38] F. Effenberger; R. Maier, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 416.

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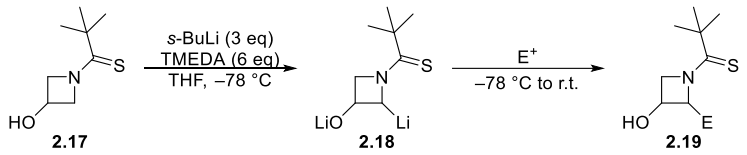
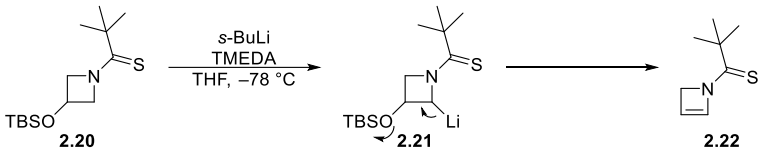
During their studies on the α-lithiation of azetidines, promoted by a protecting group at the nitrogen that double acts as an activator, the group of Hodgson discovered that free alcohols at position 3 (**2.17**) could be tolerated.[40] Protected alcohols **2.20** however underwent an elimination of the lithiated intermediates **2.21** to ultimately furnish 2-azetines **2.22**.[41]



Scheme 17: α-Lithiation of azetidine-3-ols and electrophile trapping.



Scheme 18: α-Lithiation of protected azetidin-3-ols and subsequent elimination to 2-azetines.

Another equivalent of lithium base produces α-lithiated 2-azetines, which were reacted with different electrophiles to access 2-substituted azetines.[42] Based on these findings we went on to develop a strategy for the synthesis of higher substituted 2-azetines. By using borates as electrophiles we were ultimately able to create storable azetine building blocks for further reactions.

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[41] D. M. Hodgson; C. I. Pearson; A. L. Thompson, *J. Org. Chem.* **2013**, *78*, 1098.

[42] D. M. Hodgson; C. I. Pearson; M. Kazmi, *Org. Lett.* **2014**, *16*, 856.

5 Results

5.1 Methods for the Synthesis of Substituted Azetines

Organic LETTERS
Letter
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Methods for the Synthesis of Substituted Azetines

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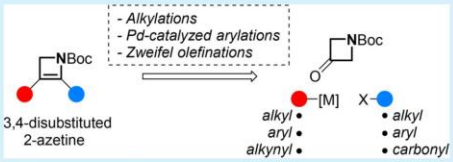
Supporting Information

ABSTRACT: Spurred on by the recent emerging interest from the chemical community for unsaturated four-membered heterocycles, an unprecedented approach to nitrogen-containing four-membered rings has been designed. 3,4-Disubstituted 2-azetines were synthesized from commercially available substrates, allowing for a straightforward access to a new library of chiral functionalized azetidines and amino alcohols. This original approach was applied to efficiently prepare functionalized azobenzenes, an emerging class of molecules with a large potential in photopharmacology.



Small, strained ring systems have recently received increased attention due to their large applicability in drug discovery and development. However, generating these systems is often limited by the availability of efficient and straightforward methods. Among them, azetidines and their unsaturated analogues 2-azetines[1−4] are particularly interesting as they represent a promising pattern for further pharmacological studies.

Apart from the well-known β-lactams penicillin and cephalosporin derivatives, several fused azetidine-containing substances have shown interesting antitumor activities[5] and antinociceptive effects[6] (Figure 1).

Fused β-lactams have also proven to be adequate precursors of azabicyclo[3.2.1]octanes.[7] In the polyoxin family, antibiotic properties were observed on 3-alkylideneazetidine-modified structures.[8]

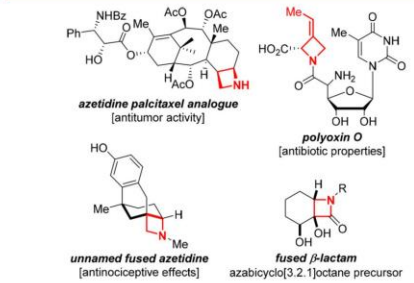


Figure 1. Examples of biologically active azetidine-containing structures or precursors.

Recently, the group of Baran et al. developed a new route for introducing 3-substituted azetidines by using the ring strain of azabicyclo[1.1.0]butane to efficiently modify lead compounds of pharmacological interests.[9] Concurrently, Carreira demonstrated the propensity of spiro-azetidines to modulate biological properties of different targets in drug discovery.[10] While smaller and larger *N*-containing heterocycles have been extensively studied,[1] only a few reports relate the general formation of azetines.[2,11]

With the ambitious objective of generalizing access to polysubstituted azetine architectures—that represent versatile building blocks en route to sophisticated azetidines—we first took on the challenge of identifying a sequence allowing for the regioselective introduction of diverse substituents at positions 3 and 4 (Scheme 1), involving a lithiated species as the key intermediate. While direct functionalization of 4-azetinyllithium could be easily performed in the presence of alkyl, silyl or carbonyl derivatives (conditions A), a more challenging arylation was designed through cross-coupling of the corresponding organoboronate derivatives, obtained through a simple transmetalation. As a matter of fact, transmetalation with $ZnCl_2$ only furnished the cross-coupled compound in low yield (27%, Hodgson et al.). Alternatively, a boron-relayed catalyst-free arylation of azetinyllithium was developed.

Starting from commercial sources of *N*-Boc-3-azetidinone **1**,[12] the introduction of the substituent at position 3 (R^1) was simply performed by employing an adequate organometallic reagent, such as organolithium, organomagnesium, or $PhMe_2SiLi$. Methylation of the resulting crude tertiary alcohol afforded **2a−f** in good to excellent yields over two steps (up to 98%, Scheme 2).[13] α-Lithiation of **2** assisted by coordination of the

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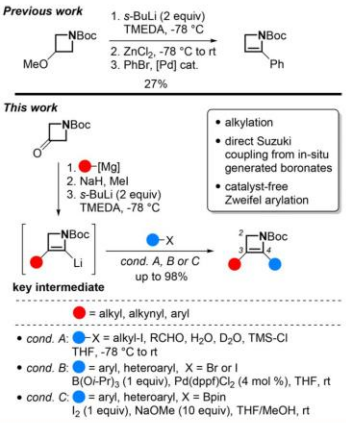
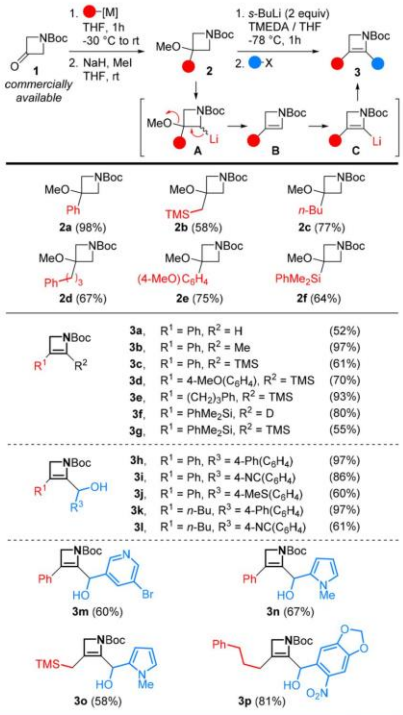
Organic Letters Letter

Scheme 1. Our Contribution to the Efficient Synthesis of Disubstituted Azetines



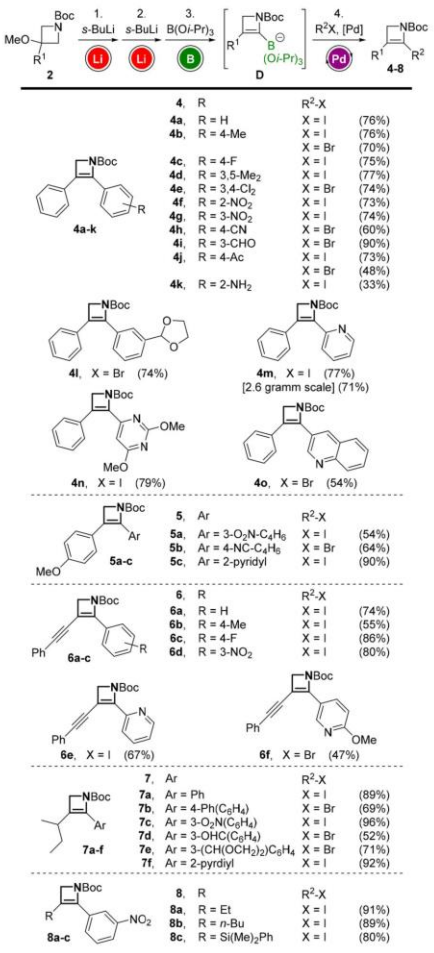
Scheme 2. Our Contribution to the Efficient Synthesis of Disubstituted Azetines



directing group (Boc) on the amine using *s*-BuLi in the presence of TMEDA triggers a β-elimination (**A**, Scheme 2) and intermediary forms a 2-azetine (**B**). With an excess of *s*-BuLi, a second α-metalation of the C(sp^2) can take place to obtain the key 4-azetinyllithium intermediate **C**. Addition of H_2O, D_2O, MeI, or TMSCl allowed the formation of 3-substituted azetines **3a–g** in up to 97% yield (Scheme 2). Aromatic and heteroaromatic aldehydes were also engaged as electrophiles in the reaction, furnishing azetinecarbinols **3h–p** with up to 97% yield.

Second, a similar sequence was designed to in situ generate a boronate derivative **D** (Scheme 3) by trapping the corresponding 4-azetinyllithium **C** with boron isopropoxide. Being a stable species at room temperature, this organoboronate is an excellent candidate to subsequently undergo a Suzuki cross-coupling in a one-pot process. Thus, following the double-lithiation/borylation sequence, a range of aromatic halides were engaged in the

Scheme 3. In Situ Generated 4-Azetinylboronates for Direct Suzuki Coupling



4,	R	R^2-X	
4a,	R = H	X = I	(76%)
4b,	R = 4-Me	X = I	(76%)
		X = Br	(70%)
4c,	R = 4-F	X = I	(75%)
4d,	R = 3,5-Me_2	X = I	(77%)
4e,	R = 3,4-Cl_2	X = Br	(74%)
4f,	R = 2-NO_2	X = I	(73%)
4g,	R = 3-NO_2	X = I	(74%)
4h,	R = 4-CN	X = Br	(60%)
4i,	R = 3-CHO	X = Br	(90%)
4j,	R = 4-Ac	X = I	(73%)
		X = Br	(48%)
4k,	R = 2-NH_2	X = I	(33%)

5,	Ar	R^2-X	
5a,	Ar = 3-O_2N-C_4H_6	X = I	(54%)
5b,	Ar = 4-NC-C_4H_6	X = Br	(64%)
5c,	Ar = 2-pyridyl	X = I	(90%)

6,	R	R^2-X	
6a,	R = H	X = I	(74%)
6b,	R = 4-Me	X = I	(55%)
6c,	R = 4-F	X = I	(86%)
6d,	R = 3-NO_2	X = I	(80%)

7,	Ar	R^2-X	
7a,	Ar = Ph	X = I	(89%)
7b,	Ar = 4-Ph(C_6H_4)	X = Br	(69%)
7c,	Ar = 3-O_2N(C_6H_4)	X = I	(96%)
7d,	Ar = 3-OHC(C_6H_4)	X = Br	(52%)
7e,	Ar = 3-(CH(OCH_2)$_2$)C_6H_4	X = Br	(71%)
7f,	Ar = 2-pyridyl	X = I	(92%)

8,	R	R^2-X	
8a,	R = Et	X = I	(91%)
8b,	R = *n*-Bu	X = I	(89%)
8c,	R = Si(Me_2)Ph	X = I	(80%)

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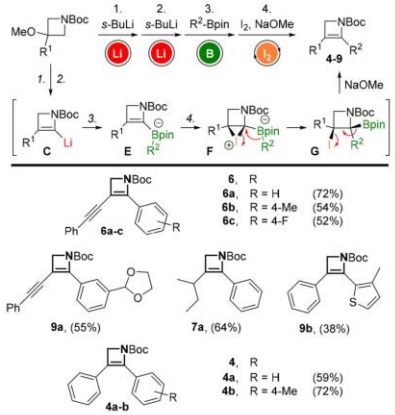
Org. Lett. 2017, 19, 5681–5684

presence of Pd(dppf)Cl_2·CH_2Cl_2 (4 mol %) in THF, and products **4**–**8** were isolated after 48 h at room temperature. Aryl iodides reacted usually faster than the corresponding bromides, leading to the expected compounds in better yields. A wide range of aromatic halides were introduced in this strategy, using 3-arylated (**4a**–**o** and **5a**–**c**), 3-alkynyl (**6a**–**f**), and 3-alkyl substrates (**7a**–**f** and **8a**,**b**), resulting in 4-arylated structures in good to excellent yields (up to 96%). Additionally, the great functional group tolerance of organoboronates allowed us to introduce aromatic aldehydes **4i** and **7d** as well as heteroaromatic moieties (**4m**–**o**, **5c**, **6e**,**f**, and **7f**) in good yields up to 92%, independently from the nature of the substituent at position 3. Structures of these unsaturated *N*-heterocycles were supported by X-ray analysis (**6d** and **8a**).[14] Although full conversion was monitored for the formation of **4k** bearing a free amine, decomposition of the product on silica was noticed and the final azetine could only be isolated in 33% yield. In a more general manner, electron-enriched aromatics led to moderate yields due to fast decomposition (mainly ring opening products) in slightly acidic conditions during purification.

We then pushed the methodology further by developing an unprecedented catalyst-free cross-coupling of the 4-azetinyllithium species, successfully adapting the Zweifel-type olefination strategy. Boronic ester was then added to the in situ generated intermediate **C** (Scheme 4), giving the bis-organoboronate **E**.

Scheme 4. Catalyst-Free Zweifel Arylation of 4-Azetinyllithium Species

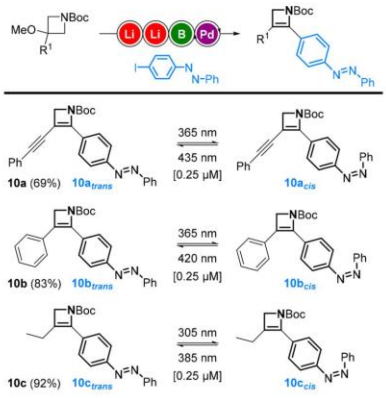


Subsequent addition of iodine furnishes an iodonium **F** that undergoes 1,2-metalate rearrangement, giving the α,β-iodoboronic ester **G**. The addition of a base finally triggers a cis-elimination, resulting in 3,4-disubstituted azetines **4**–**9**. 3-Alkyl-, alkynyl-, and arylazetinyllithium were used with aromatic boronic esters and compounds **4a**,**b**, **6a**–**c**, and **7a**, were obtained with reasonable yields (up to 72%), given the absence of a palladium catalyst. Interestingly, heteroaromatic substrates led to similar results and **9b** was isolated in 38% yield.

Considering the versatility of both arylation sequences and the recent interest brought by the community on diazobenzenes as promising photoswitchable systems for pharmacologic applications,[15] functionalization of azetines at position 4 was explored as a proof of concept.

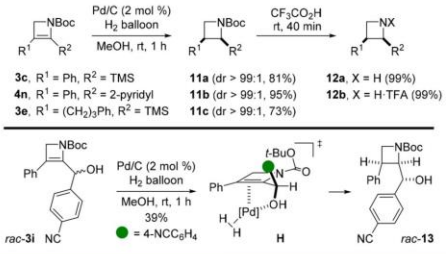
A one-pot sequence terminated by a palladium-catalyzed Suzuki coupling with 4-bromodiazobenzenes led to conjugated systems **10a**–**c** in good yields (Scheme 5). In the dark, **10a**–**c** are

Scheme 5. Application to the Synthesis of 4-Azetinylazobenzenes



present in their thermally stable *trans*-configuration. Irradiation with UV light (λ = 305–365 nm) triggers isomerization to the *cis*-configuration, while irradiation at 385–435 nm allows instant switching to the *trans*-configuration. Performing iteratively on and off photoswitching on these azetinyl-derived azobenzenes did not show any fatigue of the four-membered ring over time, proving the structural stability of the system. Finally, we showed the applicability of 3,4-substituted azetines to the formation of *syn*-2,3-disubstituted azetidines through simple hydrogenation (Scheme 6). Compounds **3e**, **3c**, and **4n** were engaged in the

Scheme 6. Straightforward Access to Stereodefined Azetidines



presence of palladium and hydrogen to give **11a**–**c** under smooth conditions in good yields and with an excellent diastereoisomeric ratio (dr >99:1).[12] Subsequent amine deprotection ultimately led to free azetidines **12a**,**b** in quantitative yields. It is worth noting that this represents a powerful approach to *syn*-azetidines, as most reports relate the formation of *anti*-azetidines.[16]

β-Amino alcohols are important functionalities in organic chemistry as they can serve as ligands in catalysis and are present in a large number of natural and bioactive substances.[17] In an attempt to synthesize stereodefined β-amino alcohols embedded in an azetidine core, we representatively demonstrated (Scheme

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6) that the reduction of chiral 4-azetinylcarbinol *rac*-**3i** could take place with high diastereoselectivities, furnishing *rac*-**13** as a single isomer (dr >99:1:0:0, the relative configuration was determined by X-ray crystallography).[14] The high degree of stereoselectivity observed in this reaction can be attributed to the coordination of the hydroxyl moiety to the palladium in the reduction process. For steric reasons, the aromatic group on the carbinol prefers to be oriented out of the plane, avoiding unfavorable interactions with the large Boc protecting group (**H**) (Scheme 6). This procedure certainly paves the way to new subclasses of chiral strained β-aminoalcohols.

In conclusion, we have demonstrated a very simple and efficient synthetic approach to novel 3,4-disubstituted azetine architectures, paving a new way toward stereodefined 2,3-azetidines. Two parallel approaches have been developed for the facile introduction of aryl and heteroaryl substituents at the position α to the nitrogen, either through a one-pot Suzuki cross-coupling or via catalyst-free arylation. Additionally, we showed the potential applicability of our system to unprecedented photoswitchable molecules, demonstrating their long-term stability. We finally illustrated an unprecedented access to stereodefined β-aminoalcohols that represent important structures in organic, organometallic and bioorganic chemistry. Paths allowing for the formation of these interesting patterns represent important advances in the chemistry of nitrogen-containing four-membered rings and their potential implications in drug-discovery processes.

■ ASSOCIATED CONTENT

Supporting Information

CThe Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02847.

Experimental procedures and characterization (IR, HRMS, and ^{1}H and ^{13}C NMR data) for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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5.2 One-Pot Preparation of Stable Organoboronate Reagents for the Functionalization of Unsaturated Four- and Five-Membered Carbo- and Heterocycles

3149

Synthesis A. N. Baumann et al. Special Topic

One-Pot Preparation of Stable Organoboronate Reagents for the Functionalization of Unsaturated Four- and Five-Membered Carbo- and Heterocycles

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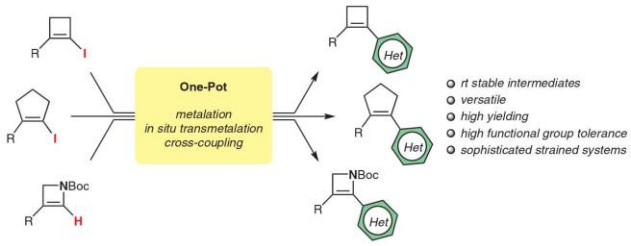

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Abstract Combining a facile preparation of organoboronates with their remarkable stability and functional group tolerance allows for the straightforward synthesis of four- and five-membered carbo- and heterocycles. While most strategies rely on the ex situ preparation of boronic acids as isolated intermediates, we demonstrate that in situ transmetalation of sensitive organometallics with boron alkoxides can lead to great stabilization of such species at room temperature. A considerable extension of the library of unsaturated strained structures is achieved through these sequences, expanding the potential applicability of such unusual building blocks.

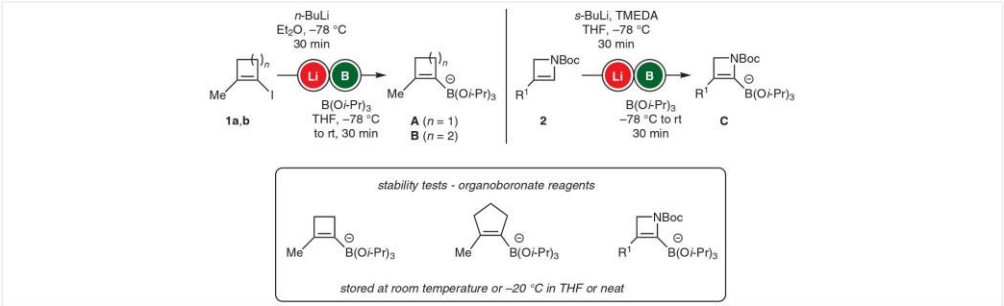
Key words cyclobutenes, cyclopentenes, azetines, organoboronates, one-pot sequences

The transition-metal-catalyzed cross-couplings of organoboronic acids with organic halides, a process developed by Suzuki et al.,[1] has become one of the most powerful tools for the creation of C–C bonds.[2] Both simplicity and functional group tolerance have made it a privileged method[3] for assembling complex structures in many fields of chemistry such as drug discovery,[4] materials science,[5] chemosensors[6] and total synthesis.[7] Spurred on by the particular stability of organoboron species, we took on the challenge of generalizing the access to classes of molecules that have been scarcely reported: strained cyclobutenes, cyclopentenes and 2-azetines. Due to their commercial availability, organoboronic acids are employed as stable substrates for numerous cross-coupling reactions. For more elaborated scaffolds however, tailor-made boronic acids must be prepared ex situ in order to be engaged in a subsequent reaction through a two-step process. For the sake of step-economy, we needed to develop a more straightforward access to the targeted compounds, avoiding an extra purification of intermediate boronic acids. Taking into account the recent work of Buchwald and co-workers on direct cross-coupling of lithium organoboronates,[8] Miyaura et al. on base-free coupling of triolborates,[9] Cammidge on coupling of ex situ generated trihydroxyborates,[10] and Knochel's group on the in situ generation of magnesium bis-organoborinates,[11] we designed different strategies in which the cross-coupling reaction would be relayed by the in situ formation of a stable intermediate boron species. Our first objective was to demonstrate the long-term stability of such strained organoboron derivatives over time, opening the strategy to reagent storage; secondly, we aimed to explore the scope and limitations of the method to complete a large library of new building blocks, being hitherto difficult to access.

Cyclobutene and cyclopentene iodides **1a**,**b** were readily prepared from procedures originally described by Negishi et al. involving π-cyclization of *gem*-bismetalated alkenes,[12] which we recently applied to the synthesis of alkylidenecyclobutanes and fused four-membered rings.[13] Halogen–lithium exchanges on **1a** and **1b** were performed employing *n*-BuLi in diethyl ether at –78 °C (as THF led to further alkylation of the newly formed cycloalkenyllithium) and the corresponding cycloalkenyl-boronates **A** and **B** were generated by addition of B(O*i*-Pr)$_3$ in THF (Scheme 1).

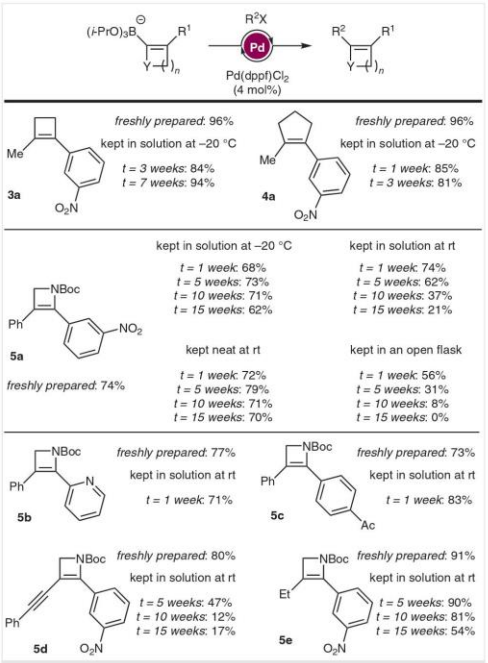
Azetinyllithium reagents were generated by α-lithiation of in situ formed azetines **2** using *s*-BuLi in the presence of TMEDA in THF at –78 °C,[14] and subsequently trapped with boron isopropoxide to give **C**.[15]

Organoboronates **A**, **B** and **C** were then stored either in solution or neat at –20 °C or room temperature before being engaged in Suzuki cross-couplings (Scheme 2).



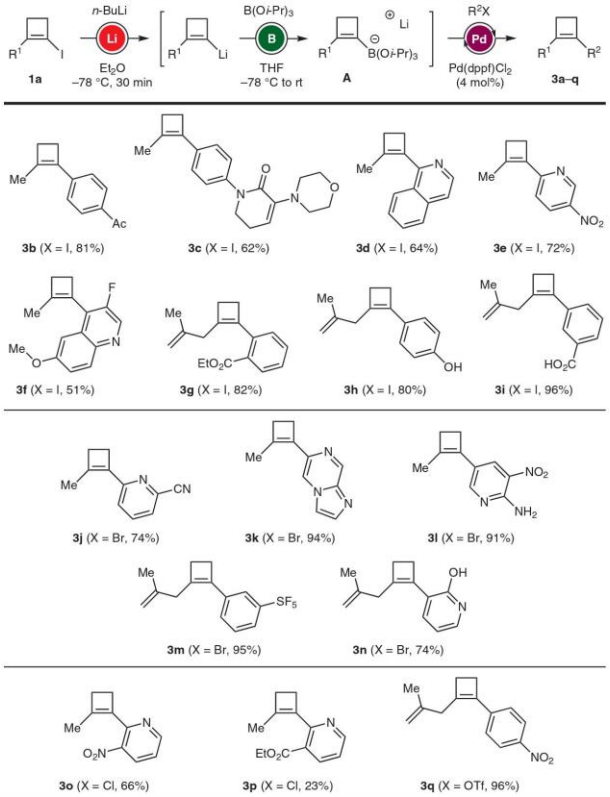
Scheme 1 Organoboronate synthesis through Li/I exchange–transmetalation or α-lithiation–transmetalation

Cyclobutenyl- and cyclopentenylboronates **A** and **B** were coupled with 1-iodo-3-nitrobenzene as a test partner. From freshly prepared solutions, both products **3a**[16] and **4a** were obtained in excellent yields (96%). Keeping solutions at –20 °C showed constancy in reactivity, delivering **3a** in 94% yield after seven weeks and **4a** (81%) after three weeks. Diverse conditions were evaluated for storage of azetinylboronates **C**. When kept in an open flask, the yields decreased drastically after only one week of storage, and a fast decrease in reactivity was also observed on storing **C** in solution at room temperature. However, reproducible results were obtained when the boronate salts were kept either in solution at –20 °C (as for **A** and **B**), or neat at room temperature. Products **5a** were isolated in constant, reasonable yields (up to 70% after fifteen weeks). Stock solutions of azetinylboronate reagents were prepared and further used in cross-coupling reactions after different storage times at room temperature. In some cases (**5b**, **5c** and **5e**), the salts gave reproducible yields after one or ten weeks of storage, showing the great potential of such reagents as building blocks. In some other cases (**5d**), the solution showed a rapid decrease of reactivity, furnishing only a 47% yield of the desired product.



Scheme 2 Stability testing of four- and five-membered carbo- and heterocyclic organoboronates

Having established the stability of strained organoboronates, we next investigated the scope of the transformation toward a new library of cyclobutenes. The protocol of Scheme 1 was used to generate in situ the cyclobutenylboronate **A**, which was then engaged directly in cross-coupling reactions in the presence of $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (Scheme 3). Aromatic and heteroaromatic iodides bearing ketone, ester, nitro or amide moieties led to the expected arylcyclobutenes **3b–g** in moderate to good yields (51 to 82%). Interestingly, an unprotected phenol and a benzoic acid furnished the desired products **3h** and **3i** in excellent yields of 80% and 96%, respectively. Not only iodides, but bromides could be engaged as cross-coupling partners with similar efficacy, furnishing **3j–n** with up to 95% yield and with exceptional functional group tolerance (SF_5, NH_2, OH). Alternatively, an aryl triflate gave a similar result (**3q**, 96%) while aryl chlorides showed decreased efficiency (**3o**,**p**, 23 to 66%).



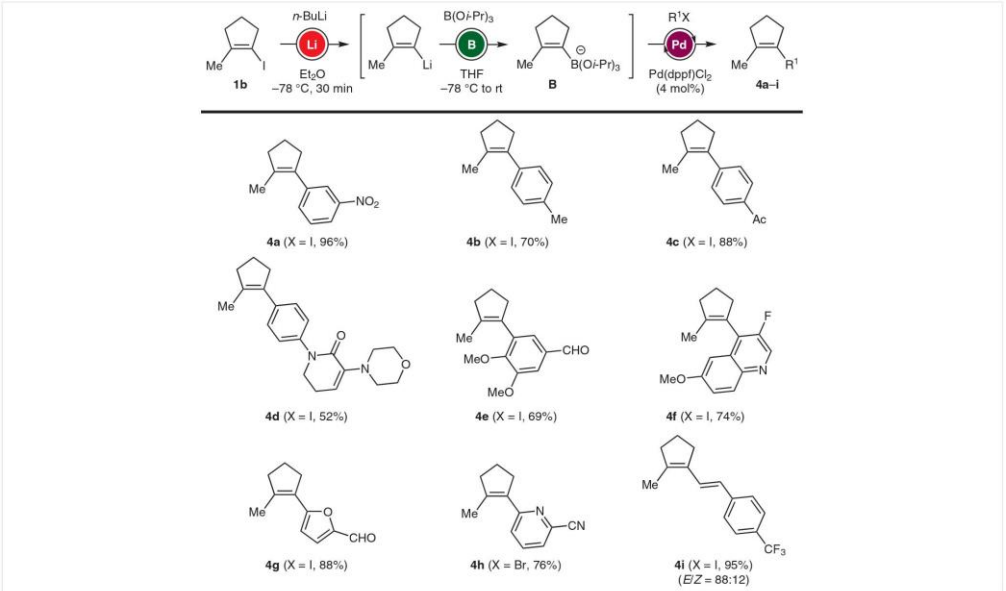
Scheme 3 In situ preparation and further Suzuki cross-coupling of cyclobutenylboronates

The study was then pursued with five-membered rings, utilizing cyclopentenyl iodides as starting materials[17] in a similar one-pot sequence (Scheme 4). Halogen–lithium exchange on **1b** was followed by transmetalation with B(O*i*-Pr)$_3$ and further palladium-catalyzed cross-coupling with diverse aromatic halides. A comparable functional group tolerance was observed for these larger cycloalkenylboronates, as ketone, nitro, amide and aldehyde moieties could be introduced, giving a wide range of unique functionalized cyclopentenes **4a–h** in moderate to excellent yields (52 to 96%).[16] When a β-styryl iodide was used, the reaction resulted in partial double bond isomerization and **4i** was obtained in 95% yield and an 82:18 *E*/*Z* ratio.

