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Cobalt-Catalyzed Cross-Coupling Reactions

von

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Erklärung

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3. D. Haas, **J. M. Hammann**, F. H. Lutter, P. Knochel, "Mild Cobalt-Catalyzed Negishi Cross-Couplings of (Hetero)Arylzinc Reagents with (Hetero)Aryl Halides", *Angew. Chem. Int. Ed.* **2016**, *55,* 3809.

2. **J. M. Hammann**, D. Haas, and P. Knochel, "Cobalt-Catalyzed Negishi Cross-Coupling Reactions of (Hetero)Arylzinc Reagents with Primary and Secondary Alkyl Bromides and Iodides", *Angew. Chem. Int. Ed.* **2015**, *54*, 4478.

1. **J. M. Hammann**, A. K. Steib, P. Knochel, "Cobalt-Mediated Diastereoselective Cross-Coupling Reactions between Cyclic Halohydrins and Arylmagnesium Reagents", *Org. Lett.* **2014**, *16*, 6500.

"Creativity is contagious. Pass it on."

– Albert Einstein

Meiner Familie

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List of Abbreviations

acac	acetylacetonate
Alk	alkyl
aq	aqueous
Ar	aryl
ATR	attenuated total reflection (IR)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
calc.	calculated
conc.	concentrated
*c*Hex	cyclohexyl
δ	chemical shifts in ppm (parts per million)
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*′-dimethylpropyleneurea
E	electrophile
EI	electron impact ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
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
MOM	methoxymethyl
MS	mass spectrometry
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
phen	phenanthroline
Piv	pivaloyl
r.t.	room temperature
sat.	saturated
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-Butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidyl
Ts	4-toluenesulfonyl

I. Introduction

Transition-metal catalyzed cross-couplings belong to the modern repertoire of organic synthesis. The agrochemical and pharmaceutical industries extensively use this powerful method for forming new carbon-carbon bonds. Palladium complexes are certainly the most frequently used catalysts and a vast range of air-stable and convenient palladium complexes are commercially available. A broad reaction scope and a large amount of literature ensure an excellent applicability of this methodology for complex and new targets.[1]

1. Recent Advances in Cobalt-Catalyzed Cross-Couplings

Most of these palladium catalysts require expensive phosphines and the palladium salts themselves are expensive and toxic, thus the search for alternative transition-metal catalysts has been extensively investigated.[2] Although nickel salts have a closely related chemical behavior and are quite inexpensive, toxicity issues as well as a more limited scope and a high ligand dependence on catalytic activity have hampered broad usage of this metal.[1a,2b,c] Alternatively, iron salts and complexes have successfully been used in several cases, nevertheless, the relative insensibility of this metal towards the addition of specific ligands and a limited reaction scope has limited their synthetic applications.[3] Cobalt salts show a similar reactivity compared to iron salts, but display in many cases a higher catalytic activity and a lower tendency to produce homo-coupling byproducts. Therefore, they have led to numerous synthetic applications and to a broad number of publications over the years.[4] Recent work from our laboratory led to the discovery of specific ligands such as *N*-heterocycles[5,6] or carboxylate

[1] a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**. b) *Organotransition Metal Chemistry* (Ed.: J. F. Hartwig), University Science Books, Sausalito, CA, **2010**.

[2] a) world markt prices: Pd ca. 8000 $/lb, ca. Co 10 $/lb; http://www.infomine.com/; retrieved December 2016. b) *Handbook on the Toxicology of Metals* (Eds.: L. Friberg, G. F. Nordberg, V. B. Vouk), Elsevier, Amsterdam, **1986**. c) M. N. Hughes, in *Comprehensive Coordination Chemistry* (Eds.: G. Wilkinson, R. D. Gillard, J. A. McCleverty), Pergamon Press, Oxford, **1987**.

[3] a) I. Bauer, H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170. b) T. L. Mako, J. A. Byers, *Inorg. Chem. Front.* **2016**, *3*, 766.

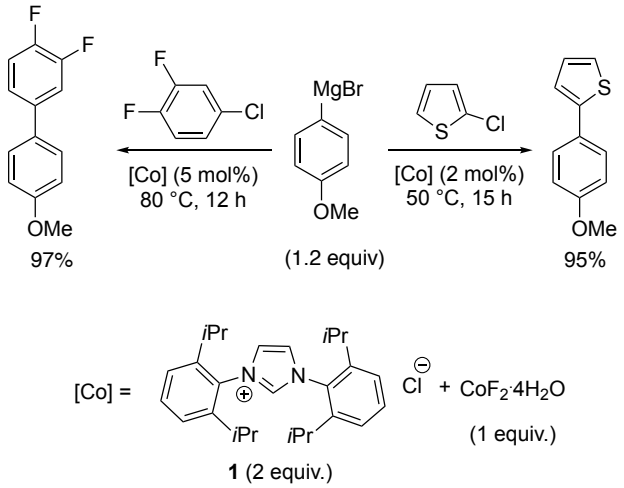
[4] a) H. Yorimitsu, K. Oshima, *Pure Appl. Chem.* **2006**, *78*, 441. b) C. Gosmini, J.-M. Bégouin, A. Moncomble, A. *Chem. Commun.* **2008**, 3221. c) G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435. d) C. Gosmini, A. Moncomble, *Isr. J. Chem.* **2010**, *50*, 568. e) A. Rudolph, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 2656.

[5] a) T. Thaler, L.-N. Guo, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 2174. b) O. M. Kuzmina,

ligands[6] allowing boosting the catalyst activity and more importantly to expand the reaction scope of cobalt-catalyzed cross-couplings. In the following sections, an overview on recent work involving cobalt-catalyzed coupling reactions and some recent advances from our laboratories will be given.[7]

1.1 Cobalt-Catalyzed Csp^2-Csp^2 Cross-Couplings

Csp^2-Csp^2 cross-couplings are difficult to realize in the absence of transition-metal catalysts. By using an *N*-heterocyclic carbene ligand such as **1**, it was possible to perform a cobalt-catalyzed cross-coupling between aryl and heteroaryl chlorides and arylmagnesium reagents. The reaction requires only a few mol% of the Co catalyst and proceeds between 50-60 °C. Nakamura showed that cobalt(II) fluoride in combination with **1** gave the best results (Scheme 1).[8] A detailed mechanistic and theoretical study is given for the corresponding Ni, Fe and Co-catalyzed reactions.

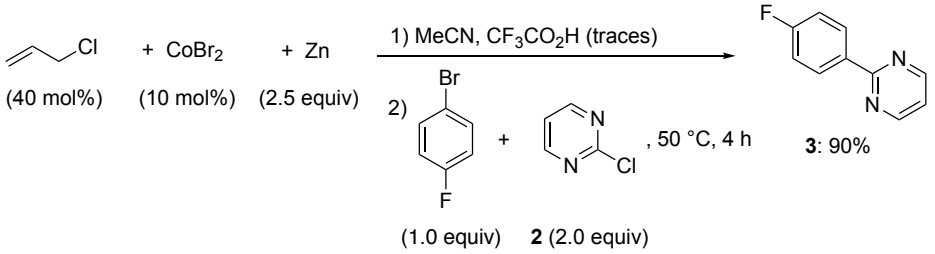


Scheme 1. Cross-couplings using $CoFe_2{\cdot}4H_2O$ and a NHC-ligand.

The fluoride ion proved to be the key for the catalytic activity of cobalt. Gosmini reported a cobalt-catalyzed cross-coupling between *in situ* prepared arylzinc halides and 2-chloropyrimidine (**2**) or 2-chloropyrazine. Using $CoBr_2$ (10 mol%) in the presence of allyl

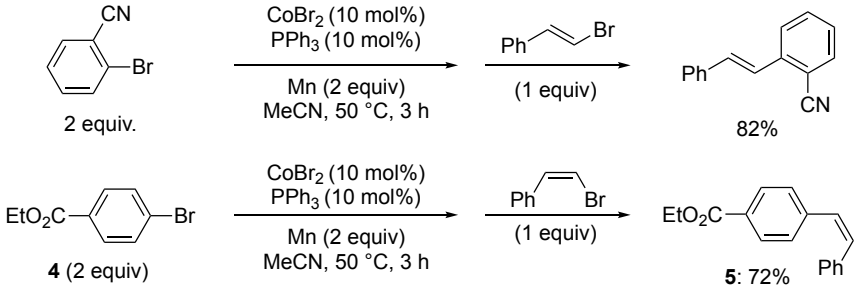
A. K. Steib, S. Fernandez, W. Boudot, J. T. Markiewicz, P. Knochel, *Chem. Eur. J.* **2015**, *21*, 8242.
[6] D. Haas, J. M. Hammann, F. H. Lutter, P. Knochel, *Angew. Chem. Int. Ed.* **2016**, *55*, 3809.
[7] J. M. Hammann, F. H. Lutter, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *129*, 1102.
[8] T. Hatakeyama, S. Hashimoto, K. Ishizuka, M. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 11949.

chloride (0.4 equiv) and zinc powder (2.5 equiv) allowed an *in situ* generation of an intermediate arylzinc reagent in acetonitrile (in the presence of traces of trifluoroacetic acid) leading to cross-coupling products such as **3** within 4 h reaction time at 50 °C (Scheme 2).[9]



Scheme 2. Cross-coupling of 2-chloropyrimidine (**2**).

Alternatively, Gosmini showed that the use of manganese metal as a reducing agent allows an efficient cross-coupling between chloro- and bromo-styrenes and various aryl bromides (Scheme 3).



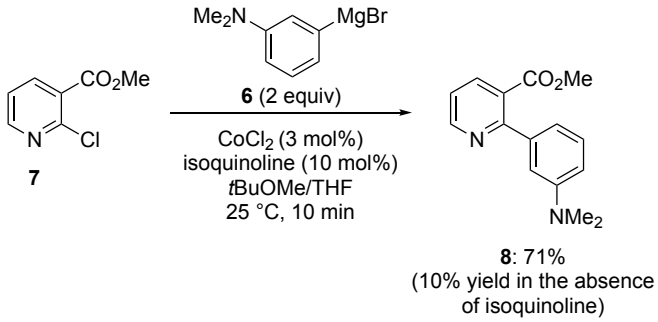
Scheme 3. Stereoselective cobalt-catalyzed alkenylation.

Remarkably, this selective cross-coupling, which proceeds rapidly in acetonitrile in a few minutes, leads to the expected stilbenes with full retention of the double bond configuration. Thus, the reductive manganation of ethyl 4-bromobenzoate (**4**) followed by the addition of *Z*-2-bromostyrene furnishes only the *Z*-stilbene **5** (Scheme 3).[10]

Instead of performing such cross-couplings in MeCN, the use of isoquinoline or quinoline (7 mol%) as a ligand, allows an efficient cross-coupling between various *N*-heteroaryl halides and arylmagnesium reagents. Thus, the cross-coupling between 3-*N,N*-dimethylaminophenylmagnesium bromide (**6**) and methyl 2-chloronicotinate (**7**) produces

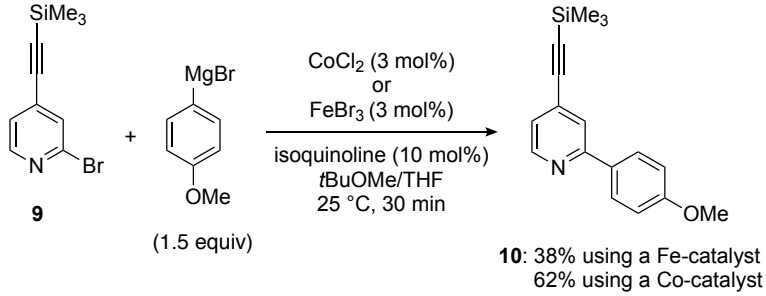
[9] J.-M. Begouin, C. Gosmini, *J. Org. Chem.* **2009**, *74*, 3221.
[10] A. Moncomble, P. Le Floch, A. Lledos, C. Gosmini, *J. Org. Chem.* **2012**, *77*, 5056.

in the presence of $CoCl_2$ (3 mol%) at 25 °C within 10 minutes the desired cross-coupling product **8** in only 10% yield. The extension of the reaction time did not increase the product formation. However, performing the reaction in the presence of isoquinoline (10 mol%) provides, at 25 °C and 10 minutes reaction time, the expected cross-coupling product in 71% isolated yield (Scheme 4).[5]



Scheme 4. Cobalt-catalyzed arylation of 2-chloropyridine **7**.

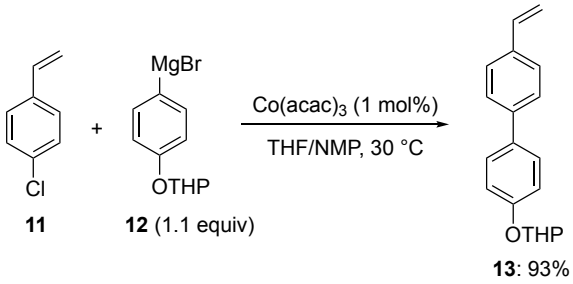
Besides displaying a superior scope and reactivity, the use of a cobalt catalyst enhances the chemoselectivity of these cross-couplings. Thus, the bromopyridine **9** bearing an alkynyl substituent at position 4, which is susceptible to undergo carbomagnesiation reactions, reacts only in modest yield in the presence of $FeBr_3$ (3 mol%). However, by using $CoCl_2$ (3 mol%) under the same reaction conditions, a yield of 62 % of the disubstituted pyridine **10** is obtained (Scheme 5).[5]



Scheme 5. Chemoselective cobalt-catalyzed cross-coupling of 4-alkynyl-2-bromopyridine (**9**).

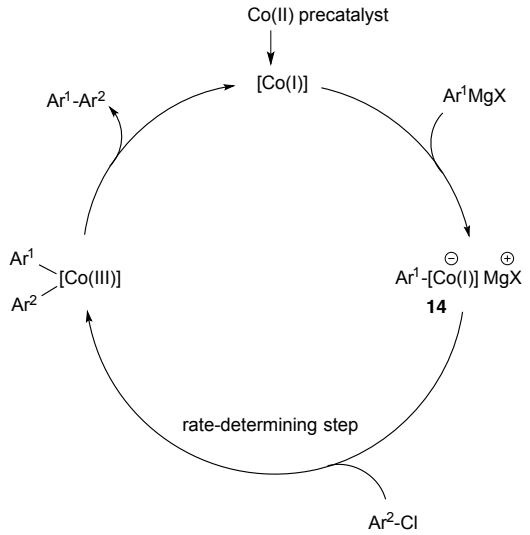
Highly chemoselective cobalt-catalyzed biaryl couplings have been reported by Jacobi von Wangelin between chloro-substituted styrenes and arylmagnesium reagents. Thus, a cross-coupling between 4-chloro-styrene (**11**) and various arylmagnesium reagents such as **12** leads,

in the presence of only 1 mol% $Co(acac)_3$ in THF/NMP at 30 °C to the desired cross-coupling product **13** in 93% yield (Scheme 6).[11]



Scheme 6. Cobalt-catalyzed cross-coupling between chlorostyrenes and Grignard reagents.

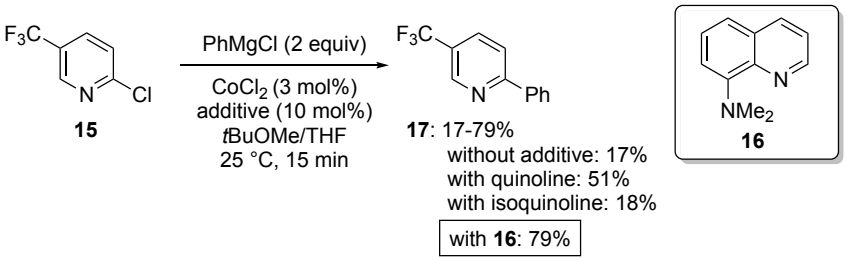
A careful mechanistic study has been performed showing that the non-innocent vinyl substituent of the chlorostyrene **11** facilitates the activation of the C-Cl bond by coordination to the cobalt-catalyst. The performance of kinetic studies supports a mechanism in which a reduced cobalt-catalyst [Co(I)] first undergoes a transmetalation with the Grignard reagent (Ar^1MgX) providing an aryl cobalt-species which in the rate-determining step undergoes an oxidative addition to the aryl chloride (Ar^2-Cl) leading to a cobalt(III)-species which after reductive elimination produces the cross-coupling product (Ar^1-Ar^2) and regenerates the Co(I)-catalyst (Scheme 7).[11]



Scheme 7. Catalytic pathway for a Co-catalyzed aryl-aryl cross-coupling.

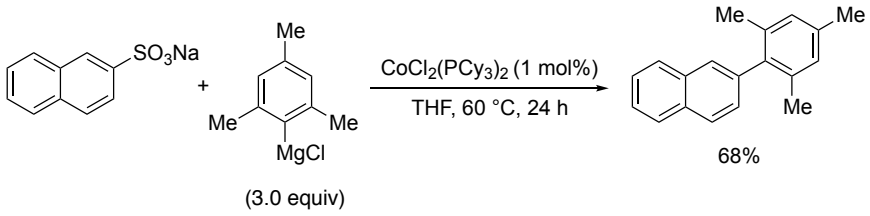
[11] S. Guelak, O. Stepanek, J. Malberg, B. R. Rad, M. Kotora, R. Wolf, A. Jacobi von Wangelin, *Chem. Sci.* **2013**, *4*, 776.

The oxidative addition step is facilitated both by the formation of a cobaltate(I) species of type **14** and by the coordination of this ate-species to the olefinic part of the styrene moiety. A similar activation may be proposed in the case of the quinoline-catalyzed cobalt cross-coupling. Thus, in the case of the electron-deficient chloropyridine **15** the use of an electron-rich substituted quinoline (*N,N*-dimethylquinoline-8-amine, **16**) is required in order to achieve a cross-coupling reaction with PhMgCl. Both quinoline and isoquinoline provide the product **17** in only modest yields (Scheme 8).[5b]



Scheme 8. Ligand influence on cobalt-catalyzed cross-couplings.

Cobalt catalysis allows also the cross-coupling of arylsulfonic acid salts with Grignard reagents. Thus, the treatment of the sodium salts of arylsulfonic acids with arylmagnesium reagents in the presence of $CoCl_2(PCy_3)_2$ (1 mol%) at 25 °C provides the desired biphenyls in excellent yields.[12] In the case of naphthylsulfonic acid salts the reaction may need to be performed at 60 °C for 24 h (Scheme 9).

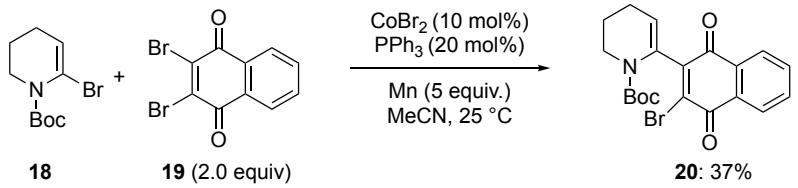


Scheme 9. Cobalt-catalyzed cross-couplings between a naphthylsulfonic acid salt and a sterically hindered Grignard reagent.

Cobalt catalysis also allows the synthesis of functionalized azepenes and piperidines using a reductive cross-coupling procedure. Thus, the cross-coupling between the heterocylic bromide **18** and the dibromonaphthoquinone (**19**) in the presence of $CoBr_2$ (10 mol%) and PPh_3

[12] C. A. Malapit, M. D. Visco, J. T. Reeves, C. A. Busacca, A. R. Howell, C. H. Senanayake, *Adv. Synth. Catal.* **2015**, *357*, 2199.

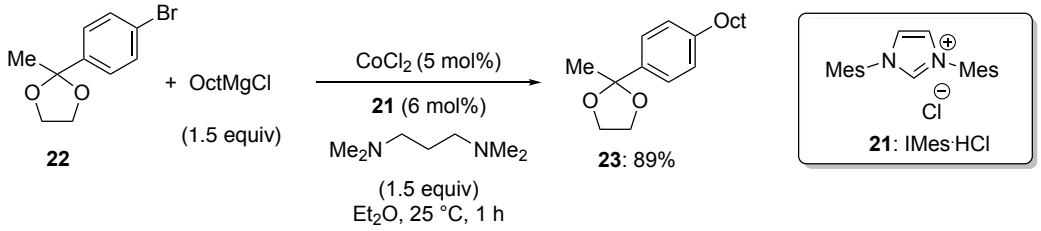
(20 mol%), using manganese powder (5 equiv) as reducing agent in MeCN at 25 °C, provides the interesting cross-coupling product **20** in 37% yield (Scheme 10).[13]



Scheme 10. Selective reductive cross-coupling of a 2-bromoenamine with a dibromonaphthoquinone in acetonitrile.

1.2 Cobalt-Catalyzed Csp^2-Csp^3 Cross-Couplings

Yorimitsu and Oshima reported the cross-coupling between aryl bromides and alkylmagnesium reagents in diethyl ether at 25 °C using $CoCl_2$ (5 mol%), 1.5 equiv TMPDA (*N,N,N',N'*-tetramethyl-1,3-propanediamine) and 6 mol% of an NHC-ligand (IMes·HCl, **21**). Under these conditions, octylmagnesium chloride reacts with the bromide **22** within 1 h at 25 °C producing the desired cross-coupling product **23** in 89% yield (Scheme 11).[14]

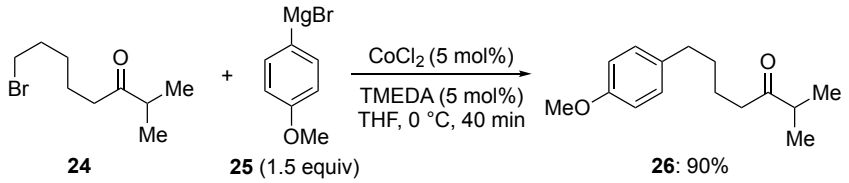


Scheme 11. $CoCl_2$-catalyzed cross-coupling between an alkylmagnesium chloride and aryl bromide (**22**).

Cahiez reported a related cross-coupling using the reaction of functionalized alkyl bromides and arylmagnesium bromides at 0 °C in THF. Thus, the bromoketone **24** reacts with

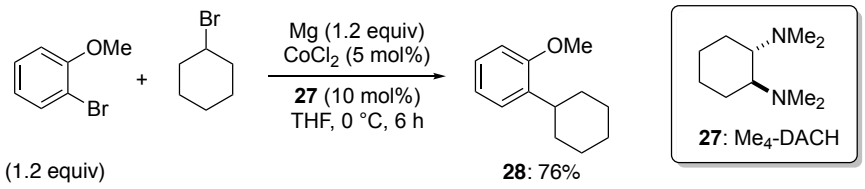
[13] T. K. Beng, K. Sincavage, A. W. V. Silaire, A. Alwali, D. P. Bassler, L. E. Spence, O. Beale, *Org. Biomol. Chem*. **2015**, *13*, 5349.
[14] H. Hamaguchi, M. Uemura, H. Yasui, H. Yorimitsu, K. Oshima, *Chem. Lett*. **2008**, *37*, 117.

anisylmagnesium bromide (**25**) in the presence of 5 mol% TMEDA providing the expected cross-coupling product **26** in 90% yield (Scheme 12).[15]

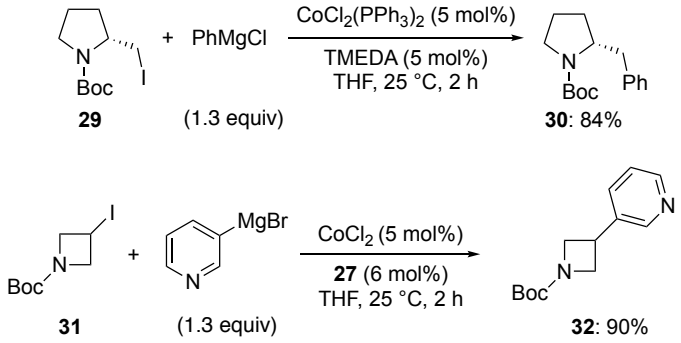


Scheme 12. Cobalt-catalyzed cross-coupling between an arylmagnesium halide and a bromoketone.

Interestingly, Jacobi von Wangelin reported a direct cobalt-catalyzed cross-coupling between aryl and alkyl halides. Thus, the reaction between *ortho*-bromoanisole with cyclohexyl bromide in the presence of magnesium powder (1.2 equiv) and Me_4-DACH (10 mol%, *N,N,N',N'*-tetramethyl-1,2-diaminocyclohexane, **27**) produces the corresponding cross-coupling product **28** in 76% yield within 6 h at 0 °C (Scheme 13).[16]



Scheme 13. Direct cobalt-catalyzed cross-coupling.

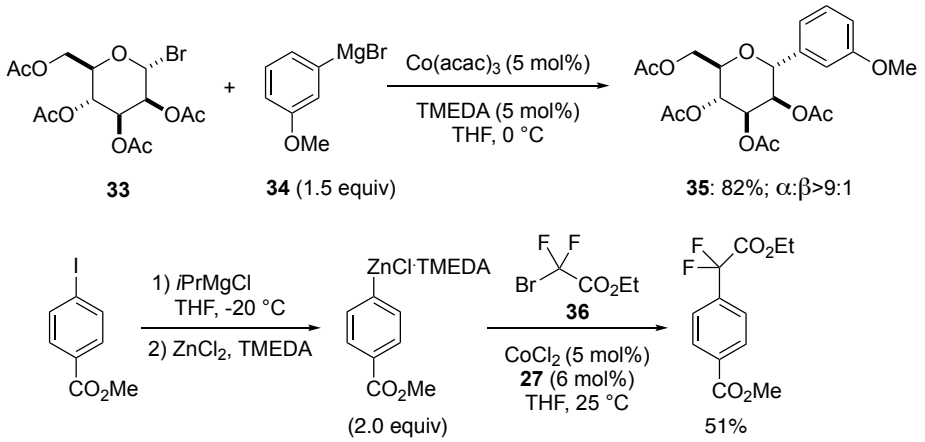


Scheme 14. Cobalt-catalyzed cross-couplings between heterocyclic iodides and arylmagnesium reagents.

[15] G. Cahiez, C. Chaboche, C. Duplais, A. Moyeux, *Org. Lett.* **2009**, *11*, 277.
[16] W. M. Czaplik, M. Mayer, A. J. von Wangelin, *Synlett* **2009**, 2931.

Such cross-couplings have been applied to the synthesis of enantiopure pyrrolidine derivatives. Thus, the reaction of the chiral iodide **29** with phenylmagnesium chloride in THF in the presence of $CoCl_2(PPh_3)_2$ (5 mol%) and TMEDA (5 mol%) furnishes the corresponding pyrrolidine **30** in 84% yield (Scheme 14).[17]

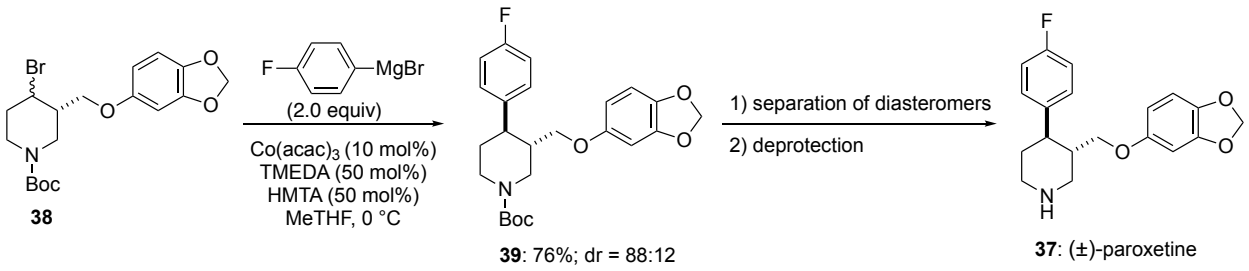
Cossy reported a straightforward cross-coupling between various iodo-azetidines, -pyrrolidines and -piperidines and a range of aryl and heteroaryl iodides.[18] Thus, the cross-coupling of the iodoazetidine (**31**) with 3-pyridylmagnesium bromide in the presence of $CoCl_2$ (5 mol%) and of ligand **27** (6 mol%) provides the coupling product **32** in 90% yield. It is worth noting that this cross-coupling can be performed with the same yield using $FeCl_2$ (10 mol%) as catalyst (Scheme 14). Such cross-couplings have been extended by Cossy and Reymond toward the diastereoselective synthesis of C-aryl glycosides. Thus, the treatment of the bromoglycoside **33** with the anisylmagnesium bromide (**34**) in the presence of 5 mol% $Co(acac)_3$ and 5 mol% TMEDA produces the α-isomer with high diastereoselectivity (**35**) in 82% yield (Scheme 15).[19]



Scheme 15. Cobalt-catalyzed cross-coupling between arylzinc and aryl magnesium reagents and functionalized bromides.

[17] S.-F. Hsu, C.-W. Ko, Y.-T. Wu, *Adv. Synth. Catal.* **2011**, *353*, 1756.
[18] B. Barre, L. Gonnard, R. Campagne, S. Reymond, J. Marin, P. Ciapetti, M. Brellier, A. Guerinot, J. Cossy, *Org. Lett.* **2014**, *16*, 6160.
[19] a) L. Nicolas, P. Angibaud, I. Stansfield, P. Bonnet, L. Meerpoel, S. Reymond, J. Cossy, *Angew. Chem. Int. Ed.* **2012**, *51*, 11101. b) L. Nicolas, E. Izquierdo, P. Angibaud, I. Stansfield, L. Meerpoel, S. Reymond, J. Cossy, *J. Org. Chem.* **2013**, *78*, 11807. c) L. Gonnard, A. Guerinot, J. Cossy, *Chem. Eur. J.* **2015**, *21*, 12797.

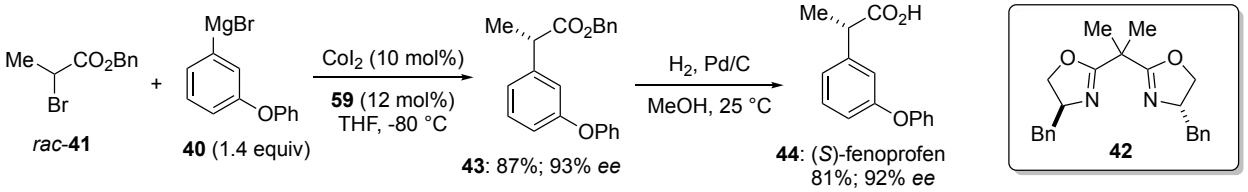
An efficient cross-coupling of various arylzinc reagents with ethyl bromodifluoroacetate (**36**), catalyzed by cobalt(II) chloride, has been reported by Inoue.[20] The method requires only 6 mol% of the ligand **27** and proceeds at 25 °C (Scheme 15). Linclau[21] has recently reported a total synthesis of (±)-paroxetine (**37**) using a stereoconvergent cobalt-catalyzed arylation reaction. Thus, the bromopiperidine **38** was converted in a stereoconvergent manner to the arylated cross-coupling product **39** by a treatment with 4-fluorophenylmagnesium bromide in the presence of 10 mol% $Co(acac)_3$, 50 mol% TMEDA and 50 mol% HMTA (hexamethylenetetramine) in methyltetrahydrofuran (25 °C, 6 h) with a diastereoselectivity of 88:12 in 76% yield. Deprotection provides the desired pharmaceutical **37** (Scheme 16).



Scheme 16. Stereoconvergent cobalt-catalyzed cross-coupling leading to (±)-paroxetine.

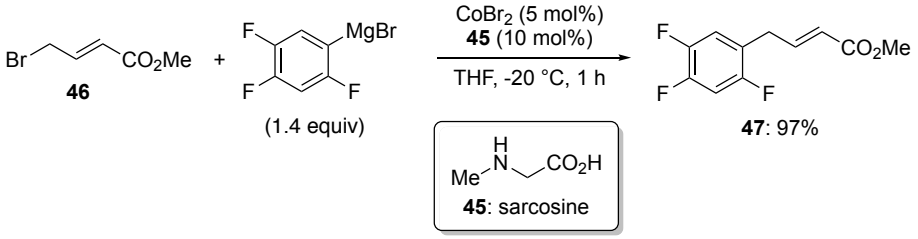
An asymmetric Kumada cross-coupling of racemic *α*-bromo esters with arylmagnesium reagents can be realized using chiral bisoxazoline ligands. Thus, the reaction of the arylmagnesium reagent **40** with the racemic bromo ester **41** in the presence of 12 mol% of ligand **42** and 10 mol% CoI_2 in THF at -80 °C leads to the optically enriched arylated ester **43** in 87% yield and 93% *ee*. Palladium-catalyzed reductive deprotection provides the pharmaceutical (*S*)-fenoprofen (**44**) in 92% *ee* (Scheme 17).[22]

[20] K. Araki, M. Inoue, *Tetrahedron* **2013**, *69*, 3913.
[21] C. F. Despiau, A. P. Dominey, D. C. Harrowven, B. Linclau, *Eur. J. Org. Chem*. **2014**, 4335.
[22] J. Mao, F. Liu, M. Wang, L. Wu, B. Zheng, S. Liu, J. Zhong, Q. Bian, P. J. Walsh, *J. Am. Chem. Soc*. **2014**, *136*, 17662.



Scheme 17. Enantioselective synthesis of (*S*)-fenoprofen using an enantioselective cobalt-catalyzed arylation.

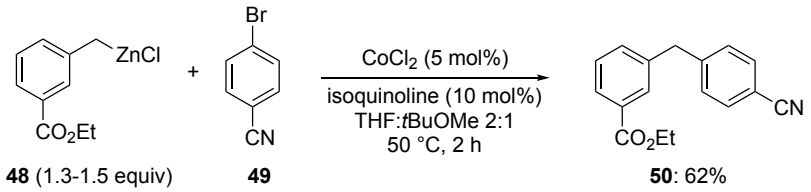
Often, cheap and structurally simple ligands can be used for cobalt-catalyzed cross-couplings. Recently, Casar has found that the naturally occurring ligand sarcosine (**45**) could be used. This ligand allows the performance of smooth cross-couplings between the functionalized allylic bromide **46** and various arylmagnesium reagents. The cross-coupling proceeds at -20 °C within 1 h and provides the desired cross-coupling product **47** in quantitative yield (Scheme 18).[23]



Scheme 18. Cobalt-catalyzed allylation using sarcosine as a ligand.

Benzylic organozinc reagents display a higher reactivity than aryl- or alkyl-zinc reagents. The use of isoquinoline as ligand in an ethereal solvent mixture (2:1 = THF : *t*BuOMe) allowed the performance of cross-couplings between various functionalized benzylic zinc chlorides and aryl bromides at 50 °C. In a typical example, the ester-substituted benzylic zinc reagent **48** reacts with 4-bromo benzonitrile **49** in the presence of 5 mol% $CoCl_2$ and 10 mol% isoquinoline furnishing after 18 h at 50 °C the expected cross-coupling product **50** in 62% yield (Scheme 19).[24]

[23] R. Frlan, M. Sova, S. Gobec, G. Stavber, Z. Casar, *J. Org. Chem.* **2015**, *80*, 7803.
[24] A. Benischke, I. Knoll, A. Rérat, C. Gosmini, P. Knochel, *Chem. Commun.* **2016**, *52*, 3171.



48 (1.3-1.5 equiv) **49** **50**: 62%

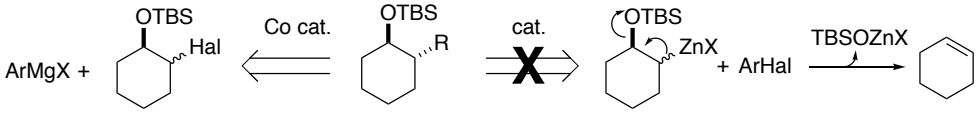
Scheme 19. Cobalt-catalyzed cross-coupling of benzylic zinc reagents.

In summary, cobalt salts are catalytically active, require only simple ligands for full activity and have already a broad application scope. It can be anticipated that future progress will be made in this attractive research field, triggered by the relative simple and practical reaction conditions, the low price of cobalt salts and the possibility of showing that cobalt-catalyzed cross-couplings can in a number of cases replace palladium catalysis.

II. Objectives

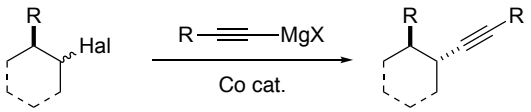
Transition-metal-catalyzed cross-coupling reactions are valuable tools for C-C bond-forming reactions and have found many applications for the syntheses of biologically active molecules. As previously mentioned, Pd- or Ni-catalyzed cross-coupling reactions dominate this field, but have several drawbacks, for example, the toxicity[2b] and the high price[2a] of these metals, as well as the requirement of sophisticated ligands to achieve a broad reaction scope. Thus, this thesis deals with the replacement of expensive and/or toxic Pd- and Ni-catalysts by environmentally more benign cobalt catalysts for such cross-coupling reactions.[4]

Recently, there has been much progress in Co-catalyzed cross-coupling reactions. However, despite the spectacular advances and insights into the role of cobalt in coupling reactions, only a few diastereoselective transformations have been described. Thus, the aim of the first part of this thesis was to develop a general method for the cobalt-catalyzed diastereoselective cross-coupling of cyclic TBS-protected halohydrins with various aryl or heteroaryl magnesium reagents (Scheme 20).



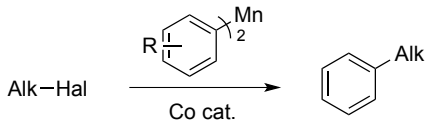
Scheme 20. Diastereoselective cross-coupling reactions between cyclic protected halohydrins and arylmagnesium reagents.

Additionally, we wanted to establish a diastereoselective cross-coupling of variously substituted cycloalkyl halides with alkynyl Grignard reagents under cobalt catalysis (Scheme 21).



Scheme 21. Diastereoselective cross-couplings of cycloalkyl iodides with alkynyl Grignard reagents.

Often however, magnesium or lithium organometallics are not the best choice for performing C-C bond formations, since homo-couplings are often observed side reactions. In comparison organomangenese reagents are considerably more stable and allow for the presence of sensitive functional groups in cross-coupling reactions even at high temperatures. Thereby, cobalt-catalyzed cross-couplings between alkyl halides and diarylmanganese reagents should be investigated (Scheme 22).[25]

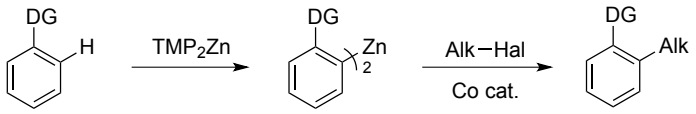


Scheme 22. Cross-coupling reactions of diarylmanganese reagents with alkyl halides.

Pd- or Ni-catalyzed cross-coupling reactions between unsaturated halides and organometallics have found broad application. Cross-coupling reactions using boronic acids or esters, known as Suzuki cross-coupling reactions, have been extensively used due to the broad availability and relative air- and moisture-stability of unsaturated boronic derivatives. Nevertheless, the fast transmetalation of organozinc reagents to palladium compared to boronic acids often allows to achieve Negishi cross-couplings between a broad range of unsaturated halides and zinc organometallics under very mild conditions. The replacement of Pd- and Ni-catalysts employed in this reaction by environmentally benign metals, such as cobalt, is therefore highly desirable.

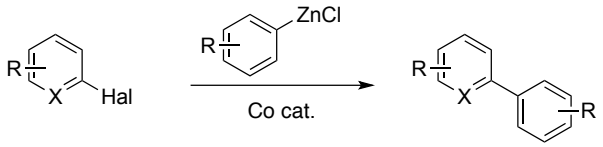
Thus, a general method for the cobalt-catalyzed cross-coupling of organozinc reagents prepared *via* directed metalation with various alkyl halides should be investigated (Scheme 23). Special attention should be drawn to the coupling of secondary alkyl halides without rearrangement from branched to unbranched.[26]

[25] This project was developed in cooperation with Maximilian S. Hofmayer, see: M. S. Hofmayer, J. M. Hammann, D. Haas, P. Knochel, *Org. Lett.* **2016**, *18*, 6456 and Maximilian S. Hofmayer, PhD Dissertation, LMU Munich.
[26] This project was developed in cooperation with Diana Haas, see: J. M. Hammann, D. Haas, and P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 4478 and Diana Haas, PhD Dissertation, LMU Munich.



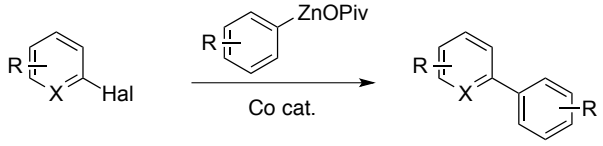
Scheme 23. Cross-coupling of organometallic reagents prepared *via* direct metalation with alkyl halides.

Due to the broad and constantly increasing availability of zinc organometallics Negishi cross-coupling reactions of (hetero)aryl halides with arylzinc reagents under cobalt-catalysis should also be investigated (Scheme 24).[27]



Scheme 24. Cross-coupling of (hetero)aryl halides and arylzinc reagents.

Boron organometallics have extensively been used for coupling reactions in medicinal chemistry, allowing for late-stage functionalizations of biologically active molecules. However, some of these boron derivatives are sensitive or difficult to prepare in high yields and in general require an additional base to achieve satisfactory cross-couplings. Hence, a robust and broadly applicable Co-catalyzed cross-coupling between functionalized air-stable aryl and heteroarylzinc reagents and various aryl or heteroaryl halides should be developed (Scheme 25).[28]



Scheme 25. Cross-coupling of (hetero)aryl halides with bench-stable arylzinc pivalates.

[27] This project was developed in cooperation with Diana Haas, see: D. Haas, J. M. Hammann, F. H. Lutter, P. Knochel, *Angew. Chem. Int. Ed.* **2016**, *55,* 3809 and Diana Haas, PhD Dissertation, LMU Munich.

[28] This project was developed in cooperation with Ferdinand H. Lutter, see: J. M. Hammann, F. H. Lutter, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, 56, 1082 and Ferdinand H Lutter, PhD Dissertation, LMU Munich.

III. Results and Discussion

1. Cobalt-Mediated Diastereoselective Cross-Coupling Reactions between Cyclic Halohydrins and Arylmagnesium Reagents

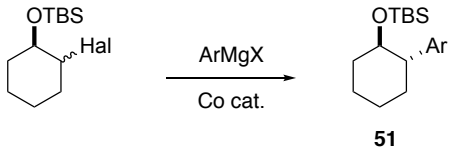
1.1 Introduction

Transition metal-catalyzed cross-coupling reactions are indispensable tools for the construction of C-C bonds in organic synthesis.[1] Recently, there has been much progress in Co-catalyzed coupling methods. However, despite the spectacular advances and insights into the role of Co in coupling reactions,[5] only a few diastereoselective Co-mediated or catalyzed transformations of this type have been described.[19,2930] Previously, we have reported a diastereoselective Fe-mediated cross-coupling of cyclic iodohydrins with aryl Grignard reagents leading to products of type **51** (Scheme 26).[31] Although very effective with electron-poor Grignard reagents, this method displays a limited reaction scope, and electron-rich arylmagnesium bromides gave unsatisfactory results. Additionally, cyclic bromohydrins did not react.

[29] For selected cobalt-catalyzed cross-couplings and related reactions, see: a) M. Lautens, C. M. Crudden, *Organometallics* **1989**, *8*, 2733. b) M. Lautens, W. Tam, C. Sood, *J. Org. Chem.* **1993**, *58*, 4513. c) G. Cahiez, H. Avedissian, *Tetrahedron Lett.* **1998**, *39*, 6159. d) K. Wakabayashi, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2001**, *123*, 5374. e) T. Tsuji, H. Yorimitsu, K. Oshima, *Angew. Chem. Int. Ed.* **2002**, *41*, 4137. f) H. Shinokubo, K. Oshima, *Eur. J. Org. Chem.* **2004**, 2081. g) H. Ohmiya, T. Tsuji, H. Yorimitsu, K. Oshima, *Chem. Eur. J.* **2004**, *10*, 5640. h) H. Ohmiya, H. Yorimitsu, K. Oshima, *Org. Lett.* **2006**, *8*, 3093. i) W. Affo, H. Ohmiya, T. Fujioka, Y. Ikeda, T. Nakamura, H. Yorimitsu, K. Oshima, Y. Imamura, T. Mizuta, K. Miyoshi, *J. Am. Chem. Soc.* **2006**, *128*, 8068. j) H. Someya, H. Ohmiya, H. Yorimitsu, K. Oshima, *Org. Lett.* **2007**, *9*, 1565. k) H. Someya, H. Ohmiya, H. Yorimitsu, K. Oshima, *Tetrahedron* **2007**, *63*, 8609. l) C. Gosmini, J.-M. Bégouin, A. Moncomble, *Chem. Commun.* **2008**, *28*, 3221. m) K. Murakami, H. Yorimitsu, K. Oshima, *Org. Lett.* **2009**, *11*, 2373. n) D. L. Usanov, H. Yamamoto, *Angew. Chem. Int. Ed.* **2010**, *49*, 8169. o) X. Qian, A. Auffrant, A. Felouat, C. Gosmini, *Angew. Chem. Int. Ed.* **2011**, *50*, 10402. p) K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208. q) L. Gonnard, A. Guérinot, J. Cossy, *Chem. - Eur. J.* **2015**, *21*, 12797. r) N. Sauermann, M. J. Gonzalez, L. Ackermann, *Org. Lett.* **2015**, *17*, 5316. s) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 8551. t) M. Moselage, N. Sauermann, S. C. Richter, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 6352. u) J. Wu, N. Yoshikai, *Angew. Chem. Int. Ed.* **2015**, *55*, 336. v) M. Moselagea, N. Sauermanna, J. Koellera, J. Liua, D. Gelmanb, L. Ackermann, *Synlett* **2015**, *26*, 1596. w) T. Yamakawa, Y. W. Seto, N. Yoshikai, *Synlett* **2015**, *26*, 340. x) J. Li, M. Tang, L. Zang, X. Zhang, Z. Zhang, L. Ackermann, *Org. Lett.* **2016**, *18*, 2742. y) J. M. Neely, M. J. Bezdek, P J. Chirik *ACS Cent. Sci.* **2016**, *2*, 935.

[30] For selected diastereoselective cobalt-catalyzed cross-coupling reactions, see: a) H. Ohmiya, K. Wakabayashi, H. Yorimitsu, K. Oshima, *Tetrahedron* **2006**, *62*, 2207. b) H. Ohmiya, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 1886.

[31] a) A. K. Steib, T. Thaler, K. Komeyama, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 3303. b) L. R. Jefferies, S. P. Cook, *Org. Lett.* **2014**, *16*, 2026. c) L. R. Jefferies, S. R. Weber, S. P. Cook, *Synlett* **2015**, *26*, 331.



Scheme 26. Diastereoselective α-arylation of alcohol derivatives.

1.2 Cobalt-Mediated Aryl-Alkyl Cross-Coupling Reactions

Herein, we report a new broadly applicable cobalt-mediated *α*-arylation of TBS-protected cyclic bromo- and iodohydrins.[32] In optimization studies, we have examined the arylation of **52a** (dr 75:25, *cis/trans*) with 4-anisylmagnesium bromide (**25a**) in the presence of various transition metal salts (Table 1). As mentioned above, the use of $FeCl_2$·2LiCl proved to be unsatisfactory, and the coupling of **52a** with **25a** furnished the expected product **51a** in only 18% yield (entry 1). Changing the iron salt or the ligand was not satisfactory (entries 2-3).[33] Therefore, we examined other metallic salts. $MnCl_2$·2LiCl[34] and $CrCl_2$[35] gave poor results (entries 4-5), in contrast to cobalt salts. Thus, $CoCl_2$·2LiCl (0.85 equiv)[36] and 4-fluorostyrene (0.5 equiv) used as an additive[37] led to the product **51a** with a dr = 99:1, but with only 44% yield (entry 6). In the absence of 4-fluorostyrene, the yield improved to 62%. Finally, adding TMEDA as a ligand gave the best results (71% isolated yield, dr 95:5; entry 8).[38]

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[32] For selected examples of α-arylations to oxygen, see: a) M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108. b) J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360. c) A. Ehrentraut, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 209. d) J. Cossy, A. de Filippis, D. G. Pardo, *Org. Lett.* **2003**, *5*, 3037. e) O. Navarro, N. Marion, Y. Onishi, R. A. Kelly, S. P. Nolan, *J. Org. Chem.* **2006**, *71*, 685. f) W. Su, S. Raders, J. G. Verkade, X. Liao, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2006**, *45*, 5852. g) X. Dai, N. A. Strotman, G. C. Fu, *J. Am. Chem Soc.* **2008**, *130*, 3302. h) P. M. Lundin, J. Esquivias, G. C. Fu, *Angew. Chem. Int. Ed.* **2009**, *48*, 154. i) S. Lou, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 1264.

[33] G. Cahiez, V. Habiak, C. Duplais, A. Moyeux, *Angew. Chem. Int. Ed.* **2007**, *46*, 4364.

[34] a) M. Alami, P. Ramiandrasoa, G. Cahiez, *Synlett* **1998**, 325. b) G. Cahiez, O. Gager, F. Lecomte, *Org. Lett.* **2008**, *10*, 5255. c) T. C. Atack, S. P. Cook *J. Am. Chem. Soc.* **2016**, *138*, 6139.

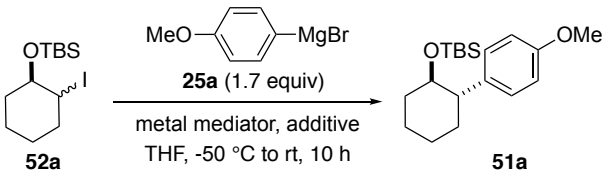
[35] A. K. Steib, O. M. Kuzmina, S. Fernandez, D. Flubacher, P. Knochel, *J. Am. Chem. Soc.* **2013**, *135*, 15346.

[36] G. Cahiez, C. Chaboche, C. Duplais, A. Giulliani, A. Moyeux, *Adv. Synth. Catal.* **2008**, *350*, 1484.

[37] A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, *67*, 79.

[38] a) The use of triisopropylsilyl-protected (TIPS-protected) 2-iodocyclohexanol led to a similar diastereoselectivity (dr 93:7), whereas protection with the bulky *tert*-butyldiphenylsilyl (TBDPS) group resulted in a decreased diastereoselectivity (dr 91:9). b) The role of *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA) is to coordinate the low-valent cobalt intermediate.

Table 1. Optimization of the diastereoselective cross-coupling of (**52a**) with (**25a**).



52a **51a**

entry	metal mediator (equiv)	additive (equiv)	yield[a] (%)	dr[a]
1	$FeCl_2$·2LiCl (0.85)	4-fluorostyrene (0.50)	18	94:6
2	$FeCl_2$·2LiCl (0.85)	TMEDA (0.30)	53	88:12
3	$Fe(acac)_3$ (0.85)	TMEDA (0.30)	24	91:9
4	$MnCl_2$·2LiCl (0.85)	TMEDA (0.30)	0	n.d.
5	$CrCl_2$ (0.20)	TMEDA (0.30)	5	99:1
6	$CoCl_2$·2LiCl (0.85)	4-fluorostyrene (0.50)	44	99:1
7	$CoCl_2$·2LiCl (0.85)	–	62	99:1
8	$CoCl_2$·2LiCl (0.85)	TMEDA (0.30)	79 (71)[b]	95:5

[a] Determined by capillary GC analysis. Undecane ($C_{11}H_{24}$) was used as internal standard.

[b] Isolated yield.

Thus, the dropwise addition of various Grignard reagents to a mixture of the protected iodohydrin **52a** (1.0 equiv), $CoCl_2$·2LiCl (0.85 equiv, 1 M in THF)[39] and TMEDA (0.3 equiv) in THF at -50 °C led to the *trans*-coupling products (**51a-k**) in 55-91% yield and excellent diastereoselectivity (dr >95:5, Table 2).[40] Both electron-poor or electron-rich arylmagnesium halides were used successfully. Furthermore, heterocylic Grignard reagents obtained either by a directed magnesiation[41] or magnesium insertion[42] led to the desired cross-coupling product in very high diastereoselectivity (up to >99:1 dr). Thus, the magnesiation of the uracil derivative **53** with TMPMgCl·LiCl (1.1 equiv, THF, 0 °C, 0.5 h) led to the heterocyclic Grignard reagent **25b** (>90% yield). Its coupling with **52a** under the standard conditions furnished the pyrimidine **51b** in 55% yield (dr >99:1). Also, *N*-methyl-5-bromoindole **54** reacted with Mg, LiCl (25 °C, 1 h) to

[39] The use of catalytic amounts of $CoCl_2$·2LiCl (0.40 equiv) did not lead to a satisfactory conversion of the starting material (54% yield).

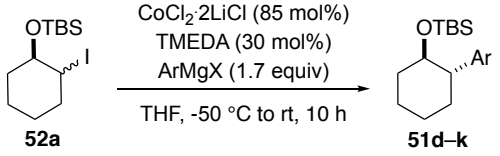
[40] Treatment of a mixture of $CoCl_2$·2LiCl (0.85 equiv), TMEDA (0.3 equiv), ArMgCl (1.7 equiv) with the protected iodohydrin (1 equiv) in THF at -50 °C did not lead to the formation of the desired product.

[41] M. Mosrin, P. Knochel, *Org. Lett.* **2008**, *10*, 2497.

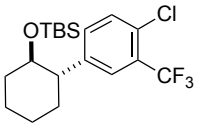
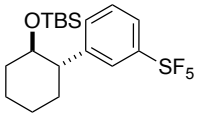
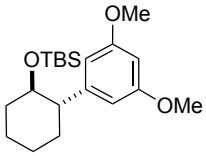
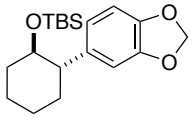
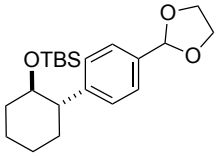
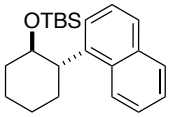
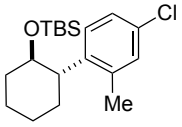
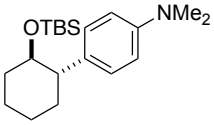
[42] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802. b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. - Eur. J.* **2009**, *15*, 7192.

produce the corresponding Grignard reagent **25c** in >90% yield. Coupling with **52a** under our standard conditions produced the indole **51c** (60% yield, dr 98:2, Scheme 27).

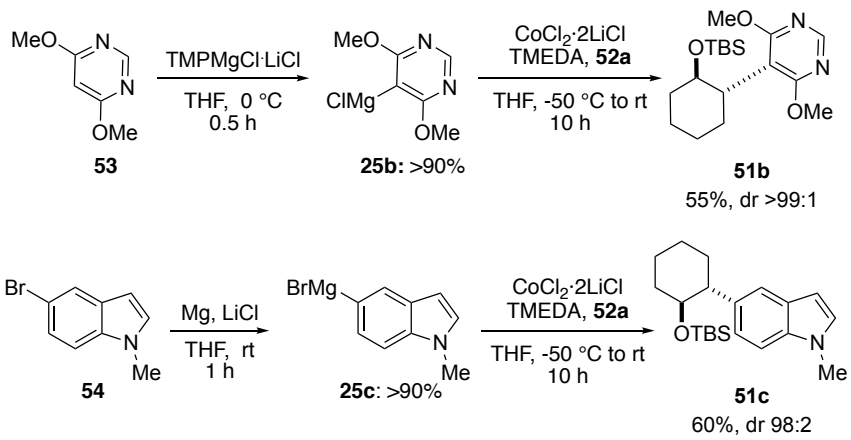
Table 2. Products obtained by the diastereoselective cross-coupling of (**52a**) with various Grignard reagents.



52a **51d–k**

entry	product	yield (%)[a] dr[b]	entry	product	yield (%)[a] dr[b]
1	 **51d**	65% >99:1	5	 **51h**	67% 98:2
2	 **51e**	71% 95:5	6	 **51i**	70% 98:2
3	 **51f**	73% 97:3	7	 **51j**	91% >99:1
4	 **51g**	71% >99:1	8	 **51k**	63% 99:1

[a] Isolated yield. [b] Determined by capillary GC and ^{1}H NMR analysis.

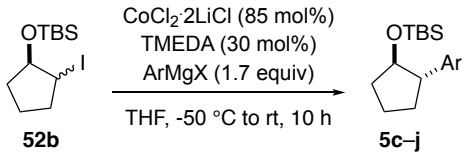


Scheme 27. Preparation of heterocyclic Grignard reagents and their diastereoselective cross-coupling with (**52a**).

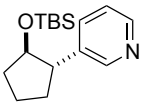
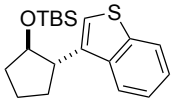
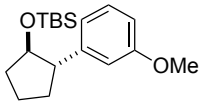
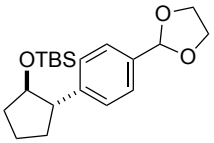
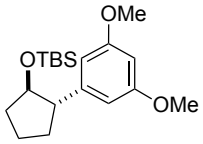
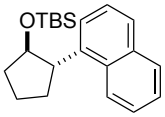
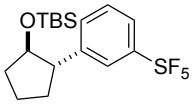
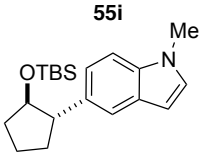
Extension of this coupling to the 5-membered iodohydrin **52b** (X = I, dr 1:99, *cis/trans*) led to the expected α-arylated or -heteroarylated cyclopentanol silyl ethers **55a-j** in 52-80% yield (dr >97:3; Table 3). The mild conditions required for this cross-coupling allowed the presence of sensitive functional groups in the Grignard reagent. Thus, the treatment of the bromobenzonitrile **56** with *i*PrMgCl·LiCl (1.1 equiv, THF, -20 °C, 0.5 h)[43] provides the corresponding Grignard reagent **25d** (>90%), which smoothly undergoes a Co-mediated cross-coupling, providing the cyclopentanol derivative **55a** in 67% yield (dr >99:1). Similarly, the arylmagnesium reagent **25e** (>90%) prepared from the iodobenzoate **57** by I/Mg-exchange furnished, after cross-coupling with **52b**, the cyclopentanol derivative **55b** in 52% yield (dr 97:3, Scheme 28).

[43] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159.

Table 3. Products obtained by the diastereoselective cross-coupling of (**52b**) with various Grignard reagents.

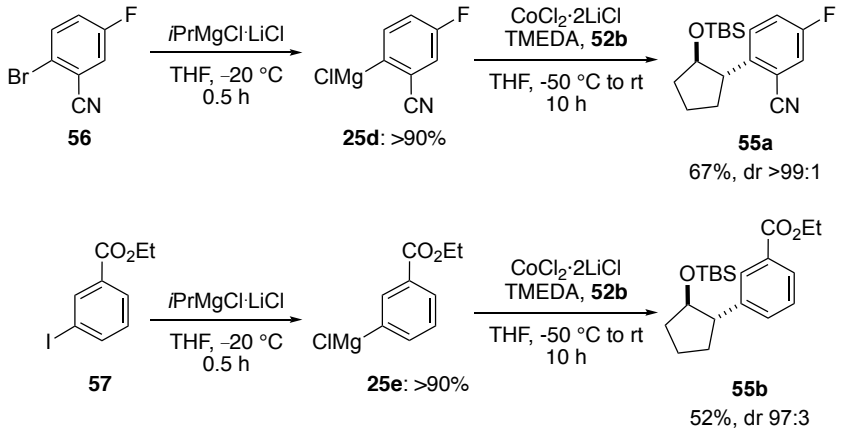


52b **5c–j**

entry	product	yield (%)[a] dr[b]	entry	product	yield (%)[a] dr[b]
1	 **55c**	73% >99:1	5	 **55g**	58% 98:2
2	 **55d**	79% >99:1	6	 **55h**	78% >99:1
3	 **55e**	74% 99:1	7	 **55i**	80%[c] >99:1
4	 **55f**	61% 99:1	8	 **55j**	65% 99:1

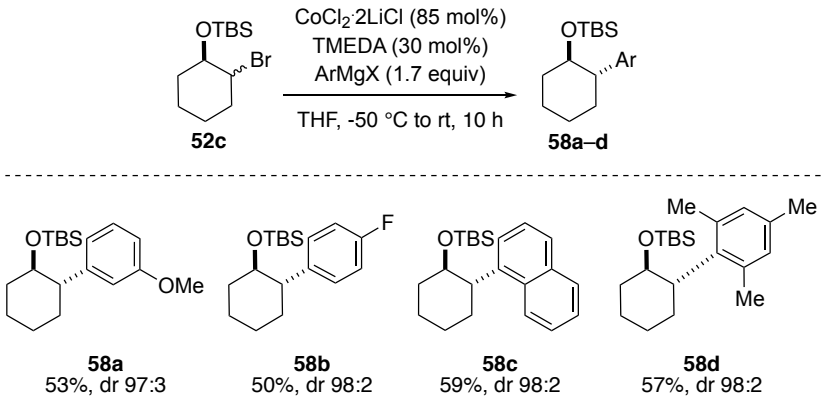
[a] Isolated yield. [b] Determined by capillary GC and ^{1}H NMR analysis. [c] Reaction performed on a 4 mmol scale.

