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Cobalt-Catalyzed Reactions utilizing Organozinc Reagents and a Tailored Magnesium Amide Base for the Regioselective Functionalization of Aryl Azoles

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(Ferdinand H. Lutter)

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3) F. H. Lutter, L. Grokenberger, P. Spieß, J. M. Hammann, K. Karaghiosoff, P. Knochel, "Cobalt-Catalyzed Cross-Coupling of Functionalized Alkylzinc Reagents with (Hetero)Aryl Halides", *Angew. Chem. Int. Ed.* **2020**, *59*, 5546-5550.

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Non quia difficilia sunt non audemus,

sed quia non audemus difficilia sunt.

L. A. Seneca the Younger

Abbreviations

1°	primary
2°	secondary
3°	tertiary
Ac	acetyl
acac	acetylacetonate
Alk	alkyl
aq	aqueous
Ar	aryl
ATR	attenuated total reflection (IR)
bipy	2,2'-bipyridine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
calc.	calculated
conc.	concentrated
Cy	cyclohexyl
DACH	(±)-*trans*-1,2-diaminocyclohexane
dba	(1*E*, 4*E*)-1,5-iphenylpenta-1,4-dien-3-one
DBDMH	1,3-dibromo-5,5-dimethyl-hydantoin
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DCM	dichloromethane
Dip	2,6-diisopropylphenyl
DIPEA	*N*,*N*-Diisopropylethylamine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)-ferrocene
dtbbpy	4,4'-di-*tert*-butyl-2,2'-dipyridyl
E	electrophile
ee	enantiomeric excess
EI	electron impact ionization
equiv	equivalent
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
Hal	halide
Het	heteroaryl
HRMS	high resolution mass spectrometry
*i*Pr	*iso*-propyl
IR	infrared
J	coupling constant (NMR)
M	molarity
m	meta
m.p.	melting point
Me	methyl
Met	metal
MS	mass spectrometry
MTBE	2-Methoxy-2-methylpropane
MW	microwave irraditation
*n*Bu	*n*-butyl
NMI	1-methylimidazole
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	ortho
o/n	overnight

p	para
Ph	phenyl
phen	phenanthroline
Phthal	Phthalimide
Piv	pivaloyl
Pr	propyl
Py	pyridyl
R	organic substituents
rt	room temperature
sat.	saturated
*s*Bu	sec-butyl
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
temp	temperature
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
Tf	triflyl
tfp	tri(2-furyl)phosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylene-diamine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
tol	toloyl
TP	typical procedure
Ts	4-toluenesulfonyl
δ	chemical shifts in ppm (parts per million)

Table of Contents

I. Introduction

1. Cobalt-Catalyzed Reactions with Functionalized Zinc Reagents

Transition-metal catalyzed C-C bond forming reactions have considerably shaped the landscape of modern synthetic organic chemistry. Their success culminated in 2003 by awarding Richard Heck, Ei-ichi Negishi and Akira Suzuki the Nobel prize in chemistry.[1] Although the discovery of transition-metal-promoted C-C bond formation reactions can be dated back to the end of the 19th century,[2] the constant need for highly active but also cheap catalytic systems is more relevant than ever. Metal complexes based on palladium salts are the most common catalysts for these transformations. Their broad reaction scope and exceptional high catalytic activity led to numerous applications in academia but also industry.[3] However, major drawbacks of palladium-based catalysis are the need of often sophisticated and costly ligands as well as the high price of the metal itself.[3] Thus, the search for viable alternatives is of huge importance for the chemical community. In this context, cobalt salts are of great interest, since their relatively high abundance makes them rather inexpensive catalysts.[4] The low price combined with a high catalytic activity have triggered research towards the usage of cobalt catalysts for several transformations.[5]

[1] The Nobel Prize in Chemistry **2010**. NobelPrize.org. Nobel Media AB **2020**. Wed. 11 Mar 2020. <https://www.nobelprize.org/prizes/chemistry/2010/summary/>.

[2] a) C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422-424; b) C. Glaser, *Ann. Chem. Pharm*. **1870**, *154*, 137-171; c) A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 50-56; d) F. Ullmann, J. Bielecki, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174-2185; e) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085.

[3] a) *Cross-Coupling Reactions: A Practical Guide*, (Ed.: N. Miyaura), Springer, Heidelberg, **2002**; b) *Metal-Catalyzed Cross-Coupling Reactions, Second Edition* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; c) *Modern Drug Synthesis* (Eds.: J. J. Li, D. S. Johnson), John Wiley & Sons, Hoboken, **2010**; d) A. Biffis, P. Centomo, A. Del Zotto, M. Zecca, *Chem. Rev.* **2018**, *118*, 2249−2295.

[4] a) H. Pellissier, H. Clavier, *Chem. Rev.* **2014**, *114*, 2775-2823; b) X.-G. Liu, C.-J. Zhou, E. Lin, X.-L. Han, S.-S. Zhang, Q. Li, H. Wang, *Angew. Chem. Int. Ed*. **2018**, *57*, 13096-13100.

[5] a) H. Shinokubo, K. Oshima, *Eur. J. Org. Chem.* **2004**, *2004*, 2081-2091; b) W. Hess, J. Treutwein, G. Hilt, *Synthesis* **2008**, *22*, 3537-3562; c) C. Gosmini, J.-M. Bégouin, A. Moncomble, *Chem. Commun.* **2008**, 3221-3233; d) G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435-1462; e) C. E. I. Knappke, S. Grupe, D. Gärtner, M. Corpet, C. Gosmini, A. J. von Wangelin, *Chem. Eur. J.* **2014**, *20*, 6828-6842; f) M. S. Hofmayer, J. M. Hammann, F. H. Lutter, P. Knochel, *Synthesis* **2017**, *49*, 3925-3930; g) *Non-Noble Metal Catalysis* (Eds.: R. J. M. Klein Gebbink, M.-E. Moret), Wile-VCH, Weinheim, **2019**; f) C. Dorval, C. Gosmini, *Low-valent Cobalt Complexes in C-X Coupling and Related Reactions in Cobalt Catalysis in Organic Synthesis* (Ed.: M. Hapke, G. Hilt), Wiley-VCH, Weinheim, **2020**.

Whereas cobalt-catalyzed reactions using organomagnesium reagents have been widely reported,[5] a growing interest in the application of organozinc reagents as reaction partners became apparent.[5f,6]

Zinc organometallics provide some highly advantageous properties. In comparison to the rather ionic carbon-metal bond of lithium or magnesium organometallics the carbon-zinc bond has a more covalent character, thus enabling the tolerance of a plethora of sensitive functional groups.[7] This, in turn, causes a comparably low reactivity with a range of electrophiles. However, the low lying *p*-orbitals of organozinc reagents enable a fast transmetalation to transition-metal catalysts, which opens the way for a variety of reactions due to the presence of empty *d*-orbitals at the transition-metal centre.[7c] Furthermore, the comparably low toxicity and constantly increasing commercial availability make zinc reagents a unique class of compounds.[7] The following part outlines the most common methods for the preparation of functionalized organozinc reagents.

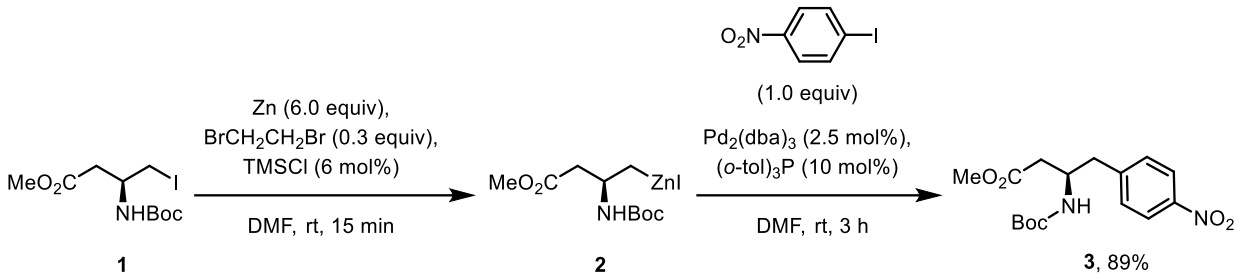
[6] a) J.-M. Bégouin, C. Gosmini, *J. Org. Chem.* **2009**, *74*, 3221-3224; b) J. M. Hammann, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 4478-4481; c) D. Haas, J. M. Hammann, F. H. Lutter, P. Knochel, *Angew. Chem. Int. Ed.* **2016**, *55*, 3809-3812; d) L. Thomas, F. H. Lutter, M. S. Hofmayer, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2018**, *20*, 2441-2444; e) F. Liu, J. Zhong, Y. Zhou, Z. Gao, P. J. Walsh, W. Wang, S. Ma, S. Hou, S. Liu, M. Wang, M. Wang, Q. Bian, *Chem. Eur. J.* **2018**, *24*, 2059-2064.

[7] a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117-2188; b) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Preparation and Applications of Functionalized Organozinc Compounds in Organic Reactions, Vol. 58* (Ed.: L. E. Overman), Wiley, New York, **2001**; c) P. Knochel, H. Leuser, L-Z. Gong, S. Perrone, F. F. Kneisel, *Polyfunctional Zinc Organometallics for Organic Synthesis in Handbook of Functionalized Organometallics,* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**; d) P. Knochel, H. Leuser, L.-Z. Gong, S. Perrone, F. F. Kneisel, *Functionalized Organozinc Compounds in Patai's Chemistry of Functional Groups: Functionalized Organozinc Compounds Part 1* (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2006**; e) A. Sidduri, J. Tilley, N. Fotouhi, *Synthesis* **2014**, *46*, 430-444; f) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540-1552; g) A. D. Dilman, V. V. Levin, *Tetrahedron Lett.* **2016**, *57*, 3986-3992; h) A. D. Benischke, M. Ellwart, M. R. Becker, P. Knochel, *Synthesis* **2016**, *48*, 1101-1107; i) F. H. Lutter, M. S. Hofmayer, J. M. Hammann, V. Malakhov, P. Knochel *Generation and Trapping of Functionalized Aryl- and Heteroarylmagnesium and -Zinc Compounds in Organic Reactions, Vol. 100* (Ed.: S. E. Denmark), Wiley, New York, **2019**.

2. Preparation of Polyfunctional Organozinc Reagents

2.1 Oxidative Insertion of Zinc Powder

Organozinc reagents can be obtained *via* oxidative insertion of zinc powder into a carbon-halide bond. However, zinc dust is often covered by an oxide layer, which significantly hampers the reaction. Thus, in order to ensure a fast and complete insertion reaction, the surface of the metal has to be activated prior to use. Treatment of the metal powder with a combination of trimethylsilyl chloride and 1,2-dibromoethane enables the preparation of various alkylzinc reagents from the corresponding iodides.[7c] Hence, the reaction of zinc with β-amino acid derivative **1** proceeded within 15 min affording the polyfunctional alkylzinc reagent **2**, which underwent a subsequent cross-coupling leading to the alkylated arene **3** in 89% yield (Scheme 1). Using DMF as solvent for the generation of **2** was crucial to avoid β-elimination of the amino group.[8]

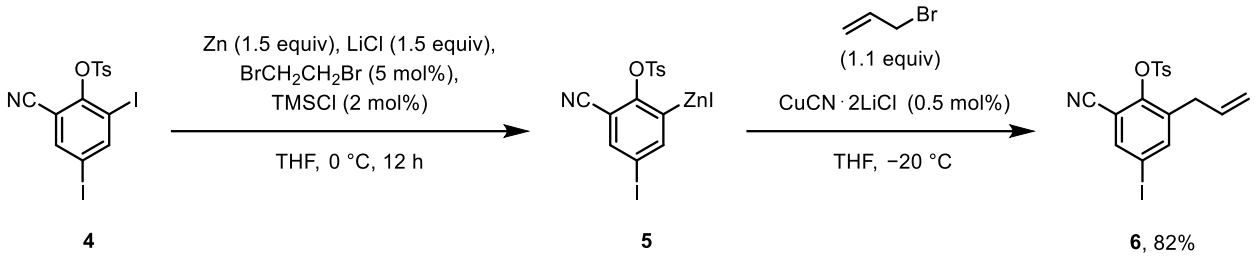


Scheme 1: Preparation of a chiral alkylzinc reagent and subsequent palladium-catalyzed cross-coupling.

Alternatively, Riecke found that *in situ* reduction of $ZnCl_2$ with alkaline metals produces highly active zinc (Riecke-zinc). This allows the formation of various zinc organometallics from alkyl iodides and even bromides. Also, (hetero)aryl halides are readily transformed into the corresponding zinc reagents.[9] A convenient alternative is the activation of the zinc surface with lithium chloride, which enables the preparation of a variety of alkyl-, alkenyl-, aryl- and heteroarylzinc reagents.[10] Mechanistic studies revealed that LiCl promotes the solubilization of surface-bound organometallic species, thus enabling the progress of the insertion reaction.[11] Under these conditions, zinc powder inserted regioselectively into the carbon-

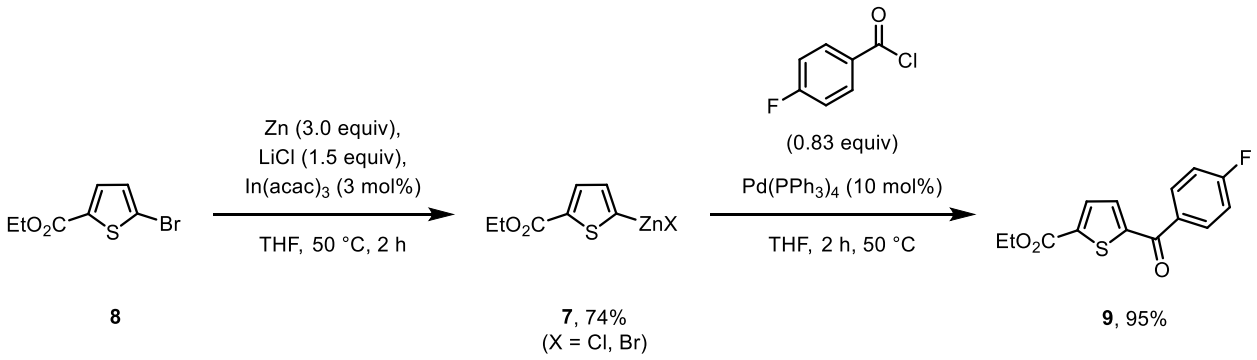
[8] C. S. Dexter, R. F. W. Jackson, J. Elliott, *J. Org. Chem.* **1999**, *64*, 7579-7585.
[9] a) R. D. Riecke, *Science* **1989**, *246*, 1260-1264; b) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925-1956.
[10] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040-6044.
[11] a) C. Feng, D. W. Cunningham, Q. T. Easter, S. A. Blum, *J. Am. Chem. Soc.* **2016**, *138*, 11156-11159; b) C. Feng, Q. T. Easter, S. A. Blum, *Organometallics* **2017**, *36*, 2389-2396.

iodine bond of the polyfunctional aryl tosylate **4** leading to the zinc reagent **5**. A copper-catalyzed allylation afforded the polyfunctional arene **6** in 82% yield (Scheme 2).[12]



Scheme 2: Regioselective zinc insertion and subsequent copper-catalyzed allylation.

Later, it was found that the addition of indium salts further accelerates the insertion reaction. Thus, thiophenylzinc reagent **7** was prepared from the corresponding heterocyclic bromide **8** within 2 h in 74% yield. Subsequent acylation in the presence of a palladium catalyst led to the unsymmetrical ketone **9** in 95% yield (Scheme 3).[13]

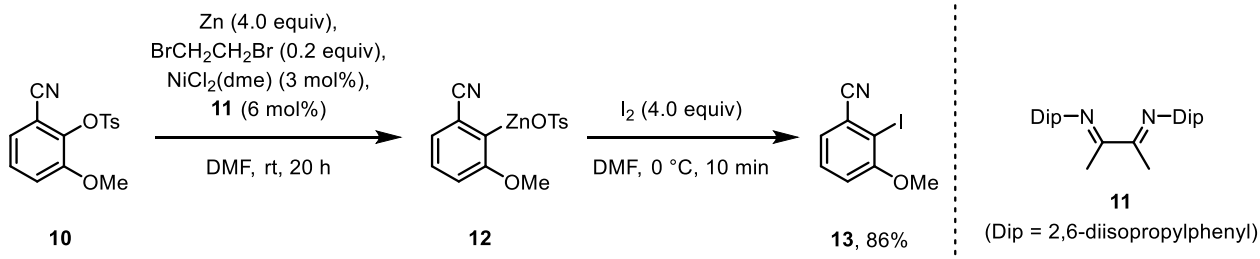


Scheme 3: Zinc insertion in the presence of indium and lithium salts.

Recently, a nickel-catalyzed generation of various arylzinc reagents from aryl sulfonates was reported. Tosylate **10** was treated with zinc powder in the presence of 1,2-dibromoethane, a nickel catalyst and diazadiene ligand **11** furnishing the corresponding arylzinc tosylate **12**. Trapping reaction with iodine afforded aryl iodide **13** in 86% yield (Scheme 4).[14] Mechanistically, the authors propose an initial reduction

[12] N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358-12359.
[13] A. D. Benischke, G. Le Corre, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 778-782.
[14] P. Klein, V. D. Lechner, T. Schimmel, L. Hintermann, *Chem. Eur. J.* **2020**, *26*, 176-180.

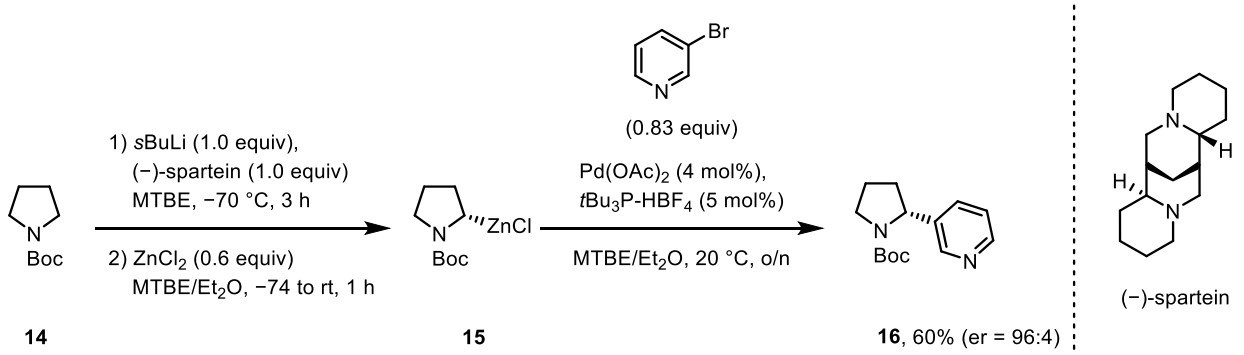
of the Ni(II) catalyst leading to the corresponding Ni(0) complex, which undergoes an oxidative addition to the aryl tosylate. Subsequent *in situ* transmetalation affords the arylzinc tosylate.



Scheme 4: Nickel-catalyzed zinc insertion into aryl sulfonates.

2.2 Transmetalation

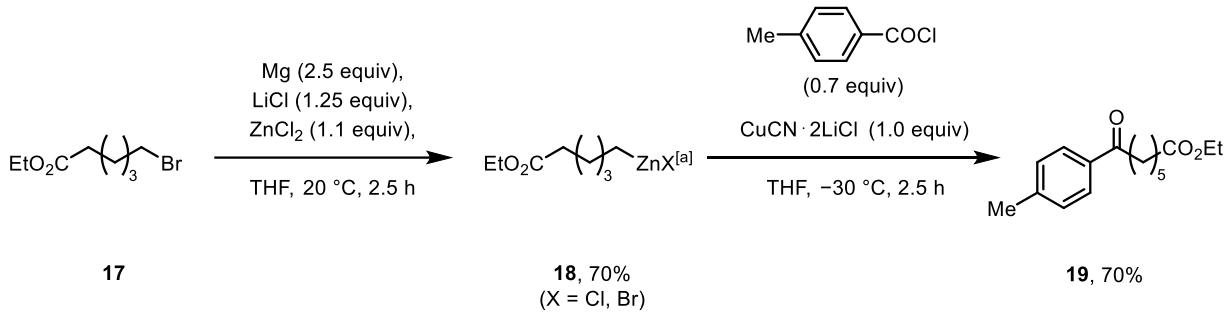
Another approach towards organozinc reagents is their preparation *via* transmetalation. Lithium or magnesium organometallics undergo fast transmetalation with zinc salts, driven by the formation of a more covalent and thus thermodynamically more stable carbon-metal bond.[7c] For example, the asymmetric lithiation of *N*-boc pyrrolidine **14** in the presence of (−)-spartein and subsequent transmetalation with $ZnCl_2$ afforded the chiral organozinc reagent **15**. A palladium-catalyzed cross-coupling of **15** with 3-bromo pyridine furnished the arylated pyrrolidine **16** in 60% yield (er = 96:4, Scheme 5).[15]



Scheme 5: Asymmetric lithiation of *N*-Boc pyrrolidine and subsequent cross-coupling of the corresponding zinc reagent.

[15] K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer, C.-Y. Chen, *J. Am. Chem. Soc.* **2006**, *128*, 3538-3539.

Also, the reaction of magnesium metal with (hetero)aryl halides in the presence of $ZnCl_2$ allowed the efficient preparation of various polyfunctional zinc organometallics.[16] Later, this method was extended to functionalized alkylzinc reagents. Thus, the reaction of ethyl 6-bromohexanoate (**17**) with a mixture of magnesium and $ZnCl_2$ provided 70% of alkylzinc reagent **18** within 2.5 h at 20 °C. Copper-catalyzed acylation led to ketone **19** in 70% yield (Scheme 6).[17] Remarkably, the related reaction of zinc powder with **17** in the presence of LiCl proceeded significantly slower furnishing 70% of reagent **18** after 70 h reaction time at 50 °C.[17]

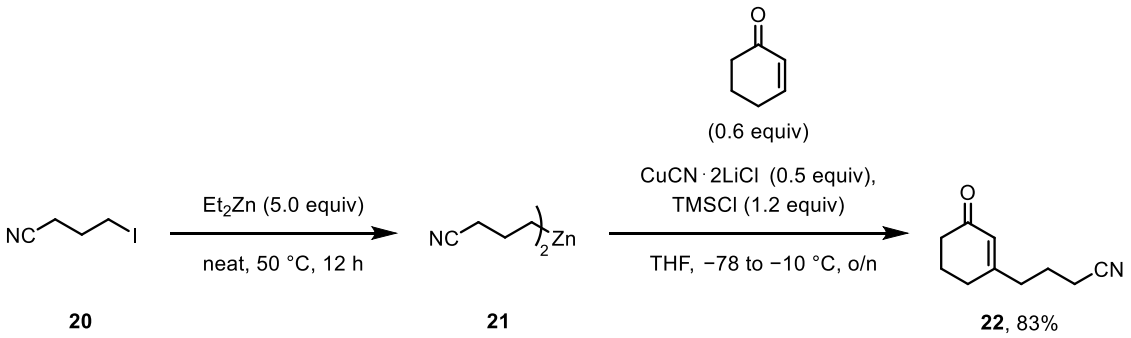


Scheme 6: Preparation of an alkylzinc reagent *via* magnesium insertion followed by *in situ* transmetalation with $ZnCl_2$. [a] Salts are omitted for clarity.

2.3 Halogen/Zinc-Exchange

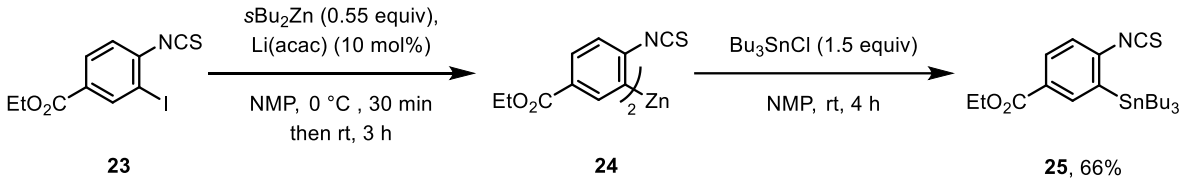
Furthermore, functionalized alkyl-, alkenyl-, aryl- and heteroarylzinc reagents can be prepared from the corresponding halides *via* halogen/zinc-exchange using diorganozinc reagents or zincates.[18] In general, the rate of halogen/metal-exchange reactions is highly dependent on the nature of the carbon-metal bond present in the exchange reagent. The more ionic this bond the faster the exchange reaction. Due to the covalent character of the carbon-zinc bond an exchange reaction is comparably slow and requires more polar solvents or rather forcing reaction conditions.[7i] Thus, performing an iodine/zinc-exchange reaction using alkyl iodide **20** required treatment with an excess Et_2Zn at 50 °C. The corresponding dialkylzinc reagent **21** was subsequently trapped with 2-cyclohexenone affording the alkylated cyclohexanone **22** in 83% yield (Scheme 7).[19]

[16] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802-6806; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192-7202.
[17] T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082-4084.
[18] M. Balkenhohl, P. Knochel, *Chem. Eur. J.* **2020**, DoI: 10.1002/chem.201904794.
[19] M. J. Rozema, A. Sidduri, P. Knochel, *J. Org. Chem.* **1992**, *57*, 1956-1958.



Scheme 7: Preparation of dialkylzinc reagents *via* iodine/zinc-exchange using Et_2Zn.

Alternatively, highly reactive alkylzincates enable the halogen/zinc-exchange of various aryl iodides. However, low reaction temperatures were required to allow the tolerance of sensitive functional groups under the reaction conditions.[20] In 2004 a mild halogen/zinc-exchange reaction of various (hetero)aryl iodides using either *i*Pr_2Zn or *s*Bu_2Zn was reported displaying an exceptional functional group tolerance. The addition of Li(acac) was found to increase the reactivity of the exchange reagent due to *in situ* formation of zincates. Treating polyfunctional aryl iodide **23** with *s*Bu_2Zn in the presence of 10 mol% Li(acac) for 3 h at room temperature provided the diarylzinc reagent **24**. Trapping reaction with Bu_3SnCl afforded arylstannane **25** in 66% yield (Scheme 8).[21]

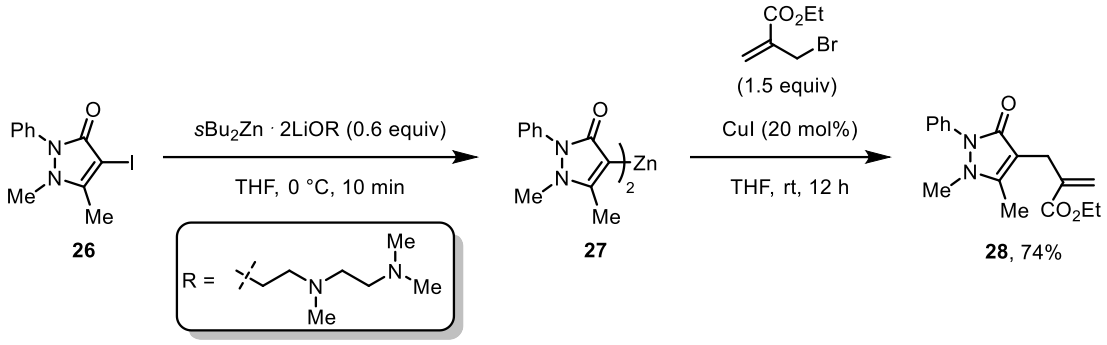


Scheme 8: Li(acac)-catalyzed preparation of diorganozinc reagents *via* iodine/zinc-exchange.

Recently, it was found that the complexation of *s*Bu_2Zn with two lithium alkoxides resulted in a highly reactive but yet selective exchange reagent, which enables the preparation of di(hetero)aryl zinc reagents from various electron-rich as well as -deficient halo arenes. Thus, iodo anitpyrine **26** underwent a fast iodine/zinc-exchange leading to **27** within 10 min. A copper-catalyzed allylation furnished the

[20] a) Y. Kondo, N. Takazawa, C. Yamazaki, T. Sakamoto, *J. Org. Chem.* **1994**, *59*, 4717-4718; b) Y. Kondo, M. Fujinami, M. Uchiyama, T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1* **1997**, 799-800; c) Kondo, N. Takazawa, A. Yoshida, T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1207-1208.
[21] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017-1021.

functionalized heterocycle **28** in 74% yield (Scheme 9). Remarkably, the bimetallic exchange reagent enabled the first halogen/zinc-exchange reaction using aryl bromides.[22]

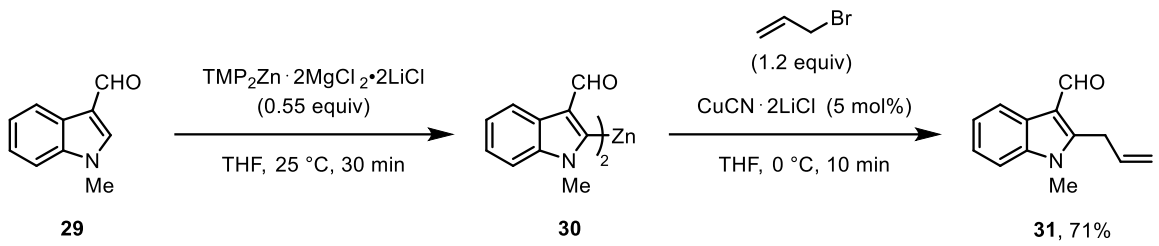


Scheme 9: Preparation of a diorganozinc reagent using *s*Bu_2Zn·2LiOR.

2.4 Directed Metalation

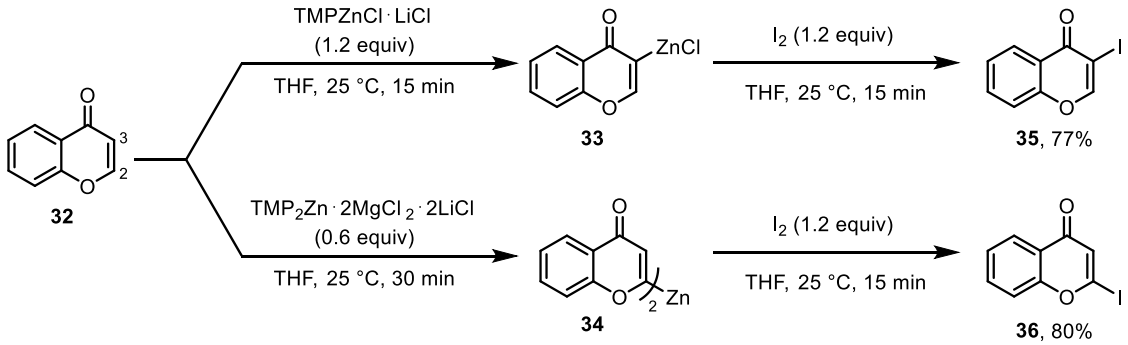
The directed metalation of arenes and heterocycles has proved to be a powerful tool for the selective functionalization of various scaffolds.[7l,23] Especially, TMP-magnesium or -zinc bases found broad application in academic as well as industrial research.[23b,c] $TMP_2Zn·2MgCl_2·2LiCl$[24] and TMPZnCl·LiCl[25], which are prepared *via* transmetalation from the corresponding Mg- or Li-amide, are the most common reagents for the mild deprotonation of various sensitive substrates. The non-nucleophilic zinc amide $TMP_2Zn·2MgCl_2·2LiCl$ enabled the selective metalation of 3-formylindole **29** affording the heteroarylzinc reagent **30** within 30 min at 25 °C. After a copper-catalyzed allylation, the functionalized indole **31** was obtained in 71% yield (Scheme 10).[24]

[22] M. Balkenhohl, D. S. Ziegler, A. Desaintjean, L. J. Bole, A. R. Kennedy, E. Hevia, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 12898-12902.
[23] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879-933; b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794-9824. b) M. Balkenhohl, P. Knochel, *SynOpen* **2018**, *2*, 78-95.
[24] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685-7688.
[25] M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837-1840.



Scheme 10: Directed metalation of an indole derivative using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.

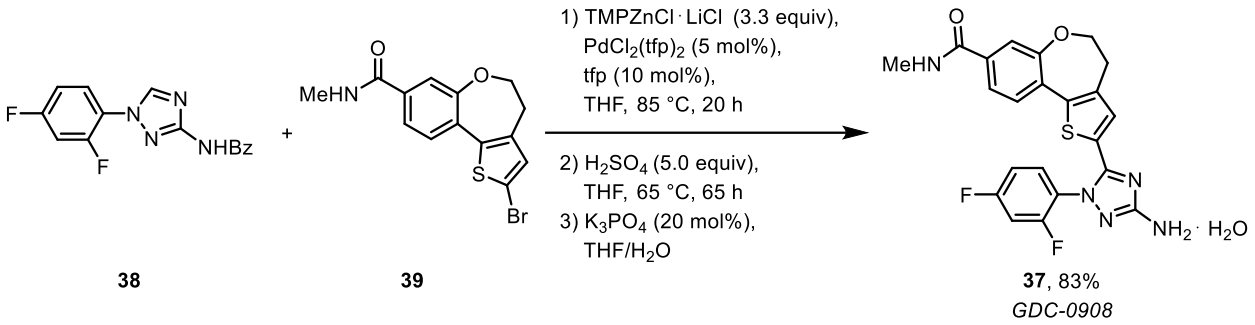
Interestingly, the regioselectivity of the metalation of chromone (**32**) can be adjusted by the composition of the metal amide used for the deprotonation. Thus, treating **32** with TMPZnCl·LiCl led to the metalation in 3-position (**33**), whereas $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ afforded the corresponding diheteroarylzinc reagent **34** in 2-position. This might be explained by the presence of the magnesium salt within the reaction mixture. $MgCl_2$ is coordinated by the ketone moiety, thus blocking the preferential coordination-site for the zinc-amide. Trapping the zinc reagents **33** and **34** with I_2 afforded iodo-chromones **35** and **36** in 77 and 80% yield, respectively (Scheme 11).[26]



Scheme 11: Regioselective metalation of chromone.

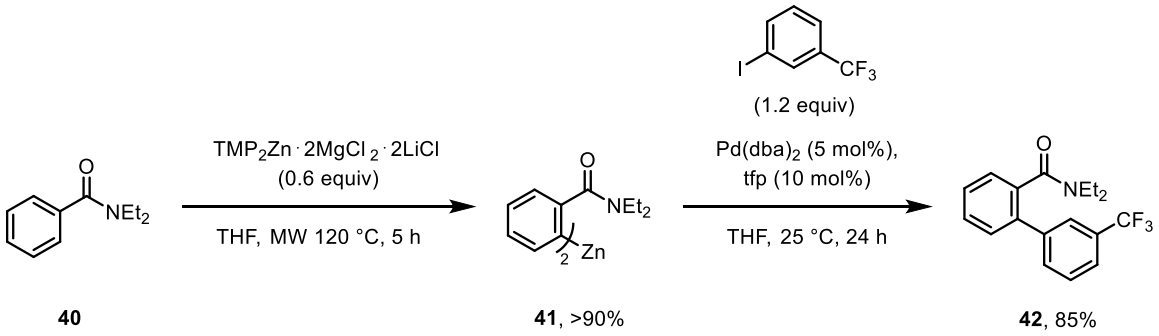
Remarkably, a one-pot late-stage zincation/cross-coupling sequence was reported for the synthesis of the PI3K inhibitor GDC-0908 (**37**). Treating 1,2,4-triazole **38** with TMPZnCl·LiCl in the presence of a palladium catalyst and heteroaryl bromide **39** led to the formation of the corresponding cross-coupling product. Subsequent benzoyl deprotection afforded GDC-0908 (**37**) in 83% yield over two steps (Scheme 12).[27]

[26] L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584-13587.
[27] H. Zhang, B. X. Li, B. Wong, A. Stumpf, C. G. Sowell, F. Gosselin, *J. Org. Chem.* **2019**, *84*, 4796-4802.



Scheme 12: Synthesis of GDC-0908 (**37**) *via* a late stage zincation/cross-coupling sequence.

Remarkably, organozinc reagents exhibit a high thermal stability enabling the zincation of less activated arenes using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ at elevated temperatures.[7i,28] Therefore, *N*,*N*-diethylbenzamide (**40**) was treated with the zinc base for 5 h at 120 °C under microwave irradiation yielding **41** in more than 90% yield. Remarkably, performing the reaction in an oil bath at the same reaction conditions only afforded 10-20% of the corresponding organozinc reagent **41**. Zincated arene **41** was used in a subsequent palladium-catalyzed cross-coupling leading to the arylated benzamide **42** in 85% yield (Scheme 13).[29]

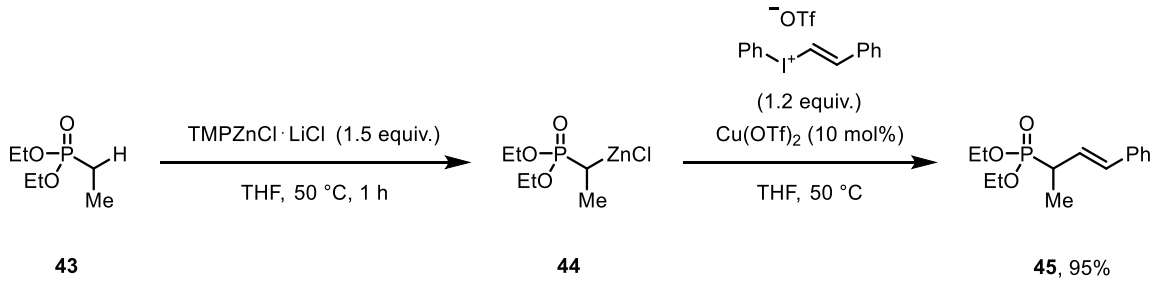


Scheme 13: High-temperature zincation of *N*,*N*-diethylbenzamide.

[28] a) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445-1453; b) M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615-5617.
[29] S. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705-4707.

Besides the directed zincation of various arenes and heterocycles, TMP-zinc bases also allow for the metalation at benzylic[30] or allylic[31] positions and the deprotonation of functionalized alkenes.[32] The metalation in α-position to several electron-withdrawing groups has also been reported.[31,33]

Recently, Wang showed that α-metalated alkyl compounds bearing phosphonate, phosphine oxide, sulfonamide or sulfoxide groups undergo a copper-catalyzed cross-coupling with alkenyl iodonium salts. Thus, treating phosphonate **43** with TMPZnCl·LiCl afforded the zinc reagent **44**, which led after copper-catalyzed alkenylation using an alkenyl iodonium salt to the β,γ-unsaturated phosphonate **45** in 95% yield (Scheme 14).[34]



Scheme 14: Metalation of an alkyl phosphonate.

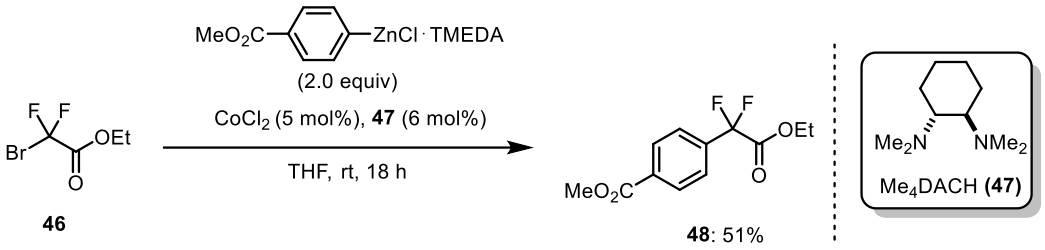
3. Cobalt Catalyzed Cross-Coupling Reactions with Organozinc Reagents

The relatively high abundance and catalytic activity of cobalt salts combined with easy accessible and mild zinc organometallics led to a rising number of publications within this field.[5f,6] In the following part, an overview on recent developments in cobalt catalyzed Negishi cross-couplings will be given.

[30] a) S. Duez, A. K. Steib, S. M. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 7686-7690; b) S. Duez, A. K. Steib, P. Knochel, *Org. Lett.* **2012**, *14*, 1951-1953; c) A. Castelló-Micó, P. Knochel, *Synthesis* **2018**, *2*, 155-169.
[31] S. Duez, S. Bernhardt, J. Heppekausen, F. F. Fleming, P. Knochel, *Org. Lett.* **2011**, *13*, 1690-1693.
[32] T. Bresser, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1914-1917.
[33] a) I. Popov, S. Lindeman, O. Daugulis, *J. Am. Chem. Soc.* **2011**, *133*, 9286-9289; b) R. J. Mycka, S. Duez, S. Bernhardt, J. Heppekausen, P. Knochel, F. F. Fleming, *J. Org. Chem.* **2012**, *77*, 7671-7676; c) T. Knauber, J. Tucker, *J. Org. Chem.* **2016**, *81*, 5636-5648; d) M. E. Dalziel, P. Chen, D. E. Carrera, H. Zhang, F. Gosselin, *Org. Lett.* **2017**, *19*, 3446-3449.
[34] C. Liu, Q. Wang, *Angew. Chem. Int. Ed.* **2018**, 57, 4727-4731.

3.1 Cobalt-Catalyzed Cross-Couplings of Sp^2-Hybridized Organozinc Reagents

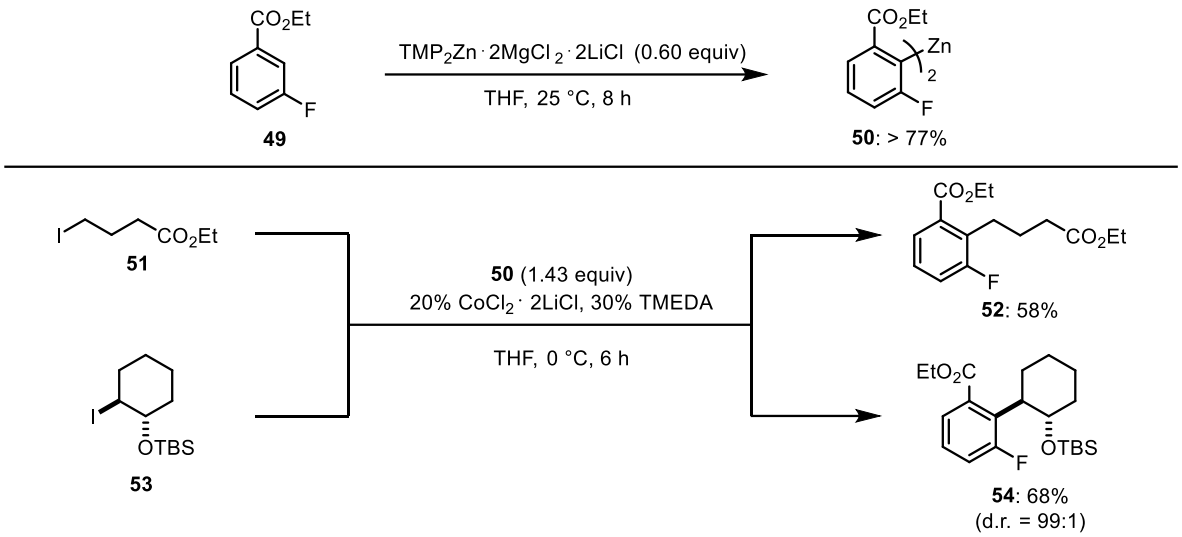
In 2013, Inoue and co-worker developed a protocol for the cobalt-catalyzed arylation of ethyl bromodifluoroacetate (**46**). A catalytic system comprising 5 mol% $CoCl_2$ and 6 mol% Me_4DACH (*Trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine, **47**) enabled the coupling of functionalized arylzinc reagents. Thus, various arylated ethyl difluoroacetates such as **48** were obtained at room temperature within 18 h (Scheme 15).[35]



Scheme 15: Cobalt-catalyzed cross-coupling of arylzinc reagents with bromo difluoroacetates.

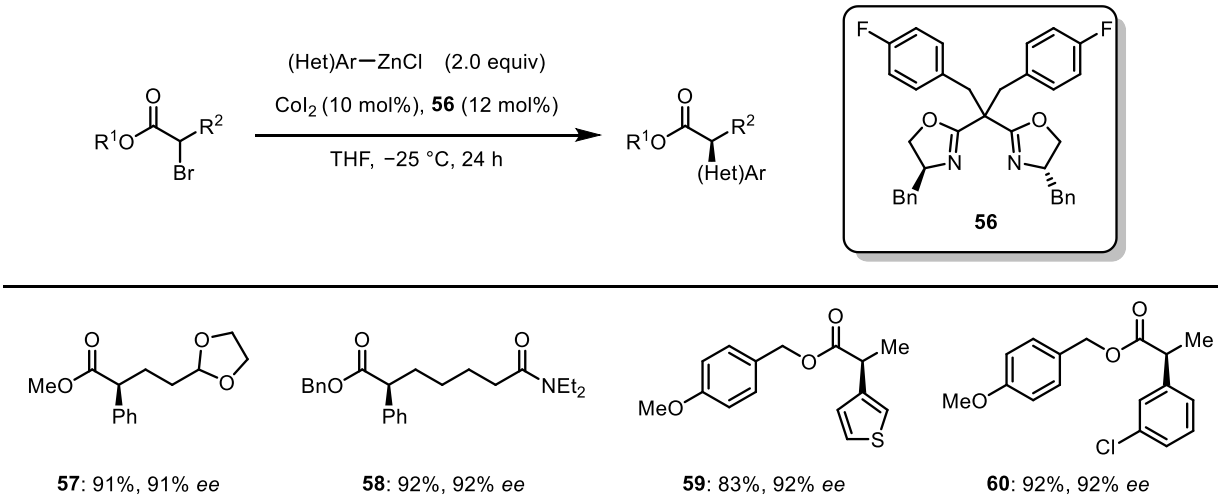
Furthermore, (hetero)aryl zinc reagents generated *via* directed deprotonation using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[24,36] as a metalation agent were efficiently coupled with various primary and secondary alkyl iodides or bromides. Thus, the conversion of ethyl 3-fluorobenzoate (**49**) to the corresponding diarylzinc derivative **50** using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ followed by the cross-coupling with the primary iodide **51** provided the alkylated benzoate **52** in 58% yield. Additionally, the coupling proceeded with high diastereoselectivity using the 1,2-disubstituted TBS protected iodohydrin **53** affording **54** in 68% yield and dr = 99:1 (Scheme 16).[6b]

[35] K. Araki, M. Inoue, *Tetrahedron* **2013**, *69*, 3913-3918.
[36] a) M. Mosrin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 1468-1477; b) S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel, *Org. Process Res. Dev.* **2010**, *14*, 339-345.



Scheme 16: Cobalt-catalyzed cross-coupling of diarylzinc **50** with primary and secondary alkyl iodides **51** and **53**.

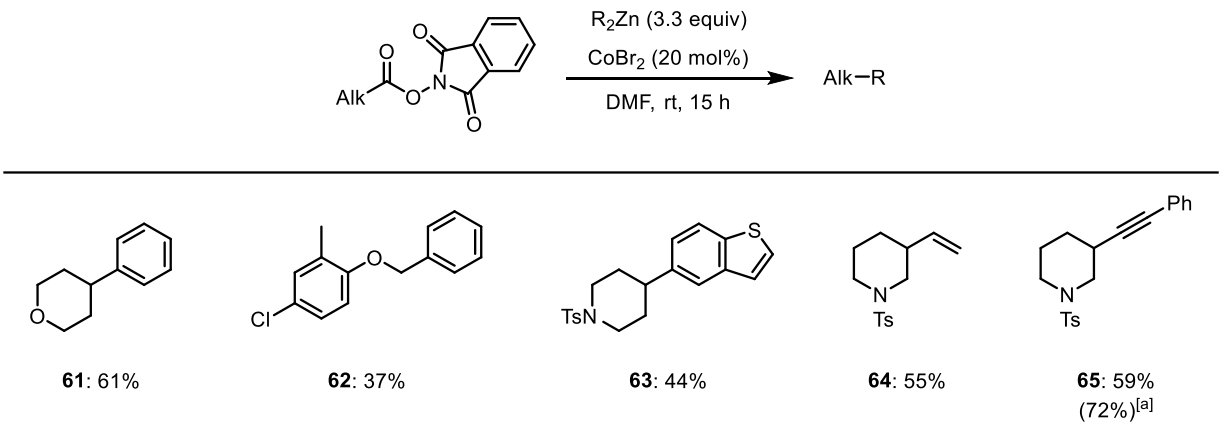
An enantioselective cobalt-catalyzed Negishi cross-coupling was reported by Bian and co-workers. A variety of racemic α-bromo esters was coupled with functionalized (hetero)aryl zinc reagents using 10 mol% CoI_2 in combination with the tailored bisoxazolidine ligand **56**. Remarkably, the protocol enabled the efficient coupling of sterically hindered *ortho*- arylzinc reagents with α-bromo esters for the first time. Thus, the method gives access to a variety of α-arylated chiral esters, such as **57-60** (Scheme 17).[6e] Later, this procedure was applied to the enantioselective synthesis of (*S*)-preclamol.[37]



Scheme 17. Enantioselective cobalt-catalyzed cross-coupling of racemic α-bromo esters.

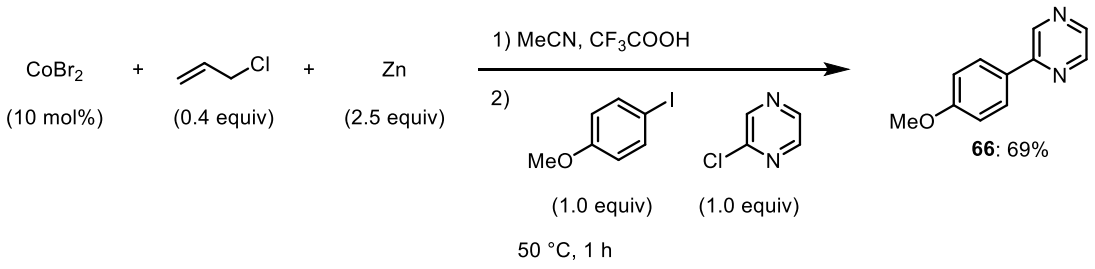
[37] Y. Zhou, C. Liu, L. Wang, L. Han, S. Hou, Q. Bian, J. Zhong, *Synlett* **2019**, *30*, 860-862.

Recently, Wang *et al.* reported a cobalt-catalyzed decarboxylative cross-coupling of functionalized *N*-hydroxyphthalimide esters with diaryl-, dialkenyl- and dialkynylzinc reagents. No additional ligand was required to obtain various arylated, olefinated and alkynylated alkyl compounds such as **61-65** (Scheme 18). Remarkably, the use of alkynylzinc pivalates instead of the corresponding dialkylzinc reagent led to improved coupling yields in some cases.[4b]



Scheme 18: Cobalt-catalyzed decarboxylative cross-coupling. [a] The corresponding alkynylzinc pivalate was used.

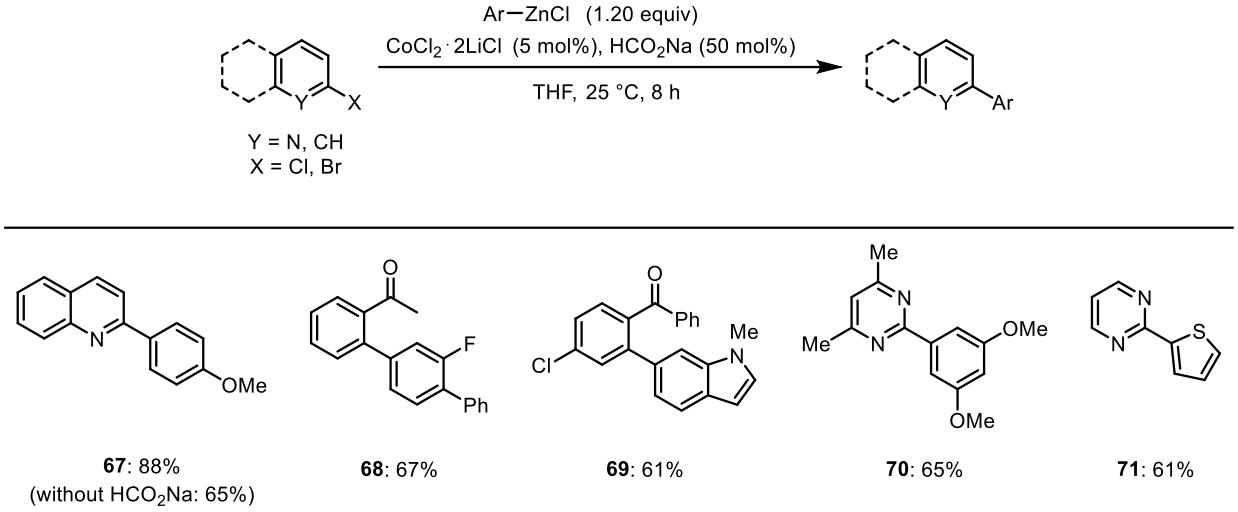
Furthermore, Gosmini described the coupling of substituted arylzinc reagents with 1-chloropyrimidine and 2-chloropyrazine. Organometallic reagents were formed *in situ* from the corresponding halide in the presence of zinc powder and 10 mol% $CoBr_2$. Subsequent addition of an *N*-heterocyclic halide to the reaction mixture led to products, such as **66** (Scheme 19).[6a]



Scheme 19: Cobalt-catalyzed cross-coupling of 2-chloropyrazine

Later, it was found that the addition of carboxylate salts, such as sodium formate or pivalate have beneficial effects on cobalt-catalyzed Csp^2-Csp^2 cross-couplings. These salts presumably act as ligands for the cobalt catalyst thus making the cross-coupling more selective by suppressing side-reactions. Various

ortho-activated halides or electron deficient *N*-heterocycles were coupled with aryl- or heteroarylzinc organometallics affording products **67-71** in 61-88% yield (Scheme 20).[6c]

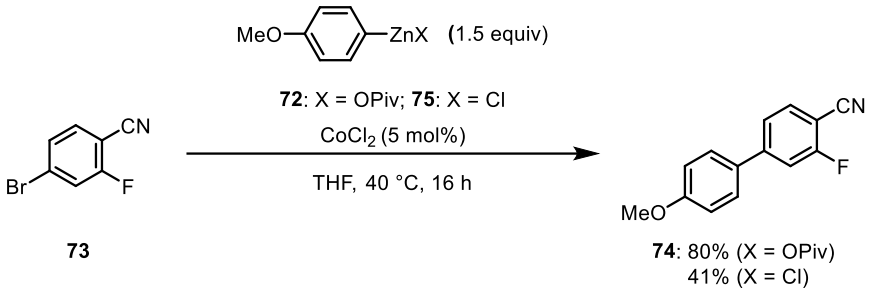


Scheme 20: Cobalt-catalyzed cross-coupling using sodium formate as additive.

These findings led to the development of a cobalt-catalyzed cross-coupling using organozinc pivalates as reaction partners. This class of organometallics show a significantly enhanced stability towards moisture and air and can be stored as solids under argon at room temperature for several months.[38] Remarkably, the use of these reagents considerably improved the yield of the coupling. Thus, the reaction of anisylzinc pivalate **72** with bromo benzonitrile **73** afforded the biaryl product **74** in 80% yield, whereas the corresponding arylzinc chloride **75** led to a significantly lower yield of 41% (Scheme 21). [39]

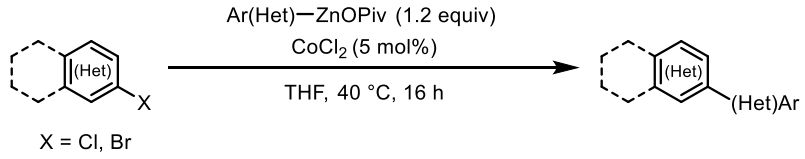
[38] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205-9209; b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9428-9432; c) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754-5757; d) C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302-1305; e) A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg, *Angew. Chem. Int. Ed.* **2014**, *53*, 2706-2710; f) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289-12297; g) M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10662-10665; h) Y.-H. Chen, M. Ellwart, V. Malakhov, P. Knochel, *Synthesis* **2017**, *49*, 3215-3223; i) Y. H. Chen, C. P. Tüllmann, M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 9236-9239; j) Y.-H. Chen, M. Ellwart, G. Toupalas, Y. Ebe, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 4612-4616; k) C. P. Tüllmann, Y.-H. Chen, R. J. Schuster, P. Knochel, *Org. Lett.* **2018**, *20*, 4601-4605;

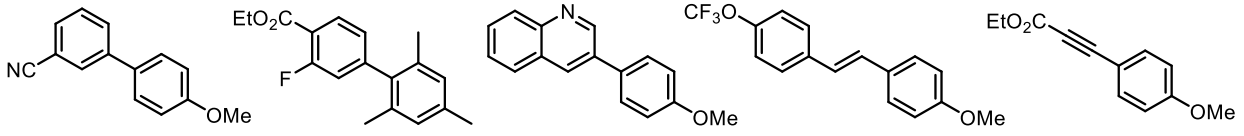
[39] J. M. Hammann, F. H. Lutter, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 1082-1086.



Scheme 21: Comparison of arylzinc pivalates and arylzinc chlorides in cobalt-catalyzed cross-couplings.

Furthermore, the combination of cobalt salts and organozinc pivalates expanded the scope of cobalt-catalyzed Csp^2-Csp^2 cross-couplings. Thus, meta-substituted halo arenes, sterically hindered metal reagents and unactivated heterocyclic halides could be used leading to functionalized coupling products, such as **76-78**. Also, alkenyl halides and bromo alkynes underwent cobalt-catalyzed cross-couplings with arylzinc pivalates leading to stilbene derivative **79** and the arylated alkyne **80** (Scheme 22).[39] Later, a further extension of the scope and the scalability of the method was reported.[5f]





76: 72% **77**: 71% **78**: 74% **79**: 97%; *E*/*Z* = 99:1 **80**: 71%[a]

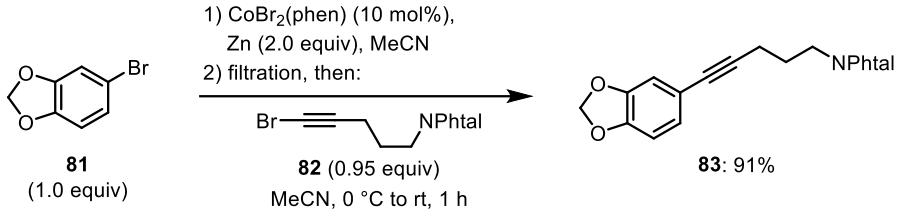
Scheme 22: Cobalt-catalyzed cross-couplings using aryl- and heteroarylzinc pivalates. [a] reaction was carried out at −40 °C

In addition, functionalized benzylzincs proved to be suitable organometallic reagents for cobalt-catalyzed couplings with various *ortho*- and *para*-activated aryl and heteroaryl halides giving access to di(hetero)aryl methane derivatives.[40]

Electron-deficient as well as electron-rich arylzinc reagents could be coupled with a variety of functionalized bromo alkynes. Hence, the reaction of the zinc reagent generated from aryl bromide **81**

[40] A. D. Benischke, I. Knoll, A. Rérat, C. Gosmini, P. Knochel, *Chem. Commun.* **2016**, *52* 3171-3174.

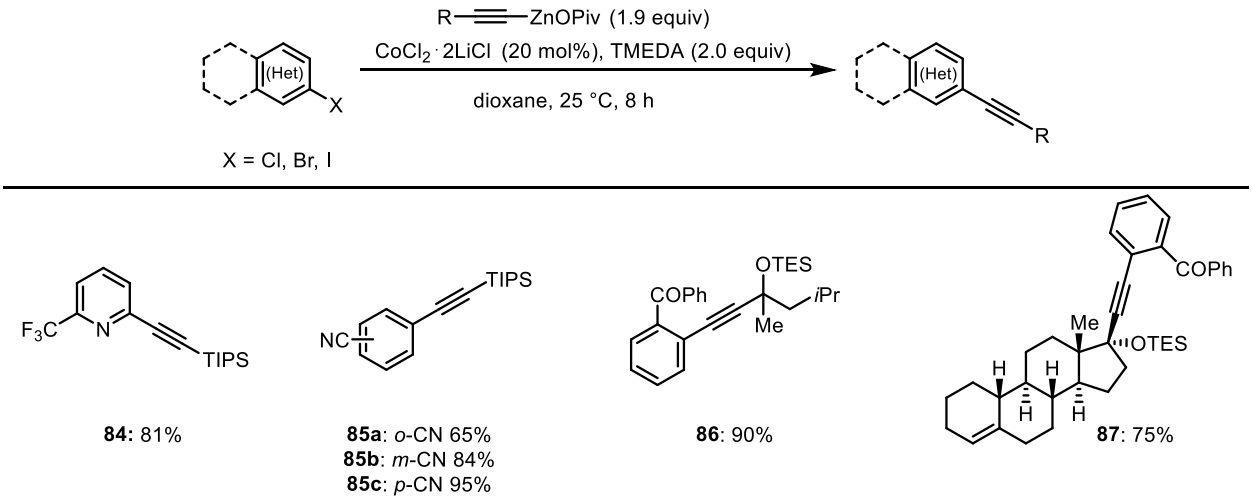
with functionalized bromo alkyne **82** proceeded smoothly in the presence of 10 mol% $CoBr_2$(phen) affording the arylated alkyne **83** in 91% yield (Scheme 23).[41]



Scheme 23: Cobalt-catalyzed coupling of arylzinc reagents with bromoalkynes.

3.2 Cobalt-Catalyzed Cross-Couplings of Sp-Hybridized Organozinc Reagents

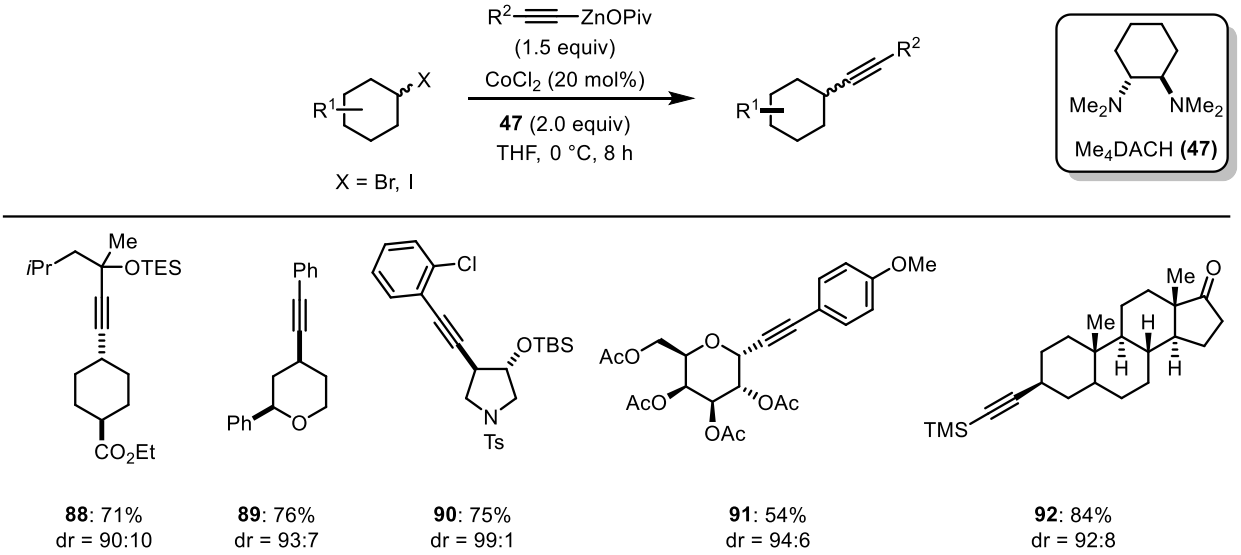
Alkynylzinc pivalates are a versatile class of organometallic reagents, which show a greatly enhanced stability towards air and moisture in comparison to the corresponding zinc halide derivatives.[42] Cobalt catalysis allows their coupling with various aryl and heteroaryl halides in the presence of TMEDA. Thus, various pyridine, benzonitrile or benzophenone halides were alkynylated furnishing the products **84-86** in up to 95% yield. Furthermore, a steroid derived alkynylzinc pivalate was coupled with chlorobenzophenone providing the cross-coupling product **87** in 75% yield (Scheme 24).[43]



Scheme 24: Cobalt-catalyzed cross-couplings of alkynylzinc pivalates with heteroaryl halides.

[41] M. Corpet., X.-Z. Bai, C. Gosmini, *Adv. Synth. Catal.* **2014**, *356*, 2937-2942.
[42] Y.-H. Chen, C. P. Tüllmann, M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 9236-9239.
[43] J. M. Hammann, L. Thomas, Y.-H. Chen, D. Haas, P. Knochel, *Org. Lett.* **2017**, *19*, 3847-3850.

Furthermore, the use of a combination of $CoCl_2$ and diamine ligand **47** allowed for the highly diastereoselective preparation of various alkynylated cycloalkyl compounds. Various 1,4-, 1,3- and 1,2-substituted cycloalkyl halides underwent highly diastereoselective cross-couplings with alkynylzinc pivalates leading to highly functionalized *anti*-1,4-, *syn*-1,3-, or *anti*-1,2-disubstituted products, such as **88-90** in 62-76% yield. Furthermore, the mild reaction conditions enabled the coupling of α-bromo gylcosides or steroid scaffolds bearing sensitive functionalities such as ketones, furnishing the coupling products **91** and **92** (Scheme 25).[6d]

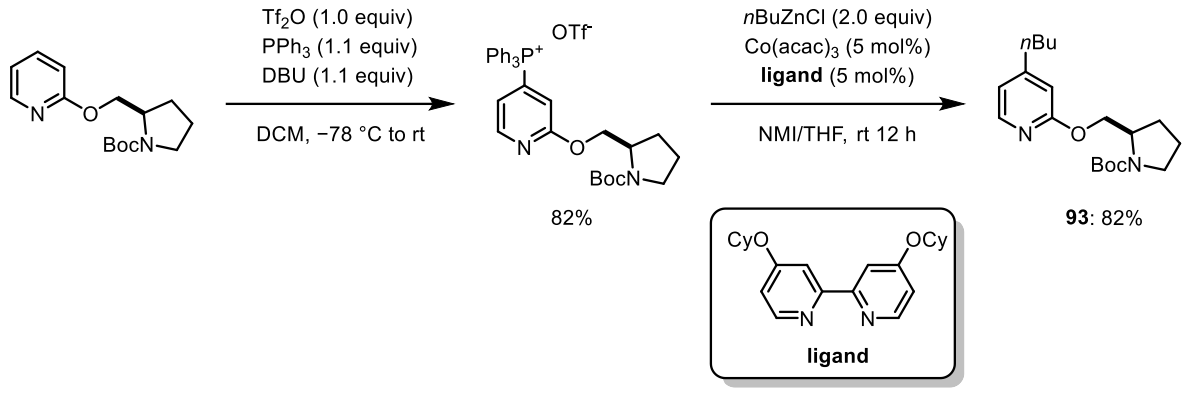


Scheme 25: Diastereoselective cobalt-catalyzed cross-couplings between alkynylzinc pivalates and iodo cycloalkanes.

3.3 Cobalt-Catalyzed Cross-Couplings of Sp^3-Hybridized Organozinc Reagents

In 1996, Knochel and Cahiez described the stereoselective alkylation of alkenyl halides.[44] However, the reaction required a high catalyst loading and a huge excess of the corresponding dialkylzinc reagent. Recently, McNally developed a cobalt catalyzed alkylation of *in situ* formed *N*-heterocyclic phosphonium salts harnessing zinc organometallics. The reaction proceeded with a variety of functionalized *N*-heterocycles providing alkylated complex molecules, such as **93** (Scheme 26).[45]

[44] H. Avedissian, L. Bérillon, G. Cahiez, P. Knochel, *Tetrahedron* **1998**, *39*, 6163-6166.
[45] X. Zhang, A. McNally *ACS Catal.* **2019**, *9*, 4862-4866.



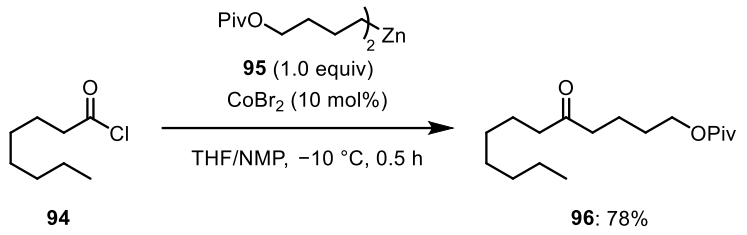
Scheme 26: Cobalt-catalyzed alkylation of heteroaryl phosphonium salts.

4. Cobalt-Catalyzed Acylation Reactions

The reaction of an activated carbonyl group, such as an acyl halide, or thioesters with highly reactive organolithium or -magnesium reagents often proceeds unselectively leading to undesired side products due to enol formation or over addition to the newly formed ketone.[46,47] However, less reactive organometallics, such as zinc reagents usually do not undergo this addition without further activation. Transition-metal catalyzed acylation reactions are a valuable alternative, since they ensure a high selectivity and enable the use of organozinc reagents, which allows the tolerance of various functional groups in both the metal reagent as well as the electrophile.[46,47] Besides well-established procedures utilizing copper,[7b,48] palladium[49] or nickel[50] catalysts, the use of cobalt salts has received growing attention.

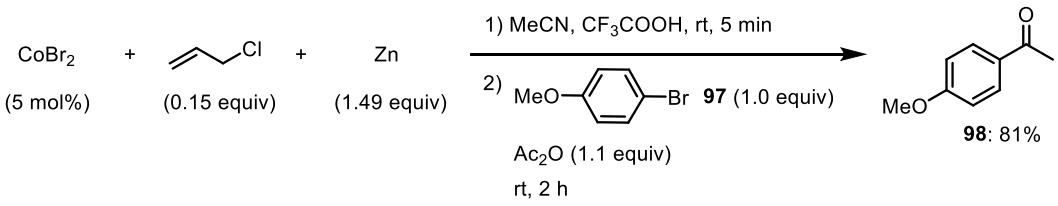
[46] R. K. Dieter *Tetrahedron,* **1999**, *55*, 4177-4236.
[47] D. A. Shirley, *Synthesis of Ketones from Acid Halides and Organometallic Compounds of Magnesium, Zinc, and Cadmium in Organic Reactions, Vol. 8* (Ed.: R. Adams), Wiley, New York, **1954**.
[48] a) J.-E. Dubois, Y. J. Bonzougou, *J. Chem. Res. (M)* **1978**, 826-835; b) J. P. Gillet, R. Sauvêtre, J. F. Normant, *Synthesis* **1982**, 297-301; c) C. R. Johnson, D. S. Dhanoa, *J. Org. Chem.* **1987**, *52*, 1885-1888; d) L. Zhu, R. M. Wehmeyer, R.D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445-1453; e) F. Langer, L. Schwink, A. Devasagayaraj, P.-Y. Chavant, P. Knochel, *J. Org. Chem.* **1996**, *61*, 8229-8243; f) R. K. Dieter, R. R. Sharma, W. Ryan, *Tetrahedron Lett.* **1997**, *38*, 783-786.
[49] a) T. Sato, K. Naruse, M. Enokiya, T. Fujisawa, *Chem. Lett.* **1981**, 1135-1138; b) E. Nakamura, I. Kuwajima, *Tetrahderon Lett.* **1986**, *27*, 83-86; c) Y. Tamaru, H. Ochiai, T. Nakamura, Z.-I. Yoshida, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1157-1158; d) M. M. Faul, L. L. Winneroski, *Tetrahedron Lett.* **1997**, *38*, 4749-4752; e) H. Tokuyama, S. Yokoshima, T. Yamashita, T. Fukuyama, *Tetrahedron Lett.* **1998**, *39*, 3189-3192; f) K. Kunchithapatham, C. C. Eichman, J. P. Stambuli, *Chem. Commun.* **2011**, *47*, 12679-12681; g) A. H. Cherney, S. E. Reisman, *Tetrahedron*, **2014**, *70*, 3259-3265.
[50] a) M. Onaka, Y. Matsuoka, T. Mukaiyama, *Chem. Lett.* **1981**, *10*, 531-534; b) C. Cardellicchio, V. Fiandanese, G. Marchese, L. Ronzini, *Tetrahedron Lett.* **1985**, *26*, 3595-3598; c) C. Malanga, L. A. Aronica, L. Lardicci, *Tetrahedron Lett.* **1995**, *36*, 9185-9188; d) T. Shimizu, M. Seki, *Tetrahedron Lett.* **2002**, *43*, 1039-1042; e) Y. Zhang, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 15964-15965; f) P. H. Gehrtz, P. Kathe, I. Fleischer, *Chem.-Eur. J.* **2018**, *24*, 8774-8778.

In 1996, a cobalt-catalyzed acylation of dialkylzincs was reported using 10 mol% $CoBr_2$ in a mixture of THF and NMP. Thus, the reaction of *n*-octanoyl chloride (**94**) with the bisalkylzinc reagent **95** afforded ketone **96** in 78% yield. (Scheme 27).[51]



Scheme 27: Cobalt-catalyzed acylation of a diorganozinc reagent.

This method was extended to aryl- and heteroarylzinc reagents. Various aromatic ketones were obtained by the acylation of arylzinc reagents, which were prepared electrochemically using a zinc anode in the presence of $ZnBr_2$ together with cobalt salt or *via* a cobalt catalyzed zinc insertion in acetonitrile from the corresponding aryl halide.[52] Later, the use of carboxylic anhydrides as acylating agents was reported, which enabled the preparation of various unsymmetrical ketones in a preparatively simple one-pot procedure. Thus, after cobalt-catalyzed activation of the zinc dust, 4-bromoanisole (**97**) and acetic anhydride were added affording the ketone **98** in 81% yield (Scheme 28).[53]

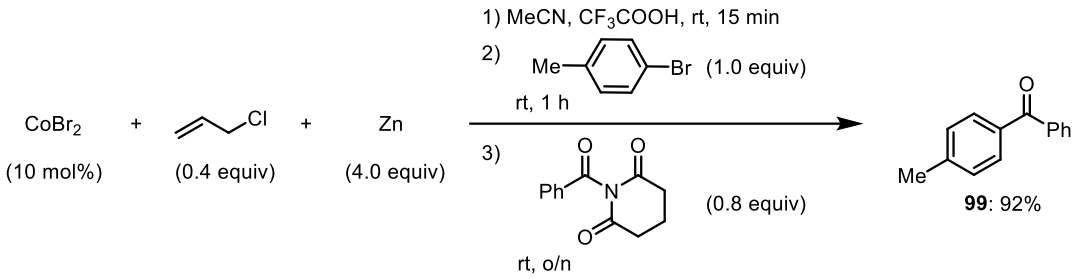


Scheme 28: Preparation of unsymmetrical ketones using a cobalt-catalyzed one-pot procedure.

This cobalt-catalyzed formation of arylzinc reagents also enabled the synthesis of symmetrical (hetero)aryl ketones by using ethyl chloroformate, which acts as a carbon monoxide surrogate in the presence of 13 mol% $CoBr_2$ and a bipyridine ligand.[54]

[51] C. K. Reddy, P. Knochel, *Angew. Chem. Int. Ed.* **1996**, *35*, 1700-1701.
[52] H. Fillon, C. Gosmini, J. Périchon, *Tetrahedron* **2003**, *59*, 8199-8202.
[53] I. Kazmierski, M. Bastienne, C. Gosmini, J.-M. Paris, J. Périchon *J. Org. Chem.* **2004**, *69*, 3, 936-942.
[54] A. Rérat, C. Michon, F. Agbossou-Niedercorn, C. Gosmini *Eur. J. Org. Chem.* **2016**, 4554-4560.

Recently, Gosmini reported a cobalt catalyzed acylation utilizing various *N*-benzoyl glutarimides as electrophilic coupling partners leading to products such as **99** (Scheme 29). Remarkably, the reaction can be performed in a simple one-pot procedure and does not require precautions towards moisture and air.[55]

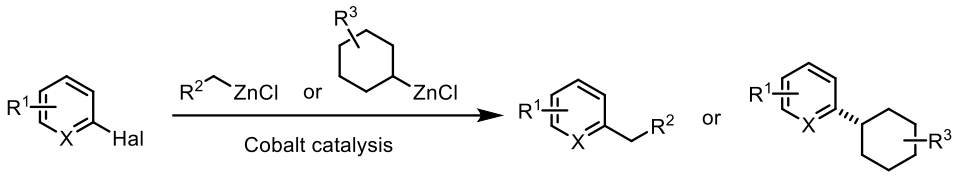


Scheme 29: Cobalt-catalyzed acylation of arylzinc reagents using amide electrophiles.

[55] C. Dorval, E. Dubois, Y. Bourne-Branchu, C. Gosmini, G. Danouna, *Adv. Synth. Catal.* **2019**, *361*, 1777-1780.

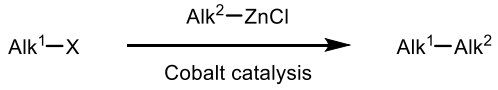
II. Objectives

Transition-metal-catalyzed C-C bond forming reactions are indispensable tools in modern synthetic organic chemistry. Cobalt catalysts proved to be auspicious alternatives to commonly used palladium and nickel catalysts. As described before, various cobalt-catalyzed Negishi-type cross-couplings utilizing (hetero)aryl and alkynyl zinc reagents have been reported. However, the usage of alkylzinc reagents in these reactions is still barley investigated. Thus, a simple and cheap catalytic system based on cobalt salts for the cross-coupling of functionalized alkyl zinc reagents with various aryl and heteroaryl halides should be developed. Furthermore, the amenability of diastereomeric cross-couplings using secondary alkylzinc reagents should be examined (Scheme 30).[56]



Scheme 30: Cobalt-catalyzed cross-coupling of alkylzinc reagents with (hetero)aryl halides.

Moreover, the application of alkylzinc reagents in cross-couplings with other electrophilic coupling partners using a non-precious cobalt catalyst is highly desirable. Therefore, the development of a cobalt-catalyzed Csp^3-Csp^3 cross-coupling utilizing functionalized alkylzinc reagents with various alkyl halides should be investigated (Scheme 31).

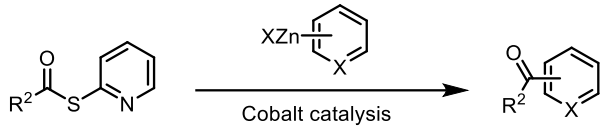


Scheme 31: Cobalt-catalyzed cross-coupling of alkylzinc reagents with alkyl halides.

A protocol developed by Fukuyama utilizes organothioester as efficient acylation agents of various zinc organometallics in the presence of a palladium catalyst. Especially, *S*-pyridyl esters can be readily prepared from the corresponding carboxylic acid without the need of harsh reaction conditions. This enables the

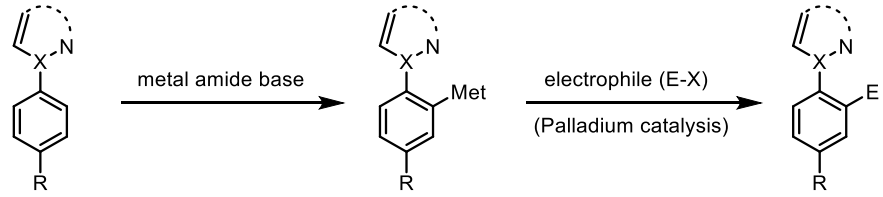
[56] This project was developed in cooperation with Lucie Grokenberger, see: F. H. Lutter, L. Grokenberger, P. Spieß, J. M. Hammann, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, DoI: 10.1002/anie.201914490 and Lucie Grokenberger, PhD Dissertation, **2020**, LMU Munich.

tolerance of various sensitive functional moieties including stereocenters, which are prone to racemization. Therefore, functionalized *S*-pyridyl esters should be tested for their suitability as acylating agents in a cobalt-catalyzed Fukuyama-type acylation using functionalized (hetero)arylzinc organometallics (Scheme 32).[57]



Scheme 32: Cobalt-catalyzed acylation of *S*-pyridyl esters with organozinc reagents.

The aim of the last part of this thesis was to develop a highly regioselective *mono*-functionalization of aryl azoles at the aryl moiety. These motifs are of great interest, since they appear as core structure in several blockbuster drugs. By now, a regioselective functionalization is enabled by transition-metal catalyzed C-H arylation. However, the need of often precious metal catalysts, the harsh reaction conditions and the predominant formation of the bis-functionalized arene significantly limits this methodology. Thus, the use of sterically hindered metal amides for a regioselective *mono*-metalation of the aryl moiety in presence of several possible metalation sites at the azole ring should be examined. The generated arylmetal reagents should be tested for their use in cross-couplings and other trapping sequences (Scheme 33).[58]



Scheme 33: Regioselective metalation of aryl azoles using metal amide bases and subsequent trapping reactions.

[57] This project was developed in cooperation with Lucie Grokenberger, see: F. H. Lutter, L. Grokenberger, M. S. Hofmayer, P. Knochel, Chem. Sci. **2019**, *10*, 8241-8245 and Lucie Grokenberger, PhD Dissertation, **2020**, LMU Munich.
[58] This project was sponsored by Janssen Pharmaceutica and Bristol-Myers Squibb and developed in cooperation with Janssen Pharmaceutica.

III. Results and Discussion

1. Cobalt-Catalyzed Cross-Coupling of Functionalized Alkylzinc Reagents with (Hetero)Aryl Halides[59]

1.1 Introduction

The transition-metal-catalyzed construction of new C-C bonds is of utmost importance in modern organic chemistry, and finds wide application in academic and industrial processes.[3c] Especially, Negishi cross-couplings are among the most versatile methods for the formation of carbon bonds to create highly functionalized scaffolds.[7f] Organozinc reagents represent an attractive class of organometallic reagents for cross-couplings, combining both, the low toxicity of zinc salts as well as a high functional group tolerance. Albeit, various examples of palladium-[7f,60] or nickel-catalyzed[7f,60e,61] Csp^2-Csp^3 cross-couplings using alkylzinc reagents have been reported, the search for cheaper and more abundant alternative catalytic systems is highly desirable. Cobalt-salts have been found to display several beneficial characteristics.[5d,6a,62] In comparison to palladium, cobalt is a fairly cheap metal and for many transformations no sophisticated ligands are required for an efficient catalysis. [5d,6a,62] Additionally, several reported protocols showed, that cobalt salts are especially well suited catalysts for various types of reactions utilizing organozinc reagents as nucleophilic coupling partners[5d,6a,62] including acylations,[52-55,63] cross-coupling reactions,[6b-f,35,39,41,43-45,64]

[59] Adapted with permission from (F. H. Lutter, L. Grokenberger, P. Spieß, J. M. Hammann, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 5546-5550). Copyright (2020) John Wiley & Sons, Inc.

[60] a) C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 2719-2724; b) C. Han, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 7532-7533; c) S. Çalimsiz, M. G. Organ, *Chem. Commun*. **2011**, *47*, 5181-5183; d) Z. Qureshi, C. Toker, M. Lautens, *Synthesis.* **2017**, *49*, 1-16; e) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev*. **2011**, *111*, 1417-1492; f) Y. Yang, K. Niedermann, C. Han, S. L. Buchwald, *Org. Lett*. **2014**, *16*, 4638-4641.

[61] a) V. B. Phapale, D. J. Cárdenas, *Chem. Soc. Rev*. **2009**, *38*, 1598-1607; b) A. Joshi-Pangu, M. Ganesh, M. R. Biscoe, *Org. Lett*, **2011**, *13*, 1218-1221; c) J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C.-M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc*, **2016**, *138*, 2174-2177; d) E. C. Hansen, C. Li, S. Yang, D. Pedro, D. J. Weix, *J. Org. Chem.* **2017**, *82*, 7085-7092.

[62] a) C. Gosmini, A. Moncomble, *Isr. J. Chem.* **2010**, *50*, 568-576; b) J. M. Hammann, M. S. Hofmayer, F. H. Lutter, L. Thomas, P. Knochel, *Synthesis* **2017**, *49*, 3887-3894. c) F. H. Lutter, S. Graßl, L. Grokenberger, M. S. Hofmayer, Y. H. Chen, P. Knochel, *ChemCatChem*, **2019**, *11*, 5188-5197.

[63] F. H. Lutter, L. Grokenberger, M. S. Hofmayer, P. Knochel, *Chem. Sci.* **2019**, *10*, 8241-8245.

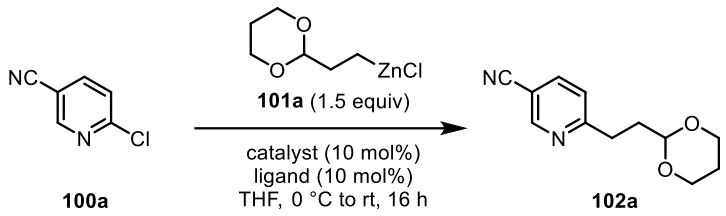
[64] a) B.-H. Tan, J. Dong, N. Yoshikai, *Angew. Chem. Int. Ed*. **2012**, *51*, 9610-9614; b) J. Yan, N. Yoshikai, *ACS Catal*. **2016**, *6*, 3738-3742; c) A. D. Benischke, I. Knoll, A. Rérat, C. Gosmini, P. Knochel, *Chem. Commun.* **2016**, *52*, 3171-3174; d) R. Sallio, M. Corpet, L. Habert, M. Durandetti, C. Gosmini, I. Gillaizeau, *J. Org. Chem*. **2017**, *82*, 1254-1259.

or aminations[65]. Using this beneficial combination, a cobalt-catalyzed cross-coupling of functionalized primary and secondary alkylzinc reagents with a variety of aryl, heteroaryl and alkynyl halides is reported.

1.2 Optimization of the Reaction Conditions

In a preliminary experiment, 6-chloronicotinonitrile (**100a**) was treated with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**101a**) under various conditions (Table 1).

Table 1: Optimization of the reaction conditions for the cross-coupling of **100a** with alkylzinc reagent **101a**.



Entry	Catalyst	Ligand	Yield of **102a** [%][a]
1	-	-	0
2	$MnCl_2$	-	0
3	$CuCl_2$	-	0
4	$FeCl_2$	-	0
5	$CrCl_2$	-	0
6	$NiCl_2$	-	51
7	$CoCl_2$	-	52
8	$CoCl_2$	bipy[b]	66
9	$CoCl_2$	dtbbpy[c]	63
10	$CoCl_2$	neocuproine	65
11	$CoCl_2$	TMEDA	39
12[d]	**$CoCl_2$**	**bipy[b]**	**80 (75)[e]**
13[d]	$CoCl_2$[f]	bipy[b]	82

[a] Reactions were performed on a 0.25 mmol scale. Yields were determined by GC-analysis. Tetradecane ($C_{14}H_{30}$) was used as internal standard. [b] 2,2'-Bipyridine. [c] 4,4'-Di-*tert*-butyl-2,2'-dipyridyl. [d] 20 mol% of bipy was used. [e] Isolated yield of the reaction performed on a 1.00 mmol scale. [f] $CoCl_2$ (99.99% purity) was used.

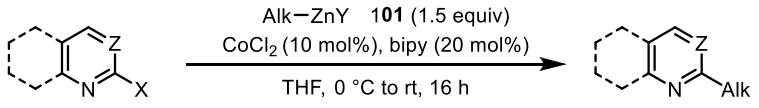
[65] a) X. Qian, Z. Yu, A. Auffrant, C. Gosmini, *Chem. Eur. J.* **2013**, *19*, 6225-6229; b) Y.-H. Chen, S. Graßl, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 1108-1111; c) S. Graßl, Y.-H. Chen, C. Hamze, C. P. Tüllmann, P. Knochel, *Org. Lett.* **2019**, *21*, 494-497.

In the absence of a catalyst, the desired coupling product **102a** could not be detected (entry 1). Various metal halides such as $MnCl_2$, $CuCl_2$, $FeCl_2$ or $CrCl_2$ were tested. However, no catalytic activity was observed for this cross-coupling (entries 2-5). As expected, $NiCl_2$ was able to catalyze the reaction leading to **102a** in 51% yield (entry 6). However, $CoCl_2$ also proved to be a suitable catalyst for this transformation affording the desired alkylated heterocycle **102a** in 52% yield (entry 7). Various ligands were tested to further improve the reaction outcome (entries 8-12). Thus, using the unsubstituted 2,2'-bipyridine led to the best coupling yield of 66% (entry 8). Increasing the amount of ligand furnished **102a** in 75% isolated yield (entry 12). Variation of the reaction solvent, the amounts of metal species or the catalyst loading did not further improve the yield.[66] At this point it was verified that no other metal contaminants are responsible for this catalysis. Using $CoCl_2$ (99.99% purity) in combination with a new stirring bar[67] and reaction vessel afforded the pyridine derivative **102a** in 82% yield (entry 13).