Next, we investigated the iodine–lithium exchange in the presence of boron isopropoxide. Given that the exchange reaction should proceed at a higher rate than the nucleophilic addition of *n*-BuLi to the boron atom, the presence of boron species should not perturb the exchange reaction, but rather promote the direct transmetalation of the newly generated lithium species (Scheme 5), as previously exemplified by Li et al.[18] As a result, the undesired alkylation reaction was to be suppressed without having to use Et$_2$O, avoiding the previously required mixture of solvents.

As a proof of concept, the halogen–metal exchange was performed on **1a** and **1b** in the presence of B(O*i*-Pr)$_3$ at –78 °C, and ultimately engaged in the cross-coupling reaction with a representative partner (1-iodo-3-nitrobenzene). Similar results were collected from this simplified procedure (93 to 96% yield).

Toward a more convenient setup, a step further was then taken by developing conditions that would not require low temperatures for the formation of organoboronates. We envisioned that room-temperature metal insertion in the presence of boron alkoxides should lead to the expected intermediate boron species through in situ transmetalation

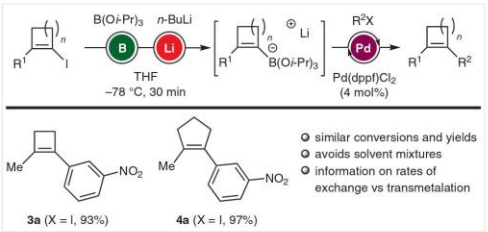


Scheme 4 In situ preparation and further Suzuki cross-coupling of cyclopentenylboronates

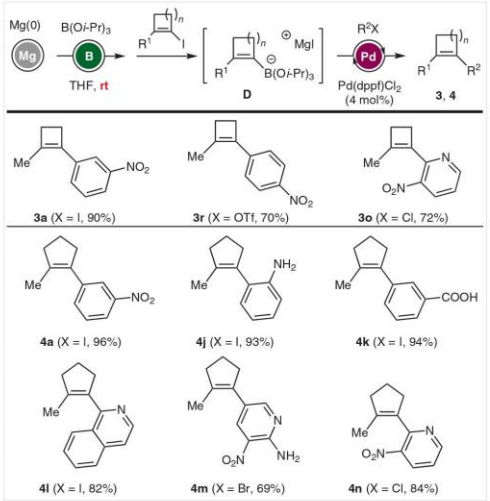
of the transitional cycloalkenylmagnesium species (Scheme 6).

Magnesium powder was then employed, furnishing the intermediary magnesium salt **D**, being an analog of **A** and **B**. Performing the full sequence at room temperature afforded the desired cross-coupling products in excellent yields, comparable to those obtained via the lithium path (up to 96%). The reaction also showed similarly high functional group tolerance, with the ability to introduce unprotected amines (**4j**, **4m**: 69 to 93%) and a carboxylic acid (**4k**, 94%).

In addition, we recently demonstrated the potential of in situ generated azetinylboronates to undergo unprecedented cross-coupling, transposing the methodology to

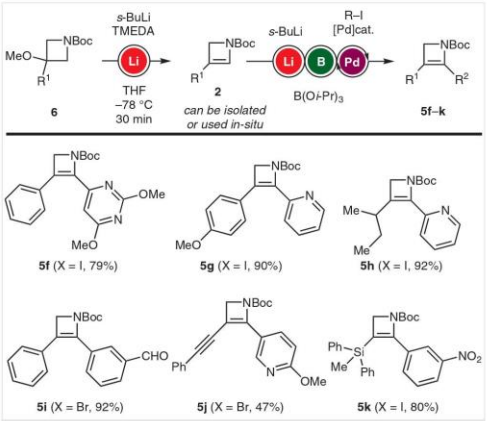


Scheme 5 Iodine–lithium exchange in the presence of $B(Oi\text{-}Pr)_3$ for direct transmetalation



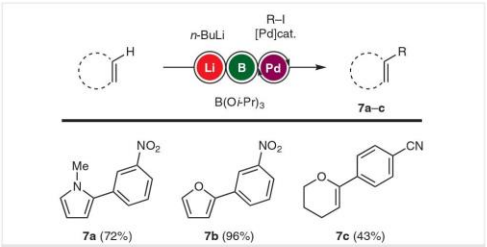
Scheme 6 Formation of organoboronates through magnesium insertion and in situ transmetalation

heterocyclic four-membered structures. A one-pot sequence was designed to access the desired boronates through a double α-lithiation of readily available azetidines **6**, followed by trapping with boron isopropoxide and palladium-catalyzed cross-coupling. Representative examples are given in Scheme 7. Alkyl, aryl, alkynyl and silyl groups were introduced at position 3, and the cross-coupling was performed using a large range of functionalized aromatic halides.[15]



Scheme 7 Single-pot access to 3,4-disubstituted azetines through a lithiation/transmetalation/cross-coupling sequence

Furthermore, we showed the applicability of this strategy to pyrroles, furans and hydropyrans to open the scope to a larger array of heterocyclic scaffolds. A simple metalation with *n*-BuLi was performed to access the initial organometallic derivatives, before transmetalation with B(O*i*-Pr)$_3$. Heteroaromatic starting materials furnished the desired cross-coupled compounds **7a**[16] and **7b** in good yields (up to 96%). However, employing hydrofuran resulted in only 43% of the substituted styrene derivative **7c** (Scheme 8).



Scheme 8 Extension to other heterocycles

In conclusion, we have assembled a new efficient one-pot sequence for the synthesis of cyclobutenes, cyclopentenes and azetines by using in situ prepared boron alkoxides possessing a remarkable functional group tolerance. Diverse conditions were successfully developed relying either on halogen/metal exchanges or on an advantageous room temperature insertion/transmetalation procedure. Through the intermediate formation of stable organoboronate building blocks, we have unlocked a wide library of unexplored strained architectures, opening modern organic chemistry to new classes of modules for further applications.

Commercially available starting materials were used without further purification unless otherwise stated. All reactions were carried out under N_2 atmospheres in flame-dried glassware. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with nitrogen prior to use. CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2. THF was refluxed and distilled from sodium benzophenone ketyl under nitrogen. Et_2O was predried over $CaCl_2$ and passed through activated Al_2O_3 (using a solvent purification system SPS-400-2 from Innovative Technologies Inc.). Toluene was predried over $CaCl_2$ and distilled from CaH_2. *n*-BuLi was purchased from Rockwood Lithium GmbH; [*n*-BuLi] = 2.44 M in hexane (titration with isopropanol/1,10-phenanthroline).

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)] or *p*-anisaldehyde (PAA) solution [concd H_2SO_4 (10 mL), EtOH (200 mL), AcOH (3 mL), *p*-anisaldehyde (4 mL)]. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Diastereoisomeric ratios were determined by ^{1}H NMR and ^{13}C NMR spectroscopy. ^{1}H and ^{13}C 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) or the solvent peak (^{13}C NMR) in deuterated chloroform ($CDCl_3$: δ 7.26 for ^{1}H NMR and δ 77.16 for ^{13}C NMR). Abbreviations for multiplicities are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet) and br (broad). Reaction endpoints were determined by GC monitoring. Gas chromatography was performed with an Agilent Technologies 7890 instrument, 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 instruments, 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 or JEOL JMS-700 instruments. Single crystals (for X-ray analysis) were grown in small quench vials with a volume of 5.0 mL from slow evaporation of dichloromethane/hexanes mixtures at room temperature. Suitable single crystals were then introduced into perfluorinated oil and mounted on top of a thin glass wire. Data collection was performed at 100 K with a Bruker D8 Venture TXS equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector operating with Mo-Kα radiation (l = 0.71071 Å).

General Procedure A

To a solution of cycloalkenyl iodide (1.00 equiv) in Et_2O (0.5 M) was slowly added a solution of *n*-BuLi (2.44 M in hexane, 1.10 equiv) at –78 °C. After stirring for 30 min at the aforementioned temperature, B(O*i*-Pr)$_3$ (1.15 equiv) and THF (total concn 0.25 M) were added and the resulting mixture stirred for an additional 1 h at room temperature. Pd(dppf)Cl_2·CH_2Cl_2 (4 mol%), the cross-coupling partner (aromatic or vinylic iodide, bromide, tosylate or chloride) (0.90 equiv) and an aqueous solution of NaOH (1.5 equiv 1.00 M) were subsequently added and the reaction mixture was stirred overnight. The crude material was extracted with Et_2O (3 × 20 mL), washed with a saturated aqueous solution of sodium chloride (20 mL), dried over magnesium sulfate, filtered, concentrated and purified via flash column chromatography.

General Procedure B

Magnesium powder (1.30 equiv) and LiCl (1.10 equiv) were placed in a reaction tube and flame-dried in vacuo three times. After cooling to ambient temperature, enough THF was added to cover the solids. The magnesium was activated by addition of a few drops of dibromoethane and heating. After cooling back to ambient temperature, B(O*i*-Pr)$_3$ (1.00 equiv) was added. The cycloalkenyl iodide was added dropwise as a solution in THF (1.00 equiv, 0.5 M) and the resulting solution stirred for 2 h, after which a grey suspension had formed, which was divided into equimolar portions in new reaction tubes. To the portions were then added Pd(dppf)Cl_2·CH_2Cl_2 (4 mol%), the cross-coupling partner (aromatic iodide, bromide, tosylate or chloride) (0.80 equiv) and an aqueous solution of NaOH (1.5 equiv 1.00 M). The reaction mixture was stirred overnight and then extracted with Et_2O (3 × 20 mL), washed with a saturated aqueous solution of sodium chloride (20 mL), dried over magnesium sulfate, filtered, concentrated and purified via flash column chromatography.

1-Iodo-2-methylcyclopent-1-ene (1b)

Commercially available 5-iodopent-1-yne (1.93 g, 10 mmol, 1.0 equiv) was dissolved in dry pentane (30 mL) in a Schlenk tube and cooled to –78 °C. *n*-BuLi (2.39 M, 10 mmol, 1.0 equiv) was then added dropwise and the reaction mixture was stirred for 30 min before being warmed to –50 °C for 5 min. The mixture was then cooled back to –78 °C and dimethylaluminum chloride (1 M in CH_2Cl_2, 10 mmol, 1.0 equiv) was added dropwise and the resulting mixture stirred for a further 30 min. The mixture was then allowed to reach room temperature. In another Schlenk flask, zirconocene dichloride (2.93 g, 10 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (25 mL) and trimethylaluminum (2 M, 20 mmol, 2.0 equiv) was added at room temperature and the mixture stirred for 1 h. The first Schlenk flask was then cooled back to –78 °C before dropwise addition of the solution from the second Schlenk flask. The combined reaction mixture was allowed to reach room temperature and stirred for 1 h. The solvent was then removed in vacuo and a red solid remained, which was dissolved in THF (50 mL). After 30 min, complete conversion into the cyclized pentene was confirmed by GC–MS. The reaction mixture was cooled to –78 °C and iodine (5.58 g, 22 mmol, 2.2 equiv) was added portionwise. The mixture was allowed to reach room temperature and then poured into ice-cold HCl (2 M, 200 mL). The layers were separated and the aqueous layer was extracted with hexane (2 × 100 mL). The combined organics were washed with a saturated sodium thiosulfate solution. The organics were dried over $MgSO_4$, filtered and the solvent evaporated at 20 °C (60 mbar) due to the volatility of the desired product. Column chromatography (hexane) yielded the desired product as a colorless oil, which was stored at –20 °C to avoid decomposition.

Yield: 1.48 g, 7.09 mmol (71%); R_f = 0.79 (hexane; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.74–2.54 (m, 2 H), 2.31 (t, *J* = 8.5 Hz, 2 H), 2.04–1.82 (m, 2 H), 1.80–1.72 (m, 3 H).

Spectroscopic data are in agreement with the previously reported characterization.[15]

1-(2-Methylcyclobut-1-en-1-yl)-3-nitrobenzene (3a)

Using 1-iodo-2-methylcyclobut-1-ene and 1-iodo-3-nitrobenzene according to general procedure A provided **3a** as a yellow solid.

Yield: 49 mg, 0.26 mmol (96%); R_f = 0.32 (hexane/EtOAc, 98:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (t, *J* = 2.0 Hz, 1 H), 8.01 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1 H), 7.60 (dt, *J* = 7.7, 1.4 Hz, 1 H), 7.47 (t, *J* = 7.9 Hz, 1 H), 2.70–2.63 (m, 2 H), 2.52–2.42 (m, 2 H), 2.08–1.99 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.6, 143.0, 137.7, 135.7, 131.2, 129.3, 121.0, 120.0, 30.2, 26.3, 16.5.

MS (EI): *m*/*z* (%) = 189 (11) $[M]^+$, 172 (43), 141 (67), 128 (100), 115 (58).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{11}NO_2$: 189.0790; found: 189.0783.

Compound **3a** was also synthesized according to general procedure B.

Yield: 41 mg, 0.22 mmol (90%); mp 115–117 °C.

1-[4-(2-Methylcyclobut-1-en-1-yl)phenyl]ethan-1-one (3b)

Using 1-iodo-2-methylcyclobut-1-ene and 1-(4-iodophenyl)ethan-1-one according to general procedure A provided **3b** as a colorless oil.

Yield: 30 mg, 0.16 mmol (81%); R_f = 0.5 (hexane/EtOAc, 95:5; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 2.66–2.63 (m, 2 H), 2.58 (s, 3 H), 2.49–2.44 (m, 2 H), 2.05–2.02 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.7, 143.4, 140.7, 137.1, 134.9, 128.7, 125.4, 30.3, 26.7, 26.2, 16.7.

MS (EI): *m*/*z* (%) = 186 $[M]^+$ (30), 171 (20), 143 (80), 128 (100), 115 (40).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{14}O$: 186.1045; found: 186.1037.

1-[4-(2-Methylcyclobut-1-en-1-yl)phenyl]-3-morpholino-5,6-dihydropyridin-2(1*H*)-one (3c)

Using 1-iodo-2-methylcyclobut-1-ene and 1-(4-iodophenyl)-3-morpholino-5,6-dihydropyridin-2(1*H*)-one according to general procedure A provided **3c** as a colorless oil.

Yield: 40 mg, 0.12 mmol (62%); R_f = 0.2 (hexane/EtOAc, 6:4; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 4 H), 5.63 (t, *J* = 4.7 Hz, 1 H), 3.84–3.80 (m, 4 H), 3.78 (t, *J* = 6.7 Hz, 2 H), 2.93–2.86 (m, 4 H), 2.64–2.55 (m, 2 H), 2.48 (td, *J* = 6.7, 4.6 Hz, 2 H), 2.44–2.39 (m, 2 H), 2.00–1.94 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.3, 143.8, 140.8, 139.0, 137.0, 134.1, 125.6, 124.7, 114.2, 66.7, 50.5, 48.6, 29.8, 26.1, 23.4, 16.2.

1-(2-Methylcyclobut-1-en-1-yl)isoquinoline (3d)

Using 1-iodo-2-methylcyclobut-1-ene and 1-iodoisoquinoline according to general procedure A provided **3d** as a colorless oil.

Yield: 25 mg, 0.13 mmol (64%); R_f = 0.3 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 5.6 Hz, 1 H), 8.30 (d, *J* = 8.5 Hz, 1 H), 7.80 (d, *J* = 7.0 Hz, 1 H), 7.67–7.63 (m, 1 H), 7.56 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H), 7.50 (d, *J* = 5.6 Hz, 1 H), 3.11–3.06 (m, 2 H), 2.63–2.57 (m, 2 H), 2.02 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.3, 147.5, 142.5, 137.8, 136.8, 129.9, 127.1, 126.9, 126.7, 126.6, 119.2, 31.1, 29.9, 17.2.

MS (EI): *m*/*z* (%) = 194 [M – H]$^+$ (100), 180 (100), 167 (30), 154 (20).

HRMS (EI): *m*/*z* [M – H]$^+$ calcd for $C_{14}H_{12}N$: 194.0970; found: 194.0962.

2-(2-Methylcyclobut-1-en-1-yl)-5-nitropyridine (3e)

Using 1-iodo-2-methylcyclobut-1-ene and 2-iodo-5-nitropyridine according to general procedure A provided **3e** as a yellow oil.

Yield: 27 mg, 0.14 mmol (72%); R_f = 0.5 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.37 (d, *J* = 2.6 Hz, 1 H), 8.39 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.26 (d, *J* = 8.7 Hz, 1 H), 2.81–2.70 (m, 2 H), 2.59–2.49 (m, 2 H), 2.21 (t, *J* = 1.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 153.3, 145.5, 141.5, 136.8, 131.4, 119.6, 31.1, 26.1, 17.2.

MS (EI): *m*/*z* (%) = 190 [M]$^+$ (40), 175 (100), 143 (60), 129 (70).

HRMS (EI): *m*/*z* [M – H]$^+$ calcd for $C_{10}H_9N_2O_2$: 189.0664; found: 189.0656.

3-Fluoro-6-methoxy-4-(2-methylcyclobut-1-en-1-yl)quinoline (3f)

Using 1-iodo-2-methylcyclobut-1-ene and 3-fluoro-4-iodo-6-methoxyquinoline according to general procedure A provided **3f** as a colorless oil.

Yield: 25 mg, 0.10 mmol (51%); R_f = 0.3 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 1.7 Hz, 1 H), 7.97 (d, *J* = 9.1 Hz, 1 H), 7.30 (dd, *J* = 9.1, 2.8 Hz, 1 H), 7.26 (d, *J* = 4.1 Hz, 1 H), 3.92 (s, 3 H), 2.98–2.89 (m, 2 H), 2.72–2.58 (m, 2 H), 1.84 (d, *J* = 1.3 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 154.0 (d, *J* = 254.5 Hz), 148.4, 141.8 (d, *J* = 2.3 Hz), 138.6 (d, *J* = 29.3 Hz), 131.4, 130.2, 128.3 (d, *J* = 3.4 Hz), 124.8 (d, *J* = 12.7 Hz), 120.8 (d, *J* = 2.7 Hz), 103.9 (d, *J* = 5.4 Hz), 55.6, 32.0, 30.5 (d, *J* = 2.8 Hz), 17.4 (d, *J* = 2.1 Hz).

MS (EI): *m*/*z* (%) = 243 [M]$^+$ (90), 228 (70), 212 (100), 200 (30).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{14}FNO$: 243.1059; found: 243.1053.

Ethyl 2-[2-(2-Methylallyl)cyclobut-1-en-1-yl]benzoate (3g)

Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and ethyl 2-iodobenzoate according to general procedure A provided **3g** as a yellowish oil.

Yield: 42 mg, 0.16 mmol (82%*), *with minor impurities due to the starting material (aryl-I); R_f = 0.6 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.6 Hz, 1 H), 7.39 (t, *J* = 8.1 Hz, 1 H), 7.31–7.19 (m, 2 H), 4.74 (d, *J* = 6.8 Hz, 2 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 2.85 (s, 2 H), 2.68–2.61 (m, 2 H), 2.46–2.36 (m, 2 H), 1.68 (s, 3 H), 1.34 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.6, 142.9, 141.9, 140.2, 136.1, 131.1, 130.3, 129.6, 129.4, 126.7, 111.6, 61.3, 38.2, 29.2, 28.7, 23.0, 14.4.

MS (EI): *m*/*z* (%) = 256 [M]$^+$ (10), 241 (5), 227 (5), 209 (30), 195 (100), 181 (20).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{20}O_2$: 256.1463; found: 256.1458.

4-[2-(2-Methylallyl)cyclobut-1-en-1-yl]phenol (3h)

Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and 4-iodophenol according to general procedure A provided **3h** as a colorless oil.

Yield: 32 mg, 0.16 mmol (80%); R_f = 0.3 (hexane/EtOAc, 8:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.21 (m, 2 H), 6.83–6.76 (m, 2 H), 4.81 (d, *J* = 5.6 Hz, 3 H), 3.04 (s, 2 H), 2.64–2.59 (m, 2 H), 2.47–2.40 (m, 2 H), 1.78 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.4, 142.9, 138.6, 137.7, 129.4, 127.2, 115.3, 111.5, 39.0, 28.3, 26.2, 23.1.

MS (EI): *m*/*z* (%) = 200 [M]$^+$ (30), 185 (80), 171 (20), 158 (100), 144 (30).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{16}O$: 200.1201; found: 200.1195.

3-[2-(2-Methylallyl)cyclobut-1-en-1-yl]benzoic Acid (3i)

Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and 3-iodobenzoic acid according to general procedure A provided **3i** as a colorless oil.

Yield: 44 mg, 0.19 mmol (96%); R_f = 0.3 (hexane/EtOAc, 95:5; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.95 (d, *J* = 7.7 Hz, 1 H), 7.57 (d, *J* = 7.7 Hz, 1 H), 7.43 (t, *J* = 7.7 Hz, 1 H), 4.84 (s, 2 H), 3.13 (s, 2 H), 2.73–2.67 (m, 2 H), 2.53–2.46 (m, 2 H), 1.80 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3, 142.4, 142.2, 138.2, 136.4, 129.5, 128.7, 128.3, 127.4, 111.9, 39.1, 28.6, 26.2, 23.1.

MS (EI): *m*/*z* (%) = 228 [M]$^+$ (5), 212 (10), 183 (100), 167 (20), 155 (50).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{16}O_2$: 228.1150; found: 228.1143.

6-(2-Methylcyclobut-1-en-1-yl)picolinonitrile (3j)

Using 1-iodo-2-methylcyclobut-1-ene and 6-bromopicolinonitrile according to general procedure A provided **3j** as a colorless oil.

Yield: 25 mg, 0.15 mmol (74%); R_f = 0.5 (hexane/EtOAc, 8:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (t, *J* = 7.8 Hz, 1 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 8.1 Hz, 1 H), 2.73–2.63 (m, 2 H), 2.53–2.44 (m, 2 H), 2.16 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.9, 149.6, 137.0, 136.2, 133.6, 125.4, 123.0, 117.8, 30.6, 26.0, 16.8.

MS (EI): *m*/*z* (%) = 170 [M]$^+$ (20), 155 (100), 142 (10), 129 (10), 115 (10).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{10}N_2$: 170.0844; found: 170.0843.

6-(2-Methylcyclobut-1-en-1-yl)imidazo[1,2-*a*]pyrazine (3k)

Using 1-iodo-2-methylcyclobut-1-ene and 6-bromoimidazo[1,2-*a*]pyrazine according to general procedure A provided **3k** as a yellowish oil.

Yield: 35 mg, 0.19 mmol (94%); R_f = 0.1 (hexane/EtOAc, 5:5; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (s, 1 H), 7.85 (s, 1 H), 7.75 (s, 1 H), 7.63 (s, 1 H), 2.72–2.61 (m, 2 H), 2.55–2.43 (m, 2 H), 2.15 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.5, 143.3, 139.8, 137.5, 135.7, 133.7, 114.1, 113.7, 30.5, 25.7, 16.5.

MS (EI): *m*/*z* (%) = 185 [M]$^+$ (70), 184 (100), 170 (100), 157 (5), 144 (5).

HRMS (EI): m/z [M – H]$^+$ calcd for $C_{11}H_{10}N_3$: 184.0875; found: 184.0869.

5-(2-Methylcyclobut-1-en-1-yl)-3-nitropyridin-2-amine (3l)

Using 1-iodo-2-methylcyclobut-1-ene and 5-bromo-3-nitropyridin-2-amine according to general procedure A provided **3l** as a yellow oil.

Yield: 37 mg, 0.18 mmol (91%); R_f = 0.1 (hexane/EtOAc, 8:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, J = 2.2 Hz, 1 H), 8.25 (d, J = 2.1 Hz, 1 H), 6.69 (s, 2 H), 2.66–2.56 (m, 2 H), 2.50–2.40 (m, 2 H), 1.99 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.3, 151.7, 140.2, 132.8, 130.5, 128.0, 123.7, 30.4, 26.1, 16.5.

MS (EI): m/z (%) = 205 [M]$^+$ (100), 190 (90), 176 (40), 157 (60), 144 (60).

HRMS (EI): m/z [M]$^+$ calcd for $C_{10}H_{11}N_3O_2$: 205.0851; found: 205.0840.

Pentafluoro{3-[2-(2-methylallyl)cyclobut-1-en-1-yl]phenyl}-λ^6-sulfane (3m)

Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and (3-bromophenyl)pentafluoro-λ^6-sulfane according to general procedure A provided **3m** as a colorless oil.

Yield: 59 mg, 0.19 mmol (95%); R_f = 0.6 (hexane; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (s, 1 H), 7.59–7.53 (m, 1 H), 7.45–7.36 (m, 2 H), 4.83 (d, J = 9.7 Hz, 2 H), 3.08 (s, 2 H), 2.73–2.63 (m, 2 H), 2.52–2.44 (m, 2 H), 1.78 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.3, 143.4, 142.0, 137.7, 136.8, 128.8, 128.5, 123.9, 123.3, 112.1, 39.1, 28.9, 26.2, 23.0.

MS (EI): m/z (%) = 310 [M]$^+$ (60), 295 (60), 282 (10), 269 (5), 253 (5).

HRMS (EI): m/z [M]$^+$ calcd for $C_{14}H_{15}F_5S$: 310.0815; found: 310.0807.

3-[2-(2-Methylallyl)cyclobut-1-en-1-yl]pyridin-2-ol (3n)

Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and 3-bromopyridin-2-ol according to general procedure A provided **3n** as a colorless oil.

Yield: 30 mg, 0.15 mmol (74%); R_f = 0.1 (hexane/EtOAc, 7:3; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (dd, J = 7.0, 2.0 Hz, 1 H), 7.21 (dd, J = 6.5, 2.0 Hz, 1 H), 6.25 (t, J = 6.7 Hz, 1 H), 4.79–4.74 (m, 2 H), 3.29 (s, 2 H), 2.68–2.63 (m, 2 H), 2.45–2.39 (m, 2 H), 1.75 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.8, 144.5, 143.9, 137.0, 135.0, 132.4, 127.7, 111.2, 106.8, 40.3, 28.5, 26.9, 23.1.

MS (EI): m/z (%) = 201 [M]$^+$ (100), 186 (50), 167 (30), 134 (30).

HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_{15}NO$: 201.1154; found: 201.1149.

2-(2-Methylcyclobut-1-en-1-yl)-3-nitropyridine (3o)

Using 1-iodo-2-methylcyclobut-1-ene and 2-chloro-3-nitropyridine according to general procedure A provided **3o** as a yellowish oil.

Yield: 25 mg, 0.13 mmol (66%).

Compound **3o** was also synthesized according to general procedure B.

Yield: 32 mg, 0.17 mmol (72%); R_f = 0.6 (hexane/EtOAc, 8:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (dd, J = 4.7, 1.6 Hz, 1 H), 7.92 (dd, J = 8.1, 1.6 Hz, 1 H), 7.21 (dd, J = 8.2, 4.7 Hz, 1 H), 2.72–2.61 (m, 2 H), 2.55–2.46 (m, 2 H), 2.10 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.6, 151.9, 147.2, 144.4, 133.6, 131.4, 120.8, 31.6, 27.5, 17.2.

MS (EI): m/z (%) = 172 (5), 160 (950), 145 (30), 130 (90), 117 (100).

HRMS (EI): m/z [M – H]$^+$ calcd for $C_{10}H_9N_2O_2$: 189.0664; found: 189.0657.

Ethyl 2-(2-Methylcyclobut-1-en-1-yl)nicotinate (3p)

Using 1-iodo-2-methylcyclobut-1-ene and ethyl 2-chloronicotinate according to general procedure A provided **3p** as a yellowish oil.

Yield: 10 mg, 0.05 mmol (23%); R_f = 0.6 (hexane/EtOAc, 8:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (dd, J = 4.8, 1.8 Hz, 1 H), 7.87 (dd, J = 7.8, 1.8 Hz, 1 H), 7.13 (dd, J = 7.8, 4.8 Hz, 1 H), 4.36 (q, J = 7.2 Hz, 2 H), 2.76–2.71 (m, 2 H), 2.48–2.42 (m, 2 H), 2.01 (s, 3 H), 1.38 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.0, 152.9, 151.1, 148.6, 137.0, 136.9, 126.0, 120.4, 61.8, 30.8, 28.3, 16.7, 14.4.

MS (EI): m/z (%) = 217 [M]$^+$ (10), 187 (100), 174 (15).

HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_{15}NO_2$: 217.1103; found: 217.1099.

1-[2-(2-Methylallyl)cyclobut-1-en-1-yl]-4-nitrobenzene (3q)

Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and 4-nitrophenyl trifluoromethanesulfonate according to general procedure A provided **3q** as a colorless oil.

Yield: 44 mg, 0.19 mmol (96%); R_f = 0.7 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, J = 8.8 Hz, 2 H), 7.42 (d, J = 8.8 Hz, 2 H), 4.83 (d, J = 16.7 Hz, 2 H), 3.12 (s, 2 H), 2.84–2.61 (m, 2 H), 2.58–2.41 (m, 2 H), 1.79 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.9, 146.0, 141.9, 141.6, 137.8, 126.1, 124.0, 112.2, 39.3, 29.1, 26.1, 23.1.