The use of $CoCl_2$·2LiCl allows further expansion of the reaction scope of this coupling, and the iodohydrins **52a-b** can be replaced advantageously by the corresponding bromohydrin (**52c**, X = Br, dr 1:99, *cis/trans*). Using the same reaction conditions, the cross-coupling products **58a-d** were obtained with high diastereoselectivities (dr >97:3, Scheme 29).

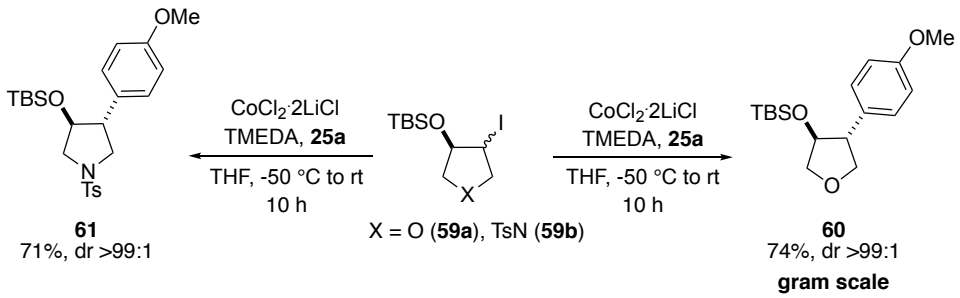


Scheme 28. Preparation of various Grignard reagents and their cross-coupling reaction.

Remarkably, this cross-coupling can also be performed with heterocyclic iodohydrins such as **59a** (dr 1:99, *cis/trans*) or **59b** (dr 1:99, *cis/trans*), leading to *trans*-3,4-disubstituted tetrahydrofurans (**60**) and pyrrolidines (**61**) as single diastereomers (71-74%, Scheme 30). The up-scaling of this cross-coupling is readily performed as indicated in Table 3 (entry 7) as well as in the synthesis of **60**, which has been performed on a 4 mmol scale (gram scale).



Scheme 29. Products of type **58** obtained by the diastereoselective cross-coupling of bromohydrin **52c** with arylmagnesium reagents.



Scheme 30. Diastereoselective cross-coupling of the heterocyclic halohydrins such as **59**.

Preliminary mechanistic studies have shown that ArMgX and $CoCl_2$ readily react with each other, leading to the homo-coupling products quantitatively. However, under the reaction conditions (slow addition of ArMgX to a mixture of the respective halohydrin, $CoCl_2$·2LiCl and TMEDA) the desired cross-coupling is much faster. The stereoconvergence of the reaction may be the result of a radical generated at the α-position to oxygen. Further extension of this method as well as mechanistic studies, are currently underway.

2. Diastereoselective Cobalt-Mediated Cross-Couplings of Cycloalkyl Iodides with Alkynyl or (Hetero)Aryl Grignard Reagents

2.1. Introduction

The formation of Csp^2-Csp^3 bonds is of great importance for the pharmaceutical industry.[1] Thus, there is a need for cheaper transition metal catalysts for such couplings, and cobalt salts have proven to be a powerful alternative.[5] Despite the diversity of various Co-catalyzed[15,18,29] cross-couplings,[19,30] only a few stereoselective transformations have been described. In the previous section, we reported a Co-mediated diastereoselective cross-coupling of substituted cyclic iodohydrins with (hetero)aryl Grignard reagents.[44] This method, however, gave unsatisfactory results with alkynylmagnesium reagents. Thus, the development of a novel method for the stereoselective C-C coupling is of great interest.

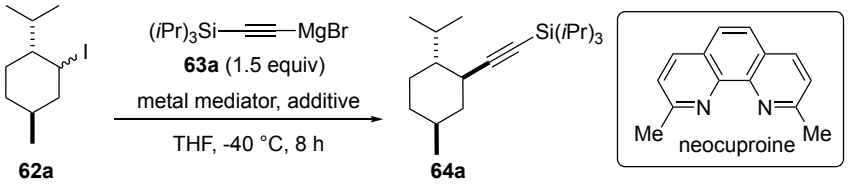
2.2. Cobalt-Mediated Alkyl-Alkynyl and Alkyl-Aryl Cross-Coupling Reactions

Herein, we report a new broadly applicable stereoconvergent cobalt-mediated cross-coupling of alkynyl or (hetero)aryl magnesium halides and variously substituted cycloalkyl iodides.

In optimization studies, we examined the alkynylation of menthyl iodide **62a** (dr 1:99, *cis/trans*) with ((triisopropylsilyl)ethynyl)magnesium bromide (1.5 equiv, **63a**) at -40 °C, in the presence of various transition metal salts (Table 4). The use of $CrCl_2$,[35] $MnCl_2$·2LiCl,[34] or $FeCl_2$·2LiCl[31] proved to be unsatisfactory, and the coupling of **62a** with **63a** furnished the expected product **64a** in only 27% yield at best when using 20 mol% of $FeCl_2$·2LiCl (entries 1-3).

[44] J. M. Hammann, A. K. Steib, P. Knochel, *Org. Lett.* **2014**, *16*, 6500.

Table 4. Optimization of the diastereoconvergent cross-coupling of **62a** with **63a**.



entry	metal mediator (equiv)	additive (equiv)	yield[a] (%)	d.r.[a]
1	$CrCl_2$ (0.20)	-	traces	n.d.
2	$MnCl_2{\cdot}2LiCl$ (0.20)	-	0	n.d.
3	$FeCl_2{\cdot}2LiCl$ (0.20)	-	19	99:1
4	$Co(acac)_3$ (0.20)	-	28	83:17
5	$CoBr_2$ (0.20)	-	22	85:15
6	$CoCl_2$ (0.20)	-	36	86:14
7	$CoCl_2{\cdot}2LiCl$ (0.20)	-	42	88:12
8	$CoCl_2{\cdot}2LiCl$ (0.20)	DMPU (0.20)	48	90:10
9	$CoCl_2{\cdot}2LiCl$ (0.20)	NMP (0.20)	41	91:9
10	$CoCl_2{\cdot}2LiCl$ (0.20)	4-fluorostyrene (0.20)	44	99:1
11	$CoCl_2{\cdot}2LiCl$ (0.20)	TMEDA (0.20)	34	90:10
12	$CoCl_2{\cdot}2LiCl$ (0.20)	neocuproine (0.20)	63	93:7
13	$CoCl_2{\cdot}2LiCl$ (0.50)	neocuproine (0.20)	88(83)[b]	99:1

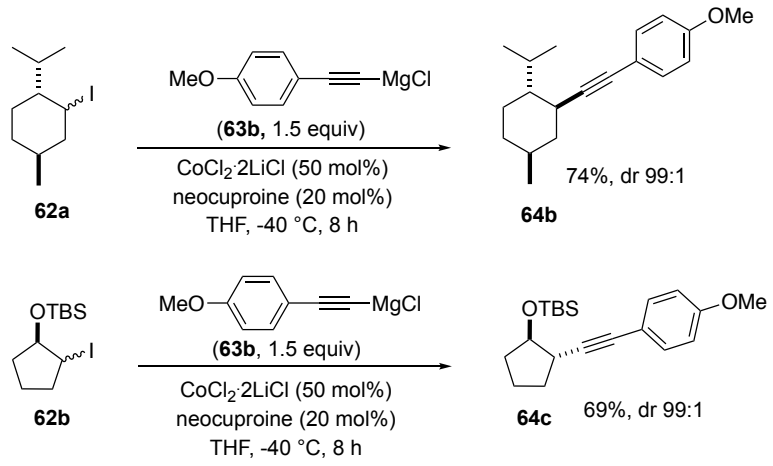
[a] Determined by capillary GC and ^{1}H NMR analysis. Undecane was used as internal standard.

[b] Isolated yield.

A general and more broad screening of reaction conditions using cobalt salts showed that $Co(acac)_3$[45] or cobalt halides[46] gave much better results (entries 4–6). Also, the THF-soluble $CoCl_2{\cdot}2LiCl$[7] afforded the coupling product **64a** in 42% yield (dr 99:1, entry 7). Switching to more polar cosolvents such as DMPU[47] or NMP[48] leads to the formation of the desired product (**64a**) in up to 48% yield and a diastereoselectivity of up to 91:9 dr (entries 8 and 9). The use of 4-fluorostyrene[10] resulted in a yield of 44% and an excellent diastereoselectivity of 99:1 (entry 10). The addition of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA)[7] leads to a deterioration of the diastereoselectivity (dr 90:10, entry 11). Changing the additive to neocuproine (20 mol%)[5] gave the best result, leading to product **64a** in 63% yield and high dr (dr = 93:7, entry 12).

[45] T. J. Korn, M. A. Schade, S. Wirth, P. Knochel, *Org. Lett.* **2006**, *8*, 725.
[46] O. M. Kuzmina, A. K. Steib, J. T. Markiewicz, D. Flubacher, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 4945.
[47] T. J. Korn, P. Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 2947.
[48] A. Fuerstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856.

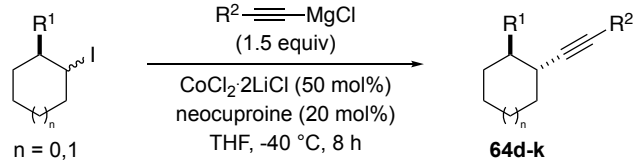
Significant improvements were achieved by using substoichiometric amounts (50 mol%) of the complex $CoCl_2 \cdot 2LiCl$, this complex leads exclusively to the thermodynamically more stable *trans*-isomer **64a** in 83% isolated yield and 99:1 dr (entry 13).

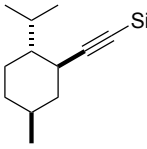
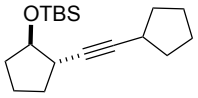
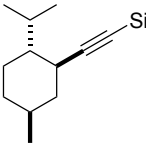
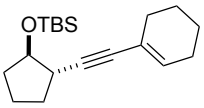
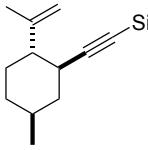
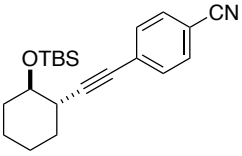
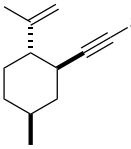
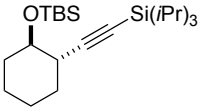


Scheme 31. Diastereoselective cross-coupling of **62a** and **62b** with the alkynyl Grignard reagent **63b.**

With these optimized reaction conditions in hand, we performed a range of coupling reactions using various alkynylmagnesium halides. Alkynyl Grignard reagents obtained by magnesiation using TMPMgCl·LiCl (1.1 equiv, THF, 0 °C, 3 h) led to the desired *trans*-cross-coupling products in very high diastereoselectivities. Thus, the coupling of ((4-methoxyphenyl)ethynyl)magnesium chloride (**63b**) with **62a** (dr 99:1, *cis/trans*) or **62b** (dr 1:99, *cis/trans*) using standard conditions furnished the coupling products **64b-c** in 69-74% yield (dr 99:1, Scheme 31).

Table 5. Coupling of 1,2-substituted cycloalkyl iodides with various alkynyl Grignard reagents.

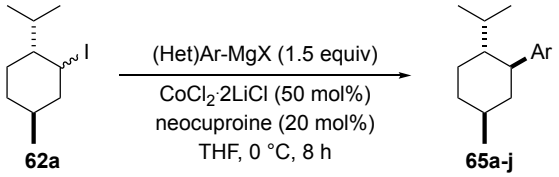


entry	product	yield (%)[a] dr[b]	entry	product	yield (%)[a] dr[b]
1	 **64d**	78% 99:1	5	 **64h**	68% 99:1
2	 **64e**	68% 99:1	6	 **64i**	68% 99:1
3	 **64f**	55% 99:1	7	 **64j**	69% 97:3
4	 **64g**	59% 99:1	8	 **64k**	77% 99:1 **gram scale**

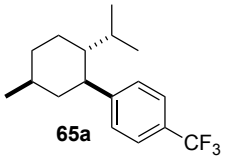
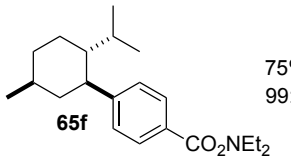
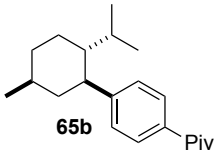
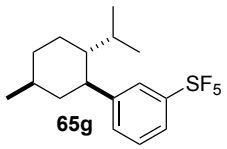
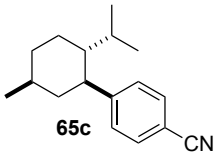
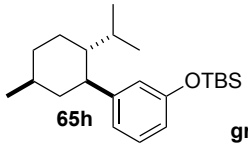
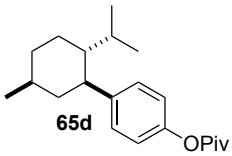
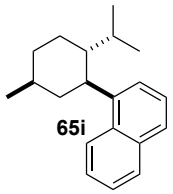
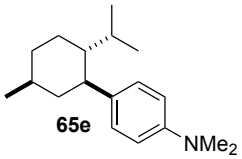
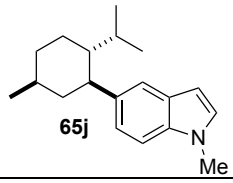
[a] Isolated yield. [b] Determined by capillary GC and ^{1}H NMR analysis.

We have further extended this Co-mediated coupling reaction to various alkynyl Grignard reagents (see Table 5).

Table 6. Products obtained by the diastereoselective cross-coupling with various substituted Grignard reagents.



62a **65a-j**

entry	product	yield (%)[a] dr[b]	entry	product	yield (%)[a] dr[b]
1	 **65a**	71% 99:1	6	 **65f**	75% 99:1
2	 **65b**	70% 99:1	7	 **65g**	68% 99:1
3	 **65c**	61% 99:1	8	 **65h**	73% 99:1 **gram scale**
4	 **65d**	75% 99:1	9	 **65i**	62% 99:1
5	 **65e**	62% 91:9	10	 **65j**	75% 96:4

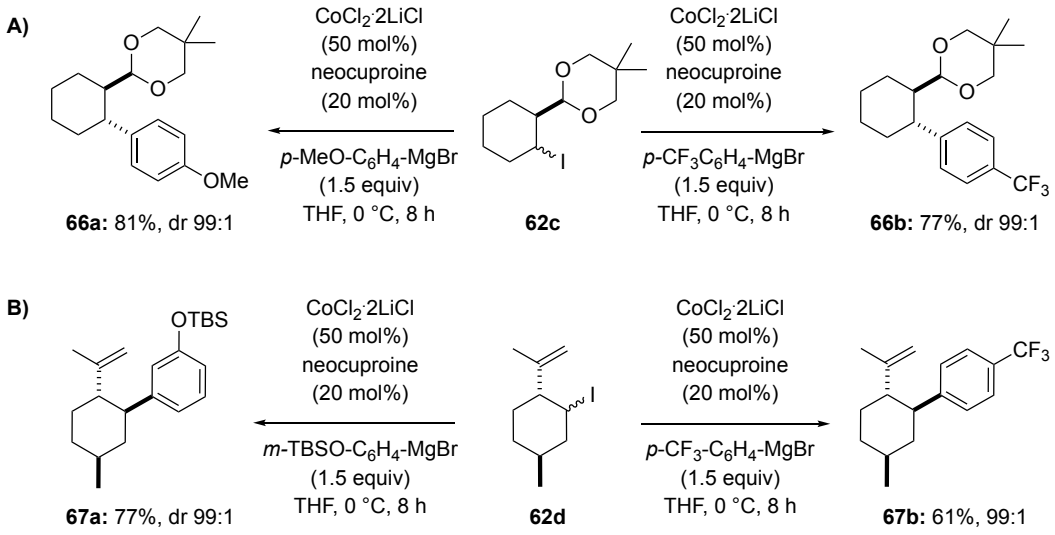
[a] Isolated yield. [b] Determined by capillary GC and ^{1}H NMR analysis.

Thus, alkynylmagnesium reagents bearing silyl (entries 1-4 and 8), aliphatic (entries 5 and 6), and aromatic substituents (entry 7) were successfully coupled, leading to the desired products **64d-k** in up to 78% yield and a dr up to 99:1 even on a gram scale (entry 8). To underline its synthetic utility, we extended this reaction to the cross-coupling of cycloalkyl iodides such as

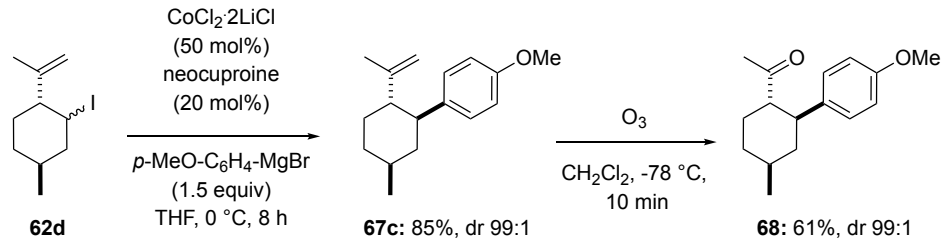
62a with heterocyclic and aryl magnesium reagents. Thus, the dropwise addition of various Grignard reagents (1.5 equiv) to a mixture of the cycloalkyl iodide **66a** (1.0 equiv), $CoCl_2$·2LiCl (50 mol%, 1 M in THF), and neocuproine (20 mol%) in THF at 0 °C led to the desired *trans*-coupling products (**65a-j**) in 61-75% yield and a dr >91:9 (Table 6).

Both, electron-poor or electron-rich arylmagnesium halides were employed successfully, and a range of functional groups such as CF_3, Piv, CN, OPiv, NMe_2, CO_2NEt_2, SF_5, and OTBS were tolerated in the Grignard reagents (entries 1-9). Additionally, a heterocyclic magnesium halide was coupled successfully, leading to the indole derivative **65j** in high diastereoselectivity with 75% isolated yield and dr 99:1 (entry 10).

Additionally, we have applied this Co-mediated cross-coupling to various substituted cycloalkyl iodides such as **62c** (dr 99:1, *cis/trans*) or **62d** (dr 99:1, *cis/trans*). To our delight, the *trans*-coupling products **66a-b** (Scheme 32A) and **67a-b** (Scheme 32B) were obtained in a dr up to 99:1. Thus, the reaction of (3-((tert-butyldimethylsilyl)oxy)-phenyl)magnesium bromide, (4-(trifluoromethyl)phenyl)- magnesium bromide, or (4-methoxyphenyl)magnesium bromide with the cycloalkyl iodides **62c** or **62d**, using $CoCl_2$·2LiCl (50 mol%) and neocuproine (20 mol%), furnished the arylated derivatives **66a-b** and **67a-b** in up to 81% yield and with a dr of 99:1.

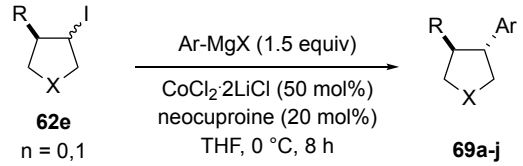


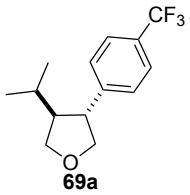
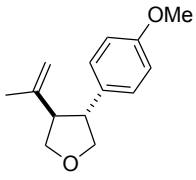
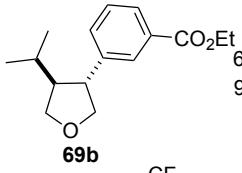
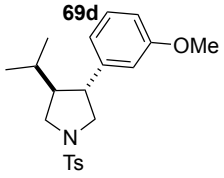
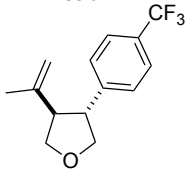
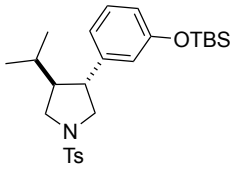
Scheme 32. Diastereoselective cross-coupling of cyclic 1,2-substituted alkyl iodides with various magnesium halides.



Scheme 33. Diastereoselective cross-coupling of **62d** with *p*-MeOC$_6$H$_4$MgBr.

Table 7. Coupling of various 1,2-substituted heterocyclic alkyl iodides with aryl Grignard reagents.



entry	product	yield (%)[a] dr[b]	entry	product	yield (%)[a] dr[b]
1	 **69a**	71% 97:3	4	 **69d**	57% 99:1
2	 **69b**	64% 99:1	5	 **69e**	66% 99:1
3	 **69c**	54% 99:1	6	 **69f**	88% 99:1

[a] Isolated yield. [b] Determined by capillary GC and ^{1}H NMR analysis.

The diastereoselective cross-coupling products of type **67** are synthetically useful and can easily be converted to the corresponding ketones. Thus, the coupling of **62d** with *p*- MeOC$_6$H$_4$MgBr

gave the desired product **67c** in 99:1 dr and 85% yield. The alkene moiety in **67c** was transformed *via* ozonolysis to ketone **68**, without loss of the stereoselectivity and in 61% isolated yield (Scheme 33).

Remarkably, this cross-coupling can also be performed with heterocyclic alkyl iodides of type **62e**, leading to *trans*-3,4-disubstituted tetrahydrofurans (**69a-d**, entries 1-4) and pyrrolidines (**69e-f**, entries 5 and 6) as single diastereomers (Table 7).

Although the mechanism of this cross-coupling was not studied in detail, experiments have shown that when R^1MgX and $CoCl_2$ readily react with each other, leading to the homocoupling products quantitatively. However, when R^1MgX is slowly added to the reaction mixture, the desired cross-coupling is faster than the biaryl (R^1-R^1) formation. The stereoconvergence of the reaction may be the result of a radical reaction pathway, as proposed by Oshima for similar reactions. Mechanistic studies, are currently underway.

3. Cobalt-Catalyzed Csp^2-Csp^3 Cross-Coupling Reactions of Diarylmanganese Reagents with Secondary Alkyl Iodides

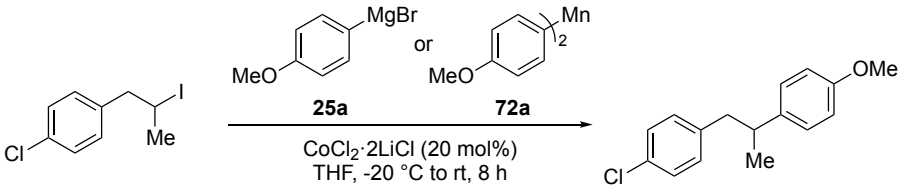
3.1. Introduction

Palladium-catalyzed cross-couplings have widely been used.[1] However, toxicity[2] and cost[3] considerations led to the search of alternative transition metal catalysts for cross coupling reactions. Especially cobalt-catalyzed transformations have shown their synthetic utility.[5] Pioneering work of several research groups demonstrated the broad field of applications of cobalt salt catalysis for forming new carbon carbon bonds.

In the previous chapters, we have shown that cobalt halides are excellent catalysts for the cross-couplings of magnesium organometallics.[6b,35,49] However, these organometallic reagents are not always the best choice for performing C-C bond formations, since homo-couplings are often observed side reactions.

3.2. Cobalt-Catalyzed Aryl-Alkyl Cross-Coupling Reactions

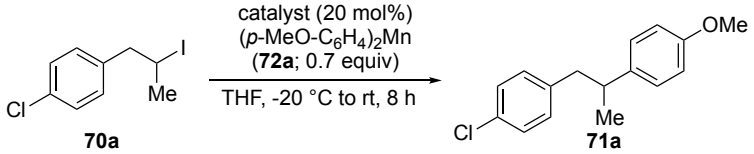
Herein, we report a new cobalt-catalyzed cross-coupling between secondary alkyl iodides and diarylmanganese reagents catalyzed by $CoCl_2 \cdot 2LiCl$ and performed in the absence of any additional ligand.



Scheme 34. Cobalt-catalyzed cross-coupling reactions of various organometallic reagents with alkyl iodide **70a**.

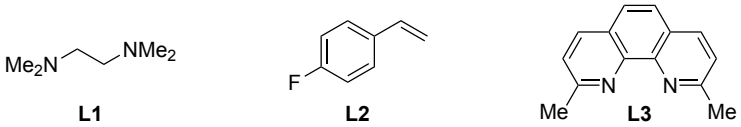
[49] a) T. J. Korn, G. Cahiez, P. Knochel, *Synlett* **2003**, 1892. b) T. J. Korn, M. A. Schade, M. N. Cheemala, S. Wirth, S. A. Guevara, G. Cahiez, P. Knochel, *Synthesis* **2006**, 3547.

Table 8. Reaction conditions optimization of the cross-coupling of alkyl iodide **70a** with the manganese reagent **72a**.



70a **71a**

entry	catalyst	ligand[a]	yield (%)[b]
1	$Co(acac)_2$	-	54
2	$Co(acac)_3$	-	82
3	$CoBr_2$	-	73
4	$CoCl_2$	-	79
5	$CoCl_2$·2LiCl	-	83 (75)[c]
6	$CoCl_2$·2LiCl[d]	-	64
7	$CoCl_2$·2LiCl	**L1**	32
8	$CoCl_2$·2LiCl	**L2**	32
9	$CoCl_2$·2LiCl	**L3**	11
10	$PdCl_2$	-	2
11	$CuCl_2$	-	3
12	$CrCl_2$	-	3
13	$NiCl_2$	-	7
14	$FeCl_2$	-	26



L1 **L2** **L3**

[a] Using 40% of the ligand. [b] Calibrated GC yield using undecane as internal standard. [c] Isolated yield. [d] Using 10% $CoCl_2$·2LiCl.

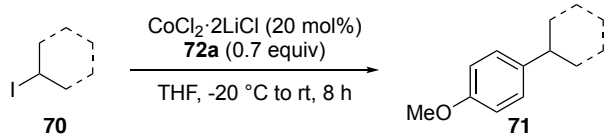
Thus, preliminary experiments have shown that the cross-coupling between the secondary alkyl iodide **70a** and *p*-anisylmagnesium bromide (**25a**) proceeds in the presence of 20 mol% $CoCl_2$·2LiCl in THF at -20 to 25 °C (8 h) to produce the substitution product **71a** in only 40% yield due to extensive homo-coupling side reactions. However, we found that by replacing **25a** with the corresponding dianisylmanganese reagent (**72a**) prepared by the transmetallation of **25a** with $MnCl_2$·2LiCl[50] (0.5 equiv), the same cross-coupling now produces **71a** in 75% isolated

[50] *Butyl Manganese Chloride and Related Reagents in Encyclopedia of Reagents for Organic Synthesis*, (Eds.: G. Cahiez, L. Paquette), Wiley-VCH, Chichester, **1995**.

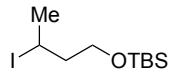
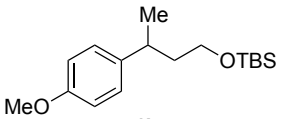
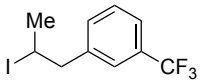
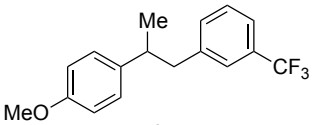
yield (Scheme 34). Remarkably, we did not observe rearrangement products (branched to unbranched) during these couplings.[51]

This encouraging result led us to examine the scope of this cross-coupling more extensively (Table 8). $CoCl_2$·2LiCl was the preferred catalyst since $Co(acac)_2$, $Co(acac)_3$, $CoBr_2$ and $CoCl_2$ gave inferior yields (entries 1-4). The use of 10 mol% $CoCl_2$·2LiCl instead of 20 mol%, reduced the yield of **71a** to 64% (compare entries 5 and 6). Attempts to improve the reaction by adding ligands such as TMEDA (**L1**),[30b] 4-fluorostyrene (**L2**),[31] or neocuproine (**L3**)[5a] did not improve the reaction yield (entries 7-9). Also alternative transition metal salts such as $PdCl_2$, $CuCl_2$, $CrCl_2$, $NiCl_2$ or $FeCl_2$ were inefficient (entries 10-14). A solvent screening showed that THF was the best solvent when compared to NMP, DMPU, DME, 1,4-dioxane and *t*-BuOMe.

Table 9. Cobalt-catalyzed cross-coupling reactions between various secondary alkyl iodides of type **70** and the diarylmanganese reagent **72a**.

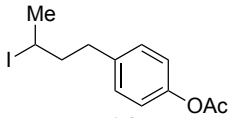
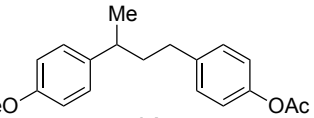
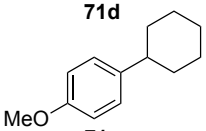
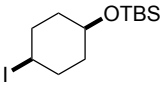
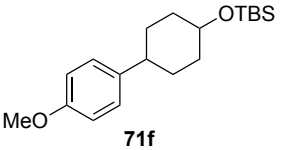
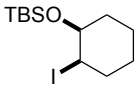
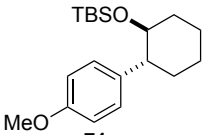
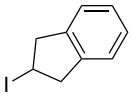
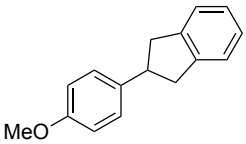
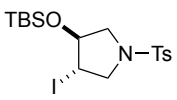
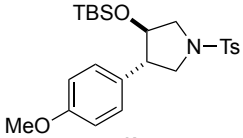


70 **71**

entry	electrophile	product	yield (%) dr
1	 **70b**	 **71b**	73% (63%)[a]
2	 **70c**	 **71c**	77%

[51] a) K. Tamao, Y. Kiso, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, 94, 9268. b) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc.* **1984**, 106, 158. c) A. Joshi-Pangu, M. Ganesh, M. R. Biscoe, *Org. Lett.* **2011**, 13, 1218. d) J. T. Binder, C. J. Cordier, G. C. Fu. *J. Am. Chem. Soc.* **2012**, 134, 17003.

Table 9 continued

3	 **70d**	 **71d**	75%
4	 **70e**	 **71e**	84% (81%)[a]
5	 **70f** (dr 99:1)	 **71f**	75%[b]
6	 **70g** (dr 75:25)	 **71g**	83% 99:1
7	 **70h**	 **71h**	70%
8	 **70i** (dr 99:1)	 **71i**	59% 95:5

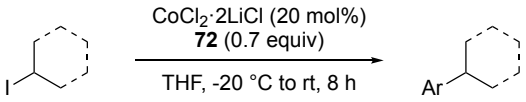
[a] $CoCl_2$ (20 mol%) was used instead of $CoCl_2 \cdot 2LiCl$. [b] dr ca. 70:30 *cis/trans*.

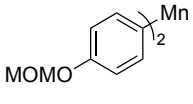
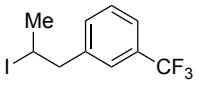
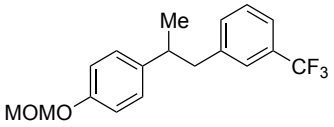
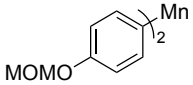
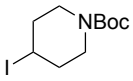
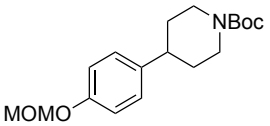
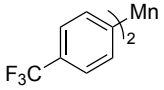
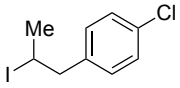
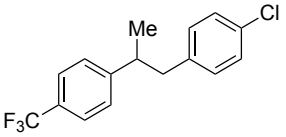
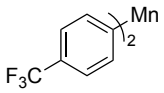
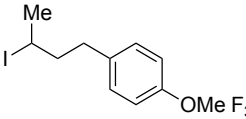
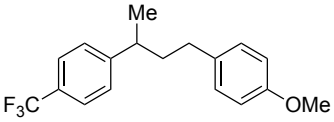
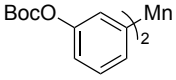
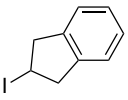
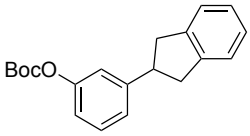
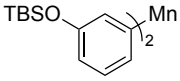
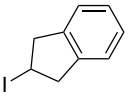
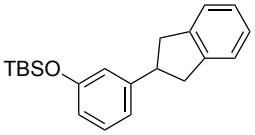
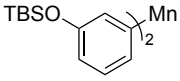
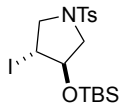
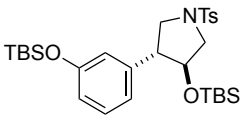
These cobalt-catalyzed alkylations proved to be general and the cross-coupling between the dianisylmanganese reagent (**72a**) and various secondary alkyl iodides has been successfully performed (Table 9).[52] Thus, various secondary alkyl iodides bearing a range of various functional groups (OTBS, CF_3, OAc; **70b-d**) reacted with the dianisylmanganese reagent (**72a**) providing the expected products **71b-d** in 73-77% yield (entries 1-3). Also, various cyclohexyl iodides underwent the cross-coupling with **72a** yielding the desired arylated products **71e-g** in 75-84% yield. Additionally, this cross-coupling can be performed with cyclopentyl iodides **70h-i**, leading to the expected products **71h** and **71i** in 59-70% yield (entries 7-8). When a TBSO

[52] Using primary or tertiary alkyl halides did not lead to a good conversion.

substituent was present in position 2 to the carbon-iodide bond, excellent diastereoselectivities were observed (dr up to 99:1, see entries 6 and 8).[53]

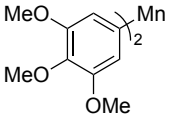
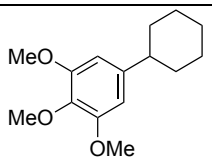
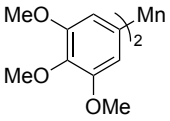
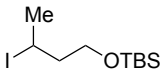
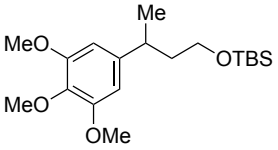
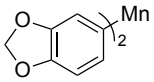
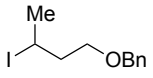
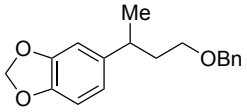
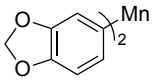
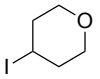
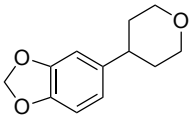
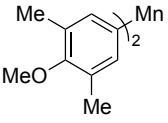
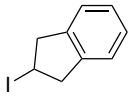
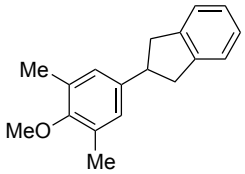
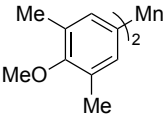
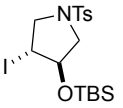
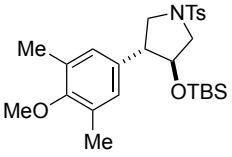
Table 10. Cobalt-catalyzed cross-couplings of diaryl manganese reagents of type **72** with secondary alkyl iodides of type **70**.



entry	manganese reagent	substrate	product / yield (%) / dr
1	 **72b**	 **70c**	 **71j**: 76%
2	 **72b**	 **70j**	 **71k**: 75%
3	 **72c**	 **70a**	 **71l**: 81%
4	 **72c**	 **70k**	 **71m**: 87%
5	 **72d**	 **70h**	 **71n**: 76%
6	 **72e**	 **70h**	 **71o**: 74%
7	 **72e**	 **70i** (dr 99:1)	 **71p**: 92%, dr 99:1

[53] The use of TIPS-protected 2-iodocyclohexanol led to a similar diastereoselectivity (dr 95:5) whereas protection with the bulky TBDPS-group resulted in a decreased diastereoselectivity (dr 90:10).

Table 10 continued

8			
	72f	**70e**	**71q**: 80% (48%)[a]
9			
	72f	**70b**	**71r**: 60% (19%)[a]
10			
	72g	**70l**	**71s:** 66%
11			
	72g	**70m**	**71t**: 70%
12			
	72h	**70h**	**71u**: 63%
13			
	72h	**70i** (dr 99:1)	**71v**: 82%, dr 99:1

[a] $CoCl_2$ (20 mol%) was used instead of $CoCl_2 \cdot 2LiCl$.

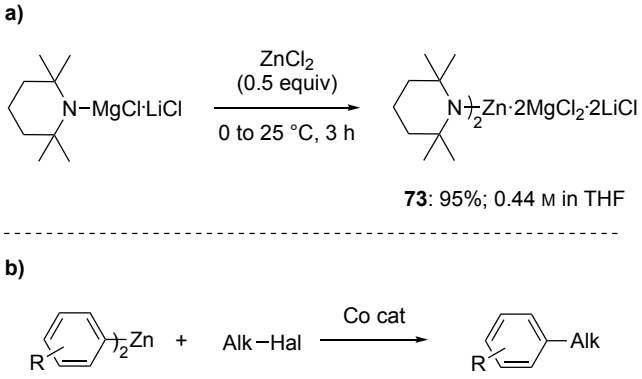
Furthermore, a range of functionalized diarylmanganese reagents could also be readily used in this reaction (Table 10). (*p*-MOMO-C_6H_4)$_2$Mn (**72b**) reacted smoothly with the alkyl iodides **70c** and **70j**, leading to the arylated products **71j-k** in 75-76% yield (entries 1-2). The coupling of the electron poor manganese reagent **72c** with **70a** or **70k** afforded the cross-coupling products **71l-m** in 81-87% yield (entries 3-4). Interestingly, the manganese reagents bearing an OBoc- (**72d**) or an OTBS-group (**72e**) were well tolerated and the cross-coupling with **70h** and **70i** (dr = 99:1) led to the desired products **71n-p** in 74-92% yield (entries 5-7). Moreover, the electron rich

diarylmanganese reagent **72f** was readily coupled with the cyclic alkyl iodides **70e** and **70b** to provide the corresponding arylated products **71q-r** in 60-80% yield. The cross-coupling of **70l** or **70m** with the di(1,3-benzodioxol-5-yl)manganese reagent (**72g**) afforded the arylated compounds **71s-t** in 66-70% yield (entries 10-11). Also, the di(4-methoxy-3,5-dimethylphenyl)manganese reagent (**72h**) was successfully coupled with **70h** and **70i** (dr = 99:1), leading to the desired products **71u-v** in 63-82% yield (entries 12-13). For the diarylmanganese reagents **72e** and **72h** using the protected heterocyclic iodohydrine **70i** (dr = 99:1) we also observed excellent diastereoselectivities (dr = 99:1, see entries 7 and 13).

4. Cobalt-Catalyzed Negishi Cross-Coupling Reactions of (Hetero)Arylzinc Reagents with Primary and Secondary Alkyl Bromides and Iodides

4.1. Introduction

Transition metal-catalyzed cross-coupling reactions are valuable tools for the syntheses of biologically active molecules. Recently, cross-coupling reactions with cobalt catalysts were found to be a valuable alternative, when compared to Pd or Ni catalysts.[1] However, despite the advances of cobalt-catalyzed cross-couplings between Csp^2 and Csp^3 centers by using magnesium reagents,[15,19,29] no Co-catalyzed Negishi-type coupling reactions using arylzinc reagents have been described.



Scheme 35. Metalation reaction using TMP_2Zn (**73**) and cobalt-catalyzed cross-coupling of the diarylzinc species. ($MgCl_2$ and LiCl are omitted for the sake of clarity)

Knochel and co-workers have reported a range of synthetic methods for the preparation of polyfunctional unsaturated zinc reagents.[54] In particular, the directed metalation[55] of polyfunctional heterocycles and aromatic substrates has a broad reaction scope, and sterically

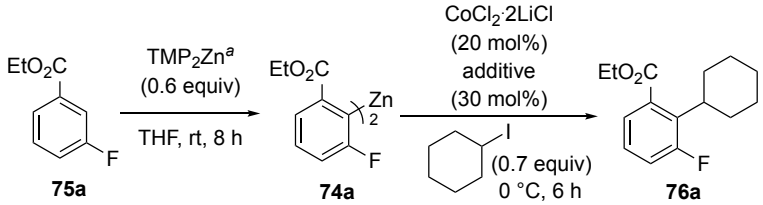
[54] a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302. b) T. Klatt, J. T. Markiewicz, C. Saemann, P. Knochel, *J. Org. Chem.* **2014**, *79*, 4253.

[55] a) P. Beak, R. A. Brown, *J. Org. Chem.* **1982**, *47*, 34. b) P. Beak, A. Tse, J. Hawkins, C. W. Chen, S. Mills, *Tetrahedron* **1983**, *39*, 1983. c) Y. Zhao, V. Snieckus, *J. Am. Chem. Soc.* **2014**, *136*, 11224. d) K. Groom, S. M. S. Hussain, J. Morin, C. Nilewski, T. Rantanen, V. Snieckus, *Org. Lett.* **2014**, *16*, 2378.

hindered bases,[56] such as $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**), have given a straightforward entry to a range of unsaturated and highly reactive diorganozinc compounds. In order to establish a cobalt-catalyzed Negishi cross-coupling it has been envisioned that diarylzinc reagents prepared by a directed C-H zincation using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**) can be employed in a cross-coupling reaction with various primary and secondary alkyl halides (Scheme 35).

4.2. Cobalt-Catalyzed Aryl-Alkyl Cross-Coupling Reactions

Table 11. Optimization of the reaction conditions for the Co-catalyzed cross-coupling.



entry	metal mediator (mol%)	additive (mol%)	yield (%)[b]
1	$FeCl_2$ (20)	4-fluorostyrene (50)	0
2	$FeCl_2$ (20)	TMEDA (30)	13
3	$Co(acac)_2$ (20)	4-fluorostyrene (50)	0
4	$Co(acac)_2$ (20)	TMEDA (30)	18
5	$CoCl_2$ (20)	4-fluorostyrene (50)	42
6	$CoCl_2$ (20)	TMEDA (30)	84
7	$CoCl_2{\cdot}2LiCl$ (20)	TMEDA (30)	94 (87)[c]
8	$CoCl_2{\cdot}2LiCl$ (20)	4-fluorostyrene (30)	38
9	$CoCl_2{\cdot}2LiCl$ (20)	**L4** (30)	40
10	$CoCl_2{\cdot}2LiCl$ (10)	TMEDA (30)	33

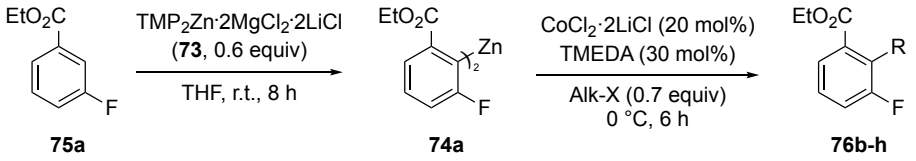
[a] $MgCl_2$ and LiCl are omitted for the sake of clarity. [b] Determined by GC using undecane as an internal standard. [c] Yield of isolated product. **L4** = *trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine.

[56] a) D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2006**, *45*, 3775. b) A. J. Martinez-Martinez, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, *Science* **2014**, *346*, 834.

In preliminary experiments, we have examined the cross-coupling of the diarylzinc reagent (**74a**) which was generated by a directed metalation of ethyl 3-fluorobenzoate (**75a**) [57] using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.6 equiv) with *c*-Hex-I in the presence of various metal catalysts (Table 11).

The addition of the zinc species to *c*-Hex-I in the presence of $Co(acac)_2$ or $FeCl_2$[18] resulted in the exclusive formation of the protonated zinc species when using 4-fluorostyrene (50 mol%) as an additive (Table 11, entries 1 and 3).[63a] Moderate yields of **76a** (13-18%) were obtained using TMEDA (30 mol%) as a ligand (entries 2 and 4). Switching to $CoCl_2$ (20 mol%) and 4-fluorostyrene (50 mol%) or TMEDA (30 mol%) in THF at 0 °C furnished the desired cross-coupling product **76a** in 42% and 84% yield, respectively (entries 5 and 6). Significant improvements were achieved by using the THF-soluble salt $CoCl_2{\cdot}2LiCl$ (20 mol%)[36] and TMEDA (30 mol%), which afforded the desired coupling product **76a** in 94% yield (entry 7). Further variation of the ligand[30b] or lowering the amount of the catalyst loading from 20 mol% to 10 mol% led only to a decrease in the yield (entries 7-10).

With these optimized reaction conditions in hand, we have performed a range of alkylations using various primary and secondary alkyl halides to afford alkylated benzoates of type **76** (Scheme 36).



Scheme 36. Zincation of ethyl 3-fluorobenzoate (**75a**) and cobalt-catalyzed cross-coupling with alkyl halides.

[57] As a consequence of its electron-acceptor properties, the fluoro-substituent facilitates the zincation, as well as the cobalt-catalyzed cross-coupling reaction and therefore ethyl 3-fluorobenzoate was chosen as the model substrate.

Table 12. Scope of various primary and secondary alkyl iodides or bromides.

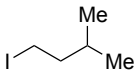
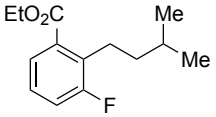
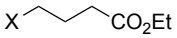
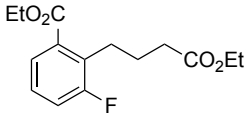
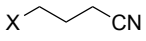
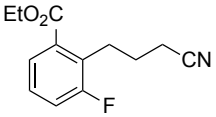
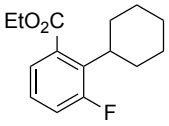
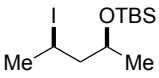
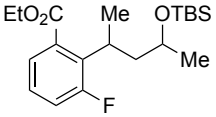
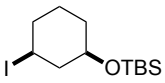
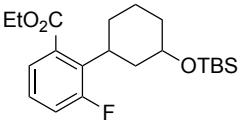
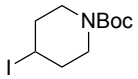
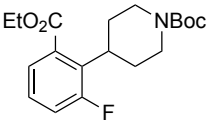
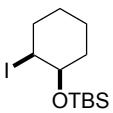
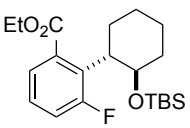
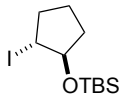
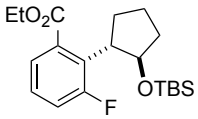
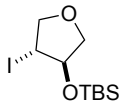
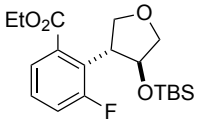
entry	Alk-X	product / yield (%)[a]
1		 **76b**: 63%
2		 **76c**: 58% (X = I) 38% (X = Br)
3		 **76d**: 71% (X = I) 51% (X = Br)
4		 **76a**: 61% (X = Br) 2% (X = Cl)[b]
5	 dr 99:1	 **76e**: 70%, dr 50:50
6	 dr 75:25	 **76f**: 79%, dr 50:50
7		 **76g**: 79%
8	 dr 75:25	 **76h**: 68%, dr 99:1

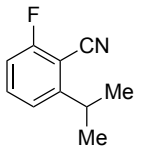
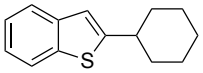
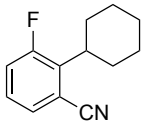
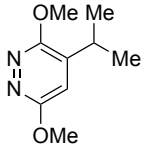
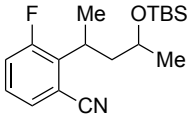
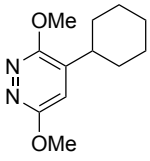
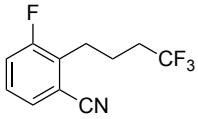
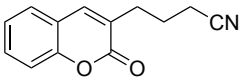
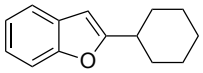
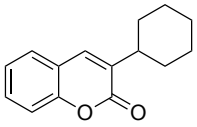
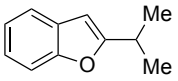
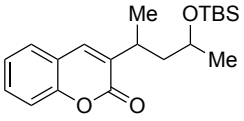
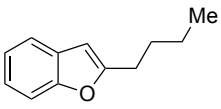
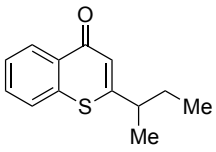
Table 12 continued

9		
	dr 99:1	**76i**: 69%, d.r. 99:1
10		
	dr 99:1	**76j**: 55 %, d.r. 99:1

[a] Isolated yield of analytically pure product. [b] The yield was determined by GC using $C_{11}H_{24}$ as an internal standard.

The reaction of the zincated species **74a** with primary alkyl iodides led to the polyfunctional alkylated benzoates (**76a**-**c**) in 58-77% yield (Table 12, entries 1-3). Remarkably, the *ortho*,*ortho'* substituents present in the diarylzinc species (**74a**) did not disturb the cross-coupling and most of the reactions were complete within 6 h at 0 °C. Primary alkyl bromides have also been successfully coupled, but with somewhat lower yields (entries 2-4), whereas cyclohexyl chloride only gave trace amounts of the desired product **76a** (compare entry 4). Functional groups, such as an ester or a nitrile, are well-tolerated in these cross-coupling reactions and products such as **76c-d** were isolated. Interestingly, also secondary alkyl iodides reacted smoothly to provide the alkylation products **76a**,**e**-**j** in 55-79% yield (entries 4-10). To our delight, no rearrangement products were observed (branched to unbranched; see entry 5 and Table 13).[51] When an oxygen substituent was present in α-position of the carbon-iodine bond, excellent diastereoselectivities were observed (dr up to 99:1, see entries 8-10) and the products **76h**-**j** were isolated in 55-69% yield. Additionally, this cross-coupling can also be performed with heterocyclic alkyl iodides, thereby leading to the expected products **76g** and **76j** in 79% and 55% yield, respectively (see entries 7 and 10).

Table 13. Cobalt-catayzed cross-coupling of various diaryl- and diheteroarylzinc reagents with alkyl iodides.

entry	product / yield (%)[a]	entry	product / yield (%)[a]
1	 **77a**: 81%	8	 **77h**: 72%
2	 **77b**: 84%	9	 **77i**: 69%
3	 **77c**: 63%[b]	10	 **77j**: 61%
4	 **77d**: 52%	11	 **77k**: 76%
5	 **77e**: 71%	12	 **77l**: 66%
6	 **77f**: 61%	13	 **77m**: 88%[b]
7	 **77g**: 63%	14	 **77n**: 51%

[a] Isolated yield of analytically pure product. [b] The starting material was 99:1 *syn*/*anti*, the product was ca. 50:50 *syn*/*anti*.

The reaction scope of this Co-catalyzed alkylation is quite broad and a range of diarylzinc reagents prepared by a directed deprotonation using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.6 equiv) provided the isolated alkylated products **77a**-**n** in 51–88% yield (Table 13). Thus, this sequential one-pot metalation/cross-coupling procedure could be extended to other 1,3-disubstituted aromatic compounds: the zincation of 2-fluorobenzonitrile or 3-fluorobenzonitrile using **73** (0.6 equiv) proceeds within 12 h at 25 °C, and the subsequent coupling reactions with secondary alkyl iodides provides the desired products **77a**-**d** in 52-84% yield (entries 1-4). Remarkably, diheteroarylzinc reagents generated by directed zincation using **73** also undergo the alkylation reactions in good yields to afford the expected products **77e**-**n** (51-88% yield, entries 5-14). Thus, zincated benzofurans or benzothiophenes reacted with secondary alkyl iodides such as *c*-Hex-I, *i*-Pr-I, or *n*-Bu-I to furnish the corresponding cross-coupling products **77e-h** in 61-76% yield (entries 5-8).

The metalation of benzofuran with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.6 equiv) was complete within 12 h at 25 °C, thereby providing the corresponding zinc reagent. This species undergoes the Co-catalyzed cross-coupling with *n*-Bu-I to afford the substituted benzofuran **77g** in 63% yield (entry 7). This alkylated benzofuran (**77g**) is a key intermediate for the synthesis of amiodarone, an active antiarrhythmic agent.[58] Similarly, 3,6-dimethoxypyridazine was zincated using **73** (0.6 equiv, 4 h, 25 °C), and the cross-coupling with 2-iodopropane or *c*-Hex-I afforded the desired polyfunctional hetereocycles **77i-j** in 69% and 61% yield, respectively (entries 9-10). Coumarin is also an excellent substrate and its zincation is complete within 1 h at 25 °C. After alkylation with various primary and secondary alkyl iodides, the substituted coumarins **77k-n** were obtained in up to 88% yield (entries 11-13). Similarly, the regioselective zincation of thiochromone (-40 °C, 1 h) at the α-position to sulfur followed by a Co-catalyzed alkylation with 2-iodobutane led to the desired product **77n** in 51% yield (entry 14).

[58] a) H. R. Ha, B. Stieger, G. Grassi, H. R. Altorfer, F. Follath, *Eur. J. Clin. Pharmacol.* **2000**, *55*, 807. b) M. Witczak, H. Kwiecien, *Synth. Commun.* **2005**, *35*, 2223. c) K. M. Zareba, *Drugs Today* **2006**, *42*, 75.

5. Mild Cobalt-Catalyzed Negishi Cross-Couplings of (Hetero)Arylzinc Reagents with (Hetero)Aryl Halides

5.1. Introduction

To date, the Negishi cross-coupling has attracted a lot of attention since a wide range of polyfunctional zinc reagents are available[59] and transmetalations with transition metal catalysts are fast and efficient. Mostly, Pd- and Ni-catalysts have been used to perform such Csp^2-Csp^2 cross-couplings, however, toxicity[3] and price[2] issues have led to the search of alternative metal catalysts, such as cobalt[5] and iron.[60] Bedford has demonstrated that iron(I)-complexes allow to achieve Negishi cross-couplings with great efficiency.[61] Gosmini has shown in one-pot procedures that organozinc reagents can be *in situ* generated and cross-coupled with heteroaryl halides.[9] Interestingly, Yoshikai has reported impressive organometallic cascade reactions, where arylzincs are generated *via* Co-catalysis, followed by cross-coupling with aryl iodides in the presence of a Pd-catalyst.[62] Also, Hayashi and Nishimura have reported novel cobalt-catalyzed asymmetric Csp^2-Csp-couplings.[63]

In the previous section, we have shown that Csp^2-Csp^3 couplings between arylzinc reagents that are prepared *via* directed metalation, undergo smooth cross-couplings with primary and secondary alkyl bromides and iodides.[64] Although, this method proceeds under mild conditions, a limited scope concerning the nature of the arylzinc reagent was observed and extension to Csp^2-Csp^2 couplings under the reported reaction conditions was difficult.

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[59] For a general overview on the generation of organometallics reagents, see: a) *Handbook of Functionalized Organometallics: Applications in Synthesis* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2004**. For representative examples, see: b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358. c) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107.

[60] For selected reviews on iron-catalyzed reactions, see: a) C. Bolm, *Nature Chem.* **2009**, 1, 420. b) A. Fürstner, *Angew. Chem. Int. Ed.* **2009**, *48*, 1364. c) W. M. Czaplik, M. Mayer, J. Cvengroš, A. Jacobi von Wangelin, *ChemSusChem* **2009**, *2*, 396. d) E. Nakamura, N. Yoshikai, *J. Org. Chem.* **2010**, 75, 6061.

[61] For representative examples, see a) C.J. Adams, R. B. Bedford, E. Carter, N. J. Gower, M. F. Haddow, J. N. Harvey, M.Huwe, M. Ángeles Cartes, S. M. Mansell, C. Mendoza, D. M. Murphy, E. Neeve, J. Nunn, *J. Am. Chem. Soc.* **2012**, *134*, 10333. b) R. B. Bedford, E. Carter, P. M. Cogswell, N. J. Gower, M. F. Haddow, J. N. Harvey, D. M. Murphy, E. C. Neeve, J. Nunn, *Angew. Chem. Int. Ed.* **2013**, *52*, 1285.

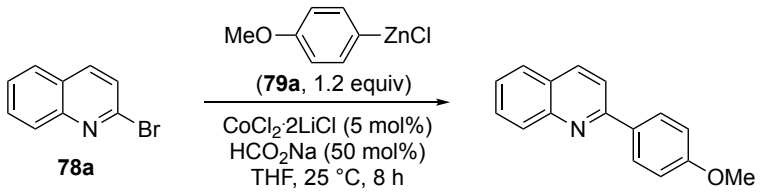
[62] B.-H. Tan, J. Dong, N. Yoshikai, *Angew. Chem. Int. Ed.* **2012**, *51*, 9610.

[63] a) T. Sawano, K. Ou, T. Nishimura, T. Hayashi, *Chem. Commun.* **2012**, *48*, 6106. b) T. Sawano, K. Ou, T. Nishimura, T. Hayashi, *J. Org. Chem.* **2013**, *78*, 8986.

[64] J. M. Hammann, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 4478.

5.2. Cobalt-Catlyzed Aryl-Aryl Cross-Coupling Reactions

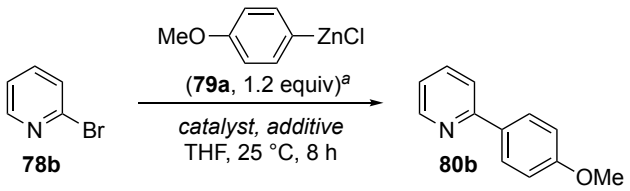
Herein, we report a new set of reaction conditions allowing for the smooth cross-coupling of various arylzinc reagents with aryl and heteroaryl chlorides or bromides within a few hours at room temperature. Thus, in a preliminary experiment, we have treated 2-bromoquinoline (**78a**) with *p*-anisylzinc chloride (**79a**, 1.2 equiv) in the presence of 5 mol% $CoCl_2{\cdot}2LiCl$ and observed a complete conversion to the desired cross-coupling product (**80a**) in 65% yield. However, the cross-coupling was too slow and side-reactions, such as homocouplings are observed. To improve the reaction outcome, our attention was attracted by the recent work of Miller, who showed that the addition of potassium formate played the role of a mild reducing agent in Suzuki reactions.[65] We anticipated that this salt could generate reduced cobalt species to which we attribute high catalytic activity. To our delight, the addition of HCO_2Na (50 mol%) led to an improved isolated yield of 88% (Scheme 37).



Scheme 37. Cobalt-catalyzed cross-coupling of 2-bromoquinoline (**78a**) and *p*-anisylzinc chloride (**80a**) with and without sodium formate.

[65] W. D. Miller, A. H. Fray, J. T. Quatroche, C. D. Sturgill, *Org. Process Res. Dev*. **2007**, *11*, 356.