1.3 Cobalt-Catalyzed Cross-Coupling of Primary Alkylzinc Reagents with *N*-Heterocyclic Halides

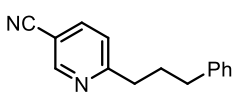
With these results in hand the scope of this cross-coupling reaction was examined (Scheme 34). *N*-heterocyclic halides of type **100** were coupled with various functionalized alkylzinc reagents of type **101**. Thus, the reaction of **100a** with (3-phenylpropyl)zinc chloride afforded **102b** in 73% yield. Also, the corresponding bromopyridine was used leading to coupling products **102c** and **102d** in 62-75% yield. Several alkylzinc reagents bearing various functional groups were excellent substrates for this cross-coupling. Zinc organometallics containing nitrile groups, masked amines, and acetates were successfully coupled furnishing the alkylated pyridines **102e**-**g** in 66-87% yield. The reactions of zinc species derived from natural products such as (1*R*)-(−)-nopol and (*S*)-citronellol with ethyl 6-chloronicotinate afforded **102h** and **102i** in 76-83% yield. Also, using 2-halonicotinic esters in combination with zinc reagents bearing a heterocyclic or an alkyne moiety coupled smoothly leading to **102j** and **102k** in 78-83% yield. Furthermore, other *N*-heterocyclic halides, such as quinoline, isoquinoline, quinazoline, and pyrimidine derivatives were successfully cross-coupled with various functionalized alkylzinc reagents furnishing products **102l**-**s** in 58-95% yield. However, the reaction with less activated heterocyclic halides led to poor coupling results.[68]

[66] For further details, see: V. Experimental Part, Table 10.
[67] E. O. Pentsak, D. B. Eremin, E. G. Gordeev, V. P. Ananikov, *ACS Catal.* **2019**, *9*, 3070-3081.
[68] For unsuccessful substrates see: V. Experimental Part, Scheme 57.

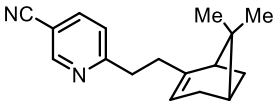


100
X, Y = Cl, Br
Z = N, CH

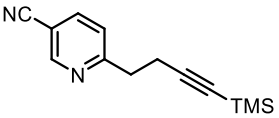
102[a]



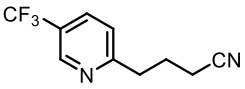
102b: 73%
(X = Cl)



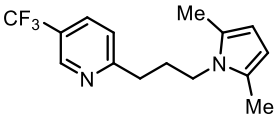
102c: 75%
(X = Br)



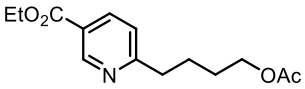
102d: 62%
(X = Br)



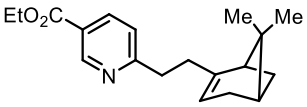
102e: 87%[b]
(X = Br)



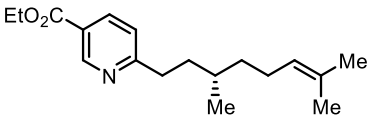
102f: 87%
(X = Br)



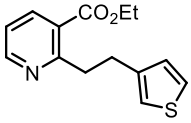
102g: 66%[b]
(X = Cl)



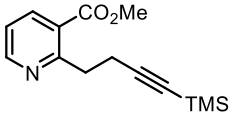
102h: 76%
(X = Cl)



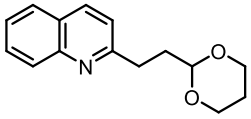
102i: 83%
(X = Cl)



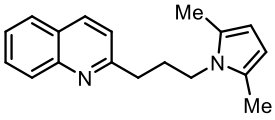
102j: 78%
(X = Cl)



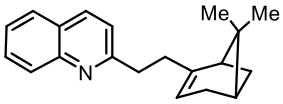
102k:
83%
(X = Br)



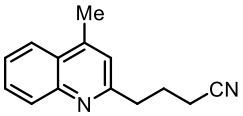
102l: 95%
(X = Br)



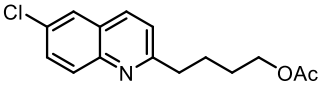
102m: 85% (X = Br)
102m: 82% (X = Cl)



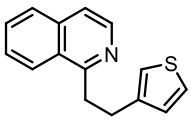
102n: 75%
(X = Br)



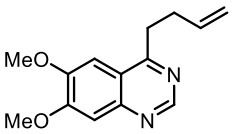
102o: 70%[b]
(X = Cl)



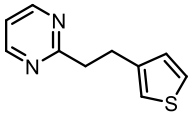
102p: 58%[b]
(X = Cl)



102q: 61%
(X = Br)



102r: 60%
(X = Cl)

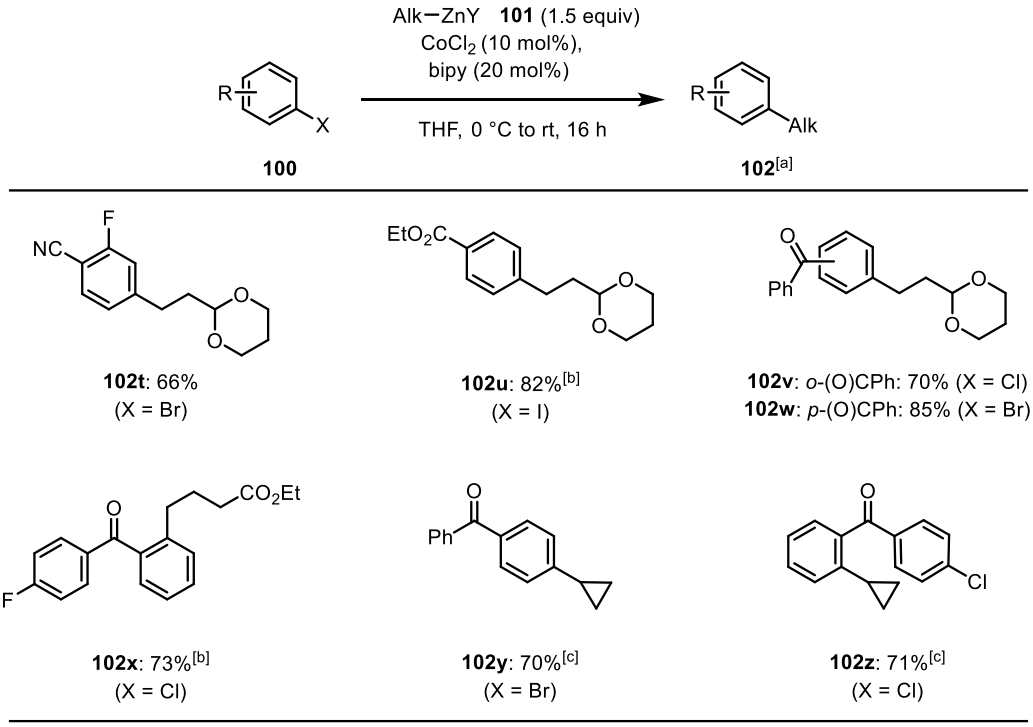


102s: 71%
(X = Br)

Scheme 34: Compounds of type **102** obtained by the Co-catalyzed reaction of *N*-heterocyclic halides of type **100** with primary alkylzinc reagents of type **101**. [a] Reactions were performed on a 0.5 mmol scale. Yields are determined from the purified and analytical pure product. [b] 20% $CoCl_2$, 40% dtbbpy and 1.9 equiv of the corresponding alkylzinc reagent were used.

1.4 Cobalt-Catalyzed Cross-Coupling of Primary and Secondary Alkylzinc Reagents with Electron-Deficient Aryl Halides

Next, this cobalt catalyzed cross-coupling was extended to various electron-deficient aryl halides as electrophilic coupling partners (Scheme 35). Thus, (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**101a**) was coupled with 4-bromo-2-fluorobenzonitrile and ethyl 4-iodobenzoate furnishing **102t-u** in 66-82% yield. Benzophenone was successfully alkylated in *ortho*- and *para*-position, respectively, starting from the corresponding halide, leading to **102v** and **102w** in 70-85% yield. The cross-coupling of a zinc reagent containing an ester moiety with a functionalized chlorobenzophenone led to **102x** in 73% yield. Also, cyclopropylzinc chloride was used in this procedure, affording the benzophenones **102y** and **102z** in 70-71% yield.



Scheme 35: Compounds of type **102** obtained by the Co-catalyzed reaction of aryl halides of type **100** with alkylzinc reagents of type **101**. [a] Reactions were performed on a 0.5 mmol scale. Yields are determined from the purified and analytical pure product. [b] 20% $CoCl_2$, 40% dtbbpy and 1.9 equiv of the corresponding alkylzinc reagent were used. [c] Dtbbpy was used instead of bipy. The reaction was performed at rt.

1.5 Diastereoselective Cobalt-Catalyzed Cross-Coupling of Secondary Alkylzinc Reagents with Heteroaryl Halides

Encouraged by the results with the secondary cyclopropylzinc reagent, the cross-coupling of various substituted six-membered cycloalkylzinc reagents was examined. In the past, several diastereoselective Csp^3-Csp^2 Negishi-type cross-couplings using palladium[33b,69] and nickel salts[70] have been reported. Also, a cobalt-catalyzed version applying diarylzinc reagents is known.[6b] However, this method only allows the coupling of 1,2-substituted cycloalkyl iodides with (hetero)aryl zinc reagents in a diastereoselective manner. To overcome this limitation, the problem was approached by using substituted cycloalkylzinc species with heteroaryl halides as coupling partners. Previous studies have shown that the carbon-zinc bond is prone for an easy epimerization in the presence of metal salts.[69a-b] Thus, a highly diastereoselective cross-coupling is only enabled by a fast transmetalation of the thermodynamically more stable alkylzinc species to the transition-metal catalyst.[69a]

To evaluate the scope of a diastereoselective cross-coupling using substituted cyclohexylzinc reagents, 2-methylcyclohexylzinc iodide was coupled with 6-bromonicotinonitrile. A short screening revealed that a catalytic system of 10% $CoCl_2$ and 20% 4,4'-di-*tert*-butyl-2,2'-dipyridyl in acetonitrile led to the best yield and diastereomeric ratio.[71] Hence, the coupling of various 1,3-, and 1,4-functionalized cycloalkylzinc reagents with *N*-heterocyclic bromides was examined (Scheme 36). The reaction of 6-bromonicotinonitrile with 3-methylcyclohexylzinc iodide led to the thermodynamically more stable *cis*-1,3-disubstituted cyclohexane **102aa** in 80% yield and dr = 91:9. However, using the corresponding zinc reagent bearing the bulkier *iso*-propyl residue led to **102ab** in 63% yield and an improved diastereomeric ratio of 96:4. Additionally, this zinc reagent was coupled with 2-bromopyrimidine furnishing **102ac** (52% yield, dr = 94:6[72]). Also, 1,4-substituted cyclohexylzinc reagents could be used in this protocol. Thus, the cross-coupling of zinc reagents bearing an ester or a pyrrole substituent with a trifluoromethylated bromopyridine led to the corresponding *trans*-1,4-bifunctionalized cyclohexanes **102ad** and **102ae** in 51-

[69] a) T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer, P. Knochel, *Nat. Chem*. **2010**, *2*, 125-130; b) T. Thaler, L.-N. Guo, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 2174-2177; c) S. Seel, T. Thaler, K. Takatsu, C. Zhang, H. Zipse, B. F. Straub, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2011**, *133*, 4774-4777; d) P. Knochel, C. Diène, *Compt. Rend. Chim.* **2011**, *14*, 842-850; e) K. Moriya, P. Knochel, *Org. Lett*. **2014**, *16*, 924-927.

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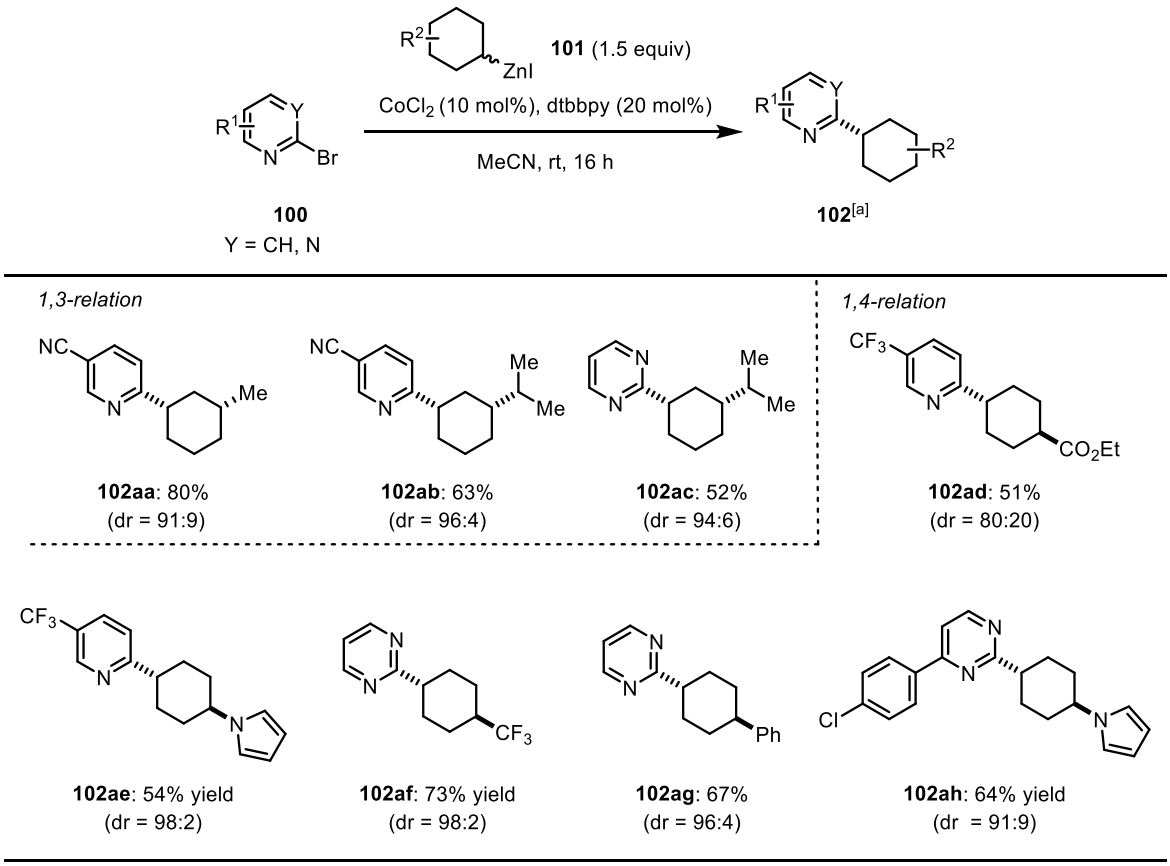
[71] For further details, see: V. Experimental Part, Table 11.

[72] The stereochemistry of **102ac** was determined by NOESY-NMR, see: VI. Appendix, 1.1 2-(3-Isopropylcyclohexyl)pyrimidine (**102ac**).

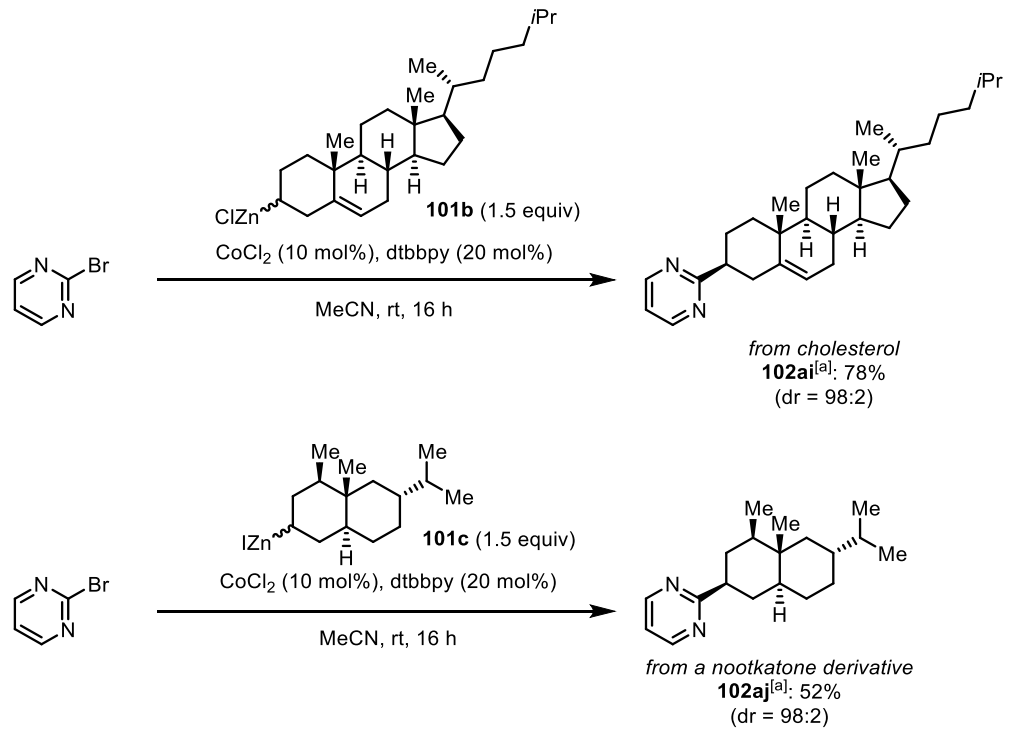
54% yield (dr = 80:20-98:2[73]). Bromopyrimidine derivatives were coupled with functionalized cyclohexyl reagents affording **102af**-**ah** in 64-73% yield and diastereomeric ratios of up to 98:2.



Scheme 36: Diastereoselective cobalt-catalyzed cross-coupling of heteroaromatic bromides of type **100** with 1,3- and 1,4-substituted secondary alkylzinc reagents of type **101** leading to products of type **102**. [a] Reactions were performed on a 0.5 mmol scale. Yields are determined from the purified and analytical pure product. The diastereomeric ratio (dr) was determined by GC analysis. The major diastereomer is shown.

Remarkably, 2-bromopyrimidine could be coupled with complex alkylzinc reagents prepared from steroid and sesquiterpene derivatives (Scheme 37). The reaction of cholesterylzinc chloride **101b** furnished **102ai** in 78% yield and a diastereomeric ratio of 98:2. Also, the corresponding coupling using zinc reagent **101c** derived from a reduced nootkaton derivative proceeded in a highly diastereoselective fashion leading to **102aj** in 52% yield (dr = 98:2).

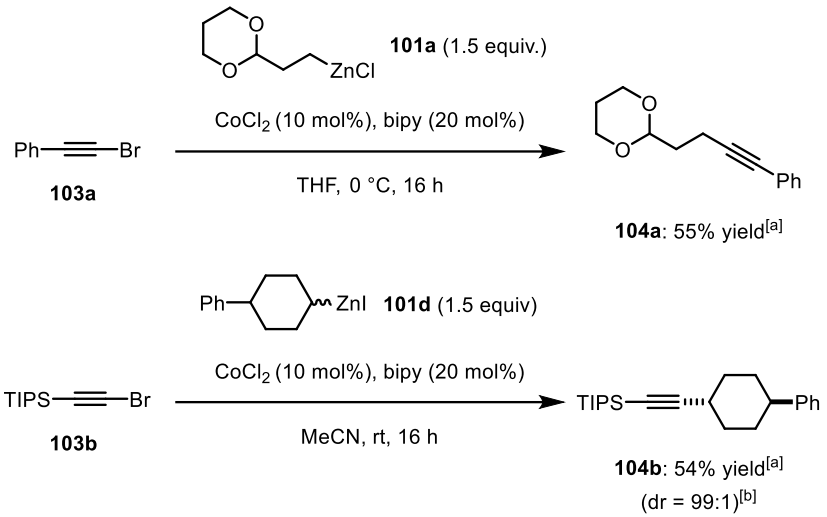
[73] The stereochemistry of **102ae** was determined by crystal structure analysis, see: VI. Appendix, 3. Single Crystal X-Ray Diffraction Studies.



Scheme 37: Diastereoselective cobalt-catalyzed cross-coupling of 2-bromopyridine with zinc organometallics **101b** and **101c** derived from cholesterol and nootkatone derivatives. [a] Reactions were performed on a 0.5 mmol scale. Yields are determined from the purified and analytically pure product. The diastereomeric ratio (dr) was determined by GC analysis. The major diastereomer is shown.

1.6 Cobalt-Catalyzed Cross-Coupling of Primary and Secondary Alkylzinc Reagents with Alkynyl Bromides

Finally, this cobalt-catalyzed cross-coupling was further extended to alkynyl bromides (Scheme 38). (Bromoethynyl)-benzene (**103a**) reacted smoothly with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**101a**) affording the alkylated alkyne **104a** in 55% yield. Interestingly, the coupling of the TIPS protected alkyne **103b** with the 1,4-phenyl substituted cyclohexylzinc reagent **101d** furnished the *trans*-1,4-alkynylated cyclohexane derivative **104b** in 54% yield and dr = 99:1.



Scheme 38: Cobalt-catalyzed cross-coupling of alkynyl bromides with primary and secondary alkylzinc reagents. [a] Reactions were performed on a 0.5 mmol scale. Yields are determined from the purified and analytical pure product. [b] The diastereomeric ratio (dr) was determined by GC analysis. The major diastereomer is shown.

1.7 Mechanistic Considerations

To gain an insight into the reaction mechanism, radical-trapping experiments using 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) were performed. Previous studies showed that TEMPO is able to significantly inhibit cobalt-catalyzed reactions, which might indicate the involvement of radical intermediates within the course of these reactions.[63,74] Thus, to a standard coupling setup of 6-chloronicotinonitrile (**100a**) with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**101a**) 2.0 equiv of TEMPO were added.[9] However, the coupling product **102a** was afforded in a similar yield, compared to the standard conditions without the radical trapping agent. This indicates that this new cobalt-catalyzed cross-coupling might not proceed *via* radical intermediates.

[74] L. Nicolas, P. Angibaud, I. Stansfield, P. Bonnet, L. Meerpoel, S. Reymond, J. Cossy, *Angew. Chem. Int. Ed.* **2012**, *51*, 11101-11104.

2. Cobalt-Catalyzed Csp^3-Csp^3 Cross-Coupling of Functionalized Alkylzinc Reagents with Alkyl Iodides[75]

2.1. Introduction

Transition-metal catalyzed cross-coupling reactions are among the most powerful tools for the construction of complex structures. Over the past decades, significant progress has been made in the formation of new C-C bonds, which led to numerous applications in academic as well as in industrial research.[3c] The most common catalysts for performing cross-couplings are palladium and nickel salts.[3b] These Csp^3-Csp^3 cross-couplings are particularly difficult due to a hampered oxidative insertion of the transition-metal catalyst into the alkyl-X bond and the propensity of the subsequently formed alkyl-transition metal species to undergo β-hydride elimination.[60e,76] Especially, the use of mild organometallic reagents in these couplings, such as organozinc compounds, is still a challenge.[76a] Zinc organometallics display several beneficial properties, including a high functional group compatibility and the ability to undergo a fast transmetalation to a transition-metal catalyst.[7,60e] Additionally, a growing commercial availability of these reagents and the low toxicity of zinc salts make them an attractive class of metal reagents. [7,60e] Various palladium and nickel catalyzed Csp^3-Csp^3 cross-couplings using zinc organometallics, including enantioselective versions have been reported by Organ[77], Fu[78], and others[60e,70b,76a,76c-e,79] However, the high price and the need of often sophisticated ligands triggered the search for cheaper and

[75] Adapted with permission from (F. H. Lutter, L. Grokenberger, M. Benz, P. Knochel, *Org. Lett.* **2020**, 22, 3028-3032). Copyright (2020) American Chemical Society.

[76] a) D. J. Cárdenas, *Angew. Chem. Int. Ed.* **2003**, *42*, 384-387; b) M. R. Netherton, G. C. Fu, *Adv. Synth. Catal.* **2004**, *346*, 1525-1532; c) A. C. Frisch, M. Beller, *Angew. Chem. Int. Ed.* **2005**, *44*, 674-688; d) A. Rudolph, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 2656-2670; e) J. Choi, G. C. Fu, *Science* **2017**, *356*, eaaf7230.

[77] a) N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *J. Org. Chem.* **2005**, *70*, 8503-8507; b) N. Hadei, E. A. B. Kantchev, C. J. O'Brie, M. G. Organ, *Org. Lett.* **2005**, *7*, 3805-3807; c) G. A. Chass, C. J. O'Brien, N. Hadei, E. A. B. Kantchev, W.-H. Mu, D.-C. Fang, A. C. Hopkinson, I. G. Csizmadia, M. G. Organ, *Chem. Eur. J.* **2009**, *15*, 4281-4288; d) G. T. Achonduh, N. Hadei, C. Valente, S. Avola, C. J. O'Brien, M. G. Organ, *Chem. Commun.* **2010**, *46*, 4109-4111; e) N. Hadei, G. T. Achonduh, C. Valente, C. J. O'Brien, M. G. Organ, *Angew. Chem. Int. Ed.* **2011**, *50*, 3896-3899; f) L. C. McCann, H. N. Hunter, J. A. C. Clyburne, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 7024-7027.

[78] a) J. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 12527-12530; b) J. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727; c) F. O. Arp, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 10482-10483; d) C. Fischer, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 4594-4595; e) S. Son, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 2756-2757; f) C. J. Cordier, R. J. Lundgren, G. C. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 10946-10949; g) J. Schmidt, J. Choi, A. T. Liu, M. Slusarczyk, G. C. Fu, *Science* **2016**, *354*, 1265-1269; h) X. Mu, Y. Shibata, Y. Makida, G. C. Fu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5821-5824; i) G. M. Schwarzwalder, C. D. Matier, G. C. Fu, *Angew. Chem. Int. Ed.* **2019**, *58*, 3571-3574.

[79] a) C. E. Tucker, P. Knochel, *J. Org. Chem.* **1993**, *58*, 4781-4782; b) A. Devasagayaraj, T. Stüdemann, P. Knochel, *Angew. Chem., Int. Ed. Engl.* **1996**, *34*, 2723-2725; c) R. Giovannini, T. Stüdemann, G. Dussin, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 2387-2390; d) A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, *67*, 79-85; e) A. Lei, X. Zhang, *Org. Lett.* **2002**, *4*, 2285-2288; f) C. F. Malosh, J. M. Ready, *J. Am. Chem. Soc.* **2004**, *126*, 10240-10241; g) V. B. Phapale, E. Buñuel, M. García-Iglesias, D. J. Cárdenas, *Angew. Chem. Int. Ed.* **2007**, *46*, 8790-8795.

more abundant metal catalysts. Although iron[80], cobalt[81], and manganese[82] salts have been found to catalyze the cross-coupling of alkyl halides with alkylmagnesium reagents there is no protocol utilizing alkylzinc organometallics as coupling reagents. However, this would be highly desirable thus enabling the tolerance of sensitive functional groups attached to the electrophile as well as in the organometallic reagent itself.

In the following the first cobalt-catalyzed Negishi type Csp^3-Csp^3 cross-coupling of various primary dialkylzinc reagents with primary and secondary iodides is reported.

2.2 Optimization of the Reaction Conditions

In preliminary experiments the coupling of (3-iodopropyl)benzene (**105a**) with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**101a**) was investigated (Table 2). Without a metal catalyst no product formation of **107a** was observed (entry 1). Transition-metal chlorides such as $CuCl_2$, $FeCl_2$ or $MnCl_2$ in combination with both, the mono-alkylzinc reagent **101a** or the dialkylzinc species **106a** did not catalyze the formation of **107a** (entries 2-4). However, $CoCl_2$ showed catalytic activity, especially in combination with the dialkylzinc reagent **106a**, furnishing the desired product **107a** in 32% yield (entries 5). Switching to acetonitrile as solvent was beneficial leading to 39% yield of **107a** (entry 6). Various ligands were tested to further improve the cross-coupling (entries 7-10). Me_4DACH (**47**)[6d,35,83] turned out to be superior to other ligands affording **107a** in 50% yield (entry 10). Previous reports showed the beneficial effects of tetrabutylammonium halides in alkyl-alkyl cross-couplings.[76b,77f,79d,84]

[80] a) K. G. Dongol, H. Koh, M. Sau, C. L. L. Chai, *Adv. Synth. Catal.* **2007**, *349*, 1015-1018; b) M. Guisán-Ceinos, F. Tato, E. Buñuel, P. Calle, D. J. Cárdenas, *Chem. Sci.* **2013**, *4*, 1098-1104.

[81] a) G. Cahiez, C. Chaboche, C. Duplais, A. Giulliani, A. Moyeux, *Adv. Synth. Catal.* **2008**, *350*, 1484-1488; b) C. Andersen, V. Ferey, M. Daumas, P. Bernardelli, A. Guérinot, J. Cossy, *Org. Lett.* **2019**, *21*, 2285-2289.

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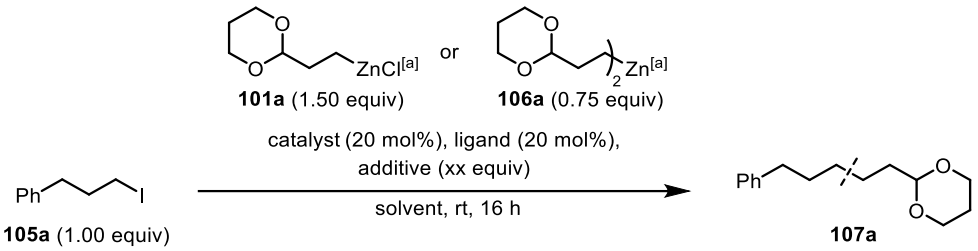
Table 2. Optimization of the reaction conditions for the cross-coupling of alkyl iodide (**105a**) with zinc reagents of type **101a** or **106a**.



Entry	Catalyst	Zinc Reagent	Solvent	Ligand	Additive	Yield of **107a** [%][b]
1	-	**101a**	THF	-	-	traces
2	$CuCl_2$	**101a** (**106a**)	THF	-	-	1 (3)[c]
3	$FeCl_2$	**101a** (**106a**)	THF	-	-	1 (2)[c]
4	$MnCl_2$	**101a** (**106a**)	THF	-	-	Traces (traces)[c]
5	$CoCl_2$	**101a** (**106a**)	THF	-	-	11 (32)[c]
6	$CoCl_2$	**106a**	MeCN	-	-	39
7	$CoCl_2$	**106a**	MeCN	neocuproine	-	46
8	$CoCl_2$	**106a**	MeCN	PPh_3[d]	-	11
9	$CoCl_2$	**106a**	MeCN	TMEDA	-	42
10	$CoCl_2$	**106a**	MeCN	Me_4DACH (**47**)	-	50
11	$CoCl_2$	**106a**	MeCN	Me_4DACH (**47**)	TBAB[e]	44
12	$CoCl_2$	**106a**	MeCN	Me_4DACH (**47**)	TBAI[e]	57
13	**$CoCl_2$**	**106a**	**MeCN**	**Me_4DACH** (**47**)	**TBAI**[f]	**74 (72)**[g] **(78)**[h]

[a] $MgX_2{\cdot}LiX$ (X = Cl or Br) is omitted for clarity. [b] Reactions were performed on a 0.25 mmol scale. Yields were determined by GC-analysis. Tetradecane ($C_{14}H_{30}$) was used as internal standard. [c] **106a** was used. [d] 40 mol% of the ligand were used. [e] 1.00 equiv. of the additive were used. [f] 2.25 equiv. of the additive were used. [g] Isolated yield. [h] $CoCl_2$ of 99.99% purity and a new stirring bar were used

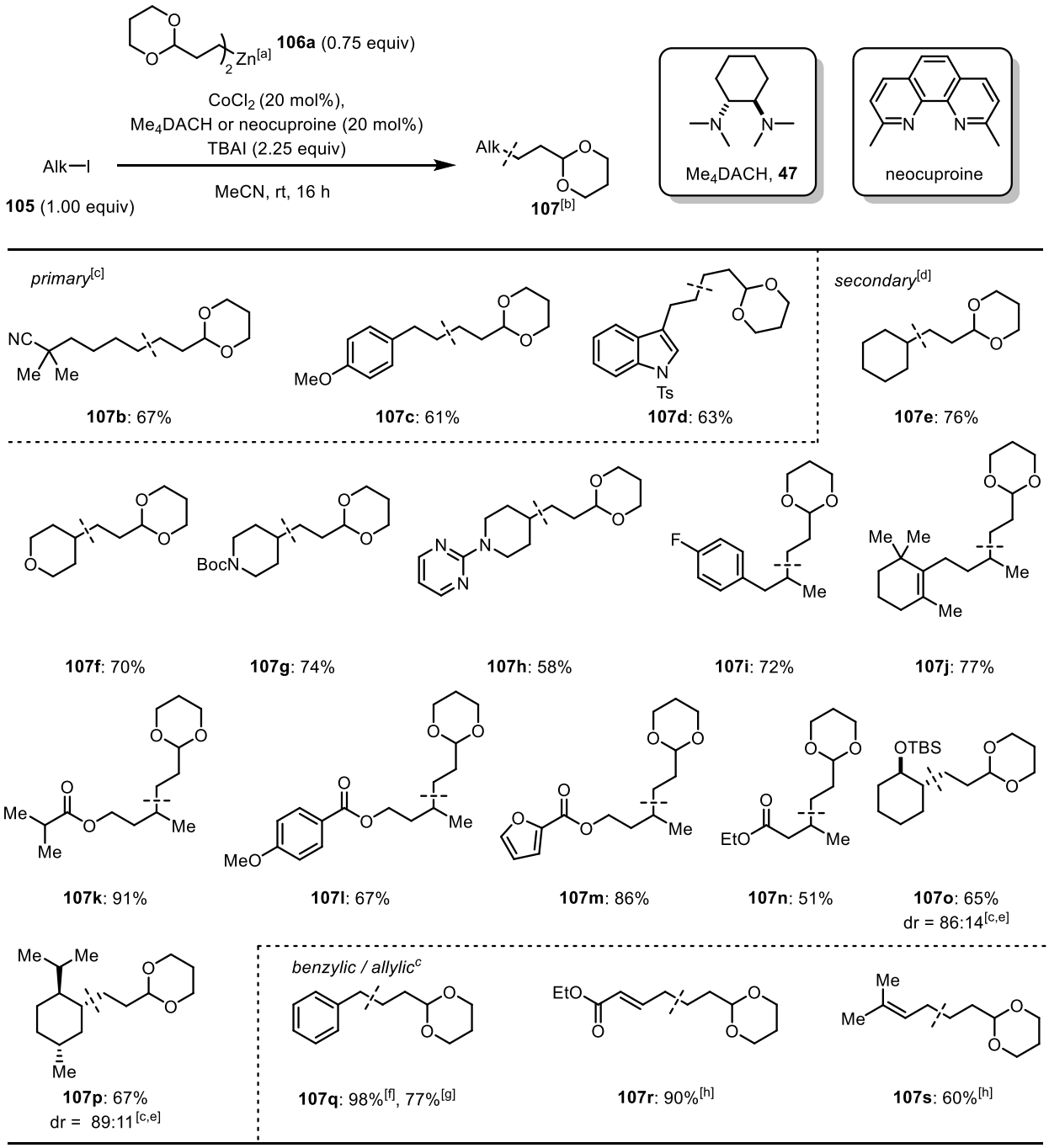
A screening revealed, that 2.25 equiv of tetrabutylammonium iodide (TBAI) significantly increased the yield leading to the coupling product **107a** in 72% (entries 11-13). Variation of the equivalents of the organozinc reagent, the cobalt source, or the amount of catalyst did not further improve the reaction yield.[85] Additionally, it was verified that no metal contaminants are responsible for the catalysis. Thus,

[85] For further details, see: V. Experimental Part, Table: 12.

performing the reaction with $CoCl_2$ (99.99% purity), a new stirring bar and reaction vessel furnished **107a** in 78% yield (entry 13).[67]

2.3 Cobalt-Catalyzed Cross-coupling of Bis(2-(1,3-dioxan-2-yl)ethyl)zinc with Primary and Secondary Alkyl Iodides

With these results in hand the scope of this cross-coupling was examined (Scheme 39). Thus, dialkylzinc reagent **106a** was coupled with primary alkyl iodides containing nitrile, aryl or heteroaryl moieties furnishing the corresponding products **107b**-**d** in 61-67% yield. Switching to neocuproine as ligand enabled the use of various secondary alkyl iodides. The coupling with cyclohexyl iodide afforded the corresponding product **107e** in 76% yield. Also, tetrahydropyranyl and piperidyl iodides underwent a smooth coupling with **106a**. Thus, the corresponding products **107f**-**h** were obtained in 58-74% yield. The coupling with secondary acyclic iodides bearing an aryl moiety or derived from β-ionone led to **107i**-**j** in 72-77% yield. Various other secondary iodides containing alkyl, aryl or heteroaryl esters were suitable electrophiles for the coupling with the dialkylzinc reagent **106a** furnishing **107k**-**n** in 51-91% yield. Interestingly, TBS-protected iodohydrin and a cyclic iodide derived from menthol could also be used for the coupling affording **107o**-**p** in 65-67% yield and up to 89:11 dr. Furthermore, benzylic and allylic halides could be coupled under these conditions furnishing the expected products **107q**-**s** in 60-98% yield.[51]

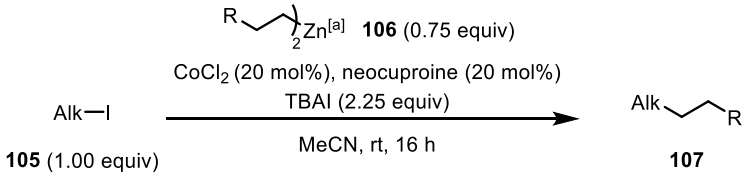


Scheme 39. Products of type **107** obtained by the cobalt-catalyzed cross-coupling of alkyl iodides (**105**) with dialkylzinc species **106a**. [a] $MgX_2 \cdot LiX$ (X = Cl or Br) is omitted for clarity. [b] All reactions were performed on a 0.5 mmol scale. Isolated yields of analytically pure products. [c] Me_4DACH (**47**) was used as a ligand. [d] Neocuproine was used as a ligand. [e] The diastereomeric ratio (dr) was determined by GC-analysis of the crude reaction mixture. The major diastereomer is shown. [f] Benzyl bromide was used as an electrophile. [g] Benzyl chloride was used as an electrophile. [h] Allyl bromide derivatives were used as electrophiles.

2.4 Cobalt-Catalyzed Cross-coupling of Dialkylzincs with Primary and Secondary Alkyl Iodides

Next, cross-couplings of various dialkylzinc reagents with secondary iodides were examined (Table 3). The reaction of iodotetrahydropyran **105b** and piperidinyl iodide **105c** with dialkylzinc reagent **106b** led to the coupling products **107t**-**u** in 66-71% yield. Also, di(4-chlorobutyl)zinc **106c** underwent a cross-coupling with iodo piperidine **105d** affording the alkylated heterocycle **107v** 66% yield. At this point the scalability of the method was examined. Thus, the reaction of **106c** with *N*-boc protected 4-iodo piperidine **105c** was performed on a 5 mmol scale, leading to the 4-alkylated piperidine **107w** in 58% yield. Zinc organometallics **106d**-**f** bearing sensitive functional groups such as acetates, carbamates and esters were conveniently prepared from the corresponding bromides performing a magnesium insertion in the presence of 0.5 equiv $ZnCl_2$.[17] The reaction of the dialkylzinc **106d** with cyclic and acyclic iodides afforded the products **107x**-**y** in 65-72% yield. The secondary iodide **105g** was coupled with the Boc-protected 4-piperidylalkylzinc **106e** leading to the product **107z** in 72% yield. Also, dialkylzinc reagent **106f** bearing an ester function was coupled with various substituted secondary alkyl iodides affording **107aa**-**ac** in 68-80% yield.

Table 3: Products of type **107** obtained by the cobalt-catalyzed cross-coupling of secondary alkyl iodides of type **105** with dialkyl zincs of type **106**.



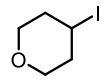
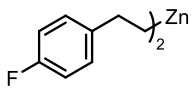
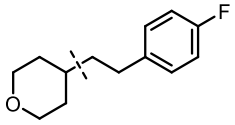
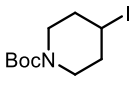
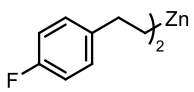
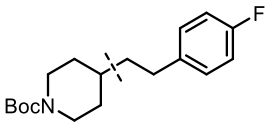
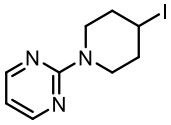
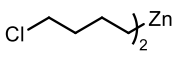
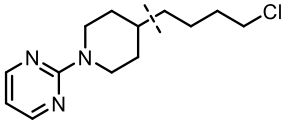
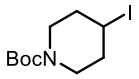
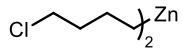
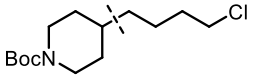
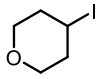
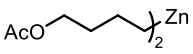
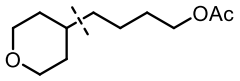
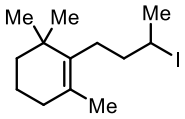
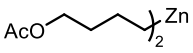
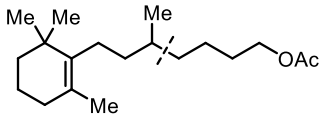
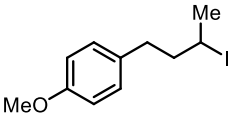
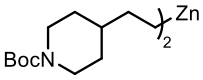
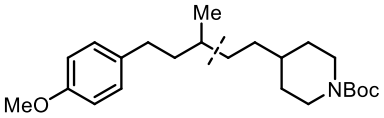
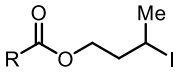
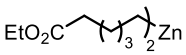
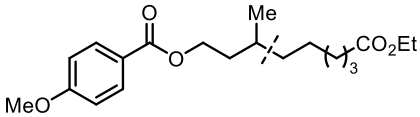
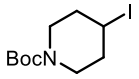
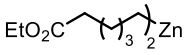
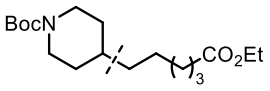
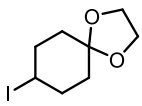
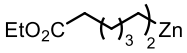
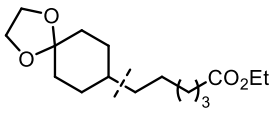
Entry	Alkyl Iodide **105**	Zinc Reagent **106**	Product **107:** yield[b]
1	 **105b**	 **106b**	 **107t**: 71%
2	 **105c**	 **106b**	 **107u**: 66%
3	 **105d**	 **106c**	 **107v**: 66%

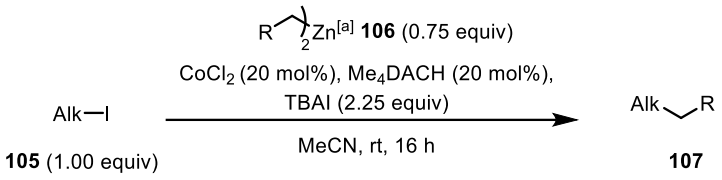
Table 3: continued

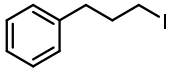
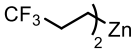
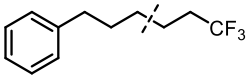
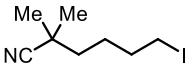
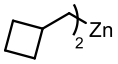
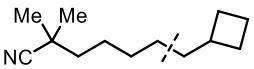
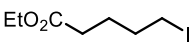
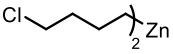
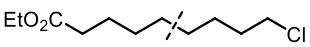
Entry	Alkyl Iodide **105**	Zinc Reagent **106**	Product **107:** yield[a]
4	 **105c**	 **106c**	 **107w**: 58% (*5 mmol scale*)
5	 **105b**	 **106d**	 **107x**: 65%
6	 **105f**	 **106d**	 **107y**: 72%
7	 **105g**	 **106e**	 **107z**: 72%
8	 **105h** R = (4-OMe)C_6H_4	 **106f**	 **107aa**: 68%
9	 **105c**	 **106f**	 **107ab**: 70%
10	 **105h**	 **106f**	 **107ac**: 80%

[a] $MgX_2 \cdot LiX$ (X = Cl or Br) is omitted for clarity. [b] All reactions were performed on a 0.5 mmol scale. Isolated yield of analytically pure products.

Additionally, primary alkyl iodides were coupled with various dialkylzinc reagents (Table 4). Thus, the coupling of di(3,3,3-trifluoropropyl)zinc (**106g**) with iodide **105a** afforded the coupling product **107ad** in 75% yield. Moreover, primary alkyl iodides containing sensitive functionalities such as nitrile (**105i**) or ester groups (**105j**) could be coupled using cobalt-catalysis leading to the corresponding products **107ae-af** in 39% and 62%, respectively.

Table 4. Products of type **107** obtained by the cobalt-catalyzed cross-coupling of primary alkyl iodides of type **105** with dialkyl zincs of type **106**.



Entry	Alkyl Iodide **105**	Zinc Reagent **106**	Product **107:** yield[b]
1	 **105a**	 **106g**	 **107ad**: 75%
2	 **105i**	 **106h**	 **107ae**: 62%
3	 **105j**	 **106c**	 **107af**: 39%

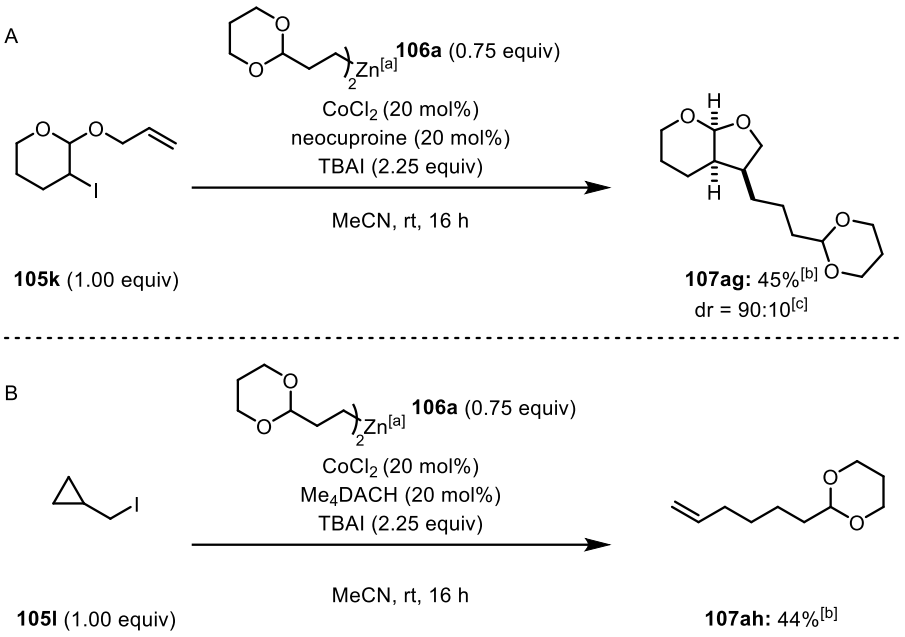
[a] $MgX_2 \cdot LiX$ (X = Cl or Br) is omitted for clarity. [b] All reactions were performed on a 0.5 mmol scale. Isolated yield of analytically pure products.

2.5 Mechanistic Considerations

To shed some light on the reaction mechanism, experiments with radical-clock precursors **105k** and **105l** were performed (Scheme 40).[80b,86] Thus, treatment of iodohydrine **105k** with dialkylzinc reagent **106a** in the presence of the cobalt catalyst only led to the cyclization product **107ag** in 45% yield (dr = 90:10). Furthermore, the reaction with (iodomethyl)cyclopropane (**105l**) afforded the ring-opening product **107ah** in 44% yield. These findings suggest the involvement of radical intermediates during the course of the reaction potentially formed *via* a stepwise one-electron oxidation of the cobalt catalyst to the alkyl iodide.[83c,86b,87]

[86] a) H. Ohmiya, H. Yorimitsu, K. Oshima, *Org. Lett.* **2006**, *8*, 3093-3096; b) H. Someya, H. Ohmiya, H. Yorimitsu, K. Oshima, *Org. Lett.* **2007**, *9*, 1565-1567; b) T. Tsuji, H. Yorimitsu, K. Oshima, *Angew. Chem. Int. Ed.* **2002**, *41*, 4137-4139; c) K. Wakabayashi, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2001**, *123*, 5374-5375.

[87] a) H. Ohmiya, K. Wakabayashi, H. Yorimitsu, K. Oshima, *Tetrahedron* **2006**, *62*, 2207-2213; b) L. Gonnard, A. Guérinot, J. Cossy, *Chem. Eur. J.* **2015**, *21*, 12797-12803; c) F. Kreyenschmidt, S. E. Meurer, K. Koszinowski, *Chem. Eur. J.* **2019**, *25*, 5912-5921.



Scheme 40. Mechanistic experiments using radical-clock precursors **105k** and **105l**. [a] $2MgX_2{\cdot}2LiX$ (X = Cl or Br) is omitted for clarity. [b] Reactions were performed on a 0.5 mmol scale. Isolated yield of analytically pure products. [c] The diastereomeric ratio (dr) was determined by GC analysis from the crude reaction mixture. The major diastereomer is shown.

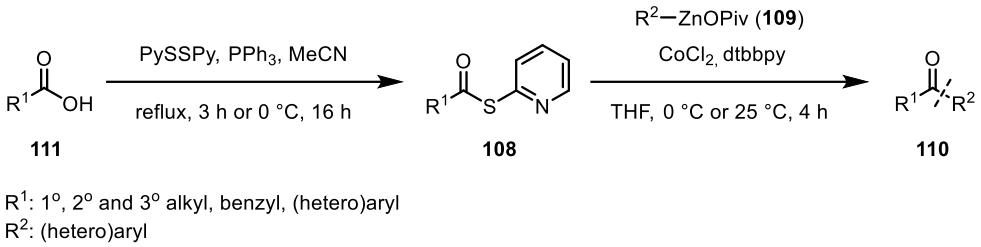
3. Cobalt-Catalyzed Acylation-Reactions of (Hetero)Arylzinc Pivalates with Thiopyridyl Ester Derivatives[88]

3.1. Introduction

The carbonyl group is a central functionality in organic chemistry and the performance of acylation reactions employing organometallic reagents represents a general access to various ketones.[46,47] A major drawback of these reactions is the moderate chemoselectivity or the use of expensive catalysts. [46,47] Acid chlorides are the most common acylation reagents. [7a,7c,46,47,51,52,89] However, their preparation requires harsh conditions, thus lowering the functional group tolerance. In contrast, the use of thioesters is a valuable alternative since Fukuyama showed in pioneering work that these acylating reagents react readily with organozinc halides in the presence of a palladium catalyst.[49e] Additionally, Seki,[50d] Rovis,[50e] Fleischer,[50f] and others[49f-g,50a-b,90] showed that these reactions can be performed using various transition-metal catalysts. Recently, it was shown that organozinc pivalates (RZnOPiv) are an attractive class of zinc organometallics due to their enhanced air- and moisture stability and their excellent compatibility with various transition metal-catalyzed transformations.[38,91] Especially, cobalt-catalyzed reactions have proved to be advantageous.[5f,6d,39,43,62c,65b]

In the following a new cobalt-catalyzed acylation reaction of various saturated and unsaturated thioesters of type $R^1C(O)SPy$ (**108**) with aryl- and heteroarylzinc pivalates of type $R^2ZnOPiv$ (**109**), leading to a broad range of polyfunctional ketones of type **110** is reported. Although thioesters are readily available from the corresponding acid chlorides and thiols,[92] the pyridyl thioesters **108** were prepared under exceedingly mild and neutral conditions from the corresponding carboxylic acid of type **111** using Mukaiyama's method (Scheme 41).[93]

[88] Adapted with permission from (F. H. Lutter, L. Grokenberger, M. S. Hofmayer, P. Knochel, *Chem. Sci.* **2019**, *10*, 8241-8245). Copyright (2019) Royal Society of Chemistry.
[89] S.-H. Kim, R. D. Rieke, *Tetrahedron Lett.* **2011**, *52*, 1523-1526.
[90] a) W. Oppolzer, C. Darcel, P. Rochet, S. Rosset, J. De Brabander, *Helv. Chim. Acta* **1997**, *80*, 1319-1337; b) B. Li, R. A. Buzon, C. K. F. Chiu, S. T. Colgan, M. L. Jorgensen, N. Kasthurikrishnan, *Tetrahedron Lett.* **2004**, *45*, 6887-6890; c) R. Haraguchi, S.-G. Tanazawa, N. Tokunaga, S.-I. Fukuzawa, *Org. Lett.* **2017**, *19*, 1646-1649.
[91] M. S. Hofmayer, F. H. Lutter, L. Grokenberger, J. M. Hammann, P. Knochel, *Org. Lett.* **2019**, *21*, 36-39.
[92] B. P. Bandgar, P. E. More, V. T. Kamble, S. S. Sawant, *Aust. J. Chem.* **2008**, *61*, 1006-1010.
[93] a) T. Endo, S. Ikenaga, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2632-2633; b) T. Mukaiyama, M. Araki, H. Takei, *J. Am. Chem. Soc.* **1973**, *95*, 4763-4765; c) T. Hofmann, P. Schieberle, *J. Agric. Food. Chem.* **1998**, *46*, 616-619.

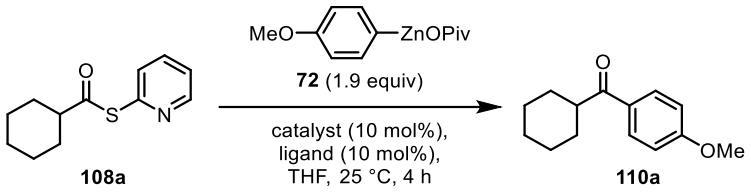


Scheme 41: Preparation of thiopyridyl esters of type **108** from carboxylic acids **111** and cobalt-catalyzed acylation with organozinc pivalates **109**, affording ketones of type **110**. Py = 2-pyridyl.

3.2 Optimization of the Reaction Conditions

In preliminary experiments, *S*-(pyridin-2-yl)-cyclohexanecarbothioate (**108a**) was treated with 4-(methoxyphenyl)zinc pivalate (**72**) under various conditions (Table 5). In the absence of a catalyst, ketone **110a** was obtained in only 9% yield (Table 5, entry 1). Although palladium and nickel are well-known metal catalysts for the Fukuyama acylation, the use of cheaper and more abundant catalysts is highly desirable. Whereas, $MnCl_2$, $CrCl_2$, $FeCl_2$ or $CuCl_2$ gave unsatisfying results (entries 2-5), $CoCl_2$ proved to be an excellent catalyst for this transformation (entry 6). Its catalytic efficiency could be further improved by the addition of various ligands. After a short screening it became clear that 4,4'-di-*tert*-butyl-2,2'-dipyridyl (dtbbpy) gave the best results leading to the ketone **110a** in 88% isolated yield (entry 11).

Table 5: Optimization of the reaction conditions for the acylation of thioester **108a** with arylzinc pivalate **72**.



108a **110a**

Entry	Catalyst	Ligand	Yield of **110a** [%][a]
1	-	-	9
2	$MnCl_2$	-	traces
3	$CrCl_2$	-	traces
4	$FeCl_2$	-	50
5	$CuCl_2$	-	29
6	$CoCl_2$	-	67
7	$CoCl_2$	PPh_3[b]	63
8	$CoCl_2$	TMEDA	64
9	$CoCl_2$	neocuproine	49
10	$CoCl_2$	bipy[c]	71
11	**$CoCl_2$**	**dtbbpy**[d]	**90 (88)**[e] **(87)**[f]
12	$CoCl_2$[g]	dtbbpy[d]	86

[a] Reactions were performed on a 0.5 mmol scale. Determined by GC-analysis. Tetradecane ($C_{14}H_{30}$) was used as internal standard. [b] 20% of the ligand was used. [c] 2,2'-Bipyridine. [d] 4,4'-Di-*tert*-butyl-2,2'-dipyridyl. [e] Isolated yield. [f] Reaction was performed on a 5 mmol scale. [g] $CoCl_2$ (99.99% purity) was used.

At this point, it was verified that no other metal contaminations are responsible for this catalysis. Thus, using $CoCl_2$ (99.99% purity) together with a new stirring bar and reaction vessel led to **110a** in 86% yield (entry 12).[67] Furthermore, a screening showed that RC(O)SPy thioesters are superior to thioesters of type RC(O)SEt or RC(O)SPh.[94]

3.3 Cobalt-Catalyzed Acylation of Alkylthiopyridyl Esters with (Hetero)Arylzinc Pivalates

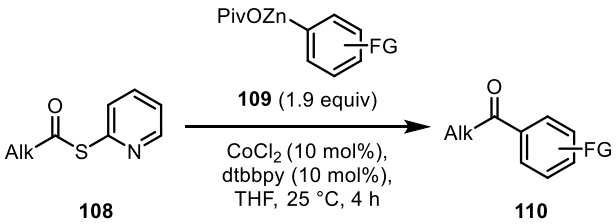
With the optimized conditions in hand, the scope of the acylation reaction was examined. In a typical experiment palmitic acid was treated with 2,2'-dipyridyl disulfide (1.1 equiv) and PPh_3 (1.5 equiv) in

[94] For further details, see: V. Experimental Part, Tables 13 and 14.

acetonitrile (0.3 M) under reflux for 3 h. Short purification using flash column chromatography afforded **108b** in 98% yield. Zinc pivalate **109a** was prepared by treating 1-bromo-3,4-(methylene-dioxy)benzene with Mg (1.2 equiv) and anhydrous LiCl (1.2 equiv) for 2 h at 0 °C leading to the corresponding arylmagnesium derivative (91% yield).[95] Transmetalation with $Zn(OPiv)_2$ (1.0 equiv) afforded the zinc organometallic **109a** in 93% yield.[95] The thioester **108b** was treated with 3,4-(methylene-dioxy)-1-phenylzinc pivalate (**109a**) in the presence of 10 % $CoCl_2$ and 10% dtbbpy in THF (25 °C, 4 h) furnishing, after standard workup and chromatographic purification the ketone **110b** in 90% yield (Table 6, entry 1). According to this procedure various ketones of type **110** were prepared. Hence, the heterocyclic indolylzinc pivalate (**109b**) was acylated with palmitic *S*-pyridyl thioate (**108b**) furnishing ketone **110c** in 74% yield (entry 2). Additionally, secondary thioesters derived from cyclobutane- (**108c**) and cyclohexanecarboxylic acid (**108a**) were employed to this acylation procedure leading to the corresponding ketones (**110d**-**g**) in 60-95% yield (entries 3-6). Tertiary *S*-pyridyl esters **108d** and **108e** derived from 1-adamantanecarboxylic acid and the lipid regulating drug gemfibrozil[96] reacted smoothly with various functionalized arylzinc pivalates affording acylation products (**110h**-**k**) in 61-81% yield (entries 7-10).

[95] A. Krasovskiy and P. Knochel, Synthesis, **2006**, 890-891.
[96] P. A. Todd, A. Ward, *Drugs* **1988**, *36*, 314-339.

Table 6: Ketones **110** obtained by the acylation of various alkylthiopyridyl esters **108** with (hetero)arylzinc pivalates **109**.[a]



108 **110**

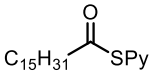
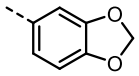
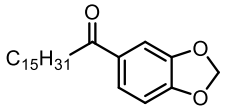
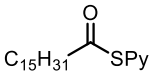
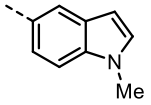
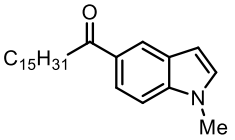
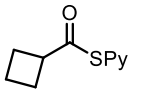
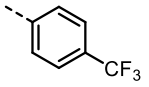
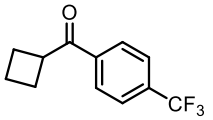
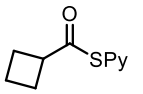
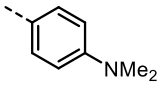
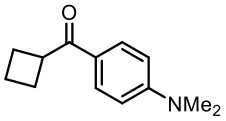
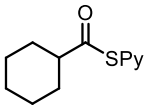
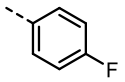
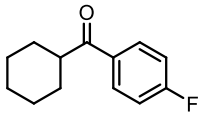
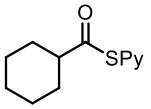
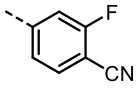
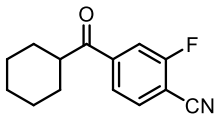
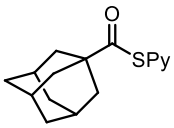
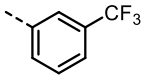
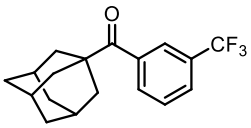
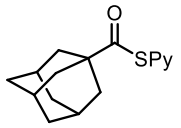
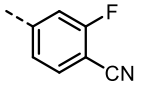
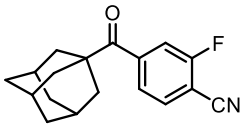
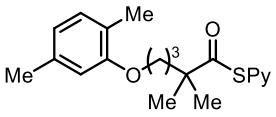
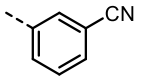
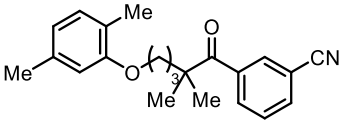
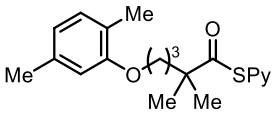
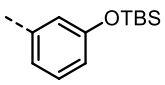
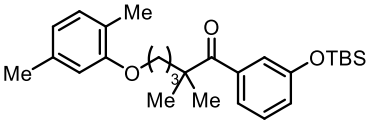
Entry	Thiopyridyl ester **108** (yield)[b]	Zinc reagent PivOZn-R **109**	Product **110**: yield[c]
1	 **108b** (98%)	 **109a**	 **110b**: 90%
2	 **108b** (98%)	 **109b**	 **110c**: 74%
3	 **108c** (79%)	 **109c**	 **110d**: 84%
4	 **108c** (79%)	 **109d**	 **110e**: 95%
5	 **108a** (76%)	 **109e**	 **110f**: 60%
6	 **108a** (76%)	 **109f**[d]	 **110g**: 79%
7	 **108d** (85%)	 **109g**	 **110h**: 61%

Table 6: continued

Entry	Thiopyridyl ester **108** (yield)[b]	Zinc reagent PivOZn-R **109**	Product **110**: yield[c]
8	 **108d** (85%)	 **109f**	 **110i**: 81%
9	 **108e** (98%)	 **109h**	 **110j**: 72%
10	 **108e** (98%)	 **109i**	 **110k**: 78%

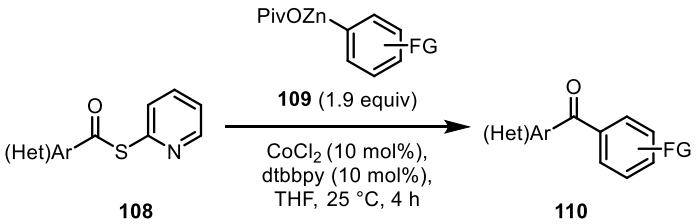
[a] The reactions were performed on a 0.5 mmol scale [b] Isolated yield of the *S*-pyridyl ester prepared from the corresponding carboxylic acid, PySSPy (1.1 equiv), PPh_3 (1.5 equiv), MeCN, reflux, 3 h. [c] Isolated yield. [d] Prepared using *i*PrMgCl·LiCl (1.1 equiv), THF, -20 °C, 2 h.

3.4 Cobalt-Catalyzed Acylation of (Hetero)Arylthiopyridyl Esters with (Hetero)Arylzinc Pivalates

Furthermore, the acylation reaction was extended to aryl- and heteroaryl-*S*-pyridyl esters (Table 7). Thus, (4-(ethoxycarbonyl)-phenyl)zinc pivalate (**109j**) prepared *via* I/Mg-exchange using *i*PrMgCl·LiCl followed by transmetalation with $Zn(OPiv)_2$[38f] was readily acylated with *S*-pyridyl ester **108f** affording the benzophenone **110l** in 71% yield (entry 1). Also, 2-benzothiophenylzinc pivalate **109k** generated *via* directed metalation of benzothiophene using TMPMgCl·LiCl and subsequent transmetalation with $Zn(OPiv)_2$[38f] underwent a cobalt catalyzed acylation reaction with **108f** leading to the ketone **110m** in 68% yield (entry 2). Various substituted aryl thioesters and ferrocenyl derivatives reacted successfully with functionalized (hetero)arylzinc pivalates affording the diaryl ketones **110n**-**r** in 81-96% yield (entries 3-7). Additionally, 4-trifluoromethoxyphenylzinc pivalate (**109n**) was acylated using quinoline thioester **108j** furnishing ketone **110s** in 68% yield (entry 8).[97]

[97] For unsuccessful acylation reactions with (hetero)arylzinc pivalates including several electron poor *N*-heterocyclic and sterically hindered organozinc reagents, see: V. Experimental Part, Scheme 58.

Table 7: Ketones **110** obtained by the acylation of (hetero)aryl-S-pyridyl thioesters **108** with (hetero)arylzinc pivalates **109**[a]



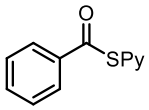
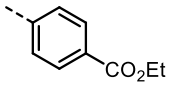
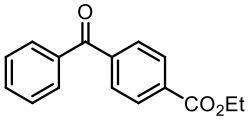
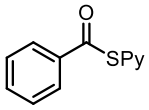
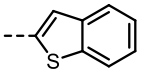
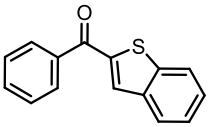
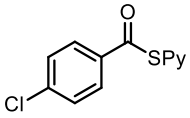
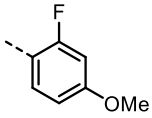
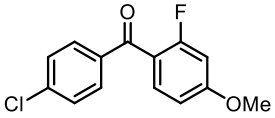
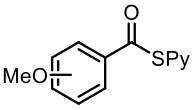
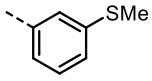
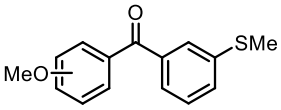
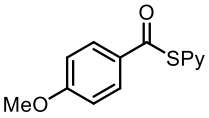
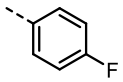
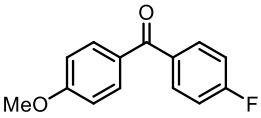
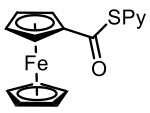
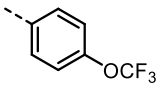
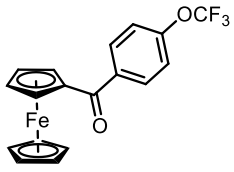
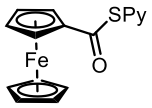
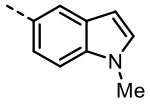
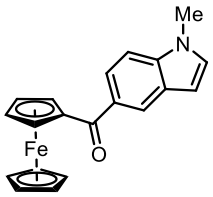
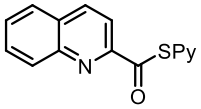
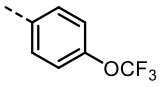
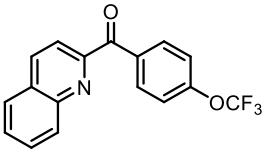
Entry	Thiopyridyl ester **108** (yield)[b]	Zinc reagent PivOZn-R **109**	Product **110**: yield[c]
1	 **108f** (84%)	 **109j**[d]	 **110l**: 71%
2	 **108f** (84%)	 **109k**[e]	 **110m**: 68%[f]
3	 **108g** (66%)	 **109l**	 **110n**: 92%
4	 *para:* **108h** (69%) *ortho:* **108h'** (96%)	 **109m**	 *para:* **110o**: 96% *ortho:* **110o'**: 71%
5	 **108h** (69%)	 **109e**	 **110p**: 86%
6	 **108i** (91%)	 **109n**	 **110q**: 81%

Table 7: continued

Entry	Thiopyridyl ester **108** (yield)[b]	Zinc reagent PivOZn-R **109**	Product **110**: yield[c]
7	 **108i** (91%)	 **109b**	 **110r**: 84%
8	 **108j** (75%)	 **109n**	 **110s**: 68%

[a] The reactions were performed on a 0.5 mmol scale [b] Isolated yield of the *S*-pyridyl ester prepared from the corresponding carboxylic acid, PySSPy (1.1 equiv), PPh_3 (1.5 equiv), MeCN, reflux, 3 h [c] Isolated yield [d] Prepared using *i*PrMgCl·LiCl (1.1 equiv), THF, -40 °C, 2 h. [e] Prepared using TMPMgCl·LiCl (1.0 equiv), THF, 0 °C, 3 h. [f] TMEDA was used instead of dtbbpy.

3.5 Cobalt-Catalyzed Acylation of α-Chiral *S*-Pyridyl Esters s with Arylzinc Pivalates

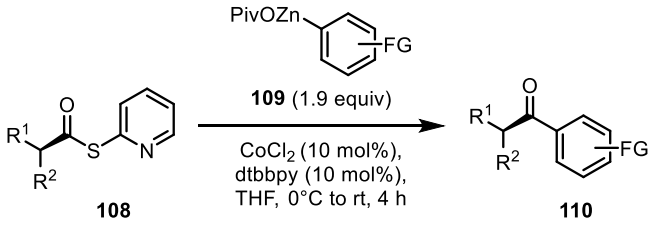
The synthesis of *α*-chiral ketones is of great interest[49e,49g,50e,90a.98] but often challenging under basic conditions due to epimerization. Also, reactions under pH-neutral conditions have been reported by Liebeskind *et al.* for the synthesis of highly enantiopure peptidyl ketones.[99] We also tested the applicability of this cobalt-catalyzed acylation to the synthesis of optically enriched α-chiral ketones. Using α-chiral *S*-pyridyl esters at 0 °C afforded several α-chiral ketones with high stereoretention (Table 8). Thus, *S*-pyridyl ester **108k** prepared from *N*-Boc protected (*S*)-proline was treated with arylzinc reagents **72** and **109a** leading to the corresponding α-chiral ketones **110t-u** in 72-82% yield and >99% *ee* (entries 1-2). Furthermore, thioester **108l** derived from enantiopure (*S*)-ibuprofen reacted smoothly with the functionalized arylzinc pivalates **109o** and **109m** leading to the products **110v-w** in 71-89% yield and 94-97% *ee* (entries 3-4). Also, arylzinc pivlalates **109p** and **109q** bearing an amide or dimethylamino

[98] a) G. T. Crisp, T. P. Bubner, *Synth. Commun.* **1990**, *20*, 1665-1670; b) G. Cahiez, E. Metais, *Tetrahedron Lett.* **1995**, *36*, 6449-6452; c) T. Fukuyama, H. Tokuyama, *Aldrichimica Acta* **2004**, *37*, 100-101; d) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc.* **2013**, *135*, 7442-7445; e) R. Oost, A. Misale, N. Maulide, *Angew. Chem. Int. Ed.* **2016**, *55*, 4587-4590.

[99] a) H. Li, H. Yang, L. S. Liebeskind, *Org. Lett.* **2008**, *10*, 4375-4378; b) L. S. Liebeskind, H. Yang, H. Li, *Angew. Chem. Int. Ed.* **2009**, *48*, 1417-1421.

functionality were acylated using optically pure *S*-(pyridin-2-yl)-(*S*)-2-methylbutanethioate furnishing the α-chiral ketones **110x-y** in 69-84% yield and 95-98% *ee* (entries 5-6).

Table 8: Preparation of *α*-chiral ketones **110** by acylation of thiopyridyl esters **108** with (hetero)arylzinc pivalates **109**.[a]



108 **110**

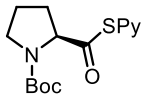
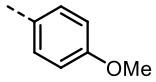
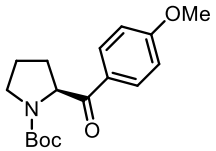
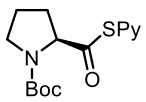
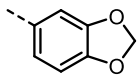
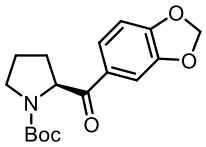
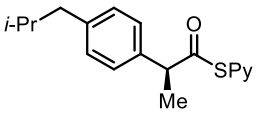
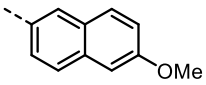
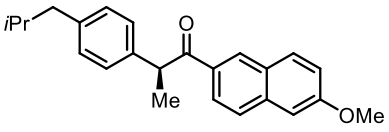
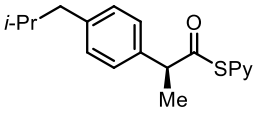
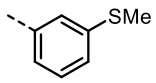
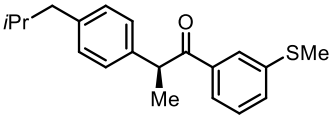
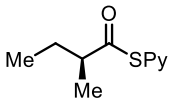
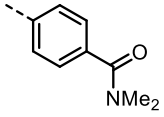
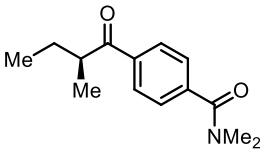
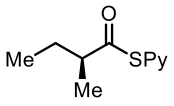
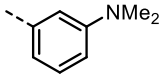
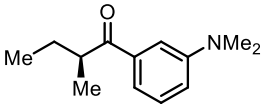
Entry	Thiopyridyl ester **108** (yield)[b]	Zinc reagent PivOZn-R **109**	Product **110**: yield[c]
			
1	**108k**, (73%; >99% *ee*)	**72**	**110t**, 72%, >99% *ee*
			
2	**108k**, (73%; >99% *ee*)	**109a**	**110u**, 82%, >99% *ee*
			
3	**108l**, (96%; 98% *ee*)	**109o**	**110v**, 89%, 97% *ee*
			
4	**108l**, (96%; 98% *ee*)	**109m**	**110w**, 71%, 94% *ee*
			
5	**108m**, (97%; 98% *ee*)	**109p**[d]	**110x**, 69%, >95% *ee*

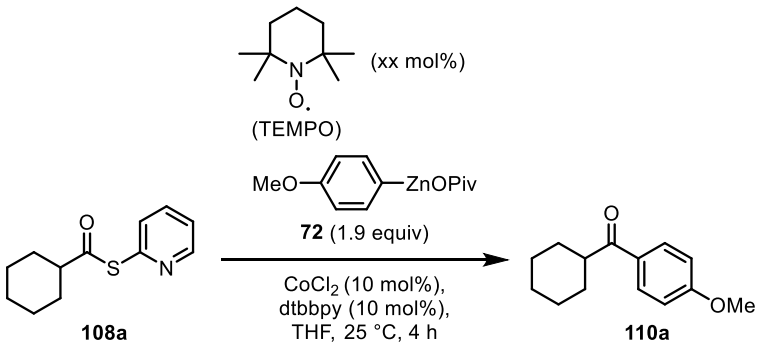
Table 8: continued

Entry	Thiopyridyl ester **108** (yield)[b]	Zinc reagent PivOZn-R **109**	Product **110**: yield[c]
6	 **108m**, (97%; 98% *ee*)	 **109q**	 **110y**, 84%, 98% *ee*

[a] The reactions were performed on a 0.5 mmol scale and at 0 °C instead of 25 °C. [b] Isolated yield of the S-pyridyl ester prepared from the corresponding carboxylic acid, PySSPy (1.0 equiv), PPh_3 (1.0 equiv), MeCN, 0 °C to 25 °C, 16 h. [c] Isolated yield. [d] Prepared using *i*PrMgCl·LiCl (1.1 equiv), THF, 0 °C, 2 h.

3.6 Mechanistic Considerations

To gain insights into the reaction mechanism, radical trapping experiments were carried out. Thus, to a standard acylation setup of the developed protocol using *S*-pyridyl ester **108a** and organozinc pivalate **72** various amounts of the radical trapping agent 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) were added (Scheme 42). With 10% of the trapping reagent a decrease of the yield by 19% was observed for the acylation product **110a**. However, using 1.5 equiv of TEMPO the product formation is almost completely suppressed. This may indicate the involvement of radical intermediates within this acylation reaction.[100]



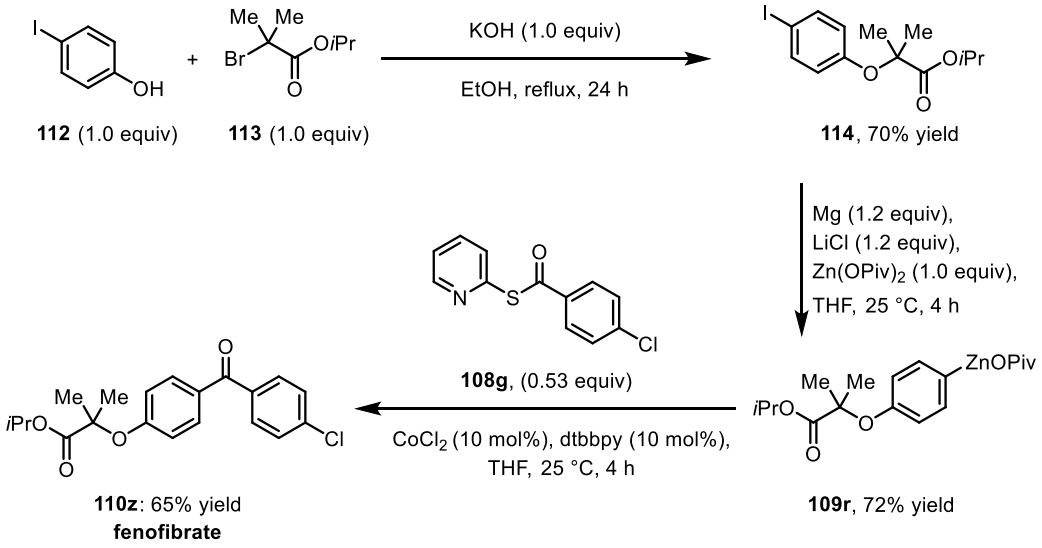
entry	TEMPO	GC-yield of **110a**[a]
1	-	90
2	10%	71
3	150%	6

Scheme 42: Cobalt-catalyzed acylation reaction in the presence of various amounts of TEMPO. [a] Tetradecane ($C_{14}H_{30}$) was used as internal standard.

[100] For further details, see: V. Experimental Part, Table 15.

3.7 Application of the Cobalt-Catalyzed Acylation Reaction to Synthesis of Fenofibrate

The utility of this acylation was demonstrated in the synthesis of the anitlipedemic drug fenofibrate[101] (**110z**, Scheme 43). Alkylation of 4-iodophenol (**112**) with isopropyl 2-bromo-2-methyl-propanoate (**113**) affords the corresponding iodo-aryl ether **114** in 70% yield. **114** was treated with Mg, LiCl and $Zn(OPiv)_2$ generating the arylzinc pivalate **109r** in 72% yield.[38a] Using the new cobalt-catalyzed acylation procedure, fenofibrate (**110z**) was obtained in 65% yield.



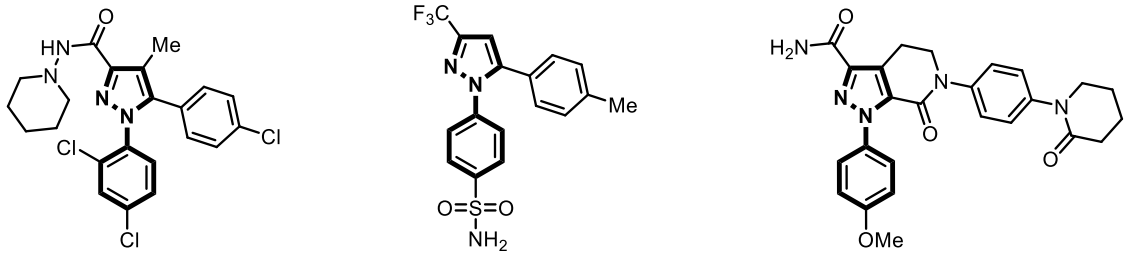
Scheme 43: Synthesis of fenofibrate (**110z**) using the Co-catalyzed acylation.

[101] G. M. Keating, K. F. Croom, *Drugs* **2007**, *67*, 121-153.

4. Mild and Regioselective Magnesiation and Functionalization of Aryl Azoles as a Powerful Tool for the Synthesis of Pharmaceutically Relevant Targets

4.1 Introduction

Aryl azoles are widely spread scaffolds in biologically active compounds. *N*-aryl azoles are present in various blockbuster drugs, such as rimonabant,[102] celecoxib[103] and apixaban[104] (Figure 1). The synthesis and future derivatization of such compounds is therefore of high importance.



Rimonabant *(antiobesity)* | Celecoxib *(anti-inflammatory)* | Apixaban *(anti-coagulant)*

Figure 1: Biologically active compounds containing an aryl azole motif.

A commonly used *ortho*-functionalization of the aryl ring in these scaffolds involves transition metal catalyzed C-H arylations.[105,106] However, these reactions usually require harsh conditions and often

[102] S. Henness, D. M. Robinson, K. A. Lyseng-Williamson, *Drugs* **2006**, *66*, 2109-2119.

[103] T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.* **1997**, *40*, 1347-1365.

[104] D. J. P. Pinto, M. J. Orwat, S. Koch, K. A. Rossi, R. S. Alexander, A. Smallwood, P. C. Wong, A. R. Rendina, J. M. Luettgen, R. M. Knabb, K. He, B. Xin, R. R. Wexler, P. Y. S. Lam, *J. Med. Chem.* **2007**, *50*, 5339-5356.

[105] For selected reviews on C-H activation: a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174-238; b) L. Ackermann, *Synlett* **2007**, *2007*, 507-526; c) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879-5918; d) N. Kuhl, N. Schröder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443-1460; e) Y. Yang, J. Lan, J. You, *Chem. Rev.* **2017**, *117*, 8787-8863; f) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192-2452.

[106] a) F. Kakiuchi, M. Matsumoto, K. Tsuchiya, K. Igi, T. Hayamizu, N. Chatani, S. Murai, *J. Organomet. Chem.* **2003**, *686*, 134-144; b) S. Oi, E. Aizawa, Y. Ogino, Y. Inoue, *J. Org. Chem.* **2005**, *70*, 3113-3119; c) L. Ackermann, A. Althammer, R. Born, *Synlett* **2007**, *2007*, 2833-2836; d) S. Oi, H. Sasamoto, R. Funayama, Y. Inoue, *Chem. Lett.* **2008**, *37*, 994-995; e) M. Simonetti, D. M. Cannas, X. Just-Baringo, I. J. Vitorica-Yrezabal, I. Larrosa, *Nat. Chem.* **2018**, *10*, 724-731; f) L. Ackermann, A. Althammer, R. Born, *Tetrahedron* **2008**, *64*, 6115-6124; g) S. H. Kwak, N. Gulia, O. Daugulis, *J. Org. Chem.* **2018**, *83*, 5844-5850; h) S. Oi, H. Sato, S. Sugawara, Y. Inoue, *Org. Lett.* **2008**, *10*, 1823-1826; i) L. Ackermann, R. Born, R. Vicente, *ChemSusChem* **2009**, *2*, 546-549; j) C. J. Teskey, S. M. A. Sohel, D. L. Bunting, S. G. Modha, M. F. Greaney, *Angew. Chem. Int. Ed.* **2017**, *56*, 5263-5266.

predominantly lead to a double arylated product, which severely limits this methodology.[105a,105c,106a-g,107] An alternative for the selective functionalization of aryl azoles may be the directed deprotonation with a sterically hindered metal amide base. Especially, magnesium- and zinc-derived TMP-bases have proved to be powerful and selective reagents for the functionalization of various (hetero)arenes.[7i,23b-c,108] However, a regioselective metalation of aryl rings linked to azole-heterocycles is especially challenging, due to the competitive metalation of the *N*-heterocycle itself. A potential approach to achieve a highly regioselective metalation at the aryl ring is the avoidance of coordinating solvents such as THF, which competes in a selective complexation of the base with the nitrogen atom of the azole ring.[109] Thus, the use of hindered magnesium amides in hydrocarbons or related solvents should be beneficial. In the past, Hagadorn showed, that TMP_2Zn is an excellent base for the α-zincation of various carbonyl compounds and the metalation of pyridine-*N*-oxide in toluene.[110] Furthermore, Mulvey and co-workers reported several mixed bimetallic amide bases, which were used for metalation reactions in non-coordinating hydrocarbon solvents.[111]

In the following a highly selective and broadly applicable magnesiation of various aryl azoles in toluene and subsequent cross-couplings and electrophilic quench reactions is reported.

4.2 Optimization of the Metalation Conditions

In preliminary experiments, the selective magnesiation of *N*-aryl-1,2,3-triazole **115a** using various metal amide bases was investigated (Table 9). As expected, the use of strong bases like TMPLi did not lead to the

[107] a) O. Daugulis, V. G. Zaitsev, *Angew. Chem. Int. Ed.* **2005**, *44*, 4046-4048; b) S. Oi, R. Funayama, T. Hattori, Y. Inoue, *Tetrahedron* **2008**, *64*, 6051-6059.

[108] For recent publications on directed metalation using TMP-metal bases, see a) D. S. Ziegler, R. Greiner, H. Lumpe, L. Kqiku, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2017**, *19*, 5760-5763; b) M. Balkenhohl, R. Greiner, I. S. Makarov, B. Heinz, K. Karaghiosoff, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 13046-13050; c) S. B. Boga, M. Christensen, N. Perrotto, S. W. Krska, S. Dreher, M. T. Tudge, E. R. Ashley, M. Poirier, M. Reibarkh, Y. Liu, E. Streckfuss, L.-C. Campeau, R. T. Ruck, I. W. Davies, P. Vachal, *React. Chem. Eng.* **2017**, *2*, 446-450; d) M. Balkenhohl, B. Salgues, T. Hirai, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2018**, *20*, 3114-3118; e) M. Balkenhohl, H. Jangra, T. Lenz, M. Ebeling, H. Zipse, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 9244-9247.

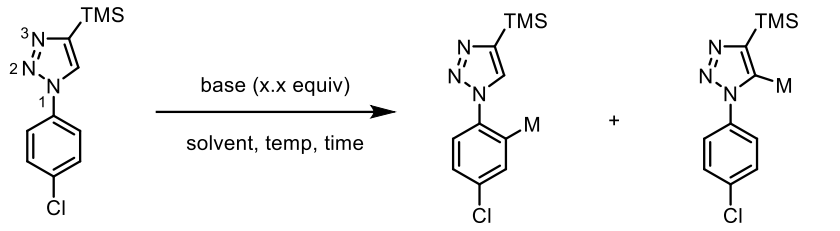
[109] M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206-2225.

[110] a) M. L. Hlavinka, J. R. Hagadorn, *Organometallics* **2007**, *26*, 4105-4108; b) M. L. Hlavinka, J. R. Hagadorn, *Tetrahedron Lett.* **2006**, *47*, 5049-5053.

[111] a) V. L. Blair, L. M. Carrella, W. Clegg, B. Conway, R. W. Harrington, L. M. Hogg, J. Klett, R. E. Mulvey, E. Rentschler, L. Russo, *Angew. Chem. Int. Ed.* **2008**, *47*, 6208-6211; b) A. J. Martínez-Martínez, S. Justice, B. J. Fleming, A. R. Kennedy, I. D. H. Oswald, C. T. O'Hara, *Science Advances* **2017**, *3*, e1700832; c) A. J. Martínez-Martínez, D. R. Armstrong, B. Conway, B. J. Fleming, J. Klett, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, C. T. O'Hara, *Chemical Science* **2014**, *5*, 771-781; d) R. E. Mulvey, *Organometallics* **2006**, *25*, 1060-1075; e) A. J. Martínez-Martínez, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, *Science* **2014**, *346*, 834; f) S. D. Robertson, M. Uzelac, R. E. Mulvey, *Chem. Rev.* **2019**, *119*, 8332-8405; g) M. A. Stevens, F. H. Hashim, E. S. H. Gwee, E. I. Izgorodina, R. E. Mulvey, V. L. Blair, *Chemistry-A European Journal* **2018**, *24*, 15669-15677; h) M. Á. Fuentes, A. Zabala, A. R. Kennedy, R. E. Mulvey, *Chemistry-A European Journal* **2016**, *22*, 14968-14978.

desired aryllithium reagent **A**, but exclusively afforded the unwanted metalation at the 1,2,3-triazole ring (**B**, entry 1). Similarly, mixtures of **A** and **B** were obtained with TMPMgCl·LiCl or TMP_2Mg in THF[112] (entries 2-3). As mentioned above, it was anticipated that the use of the highly coordinating solvent THF hampers a selective coordination at the N(2)-atom. However, TMP_2Mg in toluene proved to be too reactive, leading to extensive decomposition of the staring material **115a** (entry 4).