MS (EI): m/z (%) = 229 [M]$^+$ (2), 212 (90), 182 (100), 168 (50), 153 (50).

HRMS (EI): m/z [M]$^+$ calcd for $C_{14}H_{15}NO_2$: 229.1103; found: 229.1102.

1-(2-Methylcyclobut-1-en-1-yl)-4-nitrobenzene (3r)

Using 1-iodo-2-methylcyclobut-1-ene and 4-nitrophenyl trifluoromethanesulfonate according to general procedure B provided **3r** as a yellow oil.

Yield: 32 mg, 0.17 mmol (70%); R_f = 0.29 (hexane/EtOAc, 98:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.09 (m, 2 H), 7.46–7.28 (m, 2 H), 2.76–2.57 (m, 2 H), 2.57–2.40 (m, 2 H), 2.15–1.96 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.9, 145.8, 142.3, 136.3, 125.7, 124.0, 30.6, 26.2, 16.7.

MS (EI): m/z (%) = 189 [M]$^+$ (23), 172 (34), 143 (63), 128 (100), 115 (50), 102 (14).

HRMS (EI): m/z [M]$^+$ calcd for $C_{11}H_{11}NO_2$: 189.0790; found: 189.0783.

1-(2-Methylcyclopent-1-en-1-yl)-3-nitrobenzene (4a)

Using 1-iodo-2-methylcyclopent-1-ene and 1-iodo-3-nitrobenzene according to general procedure A provided **4a** as a light-yellow oil.

Yield: 39 mg, 0.19 mmol (96%); R_f = 0.2 (hexane/EtOAc, 99:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (t, *J* = 1.9 Hz, 1 H), 8.04 (dd, *J* = 9.1, 2.1 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.48 (t, *J* = 7.9 Hz, 1 H), 2.80–2.72 (m, 2 H), 2.54 (t, *J* = 7.9 Hz, 2 H), 1.94 (quin, *J* = 7.5 Hz, 2 H), 1.88 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.3, 140.5, 138.7, 133.7, 132.4, 129.0, 122.4, 120.9, 40.4, 37.2, 21.9, 15.6.

MS (EI): *m*/*z* (%) = 203 $[M]^+$ (80), 188 (100), 156 (20), 141 (78), 128 (58), 115 (81).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{13}NO_2$: 203.0946; found: 203.0939.

Compound **4a** was also synthesized according to general procedure B.

Yield: 39 mg, 0.19 mmol (96%).

1-Methyl-4-(2-methylcyclopent-1-en-1-yl)benzene (4b)

Using 1-iodo-2-methylcyclopent-1-ene and 1-iodo-4-methylbenzene according to general procedure A provided **4b** as a colorless oil.

Yield: 24 mg, 0.14 mmol (70%); R_f = 0.7 (hexane; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.29 (m, 4 H), 2.95–2.86 (m, 2 H), 2.73–2.60 (m, 2 H), 2.52 (s, 3 H), 2.07 (t, *J* = 7.5 Hz, 2 H), 2.05–1.99 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.9, 135.7, 134.7, 134.6, 128.8, 127.6, 40.2, 37.4, 22.0, 21.3, 15.6.

MS (EI): *m*/*z* (%) = 172 $[M]^+$ (70), 157 (100), 142 (40), 129 (40), 115 (30).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{16}$: 172.1252; found: 172.1245.

1-[4-(2-Methylcyclopent-1-en-1-yl)phenyl]ethan-1-one (4c)

Using 1-iodo-2-methylcyclopent-1-ene and 1-(4-iodophenyl)ethan-1-one according to general procedure A provided **4c** as a colorless oil.

Yield: 35 mg, 0.18 mmol (88%); R_f = 0.3 (hexane/EtOAc, 95:5; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 2.80–2.71 (m, 2 H), 2.60 (s, 3 H), 2.53 (t, *J* = 7.1 Hz, 2 H), 1.97–1.90 (m, 2 H), 1.88 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.9, 143.9, 138.5, 134.8, 134.2, 128.3, 127.7, 40.5, 37.1, 26.7, 22.0, 15.9.

MS (EI): *m*/*z* (%) = 200 $[M]^+$ (57), 185 (100), 157 (22), 142 (25), 128 (32).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{16}O$: 200.1201; found: 200.1195.

1-[4-(2-Methylcyclopent-1-en-1-yl)phenyl]-3-morpholino-5,6-dihydropyridin-2(1*H*)-one (4d)

Using 1-iodo-2-methylcyclopent-1-ene and 1-(4-iodophenyl)-3-morpholino-5,6-dihydropyridin-2-(1*H*)-one according to general procedure A provided **4d** as a light yellow sticky oil.

Yield: 35 mg, 0.10 mmol (52%); R_f = 0.3 (hexane/EtOAc, 1:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 4 H), 5.63 (t, *J* = 4.7 Hz, 1 H), 3.84–3.76 (m, 6 H), 2.91 (t, *J* = 4.4 Hz, 4 H), 2.75–2.66 (m, 2 H), 2.53–2.43 (m, 4 H), 1.95–1.84 (m, 2 H), 1.84 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.5, 143.9, 140.6, 136.6, 135.6, 134.3, 128.0, 124.5, 114.2, 66.9, 50.6, 48.7, 40.2, 37.3, 23.5, 21.9, 15.6.

MS (EI): *m*/*z* (%) = 338 $[M]^+$ (14), 320 (100), 307 (20), 281 (35), 253 (34), 239 (31), 207 (55).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{26}N_2O_2$: 338.1994; found: 338.1988.

3,4-Dimethoxy-5-(2-methylcyclopent-1-en-1-yl)benzaldehyde (4e)

Using 1-iodo-2-methylcyclopent-1-ene and 3-iodo-4,5-dimethoxybenzaldehyde according to general procedure A provided **4e** as a colorless oil.

Yield: 34 mg, 0.14 mmol (69%); R_f = 0.35 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.87 (s, 1 H), 7.34 (d, *J* = 1.9 Hz, 1 H), 7.24 (d, *J* = 1.9 Hz, 1 H), 3.92 (s, 3 H), 3.79 (s, 3 H), 2.76–2.61 (m, 2 H), 2.47 (t, *J* = 7.0 Hz, 2 H), 1.95 (quin, *J* = 7.5 Hz, 2 H), 1.65 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.6, 153.6, 152.7, 138.0, 133.6, 132.10, 132.08, 127.6, 108.7, 60.8, 56.1, 38.9, 37.8, 22.7, 15.4.

MS (EI): *m*/*z* (%) = 246 $[M]^+$ (100), 231 (27), 217 (18), 203 (18), 189 (24), 161 (26), 115 (35).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{18}O_3$: 246.1256; found: 246.1250.

3-Fluoro-6-methoxy-4-(2-methylcyclopent-1-en-1-yl)quinoline (4f)

Using 1-iodo-2-methylcyclopent-1-ene and 3-fluoro-4-iodo-6-methoxyquinoline according to general procedure A provided **4f** as colorless oil.

Yield: 38 mg, 0.15 mmol (74%); R_f = 0.3 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 9.2 Hz, 1 H), 8.00 (d, *J* = 9.2 Hz, 1 H), 7.31 (dd, *J* = 9.2, 2.8 Hz, 1 H), 6.99 (d, *J* = 2.8 Hz, 1 H), 3.89 (s, 3 H), 2.86–2.74 (m, 1 H), 2.71–2.66 (m, 1 H), 2.62 (t, *J* = 7.3 Hz, 2 H), 2.20–1.99 (m, 2 H), 1.56 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.9, 154.3 (d, *J* = 252.4 Hz), 142.0, 141.9, 138.9 (d, *J* = 29.3 Hz), 131.7, 129.4 (d, *J* = 3.6 Hz), 128.8 (d, *J* = 14.4 Hz), 126.7, 120.8 (d, *J* = 3.2 Hz), 104.1 (d, *J* = 5.9 Hz), 55.9, 39.2, 37.8 (d, *J* = 2.1 Hz), 23.5, 15.9.

MS (EI): *m*/*z* (%) = 257 $[M]^+$ (100), 242 (25), 226 (20), 214 (40), 198 (22), 184 (36), 172 (20).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{16}FNO$: 257.1216; found: 257.1210.

5-(2-Methylcyclopent-1-en-1-yl)furan-2-carbaldehyde (4g)

Using 1-iodo-2-methylcyclopent-1-ene and 5-iodofuran-2-carbaldehyde according to general procedure A provided **4g** as a crystalline solid.

Yield: 31 mg, 0.18 mmol (88%); mp 93–97 °C; R_f = 0.2 (hexane/EtOAc, 98:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.56 (s, 1 H), 7.23 (d, *J* = 3.7 Hz, 1 H), 6.34 (d, *J* = 3.7 Hz, 1 H), 2.80–2.65 (m, 2 H), 2.60–2.48 (m, 2 H), 2.12 (quin, *J* = 1.6 Hz, 3 H), 1.93 (quin, *J* = 7.6 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.0, 159.1, 151.2, 144.1, 124.1, 123.4, 109.4, 40.9, 34.4, 22.1, 16.4.

MS (EI): *m*/*z* (%) = 176 $[M]^+$ (100), 161 (50), 147 (78), 129 (21), 119 (46), 105 (22).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{12}O_2$: 176.0837; found: 176.0831.

6-(2-Methylcyclopent-1-en-1-yl)picolinonitrile (4h)

Using 1-iodo-2-methylcyclopent-1-ene and 6-bromopicolinonitrile according to general procedure A provided **4h** as a colorless oil.

Yield: 28 mg, 0.15 mmol (76%); R_f = 0.3 (hexane/EtOAc, 95:5; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 = (t, *J* = 7.9 Hz, 1 H), 7.46 (d, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 8.1 Hz, 1 H), 2.85–2.76 (m, 2 H), 2.58 (t, *J* = 7.4 Hz, 2 H), 2.10 (s, 3 H), 1.92 (quin, *J* = 7.6 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.8, 145.2, 136.9, 133.1, 132.4, 125.2, 125.1, 117.8, 41.3, 35.8, 21.7, 16.4.

MS (EI): *m*/*z* (%) = 184 $[M]^+$ (70), 169 (100), 155 (46), 142 (36), 129 (13), 118 (12), 103 (17).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{12}N_2$: 184.1000; found: 184.0994.

(*E*)-1-[2-(2-Methylcyclopent-1-en-1-yl)vinyl]-4-(trifluoromethyl)benzene (4i)

Using 1-iodo-2-methylcyclopent-1-ene and (*Z*)-1-(2-iodovinyl)-4-(trifluoromethyl)benzene according to general procedure A provided **4i** (*E*/*Z* = 88:12 by crude GC, isolated *E*/*Z* = 56:44) as a colorless oil.

Yield: 48 mg, 0.19 mmol (95%); R_f = 0.56/0,68 (hexane; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.46 (m, 3 H), 7.37–7.30 (m, 1 H), 6.46–6.33 (m, 2 H), 2.36–2.28 (m, 2 H), 2.22–2.11 (m, 2 H), 1.75 (quin, *J* = 7.4 Hz, 2 H), 1.67 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.6 (d, *J* = 1.6 Hz), 142.3, 133.8, 129.2, 128.7 (d, *J* = 5.0 Hz), 128.0, 125.9, 124.7 (q, *J* = 3.8 Hz), 123.1 (d, *J* = 1.5 Hz), 38.6, 35.8, 22.8, 15.1.

MS (EI): *m*/*z* (%) = 252 $[M]^+$ (91), 237 (100), 209 (75), 183 (53), 159 (35), 141 (34), 115 (22).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{15}F_3$: 252.1126; found: 252.1119.

2-(2-Methylcyclopent-1-en-1-yl)aniline (4j)

Using 1-iodo-2-methylcyclopent-1-ene and 2-iodoaniline according to general procedure B provided **4j** as a light yellow oil.

Yield: 32 mg, 0.19 mmol (93%); R_f = 0.2 (hexane/EtOAc, 95:5; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (td, *J* = 7.8, 1.5 Hz, 1 H), 6.98 (dd, *J* = 7.5, 1.4 Hz, 1 H), 6.79–6.69 (m, 2 H), 3.66 (s, 2 H), 2.68–2.57 (m, 2 H), 2.48 (t, *J* = 7.3 Hz, 2 H), 1.96 (quin, *J* = 7.5 Hz, 2 H), 1.61 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.6, 136.9, 133.4, 129.3, 127.7, 124.9, 118.2, 115.2, 38.8, 37.9, 22.6, 15.2.

MS (EI): *m*/*z* (%) = 173 $[M]^+$ (67), 158 (22), 144 (100), 130 (53), 117 (22), 77 (20).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{15}N$: 173.1204; found: 173.1198.

3-(2-Methylcyclopent-1-en-1yl)benzoic Acid (4k)

Using 1-iodo-2-methylcyclopent-1-ene and 3-iodobenzoic acid according to general procedure B provided **4k** as a light brown solid.

Yield: 38 mg, 0.19 mmol (94%); mp 116–120 °C; R_f = 0.4 (hexane/1% MeOH; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.39 (s, 1 H), 8.01 (s, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.47 (d, *J* = 7.4 Hz, 1 H), 7.36 (t, *J* = 7.3 Hz, 1 H), 2.72 (s, 2 H), 2.49 (s, 2 H), 1.90 (quin, *J* = 7.2 Hz, 2 H), 1.83 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8, 139.1, 136.7, 134.1, 132.7, 129.9, 129.4, 128.2, 127.9, 40.3, 37.3, 22.0, 15.6.

MS (EI): *m*/*z* (%) = 202 $[M]^+$ (100), 187 (81), 157 (52), 128 (77), 115 (67), 77 (28).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{14}O_2$: 202.0994; found: 202.0989.

1-(2-Methylcyclopent-1-en-1-yl)isoquinoline (4l)

Using 1-iodo-2-methylcyclopent-1-ene and 1-iodoisoquinoline according to general procedure B provided **4l** as a light yellow oil.

Yield: 34 mg, 0.16 mmol (82%); R_f = 0.2 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 5.7 Hz, 1 H), 7.97 (d, *J* = 8.4 Hz, 1 H), 7.82 (d, *J* = 8.2 Hz, 1 H), 7.70–7.62 (m, 1 H), 7.57–7.51 (m, 2 H), 2.97–2.82 (m, 2 H), 2.62 (t, *J* = 7.1 Hz, 2 H), 2.09 (quin, *J* = 7.5 Hz, 2 H), 1.55 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.2, 142.5, 139.9, 136.5, 134.5, 130.1, 127.5, 127.1, 127.0, 126.9, 119.3, 39.4, 38.6, 22.9, 15.6.

MS (EI): *m*/*z* (%) = 208 $[M - H]^+$ (100), 191 (11), 180 (40), 167 (15).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{15}H_{14}N$: 208.1126; found: 208.1120.

5-(2-Methylcyclopent-1-en-1-yl)-3-nitropyridin-2-amine (4m)

Using 1-iodo-2-methylcyclopent-1-ene and 5-bromo-3-nitropyridin-2-amine according to general procedure B provided **4m** as a yellow solid.

Yield: 30 mg, 0.14 mmol (69%); mp 177–180 °C; R_f = 0.2 (hexane/EtOAc, 9:1; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 2.1 Hz, 1 H), 8.31 (d, *J* = 2.0 Hz, 1 H), 6.70 (s, 2 H), 2.76–2.64 (m, 2 H), 2.51 (t, *J* = 7.1 Hz, 2 H), 1.93 (quin, *J* = 7.5 Hz, 2 H), 1.86 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.1, 151.7, 137.6, 133.0, 129.7, 127.9, 125.4, 40.2, 36.9, 21.8, 15.7.

MS (EI): *m*/*z* (%) = 219 $[M]^+$ (100), 204 (67), 173 (22), 158 (30).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{13}N_3O_2$: 219.1008; found: 219.0992.

2-(2-Methylcyclopent-1-en-1-yl)-3-nitropyridine (4n)

Using 1-iodo-2-methylcyclopent-1-ene and 2-chloro-3-nitropyridine according to general procedure B provided **4n** as a yellow oil.

Yield: 26 mg, 0.17 mmol (84%); R_f = 0.3 (hexane/EtOAc, 8:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (dd, *J* = 4.7, 1.6 Hz, 1 H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.34 (dd, *J* = 8.2, 4.7 Hz, 1 H), 2.84–2.70 (m, 2 H), 2.50 (t, *J* = 8.0 Hz, 2 H), 2.01 (quin, *J* = 7.5 Hz, 2 H), 1.61 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.9, 152.6, 146.5, 142.1, 132.2, 132.0, 121.8, 39.4, 36.7, 22.8, 15.0.

MS (EI): *m*/*z* (%) = 187 (70), 174 (35), 156 (95), 147 (100), 130 (75), 117 (65), 103 (23).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{11}H_{11}N_2O_2$: 203.0821; found: 203.0814.

1-Methyl-2-(3-nitrophenyl)-1*H*-pyrrole (7a)

To a solution of 1-methyl-1*H*-pyrrole (90 µL, 1.014 mmol) and TMEDA (200 µL, 1.33 mmol, 1.33 equiv) in Et_2O (2 mL, 0.5 M) was slowly added a solution of *n*-BuLi (410 µL, 2.44 M in hexane, 1.00 equiv) at 0 °C. After stirring for 2 h at ambient temperature, B(O*i*-Pr)$_3$ (230 µL, 1.00 mmol, 1.00 equiv) and THF (2 mL) were added and the resulting mixture stirred for another 1 h at room temperature. Pd(dppf)Cl_2 dichloromethane adduct (16 mg, 4 mol%), 1-iodo-3-nitrobenzene (125 mg, 0.5 mmol, 0.5 equiv) and an aqueous solution of sodium hydroxide (1.5 mL, 1.5 equiv 1.00 M) were subsequently added and the mixture stirred overnight. The mixture was extracted with Et_2O (3 × 20 mL), washed with a saturated aqueous solution of sodium chloride

(20 mL), dried over magnesium sulfate, filtered, concentrated and purified via flash column chromatography. Compound **7a** was obtained as a yellow solid.

Yield: 73 mg, 0.36 mmol (72%); mp 73–75 °C; R_f = 0.09 (hexane/EtOAc, 98:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (t, *J* = 2.0 Hz, 1 H), 8.13 (ddd, *J* = 8.3, 2.3, 1.1 Hz, 1 H), 7.74 (ddd, *J* = 7.7, 1.7, 1.1 Hz, 1 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 6.79 (t, *J* = 2.3 Hz, 1 H), 6.36 (dd, *J* = 3.7, 1.8 Hz, 1 H), 6.24 (dd, *J* = 3.7, 2.7 Hz, 1 H), 3.73 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.5, 135.0, 134.1, 132.1, 129.5, 125.4, 122.8, 121.4, 110.4, 108.5, 35.4.

MS (EI): *m*/*z* (%) = 202 [M]$^+$ (100), 156 (45), 141 (11), 128 (35), 115 (25).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{10}N_2O_2$: 202.0742; found: 204.0736.

2-(3-Nitrophenyl)furan (7b)

To a solution of furan (75 µL, 1.014 mmol) in Et_2O (2 mL, 0.5 M) was slowly added a solution of *n*-BuLi (410 µL, 2.44 M in hexane, 1.00 equiv) at 0 °C. After stirring for 1 h at ambient temperature, B(O*i*-Pr)$_3$ (230 µL, 1.00 mmol, 1.00 equiv) and THF (2 mL) were added and the resulting mixture stirred for another 1 h at room temperature. Pd(dppf)Cl_2 dichloromethane adduct (16 mg, 4 mol%), 1-iodo-3-nitrobenzene (125 mg, 0.5 mmol, 0.5 equiv) and an aqueous solution of sodium hydroxide (1.5 mL, 1.5 equiv 1.00 M) were subsequently added and the mixture stirred overnight. The mixture was extracted with Et_2O (3 × 20 mL), washed with a saturated aqueous solution of sodium chloride (20 mL), dried over magnesium sulfate, filtered, concentrated and purified via flash column chromatography. Compound **7b** was obtained as a colorless oil.

Yield: 91 mg, 0.48 mmol (96%); R_f = 0.14 (hexane/EtOAc, 98:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (t, *J* = 1.9 Hz, 1 H), 8.06 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 7.57–7.42 (m, 2 H), 6.79 (d, *J* = 3.5 Hz, 1 H), 6.52 (dd, *J* = 3.4, 1.8 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.6, 148.8, 143.4, 132.4, 129.8, 129.3, 121.7, 118.5, 112.2, 107.4.

MS (EI): *m*/*z* (%) = 189 [M]$^+$ (100), 143 (23), 131 (10), 115 (100), 102 (7).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_7NO_3$: 189.0426; found: 189.0420.

4-(3,4-Dihydro-2*H*-pyran-6-yl)benzonitrile (7c)

To a solution of 3,4-dihydro-2*H*-pyran (90 µL, 1.014 mmol) and TMEDA (50 µL, 0.33 mmol, 0.33 equiv) in Et_2O (2 mL, 0.5 M) was slowly added a solution of *n*-BuLi (550 µL, 2.44 M in hexane, 1.34 equiv) at ambient temperature. After stirring for 30 min, B(O*i*-Pr)$_3$ (230 µL, 1.00 mmol, 1.00 equiv) and THF (2 mL) were added and the resulting mixture stirred for 1 h at room temperature. Pd(dppf)Cl_2 dichloromethane adduct (16 mg, 4 mol%), 4-bromobenzonitrile (91 mg, 0.5 mmol, 0.5 equiv) and an aqueous solution of sodium hydroxide (1.5 mL, 1.5 equiv 1.00 M) were subsequently added and the mixture stirred overnight. The mixture was extracted with Et_2O (3 × 20 mL), washed with a saturated aqueous solution of sodium chloride (20 mL), dried over magnesium sulfate, filtered, concentrated and purified via flash column chromatography. Compound **7c** was obtained as a yellow oil.

Yield: 40 mg, 0.22 mmol (43%); R_f = 0.17 (hexane/EtOAc, 98:2; UV, $KMnO_4$, PAA).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.59 (m, 2 H), 7.59–7.54 (m, 2 H), 5.50 (t, *J* = 4.2 Hz, 1 H), 4.17 (t, *J* = 5.3 Hz, 2 H), 2.24 (td, *J* = 6.4, 4.1 Hz, 2 H), 1.96–1.85 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.2, 140.5, 132.0, 124.7, 119.2, 110.9, 101.0, 66.7, 22.2, 21.0.

MS (EI): *m*/*z* (%) = 185 [M]$^+$ (56), 170 (9), 156 (6), 140 (7), 130 (100), 116 (5), 102 (44).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{11}NO$: 185.0841; found: 185.0834.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1592004.

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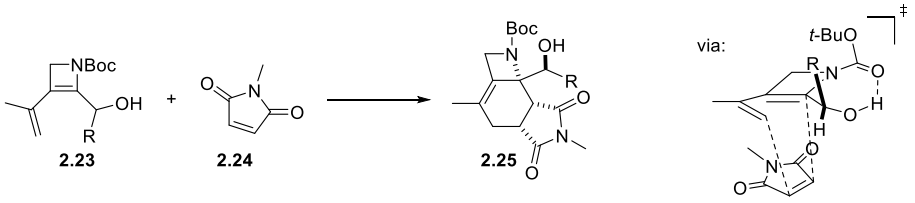
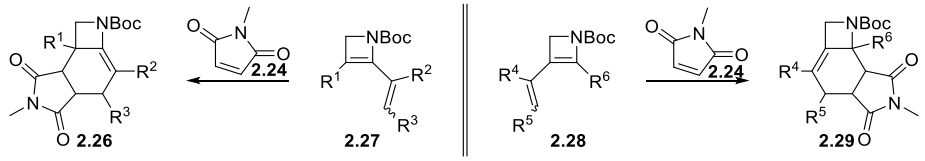
6 Outlook

The method for the synthesis of azetinecarbinols (see 5.1) was also expanded toward the synthesis of 3-vinyl azetinecarbinols **2.23**, which unfortunately were not stable to isolation, but could directly be engaged in Diels–Alder reactions to yield fused alkylidene azetidines of type **2.25**.[43] As shown through X-ray structures, the alcohol moiety shows hydrogen bonding to the *tert*-butyloxycarbonyl which we assume is crucial for the observed formation of a single diastereomer.



Scheme 19: Synthesis of alkylidene azetine carbinols and proposed transition state.

Vinylic azetines of types **2.27** and **2.28** could also be generated via Suzuki–Miyaura cross-coupling reactions and were equally prone to undergo efficient [4+2] reactions. The resulting fused 2- or 3-alkylidene azetidines (**2.26** and **2.29**, respectively) could be obtained in up to over 90% yield over five consecutive steps, requiring only one purification.



Scheme 20: Diels–Alder reaction to furnish 2- and 3-alkylidene azetines, respectively.

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CHAPTER III

Thiete dioxides

7 Introduction

Thietane dioxides, even though scarcely examined, have shown some interesting properties in biological assays. In the search for new inhibitors for HIV-1 protease, **3.01** has shown superior binding properties compared to homologs having the thietane dioxide moiety replaced by open chain sulfones, six-membered sulfones or even tetrahydrothiophenes.[44] Another interesting thietane dioxide is **3.02**, which demonstrated a significantly increased insecticidal action on *Spodootera littoralis* relative to the state of the art cyclobutene derivative.[45]

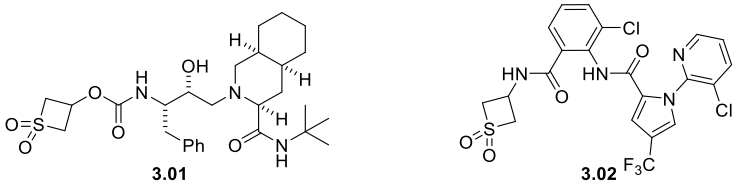

Figure 6: Biologically active thietane dioxides.

Thiete dioxides however, unlike the saturated thietane dioxides, have received no real attention in terms of biological application. This is also due to the fact that only very little reports on their modifications exist and incorporation in drugs is limited by the conditions of their syntheses.

7.1 Thiete Dioxide Syntheses

The most reported synthesis of thiete dioxides consists of a formal [2+2] cycloaddition of an alkene with an in-situ generated sulfene, mostly through deprotonation of methanesulfonylchloride giving first a thietane dioxide. The latter can undergo elimination through different methods, depending on its nature, yielding the desired thiete dioxides **3.05**. Mono amino thietans **3.03** can either be converted to thietes through Hoffmann elimination or oxidation to the corresponding amine oxide and elimination of a hydroxyl amine.[46] Aminals **3.04** can experience elimination under basic conditions to give 3-amino thietes.[47] The same behavior has been observed with ketals **3.06**, but only in a single case as the major reaction pathway.[48]

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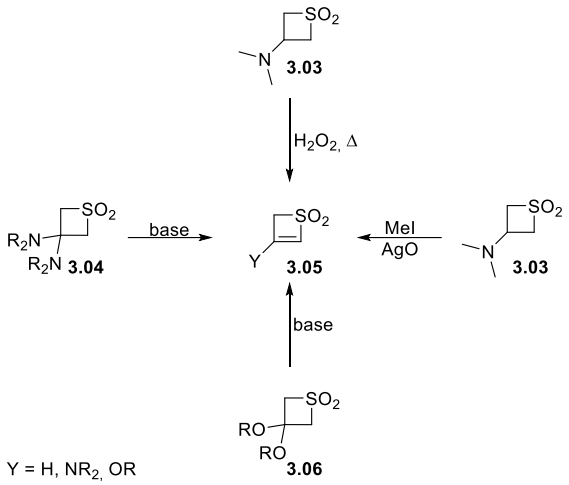
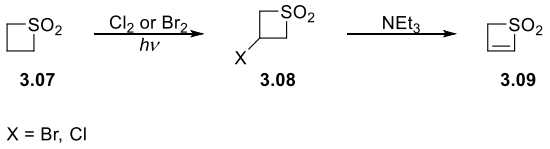


Scheme 21: Elimination reaction of thietane dioxides to thiete dioxides.

In 1968 several groups independently reported the direct synthesis of thiete dioxides through formal [2 + 2] cycloadditions of alkynes with sulfenes.[49]

The halogenation of thietan dioxides **3.07** with elemental chlorine or bromine and subsequent elimination depicts another, yet rather limiting way of synthesizing thiete dioxides **3.09**.[50]



Scheme 22: Halogenation of thietane dioxide and elimination to thiete dioxide.

The showcased methods for creating thietes all need to be applied in a synthesis' early stages, or side reactions with abundant functional groups like amines and halogens of complex molecules might occur. To overcome this issue, the aim was to develop methods for the possible late stage functionalization of thietes.

Our general approach to the desired thiete dioxide motif was an 1,2-addition of an organometallic reagent to commercially available 3-thietanone **3.10**, followed by double oxidation to the sulfone moiety and subsequent elimination.[51] This route requires only one purification step and can be conducted in less than a day's work.

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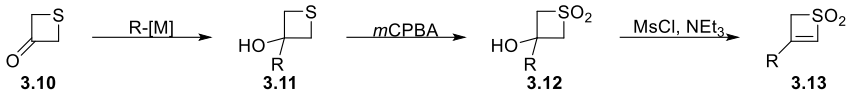

3.10 **3.11** **3.12** **3.13**

Scheme 23: Synthesis of 3-substituted thiete dioxides.

The so obtained thiete dioxides were then modified through various organometallic methods, C–H activation being one of them.

7.2 C–H Activation

C–H activation provides a method for the late-stage diversification of biologically active molecules and therefore is the ultimate tool to make a series of slightly modified analogs for activity screenings. As such it comes as no surprise that the field of C–H activation has made tremendous progress in the last few years. A recent example of how far chemists have come can be found in a report of Yu.[52] In typical examples on arenes, the transition metal catalyst inserts into the carbon-hydrogen bond *ortho* to the directing group (step *i-ii*, Scheme 24). Through introduction of a norbornene the activation site can be relayed, similar to what is observed in the Catellani reaction, thus effectively activating the *meta* position (step *iii-iv*).[53] After oxidative addition and reductive elimination (step *v-vi*) the *meta* position ends up arylated. Subsequent extrusion of the norbornene and protic termination (step *vii-viii*) gives the final product.