Table 14. Optimization of the reaction conditions for the Co-catalyzed Csp^2-Csp^2 cross-coupling of 2-bromopyridine (**78b**).



entry	catalyst (5 mol%)	additive (50 mol%)	yield (%)[b]
1	$CoCl_2$	-	82
2	$CoCl_2$[c]	-	76
3	$CoBr_2$	-	78
4	$Co(acac)_2$	-	72
5	$Co(acac)_3$	-	80
6	$CoCl_2$·2LiCl	-	81
7	$CoCl_2$·2LiCl	HCO_2Na	94 (87)[d]
8	$CoCl_2$·2LiCl	PivONa	96
9	$CoCl_2$·2LiCl	DMPU	84
10	$CoCl_2$·2LiCl	TMEDA	51
11	$Co(acac)_3$	HCO_2Na	89
12	-	HCO_2Na	0
13	$CrCl_2$	-	traces
14	$FeCl_2$	-	17

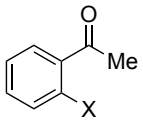
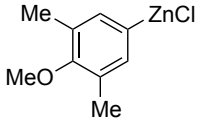
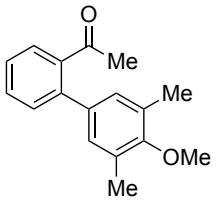
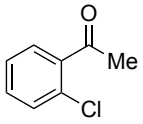
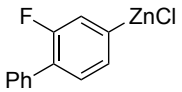
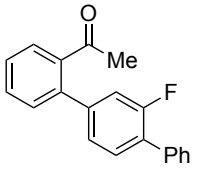
[a] $MgCl_2$ and LiCl are omitted for sake of clarity. [b] Undecane was used as an internal standard. [c] 99.99% purity. [d] Isolated yield.

Preliminary mechanistic studies showed that the main effect of HCO_2Na is to considerably reduce the occurrence of side reactions, thus, as anticipated, leading to more selective cross-couplings and higher reaction yields.[66] This effect proved to be general, and a broader screening of reaction conditions using 2-bromopyridine (**78b**) showed that cobalt halides, such as $CoCl_2$ or $CoBr_2$, as well as $Co(acac)_2$, and $Co(acac)_3$ gave good results (Table 14, entries 1-5). In particular, $CoCl_2$·2LiCl, which is conveniently soluble in THF, afforded product **80b** in excellent yield in the presence of HCO_2Na (entry 6-7). Interestingly, when sodium pivalate (*t*-$BuCO_2Na$ = PivONa) was used as an additive, the reaction was equally efficient, showing that

[66] Premixing of $CoCl_2$·2LiCl and HCO_2Na in THF using the same stoichiometry as in the standard reaction led to the same reaction outcome as the one-pot procedure (also, compare table 9, entry 7).

HCO_2Na does not act as a reducing agent, but rather as a ligand (entry 8).[67] Control experiments using ultrapure $CoCl_2$ (99.99%) confirmed that the Co salts are the active catalysts and that metal impurities do not play a role (compare with entry 2). Polar solvents, such as *N,N'*-dimethylpropylene urea (DMPU), or the use of a typical additive, such as TMEDA, did not improve the reaction outcome (entries 9-10). The use of $Co(acac)_3$ instead of $CoCl_2 \cdot 2LiCl$ was not advantageous (entry 11). Furthermore, we confirmed that HCO_2Na alone did not catalyze this coupling by additional metal impurities (entry 12). Additional control experiments indicated that Cr[35] and Fe[68] salts are not good catalysts for this reaction (entries 13-14).

Table 15. Co-catalyzed cross-coupling reactions between 2-chlorinated aromatic ketones and arylzinc reagents.

entry	electrophile	zinc reagent	product / yield (%)[a]
1	 **78c** (X = Cl) **78d** (X = Br)	 **79b**	 **81a:** 65% (X = Cl) **81b:** 74% (X = Br)
2	 **78c**	 **79c**	 **81c:** 67%

[67] We propose that the halide ligands in $CoCl_2 \cdot 2LiCl$ are replaced by carboxylate ligands (HCO_2^-), which provides a more selective cobalt catalyst. In fact, halide ligands mostly lead to tetrahedral coordination (see, for example: N. S. Gill, F. B. Taylor, *Inorg. Synth.* **1967**, *9*,136), whereas carboxylate ligands lead to an octahedral coordination (see, for example: a) A. Kaufmann, C. Afshar, M. Rossi, D. E. Zacharias, J. P. Glusker*, Struct. Chem.* **1993**, *4*, 191; b) G. Aromí, A. S. Batsanov, P. Christian, M. Helliwell, A. Parkin, S. Parsons, A. A. Smith, G. A. Timco, R. E. P. Winpenny, *Chem. Eur. J.* **2003**, *9*, 5142). Furthermore, whereas $CoCl_2 \cdot 2LiCl$ in THF is a blue solution, the addition of HCO_2Na leads to a pink solution, which is typical for a coordination change.

[68] a) O. M. Kuzmina, A. K. Steib, D. Flubacher, P. Knochel, *Org. Lett.* **2012**, *14*, 4818. b) T. C. Atack, R. M. Lecker, S. P. Cook *J. Am. Chem. Soc.* **2014**, *136*, 9521. c) T. Agrawal, S. P. Cook *Org. Lett.* **2014**, *16*, 5080.

Table 15 continued

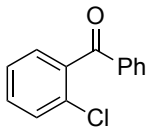
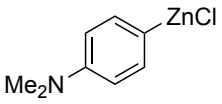
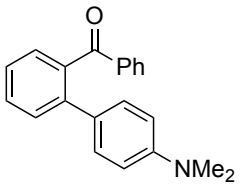
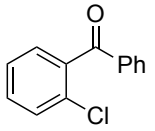
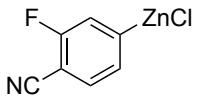
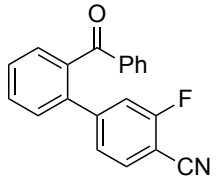
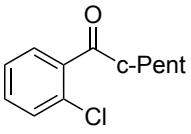
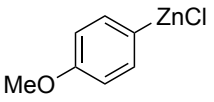
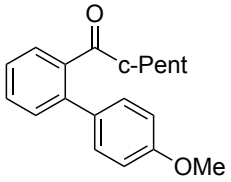
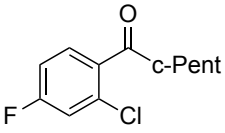
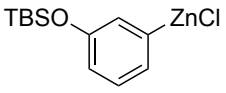
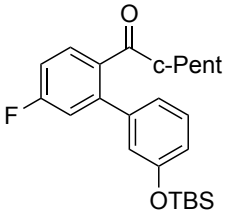
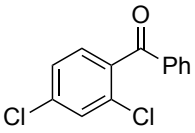
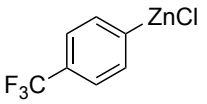
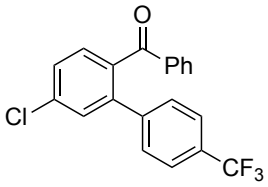
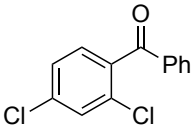
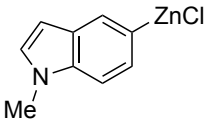
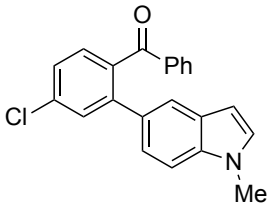
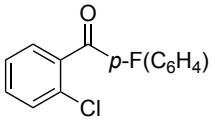
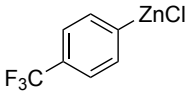
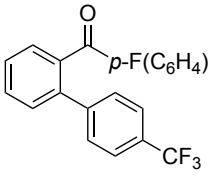
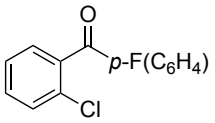
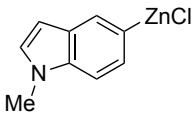
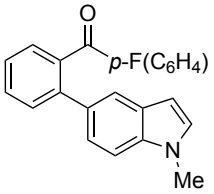
3	 **78e**	 **79d**	 **81d:** 73%
4	 **78e**	 **79e**	 **81e:** 98%
5	 **78f**	 **79a**	 **81f:** 76%
6	 **78g**	 **79f**	 **81g:** 68%
7	 **78h**	 **79g**	 **81h:** 89%
8	 **78h**	 **79h**	 **81i:** 61%

Table 15 continued

9	 **78i**	 **79g**	 **81j:** 73%
10	 **78i**	 **79h**	 **81k:** 62%

[a] Yield of isolated product.

The reaction scope of this cross-coupling proved to be quite broad. Thus, 2-halogenated functionalized aceto- and benzophenones (**78c-j**) undergo the cobalt-catalyzed cross-coupling with a range of aryl- and heteroarylzinc reagents (**79a-h**), yielding the corresponding polyfunctionalized ketones (**81a-k**) in 61-98% yield (Table 15). 2-Chloro- or 2-bromoacetophenone (**78c-d**) react with zinc reagents bearing various functional groups, such as F or MeO, providing the expected products (**81a-c**) in 65-74% yield (entries 1–2). Interestingly, a dimethylamino substituent or a cyano group were well tolerated in the zinc reagents (**79d-e**), as they reacted with 2-chlorobenzophenone (**78e**) to give the products **81d** and **81e** in 73–98% yield (entries 3-4). Remarkably, various other 2-chlorinated aromatic ketones (**78f-j**) undergo the cross-coupling with both, electron-rich and -poor substituted arylzinc reagents, leading to the desired products **81f-81k** in 61-89% yield (entries 5-10). Also, heterocyclic zinc reagents, such as **79h**, provided the new ketones **81i** and **81k** in 61-62% yield (entries 8 and 10).

Table 16. Co-catalyzed cross-coupling reactions between 2-chloropyridines and arylzinc reagents.

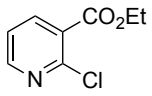
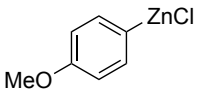
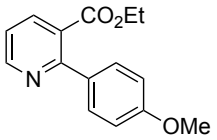
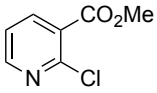
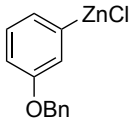
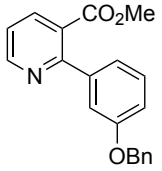
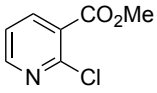
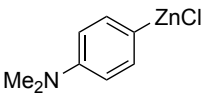
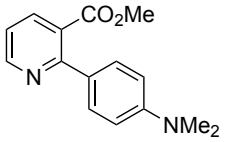
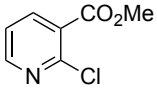
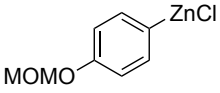
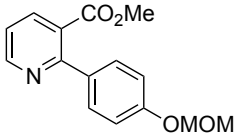
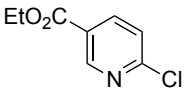
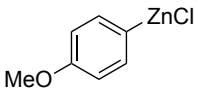
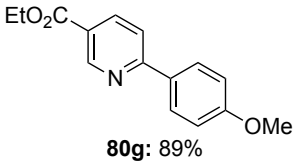
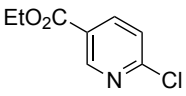
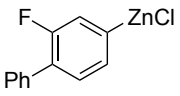
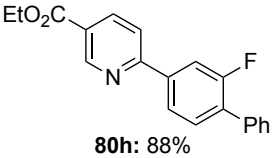
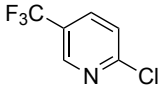
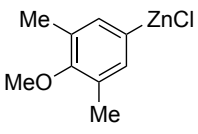
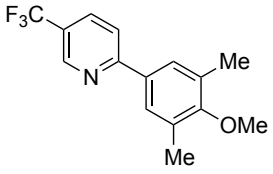
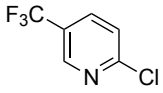
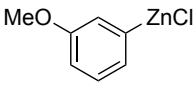
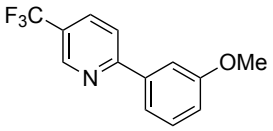
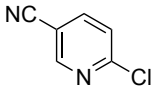
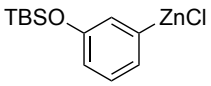
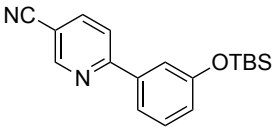
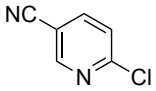
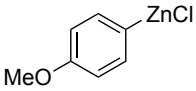
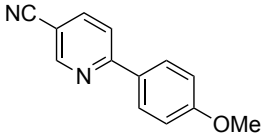
entry	electrophile	zinc reagent	product / yield (%)[a]
1	 **78k**	 **79a**	 **80c:** 70%
2	 **78l**	 **79i**	 **80d:** 71%
3	 **78l**	 **79d**	 **80e:** 91%
4	 **1m**	 **79j**	 **80f:** 60%
5	 **78n**	 **79a**	 **80g:** 89%
6	 **78n**	 **79c**	 **80h:** 88%
7	 **78o**	 **79b**	 **80i:** 86%

Table 16 continued

8	 **78o**	 **79k**	 **80j:** 73%
9	 **78p**	 **79f**	 **80k:** 84%
10	 **78p**	 **79a**	 **80l:** 84%

[a] Yield of isolated product.

Additionally, a range of 2,3-disubstituted-*N*-heterocyclic chlorides can be readily employed in this protocol (Table 16, entries 1-4). *p*-$MeOC_6H_4ZnCl$ (**79a**) undergoes a smooth cross-coupling with ethyl 2-chloronicotinate (**78k**), leading to the 2,3-disubstituted pyridine **80c** in 70% yield (entry 1). Also, the coupling of electron-rich arylzinc reagents **79i** and **79d** with methyl 2-chloronicotinate (**78l**) afforded the pyridines **80d–e** in 71-91% yield (entries 2-3). Similarly, the cross-coupling of 2-chloronicotinonitrile (**1m**) and a zinc organometallic bearing a OMOM-group (**79j**), led to the desired pyridine **80f** in 60% yield (entry 4). Furthermore, 2,5-disubstituted-*N*-heterocyclic chlorides were also good substrates producing the diarylated pyridines **80g-l** (73-89%; entries 5-10).

Table 17. Co-catalyzed cross-coupling reactions between *N*-hetereocyclic halides and arylzinc reagents.

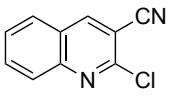
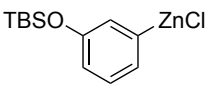
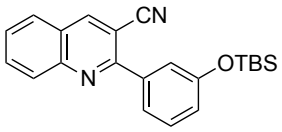
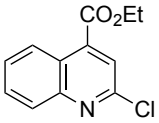
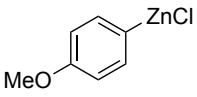
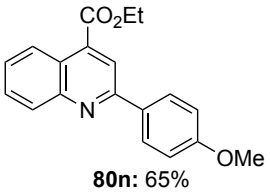
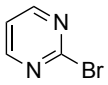
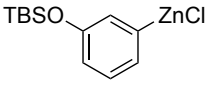
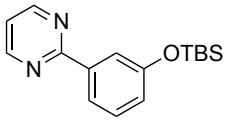
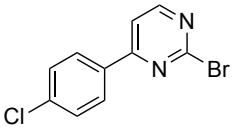
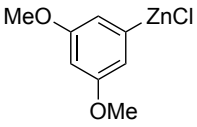
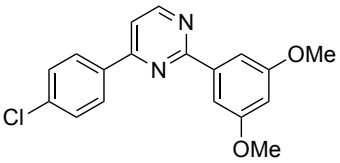
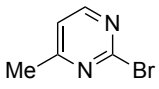
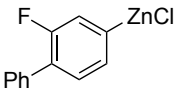
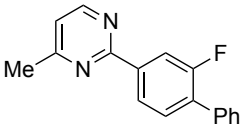
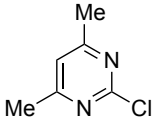
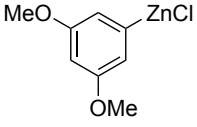
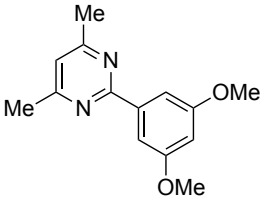
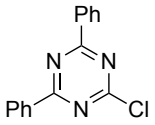
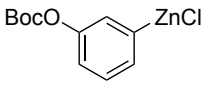
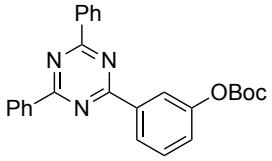
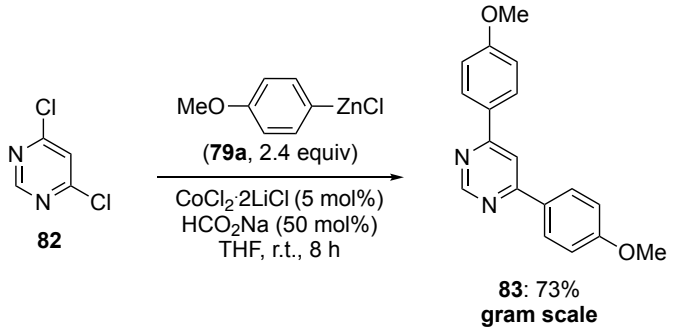
entry	electrophile	zinc reagent	product / yield (%)[a]
1	 **78q**	 **79f**	 **80m:** 92%
2	 **78r**	 **79a**	 **80n:** 65%
3	 **78s**	 **79f**	 **80o:** 92%
4	 **78t**	 **79l**	 **80p:** 86%
5	 **78u**	 **79c**	 **80q:** 76%
6	 **78v**	 **79l**	 **80r:** 65%

Table 17 continued

7			
	78w	**79m**	**80s:** 61%

[a] Yield of isolated product.

Moreover, halogenated quinolines, pyrimidines and triazines also proved to be good substrates for this cross-coupling (Table 17). Substituted quinolines, such as 2-bromoquinoline-3-carbonitrile (**78q**) and ethyl 2-bromoquinoline-4-carboxylate (**78r**), rapidly couple with the zinc organometallics **79a,f** to provide the arylated quinolines in 65-92% yield (**80m-n**; entries 1-2). Pyrimidines, which are common scaffolds found in pharmaceuticals,[69] are readily obtained by the coupling of 2-chloro- or 2-bromopyrimidines (**78s-v**) in 65-92% yield (entries 3–6). Also, triazines are of great importance as building blocks for materials and agrochemicals.[70] The cross-coupling of 2-chloro-4,6-diphenyl-1,3,5-triazine (**78w**) with the arylzinc reagent **79f** leads to the desired product **80s** in 61% yield (entry 7). 4,6-Dichloropyrimidine (**82**) also underwent a coupling reaction with *p*-$MeOC_6H_4ZnCl$ (2.4 equiv, **79a**), affording the arylated compound **83** in 73% isolated yield (Scheme 38).

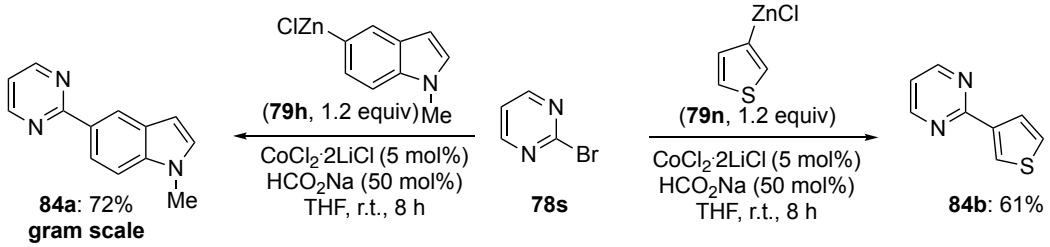


Scheme 38. Co-catalyzed cross-coupling reaction between 4,6-dichloropyrimidine (**82**) and *p*-$MeOC_6H_4ZnCl$ (**79a**).

The synthesis of heteroaryl–heteroaryl cross-coupling products is a challenge. When using Pd or Ni as catalysts, deactivation of the catalyst is often observed owing to chelation of the

[69] M. E Welsch, S. A Snyder, B. R Stockwell, *Curr. Op. Chem. Bio.* **2010**, *14*, 347.
[70] a) H. Zhong, H. Lai, Q. Fang, *J. Phys. Chem.* **2011**, *115*, 2423. b) R. V. Patel, Y.-S. Keum, S. W. Park, *Mini-Rev. Med. Chem.* **2014**, *14*, 768.

reagents with the catalyst.[71] However, the THF-soluble $CoCl_2$·2LiCl-catalyzed reaction (5 mol%) promoted by sodium formate (50 mol%) allows smooth cross-coupling of 2-bromopyrimidine (**78s**) with (1-methyl-1*H*-indol-5-yl)zinc chloride (**79h**) or thiophen-3-ylzinc chloride (**79n**) to afford the heteroaryl compounds **84a-b** in 61-66% isolated yield (Scheme 39).



Scheme 39. Heteroaryl–heteroaryl cross-coupling reactions between 2-bromopyrimidine (**78s**) and hetereoarylzinc organometallics.

[71] a) G. S. Hanan, U. S. Schubert, D. Volkmer, E. Rivière, J.-M. Lehn, N. Kyritsakas, J. Fischer, *Can. J. Chem.* **1997**, *75*, 169. b) C. Kaes, A. Katz, M.W. Hosseini, *Chem. Rev.* **2000**, *100*, 3553. c) S. Bedel, G. Ulrich, C. Picard, P. Tisnès, *Synthesis* **2002**, 1564; d) *Comprehensive Coordination Chemistry II*, Vol. 1 (Eds.: J. A. McCleverty, T. J. Meyer), Elsevier, Oxford, **2004**.

6. A Robust and Broadly Applicable Cobalt-Catalyzed Cross-Coupling of Functionalized Bench-Stable Organozinc Pivalates with Unsaturated Halides

6.1. Introduction

To date, boron organometallics have extensively been used for cross-coupling reactions in medicinal chemistry,[72] allowing late-stage functionalizations of biologically active molecules.[73] Their air and water stability has made boronic esters,[74] boronic acids,[75] as well as trifluoroboronates,[76] highly attractive for the pharmaceutical industry. However, some of these boron derivatives are sensitive or difficult to prepare in high yields and in general require an additional base to achieve satisfactory cross-couplings.[77] In comparison, organozinc reagents display an excellent functional group compatibility and a better reactivity in coupling reactions.[78] No additional base is required and the transmetalation from Zn to Pd or other transition metals is very fast. Nevertheless, standard organozinc reagents (RZnX, X = Hal), are highly air and moisture sensitive, thus limiting their synthetic applications. Recently, we demonstrated that organozinc pivalates (RZnOPiv)[79] afford, after solvent evaporation, solid organozinc compounds with greatly improved air and moisture stability, allowing them to be weighed out on the benchtop.

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[72] a) P. A. Wender, M. K. Hilinski, A. V.W. Mayweg*, Org. Lett.* **2005**, *7*, 79. b) M. G. Campbell, T. Ritter, *Org. Process Res. Dev.* **2014**, *18*, 474.

[73] a) H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7222. b) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369. c) D. A. DiRocco, K. Dykstra, S. Krska, P. Vachal, D. V. Conway, M. Tudge, *Angew. Chem. Int. Ed.* **2014**, *53*, 4802. d) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska*, Chem. Soc. Rev.* **2016**, *45*, 546.

[74] a) H. Noguchi, K. Hojo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 758. b) S. J. Lee, K. C. Gray, J. S. Paek, M. D. Burke, *J. Am. Chem. Soc.* **2008**, *130*, 466. c) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961.

[75] a) N. Miyaura, K. Yamada, H. Suginome, A. Suzuki, *J. Am. Chem. Soc.* **1985**, *107*, 972. b) A. Suzuki, *Pure Appl. Chem.* **1985**, *57*, 1749. c) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

[76] a) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302. b) G. A. Molander, B. Canturk, *Angew. Chem. Int. Ed.* **2009**, *48*, 9240.

[77] a) N. Kudo,M. Perseghini, G. C. Fu, *Angew. Chem. Int. Ed.* **2006**, *45*, 1282. b) A. J. J. Lennox,G. C. Lloyd-Jones, *Isr. J. Chem.* **2010**, *50*, 664.

[78] D. Haas, J. M. Hammann, R. Greiner, P. Knochel *ACS Catal.* **2016**, *6*, 1540.

[79] NMR experiments and crystallographic data showed that the structure of these zinc reagents is $RZnX{\cdot}Mg(OPiv)_2{\cdot}LiCl$. However, for the sake of clarity, we have named these reagents RZnOPiv, see: 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.

These organozinc pivalates readily undergo Pd-catalyzed cross-couplings.[80] However, since palladium[81] and nickel,[82] the favored transition metal catalysts for couplings, are toxic[3] and/or expensive,[2] we envisioned the performance of cross-couplings with organozinc pivalates using industry-friendly transition metal catalysts. Cobalt-catalyzed couplings are of special interest since cobalt salts are much less toxic than palladium salts and additionally are ca. 800 times cheaper. Although several Co-catalyzed Csp^2-Csp^2 cross-couplings have been reported, all these methods lack generality and a broad reaction scope is essential for an extensive use in industrial and academic research.[5,18] Also, many Co-catalyzed cross-couplings are limited to electron-deficient *N*-heterocyclic halides and ortho-activated electron-poor aromatic halides.[17] Herein, we report a practical, robust and broadly applicable Co-catalyzed Csp^2-Csp^2 cross-coupling between various aryl or heteroarylzinc pivalates and electron-poor aryl or heteroaryl iodides, bromides and chlorides. In the previous chapter, we have noticed that sodium formate was an excellent promoter for cross-couplings between *ortho*-activated heterocyclic halides and arylzinc chlorides.[83] These results encouraged us to examine the use of arylzinc pivalates as nucleophilic cross-coupling partners. The pivalate anion[10] like sodium formate may accelerate the coupling reaction. To our delight, this hypothesis was confirmed.

[80] a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205. b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9428. c) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754. d) C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302. e) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. - Eur. J.* **2014**, *20*, 12289.

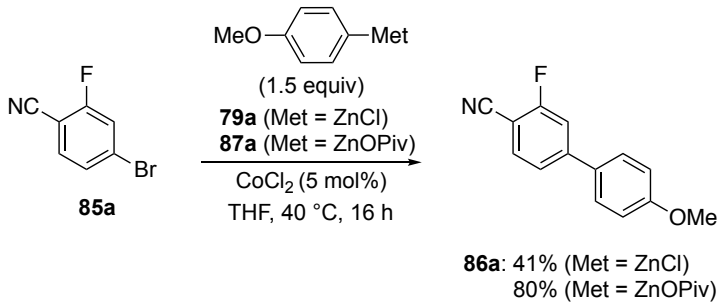
[81] a) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871. b) J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028. c) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685. d) K. L. Billingsley, K. W. Anderson, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 3484. e) Y. Yang, N. J. Oldenhuis, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 615. f) Y. Yang, K. Niedermann, C. Han, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 4638.

[82] a) M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, *Organometallics* **1995**, *14*, 3081. b) L. Melzig, T. Dennenwaldt, A. Gavryushin, P. Knochel, *J. Org. Chem.* **2011**, *76*, 8891.

[83] Although sodium formate proved to be and excellent catalyst for the cross-coupling of activated heteroaryl halides, the scope of this method was limited to activated substrates, see (6). For other realated reactions using PivOR, see: a) D. S. Roman and A. B. Charette *Org. Lett.* **2013**, *15*, 4394. b) P. Cyr, S. Régnier, W. S. Bechara, A. B. Charette *Org. Lett.* **2015**, *17*, 3386. c) C. L. Ladd, A. V. Belouin, A. B. Charette *J. Org. Chem.* **2016**, *81*, 256.

6.2. Cobalt-Catalyzed Aryl-Aryl Cross-Coupling Reactions

Preliminary experiments showed, the treatment of the bromobenzonitrile (**85a**) with *p*-anisylzinc chloride **79a** in the presence of $CoCl_2$ (5 mol%)[84] in THF (40 °C,[85] 16 h) gave the desired product **86a** in 41% yield (Scheme 40).

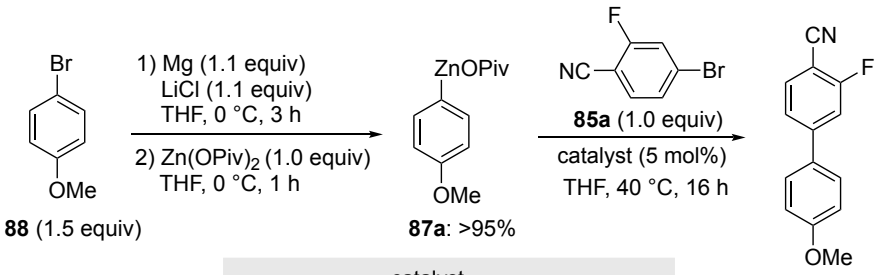


Scheme 40. Cobalt-catalyzed cross-coupling of 4-bromo-2-fluorobenzonitrile (**85a**).

During this reaction, extensive homo-coupling as well as hydrolysis of the organometallic species was observed explaining the low yield. However, using *p*-anisylzinc pivalate (**87a**) prepared from 4-bromoanisole (**88**) by Mg-insertion in the presence of LiCl[42] followed by a transmetalation with $Zn(OPiv)_2$ (>95% yield), we observed a very clean cross-coupling affording the biphenyl (**86a**) in 80% yield showing the clear superiority of ArZnOPiv over ArZnCl. Remarkably, although *ortho*-fluoro electron-deficient aromatics are known to readily undergo Co-catalyzed cross-couplings with Grignard reagents, using 4-bromo-2-fluorobenzonitrile (**85a**) only a regio- and chemoselective coupling of bromide occurs. With these results in hand, we have further optimized the reaction conditions and showed that $MnCl_2$,[34] $CrCl_2$[35] or $FeCl_2$[68] were unsuitable catalysts (Table 18, entries 2-4).

[84] See experimental part for more details (page 186).
[85] See experimental part for more details (page 185).

Table 18. Reaction conditions optimization for the cobalt-catalyzed cross-coupling of 4-bromo-2-fluorobenzonitrile (**85a**).



88 (1.5 equiv) **87a**: >95% **86a**

entry	catalyst (mol%)	yield (%)[a]
1	none	traces
2	$MnCl_2$	traces
3	$CrCl_2$	6
4	$FeCl_2$	7
5	$Co(acac)_2$	72
6	$Co(acac)_3$	74
7	$CoBr_2$	81
8	$CoCl_2 \cdot 2LiCl$	77
9	$CoCl_2$	85 (80)[b]
10	$CoCl_2$	71[c]
11	$CoCl_2$	78[d]

[a] GC yield. Undecane was used as an internal standard. [b] Isolated yield. [c] 99.99% purity. [d] Technical grade THF was used as a solvent.

We found that $CoCl_2$ is superior to other cobalt salts, such as $Co(acac)_2$, $Co(acac)_3$, $CoBr_2$ and $CoCl_2 \cdot 2LiCl$[36] (entries 5-9). At this point, we have verified that no other metal contaminant is responsible for this catalysis by using 5% $CoCl_2$ (99.99% purity) which produced **86a** in 71% yield (entry 10). Solvent screening showed that THF was the best solvent compared to NMP, DMPU, DME, 1,4-dioxane, *t*BuOMe, EtOAc.[86] Remarkably, the improved water and air stability of arylzinc pivalates allows performing these couplings in technical (undistilled) THF providing **86a** in 78% yield (compare entries 11 and 9). Additionally, whereas previous cobalt-catalyzed cross-couplings were often limited to aryl halides bearing an *ortho*-electron-withdrawing substituent, the reaction scope was found to be quite broad. Thus, not only 2-iodobenzonitrile (**85b**) underwent the described cross-coupling with **87a**, but 3-iodo and 4-iodobenzonitrile

[86] See experimental part for more details (page 186).

(**85c-d**) reacted smoothly, leading to the expected products (**86b-d**) in 71-75% yield (Table 19, entry 1).

Table 19. Cobalt-catalyzed cross-couplings between aryl halides and arylzinc pivalates.

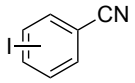
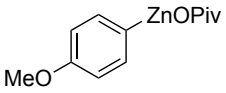
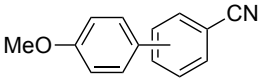
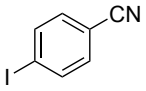
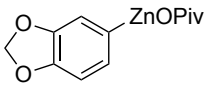
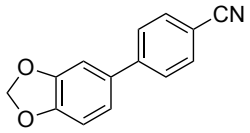
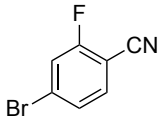
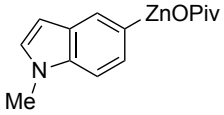
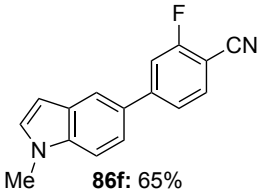
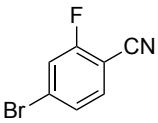
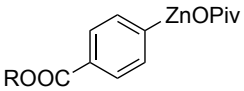
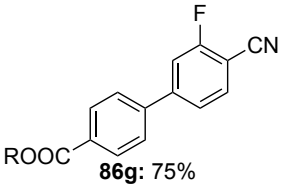
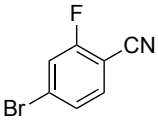
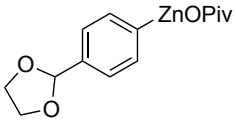
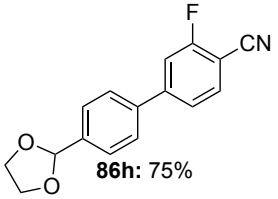
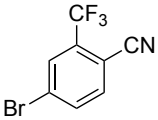
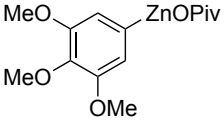
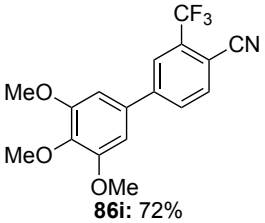
entry	electrophile	zinc reagent	product / yield (%)[a]
1	 **85b** (*ortho*) **85c** (*meta*) **85d** (*para*)	 **87a**	 **86b** 71% (*ortho*) **86c** 72% (*meta*) **86d** 75% (*para*)
2	 **85d**	 **87b**	 **86e:** 72%
3	 **85a**	 **87c**	 **86f:** 65%
4	 **85a**	 **87d**	 **86g:** 75%
5	 **85a**	 **87e**	 **86h:** 75%
6	 **85e**	 **87f**	 **86i:** 72%

Table 19 continued

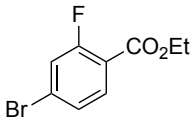
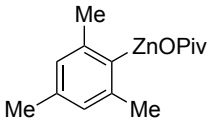
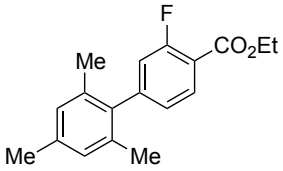
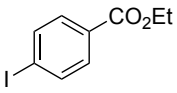
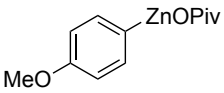
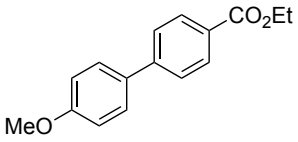
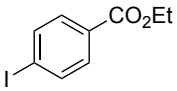
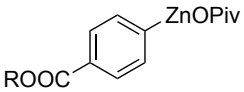
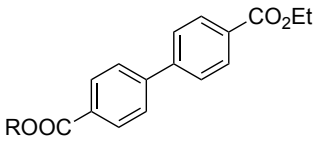
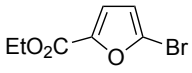
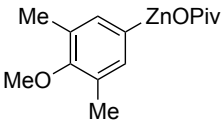
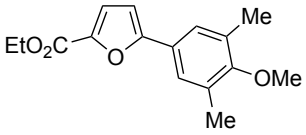
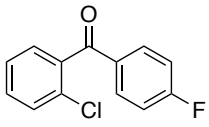
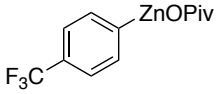
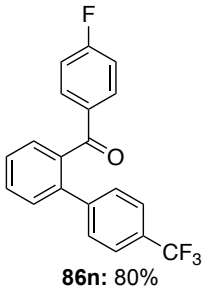
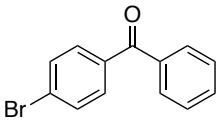
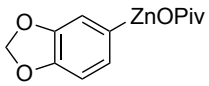
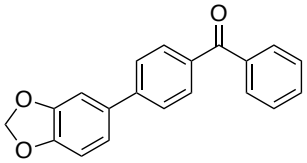
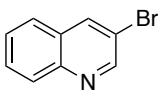
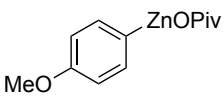
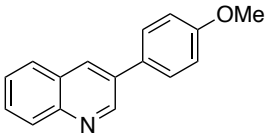
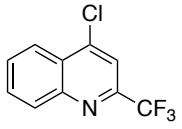
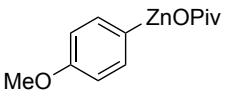
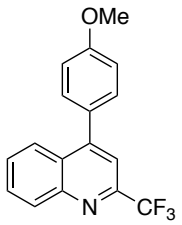
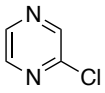
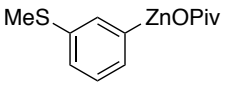
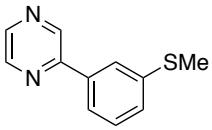
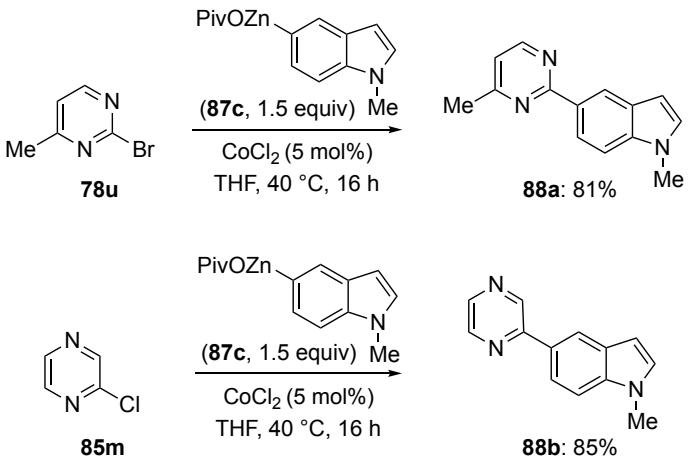
7			
	85f	**87a**	**86j:** 71%
8			
	85g	**87a**	**86k:** 61%
9			
	85g	**87d**	**86l:** 65%
10			
	85h	**87h**	**86m:** 65%
11			
	85i	**87i**	**86n:** 80%
12			
	85j	**87b**	**86o:** 81%
13			
	85k	**87a**	**86p:** 74%

Table 19 continued

14	 **85l**	 **87a**	 **86q:** 74%
15	 **85m**	 **87j**	 **86r:** 85%

[a] Yield of isolated product. R = ZnOPiv

Similarly, 4-iodobenzonitrile (**85d**) reacts with the organozinc pivalate **87b** to give **86e** in 72% yield (entry 2). Also, (1-methyl-1*H*-indol-5-yl)zinc pivalate **87c** as well as the bis-zinc pivalate (**87d**) and the functionalized arylzinc reagents (**87e-f**) undergo a regioselective cross-coupling providing the biphenyls (**86f-i**) in 65-75% yield (entries 3-6). Also, the ethyl benzoate (**85f**) bearing a 4-bromo and 2-fluoro substituent react regio- and chemo-selectively with the sterically demanding mesitylzinc pivalate (**87g**) furnishing the substituted benzoate (**86j**) in 71% yield (entry 7). Similarly, the reaction of 4-iodobenzoate (**85g**) with **87a** and **87d** provided the coupling products (**86k-l**) in 61-65% yield (entries 8-9). The bromofuran derivative (**85h**) is coupled with **87h** affording the disubstitued furan (**86m**) in 65% yield (entry 10). 2-Chloro and 4-bromobenzophenones (**85i-j**) are readily cross-coupled with **87i** and **87b** leading to the desired products (**86n-o**) in 80-81% yield (entries 11-12). Electron-deficient bromides and chlorides such as the 3-bromo- or 4-chloroquinoline (**85k-l**) undergo a smooth cross-coupling with 3a leading to the quinolines (**86p-q**) in 72-74% yield (entries 13-14). Finally, 2-chloropyridazine (**85m**) which is notoriously difficult to cross-couple, **85m** reacts with 3-thioanisylzinc pivalate (**87j**) giving the arylated pyridazine (**86r**) in 89% yield showing that thioethers do not inhibit this cobalt catalysis (entry 15).



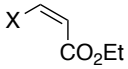
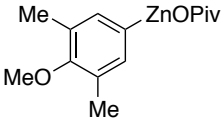
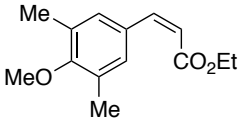
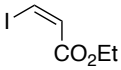
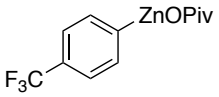
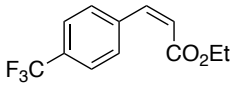
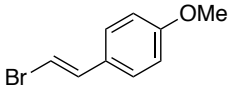
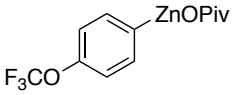
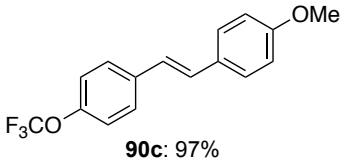
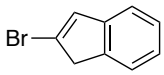
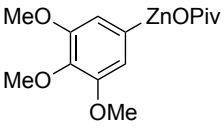
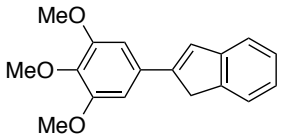
Scheme 41. Cobalt-catalyzed heteroaryl–heteroaryl cross-coupling reactions.

Cross-couplings between heterocyclic moieties is a synthetic challenge in pharmaceutical and agrochemical research[87] and this new cobalt-catalyzed cross-coupling procedure allows the linkage between 5-indolylzinc pivalate (**87c**) and 2-bromopyrimidine (**78u**) as well as 2-chloropyrazine (**85m**) leading to the complex heterocycles (**88a-b** in 81-85% yield, Scheme 41).

Additionally, this cobalt-catalyzed cross-coupling was extended to the performance of aryl-alkenyl cross-couplings (Table 20). Thus, the (*Z*)-3-iodo- and (*Z*)-3-bromo-acrylates (**89a-b**), *E/Z* = 1:99) undergo a stereoselective reaction with arylzinc pivalate (**87h**) under our standard conditions providing (*Z*)-ethyl cinnamate (**90a**) in 94-98% yield with complete rentention of the double bond geometry (*E/Z* = 1:99, entry 1).

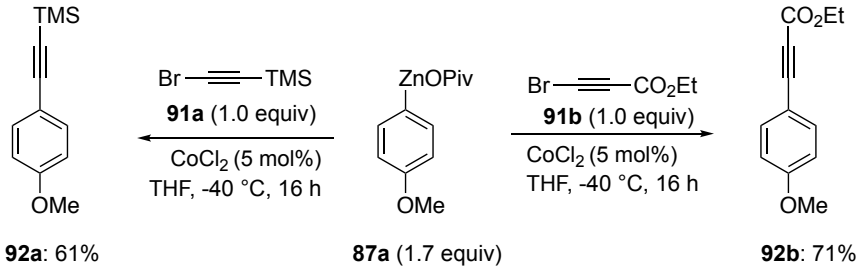
[87] a) C. Kaes, A. Katz, M. W. Hosseini, *Chem. Rev.* **2000**, *100*, 3553. b) *Comprehensive Coordination Chemistry II*, Vol. 1 (Eds.: J. A. McCleverty, T. J. Meyer), Elsevier, Oxford, **2004**. b) For additional cross-coupling reactions using heteroarylzinc pivalates, see experimental part (page 186).

Table 20. Co-catalyzed cross-coupling reactions between alkenyl halides of type **89** and arylzinc pivalates of type **87**.

entry	electrophile	zinc reagent	product / yield (%)[a]
1			
	89a (X = I) *E/Z* = 1:99 **89b** (X = Br) *E/Z* = 1:99	**87h**	**90a**: 98% *E/Z* = 1:99 **90a**: 94% *E/Z* = 1:99
2			
	89a (X = I) *E/Z* = 1:99	**87i**	**90b**: 80% *E/Z* = 3:97
3			
	89c *E/Z* = 99:1	**87k**	**90c**: 97% *E/Z* = 99:1
4			
	89d	**87f**	**90d**: 70%

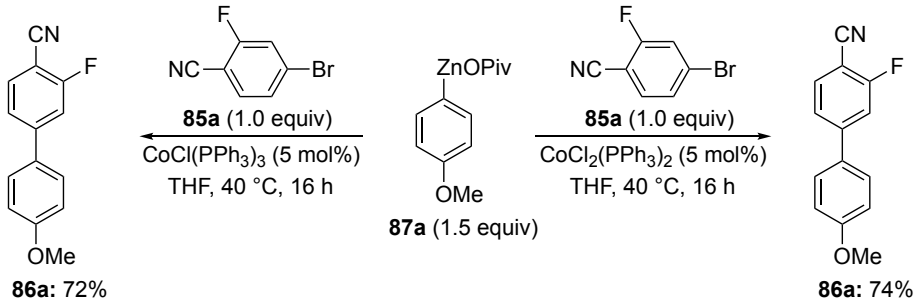
[a] Yield of isolated product.

Similarly, the arylzinc pivalate (**87i**) reacts with **89a** providing the corresponding *Z*-ester (**90b**) in 80% yield (*E/Z* = 3:97, entry 2). The *E*-styryl bromide (**89c**, *E/Z* = 99:1) cross-couples with the arylzinc pivalate (**87k**) leading to the *E*-stilbene **90c** in 97% yield (*E/Z* = 99:1, entry 3). Also, 2-bromo-indene (**89d**) reacts with pivalate **87f** providing the desired cross-coupling product (**90d**) in 70% yield (entry 4).



Scheme 42. Cobalt-catalyzed cross-couplings of organozinc pivalates with bromoalkynes.

Finally, this Co-catalyzed cross-coupling can further be extended to Csp^2-Csp couplings. Typical bromoalkynes[88] such as **91a-b** react with the arylzinc pivalate (**87a**) affording the functionalized alkynes (**92a-b**) in 61-71% yield (Scheme 42). Preliminary mechanistic studies show that Co(I)-complexes are as active as Co(II)-complexes (Scheme 43). Further studies are currently underway.

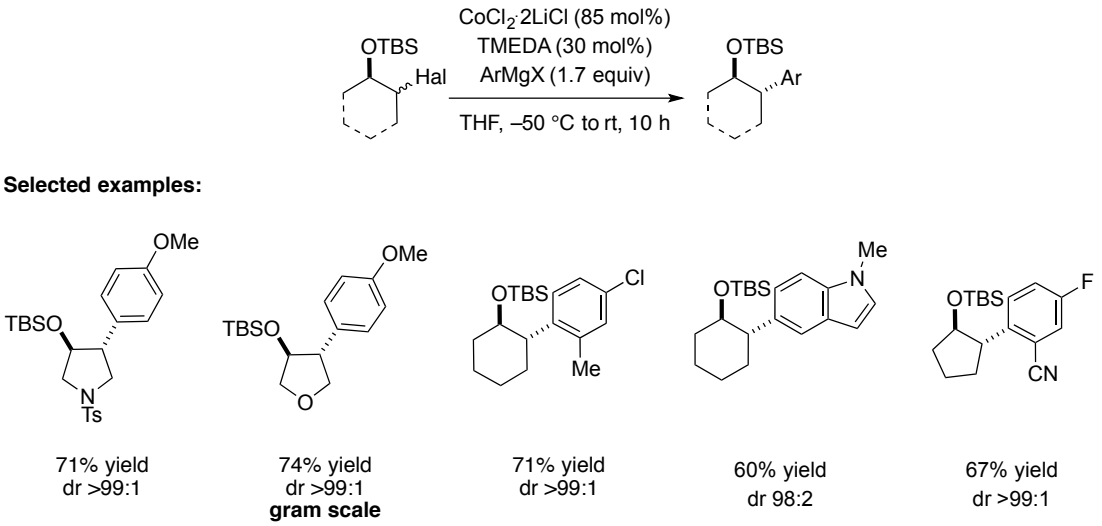


Scheme 43. Cobalt-catalyzed cross-couplings of Co(I) and Co(II)-complexes.

[88] a) D. Castagnolo, M. Botta, *Eur. J. Org. Chem.* **2010**, *17*, 3224. b) M. Corpet, X.-Z. Bai, C. Gosmini *Adv. Synth. Catal.* **2014**, *356*, 2937.

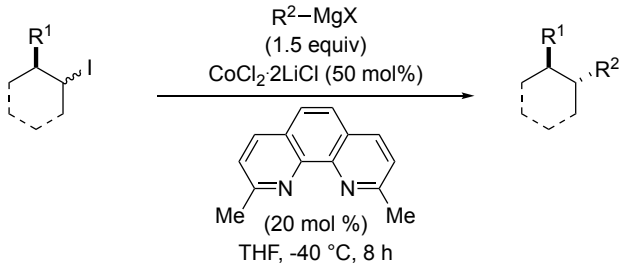
IV. Summary

The research described in this thesis focused on cobalt-catalyzed/mediated cross-coupling reactions. First, we developed a highly diastereoselective cross-coupling of cyclic TBS-protected iodohydrins (and bromohydrins) with various aryl and heteroarylmagnesium reagents in the presence of THF-soluble $CoCl_2$·2LiCl and TMEDA as a ligand leading to *trans*-2-arylcyclohexanol derivatives in good yields and a dr up to 99:1. A range of functional groups were tolerated in the Grignard reagent (e.g. COOR, CN, CF_3, SF_5). The use of heterocyclic iodohydrins leads to *trans*-3,4-disubstituted pyrrolidines and tetrahydrofurans (Scheme 44).

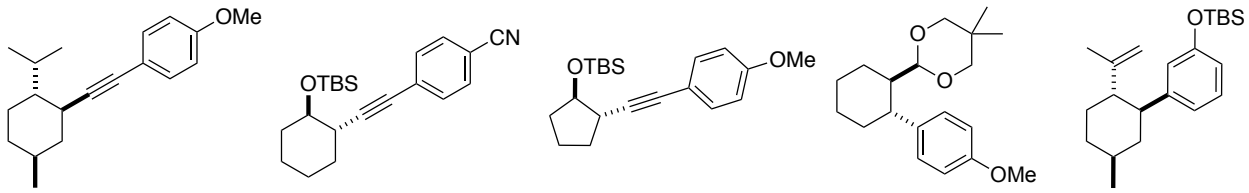


Scheme 44. Cobalt-mediated diastereoselective cross-coupling reactions between cyclic halohydrins and arylmagnesium reagents

Moreover, we have discovered a highly diastereoselective cross-coupling of variously substituted cycloalkyl iodides with alkynyl and (hetero)aryl Grignard reagents using cobalt(II) chloride. With the THF-soluble $CoCl_2$·2LiCl and the inexpensive *ortho*-phenanthroline derivative neocuproine, as a ligand, diastereomeric ratios of up to 99:1 were achieved. A range of functional groups were tolerated in the Grignard reagent (e.g., CF_3, Piv, CN, OPiv, NMe_2, CO_2NEt_2, SF_5, OTBS; Scheme 45).



Selected examples:



74% yield
dr 99:1

69% yield
dr 97:3

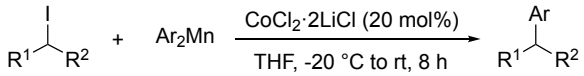
69% yield
dr 99:1

81% yield
dr 99:1

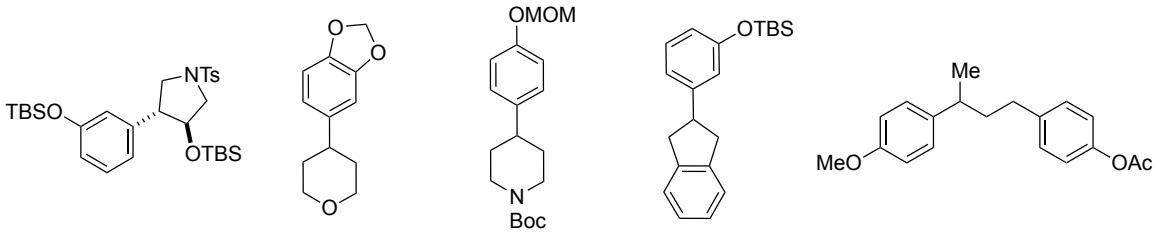
77% yield
dr 99:1

Scheme 45. Diastereoselective cobalt-mediated cross-couplings of cycloalkyl iodides with alkynyl or (hetero)aryl Grignard reagents.

We also developed a cobalt-catalyzed cross-coupling of diarylmanganese reagents with secondary alkyl iodides using $CoCl_2$·2LiCl, which leads to the cross-coupling products in up to 92% yield. High diastereoselectivities can be reached in these cross-couplings (dr up to 99:1). Remarkably, rearrangement of secondary alkyl iodides to unbranched products was not observed in these C-C forming reactions (Scheme 46).



Selected examples:



92% yield
dr 99:1

70% yield

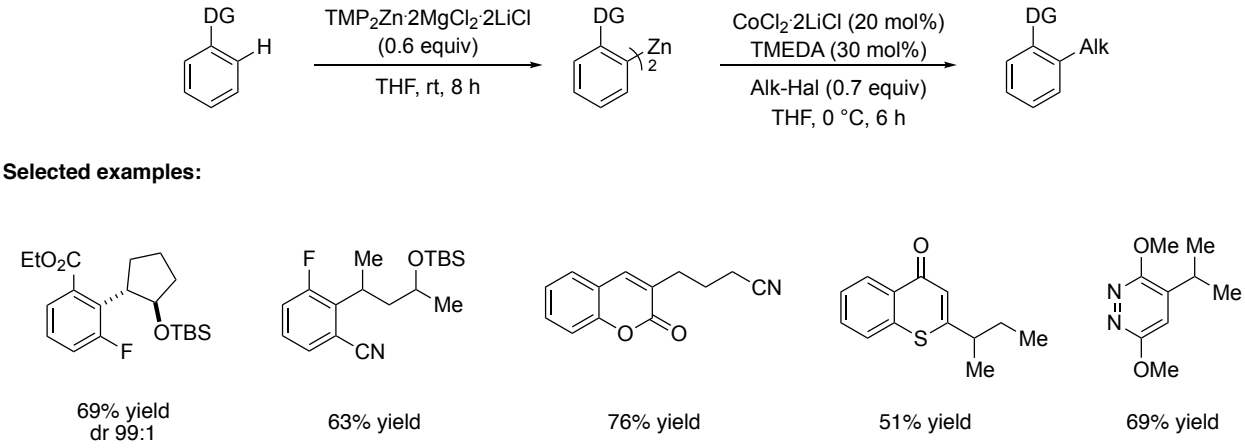
75% yield

74% yield

75% yield

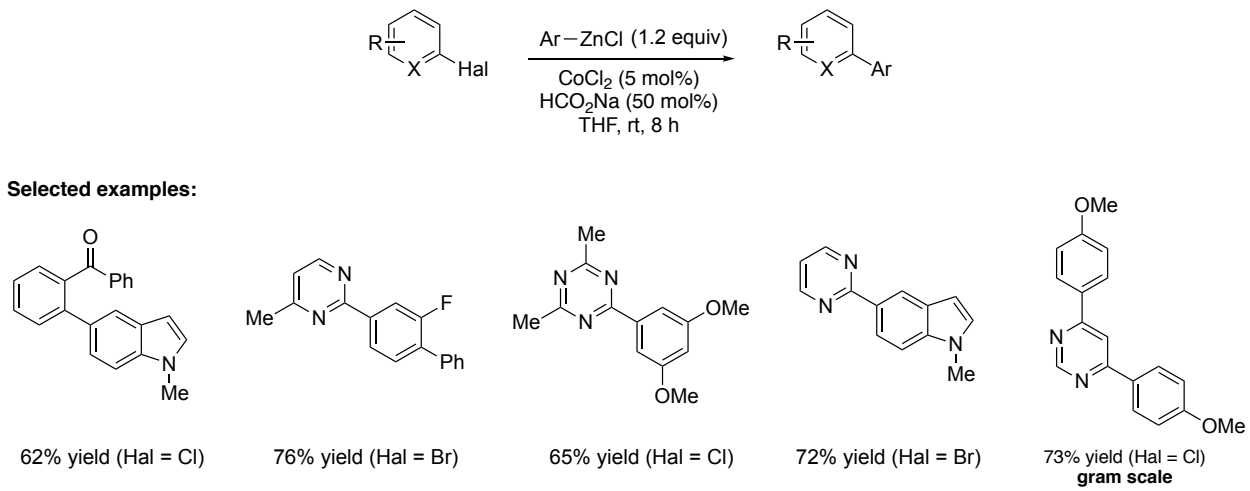
Scheme 46. Cobalt catalyzed Csp^2-Csp^3 cross-coupling reactions of diarylmanganese reagents with secondary alkyl iodides.

Furthermore, we have developed a new cobalt-catalyzed cross-coupling of polyfunctional diaryl- and diheteroarylzinc reagents prepared *via* directed zincation using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ with primary and secondary alkyl iodides or bromides using the cobalt complex $CoCl_2{\cdot}2LiCl$. Remarkably, no rearrangement of the secondary alkyl group was observed for the alkyl halides employed in this procedure. This cross-coupling proceeds under mild conditions and is compatible with various functional groups and hetereocyclic scaffolds (Scheme 47).



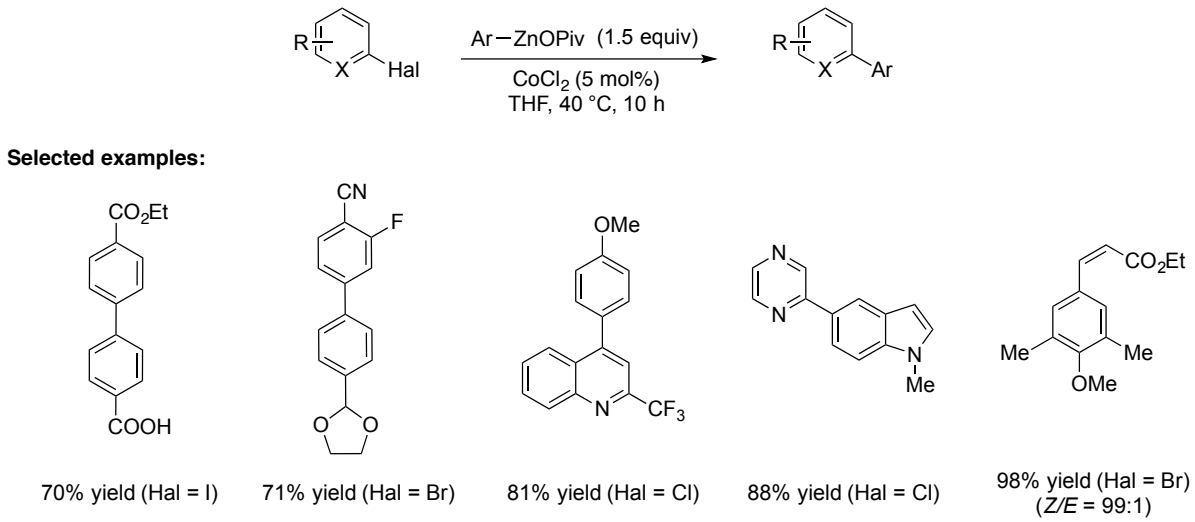
Scheme 47. Cobalt-catalyzed negishi cross-coupling reactions of (hetero)aryl-zinc reagents with primary and secondary alkyl bromides and iodides.

Also, we investigated cobalt-catalyzed Negishi cross-couplings of (hetero)arylzinc reagents with (hetero)aryl halides. A simple, practical cobalt salt-catalyzed procedure allows for cross-coupling reactions of halogenated aryl ketones, as well as *N*-heterocyclic chlorides and bromides with various electron-rich and -poor arylzinc reagents. The addition of sodium formate is essential for this cross-coupling (Scheme 48).



Scheme 48. Mild cobalt-catalyzed Negishi cross-couplings of (hetero)arylzinc reagents with (hetero)aryl halides.