Table 9: Screening of the metalation of **115a**



115a **A:** M = Li or MgX **B:** M = Li or MgX

Entry	Base	Equiv	Solvent	Time	Temp	**A**[a]	**B**[a]
1	TMPLi	1.2	THF	0.5	-78 °C	0%	99%
2	TMPMgCl·LiCl	1.2	THF	1	rt	39%	19%
3	TMP_2Mg	1.2	THF	1	rt	67%	23%
4	TMP_2Mg	1.2	toluene	1	rt	decomposition	
5	**TMPMgBu**	**1.0**	**toluene**	**1**	**rt**	**81%**	**3%**
6	TMPMgBu	1.0	THF	1	rt	78%	32%[b]
7	*i*Pr_2NMgBu	1.0	toluene	1	rt	67%	3%
8	Cy_2NMgBu	1.0	toluene	1	rt	65%	2%

[a] Metalation yields were determined from D_2O quenched reaction aliquots and subsequent ^{1}H-NMR analysis.[113] [b] including bis-metalated species.

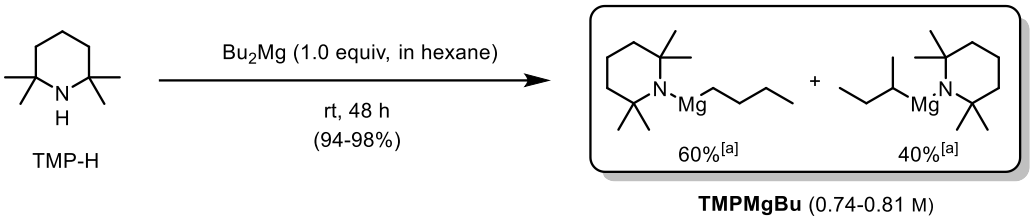
Therefore, the attention was turned to TMPMgBu[114], which was conveniently prepared by treating TMP-H with commercially available Bu_2Mg in hexane (25 °C, 48 h) affording a clear 0.74-0.81 M solution (94-98% yield, Scheme 44). An analysis of iodolyzed samples of the reagent revealed, that the reagent contains 60%

[112] a) P. E. Eaton, C. H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016-8018; b) P. E. Eaton, Y. Xiong, R. Gilardi, *J. Am. Chem. Soc.* **1993**, *115*, 10195-10202; c) T. Ooi, Y. Uematsu, K. Maruoka, *J. Org. Chem.* **2003**, *68*, 4576-4578.

[113] For further details, see: V. Experimental Part, 5.2 Preparation of Organometallic Reagents and Metalation Optimization.

[114] a) E. Hevia, A. R. Kennedy, R. E. Mulvey, S. Weatherstone, *Angew. Chem. Int. Ed.* **2004**, *43*, 1709-1712; b) B. Conway, E. Hevia, A. R. Kennedy, R. E. Mulvey, S. Weatherstone, *Dalton Trans.* **2005**, 1532-1544.

n-butylmagnesium and 40% *sec*-butylmagnesium species. This metal amide proved to be highly selective affording the desired metalated 1,2,3-triazole **A** within 1 h (**A**:**B** = 81%:3%, entry 5). The choice of the solvent was crucial in this experiment, since performing the metalation with TMPMgBu in THF provides a mixture of **A**:**B** including double metalated product (entry 6). Other alkyl magnesium amides, such as *i*Pr_2NMgBu or Cy_2NMgBu did not improve the reaction outcome (entries 7-8).[115]



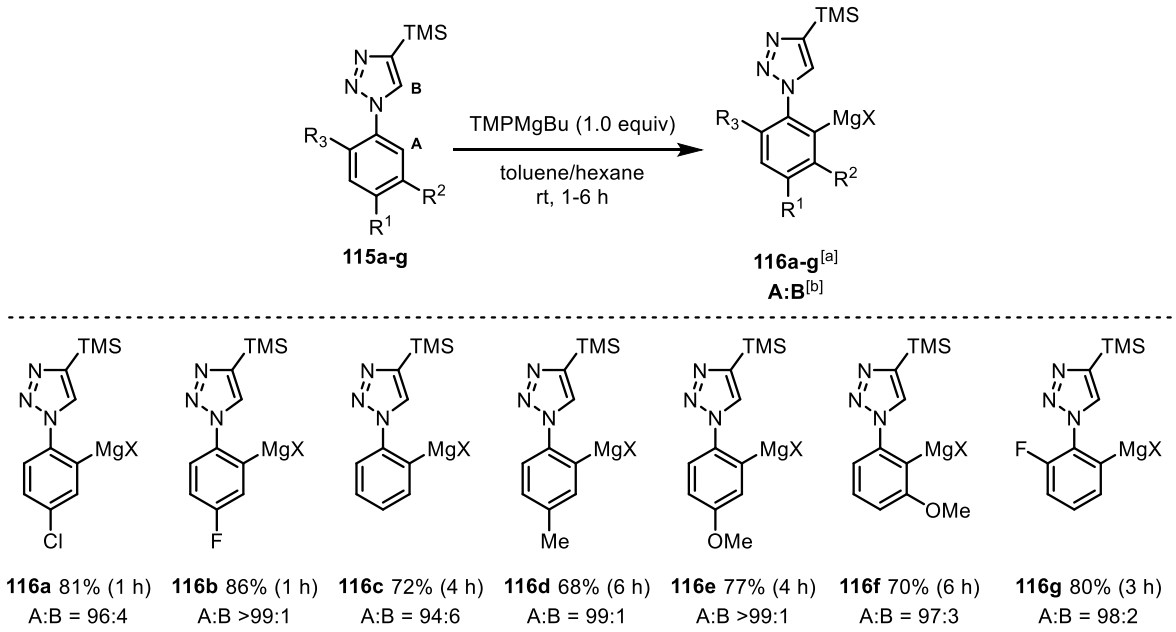
Scheme 44: Preparation and composition of TMPMgBu. [a] Yields and composition was determined by GC-analysis of iodolyzed aliquots using undecane ($C_{11}H_{24}$) as internal standard by comparison with a calibration curve of various amounts of the respective molecule and undecane.

4.3 Metalation of Functionalized Aryl Triazoles

With these results in hand, the scope of the metalation reaction was examined. Thus, various substituted aryl triazoles were successfully deprotonated using TMPMgBu (Scheme 45). The metalation of the electron-deficient 1-(4-fluorophenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**115b**) proceeded within 1 h leading to 86% of the organomagnesium reagent **116b**. The unsubstituted phenyl derivative **115c** was metalated in 4 h affording 72% of the desired metal reagent **116c**. The electron-rich 1-(*p*-tolyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**115d**) required a prolonged metalation time of 6 h furnishing **116d** in 68% yield. Interestingly, the metalation of a 4-methoxy aryl triazole **115e** proceeded significantly faster (4 h) leading to **116e** in 77% yield. This might be explained by the electron-pushing property of the methoxy group, which leads to an increased electron density in the triazole moiety, thus facilitating a coordination of the TMPMgBu base.[116] The metalation of the corresponding *meta*-methoxy derivative **115f** and the *ortho*-fluoro triazole **115g** afforded **116f** and **116g** in 70% and 80% yield, respectively. However,

[115] For further details, see: V. Experimental Part, Table 16.
[116] D. W. Slocum, E. A. Maulden, P. E. Whitley, T. K. Reinscheld, C. S. Jackson, J. B. Maddox, *Eur. J. Org. Chem.* **2017**, *2017*, 6882-6884.

using 4-butyl-1-(4-fluorophenyl)-1*H*-1,2,3-triazole only afforded mixtures of metalation at the arene and the triazole.[117]



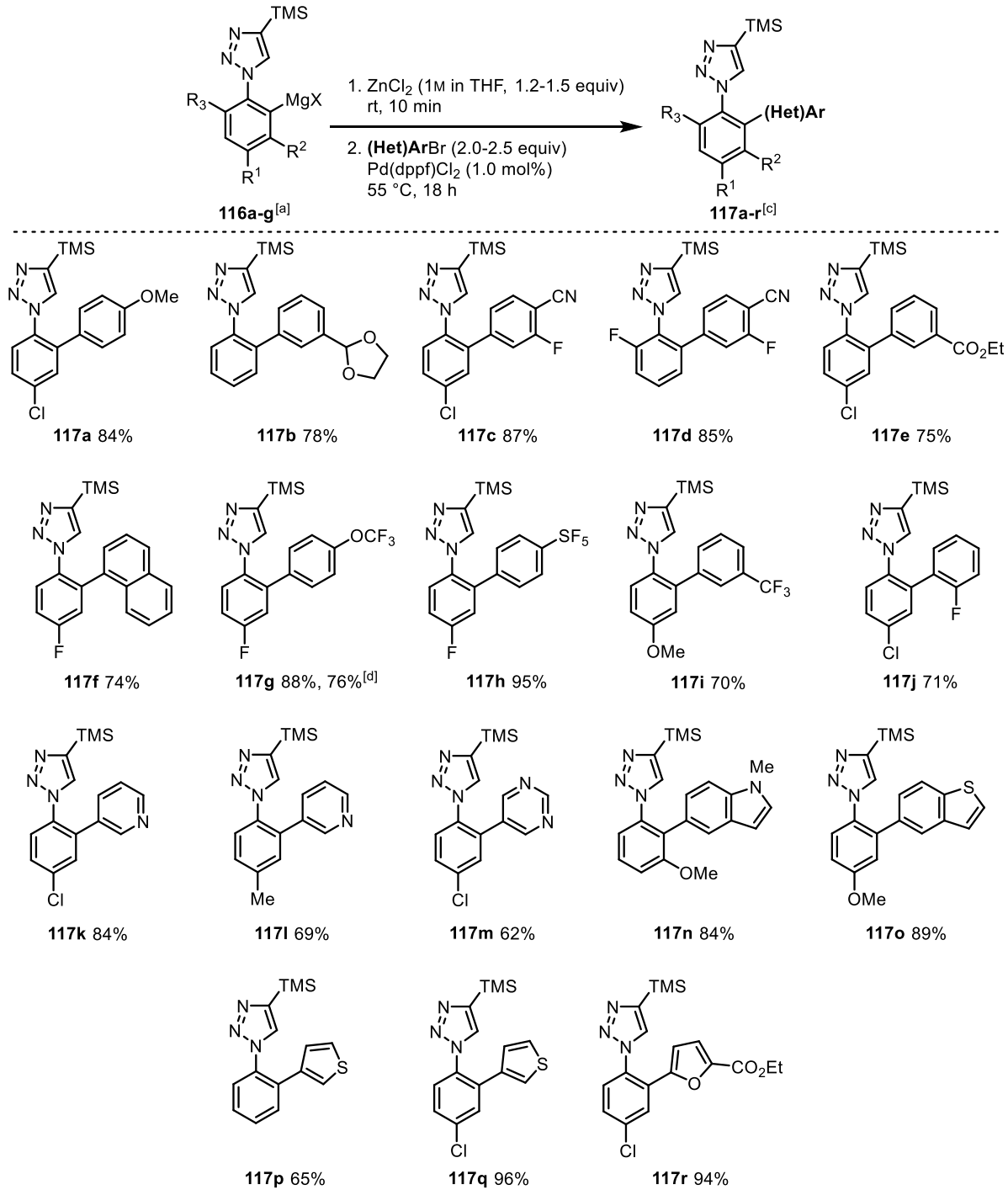
Scheme 45: Metalation of various aryl triazole derivatives of type **115**. [a] Metalation yields were determined by ^{1}H-NMR analysis of D_2O-quenched reaction aliquots. Metalation time in brackets;[113] [b] Metalation ratio in [%] determined by ^{1}H-NMR analysis of D_2O-quenched reaction aliquots.[113]

4.4 Palladium-Catalyzed Cross-Coupling of Arylzinc Reagents derived from Aryl Triazoles

Next, the applicability of the arylmetal species **116a**-**g** in palladium-catalyzed Negishi-cross-couplings was examined (Scheme 46). After transmetalation with $ZnCl_2$, the resulting arylzinc reagent was coupled with a (hetero)aryl bromide using 1% $PdCl_2$(dppf). The coupling reactions proceeded smoothly with several electron-rich and -deficient aryl bromides furnishing the corresponding products **117a**[118]**-e** in 75-87% yield. Remarkably, the reaction with the sterically demanding 2-bromo naphthalene led to **117f** in 74% yield. Also, various fluorinated aryl bromides containing a trifluoromethoxy-, pentafluorosulfinyl-, trifluoromethyl-, or fluoro-substituent were coupled with various arylzinc reagents affording the desired products **117g-j** in 70-95% yield. Furthermore, a range of heteroaryl bromides, such as pyridyl-, pyrimidyl-,

[117] For unsuccessful substrates see: V. Experimental Part, Scheme 59.
[118] The structure of **117a** was confirmed by NOESY-NMR, see, VI. Appendix, 1.2 1-(5-Chloro-4'-methoxy-[1,1'-biphenyl]-2-yl)-4-(trimethylsilyl)-1H-1,2,3-triazole (**117a**).

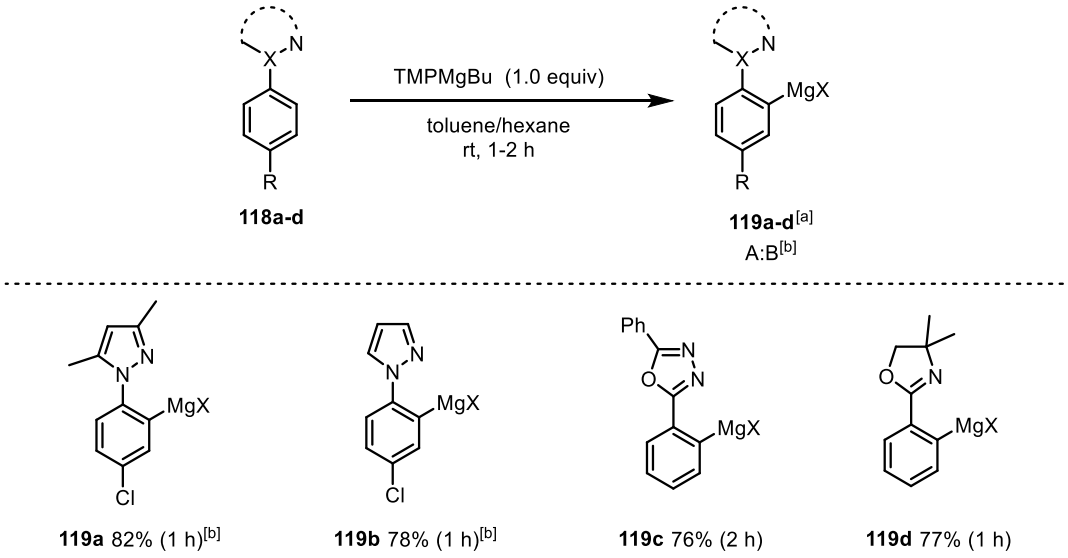
indolyl-, and various thienyl- and furyl bromides could be used as coupling partners leading to the corresponding products **117k-r** in 62-96% yield.



Scheme 46: Palladium-catalyzed cross-coupling of magnesium reagents of type **116**. [c] All yields refer to isolated analytically pure compounds; [d] Reaction performed on 5 mmol scale.

4.5 Metalation of Functionalized Aryl Azoles

The metalation was extended to other aryl azoles (Scheme 47). Treating 1-(4-chlorophenyl)-3,5-dimethyl-1*H*-pyrazole (**118a**) with TMPMgBu (1.0 equiv) for 1 h afforded **119a** in 82% yield. Also, the unsubstituted aryl pyrazole **118b** was selectively metalated at the aryl moiety leading to the magnesium reagent **119b** (78% yield). Remarkably, no competitive metalation of the azole ring was observed in any case. Furthermore, 2,5-diphenyl-1,3,4-oxadiazole (**118c**) underwent a selective mono-magnesiation affording **119c** in 76% yield after 2 h metalation time. The metalation of phenyl oxazoline **118d** proceeded within 1 h leading to the metalated substrate **119d** (77% yield).

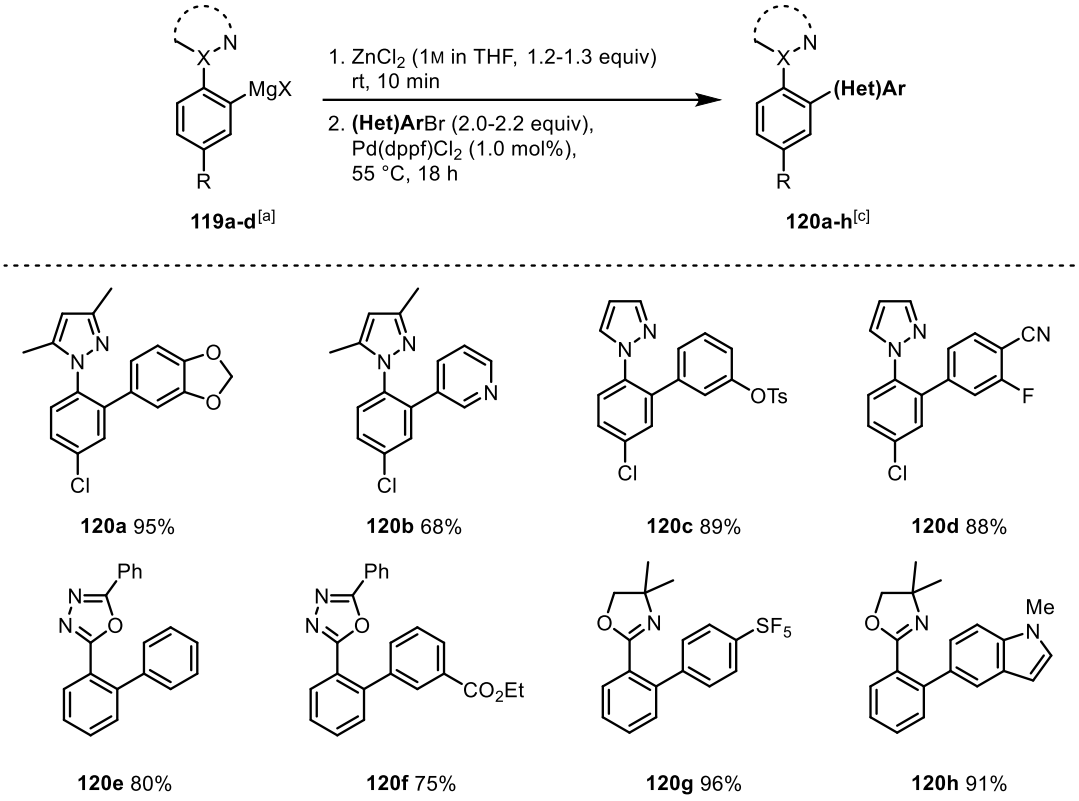


Scheme 47: Metalation of various aryl azole derivatives. [a] Metalation yields were determined by ^{1}H-NMR analysis of D_2O-quenched reaction aliquots. Metalation time in brackets;[113] [b] No metalation at the heterocycle was observed. [113]

4.6 Palladium-Catalyzed Cross-Coupling of Arylzinc reagents derived from Aryl Azoles

Negishi cross-couplings were performed with metal reagents **119a-d** after transmetalation to the corresponding arylzincs (Scheme 48). Negishi-cross-couplings starting from reagent **119a** afforded the compounds **120a-b** in 68-95% yield. Substrates containing a 3,5-dimethyl pyrazole group are of special interest, since an oxidative removal *via* ozonolysis affords the corresponding aniline.[106g] Also, the unsubstituted *N*-aryl pyrazole magnesium reagent **119b** was coupled with functionalized aryl bromides

bearing a tosyl or nitrile group leading to the products **120c** and **120d**[119] in 88-89% yield. The reaction of **119c** with phenyl bromide furnished 2-(1,1'-biphenyl-2-yl)-5-phenyl-1,3,4-oxadiazole (**120e**) in 80% yield, which is a valuable precursor for the synthesis of organic electroluminescent compounds.[120] Furthermore, a more electron-deficient derivative was synthesized following this procedure leading to **120f** in 75% yield. Finally, the cross-coupling of **119d** led to the corresponding products **120g** and **120h**[121] in 91-96% yield.



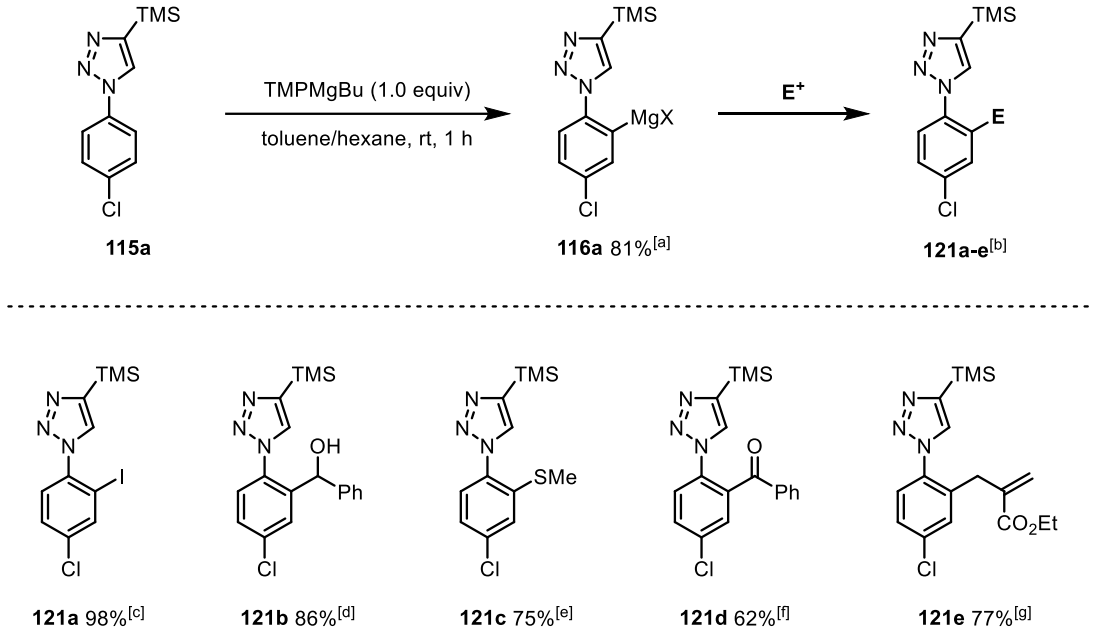
Scheme 48: Palladium-catalyzed cross-coupling of *N*-aryl azoles with (hetero)aryl bromides. [c] All yields refer to isolated yields of analytically pure compounds.

4.7 Electrophilic Trapping Reactions

The versatility of the new method was shown by performing various trapping reactions of arylmagnesium reagent **116a** with several commonly used electrophiles (Scheme 49). Thus, a reaction with I_2 afforded

[119] The structure of **120d** was confirmed by crystal structure analysis, see: VI. Appendix, 3. Single Crystal X-Ray Diffraction Studies.
[120] J. Feldmann, K. D. Dobbs, T. C. Gehret, C. D. McLaren, Y. Wang, US 20150236278 A1, **2015**.
[121] The structure of **120h** was confirmed by crystal structure analysis, see: VI. Appendix, 3. Single Crystal X-Ray Diffraction Studies.

121a in 98% yield. Addition reactions of **116a** to benzaldehyde or $MeSSO_2Me$ led to the corresponding alcohol **121b**[122] or the thioether **121c** in 75-86% yield. Also, a transmetalation with CuCN·2LiCl and subsequent reaction with benzoyl chloride or an allyl bromide derivative proceeded smoothly furnishing the products **121d-e** in 62-77% yield.



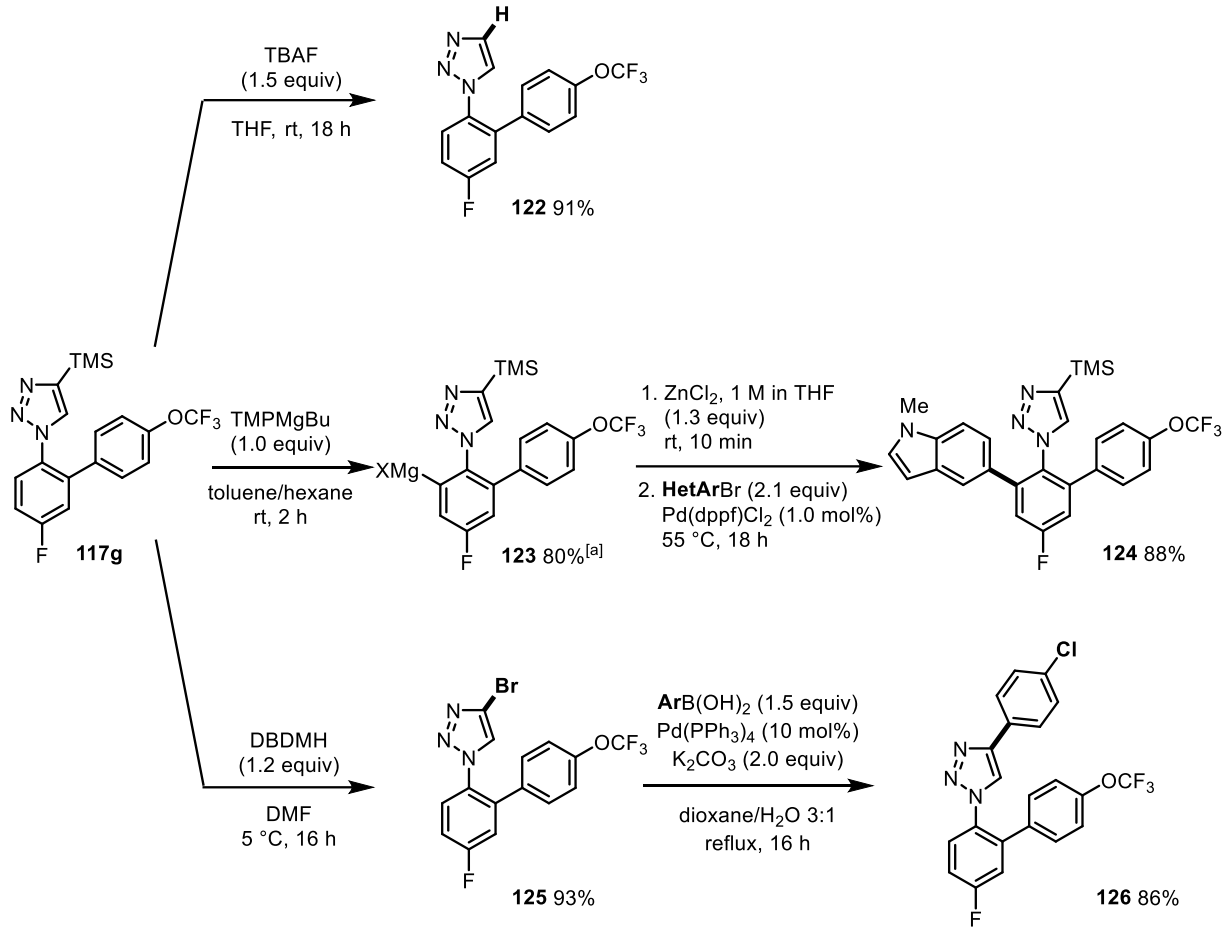
Scheme 49: Trapping of magnesium reagent **116a** with various electrophiles. [a] Metalation yields were determined by ^{1}H-NMR analysis of D_2O-quenched reaction aliquots; [113] [b] All yields refer to isolated yields of analytically pure compounds; [c] I_2 (4.3 equiv); [d] Benzaldehyde (2.5 equiv); [e] $MeSSO_2Me$ (2.5 equiv); [f] Transmetalation with CuCN·2LiCl (3.0 equiv), then benzoyl chloride (2.5 equiv); [g] Transmetalation with CuCN·2LiCl (3.0 equiv), then ethyl 2-(bromomethyl) acrylate (2.5 equiv).

4.8 Late-Stage Modifications

Demonstrating the synthetic utility of the cross-coupling products, various late-stage modifications were performed (Scheme 50). Thus, a fluoride mediated desilylation of **117g** afforded triazole **122** in 91% yield. Treating **117g** with TMPMgBu for 2 h in toluene led to the arylmagnesium reagent **123** in 80% yield. After transmetalation with $ZnCl_2$ a palladium-catalyzed cross-coupling with 5-bromo-*N*-methyl indole furnished the bis-arylated triazole **124** in 88% yield. Furthermore, the reaction of **117g** with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) led to the corresponding bromide **125** in 93% yield. A subsequent palladium-

[122] The structure of **121b** was confirmed by crystal structure analysis, see: VI. Appendix, 3. Single Crystal X-Ray Diffraction Studies.

catalyzed Suzuki-cross-coupling of bromide **125** with an aryl boronic acid allows for the smooth functionalization of the triazole moiety, affording **126**[123] in 86% yield.

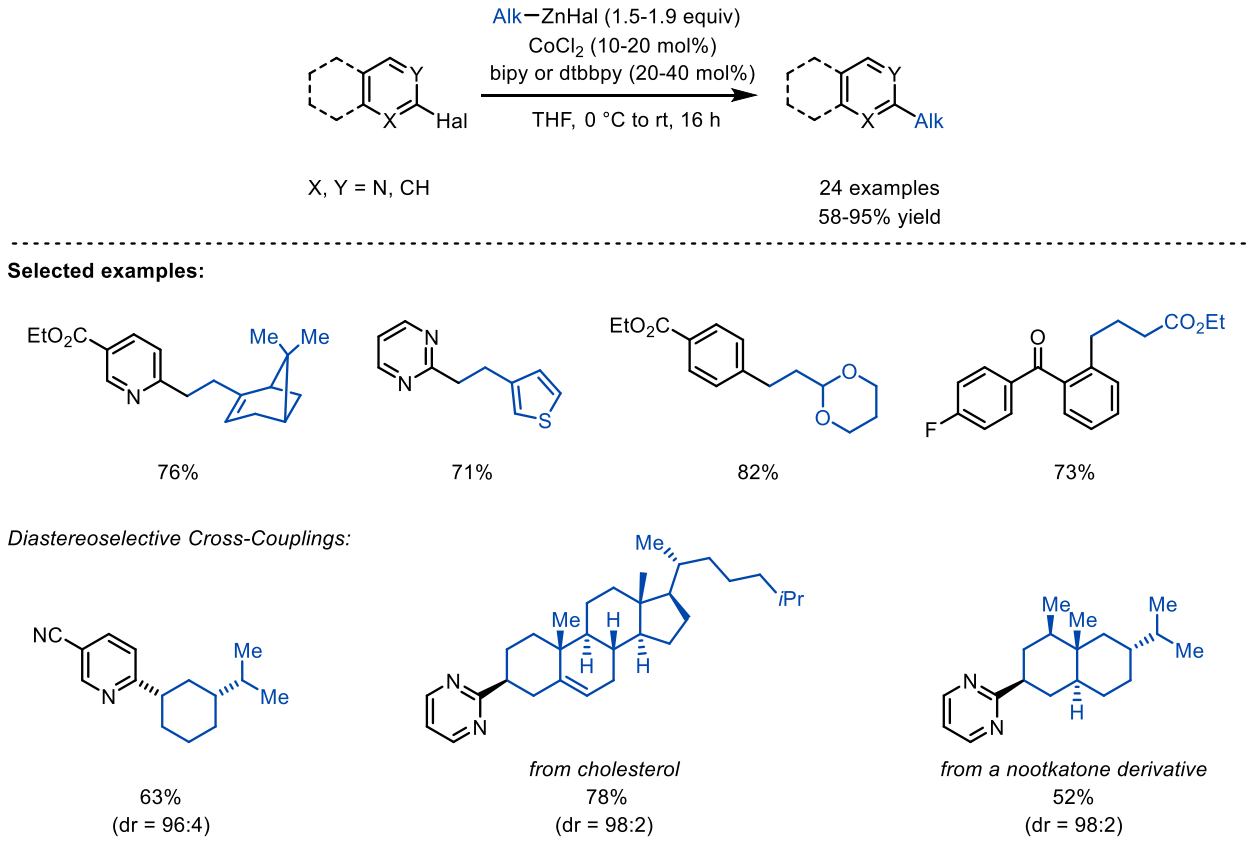


Scheme 50: Late-stage functionalization of **117g**. [a] Metalation yields was determined by ^{1}H-NMR analysis of D_2O-quenched reaction aliquots; [113] All other yields refer to isolated yields of analytically pure compounds.

[123] The structure of **126** was confirmed by crystal structure analysis, see: VI. Appendix, 3. Single Crystal X-Ray Diffraction Studies.

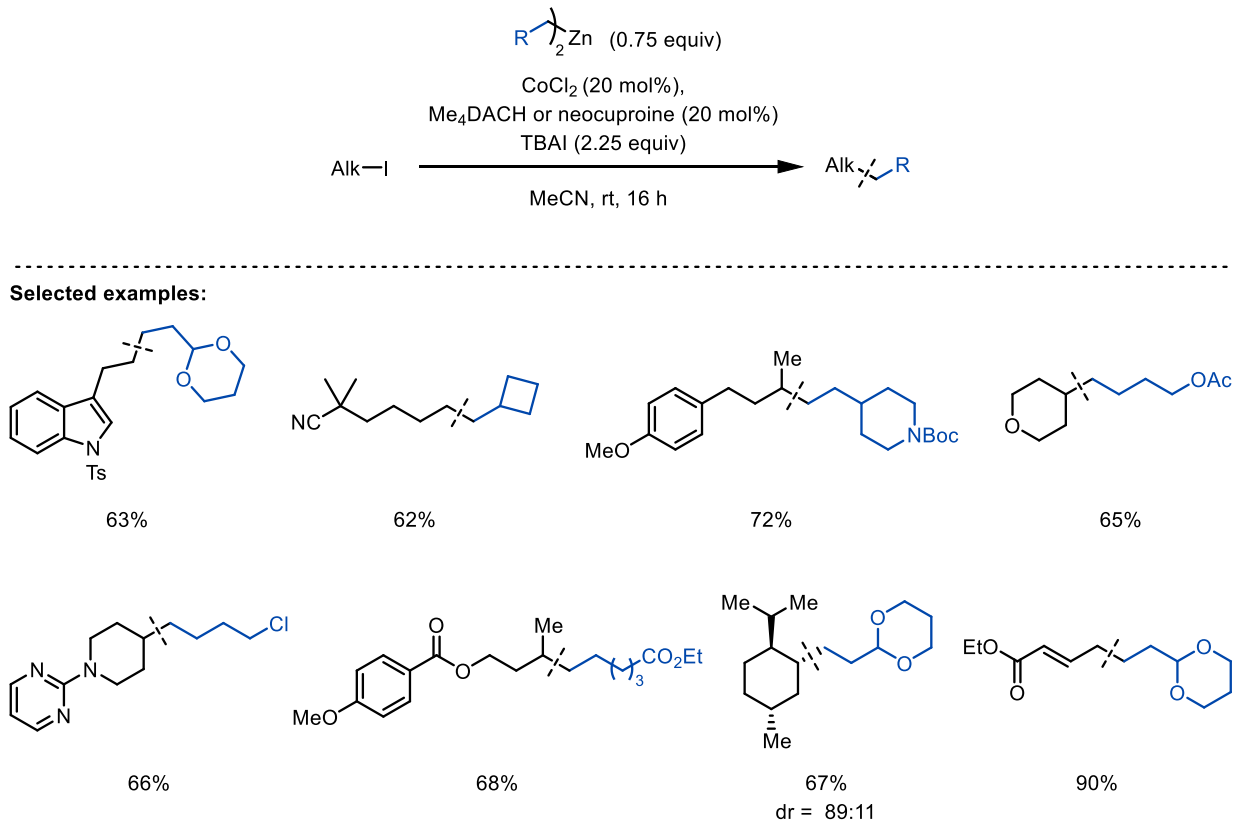
IV. Summary

The first part of this thesis was focused on the development of new cobalt-catalyzed reactions using functionalized zinc organometallics. A cobalt-catalyzed alkylation of various aryl and heteroaryl halides with functionalized primary and secondary alkylzinc reagents was developed. The catalytic system comprising an abundant cobalt catalyst and a bipyridyl ligand allowed the mild alkylation of several *N*-heterocyclic halides, such as pyridines, pyrimidines, (iso)quinolines and quinazolines, but also aryl halides bearing ester, nitrile or ketone moieties. 1,3- and 1,4-disubstituted cyclohexylzinc reagents including complex scaffolds derived from cholesterol or nootkatone were coupled with *N*-heterocyclic halides affording the corresponding products in high diasteroselectivities of up to 98:2 (Scheme 51). Furthermore, primary and secondary alkylzinc reagents were successfully coupled with alkynyl halides.



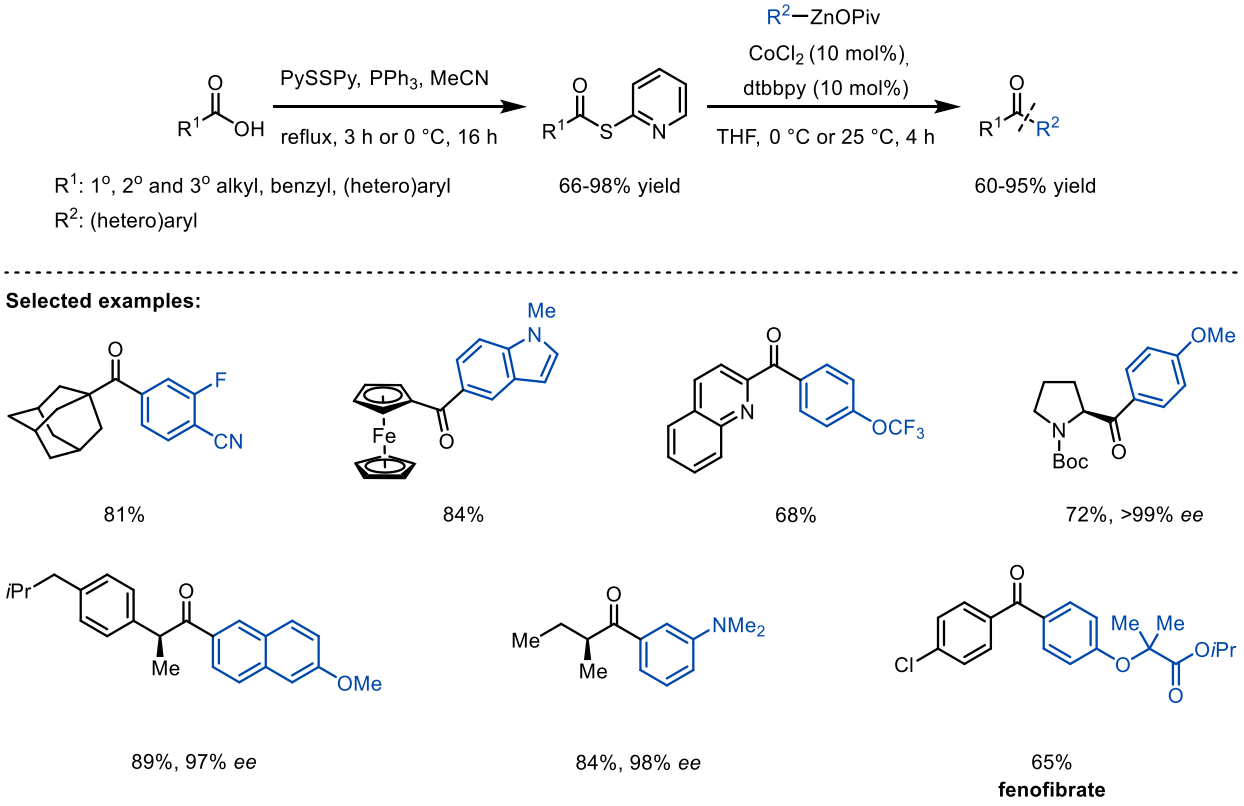
Scheme 51: Cobalt-catalyzed cross-coupling of primary alkylzinc reagents with (hetero)aryl halides.

Moreover, a cobalt-catalyzed Csp^3-Csp^3 cross-coupling of functionalized dialkylzinc reagents with various primary and secondary alkyl iodides was developed. Dialkylzinc reagents bearing sensitive functionalities, were readily prepared *via* magnesium insertion in the presence of 0.5 equiv $ZnCl_2$. With 1,2-disubstituted cyclohexyl iodides the cross-coupling proceeded in a diastereoselective fashion affording the corresponding coupling-products with diastereoselectivities up to 89:11. Furthermore, the catalytic system allowed the smooth coupling of benzylic and allylic halides (Scheme 52). Mechanistic investigations with radical-clock precursors suggest the involvement of radical intermediates within the course of the reaction.



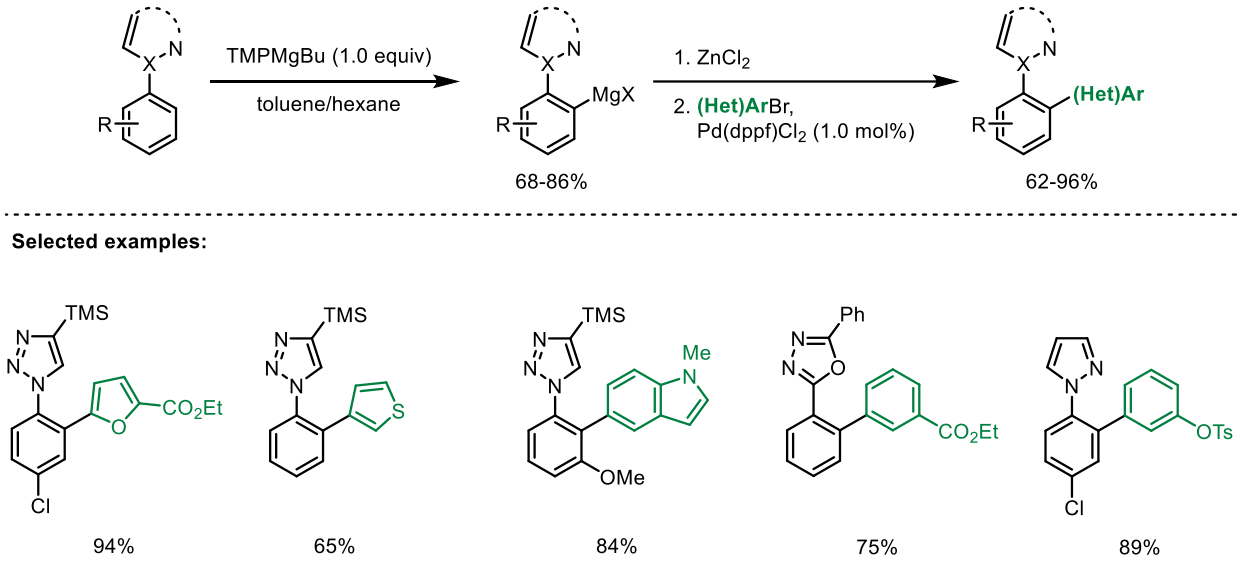
Scheme 52: Cobalt-catalyzed Csp^3-Csp^3 cross-coupling of various primary and secondary alkyl iodides with functionalized dialkylzinc reagents.

Also, a cobalt-catalyzed Fukuyama-type acylation of organo *S*-pyridyl esters with (hetero)aryl zinc pivalates was developed. The reaction proceeded with a variety of primary, secondary and tertiary alkyl, benzyl and (hetero)aryl *S*-pyridyl esters, which were readily prepared starting directly from the corresponding carboxylic acids under mild reaction conditions. This method avoids the preparation of a transient acyl chloride thus enabling a smooth synthesis of polyfunctional ketones. Furthermore, this cobalt-catalyzed acylation allow for the synthesis of several optically enriched α-chiral ketones from the corresponding enantiopure *S*-pyridyl esters with very high stereoretention (94% to >99% *ee*). Additionally, the antilipidemic drug fenofibrate was synthesized in a short sequence (Scheme 53).



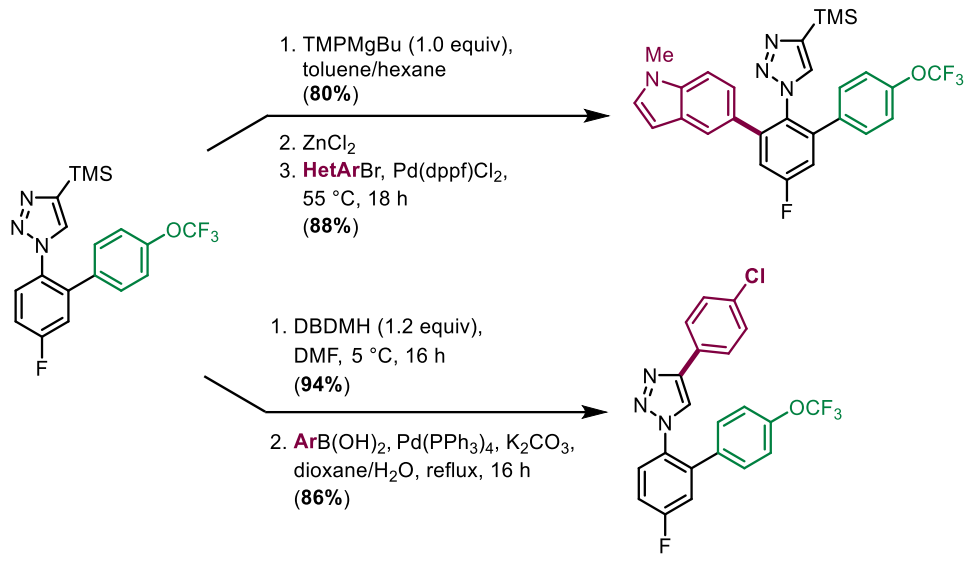
Scheme 53: Cobalt-catalyzed acylation of organo *S*-pyridyl esters using (hetero)arylzinc pivalates.

The second part of this thesis dealt with the development of a highly regioselective magnesiation of arylazoles using the mixed magnesium amide TMPMgBu. This base allows for the selective deprotonation of the aryl moiety circumventing the deprotonation of the more acidic sites at the *N*-heterocycle. The key for a high regioselectivity was the replacement of THF by the non-coordinating hydrocabons toluene and hexane as reaction solvents. The metalation proceeds with excellent regioselectivity at various substituted aryl 1,2,3-triazoles, pyrazoles, oxadiazoles and oxazolines affording, after transmetalation with $ZnCl_2$ and subsequent palladium catalyzed cross-coupling, several mono-arylated *N*-aryl azoles in high yields (Scheme 54). Furthermore, the arylmagnesium reagent was trapped with various electrophiles including iodine, thiomethylsulfonate and benzoyl chloride affording functionalized *N*-aryl azoles



Scheme 54: Regioselective magnesiation of various *N*-aryl azoles and subsequent palladium-catalyzed cross-coupling.

Finally, the versatility of the resulting scaffolds was shown by performing late-stage modifications. Thus, a second metalation and subsequent cross-coupling afforded the difunctionalized *N*-aryl triazole. Furthermore, transformation of the TMS-moiety into a bromide followed by Suzuki-cross-coupling enabled the diversification of the triazole moiety (Scheme 55).



Scheme 55: Late-stage diversification of a functionalized aryl triazole.

V. Experimental Part

1. General Considerations

All reactions were carried out with magnetic stirring and in dry glassware under an argon atmosphere using *Schlenk* technique. Syringes used to transfer solvents or reagents were purged with argon three times prior to use.

1.1 Solvents

DCM was predried over $CaCl_2$ and distilled from CaH_2.
DME was predried over $CaCl_2$ and distilled from sodium benzophenone ketyl under argon atmosphere.
DMF was refluxed over CaH_2 (14 h), distilled from CaH_2 and stored over 4 Å MS under argon atmosphere.
DMPU was predried over CaH_2 (4 h) and distilled.
MeCN was purchased from Acros (99.9+% extra dry)
THF was purchased from Acros (99.5% extra dry, stored over molecular sieve, stabilized)
Toluene was continuously refluxed and freshly distilled from sodium under nitrogen.

Solvents for column chromatography were distilled prior to use.

1.2 Reagents

Preparation of $ZnCl_2$ solution in THF (1 M)

In a dry and and argon flushed *Schlenk*-flask $ZnCl_2$ (40.9 g, 300 mmol) was dried under high vacuum at 150 °C for 4 h. After cooling to 25 °C, anhydrous THF was added until a total volume of 300 mL was reached. The suspension was left stirring overnight at 25 °C and after 12 h the salts had completely dissolved. The stirring was stopped and the solution was left for some hours to become completely clear. The solution was stored over 4 Å molecular sieve under argon upon use.

Preparation of $Zn(OPiv)_2$[124]

A dry, tared, 500 mL round-bottomed flask equipped with a magnetic stirring bar and a septum is charged with toluene (250 mL, 0.2 m). Pivalic acid (12.5 mL, 11.3 g, 110 mmol, 2.2 equiv) is added to form a colorless solution. Zinc oxide (4.07 g, 50 mmol, 1.0 equiv) is added in 1 g portions at 25 °C over 15 min to form a colorless suspension. The flask was equipped with a Dean-Stark apparatus (10 mL) wrapped in aluminum foil and topped with a reflux condenser (20 cm) and the suspension is stirred under nitrogen at reflux in an oil bath for 16 h. A viscous colorless suspension was obtained after 12 h. After cooling to 25 °C, the mixture is concentrated by rotary evaporation (50 °C/50 mmHg). The remaining pivalic acid and water were removed *in vacuo* from the reaction mixture using a vacuum line (0.1 mmHg) and a liquid nitrogen cold trap (1000 mL). The white solid was warmed to 100 °C in an oil bath and dried for at least 6 h. Zinc pivalate (13.1–13.2 g, 48.9–49.7 mmol, 98–99% yield), is obtained as a puffy amorphous white solid.

CuCN·2LiCl solution in THF (1.0 M)[125]

LiCl (8.40 g, 200 mmol) and CuCN (8.96 g, 100 mmol) were dried in a *Schlenk*-flask under high vacuum at 150 °C for 4 h. After cooling to 25 °C, dry THF was added until a total volume of 100 mL was reached. The suspension was left stirring overnight at room temperature until all salts had completely dissolved. The solution was stored under argon upon use.

Preparation of *i*PrMgCl·LiCl[126]

Magnesium turnings (2.67 g, 110 mmol) and anhydrous LiCl (4.66 g, 100 mmol) were placed in an argon-flushed flask and THF (50 mL) was added. A solution of *i*PrCl (9.13 mL, 100 mmol) in THF (50 mL) was slowly added at 25 °C. The reaction starts within a few minutes. After addition, the reaction mixture was stirred for 12 h at 25 °C. The grey solution of *i*PrMgCl·LiCl was cannulated to another flask under argon and removed in this way from excess of magnesium. A yield of ca. 95-98% of *i*PrMgCl·LiCl is obtained.

TMPH, Cy_2NH and iPr_2NH were distilled from CaH_2 under argon prior to use.

[124] M. Ellwart, Y-H. Chen, C. P. Tüllmann, V. Malakhov, P. Knochel, *Org. Synth.* **2018**, *95*, 127-141.
[125] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem*. **1988**, *53*, 2390-2392.
[126] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333-3336.

Preparation of TMPLi

nBuLi (4 mL, 10 mmol, 2.5 M in hexane) was slowly added to a solution of TMPH (1.7 mL, 10 mmol) in THF (10 mL) at −40 °C and stirred for 30 min at −40 °C.

Preparation of TMPMgCl·LiCl[127]

A dry and argon-flushed 250-mL *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with freshly titrated *i*PrMgCl·LiCl (100 mL, 1.2 m in THF, 120 mmol). TMPH (17.8 g, 126 mmol, 1.05 equiv) was added dropwise at 25 °C. The reaction mixture was stirred at 25 °C until gas evolution ceased (ca. 24 h).

Preparation of TMP_2Mg

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and rubber septum, TMPH (1.69 ml, 10.00 mmol, 2.00 equiv) was placed and Bu_2Mg (7.04 ml, 5.00 mmol, 1.00 equiv, 0.71 M in hexane) was added at 0 °C. The mixture was stirred for 48 h at room temperature resulting in a pale yellow solution.

Preparation of Cy_2NMgBu

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and rubber septum, dicyclohexylamine (1.99 ml, 10.00 mmol, 2.00 equiv) was placed and Bu_2Mg (7.04 ml, 5.00 mmol, 1.00 equiv, 0.71 M in hexane) was added at 0 °C. The mixture was stirred for 48 h at room temperature resulting in a pale yellow solution.

Preparation of *i*Pr_2NMgBu

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and rubber septum, diisopropylamine (1.41 ml, 10.00 mmol, 2.00 equiv) was placed and Bu_2Mg (7.04 ml, 5.00 mmol, 1.00 equiv, 0.71 M in hexane) was added at 0 °C. The mixture was stirred for 48 h at room temperature resulting in a pale yellow solution.

[127] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958-2961.

Preparation of TMPMgBu

In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and rubber septum, TMPH (1.18 ml, 7.00 mmol, 1.00 equiv) was placed and Bu_2Mg (9.86 ml, 7.00 mmol, 1.00 equiv, 0.71 M in hexane) was added at 0 °C. The mixture was stirred for 48 h at room temperature resulting in a pale yellow solution. The yield was determined to be 94-98% yield (0.74-0.81 M).

Preparation of the reagent $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[24]

A dry and A flame-dried and argon-flushed Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, was charged with a solution of TMPMgCl·LiCl (4.35 mL, 5 mmol, 1.00 equiv) and cooled to 0 °C. Then, $ZnCl_2$ (2.5 mL, 2.5 mmol, 0.50 equiv) was and the mixture was stirred for 2 h at 0 °C.

The content of organometallic reagent was determined either by the method of Paquette[128] using *i*PrOH and 1,10-phen as indicator (organolithium reagents) or the method of Knochel[95] using I_2 in THF (organomagnesium and -zinc reagents).

TMP-Bases were titrated against benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.

Bu_2Mg was titrated against I_2 in a 0.5 M solution of LiCl in THF.

1.3 Chromatography

Flash column chromatography was performed using silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck.

Thin layer chromatography was performed using aluminum plates covered with SiO2 (Merck 60, F-254). The chromatograms were visualized by UV detection at 254 nm and/or by staining of the TLC-plate with one of the solutions given below followed by heating with a heat gun:

- $KMnO_4$ stain: $KMnO_4$ (3.0 g), K_2CO_3 (20 g), 5% NaOH solution (5.00 mL), water (300 mL).
- PMA stain: Dissolve 10 g PMA in 100 mL absolute ethanol.

[128] H. S. Lin, A. Paquette, *Synth. Commun*. **1994**, *24*, 2503-2506.

1.4 Analytical Data

NMR spectra were recorded on Bruker Avance III HD 400 MHz, WH 400 and Bruker AMX 600 instruments. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent peak of $CHCl_3$ (δ H = 7.26, δ C = 77.0), d_6-DMSO (δ H = 2.50, δ C = 39.52) or d_6-benzene (δ H = 7.16, δ C = 128.06). For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet), br (broad).

Mass spectra and **high resolution mass spectra (HRMS)** were recorded on a Finnigan MAT 95Q (EI) or a Thermo Finnigan LTQ FT instrument (ESI). Electron impact ionization (EI) was conducted with an electron energy of 70 eV. Electrospray ionization (ESI) was conducted with an IonMax ion-source equipped with an ESI head. It was performed with a voltage of 4 kV at the spray capillary tube, a heating filament temperature of 250 °C and a nitrogen flow of 25 units.

Gas Chromatography (GC) was performed with machines of the types Hewlett-Packard 6890 or 5890 Series II (Hewlett Packard, 5% phenylmethylpolysiloxane; column length: 15 m, diameter: 0.25 mm; film thickness: 0.25 m). For the combination of gas chromatography with mass spectroscopic detection, a GC-MS from Hewlett Packard of type 6890/MSD 5973 was used.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a Perkin Elmer Spectrum BX-59343 instrument. For detection a Smiths Detection Dura Sampl*IR* II Diamond ATR sensor was used. The absorption bands ($\tilde{\nu}$) are reported in wave numbers (cm^{-1}).

Melting points (m.p.) were measured using a Büchi B-540 apparatus and are uncorrected.

Single Crystal X-Ray Diffraction Studies. Single crystals of the corresponding compounds, suitable for X-ray diffraction, were obtained by slow evaporation of a DCM, $CDCl_3$ or EtOAc solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-Kα radiation (λ = 0.71071 Å). Data collection and data reduction were performed with the CrysAlisPro software.[129] Absorption correction using the multiscan method[129] was applied. The structures were solved with

[129] Program package CrysAlisPro 1.171.39.46e (Rigaku OD, **2018**).

SHELXS-97[130], refined with SHELXL-97[131] and finally checked using PLATON[132]. Details for data collection and structure refinement are summarized in the appendix section. The single crystal structures are shown in DIAMOND109 representation.[133]

Enantiomeric excess (*ee*). The enantiomeric excess of optical enriched compounds was determined *via* chiral HPLC analysis on a Shimadzu Prominence 20A HPLC system. For developing a chiral resolution method, different chiral normal phase columns were tested with *n*-heptane and *i*PrOH as mobile phase (isocratic) using a racemic mixture of the compound.

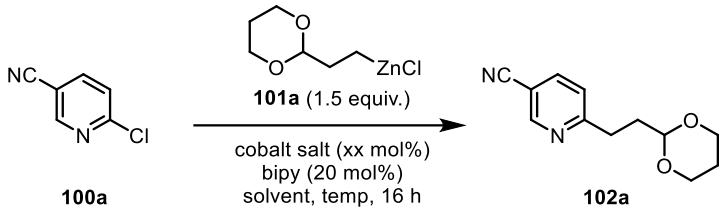
Specific Rotation $[\alpha]_D^{20}$ values of chiral products were measured in $CHCl_3$ at 20 °C using a wavelength λ = 589 nm and a 1 dm cuvette on a *Anton Paar* MCP *200* instrument. The sample concentration was 0.01 g/mL and the values are reported in $°\cdot ml\cdot dm^{-1}\cdot g^{-1}$.

[130] Sheldrick, G. M. (**1997**) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[131] Sheldrick, G. M. (**1997**) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[132] Spek, A. L. (**1999**) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.
[133] DIAMOND, Crystal Impact GbR., Version 3.2i.

2. Cobalt-Catalyzed Cross-Coupling of Functionalized Alkylzinc Reagents with (Hetero)Aryl Halides

2.1 Optimization of the Reaction Conditions

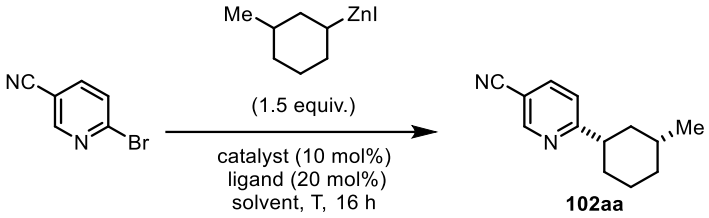
Table 10: Further optimization of the reaction conditions for the cross-coupling of **100a** with alkylzinc reagent **101a**.



Entry	Cobalt salt	$CoCl_2$ [mol%]	Amount of **101a** [equiv]	Solvent	temp [°C]	GC-Yield[a] of **102a** [%]
1	**$CoCl_2$**	**10**	**1.5**	**THF**	0	**80**
2	$CoBr_2$	10	1.5	THF	0	78
3	$Co(acac)_2$	10	1.5	THF	0	79
4	$Co(acac)_3$	10	1.5	THF	0	71
5	$CoCl_2$	2.5[b]	1.5	THF	0	51
6	$CoCl_2$	5.0[c]	1.5	THF	0	73
7	$CoCl_2$	20[d]	1.5	THF	0	12
8	$CoCl_2$	10	1.2	THF	0	62
9	$CoCl_2$	10	1.7	THF	0	81
10	$CoCl_2$	10	1.5	toluene	0	56
11	$CoCl_2$	10	1.5	MeCN	0	79
12	$CoCl_2$	10	1.5	Et_2O	0	79
13	$CoCl_2$	10	1.5	tBuOMe	0	76
14	$CoCl_2$	10	1.5	THF	-10	65
15	$CoCl_2$	10	1.5	THF	25	50

[a] Tetradecane ($C_{14}H_{30}$) was used as internal standard. [b] 5% bipy was used. [c] 10% bipy was used. [b] 40% bipy was used.

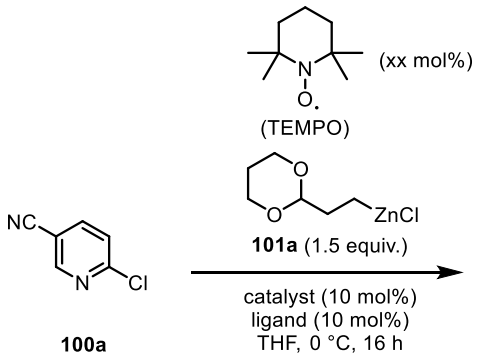
Table 11: Further optimization of the reaction conditions for the Diastereoselective formation of **102aa**.



Entry	catalyst	Ligand [mol%]	T[°C]	solvent	dr	GC-Yield[a] of **102aa** [%]
1	$CoCl_2$	-	25	THF	40:60	13
2	$CoCl_2$	neocuproine	25	THF	69:31	6
3	$CoCl_2$	bipy	25	THF	91:9	33
4	$CoCl_2$	bipy	0	THF	91:9	24
5	$CoCl_2$	dtbbpy	25	THF	90:10	28
6	$CoCl_2$	bipy	25	MeCN	79:21	81
8	$CoCl_2$	**dtbbpy**	**25**	**MeCN**	**91:9**	**85**
9	$NiCl_2$	dtbbpy	25	THF	88:12	19
10	$NiCl_2$	dtbbpy	25	MeCN	88:12	29
11	$NiCl_2(PPh_3)_2$	-	25	THF	80:20	70
12	$NiCl_2(PPh_3)_2$	-	25	MeCN	79:21	76

[a] Tetradecane ($C_{14}H_{30}$) was used as internal standard.

2.2 Mechanistic Experiments

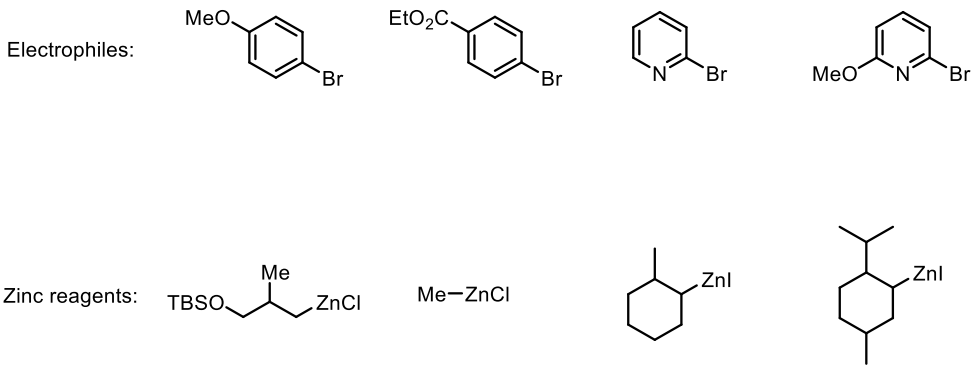


entry	TEMPO	GC-yield [%][a]
1	-	80
2	10%	69
3	100%	81
4	200%	82

Scheme 56: Radical trapping experiments using TEMPO. [a] Tetradecane ($C_{14}H_{30}$) was used as internal standard.

To gain an insight into the reaction mechanism, radical-trapping experiments using 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) were performed. To a standard coupling setup of 6-chloronicotinonitrile (**100a**) with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**101a**) various amounts of TEMPO were added (entry 2-4). However, the coupling product **102a** was obtained in a similar yield, compared to the standard conditions without the radical trapping agent. This indicates that the developed cobalt-catalyzed cross-coupling might not proceed *via* radical intermediates.

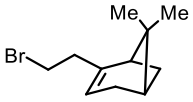
2.3 Selected Unsuccessful Substrates



Scheme 57: Selected unsuccessful substrates for the cobalt-catalyzed cross-coupling.

2.4 Preparation of Starting Materials

(1*R*,5*S*)-2-(2-bromoethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene[134]

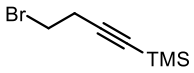


The title compound was prepared according to literature procedure from (1*R*)-(−)-nopol (6.7 mL, 40 mmol) affording (1*R*,5*S*)-2-(2-bromoethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene as pale yellow oil (8.25 g, 36.0 mmol, 90 %). The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.32 (tq, *J* = 2.9, 1.5 Hz, 1H), 3.36 (td, *J* = 7.7, 3.8 Hz, 2H), 2.56 – 2.48 (m, 2H), 2.37 (dt, *J* = 8.6, 5.6 Hz, 1H), 2.31 – 2.15 (m, 2H), 2.09 (ttd, *J* = 5.8, 2.8, 1.3 Hz, 1H), 2.01 (td, *J* = 5.6, 1.5 Hz, 1H), 1.27 (s, 3H), 1.17 (d, *J* = 8.6 Hz, 1H), 0.83 (s, 3H).

[134] B. Akgun, D. G. Hall, *Angew. Chem. Int. Ed*. **2016**, *55*, 3909-3913.

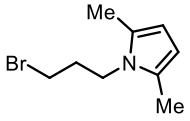
(4-Bromobut-1-yn-1-yl)trimethylsilane[135]



The title compound was prepared according to literature procedure from (4-(trimethylsilyl)-3-butyn-1-ol (3.00 g, 21 mmol), affording (4-bromobut-1-yn-1-yl)trimethylsilane as a colorless liquid (3.10 g, 16.0 mmol, 76 %). The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.43 (t, *J* = 7.5 Hz, 2H), 2.77 (t, *J* = 7.5 Hz, 2H), 0.16 (s, 9H).

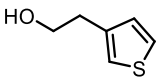
1-(3-Bromopropyl)-2,5-dimethyl-1*H*-pyrrole[136]



The title compound was prepared according to literature procedure from 3-bromopropylammonium bromide (5.00 g, 22.8 mmol) affording 1-(3-bromopropyl)-2,5-dimethyl-1*H*-pyrrole as a yellow oil (2.50 g, 11.6 mmol, 54 %). The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.77 (s, 2 H), 3.95 – 3.88 (m, 2 H,), 3.42 (m, 2 H), 2.24 (s, 6 H), 2.20 – 2.15 (m, 2 H).

3-(2-Bromoethyl)thiophene[137]



The title compound was prepared according to literature procedure from 2-(thiophen-3-yl)ethan-1-ol (2.56 g, 20 mmol), affording 3-(2-bromoethyl)thiophene as a colorless liquid (2.75 g, 14.4 mmol, 72 %). The analytical data is in full consistency with the data reported in the literature.

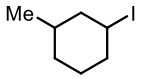
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.29 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.07 (d, *J* = 2.9 Hz, 1H), 6.98 (d, *J* = 4.9 Hz, 1H), 3.57 (t, *J* = 7.5 Hz, 2H), 3.21 (t, *J* = 7.5 Hz, 2H).

[135] H. M. Wisniewska, E. C. Swift, E. R. Jarvo, *J. Am. Chem. Soc.* **2013**, *135*, 9083–9090.
[136] S. P. Bruekelman, S. E. Leach, G. D. Meakins, M. D. Tirel, *J. Chem. Soc. Perkin Trans. 1* **1984**, 2801–2807.
[137] P. Taranekar, A. Baba, T. M. Fulghum, R. Advincula, *Macromolecules* **2005**, *38*, 3679–3687.

Preparation of cyclohexyl Iodides TP1[138]

A dry round bottom flask equipped with a magnetic stirring bar was charged with I_2 (1.20 equiv) which was dissolved in CH_2Cl_2 (0.5 m) and cooled to 0 °C. PPh_3 (1.10 equiv) was carefully added at this temperature. The resulting suspension was stirred for 1.5 h. Then, *N*-methylimidazole (1.25 equiv) was added. After 10 min of stirring, the respective cyclohexanol (1.00 equiv) was added. The reaction mixture was stirred for another 4 h, was allowed to warm to rt and stirred overnight. The reaction mixture was quenched with sat. aqueous $Na_2S_2O_3$ solution. The phases were separated and the aqueous layer was extracted 3x with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were evaporated and the crude product was subjected to column chromatography furnishing the analytical pure cyclohexyl iodide.

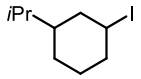
1-Iodo-3-methylcyclohexane



1-Iodo-3-methylcyclohexane was prepared according to **TP1** from 3-methylcyclohexanol (4.56 g, 40 mmol) and was obtained as a pale pink oil (6.05 g, 27 mmol, 68% yield). The analytical data is in full consistency with the data reported in the literature. [78h]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.91 – 4.79 (m, 1H), 4.15 (tt, *J* = 12.3, 4.0 Hz, 0.5H), 2.40 (ttq, *J* = 10.9, 3.6, 1.9 Hz, 1H), 2.14 – 1.80 (m, 4H), 1.80 – 1.33 (m, 5H), 1.32 – 1.18 (m, 3H), 1.07 – 0.81 (m, 5H).

1-iodo-3-isopropylcyclohexane

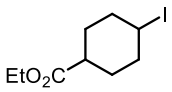


1-Iodo-3-isopropylcyclohexane was prepared according to **TP1** from 3-isopropylcyclohexanol (12.1 g, 85 mmol), which was prepared according to literature procedure[139] and was obtained as a colorless oil (15.1 g, 60 mmol, 70%) The analytical data is in full consistency with the data reported in the literature. [69a]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.93 (qt, *J* = 3.3, 2.0 Hz, 1H), 2.05 (ddtt, *J* = 14.5, 10.5, 3.5, 1.8 Hz, 2H), 1.81– 1.58 (m, 5H), 1.53 – 1.38 (m, 2H), 1.29 (ddd, *J* = 14.4, 11.0, 3.4 Hz, 1H), 1.13 – 1.00 (m, 1H), 0.87 (s, 4H), 0.85 (s, 3H).

[138] G. L. Lange, C. Gottardo, *Synth. Commun.* **1990**, *20*, 1473-1479.
[139] T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer, P. Knochel *Nat. Chem*. **2010**, *2*, 125-130.

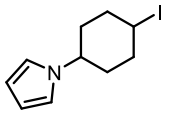
Ethyl 4-iodocyclohexane-1-carboxylate



Ethyl 4-iodocyclohexane-1-carboxylate was prepared according to **TP1** from ethyl 4-hydroxycyclohexane-1-carboxylate (2.15 g, 12.5 mmol) and was obtained as a colorless oil (2.39 g, 8.5 mmol, 68% yield). The analytical data is in full consistency with the data reported in the literature.[140]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.66 (s, 1H), 4.14 – 3.96 (m, 2H), 2.54 – 2.42 (m, 2H), 2.41 – 2.28 (m, 2H), 2.24 – 2.13 (m, 1H), 2.13 – 2.00 (m, 2H), 1.96 – 1.88 (m, 2H), 1.28 – 1.11 (m, 3H).

1-(4-Iodocyclohexyl)-1*H*-pyrrole



1-(4-Iodocyclohexyl)-1*H*-pyrrole was prepared according to **TP1** from 4-(1*H*-pyrrol-1-yl)cyclohexan-1-ol (6.60 g, 40.0 mmol), which was prepared according to literature procedure[141] from 4-aminocyclohexan-1-ol. 1-(4-iodocyclohexyl)-1*H*-pyrrole and was obtained as colorless crystals (6.08 g, 22.1 mmol, 55% yield).

Purification: *i*hexane:ethyl acetate = 95:5.

m.p.: 51.0 – 52.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.81 (t, *J* = 2.1 Hz, 2H), 6.20 (t, *J* = 2.1 Hz, 2H), 4.90 – 4.80 (m, 1H), 3.92 (tt, *J* = 11.7, 3.9 Hz, 1H), 2.38 – 2.13 (m, 4H), 2.11 – 1.95 (m, 2H), 1.82 – 1.65 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 118.6, 107.8, 57.6, 35.8, 33.2, 30.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2945, 2934, 2832, 1490, 1438, 1428, 1410, 1346, 1392, 1276, 1258, 1238, 1214, 1188, 1160, 1088, 1068, 1054, 1021, 1005, 961, 904, 875, 864, 820, 772, 723, 712, 697.

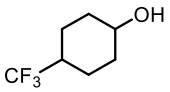
MS (EI, 70 eV): *m/z* (%) = 275 (31), 149 (11), 148 (100), 120 (11), 118 (16), 106 (10), 81 (31), 80 (17), 79 (27), 68 (16).

HR-MS (EI, 70eV): [$C_{10}H_{14}NI$], calcd.: 275.0171; found: 275.0167.

[140] K. Moriya and P. Knochel *Org Lett.* **2014**, *16*, 924-927.

[141] N.N. Bhuvan Kumar, O. A. Mukhina, and A. G. Kutateladze *J.Am.Chem.Soc.* **2013**, 135, 9608-9611.

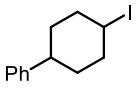
1-Iodo-4-(trifluoromethyl)cyclohexane



1-Iodo-4-(trifluoromethyl)cyclohexane was prepared according to **TP1** from ethyl 4-(trifluoromethyl)cyclohexan-1-ol (1.00 g, 6.00 mmol) and was obtained as a colorless oil (750 mg, 2.74 mmol, 46% yield). The analytical data is in full consistency with the data reported in the literature. [78h]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.74 (p, *J* = 3.4 Hz, 1H), 2.17 – 2.06 (m, 2H), 2.05 – 1.89 (m, 1H), 1.90 – 1.69 (m, 4H), 1.60 – 1.41 (m, 2H).

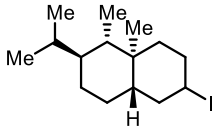
(4-Iodocyclohexyl)benzene



(4-Iodocyclohexyl)benzene was prepared according to **TP1** from (4-hydroxycyclohexyl)benzene (3.5 g, 20.0 mmol) and was obtained as colorless crystals (5.31g, 18.6 mmol, 90%). The analytical data is in full consistency with the data reported in the literature. [78h]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.37 – 6.99 (m, 5H), 2.49 (dddd, *J* = 15.4, 11.8, 7.5, 3.6 Hz, 1H), 2.11 (ddt, *J* = 18.7, 7.0, 3.3 Hz, 2H), 1.96 (qd, *J* = 12.5, 3.2 Hz, 2H), 1.88 – 1.54 (m, 4H), 0.85 – 0.70 (m, 1H).

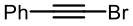
(1*S*,2*S*,4*aS*,8*aS*)-6-Iodo-2-isopropyl-1,8a-dimethyldecahydronaphthalene



(+)-Nootkatone (20.0 mmol, 4.40 g) and Pd/C (10%, 700 mg) were suspended in EtOAc (35 mL) in a 250 mL round-bottom flask charged with a stirring bar. A H_2 balloon was attached to the flask was stirred for 72 h until full reduction of the olefinic double bonds was detected according to GC-MS and NMR analysis of a crude reaction aliquot. The reaction mixture was filtered through a short silica plug using EtOAc as eluent. After solvent evaporation the obtained pale yellow oil was dissolved in MeOH (50 mL), cooled to 0 °C, $NaBH_4$ was added portion wise and the reaction mixture was stirred overnight. The reaction mixture was quenched with HCl (1.00 m) and extracted with DCM. After solvent evaporation the crude product was purified by a short silica column (9:1 hexanes/EtOAc), affording the corresponding alcohol as a colorless oil. (1*S*,2*S*,4*aS*,8*aS*)-6-Iodo-2-isopropyl-1,8a-dimethyldecahydronaphthalene was prepared according to **TP1** from the corresponding alcohol and was obtained as pink oil (14.8 mmol, 4.95 g, 75% over 3 steps). The analytical data is in full consistency with the data reported in the literature. [78h]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.88 (tt, *J* = 4.0, 2.1 Hz, 1H), 1.72 (ddt, *J* = 13.8, 10.3, 3.2 Hz, 2H), 1.67–1.54 (m, 4H), 1.40 – 1.10 (m, 6H), 0.98 (ddt, *J* = 14.3, 12.3, 5.2 Hz, 1H), 0.79 (dd, *J* = 6.8, 4.3 Hz, 6H), 0.75 (dd, *J* = 6.7, 4.2 Hz, 3H), 0.63 (s, 3H).

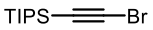
(Bromoethynyl)benzene (4a)[142]



The title compound was prepared according to literature procedure from ethynylbenzene (306 mg, 3.00 mmol), affording (bromoethynyl)benzene as a pale yellow liquid (467 mg, 2.58 mmol, 86%). The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.49 – 7.42 (m, 2H), 7.37 – 7.27 (m, 3H).

(Bromoethynyl)triisopropylsilane (4b)[142]



The title compound was prepared according to literature procedure from ethynyltriisopropylsilane (546 mg, 3.00 mmol), affording (bromoethynyl)triisopropylsilane as a colorless oil (734 mg, 2.80 mmol, 93%). The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 1.07 (s, 21H).

[142] Y. Ping, K. Wang, Q. Pan, Z. Ding, Z. Zhou, Y. Guo, and W. Kong, *ACS Catal.* **2019**, *9*, 7335-7342.

2.5 Preparation of Organometallic Reagents

Preparation of alkylzinc reagents *via* magnesium insertion and subsequent transmetalation (TP2):[16a]

Dry LiCl (1.2 equiv.) was placed in a dry and argon flushed 50 mL *Schlenk*-tube equipped with a magnetic stirring bar and a septum and was dried over 5 min at 300 °C under high vacuum (0.1 mbar). Magnesium turnings (1.2 equiv.) were added followed by dry THF (1.00 m solution relating to the aryl halide) and the respective alkyl bromide (1.0 equiv.). After the exothermic reaction started, the mixture was cooled with an ice bath. To monitor the progress of the insertion reaction, reaction aliquots quenched with iodine were analyzed as water-quenched samples by GC-analysis. When the insertion was completed, the concentrations of the magnesium reagent were determined *via* titration of a small aliquot with I_2 (50 mg in 2 mL THF). A $ZnCl_2$ solution (1.00 m in THF, 1.0 equiv.) was added at 0 °C and stirred at ambient temperature for 15 min affording the corresponding alkylzinc chloride.

Preparation of alkylzinc halides *via* zinc insertion (TP3): [10,69b]

Dry LiCl (1.5 equiv.) was placed in a dry and argon flushed 25 mL *Schlenk*-tube equipped with a magnetic stirring bar and a septum, was dried over 5 min at 300 °C under high vacuum (0.1 mbar). Zn powder (3.0 equiv.) was added under argon and the heterogeneous mixture of Zn and LiCl was dried one more time at 300 °C for 5 min under high vacuum. The reaction flask was evacuated and refilled with argon three times. THF (1.00 m solution relating to the alkyl iodide) and 1,2-dibromoethane (0.05 equiv.) were added. The mixture was then gently heated in order to activate the Zn surface. TMSCl (0.05 equiv.) was added and the reaction mixture was again gently heated.

The respective primary alkyl bromide or cyclohexyl iodide (1.0 equiv.) was added neat at rt in one portion. The resulting reaction mixture was stirred until full consumption of the alkyl halide, in case of the primary alkyl bromides the insertion reaction was stirred at 50°C. To monitor the progress of the insertion reaction, reaction aliquots quenched with iodine and quenched with sat. aqueous. NH_4Cl were analyzed by GC-analysis. When the insertion was completed the solution was then filtered from the remaining Zn powder *via* syringe filter (30 mm with 0.45 µm glass fiber membrane) and transferred to a dry argon flushed *Schlenk*-tube. The concentrations of all cyclohexylzinc reagents were determined *via* titration of a small aliquot with I_2 (50 mg in 2 mL THF).

2.6 Cobalt-Catalyzed Cross-Coupling of Polyfunctional Alkylzinc Reagents with (Hetero)Aryl Halides

Cobalt-catalyzed acylation of arylzinc pivalates with thiopyridyl esters (TP4):

A dry and argon flushed *Schlenk*-tube, equipped with a magnetic stir bar and a septum was charged with dry $CoCl_2$ (6.5 mg, 0.05 mmol, 10 mol%), which was dried at 300 °C under high vacuum prior to use.

A) For primary alkylzinc spezies:

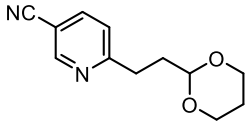
Bipyridine (17 mg, 0.1 mmol, 20 mol%) the respective (hetero)aryl halide (0.5 mmol, 1.0 equiv.) and dry THF (1.0 mL) were added. The reaction mixture was cooled to 0 °C with an ice bath and a solution of the appropriate alkylzinc halide (0.75 mmol, 1.5 equiv.) was added *via* syringe.

B) For secondary alkylzinc spezies:

4,4'-Di-*tert*-butyl-2,2'-bipyridine (27 mg, 0.1, 20 mol), the respective (hetero)aryl halide (0.5 mmol, 1.0 equiv.) and dry MeCN (1.0 mL) were added (for the synthesis of **102x** and **102y** the reaction was performed in THF). The appropriate alkylzinc halide (0.75 mmol, 1.5 equiv.) was added *via* syringe at room temperature.

In both cases the reaction was stirred for 16 h at room temperature. The solvent was removed and the crude product was subjected to column chromatography purification on silica yielding the corresponding coupling product.

6-(2-(1,3-Dioxan-2-yl)ethyl)nicotinonitrile (102a)



Following **TP4-A** 6-chloronicotinonitrile (**1a**, 138 mg, 1.00 mmol, 1.0 equiv.) was coupled with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**2a**, 1.50 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 163 mg, 0.75 mmol, 75%, white solid.

Purification: pentane:ethyl acetate = 7:3.

m.p.: 100.1 – 102.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.73 (dd, *J* = 2.2, 0.9 Hz, 1H), 7.78 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.38 – 6.90 (m, 1H), 4.50 (t, *J* = 5.0 Hz, 1H), 4.03 (ddt, *J* = 10.5, 4.9, 1.4 Hz, 2H), 3.80 – 3.52 (m, 2H), 3.00 – 2.76 (m, 2H), 2.18 – 1.89 (m, 3H), 1.28 (dtt, *J* = 13.5, 2.6, 1.4 Hz, 1H).

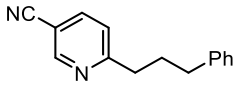
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.4, 152.2, 139.4, 123.1, 117.13, 107.3, 101.1, 67.0, 34.2, 32.8, 25.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2966, 2934, 2865, 227, 1979, 1596, 156, 1492, 1474, 1453, 1424, 1381, 1318, 1290, 1266, 1241, 1191, 1138, 1121, 1070, 1040, 1029, 998, 952, 943, 926, 888, 865, 856, 834, 758, 668.

MS (EI, 70 eV): *m/z* (%) = 217 (12), 159 (49), 143 (13), 132 (25), 131 (96), 118 (31), 101 (20), 87 (100).

HR-MS (EI, 70eV): [$C_{12}H_{13}N_2O_2$], calcd.: 217.0972; found:217.0970 [M^+-H].

6-(3-Phenylpropyl)nicotinonitrile (102b)



Following **TP4-A** 6-chloronicotinonitrile (**1a**, 69 mg, 0.50 mmol, 1.0 equiv.) was coupled with (3-phenylpropyl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 81 mg, 0.36 mmol, 73%, white solid.

Purification: *i*-hexane:ethyl acetate = 8:2.

m.p.: 62.3 – 64.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.87 – 8.74 (m, 1H), 7.84 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.33 – 7.19 (m, 3H), 7.20 – 7.16 (m, 3H), 2.96 – 2.83 (m, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.09 (p, *J* = 7.7 Hz, 2H).

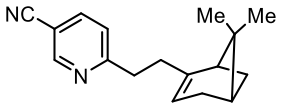
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.8, 152.3, 141.6, 139.4, 128.6, 128.6, 126.1, 123.0, 117.1, 107.3, 38.2, 35.5, 30.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3045, 3021, 2946, 2922, 2858, 2229, 1594, 1553, 1495, 1484, 1452, 1387, 1316, 1289, 1204, 1187, 1156, 1129, 1076, 1043, 1027, 1017, 934, 914, 868, 849, 827, 750, 700, 677.

MS (EI, 70 eV): *m/z* (%) = 223 (1), 131 (3), 119 (8), 118 (100), 117 (1), 91 (5).

HR-MS (EI, 70eV): [$C_{15}H_{15}N_2$], calcd.: 223.1230; found: 223.1229 [M^++H].

6-(2-((1*R*,4*R*)-5,5-Dimethylbicyclo[2.1.1]hex-2-en-2-yl)ethyl)nicotinonitrile (102c)



Following **TP4-A** 6-bromonicotinonitrile (92 mg, 0.50 mmol, 1.0 equiv.) was coupled with (2-((1*R*,4*R*)-5,5-dimethylbicyclo[2.1.1]hex-2-en-2-yl)ethyl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 98 mg, 0.39 mmol, 78%, red crystals.

Purification: *i*-hexane:ethyl acetate = 9:1.

m.p.: 34.2 – 35.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.79 (dd, *J* = 2.2, 0.9 Hz, 1H), 7.85 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.30 – 7.26 (m, 1H), 5.23 (tp, *J* = 3.0, 1.4 Hz, 1H), 2.98 – 2.86 (m, 2H), 2.44 – 2.31 (m, 3H), 2.30 – 2.12 (m, 3H), 2.11 – 2.02 (m, 2H), 1.27 (s, 3H), 1.10 (d, *J* = 8.5 Hz, 1H), 0.80 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.8, 152.1, 146.8, 139.5, 123.0, 117.2, 117.1, 107.3, 45.9, 40.8, 4.1, 36.6, 36.4, 31.7, 31.7, 26.4, 21.3.

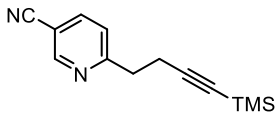
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2975 , 2925, 2834, 2231, 1595, 1554, 1482, 1447, 1382, 1364, 1338, 1304, 1264, 1202, 1119, 1098, 1025, 1003, 936, 886, 862, 838, 806, 725.

MS (EI, 70 eV): *m/z* (%) = 252 (5), 251 (6), 237 (7), 223 (7), 211 (5), 209 (52), 207 (7), 184 (13), 183 (100), 181 (7).

HR-MS (EI, 70eV): [$C_{17}H_{19}N_2$], calcd.: 251.1548; found: 251.1539.

Optical rotation: $[\alpha]_D^{20} =$ - 34 (c 0.83, $CHCl_3$).

6-(4-(Trimethylsilyl)but-3-yn-1-yl)nicotinonitrile (102d)



Following **TP4-A** 6-bromonicotinonitrile (92 mg 0.50 mmol, 1.0 equiv.) was coupled with (4-(trimethylsilyl)but-3-yn-1-yl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 71 mg, 0.31 mmol, 62%, yellow solid.

Purification: *i*-hexane:ethyl acetate = 8:2.

m.p.: 70.0 – 71.2 **°C**.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.81 (dd, *J* = 2.3, 0.9 Hz, 1H), 7.87 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.35 (dd, *J* = 8.1, 1.0 Hz, 1H), 3.05 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 0.09 (s, 9H).

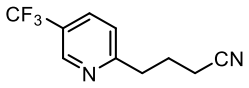
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 164.6, 152.3, 139.2, 123.5, 117.0, 107.8, 105.3, 86.4, 37.4, 19.7, 0.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925, 2231, 2172, 1591, 1551, 1482, 1434, 1384, 1242, 1048, 1025, 999, 843, 757, 699.

MS (EI, 70 eV): *m/z* (%) = 229 (3), 228 (11), 227 (93), 213 (59), 157 (12), 156 (11), 155 (100).

HR-MS (EI, 70eV): [$C_{13}H_{16}N_2Si$], calcd.: 228.1083; found: 228.1036.

4-(5-(Trifluoromethyl)pyridin-2-yl)butanenitrile (102e)



Following **TP4-A** using $CoCl_2$ (13 mg, 0.1 mmol, 20 mol%) and bipyridine (31 mg, 0.2 mmol, 40 mol%), 2-bromo-5-(trifluoromethyl)pyridine (113 mg, 0.50 mmol, 1.0 equiv.) was coupled with (3-cyanopropyl)zinc bromide (0.95 mmol, 1.9 equiv.) prepared according to **TP3** from the corresponding bromide.

Isolated yield: 93 mg, 0.43 mmol, 87%, colorless oil.

Purification: *i*-hexane:ethyl acetate = 7:3 to 6:4.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.92 – 8.73 (m, 1H), 7.86 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 3.03 (t, *J* = 7.4 Hz, 2H), 2.44 (t, *J* = 7.1 Hz, 2H), 2.17 (p, *J* = 7.2 Hz, 2H).