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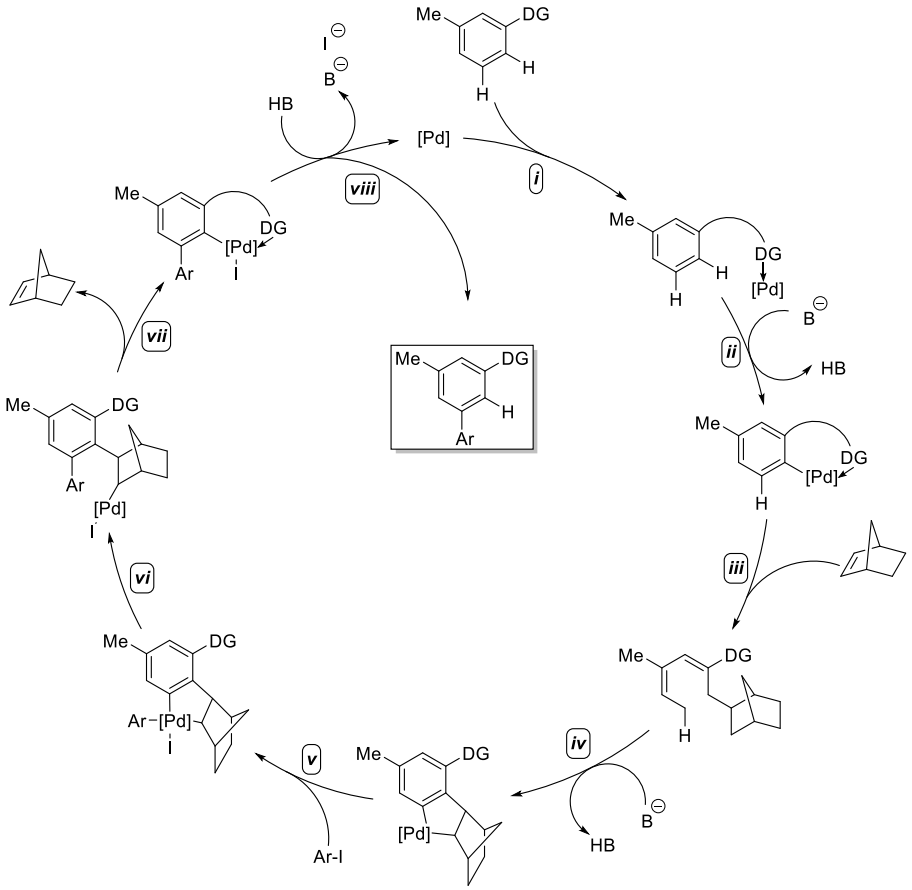
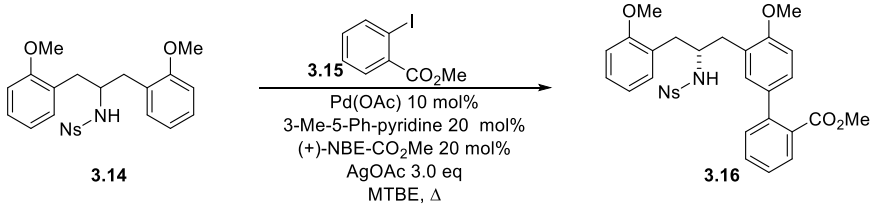
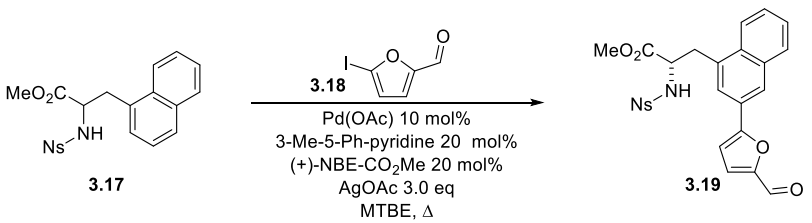


Scheme 24: Possible catalytic cycle for *meta* C–H arylation.

The group of Yu introduced a chiral norbornene derivative, which renders the reaction enantioselective (Scheme 25, up to 99:1 e.r.) and allows kinetic resolution (Scheme 26, up to 93:7 e.r.) of racemic starting materials, respectively.



Scheme 25: *meta* C–H arylation with desymmetrization.



Scheme 26: *meta* C–H arylation with kinetic resolution.

8 Results

8.1 Parallel Approaches for the Functionalization of Thietes: α-Metalation versus C–H Activation

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Parallel Approaches for the Functionalization of Thietes: α-Metalation versus C−H Activation

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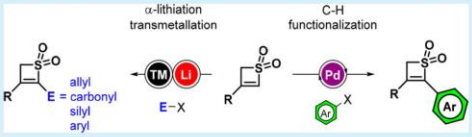
Supporting Information

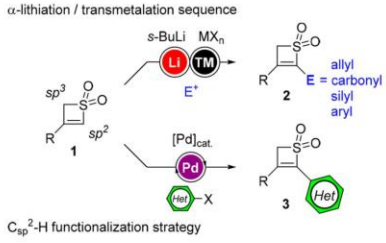
ABSTRACT: For the first time, an approach to 3,4-disubstituted thietes was developed through two complementary paths. While the first one relies on α-metalation, the second is based on direct C−H functionalization. A new library of sophisticated sulfur-containing four-membered rings is described, paving the way to new bioactive analogues and small heterocycle incorporation.



Conceptually new approaches that enable implementation of functionalities in bioactive targets have emerged as essential tools in drug discovery processes. Simplicity, versatility, selectivity, and functional group tolerance have to meet for the method to become a privileged path in organic and medicinal chemistry. Most recent examples reported by the groups of Carreira and Baran demonstrate the importance of small, strained bioisosteres, such as oxetanes,[1] azetidines,[2] or propellanes,[3] in the modulation of bioactivities. In this context, we have recently assembled strategies to broadly and selectively access cyclobutenes[4] and azetines,[5] constituting a large library of building blocks. These allowed us to open unprecedented routes toward the stereocontrolled formation of alkylidenecyclobutanes,[6] alkylideneazetidines,[7] and fused systems thereof.[8] S-containing heterocycles have vastly demonstrated their importance in fundamental and applied chemistry.[9] However, while most studied thiophene derivatives have been employed as base units in conducting or light-emitting materials[10] but also intensively in modern drug design,[11] smaller nonaromatic patterns such as thietes, have been scarcely investigated. Only a few reports describe their selective formation and in a restrained scope, limiting their potential applications. We believe that straightforward and general accesses to unsaturated S-containing four-membered heterocycles will ultimately enable their incorporation in medicinal chemistry studies.

We describe herein parallel complementary approaches toward disubstituted thietes, paving the way to new classes of functionalized heterocycles. In the first sequence (α-lithiation/transmetalation), substrate **1** was subjected to *s*-BuLi to undergo α-lithiation at the more reactive sp^2 center. The intermediate thietyllithium can then either be trapped with an electrophile or tempered by transmetalation with a metallic salt to allow the introduction of more sensitive electrophiles, as well as cross-coupling reactions (**2**). In parallel, a complementary strategy for direct arylation (**3**) was elaborated through C−H functionalization, employing inexpensive palladium catalysts (Scheme 1).

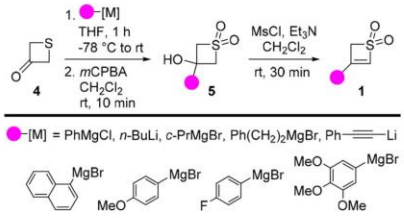
Scheme 1. Parallel Approaches toward 2,3-Disubstituted Thietes



1,2-Nucleophilic addition of a lithium or Grignard reagent on commercially available thietanone **4**,[12] followed by oxidation of the sulfide moiety gave tertiary alcohol **5** (Scheme 2). Thiete substrates **1** were obtained in reasonable yields after a simple elimination reaction.[13]

Metalation of thiete **1a** was first examined, employing *s*-BuLi as a base for selective C-sp^2 deprotonation. Direct quenching with D_2O or TMSCl afforded **2a−b** in good yields, and the

Scheme 2. Synthetic Approach to Substrates 1



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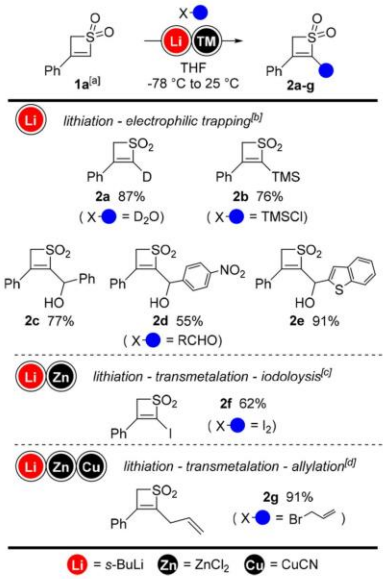
addition of aromatic and heteroaromatic aldehydes produced thiete carbinols **2c–e** with up to 91% yield (Scheme 3).[14] The

Scheme 3. α-Metalation for the Functionalization of Thietes 1[a]



[a]Reaction conditions: (a) 0.2 mmol scale; (b) *s*-BuLi (1.2 equiv), THF, −78 °C, 10 min, TMSCl and D_2O were used in excess, or 0.16 mmol of aldehydes; (c) $ZnCl_2$ (1.3 equiv), THF, −78 to −30 °C, then I_2 (0.3 mmol); and (d) $ZnCl_2$ (1.3 equiv), THF, −78 to −30 °C, CuCN·2LiCl (0.03 mmol), then allyl bromide (0.23 mmol).

versatility of this metalation process was further explored by an intermediary transmetalation with $ZnCl_2$ (Schemes 3 and 4). On the one hand, iodolysis furnished the new iodinated building block **2f**. On the other hand, allylation was performed with assistance of copper cyanide, giving structure **2g** in great yield (91%).

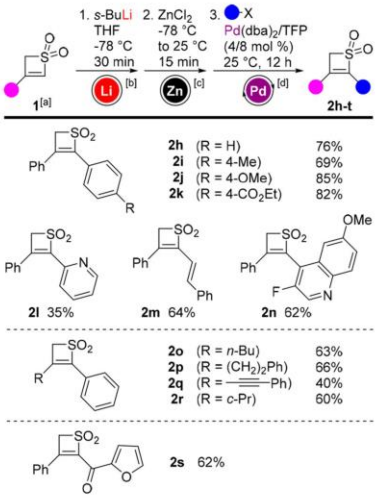
Taking advantage of such simple access to the thietylzinc species, Negishi couplings were performed to synthesize unprecedented aryl derivatives (Scheme 4).

3-Phenylthiete **1a** was first used in this sequence to establish the scope of the transformation. Electroenriched and electrodeficient aryl iodides and bromides furnished corresponding disubstituted thietes **2h–k** in high yields (up to 85%). While a lack of reactivity was observed for 2-iodopyridine (**2l**), substituted quinoline and styryl derivatives **2n** and **2m** were isolated in good yields.

Switching the substituents at position 3 for the alkyl or alkynyl groups gave the 2-phenylthietes **2o–r** with moderate yields after reaction with iodobenzene. Alternatively, the introduction of furoyl chloride furnished the corresponding conjugated ketone **2s** in 62% yield.

On the basis of these successful first results, we took on the challenge of using the potential acidity of the hydrogen atom at position 2 for direct C–H functionalization (Scheme 5).

Scheme 4. α-Lithiation/Transmetalation/Pd-Catalyzed Cross Coupling Sequence Towards Functionalized Thietes[a]



[a]Reaction conditions: (a) 0.2 mmol; (b) *s*-BuLi (1.2 equiv); (c) $ZnCl_2$ (1.3 equiv); and (d) Ar–X (0.16 mmol).

In contrast to metalation strategies that require the use of stoichiometric amounts of a strong base, direct palladium-catalyzed C–H functionalization presents attractive features in terms of functional group tolerance, versatility, and efficacy. In this context, great achievements on directed arylation have been reported since the pioneering findings of Tajima and Ames.[15] While base-assisted Pd-catalyzed arylations allowed us to broaden the application range with consequent improvement, Fagnou and co-workers[16] demonstrated the utility of carboxylic acids as cocatalysts to tremendously modulate the activity of the catalytic systems.[17] However, most methods describe the functionalization of aromatic cores. Nonaromatic sp^2-systems have received much less attention, and the scope of reported transformations remains quite limited.[18]

Optimizations on direct α-arylation of substrate **1a** led to the best conversions employing conditions described by Ackermann et al. on substituted triazoles,[19] when using pivalic acid in the presence of $Pd(OAc)_2/PCy_3$. 3-Phenylthiete **1a** was then employed first with diversely substituted aromatic bromides (Scheme 5). Both electron donor and acceptor substituents led to arylated compounds **2i–j** and **3a–f** in good-to-excellent yields (up to 96%). 5-Bromobenzothiophene was also efficiently introduced (**3j**, 80%) as well as bromopyridines (**3g–i**, up to 95%), with an exception for **2l** (40%). Moderate to good yields were obtained in the presence of electron donor substituents on the aryl group at position 3, furnishing the desired arylated or heteroarylated products **3k–n**.

Naphthyl groups were also evaluated, furnishing **3o–q** with up to 95% yield. Electron-withdrawing groups also reacted very efficiently in this C–H functionalization, giving the disubstituted structure **3r** with 95% yield. Interestingly, alkyl groups at position 3 were also tolerated, opening unique access to functionalized scaffold **3s** in high yield (87%).

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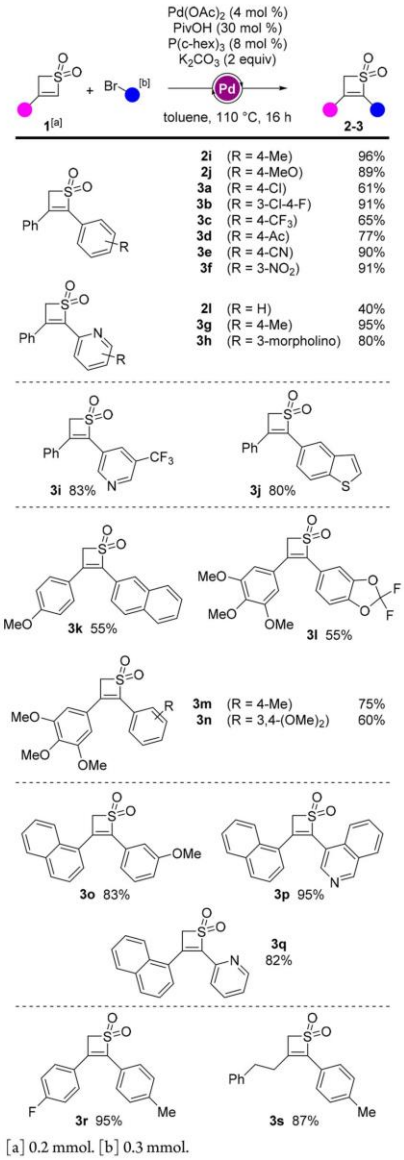
Scheme 5. Direct Pd-Catalyzed C−H Functionalization of Thiete Derivatives[a]

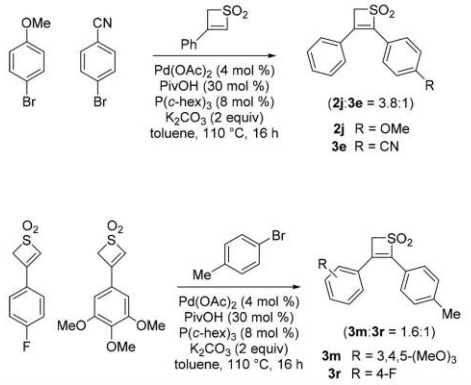


[a] 0.2 mmol. [b] 0.3 mmol.

[a]Reaction conditions: (a) 0.2 mmol and (b) 0.3 mmol.

Given the simplicity and great efficiency of the method, we were intrigued by defining its mode of action. Intermolecular competition experiments (Scheme 6) revealed electron-rich substrates to be preferentially functionalized.

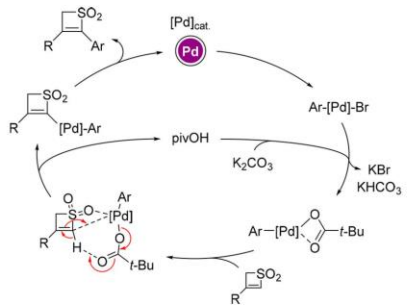
Scheme 6. Competition Experiments



Such findings indicate that the C−H activation step should occur through a base-assisted internal substitution (BIES),[20] discrediting the possibility of a concerted-metalation-deprotonation (CMD) mechanism.[21]

We thus proposed a catalytic cycle based on these observations (Scheme 7), in which the potassium carbonate

Scheme 7. Proposed Mechanism for Pivalate-Assisted Palladium-Catalyzed Functionalization of Thietes



acts as a proton-shuttle to regenerate the pivalate ligand. We assume that a π-addition of the double bond onto the palladium complex occurs (after coordination to the sulfone), followed by an intramolecular proton-abstraction by the carboxylate, rebuilding the unsaturation of the four-membered ring.

Considering the broad versatility of our synthetic methods, we finally focused on synthesizing drug analogs. In fact, compounds that disrupt tubulin dynamics by exalting π-interactions are extensively used in chemotherapy.[22] Isosteres of the original colchicine (Figure 1) have thus emerged as potential candidates for such applications.

Through simple C−H functionalization, analogs **3n** and **3t** of the metabolically unstable CA-4 were synthesized and evaluated against HL60 cell lines. While pentamethylated structure **3n** showed inefficient apoptosis (IC_{50} > 50 μM), the direct phenol analogue **3t** induced cell death at low concentration (IC_{50} = 2 μM). This new class of bioactive

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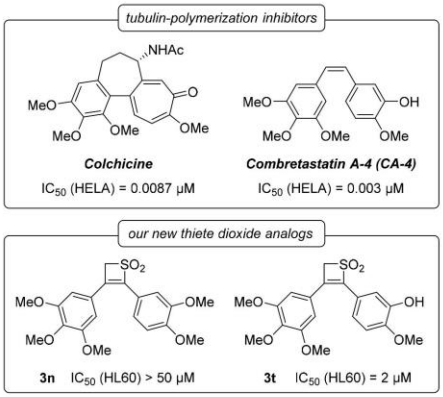

Figure 1. Known tubulin-polymerization inhibitors vs our thiete analogs.[23]

thietes surely represents a great input in drug discovery due to the continuous need for fine structural modulation.

In summary, we have unlocked two paths toward the formation of unique unsaturated four-membered S-heterocycles. While a classical strategy relying on metalation-transmetalation opened a route for electrophilic trapping or cross-coupling reactions, direct C−H functionalization allowed us to access a wide range of substituted thietes with exceptional functional group tolerance. Enabling facile structural modification ultimately led us to discover new classes of polar Combretastatin A-4 analogs possessing interesting antitumor properties.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01961.

Experimental procedures and spectroscopic characterization (IR, HRMS, and ^{1}H and ^{13}C NMR data) of all new compounds available (PDF)

Accession Codes

CCDC 1821583 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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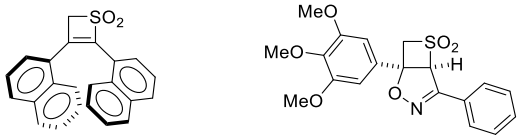
9 Outlook

Further efforts of the group concerning the thiete moiety are bound for different directions. By increasing the bulkiness of the thiete's substituent, we hope to enforce axial chirality. The proper functional groups could then allow for strong π-stacking interactions, locking the molecules in their conformation. Such products (**3.20**) pose as potential analogs for helicenes which have already found application in asymmetric catalysis, optoelectric materials and other fields.[54]

Another area of interest is the embedment of thietes in fused ring systems. Through [3+2] cycloadditions, the first isoxazoline fused thietans were synthesized (**3.21**), enabling new space for chemical explorations.[55]



3.20 **3.21**

Figure 7: Thiete **3.20** with axial chirality and isoxazoline fused thietane **3.21**.

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CHAPTER IV

Experimental Part

The following experimental part highlights some of the typical procedures applied and compounds synthesized in the course of this thesis. For full details, the respective supporting information can be downloaded free of charge from the publishers' websites.

10 General Considerations

Commercially available starting materials were used without further purification unless otherwise stated. All reactions were carried out under N_2 atmosphere in flame-dried glassware. Syringes used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use.

CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2. THF was refluxed and distilled from sodium benzophenone ketyl under nitrogen. Et_2O was predried over $CaCl_2$ and passed through activated Al_2O_3 (the solvent purification system SPS-400-2 from Innovative Technologies Inc.).

Chromatography purifications were performed using silica gel (SiO_2, 0.040–0.063 mm, 230–400 mesh ASTM) from Merck or Florisil ($MgSiO_3$, 60–100 mesh) from APOLLO. Some samples were purified with preparative-layer plates using Merck PLC silica gel 60 F_{254} (2 mm). The spots were visualized under UV (254 nm) or by staining the TLC plate with $KMnO_4$ solution (3.0 g $KMnO_4$, 300 mL H_2O, 5 drops conc. H_2SO_4), *p*-anisaldehyde solution (4 mL *p*-anisaldehyde, 200 mL ethanol, 3 mL acetic acid, 10 mL conc. H_2SO_4) and/or "Magic stain" (2.5 g phosphomolybdic acid, 1 g $Ce(SO_4)_2$, 94 mL H_2O, 6 mL conc. H_2SO_4).

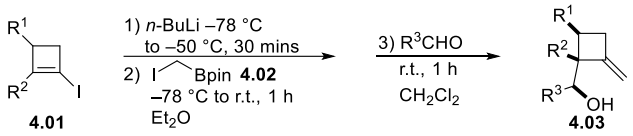
Diastereoisomeric ratios were determined by ^{1}H NMR and ^{13}C NMR. NMR spectra were recorded on Mercury 200, Varian NMR-Systtem 600 or Bruker Avance III HD 400 MHz equipped with a CryoProbe™ spectrometers. Chemical shifts are reported as δ values in ppm relative to residual solvent peak (^{1}H NMR) or solvent peak (^{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), app (apparent) and br (broad). Reaction endpoints were determined by GC or TLC monitoring of the reactions. 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 (HewlettPackard, 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 or 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; from 25% to 50% of max. intensity), vw (very weak;

below 25%) and br (broad). Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Optical rotation values were determined on a P8000-P8100-T polarimeter from A. Krüss Optronic, running software V3.0 with 5 cm path length. Enantiomeric excess was determined using a Shimadzu prominence HPLC machine running LabSolutions V5.42SP5 equipped with Chiralcel Technologies Europe columns with 0.46 cm diameter and 25 cm length, from Daicel chemical industries LTD. Single crystals were grown in small quench vials with a volume of 5.0 ml from slow evaporation of dichloromethane/hexanes mixtures at room temperature. Suitable single crystals were then introduced into perfluorinated oil and mounted on top of a thin glass wire.

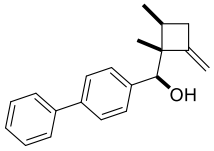
11 Experimental for Chapter I

11.1 2.1 Highly Diastereoselective Synthesis of Methylenecyclobutanes by Merging Boron-Homologation and Boron-Allylation Strategies

<u>One-pot Synthesis of Methylenecyclobutanes Starting from Cyclobutene Iodides</u>



To a stirred solution of cyclobutene iodide **4.01** (0.5 mmol, 1 eq) in 4 mL Et_2O was added a solution of *n*-BuLi in hexanes (212 µL, 0.5 mmol, 1 eq, 2.36 M) at −78 °C. After increasing the temperature to −50 °C, the yellow solution was stirred for 30 minutes. The reaction mixture was cooled down to −78 °C prior to addition of iodomethylboronic acid pinacol ester **4.02** (134 mg, 0.5 mmol, 1 eq) in 1 mL Et_2O and let warm slowly to room temperature over 2 hours. The solution was diluted with 3 mL CH_2Cl_2, followed by the addition of the aldehyde (0.5 mmol, 1 eq) at room temperature. The reaction was monitored by TLC. Consumption of the intermediate cyclobutenylmethylboronic ester was observed after 1 hour. Water was added and the mixture was extracted with Et_2O (2 × 5 mL), the combined organic phases were dried over $MgSO_4$, filtrated, concentrated under reduce pressure and purified by flash-column chromatography on silica gel with the appropriate solvent mixture.

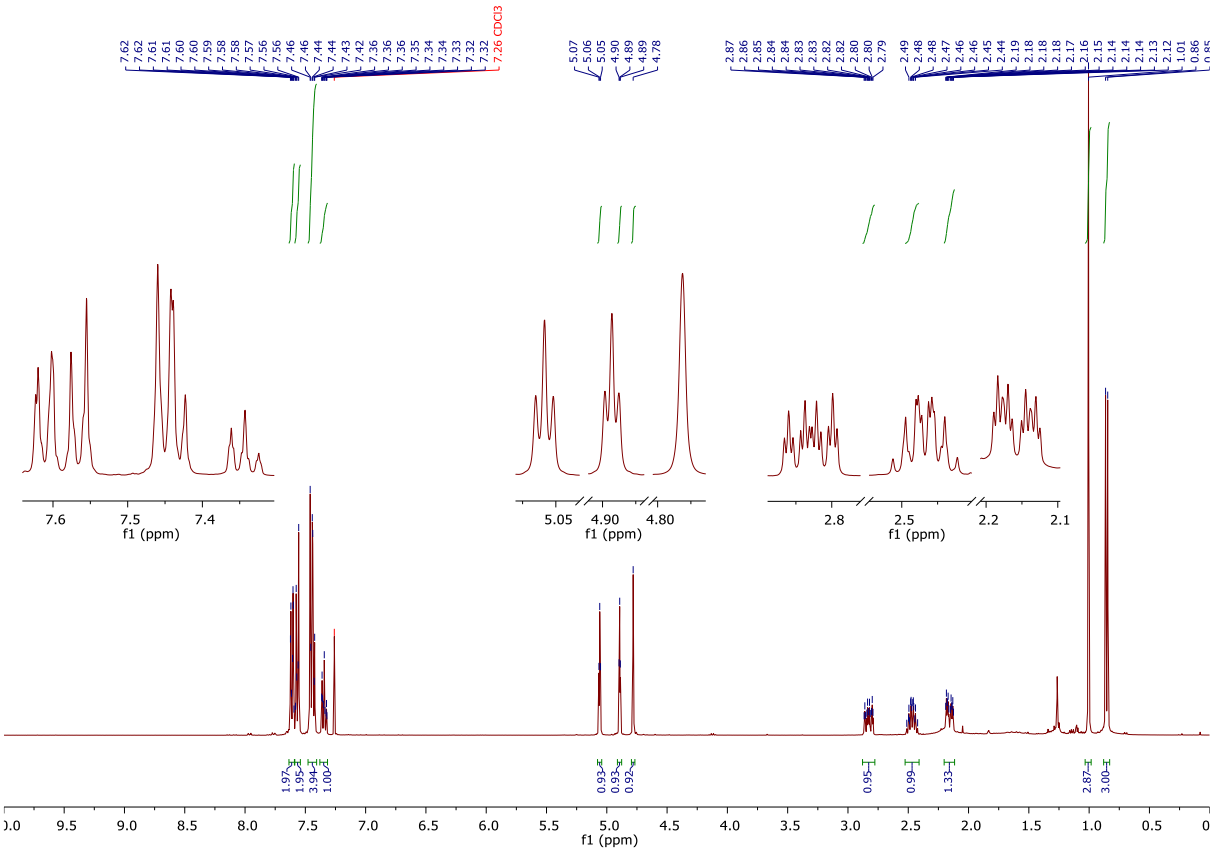


(*S**)-[1,1'-Biphenyl]-4-yl((1*R**,2*S**)-1,2-dimethyl-4-methylenecyclobutyl)methanol

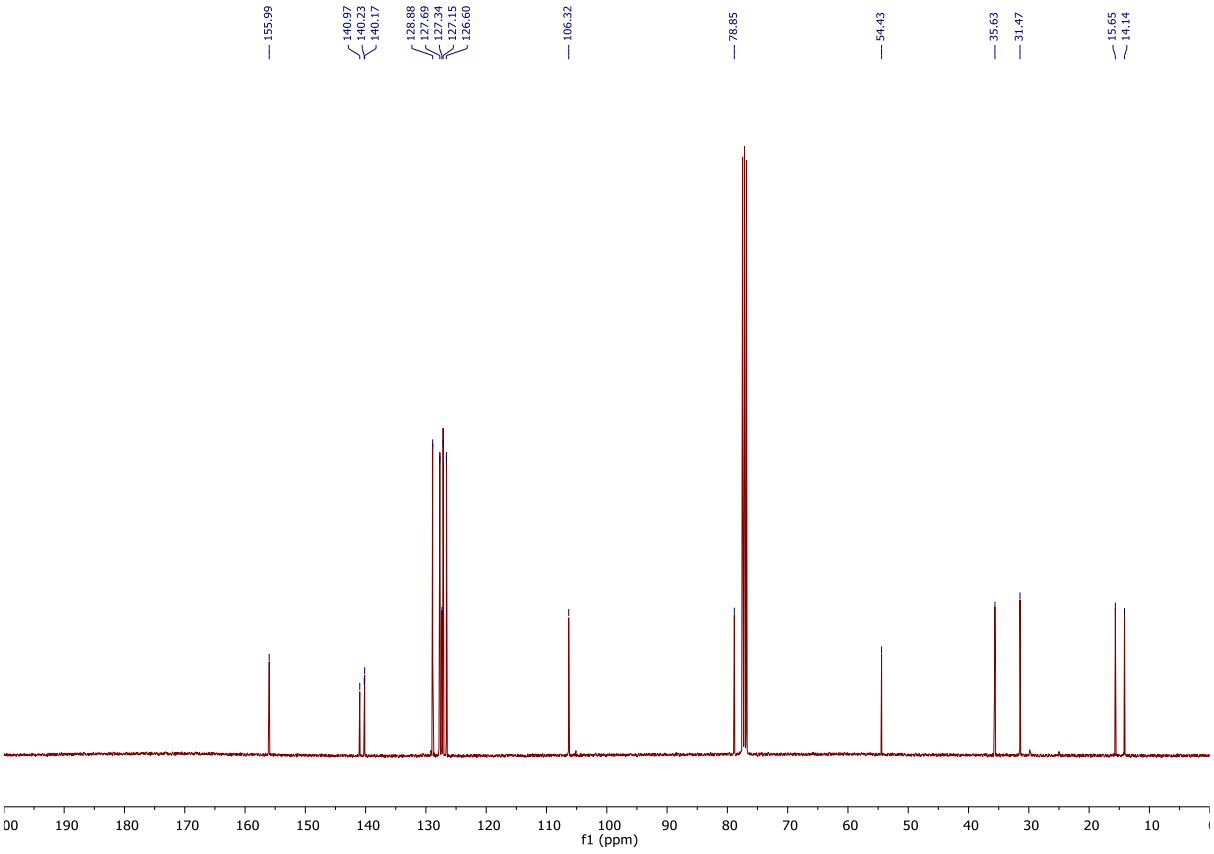
Using 1-iodo-2,3-dimethylcyclobut-1-ene and [1,1'-biphenyl]-4-carbaldehyde provided the product (67 mg, 0.24 mmol, 55%) as a colorless oil in >97:3:0:0 d.r.