Finally, we discovered a robust and broadly applicable $CoCl_2$-catalyzed cross-coupling between functionalized bench-stable aryl and heteroarylzinc reagents and various electron-poor aryl and heteroaryl halides (X = Cl, Br, I). Couplings with (*E*)- or (*Z*)-bromo- or iodo-alkenes proceed with retention of configuration. Also, alkynyl bromides react with arylzinc pivalates providing arylated alkynes (Scheme 49).



Scheme 49. Cobalt-catalyzed cross-coupling of functionalized bench-stable organozinc pivalates with unsaturated halides.

V. Experimental Part

1. General Considerations

All reactions were carried out with magnetic stirring and in flame-dried glassware under argon atmosphere using *Schlenk* technique. Syringes used to transfer reagents and solvents were purged with argon prior to use.

1.1 Solvents and Reagents

CH_2Cl_2 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. **TEA** was dried over KOH and distilled. **THF** was continuously refluxed and distilled from sodium benzophenone ketyl under nitrogen and stored over 4 Å MS under argon atmosphere. **TMEDA** was predried over CaH_2 (12 h) and distilled from sodium benzophenone ketyl under argon atmosphere. **TMPH** was distilled from CaH_2 under argon prior to use.

Solvents for reaction workups and column chromatography were distilled prior to use.

1.2 Organometallic Reagents

Commercially available starting materials were used without further purification.

***i*-PrMgCl·LiCl** was purchased as a solution in THF from Albemarle Corp. as a 14% solution in THF and was titrated with I_2 prior to use.

***n*-BuLi** was purchased as a solution in hexane from Albemarle Corp..

$ZnCl_2$ solution in THF (1.0 M) was prepared by drying $ZnCl_2$ (40.9 g, 300 mmol) in a *Schlenk*-flask 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 MS under argon upon use.

CuCN·2LiCl solution in THF (1.0 M) was prepared by drying LiCl (17.0 g, 400 mmol) and CuCN (17.9 g, 200 mmol) in a *Schlenk*-flask under high vacuum at 150 °C for 4 h. After cooling to 25 °C, anhydrous THF was added until a total volume of 200 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 more time to become completely clear. The solution was stored under argon upon use.

$CoCl_2$·2LiCl solution in THF (1.0 M) was prepared by drying LiCl (8.5 g, 200 mmol) in a *Schlenk*-flask under high vacuum at 130 °C for 3 h. After cooling to 25 °C, anhydrous $CoCl_2$ (13.0 g, 100 mmol) was added and the salts were further heated to 130 °C for 5 h under high vacuum. After cooling to 25 °C anhydrous THF (100 mL) was added. The mixture was vigorously stirred until all solids were dissolved and the reagent was obtained as a dark blue solution.

$MnCl_2$·2LiCl solution in THF (1.0 M) was prepared by drying LiCl (140 mmol, 5.94 g) in a *Schlenk*-flask under high vacuum at 130 °C for 3 h. After cooling to rt under vacuum, anhydrous $MnCl_2$ (70.0 mmol, 8.81 g) was added under argon. The *Schlenk*-flask was further heated to 130 °C for 3 h under high vacuum, cooled to 25 °C and charged with dry THF (70 mL). The mixture was stirred for at least 24 h (covered with aluminum foil) at room temperature and the resulting reagent $MnCl_2$·2LiCl (1 M in THF) was obtained as a yellow solution.

Preparation of $Zn(OPiv)_2$: Pivalic acid (20.4 g, 22.6 mL, 200 mmol) was placed in a dry and argon-flushed 500 mL three-necked round-bottom flask, equipped with a magnetic stirring bar, a septum and a pressure equalizer, and was dissolved in dry THF (120 mL). The mixture was cooled to 0 °C, and a solution of Et_2Zn (13.0 g, 10.8 mL, 105 mmol) in dry THF (120 mL) was added over a period of 30 min under vigorous stirring. Then, the ice-bath was removed and stirring was continued at 25 °C for one additional hour at which point bubbling was ceased (a thick slurry was formed). The solvent was removed *in vacuo* and the solid residue was dried for at least 4 h longer. $Zn(OPiv)_2$ was obtained in quantitative yield, as a puffy amorphous white solid.

Preparation of EtMgBr: A dry and argon-flushed 100mL flask, equipped with a stirring bar and a septum, was charged with magnesium turnings (60 mmol, 1.44 g) in THF (50 mL). Bromoethane (50 mmol, 5.4 g) was added dropwise at -20 °C and the reaction mixture was shortly heated to reflux and again cooled to -20 °C. This procedure was repeated until the reaction started. After disappearance of the Mg turnings the dark-grey solution was titrated by using a stoichiometric amount of iodine (100 mg) in THF (2 mL) and a concentration of 0.94 M was determined.

Preparation of TMPMgCl·LiCl: A 250 mL *Schlenk*-flask was charged with *i*-PrMgCl·LiCl (120 mmol, 100 mL, 1.2 M in THF). Freshly distilled 2,2,6,6-tetramethylpiperidine (TMPH; 126 mmol, 23.9 mL) was added dropwise at 25 °C and the mixture was stirred for 48 h.

Preparation of TMPZnCl·LiCl: A 250 mL *Schlenk*-flask was charged with freshly distilled TMPH (60 mmol, 10 mL) dissolved in THF (60 mL). The solution was cooled to -40 °C and *n*-BuLi (60 mmol, 25 mL, 2.4 M in hexane) was added dropwise. The reaction was allowed to warm slowly to -10 °C within 1 h. $ZnCl_2$ (66 mmol, 66 mL, 1 M in THF) was added dropwise and the resulting solution was stirred for 0.5 h at -10 °C and then 0.5 h at 25 °C. The solvents were removed *in vacuo* to afford a light yellow solid and freshly distilled THF was added under vigorous stirring until the salts were completely dissolved.

The content of organometallic reagent was determined either by the method of Paquette[89] using *i*-PrOH and 1,10-phen as indicator (organolithium reagents) or the method of Knochel[90] using I_2 in THF (organomagnesium and -zinc reagents).

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

[89] H. S. Lin, A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[90] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.

1.3 Chromatography

Flash column chromatography was performed using silica gel 60 (40 – 63 µm 230-400 mesh ASTM) from Merck.

Thin layer chromatography (TLC) was performed using aluminum plates covered with SiO_2 (Merck 60, F-254) and visualized either by UV detection or by staining with $KMnO_4$ solution (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10% NaOH solution in 200 mL H_2O).

1.4 Analytical Data

NMR spectra were recorded on Varian VXR 400S, Bruker Avance III HD 400 MHz and Bruker AMX 600 instruments. Chemical shifts (*d*) are reported in parts per million (ppm) relative to the residual solvent peak of $CHCl_3$ (d_H = 7.26, d_C = 77.0). 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 withmachines 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 mm). 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}).

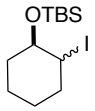
Melting points (m.p.) were measured using a Büchi B-540 apparatus and are uncorrected.

2. Cobalt-Mediated Diastereoselective Cross-Coupling Reactions between Cyclic Halohydrines and Arylmagnesium Reagents

2.1 Preparation of Starting Materials

The following starting materials were prepared according to literature procedures with only little deviation. The spectral data of known compounds were in full agreement with the literature (Signals of the main diastereomer are given).

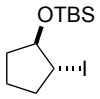
***tert*-Butyl((2-iodocyclohexyl)oxy)dimethylsilane (52a)**



dr: 25:75 (*trans*/*cis*).

^{1}H NMR (300 MHz, CDCl3) δ/ppm: 4.53 - 4.39 (m, 1 H), 3.36 (s br., 1 H), 2.32 - 2.20 (m, 1 H), 1.96 - 1.84 (m, 1 H), 1.79 - 1.60 (m, 3 H), 1.57 - 1.30 (m, 3 H), 0.95 (s, 9 H), 0.14 (s, 3 H), 0.08 (s, 3 H).

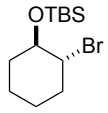
***tert*-Butyl((2-iodocyclopentyl)oxy)dimethylsilane (52b)**



dr: 99:1 (*trans*/*cis*).

^{1}H NMR (300 MHz, CDCl3) δ/ppm: 4.43 (ddd, *J*=6.3, 3.6, 3.3 Hz, 1 H), 4.06 - 3.98 (m, 1 H), 2.41 - 2.28 (m, 1 H), 2.16 - 1.97 (m, 2 H), 1.80 (quin, *J*=7.39 Hz, 2 H), 1.60 - 1.49 (m, 1 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H).

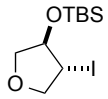
((2-Bromocyclohexyl)oxy)(*tert*-butyl)dimethylsilane (52c)



dr: 99:1 (*trans*/*cis*).

^{1}H NMR (300 MHz, CDCl3) δ/ppm: 3.90 (ddd, *J* = 9.6, 7.6, 4.1, 1H), 3.73 – 3.63 (m, 1H), 2.36 – 2.25 (m, 1H), 2.09 – 1.95 (m, 1H), 1.88 – 1.58 (m, 4H), 1.43 – 1.23 (m, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H).

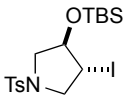
***tert*-Butyl((4-iodotetrahydrofuran-3-yl)oxy)dimethylsilane (59a)**



dr: 99:1 (*trans*/*cis*).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.01 - 0.14 (m, 6 H), 0.87 (s, 9 H), 3.66 (dd, *J*=9.26, 2.07 Hz, 1 H), 3.97 - 4.10 (m, 2 H), 4.17 - 4.36 (m, 2 H), 4.58 (dt, *J*=4.42, 2.21 Hz, 1 H).

3-((*tert*-Butyldimethylsilyl)oxy)-4-iodo-1-tosylpyrrolidine (59b)



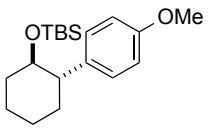
dr: 99:1 (*trans*/*cis*).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.08 - 0.02 (m, 6 H), 0.73 (s, 9 H), 2.40 (s, 3 H), 3.17 (dd, *J*=10.23, 1.94 Hz, 1 H), 3.63 - 3.71 (m, 1 H), 3.77 - 3.96 (m, 3 H), 4.34 (dt, *J*=4.70, 2.35 Hz, 1 H), 7.30 (m, *J*=8.57 Hz, 2 H), 7.70 (m, *J*=8.29 Hz, 2 H).

2.2 Cobalt-Mediated Cross-Coupling of Various Protected Cycloalcohols with (Hetero)Arylmagnesium Reagents

Typical Procedure 1 (TP1): A dry and Ar-flushed 10 mL Schlenk-tube, equipped with a stirring bar and a septum, was charged with a solution of $CoCl_2$·2LiCl (1 M in THF) (0.43 mmol, 0.43 mL, 0.85 equiv) and anhydrous THF (0.5 mL). The respective protected cyclicalcohols (0.5 mmol, 1 equiv) and TMEDA (0.15 mmol, 22.6 mg, 0.3 equiv) were added via syringe. The reaction mixture was cooled to -50 °C and a solution of the appropriate Grignard reagent (0.85 mmol, 1.7 equiv) was added dropwise over 10 min via syringe. The reaction mixture was allowed to warm to rt over 10 h. Saturated aqueous NH_4Cl solution (5 mL) and EtOAc (5 mL) was added, the phases were separated and the aqueous phase was extracted with EtOAc (4 x 50 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

***tert*-Butyl((*trans*-2-(4-methoxyphenyl)cyclohexyl)oxy)dimethylsilane (51a)**



Following **TP1**, *tert*-Butyl((2-iodocyclohexyl)oxy)dimethylsilane (**52a**, 0.5 mmol, 1.0 equiv) reacts with (4-methoxyphenyl)magnesium bromide (1.7 equiv, 0.94 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 100:1
yield: 114 mg (71 %), (colorless oil)
dr: 95:5.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.50 (s, 3 H), -0.20 (s, 3 H), 0.67 (s, 9 H), 1.27 - 1.57 (m, 4 H), 1.69 - 1.86 (m, 3 H), 1.92 - 2.02 (m, 1 H), 2.33 - 2.44 (m, 1 H), 3.47 (td, *J*=9.74, 4.56 Hz, 1 H), 3.77 (s, 3 H), 6.81 (m, 2 H), 7.09 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.5, -4.8, 17.8, 25.3, 25.7, 26.1, 32.9, 36.7, 52.1, 55.3, 76.0,

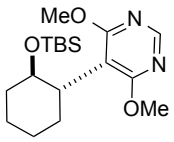
113.3, 129.0, 137.3, 158.0.

MS (70 eV, EI) m/z (%): 320 (2), 263 (100), 189 (14), 121 (32), 75 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 2855, 1612, 1513, 1471, 1462, 1448, 1361, 1282, 1245, 1177, 1124, 1091, 1040, 1006, 983, 906, 881, 856, 846, 826, 772, 666.

HRMS (EI) for $C_{19}H_{32}O_2Si$ (320.2172) $[M]^+$: 320.2231.

5-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-4,6-dimethoxypyrimidine (51b)



Following **TP1**, *tert*-Butyl((2-iodocyclohexyl)oxy)dimethylsilane (**52a**, 0.5 mmol, 1.0 equiv) reacts with (4,6-dimethoxypyrimidin-5-yl)magnesium chloride (1.7 equiv, 0.75 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 9:1

yield: 97 mg (55 %), (colorless oil)

dr: >99:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.41 (s, 3 H), -0.13 (s, 3 H), 0.61 (s, 9 H), 1.20 - 1.36 (m, 3 H), 1.52 (dt, *J*=13.14, 2.50 Hz, 1 H), 1.62 - 1.76 (m, 2 H), 1.87 - 2.00 (m, 2 H), 2.98 (ddd, *J*=12.72, 9.91, 3.74 Hz, 1 H), 3.92 (s, 6 H), 3.97 - 4.07 (m, 1 H), 8.27 (s, 1 H).

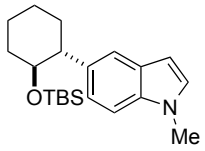
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.7, -4.3, 17.6, 25.0, 25.4, 25.9, 28.2, 36.7, 41.7, 53.8, 71.3, 107.4, 154.0, 168.4.

MS (70 eV, EI) m/z (%): 296 (19), 295 (100), 263 (25), 153 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2952, 2928, 2856, 1572, 1461, 1415, 1384, 1373, 1294, 1282, 1249, 1232, 1184, 1157, 1136, 1128, 1089, 1022, 1006, 984, 882, 864, 833, 816, 805, 793, 771, 750, 662.

HRMS (EI) for $C_{18}H_{32}N_2O_3Si$ (352.2182) $[M]^+$: 352.2236.

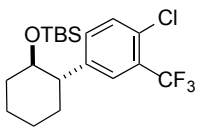
5-(*trans*-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-1-methyl-1H-indole (51c)



Following **TP1**, *tert*-Butyl((2-iodocyclohexyl)oxy)dimethylsilane (**52a**, 0.5 mmol, 1.0 equiv) reacts with (1-methyl-1H-indol-5-yl)magnesium bromide (1.7 equiv, 0.94 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 100:1
yield: 111 mg (65 %), (colorless oil)
dr: 99:1.
^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 7.41 (d, *J*=1.8 Hz, 1H), 7.19 (d, *J*=8.4 Hz, 1H), 7.06 (dd, *J*=8.5, 1.6 Hz, 1H), 6.99 - 6.96 (m, 1H), 6.38 (dd, *J*=2.9 Hz, 1.4, 1H), 3.75 (d, *J*=1.6 Hz, 3H), 3.59 (d, *J*=4.4 Hz, 1H), 2.61 - 1.30 (m, 10H), 0.63 (d, *J*=1.7 Hz, 9H), -0.27 (d, *J*=1.6 Hz, 3H), -0.65 (d, *J*=1.5 Hz, 3H).
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 135.8, 135.7, 128.5, 122.4, 120.1, 108.3, 100.4, 76.3, 52.9, 36.8, 33.5, 32.8, 26.3, 25.7, 25.4, 17.9, -4.9, -5.5.
MS (70 eV, EI) m/z (%): 288 (12), 287 (43), 286 (198), 212 (34), 210 (16), 188 (12), 182 (10), 157 (10), 144 (48), 75 (19), 73 (13), 43 (10).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 2856, 1514, 1490, 1471, 1247, 1096, 989, 905, 835, 774, 730.
HRMS (EI) for $C_{21}H_{33}NOSi$ (343.2331) $[M]^+$: 343.2339.

***tert*-Butyl((*trans*-2-(4-chloro-3-(trifluoromethyl)phenyl)cyclohexyl)oxy)dimethylsilane (51d)**



Following **TP1**, *tert*-butyl((2-iodocyclohexyl)oxy)dimethylsilane (**52a**, 0.5 mmol, 1.0 equiv) reacts with (4-chloro-3-(trifluoromethyl)phenyl)magnesium chloride (1.7 equiv, 1.07 M) at -50 °C. The

solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 100:1

yield: 128 mg (65 %), (colorless oil)

dr: >99:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.50 (s, 3 H), -0.15 (s, 3 H), 0.65 (s, 9 H), 1.25 - 1.45 (m, 3 H), 1.49 - 1.60 (m, 1 H), 1.73 - 1.89 (m, 3 H), 1.94 - 2.06 (m, 1 H), 2.50 (ddd, *J*=12.72, 9.54, 3.46 Hz, 1 H), 3.48 (td, *J*=9.81, 4.42 Hz, 1 H), 7.26 - 7.32 (m, 1 H), 7.36 - 7.43 (m, 1 H), 7.51 (d, *J*=2.21 Hz, 1 H).

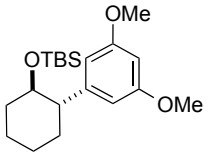
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.7, -4.5, 17.7, 25.0, 25.5, 25.7, 32.3, 36.5, 52.4, 75.7, 123.0 (q, *J*=273.2 Hz), 127.6 (q, *J*=5.3 Hz), 127.7 (q, *J*=30.9 Hz), 129.5 (q, *J*=1.9 Hz), 130.8, 132.4 (q, J=1.1 Hz), 144.2.

MS (70 eV, EI) m/z (%): 337 (35), 336 (21), 335 (100), 267 (9), 241 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2930, 2858, 1482, 1473, 1463, 1450, 1424, 1362, 1314, 1276, 1260, 1250, 1229, 1209, 1196, 1172, 1134, 1108, 1094, 1046, 1035, 1006, 990, 939, 916, 900, 872, 833, 815, 773, 732, 700, 663.

HRMS (EI) for $C_{19}H_{28}ClF_3OSi$ (392.1550) $[M]^+$: 392.1532.

***tert*-butyl((*trans*-2-(3,5-dimethoxyphenyl)cyclohexyl)oxy)dimethylsilane (51e)**



Following **TP1**, *tert*-Butyl((2-iodocyclohexyl)oxy)dimethylsilane (**52a**, 0.5 mmol, 1.0 equiv) reacts with (3,5-dimethoxyphenyl)magnesium chloride (1.7 equiv, 1.1 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 50:1

yield: 124 mg (71 %), (colorless oil)

dr: 95:5.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.44 (s, 3 H), -0.16 (s, 3 H), 0.64 - 0.72 (m, 9 H), 1.23 - 1.42 (m, 3 H), 1.45 - 1.62 (m, 1 H), 1.69 - 1.88 (m, 3 H), 1.92 - 2.03 (m, 1 H), 2.38 (ddd, *J*=12.51,

9.47, 3.46 Hz, 1 H), 3.53 (td, *J*=9.81, 4.42 Hz, 1 H), 3.76 (s, 6 H), 6.29 (t, *J*=2.21 Hz, 1 H), 6.37 (d, *J*=2.49 Hz, 2 H).

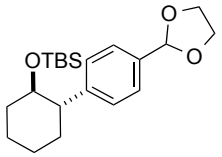
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.5, -4.7, 17.8, 25.2, 25.7, 25.9, 32.7, 36.7, 53.5, 55.2, 75.8, 98.3, 106.5, 147.5, 160.4.

MS (70 eV, EI) m/z (%): 294 (21), 293 (100), 219 (5), 151 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 2855, 2839, 1606, 1596, 1470, 1462, 1428, 1360, 1342, 1318, 1291, 1255, 1248, 1204, 1150, 1128, 1093, 1063, 1007, 992, 938, 893, 880, 832, 816, 772, 695, 666.

HRMS (EI) for $C_{20}H_{34}O_3Si$ (350.2277) $[M]^+$: 350.2271.

((*trans*-2-(4-(1,3-Dioxolan-2-yl)phenyl)cyclohexyl)oxy)(tert-butyl)dimethylsilane (51f)



Following **TP1**, *tert*-butyl((2-iodocyclohexyl)oxy)dimethylsilane (**52a**, 0.5 mmol, 1.0 equiv) reacts with (4-(1,3-dioxolan-2-yl)phenyl)magnesium chloride (1.7 equiv, 0.95 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 25:1

yield: 132 mg (73 %), (colorless oil)

dr: 97:3.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.53 (s, 3 H), -0.20 (s, 3 H), 0.65 (s, 9 H), 1.27 - 1.43 (m, 3 H), 1.51 - 1.61 (m, 1 H), 1.69 - 1.85 (m, 3 H), 1.94 - 2.02 (m, 1 H), 2.46 (ddd, *J*=12.58, 9.58, 3.46 Hz, 1 H), 3.54 (td, *J*=9.72, 4.49 Hz, 1 H), 4.00 - 4.11 (m, 4 H), 5.81 (s, 1 H), 7.20 (d, *J*=8.23 Hz, 2 H), 7.34 - 7.38 (m, 2 H).

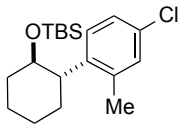
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.6, -4.7, 17.8, 25.2, 25.6, 32.8, 36.6, 52.9, 65.1, 65.3, 75.8, 103.8, 126.0, 128.3, 135.7, 146.2.

MS (70 eV, EI) m/z (%): 305 (25), 262 (32), 261 (100), 185 (6), 129 (4), 91 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 2884, 2855, 1472, 1462, 1448, 1431, 1388, 1361, 1249, 1219, 1180, 1125, 1082, 1042, 1028, 1022, 1006, 983, 939, 908, 882, 846, 833, 772, 739, 721, 698, 666.

HRMS (EI) for $C_{21}H_{34}O_3Si$ (362.2277) $[M]^+$: 362.2196.

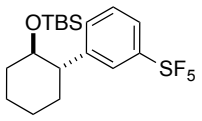
***tert*-Butyl((*trans*-2-(4-chloro-2-methylphenyl)cyclohexyl)oxy)dimethylsilane (51g)**



Following **TP1**, *tert*-butyl((2-iodocyclohexyl)oxy)dimethylsilane (**52a**, 0.5 mmol, 1.0 equiv) reacts with (4-chloro-2-methylphenyl)magnesium chloride (1.7 equiv, 0.91 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane
yield: 170 mg (71 %), (colorless oil)
dr: >99:1.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.51 (s, 3 H), -0.16 (s, 3 H), 0.65 (s, 9 H), 1.29 - 1.49 (m, 4 H), 1.69 - 1.83 (m, 4 H), 1.95 - 2.02 (m, 1 H), 2.32 (s, 3 H), 2.74 (ddd, *J*=12.44, 9.54, 3.46 Hz, 1 H), 3.52 (dt, *J*=9.74, 4.94 Hz, 1 H), 7.06 - 7.11 (m, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.6, -4.7, 17.7, 20.2, 25.2, 25.5, 25.9, 26.1, 32.7, 36.81, 46.8, 125.7, 127.2, 129.5, 130.7, 139.1, 142.3.
MS (70 eV, EI) m/z (%): 283 (35), 281 (100), 141 (8), 139 (23), 115 (6).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929, 2856, 1486, 1472, 1462, 1448, 1360, 1249, 1174, 1133, 1090, 1050, 1006, 983, 939, 908, 876, 834, 813, 800, 773, 675, 666.
HRMS (EI) for $C_{19}H_{31}ClOSi$ (338.1833) $[M]^+$: 338.1820.

***tert*-Butyldimethyl((*trans*-2-(3-(pentafluoro-λ6-sulfanyl)phenyl)cyclohexyl)oxy)silane (51h)**



Following **TP1**, *tert*-butyl((2-iodocyclohexyl)oxy)dimethylsilane (**52a**, 0.5 mmol, 1.0 equiv) reacts with (3-(pentafluoro-λ6-sulfanyl)phenyl)magnesium chloride (1.7 equiv, 0.91 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane

yield: 139 mg (67 %), (colorless oil)

dr: 98:2.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.58 (d, *J*=1.7 Hz, 2H), 7.37 - 7.30 (m, 2H), 3.54 (d, *J*=4.5, 1H), 2.53 (s, 4H), 1.51 (s, 4H), 0.63 (s, 9H), -0.15 (d, 3H), -0.51 (s, 3H).

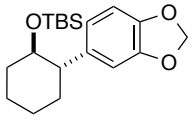
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 154.0, 146.5, 131.4, 128.1, 125.6, 123.6, 75.8, 53.2, 36.5, 32.6, 25.8, 25.4, 25.0, 17.7, -4.6, -5.9.

MS (70 eV, EI) m/z (%): 359 (9), 251 (134), 157 (108), 142 (6), 129 (179), 115 (6), 88 (5), 81 (4), 75 (9), 73 (7), 57 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 2856, 1472, 1462, 1257, 1094, 989, 872, 831, 816, 805, 788 (s) 771, 693.

HRMS (EI) for $C_{18}H_{29}F_5OSSi$ (416.1629) $[M-H]^+$: 415.1361.

((*trans*-2-(Benzo[d][1,3]dioxol-5-yl)cyclohexyl)oxy)(tert-butyl)dimethylsilane (51i)



Following **TP1**, *tert*-butyl((2-iodocyclohexyl)oxy)dimethylsilane (**52a**, 0.5 mmol, 1.0 equiv) reacts with benzo[d][1,3]dioxol-5-ylmagnesium chloride (1.7 equiv, 1.0 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 100:1

yield: 117 mg (70 %), (colorless oil)

dr: 98:2.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 6.72 - 6.68 (m, 2H), 6.64 (dd, *J*=8.0 Hz, 1.8, 1H), 5.88 (d, *J*=2.0 Hz, 2H), 3.44 (td, J=9.8, 4.2 Hz, 1H), 2.36 (ddd, *J*=12.8, 9.7, 3.5 Hz, 1H), 2.01 - 1.66 (m, 1H), 1.53 - 1.21 (m, 1H), 0.69 (t, *J*=1.7 Hz, 8H), -0.16 (d, *J*=1.9 Hz, 3H), -0.44 (d, *J*=1.9 Hz, 3H).

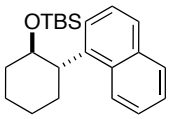
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 147.12 145.6, 139.1, 121.2, 108.7, 107.8, 100.5, 76.0, 52.7, 36.7, 33.0, 26.0, 25.7, 25.2, 17.8, -4.7, -5.5.

MS (70 eV, EI) m/z (%): 279 (3), 278 (10), 27 (42), 203 (5), 179 (9), 135 (10), 81 (4), 75 (7), 73 (4), 75 (7), 73 (4), 57 (2), 42 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2929, 2856, 1504, 1484, 1441, 1246, 1093, 1041, 939, 905, 835, 774, 710,

HRMS (EI) for $C_{19}H_{30}O_3Si$ (334.1964) $[M]^+$: 334.1959.

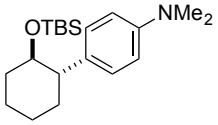
tert-Butyldimethyl((*trans*-2-(naphthalen-1-yl)cyclohexyl)oxy)silane (51j)[6]



Following **TP1**, *tert*-butyl((2-iodocyclohexyl)oxy)dimethylsilane (**52a**, 0.5 mmol, 1.0 equiv) reacts with naphthalen-1-ylmagnesium chloride (1.7 equiv, 0.94 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane
yield: with **52a**: 186 mg (**51j,** 91 %); with **52c**: 120 mg (59 %), (colorless oil)
dr: >99:1.
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.31 (d, *J*=8.46 Hz, 1H), 7.88 - 7.82 (m, 1H), 7.73 (d, *J*=7.44 Hz, 1H), 7.55 - 7.40 (m, 4H), 3.77 (br s., 1 H), 3.49 (t, *J*=9.49 Hz, 1 H), 2.16 - 2.08 (m, 1 H), 2.00 - 1.86 (m, 2 H), 1.85 (dd, *J*=8.59, 2.44 Hz, 1H), 1.81 - 1.72 (m, 1H), 1.65 - 1.46 (m, 3H), 0.49 (s, 9H), -0.22 (s, 3H), -0.81 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 142.1, 133.7, 133.3, 128.3, 126.2, 125.3, 125.2, 125.0, 124.5, 123.0, 77.2, 45.9, 37.1, 33.2, 26.4, 25.4, 25.4, 17.5, -4.9, -5.9.
MS (70 eV, EI) m/z (%): 339 (1), 325 (1), 284 (20), 283 (100), 210 (3), 208 (4), 179 (3), 165 (4), 141 (8), 75 (11), 73 (3).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 2856, 1248, 1096, 1084, 972, 880, 862, 832, 814, 792, 772 (vs), 666,
HRMS (EI) for $C_{22}H_{31}O_1Si_1$ (339.2149) $[M-H]^+$: 339.2136.

4-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-*N,N*-dimethylaniline (51k)

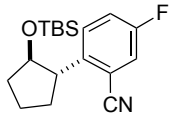


Following **TP1**, *tert*-butyl((2-iodocyclohexyl)oxy)dimethylsilane (**52a**, 0.5 mmol, 1.0 equiv) reacts with (4-(dimethylamino)phenyl)magnesium chloride (1.7 equiv, 1.0 M) at -50 °C. The solution

was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 100:2
yield: 104 mg (63 %), (colorless oil)
dr: 99:1.
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.11 - 7.02 (m, 2H), 6.72 - 6.66 (m, 2H), 3.47 (dd, *J*=4.6 Hz, 1H), 2.89 (s, 6H), 2.36 (ddd, *J*=13.0, 9.6, 3.6 Hz, 1H), 1.99 - 1.35 (m, 8H), 0.70 (s, 9H), -0.19 (s, 3H), -0.47 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 149.5, 133.8, 128.8, 113.1, 76.1, 51.9, 41.2, 36.7, 32.9, 26.2, 25.8, 25.3, 17.9, -4.8, -5.5.
MS (70 eV, EI) m/z (%): 333 (4), 277 (6), 276 (25), 203 (3), 202 (17), 200 (4), 178 (2), 160 (3), 134 (10), 75 (3), 73 (2), 57 (2).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2925, 2852, 1613, 1519, 1471, 1446, 1341, 1247, 1128, 1091, 983, 880, 846, 833, 813, 772,
HRMS (EI) for $C_{20}H_{35}NOSi$ (333.2488) $[M]^+$: 333.2482.

2-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)-5-fluorobenzonitrile (55a)

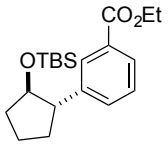


Following **TP1**, *tert*-butyl((2-iodocyclopentyl)oxy)dimethylsilane (**52b**, 0.5 mmol, 1.0 equiv) reacts with (2-cyano-4-fluorophenyl)magnesium chloride (1.7 equiv, 0.78 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 100:1
yield: 107 mg (67 %), (colorless oil)
dr: >99:1.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.27 (s, 3 H), -0.15 (s, 3 H), 0.76 (s, 9 H), 1.66 - 2.06 (m, 5 H), 2.12 - 2.24 (m, 1 H), 3.31 (dt, *J*=10.16, 8.19 Hz, 1 H), 4.10 (q, *J*=7.46 Hz, 1 H), 7.20 - 7.35 (m, 4 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.2, -4.9, 17.8, 21.7, 25.6, 30.9, 34.6, 52.1, 81.3, 114.2,

114.3, 117.1, 117.2, 119.1, 119.4, 120.2, 120.5, 129.0, 129.1, 144.1, 144.2, 158.7, 162.0.
MS (70 eV, EI) m/z (%): 304 (2), 262 (100), 188 (27), 75 (64), 69 (12).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2930, 2857, 2231, 1610, 1584, 1498, 1472, 1464, 1415, 1387, 1361, 1312, 1251, 1191, 1146, 1117, 1090, 1084, 1006, 941, 909, 885, 871, 856, 833, 774, 710, 669.
HRMS (EI) for $C_{18}H_{26}FNOSi$ (319.1768) $[M]^+$: 319.1754.

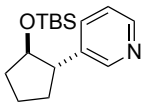
Ethyl 3-(*trans*-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)benzoate (55b)



Following **TP1**, *tert*-butyl((2-iodocyclopentyl)oxy)dimethylsilane (**52b**, 0.5 mmol, 1.0 equiv) reacts with (3-(ethoxycarbonyl)phenyl)magnesium chloride (1.7 equiv, 0.77 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 50:1
yield: 90 mg (52 %), (colorless oil)
dr: 97:3.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.26 (s, 3 H), -0.19 (s, 3 H), 0.77 (s, 9 H), 1.38 (t, *J*=7.19 Hz, 3 H), 1.61 - 1.89 (m, 4 H), 1.95 - 2.15 (m, 2 H), 2.87 - 2.98 (m, 1 H), 4.01 (q, *J*=7.19 Hz, 1 H), 4.36 (q, *J*=7.19 Hz, 2 H), 7.29 - 7.44 (m, 2 H), 7.87 (dt, *J*=7.46, 1.66 Hz, 1 H), 7.89 - 7.94 (m, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.1, -5.0, 14.3, 17.9, 21.7, 25.7, 30.6, 34.7, 54.0, 60.80, 81.3, 127.3, 128.0, 128.6, 130.3, 132.3, 144.2, 166.8.
MS (70 eV, EI) m/z (%): 333 (1), 303 (5), 291 (37), 247 (100), 231 (24), 171 (11).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956, 2930, 2857, 1719, 1606, 1587, 1472, 1463, 1443, 1389, 1367, 1284, 1251, 1201, 1172, 1105, 1086, 1025, 1006, 939, 900, 876, 834, 816, 774, 752, 696, 681, 668.
HRMS (EI) for $C_{20}H_{32}O_3Si$ (348.2121) $[M]^+$: 348.2089.

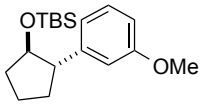
3-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)pyridine (55c)



Following **TP1**, *tert*-butyl((2-iodocyclopentyl)oxy)dimethylsilane (**52b**, 0.5 mmol, 1.0 equiv) reacts with pyridin-3-ylmagnesium chloride (1.7 equiv, 0.90 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 4:1
yield: 101 mg (73 %), (slightly yellow oil)
dr: >99:1.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.30 - -0.24 (m, 3 H), -0.18 (s, 3 H), 0.76 (s, 9 H), 1.64 - 1.91 (m, 4 H), 1.92 - 2.12 (m, 2 H), 2.79 - 2.94 (m, 1 H), 3.98 (q, *J*=7.00 Hz, 1 H), 7.18 (dd, *J*=7.60, 4.56 Hz, 1 H), 7.50 (ddd, *J*=8.02, 1.94, 1.66 Hz, 1 H), 8.38 - 8.50 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.1, -4.9, 17.9, 21.6, 25.6, 30.8, 34.6, 51.8, 81.3, 123.1, 134.7, 139.1, 147.6, 149.6.
MS (70 eV, EI) m/z (%): 262 (3), 221 (14), 220 (100), 146 (34), 75 (22).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2929, 2856, 1576, 1472, 1463, 1426, 1388, 1377, 1361, 1250, 1190, 1114, 1086, 1025, 1006, 938, 889, 860, 834, 809, 774, 714, 668.
HRMS (EI) for $C_{16}H_{27}NOSi$ (277.1862) $[M]^+$: 277.1848.

***tert*-Butyl((*trans*-2-(3-methoxyphenyl)cyclopentyl)oxy)dimethylsilane (55d)**



Following **TP1**, *tert*-butyl((2-iodocyclopentyl)oxy)dimethylsilane (**52b**, 0.5 mmol, 1.0 equiv) reacts with (3-methoxyphenyl)magnesium chloride (1.7 equiv, 1.14 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 100:1
yield: 121 mg (79 %), (colorless oil)

dr: >99:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.21 (s, 3 H), -0.17 (s, 3 H), 0.79 (s, 9 H), 1.61 - 1.88 (m, 4 H), 1.91 - 2.12 (m, 2 H), 2.81 - 2.91 (m, 1 H), 3.79 (s, 3 H), 4.03 (q, *J*=7.00 Hz, 1 H), 6.70 - 6.86 (m, 3 H), 7.20 (t, *J*=7.88 Hz, 1 H).

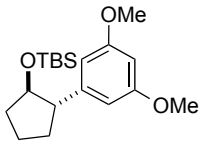
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.0, -5.0, 18.0, 21.9, 25.8, 30.9, 34.8, 54.5, 55.1, 81.51, 111.3, 113.5, 120.0, 129.1, 145.8, 159.5.

MS (70 eV, EI) m/z (%): 250 (25), 249 (54), 75 (100), 43 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 2929, 2856, 1602, 1584, 1492, 1471, 1464, 1454, 1436, 1377, 1360, 1287, 1249, 1194, 1156, 1113, 1047, 1006, 939, 902, 870, 833, 814, 772, 697, 668.

HRMS (EI) for $C_{18}H_{30}O_2Si$ (306.2015) $[M]^+$: 306.2007.

tert-Butyl((*trans*-2-(3,5-dimethoxyphenyl)cyclopentyl)oxy)dimethylsilane (55e)



Following **TP1**, *tert*-butyl((2-iodocyclopentyl)oxy)dimethylsilane (**52b**, 0.5 mmol, 1.0 equiv) reacts with (3,5-dimethoxyphenyl)magnesium chloride (1.7 equiv, 1.14 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 50:1

yield: 124 mg (74 %), (colorless oil)

dr: 99:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.18 (s, 3 H), -0.15 (s, 3 H), 0.80 (s, 9 H), 1.59 - 1.85 (m, 4 H), 1.92 - 2.11 (m, 2 H), 2.78 - 2.88 (m, 1 H), 3.77 (s, 6 H), 4.02 (q, *J*=6.73 Hz, 1 H), 6.30 (t, *J*=2.35 Hz, 1 H), 6.39 (d, *J*=2.21 Hz, 2 H).

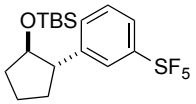
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.0, -4.9, 18.0, 22.0, 25.8, 30.9, 34.9, 54.7, 55.2, 81.38, 98.0, 105.8, 146.6, 160.5.

MS (70 eV, EI) m/z (%): 280 (21), 279 (100), 205 (7), 75 (34).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 2930, 2856, 2839, 1595, 1471, 1461, 1428, 1376, 1359, 1339, 1317, 1294, 1249, 1204, 1151, 1114, 1087, 1060, 1006, 939, 923, 872, 830, 774, 694, 668.

HRMS (EI) for $C_{19}H_{32}O_3Si$ (336.2121) $[M]^+$: 336.2115.

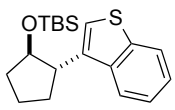
tert-Butyldimethyl((*trans*-2-(3-(pentafluoro-λ6-sulfanyl)phenyl)cyclopentyl)oxy)silane (55f)



Following **TP1**, *tert*-butyl((2-iodocyclopentyl)oxy)dimethylsilane (**52b**, 0.5 mmol, 1.0 equiv) reacts with (3-(pentafluoro-λ6-sulfanyl)phenyl)magnesium chloride (1.7 equiv, 1.0 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane
yield: 123 mg (61 %), (colorless oil)
dr: 99:1.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.64 - 7.54 (m, 2H), 7.41 - 7.33 (m, 2H), 4.00 (dd, *J*=7.4, 0.7, 1H), 2.93 (d, *J*=10.0 Hz, 1H), 2.35 - 1.50 (m, 8H), 0.77 (s, 9H), -0.16 (s, 3H), -0.26 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 154.1, 145.2, 130.7, 128.4, 125.2, 123.7, 81.4, 54.2, 34.6, 30.5, 25.6, 21.5, 17.9, -5.0, -5.4.
MS (70 eV, EI) m/z (%): 345 (18), 323 (5), 237 (40), 219 (11), 143 (65), 128 (99), 118 (39), 88 (48), 78 (22).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2857, 1604, 1471, 1250, 1257, 1110, 905, 828, 788, 773, 693,
HRMS (EI) for $C_{17}H_{27}F_5OSSi$ (402.1472) $[M\text{-}^t\text{Bu}]^+$: 345.0784.

((*trans*-2-(Benzo[b]thiophen-3-yl)cyclopentyl)oxy)(*tert*-butyl)dimethylsilane (55g)

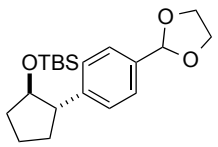


Following **TP1**, *tert*-butyl((2-iodocyclopentyl)oxy)dimethylsilane (**52b**, 0.5 mmol, 1.0 equiv) reacts with benzo[b]thiophen-3-ylmagnesium chloride (1.7 equiv, 0.84 M) at -50 °C. The solution

was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 100:1
yield: 96 mg (58 %), (colorless oil)
dr: 98:2.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.23 (s, 3 H), -0.16 (s, 3 H), 0.80 (s, 9 H), 1.68 - 2.05 (m, 5 H), 2.19 - 2.27 (m, 1 H), 3.34 - 3.44 (m, 1 H), 4.25 (q, *J*=5.99 Hz, 1 H), 7.08 (s, 1 H), 7.29 - 7.40 (m, 2 H), 7.82 - 7.91 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.9, -5.0, 18.0, 22.1, 25.8, 30.0, 34.9, 47.8, 80.2, 119.7, 122.7, 122.8, 123.6, 124.1, 139.3, 139.3, 140.5.
MS (70 eV, EI) m/z (%): 277 (8), 276(18), 275 (100), 201 (11), 147 (9), 75 (53).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 2928, 2856, 1471, 1461, 1428, 1388, 1360, 1250, 1157, 1115, 1096, 1081, 1048, 1026, 1005, 938, 903, 883, 863, 833, 813, 773, 759, 730, 715, 667.
HRMS (EI) for $C_{19}H_{28}OSSi$ (332.1630) $[M]^+$: 332.1613.

((*trans*-2-(4-(1,3-Dioxolan-2-yl)phenyl)cyclopentyl)oxy)(*tert*-butyl)dimethylsilane (55h)

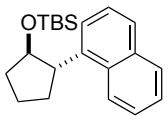


Following **TP1**, *tert*-butyl((2-iodocyclopentyl)oxy)dimethylsilane (**52b**, 0.5 mmol, 1.0 equiv) reacts with (4-(1,3-dioxolan-2-yl)phenyl)magnesium chloride (1.7 equiv, 0.95 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 25:1
yield: 135 mg (78 %), (colorless oil)
dr: >99:1.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.23 (s, 3 H), -0.18 (s, 3 H), 0.78 (s, 9 H), 1.66 - 1.89 (m, 4 H), 1.91 - 2.11 (m, 2 H), 2.84 - 2.96 (m, 1 H), 4.00 - 4.05 (m, 2 H), 4.09 - 4.13 (m, 2 H), 5.80 (s, 1 H), 7.20 - 7.25 (m, 2 H), 7.35 - 7.39 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.9, -5.0, 18.0, 22.0, 25.8, 31.1, 34.9, 54.2, 65.2, 81.4, 103.8, 126.3, 127.6, 128.3, 129.2, 135.6, 145.3.

MS (70 eV, EI) m/z (%): 291 (36), 248 (19), 247 (100), 171 (6), 149 (5), 115 (5). **IR (ATR) $\tilde{\nu}$ (cm^{-1}):** 2954, 2929, 2884, 2856, 1472, 1463, 1388, 1361, 1274, 1250, 1220, 1180, 1112, 1079, 1021, 1012, 1006, 968, 941, 911, 890, 861, 833, 774, 707, 668. **HRMS (EI)** for $C_{20}H_{32}O_3Si$ (348.2121) $[M]^+$: 348.2110.

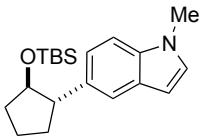
***tert*-Butyldimethyl((*trans*-2-(naphthalen-1-yl)cyclopentyl)oxy)silane (55i)**



Following **TP1**, *tert*-butyl((2-iodocyclopentyl)oxy)dimethylsilane (**4b**, 4 mmol, 1.0 equiv) reacts with naphthalen-1-ylmagnesium chloride (1.7 equiv, 1.0 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane
yield: 1.04 g (80 %), (colorless oil)
dr: >99:1.
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.30 (d, *J*=8.21 Hz, 1 H), 7.91 - 7.84 (m, 1 H), 7.74 (d, *J*=8.08 Hz, 1 H), 7.57 - 7.38 (m, 4H), 4.34 (q, *J*=6.11 Hz, 1 H), 3.91 - 3.84 (m, 1 H), 2.37 - 2.29 (m, 1 H), 2.13 - 1.87 (m, 4 H), 1.84 - 1.76 (m, 1 H), 0.80 (s, 9 H), -0.17 (s, 3 H), -0.28 (s, 3 H).
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 140.6, 133.8, 132.7, 128.5, 126.4, 125.4, 125.4, 125.3, 124.4, 122.7, 81.3, 49.0, 35.1, 31.3, 25.7, 22.5, 17.9, -5.0, -5.1.
MS (70 eV, EI) m/z (%): 326 (1), 270 (22), 269 (100), 195 (8), 193 (18), 191 (9), 165 (12), 141 (16), 115 (4), 75 (66), 73 (11), 57 (3).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (w), 2928 (w), 2856 (w), 1472 (w), 1250, 1114, 1094, 1078, 1062, 1032 (w), 1006 (w), 890, 864, 834, 810, 794, 772 (vs), 730 (w), 668,
HRMS (EI) for $C_{21}H_{30}O_1Si_1$ (326.2066) $[M]^+$: 326.2053.

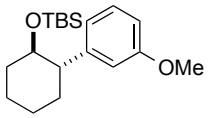
5-(*trans*-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentyl)-1-methyl-1H-indole (55j)



Following **TP1**, *tert*-butyl((2-iodocyclopentyl)oxy)dimethylsilane (**52b**, 0.5 mmol, 1.0 equiv) reacts with (1-methyl-1H-indol-5-yl)magnesium bromide (1.7 equiv, 1.0 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; n-hexane/Et_2O = 100:2
yield: 106 mg (65 %), (colorless oil)
dr: 99:1.
^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 7.44 (s, 1H), 7.22 (d, *J*=8.4 Hz, 1H), 7.10 (dt, *J*=8.6 Hz, 1.7, 1H), 7.01 - 6.98 (m, 1H), 6.40 (t, *J*=2.3 HZ, 1H), 4.10 (qd, *J*=6.6 Hz, 1.8, 1H), 3.76 (d, *J*=1.9 Hz, 3H), 2.99 (d, *J*=7.8 Hz, 1H), 2.20 - 2.07 (m, 1H), 2.00 (d, *J*=6.6 Hz, 1H), 1.92 - 1.74 (m, 3H), 1.70 - 1.63 (m, 1H), 0.82 - 0.76 (m, 10H), -0.22 (dd, *J*=13.0, 2.0 Hz, 6H).
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 135.6, 134.8, 128.7, 128.5, 121.7, 119.2, 108.7, 100.5, 81.7, 54.4, 34.9, 32.8, 31.7, 25.8, 22.2, 18.1, -4.8, -5.0.
MS (70 eV, EI) m/z (%): 329 (3) $[M]^+$, 273 (10), 272 (50), 199 (3), 198 (20), 196 (6), 157 (4), 144 (6), 75 (10), 73 (5).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954, 2929, 2856, 1491, 1247, 1113, 1079, 906, 879, 835, 775, 731.
HRMS (EI) for $C_{20}H_{31}NOSi$ (329.2175) $[M]^+$: 329.2180.

***tert*-Butyl((*trans*-2-(3-methoxyphenyl)cyclohexyl)oxy)dimethylsilane (58a)**



Following **TP1**, ((2-bromocyclohexyl)oxy)(*tert*-butyl)dimethylsilane (**52c**, 0.5 mmol, 1.0 equiv) reacts with (3-methoxyphenyl)magnesium chloride (1.7 equiv, 1.14 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 100:1
yield: 85 mg (53 %), (colorless oil)

dr: 97:3.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.49 (s, 3 H), -0.18 (s, 3 H), 0.67 (s, 9 H), 1.27 - 1.42 (m, 3 H), 1.51 - 1.61 (m, 1 H), 1.70 - 1.88 (m, 3 H), 1.94 - 2.01 (m, 1 H), 2.42 (ddd, *J*=12.65, 9.47, 3.59 Hz, 1 H), 3.53 (td, *J*=9.81, 4.42 Hz, 1 H), 3.78 (s, 3 H), 6.68 - 6.82 (m, 3 H), 7.16 (t, *J*=7.88 Hz, 1 H).

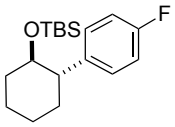
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.6, -4.7, 17.8, 25.2, 25.7, 26.0, 32.8, 36.7, 53.1, 55.2, 75.9, 111.5, 114.2, 120.7, 128.8, 146.7, 159.3.

MS (70 eV, EI) m/z (%): 264 (35), 263 (100), 189 (7), 121 (19), 75 (87).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2928, 2856, 1602, 1585, 1493, 1471, 1463, 1448, 1437, 1361, 1284, 1256, 1249, 1226, 1218, 1206, 1166, 1157, 1128, 1094, 1048, 1023, 1002, 990, 938, 926, 878, 863, 833, 815, 771, 752, 743, 698, 666.

HRMS (EI) for $C_{19}H_{32}O_2Si$ (320.2172) $[M]^+$: 320.2162.

tert-Butyl((*trans*-2-(4-fluorophenyl)cyclohexyl)oxy)dimethylsilane (58b)



Following **TP1**, ((2-bromocyclohexyl)oxy)(*tert*-butyl)dimethylsilane (**52c**, 0.5 mmol, 1.0 equiv) reacts with (4-(fluoro)phenyl)magnesium chloride (1.7 equiv, 1.0 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane

yield: 80 mg (52 %), (colorless oil)

dr: 97:3.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.18 - 7.08 (m, 1H), 6.95 (d, *J*=8.8 Hz, 1H), 3.42 - 3.52 (m, 1H), 2.48 - 2.32 (m, 1H), 2.08 - 1.60 (m, 1H), 1.60 - 1.23 (m, 1H), 0.67 (s, 9), -0.18 (s,3H), -0.50 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 159.8, 140.7, 129.4, 114.4, 75.9, 52.2, 36.6, 32.8, 26.0, 25.6, 25.2, 17.8, -4.6, -5.6.

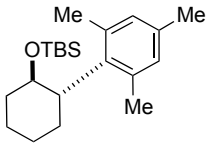
^{19}F NMR (75 MHz, $CDCl_3$) δ/ppm: -117.94.

MS (70 eV, EI) m/z (%): 251 (90), 132 (4), 183 (9), 149 (12), 109 (19), 81 (3), 75 (28), 73 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2927, 2854, 1605, 1509, 1255, 1248, 1226, 1092, 1086, 983, 827, 833, 772, 666.

HRMS (EI) for C18H29FOSi (251.1267) [M-^{t}Bu]$^+$: 251.1798.

tert-Butyl((*trans*-2-mesitylcyclohexyl)oxy)dimethylsilane (58d)



Following **TP1**, ((2-bromocyclohexyl)oxy)(*tert*-butyl)dimethylsilane (**52c**, 0.5 mmol, 1.0 equiv) reacts with mesitylmagnesium chloride (1.7 equiv, 0.95 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane

yield: 98 mg (59 %), (colorless oil)

dr: 98:2.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.76 (d, *J*=10.57 Hz, 2H), 4.11 - 4.03 (m, 1H), 3.07 - 2.98 (m, 1H), 2.43 (s, 3H), 2.33 (s, 3H), 2.22 (s, 3H), 2.05 - 1.95 (m, 2H), 1.82 - 1.69 (m, 3H), 1.38 - 1.27 (m, 3H), 0.65 (s, 9H), -0.13 (s, 3H), -0.48 (s, 3H).

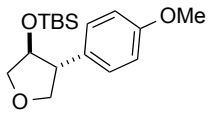
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 138.2, 137.3, 135.4, 134.7, 130.8, 128.9, 72.3, 48.2, 37.6, 29.8, 26.8, 25.5, 25.3, 22.3, 21.7, 20.6, 17.7, -4.6, -5.7.

MS (70 eV, EI) m/z (%): 332 (1), 276 (22), 275 (100), 199 (7), 157 (7), 143 (3), 133 (35), 105 (3), 75 (78), 73 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2950, 2928, 2856, 1472, 1248, 1090, 988, 880, 848, 834, 802, 772, 666.

HRMS (EI) for $C_{21}H_{36}O_1Si_1$ (332.2535) [M]$^+$: 332.2510.

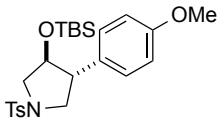
tert-Butyl((*trans*-4-(4-methoxyphenyl)tetrahydrofuran-3-yl)oxy)dimethylsilane (60)



Following **TP1**, *tert*-butyl((4-iodotetrahydrofuran-3-yl)oxy)dimethylsilane (**59a**, 4 mmol, 1.0 equiv) reacts with (4-methoxyphenyl)magnesium bromide (1.7 equiv, 0.94 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/Et_2O = 20:1
yield: 912 mg (74 %), (colorless oil)
dr: >99:1.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.05 (s, 6 H), 0.85 (s, 9 H), 3.14 - 3.23 (m, 1 H), 3.68 (dd, *J*=9.12, 3.87 Hz, 1 H), 3.78 (s, 3 H), 3.91 (dd, *J*=8.85, 5.53 Hz, 1 H), 4.03 (dd, *J*=9.12, 5.25 Hz, 1 H), 4.21 - 4.30 (m, 2 H), 6.85 (m, 2 H), 7.16 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.9, -4.7, 18.0, 25.7, 53.9, 55.2, 73.1, 74.8, 80.2, 114.0, 128.4, 133.0, 158.4.
MS (70 eV, EI) m/z (%): 251 (6), 134 (17), 121 (100), 117 (4).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2953, 2930, 2857, 1613, 1513, 1471, 1464, 1442, 1361, 1304, 1247, 1179, 1097, 1080, 1057, 1037, 1003, 939, 909, 863, 830, 811, 775, 668.
HRMS (EI) for $C_{17}H_{28}O_3Si$ (308.1808) $[M]^+$: 308.1817.

trans-3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-methoxyphenyl)-1-tosylpyrrolidine (61)



Following **TP1**, 3-((*tert*-butyldimethylsilyl)oxy)-4-iodo-1-tosylpyrrolidine (**59b**, 0.5 mmol, 1.0 equiv) reacts with (4-methoxyphenyl)magnesium bromide (1.7 equiv, 0.94 M) at -50 °C. The solution was allowed to warm to rt over 10 h and was worked-up as usual.

column chromatography: SiO_2; *n*-hexane/EtOAc = 9:1
yield: 164 mg (71 %), (white solid)
dr: >99:1.
Melting point: 129.1-131.2 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: -0.22 (s, 3 H), -0.17 (s, 3 H), 0.70 (s, 9 H), 2.43 (s, 3 H), 2.96 - 3.09 (m, 2 H), 3.45 - 3.54 (m, 1 H), 3.55 - 3.67 (m, 2 H), 3.76 (s, 3 H), 4.03 (q, *J*=5.25 Hz, 1 H),

6.81 (m, 2 H), 7.07 (m, 2 H), 7.33 (m, *J*=7.74 Hz, 2 H), 7.74 (m, *J* = 8.29 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -5.2, -5.1, 17.8, 21.5, 25.5, 51.3, 51.8, 54.3, 55.2, 77.53, 114.1, 127.6, 128.4, 129.7, 131.1, 133.8, 143.4, 158.7.

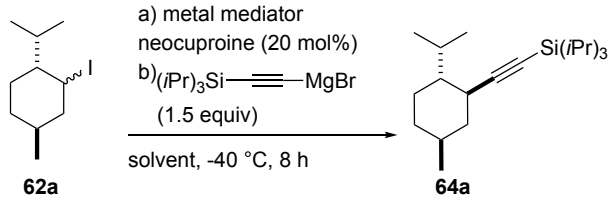
MS (70 eV, EI) m/z (%): 446 (2), 406 (14), 404 (100), 147 (11), 121 (46), 91 (26).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955, 2926, 2884, 2858, 1612, 1600, 1516, 1498, 1472, 1464, 1441, 1391, 1362, 1340, 1336, 1317, 1308, 1294, 1284, 1250, 1220, 1205, 1182, 1166, 1152, 1122, 1106, 1092, 1065, 1053, 1036, 1020, 1009, 941, 922, 861, 834, 818, 802, 778, 744, 726, 708, 664.

HRMS (EI) for $C_{24}H_{35}NO_4SSi$ (461.2056) $[M]^+$: 461.2045.

3. Diastereoselective Cobalt-Mediated Cross-Couplings of Cycloalkyl Iodides with Alkynyl or (Hetero)Aryl Grignard Reagents

3.1 Optimization of the Reaction Conditions: Solvent Screening



62a **64a**

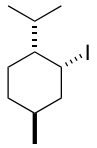
entry	metal mediator (equiv)	solvent	GC yield[a] (%)
1	$CoCl_2$·2LiCl (0.50)	THF	88
2	$CoCl_2$·2LiCl (0.20)	THF	63
3	$CoCl_2$·2LiCl (0.50)	Et_2O	85
4	$CoCl_2$·2LiCl (0.20)	Et_2O	59
5	$CoCl_2$·2LiCl (0.50)	NMP	28
6	$CoCl_2$·2LiCl (0.20)	NMP	8
7	$CoCl_2$·2LiCl (0.50)	DMPU	13
8	$CoCl_2$·2LiCl (0.20)	DMPU	3
9	$CoCl_2$·2LiCl (0.50)	DME	86
10	$CoCl_2$·2LiCl (0.20)	DME	58

[a]Determined by capillary GC and ^{1}H NMR analysis. Undecane ($C_{11}H_{24}$) was used as internal standard.

3.2 Synthesis of Starting Materials

The following starting materials were prepared according to literature procedures with only little deviation. The spectral data of known compounds are in full agreement with the literature.

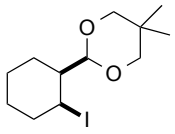
2-Iodo-1-isopropyl-4-methylcyclohexane (62a)[91]



dr = 99:1

^{1}H-NMR (300 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).

2-(2-Iodocyclohexyl)-5,5-dimethyl-1,3-dioxane (62c)[92]

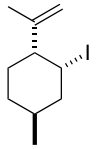


dr = 99:1

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 4.85 (dq, *J* = 3.1, 1.7 Hz, 1H), 4.07 (d, *J* = 7.5 Hz, 1H), 3.60 (ddd, *J* = 11.6, 9.3, 2.7 Hz, 2H), 3.43 (dd, *J* = 11.4, 5.0 Hz, 2H), 2.19 – 2.13 (m, 1H), 1.79 – 1.62 (m, 4H), 1.55 (s, 1H), 1.40 – 1.22 (m, 2H), 1.17 (s, 3H), 0.77 (ddt, *J* = 10.6, 7.6, 2.9 Hz, 1H), 0.72 (s, 3H).

[91] S. D. Lepore, D. Mondal, S. Y. Li, A. K. Bhunia, *Angew. Chem. Int. Ed.* **2008**, *47*, 7511.
[92] K. Moriya, P. Knochel, *Org. Lett.* **2014**, *16*, 924.

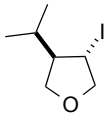
2-Iodo-4-methyl-1-(prop-1-en-2-yl)cyclohexane (62d)[1]



dr = 99:1

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 4.86 (ddd, *J* = 5.8, 3.0, 1.5 Hz, 2H), 4.66 (td, *J* = 1.7, 0.8 Hz, 1H), 2.25 (dtd, *J* = 14.4, 3.2, 2.3 Hz, 1H), 1.99 (tdt, *J* = 14.8, 6.6, 3.1 Hz, 1H), 1.87 – 1.75 (m, 1H), 1.74 (dt, *J* = 1.4, 0.7 Hz, 3H), 1.70 – 1.53 (m, 2H), 1.45 (ddd, *J* = 14.6, 11.5, 3.3 Hz, 1H), 1.30 – 1.15 (m, 1H), 1.05 (dtd, *J* = 13.3, 12.0, 4.8 Hz, 1H), 0.94 (d, J = 6.6 Hz, 3H).