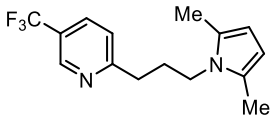
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 8.92 – 8.73 (m, 1H), 7.86 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 3.03 (t, *J* = 7.4 Hz, 2H), 2.44 (t, *J* = 7.1 Hz, 2H), 2.17 (p, *J* = 7.2 Hz, 2H).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2940, 2247, 1608, 1574, 1496, 1430, 1396, 1325, 1166, 1121, 1079, 1017, 940, 854, 750.

MS (EI, 70 eV): *m/z* (%) = 175 (4), 174 (41), 161 (100), 147 (5), 146 (5), 141 (3), 126 (3).

HR-MS (EI, 70eV): [$C_{10}H_{10}F_3N_2$], calcd.: 215.0791; found: 215.0783 [M^++H].

2-(3-(2,5-Dimethyl-1*H*-pyrrol-1-yl)propyl)-5-(trifluoromethyl)pyridine (102f)



Following **TP4-A** 2-bromo-5-(trifluoromethyl)pyridine (113 mg, 0.50 mmol, 1.0 equiv.) was coupled with (3-(2,5-dimethyl-1*H*-pyrrol-1-yl)propyl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 107 mg, 0.38 mmol, 76%, brown oil.

Purification: *i*-hexane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.80 (dt, *J* = 2.0, 1.0 Hz, 1H), 7.89 – 7.80 (m, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 5.76 (s, 2H), 3.88 – 3.77 (m, 2H), 2.92 (t, *J* = 7.7 Hz, 2H), 2.20 (s, 6H), 2.18 – 2.04 (m, 2H).

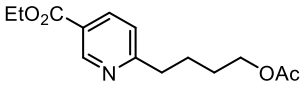
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 164.8, 146.1 (q, *J* = 4.1 Hz), 133.7 (q, *J* = 3.5 Hz), 127.4, 124.5 (q, *J* = 33.0 Hz), 123.6 (q, *J* = 272.0 Hz), 122.6, 105.3, 43.0, 35.2, 30.1, 12.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2933, 2575, 1608, 1573, 1395, 1332, 1161, 1128, 1081, 1017, 853, 750.

MS (EI, 70 eV): *m/z* (%) = 282 (42), 189 (11), 188 (100), 187 (43), 186 (25), 178 (9), 174 (73), 161 (27), 160 (10), 121 (7), 120 (9), 109 (7), 108 (32), 94 (15).

HR-MS (EI, 70eV): [$C_{15}H_{17}F_3N_2$], calcd.: 282.1344; found: 282.1335.

Ethyl 6-(4-acetoxybutyl)nicotinate (102g)



Following **TP4-A** using $CoCl_2$ (13 mg, 0.1 mmol, 20 mol%) and bipyridine (31 mg, 0.2 mmol, 40 mol%), ethyl 6-chloronicotinate (93 mg, 0.50 mmol, 1.0 equiv.) was coupled with (4-acetoxybutyl)zinc bromide (0.95 mmol, 1.9 equiv.) prepared according to **TP3** from the corresponding bromide.

Isolated yield: 87 mg, 0.33 mmol, 66%, colorless oil.

Purification: *i*-hexane:ethyl acetate = 1:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.13 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.20 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.25 – 7.20 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.08 (t, *J* = 6.5 Hz, 2H), 2.96 – 2.83 (m, 2H), 2.03 (s, 3H), 1.89 – 1.77 (m, 2H), 1.76 – 1.63 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

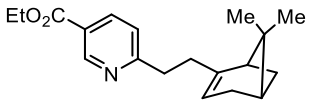
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 171.3, 166.3, 165.6, 150.7, 137.6, 124.1, 122.5, 64.3, 6.4, 38.1, 28.4, 26.1, 21.2, 14.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955, 1718, 1598, 1568, 1464, 1385, 1366, 1278, 1234, 1173, 1112, 1026, 855, 763.

MS (EI, 70 eV): *m/z* (%) = 206 (33), 192 (23), 178 (100), 165 (72), 164 (45), 150 (40), 137 (87).

HR-MS (EI, 70eV): [$C_{14}H_{20}NO_4$], calcd.: 266.1387; found: 266.1383 [M^++H].

Ethyl 6-(2-((1*R*,4*R*)-5,5-dimethylbicyclo[2.1.1]hex-2-en-2-yl)ethyl)nicotinate (102h)



Following **TP4-A** ethyl 6-chloronicotinate (93 mg, 0.50 mmol, 1.0 equiv.) was coupled with (2-((1*R*,4*R*)-5,5-dimethylbicyclo[2.1.1]hex-2-en-2-yl)ethyl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 108 mg, 0.36 mmol, 72%, yellow oil.

Purification: *i*-hexane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.12 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.22 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.29 – 7.22 (m, 1H), 5.23 (tt, *J* = 3.0, 1.5 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.99 – 2.89 (m, 2H), 2.45 – 2.30 (m, 3H), 2.28 – 2.10 (m, 2H), 2.10 – 2.01 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 3H), 1.11 (d, *J* = 8.5 Hz, 1H), 0.80 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.4, 165.4, 150.0, 147.1, 138.0, 124.2, 122.8, 117.0, 61.5, 45.8, 40.9, 38.1, 36.7, 36.2, 31.7, 31.4, 26.4, 21.3, 14.4.

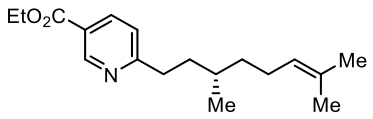
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982, 2913, 2831, 1678, 1619, 1600, 1563, 1504, 1468, 1427, 1381, 1364, 1312, 1319, 1264, 1220, 1140, 1115, 1082, 1016, 954, 886, 869, 824, 782, 753.

MS (EI, 70 eV): *m/z* (%) = 299 (10), 298 (10), 284 (15), 270 (20), 258 (13), 256 (31), 231 (13), 230 (100), 228 (36), 216 (15), 204 (12), 203 (11), 202 (84), 188 (13), 174 (11), 165 (60), 150 (10), 137 (62), 91 (12).

HR-MS (EI, 70eV): [$C_{19}H_{25}NO_2$], calcd.: 299.1885; found: 299.1885.

Optical rotation: $[\alpha]_D^{20} =$ - 23 (c 1.35, $CHCl_3$).

Ethyl (*S*)-6-(3,7-dimethyloct-6-en-1-yl)nicotinate (102i)



Following **TP4-A** ethyl 6-chloronicotinate (93 mg, 0.50 mmol, 1.0 equiv.) was coupled with (*R*)-(3,7-dimethyloct-6-en-1-yl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 120 mg, 0.42 mmol, 83%, colorless oil.

Purification: *i*-hexane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.18 – 9.04 (m, 1H), 8.18 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 5.15 – 5.01 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.85 (qdd, *J* = 13.8, 10.1, 5.6 Hz, 2H), 2.10 – 1.84 (m, 2H), 1.74 (ddq, *J* = 15.2, 9.6, 5.0, 4.5 Hz, 1H), 1.67 (s, 3H), 1.58 (s, 3H), 1.56 – 1.44 (m, 1H), 1.39 (t, *J* = 7.1 Hz, 4H), 1.44 – 1.33 (m, 1H), 1.19 (dddd, *J* = 18.8, 11.6, 9.3, 4.3 Hz, 1H), 0.95 (d, *J* = 6.3 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 167.5, 165.6, 150.6, 137.5, 131.4, 124.9, 123.9, 122.4, 61.4, 37.1, 37.0, 36.3, 32.5, 25.9, 25.6, 19.6, 17.8, 14.4.

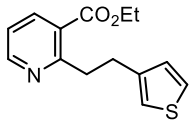
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961, 1719, 1598, 1568, 1462, 1380, 1368, 1276, 1173, 1112, 1027, 972, 856, 773, 736.

MS (EI, 70 eV): *m/z* (%) = 260 (4), 246 (31), 206 (7), 178 (37), 165 (100), 150 (17), 137 (40).

HR-MS (EI, 70eV): [$C_{16}H_{22}NO_2$], calcd.: 260.1651; found: 260.1647 [M^+-Et].

Optical rotation: $[\alpha]_D^{20} =$ 5 (c 0.75, $CHCl_3$).

Ethyl 2-(2-(thiophen-3-yl)ethyl)nicotinate (102j)



Following **TP4-A** ethyl 2-chloronicotinate (93 mg, 0.50 mmol, 1.0 equiv.) was coupled with (2-(thiophen-3-yl)ethyl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 111 mg, 0.42 mmol, 85%, pale yellow oil.

Purification: *i*-hexane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.68 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.27 – 8.18 (m, 1H), 7.32 – 7.27 (m, 1H), 7.24 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.04 – 6.95 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.57 – 3.46 (m, 2H), 3.14 – 3.04 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

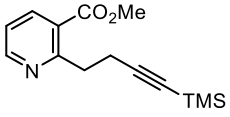
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 165.9, 161.7, 150.6, 141.6, 139.8, 128.4, 126.4, 125.3, 121.5, 120.7, 61.7, 30.4, 27.1, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982, 2118, 1714.2, 1587, 1568, 1439, 1389, 1366, 1277, 1249, 1198, 1171, 1125, 1080, 1062, 1018, 934, 858, 840, 828, 779, 741, 686, 664.

MS (EI, 70 eV): *m/z* (%) = 262 (12), 261 (62), 233 (18), 232 (100), 215 (14), 213 (23), 187 (18), 186 (2), 97 (92), 79 (15), 57 (13), 53 (23), 45 (16), 43 (17).

HR-MS (EI, 70eV): [$C_{12}H_{10}NO_2S$], calcd.: 232.0423; found: 232.0414 [M^+-Et].

Methyl 2-(4-(trimethylsilyl)but-3-yn-1-yl)nicotinate (102k)



Following **TP4-A** methyl 2-chloronicotinate (93 mg, 0.50 mmol, 1.0 equiv.) was coupled with with (4-(trimethylsilyl)but-3-yn-1-yl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 108 mg, 0.41 mmol, 83%, yellow oil

Purification: *i*-hexane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.69 – 8.62 (m, 1H), 8.23 – 8.13 (m, 1H), 7.25 – 7.22 (m, 1H), 3.93 (s, 3H), 3.44 (t, *J* = 7.6 Hz, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 0.10 (d, *J* = 1.0 Hz, 9H).

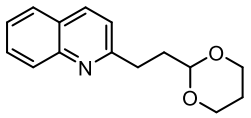
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 167.0, 161.2, 152.0, 138.6, 125.7, 121.3, 106.6, 85.0, 52.5, 35.6, 19.8, 0.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955, 2175, 1726, 1584, 1569, 1431, 1279, 1248, 1190, 1132, 1082, 1066, 1042, 1000, 964, 886, 838, 758, 698, 664.

MS (EI, 70 eV): *m/z* (%) = 261 (13), 260 (100), 246 (63), 216 (19), 214 (15), 188 (74), 186 (11), 156 (11), 142 (18).

HR-MS (EI, 70eV): [$C_{14}H_{19}NO_2Si$], calcd.: 261.1185; found: 261.1138.

2-(2-(1,3-Dioxan-2-yl)ethyl)quinoline (102l)



Following **TP4-A** 2-bromoquinoline (104 mg, 0.50 mmol, 1.0 equiv.) was coupled with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**101a**, 0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 115 mg, 0.47 mmol, 95%, colorless crystals.

m.p.: 54.8 – 56.7 °C

Purification: *i*-hexane:ethyl acetate = 7:3.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.03 (dd, *J* = 8.5, 1.8 Hz, 2H), 7.79 – 7.73 (m, 1H), 7.70 – 7.61 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 4.59 (t, *J* = 5.2 Hz, 1H), 4.10 (dd, *J* = 11.4, 4.9 Hz, 2H), 3.73 (td, *J* = 12.4, 2.5 Hz, 2H), 3.14 – 3.00 (m, 2H), 2.23 – 1.98 (m, 3H), 1.31 (ddt, *J* = 13.6, 3.1, 1.5 Hz, 1H).

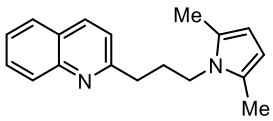
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 162.0, 148.0, 136.3, 129.4, 129.0, 127.5, 126.8, 125.8, 121.6, 101.6, 67.0, 34.8, 33.5, 25.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2971, 2922, 2856, 1732, 1618, 1601, 1563, 1505, 1469, 1444, 1426, 1407, 1380, 1292, 1247, 1213, 1198, 1144, 1082, 1055, 1044, 998, 964, 942, 922, 905, 886, 850, 822, 788, 766, 741.

MS (EI, 70 eV): *m/z* (%) = 242 (2), 158 (12), 156 (51), 144 (11), 143 (100), 128 (12).

HR-MS (EI, 70eV): [$C_{15}H_{16}NO_2$], calcd.: 242.1187; found: 242.1175 [M^+-H].

2-(3-(2,5-Dimethyl-1*H*-pyrrol-1-yl)propyl)quinoline (102m)



Following **TP4-A** 2-bromoquinoline (104 mg, 0.50 mmol, 1.0 equiv.) or 2-chloroquinoline (82 mg, 0.50 mmol, 1.0 equiv) were coupled with (3-(2,5-dimethyl-1*H*-pyrrol-1-yl)propyl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: using 2-bromoquinoline 112 mg, 0.42 mmol, 85%, yellow oil.

using 2-chloroquinoline 108 mg, 0.41 mmol, 82%, yellow oil.

Purification: *i*-hexane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.10 (t, J = 10.2 Hz, 2H), 7.81 (d, J = 8.1 Hz, 1H), 7.72 (t, J = 7.7 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 5.76 (s, 2H), 3.93 – 3.81 (m, 2H), 3.06 (t, J = 7.6 Hz, 2H), 2.22 (s, 8H).

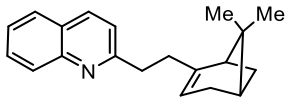
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.1, 136.8, 129.8, 128.5, 127.6, 127.4, 126.8, 126.1, 121.2, 121.2, 105.1, 43.2, 35.9, 30.3, 12.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932, 1619, 1600, 152, 1518, 1503, 1426, 1407, 1370, 1298, 1140, 1115, 1017, 974, 873, 826, 781, 743.

MS (EI, 70 eV): *m/z* (%) = 264 (5), 170 (24), 169 (19), 168 (13), 157 (12), 156 (100), 143 (54), 128 (12).

M**R-MS (EI, 70eV):** [$C_{18}H_{20}N_2$], calcd.:264.1626; found: 264.1620.

2-(2-((1*R*,4*R*)-5,5-Dimethylbicyclo[2.1.1]hex-2-en-2-yl)ethyl)quinoline (102n)



Following **TP4-A** 2-bromoquinoline (104 mg, 0.50 mmol, 1.0 equiv.) was coupled with (2-((1*R*,4*R*)-5,5-dimethylbicyclo[2.1.1]hex-2-en-2-yl)ethyl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 103 mg, 0.37 mmol, 75%, yellow oil.

Purification: *i*-hexane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.09 (d, *J* = 8.4 Hz, 2H), 7.78 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.69 (ddd, *J* = 8.3, 6.9, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 5.29 (tt, *J* = 3.0, 1.5 Hz, 1H), 3.13 – 3.00 (m, 2H), 2.47 (ddq, *J* = 10.0, 6.4, 1.8 Hz, 2H), 2.38 (dt, *J* = 8.5, 5.6 Hz, 1H), 2.29 – 2.18 (m, 2H), 2.15 (td, *J* = 5.6, 1.5 Hz, 1H), 2.08 (ttd, *J* = 5.8, 2.8, 1.2 Hz, 1H), 1.28 (s, 3H), 1.16 (d, *J* = 8.5 Hz, 1H), 0.84 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 162.7, 147.5, 136.9, 129.8, 128.5, 127.6, 126.9, 126.1, 126.1, 121.5, 116.8, 45.9, 40.9, 38.2, 37.0, 37.0, 31.8, 31.4, 26.4, 21.4.

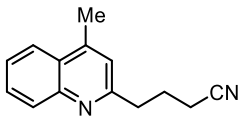
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2914.5, 1601.4, 1503.9, 1427.4, 1364.6, 1219.8, 904.6, 830.1, 731.6.

MS (EI, 70 eV): *m/z* (%) = 277 (5), 276 (9), 262 (5), 236 (8), 234 (18), 209 (15), 208 (97), 206 (8) 194 (13), 193 (8), 180 (15), 167 (8), 156 (12), 144 (11), 143 (100), 142 (6), 128 (8).

HR-MS (EI, 70eV): [$C_{20}H_{22}N$], calcd.: 276.1752; ; found: 276.1748.

Optical rotation: $[\alpha]_D^{20} =$ - 37 (c 1.36, $CHCl_3$).

4-(4-Methylquinolin-2-yl)butanenitrile (102o)



Following **TP4-A** using $CoCl_2$ (13 mg, 0.1 mmol, 20 mol%) and bipyridine (31 mg, 0.2 mmol, 40 mol%), 2-chloro-4-methylquinoline (89 mg, 0.50 mmol, 1.0 equiv.) was coupled with (3-cyanopropyl)zinc bromide (0.95 mmol, 1.9 equiv.) prepared according to **TP3** from the corresponding bromide.

Isolated yield: 73 mg, 0.35 mmol, 70%, brown oil.

Purification: *i*-hexane:ethyl acetate = 7:3.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.07 – 8.00 (m, 1H), 7.97 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.70 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.15 (d, *J* = 1.2 Hz, 1H), 3.08 (t, *J* = 7.4 Hz, 2H), 2.69 (d, *J* = 0.9 Hz, 3H), 2.48 (t, *J* = 7.2 Hz, 2H), 2.32 – 2.15 (m, 2H).

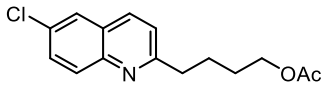
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 159.7, 147.8, 145.1, 129.5, 129.5, 127.1, 126.0, 123.8, 122.3, 119.81, 37.1, 25.0, 18.9, 16.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2931, 2246, 1602, 1562, 1508, 1448, 1412, 1380, 1346, 1159, 1123, 1026, 953, 878, 865, 757.

MS (EI, 70 eV): *m/z* (%) = 210 (3), 170 (24), 158 (12), 157 (100), 156 (10), 142 (7), 115 (18).

HR-MS (EI, 70eV): [$C_{14}H_{14}N_2$], calcd.: 210.1157; found: 210.1151.

4-(6-Chloroquinolin-2-yl)butyl acetate (102p)



Following **TP4-A** using $CoCl_2$ (13 mg, 0.1 mmol, 20 mol%) and bipyridine (31 mg, 0.2 mmol, 40 mol%), 2,6-dichloroquinoline (99 mg, 0.50 mmol, 1.0 equiv.) was coupled with (4-acetoxybutyl)zinc bromide (0.95 mmol, 1.9 equiv.) prepared according to **TP3** from the corresponding bromide.

Isolated yield: 81 mg, 0.29 mmol, 58%, yellow oil.

Purification: *i*-hexane:ethyl acetate = 7:3 to 6:4.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.97 (t, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.61 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 4.10 (t, J = 6.5 Hz, 2H), 3.08 – 2.91 (m, 2H), 2.03 (s, 3H), 1.96 – 1.82 (m, 2H), 1.80 – 1.66 (m, 2H).

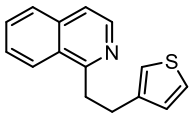
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 171.3, 162.7, 146.3, 135.6, 131.6, 130.5, 130.4, 127.4, 126.3, 122.3, 64.4, 38.7, 28.5, 26.3, 2.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2933, 1733, 1599, 1558, 1490, 1462, 1388, 1365, 1303, 1237, 1188, 1118, 1073, 1039, 959, 921, 876, 831, 745, 717, 683.

MS (EI, 70 eV): *m/z* (%) = 234 (9), 220 (11), 218 (33), 204 (19), 192 (13), 190 (40), 179 (33), 178 (11), 177 (100), 176 (13), 142 (13), 150 (12).

HR-MS (EI, 70eV): [$C_{13}H_{13}ClN$], calcd.: 218.0737; found: 218.0730 [M^+-OAc].

1-(2-(thiophen-3-yl)ethyl)isoquinoline (102q)



Following **TP4-A** 1-bromoisoquinoline (104 mg, 0.50 mmol, 1.0 equiv.) was coupled with (2-(thiophen-3-yl)ethyl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 73 mg, 0.31 mmol, 61%, brown oil.

Purification: *i*-hexane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.46 (d, J = 5.9 Hz, 1H), 8.20 – 8.11 (m, 1H), 7.92 – 7.84 (m, 1H), 7.78 – 7.70 (m, 1H), 7.64 (dddd, J = 9.9, 8.4, 5.0, 2.7 Hz, 2H), 7.29 – 7.23 (m, 1H), 7.07 – 7.01 (m, 2H), 3.76 – 3.65 (m, 2H), 3.30 – 3.20 (m, 2H).

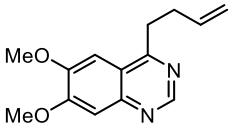
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.9, 136.8, 131.2, 128.4, 128.0, 128.0, 127.7, 127.0, 125.8, 125.8, 125.6, 120.9, 120.4, 35.6, 30.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3050, 2922, 2854, 1622, 1586, 1562, 1536, 1502, 1444, 1410, 1386, 1357, 1239, 1199, 1140, 1080, 1020, 979, 867, 822, 798, 774, 737, 684

MS (EI, 70 eV): *m/z* (%) = 241 (5), 240 (18), 239 (100), 238 (70), 224 (20), 223 (8), 206 (14), 204 (9), 156 (17), 129 (30), 114 (18), 97 (25).

HR-MS (EI, 70eV): [$C_{15}H_{13}NS$], calcd.: 239.0769; found: 239.0770.

4-(But-3-en-1-yl)-6,7-dimethoxyquinazoline (102r)



Following **TP4-A** 4-chloro-6,7-dimethoxyquinazoline (112 mg, 0.50 mmol, 1.0 equiv.) was coupled with but-3-en-1-

ylzinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 73 mg, 0.30 mmol, 60%, green solid.

Purification: *i*-hexane:ethyl acetate = 6:4.

m.p.: 66.9 – 69.1°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.02 (s, 1H), 7.45 (s, 1H), 7.21 (s, 1H), 5.88 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.10 – 4.90 (m, 1H), 4.02 (d, *J* = 13.4 Hz, 6H), 3.38 – 3.25 (m, 2H), 2.64 (tdt, *J* = 7.9, 6.6, 1.4 Hz, 2H).

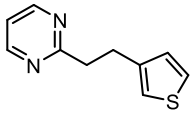
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 167.3, 156.2, 152.6, 150.6, 147.6, 137.3, 119.7, 115.9, 107.0, 101.9, 56.7, 56.4, 33.8, 32.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079, 2923, 1639, 1613, 1579, 1554, 1501, 1464, 1452, 1427, 1363, 1307, 1280, 1264, 1230, 1207, 1190, 1173, 1126, 1014, 995, 972, 890, 852, 828, 788, 760.

MS (EI, 70 eV): *m/z* (%) = 244 (61), 243 (89), 230 (13), 229 (100), 228 (10), 227 (10), 213 (12), 201 (13), 199 (11), 198 (11), 197 (16), 185 (16).

HR-MS (EI, 70eV): [$C_{14}H_{16}N_2O_2$], calcd.: 244.1212; found: 244.1209.

2-(2-(Thiophen-3-yl)ethyl)pyrimidine (102s)



Following **TP4-A** 2-bromopyrimidine (80 mg, 0.50 mmol, 1.0 equiv.) was coupled with (2-(thiophen-3-yl)ethyl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 65 mg, 0.34 mmol, 70%, yellow oil.

Purification: *i*-hexane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.69 (d, *J* = 4.9 Hz, 2H), 7.24 (dd, *J* = 4.6, 3.3 Hz, 1H), 7.16 (t, *J* = 4.9 Hz, 1H), 7.01 – 6.95 (m, 2H), 3.37 – 3.26 (m, 2H), 3.20 (ddd, *J* = 8.3, 6.2, 1.1 Hz, 2H).

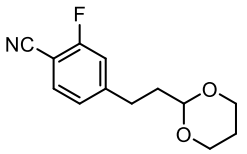
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 170.1, 157.1, 141.4, 128.3, 125.6, 120.8, 118.9, 39.9, 29.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1566, 1426, 1232, 907, 797, 731

MS (EI, 70 eV): *m/z* (%) = 191 (11), 190 (100), 189 (36), 175 (12), 157 (16), 145 (7), 107 (9), 98 (5), 97 (94), 84 (12), 80 (10), 53 (6), 45 (11).

HR-MS (EI, 70eV): [$C_{10}H_{10}N_2S$], calcd.: 190.0565; found: 190.559.

4-(2-(1,3-Dioxan-2-yl)ethyl)-2-fluorobenzonitrile (102t)



Following **TP4-A** 4-bromo-2-fluorobenzonitrile (100 mg, 0.50 mmol, 1.0 equiv.) was coupled with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**101a**, 0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 77 mg, 0.33 mmol, 66%, colorless oil.

Purification: *i*-hexane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.51 (dd, *J* = 7.9, 6.7 Hz, 1H), 7.11 – 7.00 (m, 2H), 4.50 (t, *J* = 5.0 Hz, 1H), 4.10 (ddt, *J* = 10.6, 5.1, 1.4 Hz, 2H), 3.79 – 3.67 (m, 2H), 2.83 – 2.72 (m, 2H), 2.07 (dtt, *J* = 13.6, 12.5, 5.0 Hz, 1H), 1.96 – 1.82 (m, 2H), 1.35 (dtt, *J* = 13.6, 2.7, 1.4 Hz, 1H).

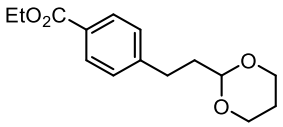
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 163.3 (d, *J* = 258.6 Hz), 151.0 (d, *J* = 7.7 Hz), 133.4, 125.1 (d, *J* = 3.2 Hz), 116.5 (d, *J* = 19.0 Hz), 114.4, 100.8 , 98.9 (d, *J* = 15.5 Hz), 67.0 , 35.8 , 30.2, 30.2, 25.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2965, 2936, 2863, 2232, 1980, 162, 1569, 1502, 1458, 1430, 1404, 1377, 1283, 1270, 1260, 1248, 1236, 1220, 1190, 1145, 1129, 1113, 1081, 1046, 995, 962, 942, 925, 890, 850, 826, 7750, 744, 729.

MS (EI, 70 eV): *m/z* (%) = 235 (2), 234 (18), 176 (20), 148 (51), 135 (35), 134 (37), 114 813), 107 (11), 87 (100).

HR-MS (EI, 70eV): [$C_{13}H_{14}FNO_2$], calcd.: 235.1009; found: 235.1003.

Ethyl 4-(2-(1,3-dioxan-2-yl)ethyl)benzoate (102u)



Following **TP4-A** using $CoCl_2$ (13 mg, 0.1 mmol, 20 mol%) and bipyridine (31 mg, 0.2 mmol, 40 mol%), ethyl 4-iodobenzoate (138 mg, 0.50 mmol, 1.0 equiv.) was coupled with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**101a**, 0.95 mmol, 1.9 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield:108 mg, 0.41 mmol, 82%, colorless oil.

Purification: *i*-hexane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ =7.98 – 7.93 (m, 2H), 7.29 – 7.23 (m, 2H), 4.49 (t, *J* = 5.2 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.11 (ddt, *J* = 10.6, 5.0, 1.4 Hz, 2H), 3.81 – 3.66 (m, 2H), 2.82 – 2.71 (m, 2H), 2.09 (dtt, *J* = 13.5, 12.5, 5.0 Hz, 1H), 1.97 – 1.85 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.33 (dq, *J* = 2.4, 1.2 Hz, 1H).

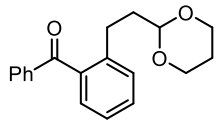
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.8, 147.3, 129.8, 128.6, 128.3, 101.3, 67.0, 60.9, 36.4, 30.2, 25.9, 14.50.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ =2963, 2849, 1712, 1611, 1367, 1308, 1271, 1177, 1146, 1132, 1101, 1038, 1021, 997, 972, 946, 926, 888, 852, 765, 705.

MS (EI, 70 eV): *m/z* (%) =263 (18), 219 (58), 218 (25), 177 (22), 161 (23), 133 (44), 115 (30), 114 (94), 105 (31), 103 (21), 91 (23), 87 (100).

HR-MS (EI, 70eV): [$C_{15}H_{20}O_4$], calcd.: 264.1362; found:264.1310.

(2-(2-(1,3-Dioxan-2-yl)ethyl)phenyl)(phenyl)methanone (102v)



Following **TP4-A** (2-chlorophenyl)(phenyl)methanone (108 mg, 0.50 mmol, 1.0 equiv.) was coupled with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**101a**, 0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 104 mg, 0.35 mmol, 70%, colorless oil.

Purification: *i*-hexane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.82 – 7.75 (m, 2H), 7.61 – 7.54 (m, 1H), 7.48 – 7.39 (m, 3H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.31 – 7.20 (m, 2H), 4.42 (t, *J* = 5.3 Hz, 1H), 4.11 – 3.97 (m, 2H), 3.67 (td, *J* = 12.4, 2.5 Hz, 2H), 2.83 – 2.69 (m, 2H), 2.03 (qt, *J* = 12.8, 5.0 Hz, 1H), 1.93 – 1.79 (m, 2H), 1.40 – 1.21 (m, 1H).

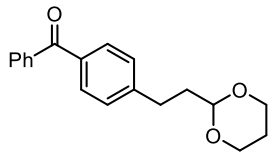
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 198.4, 140.9, 138.5, 137.8, 133.1, 130.4, 130.2, 128.7, 128.4, 125.3, 101.39, 66.8, 36.7, 27.6, 25.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961, 2850, 1661, 1597, 1580, 1484, 1448, 1403, 1378, 1314, 1265, 1239, 1196, 1178, 1145, 1132, 1104, 1078, 1048, 1028, 999, 970, 927, 886, 851, 801, 762, 700.

MS (EI, 70 eV): *m/z* (%) = 296 (2), 278 (1), 237 (2), 221 (1), 220 (4).

HR-MS (EI, 70eV): [$C_{19}H_{20}O_3$], calcd.: 296.1412; found: 296.1409.

(4-(2-(1,3-Dioxan-2-yl)ethyl)phenyl)(phenyl)methanone (102w)



Following **TP4-A** (4-bromophenyl)(phenyl)methanone (131 mg, 0.50 mmol, 1.0 equiv.) was coupled with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**101a**, 0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 126 mg, 0.43 mmol, 85%, colorless crystals.

Purification: *i*-hexane:ethyl acetate = 8:2.

m.p.: 68.6 – 70.5 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.81 – 7.77 (m, 2H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.58 (td, *J* = 7.4, 1.6 Hz, 1H), 7.52 – 7.41 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.53 (t, *J* = 5.1 Hz, 1H), 4.19 – 4.06 (m, 2H), 3.85 – 3.68 (m, 2H), 2.81 (dd, *J* = 9.3, 6.8 Hz, 2H), 2.20 – 2.01 (m, 1H), 2.01 – 1.86 (m, 2H), 1.35 (dq, *J* = 13.7, 1.9 Hz, 1H).

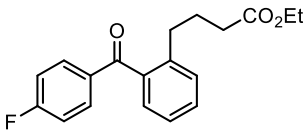
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.6, 147.1, 138.0, 135.4, 132.3, 130.5, 130.1, 128.5, 128.3, 101.3, 67.0, 36.4, 30.3, 25.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2914, 2846, 2048, 1981, 1646, 1603, 1576, 1443, 1415, 1404, 1382, 1317, 1306, 1278, 1238, 1186, 1143, 1131, 1077, 1040, 1000, 970, 940, 920, 886, 856, 786, 745, 699, 666.

MS (EI, 70 eV): *m/z* (%) = 296 (14), 237 (27), 220 (16), 167 (16), 161 (14), 114 (100), 105 (44), 87 (95), 77 (15).

HR-MS (EI, 70eV): [$C_{19}H_{20}O_3$], calcd.: 296.1412; found: 296.1407.

Ethyl 4-(2-(4-fluorobenzoyl)phenyl)butanoate (102x)



Following **TP4-A** using $CoCl_2$ (13 mg, 0.1 mmol, 20 mol%) and bipyridine (31 mg, 0.2 mmol, 40 mol%), (2-chlorophenyl)(4-fluorophenyl)methanone (117 mg, 0.50 mmol, 1.0 equiv.) was coupled with (4-ethoxy-4-oxobutyl)zinc bromide (0.95 mmol, 1.9 equiv.) prepared according to **TP3** from the corresponding bromide.

Isolated yield: 115 mg, 0.37 mmol, 73%, pale yellow oil.

Purification: *i*-hexane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.83 – 7.68 (m, 2H), 7.35 (dt, *J* = 7.7, 4.2 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.23 – 7.15 (m, 2H), 7.10 – 6.98 (m, 2H), 3.99 (q, *J* = 7.1 Hz, 2H), 2.69 – 2.47 (m, 2H), 2.18 (t, *J* = 7.4 Hz, 2H), 1.89 – 1.69 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H).

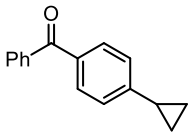
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.99, 173.42, 165.98 (d, *J* = 255.4 Hz), 140.66, 138.32, 134.25 (d, *J* = 2.9 Hz), 132.97 (d, *J* = 9.3 Hz), 130.51 (d, *J* = 7.9 Hz), 128.59, 125.66, 115.87, 115.65, 60.41, 33.92, 32.55, 26.86, 14.34.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2981, 1729, 1663, 1596, 1504, 1485, 1446, 1410, 1374, 1262, 1227, 1195, 1147, 1096, 1035, 930, 852, 810, 750, 688.

MS (EI, 70 eV): *m/z* (%) = 227 (25), 225 (249, 213 (32), 212 (100), 209 (10), 183 (15), 123 (23).

HR-MS (EI, 70eV): [$C_{19}H_{19}NO_3$], calcd.: 314.1318; found: 314.1314.

(4-Cyclopropylphenyl)(phenyl)methanone (102y)



Following **TP4-B** (4-bromophenyl)(phenyl)methanone (131 mg, 0.50 mmol, 1.0 equiv.) was coupled with cyclopropylzinc chloride (0.75 mmol, 1.5 equiv.) in THF prepared according to **TP2** from the corresponding bromide.

Isolated yield: 74 mg, 0.33 mmol, 67%, pale yellow oil.

Purification: *i*-hexane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.82 – 7.74 (m, 2H), 7.74 – 7.67 (m, 2H), 7.60 – 7.51 (m, 1H), 7.51 – 7.42 (m, 2H), 7.18 – 7.10 (m, 2H), 1.97 (tt, *J* = 8.3, 5.0 Hz, 1H), 1.12 – 1.02 (m, 2H), 0.84 – 0.74 (m, 2H).

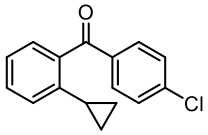
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.4, 149.9, 138.1, 134.8, 132.2, 130.5, 130.0, 128.3, 125.3, 15.8, 10.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3002, 2194, 1928, 1646, 1603, 1578, 1447, 1417, 1317, 1278, 1227, 1188, 1176, 1150, 1109, 1072, 1049, 1024, 1000, 971, 958, 971, 937, 922, 893, 840, 817, 791, 758, 741, 700, 675.

MS (EI, 70 eV): *m/z* (%) = 223 (18), 222 (69), 146 (10), 145 (100), 117 (9), 116 (8), 115 (28), 105 (49), 91 (12), 76 (33), 57 (6), 43 (10).

HR-MS (EI, 70eV): [$C_{16}H_{14}O$], calcd.: 222.1045; found: 222.1035.

(4-Chlorophenyl)(2-cyclopropylphenyl)methanone (102z)



Following **TP4-B** (2-chlorophenyl)(4-chlorophenyl)methanone (126 mg, 0.50 mmol, 1.0 equiv.) was coupled with cyclopropylzinc chloride (0.75 mmol, 1.5 equiv.) in THF prepared according to **TP2** from the corresponding bromide.

Isolated yield: 85 mg, 0.34 mmol, 68%, pale yellow oil.

Purification: *i*-hexane:ethyl acetate = 98:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.78 – 7.67 (m, 2H), 7.42 – 7.26 (m, 3H), 7.23 – 7.08 (m, 2H), 6.97 (dd, *J* = 7.9, 1.0 Hz, 1H), 1.81 (tt, *J* = 8.5, 5.2 Hz, 1H), 0.79 – 0.67 (m, 2H), 0.62 – 0.49 (m, 2H).

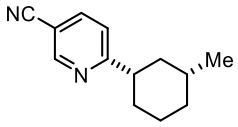
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 197.8, 142.1, 139.8, 139.4, 136.3, 131.6, 130.6, 128.9, 127.9, 125.4, 125.4, 13.8, 9.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3067, 3004, 1924, 1664, 1584, 1571, 1484, 1457, 1445, 1399, 1300, 1257, 1221, 1174, 1151, 1030, 1013, 951, 929, 897845, 822, 778, 752, 682, 656.

MS (EI, 70 eV): *m/z* (%) = 241 (10), 230 (32), 229 (15), 228 (100), 193 (41), 178 (8), 165 (23), 115 (12).

HR-MS (EI, 70eV): [$C_{16}H_{12}OCl$], calcd.: 255.0571; found: 255.0570 [M^+-H].

6-(3-Methylcyclohexyl)nicotinonitrile (102aa)



Following **TP4-B** 6-bromonicotinonitrile (91 mg, 0.50 mmol, 1.0 equiv.) was coupled with (3-methylcyclohexyl)zinc iodide (0.75 mmol, 1.5 equiv.) prepared according to **TP3** from the corresponding iodide.

Isolated yield: 80 mg, 0.40 mmol, 80%, dr = 91:1, colorless oil.

Purification: pentane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.79 (dd, *J* = 2.3, 0.9 Hz, 1H), 7.86 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.29 – 7.24 (m, 1H), 2.80 (tt, *J* = 12.0, 3.4 Hz, 1H), 1.98 – 1.79 (m, 3H), 1.75 (ddt, *J* = 12.9, 3.4, 1.8 Hz, 1H), 1.67 – 1.48 (m, 1H), 1.43 (tdd, *J* = 9.6, 4.8, 2.9 Hz, 2H), 1.28 – 1.11 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H).

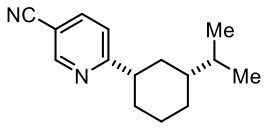
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 170.9, 152.1, 139.6, 121.4, 117.2, 107.2, 46.9, 41.0, 34.6, 32.8, 32.2, 26.2, 22.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2921, 2231, 2009, 1592, 1554, 1456, 1377, 1125, 1023, 839.

MS (EI, 70 eV): *m/z* (%) = 200 (39), 185 (54), 157 (100), 145 (32), 143 (30), 131 (84), 118 (44).

HR-MS (EI, 70eV): [$C_{13}H_{16}N_2$], calcd.: 200.1313; found: 200.1305.

6-(3-Isopropylcyclohexyl)nicotinonitrile (102ab)



Following **TP4-B** 6-bromonicotinonitrile (91 mg, 0.50 mmol, 1.0 equiv.) was coupled with (3-isopropylcyclohexyl)zinc iodide (0.75 mmol, 1.5 equiv.) prepared according to **TP3** from the corresponding iodide.

Isolated yield: 72 mg, 0.32 mmol, 63%, dr = 96:4, colorless crystals.

Purification: pentane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.80 (dd, *J* = 2.2, 0.9 Hz, 1H), 7.86 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.28 (dd, *J* = 8.2, 0.9 Hz, 1H), 2.77 (tt, *J* = 11.6, 3.4 Hz, 1H), 2.01 – 1.86 (m, 3H), 1.77 (ddq, *J* = 11.5, 4.9, 1.5 Hz, 1H), 1.56 – 1.36 (m, 3H), 1.31 – 1.19 (m, 2H), 1.02 (dddd, *J* = 15.0, 12.4, 8.9, 3.7 Hz, 1H), 0.88 (d, *J* = 3.3 Hz, 3H), 0.87 (d, *J* = 3.3 Hz, 3H).

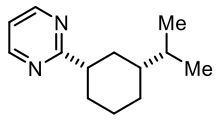
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 171.0, 152.0, 139.5, 121.4, 117.1, 107.1, 47.1, 43.9, 35.9, 33.0, 32.4, 29.1, 26.3, 19.8, 19.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927, 2854, 2231, 1592, 1478, 1462, 1447, 1384, 1368, 1023, 839.

MS (EI, 70 eV): *m/z* (%) = 228 (4), 185 (100), 157 (23), 145 (36), 143 (18), 131 (42), 118 (23).

HR-MS (EI, 70eV): [$C_{15}H_{20}N_2$], calcd.: 228.1626; found: 228.1621.

2-(3-Isopropylcyclohexyl)pyrimidine (102ac)



Following **TP4-B** 2-bromopyrimidine (80 mg, 0.50 mmol, 1.0 equiv.) was coupled with (3-isopropylcyclohexyl)zinc iodide (0.75 mmol, 1.5 equiv.) prepared according to **TP3** from the corresponding iodide.

Isolated yield: 53 mg, 0.26 mmol, 52%, dr = 94:6 colorless oil.

The *cis*-configuration of the product **102ac** was confirmed using 2D-NMR analysis, see: VI. Appendix, 1. Structure Determination using NMR-Experiments.)

Purification: pentane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.66 (d, *J* = 4.9 Hz, 2H), 7.09 (t, J = 4.9 Hz, 1H), 2.88 (tt, *J* = 11.9, 3.5 Hz, 1H), 1.98 (dddq, *J* = 10.8, 5.0, 3.4, 2.0 Hz, 2H), 1.90 (dp, J = 13.2, 3.2 Hz, 1H), 1.73 (dddd, *J* = 12.8, 4.8, 3.3, 1.6 Hz, 1H), 1.56 (ddd, *J* = 13.3, 12.2, 3.5 Hz, 1H), 1.51 – 1.44 (m, 1H), 1.44 – 1.37 (m, 1H), 1.37 – 1.30 (m, 1H), 1.30 – 1.21 (m, 1H), 1.03 (tdd, *J* = 12.6, 11.2, 3.7 Hz, 1H),), 0.87 (d, *J* = 2.2 Hz, 3H), 0.86 (d, *J* = 2.2 Hz, 3H)

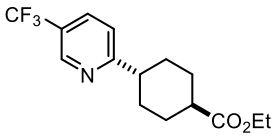
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.9, 157.1, 118.6, 48.0, 44.0, 35.4, 33.1, 32.0, 29.3, 26.4, 19.9, 19.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928, 2853, 1571, 1558, 1462, 1446, 1422, 1385, 1368, 799, 665.

MS (EI, 70 eV): *m/z* (%) = 204 (32), 162 (100), 133 (24), 121 (26), 119 (27), 107 (29).

HR-MS (EI, 70eV): [$C_{13}H_{20}N_2$], calcd.: 204.1626; found: 204.1621.

Ethyl-4-(5-(trifluoromethyl)pyridin-2-yl)cyclohexane-1-carboxylate (102ad)



Following **TP4-B** 2-bromo-5-(trifluoromethyl)pyridine (113 mg, 0.50 mmol, 1.0 equiv.) was coupled with (4-(ethoxycarbonyl)cyclohexyl)zinc iodide (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding iodide.

Isolated yield: 77 mg, 0.26 mmol, 51%, dr = 80:20, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.72 (dq, *J* = 4.1, 2.5, 1.8 Hz, 1H), 7.77 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.26 – 7.18 (m, 1H), 4.17 – 4.01 (m, 2H), 2.71 (dddd, *J* = 28.0, 24.6, 11.4, 7.3 Hz, 1H), 2.37 – 2.23 (m, 1H), 2.23 – 1.88 (m, 4H), 1.87 – 1.61 (m, 1H), 1.60 – 1.48 (m, 3H), 1.21 (td, *J* = 7.1, 1.8 Hz, 3H).

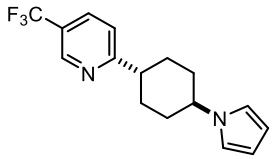
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 175.9, 169.50 (d, *J* = 1.8 Hz), 146.25 (q, *J* = 4.1 Hz), 133.69 (q, *J* = 3.5 Hz)124.5 (q, *J* = 32.9 Hz), 123.8 (q, *J* = 272.0 Hz), 121.1, 60.4, 45.7, 42.9, 31.7, 28.9, 14.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2936, 2862, 1728, 1606, 1452, 1393, 1377, 1326, 1161, 1128, 1081, 1041, 1015, 904, 842, 728.

MS (EI, 70 eV): *m/z* (%) = 301 (14) 228 (100), 200 (48), 198 (30), 186 (30), 174 (53), 161 (259).

HR-MS (EI, 70eV): [$C_{15}H_{18}F_3NO_2$], calcd.: 301.1290; found: 301.1283.

2-(4-(1*H*-Pyrrol-1-yl)cyclohexyl)-5-(trifluoromethyl)pyridine (102ae)



Following **TP4-B** 2-bromo-5-(trifluoromethyl)pyridine (113 mg, 0.50 mmol, 1.0 equiv.) was coupled with (4-(1*H*-pyrrol-1-yl)cyclohexyl)zinc iodide (0.75 mmol, 1.5 equiv.) prepared according to **TP3** from the corresponding iodide.

Isolated yield: 79 mg, 0.27 mmol, 54%, dr = 98:2, colorless crystals.

The trans-configuration of **102ae** was confirmed using X-ray structure analysis, see: VI. Appendix, 3. Single Crystal X-Ray Diffraction Studies.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 130.8 – 132.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.88 – 8.76 (m, 1H), 7.87 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 6.78 (t, J = 2.1 Hz, 2H), 6.18 (t, *J* = 2.1 Hz, 2H), 4.05 – 3.90 (m, 1H), 2.88 (tt, *J* = 11.4, 3.6 Hz, 1H), 2.38 – 2.25 (m, 2H), 2.14 (dt, *J* = 13.3, 2.7 Hz, 2H), 1.96 – 1.70 (m, 4H).

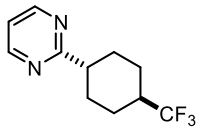
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 169.0 (d, *J* = 1.5 Hz), 146.4 (q, *J* = 4.1 Hz), 133.8 (q, J = 3.6 Hz), 123.8 (q, *J* = 272.0 Hz), 124.6 (q, *J* = 32.9 Hz), 121.2, 118.6, 107.8, 58.1, 45.5, 34.3, 31.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2940, 2860, 1706, 1605, 1571, 1489, 1452, 1399, 1366, 1325, 1272, 1259, 1243, 1197, 1161, 1128, 1097, 1079, 1013, 957, 907, 813, 766, 722, 674.

MS (EI, 70 eV): *m/z* (%) = 295 (18), 294 (100), 165 (179, 118 8249, 212 (16), 200 (16), 198 (46), 186 (19), 174 (46), 161 (19).

HR-MS (EI, 70eV): [$C_{16}H_{17}F_3N_2$], calcd.: 294.1344; found: 294.1339.

2-(4-(Trifluoromethyl)cyclohexyl)pyrimidine (102af)



Following **TP4-B** 2-bromopyrimidine (80 mg, 0.50 mmol, 1.0 equiv.) was coupled with (3-(trifluoromethyl)cyclohexyl)zinc iodide (0.75 mmol, 1.5 equiv.) prepared according to **TP3** from the corresponding iodide.

Isolated yield: 84 mg, 0.37 mmol, 73%, dr = 98:2, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.67 (d, *J* = 4.9 Hz, 2H), 7.13 (t, *J* = 4.9 Hz, 1H), 2.87 (tt, *J* = 12.2, 3.6 Hz, 1H), 2.27 – 2.03 (m, 5H), 1.75 – 1.57 (m, 2H), 1.56 – 1.41 (m, 2H).

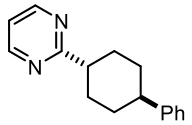
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 173.4, 157.1, 127.8 (q, *J* = 278.5 Hz), 118.8, 46.4, 41.4 (q, *J* = 26.5 Hz), 30.1, 24.8 (q, *J* = 2.6 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2950, 2926, 2858, 1571, 1558, 1451, 1438, 1423, 1390, 1370, 1337, 1271, 1249, 1220, 170, 1134, 1116, 1092, 1078, 1069, 1027, 1003, 988, 966, 902, 884, 848, 817, 805, 700.

MS (EI, 70 eV): *m/z* (%) = 231 (12), 230 (100), 229 (32), 169 (27), 133 (64), 119 (83), 107 (80), 94 (56).

HR-MS (EI, 70eV): [$C_{11}H_{13}F_3N_2$], calcd.: 230.1031; found: 230.1025.

2-(4-Phenylcyclohexyl)pyrimidine (102ag)



Following **TP4-B** 2-bromopyrimidine (80 mg, 0.50 mmol, 1.0 equiv.) was coupled with (4-phenylcyclohexyl)zinc iodide (0.75 mmol, 1.5 equiv.) prepared according to **TP3** from the corresponding iodide.

Isolated yield: 80 mg, 0.34 mmol, 67%, dr = 96:4, colorless crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 117.8 – 119.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.68 (d, *J* = 4.9 Hz, 2H), 7.36 – 7.22 (m, 4H), 7.22 – 7.15 (m, 1H), 7.12 (t, *J* = 4.9 Hz, 1H), 2.97 (tt, *J* = 12.1, 3.6 Hz, 1H), 2.63 (tt, *J* = 12.1, 3.5 Hz, 1H), 2.18 (dtd, *J* = 15.1, 4.6, 4.2, 2.2 Hz, 2H), 2.06 (dtd, *J* = 15.1, 4.9, 4.2, 2.4 Hz, 2H), 1.95 – 1.73 (m, 2H), 1.73 – 1.53 (m, 2H).

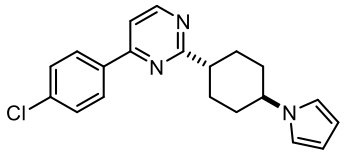
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.5, 157.1, 147.4, 128.5, 127.0, 126.1, 118.7, 47.2, 43.9, 34.0, 32.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925, 2867, 1987, 1572, 1561, 1464, 1427, 1382, 1375, 1168, 1024, 960, 832, 798.

MS (EI, 70 eV): *m/z* (%) = 238 (100), 133 (38), 121 (52), 119 (78), 115 (32), 107 898), 91 (38).

HR-MS (EI, 70eV): [$C_{16}H_{18}N_2$], calcd.: 238.1470; found: 238.1462.

2-(4-(1*H*-Pyrrol-1-yl)cyclohexyl)-4-(4-chlorophenyl)pyrimidine (102ah)



Following **TP4-B** 2-bromo-4-(4-chlorophenyl)pyrimidine (135 mg, 0.50 mmol, 1.0 equiv.) was coupled with (4-(1*H*-pyrrol-1-yl)cyclohexyl)zinc iodide (0.75 mmol, 1.5 equiv.) prepared according to **TP3** from the corresponding iodide.

Isolated yield: 108 mg, 0.32 mmol, 64%, dr = 91:9, colorless crystals.

Purification: pentane:ethyl acetate = 8:2.

m.p.: 104.0 – 105.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.43 (d, *J* = 5.2 Hz, 1H), 7.92 – 7.85 (m, 2H), 7.34 – 7.28 (m, 2H), 6.77 (d, *J* = 5.3 Hz, 1H), 6.73 (t, *J* = 2.1 Hz, 2H), 6.53 (t, *J* = 2.1 Hz, 2H), 3.61 (tt, *J* = 11.9, 3.9 Hz, 1H), 3.05 (tt, *J* = 12.1, 3.6 Hz, 1H), 2.33 – 2.18 (m, 2H), 2.13 – 1.98 (m, 2H), 1.98 – 1.82 (m, 2H), 1.74 – 1.52 (m, 2H).

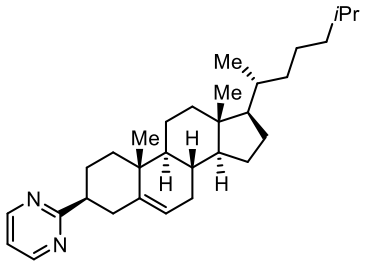
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.2, 162.2, 158.0, 137.2, 135.8, 129.3, 128.7, 118.5, 113.8, 108.3, 58.1, 46.6, 34.4, 31.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929, 2856, 1706, 1597, 1568, 1545, 1491, 1462, 1436, 1409, 1384, 1315, 1294, 1274, 1259, 1089, 1065, 1013, 962, 907, 822, 801,774, 721.

MS (EI, 70 eV): *m/z* (%) = 339 (39), 338 (27), 227 (100), 243 (229), 217 (59), 137 (26), 95 (24), 93 (27), 67 8339, 43 (31), 40 (22).

HR-MS (EI, 70eV): [$C_{20}H_{20}ClN_3$], calcd.: 337.1346; found: 337.1334.

2-((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)pyrimidine (102ai)



Following **TP4-B** 2-bromopyrimidine (80 mg, 0.50 mmol, 1.0 equiv.) was coupled with ((8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-

2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)zinc chloride (0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding chloride.

Isolated yield: 174 mg, 0.39 mmol, 78%, dr = 98:2, colorless crystals.

Purification: pentane:ethyl acetate = 95:5.

m.p.: 125.2 – 127.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.68 (d, *J* = 4.9 Hz, 2H), 7.12 (t, *J* = 4.9 Hz, 1H), 5.39 (dt, *J* = 5.3, 1.9 Hz, 1H), 2.89 (ddt, *J* = 15.9, 8.8, 4.0 Hz, 1H), 2.66 (tq, *J* = 13.2, 2.6 Hz, 1H), 2.37 – 2.25 (m, 1H), 2.10 – 1.78 (m, 7H), 1.65 – 1.44 (m, 8H), 1.44 – 1.19 (m, 6H), 1.21 – 0.95 (m, 8H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 1.9 Hz, 3H), 0.86 (d, *J* = 1.9 Hz, 3H), 0.69 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.1, 157.0, 142.3, 120.5, 118.6, 56.8, 56.2, 50.3, 48.8, 42.3, 39.8, 39.5, 39.4, 37.8, 37.0, 36.2, 35.8, 32.0, 31.9, 28.3, 28.0, 24.3, 23.9, 22.9, 22.6, 21.0, 19.7, 18.7, 11.9.

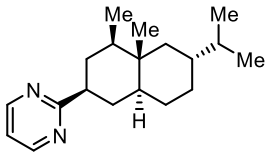
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2937, 2867, 1572, 1561, 1463, 1427, 1382, 1375, 1333, 1167, 1062, 1024, 960, 833, 797, 670.

MS (EI, 70 eV): *m/z* (%) = 448 (566), 107 (39), 94 (22), 89 (41), 55 (48), 42 (100), 41 (49).

HR-MS (EI, 70eV): [$C_{31}H_{48}N_2$], calcd.: 448.3817; found: 448.3820.

Optical rotation: $[\alpha]_D^{20} = 1$ (c 0.98, $CHCl_3$).

2-((2*S*,4R,4*aS*,6*R*)-6-Isopropyl-4,4*a*-dimethyldecahydronaphthalen-2-yl)pyrimidine (102aj)



Following **TP4-B** 2-bromopyrimidine (80 mg, 0.50 mmol, 1.0 equiv.) was coupled with ((4*R*,4*aS*,6*R*)-6-isopropyl-4,4*a*-dimethyldecahydronaphthalen-2-yl)zinc iodide (0.75 mmol, 1.5 equiv.) prepared according to **TP3** from the corresponding iodide.

Isolated yield: 149 mg, 0.26 mmol, 52%, dr = 98:2 colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.66 (d, *J* = 4.9 Hz, 2H), 7.09 (t, *J* = 4.9 Hz, 1H), 3.02 (tt, *J* = 11.9, 4.7 Hz, 1H), 1.80 – 1.52 (m, 6H), 1.46 – 1.13 (m, 6H), 0.96 (qd, *J* = 12.2, 5.1 Hz, 1H), 0.87 – 0.80 (m, 9H), 0.77 (s, 3H), 0.66 (t, *J* = 12.4 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.5, 157.1, 118.5, 47.8, 46.3, 43.3, 42.3, 39.0, 36.5, 36.1, 34.0, 33.3, 30.0, 29.8, 29.0, 20.2, 19.7, 15.2, 11.8.

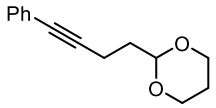
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2917, 2857, 1571, 1558, 1464, 1422, 1384, 1366, 1119, 963, 890, 780, 668.

MS (EI, 70 eV): *m/z* (%) = 287 (20), 286 (96), 243 (32), 159 (29), 147 (75), 145 (44), 135 (39), 133 (64), 131 (34), 119 (67), 107 (100), 94 (64).

HR-MS (EI, 70eV): [$C_{19}H_{30}N_2$], calcd.: 286.2409; found: 286.2404.

Optical rotation: $[\alpha]_D^{20} = 22$ (c 0.87, $CHCl_3$).

2-(4-Phenylbut-3-yn-1-yl)-1,3-dioxane (104a)



Following **TP4-A** (bromoethynyl)benzene (**103a**, 91 mg, 0.50 mmol, 1.0 equiv.) was coupled with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**101a**, 0.75 mmol, 1.5 equiv.) prepared according to **TP2** from the corresponding bromide.

Isolated yield: 59 mg, 0.28 mmol, 55%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.45 – 7.33 (m, 2H), 7.34 – 7.21 (m, 3H), 4.71 (t, *J* = 5.2 Hz, 1H), 4.12 (ddt, *J* = 10.5, 5.0, 1.4 Hz, 2H), 3.90 – 3.69 (m, 2H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.09 (dtt, *J* = 13.4, 12.4, 5.0 Hz, 1H), 1.89 (td, *J* = 7.3, 5.2 Hz, 2H), 1.36 (dtt, *J* = 13.5, 2.7, 1.4 Hz, 1H).

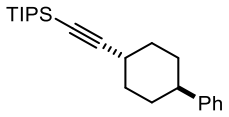
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 131.7, 128.3, 127.7, 124.0, 101.0, 89.5, 80.8, 67.1, 34.3, 26.0, 14.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2965, 2851, 1598, 1490, 1469, 1442, 1430, 1406, 1379, 1286, 1243, 1218, 1202, 1132, 1085, 1061, 1047, 1007, 971, 960, 936, 922, 882, 789, 755, 691.

MS (EI, 70 eV): *m/z* (%) = 216 (9), 215 (22), 158 (14), 157 (35), 130 (22), 129 (100), 128 (58), 115 (53).

HR-MS (EI, 70eV): [$C_{14}H_{16}O_2$], calcd.: 216.1150; found: 216.1148.

Triisopropyl((4-phenylcyclohexyl)ethynyl)silane (104b)



Following **TP4-B** (bromoethynyl)triisopropylsilane (**103b**, 131 mg, 0.50 mmol, 1.0 equiv.) was coupled with (4-phenylcyclohexyl)zinc iodide (0.75 mmol, 1.5 equiv.) prepared according to **TP3** from the corresponding iodide.

Isolated yield: 92 mg, 0.27 mmol, 54 %, dr = 99:1 colorless oil.

Purification: pentane.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.25 – 7.17 (m, 2H), 7.16 – 7.08 (m, 3H), 2.44 (tt, *J* = 11.6, 3.5 Hz, 1H), 2.26 (tt, *J* = 11.7, 3.7 Hz, 1H), 2.13 – 1.99 (m, 2H), 1.83 (dt, *J* = 12.2, 2.5 Hz, 2H), 1.58 – 1.30 (m, 4H), 1.00 (d, *J* = 5.1 Hz, 21H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 147.3, 128.5, 126.9, 126.2, 113.7, 79.3, 43.7, 33.8, 33.7, 30.5, 18.8, 11.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938, 2892, 2863, 2173, 1498, 1463, 1449, 1382, 1298, 1073, 1018, 882, 754, 697, 686, 671, 657.

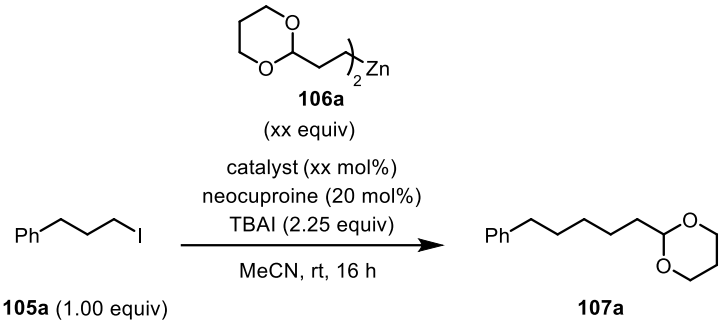
MS (EI, 70 eV): *m/z* (%) = 298 (25), 297 (100), 269 (10), 241 (9), 227 (7), 120 (8), 91 (9), 59 (14).

HR-MS (EI, 70eV): [$C_{23}H_{36}Si$], calcd.: 340.2586; found: 340.2583.

3. Cobalt-Catalyzed Csp^3-Csp^3 Cross-Coupling of Functionalized Alkylzinc Reagents with Alkyl Iodides

3.1 Optimization of the Reaction Conditions

Table 12: Further optimization of the reaction conditions.

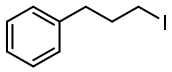


Entry	Cobalt salt	$CoCl_2$ [mol%]	Amount of **106a** [equiv]	GC-Yield[a] of **107a** [%]
1	**$CoCl_2$**	**20**	**0.75**	74
2	$CoBr_2$	20	0.75	73
3	$Co(acac)_2$	20	0.75	74
4	$CoCl_2$	10	0.75	68
5	$CoCl_2$	30	0.75	77
6	$CoCl_2$	20	0.6	71
7	$CoCl_2$	20	0.85	76

[a] Tetradecane ($C_{14}H_{30}$) was used as internal standard.

3.2 Preparation of Starting Materials

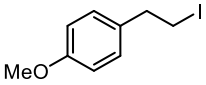
(3-iodopropyl)benzene (105a)[143]



The title compound was prepared according to literature procedure from (3-bromopropyl)benzene. The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.34 – 7.27 (m, 2H), 7.21 (td, *J* = 6.8, 1.6 Hz, 3H), 3.18 (t, *J* = 6.8 Hz, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.21 – 2.08 (m, 2H).

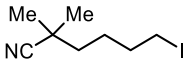
1-(2-Iodoethyl)-4-methoxybenzene[144]



The title compound was prepared according to literature procedure from 1-(2-chloroethyl)-4-methoxybenzene. The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.15 – 7.05 (m, 2H), 6.91 – 6.80 (m, 2H), 3.80 (s, 3H), 3.32 (t, *J* = 7.8 Hz, 2H), 3.12 (t, *J* = 7.8 Hz, 2H).

6-Iodo-2,2-dimethylhexanenitrile (105i)[81b]

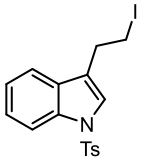


The title compound was prepared according to literature procedure from 6-hydroxy-2,2-dimethylhexanenitrile. The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.20 (t, *J* = 6.9 Hz, 2H), 1.91 – 1.81 (m, 2H), 1.66 – 1.49 (m, 4H), 1.35 (s, 6H).

[143]X. Wang, X. Ji, C. Shao, Y. Zhanga, Y. Zhang *Org. Biomol. Chem*. **2017**,*15*, 5616-5624.
[144]Q. Liu, J. Hong, B. Sun, G. Bai, Feng Li, G. Liu, Y. Yang, F. Mo *Org. Lett.* **2019** *21*, 6597-6602.

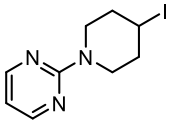
3-(2-Iodoethyl)-1-tosyl-1*H*-indole[145]



The title compound was prepared according to literature procedure from 2-(1*H*-indol-3-yl)ethan-1-ol. The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.99 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.45 (dt, *J* = 6.5, 1.0 Hz, 2H), 7.32 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.25 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.23 – 7.17 (m, 2H), 3.41 (t, *J* = 7.5 Hz, 2H), 3.24 (t, *J* = 7.5 Hz, 2H), 2.32 (s, 3H).

2-(4-Iodopiperidin-1-yl)pyrimidine (105d)



The title compound was prepared from 1-(pyrimidin-2-yl)piperidin-4-ol, which was prepared according to literature procedure.[146]

Triphenylphosphine (2.88 g, 11 mmol, 1.1 equiv) and imidazole (2.04 g, 30 mmol, 3.0 equiv) were dissolved in dichloromethane (33 mL, 0.3 M to the corresponding alcohol) and cooled to 0 °C. Iodine (2.79 g, 11 mmol, 1.1 equiv) was added over 15 min and 1-(pyrimidin-2-yl)piperidin-4-ol (1.79 g, 10 mmol, 1.0 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred overnight. Saturated aqueous sodium thiosulfate solution (30 mL) was added and the mixture was extracted with dichloromethane (3 x 20 mL). After solvent evaporation, the crude product was subjected to column chromatography with *i*-hexane and ethyl acetate (9:1) as eluent. 2-(4-Iodopiperidin-1-yl)pyrimidine was obtained as a yellow oil (2.60 g, 9.0 mmol, 90% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.30 (d, *J* = 4.7 Hz, 2H), 6.48 (t, *J* = 4.7 Hz, 1H), 4.55 (tt, *J* = 6.9, 5.1 Hz, 1H), 4.13 – 4.04 (m, 2H), 3.63 (ddd, *J* = 13.7, 6.9, 4.7 Hz, 2H), 2.17 – 2.07 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.5, 157.9, 109.9, 44.3, 37.5, 28.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2947, 2850, 1582, 1545, 1491, 1443, 1390, 1356, 1304, 1271, 1258, 1218, 1165, 1083, 1060, 1011, 993, 976, 842, 846, 794, 779, 672.

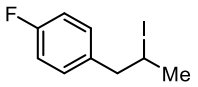
[145] S. Rezazadeh, V. Devannah, D. A. Watson *J.Am.Chem.Soc.* **2017**, *139*, 8110-8113.

[146] S. R. Katamreddy, A. J. Carpenter, C. E. Ammala, E. E. Boros, R. L. Brashear, C. P. Briscoe, S. R. Bullard, R. D. Caldwell, C. R. Conlee, D. K. Croom, S. M. Hart, D. O. Heyer, P. R. Johnson, J. A. Kashatus, D. J. Minick, G. E. Peckham, S. A. Ross, S. G. Roller, V. A. Samano, H. R. Sauls, S. M. Tadepalli, J. B. Thompson, Y. Xu, J. M. Way *J.Med.Chem.* **2012**, *55*, 10972-10994.

MS (EI, 70 eV): *m/z* (%) = 289 (6), 163 (10), 162 (100), 160 (6), 134 (29), 108 (69), 79 (6).

HR-MS (EI, 70eV): Calcd for $C_9H_{12}N_3I$ 289.0076; Found: 289.0071.

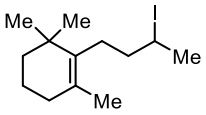
1-Fluoro-4-(2-iodopropyl)benzene[147]



The title compound was prepared according to literature procedure from 1-(4-fluorophenyl)propan-2-ol. The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.17 –7.12 (m, 2H), 7.04 –6.97 (m, 2H), 4.29 (h, *J* = 7.0, 1H), 3.22 (dd, *J* =14.2, 7.5, 1H), 3.03 (dd, *J* = 14.2, 7.1, 1H), 1.90 (d, *J* = 6.8, 3H).

2-(3-Iodobutyl)-1,3,3-trimethylcyclohex-1-ene (105f)



Dihydro-β-ionone was reduced according to literature procedure[148] by $NaBH_4$, affording 4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-ol. Triphenylphosphine (4.32 g, 16.5 mmol, 1.1 equiv) and imidazole (1.12 g, 16.5 mmol, 1.1 equiv) were dissolved in dichloromethane (50 mL, 0.3 M to the corresponding alcohol) and cooled to 0 °C. Iodine (4.19 g, 16.6 mmol, 1.1 equiv) was added over 15 min and 4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-ol (2.94 g, 15 mmol, 1.0 equiv) was added dropwise. The reaction mixture was warmed to room temperature and stirred overnight. Saturated aqueous sodium thiosulfate solution (30 mL) was added and the mixture was extracted with dichloromethane (3 x 20 mL). After solvent evaporation, the crude product was subjected to column chromatography with *i*hexane as eluent. 2-(3-Iodobutyl)-1,3,3-trimethylcyclohex-1-ene was obtained as a colorless oil (2.48 g, 8.1 mmol, 54% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.19 (dqd, *J* = 8.2, 6.9, 4.8 Hz, 1H), 2.20 (td, *J* = 12.9, 4.5 Hz, 1H), 2.03 (td, *J* = 12.9, 4.5 Hz, 1H), 1.94 (d, *J* = 6.9 Hz, 3H), 1.92 – 1.87 (m, 2H), 1.87 – 1.79 (m, 1H), 1.66 (ddt, *J* = 12.3, 9.8, 4.7 Hz, 1H), 1.59 (s, 3H), 1.58 – 1.50 (m, 2H), 1.44 – 1.37 (m, 2H), 0.99 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 136.0, 128.0, 43.0, 39.9, 35.2, 32.9, 31.3, 29.1, 29.0, 28.7, 28.7, 20.1, 19.62.

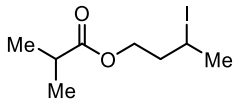
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2925, 2864, 1471, 1443, 1376, 1360, 1270, 1259, 1223, 1191, 1173, 1134, 1111, 1080, 1040, 991, 973, 902, 861, 833, 747, 704.

[147] M. S. Hofmayer, J. M. Hammann, G. Cahiez, P. Knochel *Synlett* **2018**, *29*, 65-67.
[148] P. J. Linares-Palomino, S. Salido, J. Altarejos, M. Nogueras, A. Sánchez *Flavour Fragr. J.* **2006**, *21*, 659-666.

MS (EI, 70 eV): *m/z* (%) = 291 (43), 163 (26), 137 (88), 123 (81), 121 (30), 109 (26), 107 (46), 95 (96), 93 (40), 91 (31), 81 (100), 79 (29), 67 (28).

HR-MS (EI, 70eV): Calcd for $C_{13}H_{23}I$ 306.0844; Found: 306.0838.

3-Iodobutyl isobutyrate



Butane-1,3-diol (2.23 mL, 25.0 mmol, 1.0 equiv), 4-(dimethylamino)pyridine (0.60 g, 5.00 mmol, 0.2 equiv) and triethylamine (5.05 g, 50.0 mmol, 2.0 equiv) were dissolved in DCM (50 mL) and cooled to 0 °C. Isobutyryl chloride (2.92 g, 27.5 mmol, 1.1 equiv) was dissolved in DCM (8 mL) and was added slowly to the cooled solution. The reaction mixture was warmed to room temperature and stirred overnight. The solution was washed twice with saturated $NaHCO_3$, the aqueous phase was extracted with DCM and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified *via* column chromatography using *i*hexane/EtOAc (7:3) to yield 3-hydroxybutyl isobutyrate (3.02 g, 18.8 mmol, 68%) as a colorless liquid. The analytical data is in full consistency with the data reported in the literature.[149]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.45 – 4.25 (m, 1H), 4.11 (dt, *J* = 11.2, 5.6 Hz, 1H), 3.95 – 3.76 (m, 1H), 2.53 (hd, *J* = 7.0, 1.8 Hz, 1H), 1.88 – 1.56 (m, 2H), 1.22 (dd, *J* = 6.3, 1.9 Hz, 3H), 1.19 – 1.12 (m, 6H).

Iodine (5.28, 20.6 mmol, 1.1 equiv) was dissolved in DCM (120 mL, 0.2 M with respect to the corresponding alcohol) and then cooled to 0 °C. Triphenylphosphine (5.50 g, 20.6 mmol, 1.1 equiv) was added slowly. The mixture was stirred for 1 h and cooled to -20 °C. Imidazole (1.36 g, 20.6 mmol, 1.1 equiv) was added and the mixture was stirred for 10 min. Then, 3-hydroxybutyl isobutyrate (3.02 g, 18.8 mmol, 1.0 equiv) was added and the solution was stirred overnight. The reaction mixture was washed with saturated aqueous sodium thiosulfate solution, brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was subjected to flash column chromatography using *i*hexane/EtOAc (8:2) to yield 3-iodobutyl isobutyrate as a colorless liquid (3.13 g, 11.6 mmol, 62%).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.24 (tdd, *J* = 9.3, 7.6, 5.0 Hz, 2H), 4.10 (ddd, *J* = 11.2, 7.9, 5.6 Hz, 1H), 2.54 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.12 (ddt, *J* = 14.7, 9.1, 5.3 Hz, 1H), 2.03 – 1.89 (m, 4H), 1.16 (dd, *J* = 7.0, 1.5 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 177.1, 64.1, 41.4, 34.1, 29.1, 24.4, 19.1, 19.1.

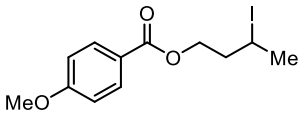
[149] Y. Toda, T. Sakamoto, Y. Komiyama, A. Kikuchi, H. Suga *ACS Catal.* **2017**, *7*, 6150-6154.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3412, 2973, 1732, 1469, 1388, 1344, 1191, 1154, 1125, 1076, 1048, 1021, 982, 929, 845, 794, 752.

MS (EI, 70 eV): *m/z* (%) = 143 (55), 89 (100), 71 (17), 55 (36), 43 (26).

HR-MS (EI, 70eV): [M+H$^+$] Calcd for $C_8H_{16}O_2I^+$ 271.0189; Found: 271.0189.

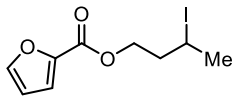
3-Iodobutyl 4-methoxybenzoate (105h)[150]



The title compound was prepared according to literature procedure from 3-hydroxybutyl 4-methoxybenzoate. The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.01 – 7.91 (m, 2H), 6.95 – 6.83 (m, 2H), 4.47 (dt, *J* = 11.2, 5.6 Hz, 1H), 4.30 (ddt, *J* = 11.8, 6.8, 4.2 Hz, 2H), 3.83 (s, 3H), 2.23 (ddt, *J* = 14.6, 9.1, 5.4 Hz, 1H), 2.09 (dddd, *J* = 15.0, 7.8, 5.9, 4.8 Hz, 1H), 1.99 (d, J = 6.9 Hz, 3H).

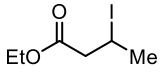
3-Iodobutyl furan-2-carboxylate[151]



The title compound was prepared according to literature procedure from 3-hydroxybutyl furan-2-carboxylate. The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.58 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.18 (dd, *J* = 3.6, 0.9 Hz, 1H), 6.51 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.50 (dt, *J* = 11.2, 5.6 Hz, 1H), 4.42 – 4.22 (m, 2H), 2.23 (ddt, *J* = 14.7, 9.2, 5.4 Hz, 1H), 2.10 (dddd, *J* = 15.1, 7.9, 6.0, 4.7 Hz, 1H), 1.99 (d, *J* = 6.9 Hz, 3H).

Ethyl 3-iodobutanoate[152]

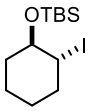


The title compound was prepared according to literature procedure from ethyl 3-hydroxybutanoate. The analytical data is in full consistency with the data reported in the literature.

[150] Y. Dai, F. Wu, Z. Zang, H. You, H. Gong *Chem. Eur. J.* **2012**, *18*, 808-812.
[151] Y. Chen, G. Ma, H. Gong *Org. Lett*. **2018**, *20*, 15, 4677-4680.
[152] C. W. Cheung, P. Ren, X. Hu, *Org. Lett.* **2014**, *16*, 2566-2569.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.45 (dp, *J* = 8.1, 6.8 Hz, 1H), 4.17 (qd, *J* = 7.1, 0.8 Hz, 2H), 2.99 (dd, *J* = 16.1, 8.0 Hz, 1H), 2.90 (dd, *J* = 16.1, 6.6 Hz, 1H), 1.94 (d, *J* = 6.9 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H).

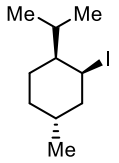
tert-Butyl((2-iodocyclohexyl)oxy)dimethylsilane[153]



The title compound was prepared according to literature procedure from cyclohexene and *N*-iodosuccinimide. The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.09 – 3.98 (m, 1H), 3.80 – 3.68 (m, 1H), 2.47 – 2.31 (m, 1H), 2.11 – 2.02 (m, 1H), 2.00 – 1.88 (m, 1H), 1.84 – 1.70 (m, 1H), 1.58 – 1.46 (m, 1H), 1.41 – 1.25 (m, 3H), 0.91 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H).

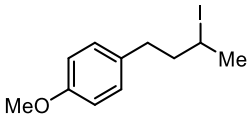
***(1S,2S,4R)*-2-Iodo-1-isopropyl-4-methylcyclohexane**[153]



The title compound was prepared according to literature procedure from (+)-menthol. The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.94 (p, J = 2.8 Hz, 1H), 2.38 (dtd, *J* = 14.5, 3.3, 2.2 Hz, 1H), 2.14 (tdd, *J* = 11.6, 5.7, 3.2 Hz, 1H), 1.92 (ttd, *J* = 12.7, 3.5, 2.2 Hz, 2H), 1.58 – 1.36 (m, 3H), 1.15 – 1.01 (m, 10H), 0.00 (ddt, *J* = 11.9, 9.1, 2.9 Hz, 1H).

1-(3-Iodobutyl)-4-methoxybenzene (105g)[151]

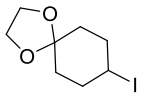


The title compound was prepared according to literature procedure from 4-(4-methoxyphenyl)butan-2-ol. The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.15 – 7.10 (m, 2H), 6.87 – 6.81 (m, 2H), 4.11 (dqd, *J* = 9.1, 6.8, 4.5 Hz, 1H), 3.79 (s, 3H), 2.79 (ddd, J = 13.9, 8.8, 5.2 Hz, 1H), 2.64 (ddd, *J* = 13.8, 8.8, 7.0 Hz, 1H), 2.13 (dtd, *J* = 14.2, 8.9, 5.2 Hz, 1H), 1.95 (d, *J* = 6.8 Hz, 3H), 1.84 (dddd, *J* = 14.6, 8.8, 7.1, 4.5 Hz, 1H).

[153] J. M. Hammann, D. Haas, C.- P. Tüllmann, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2016**, *18*, 4778-4781

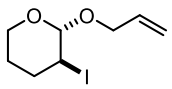
8-Iodo-1,4-dioxaspiro[4.5]decane (105h)[151]



The title compound was prepared according to literature procedure from 1,4-dioxaspiro[4.5]decan-8-ol. The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.47 – 4.36 (m, 1H), 4.01 – 3.87 (m, 4H), 2.13 (dtt, *J* = 15.7, 7.7, 4.2 Hz, 4H), 1.81 (ddd, *J* = 12.4, 7.7, 4.9 Hz, 2H), 1.61 (ddd, *J* = 13.1, 8.3, 4.6 Hz, 2H).

2-(Allyloxy)-3-iodotetrahydro-2*H*-pyran (105k)[154]



The title compound was prepared according to literature procedure from 3,4-dihydro-2*H*-pyran *N*-iodosuccinimide and prop-2-en-1-ol. The analytical data is in full consistency with the data reported in the literature.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.87 (dddd, *J* = 16.9, 10.3, 6.1, 5.2 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.15 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.62 (d, *J* = 5.3 Hz, 1H), 4.20 (ddt, *J* = 12.9, 5.3, 1.5 Hz, 1H), 4.05 (ddd, *J* = 8.1, 5.3, 4.3 Hz, 1H), 4.02 –3.94 (m, 1H), 3.94 –3.88 (m, 1H), 3.52 (ddd, *J* = 11.2, 7.4, 3.5 Hz, 1H), 2.32 (ddt, *J* = 14.9, 7.8, 4.1 Hz, 1H), 1.96 (dtd, *J* = 14.0, 8.3, 4.0 Hz, 1H), 1.71 (dtt, *J* = 14.2, 7.3, 3.8 Hz, 1H), 1.61–1.41 (m, 1H).

3.3 Preparation of Organometallic Reagents

Preparation of dialkylzinc reagents *via* magnesium insertion and subsequent transmetalation (TP1):[16a]

Dry LiCl (1.20 equiv.) was placed in a dry and argon flushed 50 mL *Schlenk*-tube equipped with a magnetic stirring bar and a septum and was dried over 5 min at 300 °C with a heat gun under high vacuum. Magnesium turnings (1.20 equiv.) were added and the flask was evacuated and back-filled with argon three times. Dry THF (1.0 M solution with respect to the alkyl halide) was added and the respective alkyl bromide (1.00 equiv). After the exothermic reaction started, the mixture was cooled with an ice bath. To monitor the progress of the insertion reaction, reaction aliquots quenched with iodine were analyzed by GC-analysis. After completion of the insertion, the concentrations of the magnesium reagent were

[154] C. Ollivier, P. Renaud. *J. Am. Chem. Soc*. **2001**, *123*, 4717-4727.

determined *via* titration with iodine (50 mg in 2 mL THF).[95] A $ZnCl_2$ solution (1.00 m in THF, 0.50 equiv.) was added at 0 °C and stirred at 0 °C for 15 min affording the corresponding dialkylzinc reagent.

Preparation of dialkylzinc reagents by magnesium insertion in the presence of $ZnCl_2$ (TP2):[17]

Dry LiCl (504 mg, 9.60 mmol, 1.50 equiv) was placed in a dry and argon flushed 50 mL *Schlenk*-tube equipped with a magnetic stirring bar and a septum and was dried over 5 min at 300 °C under high vacuum (0.1 mbar). Magnesium turnings (480 mg, 20.0 mmol, 2.50 equiv.) were added and the flask was evacuated and back-filled with argon three times. $ZnCl_2$ solution (4.00 mL, 1.00 m in THF, 0.50 equiv) was added and the respective alkyl halide (8.00 mmol, 1.00 equiv.) dissolved in THF (20.0 mL) was added *via* syringe. To monitor the progress of the insertion reaction, reaction aliquots quenched with iodine were analyzed by GC-analysis. After completion of the insertion, the black solution was filtered *via* syringe filter (30 mm with 0.45 µm glass fiber membrane) and transferred to a dry argon flushed *Schlenk*-tube. After reducing the volume to half the amount under reduced pressure, the concentrations of the dialkylzinc reagents were determined *via* titration with iodine (50 mg in 2 mL THF). [95]

3.4 Cobalt-Catalyzed Csp^3-Csp^3 Cross-Coupling of Functionalized Alkylzinc Reagents with Alkyl Iodides

Cobalt-Catalyzed Cross-Coupling of Functionalized Alkylzinc Reagents with Alkyl Iodides (TP3):

A dry and argon flushed *Schlenk*-tube, equipped with a magnetic stir bar and a septum was charged with dry $CoCl_2$ (13 mg, 0.100 mmol, 20 mol%), which was dried at 300 °C under high vacuum for 2 min prior to use.

A) For coupling of primary alkyl iodides:

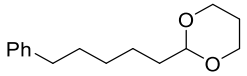
Tetrabutylammonium iodide (TBAI, 416 mg, 1.13 mmol, 2.25 equiv) the respective primary alkyl iodide (0.50 mmol, 1.00 equiv), dry MeCN (1.0 mL) and Me_4DACH (17 mg, 20 mol%) were added. Then a solution of the respective dialkylzinc reagent (0.375 mmol, 0.75 equiv.) was added *via* syringe at room temperature.

B) For coupling of secondary alkyl iodides:

Tetrabutylammonium iodide (TBAI, 416 mg, 1.13 mmol, 2.25 equiv) the respective secondary alkyl iodide (0.50 mmol, 1.00 equiv), neocuproine (21 mg, 20 mol%) and dry MeCN (1.0 mL) were added. Then a solution of the respective dialkylzinc reagent (0.375 mmol, 0.75 equiv.) was added *via* syringe at room temperature.

In both cases the reaction was stirred for 16 h at room temperature. The solvent was removed and the crude product was subjected to column chromatography purification on silica yielding the corresponding coupling product.

2-(5-Phenylpentyl)-1,3-dioxane (107a)



Following **TP3-A** (3-iodopropyl)benzene (**105a**, 123 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 84 mg, 0.360 mmol, 72%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.23 – 7.15 (m, 2H), 7.10 (m, 3H), 4.43 (t, *J* = 5.2 Hz, 1H), 4.03 (ddt, *J* = 10.5, 5.0, 1.4 Hz, 2H), 3.68 (ddt, *J* = 12.4, 10.5, 2.0 Hz, 2H), 2.53 (dd, *J* = 8.7, 6.9 Hz, 2H), 2.00 (dtt, *J* = 13.5, 12.5, 5.0 Hz, 1H), 1.63 – 1.47 (m, 4H), 1.43 – 1.20 (m, 5H).

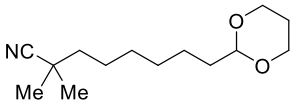
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 142.9, 128.5, 128.3, 125.7, 102.5, 67.0, 35.9, 35.3, 31.5, 29.2, 26.0, 23.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927, 2851, 1734, 1603, 1495, 1454, 1430, 1403, 1377, 1283, 1239, 1216, 1144, 1089, 1053, 1030, 995, 939, 925, 907, 892, 856, 796, 745, 697.

MS (EI, 70 eV): *m/z* (%) = 233 (16), 158 (100), 143 (41), 130 (42), 129 (48), 117 (25), 104 (32), 91 (57), 87 (86).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{15}H_{21}O_2^+$ 233.1536; Found: 233.1534.

8-(1,3-Dioxan-2-yl)-2,2-dimethyloctanenitrile (107b)



Following **TP3-A** 6-iodo-2,2-dimethylhexanenitrile (**105i**, 134 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 80 mg, 0.335 mmol, 67%, pale yellow oil.

Purification: pentane:ethyl acetate = 9:1 to 85:15.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.50 (t, *J* = 5.2 Hz, 1H), 4.09 (ddd, *J* = 12.0, 5.1, 1.5 Hz, 2H), 3.75 (tt, *J* = 10.6, 2.3 Hz, 2H), 2.07 (qt, *J* = 12.6, 5.0 Hz, 1H), 1.57 (dt, *J* = 8.8, 5.7 Hz, 2H), 1.47 (dd, *J* = 5.5, 3.3 Hz, 3H), 1.41 – 1.34 (m, 6H), 1.32 (m, 8H)

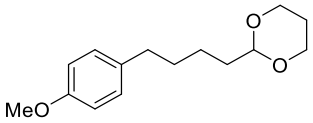
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 125.4, 102.4, 67.0, 41.2, 35.3, 32.5, 29.6, 29.4, 26.8, 26.0, 25.3, 24.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932, 2854, 1469, 1430, 1404, 1377, 1287, 1238, 1215, 1143, 1093, 1054, 997, 940, 893, 859, 834, 796, 726.

MS (EI, 70 eV): *m/z* (%) = 238 (12), 180 (5), 152 (4), 88 (5), 87 (100), 59 (9).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{14}H_{24}NO_2^+$ 238.1802; Found: 238.1801.

2-(4-(4-Methoxyphenyl)butyl)-1,3-dioxane (107c)



Following **TP3-A** 1-(2-iodoethyl)-4-methoxybenzene (131 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 76 mg, 0.304 mmol, 61 %, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.14 – 7.04 (m, 2H), 6.88 – 6.77 (m, 2H), 4.50 (t, *J* = 5.2 Hz, 1H), 4.09 (ddt, *J* = 10.5, 5.0, 1.4 Hz, 2H), 3.78 (s, 3H), 3.76 – 3.71 (m, 2H), 2.60 – 2.51 (m, 2H), 2.07 (dtt, *J* = 13.5, 12.5, 5.0 Hz, 1H), 1.67 – 1.53 (m, 4H), 1.48 – 1.37 (m, 2H), 1.33 (dtt, *J* = 13.4, 2.6, 1.4 Hz, 1H).

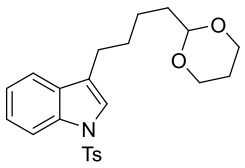
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 157.7, 134.8, 129.4, 113.8, 102.4, 67.0, 55.4, 35.3, 35.1, 31.8, 26.0, 23.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927, 2851, 1611, 1583, 1511, 1464, 1441, 1403, 1377, 1299, 1241, 1176, 1143, 1110, 1086, 1034, 992, 937, 893, 868, 830, 815, 749, 698.

MS (EI, 70 eV): *m/z* (%) = 249 (4), 175 (13), 174 (100), 173 (30), 159 (32), 147 (37), 143 (51), 132 (10), 121 (64), 91 (22), 87 (11).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{15}H_{21}O_3^+$ 249.1485; Found: 249.1483.