***R*f** = 0.24 (5% EtOAc in hexane, UV, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.64 – 7.59 (m, 2H), 7.59 – 7.54 (m, 2H), 7.48 – 7.41 (m, 4H), 7.37 – 7.31 (m, 1H), 5.06 (t, *J* = 2.6 Hz, 1H), 4.89 (t, *J* = 2.1 Hz, 1H), 4.78 (s, 1H), 2.88-2.78 (m, 1H), 2.52 – 2.41 (m, 1H), 2.20 – 2.12 (m, 1H), 1.01 (s, 3H), 0.85 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 156.0, 141.0, 140.2, 140.2, 128.9, 127.7, 127.3, 127.1, 126.6, 106.3, 78.8, 54.4, 35.6, 31.5, 15.7, 14.1. **LRMS** (DEP/EI): m/z (%): 183.2 (100) $[M]^+$, 155.2 (33), 152.2 (13), 96.2 (53), 81.2 (15). **HRMS** (EI): calcd for $C_{13}H_{11}O^+$ $[M–C_7H_{11}]^+$: 183.0810, found 183.0809. **IR**: $\tilde{\nu}$ (cm^{-1}) 3566 (w), 3454 (w), 3061 (w), 3030 (w), 2960 (m), 2868 (w), 2361 (w), 2341 (w), 1668 (w), 1600 (w), 1583 (vw), 1564 (vw), 1486 (m), 1463 (w), 1448 (w), 1428 (w), 1406 (w), 1377 (m), 1332 (w), 1302 (w), 1290 (w), 1272 (w), 1182 (w), 1143 (w), 1076 (w), 1031 (m), 1019 (m), 1008 (m), 942 (w), 874 (m), 848 (m), 835 (m), 801 (vw), 769 (m), 747 (vs), 718 (w), 697 (s).

^{1}H NMR:

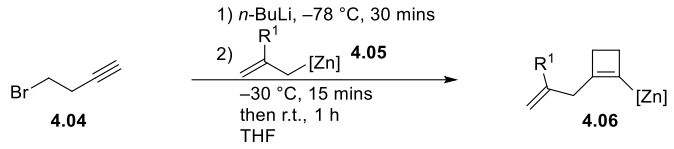


^{13}C NMR:

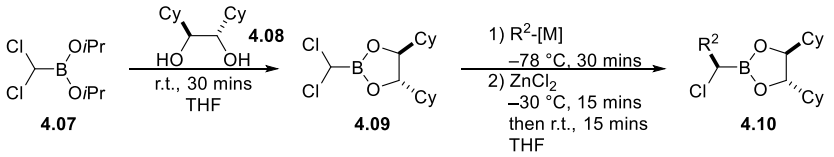


11.2 2.2 Single-Pot Asymmetric Approach toward Enantioenriched Quaternary Stereocenter-Containing Alkylidenecyclobutanes

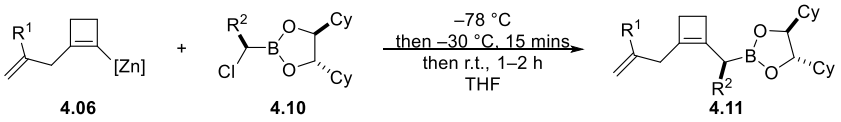
Synthesis of Enantiomerically Enriched Alkylidenecyclobutanes



To a solution of 4-bromobut-1-yne (133 mg, 1.0 mmol, 1 eq) in 2 mL THF was added dropwise a solution of *n*-BuLi in hexanes (425 µL, 1.0 mmol, 1 eq, 2.36 M) at −78 °C. After stirring for 30 minutes at aforesaid temperature, the solution was warmed to −30 °C and stirred for an additional 5 minutes. A solution of the zinc organyl **4.05** (1 eq) in THF was added slowly and the solution was stirred for another 15 minutes at −30 °C. The mixture was warmed to room temperature and allowed to react for 1 hour, to yield the metallated cyclobutenyl derivative **4.06**.

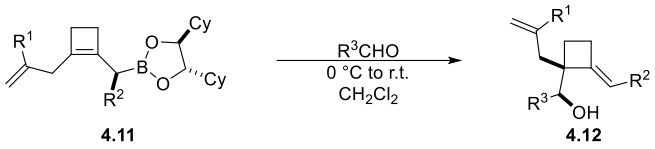


A flask was charged with a solution of di*iso*propyl (dichloromethyl)boronate (213 mg, 1.0 mmol, 1 eq) in 2 mL THF. A solution of the dicyclohexylethanediol (226 mg, 1.0 mmol, 1 eq) in 5 mL THF was added at room temperature and the mixture was stirred for 30 minutes to allow full conversion. The resulting solvent mixture was removed under reduced pressure and substituted for pure THF (2 mL, 0.5 M). The solution was cooled to −78 °C and a solution of the lithium organyl and Grignard species (1 eq), respectively, was added dropwise. After stirring for 30 minutes at aforesaid temperature, a solution of $ZnCl_2$ (1 mL, 1.0 M, 1 eq) in THF was added. The resulting mixture was then stirred for 15 minutes at −30 °C and finally for another 15 minutes at room temperature to yield the homologated alkylboronic ester **4.10**.

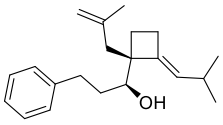


The mixture containing the metallated cyclobutenyl derivative **4.06** was then added via syringe to the mixture of the homologated alkylboronic ester **4.10** at −78 °C. After stirring for 15 minutes at −30 °C, the resulting mixture was allowed to react for another 1 – 2 hours at room temperature. Volatiles were

removed under reduced pressure to yield a pale yellow residue. The residue **4.11** was dissolved in CH_2Cl_2 (2 mL, 0.5 M) and cooled to 0 °C.



The liquid and solid aldehydes (0.5 eq) were added neat and dissolved in CH_2Cl_2, respectively. Upon full consumption of the boronate intermediate **4.11**, saturated ammonium chloride solution and Et_2O were added and the mixture was stirred vigorously. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic phases were washed with aqueous sodium metabisulfite (20 mL). The washed solution was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash-column chromatography on silica gel with the appropriate solvent mixture to afford the pure alkylidenecyclobutylcarbinols **4.12**.

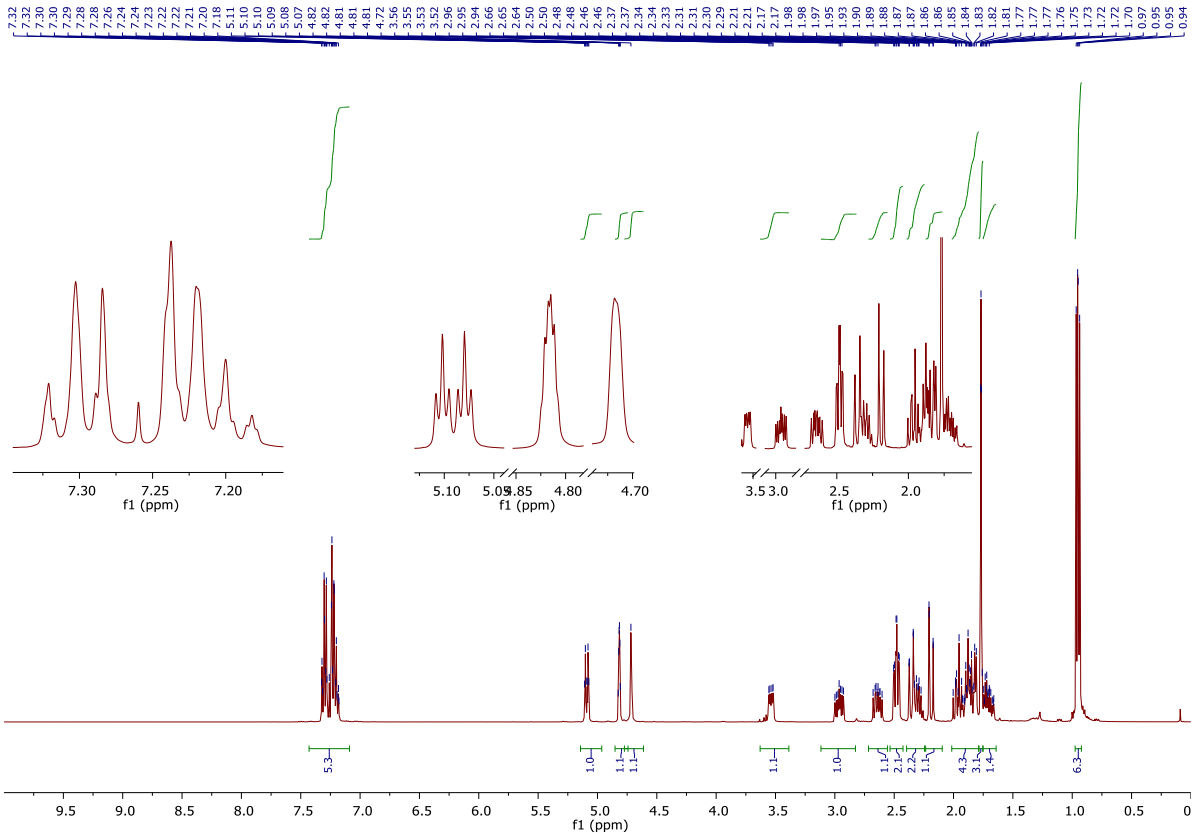


(*S*)-1-((*S*,*E*)-1-(2-Methylallyl)-2-(2-methylpropylidene)cyclobutyl)-3-phenylpropan-1-ol

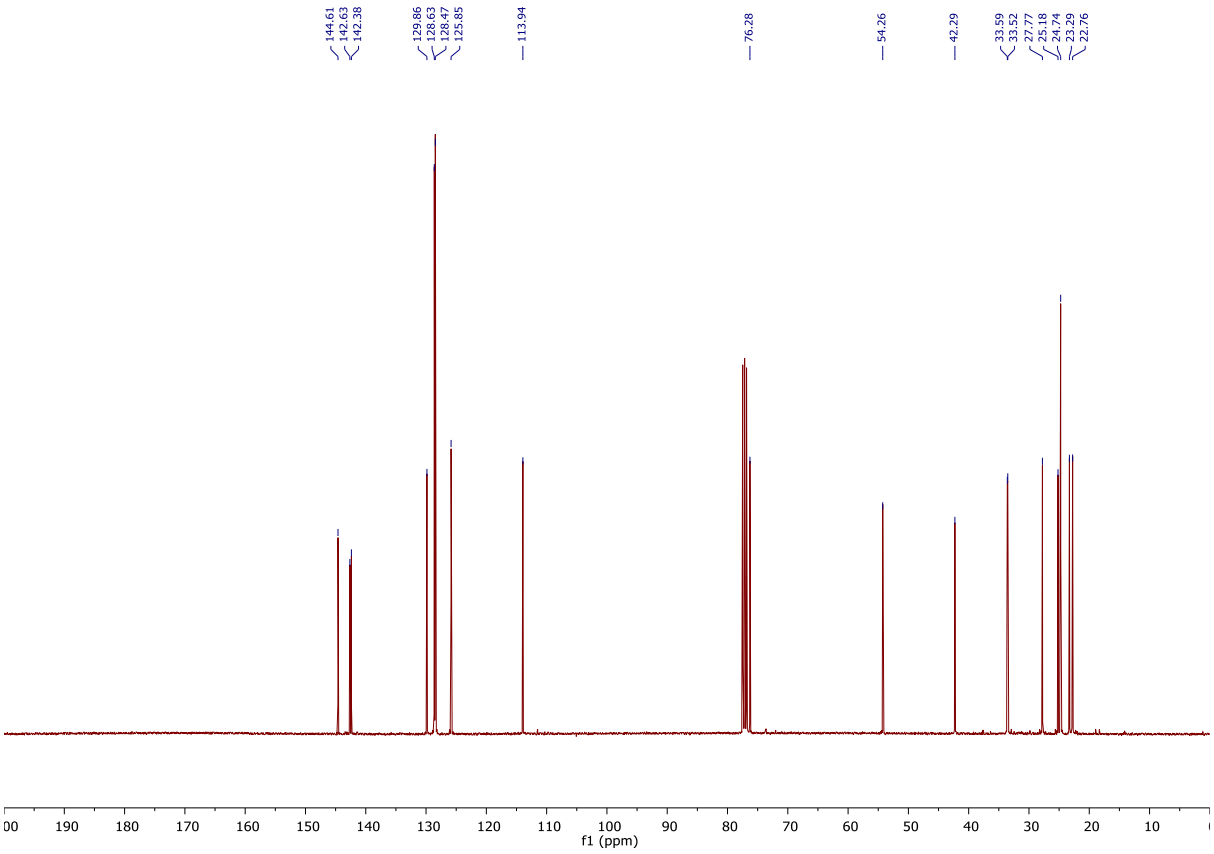
Using (2-methylallyl)zinc bromide as the zinc organyl, *iso*-propylmagnesium chloride as the magnesium species, (1*S*,2*S*)-1,2-dicyclohexylethane-1,2-diol, di*iso*propyl (dichloromethyl)boronate and 3-phenylpropanal, provided the product (118 mg, 0.40 mmol, 79%) as a colorless oil in 99:1 d.r. and 99% *ee*.

$[\alpha]_D^{19}$ = −24.63° (c = 1.34; CH_2Cl_2). R_f = 0.10 (2% EtOAc in hexanes; UV, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.43 – 7.04 (m, 5H), 5.13 – 5.05 (m, 1H), 4.83 – 4.79 (m, 1H), 4.72 (s, 1H), 3.58 – 3.50 (m, 1H), 3.02 – 2.90 (m, 1H), 2.70 – 2.58 (m, 1H), 2.52 – 2.43 (m, 2H), 2.41 – 2.25 (m, 2H), 2.27 – 2.12 (m, 1H), 2.02 – 1.80 (m, 4H), 1.77 (s, 3H), 1.75 – 1.64 (m, 1H), 0.95 (dd, *J* = 6.7, 4.9 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) 144.6, 142.6, 142.4, 129.9, 128.6, 128.5, 125.9, 113.9, 76.3, 54.3, 42.3, 33.6, 33.5, 27.8, 25.2, 24.7, 23.3, 22.8. **HRMS** (EI): calcd for $C_{21}H_{30}O^+$ $[M]^+$: 298.2297, found 298.2290. **IR**: $\tilde{\nu}$ (cm^{-1}) 3447 (br, vw), 3065 (vw), 3027 (w), 2953 (m), 2925 (m), 2866 (w), 1642 (w), 1454 (m), 1378 (w), 1362 (m), 1287 (w), 1256 (w), 1174 (w), 1040 (m), 929 (m), 889 (m), 842 (w), 747 (m), 734 (m), 698 (vs).

^{1}H NMR:

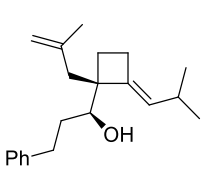


^{13}C NMR:



OF; 0.5% *i*PrOH in Heptane; 0.3 mL/min; 30 °C

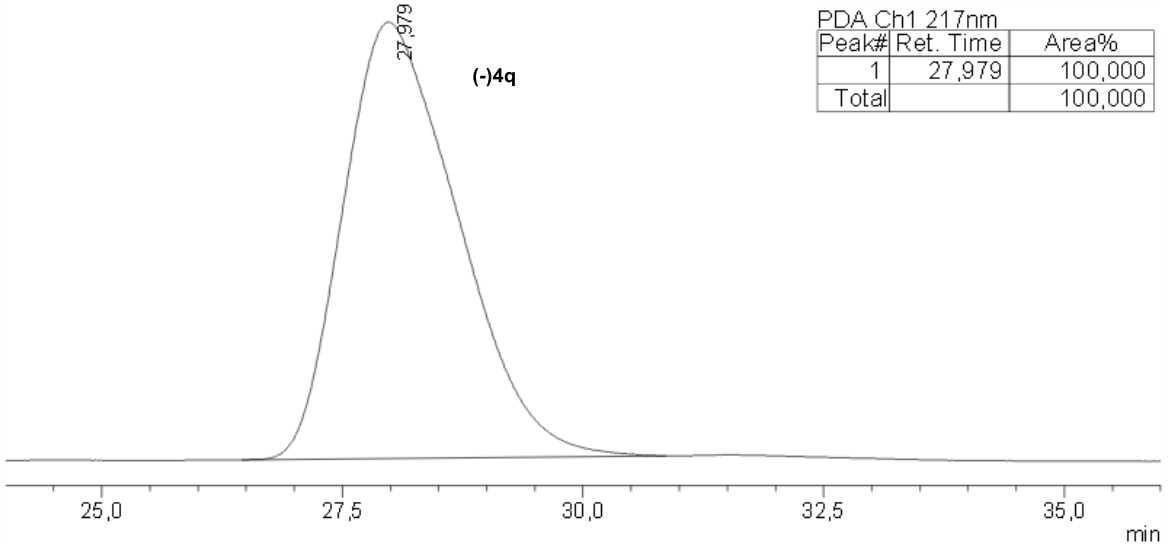
4q



PDA Ch2 217nm

Peak#	Ret. Time	Area%
1	26,594	50,041
2	30,119	49,959
Total		100,000

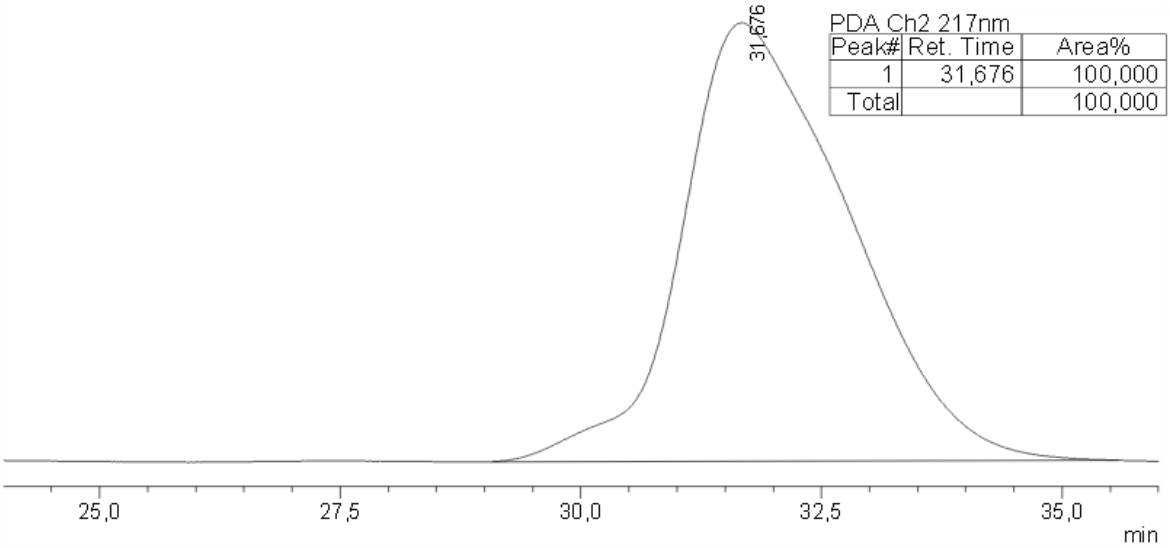
(-)4q



PDA Ch1 217nm

Peak#	Ret. Time	Area%
1	27,979	100,000
Total		100,000

(+)4q

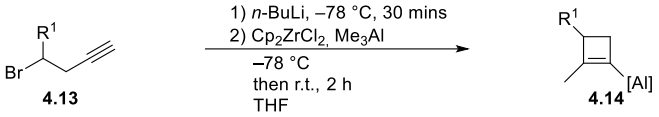


PDA Ch2 217nm

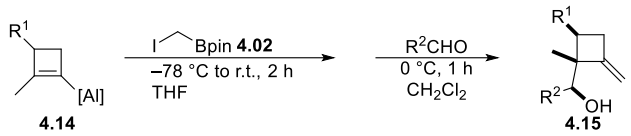
Peak#	Ret. Time	Area%
1	31,676	100,000
Total		100,000

11.3 2.3 Unsaturated Four-Membered Rings: Efficient Strategies for the Construction of Cyclobutenes and Alkylidenecyclobutanes

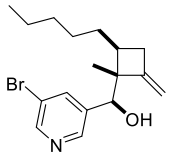
Synthesis of Methylenecyclobutanes Containing a Side Chain



To a solution of bromobutyne **4.13** (1.0 mmol, 1 eq) in 2 mL hexane was added dropwise a solution of *n*-BuLi in hexanes (425 µL, 1.0 mmol, 1 eq, 2.36 M) at −78 °C and stirred for 30 minutes. A second flask was charged with Cp_2ZrCl_2 (292 mg, 1.0 mmol, 1 eq) in 2 mL CH_2Cl_2 and a solution of Me_3Al (1 mL, 2.0 mmol, 2.0 eq, 2.0 M) in hexane was added at room temperature and stirred for 30 minutes. The second solution was transferred to the first one at −78 °C via cannula. The resulting mixture was then allowed to stir at room temperature for 2 hours to form the metallated cyclobutenyl derivative **4.14**.



The reaction mixture was cooled back to −78 °C and iodomethylboronic acid pinacol ester (268 mg, 1.0 mmol, 1 eq) in 1 mL THF was added. The solution was warmed to room temperature over 2 hours. Excess organometallic species was quenched through addition of water (very carefully) and the boronic ester intermediate was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was dissolved in 2 mL CH_2Cl_2 and cooled to 0 °C. The liquid and solid aldehydes (0.5 eq) were added neat and dissolved in CH_2Cl_2, respectively. Upon full consumption of the boronate intermediate, saturated aqueous NH_4Cl solution and Et_2O were added and the mixture was stirred vigorously. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic phases washed with aqueous $Na_2S_2O_5$ (20 mL). The washed solution was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash-column chromatography on silica gel with the appropriate solvent mixture to afford the pure alkylidenecyclobutylcarbinols **4.15**.

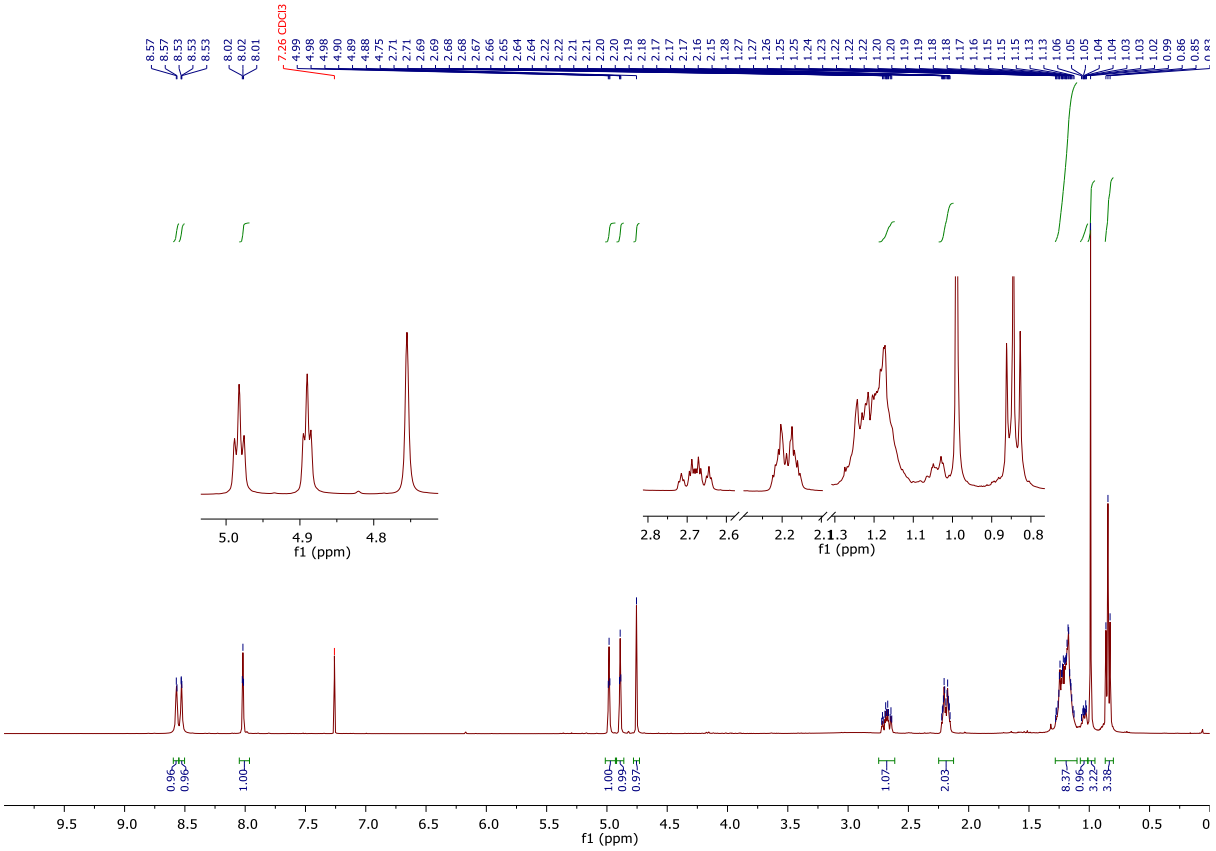


(*S**,1'*S**,4'*R**)-(5-Bromopyridin-3-yl)(1'-methyl-2'-methylene-4'-pentylcyclobutyl)methanol

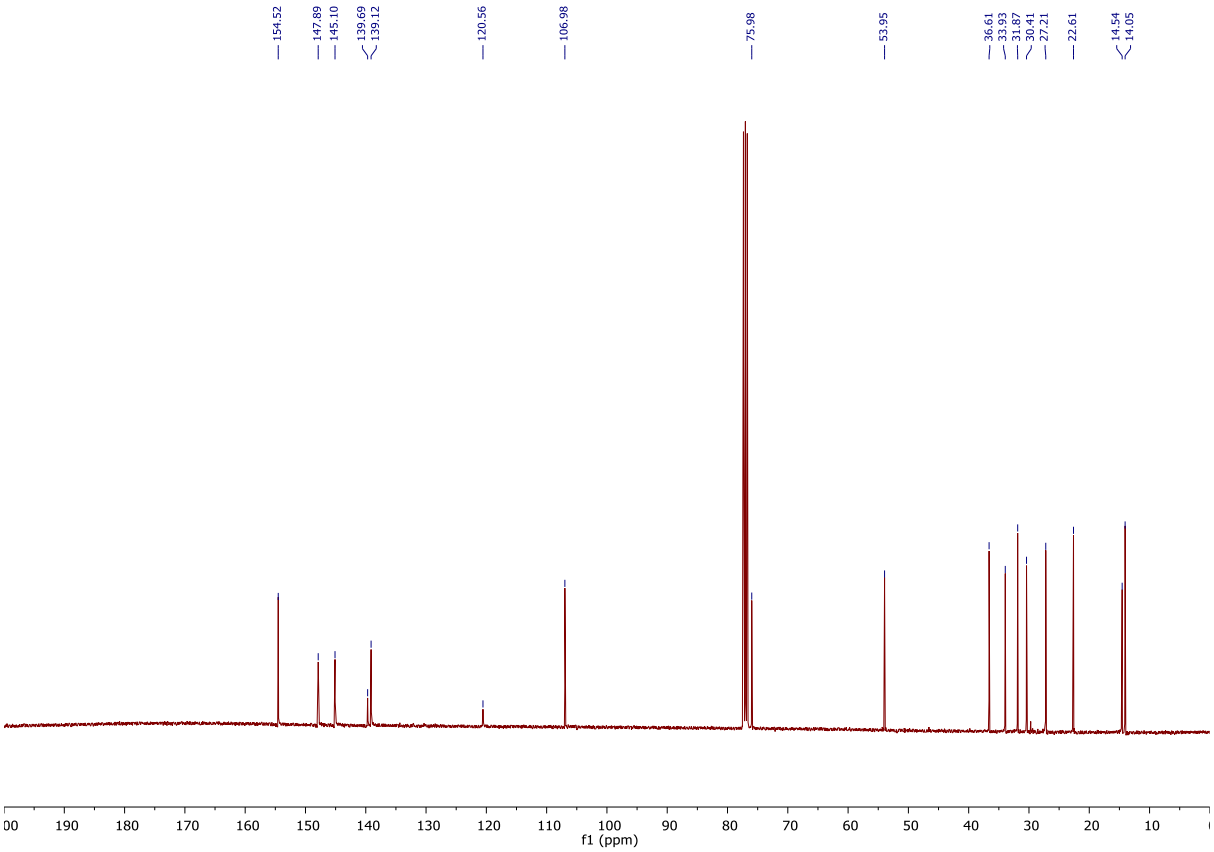
Using 4-bromonon-1-yne and 5-bromonicotinaldehyde provided the product (79 mg, 0.23 mmol, 59%) as a colorless oil in >99:1:0:0 d.r.