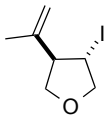
3-Iodo-4-isopropyltetrahydrofuran



dr = 99:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.21 – 4.12 (m, 1H), 3.81 – 3.67 (m, 2H), 3.43 (t, *J* = 7.9 Hz, 1H), 1.94 (d, *J* = 5.8 Hz, 1H), 1.80 (ddd, *J* = 10.9, 8.8, 5.5 Hz, 1H), 1.57 (dh, *J* = 13.5, 6.6 Hz, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).

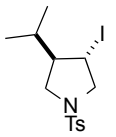
3-Iodo-4-(prop-1-en-2-yl)tetrahydrofuran



dr = 99:1

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): *d* = 5.03 – 4.91 (m, 1H), 4.62 – 4.60 (m, 1H), 4.57 (td, *J* = 4.6, 1.6 Hz, 1H), 4.52 (dd, *J* = 10.4, 4.4 Hz, 1H), 4.41 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.03 (s, 1H), 4.01 (d, *J* = 1.8 Hz, 1H), 2.34 – 2.27 (m, 1H), 1.79 (dt, *J* = 1.6, 0.8 Hz, 3H).

3-Iodo-4-isopropyl-1-tosylpyrrolidine



dr = 99:1

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.74 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 4.33 (t, *J* = 4.1 Hz, 1H), 4.16 (dd, *J* = 12.4, 4.3 Hz, 1H), 3.97 (d, *J* = 12.4 Hz, 1H), 3.56 (dd, *J* = 11.1, 9.3 Hz Hz, 1H), 3.01 (dd, *J* = 11.0, 9.3 Hz, 1H), 2.43 (s, 3H), 1.43 (dp, *J* = 9.5, 6.6 Hz, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.78 – 0.70 (m, 1H).

3.3 Preparation of Orgamometallic Reagents

Preparation of alkynyl grignard reagents:

The corresponding alkyne (1 equiv, 1 mmol) and THF (1 mL) were added to a dry and argon-flushed 10 mL *Schlenk*-flask, equipped with a stirring bar and a septum. TMPMgCl·LiCl (1.2 equiv, addition at 0 °C) or EtMgBr (1.2 equiv, addition at -20 °C) were added dropwise and the reaction mixture was allowed to warm to room temperature and stirred until a reaction aliquot quenched with I_2 in THF showed full conversion of the starting material by GC.

Preparation of aryl magnesium reagents *via* insertion of magnesium:

LiCl (1.1 equiv) was dried under high vacuum and allowed to cool to room temperature, then Mg turnings (1.2 equiv) and THF (1 M solution relating to the aryl bromide) were added. The reaction mixture was cooled to 0 °C and the corresponding aryl bromide (1.0 equiv) was added dropwise. The reaction was stirred until iodolysis of a reaction aliquot indicated full consumption of the starting material.

Preparation of aryl magnesium reagents via iodine-magnesium exchange:

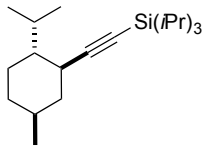
The corresponding aryl bromide (1.0 equiv) was dissolved in THF (1 M solution relating to the aryl bromide) and the reaction mixture was cooled to -30 °C. Then *i*-PrMgCl·LiCl (1.1 equiv) was

added dropwise and the reaction was stirred at this temperature until reaction aliquots quenched with iodine showed full consumption of the starting material.

3.4 Diastereoselective Cobalt-Mediated Cross-Couplings of Cycloalkyl Iodides with Alkynyl or (Hetero)Aryl Grignard Reagents

Typical procedure 2 (TP2): A dry and argon-flushed 10 mL *Schlenk*-tube was charged with $CoCl_2$·2LiCl (1.0 M in THF) (0.25 mmol, 0.25 mL, 50 mol %) and neocuproine (0.2 mmol, 21 mg, 20 mol %), in dry THF (1 mL). The respective cycloalkyl iodide (0.5 mmol) was added and the mixture was cooled to -40 °C or 0 °C. Then, a solution of the appropriate alkynyl or aryl Grignard reagent (0.75 mmol, 1.5 equiv) was added dropwise over 10 min *via* syringe. The reaction was stirred and monitored by GC-analysis ($C_{14}H_{30}$ was used as an internal standard). Upon consumption of the starting material, saturated aq. NH_4Cl solution (5 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 chromatography on silica yielding the respective title compound.

Triisopropyl(((*1R,2S,5R*)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl)ethynyl)silane (64a)



Isolated yield: 108 mg, 0.34 mmol, 68%, colorless oil

dr: 99:1.

Purification: *i*-hexane

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 2.27 (ddq, *J* = 9.9, 7.0, 3.5, 2.9 Hz, 1H), 2.11 (td, *J* = 11.5, 3.5 Hz, 1H), 1.92 (dq, *J* = 12.9, 3.4 Hz, 1H), 1.67 – 1.59 (m, 1H), 1.59 – 1.49 (m, 1H), 1.30 – 1.20 (m, 1H), 1.01 – 0.95 (m, 28H), 0.84 (d, *J* = 7.1 Hz, 3H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.71 (d, *J* = 6.9 Hz, 3H).

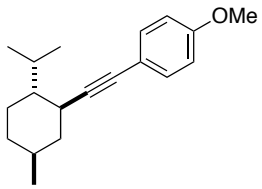
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 112.6, 80.2, 47.5, 42.6, 34.9, 34.6, 32.5, 28.7, 24.2, 22.3, 21.3, 18.6, 15.7, 11.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2942, 2924, 2891, 2865, 2170, 1647, 1462, 1375, 1259, 1060,996, 908, 884, 844, 735, 678.

MS (EI, 70 eV): *m/z* (%) = 224 (4), 323 (12), 291 (3), 278 (2), 277 (9), 276 (40), 275 (100), 273 (6).

HR-MS (EI, 70 eV): [$C_{21}H_{38}Si$], calcd.: 275.2201; found: 275.2192 [M^+-*i*Pr].

1-(((*1R,2S,5R*)-2-Isopropyl-5-methylcyclohexyl)ethynyl)-4-methoxybenzene (64b)



Isolated yield: 100 mg, 0.37 mmol, 74%, colorless oil

dr: 99:1.

Purification: *i*-hexane:ethyl acetate = 100:2

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.26 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 3.72 (s, 3H), 2.31 – 2.21 (m, 2H), 2.03 – 1.95 (m, 1H), 1.70 – 1.62 (m, 1H), 1.60 – 1.54 (m, 1H), 1.37 – 1.24 (m, 1H), 1.24 – 1.04 (m, 3H), 0.99 – 0.90 (m, 1H), 0.87 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H).

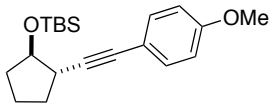
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 158.9, 132.9, 116.4, 113.7, 91.9, 81.1, 55.3, 47.5, 42.5, 34.9, 34.1, 32.5, 28.9, 24.3, 22.3, 21.4, 15.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2869, 2253, 1607, 1509, 1288, 1246, 1172, 1035, 906, 831, 731.

MS (EI, 70 eV): *m/z* (%) = 270 (15), 255 (100), 213 (14), 147 (35), 145 (9), 120 (20), 114 (2), 42 (4), 40 (8).

HR-MS (EI, 70 eV): [$C_{19}H_{26}O$], calcd.: 270.1984; found: 238.1356.

***tert*-Butyl(((*1R,2S*)-2-((4-methoxyphenyl)ethynyl)cyclopentyl)oxy)dimethylsilane (64c)**



Isolated yield: 114 mg, 0.34 mmol, 69%, colorless oil

dr: 99:1.

Purification: *i*-hexane:ethyl acetate = 100:2

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.24 – 7.18 (m, 2H), 6.73 – 6.67 (m, 2H), 4.12 (q, *J* = 5.7 Hz, 1H), 3.69 (s, 3H), 2.67 – 2.57 (m, 1H), 2.05 – 1.96 (m, 1H), 1.90 – 1.80 (m, 1H), 1.70 – 1.55 (m, 3H), 1.52 – 1.41 (m, 1H), 0.80 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

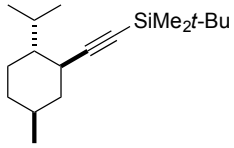
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 158.9, 132.8, 116.2, 113.8, 91.1, 81.2, 79.9, 55.3, 40.2, 34.6, 31.0, 25.9, 21.9, 18.2, -4.5, -4.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955, 2856, 2359, 1607, 1509, 1287, 1247, 1090, 1038, 906, 832, 776, 731.

MS (EI, 70 eV): *m/z* (%) = 273 (29), 200 (13), 199 (100), 171 (5), 164 (4), 121 (4), 75 (15), 73 (15).

HR-MS (EI, 70 eV): [$C_{16}H_{21}O_2Si$], calcd.: 273.1311; found: 273.1326 [M^+-*t*Bu].

***tert*-Butyl(((*1R,2S,5R*)-2-isopropyl-5-methylcyclohexyl)ethynyl)dimethylsilane (64d)**



Isolated yield: 79 mg, 0.28 mmol, 61%, colorless oil

dr: 99:1.

Purification: *i*-hexane

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 2.29 (pd, *J* = 7.0, 2.9 Hz, 1H), 2.21 – 2.13 (m, 1H), 1.98 (dtd, *J* = 13.0, 3.5, 2.2 Hz, 1H), 1.73 – 1.67 (m, 1H), 1.64 – 1.57 (m, 1H), 1.38 – 1.25 (m, 1H), 1.23 – 1.03 (m, 2H), 0.97 – 0.90 (m, 14H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.77 (d, J = 6.9 Hz, 3H), 0.07 (s, 6H).

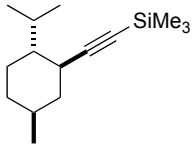
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 111.5, 82.9, 47.5, 42.6, 35.0, 34.7, 32.6, 28.8, 26.7, 26.3, 26.2, 24.4, 22.4, 21.4, 16.7, 15.9, -4.2, -4.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955, 2929, 2857, 2167, 1471, 1249, 908, 908, 837, 824, 810, 775, 735, 686.

MS (EI, 70 eV): *m/z* (%) = 221 (5), 74 (8), 73 (100), 57 (11).

HR-MS (EI, 70 eV): [$C_{18}H_{34}Si$], calcd.: 221.1720; found: 221.1720 [M^+-C_4H_9].

(((1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl)ethynyl)trimethylsilane (64e)



Isolated yield: 92 mg, 0.39 mmol, 78%, colorless oil

dr: 99:1.

Purification: *i*-hexane

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 2.25 (pd, *J* = 7.1, 2.8 Hz, 1H), 2.17 (td, *J* = 11.5, 3.5 Hz, 1H), 1.98 (dd, *J* = 12.8, 3.2 Hz, 1H), 1.75 – 1.66 (m, 1H), 1.64 – 1.57 (m, 1H), 1.39 – 1.24 (m, 1H), 1.24 – 1.10 (m, 2H), 1.01 – 0.94 (m, 2H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H), 0.14 (s, 9H).

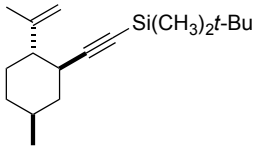
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 110.6, 84.4, 46.8, 42.0, 34.5, 34.1, 32.1, 28.3, 24.0, 22.0, 21.0, 15.5, 0.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 1704, 1456, 1407, 1386, 1368, 1248, 1131, 930, 835, 758, 696, 668.

MS (EI, 70 eV): *m/z* (%) = 237 (4), 236 (21), 222 (25), 221 (100), 163 (26), 162 (66), 147 (32), 140 (15), 109 (13), 73 (55).

HR-MS (EI, 70 eV): [$C_{15}H_{28}Si$], calcd.: 236.1960; found: 236.1945.

***tert*-Butyldimethyl(((*1R,2S,5R*)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl)ethynyl)silane (64f)**



Isolated yield: 76 mg, 0.27 mmol, 55%, colorless oil

dr: 99:1.

Purification: *i*-hexane

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 4.75 (q, *J* = 1.2 Hz, 2H), 2.29 (ddd, *J* = 11.9, 11.0, 3.5 Hz, 1H), 2.01 (dtd, *J* = 13.1, 3.5, 2.0 Hz, 1H), 1.93 (ddd, *J* = 12.0, 11.0, 3.3 Hz, 1H), 1.70 (m, 3H), 1.69 – 1.62 (m, 2H), 1.42 – 1.23 (m, 2H), 1.17 – 1.06 (m, 1H), 1.06 – 0.93 (m, 1H), 0.90 (d, *J* = 5.7 Hz, 12H), 0.04 (s, 6H).

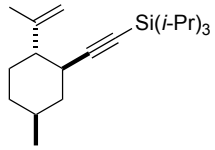
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 148.1, 111.2, 110.9, 82.7, 51.3, 41.8, 34.8, 34.7, 32.3, 32.0, 26.2, 22.4, 19.8, 16.7, 1.2, -4.2, -4.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2952, 2927, 2865, 2171, 1647, 1456, 1248, 1006, 907, 845, 825, 811, 774, 734, 685, 650.

MS (EI, 70 eV): *m/z* (%) = 276 (2), 221 (16), 220 (69), 219 (100), 217 (13), 178 (11), 177 (65), 163 (9), 160 (18), 159 (37), 157 (14), 151 (9), 149 (17), 135 (14), 123 (16), 119 (11), 109 (38), 105 (11), 98 (14), 96 (13), 83 (22), 81 (11), 73 (98), 59 (80), 57 (21), 55 (15), 43 (9), 43 (11), 41 (24).

HR-MS (EI, 70 eV): [$C_{18}H_{32}Si$], calcd.: 276.2273; found: 276.2272.

Triisopropyl(((1*S*,2*S*,5*S*)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl)ethynyl)silane (64g)



Isolated yield: 108 mg, 0.34 mmol, 68%, colorless oil

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 4.74 (dt, *J* = 5.4, 1.8 Hz, 2H), 2.36 – 2.22 (m, 1H), 2.02 (dtd, *J* = 13.1, 3.5, 1.9 Hz, 1H), 1.94 (td, *J* = 11.8, 3.3 Hz, 1H), 1.71 (t, *J* = 1.1 Hz, 3H), 1.69 – 1.62 (m, 1H), 1.44 – 1.22 (m, 2H), 1.21 – 0.92 (m, 23H), 0.90 (d, *J* = 6.5 Hz, 3H).

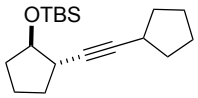
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 148.1, 112.0, 111.2, 80.0, 78.7, 51.5, 42.0, 34.8, 34.7, 32.3, 32.1, 22.4, 19.6, 18.8, 18.8, 18.8, 11.4, 11.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2942, 2924, 2891, 2865, 2170, 1647, 1462, 1375, 1259, 1060, 996, 908, 884, 844, 735, 678.

MS (EI, 70 eV): *m/z* (%) = 323 (23), 307 (3), 277 (10), 276 (40), 275 (100), 273 (6).

HR-MS (EI, 70 eV): [$C_{21}H_{38}Si$], calcd.: 275.2195; found: 275.2192 [M^+-C_3H_7].

***tert*-butyl(((1*R*,2*S*)-2-(cyclopentylethynyl)cyclopentyl)oxy)dimethylsilane (64h)**



Isolated yield: 85 mg, 0.29 mmol, 58%, colorless oil

dr: 99:1.

Purification: *i*-hexane:ethyl acetate = 99:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.99 (q, *J* = 5.7 Hz, 1H), 2.49 (pd, *J* = 7.5, 2.1 Hz, 1H), 2.41 (tdd, *J* = 7.7, 5.5, 2.1 Hz, 1H), 1.98 – 1.87 (m, 1H), 1.87 – 1.75 (m, 3H), 1.67 – 1.54 (m, 4H), 1.51 – 1.37 (m, 6H), 0.81 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

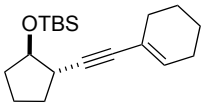
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 85.4, 82.2, 80.1, 39.6, 34.4, 34.1, 31.3, 30.4, 25.9, 24.9, 21.8, 18.2, -4.6, -4.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2931, 2858, 1710, 1472, 1361, 1251, 1085, 1005, 939, 895, 865, 835, 775, 668.

MS (EI, 70 eV): *m/z* (%) = 291 (1), 235 (28), 161 (24), 159 (63), 91 (32), 75 (100), 73 (31), 67 (12).

HR-MS (EI, 70 eV): [$C_{18}H_{32}OSi$], calcd.: 291.2148; found: 291.2144.

***tert*-butyl(((1*R*,2*S*)-2-(cyclohex-1-en-1-ylethynyl)cyclopentyl)oxy)dimethylsilane (64i)**



Isolated yield: 104 mg, 0.34 mmol, 68%, colorless oil

dr: 99:1.

Purification: *i*-hexane:ethyl acetate = 99:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.99 (dt, *J* = 4.0, 2.1 Hz, 1H), 4.13 (q, *J* = 5.4 Hz, 1H), 2.67 – 2.57 (m, 1H), 2.11 – 2.03 (m, 5H), 1.91 (ddt, *J* = 12.6, 8.6, 6.3 Hz, 1H), 1.72 – 1.51 (m, 8H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 133.2, 121.0, 89.7, 83.2, 79.9, 40.1, 34.51, 31.2, 29.6, 25.9, 25.6, 22.4, 21.9, 21.6, 18.2, -4.7, -4.8.

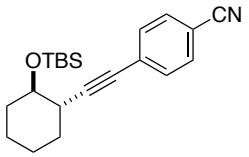
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2950, 2930, 2857, 1715, 1674, 1472, 1462, 1447, 1388, 1360, 1250,

1170, 1087, 1005, 939, 867, 834, 775, 668.

MS (EI, 70 eV): *m/z* (%) = 304 (1), 247 (47), 174 (15), 173 (100), 171 (53), 129 (15), 91 (15), 75 (68), 73 (34).

HR-MS (EI, 70 eV): [$C_{19}H_{32}OSi$], calcd.: 304.2222; found: 304.2202.

4-(((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)ethynyl)benzonitrile (64j)



Isolated yield: 105 mg, 0.31 mmol, 62%, yellow oil

dr: 99:1.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.55 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 3.69 – 3.58 (m, 1H), 2.52 (ddd, *J* = 10.0, 8.1, 3.9 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.95 – 1.86 (m, 1H), 1.78 – 1.61 (m, 2H), 1.53 – 1.40 (m, 1H), 1.37 – 1.19 (m, 3H), 0.88 (s, 9H), 0.07 (s, 6H).

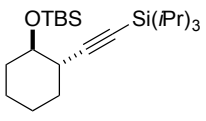
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 132.1, 131.9, 129.2, 118.7, 110.8, 98.3, 80.4, 73.1, 38.7, 34.5, 30.3, 29.7, 25.8, 24.3, 23.5, 18.1, -4.4, -4.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929, 2856, 2227, 1605, 1501, 1472, 1462, 1249, 1131, 1100, 1059, 1039, 1022, 1006, 938, 876, 833, 773, 668.

MS (EI, 70 eV): *m/z* (%) = 339 (1), 284 (14), 283 (43), 282 (22), 208 (17), 184 (25), 15 (13), 75 (100), 44.

HR-MS (EI, 70 eV): [$C_{21}H_{29}NOSi$], calcd.: 339.2018; found: 339.1996.

***tert*-Butyldimethyl((trans-2-((triisopropylsilyl)ethynyl)cyclohexyl)oxy)silane (64k)**



Isolated yield: 910 mg, 77 %, colorless oil

dr: 99:1.

Purification: *i*-hexane:*EE* = 100:2

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 3.71 (td, *J* = 6.4, 3.1 Hz, 1H), 2.44 (td, *J* = 6.8, 4.1 Hz, 1H), 2.03 – 1.85 (m, 1H), 1.73 – 1.58 (m, 2H), 1.52 –1.41 (m, 1H), 1.32 (qt, *J* = 6.2, 3.4 Hz, 3H), 1.15 – 0.96 (m, 21H), 0.89 (s, 10H), 0.08 (d, *J* = 5.6 Hz, 6H).

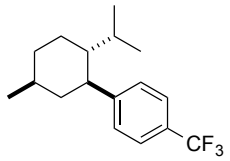
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 111.7, 81.7, 72.0, 47.8, 37.9, 32.7, 29.3, 26.1, 26.0, 23.4, 22.3, 18.8, 18.2, 11.5, -4.4, -4.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2937, 2892, 2863, 2359, 2166, 1463, 1366, 1383, 1252, 1157, 1105, 1068, 1022, 942, 908, 875, 836, 775, 735, 676.

MS (EI, 70 eV): *m/z* (%) = 394 (1), 393 (1), 337 (8), 309 (18), 296 (26), 295 (100), 267 (19), 253 (4), 225 (8).

HR-MS (EI, 70 eV): [$C_{23}H_{46}OSi_2$], calcd.: 394.3087; found: 394.3076.

1-((*1R,2S,5R*)-2-Isopropyl-5-methylcyclohexyl)-4-(trifluoromethyl)benzene (65a)



Isolated yield: 201 mg, 0.36 mmol, 71%, colorless oil

dr: 99:1.

Purification: *i*-hexane:ethyl acetate = 100:3

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): *d* = 7.55 (d, *J* = 8.5 Hz, 2H), 7.33 - 7.16 (m, 2H), 2.49 (td, *J* = 11.6, 3.5 Hz, 1H), 1.84 - 1.66 (m, 2H), 1.56 (s, 1H), 1.53 - 1.41 (m, 2H), 1.36 - 0.95 (m, 4H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.65 (d, *J* = 6.9 Hz, 3H).

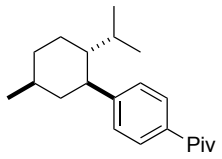
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): *d* = 152.4, 132.2, 128.3, 119.1, 109.5, 48.3, 47.2, 44.8, 35.0, 33.1, 27.6, 24.36, 22.4, 21.4, 15.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2871, 1447, 1324, 1164, 1125, 1073, 906, 799, 732, 703, 665.

MS (EI, 70 eV): *m/z* (%) = 284 (56), 199 (74), 173 (51), 172 (94), 159 (100), 112 (42), 69 (53).

HR-MS (EI, 70 eV): [$C_{17}H_{23}F_3$], calcd.: 284.1752; found: 284.1735.

1-(4-((*1R,2S,5R*)-2-Isopropyl-5-methylcyclohexyl)phenyl)-2,2-dimethylpropan-1-one (65b)



Isolated yield: 221 mg, 0.35 mmol, 70%, colorless oil

dr: 99:1.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.90 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 2.48 (td, *J* = 11.6, 3.5 Hz, 1H), 1.86 – 1.68 (m, 3H), 1.57 (s, 9H), 1.52 – 1.32 (m, 3H), 1.19 – 0.97 (m, 3H), 0.88 (d, *J* =6.5 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.65 (d, *J* = 6.9 Hz, 3H).

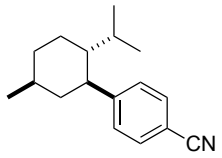
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 165.8, 151.7, 129.5, 80.5, 48.1, 47.3, 44.9, 35.2, 33.1, 28.2, 27.5, 24.5, 22.4, 21.4, 15.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2918, 1711, 1608, 1455, 1367, 1290, 1255, 1165, 1116, 1102, 908, 850, 773, 733, 708.

MS (EI, 70 eV): *m/z* (%) = 261 (33), 250 (100), 243 (56), 149 (43), 148 (73), 135 (35), 125 (26), 91 (23), 69 (37), 57 (87), 40 (32).

HR-MS (EI, 70 eV): [$C_{21}H_{32}O_2$], calcd.: 316.2402; found: 316.2387.

4-((*1R,2S,5R*)-2-Isopropyl-5-methylcyclohexyl)benzonitrile (65c)



Isolated yield: 147 mg, 0.31 mmol, 61%, colorless oil

dr: 99:1.

Purification: *i*-hexane:ethyl acetate = 100:3

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.55 (d, *J* = 8.5 Hz, 2H), 7.33 - 7.16 (m, 2H), 2.49 (td, *J* = 11.6, 3.5 Hz, 1H), 1.84 - 1.66 (m, 2H), 1.56 (s, 1H), 1.53 - 1.41 (m, 2H), 1.36 - 0.95 (m, 5H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.65 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 152.4, 132.2, 128.3, 119.1, 109.5, 48.3, 47.2, 44.8, 35.0,

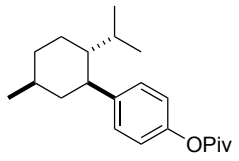
33.1, 27.6, 24.36, 22.4, 21.4, 15.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1413, 1342, 1322, 1253, 1165, 1125, 1097, 1076, 1045, 895, 796, 702, 665.

MS (EI, 70 eV): *m/z* (%) = 241 (100), 156 (73), 142 (53), 130 (95), 116 (52), 81 (53).

HR-MS (EI, 70 eV): [$C_{17}H_{23}N$], calcd.: 241.1830; found: 241.1821.

4-((1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl)phenyl pivalate (65d)



Isolated yield: 119 mg, 0.38 mmol, 75%, colorless crystals

dr: 99:1.

Purification: *i*-hexane:ethyl acetate = 96:4

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.15 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 2.43 (td, *J* = 11.7, 3.4 Hz, 1H), 1.88 – 1.67 (m, 3H), 1.52 – 1.37 (m, 3H), 1.35 (s, 9H), 1.20 – 0.94 (m, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.65 (d, *J* = 6.6 Hz, 3H).

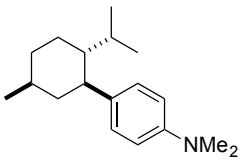
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 177.3, 148.9, 143.9, 128.2, 121.2, 47.6, 47.4, 45.3, 39.1, 35.3, 33.2, 27.3, 27.2, 27.1, 24.5, 22.6, 22.5, 21.5, 15.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 2921, 2872, 2842, 1744, 1730, 1504, 1492, 1480, 1462, 1454, 1442, 1398, 1384, 1366, 1277, 1231, 1202, 1194, 1165, 1118, 1101, 1068, 1053, 1030, 1014, 968, 944, 937, 919, 896, 872, 852, 832, 819, 808, 796, 784, 759, 723, 621, 604, 594, 585, 574, 566, 558.

MS (EI, 70 eV): *m/z* (%) = 317 (5), 316 (23), 233 (18), 232 (100), 146 (77), 107 (31), 91 (7), 95 (8), 57 (42), 41 (11).

HR-MS (EI, 70 eV): [$C_{21}H_{32}O_2$], calcd.: 316.2402; found: 316.2388.

4-((1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl)-*N*,*N*-dimethylaniline (65e)



Isolated yield: 80 mg, 0.31 mmol, 62%, white solid

dr: 91:9.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.04 (d, *J* = 8.1 Hz, 2H), 6.70 (d, *J* = 8.1 Hz, 2H), 2.92 (s, 6H), 2.33 (td, *J* = 11.6, 3.4 Hz, 1H), 1.87 – 1.65 (m, 3H), 1.54 – 1.28 (m, 3H), 1.20 – 0.94 (m, 3H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.79 (dd, *J* = 6.7 Hz, 1.2, 3H), 0.67 (dd, *J* = 7.0, 1.2 Hz, 3H).

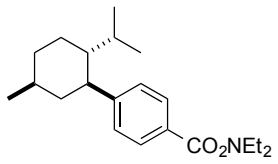
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 148.8, 134.9, 128.0, 112.8, 47.6, 46.9, 45.7, 40.9, 35.4, 33.3, 27.3, 24.6, 22.6, 21.6, 15.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951, 2913, 2868, 2844, 2798, 1613, 1565, 1519, 1493, 1480, 1461, 1452, 1444, 1383, 1366, 1344, 1277, 1206, 1191, 1162, 1138, 1097, 1082, 1059, 1038, 999, 978, 948, 935, 868, 818, 808, 749, 730, 724, 690, 642, 626, 595.

MS (EI, 70 eV): *m/z* (%) = 260 (14), 259 (72), 258 (3), 244 (6), 175 (13), 174 (100), 160 (6), 159 (5), 147 (9), 146 (10), 135 (6), 134 (52).

HR-MS (EI, 70 eV): [$C_{18}H_{29}N$], calcd.: 259.2300; found: 259.2297.

***N,N*-Diethyl-O-(4-((*1R,2S,5R*)-2-isopropyl-5-methylcyclohexyl)benzoyl)hydroxylamine (65f)**



Isolated yield: 248 mg, 0.38 mmol, 75%, colorless oil

dr: 99:1.

Purification: *i*-hexane:ethyl acetate = 100:3

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.27 – 7.22 (m, 1H), 7.00 – 6.91 (m, 3H), 3.49 – 3.37 (m, 4H), 2.44 (td, *J* = 11.6, 3.4 Hz, 1H), 1.84 – 1.70 (m, 3H), 1.55 – 1.43 (m, 3H), 1.30 – 1.10 (m, 8H), 1.01 (tdd, *J* = 12.9, 11.5, 3.4 Hz, 1H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 7.1 Hz, 3H), 0.69 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 154.2, 151.6, 148.1, 128.9, 118.9, 47.9, 47.3, 45.2, 42.1, 41.8, 35.3, 33.2, 27.4, 24.5, 22.5, 21.5, 15.4, 14.3, 13.4.

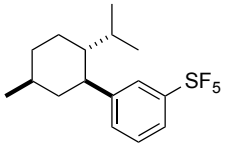
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2916, 2871, 1715, 1608, 1472, 1456, 1415, 1272, 1255, 1216,

1153, 970, 907, 773, 730, 698.

MS (EI, 70 eV): *m/z* (%) = 331 (39), 107 (11), 106 (12), 100 (34), 71 (100), 55 (11), 43 (20), 40 (13).

HR-MS (EI, 70 eV): [$C_{21}H_{33}NO_2$], calcd.: 331.2511; found: 331.2500.

Pentafluoro(3-((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl)phenyl)-λ^6-sulfane (65g)



Isolated yield: 116 mg, 0.34 mmol, 68%, colorless oil

dr: 99:1.

Purification: *i*-hexane

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ =7.55 (d, *J* = 8.1 Hz, 1H), 7.53 (s, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 2.51 (td, *J* = 11.7 Hz, 3.4 Hz, 1H), 1.88 – 1.71 (m, 3H), 1.56 – 1.28 (m, 3H), 1.25 – 0.97 (m, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.67 (d, *J* = 6.9 Hz, 3H).

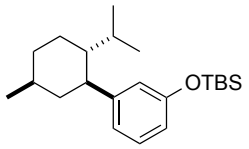
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 154.1, 147.9, 130.6, 128.6, 125.0 (m), 123.4 (p, *J* = 4.6 Hz), 48.1, 47.3, 45.1, 35.1, 33.2, 27.5, 24.5, 22.4, 21.4, 15.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 2921, 2872, 2842, 1744, 1730, 1504, 1492, 1480, 1462, 1454, 1442, 1398, 1384, 1366, 1277, 1231, 1202, 1194, 1165, 1118, 1101, 1068, 1053, 1030, 1014, 968, 944, 937, 919, 896, 872, 852, 832, 819, 808, 796, 784, 759, 723, 621, 604, 594, 585, 574, 566, 558.

MS (EI, 70 eV): *m/z* (%) = 343 (16), 342 (100), 257 (27), 230 (74), 217 (71), 130 (68), 129 (52), 116 (69), 83 (61), 55 (80).

HR-MS (EI, 70 eV): [$C_{16}H_{23}F_5S$], calcd.: 342.1441; found: 342.1430.

tert-Butyl(3-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)phenoxy)dimethylsilane (65h)



Isolated yield: 252 mg, 0.37 mmol, 73%, colorless oil

dr: 99:1.

Purification: *i*-hexane

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.30 - 7.21 (m, 1H), 7.18 - 7.10 (m, 1H), 6.87 (dq, *J* = 7.7, 0.9 Hz, 1H), 6.72 - 6.64 (m, 1H), 2.39 (td, *J* = 11.5, 3.4 Hz, 1H), 1.95 - 1.70 (m, 3H), 1.62 - 1.37 (m, 3H), 1.27 - 1.08 (m, 3H), 1.02 (dd, *J* = 1.7, 0.7 Hz, 9H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.85 - 0.80 (m, 3H), 0.71 (dd, *J* = 6.8, 0.7 Hz, 3H), 0.22 (dd, *J* = 2.7, 0.7 Hz, 6H).

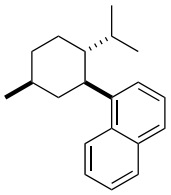
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 155.6, 148.2, 129.3, 129.1, 121.3, 120.1, 117.5, 47.9, 47.5, 45.1, 35.3, 33.2, 27.4, 25.8, 25.7, 24.5, 22.5, 21.5, 18.3, 15.4, -4.4, -4.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955, 2929, 2859, 1597, 1491, 1484, 1440, 1362, 1252, 1155, 1002, 971, 908, 867, 835, 779, 730, 801, 665.

MS (EI, 70 eV): *m/z* (%) = 346 (71), 290 (31), 289 (98), 193 (30), 179 (91), 165 (37), 75 (8).

HR-MS (EI, 70 eV): [$C_{22}H_{38}OSi$], calcd.: 346.2692; found: 346.2687.

1-((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)naphthalene (65i)



Isolated yield: 165 mg, 0.31 mmol, 62%, colorless oil

dr: 99:1.

Purification: *i*-hexane

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.20 - 8.15 (m, 1H), 7.84 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.67 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.53 - 7.42 (m, 3H), 7.38 (dd, *J* = 7.3, 1.3 Hz, 1H), 3.38 (td, *J* = 11.5, 3.4 Hz, 1H), 1.95 - 1.83 (m, 4H), 1.77 (tt, *J* = 11.5, 3.0 Hz, 1H), 1.38 - 1.23 (m, 2H), 1.13 - 1.04

(m, 2H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.61 (d, *J* = 6.9 Hz, 3H).

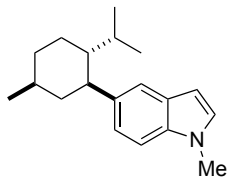
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 142.7, 134.0, 131.8, 128.9, 125.7, 125.6, 125.5, 125.1, 123.2, 122.7, 46.8, 45.8, 40.8, 35.4, 33.5, 27.3, 24.8, 22.4, 21.6, 16.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3045, 2925, 2867, 1595, 1511, 1455, 1368, 1016, 905, 794, 776, 729.

MS (EI, 70 eV): *m/z* (%) = 266 (100), 181 (86), 154 (31), 142 (60), 141 (87), 69 (12).

HR-MS (EI, 70 eV): [$C_{20}H_{26}$], calcd.: 266.2035; found: 266.2020.

5-((1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl)-1-methyl-1*H*-indole (65j)



Isolated yield: 128 mg, 0.38 mmol, 75%, white solid

dr: 96:4.

Purification: *i*-hexane: ethyl acetate 99:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.44 – 7.38 (m, 1H), 7.28 – 7.23 (m, 1H), 7.07 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.02 (d, *J* = 3.1 Hz, 1H), 6.43 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.77 (s, 3H), 2.52 (td, *J* = 11.6, 3.4 Hz, 1H), 1.89 – 1.78 (m, 2H), 1.77 (dq, *J* = 12.4, 3.1 Hz, 1H), 1.57 – 1.43 (m, 3H), 1.30 – 1.11 (m, 2H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 4H), 0.70 (d, *J* = 6.8 Hz, 3H).

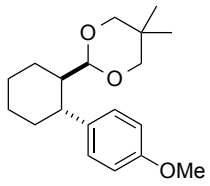
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 137.6, 135.4, 128.7, 128.6, 121.3, 119.1, 108.9, 100.5, 48.0, 47.8, 46.2, 35.5, 33.5, 32.9, 27.4, 24.7, 22.6, 21.7, 15.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2859, 1600, 1585, 1484, 1471, 1443, 1344, 1278, 1253, 1159, 1097, 1001, 908, 837, 781, 726, 700, 662.

MS (EI, 70 eV): *m/z* (%) = 270 (15), 269 (82), 185 (13), 184 (100), 169 (6), 168 (5), 158 (9), 157 (11), 145 (25), 144 (52), 131 (7).

HR-MS (EI, 70 eV): [$C_{19}H_{27}N$], calcd.: 269.2143; found: 269.2138.

2-((*1R,2R*)-2-(4-Methoxyphenyl)cyclohexyl)-5,5-dimethyl-1,3-dioxane (66a)



Isolated yield: 246 mg, 0.41 mmol, 81%, colorless oil

dr: 99:1.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.10 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 1H), 3.89 (d, *J* = 2.1 Hz, 2H), 3.80 (s, 3H), 3.50 (dd, *J* = 10.9, 2.8 Hz, 2H), 3.15 (dd, *J* = 10.9, 1.0 Hz, 2H), 2.49 (td, J = 11.9, 3.5 Hz, 1H), 2.07 (ddd, *J* = 13.4, 3.3, 1.6 Hz, 1H), 1.88 – 1.66 (m, 4H), 1.51 – 1.26 (m, 4H), 1.13 (s, 3H), 0.60 (s, 3H).

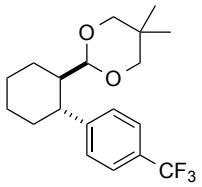
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 157.7, 137.8, 128.4, 113.6, 101.6, 55.1, 47.6, 44.7, 35.4, 30.1, 26.7, 25.94, 24.3, 22.8, 21.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2931, 2853, 2248, 1512, 1394, 1247, 114, 968, 904, 828, 727, 648.

MS (EI, 70 eV): *m/z* (%) = 304 (10), 200 (30), 196 (43), 17 (10), 120 (28), 114 (100), 69 (52), 45 (13), 41 (12).

HR-MS (EI, 70 eV): [$C_{19}H_{28}O_3$], calcd.: 304.2038; found: 304.2030.

5,5-Dimethyl-2-((*1R,2R*)-2-(4-(trifluoromethyl)phenyl)cyclohexyl)-1,3-dioxane (66b)



Isolated yield: 242 mg, 0.36 mmol, 71%, colorless oil

dr: 99:1.

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

^{1}H-NMR (600 MHz, $CDCl_3$, ppm): δ = 7.56 – 7.51 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.84 (d, *J* = 2.2 Hz, 1H), 3.49 (ddd, *J* = 30.7, 10.9, 2.8 Hz, 2H), 3.13 (ddd, *J* = 67.3, 10.9, 1.0 Hz, 2H), 2.63 (td, *J* = 11.9, 3.3 Hz, 1H), 2.10 (ddt, *J* = 13.1, 4.1, 2.9 Hz, 1H), 1.90 – 1.76 (m, 4H), 1.54 – 1.31

(m, 4H), 1.11 (s, 3H), 0.60 (s, 3H).

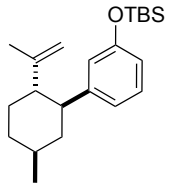
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 149.8, 127.9, 126.4, 125.2, 104.3, 101.2, 47.1, 45.5, 35.1, 30.1, 26.5, 25.8, 24.2, 22.7, 21.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2933, 2856, 2252, 1618, 1325, 112, 1116, 1069, 903, 834, 723, 649, 606.

MS (EI, 70 eV): *m/z* (%) = 341 (10), 196 (23), 158 (15), 115 (100), 69 (47), 44 (12), 40 (13).

HR-MS (EI, 70 eV): [$C_{19}H_{25}F_3O_2$], calcd.: 342.1807; found: 342.1721.

***tert*-Butyldimethyl(3-((1R,2R,5R)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl)phenoxy)silane (67a)**



Isolated yield: 264 mg, 0.39 mmol, 77%, colorless oil

dr: 99:1.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.16 - 7.06 (m, 1H), 6.79 - 6.70 (m, 1H), 6.64 (dq, *J* = 8.8, 1.3 Hz, 2H), 4.59 - 4.52 (m, 2H), 2.52 (td, *J* = 11.6, 3.4 Hz, 1H), 2.22 (td, *J* = 11.6, 3.3 Hz, 1H), 1.92 - 1.72 (m, 3H), 1.67 - 1.28 (m, 6H), 1.24 - 1.06 (m, 2H), 1.04 - 0.98 (m, 7H), 0.94 (d, *J* = 6.6 Hz, 2H), 0.89 (d, *J* = 6.7 Hz, 2H), 0.20 (d, *J* = 0.6 Hz, 6H).

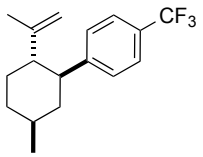
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 155.4, 148.3, 147.7, 128.8, 120.6, 119.4, 117.5, 111.1, 51.1, 47.9, 44.5, 41.4, 35.1, 33.1, 32.8, 25.7, 22.5, 19.8, 18.2, 11.5, -4.4, -4.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3072, 2951, 2926, 2857, 1645, 1601, 1483, 1440, 1374, 1270, 1252, 1156, 1002, 982, 936, 907, 866, 779, 731, 698.

MS (EI, 70 eV): *m/z* (%) = 344 (63), 288 (38), 287 (100), 191 (33), 177 (93), 163 (41), 73 (14).

HR-MS (EI, 70 eV): [$C_{22}H_{36}OSi$], calcd.: 344.2535; found: 344.2533.

1-((*1R,2R,5R*)-5-Methyl-2-(prop-1-en-2-yl)cyclohexyl)-4-(trifluoromethyl)benzene (67b)



Isolated yield: 169 mg, 0.30 mmol, 60%, colorless oil

dr: 99:1.

Purification: *i*-hexane

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.42 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.49 - 4.41 (m, 2H), 2.57 (td, *J* = 11.7, 3.4 Hz, 1H), 2.20 (td, *J* = 11.6, 3.3 Hz, 1H), 1.74 (dq, *J* = 13.4, 3.3 Hz, 3H), 1.56 - 1.35 (m, 5H), 1.13 - 0.95 (m, 2H), 0.85 (d, *J* = 6.5 Hz, 3H).

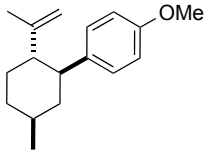
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 150.2, 147.8, 128.1, 127.8, 127.7, 125.1, 125.1, 125.0, 111.6, 50.8, 47.8, 44.5, 35.0, 323.0, 32.6, 22.4, 19.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927, 2873, 1463, 1381, 1326, 1168, 1131, 1069, 957, 890, 739, 564.

MS (EI, 70 eV): *m/z* (%) = 282 (16), 218 (35), 216 (100), 148 (32), 123 (28), 91 (36), 83 (23), 57 (22).

HR-MS (EI, 70 eV): [$C_{17}H_{21}F_3$], calcd.: 282.1595; found: 282.1570.

1-Methoxy-4-((*1R,2R,5R*)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl)benzene (67c)



Isolated yield: 104 mg, 0.43 mmol, 85%, colorless oil

dr: 99:1.

Purification: *i*-hexane:ethyl acetate = 100:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.08 - 7.06 (m, 1H), 7.05 (d, *J* = 2.2 Hz, 1H), 6.81 (d, *J* = 2.2 Hz, 1H), 6.79 (d, *J* = 2.1 Hz, 1H), 4.61 - 4.46 (m, 2H), 3.78 (s, 2H), 2.52 (td, *J* = 11.7, 3.4 Hz, 1H), 2.23 (td, *J* = 11.6, 3.4 Hz, 1H), 1.80 (dddd, *J* = 11.3, 9.6, 4.9, 2.4 Hz, 3H), 1.64 - 1.42 (m, 6H), 1.22 - 1.02 (m, 2H), 0.92 (d, *J* = 6.5 Hz, 2H), 0.91 - 0.85 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 157.5, 148.6, 138.3, 129.4, 128.2, 113.9, 113.4, 111.0,

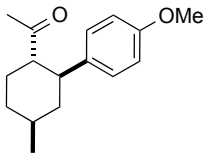
55.1, 51.1, 47.0, 45.1, 35.1, 33.1, 32.8, 22.4, 19.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3070, 2948, 2916, 1645, 1610, 1511, 1454, 1373, 1301, 1243, 1177, 1037, 906, 885, 826, 754, 729, 692.

MS (EI, 70 eV): *m/z* (%) = 244 (44), 229 (11), 173 (26), 161 (100), 134 (33), 121 (92), 91 (23), 55(23).

HR-MS (EI, 70 eV): [$C_{17}H_{24}O$], calcd.: 244.1827; found: 244.1823.

1-((1S,2S,4S)-2-(4-methoxyphenyl)-4-methylcyclohexyl)ethan-1-one (68)



Substrate **6c** (244 mg, 1 mmol) and was dissolved in dry CH_2Cl_2 (15 mL) and the solution was cooled to -78 °C, at which point a stream of O_3 was introduced through a disposable pipet for 3 min. After 15 min, the reaction was sparged with O_2 and then argon. The crude reaction mixture was diluted with CH_2Cl_2 (10 mL) and sat. aq. $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4 and filtered. The residue was purified *via* flash chromatography with hexanes/ethyl acetate 100:1 to furnish the ketone **7** as a white solid (150 mg, 0.61 mmol, 61%).

dr: 99:1.

m.p.: 102.8 – 104.5 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.01 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 3.69 (s, 3H), 2.61 – 2.65 (m, 2H), 1.89 – 1.68 (m, 6H), 1.58 – 1.34 (m, 2H), 1.18 – 0.91 (m, 2H), 0.86 (d, *J* = 6.5 Hz, 3H).

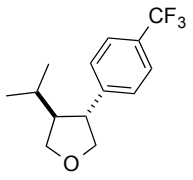
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 212.8, 157.9, 136.7, 128.2, 113.9, 57.3, 55.2, 45.6, 43.3, 34.1, 32.6, 30.1, 29.5, 22.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924, 2253, 1706, 1610, 1512, 1455, 1355, 1245, 1178, 1035, 905, 827, 726.

MS (EI, 70 eV): *m/z* (%) = 246 (77), 161 (100), 121 (84), 97 (28), 71 (28), 69 (34), 57 (54), 55 (48), 43 (44), 42 (58).

HR-MS (EI, 70 eV): [$C_{16}H_{22}O_2$], calcd.: 246.1620; found: 246.1621.

(3*S*,4*R*)-3-Isopropyl-4-(4-(trifluoromethyl)phenyl)tetrahydrofuran (69a)



Isolated yield: 92 mg, 0.36 mmol, 71%, colorless liquid

dr: 97:3.

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

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.55 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 4.18 (dd, *J* = 8.7, 7.8 Hz, 1H), 4.11 (ddd, *J* = 8.9, 7.8, 0.5 Hz, 1H), 3.74 (dd, *J* = 8.9, 6.7 Hz, 1H), 3.64 (t, *J* = 8.5 Hz, 1H), 3.14 (q, *J* = 7.3 Hz, 1H), 2.16 (p, *J* = 7.8 Hz, 1H), 1.79 – 1.60 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H).

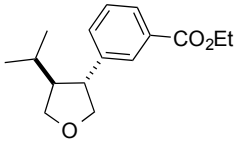
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 148.4 (q, *J* = 1.8, 1.1 Hz), 128.7 (q, *J* = 32.5 Hz), 127.9, 125.5 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 271.8 Hz), 76.3, 72.6, 50.0, 31.3, 21.6, 20.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962, 2874, 1620, 1469, 1423, 1390, 1370, 1323, 1242, 1188, 1163, 1119, 1110, 1089, 1067, 1018, 950, 927, 836, 761, 716, 670, 647, 637, 605, 576, 566, 556.

MS (EI, 70 eV): *m/z* (%) = 258 (4), 228 (6), 213 (9), 186 (7), 185 (23), 173 (10), 172 (100), 165 (7), 159 (9), 115 (8), 91 (5), 95 (6).

HR-MS (EI, 70 eV): [$C_{14}H_{17}F_3O$], calcd.: 258.1231; found: 258.1233.

Ethyl 3-((3R,4S)-4-isopropyltetrahydrofuran-3-yl)benzoate (69b)



Isolated yield: 84 mg, 0.32 mmol, 64%, colorless oil

dr: 99:1.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.94 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 4.38 (q, *J* = 7.3 Hz, 2H), 4.18 (t, *J* = 8.4 Hz, 1H), 4.13 (t, *J* = 8.3 Hz, 1H), 3.72 (t, *J* = 8.0 Hz, 1H), 3.66 (t, *J* = 8.4 Hz, 1H), 3.14 (q, *J* = 7.7 Hz, 1H), 2.20 (p, *J* = 7.9

Hz, 1H), 1.78 – 1.61 (m, *J* = 6.8 Hz, 1H), 1.40 (t, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H).

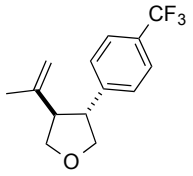
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.7, 144.1, 132.2, 130.8, 128.7, 128.7, 127.6, 72.6, 61.1, 55.0, 50.4, 31.3, 21.7, 20.5, 14.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961, 1618, 1424, 1323, 1303, 1185, 1158, 1122, 1107, 1094, 1067, 1048, 1027, 1016, 1004, 840, 814, 740, 709, 665, 653.

MS (EI, 70 eV): *m/z* (%) = 262 (17), 253 (14), 216 (28), 177 (22), 176 (100), 164 (21), 148 (27), 145 (14), 131 (37), 129 (12), 128 (11), 117 (50), 116 (15), 115 (33), 77 (17).

HR-MS (EI, 70 eV): [$C_{16}H_{22}O_3$], calcd.: 262.1569; found: 262.1562.

(3*R*,4*R*)-3-(Prop-1-en-2-yl)-4-(4-(trifluoromethyl)phenyl)tetrahydrofuran (69c)



Isolated yield: 69 mg, 0.27 mmol, 54%, colorless oil

dr: 99:1.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.49 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.75 – 4.64 (m, 1H), 4.68 (d, *J* = 0.8 Hz, 1H), 4.18 (t, *J* = 8.3 Hz, 1H), 4.11 (t, *J* = 8.3 Hz, 1H), 3.82 – 3.64 (m, 2H), 3.30 (q, *J* = 8.3 Hz, 1H), 2.94 (q, *J* = 8.6 Hz, 1H), 1.66 (s, 3H).

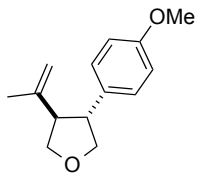
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 145.6, 142.5, 129.0 (q, *J* = 32.4 Hz), 127.8, 125.6 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 275.1 Hz), 112.6, 75.2, 72.6, 55.1, 49.5, 20.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2936, 2863, 1620, 1423, 1323, 1163, 1114, 1067, 1017, 945, 923, 896, 835.

MS (EI, 70 eV): *m/z* (%) = 256 (15), 237 (11), 212 (14), 211 (100), 198 (18), 192 (35), 188 (81), 177 (16), 172 (43), 159 (19), 157 (32), 142 (31), 141 (11).

HR-MS (EI, 70 eV): [$C_{14}H_{15}F_3O$], calcd.: 256.1075; found: 256.1068.

(3*R*,4*R*)-3-(4-Methoxyphenyl)-4-(prop-1-en-2-yl)tetrahydrofuran (69d)



Isolated yield: 62 mg, 0.29 mmol, 57%, colorless oil

dr: 99:1.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.20 – 7.13 (m, 2H), 6.88 – 6.83 (m, 2H), 4.80 – 4.74 (m, 2H), 4.23 (t, *J* = 8.2 Hz, 1H), 4.15 (t, *J* = 8.3 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.73 (m, 2H), 3.28 (q, *J* = 8.8 Hz, 1H), 2.98 (q, *J* = 8.7 Hz, 1H), 1.72 (s, 3H).

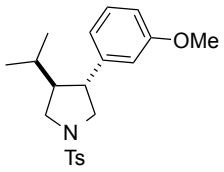
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 158.3, 143.0, 132.8, 128.4, 114.0, 112.3, 75.6, 72.6, 55.3, 54.8, 48.9, 20.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2936, 2863, 1620, 1423, 1323, 1163, 1114, 1067, 1017, 945, 923, 896, 835.

MS (EI, 70 eV): *m/z* (%) = 218 (21), 203 (15), 173 (12), 150 (28), 135 (15), 134 (16), 122 (11), 121 (100), 43 (10).

HR-MS (EI, 70 eV): [$C_{14}H_{18}O_2$], calcd.: 218.1307; found: 218.1304.

***trans*-3-Isopropyl-4-(3-methoxyphenyl)-1-tosylpyrrolidine (69e)**



Isolated yield: 246 mg, 0.33 mmol, 66%, colorless oil

dr: 99:1.

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

^{1}H-NMR (600 MHz, $CDCl_3$, ppm): δ = 7.68 – 7.62 (m, 2H), 7.29 – 7.24 (m, 2H), 7.09 (t, *J* = 7.9 Hz, 1H), 6.68 – 6.54 (m, 4H), 3.68 (s, 2H), 3.51 (ddd, *J* = 39.1, 9.9, 8.0 Hz, 2H), 3.03 (dt, *J* = 34.1, 9.6 Hz, 2H), 2.81 (td, *J* = 9.6, 8.0 Hz, 1H), 2.37 (s, 3H), 2.00 (tdd, *J* = 9.7, 8.0, 6.1 Hz, 1H),

1.52 – 1.39 (m, 1H), 0.69 (d, *J* = 6.8 Hz, 3H), 0.64 (d, *J* = 6.8 Hz, 3H).

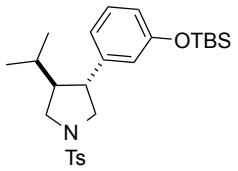
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 159.8, 143.5, 142.5, 133.6, 129.7, 127.6, 119.9, 113.7, 111.8, 55.9, 55.2, 51.7, 50.5, 48.1, 29.2, 21.5, 18.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959, 1598, 1487, 1466, 1341, 1287, 1263, 1156, 1094, 1042, 1015, 909, 814, 781, 730, 662.

MS (EI, 70 eV): *m/z* (%) = 222 (100), 219 (15), 190 (17), 146 (16), 134 (23), 121 (16), 110 (16), 91 (29), 83 (14), 42 (56).

HR-MS (EI, 70 eV): [$C_{21}H_{27}NO_3S$], calcd.: 373.1712; found: 373.1709.

***trans*-3-Isopropyl-4-(3-methoxyphenyl)-1-tosylpyrrolidine (69f)**



Isolated yield: 416 mg, 0.44 mmol, 88%, colorless oil

dr: 99:1.

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

^{1}H-NMR (600 MHz, $CDCl_3$, ppm): δ = 7.69 – 7.63 (m, 2H), 7.31 – 7.22 (m, 2H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.60 (ddt, *J* = 8.0, 3.4, 1.3 Hz, 2H), 6.51 (t, *J* = 2.0 Hz, 1H), 3.52 (ddd, *J* = 38.5, 9.9, 8.0 Hz, 2H), 3.02 (dt, *J* = 28.5, 9.7 Hz, 2H), 2.78 (td, *J* = 9.7, 7.9 Hz, 1H), 2.37 (s, 3H), 2.04 – 1.89 (m, 1H), 1.45 (dq, *J* = 13.4, 6.7 Hz, 1H), 0.89 (s, 9H), 0.69 (d, *J* = 6.7 Hz, 3H), 0.63 (d, *J* = 6.8 Hz, 3H), 0.09 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 155.9, 143.5, 142.4, 133.6, 129.7, 129.6, 127.6, 120.7, 119.2, 118.7, 55.9, 51.7, 50.6, 47.9, 29.2, 25.7, 21.6, 21.5, 18.8, 18.2, -4.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2859, 1600, 1585, 1484, 1471, 1443, 1344, 1278, 1253, 1159, 1097, 1001, 908, 837, 781, 726, 700, 662.

MS (EI, 70 eV): *m/z* (%) = 417 (26), 416 (100), 149 (13), 91 (4), 73 (3), 42 (6).

HR-MS (EI, 70 eV): [$C_{26}H_{39}NO_3SSi$], calcd.: 473.2420; found: 473.2329.

4. Cobalt-Catalyzed Csp^2-Csp^3 Cross-Coupling Reactions of Diarylmanganese Reagents with Secondary Alkyl Iodides

4.1. Additional Comments

When the diarylmanganese reagent **72a** reacted with iodide **70b** the coupling-product **71b** was obtained in only 63% yield using $CoCl_2$. In contrast, using THF soluble $CoCl_2$·2LiCl gave **71b** in 73% yield (Table 2, entry 1). The reaction of **72a** with cyclohexyl iodide (**70e**) gave **71e** in 81% yield using $CoCl_2$ compared to 84% yield when using $CoCl_2$·2LiCl in THF (Table 2, entry 4). Interestingly, the yields decreased dramatically when the organomanganese reagent **72f** reacted with iodide **70e** ($CoCl_2$: 48%; $CoCl_2$·2LiCl: 80%; Table 3, entry 8) and iodide **70b** ($CoCl_2$: 19%; $CoCl_2$·2LiCl: 60%; Table 3, entry 9) to afford the arylated products **71r**.

4.2. Preparation of Organometallic Reagents

Typical procedure 3 (TP3): Preparation of diarylmanganese reagents by magnesium-insertion and transmetallation

LiCl (1.1 equiv) was dried under high vacuum and allowed to cool to room temperature, then Mg turnings (1.2 equiv) and THF (1 M solution relating to the aryl bromide) were added. The reaction mixture was cooled to 0 °C and the corresponding aryl bromide (1.0 equiv) was added dropwise. The reaction was stirred until iodolysis of a reaction aliquot indicated full consumption of the starting material. Then a solution of $MnCl_2$·2LiCl (0.55 equiv, 1 M in THF) was added dropwise and the solution was stirred for 1 h to afford the corresponding diarylmanganese reagent (ca. 0.5 M in THF).

Typical procedure 4 (TP4): Preparation of diarylmanganese reagents b bromine-magnesium exchange and transmetallation

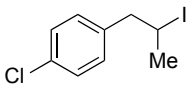
The corresponding aryl bromide (1.0 equiv) was dissolved in THF (1 M solution relating to the aryl bromide) and the reaction mixture was cooled to -30 °C. Then *i*-PrMgCl·LiCl (1.1 equiv) was added dropwise and the reaction was stirred at this temperature until reaction aliquots quenched with iodine showed full consumption of the starting material. Then a solution of $MnCl_2$·2LiCl

(0.55 equiv, 1 M in THF) was added dropwise and the solution was stirred for 1 h before use to afford the corresponding diarylmanganese reagent (ca. 0.5 M in THF).

4.2. Synthesis of Starting Materials

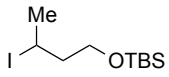
The following starting materials were prepared according to literature procedures with only little deviation.[93] The spectral data of known compounds were in full agreement with the literature.

1-Chloro-4-(2-iodopropyl)benzene (70a)



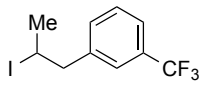
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.31 – 7.27 (m, 2H), 7.14 – 7.10 (m, 2H), 4.29 (dp, *J* = 7.6, 6.8 Hz, 1H), 3.22 (dd, *J* = 14.2, 7.6 Hz, 1H), 3.04 (dd, *J* = 14.2, 7.0 Hz, 1H), 1.90 (d, *J* = 6.8 Hz, 3H).

***tert*-Butyl(3-iodobutoxy)dimethylsilane (70b)[94]**



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.35 (dqd, *J* = 9.5, 6.9, 4.4 Hz, 1H), 3.76 (ddd, *J* = 10.3, 5.7, 4.6 Hz, 1H), 3.65 (ddd, *J* = 10.3, 8.1, 4.8 Hz, 1H), 2.04 – 1.94 (m, 4H), 1.78 (dddd, *J* = 14.6, 8.1, 5.7, 4.4 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

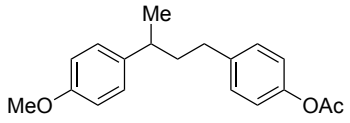
1-(2-Iodopropyl)-3-(trifluoromethyl)benzene (70c)



[93] C. W. Cheung, P. Ren, X. Hu, *Org. Lett.* **2014,** *16*, 2566.
[94] R. Yefidoff, A. Albeck, *Tetrahedron* **2004,** *60*, 8093.

