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Cobalt-Catalyzed Cross-Couplings and Acylation Reactions using Organozinc Reagents

Lucie Grokenberger (geb. Thomas)

aus München, Deutschland

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Erklärung

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‡ These authors contributed equally to the work

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LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
Alk	alkyl
aq.	aqueous
Ar	aryl
ATR	attenuated total reflection (IR)
Boc	*tert*-butyloxycarbonyl
bipy	2,2'-bipyridine
Bu	butyl
calc.	calculated
Cy	cyclohexyl
cp*	C_5Me_5
δ	chemical shifts in ppm (parts per million)
DME	1,2-dimethoxyethane
DCB	2,3-dichlorobutane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethylpropyleneurea
EI	electron impact ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
GC	gas chromatography
HRMS	high resolution mass spectrometry
i-Pr	*iso*-propyl
IR	infared
J	coupling constant (NMR)
M	molarity
m.p.	melting point
Me	methyl

MS	mass spectrometry
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
Ph	phenyl
phen	1,10-phenanthroline
Piv	pivaloyl
ppm	parts per million
py	pyridyl
pym	pyrimidyl
R	organic substituent
rt	room emperature
sat.	saturated
T	temperature
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxyl
TES	triethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
TPy	terpyridine
Ts	4-toluenesulfonyl

I INTRODUCTION

Until today more than 160 million organic and inorganic substances have been registered at the chemical abstracts service (CAS),[1] including 147 million small molecules.[2] Despite cell and gene therapy revolutionizing the drug market, small molecules still make up half the amount of the worlds 200 most selling drugs.[3] Therefore, the development of new molecules and especially efficient methods for their synthesis is of great interest. The construction of carbon bonds is crucial for the synthesis of new molecules. Palladium-catalyzed cross-coupling reactions proved to be powerful tools for the synthesis of carbon-carbon or carbon-heteroatom bonds, since they often proceed under mild reaction conditions and with high chemoselectivity.[4] The highlight in this field of research was reached in 2010, when *Richard Heck*, *Ei-ichi Negishi* and *Akira Suzuki*[5] got awarded with the Nobel prize for palladium-catalyzed cross-coupling reactions. Yet, they often require costly and sophisticated ligands and palladium itself is comparably expensive.[6] Therefore, the search for alternative transition-metals for their use in cross-coupling reactions is of great interest.

[1] https://www.cas.org/about/cas-content; retrieved March **2020**.

[2] a) Below 900 u , b) https://www.cas.org/support/documentation/cas-databases; retrieved March **2020**.

[3] https://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/2018Top200 PharmaceuticalRetailSales PosterLowResFinalV2.pdf.

[4] a) A. O. King, N. Yasuda in *Organometallics in Process Chemistry*, Springer Berlin Heidelberg, **2004**, S. 205–245; b) A. Dumrath, C. Lübbe, M. Beller in *Palladium-Catalyzed Coupling Reactions*, John Wiley & Sons, Ltd, Chichester, U.K., **2013**, Kap. 12, S. 445–489; c) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649; d) P. Devendar, R.-Y. Qu, W.-M. Kang, B. He, G.-F. Yang, *J. Agr. Food Chem.* **2018**, *66*, 8914–8934.

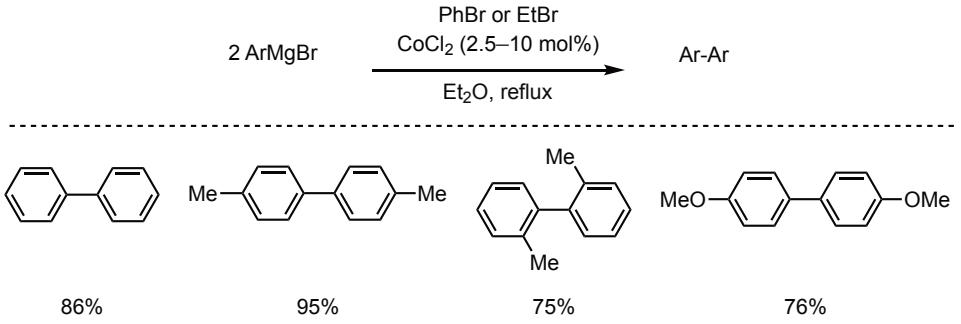
[5] https://www.nobelprize.org/uploads/2018/06/advanced-chemistryprize2010-1.pdf.

[6] a) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461–1473; b) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; c) C. A. Fleckenstein, H. Plenio, *Chem. Soc. Rev.* **2010**, *39*, 694–711; d) R. J. Lundgren, M. Stradiotto, *Chem. – Eur. J.* **2012**, *18*, 9758–9769; e) World market price: 1,449.69 €/ozt, 46.61 €/g, 4960 €/mol, from http://www.infomine.com/investment/metal-prices/palladium/ retrieved March **2020**; f) P. G. Gildner, T. J. Colacot, *Organometallics* **2015**, *34*, 5497–5508.