***R*f** = 0.23 (10% EtOAc in hexanes; UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 8.55 (s, 1H), 8.51 (s, 1H), 8.00 (s, 1H), 4.96 (s, 1H), 4.87 (s, 1H), 4.74 (s, 1H), 2.70 – 2.62 (m, 1H), 1.20 – 2.13 (m, 2H), 1.30 – 1.15 (m, 8H), 1.06 – 1.02 (m, 1H), 0.97 (s, 3H), 0.82 (t, *J* = 7.2, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) 154.5, 147.9, 145.1, 139.7, 139.1, 120.6, 107.0, 76.0, 54.0, 36.6, 33.9, 31.9, 30.4, 27.2, 22.6, 14.5, 14.1. **LRMS** (DEP/EI): *m/z* (%): 185 (100), 158 (52), 103 (12), 105 (6), 78 (39), 61 (8), 51 (42). **HRMS** (EI): calcd for $C_{17}H_{24}{}^{79}BrNO^+$ $[M]^+$: 337.1041; found: 337.1039. **IR**: $\tilde{\nu}$ (cm^{-1}) 3282 (w), 2956 (m), 2925 (s), 2854 (m), 1669 (w), 1421 (m), 1098 (w), 1042 (m), 1021 (m), 882 (m), 706 (w).

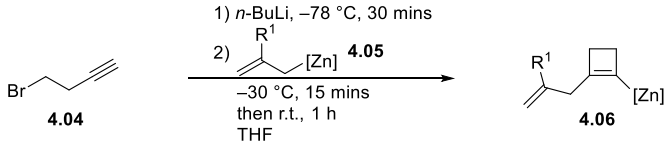
^{1}H NMR:



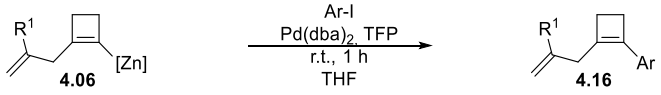
^{13}C NMR:



Negishi Cross-Coupling of in-situ Generated Cyclobutenyl Zinc Species

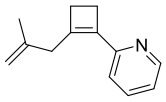


To a solution of 4-bromobut-1-yne (100 mg, 0.75 mmol, 1 eq) in 2 mL THF was added dropwise a solution of *n*-BuLi in hexanes (320 µL, 0.75 mmol, 1 eq, 2.36 M) at −78 °C. After stirring for 30 minutes at aforesaid temperature, the solution was warmed to −30 °C and stirred for an additional 5 minutes. A solution of the zinc organyl **4.05** (1 eq) in THF was added slowly and the solution was stirred for another 15 minutes at −30 °C. The mixture was warmed to room temperature and allowed to react for 1 hour to yield the metallated cyclobutenyl derivative **4.06**.



$Pd(dba)_2$ (17 mg, 4 mol%) and TFP (14 mg, 8 mol%) were dissolved in 2 mL THF in a second flask. After 10 – 20 minutes the red solution turned to yellow. The aryl iodide (0.95 eq) was added in THF to the yellow solution of the catalytic system and stirred for 10 minutes.

Finally the cyclobutenylzinc species **4.06** was quickly added to the second flask containing the aryl iodide and stirred for 1 hour. After quenching with water the crude mixture was extracted with Et_2O (2 × 10 mL) and dried over $MgsO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography or preparative layer plates on silica gel with the appropriate solvent mixture to obtain aryl-cyclobutene derivatives **4.16**.

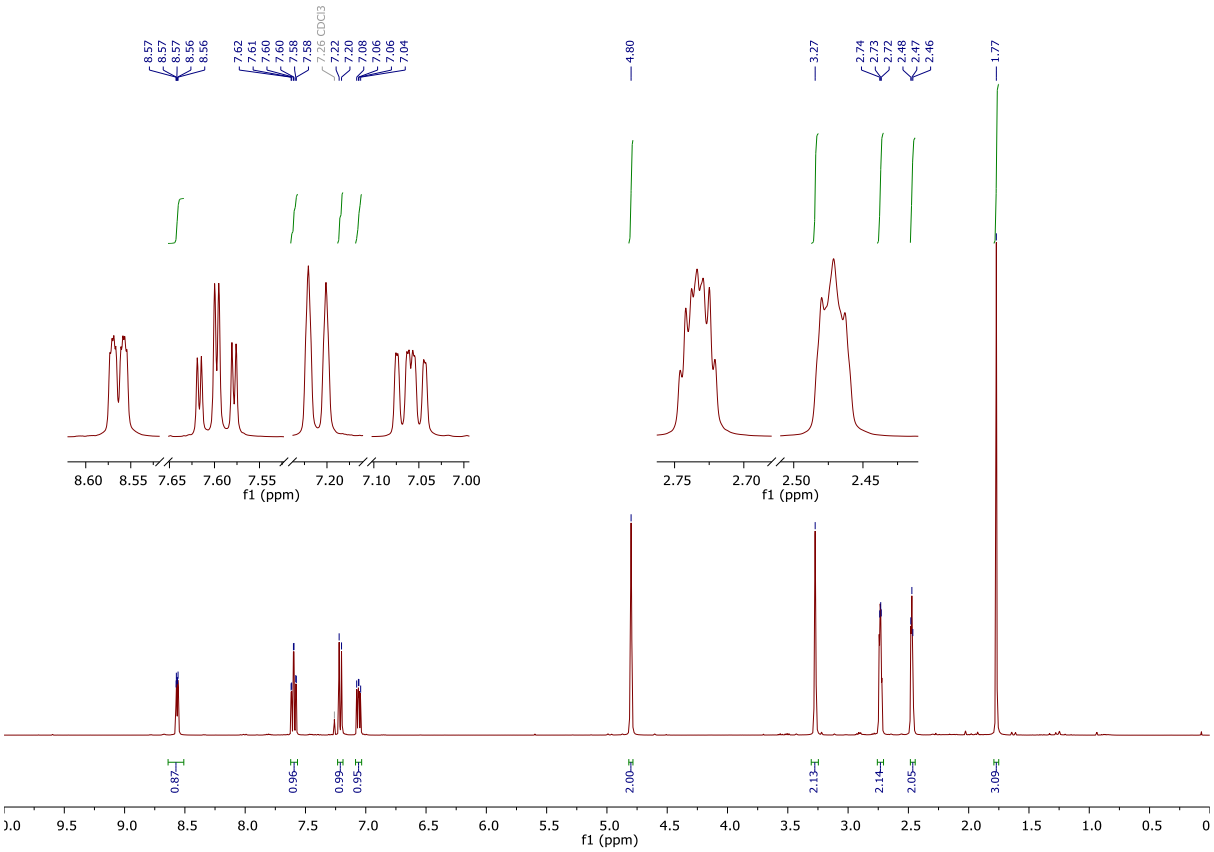


2-(2-(2-Methylallyl)cyclobut-1-en-1-yl)pyridine

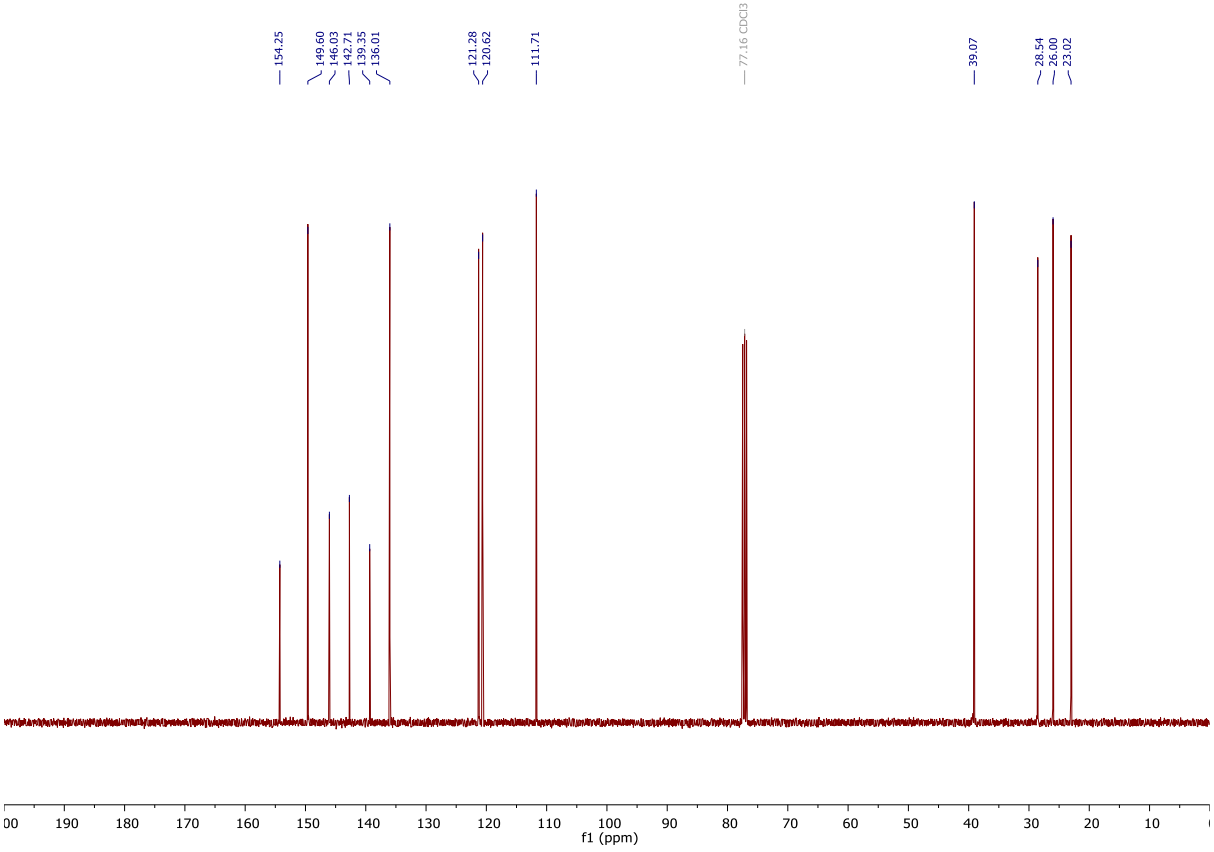
Using (2-methylallyl)zinc bromide as the zinc organyl and 2-iodopyridine provided the product (88 mg, 0.48 mmol, 80%) as an orange oil.

R_f = 0.4 (10% EtOAc in hexanes; UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 8.58 – 8.54 (m, 1H), 7.60 (td, *J* = 7.7, 1.8 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.06 (dd, *J* = 7.4, 5.8 Hz, 1H), 4.81 – 4.78 (m, 2H), 3.27 (s, 2H), 2.77 – 2.70 (m, 2H), 2.49 – 2.45 (m, 2H), 1.77 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) 154.3, 149.6, 146.0, 142.7, 139.3, 136.0, 121.3, 120.6, 111.7, 39.1, 28.5, 26.0, 23.0. **LRMS** (DEP/EI): *m/z* (%): 184.1 (35) $[M]^+$, 170.1 (100), 156.1 (20), 144.1 (30), 130.1 (20), 117.1 (15), 104.1 (10). **HRMS** (EI): calcd for $C_{13}H_{15}N^+$ $[M]^+$: 185.1204, found 185.1199. **IR**: $\tilde{\nu}$ (cm^{-1}) 3076 (w), 3008 (vw), 2914 (m), 2840 (w), 2827 (w), 2220 (vw), 1700 (vw), 1645 (m), 1583 (s), 1560 (m), 1474 (m), 1467 (m), 1435 (m), 1426 (m), 1374 (w), 1338 (w), 1200 (w), 1148 (m), 1067 (w), 988 (w), 908 (m), 888 (s), 804 (m), 776 (s), 756 (m), 731 (vs), 708 (m), 665 (w).

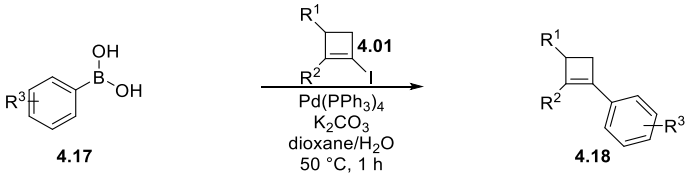
^{1}H NMR:



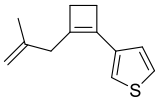
^{13}C NMR:



Suzuki Cross-Coupling of Cyclobutene Iodides



To a stirred solution of cyclobutene iodide **4.01** (0.3 mmol, 1 eq) in dioxane/H_2O (4 mL:2 mL) were added arylboronic acid **4.17** (0.4 mmol, 1.33 eq) and K_2CO_3 (112 mg, 0.8 mmol, 2.7 eq) at room temperature. The reaction mixture was stirred for 10 min before adding $Pd(PPh_3)_4$ (14 mg, 4 mol%). The cross-coupling was performed at 50 °C for 1 hour. The color of the reaction mixture changed to red or black after completion. Lastly, the reaction was treated with a small amount of water, extracted with Et_2O (2 × 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography or preparative layer plates on silica gel with the appropriate solvent mixture to obtain aryl-cyclobutene derivatives **4.18**.

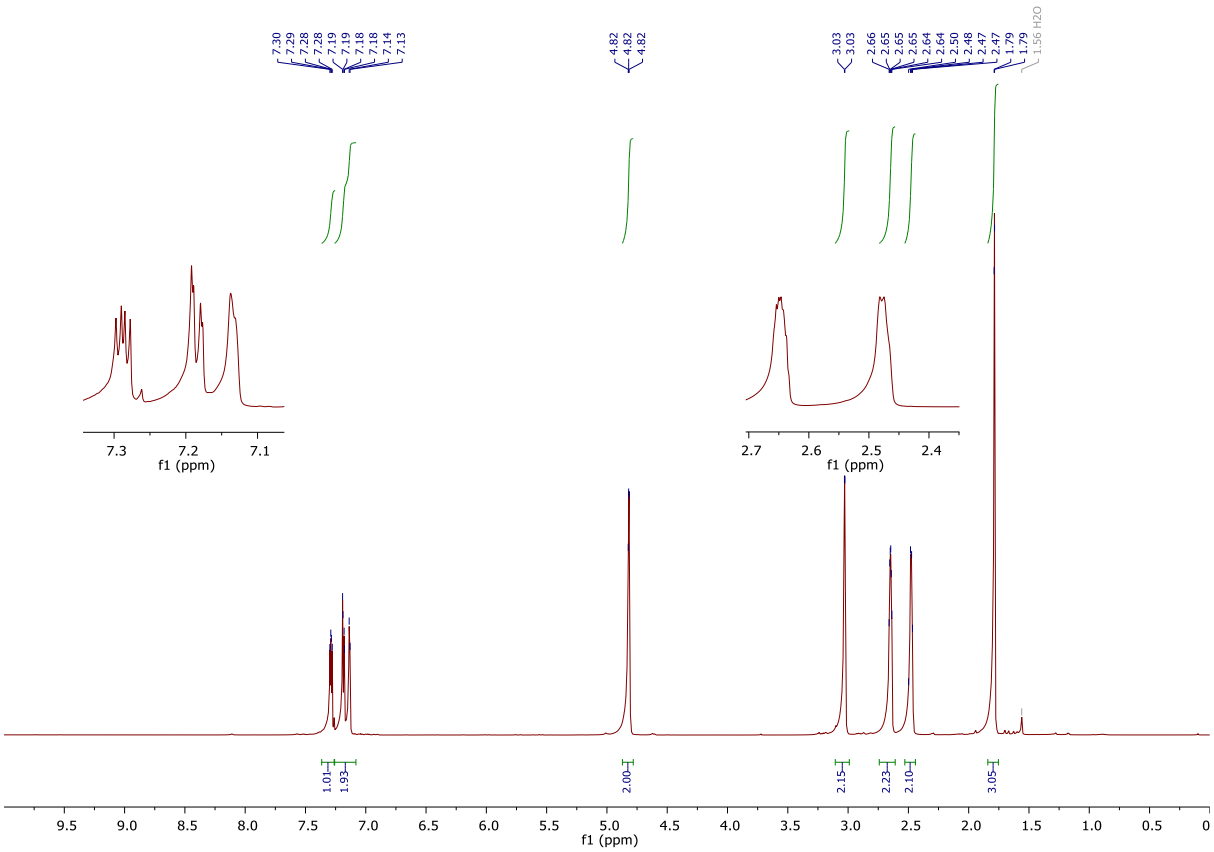


3-(2-(2-Methylallyl)cyclobut-1-en-1-yl)thiophene

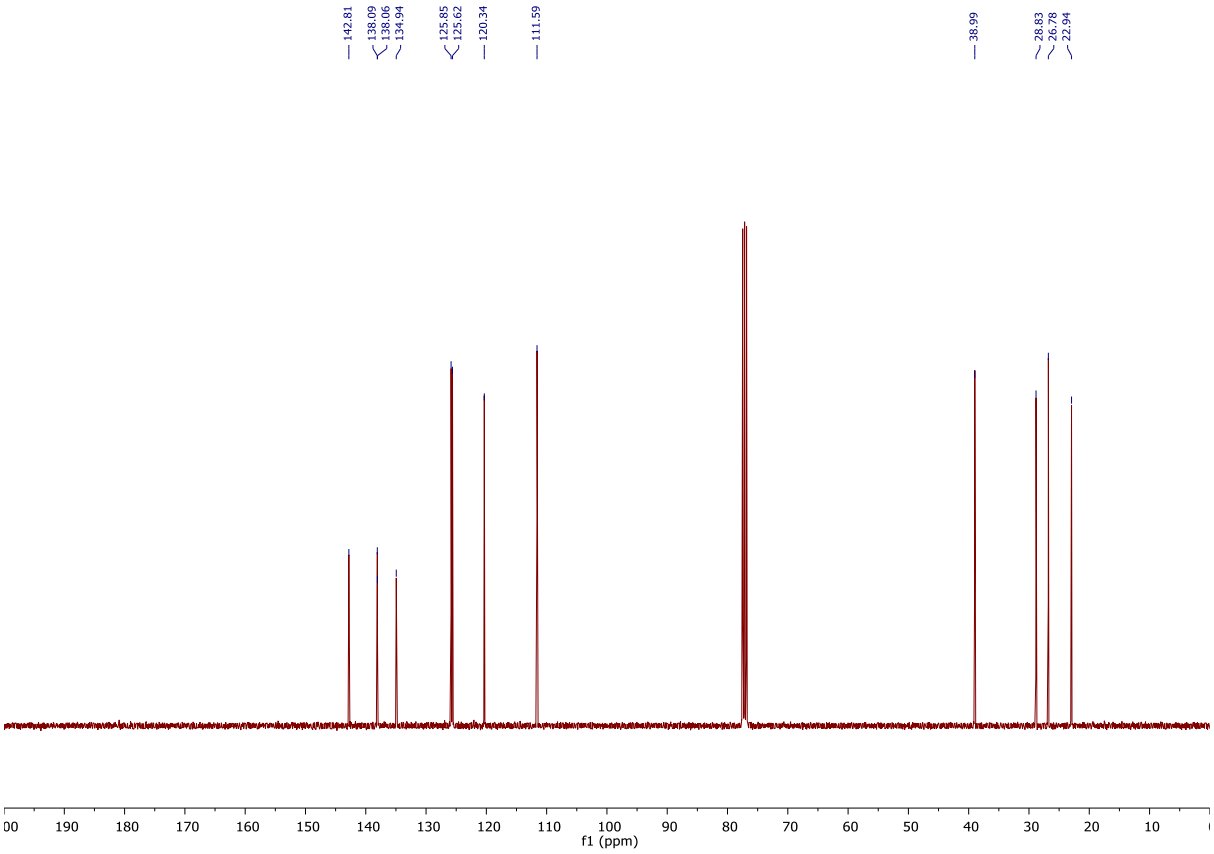
Using 1-iodo-2-(2-methylallyl)cyclobut-1-ene and thiophen-3-ylboronic acid provided the product (46 mg, 0.24 mmol, 81%) as an orange oil.

***R*f** = 0.8 (hexanes; UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.29 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.18 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.15 – 7.12 (m, 1H), 4.86 – 4.80 (m, 2H), 3.06 – 3.00 (m, 2H), 2.68 – 2.62 (m, 2H), 2.51 – 2.44 (m, 2H), 1.79 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) 142.8, 138.1, 138.1, 134.9, 125.8, 125.6, 120.3, 111.6, 39.0, 28.8, 26.8, 22.9. **LRMS** (DEP/EI): *m/z* (%): 190.1 (65) $[M]^+$, 175.1 (100), 161.1 (45), 147.0 (80), 134.0 (45), 115.1 (40), 91.1 (45), 77.1 (30), 65.1 (25). **HRMS** (EI): calcd for $C_{12}H_{14}S^+$ $[M]^+$: 190.0816, found 190.0814. **IR**: $\tilde{\nu}$ (cm^{-1}) 3101 (vw), 3075 (w), 2969 (w), 2940 (m), 2913 (m), 2835 (w), 1656 (w), 1650 (w), 1644 (w), 1442 (w), 1426 (w), 1412 (w), 1373 (w), 1302 (w), 1268 (w), 1207 (w), 1182 (w), 1082 (w), 1066 (w), 891 (m), 852 (s), 799 (w), 771 (vs), 754 (m), 683 (w), 642 (m).

^{1}H NMR:

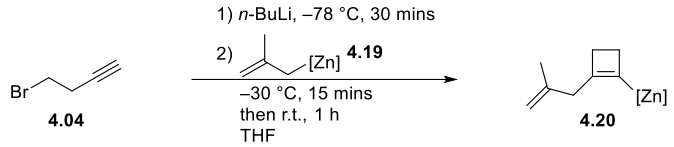


^{13}C NMR:

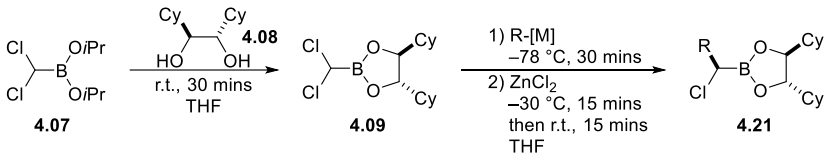


11.4 2.4 Stereoselective Access to Alkylidenecyclobutanes through γ-Selective Cross-Coupling Strategies

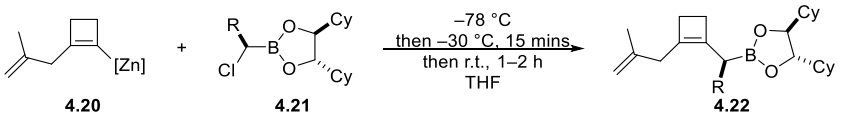
Synthesis of Enantioenriched Alkylidenecyclobutanes through γ-Selective Cross-Coupling



To a solution of 4-bromobut-1-yne (133 mg, 1.0 mmol, 1 eq) in 2 mL THF was added dropwise a solution of *n*-BuLi in hexanes (425 µL, 1.0 mmol, 1 eq, 2.36 M) at −78 °C. After stirring for 30 minutes at aforesaid temperature, the solution was warmed to −30 °C and stirred for an additional 5 minutes. A solution of 2-methylallylzinc bromide (1 eq) in THF was added slowly and the solution was stirred for another 15 minutes at −30 °C. The mixture was warmed to room temperature and allowed to react for 1 hour, to yield the metallated cyclobutenyl derivative **4.20**.

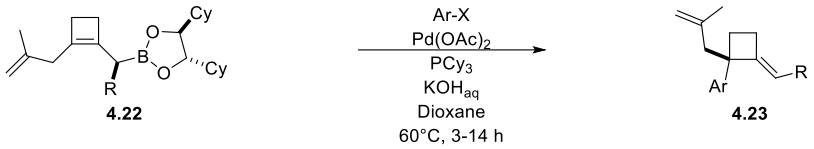


A flask was charged with a solution of di*iso*propyl (dichloromethyl)boronate (213 mg, 1.0 mmol, 1 eq) in 2 mL THF. A solution of the dicyclohexylethanediol (226 mg, 1.0 mmol, 1 eq) in 5 mL THF was added at room temperature and the mixture was stirred for 30 minutes to allow full conversion. The resulting solvent mixture was removed under reduced pressure and substituted for pure THF (2 mL, 0.5 M). The solution was cooled to −78 °C and a solution of the lithium organyl and Grignard species (1 eq), respectively, was added dropwise. After stirring for 30 minutes at aforesaid temperature, a solution of $ZnCl_2$ (1 mL, 1.0 M, 1 eq) in THF was added. The resulting mixture was then stirred for 15 minutes at −30 °C and finally for another 15 minutes at room temperature to yield the homologated alkylboronic ester **4.19**.

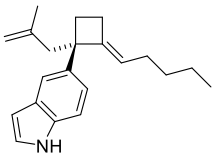


The mixture containing the metallated cyclobutenyl derivative **4.20** was then added via syringe to the mixture of the homologated alkylboronic ester **4.21** at −78 °C. After stirring for 15 minutes at −30 °C, the resulting mixture was allowed to react for another 1 – 2 hours at room temperature. The reaction was quenched by pouring onto ice-cold water while stirring vigorously. The mixture was then extracted

with Et_2O (3 × 50 mL) and the combined organic phases were washed with brine (50 mL). The washed solution was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was filtrated through silica using 2% Et_2O in hexanes as an eluent.



A nitrogen flushed flask was consecutively charged with crude cyclobutenylmethylboronic ester **4.22** in dioxane (~1.1 eq, 0.25 M), palladium acetate in dioxane (200 µL, 2 mol%, 0.02 M), tricyclohexylphosphine in dioxane (200 µL, 4 mol%, 0.04 M) and the aryl halogenide in dioxane (1 eq, 1.0 M). An aqueous solution of potassium hydroxide (115 µL, 4.5 eq, 8.0 M) was added and the resulting solution was stirred at 60 °C for 3 – 14 hours until GC showed completion. The reaction was quenched by addition of 5 mL aqueous saturated NH_4Cl solution. The mixture was then extracted with Et_2O (3 × 10 mL) and the combined organic phases were washed with brine (10 mL). The washed solution was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash-column chromatography on silica gel with the appropriate solvent mixture.

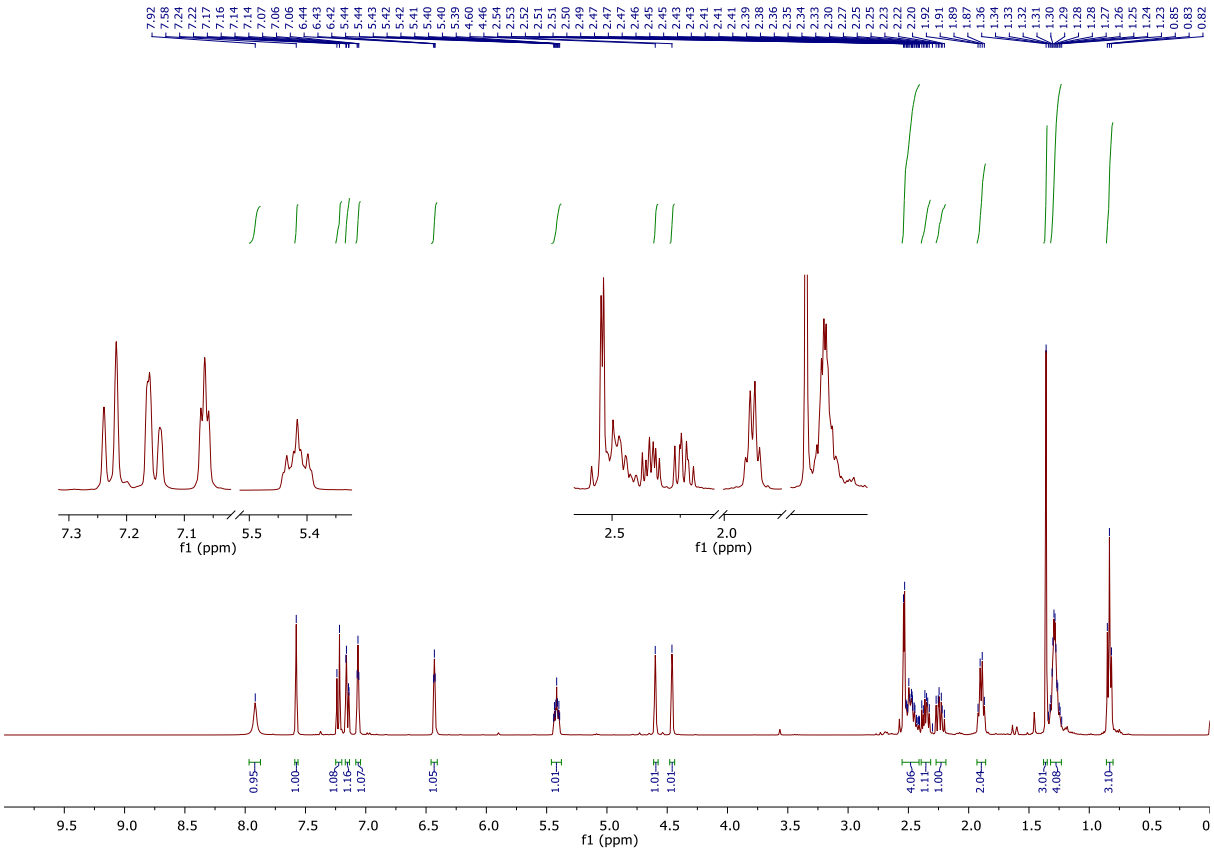


(*R*,*E*)-5-(1-(2-Methylallyl)-2-pentylidenecyclobutyl)-1*H*-indole

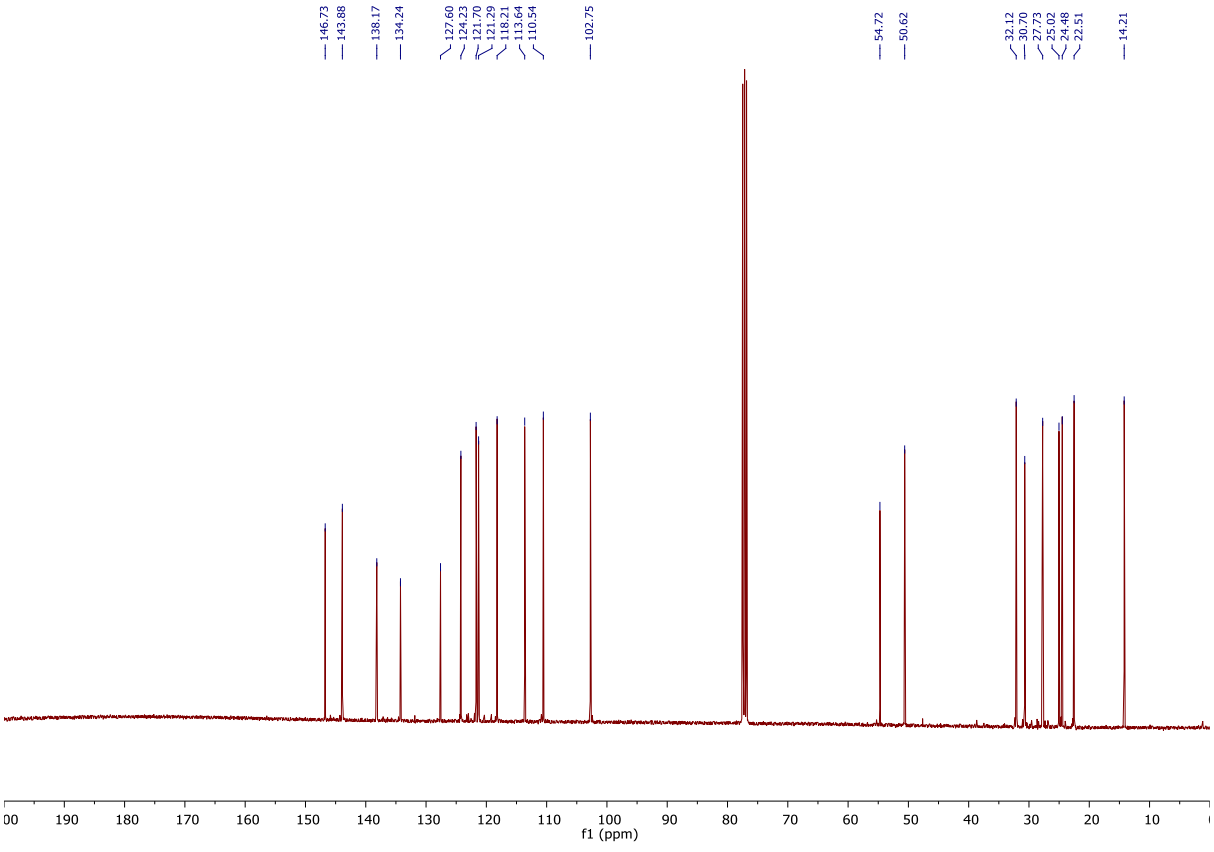
Using (1*R*,2*R*)-1,2-dicyclohexylethane-1,2-diol, *n*-BuLi as the lithium species and 5-bromo-1*H*-indole provided the product (55 mg, 0.19 mmol, 94%) as a colorless oil in 99% *ee*.