3-(4-(1,3-Dioxan-2-yl)butyl)-1-tosyl-1*H*-indole (107d)



Following **TP3-A** 3-(2-iodoethyl)-1-tosyl-1*H*-indole (213 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 130 mg, 0.315 mmol, 63 %, colorless oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.89 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.38 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.24 (d, *J* = 1.2 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.16 – 7.08 (m, 3H), 4.45 (t, *J* = 5.1 Hz, 1H), 4.04 (ddt, *J* = 10.6, 5.0, 1.3 Hz, 2H), 3.75 – 3.62 (m, 2H), 2.63 – 2.53 (m, 2H), 2.25 (s, 3H), 2.11 – 1.91 (m, 1H), 1.68 – 1.51 (m, 4H), 1.47 – 1.33 (m, 2H), 1.27 (dtt, *J* = 13.5, 2.6, 1.4 Hz, 1H).

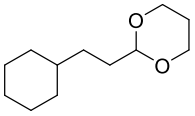
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 144.7, 135.5, 135.4, 131.3, 129.9, 126.9, 124.6, 123.5, 123.0, 122.7, 119.6, 113.9, 102.3, 67.1, 35.0, 28.8, 26.0, 24.9, 23.9, 21.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925, 2853, 1597, 1446, 1402, 1364, 1275, 1239, 1205, 1187, 1170, 1119, 1086, 1050, 1018, 975, 937, 893, 868, 844, 812, 744, 702, 666.

MS (EI, 70 eV): *m/z* (%) = 413 (7), 285 (19), 259 (17), 158 (100), 182 (16), 156 (43), 130 (23), 91 (17), 87 (25).

HR-MS (EI, 70eV): Calcd for $C_{23}H_{27}NO_4S$ 413.1661; Found: 413.1654.

2-(2-Cyclohexylethyl)-1,3-dioxane (107e)



Following **TP3-B** iodocyclohexane (105 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 75 mg, 0.381 mmol, 76%, pale yellow oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.46 (t, *J* = 5.2 Hz, 1H), 4.14 – 4.02 (m, 2H), 3.74 (ddt, *J* = 12.3, 10.4, 2.5 Hz, 2H), 2.06 (qt, *J* = 12.7, 5.0 Hz, 1H), 1.77 – 1.62 (m, 4H), 1.61 – 1.52 (m, 2H), 1.31 (dtt, *J* = 13.5, 2.6, 1.4 Hz, 1H), 1.28 – 1.04 (m, 7H), 0.85 (qd, *J* = 13.7, 12.5, 3.6 Hz, 2H).

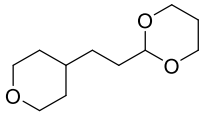
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 102.9, 67.0, 37.6, 33.3, 32.8, 31.6, 26.8, 26.5, 26.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920, 2847, 1448, 1403, 1376, 1237, 1144, 1098, 1074, 1054, 1001, 965, 1001, 965, 941, 926, 893, 863, 840.

MS (EI, 70 eV): *m/z* (%) = 197 (17), 121 (19), 93 (13), 87 (100), 81 (11), 79 (11), 59 (15).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{12}H_{21}O_2^+$ 197.1536; Found: 197.1534.

2-(2-(Tetrahydro-2*H*-pyran-4-yl)ethyl)-1,3-dioxane (107f)



Following **TP3-B** 4-iodotetrahydro-2*H*-pyran (**105b**, 106 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 70 mg, 0.350 mmol, 70%, colorless oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.50 (t, *J* = 5.1 Hz, 1H), 4.18 – 4.02 (m, 2H), 3.99 – 3.87 (m, 2H), 3.76 (ddt, *J* = 12.3, 10.3, 2.4 Hz, 2H), 3.35 (td, *J* = 11.8, 2.1 Hz, 2H), 2.15 – 1.98 (m, 1H), 1.66 – 1.53 (m, 4H), 1.45 (dtt, *J* = 17.1, 10.5, 3.6 Hz, 1H), 1.38 – 1.29 (m, 3H), 1.24 (ddd, *J* = 13.1, 11.2, 4.5 Hz, 2H).

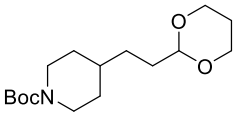
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 102.6, 68.2, 67.1, 35.0, 33.2, 32.3, 31.1, 26.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951, 2924, 2842, 1455, 1430, 1404, 1376, 1282, 1239, 1215, 1202, 1142, 1117, 1094, 1074, 1041, 1010, 977, 942, 926, 908, 887, 860, 843, 813.

MS (EI, 70 eV): *m/z* (%) = 199 (5), 123 (19), 96 (37), 87 (100), 59 (22).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{11}H_{19}O_3^+$ 199.1329; Found: 199.1329.

***tert*-Butyl 4-(2-(1,3-dioxan-2-yl)ethyl)piperidine-1-carboxylate (107g)**



Following **TP3-B** *tert*-butyl 4-iodopiperidine-1-carboxylate (**105c**, 156 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 111 mg, 0.371 mmol, 74%, yellow oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.49 (t, *J* = 5.1 Hz, 1H), 4.17 – 3.97 (m, 4H), 3.81 – 3.67 (m, 2H), 2.65 (t, *J* = 12.4 Hz, 2H), 2.16 – 1.93 (m, 1H), 1.72 – 1.52 (m, 4H), 1.44 (d, *J* = 0.9 Hz, 9H), 1.39 – 1.26 (m, 4H), 1.14 – 0.98 (m, 2H).

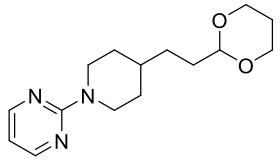
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 154.9, 102.4, 79.1, 66.9, 44.80 – 43.37 (br), 35.9, 32.4, 32.1, 30.6, 28.5, 25.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929, 2853, 1678, 1469, 1454, 1425, 1366, 1277, 1244, 1170, 1143, 1091, 1076, 1010, 967, 909, 865, 770, 727.

MS (EI, 70 eV): *m/z* (%) = 198 (33), 140 (40), 139 (19), 125 (30), 122 (46), 122 (60), 84 (19), 82 (100), 57 (18).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{16}H_{28}NO_4^+$ 298.2013; Found: 298.2007.

2-(4-(2-(1,3-Dioxan-2-yl)ethyl)piperidin-1-yl)pyrimidine (107h)



Following **TP3-B** 2-(4-iodopiperidin-1-yl)pyrimidine (**105d**, 145 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 80 mg, 0.289 mmol, 58%, pale yellow oil.

Purification: pentane:ethyl acetate = 7:3.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.28 (d, *J* = 4.7 Hz, 2H), 6.43 (t, J = 4.7 Hz, 1H), 4.72 (dq, *J* = 13.4, 2.2 Hz, 2H), 4.51 (t, J = 5.1 Hz, 1H), 4.15 – 4.02 (m, 2H), 3.76 (tt, *J* = 10.6, 2.4 Hz, 2H), 2.85 (td, *J* = 12.9, 2.7 Hz, 2H), 2.18 – 1.99 (m, 1H), 1.84 – 1.71 (m, 2H), 1.70 – 1.57 (m, 2H), 1.50 (dtq, *J* = 14.8, 7.1, 3.5 Hz, 1H), 1.44 – 1.29 (m, 3H), 1.16 (qd, *J* = 12.6, 4.4 Hz, 2H).

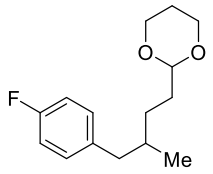
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.6, 157.7, 109.2, 102.5, 67.0, 44.1, 36.2, 32.5, 32.1, 30.7, 25.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923, 2846, 1583, 1544, 1504, 1452, 1392, 1360, 1304, 1282, 1266, 1252, 1239, 1218, 1201, 1181, 1142, 1110, 1074, 1044, 1002, 966, 943, 881, 852, 795, 777.

MS (EI, 70 eV): *m/z* (%) = 277 (15), 218 (34), 200 (18), 176 (51), 163 (20), 160 (100), 134 (30), 122 (20), 108 (38), 87.

HR-MS (EI, 70eV): Calcd for $C_{15}H_{23}N_3O_2$ 277.1790; Found: 277.1786.

2-(4-(4-Fluorophenyl)-3-methylbutyl)-1,3-dioxane (107i)



Following **TP3-B** 1-fluoro-4-(2-iodopropyl)benzene (132 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**2b**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 91 mg, 0.361 mmol, 72%, brown oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.13 – 7.03 (m, 2H), 6.99 – 6.90 (m, 2H), 4.48 (t, *J* = 5.2 Hz, 1H), 4.10 (ddd, *J* = 11.8, 5.0, 1.5 Hz, 2H), 3.75 (td, *J* = 12.2, 2.5 Hz, 2H), 2.62 (dd, *J* = 13.5, 5.9 Hz, 1H), 2.32 (dd, *J* = 13.5, 8.3 Hz, 1H), 2.07 (dtt, *J* = 13.4, 12.5, 5.0 Hz, 1H), 1.74 – 1.51 (m, 3H), 1.44 (ddt, *J* = 13.4, 11.5, 5.2 Hz, 1H), 1.33 (dtt, *J* = 13.4, 2.7, 1.4 Hz, 1H), 1.29 – 1.17 (m, 1H), 0.83 (d, J = 6.6 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.3 (d, J = 242.9 Hz), 137.1 (d, J = 3.3 Hz), 130.5 (d, J = 7.7 Hz), 114.9 (d, J = 21.0 Hz), 102.7, 67.1, 42.8, 35.2, 33.1, 30.8, 26.0, 19.2.

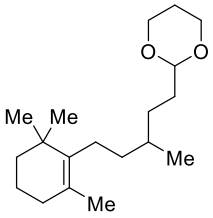
^{19}F-NMR (376 MHz, $CDCl_3$, ppm): δ = -117.95 (tt, *J* = 8.8, 5.4 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2926, 2851, 1600, 1509, 1460, 1431, 1404, 1378, 1283, 1220, 1145, 1103, 1079, 1003, 935, 877, 846, 812, 763.

MS (EI, 70 eV): *m/z* (%) = 176 (39), 161 (29), 149 (9), 147 (12), 146 (12), 136 (6), 135 (31), 133 (12), 122 (10), 110 (12), 109 (100), 87 (47), 83 (17), 59 (14), 41 (12).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{16}H_{28}NO_4^+$ 251.1442; Found: 251.1442.

2-(3-Methyl-5-(2,6,6-trimethylcyclohex-1-en-1-yl)pentyl)-1,3-dioxane (107j)



Following **TP3-B** 2-(3-iodobutyl)-1,3,3-trimethylcyclohex-1-ene (**105f**, 153 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 113 mg, 0.384 mmol, 77%, colorless oil

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.49 (t, *J* = 5.2 Hz, 1H), 4.17 – 4.02 (m, 2H), 3.76 (td, *J* = 12.3, 2.4 Hz, 2H), 2.17 – 1.94 (m, 2H), 1.88 (m, 3H), 1.67 – 1.48 (m, 7H), 1.47 – 1.29 (m, 7H), 1.28 – 1.09 (m, 1H), 0.96 (s, 6H), 0.90 (d, *J* = 6.0 Hz, 3H).

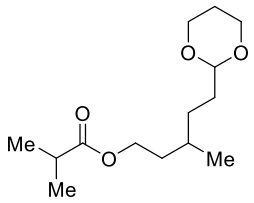
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 137.8, 126.5, 102.9, 67.1, 40.0, 37.5, 35.1, 34.1, 33.2, 32.9, 31.1, 28.8, 28.8, 26.5, 26.0, 20.0, 19.7, 19.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2868, 1731, 1662, 1459, 1377, 1336, 1239, 1143, 1108, 1075, 998, 936, 880, 848.

MS (EI, 70 eV): *m/z* (%) = 218 (50), 162 (39), 147 (49), 123 (97), 121 (100), 119 (65), 107 (60), 95 (65), 81 (100).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{19}H_{33}O_2^+$ 293.2475; Found: 293.2474.

5-(1,3-Dioxan-2-yl)-3-methylpentyl isobutyrate (107k)



Following **TP3-B** 3-iodobutyl isobutyrate (135 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 117 mg, 0.453 mmol, 91%, yellow oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.49 (t, *J* = 5.1 Hz, 1H), 4.14 – 4.06 (m, 4H), 3.75 (ddt, *J* = 12.4, 10.4, 2.4 Hz, 2H), 2.52 (hept, *J* = 7.0 Hz, 1H), 2.07 (dtt, *J* = 13.2, 12.3, 5.0 Hz, 1H), 1.73 – 1.46 (m, 4H), 1.47 – 1.38 (m, 2H), 1.33 (dtt, *J* = 13.5, 2.7, 1.4 Hz, 1H), 1.24 (dddd, *J* = 13.2, 11.3, 7.7, 5.4 Hz, 1H), 1.15 (d, *J* = 7.0 Hz, 6H), 0.90 (d, *J* = 6.5 Hz, 3H).

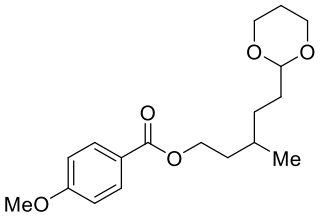
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 177.4, 102.7, 67.1, 62.8, 35.6, 34.2, 32.84, 31.0, 29.9, 26.0, 19.5, 19.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960, 2930, 2852, 1733, 1470, 1432, 1404, 1379, 1346, 1259, 1241, 1193, 1147, 1113, 1078, 1004, 929, 881, 850, 831.

MS (EI, 70 eV): *m/z* (%) = 113 (6), 95 (7), 94 (6), 88 (5), 87 (100), 79 (5), 59 (8).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{14}H_{25}O_4^+$ 257.1747; Found: 257.1738.

5-(1,3-Dioxan-2-yl)-3-methylpentyl 4-methoxybenzoate (107l)



Following **TP3-B** 3-iodobutyl 4-methoxybenzoate (**105g**, 167 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 108 mg, 0.335 mmol, 67%, yellow oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.01 – 7.95 (m, 2H), 6.93 – 6.87 (m, 2H), 4.50 (t, *J* = 5.1 Hz, 1H), 4.32 (ddd, *J* = 7.6, 6.5, 1.6 Hz, 2H), 4.09 (ddt, *J* = 10.5, 5.0, 1.4 Hz, 2H), 3.85 (s, 3H), 3.81 – 3.65 (m, 2H), 2.15 – 1.99 (m, 1H), 1.79 (dtd, *J* = 12.5, 7.0, 4.9 Hz, 1H), 1.74 – 1.42 (m, 5H), 1.38 – 1.19 (m, 2H), 0.95 (d, *J* = 6.4 Hz, 3H).

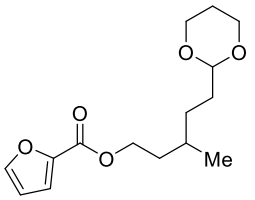
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.4, 163.2, 131.5, 122.9, 113.5, 102.5, 66.9, 63.1, 55.4, 35.5, 32.7, 30.9, 29.9, 25.9, 19.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2928, 2848, 1708, 1606, 1582, 1512, 1460, 1420, 1404, 1379, 1316, 1274, 1253, 1167, 1144, 1101, 1078, 1029, 1006, 938, 881, 848, 770, 697.

MS (EI, 70 eV): *m/z* (%) = 153 (5), 152 (36), 136 (6), 135 (72), 113 (30), 92 (6), 88 (5), 87 (100), 77 (10), 59 (8).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{18}H_{25}O_5^+$ 321.1697; Found: 321.1682.

5-(1,3-Dioxan-2-yl)-3-methylpentyl furan-2-carboxylate (107m)



Following **TP3-B** 3-iodobutyl furan-2-carboxylate (147 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 121 mg, 0.429 mmol, 86%, yellow oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.57 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.15 (dd, *J* = 3.5, 0.9 Hz, 1H), 6.50 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.49 (t, J = 5.1 Hz, 1H), 4.33 (td, *J* = 6.6, 1.4 Hz, 2H), 4.09 (ddt, *J* = 10.5, 5.0, 1.4 Hz, 2H), 3.82 – 3.69 (m, 2H), 2.16 – 1.99 (m, 1H), 1.85 – 1.73 (m, 1H), 1.73 – 1.42 (m, 5H), 1.38 – 1.27 (m, 1H), 1.26 (tdd, *J* = 10.7, 6.6, 3.6 Hz, 1H), 0.94 (d, *J* = 6.3 Hz, 3H).

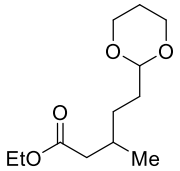
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 158.8, 146.2, 144.9, 117.7, 111.8, 102.5, 66.9, 63.4, 35.4, 32.7, 30.8, 29.8, 25.8, 19.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2929, 2854, 1727, 1582, 1474, 1431, 1400, 1380, 1296, 1232, 1180, 1145, 1117, 1077, 1011, 942, 884, 852, 813, 764.

MS (EI, 70 eV): *m/z* (%) = 113 (17), 112 (5), 95 (29), 88 (5), 87 (100), 59 (9).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{15}H_{21}O_5^+$ 281.1384; Found: 281.1375.

Ethyl 5-(1,3-dioxan-2-yl)-3-methylpentanoate (107n)



Following **TP3-B** ethyl 3-iodobutanoate (121 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 59 mg, 0.256 mmol, 51%, yellow oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.49 (t, *J* = 5.1 Hz, 1H), 4.15 – 4.06 (m, 4H), 3.75 (ddt, *J* = 12.4, 10.5, 2.1 Hz, 2H), 2.30 (dd, *J* = 14.7, 5.7 Hz, 1H), 2.14 – 2.00 (m, 2H), 1.95 (qt, *J* = 7.9, 6.0 Hz, 1H), 1.70 – 1.51 (m, 2H), 1.43 (ddt, *J* = 13.3, 11.0, 5.4 Hz, 1H), 1.38 – 1.25 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H).

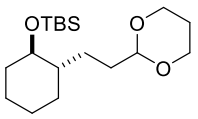
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 173.2, 102.4, 66.9, 60.1, 41.8, 32.7, 30.8, 30.2, 25.8, 19.5, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2931, 2851, 1731, 1461, 1430, 1404, 1375, 1283, 1240, 1212, 1178, 1143, 1108, 1095, 1074, 1031, 1003, 944, 929, 879, 849.

MS (EI, 70 eV): *m/z* (%) = 115 (4), 88(5), 87 (100), 83 (7), 81 (16), 79 (7), 69 (15), 67 (7), 59 (10), 55 (10), 41 (5).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{12}H_{21}O_4^+$ 229.1434; Found: 229.1430.

2-(2-(1,3-Dioxan-2-yl)ethyl)cyclohexyl)oxy)(tert-butyl)dimethylsilane (107o)



Following **TP3-A** *tert*-butyl((2-iodocyclohexyl)oxy)dimethylsilane (170 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 107 mg, 0.326 mmol, 65%, dr = 86:14, pale yellow oil.

Purification: pentane:ethyl acetate = 95:5

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.43 (dd, *J* = 5.8, 4.7 Hz, 1H), 4.05 (ddt, *J* = 10.6, 5.2, 1.4 Hz, 2H), 3.78 – 3.67 (m, 2H), 3.17 (td, *J* = 9.2, 4.0 Hz, 1H), 2.03 (dtt, *J* = 13.5, 12.5, 4.9 Hz, 1H), 1.89 – 1.70 (m, 4H), 1.69 – 1.51 (m, 3H), 1.44 (dddd, *J* = 13.5, 10.4, 5.5, 4.6 Hz, 1H), 1.34 – 1.26 (m, 1H), 1.26 – 1.10 (m, 4H), 1.11 – 0.94 (m, 1H), 0.85 (s, 9H), 0.01 (s, 3H), -0.00 (s, 3H).

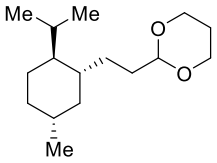
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 103.1, 75.3, 67.0, 44.9, 35.8, 32.6, 29.8, 26.7, 26.1, 26.0, 25.4, 24.8, 18.3, -3.8, -4.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927, 2854, 1737, 1471, 1462, 1448, 1403, 1377, 1360, 1249, 1205, 1145, 1120, 1082, 1004, 954, 933, 878, 831, 814, 772, 666.

MS (EI, 70 eV): *m/z* (%) = 287 (20), 211 (14), 139 (100), 133 (31), 121 (41), 105 (21), 95 (17), 87 821), 75 (62), 73 (30).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{18}H_{35}O_3Si^+$ 327.2350; Found: 327.2345.

2-(2-((1*R*,2*S*,5*R*)-2-*iso*-Propyl-5-methylcyclohexyl)ethyl)-1,3-dioxane (107p)



Following **TP3-A** (1*S*,2*R*,4*R*)-2-iodo-1-*iso*-propyl-4-methylcyclohexane (133 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 85 mg, 0.335 mmol, 67%, dr = 89:11, pale yellow oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.46 (t, *J* = 4.9 Hz, 1H), 4.08 (ddt, *J* = 10.6, 5.0, 1.4 Hz, 2H), 3.73 (ddq, *J* = 12.4, 10.5, 2.1 Hz, 2H), 2.14 – 1.89 (m, 2H), 1.72 – 1.41 (m, 7H), 1.37 – 1.09 (m, 4H), 1.01 – 0.73 (m, 9H), 0.69 (d, *J* = 6.9 Hz, 3H).

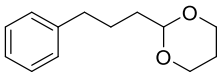
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 103.2, 67.0, 46.4, 41.3, 38.4, 35.5, 33.0, 31.6, 26.9, 26.4, 26.0, 24.4, 22.9, 21.8, 15.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2917, 2844, 1737, 1455, 1402, 1376, 1283, 1239, 1216, 1144, 1129, 1103, 1080, 1056, 1018, 997, 943, 927, 892, 870, 847.

MS (EI, 70 eV): *m/z* (%) = 253 (6), 163 (59), 135 (100), 107 (25), 93 (24), 87 (77), 81 (18).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{16}H_{29}O_2^+$ 253.2162; Found: 253.2160.

2-(3-Phenylpropyl)-1,3-dioxane (107q)



Following **TP3-B** (bromomethyl)benzene (86 mg, 0.50 mmol, 1.0 equiv.) or (chloromethyl)benzene (63 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 101 mg, 0.490 mmol, 98%, using (bromomethyl)benzene, 79 mg, 0.385 mmol, 77 %, using (chloromethyl)benzene, yellow oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.22 – 7.14 (m, 2H), 7.13 – 7.06 (m, 3H), 4.45 (t, *J* = 5.0 Hz, 1H), 4.02 (ddt, *J* = 10.5, 5.1, 1.4 Hz, 2H), 3.73 – 3.61 (m, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 1.99 (dtt, *J* = 13.5, 12.5, 5.0 Hz, 1H), 1.72 – 1.53 (m, 4H), 1.26 (dtt, *J* = 13.5, 2.6, 1.4 Hz, 1H).

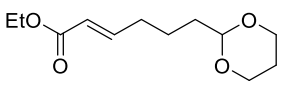
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 142.4, 128.6, 128.4, 125.8, 102.3, 67.0, 35.9, 35.0, 26.0, 26.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3026, 2955, 2925, 2850, 1603, 1496, 1454, 1430, 1404, 1378, 1283, 1242, 1217, 1188, 1144, 1130, 1082, 1050, 1030, 1009, 988, 975, 941, 911, 892, 858, 807, 748, 733, 698.

MS (EI, 70 eV): *m/z* (%) = 205 (5), 147 (5), 131 (7), 130 (67), 129 (13), 128 (10), 105 (22), 104 (100), 103 (7), 100 (20), 91 (52), 87 (52), 78 (13), 77 (7), 65 (11), 59 (11), 58 (7).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{13}H_{17}O_2^+$ 205.1223; Found: 205.1218.

Ethyl (*E*)-6-(1,3-dioxan-2-yl)hex-2-enoate (107r)



Following **TP3-B** ethyl (*E*)-4-bromobut-2-enoate (97 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 10,3 mg, 0.450 mmol, 90%, yellow oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.94 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.81 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.51 (t, *J* = 4.7 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.09 (ddt, *J* = 10.4, 5.0, 1.4 Hz, 2H), 3.80 – 3.67 (m, 2H), 2.21 (qd, *J* = 7.0, 1.6 Hz, 2H), 2.06 (dtt, *J* = 13.4, 12.4, 5.0 Hz, 1H), 1.65 – 1.50 (m, 4H), 1.33 (dtt, *J* = 13.5, 2.7, 1.4 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H).

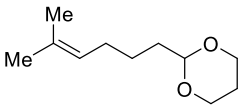
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.8, 148.9, 121.7, 102.0, 67.0, 60.3, 34.7, 32.1, 25.9, 22.5, 14.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2929, 2853, 2733, 2251, 1717, 1654, 1461, 1432, 1405, 1369, 1310, 1268, 1242, 1200, 1177, 1146, 1096, 1084, 1046, 987, 914, 864, 850, 732.

MS (EI, 70 eV): *m/z* (%) = 227 (5), 113 (12), 102 (5), 97 (7), 87 (100), 81 (18), 71 (11), 69 (12), 59 (23), 58 (23), 57 (22), 55 (20), 43 (12), 43 (24), 41 (25).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{12}H_{19}O_4^+$ 227.1278; Found: 227.1278.

2-(5-Methylhex-4-en-1-yl)-1,3-dioxane (107s)



Following **TP3-B** 1-bromo-3-methylbut-2-ene (75 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 55 mg, 0.299 mmol, 60%, yellow liquid.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.10 (dddd, *J* = 8.8, 5.9, 3.0, 1.5 Hz, 1H), 4.51 (t, *J* = 5.2 Hz, 1H), 4.10 (ddt, *J* = 10.5, 5.1, 1.4 Hz, 2H), 3.82 – 3.69 (m, 2H), 2.15 – 2.02 (m, 1H), 1.98 (q, *J* = 7.8, 7.3 Hz, 2H), 1.67 (d, *J* = 1.5 Hz, 3H), 1.62 – 1.55 (m, 5H), 1.47 – 1.37 (m, 2H), 1.33 (dtt, *J* = 13.4, 2.6, 1.4 Hz, 1H).

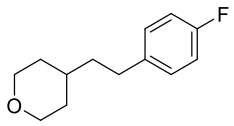
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 131.9, 124.4, 102.6, 67.1, 34.9, 27.9, 26.0, 25.9, 24.4, 17.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2925, 2850, 2731, 1457, 1432, 1404, 1378, 1286, 1243, 1217, 1146, 1111, 1086, 1052, 990, 929, 893, 862, 826.

MS (EI, 70 eV): *m/z* (%) = 113 (42), 100 (9), 93 (7), 91 (7), 87 (37), 83 (5),82 (79), 81 (6), 79 (8), 77 (5), 69 (5), 68 (5), 67 (100), 65 (5), 59 (11), 55 (15),41 (13).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{11}H_{19}O_2^+$ 183.1380; Found: 183.1375.

4-(4-Fluorophenethyl)tetrahydro-2*H*-pyran (107t)



Following **TP3-B** 4-iodotetrahydro-2*H*-pyran (**105b**, 106 mg, 0.50 mmol, 1.0 equiv.) was coupled with di(4-fluorophenethyl)zinc (**106b**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 74 mg, 0.356 mmol, 71%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.16 – 7.08 (m, 2H), 7.00 – 6.92 (m, 2H), 4.04 – 3.90 (m, 2H), 3.36 (td, *J* = 11.8, 2.0 Hz, 2H), 2.66 – 2.52 (m, 2H), 1.69 – 1.60 (m, 2H), 1.59 – 1.44 (m, 3H), 1.38 – 1.24 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.3 (d, *J* = 243.2 Hz), 138.2 (d, *J* = 3.2 Hz), 129.7 (d, *J* = 7.6 Hz), 115.2 (d, *J* = 21.1 Hz), 68.2, 39.0, 34.6, 33.2, 32.0.

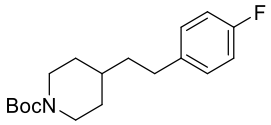
^{19}F-NMR (376 MHz, $CDCl_3$, ppm): δ = -117.98 (tt, J = 8.8, 5.4 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926, 2843, 1600, 1508, 1455, 1443, 1387, 1366, 1296, 1218, 1157, 1136, 1093, 1014, 980, 904, 864, 846, 824, 767, 745, 705.

MS (EI, 70 eV): *m/z* (%) = 208 (5), 161 (100), 147 (19), 146 (15), 135 (19), 122 (57), 109 (53).

HR-MS (EI, 70eV): Calcd for $C_{13}H_{17}FO$ 208.1263; Found: 208.1255.

***tert*-Butyl 4-(4-fluorophenethyl)piperidine-1-carboxylate (107u)**



Following **TP3-B** *tert*-butyl 4-iodopiperidine-1-carboxylate (**105c**, 156 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(4-fluorophenethyl)zinc (**106b**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 101 mg, 0.329 mmol, 66%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.14 – 7.07 (m, 2H), 7.00 – 6.90 (m, 2H), 4.15 – 4.00 (m, 2H), 2.75 – 2.52 (m, 4H), 1.78 – 1.63 (m, 2H), 1.60 – 1.49 (m, 2H), 1.45 (s, 10H), 1.12 (qd, *J* = 12.3, 4.3 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.3 (d, *J* = 243.5 Hz), 155.0, 138.2 (d, *J* = 3.2 Hz), 129.7 (d, *J* = 7.7 Hz), 115.2 (d, *J* = 21.1 Hz), 79.4, 44.1, 38.6, 35.6, 32.2, 32.2, 28.6.

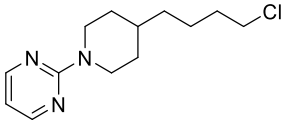
^{19}F-NMR (376 MHz, $CDCl_3$, ppm): δ = -117.95 (tt, J = 8.8, 5.4 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927, 2852, 1688, 1601, 1509, 1418, 1391, 1364, 1276, 1219, 1155, 1119, 1090, 1015, 966, 932, 865, 824, 768, 705.

MS (EI, 70 eV): *m/z* (%) = 251 (33), 129 (12), 109 (37), 85 (14), 57 (100), 41 (20).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{18}H_{25}FNO_2^+$ 306.1864; Found: 306.1866.

2-(4-(4-Chlorobutyl)piperidin-1-yl)pyrimidine (107v)



Following **TP3-B** 2-(4-iodopiperidin-1-yl)pyrimidine (**105d**, 145 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(4-chlorobutyl)zinc (**106c**, 0.375 mmol, 0.75 equiv.) prepared from the corresponding bromide according to **TP1** using 1.0 equiv magnesium turnings.

Isolated yield: 83 mg, 0.328 mmol, 66%, colorless oil.

Purification: pentane:ethyl acetate = 7:3.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.28 (d, *J* = 4.7 Hz, 2H), 6.42 (t, *J* = 4.7 Hz, 1H), 4.73 (ddt, *J* = 13.3, 4.3, 1.9 Hz, 2H), 3.54 (t, *J* = 6.6 Hz, 2H), 2.92 – 2.73 (m, 2H), 1.85 – 1.70 (m, 4H), 1.59 – 1.41 (m, 3H), 1.33 – 1.22 (m, 2H), 1.22 – 1.10 (m, 2H).

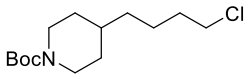
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.6, 157.8, 109.3, 45.2, 44.3, 36.3, 36.0, 32.9, 32.2, 24.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920, 2845, 1583, 1543, 1502, 1455, 1445, 1392, 1360, 1304, 1241, 1218, 1176, 1082, 1051, 973, 947, 795, 778, 734.

MS (EI, 70 eV): *m/z* (%) = 253 (4), 238 (11), 219 (14), 218 (100), 134 (18), 122 (9), 108 (29).

HR-MS (EI, 70eV): Calcd for $C_{13}H_{20}ClN_3$ 253.1346; Found: 253.1341.

***tert*-Butyl 4-(4-chlorobutyl)piperidine-1-carboxylate (107w)**



Following **TP3-B** using $CoCl_2$ (130 mg, 20 mol%), neocuproine (208 mg, 20 mol%), TBAI (4.16 g, 2.25 equiv) 4-iodopiperidine-1-carboxylate (**105c**, 1.56 g 5.00 mmol, 1.00 equiv.) in MeCN (10 ml) with di(4-chlorobutyl)zinc (**106c**, 3.75 mmol, 0.75 equiv.) prepared from the corresponding bromide according to **TP1** using 1.0 equiv magnesium turnings.

Isolated yield: 900 mg, (11% of the corresponding Iodide, due to nucleophilic substitution reaction with iodide in the reaction solution, which could not be separated by column chromatography, determined *via* NMR Analysis) → 2.9 mmol, 58%, pale yellow oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.20 – 3.94 (m, 2H), 3.53 (td, *J* = 6.7, 1.2 Hz, 2H), 2.74 – 2.57 (m, 2H), 1.85 – 1.70 (m, 2H), 1.69 – 1.57 (m, 3H), 1.45 (d, *J* = 1.2 Hz, 11H), 1.31 – 1.18 (m, 2H), 1.14 – 1.00 (m, 2H).

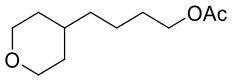
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 154.9, 79.2, 45.1, 44.0, 35.9, 35.7, 32.7, 32.1, 28.5, 23.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2975, 2929, 2849, 1687, 1447, 1419, 1364, 1276, 1235, 1153, 1120, 1087, 1009, 973, 936, 866, 768, 735.

MS (EI, 70 eV): *m/z* (%) = 275 (4), 221 (10), 220 (24), 219 (17), 218 (17), 202 (19), 184 (100), 174 (10), 140 (44), 112 (13), 57 (61).

HR-MS (EI, 70eV): Calcd for $C_{14}H_{26}ClNO_2$ 275.1652; Found: 275.1642.

4-(Tetrahydro-2*H*-pyran-4-yl)butyl acetate (107x)



Following **TP3-B** 4-iodotetrahydro-2*H*-pyran (**105b**, 106 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(4-acetoxybutyl)zinc (**106d**, 0.375 mmol, 0.75 equiv.) prepared according to **TP2** (3 h at room temperature) from the corresponding bromide.

Isolated yield: 65 mg, 0.325 mmol, 65%, yellow oil.

Purification: pentane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.03 (t, *J* = 6.7 Hz, 2H), 3.96 – 3.81 (m, 2H), 3.33 (td, *J* = 11.8, 2.0 Hz, 2H), 2.02 (s, 3H), 1.64 – 1.52 (m, 4H), 1.51 – 1.39 (m, 1H), 1.39 – 1.29 (m, 2H), 1.24 (dtd, *J* = 12.5, 6.7, 3.3 Hz, 4H).

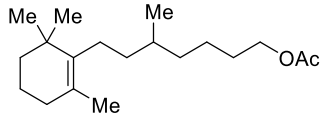
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 171.3, 68.2, 64.6, 36.6, 35.0, 33.2, 28.8, 22.8, 21.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 292, 2857, 1732, 1710, 1606, 1581, 1511, 1461, 1419, 1375, 1315, 1273, 1253, 1165, 1100, 1028, 953, 847, 769, 696.

MS (EI, 70 eV): *m/z* (%) = 199 (4), 96 (22), 87 (100), 83 (12), 59 (11).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{11}H_{29}O_3^+$ 199.1329; Found: 199.1328.

5-Methyl-7-(2,6,6-trimethylcyclohex-1-en-1-yl)heptyl acetate (107y)



Following **TP3-B** 2-(3-iodobutyl)-1,3,3-trimethylcyclohex-1-ene (**105f**, 153 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(4-acetoxybutyl)zinc (**106d**, 0.375 mmol, 0.75 equiv., 0.37 m) prepared according to **TP2** (3 h at room temperature) from the corresponding bromide.

Isolated yield: 106 mg, 0.361 mmol, 72%, yellow oil.

Purification: pentane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.05 (t, *J* = 6.7 Hz, 2H), 2.04 (s, 3H), 1.97 (dd, *J* = 12.8, 5.0 Hz, 1H), 1.94 – 1.83 (m, 3H), 1.56 (s, 3H), 1.68 – 1.49 (m, 5H), 1.45 – 1.25 (m, 6H), 1.16 (dddd, *J* = 15.8, 10.8, 8.4, 5.2 Hz, 2H), 0.97 (s, 6H), 0.89 (d, *J* = 6.2 Hz, 3H).

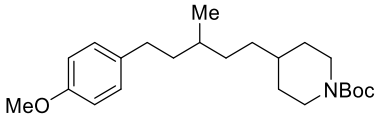
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 13C NMR (101 MHz, CDCl3) δ 171.36, 137.76, 126.51, 64.80, 39.97, 37.47, 36.55, 35.05, 33.95, 32.86, 29.03, 28.79, 28.76, 26.40, 23.58, 21.16, 19.93, 19.69, 19.62.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927, 2865, 1741, 1458, 1363, 1234, 1113, 1036, 974, 889, 735.

MS (EI, 70 eV): *m/z* (%) = 149 (26), 123 (100), 109 (20), 95 (29), 81 (60).

HR-MS (EI, 70eV): Calcd for $C_{19}H_{34}O_2$ 294.2559; Found: 294.2553.

***tert*-Butyl 4-(5-(4-methoxyphenyl)-3-methylpentyl)piperidine-1-carboxylate (107z)**



Following **TP3-B** 1-(3-iodobutyl)-4-methoxybenzene (**105g**, 145 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)ethyl)zinc (**106e**, 0.375 mmol, 0.75 equiv., 0.26 m) prepared according to **TP2** (4.5 h at room temperature) from the corresponding bromide.

Isolated yield: 135 mg, 0.360 mmol, 72%, yellow oil.

Purification: pentane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.12 – 7.05 (m, 2H), 6.86 – 6.78 (m, 2H), 4.06 (s, 2H), 3.78 (s, 3H), 2.76 – 2.43 (m, 4H), 1.69 – 1.51 (m, 4H), 1.45 (s, 9H), 1.43 – 0.98 (m, 8H), 0.91 (d, *J* = 6.0 Hz, 3H).

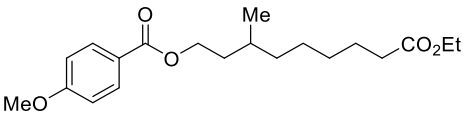
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 157.7, 155.1, 135.2, 129.3, 113.8, 79.3, 55.4, 44.2 (br), 39.2, 36.4, 33.9, 32.6, 32.6, , 32.5 (br), 28.6, 19.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920, 2850, 1389, 1612, 1511, 1453, 1420, 1364, 1299, 1276, 1242, 1159, 1090, 1036, 965, 866, 821, 767.

MS (EI, 70 eV): *m/z* (%) = 319 (24), 154 (25), 121 (100), 112 (16), 82 (14), 57 (71), 56 (14), 55 (11), 40 (20).

HR-MS (EI, 70eV): Calcd for $C_{23}H_{37}NO_3$ 375.2773; Found: 375.2775.

9-Ethoxy-3-methyl-9-oxononyl 4-methoxybenzoate (107aa)



Following **TP3-B** 3-iodobutyl 4-methoxybenzoate (**105h**, 167 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(6-ethoxy-6-oxohexyl)zinc (**106f**, 0.375 mmol, 0.75 equiv., 0.57 m) prepared according to **TP2** (2 h at room temperature) from the corresponding bromide.

Isolated yield: 119 mg, 0.340 mmol, 68%, colorless oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.01 – 7.96 (m, 2H), 6.95 – 6.88 (m, 2H), 4.35 – 4.29 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.78 (dtd, *J* = 13.2, 7.1, 4.8 Hz, 1H), 1.68 – 1.48 (m, 5H), 1.42 – 1.28 (m, 5H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H).

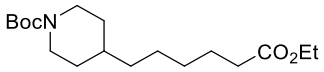
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 173.9, 166.5, 163.2, 131.5, 122.9, 113.6, 63.2, 60.2, 55.4, 36.8, 35.6, 34.37, 30.0, 29.4, 26.6, 25.0, 19.6, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924, 2855, 1693, 1669, 1421, 1391, 1364, 1276, 1244, 1159, 1093, 1034, 964, 865, 808, 768.

MS (EI, 70 eV): *m/z* (%) = 350 (3), 153 (29), 152 (21), 152 (100), 135 (100).

HR-MS (EI, 70eV): Calcd for $C_{20}H_{30}O_5$ 350.2093; Found: 350.2087.

***tert*-Butyl 4-(6-ethoxy-6-oxohexyl)piperidine-1-carboxylate (107ab)**



Following **TP3-B** 4-iodopiperidine-1-carboxylate (**105c**, 156 mg 5.00 mmol, 1.00 equiv.) was coupled with di(6-ethoxy-6-oxohexyl)zinc (**106f**, 0.375 mmol, 0.75 equiv., 0.57 m) prepared according to **TP2** (2 h at room temperature) from the corresponding bromide.

Isolated yield: 115 mg, 0.352 mmol, 70%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.12 (q, *J* = 7.1 Hz, 3H), 4.06 (s, 2H), 2.65 (t, *J* = 12.6 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.62 (dq, *J* = 7.1, 3.5, 3.1 Hz, 4H), 1.45 (s, 9H), 1.30 (tt, *J* = 4.2, 2.5 Hz, 4H), 1.25 (t, *J* = 7.1 Hz, 6H), 1.14 – 0.98 (m, 2H).

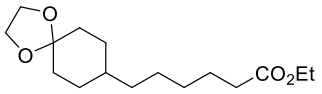
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.0, 155.1, 79.3, 60.3, 44.7 – 43.6 (br), 36.5, 36.1, 34.5, 32.3, 29.4, 28.6, 26.4, 25.1, 14.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2976, 2927, 2853, 1734, 1690, 1447, 1419, 1391, 1364, 1276, 1243, 1153, 1123, 1092, 1028, 963, 866, 809, 768, 729.

MS (EI, 70 eV): *m/z* (%) = 254 (16), 226 (67), 212 (53), 182 (58), 140 (100), 112 (31), 98 (30), 84 (33).

HR-MS (EI, 70eV): [M- O*t*-Bu] Calcd for $C_{14}H_{24}NO_3^{\bullet}$ 254.1756; Found: 254.1752.

Ethyl 6-(1,4-dioxaspiro[4.5]decan-8-yl)hexanoate (107ac)



Following **TP3-B** 8-iodo-1,4-dioxaspiro[4.5]decane (**105h**, 119 mg, 0.50 mmol, 1.00 equiv.) was coupled with (6-ethoxy-6-oxohexyl)zinc (**106f**, 0.375 mmol, 0.75 equiv., 0.57 m) prepared according to **TP2** (2 h at room temperature) from the corresponding bromide.

Isolated yield: 114 mg, 0.401 mmol, 80%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.12 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 4H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.77 – 1.65 (m, 4H), 1.61 (p, *J* = 7.4 Hz, 3H), 1.50 (td, *J* = 14.0, 13.1, 4.6 Hz, 2H), 1.35 – 1.14 (m, 13H).

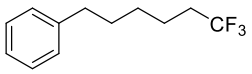
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.1, 109.4, 64.3, 60.3, 36.4, 36.2, 34.7, 34.5, 30.3, 29.5, 27.0, 25.1, 14.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927, 2856, 1732, 1446, 1373, 1336, 1175, 1135, 1106, 1089, 1033, 928, 910, 859, 766, 729, 662.

MS (EI, 70 eV): *m/z* (%) =239 (10), 213 (23), 141 (7), 100 (5), 99 (100), 55 (12).

HR-MS (EI, 70eV): Calcd for $C_{16}H_{28}O_4$ 284.1988; Found: 284.1987.

(6,6,6-Trifluorohexyl)benzene (107ad)



Following **TP3-B** (3-iodopropyl)benzene (**105a**, 123 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(3,3,3-trifluoropropyl)zinc (**106g**, 0.375 mmol, 0.75 equiv., 0.36 m) prepared according to **TP2** (1 h at room temperature) from the corresponding bromide.

Isolated yield: 83 mg, 0384 mmol, 75%, colorless oil.

Purification: pentane.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.33 – 7.24 (m, 3H), 7.22 – 7.14 (m, 3H), 2.62 (t, *J* = 7.7 Hz, 2H), 2.14 – 1.97 (m, 2H), 1.72 – 1.51 (m, 5H), 1.41 (q, *J* = 8.3 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 142.38, 128.51, 128.48, 131.54 – 123.08 (q, *J* = 276.3 Hz), 125.93, 35.78, 33.81 (q, *J* = 28.4 Hz), 31.16, 28.42, 21.90 (q, *J* = 2.9 Hz).

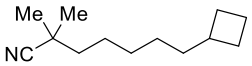
^{19}F-NMR (376 MHz, $CDCl_3$, ppm): δ = -66.51 (t, *J* = 11.1 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2873, 1496, 1454, 1385, 1335, 1254, 1175, 1135, 1033, 743, 697.

MS (EI, 70 eV): *m/z* (%) = 217 (5), 216 (35), 105 (4), 92 (31), 91 (100), 78 (3).

HR-MS (EI, 70eV): Calcd for $C_{12}H_{15}F_3$ 216.1126; Found: 216.1119.

7-cyclobutyl-2,2-dimethylheptanenitrile (107ae)



Following **TP3-B** 6-iodo-2,2-dimethylhexanenitrile (**105i**, 126 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(cyclobutylmethyl)zinc (**106h**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 60 mg, 0311 mmol, 62%, colorless oil.

Purification: pentane.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 2.22 (hept, *J* = 7.6 Hz, 1H), 2.07 – 1.96 (m, 2H), 1.91 – 1.71 (m, 2H), 1.63 – 1.40 (m, 7H), 1.40 – 1.35 (m, 1H), 1.33 (s, 6H), 1.33 – 1.14 (m, 4H).

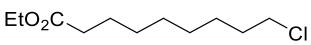
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 125.5, 41.2, 37.1, 36.3, 32.6, 29.8, 28.5, 27.1, 26.8, 25.5, 18.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2971, 2927, 2855, 2234, 1693, 1469, 1391, 1368, 1079, 966, 802, 725.

MS (EI, 70 eV): *m/z* (%) = 164 (28), 150 (100), 136 (36), 124 (28), 122 (70), 110 (33), 108 (100), 80 (38), 41 (27).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{13}H_{22}N^+$ 192.1747; Found: 192.1744.

(6,6,6-Trifluorohexyl)benzene (107af)



Following **TP3-B** ethyl 5-iodopentanoate (**105j**, 128 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(4-chlorobutyl)zinc (**106c**, 0.375 mmol, 0.75 equiv.) prepared from the corresponding bromide according to **TP1** using 1.0 equiv magnesium turnings.

Isolated yield: 55 mg, (17% of the corresponding Iodide, due to nucleophilic substitution reaction with iodide in the reaction solution, which couldn't be separated by column chromatography, determined due to NMR Analysis) 0.195 mmol, 39%, colorless oil.

Purification: pentane.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.06 (q, *J* = 7.1 Hz, 2H), 3.46 (t, *J* = 6.7 Hz, 2H), 2.22 (t, *J* = 7.5 Hz, 2H), 1.79 – 1.64 (m, 2H), 1.55 (p, *J* = 7.5 Hz, 2H), 1.41 – 1.29 (m, 2H), 1.24 (d, *J* = 2.6 Hz, 6H), 1.19 (t, *J* = 7.1 Hz, 3H).

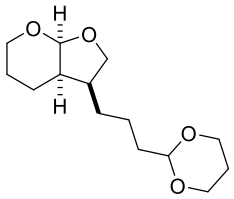
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.0, 60.3, 45.3, 34.5, 32.7, 29.2, 29.2, 28.8, 26.9, 25.1, 14.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930, 2856, 1732, 1463, 1372, 1348, 1301, 1176, 1121, 1096, 1033, 859, 724.

MS (EI, 70 eV): *m/z* (%) = 185 (16), 177 (17), 175 (41), 139 (19), 101 (39), 88 (100), 73 (16), 70 (15), 69 (22), 61 (12), 60 (11), 55 (21).

HR-MS (EI, 70eV): Calcd for $C_{11}H_{21}O_2Cl$ 220.1230; Found: 220.1224.

3-(3-(1,3-Dioxan-2-yl)propyl)hexahydro-4*H*-furo[2,3-b]pyran (107ag)



Following **TP3-B** 2-(allyloxy)-3-iodotetrahydro-2*H*-pyran (**105k**, 134 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 58 mg, 0.227 mmol, 45%, dr = 9:1, colorless oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.25 (d, *J* = 3.7 Hz, 1H, major), 4.96 (d, *J* = 3.6 Hz, 0.11H, minor), 4.48 (t, *J* = 5.1 Hz, 1H, major), 4.26 (t, *J* = 8.3 Hz, 0.12H, minor), 4.07 (ddd, *J* = 12.1, 5.0, 1.5 Hz, 2H, major), 3.92 (t, *J* = 8.0 Hz, 1H, major), 3.84 (dt, *J* = 11.7, 3.4 Hz, 0.13H, minor), 3.78 – 3.67 (m, 4H, major/minor), 3.64 – 3.56 (m, 2H, major), 3.51 (t, *J* = 8.2 Hz, 0.11H, minor), 3.38 (td, *J* = 11.6, 2.3 Hz, 0.12H, minor), 2.37 – 2.21 (m, 1H, major/minor), 2.04 (qt, *J* = 12.7, 5.0 Hz, 1H, major/minor), 1.92 (dtd, *J* = 12.0, 6.1, 3.7 Hz, 1H, major), 1.80 (dt, *J* = 8.6, 4.4 Hz, 0.34H, minor), 1.68 – 1.47 (m, 6H, major/minor), 1.44 – 1.18 (m, 7H, major/minor).

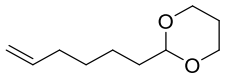
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 102.2 (minor), 102.11 (major), 102.1 (major), 74.3 (minor), 70.1 (major), 67.0 (major), 64.6 (minor), 61.0 (major), 44.2 (minor), 41.1 (major), 38.0 (minor), 36.5 (major), 35.6 (minor), 35.4 (major), 32.9 (minor), 27.0 (major), 25.9 (major), 23.30 (major), 23.0 (minor), 22.7 (major), 22.5 (minor), 20.8 (minor), 19.2 (major).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925, 2853, 1461, 1437, 1403, 1377, 1279, 1243, 1216, 1201, 1141, 1111, 1081, 1050, 1009, 993, 946, 927, 892, 870, 808.

MS (EI, 70 eV): *m/z* (%) = 180 (54), 179 (18), 151 (36), 125 (37), 113 (26), 93 (41), 87 (100), 59 (21).

HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{14}H_{23}O_4^+$ 255.1591; Found: 255.1589.

2-(Hex-5-en-1-yl)-1,3-dioxane (107ah)



Following **TP3-B** (iodomethyl)cyclopropane (**105l**, 91 mg, 0.50 mmol, 1.00 equiv.) was coupled with di(2-(1,3-dioxan-2-yl)ethyl)zinc (**106a**, 0.375 mmol, 0.75 equiv.) prepared according to **TP1** from the corresponding bromide.

Isolated yield: 37 mg, 0.218 mmol, 44%, colorless oil.

Purification: pentane:ethyl acetate = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 4.50 (t, *J* = 5.2 Hz, 1H), 4.09 (ddt, *J* = 10.6, 5.1, 1.4 Hz, 2H), 3.82 – 3.69 (m, 2H), 2.07 (tdt, *J* = 12.6, 11.1, 5.0 Hz, 3H), 1.66 – 1.52 (m, 2H), 1.40 (td, *J* = 8.2, 7.3, 4.8 Hz, 4H), 1.33 (dtt, *J* = 13.5, 2.7, 1.4 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 139.0, 114.5, 102.5, 67.0, 35.2, 33.8, 28.9, 26.0, 23.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951, 2925, 2849, 1640, 1459, 1431, 1404, 1377, 1283, 1240, 1216, 1142, 1116, 1086, 1053, 993, 936, 908, 868, 843.

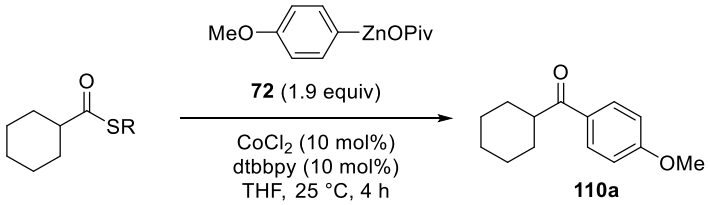
MS (EI, 70 eV): *m/z* (%) = 169 (15); 87 (100), 59 (15), 41 (7).

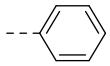
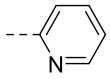
HR-MS (EI, 70eV): [M-H$^+$] Calcd for $C_{10}H_{18}O_2^+$ 169.1223; Found: 169.1221.

4. Cobalt-Catalyzed Acylation-Reactions of (Hetero)Arylzinc Pivalates with Thiopyridyl Ester Derivatives

4.1 Optimization of the Reaction Conditions

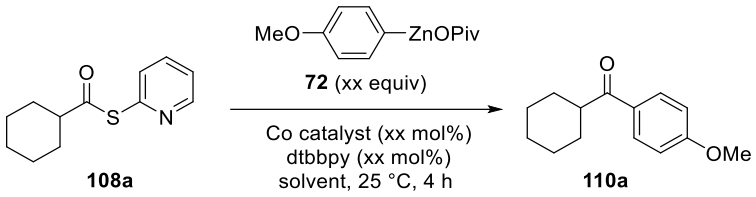
Table 13: Screening of various thioesters for the cobalt-catalyzed acylation.



Entry	R =	GC-Yield[a] [%]
1	Et	8
2		53
3		90

[a] Tetradecane ($C_{14}H_{30}$) was used as internal standard.

Table 14: Optimization of the acylation conditions.



Entry	Cobalt salt	$CoCl_2$ [mol%]	dtbbpy [mol%]	Solvent	Amount of **72** [equiv]	GC-Yield[a] [%]
1	$CoCl_2$	5	5	THF	1.9	81
2	**$CoCl_2$**	**10**	**10**	**THF**	**1.9**	**90**
3	$CoCl_2$	20	20	THF	1.9	92
4	$CoCl_2$	10	10	THF	1.5	85
5	$CoCl_2$	10	10	THF	2.5	87
6	$CoCl_2$	10	10	MeCN	1.9	89
7	$CoCl_2$	10	10	1,4-dioxane	1.9	90

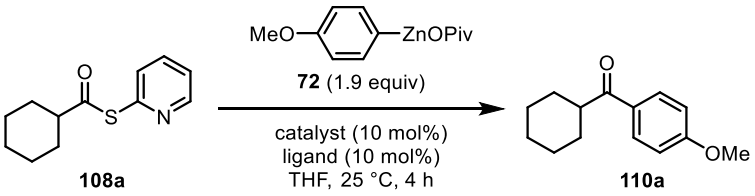
Table 14 continued.

Entry	Cobalt salt	$CoCl_2$ [mol%]	dtbbpy [mol%]	Solvent	Amount of **72** [equiv]	GC-Yield[a] [%]
9	$CoCl_2$	10	10	2-MeTHF	1.9	87
10	$CoCl_2$	10	10	THF	1.9	80[b]
11	$CoCl_2$	10	10	THF	1.9	82[c]
12	$CoBr_2$	10	10	THF	1.9	86
13	$Co(acac)_2$	10	10	THF	1.9	86
14	$Co(acac)_3$	10	10	THF	1.9	84

[a] Tetradecane ($C_{14}H_{30}$) was used as internal standard. [b] ArZnCl was used instead of ArZnOPiv. [c] The solid zinc pivalate **72** was weighed out on the bench and added to the reaction mixture under air.

4.2 Mechanistic Experiments

Table 15: Mechanistic experiments using cobalt salts of various oxidation states.

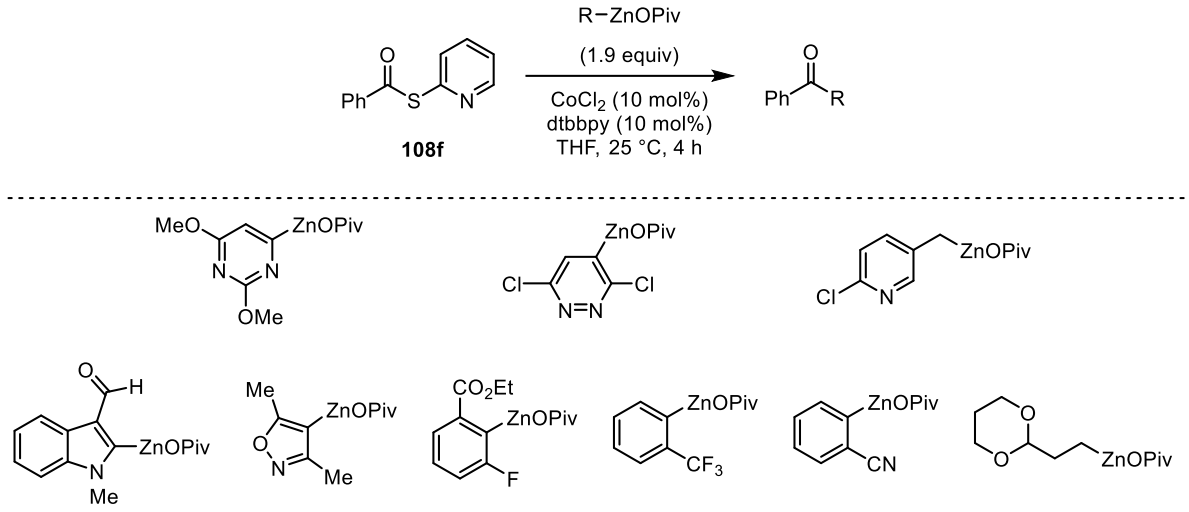


entry	cobalt salt	ligand	GC-yield[a] of **110a**
1	$CoCl_2$	dtbbpy	90
2	Co powder	dtbbpy	2
3	$CoCl(PPh_3)_3$	-	64
4	$CoCl_2(PPh_3)_3$	-	73

[a] Tetradecane ($C_{14}H_{30}$) was used as internal standard.

These experiments might indicate the involvement of a Co(I) species within the catalytic cycle (Table 15).

4.3 Unsuccessful Acylation Reactions with Several Heterocyclic and Sterically Hindered Organozinc Pivalates



Scheme 58: Unsuccessful substrates for the cobalt-catalyzed acylation reaction.

4.4 Preparation of Starting Materials

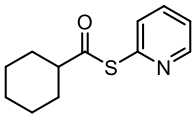
Preparation of thiopyridyl esters (TP1):[93a]

The corresponding carboxylic acid (1.0 equiv), PPh_3 (1.5 equiv) and 2,2'-dipyridyl disulfide (1.1 equiv) were added to a round bottom flask equipped with a magnetic stirring bar. The mixture was dissolved in MeCN (0.3 M) and heated to reflux for 3 h. After solvent evaporation, the resulting thiopyridyl ester was purified by column chromatography (SiO_2, *i*hexane/ethyl acetate) yielding the pure thioester.

Preparation of α-chiral-thiopyridyl esters (TP2):

The corresponding α-chiral-carboxylic acid (1.0 equiv), PPh_3 (1.0 equiv) and 2,2'-dipyridyl disulfide (1.0 equiv) were added to a round bottom flask equipped with a magnetic stirring bar. The mixture was dissolved in MeCN (0.3 M), cooled to 0 °C and stirred for 16 h. After solvent evaporation, the resulting substrate was purified by column chromatography (SiO_2, *i*hexane/ethyl acetate) yielding the corresponding thioester.

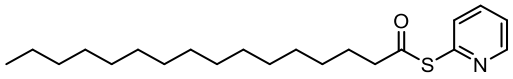
_S_-(Pyridin-2-yl) cyclohexanecarbothioate (108a)



_S_-(Pyridin-2-yl) cyclohexanecarbothioate was prepared according to **TP1** from cyclohexanecarboxylic acid (2.21 g, 10.00 mmol) and was obtained as a yellow solid (1.68 g, 7.60 mmol, 76% yield. The analytical data is in full consistency with the data reported in the literature.[155]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.61 (dd, J = 5.2, 1.9 Hz, 1H), 7.71 (tt, J = 7.7, 1.4 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.35 – 7.17 (m, 1H), 2.62 (tt, J = 11.4, 3.5 Hz, 1H), 2.08 – 1.96 (m, 2H), 1.81 (dt, J = 12.8, 3.4 Hz, 2H), 1.67 (dt, J = 12.6, 3.6 Hz, 1H), 1.53 (qd, J = 12.0, 3.3 Hz, 2H), 1.40 – 1.12 (m, 3H).

_S_-(Pyridin-2-yl) hexadecanethioate (108b)



_S_-(Pyridin-2-yl) hexadecanethioate was prepared according to **TP1** from palmitic acid (512 mg, 2.00 mmol) and was obtained as a yellow powder (684 mg, 1.96 mmol, 98% yield).

Purification: _i_hexane:ethyl acetate = 8:2.

m.p.: 62.0 – 63.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.66 – 8.58 (m, 1H), 7.73 (td, J = 7.7, 1.9 Hz, 1H), 7.61 (dd, J = 7.9, 1.1 Hz, 1H), 7.33 – 7.26 (m, 1H), 2.69 (t, J = 7.5 Hz, 2H), 1.72 (p, J = 7.5 Hz, 2H), 1.25 (s, 24H), 0.87 (t, J = 6.7 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.8, 151.8, 150.5, 137.2, 130.3, 123.6, 44.4, 32.1, 29.9, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.1, 25.6, 22.9, 14.3.

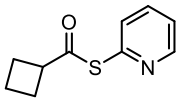
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ =2916, 2848, 1796, 1739, 1696, 1571, 1472, 1463, 1446, 1421, 1382, 1124, 1107, 1092, 1061, 1049, 981, 945, 905, 762, 718.

MS (EI, 70 eV): _m/z_ (%) = 239 (9), 112 (32), 111 (100), 98 (16), 57 (11), 43 (25).

HR-MS (EI, 70eV): [$C_{21}H_{35}NOS$], calcd.: 349.2439; found: 349.2432.

[155] B. Neises, W. Steglich, T. Van Ree, *S. Afr. J. Chem.* **1981**, *34*, 58-59.

_S_-(pyridin-2-yl) cyclobutanecarbothioate (108c)



_S_-(pyridin-2-yl) cyclobutanecarbothioate was prepared according to **TP1** from cyclobutanecarboxylic acid (200 mg, 2.00 mmol) and was obtained as a yellow oil (305 mg, 1.58 mmol, 79%).

Purification: _i_hexaner:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.66 – 8.50 (m, 1H), 7.67 (td, J = 7.7, 1.9 Hz, 1H), 7.55 (dt, J = 8.0, 1.1 Hz, 1H), 7.24 – 7.18 (m, 1H), 3.43 (pd, J = 8.5, 1.0 Hz, 1H), 2.45 – 2.27 (m, 2H), 2.20 (dtdd, J = 12.6, 8.3, 4.2, 2.3 Hz, 2H), 2.02 – 1.72 (m, 2H).

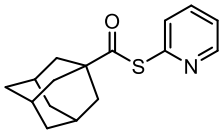
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 198.4, 151.6, 150.4, 137.1, 130.2, 123.4, 47.0, 26.0, 18.00.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2986, 2944, 1698, 1572, 1562, 1448, 1420, 1334, 1280, 1245, 1186, 1139, 1105, 1059, 1046, 988, 956, 885, 813, 763, 722, 677.

MS (EI, 70 eV): _m/z_ (%) = 258 (36), 211 (19), 136 (9) 135 (100), 77 (11).

HR-MS (EI, 70eV): [$C_{10}H_{12}NOS$], calcd.: 194.0634; found: 194.0634 [M^++H].

_S_-(pyridin-2-yl)-adamantane-1-carbothioate (108d)



_S_-(pyridin-2-yl)-adamantane-1-carbothioate was prepared according to **TP1** from adamantane-1-carboxylic acid (360 mg, 2.00 mmol) and was obtained as a pale yellow powder (464 mg, 1.70 mmol, 85% yield).

Purification: _i_hexane:ethyl acetate = 9:1 → 8:2.

m.p.: 73.2 – 75.6 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.62 (dd, J = 5.0, 1.9 Hz, 1H), 7.71 (td, J = 7.7, 1.9 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.35 – 7.17 (m, 1H), 2.09 (p, J = 3.1 Hz, 3H), 2.00 (d, J = 3.0 Hz, 6H), 1.83 – 1.63 (m, 6H).

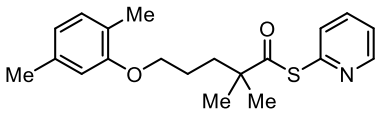
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 203.5, 152.0, 150.5, 137.0, 131.1, 123.4, 49.6, 39.3, 36.5, 28.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ =2909, 2848, 1689, 1572, 1562, 1449, 1421, 1342, 1280, 1250, 1188, 1138, 1116, 1102, 1084, 1045, 986, 946, 918, 822, 795, 760, 742, 724, 671.

MS (EI, 70 eV): _m/z_ (%) = 273 (2), 244 (6), 136 (8), 135 (100), 93 (8), 79 (9).

HR-MS (EI, 70eV): [$C_{16}H_{19}NOS$], calcd.: 273.1187; found: 273.1176.

_S_-(Pyridin-2-yl) 3-(2,5-dimethylphenoxy)-2,2-dimethylpropanethioate (108e)



_S_-(Pyridin-2-yl) 3-(2,5-dimethylphenoxy)-2,2-dimethylpropanethioate was prepared according to **TP1** from 3-(2,5-dimethylphenoxy)-2,2-dimethylpropanoic acid (444 mg, 2.00 mmol) and was obtained as a yellow oil (617 mg, 1.96 mmol, 98% yield).

Purification: *i*hexane:ethyl acetate = 9:1 → 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.64 (ddd, *J* = 4.8, 2.0, 0.8 Hz, 1H), 7.73 (td, *J* = 7.7, 2.0 Hz, 1H), 7.53 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.29 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.69 – 6.64 (m, 1H), 6.61 (d, *J* = 1.5 Hz, 1H), 3.95 (t, *J* = 5.4 Hz, 2H), 2.31 (s, 3H), 2.19 (s, 3H), 1.91 – 1.79 (m, 4H), 1.36 (s, 6H).

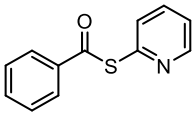
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 203.6, 157.0, 151.9, 150.6, 137.1, 136.6, 131.0, 130.4, 123.7, 123.5, 120.8, 112.0, 67.8, 50.6, 37.6, 25.4, 25.0, 21.6, 16.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2966, 2922, 1693, 1614, 1583, 1573, 1563, 1509, 1448, 1419, 1389, 1366, 1285, 1263, 1156, 1129, 1044, 1000, 988, 931, 906, 803, 764, 724.

MS (EI, 70 eV): *m/z* (%) = 258 (36), 211 (19), 136 (9) 135 (100), 77 (11).

HR-MS (EI, 70eV): [$C_{20}H_{26}NO_2S$], calcd.: 344.1679; found: 344.1678 [M^++H].

_S_-(Pyridin-2-yl) benzothioate (108f)

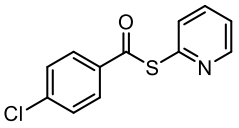


_S_-(Pyridin-2-yl) benzothioate was prepared according to **TP1** from benzoic acid (1.22 g, 10.0 mmol) and was obtained as a yellow solid (1.81 g, 8.4 mmol, 84% yield). The analytical data was in full consistency with the data reported in the literature.[156]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.72 – 8.62 (m, 1H), 8.08 – 7.97 (m, 2H), 7.79 (td, J = 7.7, 1.9 Hz, 1H), 7.73 (dt, J = 8.0, 1.0 Hz, 1H), 7.67 – 7.56 (m, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.33 (ddt, J = 7.1, 4.8, 1.0 Hz, 1H).

[156] C. M. Lemon, E. Karnas, M. G. Bawendi, D. G. Nocera, *Inorg. Chem.* 2013, **52**, 10394-10406.

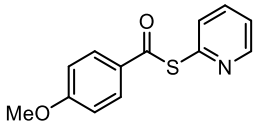
_S_-(Pyridin-2-yl) 4-chlorobenzothioate (108g)



S-(Pyridin-2-yl) 4-chlorobenzothioate was prepared according to **TP1** from 4-chlorobenzoic acid (1.55 g, 10.0 mmol) and was obtained as pale yellow needles (1.64 g, 6.6 mmol, 66 % yield). The analytical data was in full consistency with the data reported in the literature.[157]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.68 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 8.03 – 7.92 (m, 2H), 7.79 (td, *J* = 7.7, 1.9 Hz, 1H), 7.71 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.34 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H).

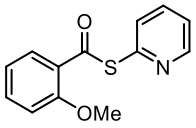
_S_-(Pyridin-2-yl) 4-methoxybenzothioate (108h)



S-(Pyridin-2-yl) 4-methoxybenzothioate was prepared according to **TP1** from 4-methoxybenzoic acid (304 mg, 2.00 mmol) and was obtained as a yellow solid (338 mg, 1.38 mmol, 69% yield). The analytical data was in full consistency with the data reported in the literature.[158]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.59 (ddt, *J* = 3.6, 2.6, 1.4 Hz, 1H), 7.93 (dd, *J* = 9.0, 2.2 Hz, 2H), 7.77 – 7.59 (m, 2H), 7.25 (dtd, *J* = 6.8, 3.2, 1.6 Hz, 1H), 6.89 (dd, *J* = 9.1, 2.6 Hz, 2H), 3.81 (s, 3H).

_S_-(Pyridin-2-yl) 4-methoxybenzothioate (108h')

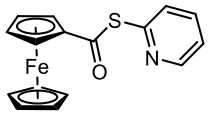


S-(Pyridin-2-yl) 2-methoxybenzothioate was prepared according to **TP1** from 2-methoxybenzoic acid (304 mg, 2.00 mmol) and was obtained as a yellow oil (470 mg, 1.92 mmol, 96% yield). The analytical data was in full consistency with the data reported in the literature.[157]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.74 – 8.58 (m, 1H), 7.86 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.80 – 7.70 (m, 2H), 7.51 (ddd, *J* = 7.9, 7.0, 1.8 Hz, 1H), 7.30 (ddd, *J* = 6.7, 4.8, 1.9 Hz, 1H), 7.07 – 6.98 (m, 2H), 3.96 (s, 3H).

[157] M. Ociepa, O. Baka, J. Nardodowiec, D. Gryko, *Adv. Synth. Catal.* 2017, **359**, 3560-3565.
[158] S. H. H. Zaidi, K. Muthukumaran, S.-I. Taimaru, J. S. Lindsey, *J. Org. Chem.* 2004, **69**, 8356-8365.

_S_-(Pyridin-2-yl) ferrocenecarbothioate (108i)



S-(Pyridin-2-yl) ferrocene was prepared according to **TP1** from ferrocene monocarboxylic acid (460 mg, 2.00 mmol) and was obtained as red crystals (588 mg, 1.82 mmol, 91% yield).

Purification: *i*hexane:ethyl acetate = 9:1 → 8:2.

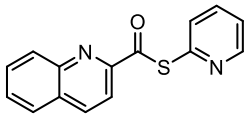
m.p.: 84.6 – 86.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.64 (d, *J* = 5.1 Hz, 1H), 7.75 (d, *J* = 6.5 Hz, 2H), 7.28 (dd, *J* = 11.8, 5.0 Hz, 1H), 4.94 (s, 2H), 4.55 (s, 2H), 4.31 (s, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 190.9, 152.4, 150.4, 150.3, 137.0, 130.4, 123.3, 123.3, 123.3, 78.8, 72.4, 72.4, 71.0, 70.8, 69.4, 69.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ =2923, 1652, 1570, 1446, 1422, 1369, 1239, 1121, 1106, 1045, 1024, 1002, 986, 942, 837, 810, 762, 721, 693.

_S_-(Pyridin-2-yl) quinoline-2-carbothioate (108j)



S-(Pyridin-2-yl) quinoline-2-carbothioate was prepared accordning to **TP1** from quinoline-2-carboxylic acid (856 mg, 5.00 mmol) and was obtained as yellow crystals (998 mg, 3.75 mmol, 75%).

Purification: *i*hexane:ethyl acetate = 9:1 → 8:2.

m.p.: 142.8– 144.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.80 – 8.70 (m, 1H), 8.38 – 8.25 (m, 2H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.90 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.87 – 7.73 (m, 3H), 7.69 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.35 (ddd, *J* = 7.3, 4.8, 1.4 Hz, 1H).

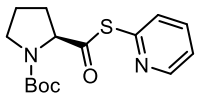
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 192.1, 152.5, 151.1, 150.6, 147.9, 137.8, 137.4, 131.0, 130.7, 130.6, 130.5, 129.2, 127.9, 123.7, 117.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926, 1682, 1668, 1572, 1561, 1502, 1461, 1448, 1419, 1378, 1305, 1279, 1263, 1227, 1206, 1142, 1108, 1082, 1046, 988, 964, 912, 834, 792, 763, 738, 722,702.

MS (EI, 70 eV): *m/z* (%) = 266 (3), 238 (19), 237 (40), 206 (40), 205 (23).

HR-MS (EI, 70eV): [$C_{15}H_{10}N_2OS$], calcd.: 266.0514; found: 266.0509.

***tert*-Butyl (*S*)-2-((pyridin-2-ylthio)carbonyl)pyrrolidine-1-carboxylate (108k)**



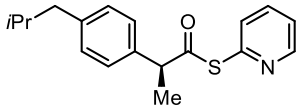
tert-Butyl (*S*)-2-((pyridin-2-ylthio)carbonyl)pyrrolidine-1-carboxylate was prepared according to **TP2** from (*tert*-butoxycarbonyl)-*L*-proline (2.15 g, 10.0 mmol) and was obtained as a yellow solid (2.24 g, 7.3 mmol, 73% yield). The analytical data is in full consistency with the data reported in the literature.[93c]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm, mixture of rotamers)**:** δ = 8.61 (dd, *J* = 5.0, 2.0 Hz, 0.6 H), 8.60 – 8.56 (m, 0.4 H), 7.72 (qd, *J* = 7.1, 6.5, 1.9 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 0.4 H), 7.55 (d, *J* = 7.9 Hz, 0.6 H), 7.26 (td, *J* = 9.7, 8.7, 5.0 Hz, 1.1 H), 4.57 (dd, *J* = 8.3, 3.4 Hz, 0.4 H), 4.44 (dd, *J* = 8.8, 3.8 Hz, 0.6 H), 3.54 (dtdd, *J* = 37.3, 18.1, 9.0, 6.1 Hz, 2H), 2.36 – 1.99 (m, 3H), 1.91 (pd, *J* = 7.6, 3.8 Hz, 1H), 1.48 (d, *J* = 7.1 Hz, 9H).

Optical rotation: $[\alpha]_D^{20} =$ -118 (c 1.17, $CHCl_3$).

Chiral HPLC: >99% *ee*, AD-H column, heptane:*i*PrOH = 95:5, 1.5 mL/min, 30 °C.

***S*-(Pyridin-2-yl) (S)-2-(4-isobutylphenyl)propanethioate (108l)**



(*S*)-2-(4-Isobutylphenyl)propanethioate was prepared according to **TP2** at 0 °C from (*S*)-2-(4-isobutylphenyl)-propanoic acid (412 mg, 2.00 mmol) and was obtained as a yellow oil (574 mg, 1.96 mmol, 96% yield).

Purification: *i*hexane:ethyl acetate = 9:1 → 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.80 (t, *J* = 1.8 Hz, 1H), 7.69 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.34 (ddd, *J* = 7.8, 2.0, 1.1 Hz, 1H), 7.32 – 7.23 (m, 1H), 7.20 – 7.14 (m, 2H), 7.09 – 7.02 (m, 2H), 4.01 (q, *J* = 7.1 Hz, 1H), 2.47 (d, *J* = 7.1 Hz, 2H), 1.86 (dp, *J* = 13.6, 6.8 Hz, 1H), 1.60 (d, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 198.5, 151.8, 150.2, 141.3, 137.1, 136.2, 130.1, 129.6, 127.9, 123.4, 54.2, 45.1, 30.2, 22.4, 18.4.

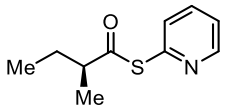
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2928, 2868, 1706, 1573, 1563, 1511, 1448, 1420, 1368, 1240, 1217, 1183, 1168, 1140, 121, 1097, 1084, 1066, 1045, 998, 988, 930, 847, 802, 763, 738, 724, 663.

HR-MS (ESI, 70eV): [$C_{18}H_{22}NOS$], calcd.: 300.1417; found: 300.1416 [M^++H].

Optical rotation: $[\alpha]_D^{20} =$ 104 (c 1.24, $CHCl_3$).

Chiral HPLC: 98% *ee*, OD-H column, heptane:*i*PrOH = 90:10, 1.0 mL/min, 30 °C.

***S*-(Pyridin-2-yl) (*S*)-2-methylbutanethioate (108m)**



S-(Pyridin-2-yl) (*S*)-2-methylbutanethioate was prepared according to **TP2** at 0 °C from *(S)*-2-methylbutanoic acid (510 mg, 5 mmol) and was obtained as a yellow oil (950 mg, 4.87 mmol, 97% yield).

Purification: *i*hexane:ethyl acetate = 9:1 → 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.61 (ddd, *J* = 5.1, 1.8, 0.9 Hz, 1H), 7.72 (td, *J* = 7.7, 1.9 Hz, 1H), 7.60 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.26 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H), 2.70 (h, *J* = 6.9 Hz, 1H), 1.82 (dt, *J* = 13.7, 7.2 Hz, 1H), 1.54 (tt, *J* = 14.4, 7.1 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 200.8, 151.8, 150.4, 137.1, 130.3, 123.5, 50.6, 27.2, 17.1, 11.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2968, 2934, 2877, 1702, 1573, 15622, 1448, 1418, 1380, 1260, 1201, 1139, 1118, 1084, 1045, 987, 967, 939, 829, 807, 762, 732, 719, 669, 670.

MS (EI, 70 eV): *m/z* (%) = 196 (2), 166 (15), 139 (18), 134 (65), 112 (91), 111 (100), 67 (26).

HR-MS (EI, 70eV): [$C_{10}H_{14}NOS$], calcd.: 196.0791; found: 196.0789 [M^++H].

Optical rotation: $[\alpha]_D^{20} = 19$ (c 1.20, $CHCl_3$).

Chiral HPLC: 98% *ee*, OD-H column, heptane:*i*PrOH = 98:2, 1.0 mL/min, 30 °C.

4.5 Preparation of Organometallic Reagents

Preparation of arylzinc pivalates by insertion (TP3):[38f]

Magnesium turnings (1.2 equiv), dry LiCl (1.2 equiv) and dry THF (1.00 M solution relating to the aryl halide) were added to a dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum. The tube was charged with the aromatic bromide (1.0 equiv). For controlling the following initial heat evolution of the insertion reaction, the Schlenk-tube was placed in an ice bath for cooling. To monitor the progress of the insertion reaction, reaction aliquots quenched with iodine and were analyzed as water-quenched samples by GC-analysis. When the insertion was completed, solid $Zn(OPiv)_2$ (1.0 equiv) was added in one portion at 0 °C and stirred at ambient temperature for 15 min.

Preparation of arylzinc pivalates by halogen/magnesium exchange (TP4):[38f]

A dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum was charged with the corresponding aryl halide (1.00 mmol) in THF (0.50 M) Then, after stirring for 5 min at ambient temperature, the resulting solution was cooled to -20 °C, *i*PrMgCl (1.11 m in THF, 1.1 equiv) was added

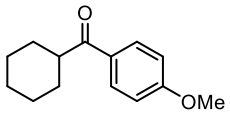
dropwise. GC-analysis was used to monitor the progress of the halogen-magnesium exchange, by analysis of reaction aliquots quenched with I_2. The reaction was completed within 60 min. $Zn(OPiv)_2$ (1.0 equiv) was added in one portion at 0 °C and the mixture was slowly warmed to room temperature.

4.6 Cobalt-Catalyzed Acylation-Reactions of (Hetero)arylzinc Pivalates with Organic Thiopyridylester derivatives

Cobalt-catalyzed acylation of arylzinc pivalates with thiopyridyl esters (TP5):

A dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum was charged with $CoCl_2$ (6.5 mg, 0.05 mmol, 0.10 equiv, dried in *vacuo* at 400 °C prior to use). Then, the ligand 4,4'-di-*tert*-butyl-2,2'-dipyridyl (13.0 mg, 0.05 mmol, 0.10 equiv) and the corresponding thiopyridyl ester (**108**, 0.50 mmol, 1.0 equiv) were added to the *Schlenk*-tube. The resulting mixture was dissolved in dry THF (1 mL). Then, the organozinc pivalate, synthesized *via* **TP2** or **TP3** (0.95 mmol, 1.9 equiv) was added and stirring was continued for 4 h, at 25 °C. For substance **110t-y** the reaction was carried out at 0 °C. The reaction conversion was monitored by GC-analysis of water-quenched reaction aliquots ($C_{14}H_{30}$ was used as an internal standard). Upon consumption of the starting material, sat. aq. NH_4Cl solution (10 mL) was added, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the residue was subjected to column chromatographical purification (pentane/ethyl acetate) on silica yielding the corresponding title compound.

Cyclohexyl(4-methoxyphenyl)methanone (110a)



Following **TP5** *S*-(pyridin-2-yl) cyclohexanecarbothioate (**108a**, 111 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-(methoxy)phenylzinc pivalate (**72**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 96 mg, 0.44 mmol, 88%, colorless crystals.

Purification: pentane:ethyl acetate = 99:1.

m.p.: 64.2 – 66.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.94 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 3.22 (tt, *J* = 11.5, 3.2 Hz, 1H), 1.85 (tdd, *J* = 11.7, 6.2, 3.0 Hz, 4H), 1.73 (dddt, *J* = 12.8, 5.0, 3.3, 1.7 Hz, 1H), 1.57 – 1.38 (m, 3H), 1.36 – 1.19 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 202.6, 163.3, 130.6, 129.4, 113.8, 55.6, 45.4, 29.7, 26.1, 26.1.

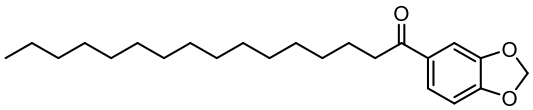
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3065, 3019, 2973, 2944, 2916, 2846, 1639, 1628, 1594, 1573, 1504, 1499, 1466, 1454, 1442, 1416, 1405, 1302, 1296, 1284, 1256, 1224, 1182, 1175, 1148, 1116, 1094, 1064, 1028, 1013, 967, 959, 949, 928, 856, 842, 828, 815, 789, 763, 682.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923, 2851, 1658, 1598, 1571, 1505, 1458, 1420, 1370, 1334, 1313, 1299, 1251, 1208, 1163, 1133, 1103, 1025, 972, 896, 844, 825, 791, 770, 742, 687.

MS (EI, 70 eV): *m/z* (%) = 135 (100), 150 (13), 187 (8), 218 (6).

HR-MS (EI, 70eV): [$C_{14}H_{18}O_2$], calcd.: 218.1307; found: 218.1302.

1-(Benzo[*d*][1,3]dioxol-5-yl)hexadecan-1-one (110b)



Following **TP5** *S*-(pyridin-2-yl) hexadecanethioate (**108b**, 175 mg, 0.50 mmol, 1.0 equiv) was coupled with (benzo[*d*][1,3]dioxol-5-yl)zinc pivalate (**109a**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 162 mg, 0.45 mmol, 90%, white solid.

Purification: pentan*e*:ethyl acetate = 100:2.

m.p.: 73.5 – 75.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.56 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.44 (d, *J* = 1.7 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.04 (s, 2H), 2.87 (t, *J* = 7.5 Hz, 2H), 1.70 (p, *J* = 7.4 Hz, 2H), 1.25 (s, 26H), 0.88 (t, *J* = 6.7 Hz, 3H).

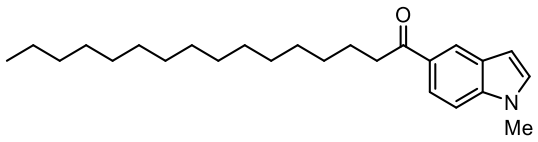
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 198.9, 151.7, 148.3, 132.1, 124.4, 108.1, 108.0, 101.9, 38.6, 32.1, 29.9, 29.8, 29.8, 29.8, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 24.8, 22.9, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961, 2952, 2914, 2868, 2847, 2774, 1675, 1604, 1497, 1488, 1472, 1462, 1444, 1418, 1373, 1359, 1285, 1279, 1263, 1258, 1250, 1200, 1110, 1092, 1051, 1004, 990, 940, 900, 889, 824, 811, 805, 780, 757, 742, 730, 719, 655.

MS (EI, 70 eV): *m/z* (%) = 281 (21), 225 (8), 209 (8), 208 (10), 207 (84), 191 (16), 165 (10), 164 (100), 149 (57), 121 (12), 44 (7).

HR-MS (EI, 70eV): [$C_{23}H_{36}O_3$], calcd.: 360.2664; found: 360.2662.

1-(1-Methyl-1*H*-indol-5-yl)hexadecan-1-one (110c)



Following **TP5** *S*-(pyridin-2-yl) hexadecanethioate (**108b**, 175 mg, 0.50 mmol, 1.0 equiv) was coupled with ((1-methyl-1*H*-indol-5-yl)zinc pivalate (**109b**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 137 mg, 0.37 mmol, 74%, pale yellow crystals.

Purification: pentan*e*:ethyl acetate = 9:1.

m.p.: 71.6 – 73.5 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 8.31 (d, *J* = 1.6 Hz, 1H), 7.91 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.11 (d, *J* = 3.2 Hz, 1H), 6.61 (d, *J* = 3.1 Hz, 1H), 3.82 (s, 3H), 3.03 (t, *J* = 7.5 Hz, 2H), 1.77 (p, *J* = 7.5 Hz, 2H), 1.26 (s, 18H), 0.88 (t, *J* = 6.7 Hz, 3H).

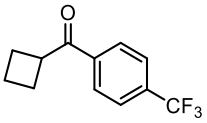
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 200.9, 139.2, 130.4, 129.4, 128.0, 122.9, 121.9, 109.2, 103.1, 38.7, 33.2, 32.1, 29.8, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 25.1, 22.9, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2948, 2920, 2848, 1657, 1606, 1556, 1513, 1464, 1450, 1212, 1412, 1368, 1343, 1309, 1297, 1264, 1249, 1229, 1163, 1145, 1090, 968, 821, 803, 780, 766, 733, 724.

MS (EI, 70 eV): *m/z* (%) = 130 (14), 158 (72), 173 (100), 174 (14), 369 (11).

HR-MS (EI, 70eV): [$C_{25}H_{39}NO$], calcd.: 369.3032; found: 369.3037.

Cyclobutyl(4-(trifluoromethyl)phenyl)methanone (110d)



Following **TP5** *S*-(pyridin-2-yl) cyclobutanecarbothioate (**108c**, 97 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-(trifluoromethyl)phenyl)zinc pivalate (**109c**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 96 mg, 0.42 mmol, 84% yield, colorless oil.

Purification: pentan*e*:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.99 (dt, *J* = 8.1, 1.0 Hz, 2H), 7.74 – 7.68 (m, 2H), 4.13 – 3.93 (m, 1H), 2.50 – 2.26 (m, 4H), 2.18 – 2.05 (m, 1H), 1.99 – 1.86 (m, 1H).

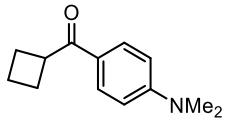
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 199.92, 138.26 , 134.15 (q, *J* = 32.6 Hz), 128.64 , 125.65 (q, *J* = 3.8 Hz), 123.63 (q, *J* = 272.7 Hz), 42.36 , 24.97 , 18.13 .

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951, 1674, 1510, 1410, 1322, 1252, 1227, 1212, 1166, 1125, 1108, 1065, 1015, 967, 949, 922, 893, 856, 842, 783, 774, 762, 731, 684, 671.

MS (EI, 70 eV): *m/z* (%) = 227 (1), 174 (8), 173 (11), 173 (100), 145 (25).

HR-MS (EI, 70eV): [$C_{12}H_{11}F_3O$], calcd.: 228.0762, found: 228.0758.

Cyclobutyl(4-(dimethylamino)phenyl)methanone (110e)



Following **TP5** *S*-(pyridin-2-yl) cyclobutanecarbothioate (**109c**, 97 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-(dimethylamino)phenyl)zinc pivalate (**109d**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 97 mg, 0.48 mmol, 95% yield, white solid.