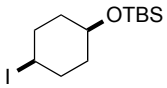
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ =7.57 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 7.41 – 7.36 (m, 1H), 4.32 (dp, *J* = 7.7, 6.8 Hz, 1H), 3.30 (dd, *J* = 14.3, 7.7 Hz, 1H), 3.13 (dd, *J* = 14.2, 6.9 Hz, 1H), 1.93 (d, *J* = 6.8 Hz, 3H).

4-(3-Iodobutyl)phenyl acetate (70d)



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.23 – 7.19 (m, 2H), 7.03 – 6.98 (m, 2H), 4.10 (dqd, *J* = 9.2, 6.8, 4.4 Hz, 1H), 2.84 (ddd, *J* = 14.0, 9.0, 5.1 Hz, 1H), 2.69 (ddd, *J* = 13.9, 9.0, 7.0 Hz, 1H), 2.29 (s, 3H), 2.19 – 2.08 (m, 1H), 1.94 (d, *J* = 6.8 Hz, 3H), 1.86 (dddd, *J* = 14.6, 9.0, 7.0, 4.4 Hz, 1H).

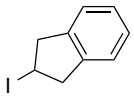
***tert*-Butyl((4-iodocyclohexyl)oxy)dimethylsilane (70f)[4]**



dr = 99:1 (*cis*:*trans*)

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.44 – 4.32 (m, 1H), 3.96 – 3.82 (m, 1H), 2.30 (dtd, *J* = 13.1, 9.0, 3.8 Hz, 2H), 1.97 – 1.87 (m, 2H), 1.72 – 1.62 (m, 2H), 1.63 – 1.52 (m, 2H), 0.90 (s, 9H), 0.04 (s, 6H).

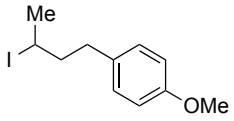
2-Iodo-2,3-dihydro-1*H*-indene (70h)[95]



[95] Y. Dai, F. Wu, Z. Zang, H. You, H. Gong, *Chem. - Eur. J.* **2012,** *18*, 808.

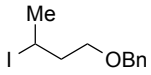
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.28 – 7.23 (m, 2H), 7.23 – 7.18 (m, 2H), 4.71 (tt, *J* = 6.5, 5.0 Hz, 1H), 3.48 (dd, *J* = 16.8, 6.5 Hz, 2H), 3.39 (dd, *J* = 16.8, 5.0 Hz, 2H).

1-(3-Iodobutyl)-4-methoxybenzene (70k)



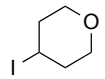
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.15 – 7.10 (m, 2H), 6.87 – 6.81 (m, 2H), 4.11 (dqd, *J* = 9.1, 6.8, 4.5 Hz, 1H), 3.79 (s, 3H), 2.79 (ddd, *J* = 13.9, 8.8, 5.2 Hz, 1H), 2.64 (ddd, *J* = 13.8, 8.8, 7.0 Hz, 1H), 2.13 (dtd, *J* = 14.2, 8.9, 5.2 Hz, 1H), 1.95 (d, *J* = 6.8 Hz, 3H), 1.84 (dddd, *J* = 14.6, 8.8, 7.1, 4.5 Hz, 1H).

((3-Iodobutoxy)methyl)benzene (70m)



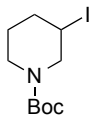
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.39 – 7.27 (m, 5H), 4.64 – 4.44 (m, 2H), 4.39 (dqd, *J*=9.5, 6.9, 4.6, 1H), 3.67 – 3.61 (m, 1H), 3.55 (ddd, *J*=9.6, 8.0, 5.0, 1H), 2.15 – 2.03 (m, 1H), 2.00 – 1.86 (m, 4H).

4-Iodotetrahydro-2H-pyran (70n)



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.45 (tt, *J* = 7.7, 5.5 Hz, 1H), 3.87 – 3.76 (m, 2H), 3.57 – 3.48 (m, 2H), 2.18 – 2.12 (m, 4H).

***tert*-Butyl 3-iodopiperidine-1-carboxylate (70o)**

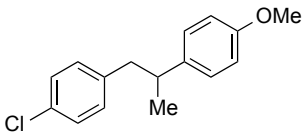


^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.29 – 3.92 (m, 2H), 3.78 (d, *J* = 13.0 Hz, 1H), 3.53 – 3.24 (m, 1H), 3.09 (s, 1H), 2.26 (s, 1H), 2.10 – 1.95 (m, 1H), 1.72 (d, *J* = 13.5 Hz, 1H), 1.57 (s, 1H), 1.46 (s, 9H).

4.3. Cobalt-Catalyzed Cross-Coupling of Diarylmanganese Reagents with Secondary Alkyl Halides

Typical Procedure 5 (TP5): A dry and argon-flushed 10 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with $CoCl_2$·2LiCl (1 M in THF, 0.1 mL, 0.10 mmol, 20 mol%). The secondary alkyl halide (0.50 mmol, 1.0 equiv) and THF (1 mL) were added and the mixture was cooled to -20 °C. The diarylmanganese reagent (0.35 mmol, 0.7 equiv) was added dropwise and the mixture was allowed to warm to room temperature overnight. A sat. aq. solution of NH_4Cl (5 mL) and EtOAc (5 mL) were added and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and the solvents were evaporated. The residue was subjected to column chromatography purification (SiO_2; *i*-hexane/EtOAc) yielding the corresponding title compound.

1-Chloro-4-(2-(4-methoxyphenyl)propyl)benzene (71a)



Following **TP5** 1-Chloro-4-(2-iodopropyl)benzene (**70a**, 140 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(*p*-anisyl)manganese reagent (**72a**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under

stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:1.5) as an eluent to afford **71a** as a colorless solid (75%, 98 mg, 0.38 mmol).

Mp.: 62.2 – 63.5 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.21 – 7.16 (m, 2H), 7.08 – 7.03 (m, 2H), 6.98 – 6.93 (m, 2H), 6.85 – 6.79 (m, 2H), 3.79 (s, 3H), 2.92 (h, *J* = 6.9 Hz, 1H), 2.84 (dd, *J* = 13.3, 7.0 Hz, 1H), 2.74 (dd, *J* = 13.2, 7.6 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 3H).

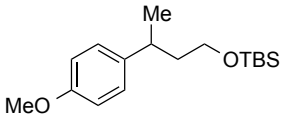
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.0, 139.4, 138.6, 131.7, 130.6, 128.3, 128.0, 113.8, 55.4, 44.7, 41.1, 21.6.

FT-IR (ATR, cm^{-1}): 2956, 2925, 2852, 1513, 1490, 1455, 1440, 1259, 1241, 1177, 1088, 1031, 1008, 829, 814, 806, 798, 698, 656.

MS (EI, 70 eV): m/z (%) = 260 (2), 136 (8), 135 (100), 125 (4), 105 (5), 103 (4), 91 (5), 77 (3).

HR-MS (EI, 70 eV): [$C_{16}H_{17}ClO$], calcd.: 260.0968; found: 260.0952.

***tert*-Butyl(3-(4-methoxyphenyl)butoxy)dimethylsilane (71b)**



Following **TP5** *tert*-butyl(3-iodobutoxy)dimethylsilane (**70b**, 157 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(*p*-anisyl)manganese reagent (**72a**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:2) as an eluent to afford **71b** as a yellowish oil (73%, 108 mg, 0.37 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.14 – 7.08 (m, 2H), 6.86 – 6.81 (m, 2H), 3.79 (s, 3H), 3.57 – 3.43 (m, 2H), 2.84 (h, *J* = 7.1 Hz, 1H), 1.80 – 1.73 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.00 (d, *J* = 0.8 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.9, 139.5, 128.0, 113.8, 61.4, 55.4, 41.5, 35.4, 26.1, 22.7, 18.4, -5.1.

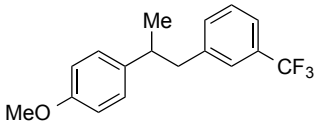
FT-IR (ATR, cm^{-1}): 2953, 2927, 2856, 2834, 1612, 1512, 1462, 1245, 1176, 1095, 1037, 899,

827, 773.

MS (EI, 70 eV): m/z (%) = 237 (100), 165 (20), 135 (22), 97 (20), 89 (56), 85 (42), 84 (31), 83 (29), 71 (49), 69 (32), 57 (89), 55 (29), 44 (25), 43 (46), 41 (28).

HR-MS (EI, 70 eV): [$C_{13}H_{21}O_2Si$], calcd.: 237.1305; found: 237.1314 [M^+-*t*Bu].

1-(2-(4-Methoxyphenyl)propyl)-3-(trifluoromethyl)benzene (71c)



Following **TP5** 1-(2-Iodopropyl)-3-(trifluoromethyl)benzene (**70c**, 157 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(*p*-anisyl)manganese reagent (**72a**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:5) as an eluent to afford **71c** as a colorless oil (77%, 114 mg, 0.39 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.44 – 7.39 (m, 1H), 7.35 – 7.27 (m, 2H), 7.21 – 7.17 (m, 1H), 7.09 – 7.03 (m, 2H), 6.85 – 6.80 (m, 2H), 3.79 (s, 3H), 3.02 – 2.89 (m, 2H), 2.88 – 2.79 (m, 1H), 1.24 (d, *J* = 6.8 Hz, 3H).

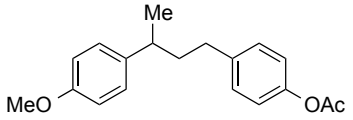
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.2, 141.8, 138.3, 132.7, 130.5 (q, *J* = 31.9 Hz), 128.5, 128.0, 126.0 (q, *J* = 3.9 Hz), 124.4 (q, *J* = 272.2 Hz), 122.8 (q, *J* = 3.9 Hz), 113.9, 55.4, 45.2, 41.0, 21.4.

FT-IR (ATR, cm^{-1}): 2959, 2929, 2836, 2360, 1611, 1512, 1449, 1326, 1245, 1176, 1159, 1118, 1072, 1037, 904, 827, 796, 702, 661.

MS (EI, 70 eV): m/z (%) = 158 (4), 136 (8), 135 (100), 105 (5), 103 (4), 91 (6), 79 (3), 77 (4), 42 (3).

HR-MS (EI, 70 eV): [$C_{17}H_{17}F_3O$], calcd.: 294.1231; found: 294.1232.

4-(3-(4-Methoxyphenyl)butyl)phenyl acetate (71d)



Following **TP5** 4-(3-Iodobutyl)phenyl acetate (**70d**, 159 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(*p*-anisyl)manganese reagent (**72a**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:5) as an eluent to afford **71d** as a colorless oil (75%, 112 mg, 0.37 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.16 – 7.09 (m, 4H), 7.00 – 6.94 (m, 2H), 6.90 – 6.84 (m, 2H), 3.81 (s, 3H), 2.68 (h, *J*=7.1, 1H), 2.49 (td, *J*=7.9, 1.8, 2H), 2.29 (s, 3H), 1.93 – 1.82 (m, 2H), 1.25 (d, *J*=6.9, 3H).

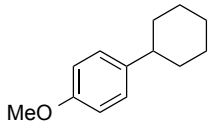
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 169.8, 158.0, 148.7, 140.3, 139.4, 129.4, 128.0, 121.3, 113.9, 55.4, 40.2, 38.8, 33.4, 22.9, 21.3.

FT-IR (ATR, cm^{-1}): 3032, 2995, 2955, 2928, 2866, 2835, 1758, 1610, 1510, 1507, 1368, 1244, 1213, 1189, 1164, 1031, 1017, 1010, 910, 828, 808.

MS (EI, 70 eV): m/z (%) = 299 (4), 298 (22), 256 (14), 148 (5), 136 (10), 135 (100), 121 (8), 107 (12), 105 (4), 91 (5), 77 (5), 43 (8).

HR-MS (EI, 70 eV): [$C_{19}H_{22}O_3$], calcd.: 298.1569; found: 298.1565.

1-Cyclohexyl-4-methoxybenzene (71e)[96]



Following **TP5** iodocyclohexane (**70e**, 105 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(*p*-anisyl)manganese reagent (**72a**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was

[96] M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* **2004,** *126*, 3686.

worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:2) as an eluent to afford **71e** as a colorless solid (84%, 80 mg, 0.42 mmol).

Mp.: 58.1-58.7 °C

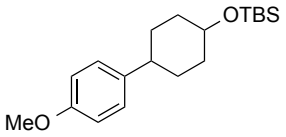
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.17 – 7.11 (m, 2H), 6.87 – 6.82 (m, 2H), 3.79 (s, 3H), 2.46 (ddq, *J*=11.7, 8.7, 3.3, 1H), 1.91 – 1.81 (m, 4H), 1.79 – 1.71 (m, 1H), 1.47 – 1.32 (m, 4H), 1.31 – 1.20 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.8, 140.5, 127.8, 113.8, 55.4, 43.8, 34.9, 27.1, 26.3.

MS (EI, 70 eV): m/z (%) = 190 (56), 147 (97), 121 (34), 111 (36), 97 (59), 95 (47), 85 (51), 84 (93), 83 (45), 71 (65), 69 (68), 57 (100), 55 (74), 43 (71), 42 (62), 39 (72).

HR-MS (EI, 70 eV): [$C_{13}H_{18}O$], calcd.: 190.1358; found: 190.1349.

***tert*-Butyl((4-(4-methoxyphenyl)cyclohexyl)oxy)dimethylsilane (71f)**



Following **TP5** *tert*-Butyl((4-iodocyclohexyl)oxy)dimethylsilane (**70f**, 170 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(*p*-anisyl)manganese reagent (**72a**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:2) as an eluent to afford **71f** as a colorless oil (75%, 120 mg, 0.37 mmol).

Signals of both diasteriomers are given (dr = 70:30).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.18 – 7.09 (m, 2H), 6.89 – 6.79 (m, 2H), 3.79 (d, *J*=1.9, 3H), 4.09 – 3.58 (m, 1H), 2.51 – 2.38 (m, 1H), 2.03 – 1.72 (m, 4H), 1.64 – 1.37 (m, 4H), 0.92 (s, 9H), 0.07 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.9, 157.8, 140.4, 139.2, 127.8, 127.7, 113.8, 113.8, 71.6, 66.0, 55.4, 43.3, 42.8, 36.5, 34.0, 33.1, 28.3, 26.1, 26.0, 18.4, 18.3, -4.4, -4.7.

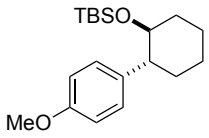
FT-IR (ATR, cm^{-1}): 2927, 2855, 1612, 1582, 1512, 1471, 1462, 1450, 1441, 1420, 1387, 1375, 1360, 1304, 1281, 1245, 1177, 1117, 1091, 1040, 1019, 1005, 988, 938, 891, 859, 833, 824,

805, 793, 772, 749, 668.

MS (EI, 70 eV): m/z (%) = 263 (18), 189 (8), 188 (50), 187 (100), 173 (5), 134 (15), 121 (17), 75 (39), 73 (8).

HR-MS (EI, 70 eV): [$C_{19}H_{32}O_2Si$], calcd.: 320,2172; found: 320.2168.

tert-Butyl((2-(4-methoxyphenyl)cyclohexyl)oxy)dimethylsilane (71g)



Following **TP5** *tert*-Butyl((*cis*-2-iodocyclohexyl)oxy)dimethylsilane (**70g**, 170 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(*p*-anisyl)manganese reagent (**72a**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:2) as an eluent to afford **71g** as a colorless oil (83%, 133 mg, 0.41 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.13 – 7.07 (m, 2H), 6.84 – 6.78 (m, 2H), 3.78 (s, 3H), 3.47 (td, *J*=9.8, 4.5, 1H), 2.39 (ddd, *J*=13.1, 9.6, 3.6, 1H), 2.03 – 1.93 (m, 1H), 1.87 – 1.76 (m, 2H), 1.76 – 1.70 (m, 1H), 1.53 (qd, *J*=13.0, 3.6, 1H), 1.44 – 1.24 (m, 3H), 0.68 (s, 9H), -0.19 (s, 3H), -0.50 (s, 3H).

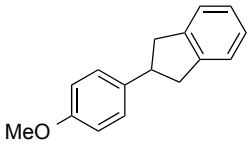
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.1, 137.5, 129.3, 113.5, 76.2, 55.5, 52.2, 36.9, 33.1, 26.3, 25.9, 25.4, 18.0, -4.6, -5.4.

FT-IR (ATR, cm^{-1}): 2926, 2854, 2360, 2341, 1512, 1360, 1244, 1176, 1124, 1090, 1039, 983, 881, 857, 846, 831, 813, 772, 753, 666.

MS (EI, 70 eV): m/z (%) = 305 (1), 265 (6), 264 (22), 263 (100), 189 (12), 187 (7), 165 (7), 121 (33), 75 (33), 73 (12).

HR-MS (EI, 70 eV): [$C_{18}H_{29}O_2Si$], calcd.: 305.1931; found: 305.1936 [M^+-CH_3].

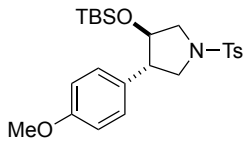
2-(4-Methoxyphenyl)-2,3-dihydro-1*H*-indene (71h)



Following **TP5** 2-Iodo-2,3-dihydro-1*H*-indene (**70h**, 122 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(*p*-anisyl)manganese reagent (**72a**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:2) as an eluent to afford **71h** as a colorless oil (70%, 78 mg, 0.35 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.29 – 7.19 (m, 4H), 7.22 – 7.17 (m, 2H), 6.90 – 6.84 (m, 2H), 3.81 (s, 3H), 3.66 (p, *J*=8.6, 1H), 3.33 (dd, *J*=15.4, 8.0, 2H), 3.06 (dd, *J*=15.5, 9.0, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.1, 143.2, 137.7, 128.1, 126.5, 124.4, 114.0, 55.4, 45.0, 41.2.
FT-IR (ATR, cm^{-1}): 3066, 3019, 2932, 2903, 2833, 1611, 1511, 1482, 1458, 1441, 1243, 1220, 1177, 1034, 825, 741.
MS (EI, 70 eV): m/z (%) = 225 (19), 224 (100), 209 (34), 116 (36), 115 (30), 82 (18), 57 (23), 55 (21), 43 (47), 42 (14).
HR-MS (EI, 70 eV): [$C_{16}H_{16}O$], calcd.: 224.1201; found: 224.1193.

3-((*tert*-Butyldimethylsilyl)oxy)-4-(4-methoxyphenyl)-1-tosylpyrrolidine (71i)



Following **TP5** 3-((*tert*-Butyldimethylsilyl)oxy)4-iodo-1-tosylpyrrolidine (**70i**, 241 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(*p*-anisyl)manganese reagent (**72a**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was

purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **71i** as a colorless solid (59%, 136 mg, 0.29 mmol).

Signals of the main diastereomer are given (dr = 95:5).

Mp.: 124.3-126.1 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.78 – 7.74 (m, 2H), 7.37 – 7.32 (m, 2H), 7.15 – 7.05 (m, 2H), 6.86 – 6.80 (m, 2H), 4.04 (q, *J*=5.3, 1H), 3.78 (s, 3H), 3.67 – 3.58 (m, 2H), 3.51 (dd, *J*=9.8, 6.2, 1H), 3.10 – 2.97 (m, 2H), 2.45 (s, 3H), 0.71 (s, 9H), -0.16 (s, 3H), -0.21 (s, 3H).

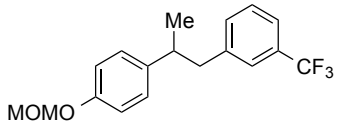
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 158.9, 143.6, 134.0, 131.2, 129.8, 128.6, 127.7, 114.2, 77.7, 55.4, 54.4, 51.9, 51.5, 25.7, 21.7, 17.9, -4.9, -5.0.

FT-IR (ATR, cm^{-1}): 2953, 2929, 2885, 2856, 1515, 1346, 1250, 1161, 1093, 1034, 834, 778, 666.

MS (EI, 70 eV): m/z (%) = 406 (10), 405 (24), 400 (100), 270 (3), 174 (3), 149 (4), 147 (5), 134 (5), 125 (6), 121 (17), 91 (8), 72 (8), 42 (7).

HR-MS (EI, 70 eV): [$C_{23}H_{32}NO_4SSi$], calcd.: 446.1816; found: 446.1805 [M^+-CH_3].

1-(2-(4-(Methoxymethoxy)phenyl)propyl)-3-(trifluoromethyl)benzene (71j)



Following **TP5** 1-(2-Iodopropyl)-3-(trifluoromethyl)benzene (**70c**, 314 mg, 1 mmol, 1 equiv, in 2 mL THF) reacts with the di(4-(methoxymethoxy)benzene)manganese reagent (**72b**, 0.7 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:2) as an eluent to afford **71j** as a colorless oil (76%, 246 mg, 0.76 mmol).

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.42 (d, *J*=7.7, 1H), 7.33 (t, *J*=7.7, 1H), 7.27 (s, 1H), 7.22 (d, *J*=7.6, 1H), 7.08 – 7.03 (m, 2H), 6.98 – 6.93 (m, 2H), 5.15 (s, 2H), 3.48 (s, 3H), 3.02 – 2.88 (m, 2H), 2.87 – 2.79 (m, 1H), 1.24 (d, *J*=6.7, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 155.8, 141.8, 139.7, 132.7 (d, *J* = 1.2 Hz), 130.5 (q, *J* =

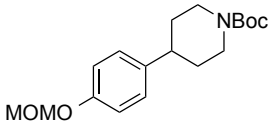
31.9 Hz), 128.6, 128.1, 126.0 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 272.3 Hz), 122.9 (q, *J* = 3.8 Hz), 116.3, 94.7, 56.1, 45.1, 41.1, 21.4.

FT-IR (ATR, cm^{-1}): 2961, 2930, 2899, 1511, 1328, 1314, 1234, 1200, 1152, 1120, 1073, 1019, 999, 921, 831, 796, 702, 661.

MS (EI, 70 eV): m/z (%) = 324 (2), 293 (2), 166 (9), 165 (100), 159 (10), 136 (4), 135 (42), 91 (6), 77 (2), 45 (80).

HR-MS (EI, 70 eV): [$C_{18}H_{19}F_3O_2$], calcd.: 324.1337; found: 324.1334.

***tert*-Butyl 4-(4-(methoxymethoxy)phenyl)piperidine-1-carboxylate (71k)**



Following **TP5** tert-butyl 4-iodopiperidine-1-carboxylate (**70j**, 156 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-(methoxymethoxy)benzene)manganese reagent (**72b**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (10:1) as an eluent to afford **71k** as a colorless solid (75%, 121 mg, 0.38 mmol).

Mp.: 84.8 – 86.6 °C

^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.14 – 7.09 (m, 2H), 7.00 – 6.97 (m, 2H), 5.15 (s, 2H), 4.23 (s, 2H), 3.47 (s, 3H), 2.85 – 2.73 (m, 2H), 2.59 (tt, *J* = 12.2, 3.6 Hz, 1H), 1.79 (d, *J* = 12.6 Hz, 2H), 1.63 – 1.54 (m, 2H), 1.48 (s, 9H).

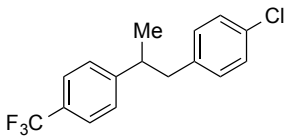
^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 155.8, 155.0, 139.4, 127.8, 116.4, 94.7, 79.5, 56.1, 44.7, 42.1, 33.5, 28.6.

FT-IR (ATR, cm^{-1}): 2974, 2932, 2850, 1687, 1511, 1422, 1365, 1279, 1228, 1198, 1151, 1123, 1106, 1077, 1001, 985, 922, 831, 762.

MS (EI, 70 eV): m/z (%) = 321 (7), 265 (22), 248 (14), 221 (22), 220 (15), 203 (17), 189 (6), 176 (14), 82 (13), 57 (89), 56 (15), 45 (100), 41 (17).

HR-MS (EI, 70 eV): [$C_{18}H_{27}NO_4$], calcd.: 321.1940; found: 321.1931.

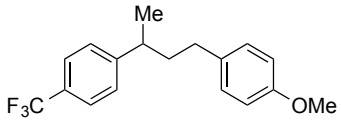
1-Chloro-4-(2-(4-(trifluoromethyl)phenyl)propyl)benzene (71l)



Following **TP5** tert-butyl 4-iodopiperidine-1-carboxylate (**70a**, 140 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-(trifluoromethyl)benzene)manganese reagent (**72c**, 0.35 mmol, 0.7 equiv) prepared according to **TP4**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane as an eluent to afford **71l** as a colorless oil (81%, 106 mg, 0.41 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.52 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 7.22 – 7.17 (m, 2H), 7.00 – 6.93 (m, 2H), 3.04 (h, J = 7.1 Hz, 1H), 2.92 – 2.77 (m, 2H), 1.27 (d, J = 6.9 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 150.5 (d, J = 1.5 Hz), 138.6, 132.0, 130.5, 128.7 (q, J = 30.7 Hz), 128.5, 127.5, 125.4 (q, J = 4.0 Hz), 124.4 (q, J = 272.0 Hz), 44.2, 41.9, 21.2.
FT-IR (ATR, cm^{-1}): 2964, 2928, 2874, 2856, 1618, 1491, 1322, 1161, 1114, 1105, 1093, 1068, 1014, 834, 801.
MS (EI, 70 eV): m/z (%) = 298 (10), 174 (35), 173 (35), 153 (11), 133 (14), 127 (36), 126 (18), 125 (100), 103 (4), 90 (4), 89 (9), 44 (5), 43 (7).
HR-MS (EI, 70 eV): [$C_{16}H_{14}ClF_3$], calcd.: 298.0736; found: 298.0736.

1-Methoxy-4-(3-(4-(trifluoromethyl)phenyl)butyl)benzene (71m)

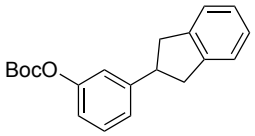


Following **TP5** 1-(3-iodobutyl)-4-methoxybenzene (**70k**, 145 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(4-(trifluoromethyl)benzene)manganese reagent (**72c**, 0.35 mmol, 0.7 equiv) prepared according to **TP4**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified

by column chromatography on silica using *i*-hexane:ethyl acetate (100:2) as an eluent to afford **72m** as a colorless oil (87%, 134 mg, 0.43 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.57 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.06 – 7.01 (m, 2H), 6.84 – 6.80 (m, 2H), 3.79 (s, 3H), 2.78 (h, *J* = 7.1 Hz, 1H), 2.52 – 2.41 (m, 2H), 1.98 – 1.85 (m, 2H), 1.28 (d, *J* = 6.9 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 157.9, 151.6 (d, *J* = 1.5 Hz), 134.2, 129.3, 128.4 (q, *J* = 32.2 Hz), 127.6, 125.5 (q, *J* = 4.0 Hz), 124.5 (q, *J* = 272.0 Hz), 113.9, 55.4, 40.0, 39.5, 33.0, 22.4.
FT-IR (ATR, cm^{-1}): 2958, 2931, 2835, 2360, 2332, 1511, 1323, 1243, 1161, 1115, 1066, 1036, 1016, 837, 820.
MS (EI, 70 eV): m/z (%) = 309 (5), 308 (23), 135 (17), 134 (12), 122 (16), 121 (100), 108 (6), 91 (10), 78 (7), 77 (8), 57 (6).
HR-MS (EI, 70 eV): [$C_{18}H_{19}F_3O$], calcd.: 308.1388; found: 308.1383.

***tert*-Butyl (3-(2,3-dihydro-1*H*-inden-2-yl)phenyl) carbonate (71n)**



Following **TP5** 2-iodo-2,3-dihydro-1H-indene (**70h**, 122 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(3-(BocO)benzene-1-yl)manganese reagent (**72d**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:2) as an eluent to afford **71n** as a colorless oil (76%, 118 mg, 0.38 mmol).

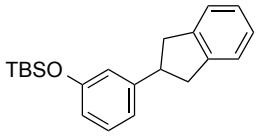
^{1}H-NMR (599 MHz, $CDCl_3$, ppm): δ = 7.30 (t, *J* = 7.9 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.21 – 7.14 (m, 3H), 7.12 – 7.10 (m, 1H), 7.03 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1H), 3.70 (p, *J* = 8.6 Hz, 1H), 3.36 (dd, *J* = 15.5, 8.2 Hz, 2H), 3.08 (dd, *J* = 15.5, 8.9 Hz, 2H), 1.56 (s, 9H).
^{13}C-NMR (151 MHz, $CDCl_3$, ppm): δ = 152.1, 151.3, 147.4, 142.8, 129.4, 126.6, 124.5, 124.5, 120.1, 119.2, 83.6, 45.4, 40.9, 27.9.

FT-IR (ATR, cm^{-1}): 2980, 2934, 2907, 2844, 2361, 2332, 1753, 1586, 1369, 1269, 1253, 1232, 1138, 1002, 780, 742, 692.

MS (EI, 70 eV): m/z (%) = 211 (11), 210 (84), 195 (15), 178 (8), 165 (11), 117 (9), 116 (27), 115 (11), 57 (100), 40 (11).

HR-MS (EI, 70 eV): [$C_{20}H_{22}O_3$], calcd.: 310.1569; found: 310.1556.

***tert*-Butyl(3-(2,3-dihydro-1*H*-inden-2-yl)phenoxy)dimethylsilane (71o)**



Following **TP5** 2-iodo-2,3-dihydro-1H-indene (**70h**, 122 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(3-(TBSO)benzene-1-yl)manganese reagent (**72e**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane as eluent to afford **71o** as a colorless oil (74%, 120 mg, 0.37 mmol).

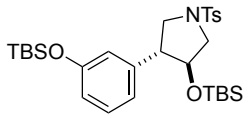
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.29 – 7.21 (m, 2H), 7.21 – 7.14 (m, 3H), 6.92 – 6.88 (m, 1H), 6.79 (t, J = 2.2 Hz, 1H), 6.70 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H), 3.65 (p, J = 8.5 Hz, 1H), 3.34 (dd, J = 15.5, 8.1 Hz, 2H), 3.07 (dd, J = 15.5, 8.8 Hz, 2H), 0.98 (s, 9H), 0.18 (s, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 155.8, 147.2, 143.1, 129.4, 126.6, 124.4, 120.2, 118.8, 117.9, 45.5, 41.0, 25.9, 18.4, -4.2.

FT-IR (ATR, cm^{-1}): 3069, 3023, 2954, 2930, 2857, 1602, 1584, 1483, 1472, 1278, 1252, 1158, 899, 836, 808, 779, 740, 695.

MS (EI, 70 eV): m/z (%) = 325 (5), 324 (20), 269 (6), 268 (21), 267 (100), 134 (4), 117 (32), 115 (9), 91 (4).

HR-MS (EI, 70 eV): [$C_{21}H_{28}OSi$], calcd.: 324.1909; found: 324.1904.

3-((*tert*-Butyldimethylsilyl)oxy)-4-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)-1tosylpyrrolidine (71p)



Following **TP5** 3-((*tert*-Butyldimethylsilyl)oxy)4-iodo-1-tosylpyrrolidine (**70i**, 241 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(3-(TBSO)benzene-1-yl)manganese reagent (**72e**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:5) as eluent to afford **71p** as a colorless solid (92%, 257 mg, 0.46 mmol).

Mp.: 96.6-97.2 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.79 – 7.73 (m, 2H), 7.37 – 7.32 (m, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.77 – 6.67 (m, 3H), 4.07 (dt, *J* = 5.6 Hz, 1H), 3.67 – 3.59 (m, 2H), 3.50 (dd, *J* = 10.0, 6.6 Hz, 1H), 3.05 (dd, *J* = 10.2, 5.2 Hz, 1H), 2.99 (dt, *J* = 7.8, 6.2 Hz, 1H), 2.45 (s, 3H), 0.98 (s, 9H), 0.72 (s, 9H), 0.18 (s, 6H), -0.16 (s, 3H), -0.21 (s, 3H).

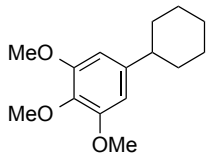
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 156.1, 143.6, 140.7, 133.9, 129.8, 129.8, 127.7, 120.5, 119.3, 119.0, 77.6, 54.5, 52.6, 51.4, 25.8, 25.7, 21.7, 18.4, 17.9, -4.2, -4.9, -5.0.

FT-IR (ATR, cm^{-1}): 2954, 2929, 2886, 2857, 1602, 1585, 1485, 1472, 1463, 1347, 1280, 1252, 1160, 1143, 1093, 1003, 905, 861, 834, 813, 778, 732, 699, 663, 608, 589.

MS (EI, 70 eV): m/z (%) = 507 (4), 506 (19), 505 (33), 504 (100), 224 (8), 149 (3), 91 (3), 73 (4).

HR-MS (EI, 70 eV): [$C_{28}H_{44}NO_4SSi_2$], calcd.: 546.2524; found: 546.2526 [M^+ -CH_3]

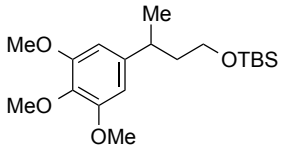
5-Cyclohexyl-1,2,3-trimethoxybenzene (70q)



Following **TP5** iodocyclohexane (**70e**, 105 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(3,4,5-(trimethoxy)benzene)manganese reagent (**72f**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:5) as eluent to afford **71q** as a colorless oil (80%, 101 mg, 0.40 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.43 (s, 2H), 3.86 (s, 6H), 3.83 (s, 3H), 2.50 – 2.38 (m, 1H), 1.94 – 1.80 (m, 4H), 1.79 – 1.70 (m, 1H), 1.47 – 1.34 (m, 4H), 1.31 – 1.19 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 153.2, 144.1, 136.2, 103.9, 61.0, 56.2, 45.2, 34.8, 27.0, 26.3.
FT-IR (ATR, cm^{-1}): 2923, 2850, 2363, 2341, 1587, 1508, 1449, 1418, 1330, 1238, 1184, 1133, 1121, 1103, 1009,956, 822, 775, 689.
MS (EI, 70 eV): m/z (%) = 251 (25), 250 (100), 236 (9), 235 (51), 207 (13), 181 (16), 176 (10), 153 (22), 151 (15), 57 (8).
HR-MS (EI, 70 eV): [$C_{15}H_{22}O_3$], calcd.: 250.1569; found: 250.1562.

***tert*-Butyldimethyl(3-(3,4,5-trimethoxyphenyl)butoxy)silane (71r)**



Following **TP5** *tert*-butyl(3-iodobutoxy)dimethylsilane (**70b**, 157 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(3,4,5-(trimethoxy)benzene)manganese reagent (**72f**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:8) as eluent to afford **71r** as a colorless oil (60%, 157 mg, 0.30 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.40 (s, 2H), 3.85 (s, 6H), 3.83 (s, 3H), 3.60 – 3.44 (m, 2H), 2.82 (h, J = 7.1 Hz, 1H), 1.77 (q, J = 6.8 Hz, 2H), 1.24 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.01 (d, J = 2.0 Hz, 6H).

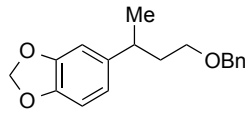
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 153.2, 143.3, 136.3, 104.1, 61.3, 61.0, 56.2, 41.4, 36.7, 26.1, 22.5, 18.4, -5.1.

FT-IR (ATR, cm^{-1}): 2954, 2929, 2856, 1588, 1510, 1459, 1420, 1322, 1236, 1128, 1100, 1010, 982, 899, 832, 811, 773, 664.

MS (EI, 70 eV): m/z (%) = 354 (8), 299 (7), 298 (20), 297 (100), 282 (12), 252 (13), 196 (11), 195 (10), 191 (8), 89 (14), 73 (5).

HR-MS (EI, 70 eV): [$C_{19}H_{34}O_4Si$], calcd.: 354.2226; found: 354.2226.

5-(4-(Benzyloxy)butan-2-yl)benzo[*d*][1,3]dioxole (71s)



Following **TP5** ((3-iodobutoxy)methyl)benzene (**70l**, 145 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(1,3-benzodioxol-5-yl)manganese reagent (**72g**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:1) as eluent to afford **71s** as a colorless oil (66%, 93 mg, 0.33 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.38 – 7.26 (m, 5H), 6.75 – 6.68 (m, 2H), 6.63 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 4.44 (d, *J* = 2.2 Hz, 2H), 3.45 – 3.29 (m, 2H), 2.86 (dp, *J* = 9.0, 6.9 Hz, 1H), 1.95 – 1.75 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 3H).

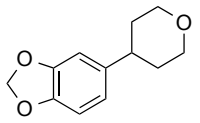
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 147.7, 145.7, 141.1, 138.7, 128.5, 127.8, 127.6, 120.1, 108.2, 107.4, 100.9, 73.1, 68.6, 38.4, 36.5, 22.7.

FT-IR (ATR, cm^{-1}): 3030, 2958, 2926, 2868, 1503, 1486, 1453, 1439, 1363, 1241, 1204, 1189, 1093, 1075, 1060, 1038, 937, 912, 860, 808, 734, 697.

MS (EI, 70 eV): m/z (%) = 285 (11), 284 (65), 192 (52), 176 (21), 163 (30), 150 (30), 149 (100), 135 (27), 119 (19), 91 (88), 65 (18), 43 (20).

HR-MS (EI, 70 eV): [$C_{18}H_{20}O_3$], calcd.: 284.1412; found: 284.1406.

5-(Tetrahydro-2*H*-pyran-4-yl)benzo[*d*][1,3]dioxole (71t)



Following **TP5** 4-iodotetrahydro-2*H*-pyran (**70m**, 106 mg, 0.5 mmol, 1 equiv, in 1 mL THF) reacts with the di(1,3-benzodioxol-5-yl)manganese reagent (**72g**, 0.35 mmol, 0.7 equiv) prepared according to **TP3**, at -20 °C. The solution was allowed to warm to room temperature under stirring for 8 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as eluent to afford **71t** as a colorless solid (70%, 72 mg, 0.35 mmol).

Mp.: 73.4-74.2 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.76 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 1.8 Hz, 1H), 6.67 (ddd, *J* = 8.0, 1.8, 0.6 Hz, 1H), 5.93 (s, 2H), 4.08 (td, *J* = 3.0, 0.9 Hz, 1H), 4.06 – 4.03 (m, 1H), 3.54 – 3.46 (m, 2H), 2.68 (tt, *J* = 10.6, 5.3 Hz, 1H), 1.84 – 1.69 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 147.8, 146.0, 140.2, 119.6, 108.4, 107.4, 101.0, 68.5, 41.5, 34.4.

FT-IR (ATR, cm^{-1}): 2935, 2915, 2841, 1503, 1487, 1440, 1385, 1262, 1247, 1227, 1189, 1129, 1085, 1037, 1020, 980, 930, 911, 875, 806, 776.

MS (EI, 70 eV): m/z (%) = 207 (13), 206 (100), 162 (39), 161 (24), 149 (13), 148 (45), 146 (27), 135 (26), 132 (12), 119 (13), 91 (13), 89 (12).

HR-MS (EI, 70 eV): [$C_{12}H_{14}O_3$], calcd.: 206.0943; found: 206.0934.

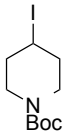
5. Cobalt-Catalyzed Negishi Cross-Coupling Reactions of (Hetero)Arylzinc Reagents with Primary and Secondary Alkyl Bromides and Iodides

5.1 Synthesis of Starting Materials

The following starting materials were prepared according to literature procedures with only little deviation. The spectral data of known compounds were in full agreement with the literature

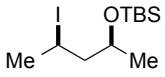
(Signals of the main diastereomer are given).

***tert*-butyl 4-iodopiperidine-1-carboxylate**



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.38 (quin, J = 5.9 Hz, 1 H) 3.43 - 3.60 (m, 2 H) 3.14 - 3.29 (m, 2 H) 1.96 (q, J = 5.6 Hz, 4 H) 1.39 (s, 9 H).

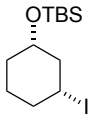
***tert*-butyl((4-iodopentan-2-yl)oxy)dimethylsilane**



d.r.: 99:1 (*syn*/*anti*)

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 4.17 (ddq, J = 7.9, 6.85, 6.84 Hz, 1H), 3.92 (qt, J = 6.11, 6.10 Hz, 1H), 2.19 (ddd, J = 14.4, 8.0. 6.6 Hz, 1H), 1.93 (d, J = 6.8 Hz, 3H), 1.70 (dt, J = 14.1, 6.5 Hz, 1H), 1.12 (d, J = 6.0 Hz, 3H), 0.89 (s, 9H), 0.074 (s, 3H), 0.068 (s, 3H).

***tert*-butyl((3-iodocyclohexyl)oxy)dimethylsilane**



d.r.: 22:78 (*syn*/*anti*).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.66 (tt, J = 8.4, 4.2 Hz, 1 H) 3.93 - 4.03 (m, 1 H) 1.89 - 2.21 (m, 3 H) 1.57 (m, 3 H) 0.90 (s, 9 H) 0.06 (d, 6 H).

5.2 Cobalt-Catalyzed Cross-Coupling of (Hetero)Arylzinc Reagents with Alkyl Iodides and Bromides

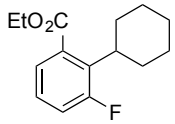
Typical procedure 6 (TP6): Metalation using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$:

A dry and argon-flushed 10 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with a solution of the corresponding (hetero)arene (1.4 mmol, 1.0 equiv) in dry THF (1 mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**1**, 0.84 mmol, 0.44 M, 1.91 mL, 0.6 equiv) was added dropwise at the given temperature and the reaction mixture was stirred at this temperature. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

Typical procedure 7 (TP7): Cobalt-catalyzed cross-coupling of organozinc reagents:

A dry and argon-flushed 10 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with a solution of $CoCl_2{\cdot}2LiCl$ (1 M in THF) (0.2 mmol, 0.2 mL, 20 mol%) and dry THF (1.0 mL). The respective alkyl iodide or bromide (1.0 mmol, 1.0 equiv) and TMEDA (0.3 mmol, 45 mg, 30 mol%) were added *via* syringe. The reaction mixture was cooled to 0 °C and a solution of the appropriate zinc reagent (1.4 mmol, 1.4 equiv) was added dropwise over 5 min *via* syringe. The reaction was allowed to warm to 25 °C and was monitored by GC-analysis (undecane $C_{11}H_{24}$ was used as an internal standard). Upon consumption of the starting material, saturated aqueous NH_4Cl solution (5 mL) and ethyl acetate (5 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography yielding the respective title compound.

Ethyl 2-cyclohexyl-3-fluorobenzoate (76a)[97]



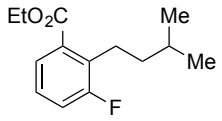
$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed

[97] S. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.

to warm to 25 °C, stirred for 8 h and was then added dropwise according to **TP7** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (99:1) as an eluent to afford **76a** as a colorless oil (87%, 218 mg, 0.87 mmol).

^{1}H-NMR 300 MHz, $CDCl_3$, ppm): δ = 7.35 (ddd, *J* = 7.6, 1.5, 0.4 Hz, 1 H), 7.04-7.20 (m, 2 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 3.01-3.13 (m, 1 H), 1.68-1.93 (m, 7 H), 1.39 (t, *J* = 7.1 Hz, 3 H), 1.26-1.37 (m, 3 H).

Ethyl 3-fluoro-2-isopentylbenzoate (76b)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP7** to 1-iodo-3-methylbutane (198 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (9:1) as an eluent to afford **76b** as a colorless oil (63%, 150 mg, 0.63 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.62 – 7.58 (m, 1H), 7.23 – 7.11 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 0.4, 2H), 3.03 – 2.89 (m, 2H), 1.71 – 1.59 (m, 1H), 1.51 – 1.43 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.08 – 0.88 (d, J = 6.4 Hz, 6 H).

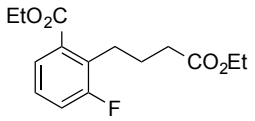
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 167.0, 161.2 (d, *J* = 246.1 Hz), 132.3 (d, *J* = 4.6 Hz), 131.8 (d, *J* = 17.3 Hz), 126.5 (d, *J* = 9.3 Hz), 125.9 (d, *J* = 3.5 Hz), 118.4 (d, *J* = 23.9 Hz), 61.1, 39.7, 28.5, 24.1, 22.4, 14.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2871, 1456, 1366, 1257, 1172, 1257, 1099, 1025, 907, 755.

MS (EI, 70 eV): *m/z* (%) = 238 (20), 195 (20), 193 (18), 183 (10), 182 (86), 167 (52), 163 (17), 154 (20), 153 (41), 149 (59), 08 (12).

HR-MS (EI, 70 eV): [$C_{14}H_{19}FO_2$], calcd.: 238.1369; found: 238.1356.

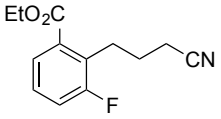
Ethyl 2-(4-ethoxy-4-oxobutyl)-3-fluorobenzoate (76c)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP7** to either ethyl 4-iodobutanoate (X = I, 242 mg, 1.0 mmol) or 4-ethyl bromobutanoate (X = Br, 195 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (92:8) as an eluent to afford **76c** as a colorless oil (X = I: 58%, 164 mg, 0.58 mmol; X = Br: 38%, 107 mg, 0.38 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.67 – 7.60 (m, 1H), 7.25 – 7.11 (m, 2H), 4.34 (q, *J* = 7.1 Hz, 0.4, 2H), 4.17 – 4.04 (m, 2H), 3.00 (q, *J* = 7.3 Hz, 2H), 2.35 (t, *J* = 7.7 Hz, 2H), 1.99 – 1.86 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 173.3, 166.6 (d, *J* = 3.5 Hz), 161.3 (d, *J* = 244.6 Hz), 132.2 (d, *J* = 4.2 Hz), 130.4 (d, *J* = 17.6 Hz), 127.0 (d, *J* = 9.0 Hz), 126.2 (d, *J* = 3.4 Hz), 118.6 (d, *J* = 24.0 Hz), 61.1, 60.2, 34.1, 25.6, 25.1, 14.2.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2981, 1720, 1456, 1367, 1258, 1174, 1129, 1059, 1024, 934, 757, 732.
MS (EI, 70 eV): *m/z* (%) = 237 (45), 236 (55), 208 (15), 194 (21), 191 (15), 190 (18), 163 (31), 162 (12), 153 (16), 149 (32), 135 (16), 133 (11).
HR-MS (EI, 70 eV): [$C_{15}H_{19}FO_4$], calcd.: 282.1267; found: 282.1271.

Ethyl 2-(3-cyanopropyl)-3-fluorobenzoate (76d)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP7** to either 4-iodobutanenitrile (X = I, 195 mg, 1.0 mmol) or 4-bromobutanenitrile (X = Br, 148 mg, 1.0 mmol)

in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (97:3) as an eluent to afford **76d** as a colorless oil (X = I: 71%, 167 mg, 0.71 mmol; X = Br: 51%, 120 mg, 0.51 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.04 - 7.96 (m, 1H), 7.05 – 6.90 (m, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.18 – 3.03 (m, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 2.06 – 1.88 (m, 2H), 1.40 (t, *J* = 7.2 Hz, 3H).

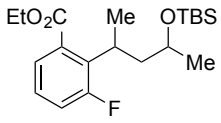
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 166.1, 165.2 (d, *J* = 254.1 Hz), 154.5 (d, *J* = 8.4 Hz), 133.8 (d, *J* = 9.3 Hz), 125.6 (d, *J* = 2.8 Hz), 119.4, 117.8 (d, *J* = 21.6 Hz), 113.7 (d, *J* = 21.0 Hz), 61.1, 33.5, 26.7, 16.9, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2254, 1715, 1458, 1261, 1139, 1056, 1020, 905, 760, 725.

MS (EI, 70 eV): *m/z* (%) = 235 (2), 217 (4), 190 (16), 189 (25), 188 (5), 167 (45), 109 (5).

HR-MS (EI, 70 eV): [$C_{13}H_{14}FNO_2$], calcd.: 235.1009; found: 235.1006.

Ethyl 2-(4-((tert-butyldimethylsilyl)oxy)pentan-2-yl)-3-fluorobenzoate (76e)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP7** to *tert*-butyl((4-iodopentan-2-yl)oxy)dimethylsilane (328 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (95:5) as an eluent to afford **76e** as a colorless oil (70%, 258 mg, 0.70 mmol, d.r. 52:48).

Signals of both diastereomers are given:

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.38 (dddd, *J* = 13.3, 7.6, 1.5, 0.6 Hz, 2H), 7.25 – 7.02 (m, 4H), 4.34 (qdd, *J* = 7.1, 4.1, 2.1 Hz, 4H), 3.85 – 3.64 (m, 2H), 3.56 – 3.43 (m, 2H), 2.07 – 1.70 (m, 5H), 1.47 – 1.30 (m, 13H), 1.10 (dd, *J* = 6.1, 1.7 Hz, 6H), 0.92 – 0.81 (m, 18H), 0.04 – -

0.07 (m, 12H).

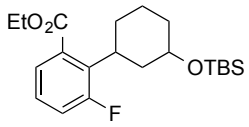
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 167.9 (d, *J* = 3.8 Hz), 167.9 (d, *J* = 3.9 Hz), 162.4 (d, *J* = 248.3 Hz), 162.1 (d, *J* = 247.1 Hz), 134.5 (d, *J* = 14.9 Hz), 134.0 (d, *J* = 6.5 Hz), 133.8 (d, *J* = 14.8 Hz), 133.5 (d, *J* = 6.6 Hz), 127.0 (d, *J* = 9.4 Hz), 126.8 (d, *J* = 9.4 Hz), 125.1 (d, *J* = 3.5 Hz), 124.8 (d, *J* = 3.5 Hz), 118.9 (d, *J* = 24.0 Hz), 118.6 (d, *J* = 23.8 Hz), 67.9, 66.7, 61.3 45.5, 45.1, 31.0, 30.5, 25.9, 25.8, 23.8, 23.7, 20.3, 19.4, 18.0, 18.0, 14.2, -4.4, -4.5, -4.8, -4.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959, 2930, 2857, 1723, 1451, 1367, 1278, 1255, 1178, 1142, 1037, 909, 834, 808, 773, 733.

MS (EI, 70 eV): *m/z* (%) = 311 (73), 265 (27), 223 (19), 163 (24), 159 (6), 149 (19), 121 (4), 103 (10), 75 (24), 73 (16).

HR-MS (EI, 70 eV): [$C_{16}H_{24}FO_3Si$], calcd.: 311.1479; found: 311.1488.

Ethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-3-fluorobenzoate (76f)



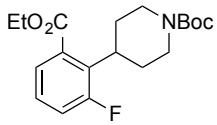
$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP7** to *tert*-butyl((3-iodocyclohexyl)oxy)dimethylsilane (340 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (98:2) as an eluent to afford **76f** as a colorless oil (79%, 301 mg, 0.79 mmol, d.r. 51:49).

Signals of both diastereomers are given:

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.41 (d, *J* = 7.3 Hz, 1 H), 7.32 (d, *J* = 7.6 Hz, 1 H), 7.16 - 7.25 (m, 2 H), 7.05 - 7.15 (m, 2 H), 4.24 - 4.48 (m, 4 H), 4.15 (br., 1 H), 3.54 - 3.68 (m, 2 H), 3.13 - 3.24 (m, 1 H), 2.05 - 2.16 (m, 1 H), 1.64 - 2.01 (m, 12 H), 1.44 - 1.61 (m, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 1.33 - 1.37 (m, 1 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 168.5 (d, *J* = 3.7 Hz), 168.2 (d, *J* = 3.7 Hz), 162.6 (d, *J* = 248.0 Hz), 162.3 (d, *J* = 248.0 Hz), 134.8 (d, *J* = 6.6 Hz), 133.6 (d, *J* = 6.6 Hz), 132.9 (d, *J* = 14.7 Hz), 132.4 (d, *J* = 14.7 Hz), 127.2 (d, *J* = 8.8 Hz), 127.0 (d, *J* = 9.5 Hz), 125.1 (d, *J* = 3.7 Hz), 124.5 (d, *J* = 3.70 Hz), 119.1 (d, *J* = 24.2 Hz), 118.6 (d, *J* = 24.2 Hz), 71.7, 67.0, 61.4, 40.1 (d, *J* = 4.4 Hz), 37.8 (d, *J* = 1.5 Hz), 37.7, 37.6, 35.7, 33.1 (d, *J* = 1.5 Hz), 32.9, 30.7 (d, *J* = 2.9 Hz), 29.8 (d, *J* = 4.4 Hz), 25.9, 25.8, 24.8, 20.4, 18.2, 18.1, 14.3, 14.3, -4.6, -4.9.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930, 2857, 1724, 1453, 1367, 1280, 1269, 1251, 1230, 1174, 1140, 1120, 1091, 1057, 1038, 1026, 981, 856, 834, 805, 773, 758.
MS (EI, 70 eV): m/z (%) = 365 (2), 335 (8), 325 (7), 324 (24), 323 (100), 305 (5), 278 (9), 277 (43), 260 (5), 259 (25), 249 (19), 235 (9), 227 (10), 221 (10), 203 (19)m 202 (8), 185 (29), 183 (22), 175 (12), 165 (15), 147 (19), 133 (13).
HR-MS (EI, 70 eV): [$C_{21}H_{33}FO_3{}^{28}Si$], calc.: 365.1948; found: 365.1939 [M^+-CH_3].

***tert*-Butyl 4-(2-(ethoxycarbonyl)-6-fluorophenyl)piperidine-1-carboxylate (76g)**



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP7** to *tert*-butyl 4-iodopiperidine-1-carboxylate (311 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (9:1) as an eluent to afford **76g** as a colorless oil (79%, 277 mg, 0.79 mmol).

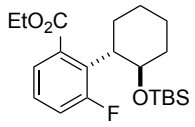
^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.41 (d, *J* = 1.4 Hz, 1H), 7.27 – 7.06 (m, 2H), 4.36 (q, *J* = 7.1, 2H), 4.21 (d, *J* = 13.2 Hz, 2H), 3.40 – 3.25 (m, 1H), 2.82 – 2.65 (m, 2H), 2.17 – 1.95 (m, 2H), 1.72 (d, *J* = 1.7 Hz, 2H), 1.47 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 167.8, 162.1 (d, *J* = 249.1 Hz), 154.9, 133.6 (d, *J* = 6.9 Hz), 131.9 (d, *J* = 14.3 Hz), 127.5 (d, *J* = 8.9 Hz), 125.3 (d, *J* = 3.8 Hz), 119.2 (d, *J* = 23.9 Hz), 79.3, 61.4, 44.7, 37.9, 29.9, 28.5, 14.2.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2978, 2863, 1719, 1684, 1450, 1424, 1366, 1275, 1244, 1165, 1118,

1018, 905, 758, 728.

MS (EI, 70 eV): *m/z* (%) = 292 (3), 278 (5), 252 (6), 251 (26), 250 (6), 222 (31), 203 (5), 132 (3), 57 (11).

HR-MS (EI, 70 eV): [$C_{19}H_{26}FNO_4$], calcd.: 351.1846; found: 351.1831.

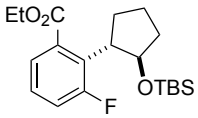
Ethyl 2-((1R,2S)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)-3-fluorobenzoate (76h)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP7** to *tert*-butyl((2-iodocyclohexyl)oxy)dimethylsilane (340 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (99:1) as an eluent to afford **76h** as a colorless oil (68%, 259 mg, 0.68 mmol, d.r. 99:1 (*trans*:*cis*)).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.39 (d, *J* = 7.7 Hz, 1H), 7.22 – 7.05 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.03 – 4.12 (m, 1H), 3.21 – 3.31 (m, 1H), 1.86 – 2.01 (m, 3H), 1.70 – 1.82 (m, 2H), 1.27 – 1.42 (m, 6H), 0.61 (s, 9H), -0.10 (s, 3H), -0.42 (s, 3H).

Ethyl 2-((1*R*,2*S*)-2-((tert-butyldimethylsilyl)oxy)cyclopentyl)-3-fluorobenzoate (76i)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP7** to *tert*-butyl((2-iodocyclopentyl)oxy)dimethylsilane (326 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (98:2) as an eluent to afford **76i** as a colorless oil (69%, 253 mg, 0.69 mmol, d.r. 99:1 (*trans*:*cis*)).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.43 (d, *J* = 7.6 Hz, 1 H), 7.21 (td, *J* = 7.9, 5.3 Hz, 1 H), 7.09 - 7.17 (m, 1 H), 4.42 - 4.50 (m, 1 H), 4.34 (qdd, *J* = 13.1, 8.4, 4.8 Hz, 2 H), 3.51 - 3.66 (m, 1 H), 2.10 - 2.21 (m, 1 H), 2.04 (dq, *J* = 12.8, 6.4 Hz, 1 H), 1.75 - 1.96 (m, 3 H), 1.58 - 1.70 (m, 1 H), 1.38 (t, *J* = 7.1 Hz, 3 H), 0.74 (s, 9 H) -0.20 (s, 3 H), -0.31 (s, 3 H).

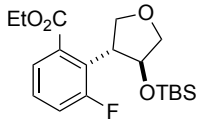
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 167.9 (d, *J* = 4.4 Hz), 161.9 (d, *J* = 246.5 Hz), 135.1 (d, *J* = 6.6 Hz), 131.58 (d, *J* = 13.2 Hz), 127.0 (d, *J* = 9.5 Hz), 124.9 (d, *J* = 2.9 Hz), 118.5 (d, *J* = 23.5 Hz), 79.0 (d, *J* = 5.1 Hz), 61.3, 48.4 (d, *J* = 2.2 Hz), 36.0, 30.3 (d, *J* = 3.7 Hz), 25.7, 22.9, 17.9, 14.2, -5.25, -5.34.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2930, 2857, 1724, 1472, 1454, 1283, 1250, 1181, 1128, 1112, 1084, 1061, 1025, 1007, 937, 892, 866, 835, 813, 774, 758, 668.

MS (EI, 70 eV): m/z (%) = 351 (1), 321 (6), 311 (5), 310 (17), 309 (71), 265 (7), 264 (23), 263 (100), 245 (9), 235 (15), 221 (10), 189 (28), 171 (27), 75 (26), 73 (23).

HR-MS (EI, 70 eV): [$C_{20}H_{31}FO_3{}^{28}Si$], calc.: 351.1792; found: 351.1785 [M^+-CH_3].

Ethyl-2-((3*S*,4*R*)-4-((tert-butyldimethylsilyl)oxy)tetrahydrofuran-3-yl)-3-fluorobenzoate (76j)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to ethyl 3-fluorobenzoate (235 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 8 h and was then added dropwise according to **TP7** to *tert*-butyl((4-iodotetrahydrofuran-3-yl)oxy)dimethylsilane (328 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (95:5) as an eluent to afford **76j** as a colorless oil (55%, 202 mg, 0.55 mmol, d.r. 99:1 (*trans*:*cis*)).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.84 (dd, *J* = 8.7, 6.1 Hz, 1H), 7.08 (dd, *J* = 10.5, 2.6 Hz, 1H), 6.95 (dd, *J* = 8.7, 7.7 Hz, 1H), 4.40 – 4.28 (m, 4H), 4.23 – 4.19 (m, 1H), 4.12 – 4.01 (m, 1H), 3.86 (dd, *J* = 8.7, 3.9 Hz, 1H), 3.75 – 3.65 (m, 1H), 1.44 – 1.33 (m, 3H), 0.84 (d, *J* = 0.6 Hz, 9H), -0.01 – -0.08 (m, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 166.7, 165.1 (d, *J* = 252.4 Hz), 146.1 (d, *J* = 8.1 Hz), 132.6 (d, *J* = 9.3 Hz), 126.8 (d, *J*=3.3 Hz), 114.5 (d, *J*=23.1 Hz), 113.4 (d, *J*=21.6 Hz), 79.8,

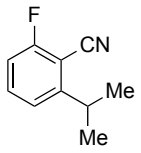
75.1, 73.6, 61.1, 50.7, 25.7, 17.9, 14.2, -4.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930, 2857, 1719, 1608, 1585, 1472, 1272, 1248, 1112, 1084, 1009, 906, 835, 777, 729.