$[\alpha]_D^{19}$ = +33.33° (c = 0.12; CH_2Cl_2). R_f = 0.22 (5% EtOAc in hexanes; UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.92 (s, 1H, NH), 7.58 (s, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.15 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.06 (app t, *J* = 2.8 Hz, 1H), 6.43 (app t, *J* = 2.5 Hz, 1H), 5.42 (app tt, *J* = 7.3, 2.6 Hz, 1H), 4.60 (s, 1H), 4.46 (s, 1H), 2.56 – 2.42 (m, 4H), 2.36 (app td, *J* = 9.8, 5.3 Hz, 1H), 2.24 (app td, *J* = 10.1, 7.3 Hz, 1H), 1.90 (q, *J* = 7.0 Hz, 2H), 1.36 (s, 3H), 1.34 – 1.22 (m, 4H), 0.83 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) 146.7, 143.9, 138.2, 134.2, 127.6, 124.2, 121.7, 121.3, 118.2, 113.6, 110.5, 102.7, 54.7, 50.6, 32.1, 30.7, 27.7, 25.0, 24.5, 22.5, 14.2. **LRMS** (DEP/EI) *m/z* (%): 293.3 (16) $[M]^+$, 265.1 (14), 238.3 (100), 222.2 (17), 208.2 (19), 194.2 (49), 182.1 (66), 167.1 (60), 154.1 (30), 141.1 (15), 130.1 (31), 115.1 (20), 55.1 (28). **HRMS** (EI): calcd for $C_{21}H_{27}N^+$ $[M]^+$: 293.2143, found 293.2137. **IR**: $\tilde{\nu}$ (cm^{-1}) 3412 (m), 3072 (w), 2956 (s), 2922 (s), 2872 (m), 2854 (m), 1642 (w), 1578 (w), 1468 (s), 1454 (m), 1414 (m), 1374 (w), 1342 (w), 1318 (m), 1250 (w), 1094 (m), 1066 (w), 888 (s), 804 (m), 764 (m), 726 (vs).

^{1}H NMR:



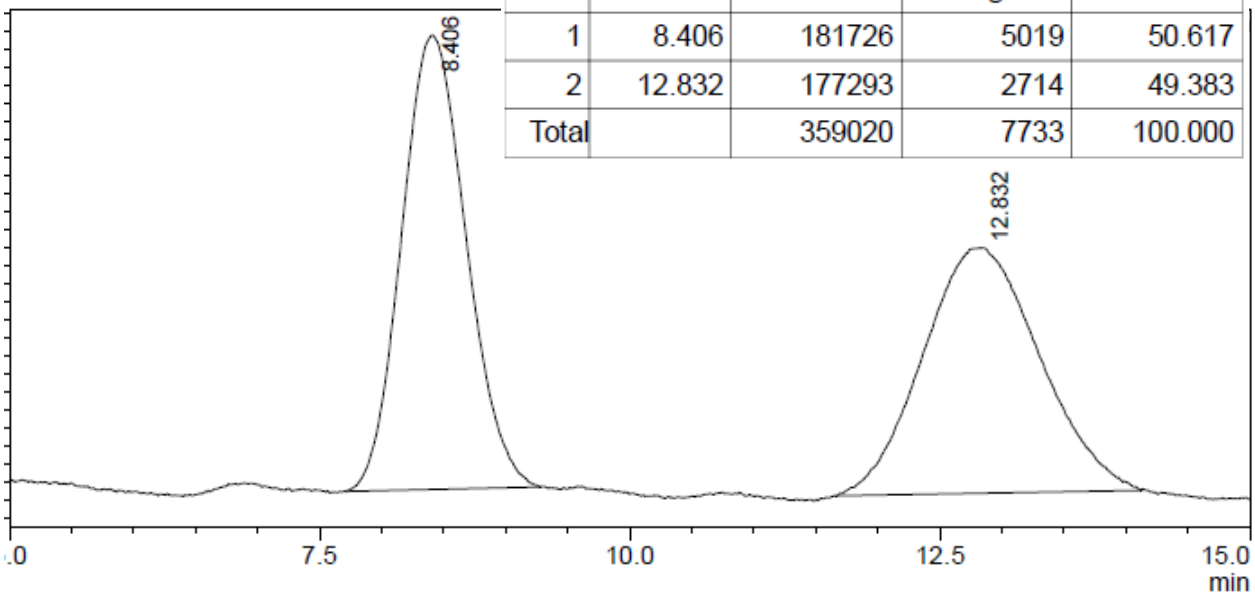
^{13}C NMR:



OJ; 5% *i*PrOH in Heptane; 1.5 mL/min; 30 °C

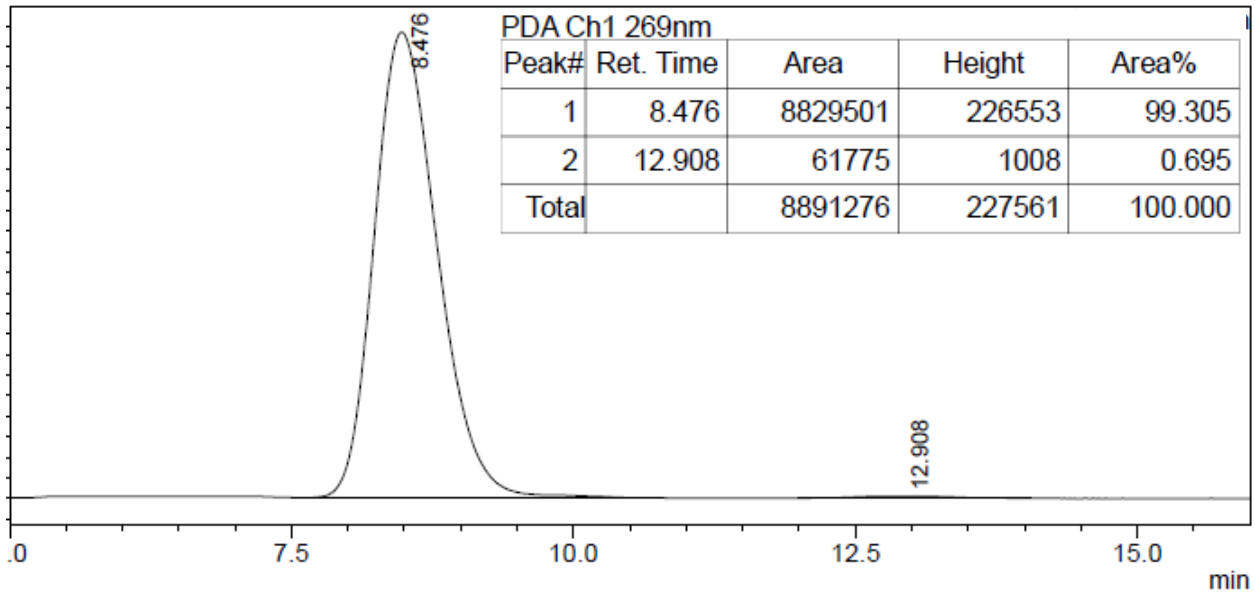
PDA Ch1 269nm

Peak#	Ret. Time	Area	Height	Area%
1	8.406	181726	5019	50.617
2	12.832	177293	2714	49.383
Total		359020	7733	100.000



PDA Ch1 269nm

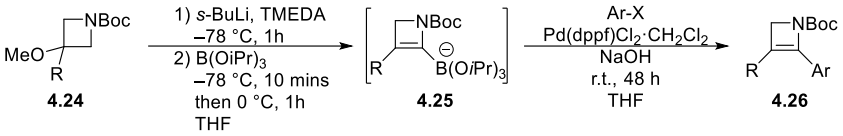
Peak#	Ret. Time	Area	Height	Area%
1	8.476	8829501	226553	99.305
2	12.908	61775	1008	0.695
Total		8891276	227561	100.000



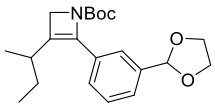
12 Experimental for Chapter II

12.1 5.1 Methods for the Synthesis of Substituted Azetines

Suzuki Cross-Coupling of in-situ Generated 2-Azetines



Azetidines **4.24** (0.5 mmol, 1 eq) were dissolved in 5 mL THF and the solution was cooled down to −78 °C. After the addition of TMEDA (0.19 ml, 1.3 mmol, 2.5 eq), a solution of *s*-BuLi in cyclohexane (1.9 mL, 1.3 mmol, 2.5 eq, 1.31 M) was added dropwise and the mixture stirred for 1 hour. B(O*i*Pr)$_3$ (230 µL, 1.0 mmol, 2.0 eq) was then added and the resulting mixture stirred for 10 minutes at −78 °C before being warmed to 0 °C and stirred for another hour. Pd(dppf)Cl_2·CH_2Cl_2 (16 mg, 0.02 mmol, 4 mol%), the corresponding aryl halide (1.0 mmol, 2.0 eq) and an aqueous solution of sodium hydroxide (1.5 mL, 1.5 mmol, 3.0 eq, 1 M) were consecutively added. The reaction mixture was then stirred for 48 hours at ambient temperature. After aqueous workup and extraction with Et_2O (2 × 10 ml), the organic phases were combined and dried over Na_2SO_4. The solvents were evaporated and the crude product was purified by column chromatography on preneutralized silica gel (1% NEt_3) with the appropriate solvent mixture to yield compounds **4.26**.

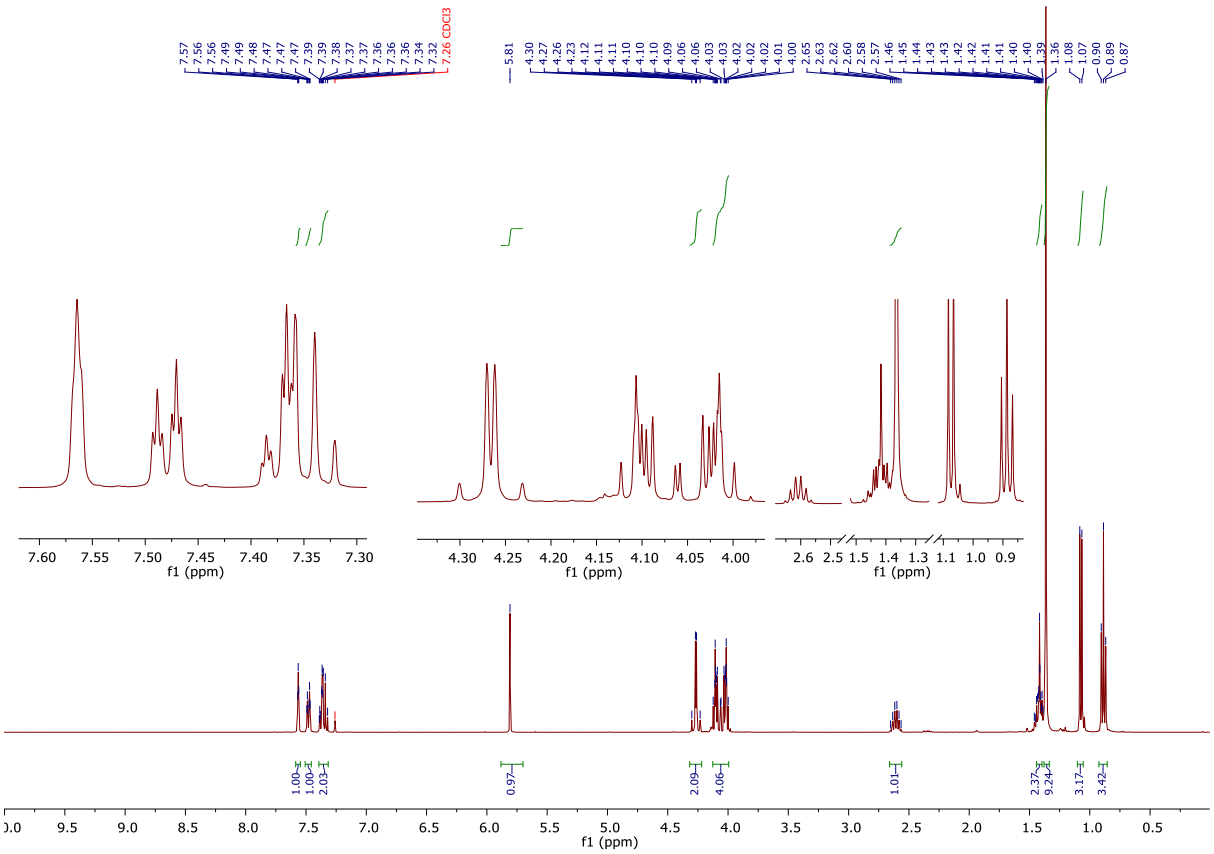


tert-Butyl 4-(3-(1,3-dioxolan-2-yl)phenyl)-3-(*sec*-butyl)azete-1(2*H*)-carboxylate

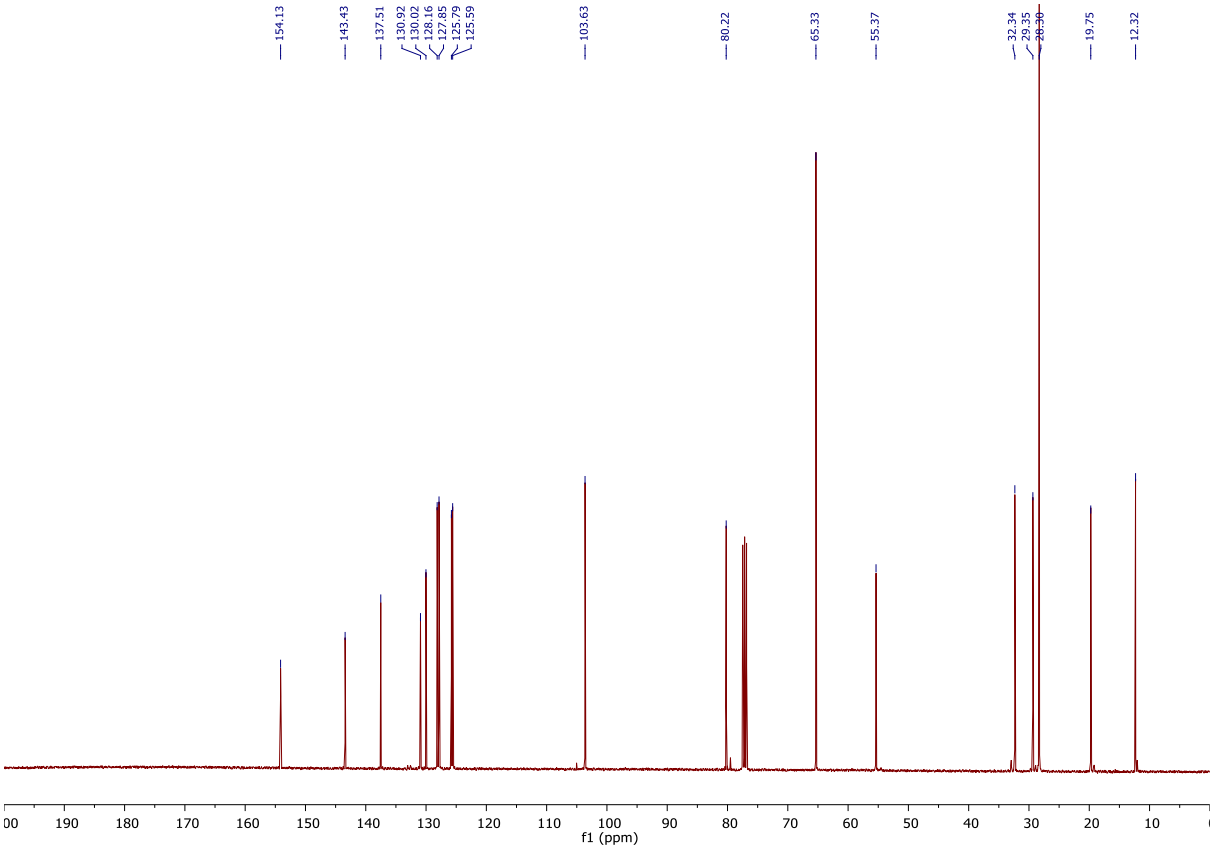
Using *tert*-butyl 3-(*sec*-butyl)-3-methoxyazetidine-1-carboxylate and 2-(3-bromophenyl)-1,3-dioxolane provided the product (128 mg, 0.36 mmol, 71%) as a colorless oil.

***R*$_f$** = 0.48 (20% EtOAc in hexanes; UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.56 (t, *J* = 1.7 Hz, 1H), 7.48 (dt, *J* = 7.1, 1.7 Hz, 1H), 7.39 – 7.31 (m, 2H), 5.81 (s, 1H), 4.33 – 4.20 (m, 2H), 4.16 – 3.97 (m, 4H), 2.68 – 2.51 (m, 1H), 1.48 – 1.39 (m, 2H), 1.36 (s, 9H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) 154.1, 143.4, 137.5, 130.9, 130.0, 128.2, 127.9, 125.8, 125.6, 103.6, 80.2, 65.3, 55.4, 32.3, 29.4, 28.3, 19.8, 12.3. **LRMS** (ESI pos) *m/z* (%): 360.2 (11) $[M]^+$, 304.2 (100), 260.1 (10). **HRMS** (ESI pos): calcd for $C_{21}H_{30}NO_4^+$ $[M]^+$: 360.2169, found 360.2174. **IR**: $\tilde{\nu}$ (cm^{-1}) 2964 (m), 2932 (w), 2876 (w), 1700 (vs), 1478 (w), 1454 (m), 1364 (vs), 1344 (s), 1284 (w), 1250 (m), 1222 (m), 1170 (s), 1134 (vs), 1098 (s), 1076 (s), 1048 (w), 1016 (m), 970 (m), 944 (m), 912 (w), 894 (m), 854 (w), 798 (m), 770 (m), 730 (m), 696 (m), 660 (w).

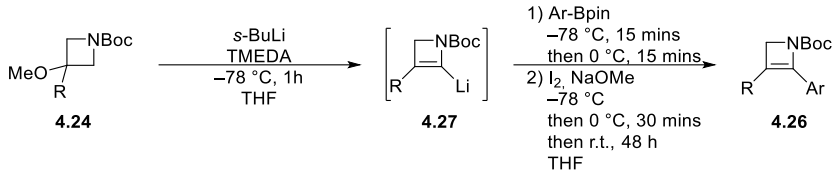
^{1}H NMR:



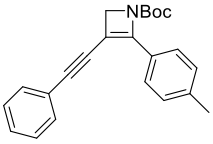
^{13}C NMR:



Zweifel Olefination of in-situ Generated 2-Azetines



Azetidines **4.24** (0.5 mmol, 1 eq) were dissolved in 5 mL THF and the solution was cooled down to −78 °C. After the addition of TMEDA (0.19 ml, 1.3 mmol, 2.5 eq), a solution of *s*-BuLi in cyclohexane (1.9 mL, 1.3 mmol, 2.5 eq, 1.31 M) was added dropwise and the mixture stirred for 1 hour. The corresponding pinacol arylboronate was added in THF (0.5 mmol, 1 eq, 0.25 M) and the resulting mixture stirred at −78 °C and then at 0 °C for 15 minutes each. The mixture was then cooled back to −78 °C and a solution of iodine in THF (0.5 mmol, 1 eq, 0.25 M) was added dropwise, followed by the addition of a suspension of sodium methoxide in methanol (5.0 mmol, 10 eq, 2.5 M). The mixture was then stirred at 0 °C for 30 minutes and subsequently at ambient temperature for 48 hours. After aqueous workup and extraction with Et_2O (2 × 10 ml), the organic phases were combined and dried over Na_2SO_4. The solvents were evaporated and the crude product was purified by column chromatography on preneutralized silica gel (1% NEt_3) with the appropriate solvent mixture to yield compounds **4.26**.

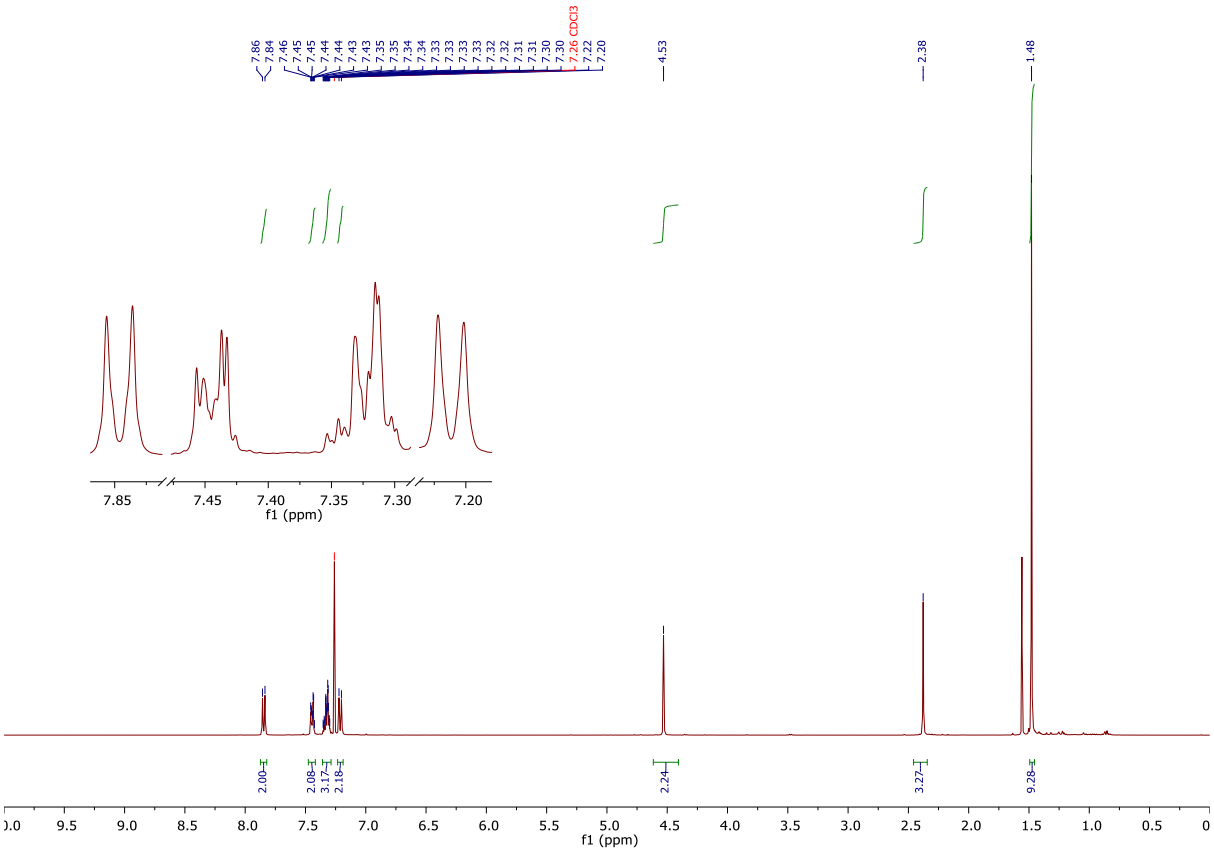


tert-Butyl 3-(phenylethynyl)-4-(*p*-tolyl)azete-1(2*H*)- carboxylate

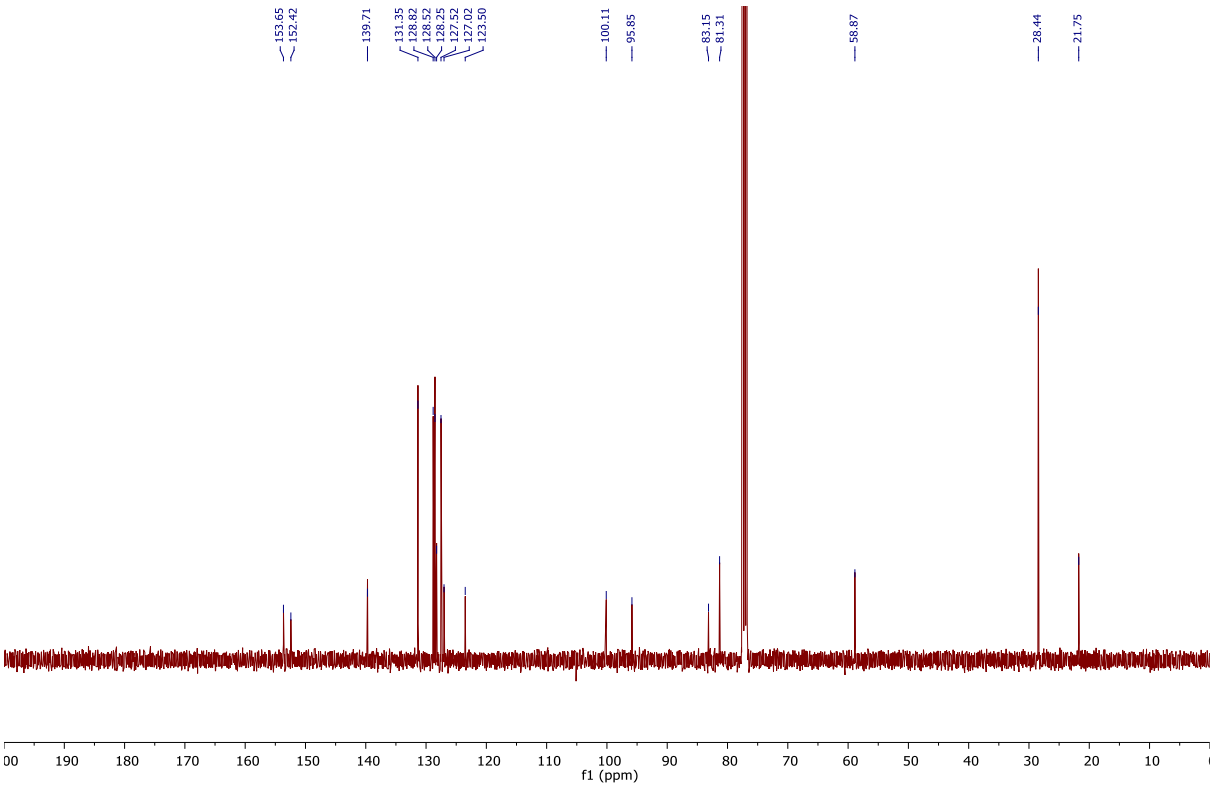
Using *tert*-butyl 3-methoxy-3-(phenylethynyl)azetidine-1-carboxylate and 4,4,5,5-tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane provided the product (93 mg 0.27 mmol, 54%) as a colorless oil.