Purification: pentane:ethyl acetate = 95:5.

m.p.: 75.2– 77.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.82 – 7.71 (m, 2H), 6.67 – 6.57 (m, 2H), 3.88 (pd, *J* = 8.6, 1.1 Hz, 1H), 2.98 (s, 6H), 2.42 – 2.27 (m, 2H), 2.18 (dddd, *J* = 12.4, 10.6, 8.8, 3.9 Hz, 2H), 2.08 – 1.91 (m, 1H), 1.81 (ddddd, *J* = 14.6, 9.2, 7.9, 4.0, 1.1 Hz, 1H).

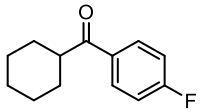
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 199.4, 153.0, 130.4, 111.0, 110.9, 41.7, 40.3, 25.3, 18.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959, 1667, 1622, 1478, 1387, 1261, 1195, 1167, 1025, 909, 856, 819.

MS (EI, 70 eV): *m/z* (%) = 203 (16), 148 (100), 44 (12), 42 (39).

HR-MS (EI, 70eV): [$C_{13}H_{17}NO$], calcd.: 203.1310, found: 203.1305.

Cyclohexyl(4-fluorophenyl)methanone (110f)



Following **TP5** *S*-(pyridin-2-yl) cyclohexanecarbothioate (**108a**, 111 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-fluorophenyl)zinc pivalate (**109e**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 62 mg, 0.30 mmol, 60%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.07 – 7.85 (m, 2H), 7.21 – 7.03 (m, 2H), 3.21 (tt, *J* = 11.4, 3.2 Hz, 1H), 1.95 – 1.79 (m, 4H), 1.74 (dtt, *J* = 13.0, 3.5, 1.8 Hz, 1H), 1.58 – 1.16 (m, 5H).

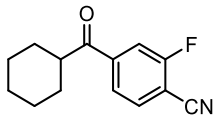
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 202.4, 165.7 (d, J = 254.0 Hz), 132.8 (d, J = 3.0 Hz), 131.0 (d, J = 9.2 Hz), 115.8 (d, J = 21.7 Hz), 45.7, 29.6, 26.1, 26.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068, 2929, 2853, 1678, 1596, 1505, 1463, 1450, 1409, 1371, 1332, 1312, 1295, 1289, 1249, 1233, 1205, 1176, 1154, 1134, 1102, 1027, 1012, 974, 893, 860, 841, 824, 806, 800, 776, 738, 675.

MS (EI, 70 eV): *m/z* (%) = 206 (9), 151 (21), 138 (9), 124 (8), 123 (100), 95 (8).

HR-MS (EI, 70eV): [$C_{13}H_{15}FO$], calcd.: 206.1107; found: 206.1101.

4-(Cyclohexanecarbonyl)-2-fluorobenzonitrile (110g)



Following **TP5** *S*-(pyridin-2-yl) cyclohexanecarbothioate (**108a**, 111 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-cyano-3-fluorophenyl)zinc pivalate (**109f**, 0.95 mmol, 1.9 equiv)prepared according to **TP4** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 91 mg, 0.39 mmol, 79%, colorless crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 54.4 – 56.2 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.85 – 7.68 (m, 3H), 3.16 (tt, *J* = 11.3, 3.1 Hz, 1H), 1.86 (dp, *J* = 9.5, 3.4 Hz, 4H), 1.75 (dddd, *J* = 11.5, 5.2, 3.3, 1.7 Hz, 1H), 1.58 – 1.16 (m, 5H).

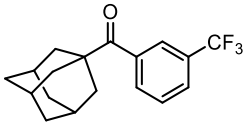
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 201.2 (d, *J* = 1.6 Hz), 163.4 (d, *J* = 261.1 Hz), 142.2 (d, *J* = 6.1 Hz), 134.1, 124.3 (d, *J* = 3.7 Hz), 116.1 (d, *J* = 20.5 Hz), 113.4, 105.2 (d, *J* = 15.9 Hz), 46.2, 29.2, 25.9, 25.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3076, 2930, 2855, 2239, 1686, 1618, 1567, 1495, 1463, 1450, 1421, 1415, 1373, 1331, 1313, 1299, 1290, 1274, 1253, 1230, 1192, 1157, 1133, 1120, 1103, 996, 988, 921, 908, 901, 873, 836, 797, 772, 734, 706.

MS (EI, 70 eV): *m/z* (%) = 231 (43), 225 (8), 216 (9), 213 (18), 190 (31), 189 (12), 188 (12), 177 (10), 176 (100), 165 (7), 164 (26), 163 (26), 158 (7), 148 (86), 121 (59), 129 (10), 105 (24), 100 (21), 83 (16), 77 (9), 68 (8), 67 (11), 55 (27).

HR-MS (EI, 70eV): [$C_{14}H_{14}FNO$], calcd.: 231.1059; found: 231.1054.

(Adamantan-1-yl)(3-(trifluoromethyl)phenyl)methanone (110h)



Following **TP5** *S*-(pyridin-2-yl)-adamantane-1-carbothioate (**108d**, 137 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-(trifluoromethyl)phenyl) zinc pivalate (**109g**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 94 mg, 0.31 mmol, 61%, white solid.

Purification: pentane:ethyl acetate = 98:2.

m.p.: 63.6 – 65.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.76 (d, *J* = 2.0 Hz, 1H), 7.70 (t, *J* = 8.4 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 1H), 2.09 (q, *J* = 3.1 Hz, 3H), 1.99 (d, *J* = 2.9 Hz, 6H), 1.82 – 1.68 (m, 6H).

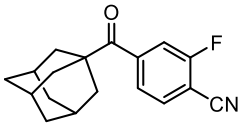
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 209.0, 140.3, 131.7 – 129.7 (m), 130.4 (d, *J* = 1.4 Hz), 128.7, 126.9 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 3.9 Hz), 123.9 (q, *J* = 272.5 Hz), 47.1, 39.1, 36.5, 28.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2943, 2914, 2854, 1661, 1605, 1453, 1329, 1309, 1261, 1225, 1184, 1162, 1119, 1102, 1071, 998, 922, 808, 778, 762, 734, 695, 659.

MS (EI, 70 eV): *m/z* (%) = 308 (1), 136 (12), 135 (100), 93 (12), 79 (12).

HR-MS (EI, 70eV): [$C_{18}H_{19}F_3O$], calcd.: 308.1388; found: 308.1382.

4-(Adamantane-1-carbonyl)-2-fluorobenzonitrile (110i)



Following **TP5** *S*-(pyridin-2-yl)-adamantane-1-carbothioate (**108d**, 137 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-cyano-3-fluorophenyl)zinc pivalate (**109f**, 0.95 mmol, 1.9 equiv) prepared according to **TP4** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 114 mg, 0.41 mmol, 81%, colorless crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 103.9 -105.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.66 (dd, *J* = 7.9, 6.2 Hz, 1H), 7.31 (ddd, *J* = 21.5, 8.5, 1.4 Hz, 2H), 2.07 (q, *J* = 3.1 Hz, 3H), 1.93 (d, *J* = 3.0 Hz, 6H), 1.81 – 1.65 (m, 6H).

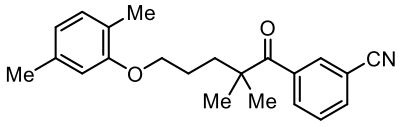
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 207.6 (d, *J* = 1.4 Hz), 162.6 (d, *J* = 261.2 Hz), 146.3 (d, *J* = 6.2 Hz), 133.5, 123.2 (d, *J* = 3.9 Hz), 115.1 (d, *J* = 20.9 Hz), 113.4, 102.8 (d, *J* = 15.6 Hz), 47.2, 38.8, 36.3, 27.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3053, 2930, 2901, 2858, 2849, 2673, 2652, 2241, 1682, 1620, 1561, 1497, 1451, 1413, 1344, 1323, 1297, 1276, 1269, 1252, 1225, 1209, 1191, 1179, 1171, 1106, 1099, 1003, 968, 938, 902, 884, 879, 851, 819, 793, 764, 751, 732, 718, 677, 661.

MS (EI, 70 eV): *m/z* (%) = 136 (11), 135 (100), 107 (14), 93 (16), 79 (13).

HR-MS (EI, 70eV): [$C_{18}H_{18}FNO$], calcd.: 283.1372; found: 283.1266.

3-(5-(2,5-Dimethylphenoxy)-2,2-dimethylpentanoyl)benzonitrile (110j)



Following **TP5** *S*-(pyridin-2-yl) 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanethioate (**108e**, 172 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-cyanophenyl)zinc pivalate (**109h**, 0.95 mmol, 1.9 equiv) prepared according to **TP4** from the corresponding iodide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 110 mg, 0.33 mmol, 66%, yellow oil.

Purification: pentane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.97 (d, *J* = 1.8 Hz, 1H), 7.92 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.74 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.66 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.60 – 6.54 (m, 1H), 3.90 (t, *J* = 6.0 Hz, 2H), 2.29 (s, 3H), 2.13 (s, 3H), 2.02 – 1.91 (m, 2H), 1.80 – 1.67 (m, 2H), 1.37 (s, 6H).

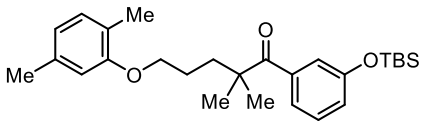
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 206.7, 156.8, 139.8, 136.6, 134.2, 131.8, 131.4, 130.4, 129.3, 123.4, 120.9, 118.2, 112.8, 111.8, 67.5, 47.9, 37.4, 26.0, 25.1, 21.5, 16.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922, 2230, 1677, 1677, 1583, 1508, 1470, 1414, 1388, 1309, 1284, 1262, 1223, 1156, 1128, 1043, 1017, 999, 844, 803, 752, 683.

MS (EI, 70 eV): *m/z* (%) = 335 (4), 214 (100), 144 (13), 130 (26), 122 (17), 102 (10), 83 (12), 55 (15).

HR-MS (EI, 70eV): [$C_{22}H_{25}NO_2$], calcd.: 335.1885, found: 335.1888.

1-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)-5-(2,5-dimethylphenoxy)-2,2-dimethylpentan-1-one (110k)



Following **TP5** *S*-(pyridin-2-yl) 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanethioate (**108e**, 172 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-((*tert*-butyldimethylsilyl)oxy)phenyl)zinc pivalate (**109i**,

0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 158 mg, 0.36 mmol, 78%, pale yellow oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.13 – 6.99 (m, 2H), 6.93 (t, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.73 (ddd, *J* = 7.8, 2.5, 1.3 Hz, 1H), 6.44 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.37 (d, *J* = 1.5 Hz, 1H), 3.68 (t, *J* = 6.1 Hz, 2H), 2.09 (s, 3H), 1.94 (s, 3H), 1.79 – 1.68 (m, 2H), 1.59 – 1.48 (m, 2H), 1.14 (s, 6H), 0.78 (s, 9H), 0.00 (s, 6H).

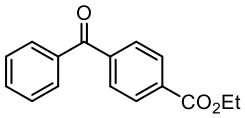
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 208.6, 156.9, 155.4, 140.3, 136.4, 130.3, 129.2, 123.5, 122.7, 120.7, 120.5, 119.3, 111.8, 67.8, 47.7, 37.5, 26.2, 25.7, 25.1, 21.4, 18.2, 15.8, -4.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953, 2927, 1672, 1594, 1576, 1508, 1470, 1421, 1388, 1362, 1251, 1183, 1156, 1129, 1044, 1000, 913, 834, 800, 779, 759, 685.

MS (EI, 70 eV): *m/z* (%) = 320 (23), 319 (100), 235 (32), 83 (8), 73 (14).

HR-MS (EI, 70eV): [$C_{27}H_{40}O_3Si$], calcd.: 440.2747, found: 440.2751.

Ethyl 4-benzoylbenzoate (110l)



Following **TP5** **S**-(pyridin-2-yl) benzothioate (**108f**, 108 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-(ethoxycarbonyl)phenyl)zinc pivalate (**109j**, 0.95 mmol, 1.9 equiv) prepared according to **TP4** at -40 °C from the corresponding iodide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 90 mg, 0.35 mmol, 71% yield, colorless crystals.

Purification: pentane:ethyl acetate = 95:5.

m.p.: 93.6 – 95.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.20 – 8.11 (m, 2H), 7.82 (ddd, *J* = 14.6, 7.6, 1.8 Hz, 4H), 7.66 – 7.57 (m, 1H), 7.50 (dd, *J* = 8.4, 7.1 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

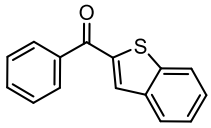
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.2, 166.0, 141.3, 137.1, 133.7, 133.1, 130.3, 129.9, 129.6, 128.6, 61.6, 14.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2979, 1704, 1660, 1604, 1480, 1446, 1399, 1367, 1266, 1179, 1102, 1019, 1004, 937, 925, 845, 752, 712, 695, 656.

MS (EI, 70 eV): *m/z* (%) = 177 (28), 105 (100), 149 (59), 152 (39), 181 (59), 209 (59), 226 (30), 254 (35).

HR-MS (EI, 70eV): [$C_{16}H_{14}O_3$], calcd.: 254.0943; found:254.0939.

Benzo[*b*]thiophen-2-yl(phenyl)methanone (110m)



Following **TP5**, using TMEDA (10 mol%, 0.05 mmol, 6 mg) as ligand, *S*-(pyridin-2-yl) benzothioate (**108f**, 108 mg, 0.50 mmol, 1.0 equiv) was coupled with (benzo[*b*]thiophen-2-yl)zinc pivalate (**109k**, 0.95 mmol, 1.9 equiv) prepared by directed metalation from benzo[*b*]thiophen and TMPMgCl (1.0 equiv) at 0 °C for 3 h, followed by transmetalation with $Zn(OPiv)_2$ (1.0 equiv) The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 81 mg, 0.34 mmol, 68%, orange oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.96 – 7.85 (m, 5H), 7.68 – 7.60 (m, 1H), 7.54 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.49 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H).

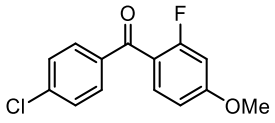
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 189.8, 143.2, 142.8, 139.2, 138.0, 132.6, 132.4, 129.4, 128.7, 127.6, 126.2, 125.2, 123.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1631, 1593, 1576, 1509, 1455, 1444, 1425, 1314, 1285, 1245, 1187, 1175, 1157, 1114, 1066, 1025, 880, 869, 833, 790, 746, 731, 708, 701, 664.

MS (EI, 70 eV): *m/z* (%) = 238 (100), 23 (11), 210 (10), 161 (97), 133 (16), 105 (40), 89 (23), 77 (31).

HR-MS (EI, 70eV): [$C_{15}H_{10}OS$], calcd.: 238.0452, found: 238.0454.

(4-Chlorophenyl)(2-fluoro-4-methoxyphenyl)methanone (110n)



Following **TP5** *S*-(pyridin-2-yl) 4-chlorobenzothioate (**108g**, 125 mg, 0.50 mmol, 1.0 equiv) was coupled with (2-fluoro-4-methoxyphenyl)zinc pivalate (**109l**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 121 mg, 0.46, 92%, colorless oil.

Purification: pentan*e*:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.74 (dd, J = 8.5, 1.6 Hz, 2H), 7.57 (t, *J* = 8.4 Hz, 1H), 7.46 – 7.40 (m, 2H), 6.80 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.66 (dd, *J* = 12.0, 2.4 Hz, 1H), 3.88 (s, 3H).

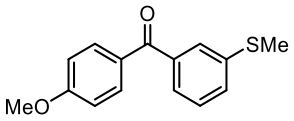
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 191.5 (d, J = 1.0 Hz), 164.2 (d, J = 11.3 Hz), 163.1, 161.9 (d, J = 254.1 Hz), 139.2, 136.7, 132.7 (d, J = 4.4 Hz), 130.9 (d, J = 1.7 Hz), 128.6, 118.9 (d, J = 13.6 Hz), 101.9 (d, J = 25.7 Hz), 55.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1671, 1588, 1570, 1560, 1544, 1446, 1426, 1340, 1282, 1235, 1218, 1154, 1116, 1069, 1054, 986, 916, 885, 791, 58, 733, 690.

MS (EI, 70 eV): *m/z* (%) = 139 (16), 153 (100), 154 (9), 187 (9), 220 (11), 264 (25), 266 (8).

HR-MS (EI, 70eV): [$C_{14}H_{10}ClFO_2$], calcd.: 264.0353, found: 264.0351.

(4-Methoxyphenyl)(3-(methylthio)phenyl)methanone (110o)



Following **TP5** *S*-(pyridin-2-yl) 4-methoxybenzothioate (**108h**, 123 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-(methylthio)phenylzinc pivalate (**109m**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 123 mg, 0.48 mmol, 96%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.89 – 7.77 (m, 2H), 7.62 (t, *J* = 1.7 Hz, 1H), 7.55 – 7.30 (m, 3H), 7.05 – 6.88 (m, 2H), 3.89 (s, 3H), 2.52 (s, 3H).

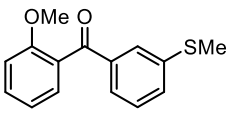
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 195.3, 163.5, 139.3, 139.0, 132.7, 130.1, 129.8, 128.6, 127.1, 126.5, 113.7, 55.7, 15.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2916, 2847, 1650, 1597, 1567, 1507, 1419, 1315, 1282, 1256, 1175, 1154, 1026, 842, 756, 710.

MS (EI, 70 eV): *m/z* (%) = 258 (36), 211 (19), 136 (9) 135 (100), 77 (11).

HR-MS (EI, 70eV): [$C_{15}H_{14}O_2S$], calcd.: 258.0715; found: 258.0709.

(2-Methoxyphenyl)(3-(methylthio)phenyl)methanone (110o')



Following **TP5** *S*-(pyridin-2-yl) 2-methoxybenzothioate (**108h'**, 123 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-(methylthio)phenylzinc pivalate (**109m**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 91 mg, 0.35 mmol, 71%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 7.74 (t, *J* = 1.8 Hz, 1H), 7.54 – 7.40 (m, 3H), 7.39 – 7.29 (m, 2H), 7.04 (td, *J* = 7.4, 0.9 Hz, 1H), 6.99 (dd, *J* = 8.5, 0.9 Hz, 1H), 3.73 (s, 3H), 2.50 (s, 3H).

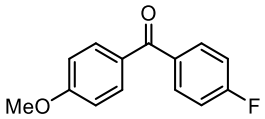
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 196.2, 157.5, 139.3, 138.5, 132.2, 130.9, 129.8, 128.7, 128.7, 127.0, 127.0, 120.7, 111.6, 55.7, 15.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920, 2836, 1659, 1597, 1581, 1567, 1486, 1462, 1434, 1413, 1294, 1241, 1180, 1154, 1111, 1077, 1047, 1020, 994, 973, 959, 949, 936, 889, 809, 750, 716, 672.

MS (EI, 70 eV): *m/z* (%) = 258 (32), 211 (43), 138 (23), 135 (100), 121 (58), 79 (26), 77 (38)

HR-MS (EI, 70eV): [$C_{15}H_{14}O_2S$], calcd.: 258.0715; found: 258.0707.

(4-Fluorophenyl)(4-methoxyphenyl)methanone (110p)



Following **TP5** *S*-(pyridin-2-yl) 4-methoxybenzothioate (**108h**, 123 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-fluorophenyl)zinc pivalate (**109e**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 99 mg, 0.43 mmol, 86% yield, white solid.

Purification: pentan*e*:ethyl acetate = 9:1.

m.p.: 97.1 – 98.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.80 (dt, *J* = 8.7, 2.7 Hz, 4H), 7.15 (t, *J* = 8.6 Hz, 2H), 7.03 – 6.92 (m, 2H), 3.89 (s, 3H).

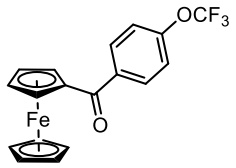
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 194.3, 165.2 (d, *J* = 253.2 Hz), 163.4, 134.6 (d, *J* = 3.1 Hz), 132.6, 132.4 (d, *J* = 9.1 Hz), 130.1, 115.5 (d, *J* = 21.8 Hz), 113.8, 55.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3065, 3019, 2973, 2944, 2916, 2846, 1639, 1628, 1594, 1573, 1504, 1499, 1466, 1454, 1442, 1416, 1405, 1302, 1296, 1284, 1256, 1224, 1182, 1175, 1148, 1116, 1094, 1064, 1028, 1013, 967, 959, 949, 928, 856, 842, 828, 815, 789, 763, 682.

MS (EI, 70 eV): *m/z* (%) = 231 (7), 230 (43), 199 (13), 136 (9), 135 (100), 123 (16), 77 (9).

HR-MS (EI, 70eV): [$C_{14}H_{11}FO_2$], calcd.: 230.0743; found: 230.0737.

Ferrocenyl-(4-(trifluoromethoxy)phenyl)methanone (110q)



Following **TP5** *S*-(pyridin-2-yl) ferrocenecarbothioate (**108i**, 162 mg, 0.50 mmol, 1.0 equiv) was coupled with 4-(trifluoromethoxy)phenyl)zinc pivalate (**109n**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 151 mg, 0.40 mmol, 81%, red solid.

Purification: pentan*e*:ethyl acetate = 9:1.

m.p.: 38.2 – 40.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.03 – 7.91 (m, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 4.89 (t, *J* = 1.9 Hz, 2H), 4.62 (t, *J* = 2.0 Hz, 2H), 4.21 (s, 5H).

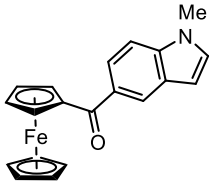
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 197.7, 153.8 – 150.2 (m), 138.2, 130.1, 120.5 (q, *J* = 258.3 Hz), 120.4, 77.9, 73.0, 71.6, 70.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924, 1627, 1598, 1447, 1251, 1213, 1152, 1104, 1054, 1027, 1014, 1002, 968, 951, 923, 852, 822, 767, 713.

MS (EI, 70 eV): *m/z* (%) = 375 (20), 374 (100), 372 (6), 212 (7), 185 (9), 139 (24).

HR-MS (EI, 70eV): [$C_{18}H_{13}F_3FeO_2$], calcd.: 374.0217, found: 374.0214.

Ferrocenyl-(1-methyl-1H-indol-5-yl)methanone (110r)



Following **TP5** *S*-(pyridin-2-yl) ferrocenecarbothioate (**108i**, 162 mg, 0.50 mmol, 1.0 equiv) was coupled with ((1-methyl-1*H*-indol-5-yl)zinc pivalate (**109b**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 144 mg, 0.42, 84%, red oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.32 (d, *J* = 1.8 Hz, 1H), 7.87 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.14 (d, *J* = 3.1 Hz, 1H), 6.62 (d, *J* = 3.1 Hz, 1H), 4.98 (t, *J* = 2.0 Hz, 2H), 4.56 (t, *J* = 2.0 Hz, 2H), 4.21 (s, 5H), 3.85 (s, 3H).

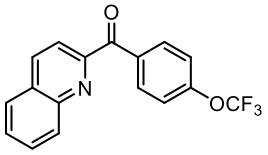
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 199.1, 138.6, 131.6, 130.3, 127.7, 122.7, 122.5, 109.0, 102.7, 79.5, 72.0, 71.9, 70.3, 33.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3093, 2920, 1624, 1597, 1564, 1511, 1489, 1441, 1416, 1373, 1337, 1305, 1286, 1267, 1242, 1210, 1149, 1135, 1098, 1081, 1044, 1025, 1000, 900, 841, 818, 776, 753, 736, 722.

MS (EI, 70 eV): *m/z* (%) = 344 (23), 343 (100), 341 (7), 194 (9), 130 (9).

HR-MS (EI, 70eV): [$C_{20}H_{17}FeNO$], calcd.: 343.0660, found: 343.0659.

Quinolin-2-yl(4-(trifluoromethoxy)phenyl)methanone (110s)



Following **TP5** *S*-(pyridin-2-yl) quinoline-2-carbothioate (**108j**, 133 mg, 0.50 mmol, 1.0 equiv) was coupled with 4-(trifluoromethoxy)phenyl)zinc pivalate (**109n**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 108 mg, 0.34 mmol, 68%, colorless oil.

Purification: pentane:ethyl acetate = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.41 – 8.33 (m, 3H), 8.20 (dq, *J* = 8.6, 0.9 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.93 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.81 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.69 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.35 (dq, *J* = 9.1, 1.1 Hz, 2H).

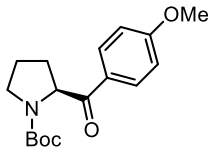
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 192.12, 154.22, 152.76, 152.74, 146.79, 137.48, 134.52, 133.72, 130.65, 130.42, 129.17, 128.85, 127.84, 121.90 – 119.05 (m, 2C)

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1662, 1605, 1587, 1508, 1309, 1295, 1202, 1140, 1112, 967, 957, 920, 850, 835, 794, 769, 743, 669.0

MS (EI, 70 eV): *m/z* (%) = 95, (12), 189 (100), 189 (29), 191 (15), 204 (42), 232 (17), 288 (69), 289 (53), 316 (28), 317 (30).

HR-MS (EI, 70eV): [$C_{17}H_{10}F_3NO_2$], calcd.: 317.0664, found: 317.0660.

***tert*-Butyl (*S*)-2-(4-methoxybenzoyl)pyrrolidine-1-carboxylate (110t)**



Following **TP5** *tert*-butyl (*S*)-2-((pyridin-2-ylthio)carbonyl)pyrrolidine-1-carboxylate (**108k**, 154 mg, 0.50 mmol, 1.0 equiv) was coupled with ((4-methoxyphenyl)zinc pivalate (**72**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 110 mg, 0.36 mmol, 72%, pale yellow crystals.

Purification: pentane:ethyl acetate = 8:2 → 6:4.

m.p.: 124.8– 126.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): (mixture of rotamers) δ = 8.06 – 7.85 (m, 2H), 7.04 – 6.82 (m, 2H), 5.29 (dd, *J* = 9.3, 2.9 Hz, 0H), 5.15 (dd, *J* = 8.8, 3.8 Hz, 1H), 3.87 (s, 2H), 3.85 (s, 1H), 3.71 – 3.58 (m, 1H), 3.54 (dt, *J* = 10.6, 6.6 Hz, 1H), 3.46 (dt, *J* = 10.3, 7.3 Hz, 0H), 2.41 – 2.18 (m, 1H), 1.91 (ttd, *J* = 15.0, 7.2, 3.5 Hz, 3H), 1.46 (s, 3H), 1.25 (s, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): (mixture of rotamers) δ = 197.5, 197.0, 163.7, 163.6, 154.6, 154.0, 130.9, 130.6, 128.3, 128.1, 114.0, 113.9, 79.8, 79.7, 61.1, 60.9, 55.6, 55.6, 46.9, 46.7, 31.1, 30.1, 28.6, 28.3, 24.3, 23.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2972, 1680, 1597, 1574, 1510, 1477, 1455, 1391, 1363, 1307, 1254, 1228, 1158, 1115, 1080, 1025, 1010, 988, 918, 880, 838, 809, 771, 688.

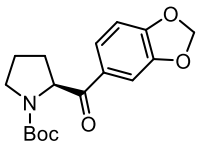
MS (EI, 70 eV): *m/z* (%) = 170 (34), 125 (81), 114 (89), 77 (13), 70 (100), 57 (67), 41 (14).

HR-MS (EI, 70eV): [$C_{17}H_{23}NO_4$], calcd.: 305.1627, found: 305.1624.

Optical rotation: $[\alpha]_D^{20}$ = -23 (c 1.02, $CHCl_3$).

Chiral HPLC: 99% *ee*, OJ-H column, heptane:*i*PrOH = 95:5, 1.0 mL/min, 30 °C.

***tert*-Butyl (*S*)-2-(benzo[*d*][1,3]dioxole-5-carbonyl)pyrrolidine-1-carboxylate (110u)**



Following **TP5** *tert*-butyl 2-((pyridin-2-ylthio)carbonyl)pyrrolidine-1-carboxylate (**108k**, 154 mg, 0.50 mmol, 1.0 equiv) was coupled with (benzo[*d*][1,3]dioxol-5-yl)zinc pivalate (**109a**, 0.95 mmol,

1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 130 mg, 0.41 mmol, 82%, brown oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, DMSO-d6**, ppm):** (mixture of rotamers) δ = 7.66 (ddd, *J* = 8.2, 2.8, 1.7 Hz, 1H), 7.49 (t, *J* = 1.9 Hz, 1H), 7.06 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.15 (s, 2H), 5.25 (ddd, *J* = 10.8, 9.0, 3.8 Hz, 1H), 3.39 (dddd, *J* = 14.2, 11.8, 7.3, 4.6 Hz, 2H), 2.37 – 2.23 (m, 1H), 1.91 – 1.63 (m, 4H), 1.38 (s, 4H), 1.17 (s, 6H).

^{13}C-NMR (100 MHz, DMSO-d$_6$, ppm): (mixture of rotamers) δ = 197.3, 196.5, 153.8, 153.4, 152.1, 148.4, 129.7, 129.5, 125.2, 125.0, 108.7, 108.7, 108.2, 108.0, 102.6, 102.6, 79.0, 78.8, 61.0, 61.0, 47.0, 46.9, 31.0, 30.1, 28.6, 28.3, 27.5, 24.3, 23.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2974, 1682, 1614, 1605, 1505, 1488, 1442, 1392, 1364, 1245, 1160, 1120, 1108, 1097, 1034, 1000, 973, 927, 910, 884, 856, 807, 772, 740, 718.

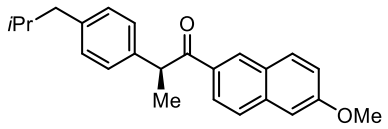
MS (EI, 70 eV): *m/z* (%) = 319 (4), 246 (11), 170 (48), 149 (100), 121 (18), 70 (75), 58 (23), 57 (48), 43 (53).

HR-MS (EI, 70eV): [$C_{17}H_{21}NO_5$], calcd.: 319.1420, found: 319.1411.

Optical rotation: $[\alpha]_D^{20}$ = -29 (c 0,4 $CHCl_3$).

Chiral HPLC: >99% *ee*, OJ-H column, heptane:*i*PrOH = 99:1, 1.0 mL/min, 30 °C.

(*S*)-2-(4-Isobutylphenyl)-1-(6-methoxynaphthalen-2-yl)propan-1-one (110v)



Following **TP5** *S*-(pyridin-2-yl) (*S*)-2-(4-isobutylphenyl)propanethioate (**108l**, 150 mg, 0.50 mmol, 1.0 equiv) was coupled with (6-methoxynaphthalen-2-yl)zinc pivalate (**109o**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 144 mg, 0.42 mmol, 89%, white solid.

Purification: *pentane*:ethyl acetate = 95:5 → 9:1.

m.p.: 70.1 – 72.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.34 (d, J = 1.7 Hz, 1H), 7.92 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.20 – 7.13 (m, 2H), 7.07 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.01 (d, *J* = 2.6 Hz, 1H), 7.00 – 6.96 (m, 2H), 4.72 (q, *J* = 6.8 Hz, 1H), 3.83 (s, 3H), 2.31 (d, *J* = 7.2 Hz, 2H), 1.71 (dp, *J* = 13.5, 6.7 Hz, 1H), 1.49 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 200.4, 159.8, 140.4, 139.1, 137.2, 132.0, 131.3, 130.4, 129.8, 127.9, 127.6, 127.1, 125.5, 119.7, 105.7, 77.1, 55.5, 47.4, 5.1, 30.3, 22.5, 22.5, 19.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2923, 1670, 1622, 1508, 1480, 1458, 1438, 1389, 1369, 1337, 1271, 1264, 1231, 1200, 1167, 1150, 1061, 1024, 945, 911, 901, 893, 864, 856, 849, 830, 817, 801, 776, 770, 762, 738, 698.

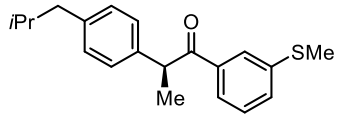
MS (EI, 70 eV): *m/z* (%) = 142 (7), 157 (13), 185 (100), 186 (13), 346 (1).

HR-MS (EI, 70eV): [$C_{24}H_{26}O_2$], calcd.: 346.1933, found: 346.1927.

Optical rotation: $[\alpha]_D^{20} =$ -89 (c 1.02, $CHCl_3$).

Chiral HPLC: 97% *ee*, OD-H column, heptane:*i*PrOH = 98:2, 1.0 mL/min, 30 °C.

(*S*)-2-(4-*iso*-Butylphenyl)-1-(3-(methylthio)phenyl)propan-1-one (110w)



Following **TP5** *S*-(pyridin-2-yl) 2-(4-isobutylphenyl)propanethioate (**108l**, 150 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-(methylthio)phenylzinc pivalate (**109m**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 110 mg, 0.35 mmol, 71%, colourless oil

Purification: pentane:ethyl acetate = 98:2

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.80 (t, J = 1.8 Hz, 1H), 7.69 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.34 (ddd, *J* = 7.8, 2.0, 1.1 Hz, 1H), 7.32 – 7.23 (m, 1H), 7.20 – 7.14 (m, 2H), 7.09 – 7.02 (m, 2H), 4.61 (q, *J* = 6.9 Hz, 1H), 2.45 (s, 3H), 2.40 (d, *J* = 7.2 Hz, 2H), 1.80 (dp, *J* = 13.6, 6.8 Hz, 1H), 1.51 (d, *J* = 6.9 Hz, 3H), 0.86 (dd, J = 6.6, 0.8 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 200.1, 140.4, 139.4, 138.5, 137.1, 130.6, 129.8, 128.7, 127.4, 126.1, 125.4, 47.7, 45.0, 30.2, 22.4, 22.4, 19.5, 15.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2926, 1682, 1584, 1569, 1509, 1465, 1453, 1415, 1384, 1373, 1333, 1215, 1080, 1061, 1014, 960, 882, 848, 795, 747, 686, 667.

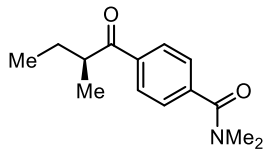
MS (EI, 70 eV): *m/z* (%) = 312 (4), 161 (35), 152 (9), 151 (100), 123 (10).

HR-MS (EI, 70eV): [$C_{20}H_{24}O_S$], calcd.: 312. 1548, found: 312.2539.

Optical rotation: $[\alpha]_D^{20} =$ 107 (c 0.53, $CHCl_3$).

Chiral HPLC: 94% *ee*, OD-H column, heptane:*i*PrOH = 98:2, 1.0 mL/min, 30 °C.

(*S*)-*N*,*N*-Dimethyl-4-(2-methylbutanoyl)benzamide (110x)



Following **TP5** *S*-(pyridin-2-yl) (*S*)-2-methylbutanethioate (**108m**, 98 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-(dimethylcarbamoyl)phenyl)zinc pivalate (**109p**, 0.95 mmol, 1.9 equiv) prepared according to **TP4** from the corresponding iodide at 0 °C in 2 h. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 80 mg, 0.34 mmol, 69%, yellow oil

Purification: pentane:ethyl acetate = 6:4, 5% NEt_3

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.03 – 7.94 (m, 2H), 7.54 – 7.47 (m, 2H), 3.38 (h, *J* = 6.7 Hz, 1H), 3.13 (s, 3H), 2.96 (s, 3H), 1.82 (dqd, *J* = 13.8, 7.4, 6.3 Hz, 1H), 1.49 (ddd, *J* = 14.0, 7.6, 6.8 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 203.9, 170.6, 140.4, 137.4, 128.4, 127.3, 42.3, 26.6, 16.6, 11.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 2933, 2363, 1684, 1636, 1508, 1458, 1396, 1266, 1219, 1081, 1015, 971, 861, 839, 709, 699.

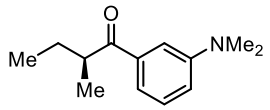
MS (EI, 70 eV): *m/z* (%) = 233 (7), 189 (5), 177 (11), 176 (100), 120 (6), 104 (11).

HR-MS (EI, 70eV): [$C_{14}H_{19}NO_2$], calcd.: 233.1416, found: 233.1407.

Optical rotation: $[\alpha]_D^{20} = 13$ (c 0.1, $CHCl_3$).

Chiral HPLC: >95% *ee*, AD-H column, heptane:*i*PrOH = 99:1, 2.0 mL/min, 30 °C.

(*S*)-1-(3-(Dimethylamino)phenyl)-2-methylbutan-1-one (110y)



Following **TP5** *S*-(pyridin-2-yl) 2-(4-isobutylphenyl)propanethioate (**108m**, 150 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-(dimethylamino)phenyl)zinc pivalate (**109q**, 0.95 mmol, 1.9 equiv) prepared according to **TP3** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 110 mg, 0.35 mmol, 71%, colorless oil

Purification: pentane:ethyl acetate = 98:2

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.35 – 7.15 (m, 3H), 6.86 (ddd, *J* = 8.0, 2.6, 1.3 Hz, 1H), 3.34 (h, *J* = 6.7 Hz, 1H), 2.94 (s, 6H), 1.78 (ddd, *J* = 13.9, 7.5, 6.5 Hz, 1H), 1.52 – 1.37 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 205.3, 150.7, 137.6, 129.1, 116.8, 116.5, 111.5, 42.2, 40.6, 39.4, 35.3, 26.8, 17.0, 11.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2965, 2932, 2874, 1677, 1597, 1574, 1496, 1460, 1434, 1353, 1261, 1213, 1146, 1062, 986, 943, 865, 773, 7421, 682.

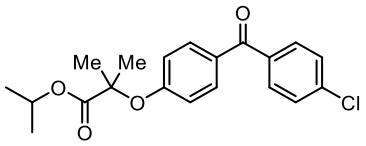
MS (EI, 70 eV): *m/z* (%) = 205 (77), 149 (12), 148 (74), 137 (22), 136 (14), 121 (38), 120 (100), 77 (15).

HR-MS (EI, 70eV): [$C_{13}H_{19}NO$], calcd.: 205.1467, found: 205.1460.

Optical rotation: $[\alpha]_D^{20} = 41$ (c 1.05, $CHCl_3$).

Chiral HPLC: 98% *ee*, OD-H column, heptane:*i*PrOH = 99:1, 1.0 mL/min, 30 °C.

Fenofibrate (110z)



KOH (560 mg, 1.0 equiv, 10 mmol) was added to a solution of 4-iodophenol (**112**, 2.2 g, 10 mmol, 1.0 equiv) in EtOH (20 mL) at 0 °C. After 30 min, isopropyl 2-bromo-2-methylpropanoate (**113**, 2.09 g, 10 mmol, 1.0 equiv) was added and the mixture was refluxed for 16 h. After solvent evaporation the product was subjected to column chromatographical purification with *i*hexane/EtOAc (98:2) as eluent. Isopropyl 2-(4-iodophenoxy)-2-methylpropanoate (**114**) was obtained as a yellow oil (2.44 g, 7 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.57 – 7.44 (m, 2H), 6.71 – 6.51 (m, 2H), 5.17 – 4.95 (m, 1H), 1.57 (s, 7H), 1.21 (d, J = 6.3 Hz, 6H).

Magnesium turnings (1.2 equiv), dry LiCl (1.2 equiv), $Zn(OPiv)_2$ (1.0 equiv) and dry THF (0.5 M) were added to a dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum. The tube was charged with isopropyl 2-(4-iodophenoxy)-2-methylpropanoate (**114**, 1.0 equiv) at room temperature. To monitor the progress of the insertion reaction, reaction aliquots were quenched with iodine and analyzed by GC-analysis. The insertion was completed within 4 h and the concentration was determined by titration with iodine, yielding (4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)phenylzinc pivalate **109r** in 72%.

A dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum was charged with $CoCl_2$ (3.25 mg, 0.025 mmol, 0.10 equiv, dried in *vacuo* at 400 °C prior to use). Then, the ligand 4,4'-di-*tert*-butyl-2,2'-dipyridyl (6.5 mg, 0.25 mmol, 0.10 equiv) and *S*-(pyridin-2-yl) 4-chlorobenzothioate (**108g**, 63 mg, 0.25 mmol, 1.0 equiv) added to the *Schlenk*-tube. The resulting mixture was dissolved in dry

THF (0.5 mL). Then, (4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)phenylzinc pivalate (**109r**, 0.48 mmol, 1.9 equiv) was added and stirring was continued for 4 h, at 25 °C. Upon consumption of the starting material, satured aq. NH_4Cl solution (10 mL) was added, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the residue was subjected to column chromatographical purification.

Isolated yield: 59 mg, 0.16 mmol, 64% yield, colorless solid.

Purification: pentane:ethyl acetate = 90:10.

m.p.:65.6 – 67.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.75 – 7.71 (m, 2H), 7.71 – 7.66 (m, 2H), 7.50 – 7.41 (m, 2H), 6.91 – 6.82 (m, 2H), 5.08 (h, *J* = 6.3 Hz, 1H), 1.66 (s, 6H), 1.20 (d, *J* = 6.2 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 194.3, 173.1, 159.7, 138.4, 136.4, 132.0, 131.2, 130.2, 128.5, 117.2, 79.4, 69.4, 25.4, 21.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2983, 2932, 1728, 1653, 1898, 1496, 1466, 1384, 1285, 1242, 1173, 1143, 4401, 1090, 1014, 972, 926, 898, 843, 825, 762, 740, 682, 655.

MS (EI, 70 eV): *m/z* (%) = 121 (100), 138 (78), 140 26), 197 (70), 232 (66), 234 (21), 273 (65), 275 (26), 360 (5).

HR-MS (EI, 70eV): [$C_{20}H_{21}ClO_4$], calcd.: 360.1128, found: 360.1125.

5. Mild and Regioselective Magnesiation and Functionalization of Aryl Azoles as a Powerful Tool for the Synthesis of Pharmaceutically Relevant Targets

5.1 Preparation of Starting Materials[159]

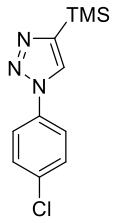
Preparation of Triazoles – General procedure TP1

A glass flask of suitable size equipped with a magnetic stirring bar, nitrogen inlet tube and a septum cap was charged with a commercially available (substituted) azidobenzene solution (approximately 0.5 M in MTBE or MeTHF). The flask was immersed in a water bath kept at room temperature. A brisk stream of dry nitrogen was bubbled through the solution to evaporate the solvent until the volume of the solution approximately halved. Then, acetonitrile was added to restore the original volume of the solution and nitrogen was again bubbled until the volume approximately halved. Dilution with MeCN and evaporation was repeated twice and finally the volume was reduced so as to obtain a solution of the (substituted) azidobenzene having a concentration of approximately 20% (w/V) in acetonitrile. Then, while keeping the inert atmosphere, the alkyne (3.0 equiv) and *N,N*-diisopropylethylamine (DIPEA, 0.5 equiv) were added by syringe, followed by the addition of CuI (0.10 equiv). The resulting mixture was stirred at room temperature until LC analysis showed complete conversion (12-72 h).

Finely ground 1,3,5-triazine-2,4,5-trithiol trisodium salt hydrate (Na_3TMT, approximately 55% assay, 100 mg per mmol of azidobenzene) was added and the mixture was stirred at room temperature for at least 1 h to precipitate copper in the form of insoluble complexes. The mixture was filtered through a short pad of diatomaceous earth, the filter pad washed with MTBE and the combined filtrates were evaporated to dryness. The residue was purified as detailed below for each compound to give the required triazole.

[159] All triazole starting materials (**115a**-**g**) were prepared by Janssen Pharmaceutica.

1-(4-Chlorophenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (115a)



The title compound was prepared according to **TP1** from commercially available 1-azido-4-chlorobenzene solution (0.54 M in MTBE, 10 mL, 5.37 mmol, 1.0 equiv) and ethynyltrimethylsilane (1.58 g, 16.1 mmol, 3.0 equiv) and was obtained in the form of straw-colored plates (1.08 g, 4.29 mmol, 80% yield). Spectral data were in agreement with the literature.[160]

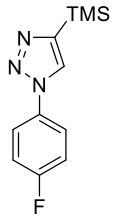
Purification: recrystallization from *i*PrOH/water (50:50, 20 mL, from reflux temperature to 20 °C).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.93 (s, 1H), 7.67–7.73 (m, 2H), 7.46 – 7.53 (m, 2H), 0.38 (m, 9H)

^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 147.6, 135.5, 134.0, 129.7, 126.9, 121.8, −1.3.

MS (ESI+): *m/z* (%) = 252.1 $[M+H]^+$.

1-(4-Fluorophenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (115b)



The title compound was prepared according to **TP1** from commercially available 1-azido-4-fluorobenzene solution (0.5 M in MTBE, 21.5 mL, 10.8 mmol,1.0 equiv) and ethynyltrimethylsilane (3.18 g, 32.4 mmol, 3.0 equiv) and was obtained in the form of beige plates (2.34 g, 9.94 mmol, 92% yield). Spectral data were in agreement with the literature.[162]

Purification: recrystallization from *i*PrOH/water (50:50, 25 mL, from reflux temperature to –20 °C).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.90 (s, 1H), 7.66 – 7.78 (m, 2H), 7.26 – 7.16 (m, 2H), 0.38 (s, 9H)

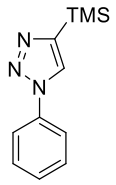
^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$, ppm): δ = −112.7.

^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 162.3 (d, $^1J_{CF}$ = 248.4 Hz), 147.5, 133.4 (d, $^4J_{CF}$ = 2.3) Hz, 127.3, 122.7 (d, $^3J_{CF}$ = 8.30 Hz), 116.6 (d, $^2J_{CF}$ = 23.4 Hz), 77.2, −1.2.

MS (ESI+): *m/z* (%) = 236.1 $[M+H]^+$.

[160] S. Wang, L.-J. Yang, J.-L. Zeng, Y. Zheng, J.-A. Ma *Org. Chem. Front.* **2015**, *2*, 1468–1474.

1-Phenyl-4-(trimethylsilyl)-1*H*-1,2,3-triazole (115c)



The title compound was prepared according to **TP1** from commercially available azidobenzene solution (0.5 M in MeTHF, 10 mL, 5.0 mmol, 1.0 equiv) and ethynyltrimethylsilane (1.47 g, 15 mmol, 3.0 equiv) and was obtained in the form of light brown plates (460 mg, 2.12 mmol, 42% yield). Spectral data were in agreement with the literature.[161]

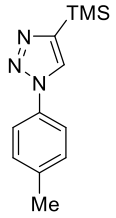
Purification: recrystallization from *i*PrOH/water (50:50, 10 mL, from reflux temperature to –20 °C).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.95 (s, 1H), 7.75 (d, *J* = 7.7 Hz, 2H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 1H), 0.39 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 147.3, 137.1, 129.7, 128.5, 127.1, 120.8, −1.2.

MS (ESI+): *m/z* (%) = 218.1 $[M+H]^+$.

1-(*p*-Tolyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (115d)



The title compound was prepared according to **TP1** from commercially available 4-azidotoluene solution (0.5 M in MTBE, 10 mL, 5.0 mmol, 1.0 equiv) and ethynyltrimethylsilane (1.47 g, 15 mmol, 3.0 equiv) and was obtained in the form of light brown needles (710 mg, 3.07 mmol, 61% yield). Spectral data were in agreement with the literature.[160]

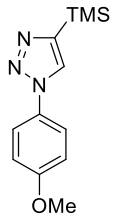
Purification: recrystallization from *i*PrOH/water (50:50, 10 mL, from reflux temperature to −20 °C).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.91 (br s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 2.43 (s, 3H), 0.39 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 138.6, 134.8, 130.2, 127.2, 120.7, 77.2, 21.1, −1.1.

MS (ESI+): *m/z* (%) = 232.1 $[M+H]^+$.

1-(4-Methoxyphenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (115e)



The title compound was prepared according to **TP1** from commercially available 4-azidoanisole solution (0.5 M in MTBE, 10 mL, 5.0 mmol, 1.0 equiv) and ethynyltrimethylsilane (1.47 g, 15 mmol, 3.0 equiv) and was obtained as a solid (900 mg, 3.64 mmol, 73% yield). Spectral data were in agreement with the literature.[161]

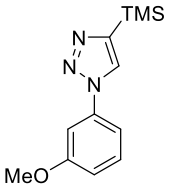
Purification: recrystallization from boiling heptane (5 mL, from reflux to room temperature) provided the title compound in the form of light brown plates (680 mg, 2.75 mmol, 55%). The mother liquor was evaporated to dryness and the residue was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc 80:20) to provide a further portion of the target compound in the form of an orange solid (220 mg, 0.889 mmol, 18%).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.86 (s, 1H), 7.63 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 3.88 (s, 3H), 0.39 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 159.6, 147.0, 130.5, 127.3, 122.4, 114.7, 55.6, −1.1.

MS (ESI+): *m/z* (%) = 248.1 $[M+H]^+$.

1-(3-Methoxyphenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (115f)



The title compound was prepared according to **TP1** from commercially available 3-azidoanisole solution (0.5 M in MTBE, 30 mL, 15.0 mmol, 1.0 equiv) and ethynyltrimethylsilane (4.41 g, 45 mmol, 3.0 equiv) was obtained as a brown oil (3.64 g, 14.7 mmol, 98% yield).

Purification: flash chromatography on silica gel (eluent: hexanes/EtOAc 90:10).

m.p.: 38.4 – 40.0 °C.

[161] P. Eisenberger, B. P. Bestvater, E. C. Keske, C. M. Crudden *Angew. Chem. Int. Ed.* **2015**, 54, 2467–2471.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.01 (s, 1H), 7.30 – 7.37 (m, 2H), 7.28 – 7.22 (m, 1H), 6.86–6.94 (m, 1H), 3.81 (s, 3H), 0.36 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 160.2, 146.9, 137.8, 130.1, 127.1, 113.9, 112.3, 106.3, 55.2, −1.4.

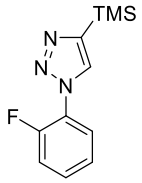
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 295, 1609, 1594, 1500, 1487, 1466, 1440, 1410, 1384, 1314, 1279, 1246, 1235, 1201, 1179, 1136, 1093, 1049, 1041, 997, 991, 997, 869, 838, 818, 769, 756, 707, 695, 680.

MS (ESI+): *m/z* (%) = 248.2 $[M+H]^+$.

MS (EI, 70 eV): *m/z* (%) =219 (119, 209 (16), 208 (100), 177 (9).

HR-MS (EI, 70 eV): $[C_{12}H_{17}N_3OSi]$, calcd.: 247.1141; found: 247.1225.

1-(2-Fluorophenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (115g)



The title compound was prepared according to **TP1** from commercially available 1-azido-2-fluorobenzene solution (0.5 M in MTBE, 30 mL, 15.0 mmol, 1.0 equiv) and ethynyltrimethylsilane (4.41 g, 45 mmol, 3.0 equiv) and was obtained as a pale yellow oil (3.18 g, 13.5 mmol, 90% yield). Spectral data were in agreement with the literature.[162]

Purification: flash chromatography on silica gel (eluent: hexanes/EtOAc 9:1).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.86 (d, *J* = 2.8 Hz, 1H), 7.79 – 7.70 (m, 1H), 7.16 – 7.28 (m, 1H), 7.03 – 7.16 (m, 2H), 0.20 (s, 9H).

^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$, ppm): δ = −123.6.

^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 153.3 (d, $^1J_{CF}$ = 250.7 Hz), 146.8, 129.9 (d, $^3J_{CF}$ = 7.6 Hz), 129.8 (d, $^3J_{CF}$ = 7.6 Hz), 125.2 (d, $^2J_{CF}$ = 10.6 Hz), 125.04 (d, $^4J_{CF}$ = 3.0 Hz), 125.01, 116.8 (d, $^2J_{CF}$ = 19.6 Hz), −1.3.

MS (ESI+): *m/z* (%) = 236.1 $[M+H]^+$.

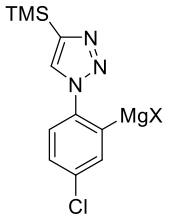
[162] S. Businelli, E. Di Martino, P. Zanirato *ARKIVOC* **2001**, *1*, 131-143.

5.2 Preparation of Organometallic Reagents and Metalation Optimization

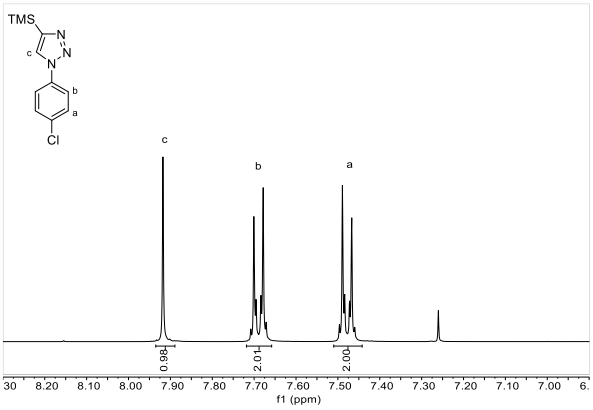
Directed *ortho*-metalation (**TP2**)

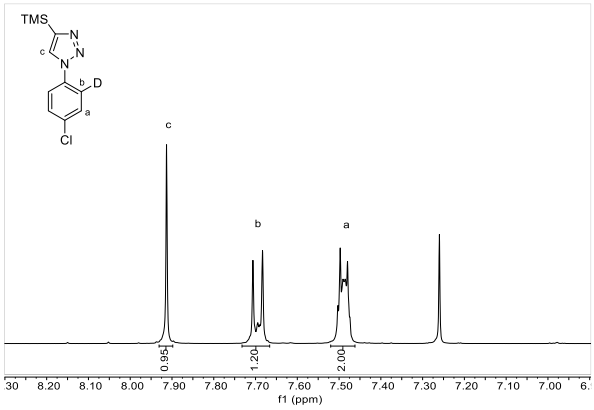
The corresponding substrate was placed in a dry and argon flushed 10 mL *Schlenk*-tube equipped with a magnetic stirring bar and a septum and was suspended in toluene (1.00 M). TMPMgBu (1.0 equiv) was added and the mixture was stirred for the appropriate time. To monitor the process of metalation aliquots quenched with D_2O were analyzed using ^{1}H-NMR.

(5-Chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (116a)



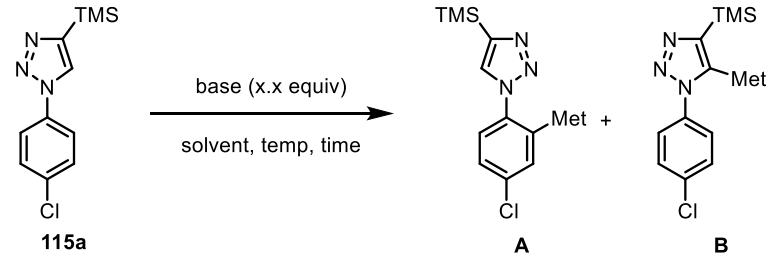
The title compound was prepared according to **TP2** from 1-(4-chlorophenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**115a**, 126 mg, 0.5 mmol) affording the corresponding magnesium reagent in 81% yield. The yield was determined *via* deuterolysis.





Optimization of the metalation of 115a:

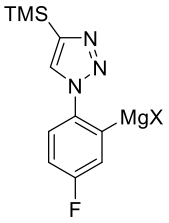
Table 16: Optimization of the metalation conditions.[a]



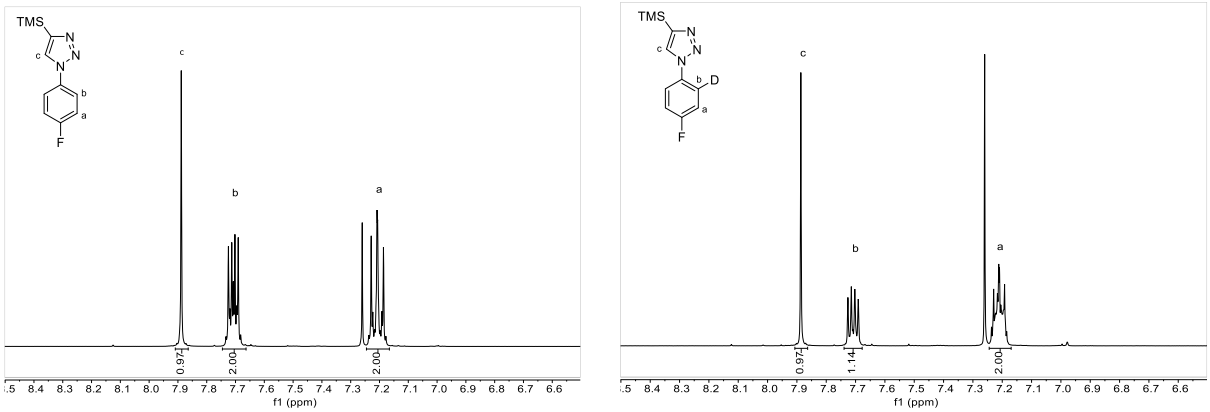
entry	base	equivalents	solvent	temperature	time	A	B
1	TMPLi	1.2	THF	-78 °C	0.5 h	0%	99%
2	TMPMgCl·LiCl	1.2	THF	rt	1 h	19%	39%
3	$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$	1.2	THF	0 °C	1 h	0%	0%
4	TMP_2Mg	1.2	THF	rt	1 h	32%	67%
5	TMPMgBu	1.0	THF	-40 °C	0.5 h	35%	3%
6	TMPMgBu	1.0	THF	-20 °C	0.5 h	57%	7%
7	TMPMgBu	1.0	THF	0 °C	0.5 h	63%	8%
8	TMPMgBu	1.0	THF	rt	0.5 h	68%	11%
9	TMPMgBu	1.0	THF	rt	1 h	75%	15%
10	TMPMgBu	1.0	THF	rt	4 h	78%	32%
11	TMPMgBu	1.0	THF	rt	6 h	76%	38%
12	TMPMgBu	1.2	THF	rt	0.5 h	78%	28%
13	TMPMgBu	1.2	THF	rt	1 h	78%	40%
14	TMPMgBu	1.0	toluene	rt	0.5 h	70%	2%
15	**TMPMgBu**	**1.0**	**toluene**	**rt**	**1 h**	**81%**	**3%**
16	TMPMgBu	1.0	toluene	rt	3 h	81%	3%
17	TMPMgBu	1.0	toluene	40°C	1 h	84%	6%
18	TMPMgBu	1.2	toluene	rt	1 h	85%	3%
19	TMPMgBu	0.8	toluene	rt	1 h	67%	2%
20	TMPMgBu	1.0	hexane	rt	1 h	75%	2%
21	TMPMgBu	1.0	fluorobenzene	rt	1 h	79%	2%
22	TMPMgBu	1.0	benzotrifluoride	rt	1 h	80%	2%
23	Cy_2NMgBu	1.0	toluene	rt	1 h	65%	2%
24	$i Pr_2NMgBu$	1.0	toluene	rt	1 h	67%	3%
25	TMP_2Mg	1.2	toluene	rt	1 h	decomposition	

[a] For values of A+B > 100% bis-metalated species was observed.

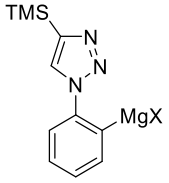
(5-Fluoro-2-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)phenyl)magnesium reagent (116b)



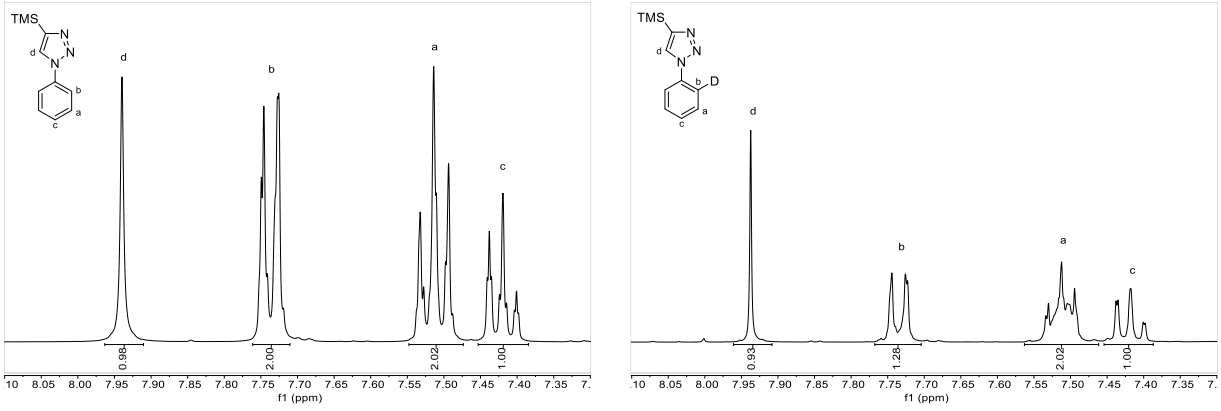
The title compound was prepared according to **TP2** from 1-(4-fluorophenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**115b**, 118 mg, 0.5 mmol) affording the corresponding magnesium reagent in 86% yield. The yield was determined *via* deuterolysis.



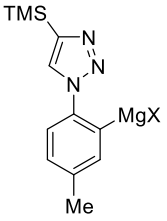
(2-(4-(Trimethylsilyl)-1H-1,2,3-triazol-1-yl)phenyl)magnesium reagent (116c)



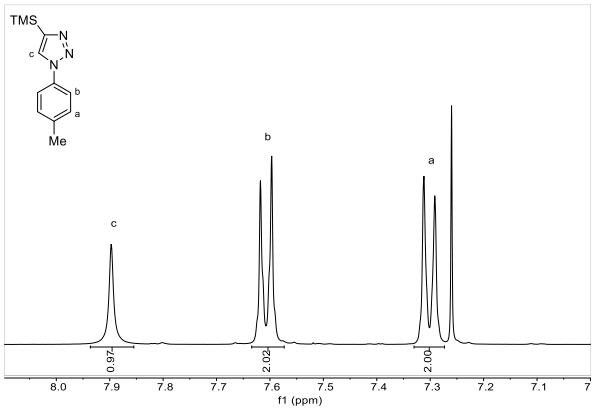
The title compound was prepared according to **TP2** from 1-phenyl-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**115c**, 109 mg, 0.5 mmol) affording the corresponding magnesium reagent in 72% yield. The yield was determined *via* deuterolysis.

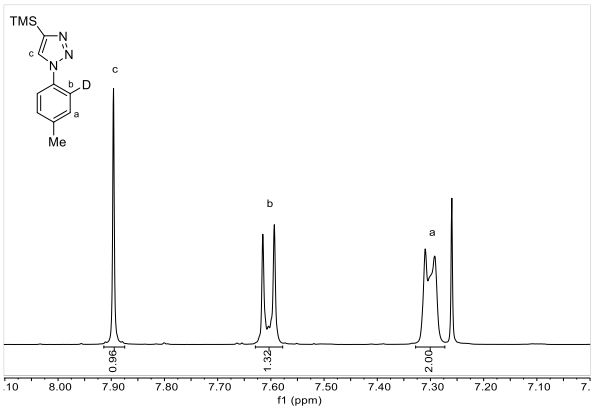


(5-Methyl-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (116d)

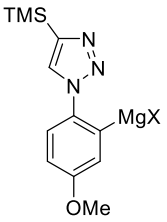


The title compound was prepared according to **TP2** from 1-(*p*ara-tolyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**115d**, 116 mg, 0.5 mmol) affording the corresponding magnesium reagent in 68% yield. The yield was determined *via* deuterolysis.

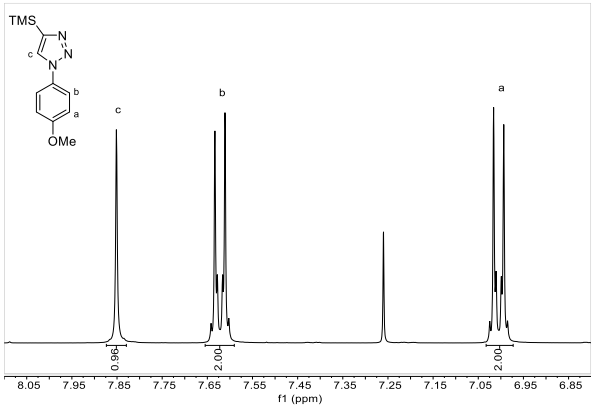


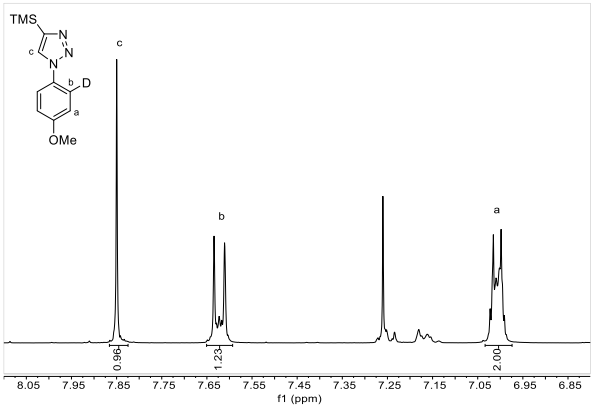


(5-Methoxy-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (116e)

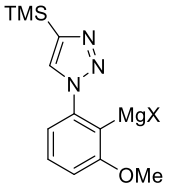


The title compound was prepared according to **TP2** from 1-(4-methoxyphenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**115e**, 124 mg, 0.5 mmol) affording the corresponding magnesium reagent in 77% yield. The yield was determined *via* deuterolysis.

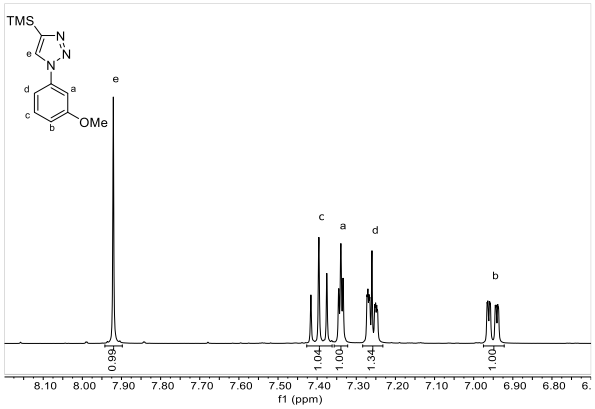


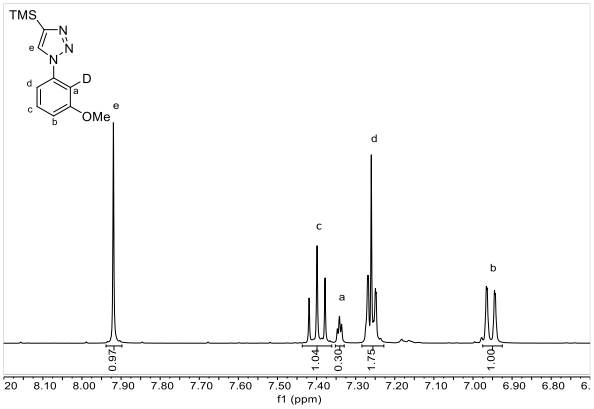


(2-Methoxy-6-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (116f)

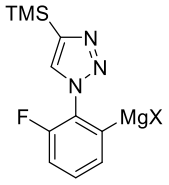


The title compound was prepared according to **TP2** from 1-(3-methoxyphenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**115f**, 124 mg, 0.5 mmol) affording the corresponding magnesium reagent in 70% yield. The yield was determined *via* deuterolysis.

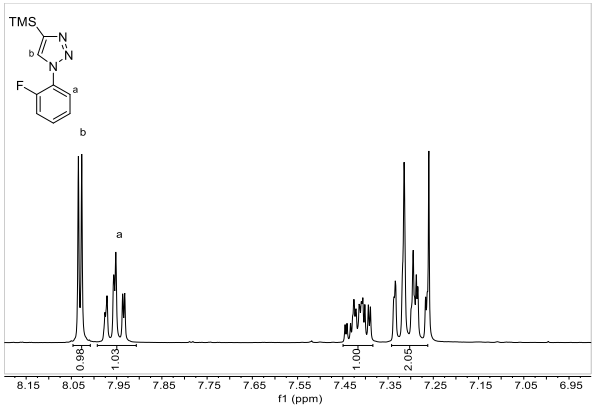


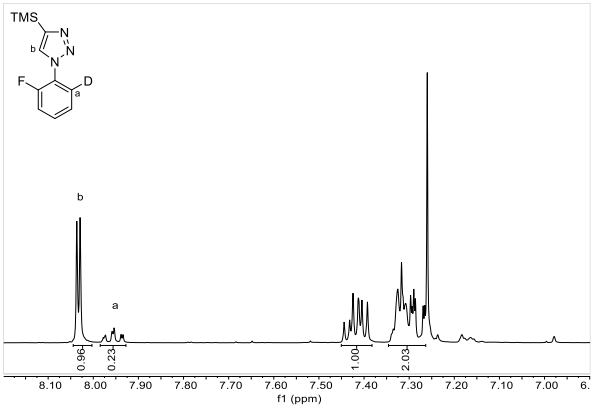


(3-Fluoro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (116g)

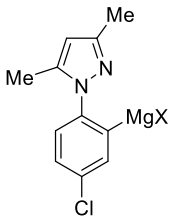


The title compound was prepared according to **TP2** from 1-(2-fluorophenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**115g**, 118 mg, 0.5 mmol) affording the corresponding magnesium reagent in 80% yield. The yield was determined *via* deuterolysis.

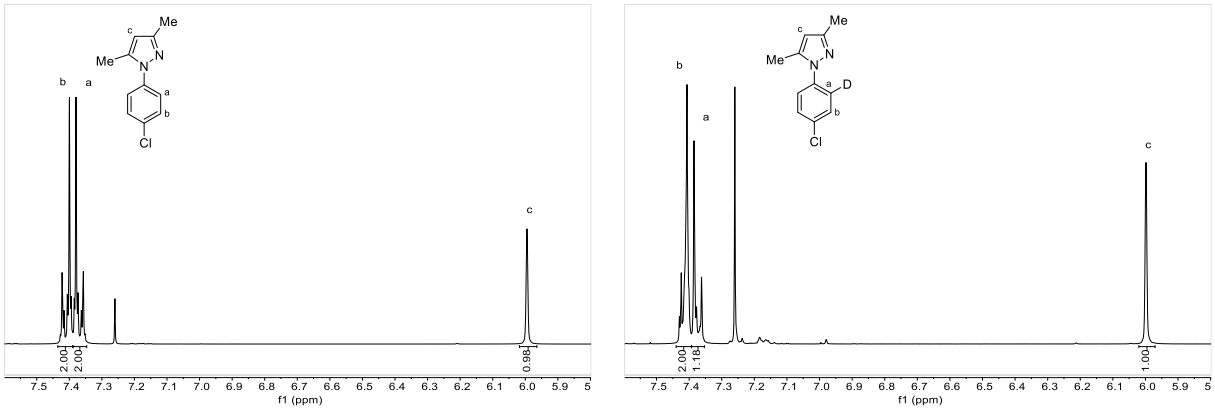




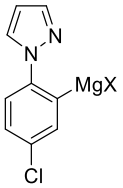
(5-Chloro-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)magnesium reagent (119a)



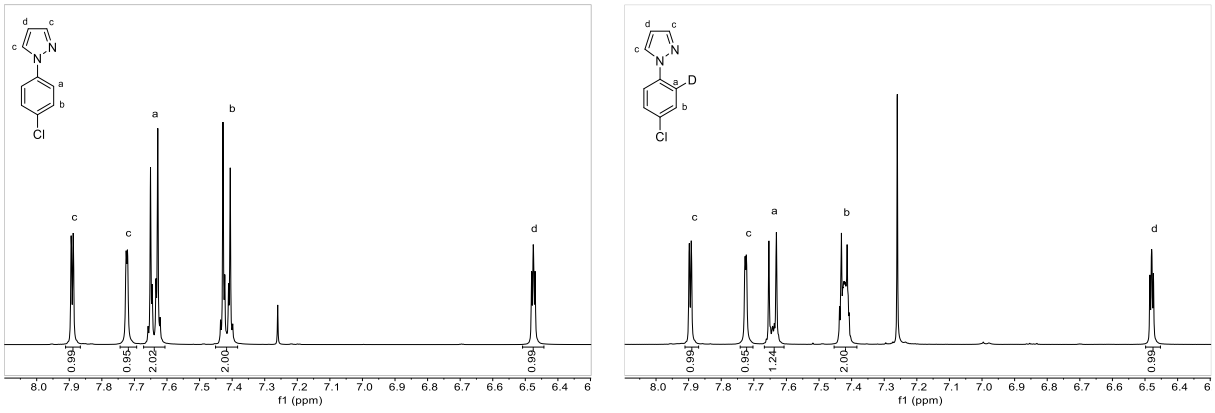
The title compound was prepared according to **TP2** from 1-(4-chlorophenyl)-3,5-dimethyl-1*H*-pyrazole (**118a**, 104 mg, 0.5 mmol) affording the corresponding magnesium reagent in 82% yield. The yield was determined *via* deuterolysis.



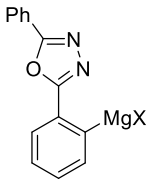
(5-Chloro-2-(1*H*-pyrazol-1-yl)phenyl)magnesium reagent (119b)



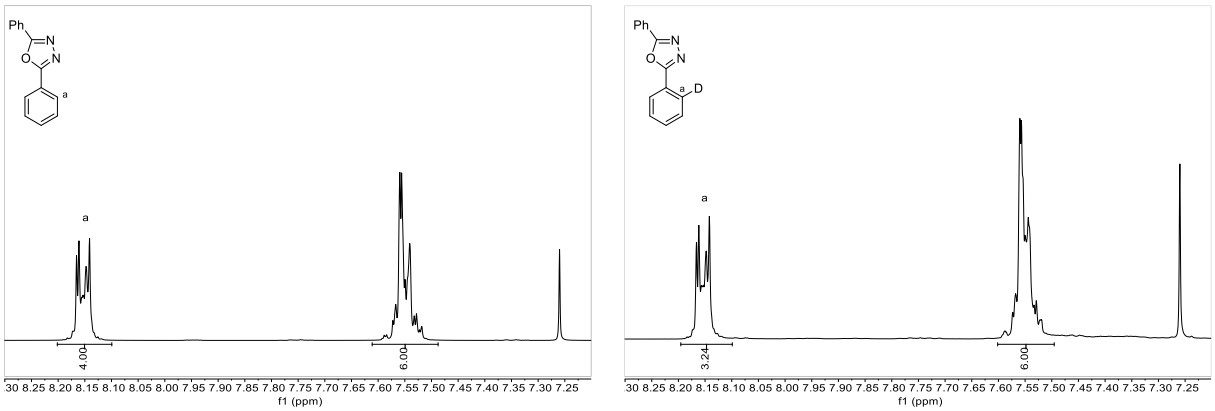
The title compound was prepared according to **TP2** from 1-(4-chlorophenyl)-1H-pyrazole (**118b**, 89 mg, 0.5 mmol) affording the corresponding magnesium reagent in 78% yield. The yield was determined *via* deuterolysis.



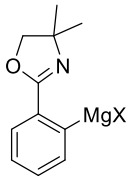
(2-(5-Phenyl-1,3,4-oxadiazol-2-yl)phenyl)magnesium reagent (119c)



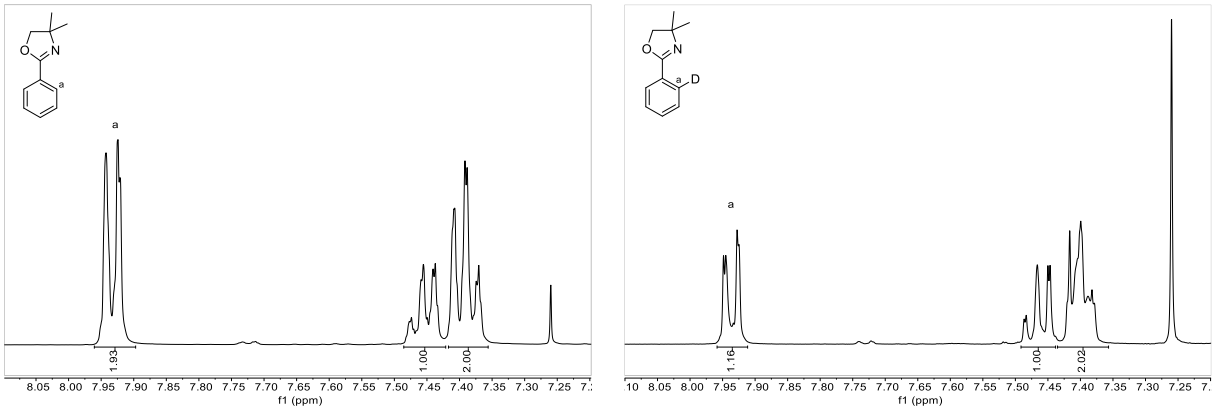
The title compound was prepared according to **TP2** from 2,5-diphenyl-1,3,4-oxadiazole (**118c**, 111 mg, 0.5 mmol) affording the corresponding magnesium reagent in 76% yield. The yield was determined *via* deuterolysis.



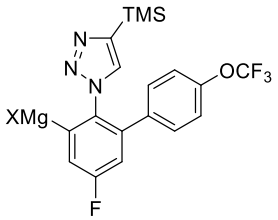
(2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl)magnesium reagent (119d)



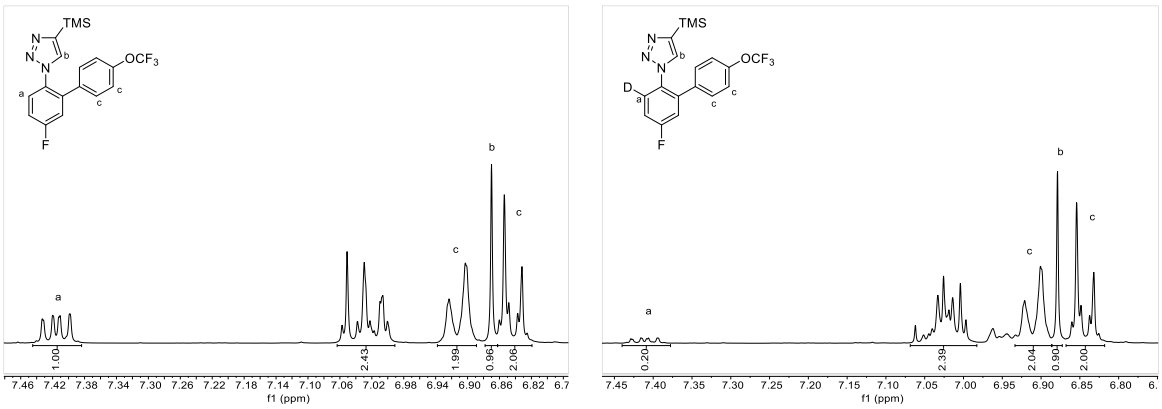
The title compound was prepared according to **TP2** from 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole (**118d**, 88 mg, 0.5 mmol) affording the corresponding magnesium reagent in 77% yield. The yield was determined *via* deuterolysis.



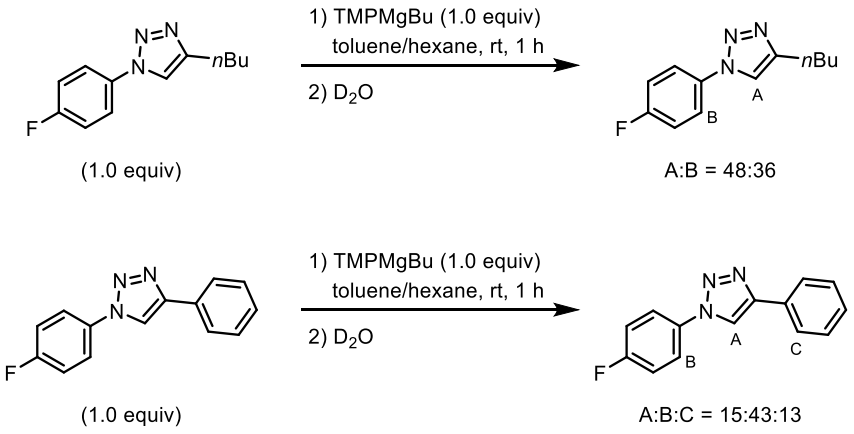
(5-Fluoro-4'-(trifluoromethoxy)-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)-[1,1'-biphenyl]-3-yl)magnesium reagent (123)



The title compound was prepared according to **TP2** from 1-(5-fluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**117g**, 99 mg, 0.5 mmol) affording the corresponding magnesium reagent in 80% yield. The yield was determined *via* deuterolysis.



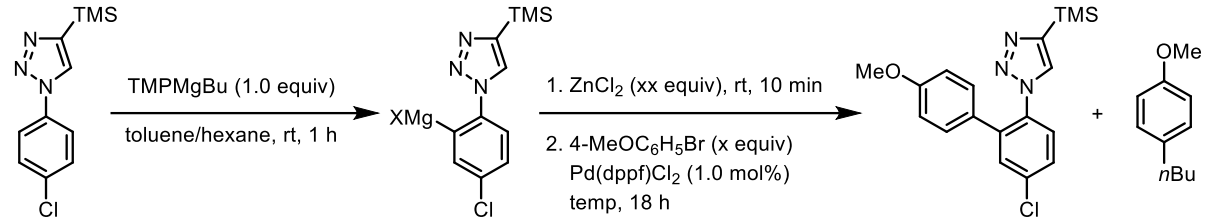
5.3 Unsuccessful Metalation Reactions



Scheme 59: Unsuccessful substrates for a regioselective metalation.

5.4 Palladium-Catalyzed Negishi-Cross-Coupling of Arylmagnesium Aryl Azoles with Aryl Bromides

Optimization of the cross-coupling reaction



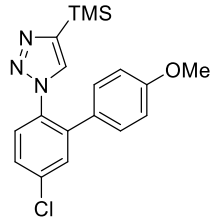
115a **116a** **SP** **117a**

entry	$ZnCl_2$ (xx equiv)	Ar-Br (xx equiv)	temp	**117a**	**SP**
1	1.0	1.5	55 °C	65%	34%
2	2.0	1.5	55 °C	68%	31%
3	1.0	1.5	rt	traces	6%
4	**1.0**	**2.1**	**55 °C**	**84%**	**28%**

Palladium-catalyzed Negishi-cross-coupling of arylmagnesium aryl azoles with aryl bromides TP3

The corresponding arylmagnesium reagent, prepared according to **TP1**, was transmetalated with a $ZnCl_2$ solution (1.00 M in THF, 1.0 equiv) and THF (1.0 ml/0.5 mmol) was added. A dry and argon-flushed *Schlenk*-tube, equipped with a magnetic stirring bar and a septum was charged with $Pd(dppf)Cl_2$ (1.0 mol%, 0.005 mmol, 3.7 mg) and the respective aryl bromide (1.00-1.25 mmol, 1.98 – 2.5 equiv). The freshly prepared arylzinc reagent was added and the reaction mixture was placed in an oil bath at 55 °C. After 16 h, saturated aq. NH_4Cl solution (5 mL) was added, the phases where separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was subjected to column chromatography on silica yielding the respective title compound.

1-(5-Chloro-4'-methoxy-[1,1'-biphenyl]-2-yl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (117a)



Following **TP3** (5-chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116a**, 0.405 mmol, 1.00 equiv) was coupled with 1-bromo-4-methoxybenzene (0.850 mmol, 159 mg, 2.10 equiv).

Isolated yield: 122 mg, 0.341 mmol, 84%, colorless crystals

m.p.: 74.1 – 75.6 °C.

Purification: pentane:ethyl acetate = 95:5 to 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.56 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.44 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.09 (s, 1H), 6.95 – 6.90 (m, 2H), 6.81 – 6.76 (m, 2H), 3.77 (s, 3H), 0.22 (s, 9H).

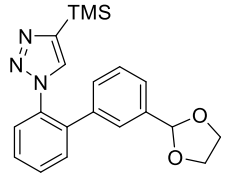
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 159.9, 146.6, 138.5, 135.5, 133.8, 131.2, 130.8, 129.7, 128.5, 128.2, 127.9, 114.3, 55.5, −1.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3105, 2956, 1610, 1514, 1490, 1473, 1463, 1455, 1442, 1404, 1288, 1254, 1241, 1198, 1151, 1124, 1113, 1095, 1037, 1022, 1009, 1000, 982, 906, 819, 775, 762, 755, 724, 711, 680.

MS (EI, 70 eV): *m/z* (%) = 330 (26), 328 (65), 314 (65), 283 (69), 279 (86), 271 (34), 139 (63), 73 (100), 43 (30).

HR-MS (EI, 70 eV): [$C_{18}H_{20}N_3OClSi$], calcd.: 357.1064; found: 357.1051.

1-(3'-(1,3-Dioxolan-2-yl)-[1,1'-biphenyl]-2-yl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (117b)



Following **TP3** (2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116c**, 0.360 mmol, 1.00 equiv) was coupled with 2-(3-bromophenyl)-1,3-dioxolane (0.850 mmol, 195 mg, 2.36 equiv).

Isolated yield: 103 mg, 0.281 mmol, 78%, colorless oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, benzene-d_6, ppm): δ = 7.19 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.07 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.04 (t, *J* = 1.8 Hz, 1H), 6.89 (d, *J* = 1.5 Hz, 1H), 6.85 – 6.69 (m, 2H), 6.71 – 6.66 (m, 1H), 6.62 (dt, *J* = 7.7, 1.6 Hz, 1H), 6.49 (s, 1H), 5.32 (s, 1H), 3.32 (ddd, *J* = 6.6, 5.1, 2.6 Hz, 2H), 3.21 – 3.13 (m, 2H), 0.00 (s, 9H)

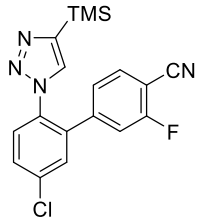
^{13}C-NMR (100 MHz, benzene-d_6, ppm): δ = 145.9, 139.6, 138.0, 137.2, 136.0, 131.2, 131.0, 129.5, 129.4, 128.6, 128.6, 127.3, 127.0, 126.4, 103.6, 65.2, -1.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2893, 1717, 1504, 1487, 1376, 1248, 1199, 1079, 1054, 1036, 983, 943, 901, 839, 802, 756, 704, 661.

MS (EI, 70 eV): *m/z* (%) = 337 (14), 295 (28), 294 (100), 278 (48), 265 (18), 254 (47), 251 (18), 250 (749, 220 (17), 218 (15), 204 (85), 192 (16), 174 (13), 152 (11), 75 (15), 73 (16).

HR-MS (EI, 70 eV): [$C_{20}H_{23}N_3O_2Si$], calcd.: 365.1560; found: 365.1565.

5'-Chloro-3-fluoro-2'-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)-[1,1'-biphenyl]-4-carbonitrile (117c)



Following **TP3** (5-chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116a**, 0.405 mmol, 1.00 equiv) was coupled with 4-bromo-2-fluorobenzonitrile (0.850 mmol, 170 mg, 2.10 equiv).

Isolated yield: 131 mg, 0.353 mmol, 87%, orange crystals.

Purification: pentane:ethyl acetate = 95:5 to 9:1.

m.p.: 98.6 – 100.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.59 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.55 (dd, *J* = 8.6, 0.6 Hz, 1H), 7.54 – 7.49 (m, 1H), 7.51 (d, *J* = 2.5 Hz, 1H), 7.29 (s, 1H), 6.95 – 6.92 (m, 1H), 6.92 – 6.89 (m, 1H), 0.27 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.0 (d, *J* = 260.8 Hz), 147.6, 143.6 (d, *J* = 8.2 Hz), 136.4, 136.2 (d, *J* = 1.9 Hz), 133.7, 133.6, 130.7 (d, *J* = 10.4 Hz), 130.3, 128.4, 125.0 (d, *J* = 3.7 Hz), 116.6 (d, *J* = 20.8 Hz), 113.4, 101.5 (d, *J* = 15.4 Hz), −1.1.

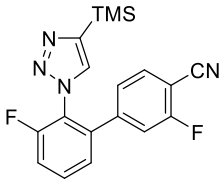
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ = −105.16 (dd, *J* = 9.5, 6.5 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2233, 1619, 1556, 1506, 1421, 1245, 1198, 1186, 1145, 1114, 1029, 993, 982, 923, 883, 871, 840, 830, 814, 784, 758, 733, 709, 676, 660.

MS (EI, 70 eV): *m/z* (%) = 343 (20), 330 (35), 329 (29), 327 (22), 293 (41), 234 (14), 195 (24), 77 (30), 73 (40), 45 (20), 43 (22).

HR-MS (EI, 70 eV): [$C_{18}H_{17}N_4ClFSi^+$], calcd.: 371.0890; found: 371.0898 [M+H$^+$].