MS (EI, 70 eV): *m/z* (%) = 311 (64), 237 (8), 235 (7), 191 (18), 163 (18), 149 (7), 117 (8), 75 (12).

HR-MS (EI, 70 eV): [$C_{15}H_{20}FO_4Si$], calcd.: 311.1115; found: 311.1088 [M^+-*t*-Bu].

2-Fluoro-6-*iso*-propylbenzonitrile (77b)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to 2-fluorobenzonitrile (170 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was stirred at r.t. for 12 h and was then added dropwise according to **TP7** to 2-iodopropane (170 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (15:1) as an eluent to afford **77a** as a colorless oil (81%, 132 mg, 0.81 mmol).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.49 - 7.57 (m, 1 H) 7.42 - 7.48 (m, 1 H) 7.20 (t, *J*=7.7 Hz, 1 H) 3.28 (spt, 1 H) 1.28 (d, *J* = 7.1 Hz, 6 H).

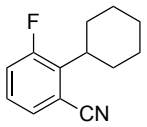
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 160.9 (d, *J* = 256.8 Hz), 136.7 (d, *J* = 13.2 Hz), 132.5 (d, *J* = 6.6 Hz), 130.7, 124.7 (d, *J* = 3.7 Hz), 114.4 (d, *J* = 1.5 Hz), 101.2 (d, *J* = 16.9 Hz), 27.1, 22.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2970, 2936, 2237, 1612, 1462, 1455, 1388, 1367, 1348, 1292, 1245, 1221, 1201, 1175, 1100, 1049, 1036, 843, 821, 794, 739, 656.

MS (EI, 70 eV): m/z (%) = 163 (25), 149 (9), 148 (100), 147 (4), 128 (15), 122 (7), 121 (7), 101 (4), 69 (8), 57 (5), 43 (8).

HR-MS (EI, 70 eV): [$C_{10}H_{10}FN$], calc.: 163.0797; found: 163.0790.

2-Cyclohexyl-3-fluorobenzonitrile (77b):



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to 3-fluorobenzonitrile (170 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was stirred at r.t. for 12 h and was then added dropwise according to **TP7** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (20:1) as an eluent to afford **77b** as a white solid (84%, 171 mg, 0.84 mmol).

m.p.: 73-74 °C

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.40 - 7.47 (m, 1 H), 7.21 - 7.31 (m, 2 H), 3.02 - 3.17 (m, 1 H), 1.84 - 2.04 (m, 4 H), 1.80 (m, 3 H), 1.23 - 1.54 (m, 3 H).

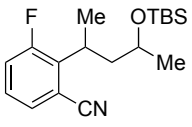
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 161.3 (d, *J* = 248.7 Hz), 137.8 (d, *J* = 16.9 Hz), 129.4 (d, *J* = 3.7 Hz), 128.0 (d, *J* = 9.5 Hz), 121.0 (d, *J* = 24.2 Hz), 117.7 (d, *J* = 3.7 Hz), 113.5 (d, *J* = 8.8 Hz), 30.8, 30.7, 26.7, 25.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2935, 2854, 2232, 1572, 1462, 1449, 1248, 1240, 1223, 1193, 1160, 1135, 1002, 948, 890, 860, 795, 733.

MS (EI, 70 eV): m/z (%) = 204 (5), 203 (33), 202 (19), 188 (12), 186 (7), 175 (17), 174 (31), 162 (34), 161 (21), 160 (14), 149 (22), 148 (43), 147 (100), 146 (10), 135 (17), 134 (38), 133 (13), 120 (10), 107 (9).

HR-MS (EI, 70 eV): [$C_{13}H_{14}FN$], calc.: 203.1110; found: 203.1107.

2-(4-((*tert*-butyldimethylsilyl)oxy)pentan-2-yl)-3-fluorobenzonitrile (77c)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to 3-fluorobenzonitrile (170 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was stirred at r.t. for 12 h and was then added dropwise according to **TP7** to *tert*-butyl((4-iodopentan-2-yl)oxy)dimethylsilane (328 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica

using hexane:ethyl acetate (9:1) as an eluent to afford **77c** as a colorless oil (63%, 202 mg, 0.63 mmol, d.r. 52:48).

Signals of both diastereomers are given:

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 7.43 – 7.19 (m, 6H), 3.86 – 3.58 (m, 3H), 3.53 – 3.21 (m, 3H), 2.13 – 1.57 (m, 6H), 1.41 – 1.32 (m, 3H), 1.23 (dd, *J* = 7.0, 2.7 Hz, 3H), 1.19 – 1.09 (m, 8H), 0.90 – 0.79 (m, 18H), 0.07 – -0.12 (m, 12H).

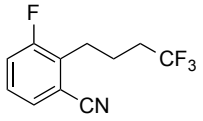
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 162.8, 161.9, 161.6, 159.5, 158.6, 158.3, 141.0, 140.8, 140.5, 140.3, 138.3, 138.1, 137.8, 129.4, 129.3, 129.3, 129.2, 129.2, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 121.0, 120.6, 119.3, 119.3, 119.0, 118.9, 117.8, 117.8, 117.5, 117.5, 117.4, 117.3, 113.7, 113.6, 110.9, 110.9, 110.8, 110.7, 68.1, 67.9, 67.4, 66.6, 66.4, 66.1, 65.3, 47.8, 46.5, 46.0, 45.0, 44.9, 30.0, 29.3, 25.9, 25.8, 25.8, 24.1, 24.0, 23.7, 21.9, 20.6, 20.2, 19.2, 18.0, 18.0, -4.1, -4.2, -4.3, -4.4, -4.8, -4.8, -4.9, -5.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2857, 1462, 1362, 1252, 1091, 1050, 1038, 906, 834, 774, 797, 730.

MS (EI, 70 eV): *m/z* (%) = 264 (17), 222 (26), 208 (12), 130 (13), 77 (6), 75 (22), 73 (8), 57 (5), 43 (6).

HR-MS (EI, 70 eV): [$C_{14}H_{19}FNOSi$], calcd.: 264.1220; found: 264.1259.

3-Fluoro-2-(4,4,4-trifluorobutyl)benzonitrile (77d)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to 3-fluorobenzonitrile (170 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was stirred at r.t. for 12 h and was then added dropwise according to **TP7** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (20:1) as an eluent to afford **77d** as a yellow oil (52%, 120 mg, 0.52 mmol).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.44 - 7.51 (m, 1 H), 7.28 - 7.40 (m, 2 H) 2.97 (t, *J* = 7.70 Hz, 2 H), 2.09 - 2.29 (m, 2 H), 1.85 - 2.02 (m, 2 H).

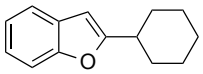
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 160.8 (d, *J* = 248.7 Hz), 132.0 (d, *J* = 19.1 Hz), 129.0 (d, *J* = 5.1 Hz), 128.9, 126.8 (q, *J* = 276.1 Hz), 120.5 (d, *J* = 22.7 Hz), 116.7 (d, *J* = 4.40 Hz), 114.5 (d, *J* = 5.9 Hz) 33.3 (q, *J* = 29.1 Hz), 26.9 (d, *J* = 2.2 Hz), 22.3 - 22.2 (m).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2950, 2232, 1578, 1465, 1441, 1392, 1339, 1316, 1279, 1251, 1208, 1131, 1112, 1021, 970, 936, 793, 733, 681, 658.

MS (EI, 70 eV): m/z (%) = 231 (13), 148 (3), 147 (3), 135 (8), 134 (100), 107 (11), 97 (5), 83 (6), 71 (6), 69 (13), 57 (11), 55 (7), 44 (34), 43 (12).

HR-MS (EI, 70 eV): [$C_{11}H_9F_4N$], calc.: 231.0671; found: 231.0665.

2-Cyclohexylbenzofuran (77e)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to benzofuran (165 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 12 h and was then added dropwise according to **TP7** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane as an eluent to afford **77e** as a colorless oil (71%, 142 mg, 0.70 mmol).

m.p.: 35-37 °C

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.47 - 7.56 (m, 1 H), 7.43 (d, *J* = 7.3 Hz, 1 H), 7.13 - 7.25 (m, 2 H), 6.36 (s, 1 H), 2.78 (tt, *J* = 11.1, 3.4 Hz, 1 H), 2.07 - 2.23 (m, 2 H), 1.86 (ddd, *J* = 12.5, 3.1, 2.9 Hz, 2 H), 1.71 - 1.81 (m, 1 H), 1.22 - 1.59 (m, 5 H).

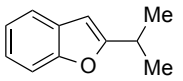
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 164.1, 154.3, 128.9, 123.0, 122.3, 120.2, 110.7, 99.7, 37.6, 31.3, 26.1, 25.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3048, 2932, 2925, 2854, 2847, 1599, 1592, 1584, 1471, 1453, 1421, 1299, 1256, 1248, 1220, 1183, 1162, 1149, 1124, 1104, 1007, 946, 922, 890, 883, 856, 830, 797, 786, 749, 736, 728, 690, 685.

MS (EI, 70 eV): m/z (%) = 201 (10), 200 (72), 199 (3), 171 (10), 158 (14), 157 (100), 145 (10), 144 (41), 132 (13), 131 (31), 128 (11), 115 (20).

HR-MS (EI, 70 eV): [$C_{14}H_{16}O$], calc.: 200.1201; found: 200.1191.

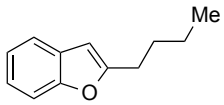
2-*iso*-Propylbenzofuran (77f)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to benzofuran (165 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 12 h and was then added dropwise according to **TP7** to 2-iodopropane (170 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane as an eluent to afford **77f** as a colorless oil (61%, 98 mg, 0.61 mmol).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.47 - 7.53 (m, 1 H), 7.43 (d, J = 7.8 Hz, 1 H), 7.13 - 7.26 (m, 2 H), 6.38 (s, 1 H), 3.09 (spt, J = 6.9 Hz, 1 H), 1.36 (d, J = 6.9 Hz, 6 H).
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 164.9, 154.5, 128.8, 123.0, 122.3, 120.3, 110.7, 99.7, 28.2, 20.9.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2967, 2929, 2874, 1586, 1467, 1454, 1385, 1301, 1253, 1236, 1182, 1167, 1127, 1105, 1067, 1045, 1009, 942, 926, 884, 795, 750, 738, 684.
MS (EI, 70 eV): m/z (%) = 160 (15), 146 (11), 145 (74), 125 (16), 115 (21), 113 (17), 111 (18), 97 (30), 95 (12), 85 (28), 57 (100), 83 (22), 82 (11), 81 (25), 71 (53), 70 (22), 69 (41), 67 (17), 56 (28), 55 (40), 43 (86), 43 (17), 41 (58).
HR-MS (EI, 70 eV): [$C_{11}H_{12}O$], calc.: 160.0888; found: 160.0887.

2-Butylbenzofuran (77g)

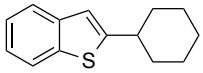


$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to benzofuran (165 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 12 h and was then added dropwise according to **TP7** to 1-iodobutane (184 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The

crude product was purified by column chromatography on silica using hexane:ethyl acetate (95:5) as an eluent to afford **77g** as a colorless oil (63%, 110 mg, 0.63 mmol).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.56 – 7.41 (m, 2H), 7.28 – 7.14 (m, 2H), 6.40 (s 1H), 2.85 – 2.72 (t, *J* = 7.4 Hz, 2H), 1.85 – 1.67 (m, 2H), 1.55 – 1.35 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 159.7, 154.6, 129.0, 123.0, 122.3, 120.1, 110.6, 101.7, 29.8, 28.1, 22.3, 13.8.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2930, 1601, 1587, 1454, 1252, 1168, 945, 905, 795, 749, 738.
MS (EI, 70 eV): m/z (%) = 174 (12), 133 (1), 132 (13), 131 (54), 115 (21), 103 (16), 77 (31).
HR-MS (EI, 70 eV): [$C_{12}H_{14}O$], calc.: 174.1045; found: 174.1054.

2-Cyclohexylbenzothiophene (77h)

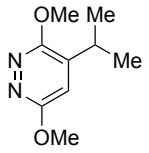


$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to thiobenzofuran (188 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t., stirred for 12 h and was then added dropwise according to **TP7** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane as an eluent to afford **77h** as a white solid (72%, 156 mg, 0.72 mmol).

m.p.: 60-62 °C
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.78 (d, *J* = 8.1 Hz, 1 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 7.21 - 7.28 (m, 1 H), 7.02 (s, 1 H), 2.89 (tt, *J* = 11.3, 3.4 Hz, 1 H), 2.04 - 2.19 (m, 2 H), 1.87 (dt, *J* = 12.7, 3.1 Hz, 2 H), 1.71 - 1.81 (m, 1 H), 1.37 - 1.60 (m, 4 H), 1.20 - 1.36 (m, 1 H).
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 153.0, 140.0, 138.6, 123.9, 123.3, 122.7, 122.2, 118.1, 40.0, 35.0, 26.4, 26.0.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3056, 2938, 2922, 2853, 2844, 1534, 1456, 1446, 1436, 1295, 1264, 1234, 1194, 1172, 1128, 1067, 1016, 987, 930, 892, 861, 846, 819, 798, 736, 725, 706, 658.
MS (EI, 70 eV): m/z (%) = 217 (12), 216 (67), 187 (7), 175 (6), 174 (17), 173 (100), 171 (5), 161

(19), 160 (27), 148 (21), 147 (36), 134 (22), 129 (10), 128 (9), 115 (17), 45 (10).
HR-MS (EI, 70 eV): [$C_{14}H_{16}S$], calc.: 216.0973; found: 216.0966.

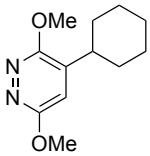
4-*iso*-Propyl-3,6-dimethoxypyridazine (77i)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to 3,6-dimethoxypyridazine (196 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was allowed to warm to r.t. for 4 h and was added dropwise according to **TP7** to 2-iodopropane (170 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (9:1) as an eluent to afford **77i** as a colorless oil (69%, 126 mg, 0.69 mmol).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 6.75 (s, 1 H), 4.06 (s, 3 H), 4.02 (s, 3 H), 3.07 (spt, J = 6.9 Hz, 1 H), 1.20 (d, J = 6.9 Hz, 6 H).
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 162.6, 160.5, 142.0, 116.2, 54.5, 54.3, 27.0, 21.1.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951, 2875, 1617, 1462, 1390, 1381, 1367, 1330, 1231, 1202, 1183, 1139, 1122, 1094, 1081, 1054, 1026, 1012, 927, 892, 771, 724, 666.
MS (EI, 70 eV): m/z (%) = 182 (100), 181 (87), 167 (91), 154 (23), 153 (16), 151 (14), 137 (21), 96 (12), 86 (12), 84 (19), 83 (15), 74 (12), 71 (13), 69 (34), 67 (25), 59 (19), 57 (23), 56 (14), 55 (24), 53 (27), 45 (90), 45 (17), 44 (33).
HR-MS (EI, 70 eV): [$C_9H_{14}N_2O_2$], calc.: 182.1055; found: 182.1052.

4-Cyclohexyl-3,6-dimethoxypyridazine (77j)

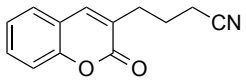


$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to 3,6-dimethoxypyridazine (196 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6.** The reaction mixture was allowed

to warm to r.t. for 4 h and was added dropwise according to **TP7** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (8:2) as an eluent to afford **77j** as a colorless oil (61%, 135 mg, 0.61 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 6.64 (d, J = 0.9 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 2.73 – 2.48 (m, 1H), 1.86 – 1.64 (m, 5H), 1.45 – 1.06 (m, 5H).
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 162.5, 160.4, 140.9, 116.5, 54.4, 54.2, 36.6, 31.6, 26.3, 25.9.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929, 2854, 1617, 1465, 1389, 1370, 1247, 1227, 1150, 1038, 1013, 1006, 906, 879, 750, 726.
MS (EI, 70 eV): *m/z* (%) = 222 (64), 221 (62), 193 (26), 191 (38), 167 (15), 163 (13), 154 (10), 40 (14).
HR-MS (EI, 70 eV): [$C_{12}H_{18}N_2O_2$], calcd.: 222.1368; found: 222.1366.

4-(2-Oxo-2H-chromen-3-yl)butanenitrile (77k)



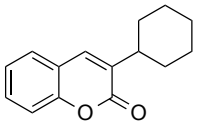
$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to coumarin (204 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was stirred for 1 h at r.t. and was then added dropwise according to **TP7** to 4-iodobutanenitril (195 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (9:1) as an eluent to afford **77k** as a yellowish solid (76%, 162 mg, 0.76 mmol).

m.p.: 102-104 °C
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.61 (s, 1 H) 7.44 - 7.55 (m, 2 H) 7.25 - 7.36 (m, 2 H) 2.76 (t, J = 7.5 Hz, 2 H) 2.44 (t, J = 7.0 Hz, 2 H) 2.06 (qd, J = 7.3, 7.1 Hz, 2 H).
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 161.4, 153.3, 140.2, 131.2, 127.4, 127.2, 124.5, 119.2, 119.1, 116.5, 30.2, 23.6, 16.7.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923, 2360, 2244, 1716, 1634, 1620, 1605, 1455, 1421, 1284, 1175, 1069, 1016, 922, 772, 763, 742, 712.

MS (EI, 70 eV): m/z (%) = 234 (5), 214 (13), 213 (56), 212 (7), 174 (12), 173 (100), 172 (8), 161 (11), 160 (92), 259 (61), 144 (10), 132 (15), 131 (42), 128 (7), 126 (8), 115 (42), 102 (8), 77 (17), 63 (7).

HR-MS (EI, 70 eV): [$C_{13}H_{11}NO_2$], calc.: 213.0790; found: 213.0790.

3-Cyclohexyl-2H-chromen-2-one (77l)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to coumarin (204 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was stirred for 1 h at r.t. and was then added dropwise according to **TP7** to iodocyclohexane (210 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (95:5) as an eluent to afford **77l** as a white solid (66%, 151 mg, 0.66 mmol).

m.p.: 93-95 °C

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.47 – 7.36 (m, 3H), 7.29 – 7.17 (m, 2H), 2.82 – 2.68 (m, 1H), 2.00 – 1.66 (m, 5H), 1.50 – 1.15 (m, 5H).

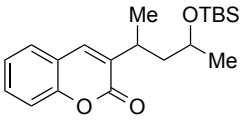
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.5, 152.7, 136.3, 134.8, 130.4, 127.3, 124.10, 119.6, 116.2, 38.2, 32.1, 26.5, 26.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1706, 1609, 1456, 988, 904, 755, 726.

MS (EI, 70 eV): *m/z* (%) = 228 (46), 227 (9), 171 (34), 146 (13), 128 (9), 115 (24), 43 (19).

HR-MS (EI, 70 eV): [$C_{15}H_{16}O_2$], calcd.: 228.1150; found: 228.1145.

3-(4-((*tert*-Butyldimethylsilyl)oxy)pentan-2-yl)-2H-chromen-2-one (77)



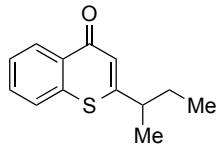
$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to coumarin (204 mg, 1.4 mmol) in THF (1.0 mL) at 0 °C according to **TP6**. The reaction mixture was stirred for 1 h at r.t.

and was then added dropwise according to **TP7** to *tert*-butyl((4-iodopentan-2-yl)oxy)dimethylsilane (328 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (9:1) as an eluent to afford **77m** as a colorless oil (88%, 305 mg, 0.88 mmol, d.r. 62:38).

Signals of both diastereomers are given:

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.42 - 7.51 (m, 6 H), 7.32 (d, *J* = 8.3 Hz, 2 H), 7.23 - 7.29 (m, 2 H), 3.76 - 3.95 (m, 2 H), 3.02 - 3.18 (m, 2 H), 1.83 - 1.95 (m, 2 H), 1.59 - 1.71 (m, 2 H), 1.26 (m, 6 H), 1.19 (d, *J* = 6.1 Hz, 6 H), 0.89 (d, *J* = 2.5 Hz, 9 H), -0.08 - 0.12 (m, 12 H).
^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 161.1 (2 C), 152.9, 137.1, 136.9, 134.9, 1345, 130.5 (2 C), 127.2 (2 C), 124.2 (2 C), 119.5 (2 C), 116.3, 67.0, 66.4, 45.2, 45.0, 31.8, 31.2, 25.9 (2 C), 24.1, 23.9, 20.4, 19.8, 18.1, -4.2 (2 C), -4.7 (2 C).
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958, 2928, 2856, 1722, 1610, 1456, 1373, 1254, 1177, 1142, 1132, 1121, 1094, 1051, 1030, 1006, 989, 972, 922, 834, 807, 773, 753, 735, 721.
MS (EI, 70 eV): m/z (%) = 331 (2), 291 (7), 290 (23), 289 (100), 216 (7), 215 (35), 179 (20), 173 (8), 157 (5), 115 (12), 75 (27), 73 (15), 57 (5), 41 (9).
HR-MS (EI, 70 eV): [$C_{20}H_{30}O_3{}^{28}Si$], calc.: 331.1729; found: 331.1720 [M^+-CH_3].

2-(*sec*-Butyl)-4H-thiochromen-4-one (77n)



$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**73**, 0.84 mmol, 0.44 M, 1.91 mL) was added to thiochromone (227 mg, 1.4 mmol) in THF (1.0 mL) at -40 °C according to **TP6**. The reaction mixture was stirred for 1 h and was then added dropwise according to **TP7** to 2-iodobutane (184 mg, 1.0 mmol) in THF (1.0 mL). After standard work-up, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography on silica using hexane:ethyl acetate (8:2) as an eluent to afford **77n** as a colorless oil (51%, 111 mg, 0.51 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.46 (d, *J* = 7.8 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.45 – 7.42 (m, 1H), 6.86 (s, 1H), 2.76 – 2.43 (m, 1H), 1.79 – 1.56 (m, 2H), 1.31 (d, *J* = 6.9 Hz, 3H), 0.90 (t,

J = 7.4 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 180.7, 161.9, 137.6, 131.2, 128.4, 127.4, 126.4, 122.7, 44.1, 30.0, 21.0, 11.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1617, 1591, 1439, 1326, 1100, 904, 778, 723, 689, 668.

MS (EI, 70 eV): *m/z* (%) = 218 (77), 190 (92), 176 (62), 161 (51), 136 (41), 128 (19), 69 (7).

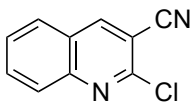
HR-MS (EI, 70 eV): [$C_{13}H_{14}OS$], calc.: 218.0767**;** found: 218.0765.

6. Mild Cobalt-Catalyzed Negishi Cross-Couplings of (Hetero)Arylzinc Reagents with (Hetero)Aryl Halides

6.1. Synthesis of Starting Materials

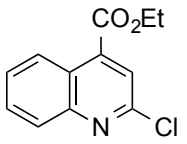
The following starting materials were prepared according to literature procedures with only little deviation. The spectral data of known compounds are in full agreement with the literature.

2-Bromoquinoline-3-carbonitrile (78q)[98]



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.51 (s, 1H), 8.12 – 8.09 (m, 1H), 7.95 – 7.87 (m, 2H), 7.72 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H).

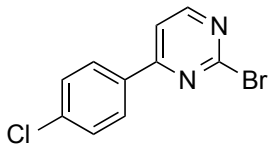
Ethyl 2-bromoquinoline-4-carboxylate (78r)



[98] N. Boudet, J. R. Lachs, P. Knochel *Org. Lett.* **2007**, *9*, 5525.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.66 (s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.88 (ddd, J = 8.5, 7.0, 1.4 Hz, 1H), 7.68 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 4.49 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.1 Hz, 3H).

2-Bromo-4-(4-chlorophenyl)pyrimidine (78t)[99]



^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.58 (d, J = 5.2 Hz, 1H), 8.04 (m, 2H), 7.65 (d, J = 5.2 Hz, 1H), 7.52 – 7.43 (m, 2H).

6.2 Preparation of Organometallic Reagents

Preparation of zinc reagents (79a-d, f, h-n):

LiCl (1.1 equiv) was dried under high vacuum and allowed to cool to room temperature, then Mg turnings (1.2 equiv), $ZnCl_2$ solution (1 M in THF, 1.1 equiv) and THF (1 M solution relating to the aryl bromide) were added. The reaction mixture was cooled to 0 °C and the corresponding aryl bromide (1.0 equiv) was added dropwise. The reaction was stirred until iodolysis of a reaction aliquot indicated full consumption of the starting material.

Preparation of zinc reagents (79e, g):

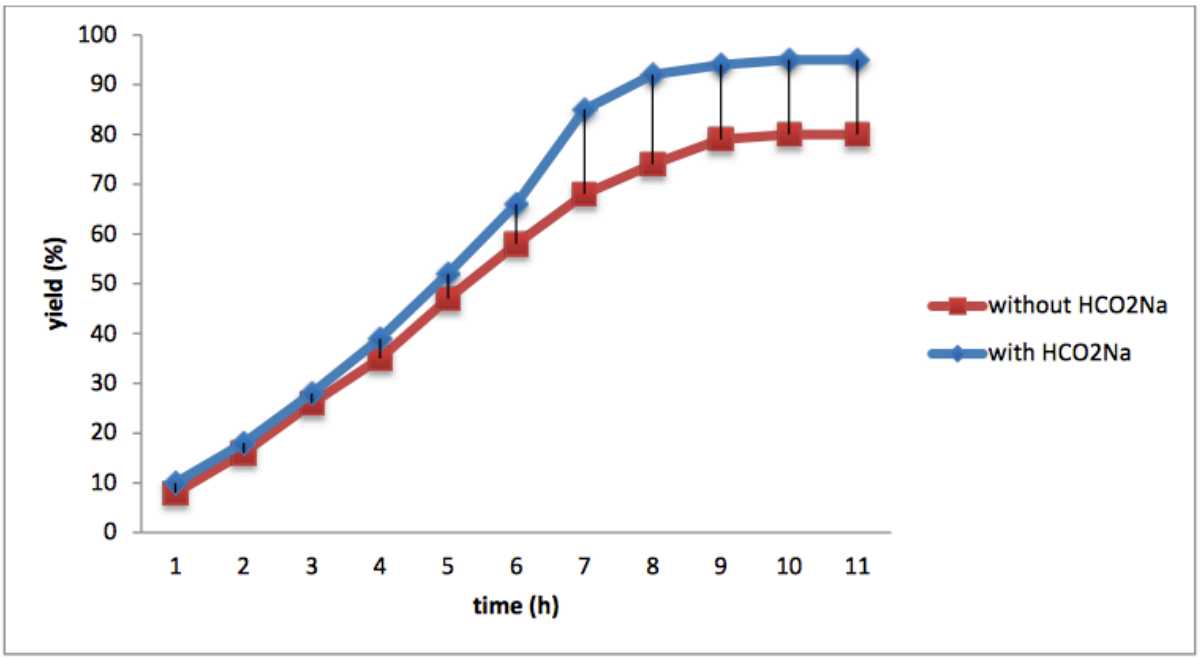
The corresponding aryl bromide (1.0 equiv) was dissolved in THF (1 M solution relating to the aryl bromide) and the reaction mixture was cooled to -30 °C. Then *i*-PrMgCl·LiCl was added dropwise and the reaction was stirred at this temperature until reaction aliquots quenched with iodine showed full consumption of the starting material. Transmetalation with $ZnCl_2$ solution (1 M in THF, 1.1 equiv) at 0 °C (1 h) provided the corresponding zinc reagent.

[99] M. Mosrin, M. Petrera, P. Knochel *Synthesis* **2008**, 22, 3697.

6.3. Cobalt-Catalyzed Cross-Coupling of (Hetero)Arylzinc Reagents with Alkyl Iodides and Bromides

Investigation of the time course of the reaction with or without sodium formate:

For this experiment, the reactions were performed as described above on a 1 mmol scale and the average GC-yields of three runs were used.

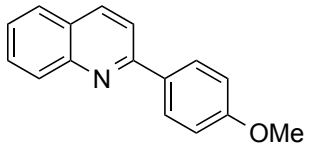


Typical procedure 8 (TP8) for the cobalt-catalyzed cross-coupling of organozinc reagents:

A dry and argon-flushed 10 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with a solution of $CoCl_2 \cdot 2LiCl$ (1 M in THF) (0.05 mmol, 50 mL, 5 mol%) and dry THF (1.0 mL). The respective aryl halide (1.0 mmol, 1.0 equiv) and HCO_2Na (0.5 mmol, 34 mg, 50 mol%) were added at room temperature. Then, a solution of the appropriate zinc reagent (1.2 mmol, 1.2 equiv) was added dropwise over 15 min *via* syringe. The reaction was stirred and monitored by GC-analysis ($C_{11}H_{24}$ was used as an internal standard). Upon consumption of the starting material, saturated aqueous NH_4Cl solution (5 mL) and ethyl acetate (5 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated

and the residue was subjected to column chromatography on silica yielding the respective title compound.

2-(4-Methoxyphenyl)quinoline (80a)



Isolated yield: 207 mg, 0.88 mmol, 88% yield; colorless crystals

Purification: *i*-hexane/EtOAc 7:3

m.p.: 123.7 – 124.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, ppm): δ = 8.20 – 8.09 (m, 4H), 7.84 – 7.76 (m, 2H), 7.71 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.08 – 6.99 (m, 2H), 3.87 (s, 3H).

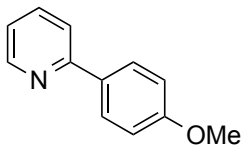
^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ = 160.8, 156.9, 148.3, 136.6, 132.3, 129.6, 129.5, 128.9, 127.5, 126.9, 125.91, 118.5, 114.2, 55.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960, 2920, 1594, 1495, 1467, 1430, 1289, 1247, 1174, 1156, 1028, 975, 948, 811, 789, 748, 726.

MS (EI, 70 eV): *m/z* (%) = 237 (2), 236 (16), 235 (100), 234 (3), 220 (21), 192 (23), 191 (24), 190 (6).

HR-MS (EI, 70 eV): [$C_{16}H_{13}ON$], calcd.: 235.0997; found: 235.0998.

2-(4-Methoxyphenyl)pyridine (80b)



Isolated yield: 161 mg, 0.87 mmol, 87% yield; white solid

Purification: *i*-hexane/EtOAc 4:1

m.p.: 53.2 – 54.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.65 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.99 – 7.91 (m, 2H), 7.75 – 7.62 (m, 2H), 7.17 (ddd, *J* = 7.1, 4.8, 1.5 Hz, 1H), 7.05 – 6.94 (m, 2H), 3.86 (s, 3H).

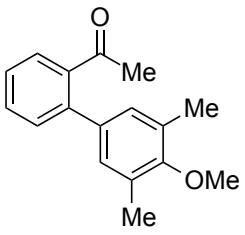
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.5, 157.1, 149.5, 136.7, 132.0, 128.2, 121.4, 119.8, 114.1, 55.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2997, 2836, 1603, 1586, 1512, 1460, 1432, 1272, 1243, 1175, 1151, 1112, 1036, 1021, 1005, 838, 776, 736, 717.

MS (EI, 70 eV): *m/z* (%) = 186 (12), 185 (100), 170 (22), 142 (29), 141 (15), 61 (9).

HR-MS (EI, 70 eV): [$C_{12}H_{11}NO$], calcd.: 185.0841; found: 185.0836.

1-(4'-Methoxy-3',5'-dimethyl-[1,1'-biphenyl]-2-yl)ethan-1-one (81a,b)



Isolated yield: 165 mg, 0.65 mmol, 65% yield for X = Cl (**81a**) colorless oil

188 mg, 0.74 mmol, 74% yield for X = Br (**81b**)

Purification: *i*-hexane/EtOAc 9:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.51 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.47 (td, *J* = 7.5, 1.5 Hz, 1H), 7.40 – 7.33 (m, 2H), 6.98 (s, 2H), 3.76 (s, 3H), 2.32 (s, 6H), 2.02 (s, 3H).

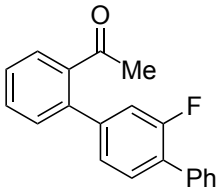
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 205.2, 156.9, 140.8, 140.3, 136.1, 131.2, 130.6, 130.1, 129.3, 127.7, 127.1, 59.8, 30.4, 16.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932, 1684, 1471, 1443, 1419, 1353, 1276, 1235, 1194, 1165, 1116, 1088, 1007, 966, 889, 871, 761, 741, 700.

MS (EI, 70 eV): *m/z* (%) = 255 (12), 254 (67), 253 (10), 240 (12), 239 (73), 224 (14), 196 (10), 165 (10), 70 (12), 61 (17), 45 (15), 43 (100).

HR-MS (EI, 70 eV): [$C_{17}H_{18}O_2$], calcd.: 254.1307; found: 254.1301.

1-(3'-Fluoro-[1,1':4',1''-terphenyl]-2-yl)ethan-1-one (81c)



Isolated yield: 194 mg, 0.67 mmol, 67% yield; white solid

Purification: *i*-hexane/EtOAc 98:2 to 90:10

m.p.: 85.1 – 87.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.65 – 7.56 (m, 3H), 7.59 – 7.50 (m, 1H), 7.53 – 7.35 (m, 6H), 7.22 – 7.16 (m, 1H), 7.17 (s, 1H), 2.19 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 204.1, 159.6 (d, J = 249.5 Hz), 141.8 (d, J = 8.1 Hz), 140.6, 138.9 (d, J = 1.8 Hz), 135.2 (d, J = 1.4 Hz), 130.9, 130.8 , 130.3, 129.0 (d, J = 3.0 Hz), 128.5, 128.49, 128.3, 128.1, 127.9 (d, J = 6.4 Hz), 125.0 (d, J = 3.4 Hz), 116.4 (d, J = 23.7 Hz), 30.5.

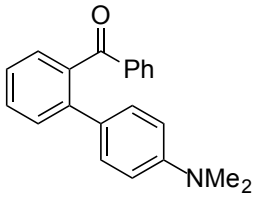
^{19}F (376 MHz, $CDCl_3$, ppm): δ = -117.39.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060, 1686, 1474, 1404, 1354, 1274, 1235, 1183, 893, 834, 759, 746, 722, 696, 682.

MS (EI, 70 eV): *m/z* (%) = 292 (6), 291 (33), 290 (73), 289 (16), 276 (23), 275 (100), 273 (10), 255 (13), 246 (22), 225 (22), 141 (14), 139 (49), 111 (15).

HR-MS (EI, 70 eV): [$C_{20}H_{15}FO$], calcd.: 290.1107; found: 290.1103.

(4'-(Dimethylamino)-[1,1'-biphenyl]-2-yl)(phenyl)methanone (81d)



Isolated yield: 219 mg, 0.73 mmol, 73% yield; yellowish crystals

Purification: *i*-hexane/EtOAc 9:1

m.p.: 114.2 – 116.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.67 – 7.61 (m, 2H), 7.49 (td, J = 7.5, 1.5 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.40 – 7.31 (m, 2H), 7.25 – 7.21 (m, 2H), 7.13 – 7.07 (m, 2H), 6.56 – 6.48 (m, 2H), 2.83 (s, 6H).

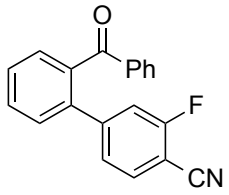
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 199.3, 149.7, 141.2, 138.6, 137.5, 132.7, 130.2, 130.0, 129.8, 129.7, 128.7, 128.1, 128.1, 126.0, 112.2, 40.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1664, 1613, 1594, 1526, 1479, 1448, 1350, 1315, 1281, 1247, 1222, 1204, 1169, 1161, 1149, 932, 922, 824, 776, 766, 720, 704, 690, 676.

MS (EI, 70 eV): *m/z* (%) = 303 (3), 302 (25), 301 (100), 300 (38), 224 (9), 180 (5), 152 (7), 105 (7).

HR-MS (EI, 70 eV): [$C_{21}H_{19}NO$], calcd.: 301.1467; found: 301.1462.

2'-Benzoyl-3-fluoro-[1,1'-biphenyl]-4-carbonitrile (81e)



Isolated yield: 295 mg, 0.98 mmol, 98% yield; colorless oil

Purification: *i*-hexane/EtOAc 8:2

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.70 – 7.64 (m, 2H), 7.65 – 7.60 (m, 1H), 7.58 – 7.41 (m, 5H), 7.39 – 7.32 (m, 2H), 7.18 – 7.10 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 197.5, 162.7 (d, *J* = 259.7 Hz), 147.9 (d, *J* = 8.2 Hz), 138.8, 138.4 (d, *J* = 1.9 Hz), 137.0, 133.5, 133.2, 130.9, 129.9, 129.9, 129.4, 128.6, 128.5, 125.5 (d, *J* = 3.4 Hz), 116.9 (d, *J* = 20.2 Hz), 113.8, 100.1 (d, *J* = 15.5 Hz).

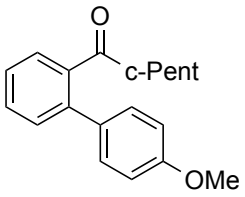
^{19}F (376 MHz, $CDCl_3$, ppm): δ = -106.19 – -106.31 (m).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3061, 1660, 1619, 1448, 1412, 1279, 1260, 928, 902, 832, 762, 737, 724, 703, 689, 680.

MS (EI, 70 eV): *m/z* (%) = 302 (19), 301 (88), 300 (19), 273 (8), 272 (16), 225 (11), 224 (77), 196 (19), 195 (21), 105 (100), 76 (43).

HR-MS (EI, 70 eV): [$C_{20}H_{12}FNO$], calcd.: 301.0903; found: 301.0897.

Cyclopentyl(4'-methoxy-[1,1'-biphenyl]-2-yl)methanone (81f)



Isolated yield: 213 mg, 0.76 mmol, 76% yield; white solid

Purification: *i*-hexane/EtOAc 95:5

m.p.: 99.4 – 101.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.51 – 7.42 (m, 1H), 7.44 – 7.33 (m, 3H), 7.30 – 7.22 (m, 2H), 6.98 – 6.91 (m, 2H), 3.85 (s, 3H), 2.79 – 2.65 (m, 1H), 1.74 – 1.53 (m, 4H), 1.51 – 1.29 (m, 4H).

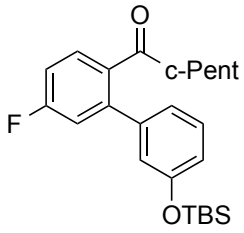
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 212.2, 159.3, 141.4, 139.3, 132.9, 130.0, 130.0, 129.9, 127.7, 126.9, 114.1, 55.3, 51.1, 30.3, 26.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2941, 1673, 1609, 1518, 1463, 1439, 1307, 1256, 1211, 1186, 1180, 1039, 998, 834, 822, 781, 766, 727.

MS (EI, 70 eV): *m/z* (%) = 281 (4), 280 (21), 212 (19), 211 (100), 168 (14), 139 (9), 61 (9), 43 (53).

HR-MS (EI, 70 eV): [$C_{19}H_{20}O_2$], calcd.: 280.1463; found: 280.1458.

1-(3'-((*tert*-Butyldimethylsilyl)oxy)-5-fluoro-[1,1'-biphenyl]-2-yl)ethan-1-one (81g)



Isolated yield: 224 mg, 0.68 mmol, 68% yield; colorless oil

Purification: *i*-hexane/EtOAc 95:5

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.57 (dd, *J* = 8.5, 5.8 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.13 – 7.03 (m, 2H), 6.92 – 6.86 (m, 2H), 6.81 (t, *J* = 2.0 Hz, 1H), 1.99 (s, 3H), 0.99 (s, 9H), 0.21 (s, 6H).

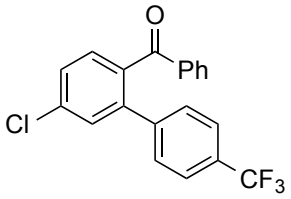
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 203.3, 163.6 (d, *J* = 252.0 Hz), 156.0, 143.1 (d, *J* = 8.5 Hz), 141.1 (d, *J* = 1.7 Hz), 137.0 (d, *J* = 3.1 Hz), 130.5 (d, *J* = 9.2 Hz), 129.9, 121.9, 120.4, 120.3, 116.9 (d, *J* = 22.0 Hz), 114.5 (d, *J* = 21.5 Hz), 30.4, 25.7, 18.2, -4.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930, 2859, 1688, 1600, 1572, 1473, 1307, 1279, 1260, 1241, 1216, 1174, 968, 872, 838, 823, 810, 780, 706, 694.

MS (EI, 70 eV): *m/z* (%) = 344 (15), 288 (18), 287 (73), 272 (26), 271 (54), 269 (32), 253 (28), 213 (24), 75 (15), 70 (11), 61 (15), 45 (12), 43 (100).

HR-MS (EI, 70 eV): [$C_{20}H_{25}FO_2Si$], calcd.: 344.1608; found: 344.1603.

(5-Chloro-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)(phenyl)methanone (81h)



Isolated yield: 321 mg, 0.89 mmol, 89% yield; white solid

Purification: *i*-hexane/EtOAc 9:1

m.p.: 79.5 – 81.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.68 – 7.61 (m, 2H), 7.52 – 7.45 (m, 6H), 7.39 – 7.29 (m, 4H).

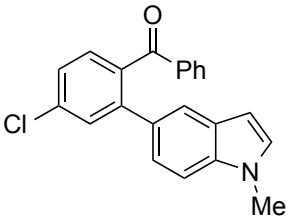
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 197.0, 142.5, 141.7, 137.2, 137.0, 136.6, 133.4, 130.5, 130.1, 129.8, 129.9 (q, *J* = 32.4 Hz), 129.2, 128.4, 127.9, 125.4 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.1 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1666, 1591, 1581, 1321, 1278, 1247, 1166, 1152, 1109, 1096, 1066, 1031, 1014, 928, 896, 844, 828, 815, 800, 767, 704, 686, 675.

MS (EI, 70 eV): *m/z* (%) = 362 (13), 361 (16), 360 (42), 359 (23), 325 (20), 284 (18), 282 (53), 220 (24), 105 (47), 77 (20), 70 (14), 61 (18), 45 (14), 43 (100).

HR-MS (EI, 70 eV): [$C_{20}H_{12}ClF_3O$], calcd.: 360.0529; found: 360.0522.

(4-Chloro-2-(1-methyl-1H-indol-6-yl)phenyl)(phenyl)methanone (81i)



Isolated yield: 210 mg, 0.61 mmol, 61% yield; yellow oil

Purification: *i*-hexane/EtOAc 8:2

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.61 – 7.55 (m, 2H), 7.52 – 7.47 (m, 2H), 7.43 (tdd, *J* = 4.4, 1.4, 0.7 Hz, 2H), 7.36 (ddd, *J* = 7.6, 6.2, 2.2 Hz, 1H), 7.07 – 7.04 (m, 2H), 6.92 (d, *J* = 3.1 Hz, 1H), 6.81 – 6.75 (m, 2H), 6.32 (dd, *J* = 3.1, 0.7 Hz, 1H), 3.65 (s, 3H).

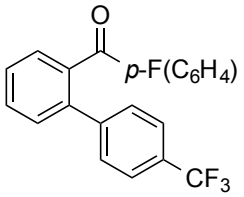
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 197.9, 166.5, 163.9, 142.1, 138.9, 136.0, 132.4, 132.3, 131.4, 130.5, 130.3, 128.5, 126.4, 122.9, 121.5, 115.1, 114.9, 109.0, 101.2, 32.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2943, 2252, 1662, 1586, 1470, 1448, 1280, 1245, 1091, 905, 727.

MS (EI, 70 eV): *m/z* (%) = 347 (11), 346 (10), 345 (28), 344 (15), 267 (6), 104 (4), 76 (40< 58 (4), 42 (11).

HR-MS (EI, 70 eV): [$C_{22}H_{16}ClNO$], calcd.: 345.0920; found: 345.0919.

(4-Fluorophenyl)(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)methanone (81j)



Isolated yield: 251 mg, 0.73 mmol, 73% yield; white solid

Purification: *i*-hexane/EtOAc 95:5

m.p.: 97.8 – 99.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.65 – 7.58 (m, 2H), 7.55 (ddd, *J* = 7.6, 5.4, 3.5 Hz, 1H), 7.48 – 7.38 (m, 5H), 7.33 – 7.27 (m, 2H), 6.96 – 6.88 (m, 2H).

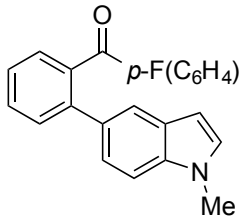
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.6, 166.9, 164.4, 143.7, 139.7, 138.7, 133.7, 132.6 (d, *J* = 9.4 Hz), 130.2, 129.7, 129.4 (q, *J* = 283 Hz), 129.2, 128.8, 125.3 (q, *J* = 4.3 Hz), 122.3, 115.6 (d, *J* = 24.1 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3061, 1660, 1617, 1596, 1504, 1407, 1325, 1304, 1259, 1225, 1160, 1113, 1104, 1067, 926, 843, 838, 765, 745, 733, 673.

MS (EI, 70 eV): *m/z* (%) = 345 (12), 344 (53), 343 (23), 275 (15), 249 (38), 201 (15), 152 (10), 123 (54), 95 (20), 85 (10), 83 (16).

HR-MS (EI, 70 eV): [$C_{20}H_{12}F_4O$], calcd.: 344.0824; found: 344.0818.

(4-Fluorophenyl)(2-(1-methyl-1H-indol-6-yl)phenyl)methanone (81k)



Isolated yield: 204 mg, 0.62 mmol, 62% yield; orange oil

Purification: *i*-hexane/EtOAc 8:2

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.59 – 7.54 (m, 2H), 7.48 (dd, *J* = 2.0, 0.5 Hz, 1H), 7.44 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.38 – 7.25 (m, 3H), 7.17 – 7.12 (m, 2H), 7.08 – 7.00 (m, 2H), 6.92 (d, *J* = 3.1 Hz, 1H), 6.32 (dd, *J* = 3.2, 0.8 Hz, 1H), 3.64 (s, 3H).

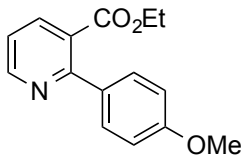
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 198.2, 144.2, 137.5, 137.2, 136.2, 135.9, 132.8, 130.4, 130.2, 130.0, 129.8, 129.5, 128.5, 128.0, 126.3, 122.7, 121.5, 109.1, 101.4, 32.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2943, 2250, 1661, 1597, 1503, 1473, 1303, 1284, 1240 , 1148, 931, 907, 756, 729.

MS (EI, 70 eV): *m/z* (%) = 330 (20), 329 (87), 328 (43), 300 (17), 234 (16), 165 (10), 164 (11), 95 (7), 58 (7), 42 (17).

HR-MS (EI, 70 eV): [$C_{22}H_{16}FNO$], calcd.: 329.1216; found: 329.1214.

Ethyl 2-(4-methoxyphenyl)nicotinate (80c)



Isolated yield: 180 mg, 0.70 mmol, 70% yield; colorless oil

Purification: *i*-hexane/EtOAc 95:5

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.64 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.96 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.47 – 7.36 (m, 2H), 7.18 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.95 – 6.78 (m, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H).

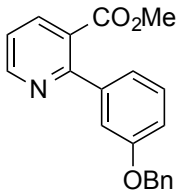
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 168.4, 160.2, 158.2, 151.0, 137.7, 132.5, 130.0, 127.1, 121.0, 113.6, 61.5, 55.2, 13.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982, 1714, 1608, 1582, 1515, 1428, 1298, 1280, 1250, 1175, 1130,1095, 1054, 1024, 838, 780.

MS (EI, 70 eV): *m/z* (%) = 257 (13), 229 (13), 228 (100), 212 (11), 185 (18), 169 (12), 142 (13), 141 (19), 114 (14).

HR-MS (EI, 70 eV): [$C_{15}H_{15}NO_3$], calcd.: 257.1052; found: 257.1053.

Methyl 2-(3-(benzyloxy)phenyl)nicotinate (80d)



Isolated yield: 226 mg, 0.71 mmol, 71% yield; yellow oil

Purification: *i*-hexane/EtOAc 7:3

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.71 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.01 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.40 – 7.25 (m, 7H), 7.18 – 7.17 (m, 1H), 7.04 – 6.96 (m, 2H), 5.05 (s, 2H), 3.62 (s, 3H).

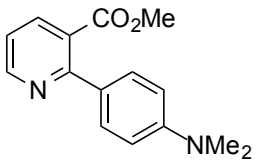
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 168.5, 158.8, 158.5, 151.2, , 141.4, 137.8, 136.9, 129.2, 128.6, 127.9, 127.6, 127.2, 121.6, 121.3, 115.7, 114.6, 70.0, 52.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960, 2254, 1635, 1587, 1560, 1483, 1403, 1313, 1190, 1078, 968, 952, 902, 722.

MS (EI, 70 eV): *m/z* (%) = 319 (28), 161 (8), 91 (8), 90 (103), 83 (5), 58 (6), 43 (11).

HR-MS (EI, 70 eV): [$C_{20}H_{17}NO_3$], calcd.: 319.1208; found: 319.1203.

Methyl 2-(4-(dimethylamino)phenyl)nicotinate (80e)



Isolated yield: 232 mg, 0.91 mmol, 91% yield; yellow oil

Purification: *i*-hexane/EtOAc 9:1 to 2:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.71 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.98 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.81 – 6.70 (m, 2H), 3.76 (s, 3H), 3.01 (s, 6H).

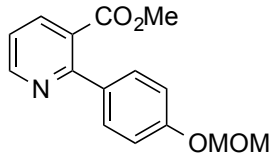
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 169.7, 158.4, 151.1, 150.9, 137.7, 129.7, 127.4, 126.1, 120.1, 111.8, 52.4, 40.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1717, 1607, 1579, 1565, 1525, 1422, 1356, 1313, 1282, 1216, 1193, 1169, 1122, 1094, 1053, 945, 824, 777, 751.

MS (EI, 70 eV): *m/z* (%) = 257 (17), 256 (100), 255 (53), 241 (43), 225 (14), 98 (12), 44 (15).

HR-MS (EI, 70 eV): [$C_{15}H_{16}N_2O_2$], calcd.: 256.1212; found: 256.1208.

2-(4-(Methoxymethoxy)phenyl)nicotinonitrile (80f)



Isolated yield: 145 mg, 0.60 mmol, 60% yield; white solid

Purification: *i*-hexane/EtOAc 2:1

m.p.: 83.7 – 85.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.84 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.04 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.95 – 7.87 (m, 2H), 7.32 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.20 – 7.12 (m, 2H), 5.25 (s, 2H), 3.50 (s, 3H).

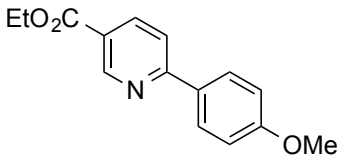
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.5, 159.0, 152.6, 141.9, 130.7, 130.4, 121.1, 118.0, 116.3, 106.8, 94.2, 56.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2225, 1607, 1581, 1574, 1552, 1517, 1432, 1410, 1306, 1256, 1248, 1209, 1178, 1155, 1108, 1038, 982, 948, 934, 851, 828, 812, 803, 771, 719.

MS (EI, 70 eV): *m/z* (%) = 241 (4), 240 (27), 210 (24), 179 (5), 167 (5), 45 (100), 43 (23).

HR-MS (EI, 70 eV): [$C_{14}H_{12}N_2O_2$], calcd.: 240.0899; found: 240.08942.

Ethyl 6-(4-methoxyphenyl)nicotinate (80g)



Isolated yield: 230 mg, 0.89 mmol, 89% yield; white solid

Purification: *i*-hexane/EtOAc 4:1

m.p.: 81.5 – 82.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.24 (dd, *J* = 2.2, 0.8 Hz, 1H), 8.30 (dd, *J* = 8.3, 2.2 Hz, 1H), 8.08 – 7.99 (m, 2H), 7.74 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.06 – 6.96 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).

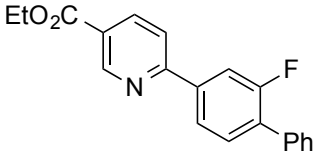
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 165.5, 161.2, 160.4, 150.9, 137.7, 130.9, 128.8, 123.7, 118.9, 114.3, 61.3, 55.4, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2839, 1706, 1592, 1583, 1561, 1475, 1461, 1379, 1366, 1285, 1247, 1182, 1144, 1131, 1112, 1033.

MS (EI, 70 eV): *m/z* (%) = 259 (17), 257 (100), 256 (3), 231 (30), 215 (9), 214 (10), 213 (51), 186 (10), 184 (9), 157 (15).

HR-MS (EI, 70 eV): [$C_{15}H_{15}NO_3$], calcd.: 257.1052; found: 257.1048.

Ethyl 6-(2-fluoro-[1,1'-biphenyl]-4-yl)nicotinate (80h)



Isolated yield: 283 mg, 0.88 mmol, 88% yield; white solid

Purification: *i*-hexane/EtOAc 9:1

m.p.: 111.7 – 112.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.30 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.37 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.97 – 7.90 (m, 1H), 7.91 (t, *J* = 0.9 Hz, 1H), 7.83 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.65 – 7.54 (m, 3H), 7.52 – 7.44 (m, 2H), 7.44 – 7.37 (m, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 165.2, 161.4, 159.0 (d, *J* = 2.5 Hz), 158.9, 151.1, 139.3 (d, *J* = 7.9 Hz), 138.0, 135.2 (d, *J* = 1.4 Hz), 131.1 (d, *J* = 3.8 Hz), 130.5 (d, *J* = 13.7 Hz), 129.0 (d, *J* = 3.1 Hz), 128.6, 128.1, 127.9, 125.0, 123.0 (d, *J* = 3.3 Hz), 119.7, 115.0 (d, *J* = 24.9 Hz).

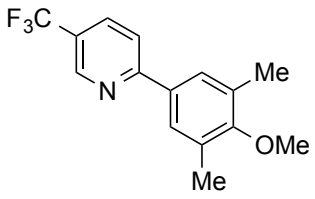
^{19}F-NMR (375 MHz, CDCl, ppm): δ = -117.20.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1712, 1593, 1470, 1417, 1380, 1287, 1274, 1261, 1155, 1124, 1024, 1011, 897, 851, 829, 780, 761, 740, 728, 718, 694.

MS (EI, 70 eV): *m/z* (%) = 322 (19), 321 (100), 293 (35), 277 (11), 276 (57), 248 (14), 221 (21), 220 (18), 170 (13), 44 (10), 43 (24).

HR-MS (EI, 70 eV): [$C_{20}H_{16}FNO_2$], calcd.: 321.1165; found: 321.1158.

2-(4-Methoxy-3,5-dimethylphenyl)-5-(trifluoromethyl)pyridine (80i)



Isolated yield: 242 mg, 0.86 mmol, 86% yield; colorless oil

Purification: *i*-hexane/EtOAc 4:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.90 (dt, *J* = 2.5, 0.9 Hz, 1H), 7.93 (ddd, *J* = 8.3, 2.4, 0.7 Hz, 1H), 7.82 – 7.75 (m, 1H), 7.69 (2H), 3.77 (s, 3H), 2.37 (s, 6H).

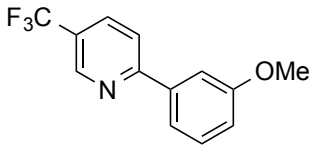
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.5 (d, *J* = 1.5 Hz), 158.9, 146.4 (q, *J* = 4.1 Hz), 133.8 (q, *J* = 3.5 Hz), 133.4, 131.5, 127.9, 124.3 (q, *J* = 33.0 Hz), 123.9 (q, *J* = 272.8 Hz), 119.6, 59.7, 16.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929, 1606, 1567, 1476, 1326, 1199, 1164, 1125, 1075, 1012, 839, 718.

MS (EI, 70 eV): *m/z* (%) = 282 (16), 281 (100), 280 (3), 267 (16), 266 (79), 238 (34), 222 (15), 61 (12).

HR-MS (EI, 70 eV): [$C_{15}H_{14}ClF_3NO$], calcd.: 281.1027; found: 281.1020.

2-(3-Methoxyphenyl)-5-(trifluoromethyl)pyridine (80j)



Isolated yield: 185 mg, 0.73 mmol, 73% yield; colorless crystals

Purification: *i*-hexane/Et_2O 10:1

m.p.: 53.4 – 55.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.95 – 8.93 (m, 1H), 7.98 (ddd, *J* = 8.3, 2.4, 0.8 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.63 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.58 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.03 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 3.91 (s, 3H).

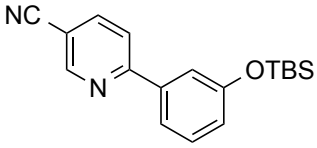
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.4 (d, *J* = 1.4 Hz), 160.2, 146.5 (q, *J* = 4.1 Hz), 139.4, 133.9 (q, *J* = 3.5 Hz), 130.0, 124.9 (td, *J* = 31.4 Hz), 123.8 (q, *J* = 273.9 Hz), 120.1, 119.6, 116.1, 112.4, 55.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956, 2838, 1608, 1589, 1566, 1476, 1328, 1304, 1296, 1242, 1220, 1180, 1166, 1124, 1082, 1052, 1033, 1014, 945, 881, 853, 843, 793, 782, 764, 717, 691.

MS (EI, 70 eV): *m/z* (%) = 254 (12), 253 (100), 252 (95), 224 (51), 223 (54), 222 (54), 154 (20), 141 (21), 44 (23), 43 (64).

HR-MS (EI, 70 eV): [$C_{13}H_{10}F_3NO$], calcd.: 253.0714; found: 253.0716.

6-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)nicotinonitrile (80k)



Isolated yield: 261 mg, 0.84 mmol, 84% yield; white solid

Purification: *i*-hexane/EtOAc 95:5

m.p.: 69.4 – 70.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.93 (dd, *J* = 2.2, 0.9 Hz, 1H), 7.99 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.81 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.61 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 7.54 (t, *J* = 2.1 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 6.97 (ddd, *J* = 8.1, 2.5, 1.0 Hz, 1H), 1.01 (s, 9H), 0.24 (s, 6H).

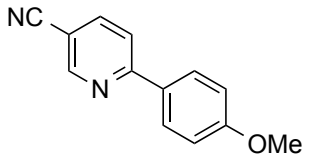
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.3, 156.4, 152.4, 139.8, 138.8, 130.1, 122.3, 120.3, 120.1, 119.1, 117.1, 107.9, 25.7, 18.2, -4.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928, 2857, 2229, 1594, 1582, 1553, 1464, 1432, 1373, 1310, 1288, 1259, 1252, 1236, 1217, 1206, 936, 892, 830, 799, 779, 760, 739, 690, 681, 662.

MS (EI, 70 eV): *m/z* (%) = 311 (2), 310 (6), 295 (2), 254 (19), 253 (100), 43 (11).

HR-MS (EI, 70 eV): [$C_{18}H_{22}N_2OSi$], calcd.: 310.1501; found: 310.1499.

6-(4-Methoxyphenyl)nicotinonitrile (80l)



Isolated yield: 176 mg, 0.84 mmol, 84% yield; white solid

Purification: *i*-hexane/EtOAc 9:1

m.p.: 104.3 – 106.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.88 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.03 – 7.99 (m, 2H), 7.96 – 7.90 (m, 1H), 7.78 – 7.73 (m, 1H), 7.03 – 6.99 (m, 2H), 3.87 (s, 3H).