1 Beginnings of Cobalt-Catalyzed Carbon-Carbon Bond Forming Reactions

One transition-metal, which has recently attracted a lot of attention in cross-coupling reactions is cobalt. Cobalt has only one stable isotope (^{59}Co) and is able to form the oxidation states -I, 0, +I, +II, +III, +IV, +V of which oxidation states +II, +III are the most frequent ones.[7] The occurrence of cobalt is about 40 ppm in the earth crust and only in chemically combined form.[7] The main cobalt mining country is the DR Congo and the total worldwide mine production is about 120 0000 tons.[7] Cobalt salts often have characteristic color, thus finding broad application as dyes until now. In fact, more than 3000 years old shards were found covered with *cobalt blue* ($CoAl_2O_4$) also known as *Thénard blue* after *Louis Jacques Thénard*, who rediscovered it in 1802.[8] Today cobalt is applied in lithium-ion batteries, alloys and it is still used for its blue color in ceramics, inks and paints.[7] Furthermore, it became a popular catalyst in organic chemistry, especially for cross-coupling reactions.[9]

The first cobalt-catalyzed carbon-carbon bond formation were homocoupling reactions.[10] In 1941 *Kharasch et al.* showed that only a catalytic amount of $CoCl_2$ is needed, to enable the homo-coupling of aryl magnesium reagents in the presence of an organic halide such as phenyl or ethyl bromide (see Scheme 1).

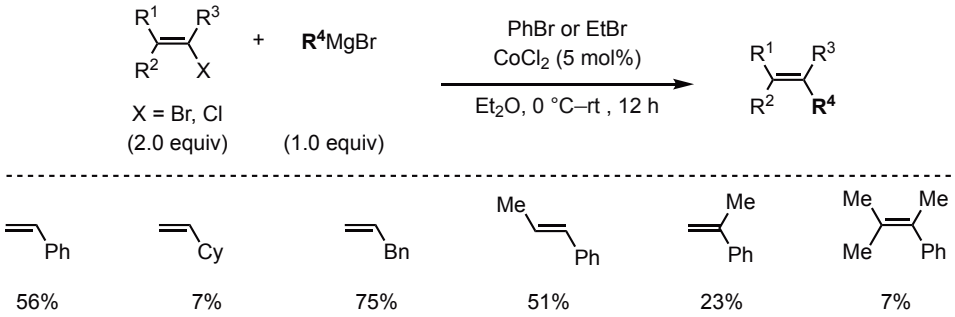


Scheme 1 Cobalt-catalyzed homocoupling reaction of aromatic *Grignard* reagents.[10]

Just two years later the first cobalt-catalyzed cross-coupling was discovered.[11] The same conditions allowed the cross-coupling of *Grignard* reagents with vinyl halides (see Scheme 2). However, this reaction gave moderate yields and proceeded only by using a large excess of vinyl

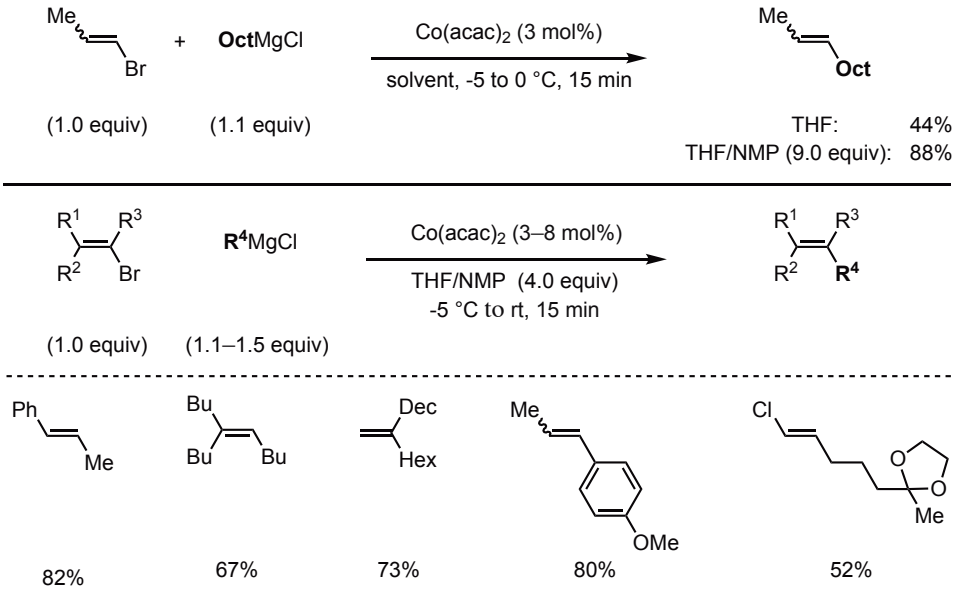
[7] H. Sicius in *Handbuch der chemischen Elemente*, Springer Berlin Heidelberg, Berlin, Heidelberg, **2019**, S. 1–37.
[8] G. Schwedt in *Chemische Experimente in Schlössern, Klöstern und Museen*, Wiley-VCH, Weinheim, Berlin, Heidelberg, **2009**.
[9] a) C. Gosmini, J.-M. Bégouin, A. Moncomble, *Chem. Commun.* **2008**, 3221–3233; b) G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435–1462; c) J. M. Hammann, M. S. Hofmayer, F. H. Lutter, L. Thomas, P. Knochel, *Synthesis* **2017**, *49*, 3887–3894; d) G. Dorval, C. Gosmini in *Cobalt Catalysis in Organic Synthesis*, (ed.: G. Hilt), Wiley-VCH, Weinheim, **2020**, pp. 163–205
[10] M. S. Kharasch, E. K. Fields, *J. Am. Chem. Soc.* **1941**, *63*, 2316–2320.
[11] M. S. Kharasch, C. F. Fuchs, *J. Am. Chem. Soc.* **1943**, *65*, 504–507.