3,3'-Difluoro-2'-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)-[1,1'-biphenyl]-4-carbonitrile (117d)



Following **TP3** (3-fluoro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116g**, 0.400 mmol, 1.00 equiv) was coupled with 4-bromo-2-fluorobenzonitrile (0.850 mmol, 170 mg, 2.13 equiv).

Isolated yield: 120 mg, 0.339 mmol, 85%, pale yellow oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.62 (td, *J* = 8.1, 5.3 Hz, 1H), 7.54 (d, *J* = 1.1 Hz, 1H), 7.48 (dd, *J* = 8.0, 6.6 Hz, 1H), 7.39 (td, *J* = 8.6, 1.3 Hz, 1H), 7.32 (dt, *J* = 7.9, 1.2 Hz, 1H), 6.97 – 6.87 (m, 2H), 0.31 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 162.8 (d, *J* = 260.2 Hz), 157.2 (d, *J* = 255.1 Hz), 147.2, 143.84 (dd, *J* = 8.2, 2.6 Hz), 138.2 (d, *J* = 2.0 Hz), 133.5, 131.8 (d, *J* = 8.6 Hz), 131.7 (d, *J* = 1.2 Hz), 126.0 (d, *J* = 3.6 Hz), 124.9 (d, *J* = 3.6 Hz), 123.7 (d, *J* = 13.7 Hz), 117.4 (d, *J* = 20.1 Hz), 116.5 (d, *J* = 20.8 Hz), 113.6, 101.2 (d, *J* = 15.5 Hz), −1.1.

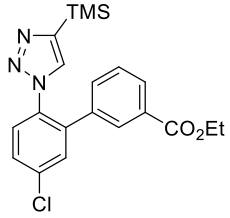
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ = −105.64 (dd, *J* = 9.6, 6.6 Hz), −119.96 (dd, *J* = 9.0, 5.4 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2234, 1619, 1589, 1561, 1511, 1497, 1470, 1417, 1387, 1265, 1247, 1201, 1170, 1142, 1125, 1075, 1083, 1034, 999, 985, 958, 835, 797, 763, 744, 721, 711, 701, 665.

MS (EI, 70 eV): *m/z* (%) = 326 (55), 312 (61), 311 (45), 311 (45), 311 (45), 311 (62), 311 (64), 311 (65), 310 (32), 249 (24), 215 (29), 208 (28), 195 (26), 77 (100).

HR-MS (EI, 70 eV): [$C_{18}H_{16}F_2N_4Si$], calcd.: 354.1112; found: 354.1110.

Ethyl 5'-chloro-2'-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)-[1,1'-biphenyl]-3-carboxylate (117e)



Following **TP3** (5-chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116a**, 0.405 mmol, 1.00 equiv) was coupled with ethyl 3-bromobenzoate (0.850 mmol, 195 mg, 2.10 equiv).

Isolated yield: 122 mg, 0.305 mmol, 75%, pale yellow solid.

Purification: pentane:ethyl acetate = 95 :5.

m.p.: 97.0 – 98.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.99 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.81 (td, *J* = 1.8, 0.5 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 7.52 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.30 (td, *J* = 7.8, 0.6 Hz, 1H), 7.11 (s, 1H), 7.10 – 7.07 (m, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 0.20 (s, 9H).

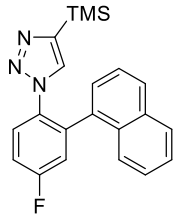
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 165.9, 146.8, 137.9, 136.6, 135.8, 133.8, 132.7, 131.3, 131.1, 130.9, 129.6, 129.1, 128.8, 128.1, 61.4, 14.4, −1.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 1715, 1500, 1484, 1490, 1366, 1296, 1285, 1266, 1249, 1236, 1200, 1172, 1148, 1133, 1124, 1109, 1096, 1049, 1034, 996, 982, 927, 903, 871, 838, 808, 777, 758, 735, 708, 673, 659.

MS (EI, 70 eV): *m/z* (%) = 371 (10), 356 (12), 254 (11), 190 (16), 103 (100), 75 (63), 73 (28), 59 (12).

HR-MS (EI, 70 eV): [$C_{20}H_{22}ClN_3O_2Si$], calcd.: 399.1170; found: 399.1120.

1-(4-Fluoro-2-(naphthalen-1-yl)phenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (117f)



Following **TP3** (5-fluoro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116b**, 0.430 mmol, 1.00 equiv) was coupled with 1-bromonaphthalene (0.850 mmol, 176 mg, 1.98 equiv).

Isolated yield: 115 mg, 0.318 mmol, 74%, pale yellow oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.92 – 7.85 (m, 3H), 7.52 – 7.44 (m, 3H), 7.41 – 7.28 (m, 4H), 6.73 (s, 1H), 0.00 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 162.4 (d, *J* = 250.6 Hz), 145.8, 137.1 (d, *J* = 8.6 Hz), 134.2 (d, *J* = 1.4 Hz), 133.3, 132.7 (d, *J* = 3.1 Hz), 131.0, 130.4, 129.1, 128.3, 127.6 (d, *J* = 9.0 Hz), 127.5, 127.0, 126.4, 125.3, 124.5, 118.7 (d, *J* = 23.0 Hz), 116.1 (d, *J* = 22.7 Hz), −1.5.

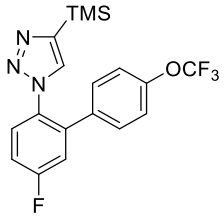
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ = −111.63 (m).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 1614, 1585, 1502, 1402, 1301, 1248, 1197, 1171, 1146, 1033, 1020, 983, 894, 878, 838, 798, 775, 757, 731, 709, 696, 688, 667.

MS (EI, 70 eV): *m/z* (%) = 334 (24), 333 (100), 332 (62), 320 (20), 319 (93), 318 (57), 318 (57), 318 (57), 318 (87), 318 (52), 318 (54), 318 (55), 317 (50), 302 (29), 288 (20), 258 (14), 240 (19), 220 (33).

HR-MS (EI, 70 eV): [$C_{21}H_{20}FN_3Si$], calcd.: 361.1411; found: 361.1398.

1-(5-Fluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (117g)



Following **TP3** (5-fluoro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116b**, 0.430 mmol, 1.00 equiv) was coupled with 1-bromo-4-(trifluoromethoxy)benzene (0.850 mmol, 205 mg, 1.98 equiv).

Isolated yield: 150 mg, 0.379 mmol, 88% colorless crystals.

Large scale-experiment: Following **TP3** (5-fluoro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**2b**, 4.30 mmol, 1.00 equiv) was coupled with 1-bromo-4-(trifluoromethoxy)benzene (8.5 mmol, 2.05 g, 1.98 equiv).

Isolated yield: 1.29 g, 3.262 mmol, 76%, colorless crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 74.6 – 76.6 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.60 (ddd, *J* = 8.3, 5.2, 0.9 Hz, 1H), 7.25 – 7.17 (m, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.12 – 7.07 (m, 2H), 7.06 (s, 1H), 7.05 – 7.01 (m, 2H), 0.19 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 162.9 (d, *J* = 251.2 Hz), 149.4 (q, *J* = 1.9 Hz), 146.9, 138.4 (d, *J* = 8.6 Hz), 135.1 (d, *J* = 1.6 Hz), 131.5 (d, *J* = 3.2 Hz), 131.2, 130.0, 128.9 (d, *J* = 9.2 Hz), 121.3 (q, *J* = 1.0 Hz), 120.5 (q, *J* = 257.7 Hz), 117.6 (d, *J* = 23.5 Hz), 116.0 (d, *J* = 22.7 Hz), −1.3.

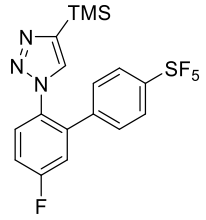
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ = −58.04 (t, *J* = 1.1 Hz), −109.19 – −111.70 (m).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1582, 1517, 1501, 1391, 1302, 1263, 1247, 1217, 1198, 1185, 1165, 1147, 1117, 1104, 1037, 1018, 999, 986, 958, 921, 889, 879, 843, 831, 815, 807, 767, 756, 677, 662.

MS (EI, 70 eV): *m/z* (%) = 367 (10), 366 (41), 365 (26), 313 (12), 287 (20), 286 (100), 270 (13), 259 (15), 257 (65), 224 (11), 222 (18), 190 (10), 77 (22), 73 (11).

HR-MS (EI, 70 eV): [$C_{18}H_{17}F_4N_3OSi$], calcd.: 395.1077; found: 395.1074.

1-(5-Fluoro-4'-(pentafluoro-λ^6-sulfaneyl)-[1,1'-biphenyl]-2-yl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (117h)



Following **TP3** (5-fluoro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116b**, 0.430 mmol, 1.00 equiv) was coupled with (4-bromophenyl)pentafluoro- λ^6-sulfane (0.850 mmol, 241 mg, 1.98 equiv).

Isolated yield: 178 mg, 0.407 mmol, 95%, pale yellow crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 84.1 – 85.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.65 (ddd, *J* = 8.3, 2.3, 1.0 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.42 – 7.34 (m, 1H), 7.30 (t, *J* = 1.9 Hz, 1H), 7.26 (s, 1H), 7.26 – 7.20 (m, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 0.19 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 163.0 (d, *J* = 251.8 Hz), 154.0 (p, *J* = 17.8 Hz), 147.0, 137.96 (d, *J* = 8.6 Hz), 137.4 (d, *J* = 1.6 Hz), 131.6, 131.53 (d, *J* = 3.3 Hz), 131.0, 129.3, 129.1 (d, *J* = 9.1 Hz), 125.8 (m) 117.7 (d, *J* = 23.7 Hz), 116.4 (d, *J* = 22.7 Hz), −1.3.

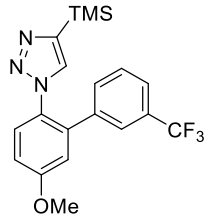
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ = 85.25 – 81.34 (m), 62.70 (d, *J* = 150.3 Hz), −109.90 (td, *J* = 8.0, 5.1 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1511, 1486, 1475, 1387, 1281, 1249, 1200, 1192, 1146, 1112, 1035, 983, 923, 915, 905, 880, 875, 863, 826, 791, 761, 745, 761, 745, 692, 709, 6679, 668.

MS (EI, 70 eV): *m/z* (%) = 409 (50), 285 (72), 271 (18), 270 (100), 258 (20), 256 (27), 224 (44), 222 26), 77 (22).

HR-MS (EI, 70 eV): [$C_{17}H_{17}F_6N_3SSi$], calcd.: 437.0817; found: 437.0824.

1-(5-Methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (117i)



Following **TP3** (5-methoxy-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116e**, 0.385 mmol, 1.00 equiv) was coupled with 1-bromo-3-(trifluoromethyl)benzene (0.850 mmol, 191 mg, 2.21 equiv).

Isolated yield: 106 mg, 0.271 mmol, 70%, colorless crystals.

Purification: pentane:ethyl acetate = 9:1 to 85:15.

m.p.:.98.8 – 100.2 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.31 (d, *J* = 8.6 Hz, 2H), 7.20 – 7.13 (m, 1H), 7.07 – 7.01 (m, 2H), 6.95 (s, 1H), 6.87 – 6.79 (m, 2H), 3.70 (s, 3H), 0.00 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.5, 146.5, 138.3, 137.5, 131.9 (d, *J* = 1.5 Hz), 131.3, 131.0 (q, *J* = 32.5 Hz), 129.1, 128.4, 128.3, 125.3 – 125.1 (m), 124.7 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 272.9 Hz), 116.0, 114.2, 56.0, −1.22.

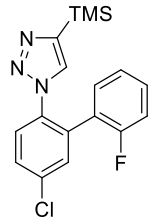
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ = −62.74 (s).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1606, 1576, 1513, 1486, 1455, 1442, 1332, 1296, 1275, 1249, 1214, 4201, 1164, 1123, 10075, 1035, 996, 983, 909, 878, 839, 804, 788, 759, 732, 715, 702, 658, 676.

MS (EI, 70 eV): *m/z* (%) = 364 (15), 363 (61), 333 (25), 253 (12), 252 (70), 237 (12), 209 (58), 45 (16), 42 (100).

HR-MS (EI, 70 eV): [$C_{19}H_{20}F_3N_3OSi$], calcd.: 391.1328; found: 391.1320.

1-(5-Chloro-2'-fluoro-[1,1'-biphenyl]-2-yl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (117j)



Following **TP3** (5-chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116a**, 0.405 mmol, 1.00 equiv) was coupled with 1-bromo-2-fluorobenzene (0.850 mmol, 149 mg, 2.10 equiv).

Isolated yield: 100 mg, 0.289 mmol, 71%, yellow crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 111.0 – 113.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.64 (dd, J = 8.2, 0.8 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.32 (dddd, J = 8.2, 7.3, 5.2, 2.1 Hz, 1H), 7.17 (s, 1H), 7.12 – 6.98 (m, 3H), 0.20 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 159.5 (d, *J* = 248.2 Hz), 146.5, 135.2, 134.6, 132.4, 131.6 (d, *J* = 1.6 Hz), 131.0 (d, *J* = 2.6 Hz), 130.8 (d, *J* = 8.1 Hz), 130.3, 129.5, 127.4, 124.6 (d, *J* = 3.7 Hz), 124.0 (d, *J* = 15.4 Hz), 115.9 (d, *J* = 21.8 Hz), −1.2.

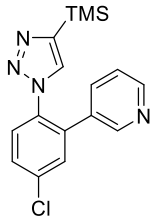
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ = −115.51 (ddd, *J* = 9.9, 7.0, 5.3 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1507, 1490, 1454, 1447, 1399, 1264, 1249, 1207, 1196, 1154, 1130, 1108, 1041, 984, 8887, 835, 827, 786, 753, 743, 704, 694, 657.

MS (EI, 70 eV): *m/z* (%) = 319 (14), 317 (43), 267 (14), 191 (15), 190 (100), 170 (24), 77 (37), 77 (37), 77 (56), 77 (56), 77 (56), 73 (18).

HR-MS (EI, 70 eV): [$C_{17}H_{18}ClFN_3Si^+$], calcd.: 346.0937; found: 346.0955 [M+H$^+$].

3-(5-Chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)pyridine (117k)



Following **TP3** (5-chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116a**, 0.405 mmol, 1.00 equiv) was coupled with 3-bromopyridine (0.850 mmol, 134 mg, 2.10 equiv).

Isolated yield: 112 mg, 0.341 mmol, 84%, colorless crystals.

Purification: pentane:ethyl acetate = 7:3.

m.p.: 129.5 – 131.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.55 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.44 (dd, *J* = 2.4, 0.9 Hz, 1H), 7.58 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.53 (dd, *J* = 2.3, 0.9 Hz, 1H), 7.23 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.18 (s, 1H), 7.15 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 0.22 (s, 9H).

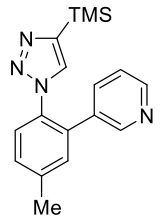
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 149.7, 149.0, 147.2, 136.1, 135.8, 135.6, 134.1, 132.3, 131.0, 130.9, 129.6, 128.4, 123.3, −1.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1501, 1473, 1411, 1250, 1201, 1154, 1125, 1097, 1042, 1014, 979, 911, 832, 814, 757, 741, 714, 741, 668.

MS (EI, 70 eV): *m/z* (%) = 300 (14), 287 (31), 286 (57), 285 (100), 284 (20), 284 (20), 284 (20), 284 (48), 284 (49), 255 (11), 73 (15).

HR-MS (EI, 70 eV): [$C_{16}H_{18}ClN_4Si^+$], calcd.: 329.0984; found: 329.0985 [M+H$^+$].

3-(5-Methyl-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)pyridine (117l)



Following **TP3** 1-(*p*ara-tolyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**116d**, 0.340 mmol, 1.00 equiv) was coupled with 3-bromopyridine (0.850 mmol, 134 mg, 2.50 equiv).

Isolated yield: 72 mg, 0.233 mmol, 69%, yellow solid.

Purification: pentane:ethyl acetate = 8:2.

m.p.: 72.2 - 74.0.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.29 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.24 (dd, *J* = 2.4, 0.9 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.14 (ddd, *J* = 8.1, 2.0, 0.9 Hz, 1H), 7.10 (d, *J* = 1.9 Hz, 1H), 7.01 – 6.95 (m, 2H), 6.89 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 2.27 (s, 3H), 0.00 (s, 9H).

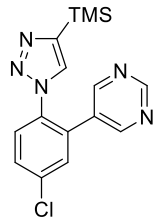
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 149.2, 149.1, 146.7, 140.5, 135.9, 133.8, 133.6, 133.1, 131.4, 131.2, 130.0, 126.9, 123.1, 21.4, −1.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 1512, 1409, 1248, 1205, 1156, 1134, 1039, 102, 997, 981, 832, 816, 755, 714, 668.

MS (EI, 70 eV): *m/z* (%) = 280 (18), 266 (16), 365 (72), 264 (100), 235 (10).

HR-MS (EI, 70 eV): [$C_{17}H_{20}N_4Si$], calcd.: 308.1457; found: 308.1451.

(5-Methyl-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (117m)



Following **TP3** (5-chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116a**, 0.405 mmol, 1.00 equiv) was coupled with 5-bromopyrimidine (0.850 mmol, 135 mg, 2.10 equiv).

Isolated yield: 83 mg, 0.252 mmol, 62%, yellow crystals.

Purification: pentane:ethyl acetate = 8:2.

m.p.: 125.8 – 127.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.15 (s, 1H), 8.44 (s, 2H), 7.60 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 2.2 Hz, 1H), 7.38 (s, 1H), 0.27 (s, 9H).

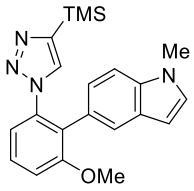
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 158.4, 155.9, 147.7, 136.5, 134.0, 132.5, 131.0, 130.7, 130.7, 130.3, 128.5, −1.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3103, 1548, 1507, 1218, 1404, 1386, 1247, 1205, 1185, 1157, 1115, 1037, 1018, 986, 979, 953, 890, 843, 822, 759, 737, 728, 737, 667.

MS (EI, 70 eV): *m/z* (%) = 301 (13), 288 (32), 287 (47), 286 (100), 285 (97), 259 (16), 73 (19).

HR-MS (EI, 70 eV): [$C_{15}H_{16}ClN_5Si$], calcd.: 329.0863; found: 329.0858

5-(2-Methoxy-6-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)-1-methyl-1*H*-indole (117n)



Following **TP3** (2-methoxy-6-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium (**116f**, 0.350 mmol, 1.00 equiv) was coupled with 5-bromo-1-methyl-1*H*-indole (0.850 mmol, 179 mg, 2.43 equiv).

Isolated yield: 111 mg, 0.295 mmol, 84%, pale yellow oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.45 (t, *J* = 8.1 Hz, 1H), 7.34 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.27 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.19 (dt, *J* = 8.4, 0.8 Hz, 1H), 7.10 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.00 (d, *J* = 3.1 Hz, 1H), 6.87 (dd, *J* = 8.5, 1.6 Hz, 1H), 6.82 (s, 1H), 6.36 (dd, *J* = 3.2, 0.8 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 0.00 (s, 9H).

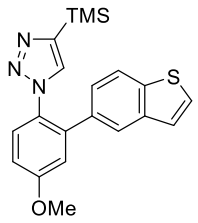
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 157.7, 145.4, 137.4, 136.2, 131.3, 129.3, 128.6, 128.6, 127.4, 123.8, 123.4, 122.5, 118.2, 111.7, 109.1, 101.4, 56.3, 32.9, −1.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953, 1598, 1581, 1513, 1488, 1473, 1438, 1422, 1331, 1300, 1246, 4210, 1181, 1092, 1037, 1014, 989, 839, 803, 792, 778, 760, 735, 719, 697, 667.

MS (EI, 70 eV): *m/z* (%) = 348 (25), 347 (34), 334 (25), 333 (100), 319 (11), 318 (42), 301 (7), 290 (6), 73 (7).

HR-MS (EI, 70 eV): [$C_{21}H_{24}N_4OSi$], calcd.: 376.1719; found: 376.1713.

1-(2-(Benzo[*b*]thiophen-5-yl)-4-methoxyphenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazol (117o)



Following **TP3** (5-methoxy-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116e**, 0.385 mmol, 1.00 equiv) was coupled with 5-bromobenzo[*b*]thiophene (0.850 mmol, 181 mg, 2.21 equiv).

Isolated yield: 130 mg, 0.343 mmol, 89%, pale yellow oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.73 (dt, *J* = 8.4, 0.7 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.48 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.44 (d, *J* = 5.4 Hz, 1H), 7.23 (dd, *J* = 5.5, 0.8 Hz, 1H), 7.09 (d, *J* = 2.8 Hz, 1H), 7.05 (s, 1H), 7.04 – 6.94 (m, 2H), 3.91 (s, 3H), 0.12 (s, 9H).

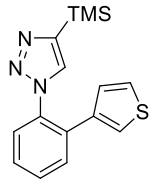
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.4, 146.2, 139.8, 139.4, 138.8, 133.6, 131.6, 128.7, 128.1, 127.4, 124.6, 124.0, 123.5, 122.6, 116.2, 113.7, 55.9, −1.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953, 1603, 1575, 1544, 1513, 1500, 1463, 1436, 1412, 1328, 1291, 1247, 1220, 1199, 1183, 1168, 1154, 1128, 1090, 1055, 1037, 995, 983, 837, 814, 755, 739, 702, 667.

MS (EI, 70 eV): *m/z* (%) = 358 (25), 357 (80), 355 (100), 340 (16), 339 (63), 337 (16), 320 (17), 306 (20), 306 (20), 305 (80), 246 (18), 73 (12).

HR-MS (EI, 70 eV): [$C_{20}H_{21}N_3OSSi$], calcd.: 379.1175; found: 379.1170.

1-(2-(Thiophen-3-yl)phenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (117p)



Following **TP3** (2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116c**, 0.360 mmol, 1.00 equiv) was coupled with 3-bromothiophene (0.850 mmol, 139 mg, 2.36 equiv).

Isolated yield: 70 mg, 0.234 mmol, 65%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.60 – 7.56 (m, 2H), 7.50 (m, 2H), 7.24 (s, 1H), 7.20 (dd, *J* = 5.0, 3.0 Hz, 1H), 6.96 (dd, *J* = 3.0, 1.3 Hz, 1H), 6.62 (dd, *J* = 5.0, 1.3 Hz, 1H), 0.26 (s, 9H).

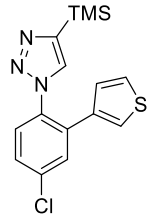
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 146.6, 137.6, 135.1, 132.5, 131.2, 130.5, 129.9, 128.5, 127.5, 127.0, 126.0, 123.6, −1.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 1495, 1364, 1248, 1200, 1150, 1112, 1084, 1053, 1036, 983, 838, 792, 756, 740, 704, 664.

MS (EI, 70 eV): *m/z* (%) = 271 (24), 270 (76), 258 89), 257 (20), 256 (100), 255 (26), 239 (21), 225 (15), 166 (13), 115 (9).

HR-MS (EI, 70 eV): [$C_{15}H_{17}N_3SSi$], calcd.: 299.0912; found: 299.0912.

1-(4-Chloro-2-(thiophen-3-yl)phenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (117q)



Following **TP3** (5-chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116a**, 0.405 mmol, 1.00 equiv) was coupled with 3-bromothiophene (0.850 mmol, 139 mg, 2.10 equiv).

Isolated yield: 130 mg, 0.389 mmol, 96%, pale yellow crystals

m.p.: 57.5 – 59.7 °C.

Purification: pentane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.56 (d, *J* = 2.3 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.21 (m, 2H), 6.97 (dd, *J* = 2.9, 1.3 Hz, 1H), 6.59 (dd, *J* = 5.0, 1.4 Hz, 1H), 0.25 (s, 9H).

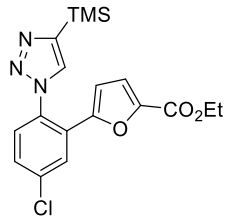
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 146.8, 136.2, 135.6, 133.9, 133.5, 131.1, 130.3, 128.4, 128.2, 127.2, 126.5, 124.3, −1.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3108, 2956, 1533, 1497, 1471, 1247, 1204, 1152, 1126, 1091, 1082, 1041, 1000, 979, 908, 890, 830, 787, 754, 736, 708, 694, 673.

MS (EI, 70 eV): *m/z* (%) = 307 (12), 306 (41), 305 (31), 304 (99), 292 (35), 291 (34), 290 (100), 289 (13), 261 (11), 256 (14), 255 (42), 240 (29), 208 (11), 73 (23), 44 (11).

HR-MS (EI, 70 eV): [$C_{15}H_{16}ClN_3SSi$], calcd.: 333.0523; found: 333.0529.

Ethyl 5-(5-chloro-2-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)phenyl)furan-2-carboxylate (117r)



Following **TP3** (5-chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**a**, 0.405 mmol, 1.00 equiv) was coupled with ethyl 5-bromofuran-2-carboxylate (0.850 mmol, 186 mg, 2.07 equiv).

Isolated yield: 149 mg, 0.381 mmol, 94%, orange crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 136.6 – 138.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.05 (d, *J* = 2.3 Hz, 1H), 7.60 (s, 1H), 7.46 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 3.7 Hz, 1H), 5.26 (d, *J* = 3.7 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 0.36 (s, 9H).

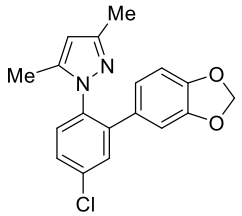
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 158.4, 150.6, 147.7, 145.0, 136.9, 132.2, 131.0, 129.4, 129.4, 128.4, 128.2, 119.5, 111.5, 61.4, 14.5, −1.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ =1726, 1499, 1468, 1386, 1297, 1148, 1215, 1199, 1158, 1149, 1124, 1114, 1098, 1058, 1035, 1024, 996, 968, 980, 935, 883, 826, 834, 819, 784, 762, 710, 678, 668.

MS (EI, 70 eV): *m/z* (%) = 361 (17), 348 (27), 332 (77), 318 (14), 303 (38), 288 (25), 258 (20), 253 (15), 103 (45), 75 (100), 73 (83).

HR-MS (EI, 70 eV): [$C_{18}H_{20}ClN_3O_3Si$], calcd.: 389.0962; found: 389.0943.

1-(2-(Benzo[*d*][1,3]dioxol-5-yl)-4-chlorophenyl)-3,5-dimethyl-1*H*-pyrazole (120a)



Following **TP3** (5-chloro-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)magnesium reagent (**119a**, 0.410 mmol, 1.00 equiv) was coupled with 5-bromobenzo[*d*][1,3]dioxole (0.850 mmol, 171 mg, 2.07 equiv).

Isolated yield: 127 mg, 0.389 mmol, 95%, pale yellow oil.

Purification: pentane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.45 (dd, *J* = 1.8, 1.0 Hz, 1H), 7.40 – 7.33 (m, 2H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.59 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.50 (d, *J* = 1.8 Hz, 1H), 5.94 (s, 2H), 5.79 (s, 1H), 2.28 (s, 3H), 1.66 (s, 3H).

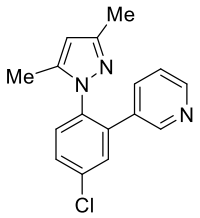
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 149.2, 147.9, 147.5, 140.8, 140.4, 136.0, 134.8, 131.2, 130.4, 130.2, 128.0, 122.4, 108.8, 108.5, 106.0, 101.3, 13.7, 11.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2898, 1608, 1594, 1553, 1499, 1483, 1434, 1401, 1364, 1335, 1277, 1251, 1238, 1220, 1149, 1134, 1105, 1094, 1037, 1023, 1012, 973, 934, 906, 862, 824, 814, 797, 759, 738, 718, 689, 667.

MS (EI, 70 eV): *m/z* (%) = 328 (14), 327 (13), 326 (43), 325 (16), 313 (29), 312 (16), 311 (100), 138 (7).

HR-MS (EI, 70 eV): [$C_{18}H_{15}ClN_2O_2$], calcd.: 326.0822; found: 326.0822.

3-(5-Chloro-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)pyridine (120b)



Following **TP3** (5-chloro-2-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)magnesium reagent (**119a**, 0.410 mmol, 1.00 equiv) was coupled with 3-bromopyridine (0.850 mmol, 134 mg, 2.07 equiv).

Isolated yield: 79 mg, 0.277 mmol, 68%, pale yellow oil.

Purification: pentane:ethyl acetate = 8:2 to 7:3.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.52 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.39 (dd, *J* = 2.4, 0.9 Hz, 1H), 7.51 (d, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.31 (ddd, *J* = 8.0, 2.4, 1.7 Hz, 1H), 7.18 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 5.79 (s, 1H), 2.25 (s, 3H), 1.75 – 1.60 (m, 3H).

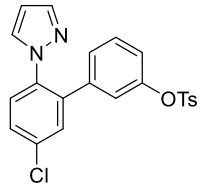
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 149.5, 149.2, 149.1, 140.6, 137.6, 136.4, 135.8, 135.3, 133.2, 130.6, 130.2, 129.3, 123.4, 106.4, 13.6, 11.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1588, 1553, 1499, 1473, 1415, 1393, 1363, 1332, 1292, 1252, 1190, 1131, 1096, 1028, 1017, 1010, 972, 882, 821, 808, 781, 740, 712, 668, 653.

MS (EI, 70 eV): *m/z* (%) = 270 (30), 269 (16), 268 (100), 192 (9).

HR-MS (EI, 70 eV): [$C_{15}H_{11}ClN_3^+$], calcd.: 268.0636; found:268.0633 [M-Me$^-$]

5'-Chloro-2'-(1*H*-pyrazol-1-yl)-[1,1'-biphenyl]-3-yl 4-methylbenzenesulfonate (120c)



Following **TP3** (5-chloro-2-(1*H*-pyrazol-1-yl)phenyl)magnesium reagent (**119b**, 0.390 mmol, 1.00 equiv) was coupled with 3-bromophenyl 4-methylbenzenesulfonate (0.850 mmol, 278 mg, 2.18 equiv).

Isolated yield: 148 mg, 0.348 mmol, 89%, colorless oil.

Purification: pentane:ethyl acetate = 85:15.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.66 – 7.56 (m, 2H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.15 – 7.06 (m, 2H), 6.96 – 6.86 (m, 2H), 6.77 (dt, *J* = 7.8, 1.3 Hz, 1H), 6.68 (t, *J* = 2.0 Hz, 1H), 6.13 (t, *J* = 2.1 Hz, 1H), 2.40 (s, 3H),

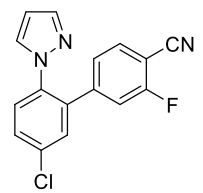
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 149.8, 145.8, 140.9, 139.0, 137.1, 136.6, 134.0, 132.2, 131.2, 130.7, 130.0, 129.9, 129.0, 128.7, 128.0, 127.2, 122.6, 122.2, 107.1, 21.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1596, 1580, 1566, 1517, 1476, 1430, 1371, 1329, 1307, 1293, 1263, 1211, 1192, 1179, 1147, 1110, 1091, 1042, 1019, 1002, 936, 916, 893, 877, 805, 793, 746, 695, 659.

MS (EI, 70 eV): *m/z* (%) = 271 (32), 270 (17), 269 (100), 90 (16), 61 (9), 43 (52), 42 (18).

HR-MS (EI, 70 eV): [$C_{22}H_{17}ClN_2O3S$], calcd.: 424.0648; found: 424.0626.

5'-Chloro-3-fluoro-2'-(1*H*-pyrazol-1-yl)-[1,1'-biphenyl]-4-carbonitrile (120d)



Following **TP3** (5-chloro-2-(1*H*-pyrazol-1-yl)phenyl)magnesium reagent (**119b**, 0.390 mmol, 1.00 equiv) was coupled with 4-bromo-2-fluorobenzonitrile (0.850 mmol, 170 mg, 2.18 equiv).

Isolated yield: 102 mg, 0.342 mmol, 88%, yellow crystals.

Purification: pentane:ethyl acetate = 85:15.

m.p.: 128.8 – 130.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.61 (d, *J* = 1.8 Hz, 1H), 7.57 – 7.49 (m, 3H), 7.45 (dd, *J* = 1.8, 1.0 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 6.98 – 6.90 (m, 2H), 6.31 (t, *J* = 2.1 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 163.0 (d, *J* = 259.9 Hz), 144.8 (d, *J* = 8.4 Hz), 141.3, 137.2, 135.7 (d, *J* = 1.9 Hz), 134.7, 133.6 (d, *J* = 0.8 Hz), 131.1, 130.5, 130.1, 128.4, 124.9 (d, *J* = 3.5 Hz), 116.5 (d, *J* = 20.7 Hz), 113.7, 107.7, 101.0 (d, *J* = 15.5 Hz).

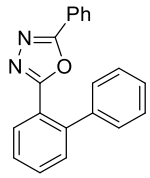
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ = −105.54 (dd, *J* = 9.7, 6.6 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2232, 1622, 1575, 1558, 1550, 1486, 1421, 1392, 1325, 1300, 1259, 1203, 1191, 1185, 1121, 1111, 1095, 1048, 1041, 1022, 937, 913, 894, 848, 833, 779, 763, 749, 732, 719, 689.

MS (EI, 70 eV): *m/z* (%) = 298 (32), 297 (16), 296 (100), 261 (15), 234 (12), 233 (11), 195 (7).

HR-MS (EI, 70 eV): [$C_{16}H_8ClFN_3^-$], calcd.: 296.0396; found: 296.0384 [M-H$^+$]

2-([1,1'-Biphenyl]-2-yl)-5-phenyl-1,3,4-oxadiazole (120e)



Following **TP3** (2-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl)magnesium reagent (**119c**, 0.380 mmol, 1.00 equiv) was coupled with bromobenzene (0.850 mmol, 133 mg, 2.24 equiv).

Isolated yield: 91 mg, 0.305 mmol, 80%, pale yellow oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.19 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.63 – 7.57 (m, 3H), 7.56 – 7.42 (m, 3H), 7.42 – 7.34 (m, 5H), 7.34 – 7.29 (m, 2H).

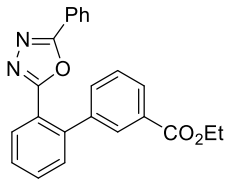
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 165.2, 164.7, 142.1, 140.9, 131.6, 131.5, 131.1, 130.2, 128.9, 128.8, 128.3, 127.9, 127.6, 126.7, 123.8, 122.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3057, 1607, 1598, 1571, 150, 1488, 1461, 1448, 1437, 1362, 1315, 1292, 1272, 1249, 1178, 1159, 1116, 1107, 1069, 1043, 1026, 1009, 988, 965, 924, 842, 778, 769, 758, 742, 715, 696, 669.

MS (EI, 70 eV): *m/z* (%) = 298 (21), 297 (100), 166 (28), 153 (5), 152 (18).

HR-MS (EI, 70 eV): [$C_{20}H_{13}N_2O^-$], calcd.: 297.1033; found: 297.1021 [M-H$^+$].

Ethyl 2'-(5-phenyl-1,3,4-oxadiazol-2-yl)-[1,1'-biphenyl]-3-carboxylate (120f)



Following **TP3** (2-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl)magnesium reagent (**119c**, 0.380 mmol, 1.00 equiv) was coupled with ethyl 3-bromobenzoate (0.850 mmol, 195 mg, 2.24 equiv).

Isolated yield: 106 mg, 0.286 mmol, 75%, yellow solid.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 121.9 – 123.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.24 – 8.18 (m, 1H), 8.12 – 8.05 (m, 2H), 7.65 – 7.52 (m, 4H), 7.51 – 7.41 (m, 4H), 7.38 (ddt, *J* = 8.5, 6.8, 1.3 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

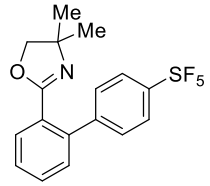
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.3, 164.7, 164.7, 141.0, 140.8, 133.3, 131.6, 131.5, 131.2, 130.6, 130.1, 129.9, 128.9, 128.8, 128.3, 126.6, 123.6, 122.7, 61.2, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1709, 1597, 1582, 1543, 1496, 1489, 1474, 1448, 1414, 1393, 1367, 1311, 1301, 1277, 1245, 1168, 1138, 1107, 1072, 1049, 1024, 990, 964, 908, 882, 865, 851, 828, 786, 736, 748, 714, 702, 691, 656.

MS (EI, 70 eV): *m/z* (%) = 370 (29), 369 (100), 152 (7), 151 (7), 105 (19), 77 (12).

HR-MS (EI, 70 eV): [$C_{23}H_{17}N_2O_3$], calcd.: 369.1245; found: 369.1233.

4,4-Dimethyl-2-(4'-(pentafluoro-λ^6-sulfaneyl)-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (120g)



Following **TP3** (2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl)magnesium reagent (**119d**, 0.385 mmol, 1.00 equiv) was coupled with (4-bromophenyl)pentafluoro-λ^6-sulfane (0.850 mmol, 241 mg, 2.21 equiv).

Isolated yield: 90 mg, 0.238 mmol, 62%, pale yellow oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.81 – 7.72 (m, 3H), 7.52 (td, *J* = 7.6, 1.5 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.34 (dd, *J* = 7.6, 1.3 Hz, 1H), 3.82 (s, 2H), 1.27 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 163.0, 152.9 (p, *J* = 17.2 Hz), 144.9, 139.7, 130.8, 130.5, 130.2, 128.8, 128.2, 128.1, 125.7 (p, *J* = 4.7 Hz), 79.6, 67.9, 28.1.

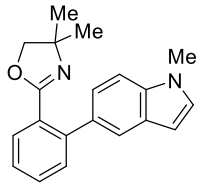
^{19}F NMR (377 MHz, CDCl3, ppm): δ = 85.77 – 83.67 (m), 63.13 (d, *J* = 150.1 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2967, 1654, 1598, 1784, 1463, 1448, 1399, 1365, 1349, 1310, 1213, 1189, 1100, 1076, 1061, 1037, 963, 822, 770, 754, 730, 699, 683, 662.

MS (EI, 70 eV): *m/z* (%) = 376(100), 322 (22), 291 (75), 250 (23), 220 (29), 183 (60), 180 (23), 179 (19), 178 (45), 177 (48), 163 (25), 152 (31), 151 (72), 150 (36).

HR-MS (EI, 70 eV): [$C_{17}H_{15}F_5NO_2S^-$], calcd:. 376.0800; found: 376.0793 [M-H$^+$].

4,4-Dimethyl-2-(2-(1-methyl-1*H*-indol-5-yl)phenyl)-4,5-dihydrooxazole (120h)



Following **TP3** (2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl)magnesium reagent (**119d**, 0.385 mmol, 1.00 equiv) was coupled with 5-bromo-1-methyl-1*H*-indole (0.850 mmol, 179 mg, 2.18 equiv).

Isolated yield: 107 mg, 0.352 mmol, 91%, orange crystals.

Purification: pentane:ethyl acetate = 8:2.

m.p.: 154.1 – 155.9 °C.

^{1}H-NMR (400 MHz, CDCl$_3$, ppm): *δ* = 7.72 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.69 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.37 – 7.32 (m, 2H), 7.30 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.08 (d, *J* = 3.1 Hz, 1H), 6.49 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 2H), 1.31 (s, 6H).

^{13}C-NMR (100 MHz, CDCl$_3$, ppm): *δ* = 164.6, 142.8, 136.2, 132.6, 130.7, 130.4, 130.3, 129.4, 128.5, 128.3, 126.4, 122.6, 120.7, 108.8, 101.3, 79.7, 67.4, 33.1, 28.2.

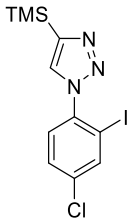
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2968, 1658, 1615, 1509, 1470, 1436, 1212, 1365, 1334, 138, 1299, 1246, 1181, 1155, 1107, 1083, 1066, 1032, 963, 920, 871, 810, 774, 755, 718, 691, 655.

MS (EI, 70 eV): *m/z* (%) = 304 (20), 303 (100), 248 (61), 231 (19), 218 (36), 217 (13), 190 (13).

HR-MS (EI, 70 eV): [$C_{20}H_{19}N_2O^-$], calcd.: 303.1503; found: 303.1493 [M-H$^+$].

5.5 Trapping of the Magnesium Reagent 116a with Electrophiles

1-(4-Chloro-2-iodophenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (121a)



(5-Chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116a**, 0.405 mmol, 1.00 equiv) was cooled to 0 °C and quenched with an iodine solution (1.75 mmol, 4.32 equiv) in THF (2 mL). The reaction mixture was stirred for 15 min and the remaining iodine was quenched with saturated aq. $Na_2S_2O_3$ solution (15 mL). The mixture was extracted with DCM (3 x 25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was subjected to column chromatography on silica yielding 1-(4-chloro-2-iodophenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole.

Isolated yield: 150 mg, 0.397 mmol, 98%, white crystals.

Purification: pentane:ethyl acetate = 95:5.

m.p.: 111.0 – 113.2 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.98 (d, *J* = 2.2 Hz, 1H), 7.80 (s, 1H), 7.47 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 0.38 (s, 9H).

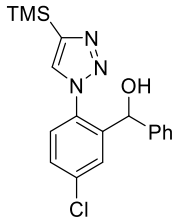
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 146.8, 139.6, 139.1, 136.5, 130.9, 129.5, 128.4, 94.4, −1.00.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3076, 2957, 1574, 1495, 1473, 1436, 1401, 1372, 1250, 1204, 1160, 1101, 1047, 1040, 1005, 999, 985, 875, 835, 825, 773, 756, 710, 672, 697.

MS (EI, 70 eV): *m/z* (%) = 348 (12), 335 (29), 334 (60), 209 (32), 208 (19), 207 (100), 194 (18), 192 (55), 73 (19).

HR-MS (EI, 70 eV): [$C_{11}H_{14}N_3ClSi^+$], calcd.: 377.9685; found: 377.9669 [M+H$^+$].

(5-Chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)(phenyl)methanol (121b)



(5-Chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116a**, 0.405 mmol, 1.00 equiv) was cooled to 0 °C and benzaldehyde (0.10 mL, 1.00 mmol, 2.47 equiv) was added dropwise. The reaction was stirred for 1.5 h at this temperature and was then allowed to warm to room temperature. Saturated aq. NH_4Cl solution (5 mL) was added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was subjected to column chromatography on silica yielding (5-chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)(phenyl)methanol.

Isolated yield: 125 mg, 0.349 mmol, 86%, pale yellow crystals.

Purification: pentane:ethyl acetate = 8:2.

m.p.: 103.8 – 105.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.83 (d, *J* = 2.4 Hz, 1H), 7.35 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.22 (s, 1H), 7.17 – 7.08 (m, 4H), 6.97 – 6.89 (m, 2H), 5.87 (d, *J* = 5.6 Hz, 1H), 4.80 (d, *J* = 5.7 Hz, 1H), 0.26 (s, 9H).

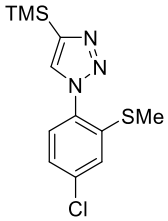
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 146.7, 142.4, 141.8, 136.2, 133.4, 131.0, 129.2, 128.4, 128.3, 127.5, 127.26, 126.5, 71.2, −1.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3220, 1493, 1448, 1403, 1345, 1268, 1251, 1235, 1209, 1179, 1157, 1119, 1096, 1054, 1046, 1027, 1016, 986, 926, 906, 883, 836, 821, 772, 759, 736, 726, 700, 661.

MS (EI, 70 eV): *m/z* (%) = 314 (18), 312 (40), 254 (26), 252 (54), 241 (31), 239 (90), 237 (35), 235 (46), 203 (34), 76 (29), 75 (80), 73 (100).

HR-MS (EI, 70 eV): [$C_{18}H_{20}ClN_3OSi$], calcd.: 357.1064; found: 357.1065.

1-(4-Chloro-2-(methylthio)phenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (121c)



(5-Chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116a**, 0.405 mmol, 1.00 equiv) was cooled to 0 °C and $MeSSO_2Me$ (1.00 mmol, 126 mg, 2.47 equiv) was added portionwise.

The reaction was stirred for 1 h at this temperature and was allowed to warm to room temperature. Saturated aq. NH_4Cl solution (5 mL) was added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was subjected to column chromatography on silica yielding 1-(4-chloro-2-(methylthio)phenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole.

Isolated yield: 90 mg, 0.302 mmol, 75%, colorless crystals.

Purification: pentane:ethyl acetate = 95:5.

m.p.: 84.0 – 85.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.84 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 2.2 Hz, 1H), 7.26 – 7.23 (m, 1H), 2.39 (s, 3H), 0.38 (s, 9H).

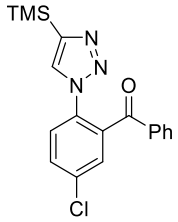
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 146.6, 137.6, 136.2, 133.7, 130.9, 127.9, 126.3, 125.7, 15.7, −0.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3077, 1583, 1493, 1472, 1437, 1426, 1400, 1382, 1249, 1204, 1191, 1154, 1096, 1075, 7039, 1005, 987, 980, 955, 822, 796, 756, 711, 699, 680, 655.

MS (EI, 70 eV): *m/z* (%) = 253 (22), 240 (38), 239 (17), 238 (100), 223 (10), 73 (17).

HR-MS (EI, 70 eV): [$C_{12}H_{16}ClN_3SSi$], calcd.: 297.0523; found: 297.0513.

(5-Chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)(phenyl)methanone (121d)



(5-Chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116a**, 0.405 mmol, 1.00 equiv) was cooled to -40 °C, CuCN·2·LiCl solution (1 M in THF, 1.20 mmol, 2.96 equiv) was added and the reaction mixture was for 30 min. Benzoyl chloride (0.12 mL, 1.00 mmol, 2.47 equiv) was added dropwise and the reaction mixture was allowed to come to room temperature for 16 h. Saturated aq. NH_4Cl solution (5 mL) was added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was subjected to column chromatography on silica yielding (5-chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)(phenyl)methanone.

Isolated yield: 89 mg, 0.250 mmol, 62%, colorless crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 127.1 – 128.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.68 – 7.63 (m, 2H), 7.61 – 7.54 (m, 4H), 7.46 (ddt, *J* = 8.8, 7.0, 1.3 Hz, 1H), 7.33 – 7.27 (m, 2H), 0.18 (s, 9H).

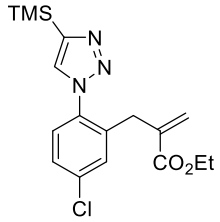
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 193.7, 147.4, 135.9, 135.8, 135.5, 133.8, 133.6, 131.7, 130.2, 129.9, 129.3, 128.6, 126.2, −1.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3116, 1656, 1594, 1495, 1448, 1393, 1313, 1244, 1201, 1157, 1112, 1040, 984, 956, 891, 832, 785, 759, 739, 709, 694, 668, 660.

MS (EI, 70 eV): *m/z* (%) = 327 (28), 315 817), 314 (100), 313 (43), 312 (50), 203 (11), 77 (19).

HR-MS (EI, 70 eV): [$C_{18}H_{18}N_3Cl_2Si$], calcd.: 355.0908; found: 355.0898.

Ethyl 2-(5-chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)benzyl)acrylate (121e)



(5-Chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)magnesium reagent (**116a**, 0.405 mmol, 1.00 equiv) was cooled to -30 °C and CuCN·2 LiCl solution (1 M in THF, 1.20 mmol, 2.96 equiv) was added dropwise. The reaction mixture was stirred at this temperature for 30 min and ethyl 2-(bromomethyl)acrylate (193 mg, 1.0 mmol, 2.47 equiv) was added. The reaction mixture was allowed to come to room temperature for 16 h. Saturated aq. NH_4Cl solution (5 mL) was added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was subjected to column chromatography on silica yielding ethyl 2-(5-chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)benzyl)acrylate.

Isolated yield: 113 mg, 0.311 mmol, 77%, colorless oil.

Purification: pentane:ethyl acetate = 7:3.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.72 (s, 1H), 7.38 (d, *J* = 2.3 Hz, 1H), 7.34 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 6.18 (d, *J* = 1.2 Hz, 1H), 5.27 (q, *J* = 1.3 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.52 (s, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.36 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.2, 146.7, 137.8, 136.9, 135.7, 135.1, 131.1, 130.9, 127.8, 127.8, 127.8, 61.1, 33.8, 14.3, −1.00.

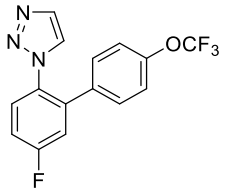
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 1713, 1631, 1598, 1499, 1478, 1407, 1368, 1327, 1300, 1249, 1203, 1186, 1145, 1114, 1094, 1033, 997, 983, 997, 983, 951, 932, 838, 818, 757, 709, 697, 662, 677.

MS (EI, 70 eV): *m/z* (%) = 306 (15), 263 (23), 261 (55), 249 (24), 248 (28), 215 (25), 190 (23), 189 (33), 75 (66), 73 (100).

HR-MS (EI, 70 eV): [$C_{17}H_{22}ClN_3O_2Si$], calcd.: 363.1170; found: 363.1156.

5.6 Late-Stage Modifications

1-(5-fluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazole (122)



According to the literature[163], 1-(5-fluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**117g**, 119 mg, 0.3 mmol, 1.00 equiv) was dissolved in THF (0.3 mL) and TBAF (1 M in THF, 0.45 mmol, 1.50 equiv) was added. The reaction mixture was stirred for 16 h. Saturated aq. $NaHCO_3$ solution (5 mL) was added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was subjected to column chromatography on silica yielding the title compound.

Isolated yield: 88 mg, 0.27 mmol, 91%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.55 (d, *J* = 1.1 Hz, 1H), 7.52 (dd, *J* = 8.6, 5.1 Hz, 1H), 7.19 (d, *J* = 1.1 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.04 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 163.0 (d, *J* = 251.7 Hz), 149.4 (q, *J* = 1.9 Hz), 138.4 (d, *J* = 8.6 Hz), 134.8 (d, *J* = 1.5 Hz), 133.9, 131.3 (d, *J* = 3.3 Hz), 129.9, 129.1 (d, *J* = 9.2 Hz), 125.9, 121.2, 120.4 (q, *J* = 258.0 Hz), 117.9 (d, *J* = 23.5 Hz), 116.0 (d, *J* = 22.6 Hz).

^{19}F NMR (377 MHz, CDCl3, ppm): δ = −57.81 (s), −109.88 (td, J = 8.3, 5.1 Hz).

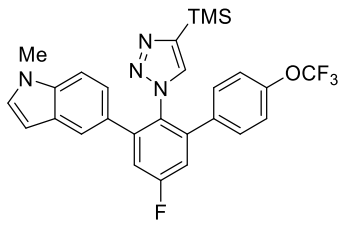
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1617, 1593, 1580, 1519, 1501, 1474, 1001, 1253, 1206, 1161, 1107, 1089, 1039, 1026, 1018, 982, 945, 922, 890, 853, 826, 806, 780, 701, 674, 660.

MS (EI, 70 eV): *m/z* (%) = 323 (40), 295 (100), 226 (13), 210 (61), 208 (29), 198 (56), 183 (19), 170 (32), 157 (38).

HR-MS (EI, 70 eV): [$C_{15}H_9N_3OF_4$], calcd.: 323.0682; found: 323.0677.

[163] Y. Jeong, J.-S. Ryu *J. Org. Chem.* **2010**, *75*, 4183–4191

5-(5-fluoro-4'-(trifluoromethoxy)-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)-[1,1'-biphenyl]-3-yl)-1-methyl-1*H*-indole (124)



Following **TP3** (5-fluoro-4'-(trifluoromethoxy)-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)-[1,1'-biphenyl]-3-yl)magnesium reagent (**123**, 0.400 mmol, 1.00 equiv) was coupled with 5-bromo-1-methyl-1*H*-indole (0.85 mmol, 179 mg, 2.34 equiv).

Isolated yield: 184 mg, 0.351 mmol, 88%, pale yellow crystals.

Purification: pentane:ethyl acetate = 8:2.

m.p.: 64.9 – 66.6 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.37 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.33 (dd, *J* = 8.9, 2.9 Hz, 1H), 7.19 – 7.11 (m, 4H), 7.10 – 7.04 (m, 3H), 7.03 (d, *J* = 3.1 Hz, 1H), 6.89 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.39 (dd, *J* = 3.2, 0.9 Hz, 1H), 3.74 (s, 3H), 0.08 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 162.5 (d, J = 251.1 Hz), 149.0 (d, J = 2.0 Hz), 146.1, 144.2 (d, J = 9.2 Hz), 141.1 (d, J = 9.2 Hz), 136.4, 135.87 (d, J = 1.8 Hz), 132.6, 129.9, 129.7, 128.5, 127.9 (d, J = 1.6 Hz), 121.8, 121.1, 120.7, 120.5 (q, J = 257.7 Hz), 117.6 (d, J = 22.4 Hz), 115.8 (d, J = 23.3 Hz), 109.2, 101.5, 33.0, -1.3.

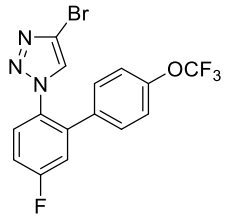
^{19}F NMR (377 MHz, CDCl3, ppm): δ = −57.86 (s), −110.53 (t, *J* = 8.7 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 1594, 1511, 1511, 1494, 1463, 1446, 1422, 1325, 1247, 1204, 1160, 1103, 1080, 1035, 1019, 984, 955, 921, 873, 838, 801, 760, 722, 679.

MS (EI, 70 eV): *m/z* (%) = 524 (6), 497 (22), 496 (64), 495 (100), 482 (29), 481 (87), 424 (18), 415 (32), 338 (23), 337 (24), 335 (59).

HR-MS (EI, 70 eV): [$C_{27}H_{24}N_4OSi$], calcd.: 524.1656; found: 524.1645.

4-Bromo-1-(5-fluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazole (125)



1-(5-fluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**117g**, 790 mg, 2.00 mmol, 1.00 equiv) was dissolved in DMF (4 mL) cooled with an icebath to 5 °C and DBDMH (686 mg, 2.40 mmol, 1.20 equiv) was added and the reaction mixture was stirred for 16 h. After removal of the solvent the crude product was subjected to column chromatography on silica yielding the title compound.

Isolated yield: 769 mg, 1.92 mmol, 93%, pale yellow crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 77.8 – 79.5 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.37 (dd, *J* = 8.6, 5.1 Hz, 1H), 7.08 – 7.00 (m, 3H), 6.99 – 6.94 (m, 2H), 6.93 – 6.88 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 163.3 (d, *J* = 252.7 Hz), 149.6 (t, *J* = 1.9 Hz), 138.6 (d, *J* = 8.6 Hz), 134.4 (d, *J* = 1.5 Hz), 130.8 (d, *J* = 3.4 Hz), 129.9, 129.1 (d, *J* = 9.3 Hz), 126.0, 121.4, 120.8, 120.5 (q, *J* = 258.1 Hz), 118.1 (d, *J* = 23.7 Hz), 116.2 (d, *J* = 22.8 Hz).

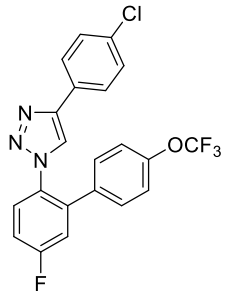
^{19}F NMR (377 MHz, CDCl3, ppm): δ = −57.81 (s), −108.80 (td, *J* = 7.9, 5.1 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3158, 1615, 1594, 1580, 1516, 1500, 1478, 1442, 1395, 1278, 1246, 1221, 1205, 1190, 1164, 1104, 1040, 1034, 1017, 991, 976, 951, 921, 893, 881, 853, 830, 817, 806, 746, 698, 658, 676.

MS (EI, 70 eV): *m/z* (%) = 375 (38), 372 (37), 295 (21), 294 (100), 290 (26), 288 (27), 266 (18), 209 (50), 208 (98), 197 (20), 196 (24), 169 (24), 158 (11), 157 (33).

HR-MS (EI, 70 eV): [$C_{15}H_8N_3O_2BrF_4$], calcd.: 400.9787; found: 400.9786.

4-(4-Chlorophenyl)-1-(5-fluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazole (126)



According to the literature[164], 4-bromo-1-(5-fluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazole was (**117g**, 99 mg, 0.250 mmol, 1.00 equiv), K_2CO_3 (69 mg. 0.500 mmol, 2.00 equiv), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol 10 mol%) and (4-chlorophenyl)boronic acid (59 mg, 0.375, 1.5 equiv) were added to a flask under argon. Then dioxane (2.25 ml) and water (0.75 ml) were added and the reaction mixture was heated for 16 h at 100 °C. Saturated aq. NH_4Cl solution (5 mL) was added and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was subjected to column chromatography on silica yielding 4-(4-chlorophenyl)-1-(5-fluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)-1H-1,2,3-triazole.

Isolated yield: 93 mg, 0.22 mmol, 86%, pale orange crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 144.7 – 146.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.47 – 7.42 (m, 1H), 7.42 – 7.37 (m, 2H), 7.19 (s, 1H), 7.17 – 7.12 (m, 2H), 7.10 – 7.02 (m, 2H), 6.95 (s, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 163.1 (d, *J* = 252.0 Hz), 149.5 (d, *J* = 2.0 Hz), 147.9, 138.3 (d, *J* = 8.6 Hz), 134.9 (d, *J* = 1.5 Hz), 134.4, 131.2 (d, *J* = 3.2 Hz), 130.0, 129.2, 129.0 (d, *J* = 9.2 Hz), 128.5, 127.1, 121.8, 121.4, 120.5 (q, *J* = 257.9 Hz), 118.0 (d, *J* = 23.6 Hz), 116.2 (d, J = 22.8 Hz).

^{19}F NMR (377 MHz, CDCl3, ppm): δ = −58.32 , −110.08 (ddd, *J* = 8.6, 7.6, 5.1 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1610, 1519, 1054, 1475, 1426, 2317, 1301, 1279, 1239, 1224, 1206, 1182, 1112, 1095, 1083, 1035, 1018, 1011, 993, 967, 945, 924, 893, 82, 843, 832, 846, 824, 805, 138, 719, 704, 686, 675, 662.

MS (EI, 70 eV): *m/z* (%) = 407 (32), 406 (30), 405 (100), 370 (32), 369 (52), 318 (11), 286 (11), 285 (44), 272 (17), 170 (11), 150 (18).

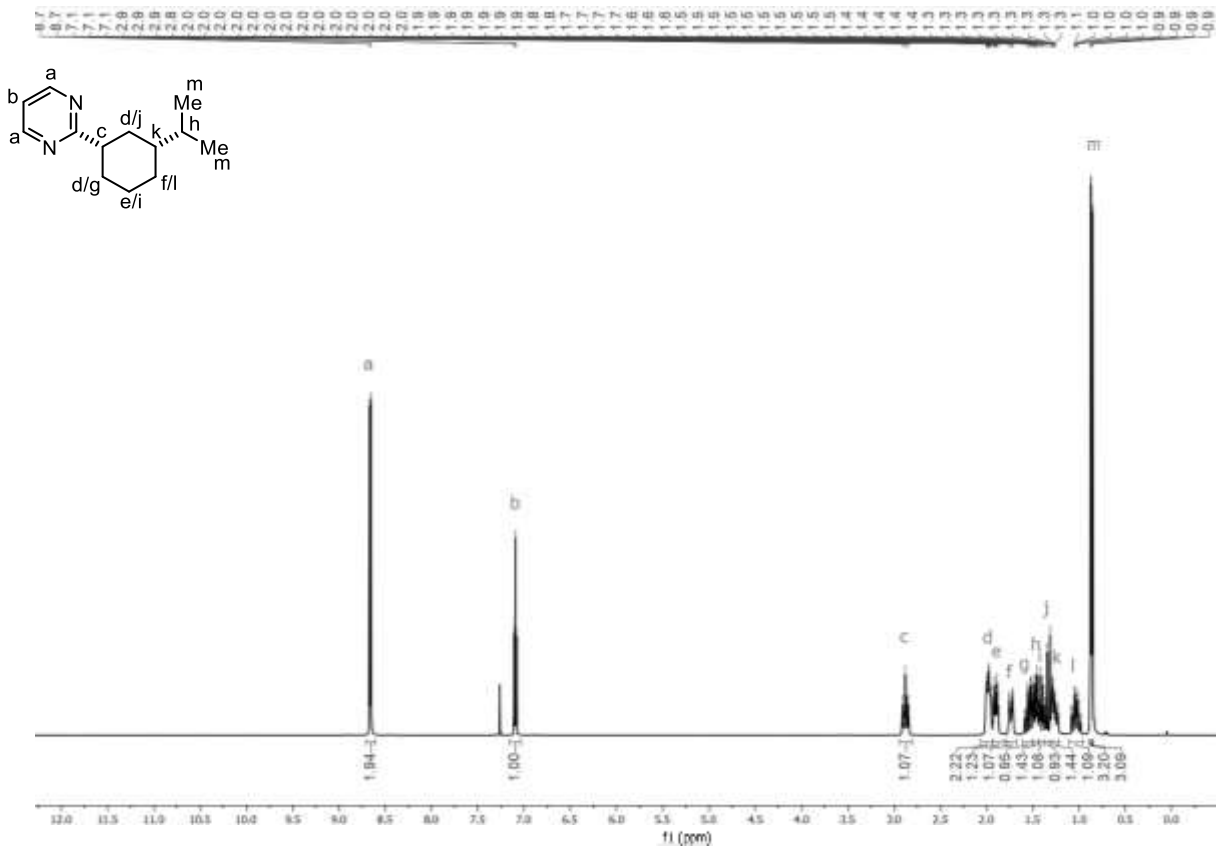
HR-MS (EI, 70 eV): [$C_{21}H_{12}N_3O_2ClF_4$], calcd.: 433.0605; found: 433.0600.

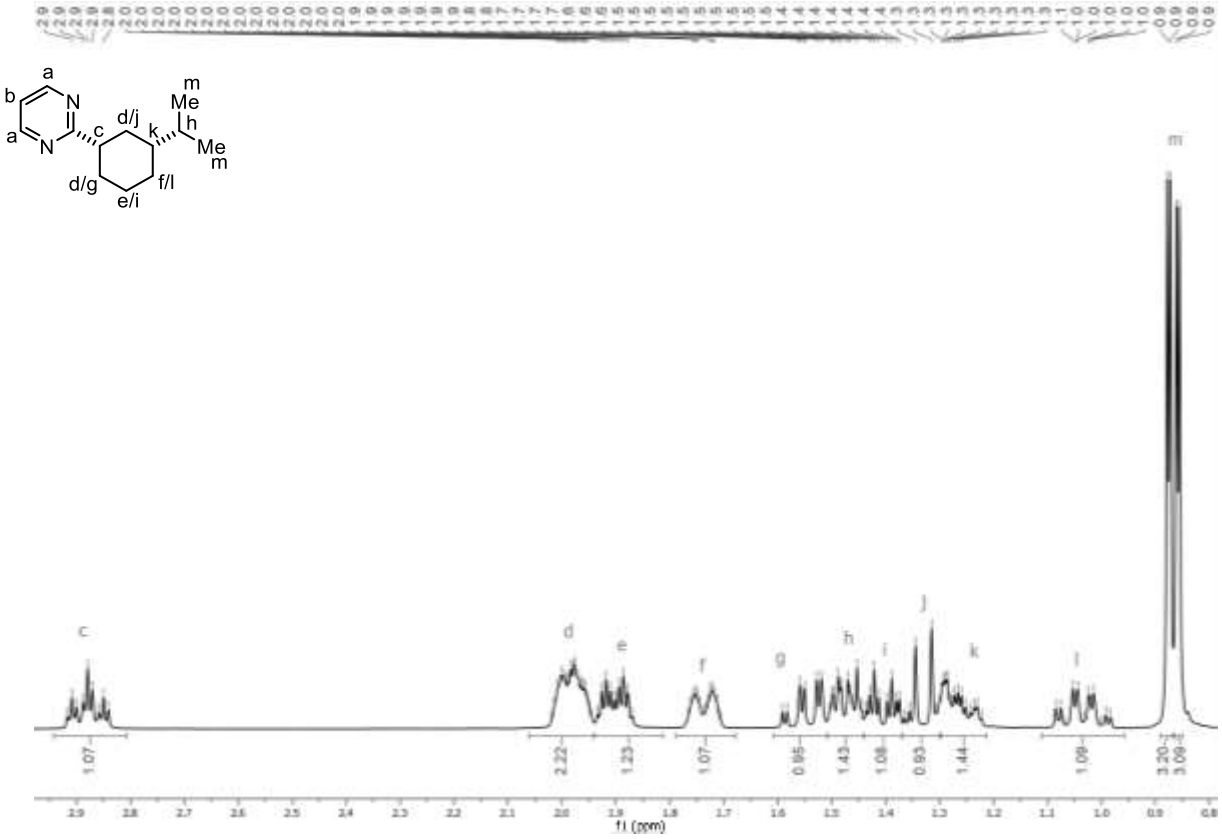
[164] Z. Shan, M. Peng, H. Fan, Q. Lu, P. Lu, C. Zhao, Y. Chen *Bioorg. Med. Chem. Lett.* **2011,** *21*,1731–1735.

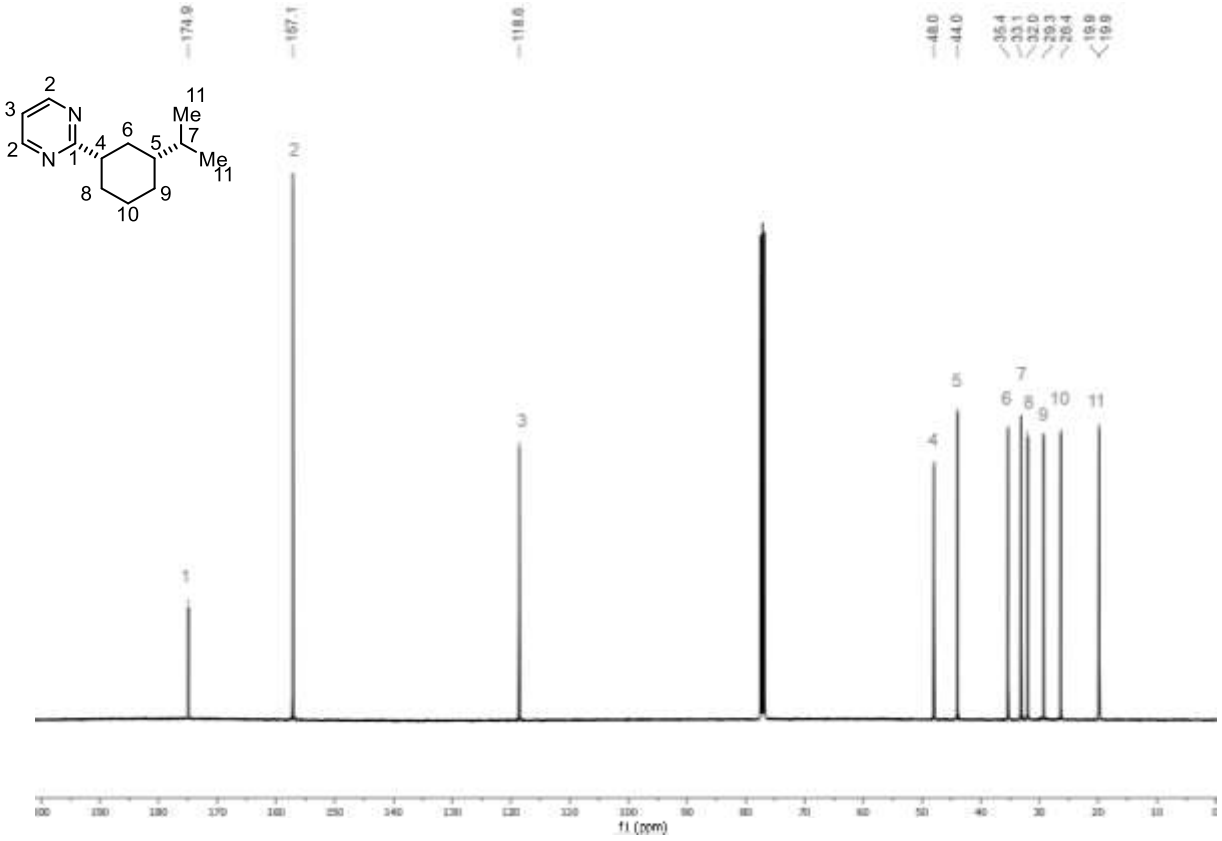
VI. Appendix

1. Structure Determination using NMR-Experiments

1.1 2-(3-Isopropylcyclohexyl)pyrimidine (102ac)




a
b
a
N
N
c
d/j
k
m
Me
h
Me
m
d/g
e/i
f/l
m
c
d
e
f
g
h
i
j
k
l
1.07
2.22
1.23
1.07
0.95
1.43
1.08
0.93
1.44
1.09
3.20
3.09
f1 (ppm)


174.9
167.1
118.6
48.0
44.0
35.4
33.1
32.0
29.3
26.4
19.9
19.9
2
3
N
N
1
4
6
5
11
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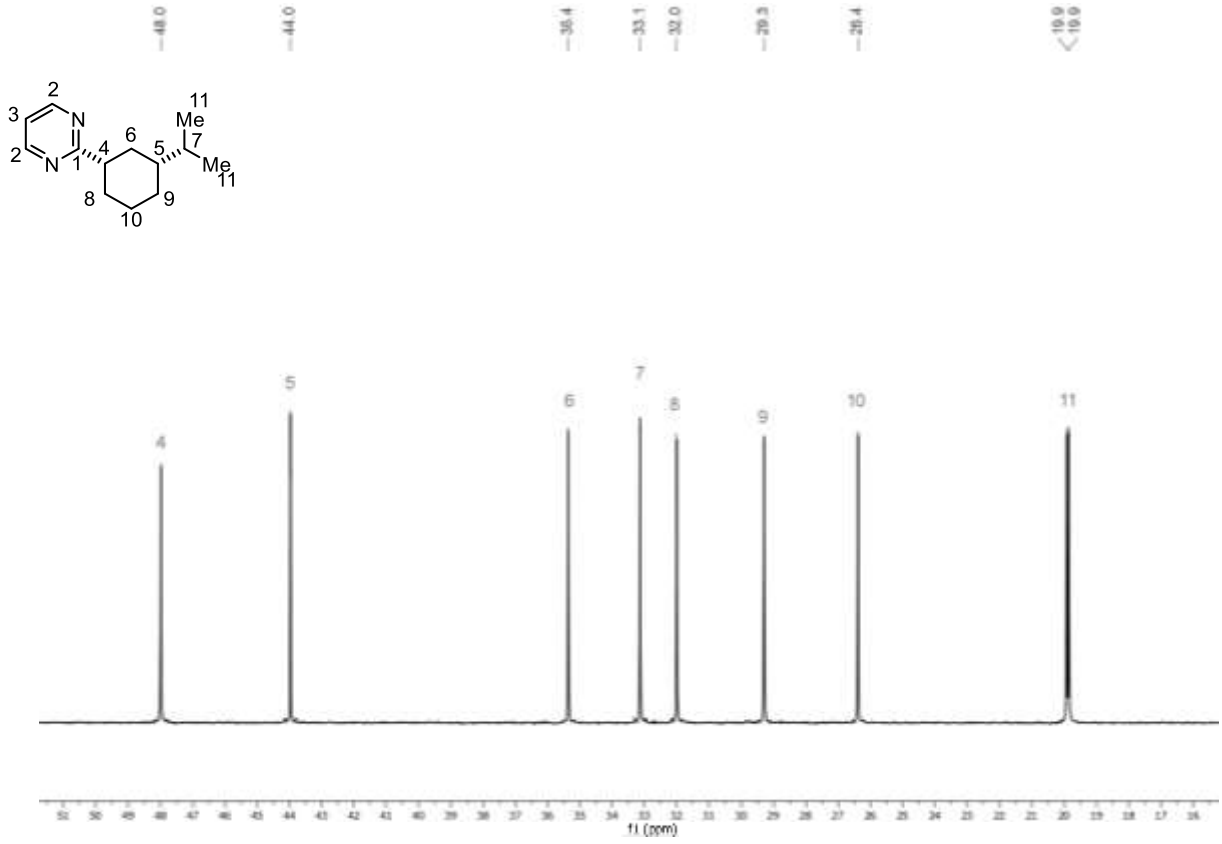
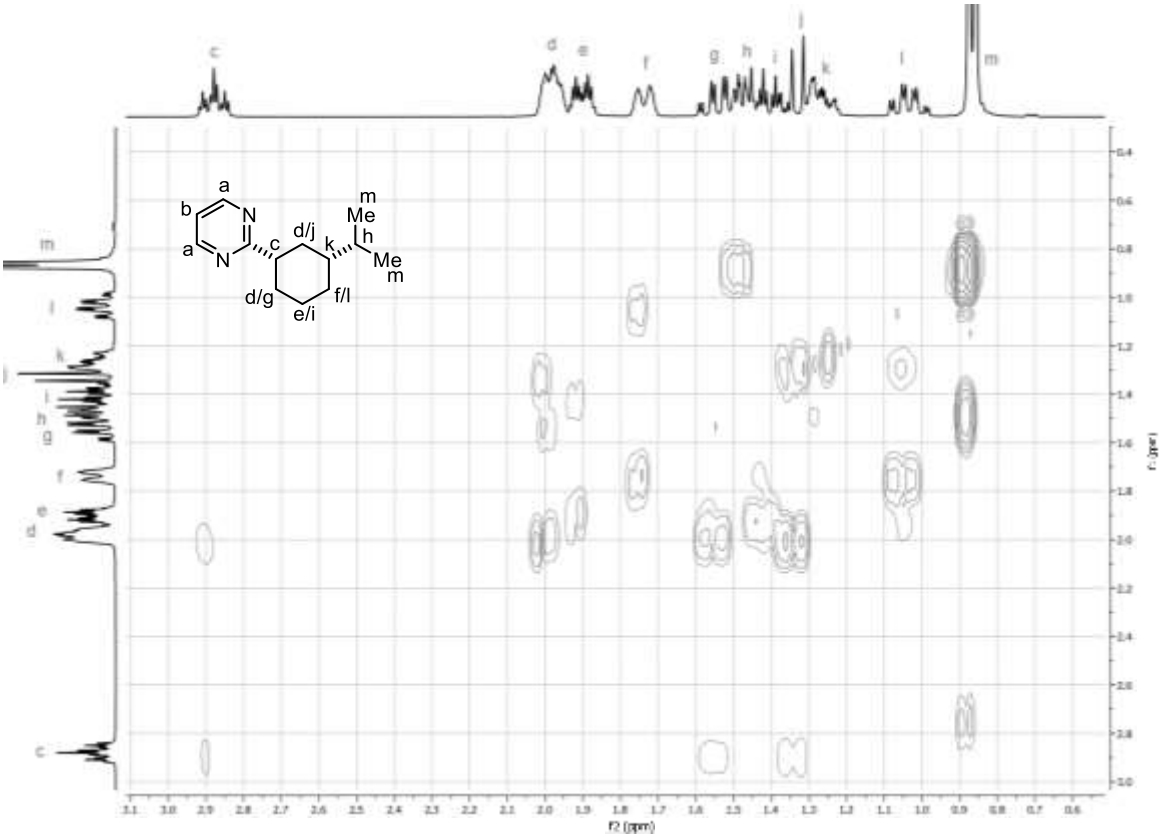
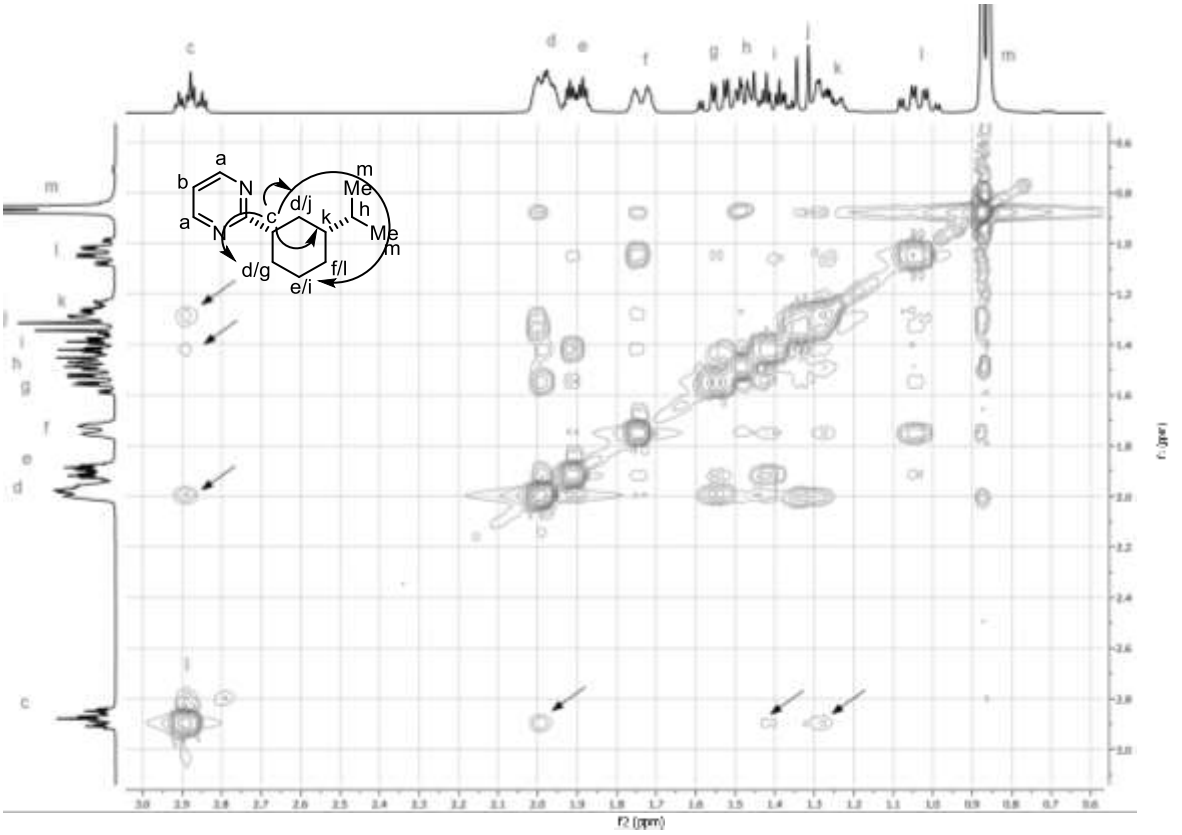
5
6
7
8
9
10
11
f1 (ppm)



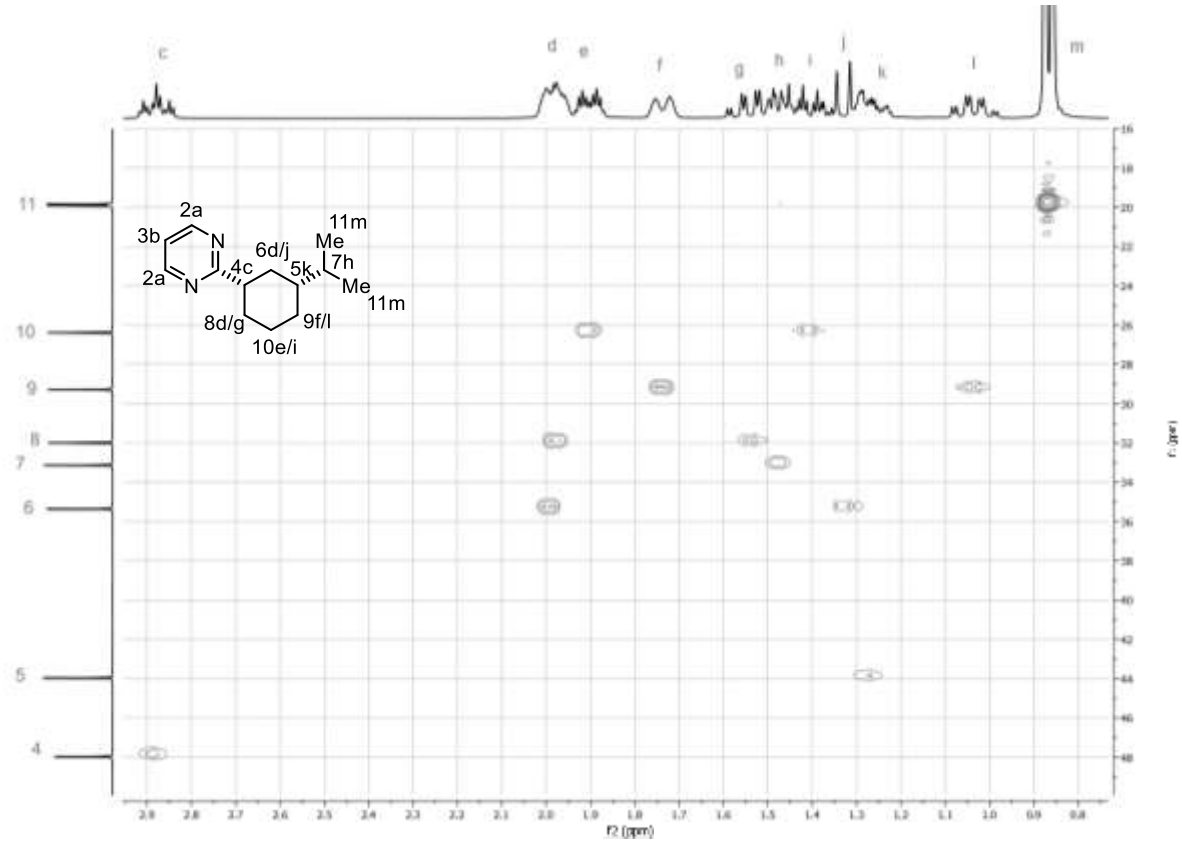
COSY-NMR spectrum



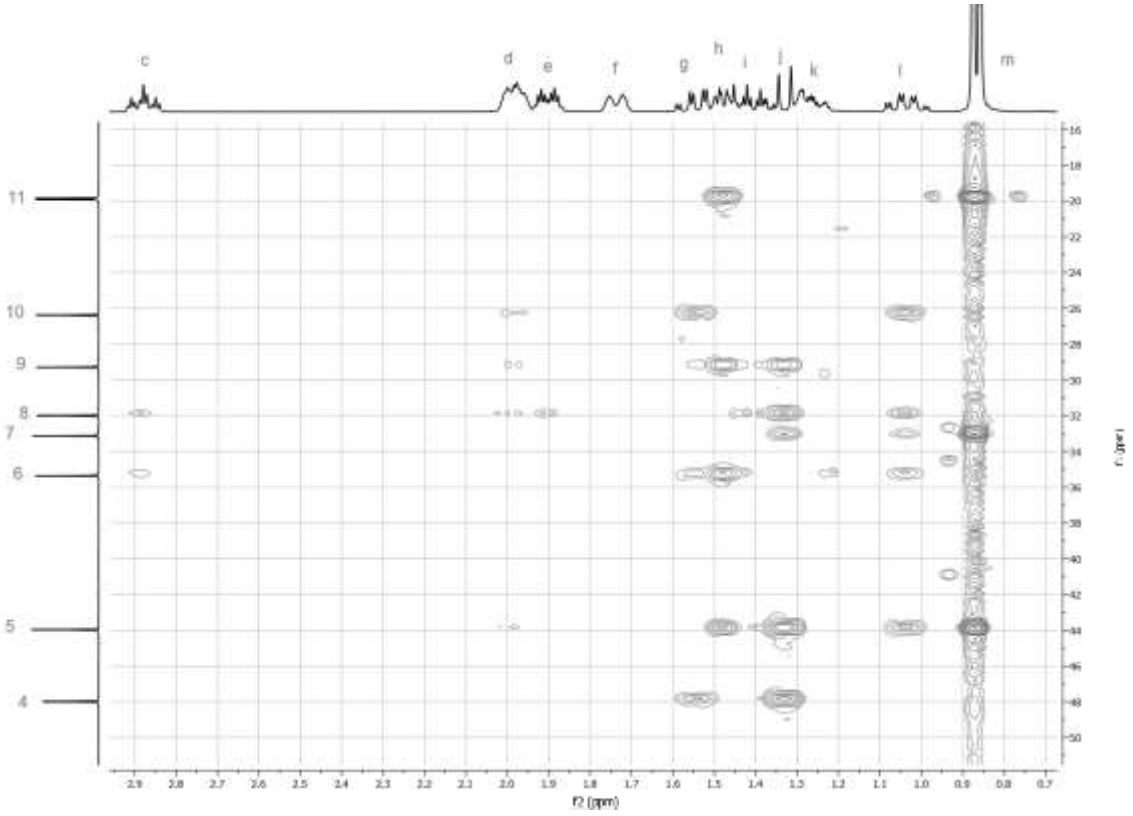
NOESY-NMR spectrum



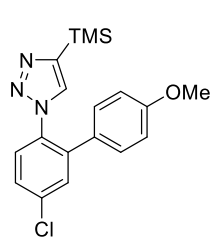
HSQC-NMR spectrum

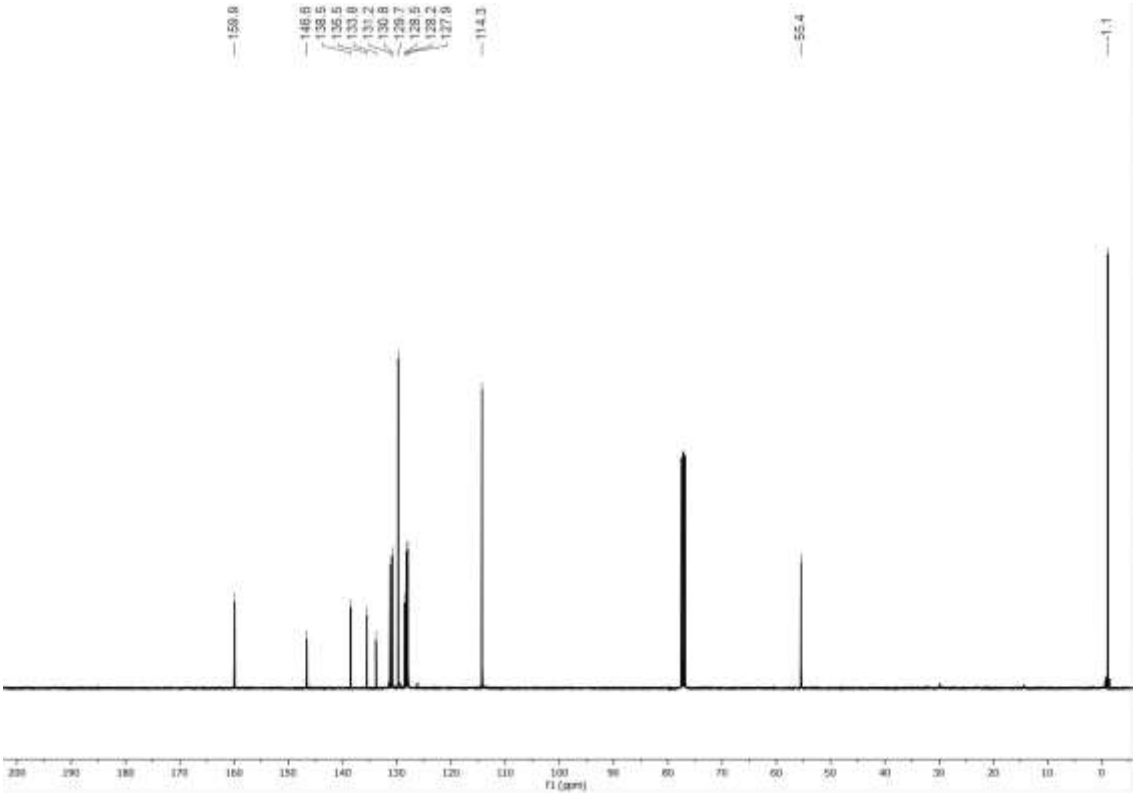


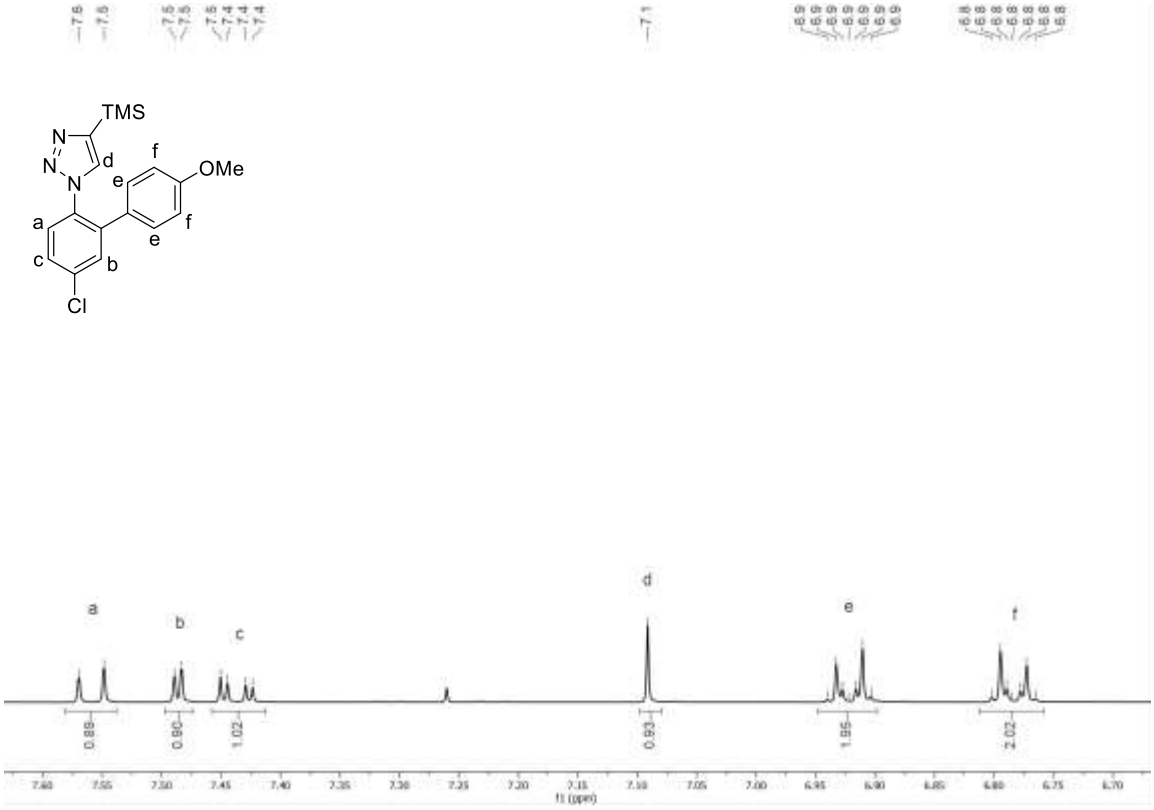
HMBC-NMR spectrum



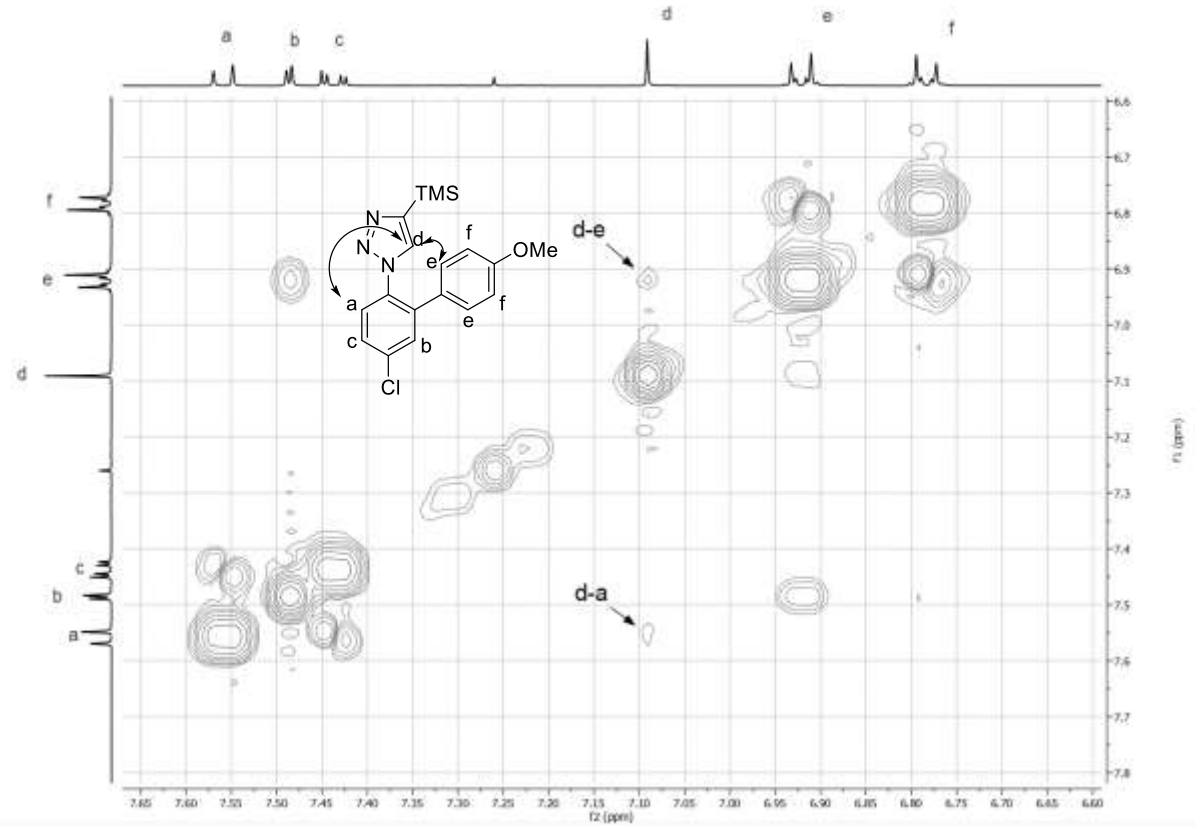
1.2 1-(5-Chloro-4'-methoxy-[1,1'-biphenyl]-2-yl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (117a)