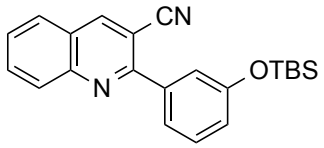
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.8, 160.0, 152.4, 139.6, 129.8, 128.86, 118.9, 117.2, 114.4, 106.8, 55.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3053, 2841, 2220, 1607, 1587, 1515, 1474, 1442, 1378, 1303, 1245, 1169, 1113, 1042, 1017, 817, 757.

MS (EI, 70 eV): *m/z* (%) = 210 (22), 196 (1), 195 (5), 179 (1), 168 (1), 167 (9), 166 (4), 141 (1), 140 (2), 86 (3), 84 (5)

HR-MS (EI, 70 eV): [C13H10N2O], calcd.: 210.0793 found: 210.0788.

2-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)quinoline-3-carbonitrile (80m)



Isolated yield: 328 mg, 0.92 mmol, 92% yield; yellow oil

Purification: *i*-hexane/EtOAc 8:2

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.59 (d, *J* = 0.8 Hz, 1H), 8.14 (dq, *J* = 8.2, 1.0 Hz, 1H), 7.86 - 7.80 (m, 2H), 7.60 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.52 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 7.42 - 7.32 (m, 2H), 6.95 (ddd, *J* =8.1, 2.5, 1.0 Hz, 1H), 0.95 (s, 9H), 0.20 (s, 6H).

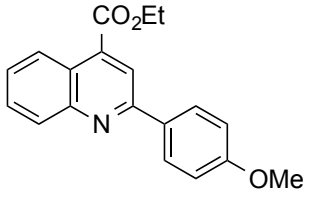
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 157.7, 155.9, 148.6, 144.2, 139.0, 132.9, 130.0, 129.8, 128.0, 127.7, 125.1, 122.1, 121.9, 120.8, 117.9, 105.6, 25.7, 18.2, -4.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3064, 2856, 2225, 1715, 1619, 1582, 1557, 1460, 1440, 1287, 1250, 1220, 944, 900, 831, 774, 730.

MS (EI, 70 eV): *m/z* (%) = 305 (17), 304 (71), 303 (237), 287 (23), 274 (14), 273 (35), 144 (14).

HR-MS (EI, 70 eV): [$C_{22}H_{24}N_2OSi$], calcd.: 360.1658; found: 360.1657.

ethyl 2-(4-Methoxyphenyl)quinoline-4-carboxylate (80n)



Isolated yield: 199 mg, 0.65 mmol, 65% yield; white solid

Purification: *i*-hexane/EtOAc 9:1

m.p.: 80.1 – 82.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.66 (dd, *J* = 8.6, 0.7 Hz, 1H), 8.30 (s, 1H), 8.17 – 8.08 (m, 3H), 7.70 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.04 – 6.94 (m, 2H), 4.50 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H).

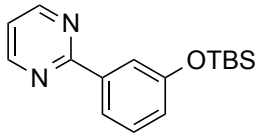
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.6, 161.1, 156.3, 149.2, 136.0, 131.4, 130.1, 129.8, 128.9, 127.3, 125.4, 123.7, 119.8, 114.3, 61.9, 55.4, 14.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2981, 1714, 1504, 1271, 1244, 1232, 1194, 1178, 1151, 1136, 1113, 1023, 835, 797, 780, 736, 678.

MS (EI, 70 eV): *m/z* (%) = 309 (2), 308 (24), 307 (100), 236 (12), 235 (57), 234 (12), 191 (23), 190 (10).

HR-MS (EI, 70 eV): [$C_{19}H_{17}NO_3$], calcd.: 307.1208; found: 307.1203.

2-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)pyrimidine (80o)



Isolated yield: 264 mg, 0.92 mmol, 92% yield; colorless oil

Purification: *i*-hexane/EtOAc 9:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.80 (d, *J* = 4.8 Hz, 2H), 8.04 (ddd, *J* = 7.8, 1.6, 1.0 Hz, 1H), 7.94 (dd, *J* = 2.5, 1.6 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.18 (t, *J* = 4.8 Hz, 1H), 6.97 (ddd, *J* = 8.1, 2.6, 1.0 Hz, 1H), 1.01 (s, 9H), 0.24 (s, 6H).

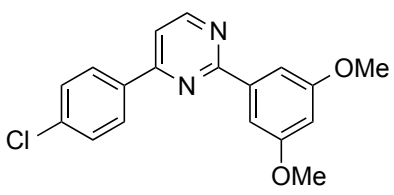
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 164.6, 157.2, 156.1, 139.1, 129.5, 122.6, 121.2, 119.8, 119.1, 25.7, 18.2, -4.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2931, 2858, 1713, 1553, 1450, 1422, 1409, 1281, 1250, 1225, 1177, 1150, 939, 834, 816, 796, 779, 690.

MS (EI, 70 eV): *m/z* (%) = 287 (3), 286 (12), 230 (6), 229 (20), 288 (100), 213 (5), 167 (5).

HR-MS (EI, 70 eV): [$C_{16}H_{22}N_2OSi$], calcd.: 286.1501; found: 286.1496.

4-(4-Chlorophenyl)-2-(3,5-dimethoxyphenyl)pyrimidine (80p)



Isolated yield: 281 mg, 0.89 mmol, 86% yield; white solid

Purification: *i*-hexane/EtOAc 4:1

m.p.: 113.3 – 113.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.84 (dd, *J* = 5.3, 0.9 Hz, 1H), 8.21 – 8.11 (m, 2H), 7.76 (d, *J* = 2.4 Hz, 2H), 7.57 (dd, *J* = 5.3, 1.1 Hz, 1H), 7.55 – 7.46 (m, 2H), 6.63 (t, *J* = 2.4 Hz, 1H), 3.92 (s, 6H).

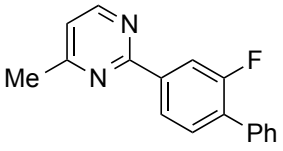
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 164.3, 162.6, 161.0, 157.9, 139.8, 137.3, 135.3, 129.2, 128.5, 114.5, 106.1, 103.5, 55.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3019, 2840, 1604, 1595, 1568, 1543, 1493, 1471, 1435, 1421, 1405, 1380, 1291, 1208, 1158, 1088, 1068, 1045, 1011, 930, 869, 828, 810, 791, 774, 702, 689, 663.

MS (EI, 70 eV): *m/z* (%) = 329 (7), 328 (36), 327 (38), 326 (100), 325 (64), 298 (8), 297 (19), 296 (17), 295 (10), 163 (11).

HR-MS (EI, 70 eV): [$C_{18}H_{15}ClN_2O_2$], calcd.: 326.0822; found: 326.0814.

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-4-methylpyrimidine (80q)



Isolated yield: 200 mg, 0.76 mmol, 76% yield; white solid

Purification: *i*-hexane/EtOAc 9:1

m.p.: 93.7 – 94.6 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.66 (d, *J* = 5.1 Hz, 1H), 8.34 – 8.23 (m, 2H), 7.67 – 7.60 (m, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.43 – 7.36 (m, 1H), 7.08 (d, *J* = 5.0 Hz, 1H), 2.61 (s, 3H).

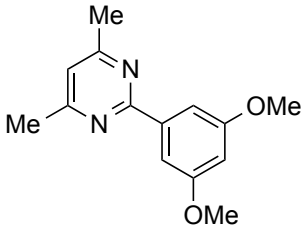
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 167.4, 163.0 (d, *J* = 2.9 Hz), 160.0 (d, *J* = 247.2 Hz), 156.9, 139.1 (d, *J* = 8.1 Hz), 135.5 (d, *J* = 1.5 Hz), 131.0 (d, *J* = 13.7 Hz), 130.8 (d, *J* = 3.7 Hz), 129.0 (d, *J* = 3.1 Hz), 128.5, 128.0, 124.0 (d, *J* = 3.3 Hz), 119.0, 115.8 (d, *J* = 25.1 Hz), 24.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2252, 1578, 1557, 1436, 1416, 1390, 904, 832, 828, 797, 768, 723, 697.

MS (EI, 70 eV): *m/z* (%) = 266 (1), 265 (20), 264 (100), 263 (4), 249 (11), 198 (6), 197 (27), 196 (6), 170 (6).

HR-MS (EI, 70 eV): [$C_{17}H_{13}FN_2$], calcd.: 264.1063; found: 264.1056.

2-(3,5-Dimethoxyphenyl)-4,6-dimethylpyrimidine (80r)



Isolated yield: 158 mg, 0.65 mmol, 65% yield; white solid

Purification: *i*-hexane/EtOAc 4:1

m.p.: 127.7 – 128.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.63 (d, J = 2.4 Hz, 2H), 6.93 (s, 1H), 6.58 (t, J = 2.4 Hz, 1H), 3.89 (s, 6H), 2.53 (s, 6H).

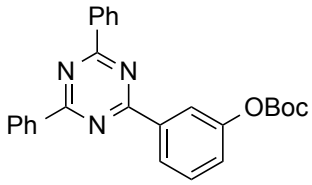
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.7, 163.8, 160.9, 140.3, 118.2, 105.9, 103.3, 55.5, 24.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926, 2834, 1610, 1584, 1540, 1465, 1450, 1440, 1427, 1384, 1360, 1318, 1284, 1240, 1203, 1170, 1154, 1096, 1057, 1002, 985, 941, 926, 877, 867, 835, 812, 794, 754, 690.

MS (EI, 70 eV): *m/z* (%) = 245 (4), 244 (25), 243 (23), 215 (6), 214 (7), 191 (8), 88 (5), 70 (10).

HR-MS (EI, 70 eV): [$C_{14}H_{16}N_2O_2$], calcd.: 244.1212; found: 244.1204.

***tert*-Butyl (3-(4,6-diphenyl-1,3,5-triazin-2-yl)phenyl) carbonate (80s)**



Isolated yield: 260 mg, 0.61 mmol, 61% yield; white solid

Purification: *i*-hexane/EtOAc 4:1

m.p.: 182.3 – 183.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.81 – 8.73 (m, 4H), 8.67 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.56 (dd, *J* = 2.5, 1.6 Hz, 1H), 7.67 – 7.54 (m, 7H), 7.46 (ddd, *J* = 8.1, 2.5, 1.1 Hz, 1H), 1.62 (s, 9H).

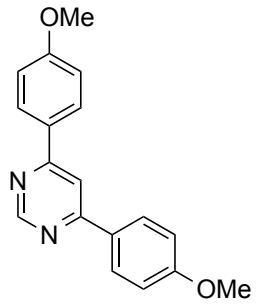
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 171.7, 170.8, 151.8, 151.5, 138.0, 136.1, 132.6, 129.6, 129.0, 128.7, 126.3, 125.5, 121.7, 83.9, 27.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982, 1757, 1519, 1447, 1363, 1253, 1218, 1147, 909, 770, 732, 689.

MS (EI, 70 eV): *m/z* (%) = 426 (1), 326 (21), 325 (100), 104 (18), 103 (21), 57 (33).

HR-MS (EI, 70 eV): [$C_{26}H_{23}N_3O_3$+H^+], calcd.: 426.1812; found: 426.1811.

4,6-Bis(4-methoxyphenyl)pyrimidine (83)



Isolated yield: 225 mg, 0.77 mmol, 77% yield; white solid

Purification: *i*-hexane/EtOAc 7:1

m.p.: 146.8 – 148.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.14 (d, *J* = 1.3 Hz, 1H), 8.09 – 8.01 (m, 4H), 7.91 (d, *J* = 1.3 Hz, 1H), 7.03 – 6.93 (m, 4H), 3.83 (s, 6H).

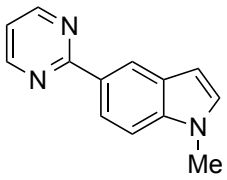
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 163.9, 161.9, 159.0, 129.6, 128.7, 114.4, 111.0, 55.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3009, 1602, 1583, 1506, 1457, 1443, 1379, 1298, 1255, 1231, 1170, 1112, 1021, 825, 804, 780.

MS (EI, 70 eV): *m/z* (%) = 293 (20), 292 (100), 277 (19), 41 (9), 249 (6), 234 (5), 146 (8).

HR-MS (EI, 70 eV): [$C_{18}H_{16}N_2O_2$], calcd.: 292.1212; found: : 292.1205.

1-Methyl-6-(pyrimidin-2-yl)-1*H*-indole (84a)



Isolated yield: 144 mg, 0.69 mmol, 69% yield; white solid

Purification: *i*-hexane/EtOAc 7:3

m.p.: 122.6 – 124.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.75 – 8.67 (m, 3H), 8.29 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.34 (dt, *J* = 8.8, 0.8 Hz, 1H), 7.09 – 6.99 (m, 2H), 6.53 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.77 (s, 3H).

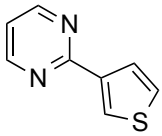
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.0, 157.1, 138.4, 129.7, 129.1, 128.7, 121.9, 121.8, 118.1, 109.2, 102.5, 33.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3098, 1612, 1563, 1552, 1433, 1404, 1339, 1277, 1240, 1148, 919, 790, 769, 728, 698.

MS (EI, 70 eV): *m/z* (%) = 209 (100), 208 (24), 156 (24), 155 (12), 104 (10), 85 (20), 83 (30).

HR-MS (EI, 70 eV): [$C_{13}H_{11}N_3$], calcd.: 209.0953; found: 209.0950.

2-(Thiophen-3-yl)pyrimidine (84b)



Isolated yield: 99 mg, 0.61 mmol, 61% yield; white solid

Purification: *i*-hexane/EtOAc 8:2

m.p.: 96.8 – 98.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.67 (d, *J* = 4.9 Hz, 2H), 8.23 (dd, *J* = 3.1, 1.2 Hz, 1H), 7.83 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.32 (dd, *J* = 5.1, 3.1 Hz, 1H), 7.06 (t, *J* = 4.9 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.9, 157.2, 141.5, 127.9, 127.3, 126.1, 118.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3117, 2925, 2360, 1566, 1557, 1530, 1435, 1376, 866, 804, 773, 698.

MS (EI, 70 eV): *m/z* (%) = 244 (11), 163 (15), 162 (19), 161 (42), 135 (12), 110 (12), 109 (78), 58 (41), 57 (12), 49 (11), 42 (9).

HR-MS (EI, 70 eV): [$C_8H_6N_2S$], calcd.: 162.0252; found: 162.0243.

7. A Robust and Broadly Applicable Cobalt-Catalyzed Cross-Coupling of Functionalized Bench-Stable Organozinc Pivalates with Unsaturated Halides

7.1 Preparation of Organometallic Reagents

Typical procedure 9 (TP9) for the preparation of organozinc pivalates (3a-c, e-f):

A dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum was charged with magnesium turnings (1.1 equiv), dry LiCl (1.1 equiv) and dry THF (1 M solution relating to the aryl halide). The aromatic halide (1.0 equiv) was added. If necessary the *Schlenk*-tube was placed in a water bath for cooling during the initial heat evolution of the insertion reaction. The progress of the insertion reaction was monitored by GC-analysis of reaction aliquots quenched with I_2. Upon completion of the insertion, solid $Zn(OPiv)_2$ (1.0 equiv) was added in one portion and stirred at ambient temperature for 15 min. Solvent removal affords the solid organozinc pivalates.

Typical procedure 10 (TP10) for the preparation of organozinc pivalates (3d)[100]:

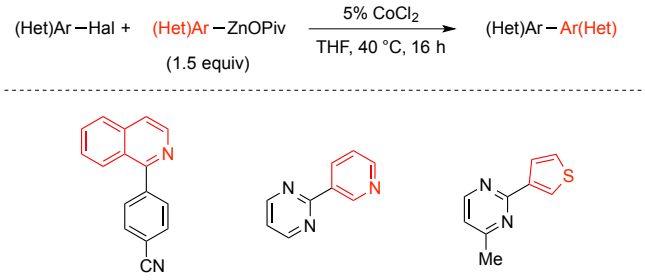
The iodobenzoic acid (1.6 mmol) was placed in a dry and argon-flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M, 3.2 mL, 1.6 mmol) was added and after stirring for 5 min at rt, the resulting solution was cooled to –20 °C and MeMgCl (2.83 M in THF; 0.85 mL, 1.6 mmol) was added dropwise. After completion of the addition, the mixture was stirred at –20 °C for further 20 min. Then *i*-PrMgCl·LiCl (1.15 M in THF; 1.53 mL, 1.76 mmol) was added slowly and the resulting mixture was allowed to warm up to room temperature. The progress of the halogen-magnesium exchange was monitored by GC-

[100] F. Kopp, S. Wunderlich, P.Knochel, *Chem. Commun*. **2007**, 2075.

analysis of reaction aliquots quenched with I_2 and found to be completed within 45 min. Solid $Zn(OPiv)_2$ (2.0 equiv) was added at 0 °C in one portion and the mixture was allowed to slowly warm up to 25 °C.

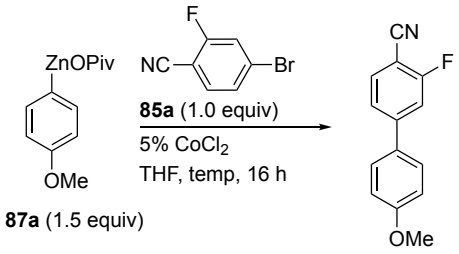
7.2. Optimization of the Reaction Conditions

Additional Co-catalyzed cross-couplings using heteroarylzinc pivalates:



19% yield (Hal = I) 70% yield (Hal = Br) 65% yield (Hal = Br)

Temperature screening:

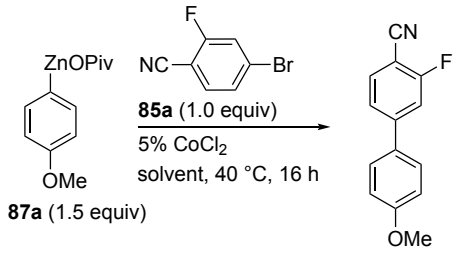


86a

entry	temp (°C)	yield of **86a** [a] (%)
1	0	31
2	25	59
3	40	85
4	60	69

[a] GC yield. Undecane was used as an internal standard.

Solvent screening:



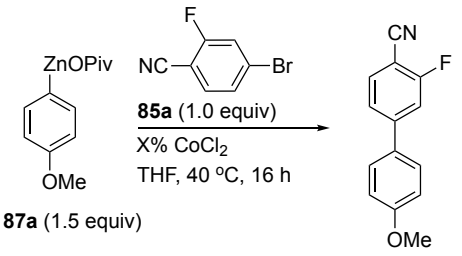
87a (1.5 equiv)

86a

entry	solvent	yield of **86a** [a] (%)
1	THF	85
2	NMP	42
3	DMPU	17
4	DME	47
5	1,4-Dioxane	42
6	*t*BuOMe	61
7	EtOAc	56
8	THF_{tec}	71
9	toluene	70

[a] GC yield. Undecane was used as an internal standard.

Catalyst screening:



87a (1.5 equiv)

86a

entry	$CoCl_2$ (mol%)	yield of **86a** [a] (%)
1	2.5	77
2	5	85
3	10	81
4	20	81

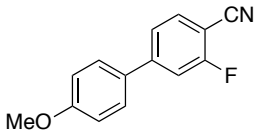
[a] GC yield. Undecane was used as an internal standard.

7.3. A Robust and Broadly Applicable Cobalt-Catalyzed Cross-Coupling of Functionalized Bench-Stable Organozinc Pivalates with Unsaturated Halides

Typical procedure 11 (TP11) for the cobalt-catalyzed cross-coupling of organozinc pivalates:

A dry and argon-flushed 10 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with dry $CoCl_2$ (6.5 mg, 0.05 mmol, 5 mol%) and dry THF (2.0 mL). The respective aryl halide (1.0 mmol, 1.0 equiv) was added at room temperature. Then, a solution of the appropriate (hetero)aryl zinc pivalate (1.5 mmol, 1.5 equiv) was added dropwise over 5 min *via* syringe. The reaction was stirred at 40 °C and monitored by GC-analysis ($C_{11}H_{24}$ was used as an internal standard). Upon consumption of the starting material, saturated aqueous NH_4Cl solution (5 mL) and ethyl acetate (5 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with aqueous NaOH solution (2 M, 50 mL) and dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography purification on silica yielding the respective title compound.

3-Fluoro-4'-methoxy-[1,1'-biphenyl]-4-carbonitrile (86a)



Following **TP11** 4-bromo-2-fluorobenzonitrile (**85a**, 200 mg, 1 mmol, 1.0 equiv, in 2 mL of THF) reacts with (4-methoxyphenyl)zinc pivalate, (**87a**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **86a** as a white solid (80%, 181 mg, 0.80 mmol).

m.p.: 150.9 – 152.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.64 (dd, *J* = 8.1, 6.7 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.43 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.38 (dd, *J* = 10.5, 1.6 Hz, 1H), 7.04 – 6.97 (m, 2H), 3.87 (s, 3H).

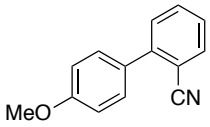
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 163.7 (d, *J* = 258.1 Hz), 160.8, 148.3 (d, *J* = 8.2 Hz), 133.8 (d, *J* = 1.1 Hz), 130.4 (d, *J* = 2.1 Hz), 128.5, 122.9 (d, *J* = 3.1 Hz), 114.8, 114.4, 114.2 (d, *J* = 20.2 Hz), 99.1 (d, *J* = 15.6 Hz), 55.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2941, 2839, 2224, 1618, 1608, 1582, 1560, 1524, 1493, 1467, 1436, 1407, 1315, 1298, 1276, 1250, 1223, 1210, 1180, 1120, 1040, 1026, 900, 881, 844, 813, 795, 736, 562.

MS (EI, 70 eV): *m/z* (%) = 228 (15), 227 (100), 121 (17), 184 (47), 158 (25).

HR-MS (EI, 70 eV): [$C_{14}H_{10}FNO$], calcd.: 227.0746; found: 227.0741.

4'-Methoxy-[1,1'-biphenyl]-2-carbonitrile (86b)



Following **TP11** 2-iodobenzonitrile (**85b**, 229 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (4-methoxyphenyl)zinc pivalate (**87a**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 36 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **86b** as a white solid (71%, 148 mg, 0.71 mmol).

m.p.: 85.0 – 85.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.74 (ddd, *J* = 7.8, 1.4, 0.5 Hz, 1H), 7.62 (td, *J* = 7.7, 1.4 Hz, 1H), 7.54 – 7.47 (m, 3H), 7.40 (td, *J* = 7.6, 1.2 Hz, 1H), 7.05 – 6.99 (m, 2H), 3.87 (s, 3H).

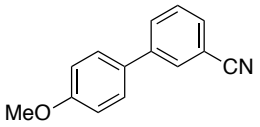
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.2, 145.3, 133.9, 132.9, 130.7, 130.1, 130.0, 127.2, 119.1, 114.3, 111.2, 55.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2937, 2224, 1610, 1580, 1517, 1479, 1465, 1443, 1306, 1294, 1269, 1247, 1180, 1048, 1035, 1018, 1001, 907, 834, 811, 764, 729, 649, 600.

MS (EI, 70 eV): *m/z* (%) = 210 (16), 209 (100), 194 (8), 166 (39), 140 (14), 139 (7), 43 (22).

HR-MS (EI, 70 eV): [$C_{14}H_{11}NO$], calcd.: 209.0841; found: 209.0837.

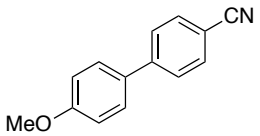
4'-Methoxy-[1,1'-biphenyl]-3-carbonitrile (86c)



Following **TP11** 3-iodobenzonitrile (**85c**, 229 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (4-methoxyphenyl)zinc pivalate (**87a**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 36 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **86c** as a slightly yellow oil (72%, 150 mg, 0.72 mmol). The remaining impurity was deducted from the final yield. The spectral data of this known compound was in full agreement with the literature.[101]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.81 – 7.78 (m, 1H), 7.77 – 7.73 (m, 1H), 7.56 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.52 – 7.45 (m, 3H), 7.03 – 6.96 (m, 2H), 3.85 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.1, 142.2, 131.4, 131.1, 130.3, 130.2, 129.7, 128.3, 119.1, 114.7, 113.0, 55.5.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959, 2230, 1610, 1516, 1479, 1442, 1434, 1296, 1269, 1247, 1182, 1114, 1049, 1029, 908, 832, 796, 731, 690.
MS (EI, 70 eV): *m/z* (%) = 210 (15), 209 (100), 194 (22), 166 (32), 140 (17), 44 (9), 43 (28).
HR-MS (EI, 70 eV): [$C_{14}H_{11}NO$], calcd.: 209.0841; found 209.0833.

4'-Methoxy-[1,1'-biphenyl]-4-carbonitrile (86d)



Following **TP11** 4-iodobenzonitrile (**85d**, 229 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (4-methoxyphenyl)zinc pivalate (**87a**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 36 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **86d** as a white solid (75%, 156 mg, 0.75 mmol).

m.p.: 99.4 – 101.4 °C.

[101] I. Stibingerov, S. Voltrova, S.Kocova, M. Lindale, J. Srogl, *Org. Lett.* **2016**, 18, 312.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.71 – 7.61 (m, 4H), 7.57 – 7.51 (m, 2H), 7.04 – 6.98 (m, 2H), 3.86 (s, 3H).

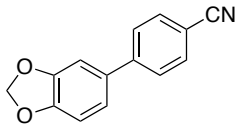
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.3, 145.3, 132.7, 131.6, 128.5, 127.2, 119.2, 114.7, 110.2, 55.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2964, 2840, 2225, 1605, 1580, 1515, 1494, 1468, 1446, 1398, 1313, 1306, 1294, 1267, 1247, 1179, 1112, 1038, 1021, 1016, 1001, 907, 854, 823, 770, 728, 649, 639, 628, 564.

MS (EI, 70 eV): *m/z* (%) = 210 (15), 209 (100), 194 (20), 166 (32), 140 (14).

HR-MS (EI, 70 eV): [$C_{14}H_{11}NO$], calcd.: 209.0841; found: 209.0831.

4-(Benzo[d][1,3]dioxol-5-yl)benzonitrile (86e)



Following **TP11** 4-iodobenzonitrile (**85d**, 229 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with benzo[d][1,3]dioxol-5-ylzinc pivalate (**87b**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **86e** as a white solid (72%, 161 mg, 0.72 mmol).

m.p.: 125.6 – 126.7°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.74 – 7.57 (m, 4H), 7.10 – 7.04 (m, 2H), 6.91 (dd, *J* = 7.9, 0.6 Hz, 1H), 6.03 (s, 2H).

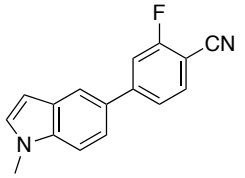
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 148.6, 148.4, 145.4, 133.5, 132.7, 127.5, 121.3, 119.1, 110.6, 109.0, 107.6, 101.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2898, 2227, 1604, 1501, 1480, 1442, 1412, 1341, 1306, 1294, 1275, 1252, 1228, 1181, 1108, 1038, 1011, 932, 906, 871, 841, 808, 729.

MS (EI, 70 eV): *m/z* (%) = 224 (14), 223 (100), 222 (47), 164 (25), 112 (6), 111 (6).

HR-MS (EI, 70 eV): [$C_{14}H_9NO_2$], calcd.: 223,0633; found: 223,0629.

2-Fluoro-4-(1-methyl-1H-indol-5-yl)benzonitrile (86f)



Following **TP11** 4-bromo-2-fluorobenzonitrile (**85a**, 200 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (1-methyl-1H-indol-5-yl)zinc pivalate (**87c**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 36 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (8.5:1.5) as an eluent to afford **86f** as a white solid (65%, 162 mg, 0.65 mmol).

m.p.: 139.8 – 141.6°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.85 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.64 (dd, *J* = 8.1, 6.7 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.49 – 7.39 (m, 3H), 7.13 (d, *J* = 3.1 Hz, 1H), 6.57 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.85 (s, 3H).

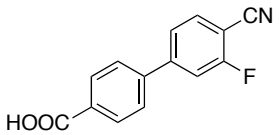
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 163.6 (d, *J* = 257.6 Hz), 150.3 (d, *J* = 8.5 Hz), 137.3, 133.6 (d, *J* = 1.4 Hz), 130.4, 129.6 (d, *J* = 2.3 Hz), 129.2, 123.4 (d, *J* = 3.3 Hz), 120.9, 120.1, 114.7 (d, *J* = 20.2 Hz), 114.6, 110.1, 102.0, 98.5 (d, *J* = 15.8 Hz), 33.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2946, 2230, 1609, 1574, 1557, 1514, 1483, 1449, 1425, 1362, 1337, 1311, 1281, 1260, 1247, 1212, 1160, 1119, 1105, 1081, 908, 871, 833, 800, 762, 746, 729.

MS (EI, 70 eV): *m/z* (%) = 252 (1), 251 (20), 250 (100), 249 (29), 208 (9), 125 (8), 42 (7).

HR-MS (EI, 70 eV): [$C_{14}H_9NO_2$], calcd.: 250,0906 ; found 250,0899:

4'-Cyano-3'-fluoro-[1,1'-biphenyl]-4-carboxylic acid (86g)



Following **TP11** 4-bromo-2-fluorobenzonitrile (**85a**, 200 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with the bis-zinc pivalate **87d** (1.6 mmol, 1.6 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (6:4) with 1% acetic acid as an eluent to afford **86g** as a white solid (70%, 168 mg, 0.70 mmol).

m.p.: 246 – 248°C.

^{1}H-NMR (400 MHz, DMSO–d_6, ppm): δ = 13.11 (s, 1H), 8.07 – 8.01 (m, 3H), 7.98 – 7.89 (m, 3H), 7.81 (dd, *J* = 8.2, 1.6 Hz, 1H).

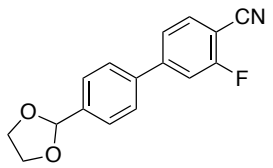
^{13}C-NMR (101 MHz, DMSO–d_6, ppm): δ = 166.8, 162.9 (d, *J* = 255.1 Hz), 146.5 (d, *J* = 8.5 Hz), 140.9 (d, *J* = 2.1 Hz), 134.4, 131.4, 130.0, 127.5, 123.9 (d, *J* = 3.1 Hz), 114.8 (d, *J* = 20.7 Hz), 114.0, 99.4 (d, *J* = 15.2 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3074, 2671, 2236, 1723, 1689, 1620, 1609, 1578, 1559, 1493, 1432, 1423, 1400, 1321, 1314, 1292, 1268, 1236, 1206, 1196, 1184, 1121, 1111, 904, 881, 858, 828, 808, 785, 772, 737, 721, 702, 684.

MS (ESI–): 240 [M–H]

HR-MS (ESI–): [$C_{14}H_{17}FNO_2^-$], calcd.: 240.0466; found: 240.0466.

4'-(1,3-dioxolan-2-yl)-3-fluoro-[1,1'-biphenyl]-4-carbonitrile (86h)



Following **TP11** 4-bromo-2-fluorobenzonitrile (**85a**, 200 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (4-(1,3-dioxolan-2-yl)phenyl)zinc pivalate (**87e**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 36 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (7:3) as an eluent to afford **86h** as a white solid (75%, 202 mg, 0.75 mmol).

m.p.: 132 – 133.3°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.68 (dd, *J* = 8.1, 6.6 Hz, 1H), 7.64 – 7.56 (m, 4H), 7.47 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.42 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.87 (s, 1H), 4.19 – 4.03 (m, 4H).

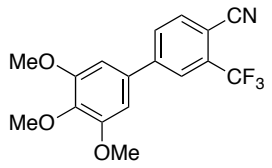
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 163.6 (d, *J* = 258.8 Hz), 148.2 (d, *J* = 8.1 Hz), 139.3, 139.0 (d, *J* = 2.1 Hz), 133.9 (d, *J* = 1.0 Hz), 127.4 (d, *J* = 13.4 Hz), 123.6 (d, *J* = 3.3 Hz), 115. 1, 114.9, 114.1, 103.3, 100.2 (d, *J* = 15.7 Hz), 65.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961, 2893, 2234, 1618, 1558, 1493, 1434, 1400, 1311, 1265, 1224, 1207, 1194, 1184, 1122, 1084, 1029, 1020, 974, 945, 903, 891, 842, 810, 734, 684.

MS (EI, 70 eV): *m/z* (%) = 270 (9), 269 (46), 268 (100), 224 (28), 210 (11), 108 (26), 198 (13), 197 (74), 196 (16), 195 (20), 73 (15).

HR-MS (EI, 70 eV): [$C_{16}H_{11}FNO_2$], calcd.: 269.0852; found: 269.0757.

3',4',5'-Trimethoxy-3-(trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile (86i)



Following **TP11** 4-iodo-2-(trifluoromethyl)benzonitrile (**85e**, 297 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (3,4,5-trimethoxyphenyl)zinc pivalate (**87f**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 36 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (7:3) as an eluent to afford **86i** as a white solid (72%, 241 mg, 0.72 mmol).

m.p.: 137.7 – 138.6°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.94 – 7.87 (m, 2H), 7.84 – 7.83 (m, 1H), 6.76 (s, 2H), 3.95 (s, 6H), 3.91 (s, 3H).

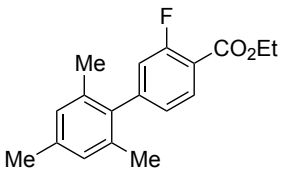
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 154.1, 146.4, 139.6, 135.3, 133.7, 133.4 (q, J = 32.5 Hz), 130.5, 125.3 (q, J = 4.7 Hz), 122.5 (q, J = 274.0 Hz), 115.7, 108.4 (q, J = 2.1 Hz), 104.9, 61.2, 56.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2940, 2839, 2231, 1611, 1588, 1562, 1516, 1494, 1463, 1429, 1403, 1349, 1313, 1274, 1247, 1218, 1179, 1128, 1082, 1054, 1003, 907, 828, 768, 730, 686.

MS (EI, 70 eV): *m/z* (%) = 339 (2), 338 (15), 337 (100), 322 (45), 294 (24), 264 (24), 208 (22).

HR-MS (EI, 70 eV): [$C_{17}H_{14}F_3NO_3$], calcd.: 337.0926; found: 337.0926.

Ethyl 3-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-4-carboxylate (86j)

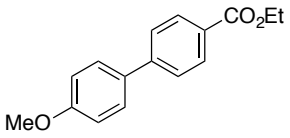


Following **TP11** ethyl 4-bromo-2-fluorobenzoate (**85f**, 247 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with mesitylzinc pivalate (**87g**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude

product was purified by column chromatography on silica using *i*-hexane:diethylether (100:3) as an eluent to afford **86j** as a colorless oil (71%, 202 mg, 0.71 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.99 (t, *J* = 7.8 Hz, 1H), 7.00 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.97 – 6.93 (m, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 2.00 (s, 6H), 1.43 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 164.6 (d, *J* = 3.7 Hz), 162.1 (d, *J* = 260.6 Hz), 148.5 (d, *J* = 8.7 Hz), 137.6, 136.9 (d, *J* = 1.5 Hz), 135.5, 132.2 (d, *J* = 1.6 Hz), 128.4, 125.4 (d, *J* = 3.5 Hz), 118.1 (d, *J* = 21.9 Hz), 117.4 (d, *J* = 9.9 Hz), 61.4, 21.2, 20.7, 14.5.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2980, 2921, 1729, 1715, 1619, 1561, 1508, 1476, 1465, 1445, 1410, 1380, 1366, 1284, 1259, 1247, 1240, 1193, 1172, 1157, 1136, 1092, 1035, 1018, 897, 876, 868, 850, 780, 743, 710, 696.
MS (EI, 70 eV): *m/z* (%) = 288 (2), 287 (19), 286 (100), 242 (15), 241 (88), 213 (12), 198 (10), 197 (12), 183 (17).
HR-MS (EI, 70 eV): [$C_{18}H_{19}FO$], calcd.: 286.1369; found: 286.1362.

Ethyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (86k)



Following **TP11** ethyl 4-iodobenzoate (**85g**, 276 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (4-methoxyphenyl)zinc pivalate (**87a**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (100:4) as an eluent to afford **86k** as a colorless crystals (61%, 155 mg, 0.71 mmol).

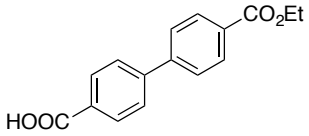
m.p.: 104.7 – 105.7°C.
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.12 – 8.06 (m, 2H), 7.65 – 7.55 (m, 4H), 7.02 – 6.97 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.7, 160.0, 145.2, 132.6, 130.2, 128.8, 128.5, 126.6, 114.5, 61.0, 55.5, 14.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 1706, 1604, 1582, 1564, 1529, 1497, 1465, 1445, 1426, 1401, 1369, 1312, 1286, 1278, 1252, 1198, 1186, 1110, 1035, 1014, 1001, 907, 861, 828, 807, 772, 730, 699, 650.

MS (EI, 70 eV): *m/z* (%) = 258 (2), 257 (20), 256 (100), 228 (20), 212 (11), 211 (61), 168 (13), 140 (12), 139 (22), 43 (11).

HR-MS (EI, 70 eV): [$C_{16}H_{16}O_3$], calcd.: 256.1099; found: 256.1080.

4'-(Ethoxycarbonyl)-[1,1'-biphenyl]-4-carboxylic acid (86l)



Following **TP11** ethyl 4-iodobenzoate (**85g**, 276 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with the bis-zinc pivalate **87d** (1.6 mmol, 1.6 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (6:4) with 1% acetic acid as an eluent to afford **86l** as a white solid (65%, 177 mg, 0.65 mmol).

m.p.: 238 – 240°C.

^{1}H-NMR (400 MHz, DMSO–d$_6$, ppm): δ = 13.03 (s, 1H), 8.07 – 8.04 (m, 4H), 7.92 – 7.82 (m, 4H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, DMSO–d$_6$, ppm): δ = 167.0, 165.4, 143.4, 142.9, 130.5, 130.0, 129.8, 129.4, 127.2, 127.1, 60.8, 14.2.

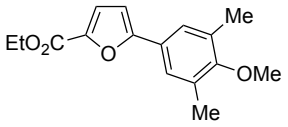
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2980, 2928, 2847, 2671, 2546, 1707, 1672, 1606, 1579, 1560, 1430, 1401, 1371, 1324, 1314, 1270, 1191, 1176, 1099, 1028, 1007, 932, 878, 845, 783, 754, 708, 697, 672.

MS (ESI–): 269 [M–H]

MS (ESI+): 288 [M+NH$_4$]

HR-MS (ESI–): [$C_{16}H_{13}O_4^-$], calcd.: 269,0819 found: 269,0818.

Ethyl 5-(4-methoxy-3,5-dimethylphenyl)furan-2-carboxylate (86m)



Following **TP11** ethyl 5-bromofuran-2-carboxylate (**85h**, 219 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (4-methoxy-3,5-dimethylphenyl)zinc pivalate (**87h**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (95:5) as an eluent to afford **86m** as a slightly yellow solid (65%, 177 mg, 0.65 mmol).

m.p.: 97.9 – 99.0°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.47 – 7.40 (m, 2H), 7.21 (d, J = 3.6 Hz, 1H), 6.62 (d, J = 3.6 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 2.32 (t, J = 0.7 Hz, 6H), 1.39 (t, J = 7.1 Hz, 3H).

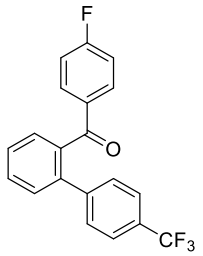
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 159.1, 157.9, 157.8, 143.6, 131.6, 125.6, 125.3, 120.0, 106.2, 60.9, 59.9, 16.3, 14.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 1605, 1515, 1466, 1309, 1254, 1204, 1175, 1106, 1028, 971, 903, 838, 810, 729.

MS (EI, 70 eV): *m/z* (%) = 275 (21), 274 (100), 260 (16), 259 (89), 227 (43), 115 (11), 107 (11), 43 (36).

HR-MS (EI, 70 eV): [$C_{16}H_{18}O_4$], calcd.: 274.1205; found: 274.1198.

(4-Fluorophenyl)(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)methanone (86n)



Following **TP11** (2-chlorophenyl)(4-fluorophenyl)methanone (**85i**, 235 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (4-trifluormethylphenyl)zinc pivalate (**87i**, 1.5 mmol, 1.5 equiv) prepared according to **TP1** at 40 °C. The solution was stirred at this temperature for 16 h and was

worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (95:5) as an eluent to afford **86n** as a white solid (80%, 276 mg, 0.80 mmol).

m.p.: 97.8 – 99.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.73 – 7.65 (m, 2H), 7.61 (ddd, *J* = 7.6, 6.3, 2.7 Hz, 1H), 7.55 – 7.45 (m, 5H), 7.41 – 7.35 (m, 2H), 7.01 – 6.93 (m, 2H).

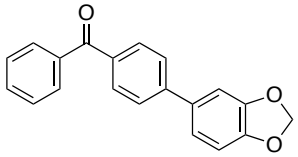
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 196.6, 165.8 (d, *J* = 255.8 Hz), 143.9 (q, *J* = 1.4 Hz), 139.8, 138.8, 133.8 (d, *J* = 2.9 Hz), 132.63 (d, *J* = 9.4 Hz), 130.8, 130.3, 129.6 (q, *J* = 32.6 Hz), 129.4, 128.9, 128.0, 125.4 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.1 Hz), 115.6 (d, *J* = 22.0 Hz).

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3061, 1660, 1617, 1596, 1504, 1407, 1325, 1304, 1259, 1225, 1160, 1113, 1104, 1067, 926, 843, 838, 765, 745, 733, 673.

MS (EI, 70 eV): *m/z* (%) = 345 (12), 344 (53), 343 (23), 275 (15), 249 (38), 201 (15), 152 (10), 123 (54), 95 (20), 85 (10), 83 (16).

HR-MS (EI, 70 eV): [$C_{20}H_{12}F_4O$], calcd.: 344.0824; found: 344.0818.

(4-(Benzo[d][1,3]dioxol-5-yl)phenyl)(phenyl)methanone (86o)



Following **TP11** (4-bromophenyl)(phenyl)methanone (**87j**, 261 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with benzo[d][1,3]dioxol-5-ylzinc pivalate (**85b**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **86o** as a white solid (81%, 244 mg, 0.81 mmol).

m.p.: 111.6 – 112.7°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.89 – 7.80 (m, 4H), 7.65 – 7.56 (m, 3H), 7.53 – 7.47 (m, 2H), 7.14 (d, *J* = 7.4 Hz, 2H), 6.94 – 6.88 (m, 1H), 6.03 (s, 2H).

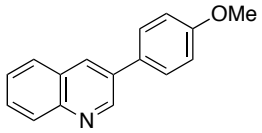
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 196.4, 148.5, 148.0, 145.0, 137.9, 136.0, 134.4, 132.4, 130.9, 130.1, 128.4, 126.7, 121.2, 108.9, 107.8, 101.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2894, 2253, 1652, 1601, 1502, 1481, 1441, 1313, 1276, 1250, 1226, 1039, 938, 905, 849, 813, 792, 755, 726, 701, 682.

MS (EI, 70 eV): *m/z* (%) = 303 (27), 302 (100), 225 (56), 139 (28), 105 (15), 77 (18), 43 (36).

HR-MS (EI, 70 eV): [$C_{20}H_{14}O_3$], calcd.: 302.0943; found: 302.0953.

3-(4-Methoxyphenyl)quinoline (86p)



Following **TP11** 3-bromoquinoline (**85k**, 208 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (4-methoxyphenyl)zinc pivalate (**87a**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (6:4) as an eluent to afford **86p** as a yellow solid (74%, 173 mg, 0.74 mmol).

m.p.: 99.4 – 101.4°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.16 (d, *J* = 2.3 Hz, 1H), 8.22 – 8.21 (m, 1H), 8.14 – 8.11 (m, 1H), 7.86 – 7.80 (m, 1H), 7.69 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.55 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.08 – 7.01 (m, 2H), 3.86 (s, 3H).

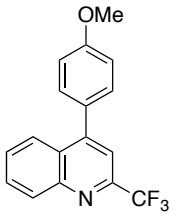
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 159.9, 149.9, 147.1, 133.5, 132.4, 130.4, 129.3, 129.1, 128.6, 128.2, 128.0, 127.0, 114.8, 55.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2934, 1609, 1516, 1492, 1462, 1431, 1440, 1341, 1285, 1250, 1180, 1045, 1029, 954, 906, 829, 785, 751, 727.

MS (EI, 70 eV): *m/z* (%) = 237 (2), 236 (21), 235 (100), 221 (8), 220 (31), 192 (13), 191 (8), 191 (8), 190 (9), 165 (8), 163 (6), 117 (8).

HR-MS (EI, 70 eV): [$C_{16}H_{13}ON$], calcd.: 235.0997; found: 235.0994.

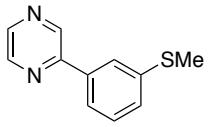
4-(4-Methoxyphenyl)-2-(trifluoromethyl)quinoline (86q)



Following **TP11** 4-chloro-2-(trifluoromethyl)quinoline (**85l**, 232 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (4-methoxyphenyl)zinc pivalate (**87a**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **86q** as a slightly yellow oil (72%, 217 mg, 0.72 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.31 – 8.26 (m, 1H), 8.05 – 8.03 (m, 1H), 7.82 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.66 (s, 1H), 7.62 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.12 – 7.06 (m, 2H), 3.92 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 160.5, 150.8, 148.0, 147.7 (q, *J* = 34.3 Hz), 131.0, 130.7, 130.6, 129.6, 128.6, 127.7, 126.1, 121.8 (q, *J* = 275.5 Hz), 117.0 (q, *J* = 2.1 Hz), 114.5, 55.6.
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2933, 1610, 1518, 1506, 1466, 1384, 1342, 1296, 1268, 1250, 1188, 1168, 1138, 1094, 1033, 908, 876, 836, 769, 732.
MS (EI, 70 eV): *m/z* (%) = 304 (19), 303 (100), 190 (16), 44 (14), 43 (44).
HR-MS (EI, 70 eV): [$C_{11}H_{15}O_3N_2$], calcd.: 303.0871; found: 303.0864.

2-(3-(Methylthio)phenyl)pyrazine (86r)



Following **TP11** 2-chloropyrazine (**85m**, 115 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (3-(methylthio)phenyl)zinc pivalate (**87j**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1 to 7:3) as an eluent to afford **86r** as a colorless oil (89%, 179 mg, 0.89 mmol; or 85% on a 10 mmol scale).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.02 (d, *J* = 1.5 Hz, 1H), 8.63 (dd, *J* = 2.5, 1.6 Hz, 1H), 8.52 (d, *J* = 2.5 Hz, 1H), 7.95 – 7.91 (m, 1H), 7.75 (ddd, *J* = 7.6, 1.7, 1.2 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.36 (ddd, *J* = 7.8, 2.0, 1.2 Hz, 1H), 2.56 (s, 3H).

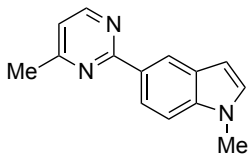
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 152.5, 144.3, 143.3, 142.4, 140.0, 137.1, 129.5, 128.0, 125.0, 123.6, 15.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3055, 2923, 2236, 1591, 1580, 1567, 1523, 1470, 1460, 1427, 1411, 1394, 1380, 1304, 1292, 1147, 1084, 1036, 1015, 968, 907, 848, 819, 786, 729, 700, 691.

MS (EI, 70 eV): *m/z* (%) = 204 (5), 203 (17), 202 (100), 201 (20), 169 (24), 157 (11), 148 (14), 85 (12).

HR-MS (EI, 70 eV): [$C_{11}H_{10}SN_2$], calcd.: 202.0565; found: 202.0555.

1-Methyl-6-(4-methylpyrimidin-2-yl)-1H-indole (88a)



Following **TP11** 2-bromo-4-methylpyrimidine (**78u**, 173 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (1-methyl-1H-indol-5-yl)zinc pivalate (**87c**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane: ethyl acetate (7:3) as an eluent to afford **86a** as a white solid (81%, 180 mg, 0.81 mmol).

m.p.: 149.5 – 151.4°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.78 (dd, *J* = 1.7, 0.7 Hz, 1H), 8.62 (d, *J* = 5.0 Hz, 1H), 8.37 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.39 (dt, *J* = 8.8, 0.8 Hz, 1H), 7.07 (d, *J* = 3.1 Hz, 1H), 6.98 (d, *J* = 5.0 Hz, 1H), 6.59 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.82 (s, 3H), 2.59 (s, 3H).

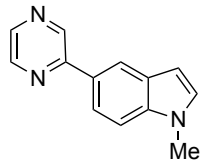
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 167.1, 165.7, 156.8, 138.5, 129.7, 129.5, 128.8, 122.1, 121.9, 117.7, 109.2, 102.5, 33.1, 24.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2927, 1615, 1578, 1565, 1551, 1515, 1450, 1432, 1387, 1370, 1354, 1344, 1275, 1242, 1148, 1080, 907, 818, 790, 775, 763, 727, 694.

MS (EI, 70 eV): *m/z* (%) = 225 (2), 224 (17), 223 (100), 222 (14), 208 (15), 156 (20).

HR-MS (EI, 70 eV): [$C_{11}H_{15}O_3N_2$], calcd.: 223,1109; found: 223,1079.

1-Methyl-6-(pyrazin-2-yl)-1H-indole (88b)



Following **TP11** 2-chloropyrazine (**85m**, 115 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (1-methyl-1H-indol-5-yl)zinc pivalate (**87c**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (7:3) as an eluent to afford **88b** as a slightly brown solid (85%, 178 mg, 0.85 mmol).

m.p.: 108.9 – 110.2°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.09 (d, *J* = 1.5 Hz, 1H), 8.60 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.43 (d, *J* = 2.5 Hz, 1H), 8.31 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.92 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.11 (d, *J* = 3.1 Hz, 1H), 6.59 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.83 (s, 3H).

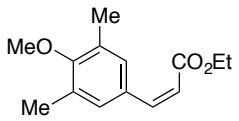
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 154.3, 144.1, 142.3, 141.8, 137.8, 130.1, 129.1, 127.9, 120.8, 120.1, 110.0, 102.2, 33.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928, 1616, 1575, 1517, 1466, 1448, 1424, 1404, 1340, 1312, 1246, 1164, 1142, 1107, 1081, 1012, 906, 846, 803, 906, 846, 803, 723.

MS (EI, 70 eV): *m/z* (%) = 211 (1), 210 (14), 209 (100), 208 (12), 156 (25).

HR-MS (EI, 70 eV): [$C_{13}H_{11}N_3$], calcd.: 209.0953; found: 209.0952.

Ethyl (*Z*)-3-(4-methoxy-3,5-dimethylphenyl)acrylate (90a)



Following **TP11** ethyl (*Z*)-3-iodoacrylate (**89a**, 226 mg, 1 mmol, 1.0 equiv, *E/Z* 1:99, in 2 mL THF) or ethyl (*Z*)-3-bromoacrylate (**89b**, 179 mg, 1 mmol, 1.0 equiv, *E/Z* 1:99, in 2 mL THF) reacts with (4-methoxy-3,5-dimethylphenyl)zinc pivalate (**87h**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was

worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (95:5) as an eluent to afford **90a** as a slightly yellow oil (starting with **89a**: 98%, 230 mg, 0.98 mmol, *E/Z* 1:99; starting with **89b**: 94%, 220 mg, 0.94 mmol, *E/Z* 1:99;).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.31 (q, *J* = 0.7 Hz, 2H), 6.81 (dt, *J* = 12.7, 0.7 Hz, 1H), 5.85 (d, *J* = 12.7 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 2.28 (s, 6H), 1.27 (t, *J* = 7.1 Hz, 3H).

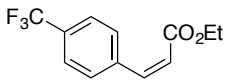
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 166.6, 157.9, 142.8, 130.9, 130.5, 130.5, 118.7, 60.3, 59.8, 16.2, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982, 2939, 1714, 1627, 1600, 1485, 1445, 1388, 1286, 1228, 1174, 1136, 1096, 1033, 1014, 907, 826, 767, 729.

MS (EI, 70 eV): *m/z* (%) = 235 (17), 234 (100), 219 (10), 191 (16), 189 (59), 162 (19), 147 (10), 91 (12).

HR-MS (EI, 70 eV): [$C_{14}H_{18}O_3$], calcd.: 234.1256; found: 234.1251.

Ethyl (*Z*)-3-(4-(trifluoromethyl)phenyl)acrylate (90b)



Following **TP11** ethyl (*Z*)-3-iodoacrylate (**89a**, 226 mg, 1 mmol, 1.0 equiv, *E/Z* 1:99, in 2 mL THF) reacts with (4-trifluormethylphenyl)zinc pivalate (**87i**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (97:3) as an eluent to afford **90b** as a colorless oil (80%, 195 mg, 0.80 mmol, *E/Z* 3:97).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.62 (d, *J* = 6.7 Hz, 4H), 6.98 (d, *J* = 12.6 Hz, 1H), 6.06 (d, *J* = 12.6 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

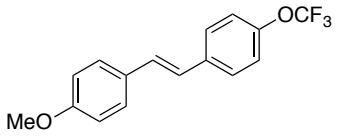
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 165.7, 141.5, 138.5 (d, *J* = 1.7 Hz), 130.5 (q, *J* = 32.6 Hz), 129.7, 124.9 (q, *J* = 3.9 Hz), 124.0 (q, *J* = 272.1 Hz), 12.1, 60.6, 14.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2986, 2362, 2349, 2256, 1721, 1637, 1617, 1407, 1324, 1200, 1185, 1166, 1127, 1114, 1068, 1019, 909, 858, 732.

MS (EI, 70 eV): *m/z* (%) = 244 (27), 225 (6), 216 (25), 215 (10), 200 (6), 199 (100), 172 (13), 171 (32), 151 (36), 147 (7), 145 (7), 109 (7), 102 (12), 97 (10), 83 (14).

HR-MS (EI, 70 eV): [$C_{12}H_{11}F_3O_2$], calcd.: 244.0711; found: 244.0700.

(*E*)-1-Methoxy-4-(4-(trifluoromethoxy)styryl)benzene (90c)



Following **TP11** (*E*)-1-(2-bromovinyl)-4-methoxybenzene (**89c**, 213 mg, 1 mmol, 1.0 equiv, *E/Z* 99:1, in 2 mL THF) reacts with (4-(trifluoromethoxy)phenyl)zinc pivalate (**87k**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (95:5) as an eluent to afford **90c** as a white solid (97%, 285 mg, 0.97 mmol, *E/Z* 99:1).

m.p.: 149.2 – 151.1°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.52 – 7.42 (m, 4H), 7.21 – 7.17 (m, 2H), 7.07 – 6.89 (m, 4H), 3.84 (s, 3H).

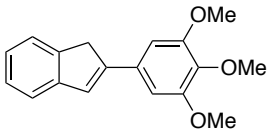
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 159.7, 148.3 (d, J = 1.9 Hz), 136.6, 129.9, 129.4, 128.0, 127.5, 125.1, 121.3 (d, J = 1.1 Hz), 120.7 (q, J = 257.0 Hz), 114.3, 55.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 1605, 1515, 1309, 1254, 1204, 1175, 1106, 1028, 971, 903,838, 810, 729.

MS (EI, 70 eV): *m/z* (%) = 295 (20), 294 (100), 279 (23), 251 (5), 166 (9), 165 (28), 153 (5), 152 (6).

HR-MS (EI, 70 eV): [$C_{16}H_{13}F_3O_2$], calcd.: 294.0868; found: 294.0862.

2-(3,4,5-Trimethoxyphenyl)-1H-indene (90d)



Following **TP11** 2-bromo-1H-indene (**89d**, 195 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (3,4,5-trimethoxyphenyl)zinc pivalate (**87f**, 1.5 mmol, 1.5 equiv) prepared according to **TP9**, at 40 °C. The solution was stirred at this temperature for 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (85:15) as an eluent to afford **90d** as a white solid (83%, 234 mg, 0.83 mmol).

m.p.: 115.6 – 117.8°C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.49 – 7.46 (m, 1H), 7.42 – 7.38 (m, 1H), 7.29 (td, *J* = 7.5, 1.1 Hz, 1H), 7.23 – 7.15 (m, 2H), 3.94 (s, 6H), 3.90 (s, 3H), 3.78 – 3.77 (m, 2H).

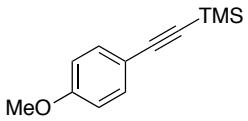
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 153.4, 146.4, 145.4, 143.0, 138.0, 131.9, 126.7, 126.4, 124.8, 123.7, 121.0, 102.9, 61.1, 56.2, 39.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938, 2250, 1581, 1562, 1504, 1460, 1431, 1415, 1395, 1354, 1340, 1297, 1240, 1203, 1187, 1162, 1125, 1058, 1030, 1004, 906, 820, 752, 727, 717.

MS (EI, 70 eV): *m/z* (%) = 283 (20), 282 (100), 268 (14), 267 (67), 165 (12), 153 (13), 152 (14), 141 (15), 43 (11).

HR-MS (EI, 70 eV): [$C_{18}H_{18}O_3$], calcd.: 282.1256; found: 282.1253.

((4-Methoxyphenyl)ethynyl)trimethylsilane (92a)



Following **TP11** (bromoethynyl)trimethylsilane (**91a**, 177 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (4-methoxyphenyl)zinc pivalate (**87a**, 1.7 mmol, 1.7 equiv) prepared according to **TP9**, at – 40 °C. The solution was allowed to warm to room temperature over 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **92a** as a yellow oil (61%, 124 mg, 0.61 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.36 – 7.30 (m, 2H), 6.79 – 6.70 (m, 2H), 3.73 (s, 3H), 0.17 (s, 9H).

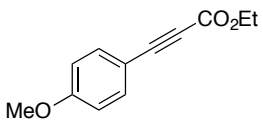
^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 159.6, 133.4, 115.2, 113.7, 105.1, 92.4, 55.2, 0.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959, 2936, 2901, 2838, 2361, 2156, 1606, 1572, 1508, 1465, 1442, 1293, 1249, 1231, 1180, 1172, 1107, 1034, 909, 864, 834, 756, 734, 700.

MS (EI, 70 eV): *m/z* (%) = 206 (3), 205 (11), 294 (65), 190 (33), 189 (100), 173 (11), 146 (9), 94 (9).

HR-MS (EI, 70 eV): [$C_{12}H_{16}O_2Si$], calcd.: 204.0970; found: 204.0960.

Ethyl 3-(4-methoxyphenyl)propiolate (92b)



Following **TP11** ethyl 3-bromopropiolate (**91b**, 177 mg, 1 mmol, 1.0 equiv, in 2 mL THF) reacts with (4-methoxyphenyl)zinc pivalate (**87a**, 1.7 mmol, 1.7 equiv) prepared according to **TP9**, at – 40 °C. The solution was allowed to warm to room temperature over 16 h and was worked-up as usual. The crude product was purified by column chromatography on silica using *i*-hexane:ethyl acetate (9:1) as an eluent to afford **92b** as a yellow oil (71%, 144 mg, 0.71 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.58 – 7.49 (m, 2H), 6.92 – 6.83 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$, ppm): δ = 161.6, 154.5, 135.0, 114.4, 111.6, 87.0, 80.3, 62.0, 55.5, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982, 2236, 2205, 1703, 1604, 1510, 1463, 1443, 1367, 1287, 1253, 1194, 1163, 1025, 834, 748.

MS (EI, 70 eV): *m/z* (%) = 205 (4), 204 (29), 160 (8), 159 (73), 144 (9), 133 (11), 132 (100), 117 (8), 116 (9), 88 (9).

HR-MS (EI, 70 eV): [$C_{12}H_{12}O_3$], calcd.: 204.0786; found: 204.0780.