***R*f** = 0.74 (20% EtOAc in hexanes; UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.85 (d, *J* = 8.2 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.36 – 7.29 (m, 3H), 7.21 (d, *J* = 8.1 Hz, 2H), 4.53 (s, 2H), 2.38 (s, 3H), 1.48 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) 153.7, 152.4, 139.7, 131.3, 128.8, 128.5, 128.3, 127.5, 127.0, 123.5, 100.1, 95.9, 83.2, 81.3, 58.9, 28.4, 21.7. **LRMS** (ESI pos) *m/z* (%): not found. **HRMS** (ESI pos): not found. **IR**: $\tilde{\nu}$ (cm^{-1}) 2978 (w), 2936 (w), 2202 (m), 1744 (m), 1710 (s), 1684 (s), 1490 (w), 1444 (w), 1394 (m), 1362 (s), 1324 (m), 1260 (m), 1228 (s), 1148 (vs), 1086 (s), 1038 (m), 1024 (m), 1000 (m), 974 (m), 954 (m), 904 (m), 848 (m), 802 (m), 774 (m), 758 (s), 690 (s).

^{1}H NMR:

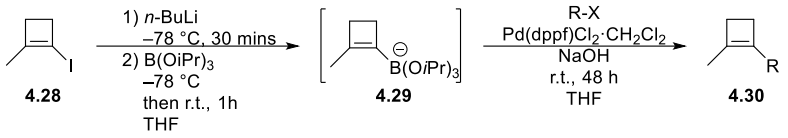


^{13}C NMR:



12.2 5.2 One-Pot Preparation of Stable Organoboronate Reagents for the Functionalization of Unsaturated Four- and Five-Membered Carbo- and Heterocycles

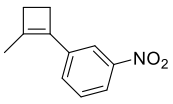
Suzuki Cross-Coupling of Storable Cyclobutenylboronates



4.28 **4.29** **4.30**

To a solution of cyclobutene iodide **4.28** (58 mg, 0.30 mmol, 1 eq) in 0.6 mL Et_2O was slowly added a solution of *n*-BuLi (135 μL, 0.33 mmol, 1.10 eq, 2.44 M) in hexane at −78 °C. After stirring for 30 minutes at aforementioned temperature, $B(OiPr)_3$ (80 μL, 0.35 mmol, 1.15 eq) and 0.6 mL THF were added and the resulting mixture stirred for another hour at room temperature and then stored in the freezer at −20 °C until used.

$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mg, 4 mol%), cross-coupling partner (aromatic and vinylic iodide, bromide, tosylate or chloride) (0.90 eq) and an aqueous solution of NaOH (0.9 mL, 1.50 eq, 1.00 M) were subsequently added and the reaction mixture stirred for 48 hours. The mixture was extracted with Et_2O (3 × 20 mL), washed with brine (20 mL), dried with $MgSO_4$, concentrated and purified by flash-column chromatography on silica gel with the appropriate solvent mixture.

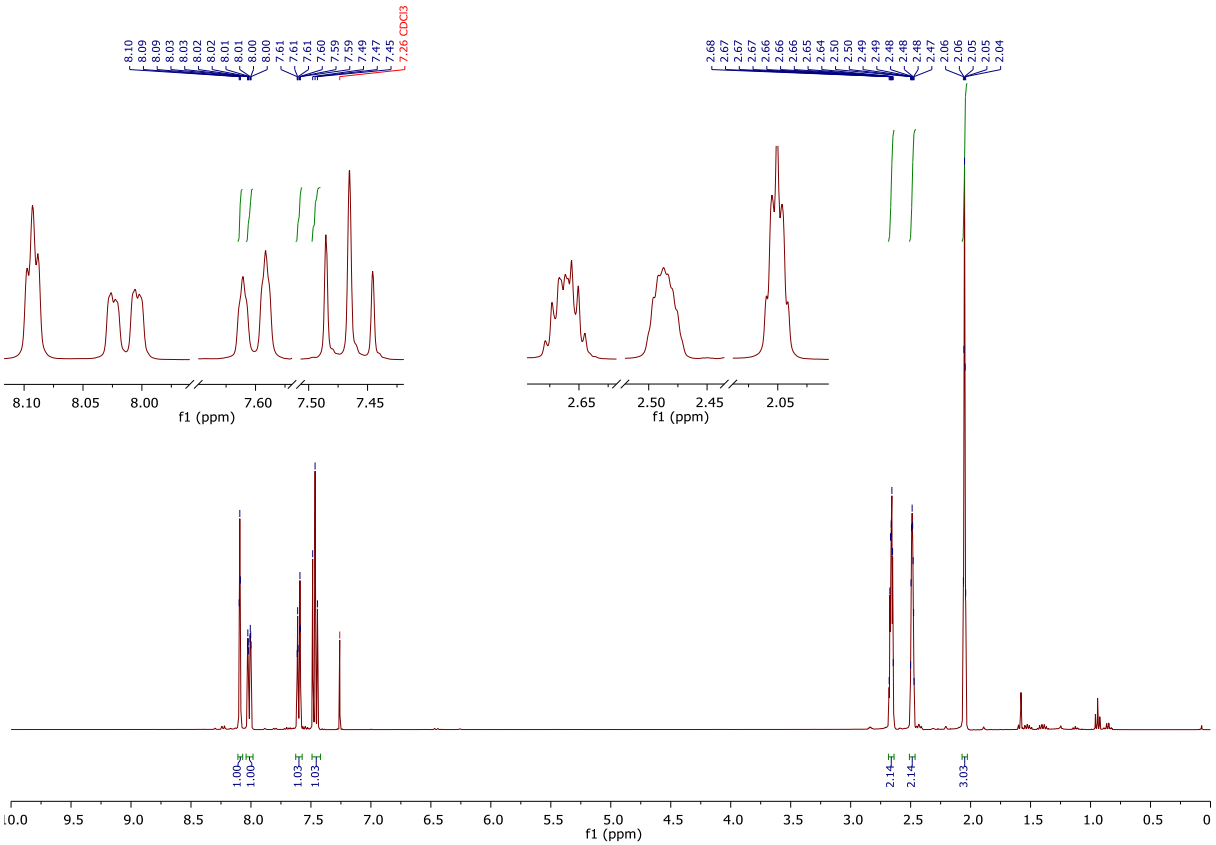


1-(2-Methylcyclobut-1-en-1-yl)-3-nitrobenzene

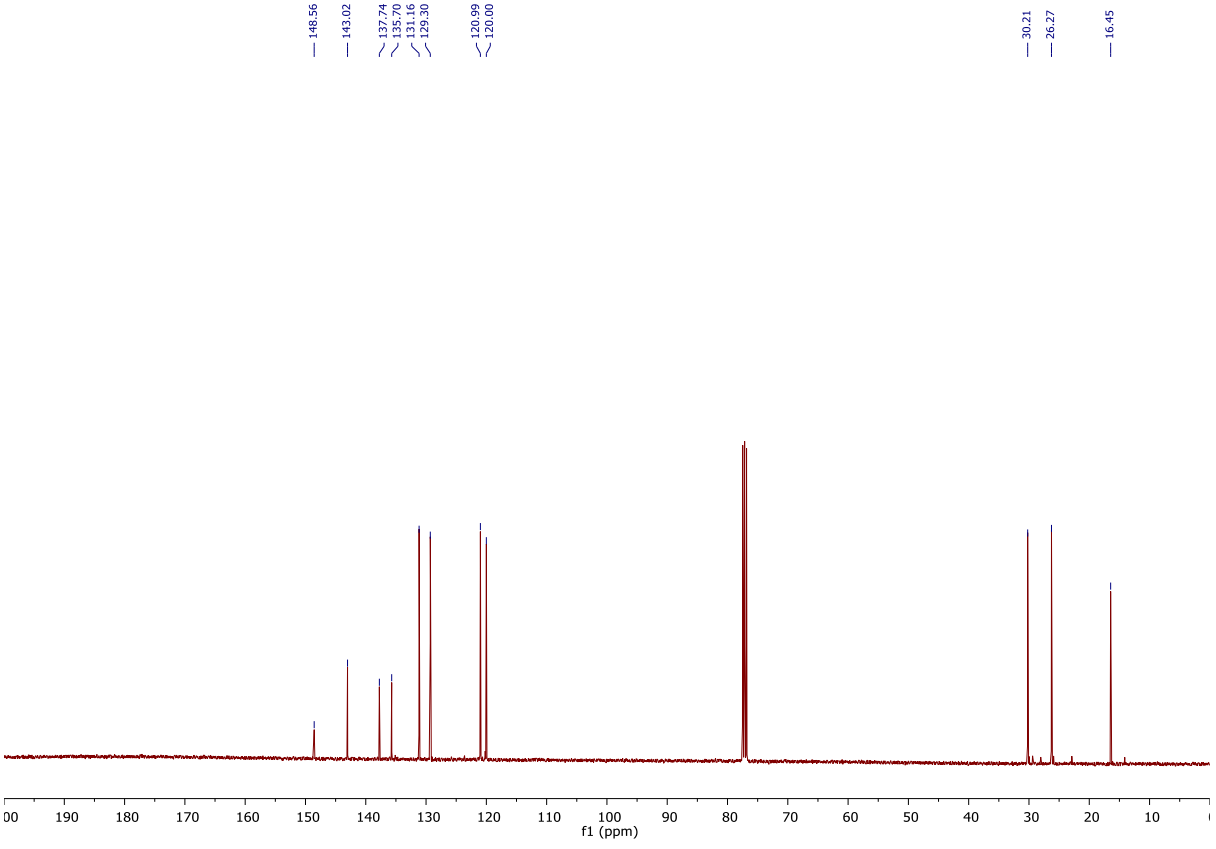
Using 1-iodo-2-methylcyclobute-1-ene and 1-iodo-3-nitrobenzene provided the product (49 mg, 0.26 mmol, 96%) as a yellow solid.

***R*f** = 0.32 (2% EtOAc in hexanes; UV, $KMnO_4$, PAA). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 8.09 (t, *J* = 2.0 Hz, 1H), 8.01 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1H), 7.60 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 2.70 – 2.63 (m, 2H), 2.52 – 2.42 (m, 2H), 2.08 – 1.99 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) 148.6, 143.0, 137.7, 135.7, 131.2, 129.3, 121.0, 120.0, 30.2, 26.3, 16.5. **LRMS** (EI): *m*/z (%) = 189 (11) $[M]^+$, 172 (43), 141 (67), 128 (100), 115 (58). **HRMS** (EI): calcd for $C_{11}H_{11}NO_2^+$ $[M]^+$: 189.0790; found: 189.0783. mp 115 – 117 °C.

^{1}H NMR:



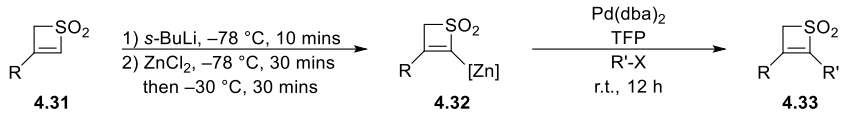
^{13}C NMR:



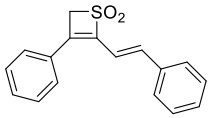
13 Experimental for Chapter III

13.1 8.1 Parallel Approaches for the Functionalization of Thietes: α-Metalation versus C–H Activation

Negishi Cross-Coupling of Thiete Dioxides



A flask was charged with 1,1-dioxothiete derivative **4.31** (0.20 mmol, 1 eq) and 2 mL THF was added. The reaction mixture was cooled to −78 °C and a solution of *s*-BuLi (190 µL, 0.24 mmol, 1.20 eq, 1.25 M) in cyclohexane was added dropwise. After 10 minutes, a solution of $ZnCl_2$ (0.26 mL, 0.26 mmol, 1.30 eq, 1.0 M) in THF was added dropwise and the solution was stirred another 30 minutes at –78 °C. Then the cooling bath was changed to −30 °C and the reaction was stirred for another 30 minutes. In parallel, a separate flask was charged with $Pd(dba)_2$ (4.6 mg, 8 µmol, 4 mol%) and 0.5 mL THF and tri(furan-2-yl)phosphane (TFP) (4.0 mg, 16 µmol, 8 mol%) in 0.5 mL THF was added at ambient temperature. The mixture was stirred until a color change form dark red to yellow was observed. Then the desired halogenide (0.16 mmol, 0.80 eq) in 0.5 mL THF was added and the solution was stirred for 15 minutes. Subsequently, the solution containing the metal-species was added dropwise to the Pd/TFP/halogenide solution. The reaction mixture was stirred at ambient temperature for 12 hours. Upon completion, it was quenched with water and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtrated, concentrated in vacuo and purified by flash-column chromatography on silica gel with the appropriate solvent mixture.



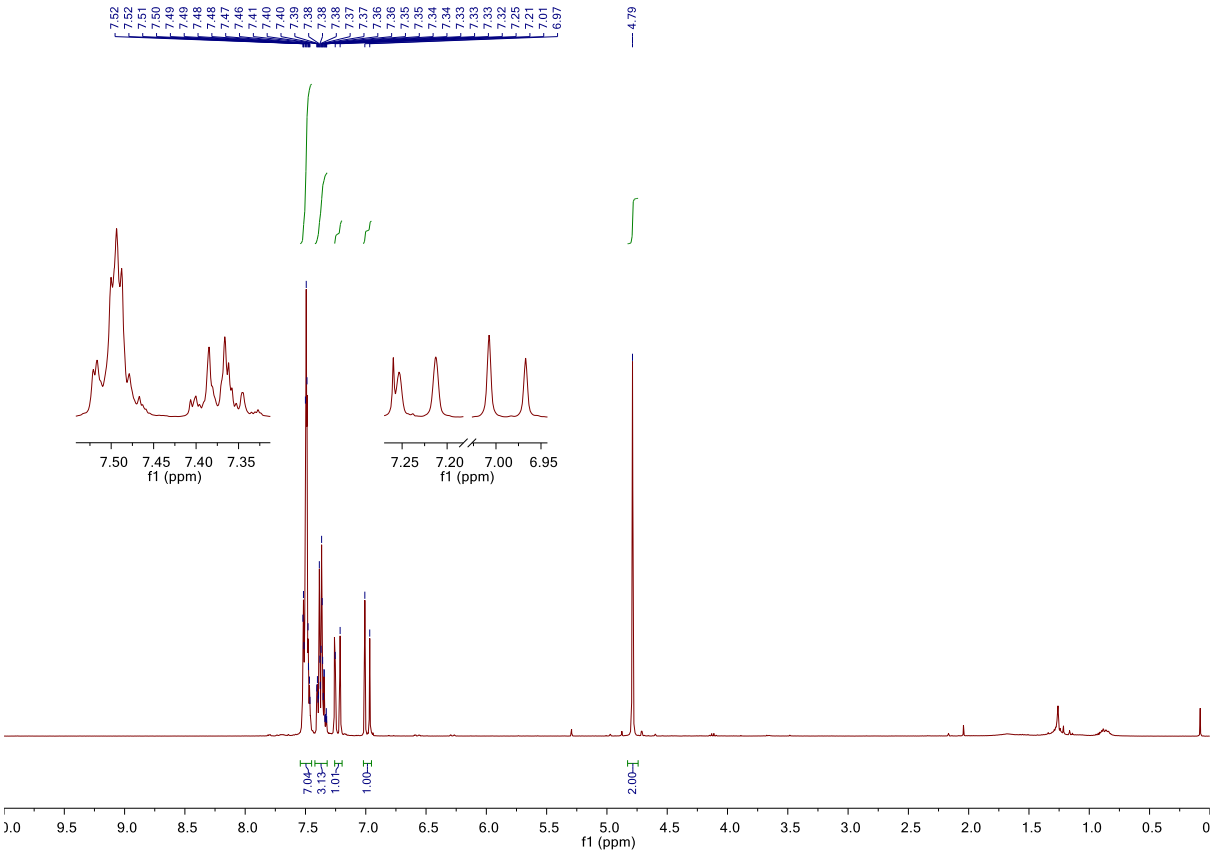
(*E*)-3-Phenyl-4-styryl-2*H*-thiete 1,1-dioxide

Using 3-phenyl-2*H*-thiete 1,1-dioxide and (*E*)-(2-iodovinyl)benzene provided the product (29 mg, 0.10 mmol, 64%) as a colorless oil.

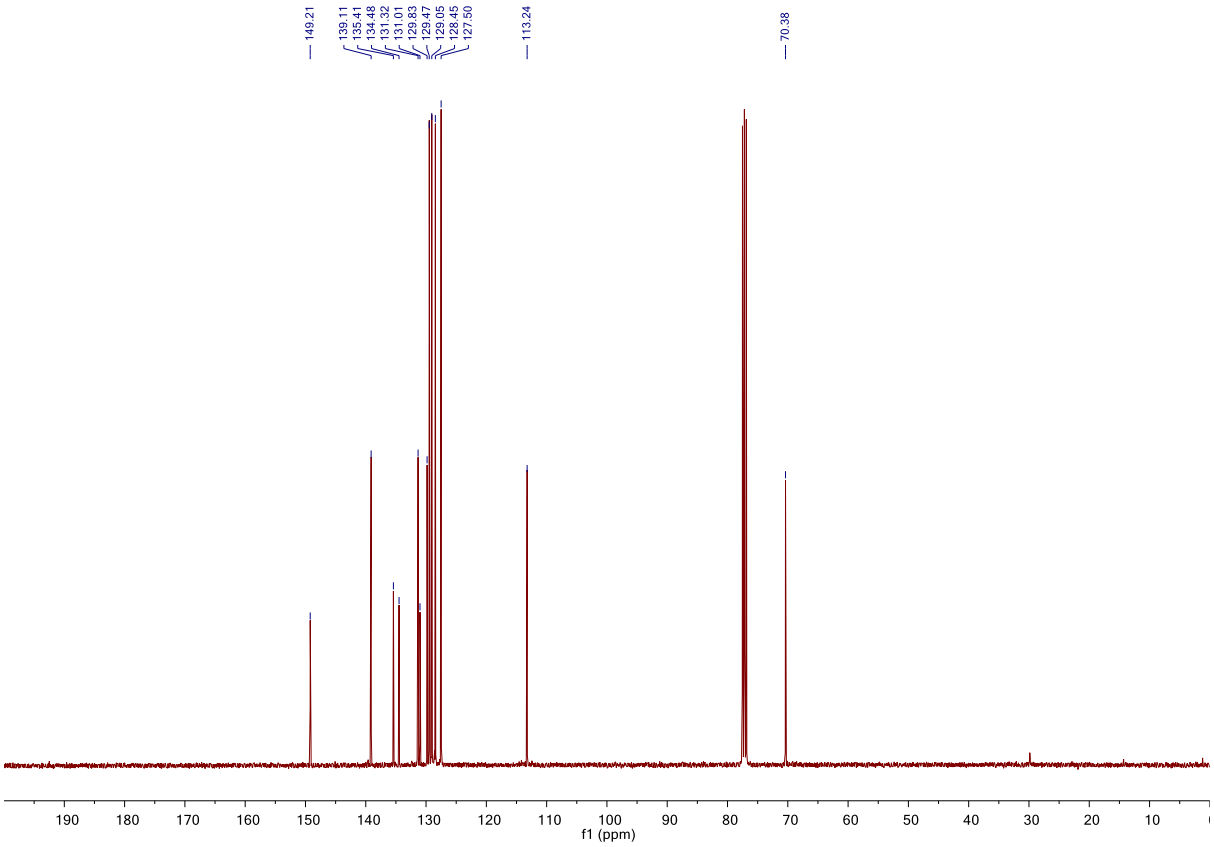
***R*f** = 0.25 (15% EtOAc in hexanes; UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.58 – 7.44 (m, 7H), 7.42 – 7.31 (m, 3H), 7.23 (d, *J* = 16.3 Hz, 1H), 6.99 (d, *J* = 16.3 Hz, 1H), 4.79 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) 149.2, 139.1, 135.4, 134.5, 131.3, 131.0, 129.8, 129.5, 129.0, 128.5, 127.5, 113.2, 70.4. **LRMS** (DEP/EI): *m/z* (%): 282 (14) $[M]^+$, 207 (70), 181 (100), 165 (38), 152 (18), 135 (17). **HRMS** (EI): calcd for $C_{17}H_{14}O_2S^+$ $[M]^+$: 282.0715; found: 282.0710. **IR**: $\tilde{\nu}$ (cm^{-1}) 2954 (w), 2923 (w), 2853 (w), 1615 (w), 1594 (vw), 1568 (vw), 1498 (w), 1492 (w), 1450 (w), 1446 (w), 1404 (vw), 1346 (w), 1340 (w), 1291

(vs), 1216 (w), 1186 (s), 1180 (s), 1121 (vs), 1076 (w), 1048 (w), 1040 (w), 1022 (w), 947 (s), 883 (w), 849 (w), 818 (w), 765 (vs), 759 (s), 736 (m), 720 (s), 694 (s), 684 (vs).

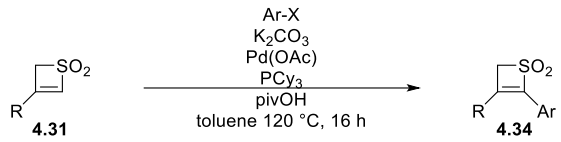
^{1}H NMR:



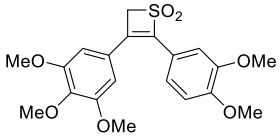
^{13}C NMR:



C–H-Functionalization of Thiete Dioxides



A pressure tube was charged with 1,1-dioxothiete derivative **4.31** (0.2 mmol, 1 eq) and 2 mL toluene was added. Subsequently were added K_2CO_3 (55 mg, 0.4 mmol, 2.0 eq), $Pd(OAc)_2$ (1.8 mg, 8 µmol, 4 mol%), tricyclohexylphosphane (PCy_3) (4.5 mg, 16 µmol, 8 mol%), the corresponding halogenide (0.3 mmol, 1.5 eq) and a few drops of pivalic acid (~7 µL, 30 mol%). The mixture was stirred at 120 °C in the sealed pressure tube until TLC showed consumption of the starting 1,1-dioxothiete (approx. 16 hours). After cooling to ambient temperature, the tube was opened and a 1:1 mixture of H_2O:Et_2O (4 mL) was added. The aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtrated, concentrated in vacuo and purified by flash-column chromatography on silica gel with the appropriate solvent mixture.

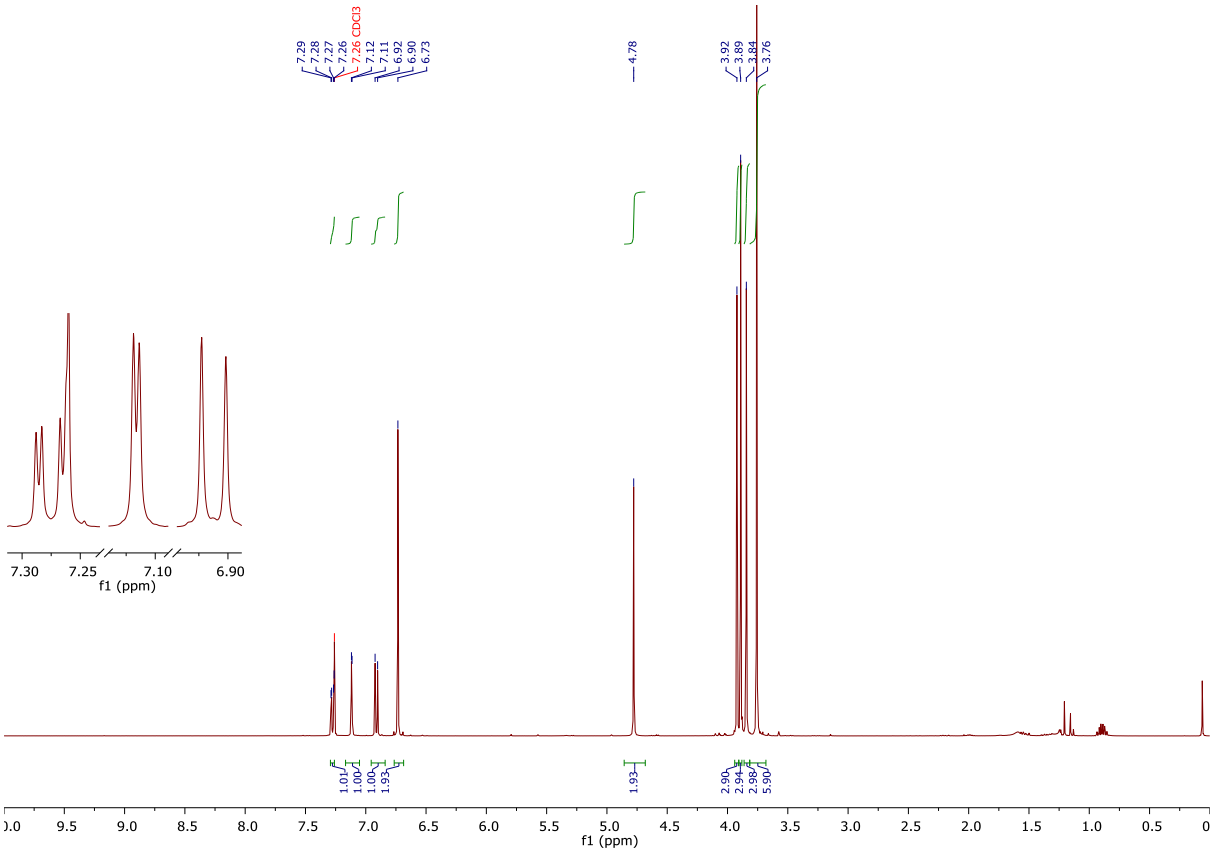


4-(3,4-Dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-2*H*-thiete 1,1-dioxide

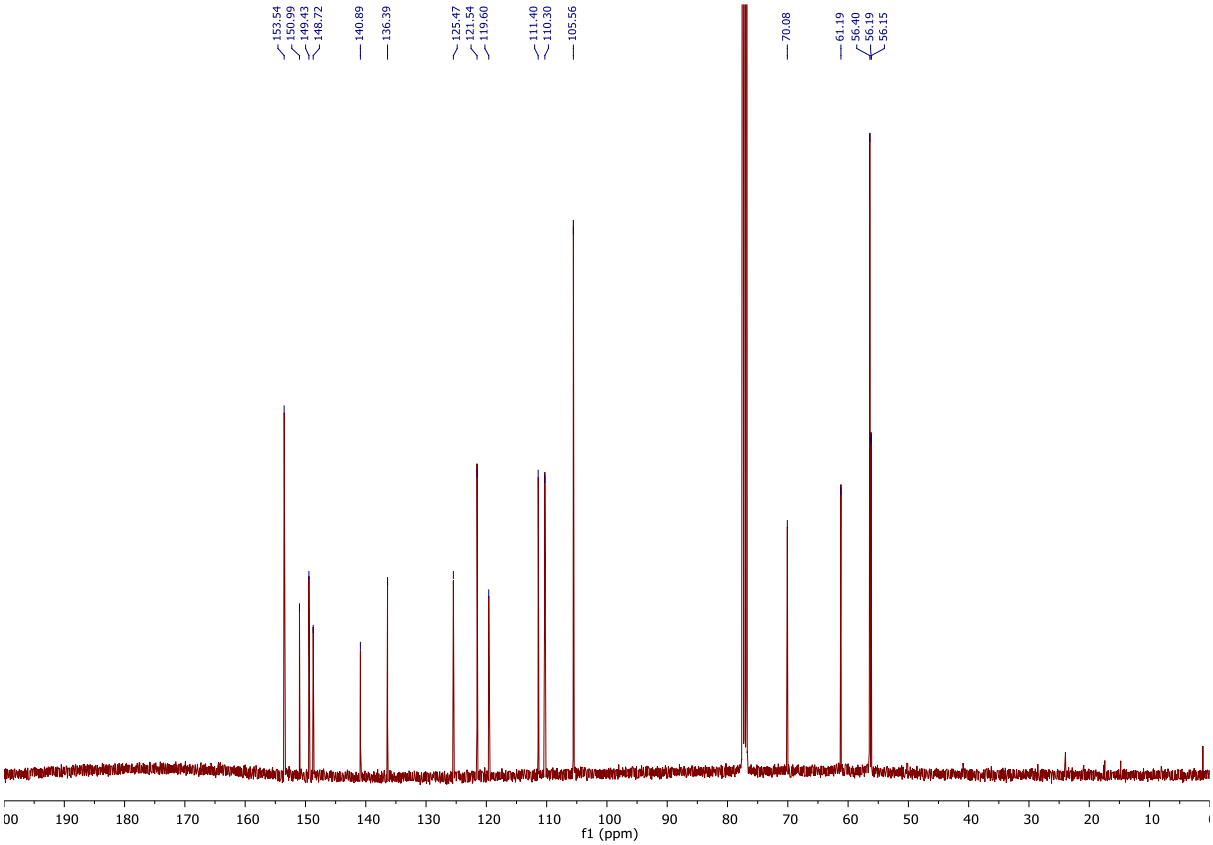
Using 2-(3,4,5-trimethoxyphenyl)-2*H*-thiete 1,1-dioxide and 4-bromo-1,2-dimethoxybenzene provided the product (49 mg, 0.12 mmol, 60%) as a colorless oil.

***R*f** = 0.19 (40% EtOAc in hexanes; UV, $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.28 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.12 (d, *J* = 2.0 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.73 (s, 2H), 4.78 (s, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.76 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) 153.5, 151.0, 149.4, 148.7, 140.9, 136.4, 125.5, 121.5, 119.6, 111.4, 110.3, 105.6, 70.1, 61.2, 56.4, 56.2, 56.2. **LRMS** (DEP/EI): *m/z* (%):406 (1) $[M]^+$, 358 (68), 327 (29), 281 (10), 192 (28), 165 (100), 137 (13). **HRMS** (EI): calcd for $C_{20}H_{22}O_7S^+$ $[M]^+$: 406.1086; found: 406.1081 **IR**: $\tilde{\nu}$ (cm^{-1}) 2936 (w), 1580 (w), 1514 (m), 1462 (m), 1416 (m), 1298 (m), 1275 (w), 1257 (w), 1249 (m), 1186 (w), 1124 (vs), 1000 (w).

^{1}H NMR:



^{13}C NMR:


153.54
150.99
149.43
148.72
140.89
136.39
125.47
121.54
119.60
111.40
110.30
105.56
70.08
61.19
56.40
56.19
56.15
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)