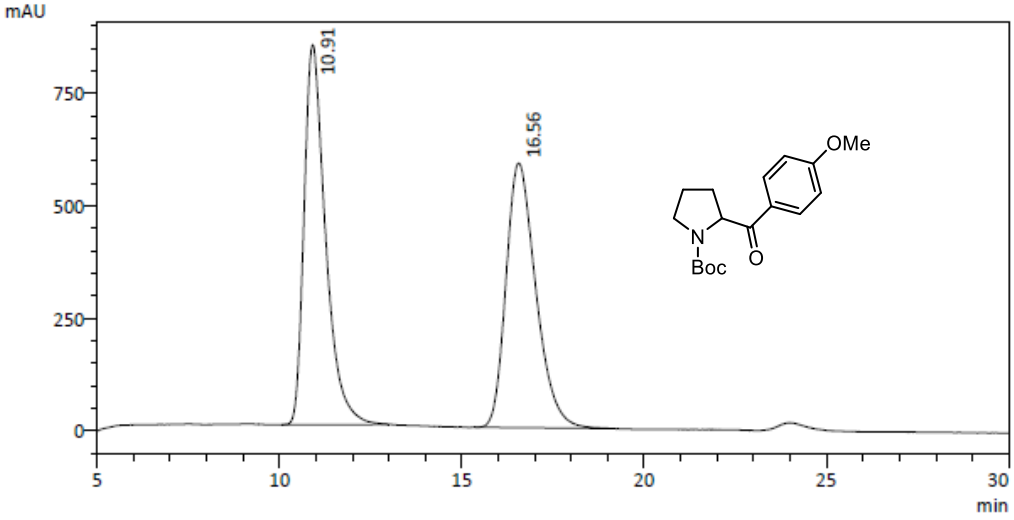


NOESY-NMR spectrum



2. Chiral HPLC Analysis

tert-Butyl (R/*S*)-2-(4-methoxybenzoyl)pyrrolidine-1-carboxylate (110t)



PDA Ch2 205nm

Peak#	Ret. Time	Area	Height	Area%
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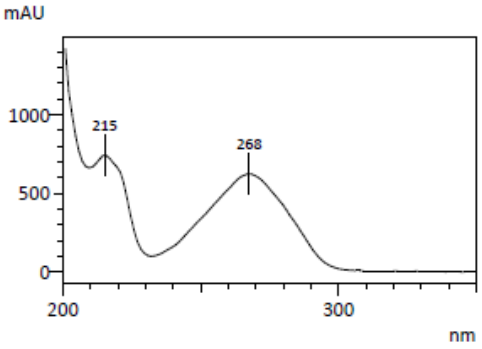
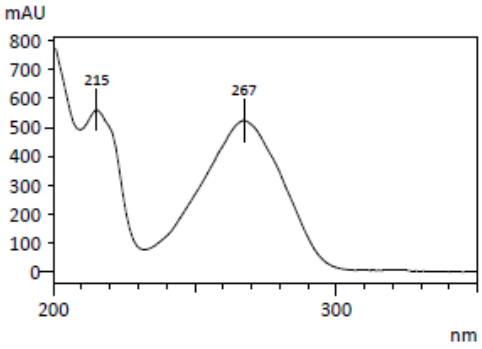
2	16.56	33536738	588075	49.2
Total				100.0

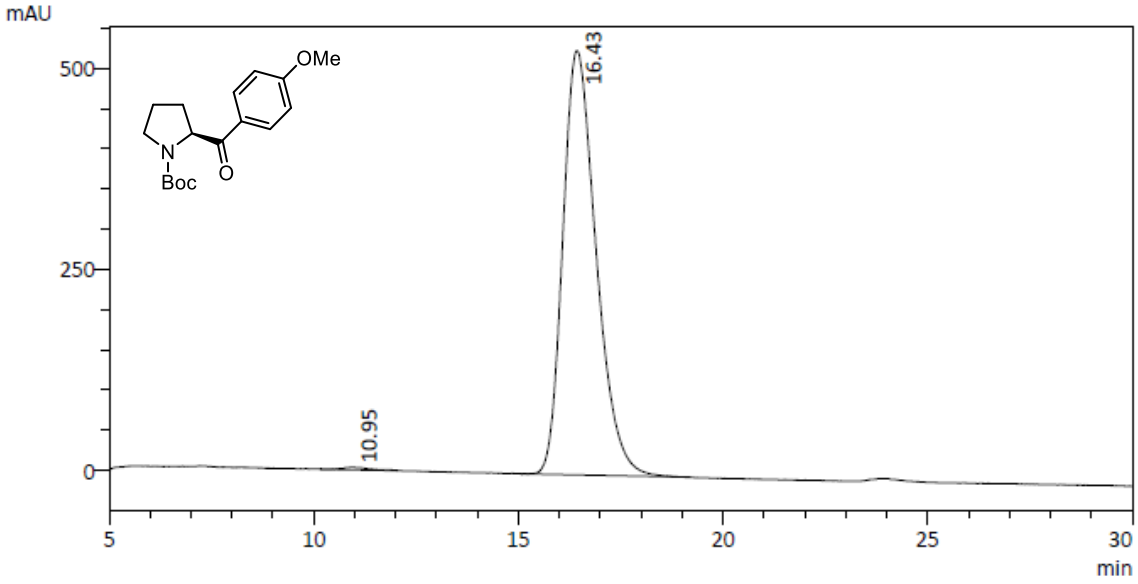
UV Spectrum
Peak#: 1
Retention Time: 10.912 min



UV Spectrum
Peak#: 2
Retention Time: 16.560 min



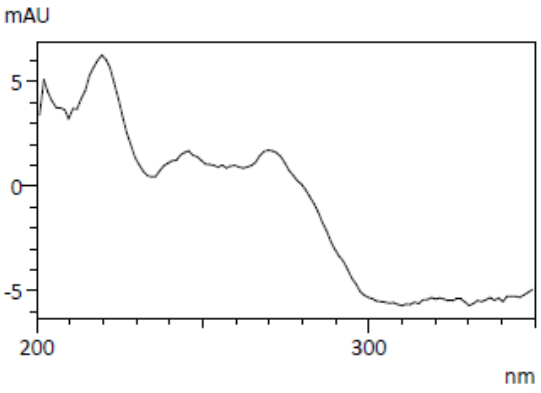
tert-Butyl (_S_)-2-(4-methoxybenzoyl)pyrrolidine-1-carboxylate (110t)



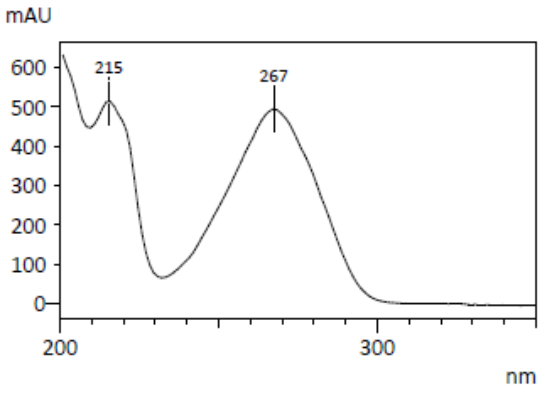
PDA Ch2 205nm

Peak#	Ret. Time	Area	Height	Area%
1	10.95	144744	3265	0.5
2	16.43	29893047	527759	99.5
Total				100.0

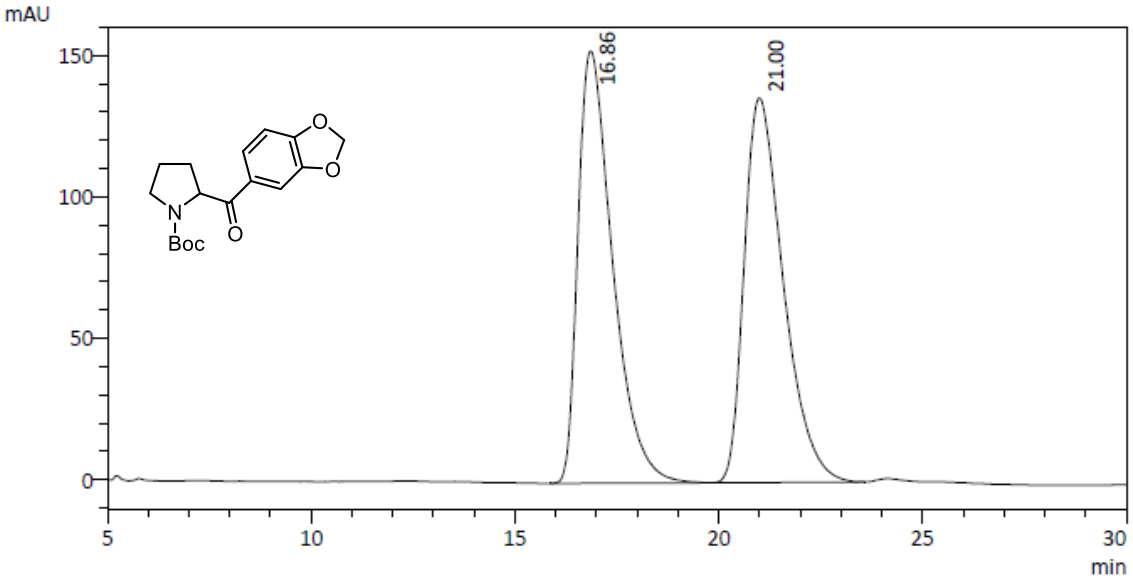
UV Spectrum
Peak#: 1
Retention Time: 10.947 min



UV Spectrum
Peak#: 2
Retention Time: 16.429 min



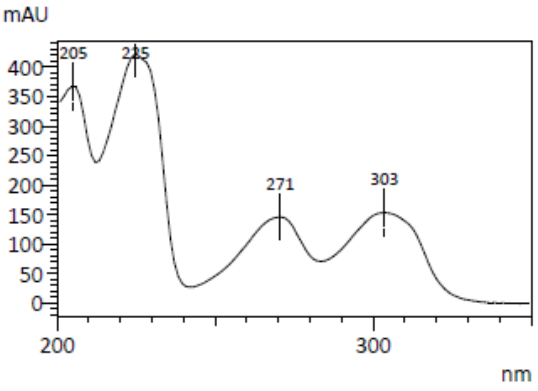
tert-Butyl (R/S)-2-(benzo[_d_][1,3]dioxole-5-carbonyl)pyrrolidine-1-carboxylate (110u)



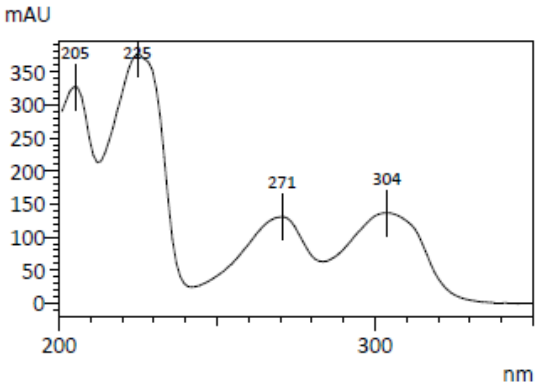
PDA Ch2 303nm

Peak#	Ret. Time	Area	Height	Area%
1	16.86	9027923	152766	49.9
2	21.00	9081683	135945	50.1
Total				100.0

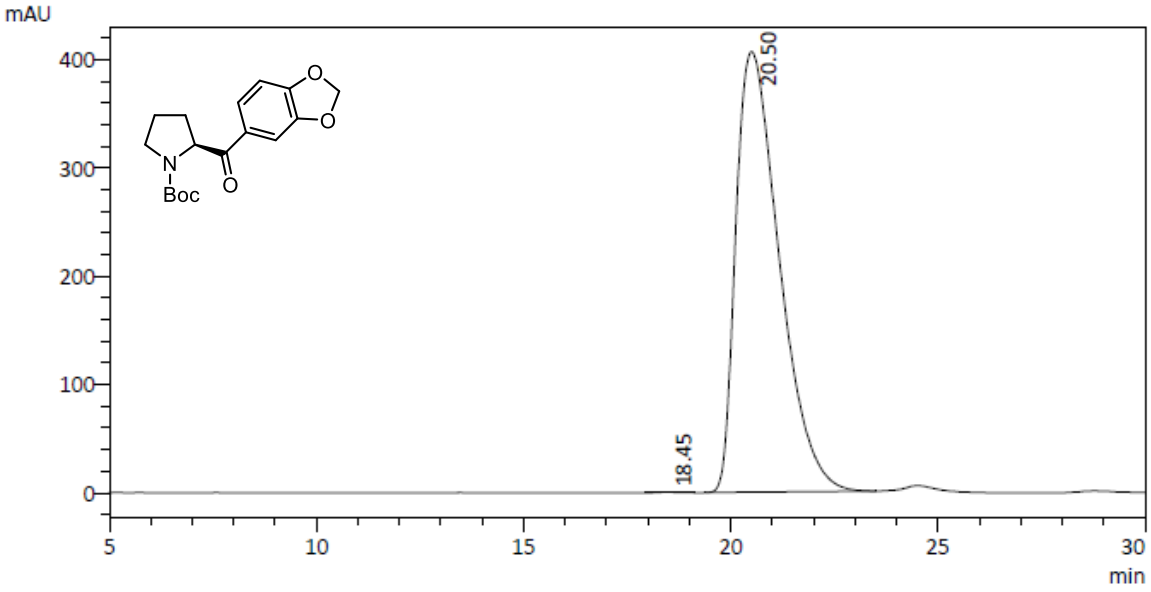
UV Spectrum
Peak#: 1
Retention Time: 16.859 min



UV Spectrum
Peak#: 2
Retention Time: 20.998 min



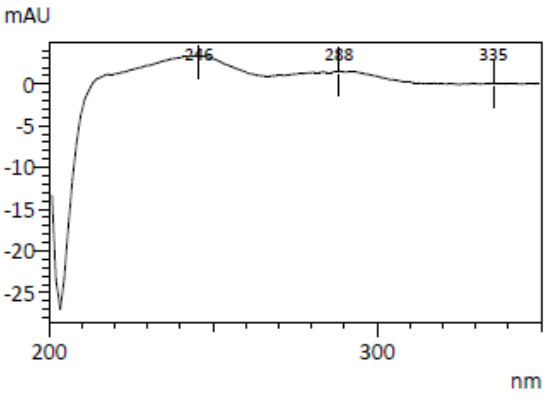
tert-Butyl (S)-2-(benzo[_d_][1,3]dioxole-5-carbonyl)pyrrolidine-1-carboxylate (110u)



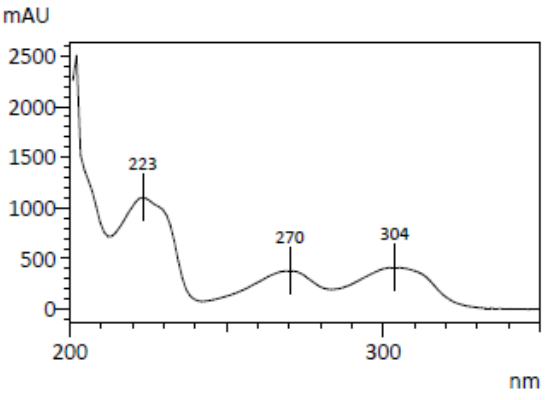
PDA Ch2 303nm

Peak#	Ret. Time	Area	Height	Area%
1	18.45	15261	456	0.1
2	20.50	29617587	406667	99.9
Total				100.0

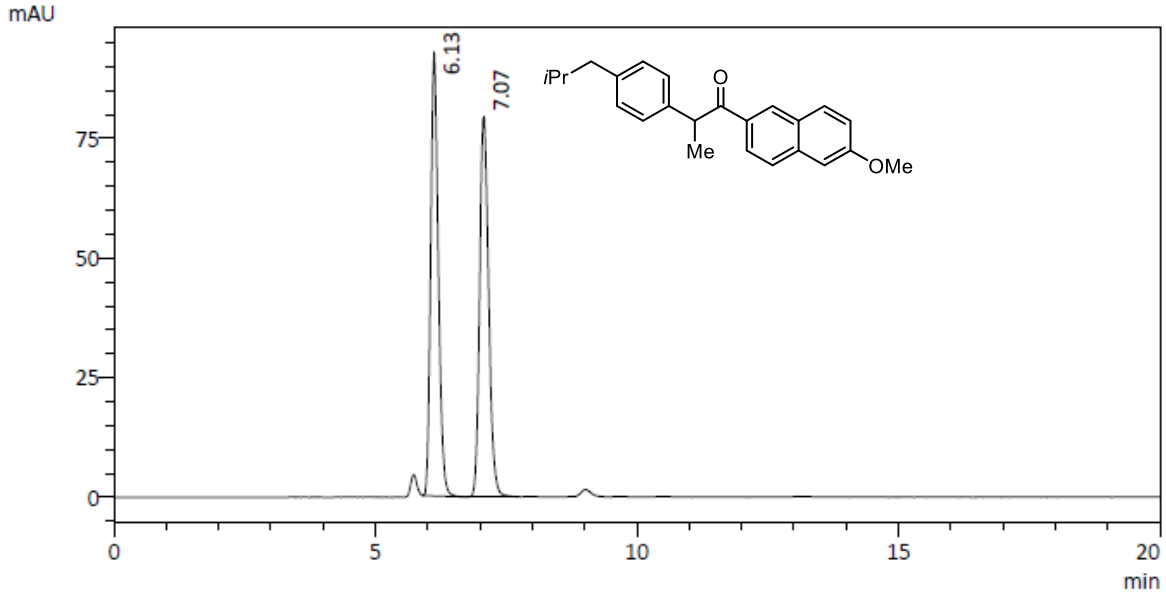
UV Spectrum
Peak#: 1
Retention Time: 18.446 min



UV Spectrum
Peak#: 2
Retention Time: 20.503 min



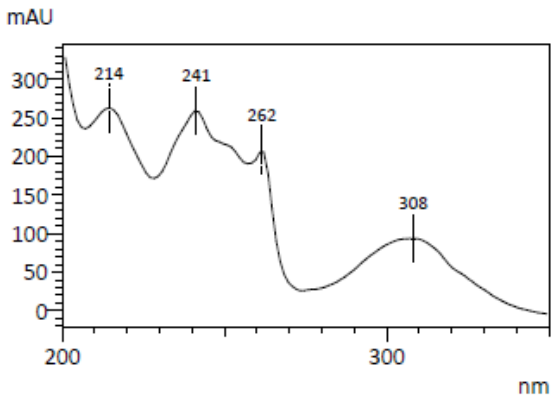
(R/*S*)-2-(4-*iso*-Butylphenyl)-1-(6-methoxynaphthalen-2-yl)propan-1-one (110v)



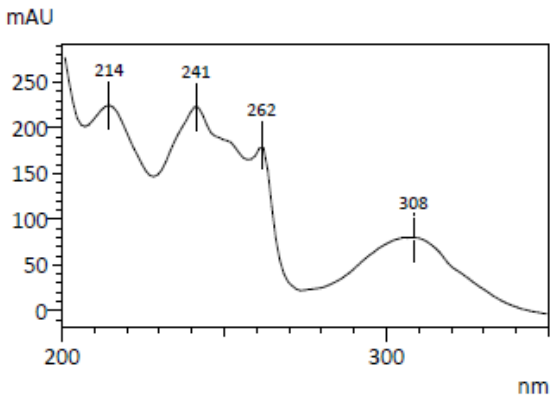
PDA Ch2 308nm

Peak#	Ret. Time	Area	Height	Area%
1	6.13	940487	92827	49.8
2	7.07	948746	79468	50.2
Total				100.0

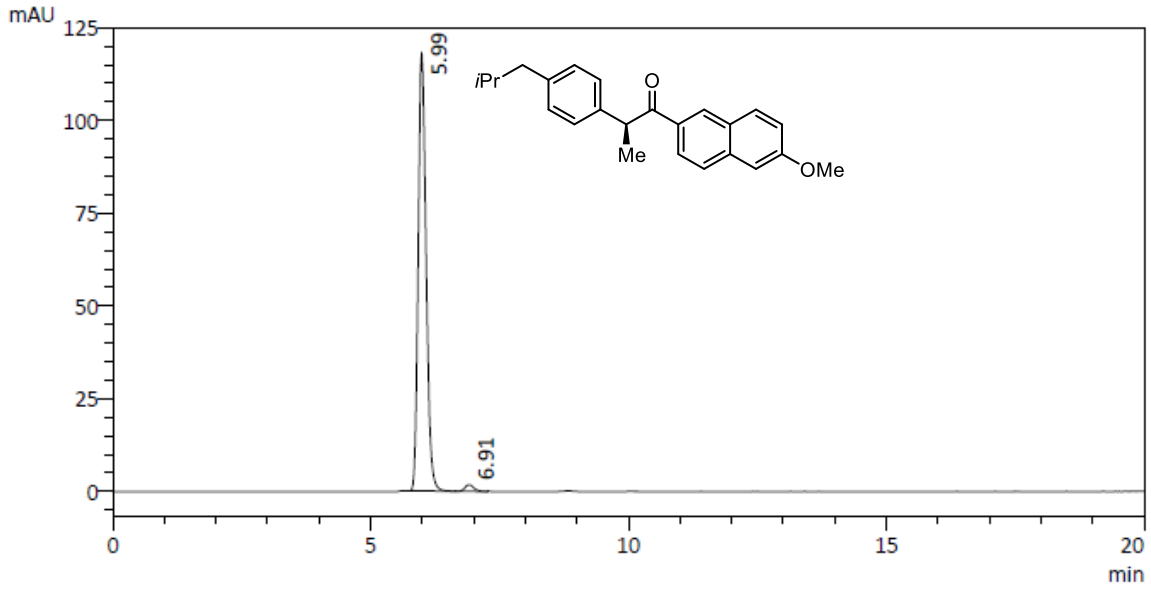
UV Spectrum
Peak#: 1
Retention Time: 6.125 min



UV Spectrum
Peak#: 2
Retention Time: 7.074 min



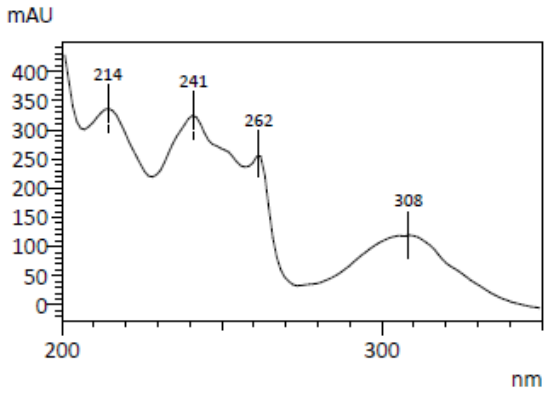
(R/*S*)-2-(4-*iso*-Butylphenyl)-1-(6-methoxynaphthalen-2-yl)propan-1-one (110v)



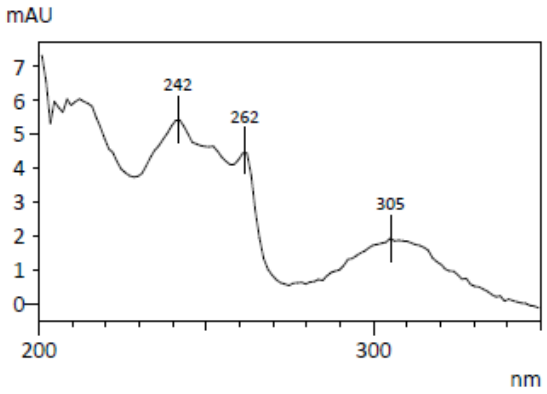
PDA Ch2 308nm

Peak#	Ret. Time	Area	Height	Area%
1	5.99	1260220	118202	98.3
2	6.91	21578	1804	1.7
Total				100.0

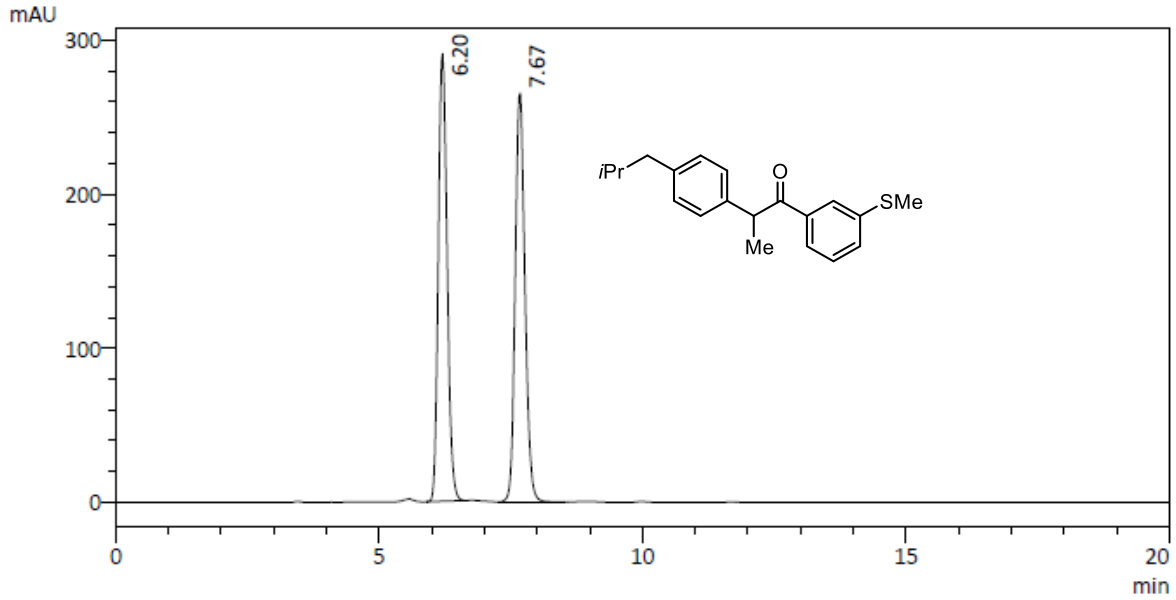
UV Spectrum
Peak#: 1
Retention Time: 5.994 min



UV Spectrum
Peak#: 2
Retention Time: 6.913 min



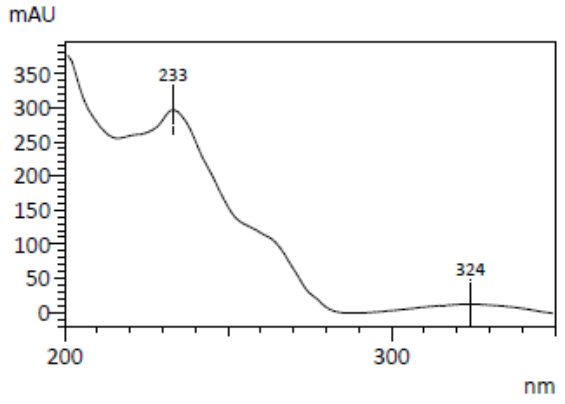
(R/*S*)-2-(4-*iso*-Butylphenyl)-1-(3-(methylthio)phenyl)propan-1-one (110w)



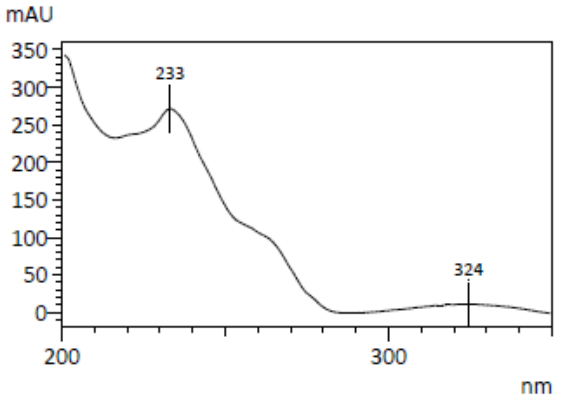
PDA Ch2 233nm

Peak#	Ret. Time	Area	Height	Area%
1	6.20	3372405	290642	49.7
2	7.67	3419067	265543	50.3
Total				100.0

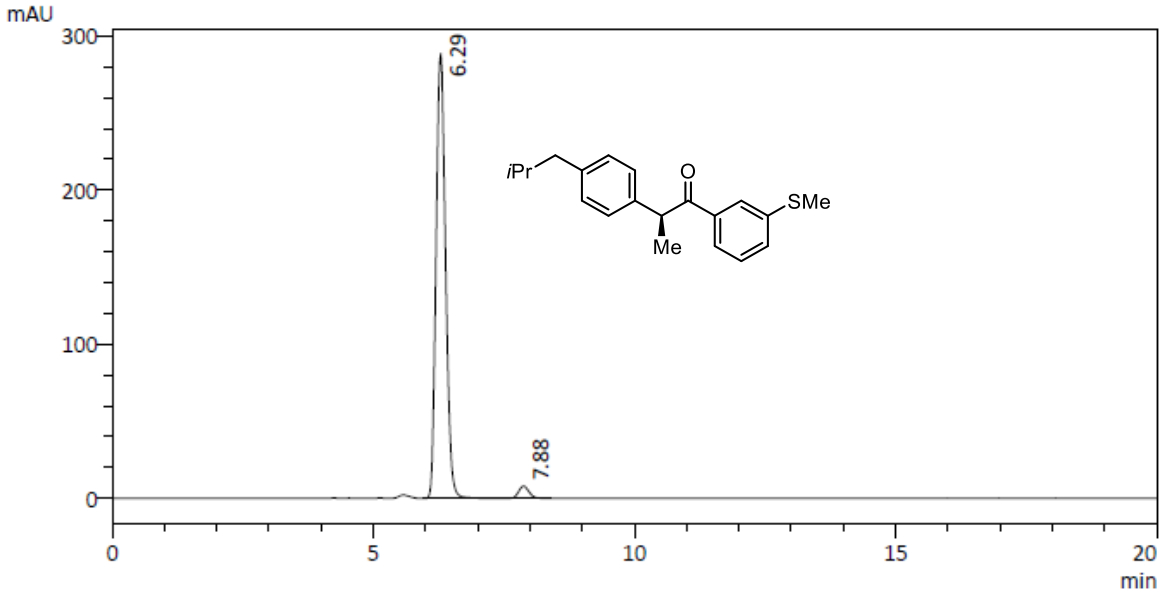
UV Spectrum
Peak#: 1
Retention Time: 6.203 min



UV Spectrum
Peak#: 2
Retention Time: 7.672 min



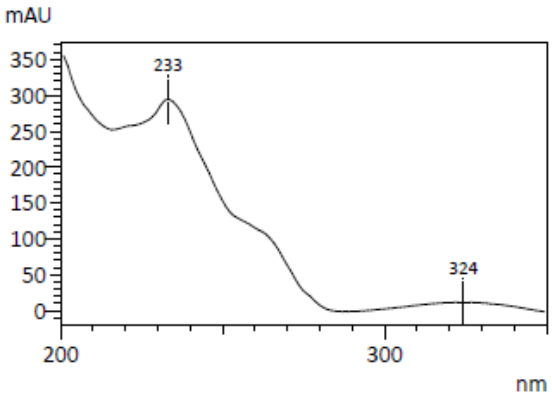
(*S*)-2-(4-*iso*-Butylphenyl)-1-(3-(methylthio)phenyl)propan-1-one (110w)



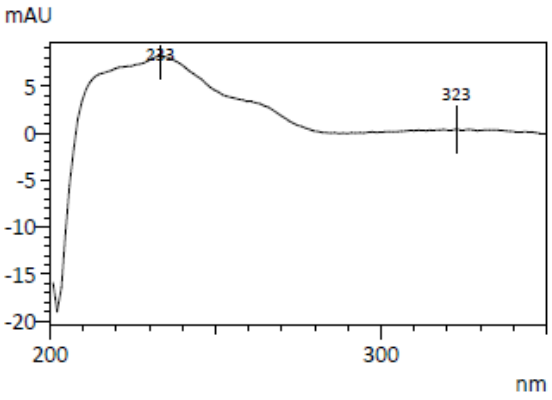
PDA Ch2 233nm

Peak#	Ret. Time	Area	Height	Area%
1	6.29	3644451	288696	97.0
2	7.88	111762	8053	3.0
Total				100.0

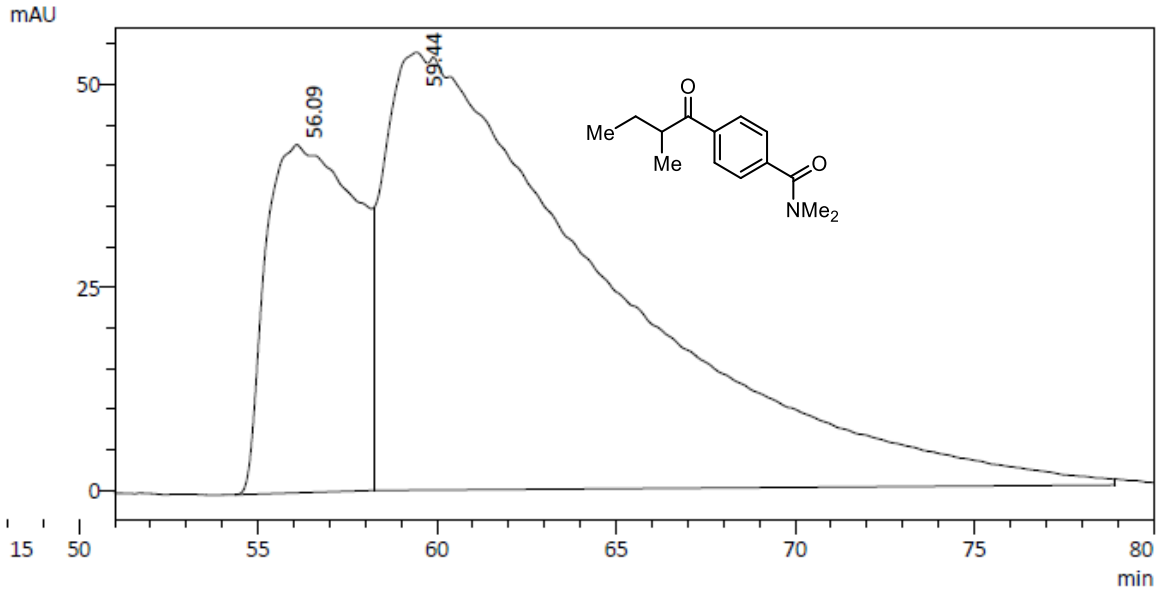
UV Spectrum
Peak#: 1
Retention Time: 6.289 min



UV Spectrum
Peak#: 2
Retention Time: 7.877 min



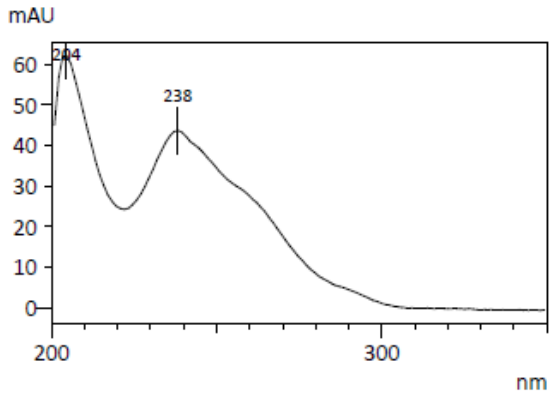
(R/*S*)-*N*,*N*-Dimethyl-4-(2-methylbutanoyl)benzamide (110x)



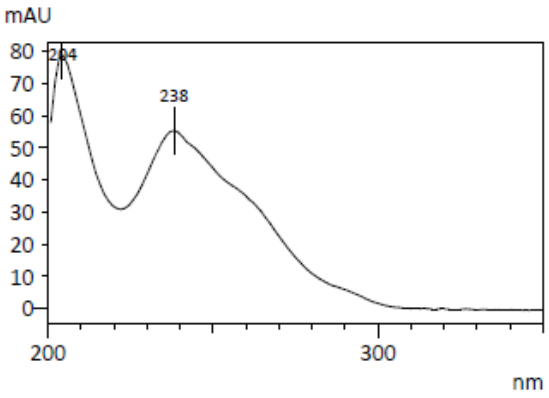
PDA Ch2 238nm

Peak#	Ret. Time	Area	Height	Area%
1	56.09	7545482	42833	24.3
2	59.44	23532946	53869	75.7
Total				100.0

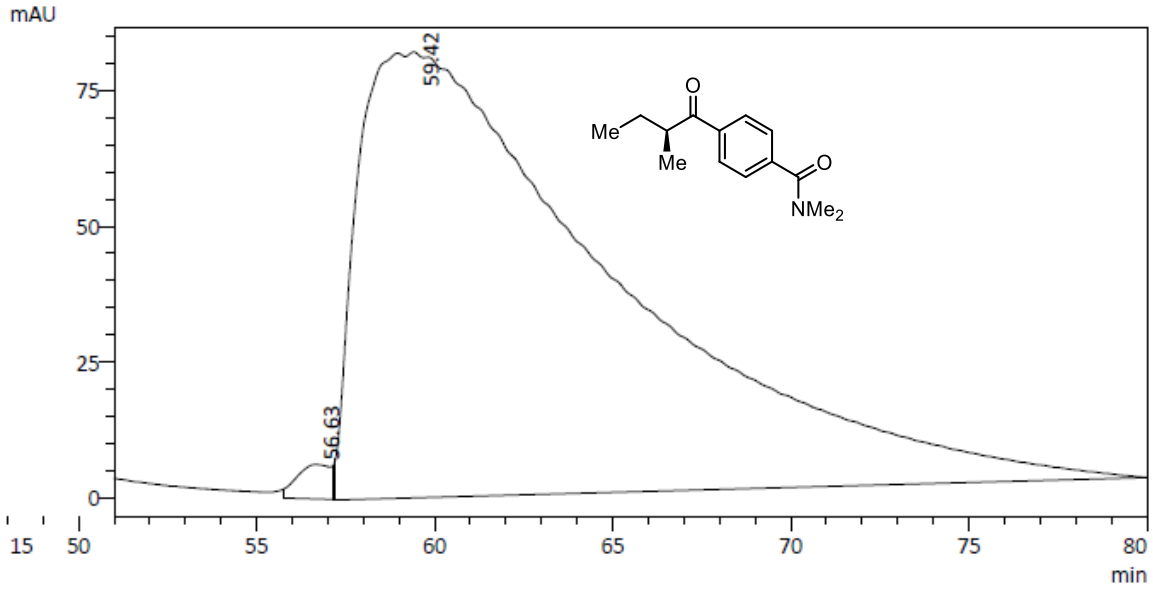
UV Spectrum
Peak#: 1
Retention Time: 56.086 min



UV Spectrum
Peak#: 2
Retention Time: 59.443 min



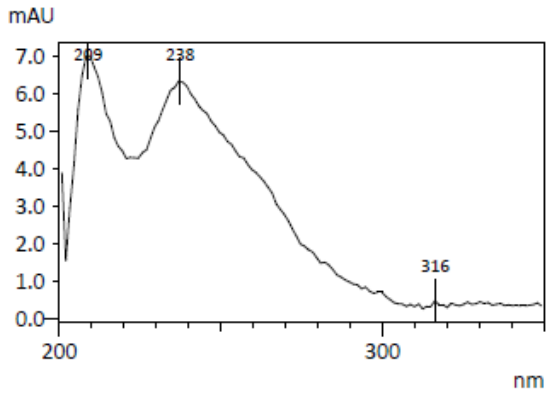
(*S*)-*N*,*N*-Dimethyl-4-(2-methylbutanoyl)benzamide (110x)



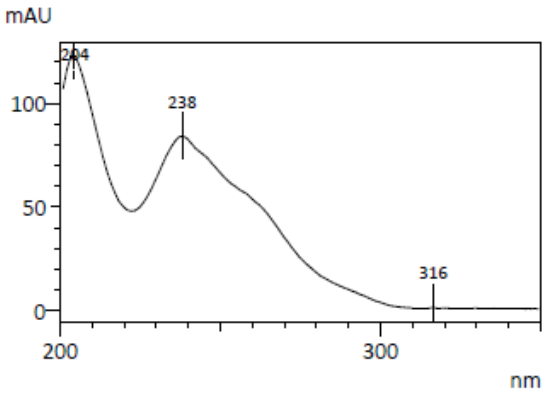
PDA Ch2 238nm

Peak#	Ret. Time	Area	Height	Area%
1	56.63	416671	6326	1.0
2	59.42	41146287	82083	99.0
Total				100.0

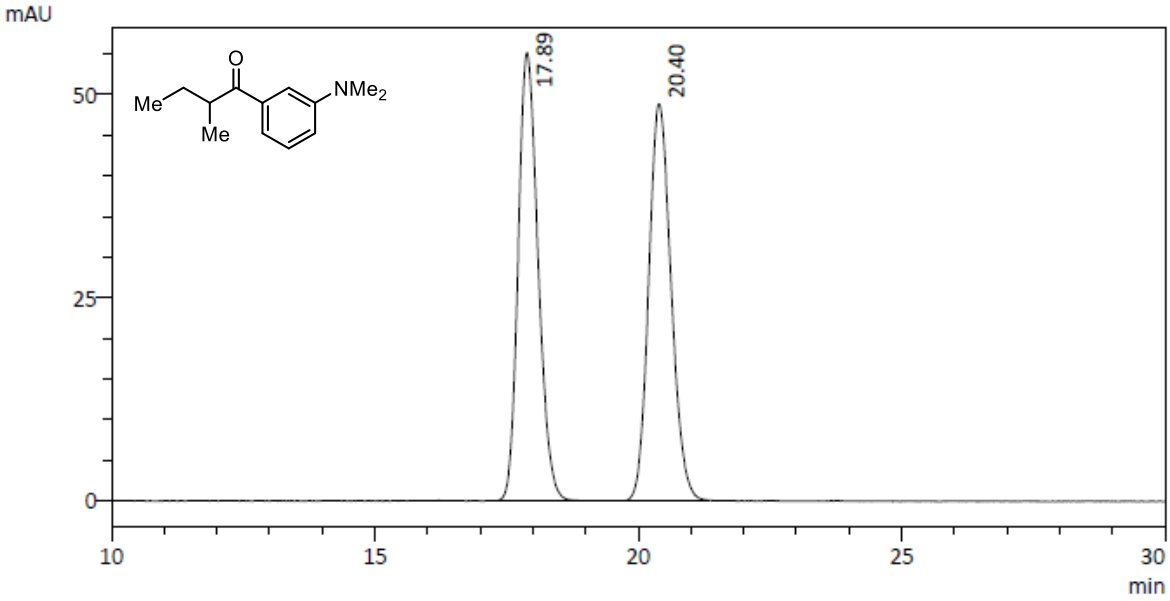
UV Spectrum
Peak#: 1
Retention Time: 56.629 min



UV Spectrum
Peak#: 2
Retention Time: 59.421 min



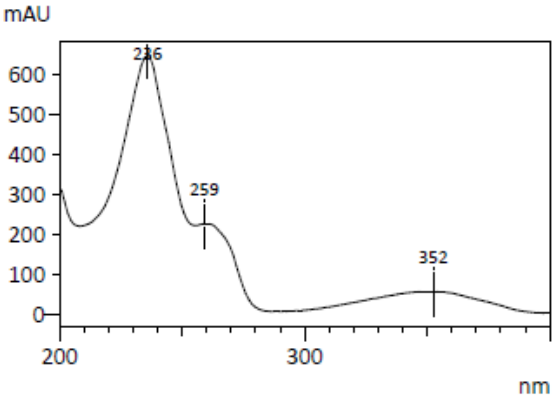
(R/*S*)-1-(3-(Dimethylamino)phenyl)-2-methylbutan-1-one (110y)



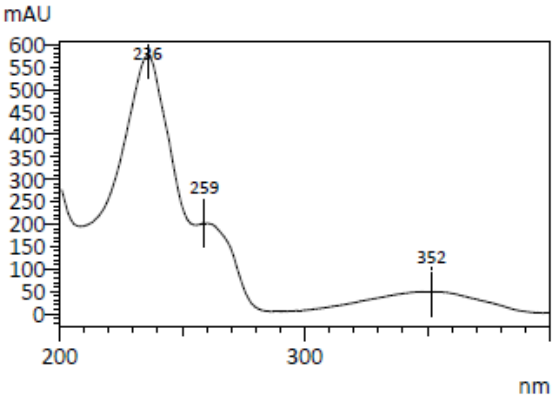
PDA Ch2 352nm

Peak#	Ret. Time	Area	Height	Area%
1	17.89	1445365	55158	50.0
2	20.40	1445361	48838	50.0
Total				100.0

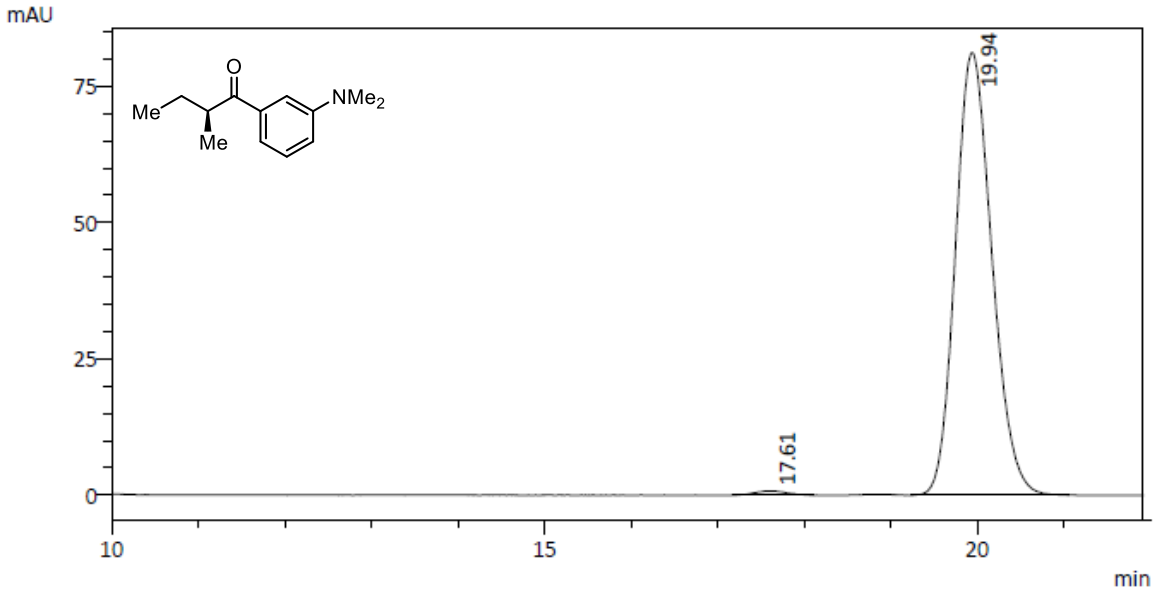
UV Spectrum
Peak#: 1
Retention Time: 17.890 min



UV Spectrum
Peak#: 2
Retention Time: 20.398 min



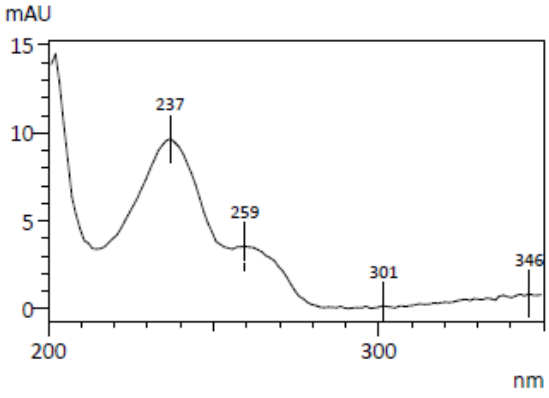
(*S*)-1-(3-(Dimethylamino)phenyl)-2-methylbutan-1-one (110y)



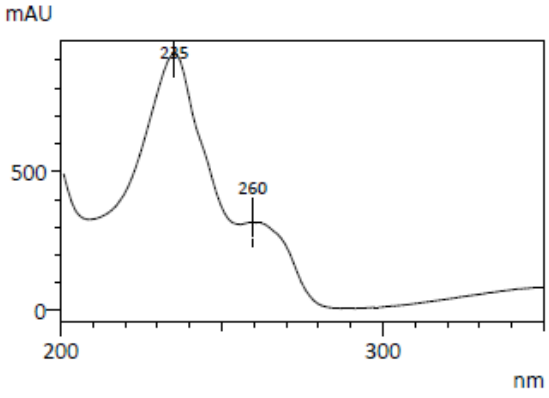
PDA Ch2 353nm

Peak#	Ret. Time	Area	Height	Area%
1	17.61	19705	797	0.8
2	19.94	2384952	81203	99.2
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 17.610 min

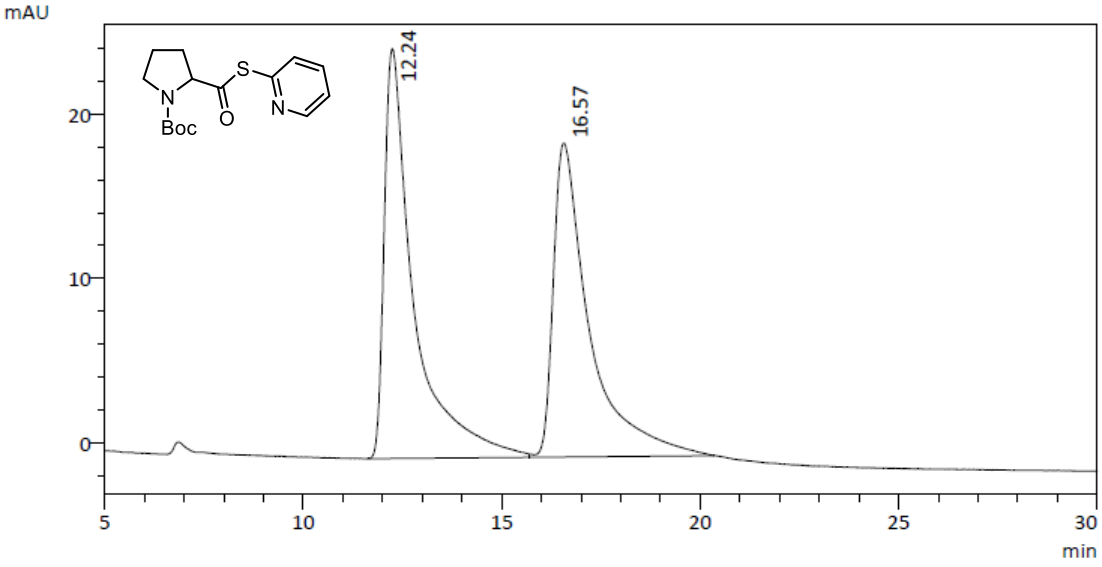


UV Spectrum
Peak#: 2
Retention Time: 19.943 min



tert-Butyl (R/_S_)-2-((pyridin-2-ylthio)carbonyl)pyrrolidine-1-carboxylate (108k)

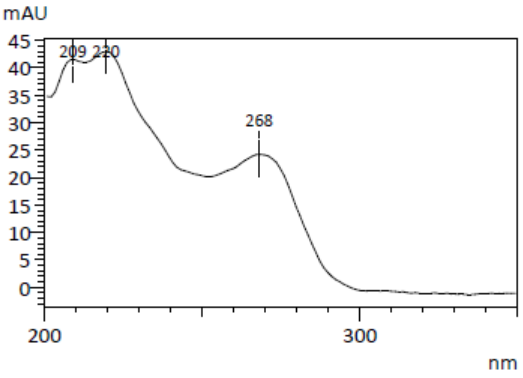
Method File : AD-H_H95_30min.lcm
Date Processed : 03/04/2019 09:07:51



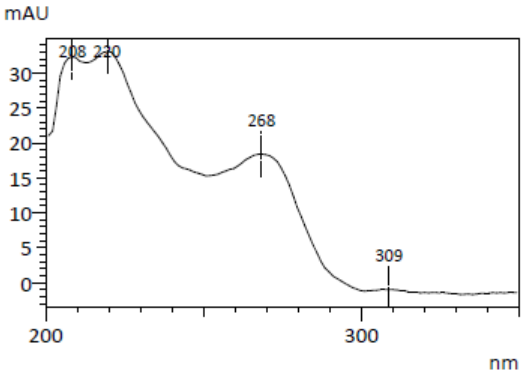
PDA Ch2 268nm

Peak#	Ret. Time	Area	Height	Area%
1	12.24	1282884	24914	51.6
2	16.57	1201484	19082	48.4
Total				100.0

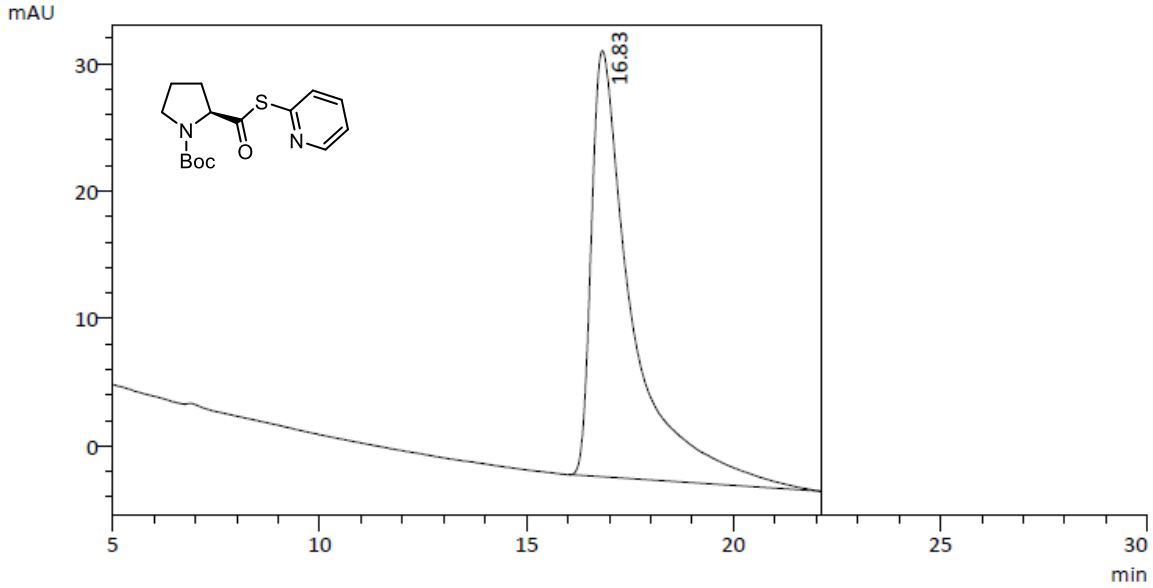
UV Spectrum
Peak#: 1
Retention Time: 12.245 min



UV Spectrum
Peak#: 2
Retention Time: 16.565 min



***tert*-Butyl (*S*)-2-((pyridin-2-ylthio)carbonyl)pyrrolidine-1-carboxylate (108k)**

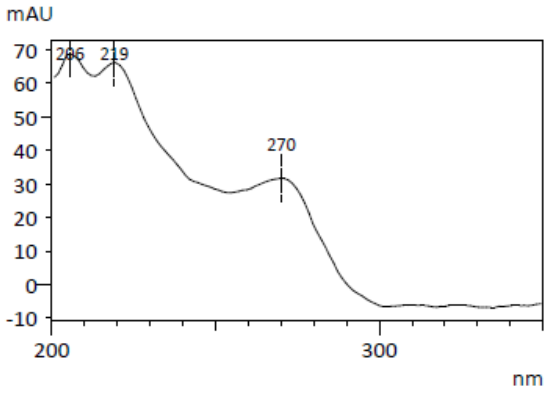


PDA Ch2 267nm

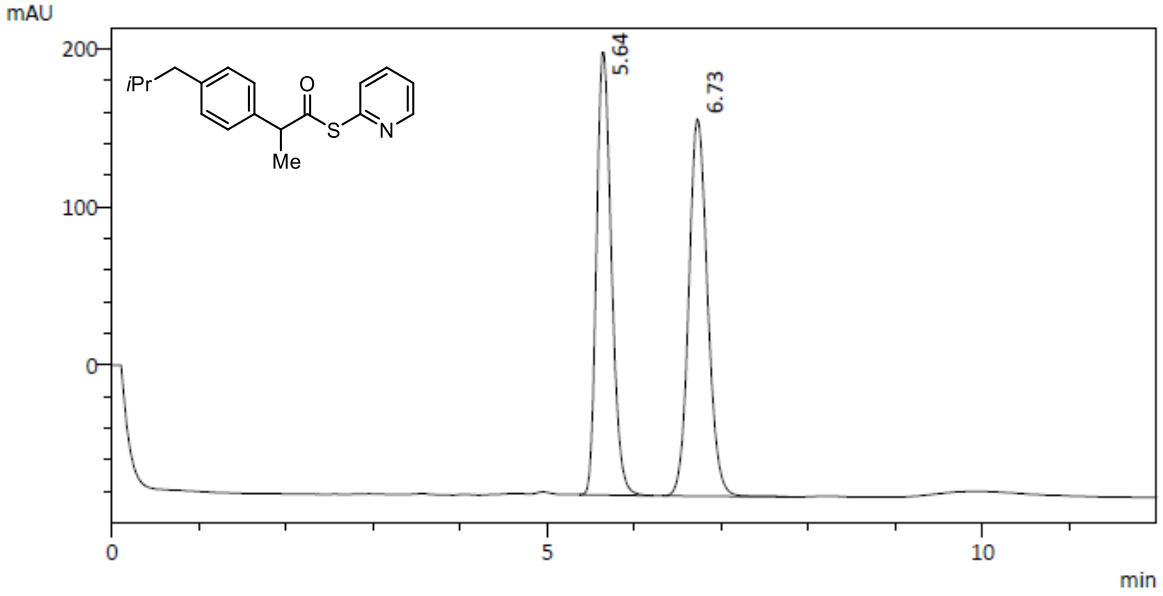
Peak#	Ret. Time	Area	Height	Area%
1	16.83	2292279	33483	100.0
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 16.833 min

UV Spectrum



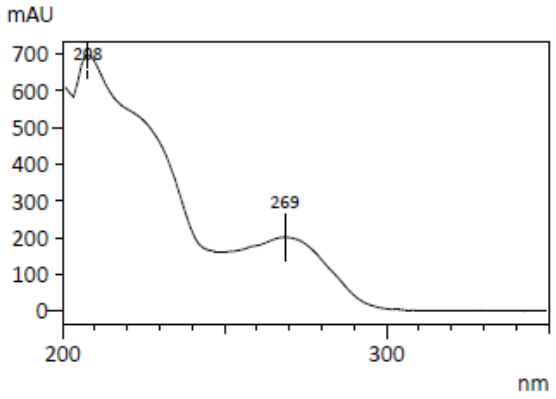
***S*-(Pyridin-2-yl) (R/S)-2-(4-isobutylphenyl)propanethioate (108l)**



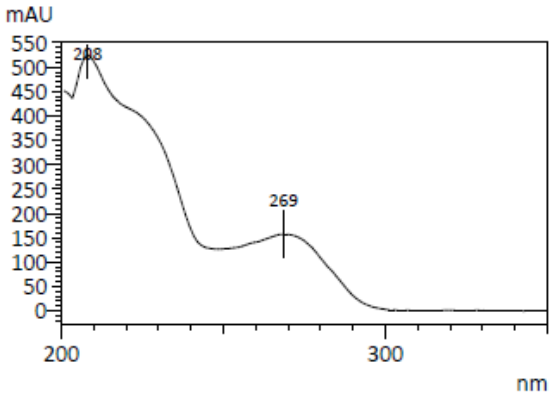
PDA Ch2 268nm

Peak#	Ret. Time	Area	Height	Area%
1	5.64	3345973	279898	48.4
2	6.73	3571156	238609	51.6
Total				100.0

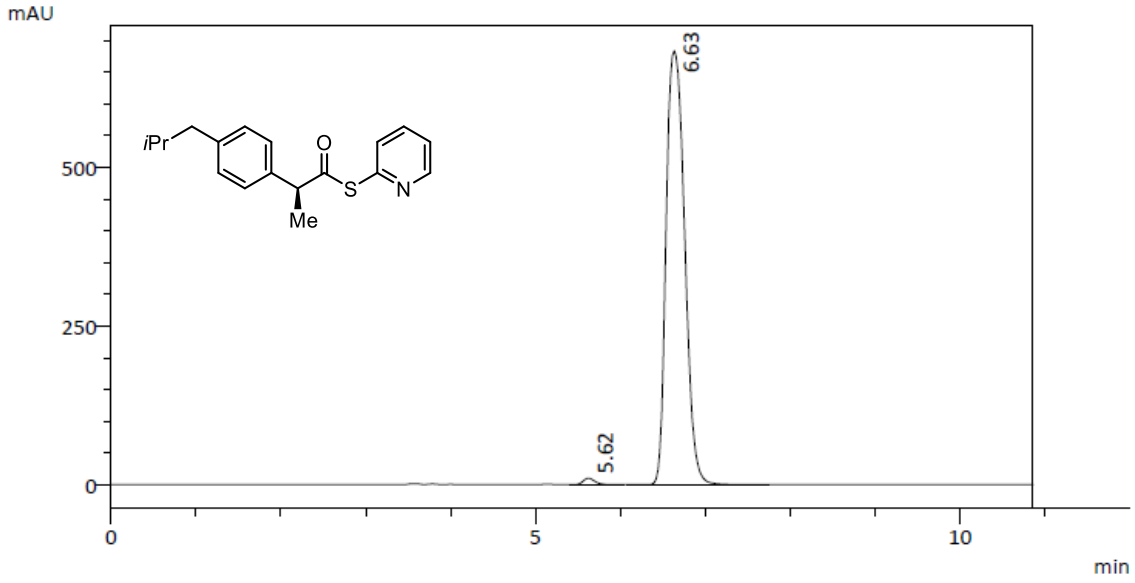
UV Spectrum
Peak#: 1
Retention Time: 5.643 min



UV Spectrum
Peak#: 2
Retention Time: 6.727 min



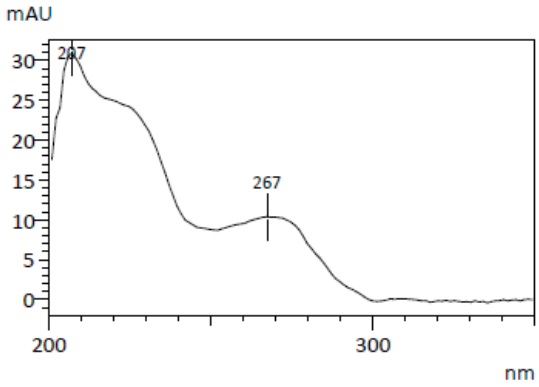
S-(Pyridin-2-yl) (S)-2-(4-isobutylphenyl)propanethioate (108l)



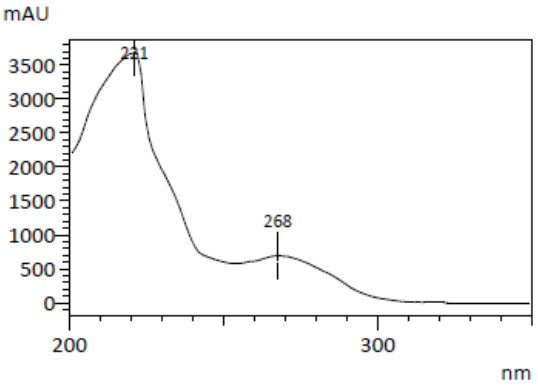
PDA Ch2 268nm

Peak#	Ret. Time	Area	Height	Area%
1	5.62	98756	10149	0.9
2	6.63	10337718	684373	99.1
Total				100.0

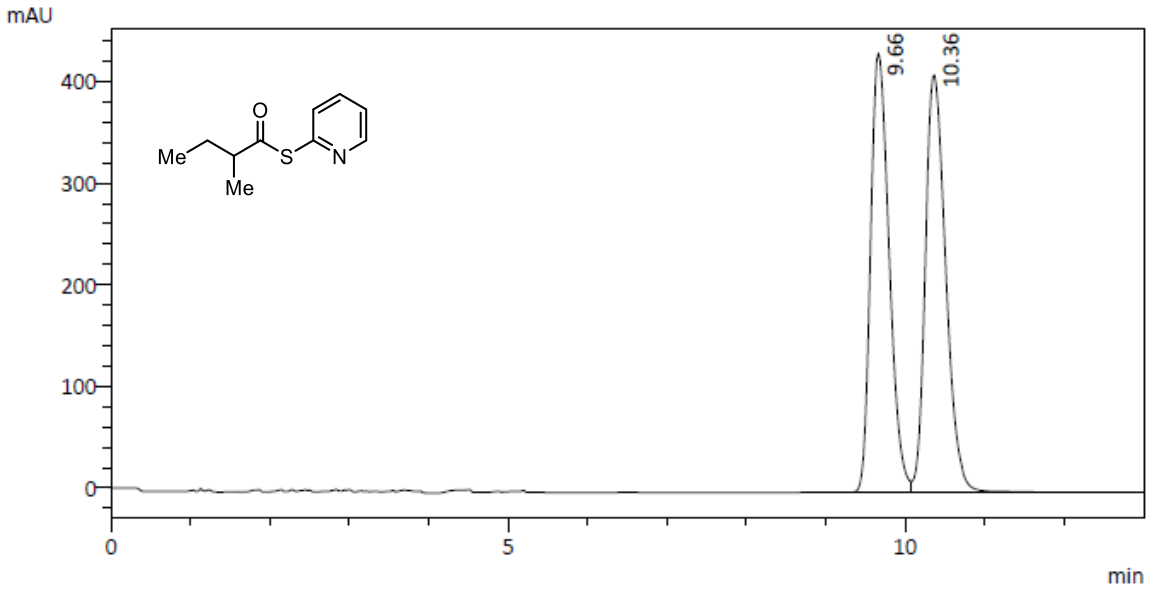
UV Spectrum
Peak#: 1
Retention Time: 5.625 min



UV Spectrum
Peak#: 2
Retention Time: 6.634 min



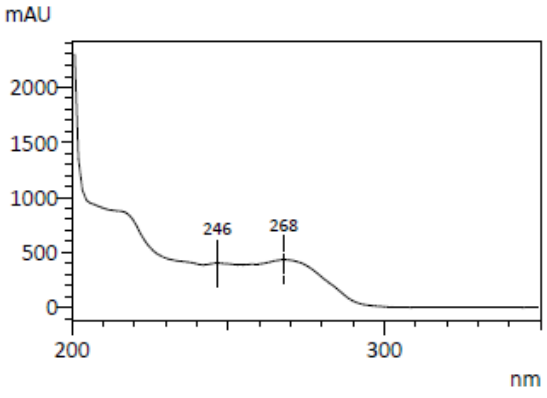
S-(Pyridin-2-yl) (R/S)-2-methylbutanethioate (108m)



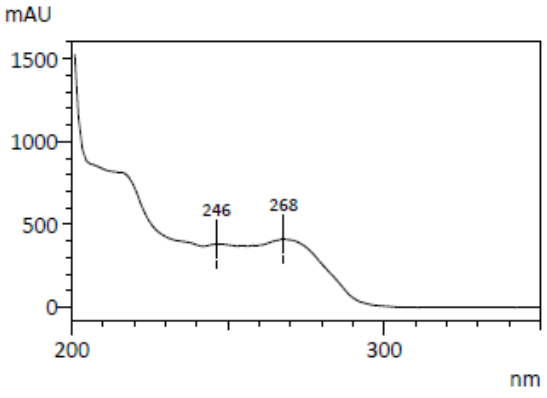
PDA Ch2 268nm

Peak#	Ret. Time	Area	Height	Area%
1	9.66	7082537	432518	49.0
2	10.36	7374118	410870	51.0
Total				100.0

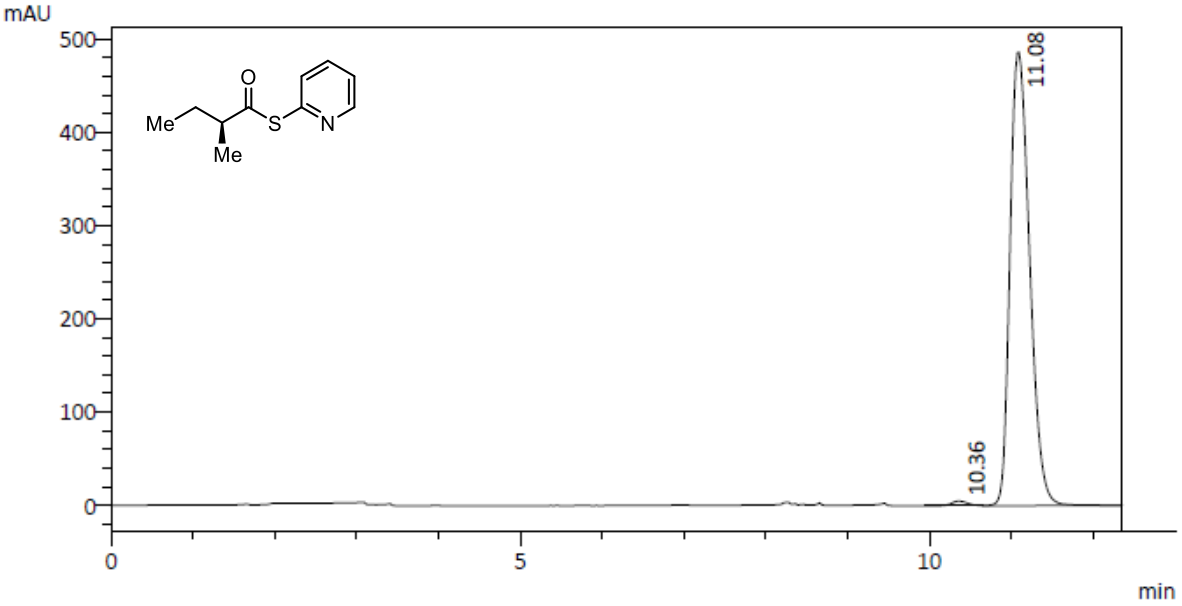
UV Spectrum
Peak#: 1
Retention Time: 9.663 min



UV Spectrum
Peak#: 2
Retention Time: 10.362 min



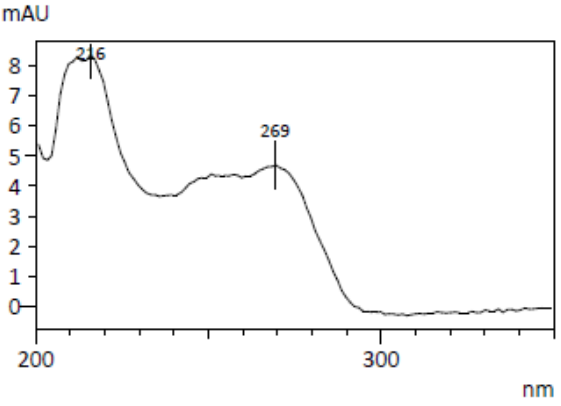
_S_-(Pyridin-2-yl) (_S_)-2-methylbutanethioate (108m)



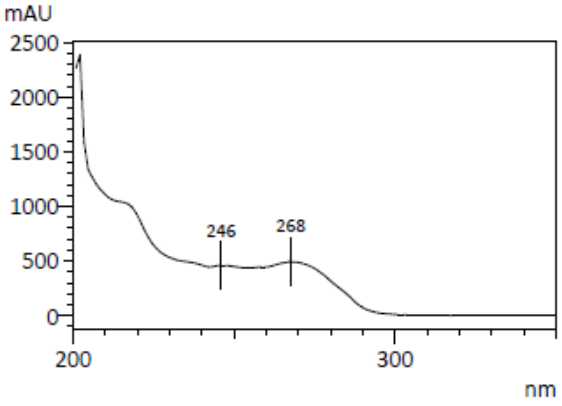
PDA Ch2 268nm

Peak#	Ret. Time	Area	Height	Area%
1	10.36	67843	5002	0.8
2	11.08	8089331	486237	99.2
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 10.363 min



UV Spectrum
Peak#: 2
Retention Time: 11.084 min



3. Single Crystal X-Ray Diffraction Studies

1. 2-(4-(1*H*-Pyrrol-1-yl)cyclohexyl)-5-(trifluoromethyl)pyridine (102ae)

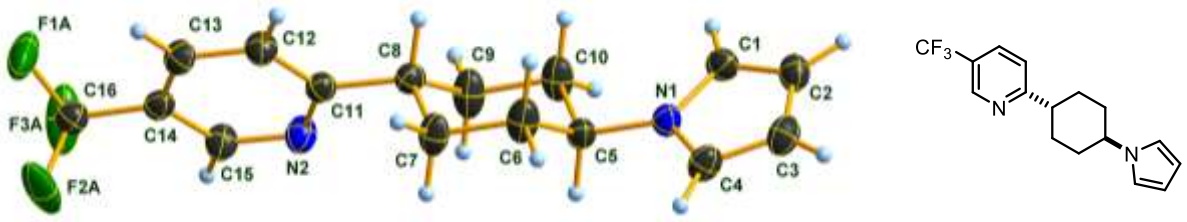


Figure 2: Molecular structure of compound **102ae** in the crystal, DIAMOND[165] representation; thermal ellipsoids are drawn at 50 % probability level. The fluorine atoms are disordered over two positions; only one position has been shown for clarity.

Table 17: Details for X-ray data collection and structure refinement for compound **102ae**.

Empirical formula	$C_{16}H_{17}F_3N_2$	$\rho_{calcd.}$ [g cm^{-3}]	1.392
Formula mass	294.32	μ [mm^{-1}]	0.111
T[K]	123(2)	*F*(000)	308
Crystal size [mm]	0.25 × 0.20 × 0.03	Θ range [°]	2.31 – 25.24
Crystal description	colorless block	Index ranges	-11 ≤ *h* ≤ 11
Crystal system	triclinic		-11 ≤ *k* ≤ 11
Space group	*P*-1		-11 ≤ *l* ≤ 10
a [Å]	9.3100(9)	Reflns. collected	4530
b [Å]	9.3232(11)	Reflns. obsd.	1669
c [Å]	9.3565(9)	Reflns. unique	2670
α [°]	66.006(10)		(R_{int} = 0.0288)
β [°]	72.336(9)	R_1, wR_2 (2σ data)	0.0548, 0.0923
γ [°]	76.892(9)	R_1, wR_2 (all data)	0.1003, 0.1093
V [Å^3]	701.97(14)	GOOF on F^2	1.028
Z	2	Peak/hole [e Å^{-3}]	0.193 / -0.211

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

2. 5'-Chloro-3-fluoro-2'-(1*H*-pyrazol-1-yl)-[1,1'-biphenyl]-4-carbonitrile (120d)

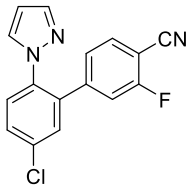


Figure 3: Molecular structure of compound **120d** in the crystal, DIAMOND[165] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 18: Details for X-ray data collection and structure refinement for compound **120d**.

Empirical formula	$C_{16}H_9ClFN_3$	$\rho_{calcd.}$ [g cm^{-3}]	1.400
Formula mass	297.71	μ [mm^{-1}]	0.277
T[K]	123(2)	*F*(000)	608
Crystal size [mm]	0.20 × 0.10 × 0.05	Θ range [°]	2.05 – 25.24
Crystal description	colorless block	Index ranges	-12 ≤ *h* ≤ 12
Crystal system	monoclinic		-9 ≤ *k* ≤ 9
Space group	*P*21/*n*		-26 ≤ *l* ≤ 26
a [Å]	9.6679(4)	Reflns. collected	21202
b [Å]	7.3579(2)	Reflns. obsd.	2448
c [Å]	20.1976(8)	Reflns. unique	3496 (R_{int} = 0.0619)
α [°]	90.0		
β [°]	100.596(4)	R_1, wR_2 (2σ data)	0.0480, 0.0931
γ [°]	90.0	R_1, wR_2 (all data)	0.0805, 0.1058
V [Å^3]	1412.27(9)	GOOF on F^2	1.007
Z	4	Peak/hole [e Å^{-3}]	0.275 / -0.294

3. 4,4-Dimethyl-2-(2-(1-methyl-1*H*-indol-5-yl)phenyl)-4,5-dihydrooxazole (120h)

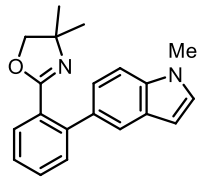
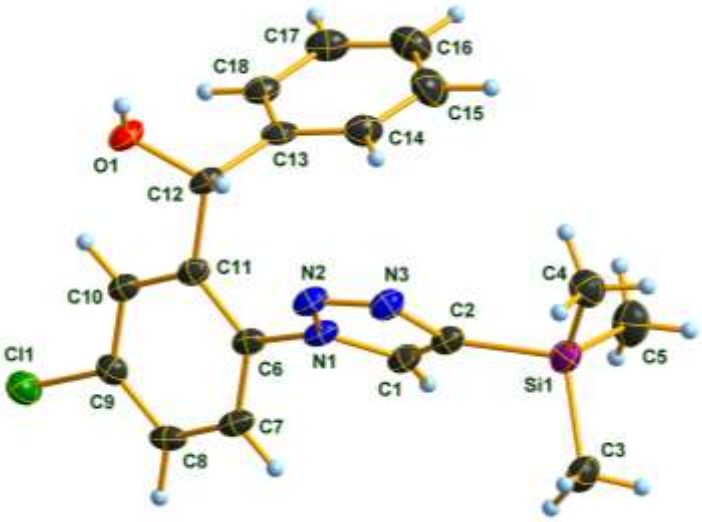


Figure 4: Molecular structure of compound **120h** in the crystal, DIAMOND[165] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 19: Details for X-ray data collection and structure refinement for compound **120h**.

Empirical formula	$C_{20}H_{20}N_2O$	$\rho_{calcd.}$ [g cm^{-3}]	1.238
Formula mass	304.38	μ [mm^{-1}]	0.077
T[K]	123(2)	*F*(000)	1296
Crystal size [mm]	0.40 × 0.20 × 0.10	Θ range [°]	2.98 – 25.24
Crystal description	colorless block	Index ranges	-10 ≤ *h* ≤ 6
Crystal system	orthorhombic		-18 ≤ *k* ≤ 18
Space group	*Pbca*		-39 ≤ *l* ≤ 40
a [Å]	7.6428(4)	Reflns. collected	29083
b [Å]	14.0522(8)	Reflns. obsd.	2866
c [Å]	30.4091(16)	Reflns. unique	4040
α [°]	90.0		(R_{int} = 0.0607)
β [°]	90.0	R_1, wR_2 (2σ data)	0.0500, 0.1126
γ [°]	90.0	R_1, wR_2 (all data)	0.0768, 0.1280
V [Å^3]	3265.9(3)	GOOF on F^2	1.020
Z	8	Peak/hole [e Å^{-3}]	0.256 / -0.243

4. (5-Chloro-2-(4-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)phenyl)(phenyl)methanol (121b)



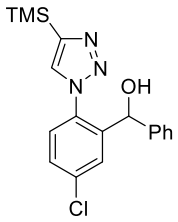
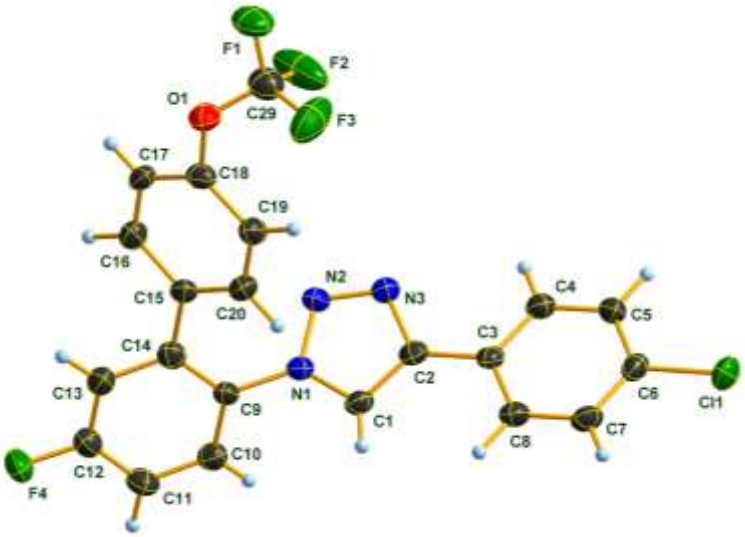


Figure 5: Molecular structure of compound **121b** in the crystal, DIAMOND[165] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 20: Details for X-ray data collection and structure refinement for compound **121b**.

Empirical formula	$C_{18}H_{20}ClN_3OSi$	$\rho_{calcd.}$ [g cm^{-3}]	1.280
Formula mass	357.91	μ [mm^{-1}]	0.280
T[K]	123(2)	*F*(000)	752
Crystal size [mm]	0.35 × 0.30 × 0.05	Θ range [°]	2.07 – 25.24
Crystal description	colorless block	Index ranges	-14 ≤ *h* ≤ 14
Crystal system	monoclinic		-25 ≤ *k* ≤ 26
Space group	*P*21/*c*		-9 ≤ *l* ≤ 9
a [Å]	11.6823(5)	Reflns. collected	16290
b [Å]	21.2482(6)	Reflns. obsd.	2927
c [Å]	7.8984(3)	Reflns. unique	3775 (R_{int} = 0.0477)
α [°]	90.0		
β [°]	108.644(4)	R_1, wR_2 (2σ data)	0.0426, 0.1009
γ [°]	90.0	R_1, wR_2 (all data)	0.0613, 0.1120
V [Å^3]	1857.72(13)	GOOF on F^2	1.026
Z	4	Peak/hole [e Å^{-3}]	0.487 / -0.227

5. 4-(4-Chlorophenyl)-1-(5-fluoro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)-1*H*-1,2,3-triazole (126)



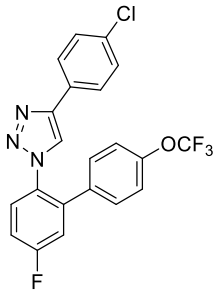


Figure 6: Molecular structure of compound **126** in the crystal, DIAMOND[165] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 21: Details for X-ray data collection and structure refinement for compound **126**.

Empirical formula	$C_{21}H_{12}ClF_4N_3O$
Formula mass	433.79
T[K]	123(2)
Crystal size [mm]	0.25 × 0.06 × 0.03
Crystal description	colorless rod
Crystal system	triclinic
Space group	*P*-1
a [Å]	5.8604(5)
b [Å]	10.0154(8)
c [Å]	16.5065(17)
α [°]	104.125(8)
β [°]	98.795(8)
γ [°]	97.054(7)
V [Å^3]	915.45(15)
Z	2

$\rho_{calcd.}$ [g cm^{-3}]	1.574
μ [mm^{-1}]	0.267
F(000)	440
Θ range [°]	2.13 – 25.24
Index ranges	$-7 \le h \le 7$
	$-12 \le k \le 8$
	$-16 \le l \le 20$
Reflns. collected	6200
Reflns. obsd.	2335
Reflns. unique	3609 (R_{int} = 0.0388)
R_1, wR_2 (2σ data)	0.0606, 0.1211
R_1, wR_2 (all data)	0.1025, 0.1431
GOOF on F^2	1.022
Peak/hole [e Å^{-3}]	0.517 / -0.348