halide, due to high homocoupling products formation. Also, sterically hindered vinyl halides only were coupled in poor yields.



Scheme 2 Cobalt-catalyzed cross-coupling of vinyl halides and *Grignard* reagents.[11]

It took more than 50 years until this drawback could be overcome. The key to a higher selectivity was the use of a NMP-THF 1:1 solvent mixture, which doubled the yield, compared to THF. Thus, various alkenyl halides could be coupled with several *Grignard* reagents in good yields.[12]



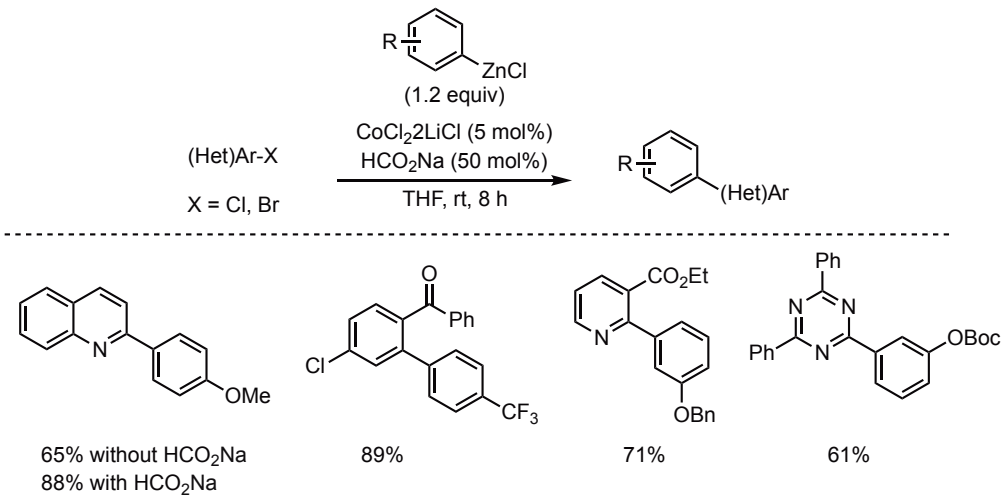
Scheme 3 Cobalt-catalyzed alkenylation of *Grignard* regents.[12]

From the beginnings to date, cobalt-catalyzed cross couplings have been refined. The addition of ligands and additives, the use of different organometallics and also the application to stereoselective reactions led to numerous publications. In the following part a short summary of the highlights in cobalt catalyzed cross-coupling reactions of the last decade will be given.

[12] G. Cahiez, H. Avedissian, *Tetrahedron Lett.* **1998**, *39*, 6159–6162.

2 Recent Advances in Cobalt-Catalyzed Carbon-Carbon Bond Forming Reactions

The construction of carbon-carbon bonds is one of the most versatile and popular cross-coupling reaction. Especially the preparation of biaryl compounds is of great interest, since they are scaffolds in natural products, pharmaceuticals or ligands.[13] Whereas, *Kumada*-type cobalt-catalyzed C(sp^2)-C(sp^2) cross-couplings were already discovered earlier,[11] the development of *Negishi* and *Suzuki-Miyaura* type reaction seemed to be more challenging to achieve. *Gosmini* and co-workers discovered the beneficial effect of cobalt bromide for the generation of arylzinc reagents.[14] Those could be generated by reduction of the aryl halide by a zinc anode[14a,b] or by zinc dust[14c] in the presence of $CoBr_2$ and $ZnBr_2$ in acetonitrile at rt. A few years later this method was applied to cobalt-catalyzed cross-couplings with 2-chloropyrimidine or 2-chloropyrazine.[15] In 2016, *Knochel* and co-workers could broaden the scope of the cobalt-catalyzed *Negishi* cross-coupling. A catalytic system consisting of the THF-soluble $CoCl_2$·LiCl and HCO_2Na enabled the cross-coupling of *N*-heterocyclic chlorides, as well as, bromides and aromatic halogenated ketones. The cross-coupling proceeded smoothly with various electron-rich and -poor arylzinc reagents (see Scheme 4).[16]



Scheme 4 Cobalt-catalyzed *Negishi* cross-coupling of (hetero)arylzinc reagents with (hetero) aryl halides.[16]

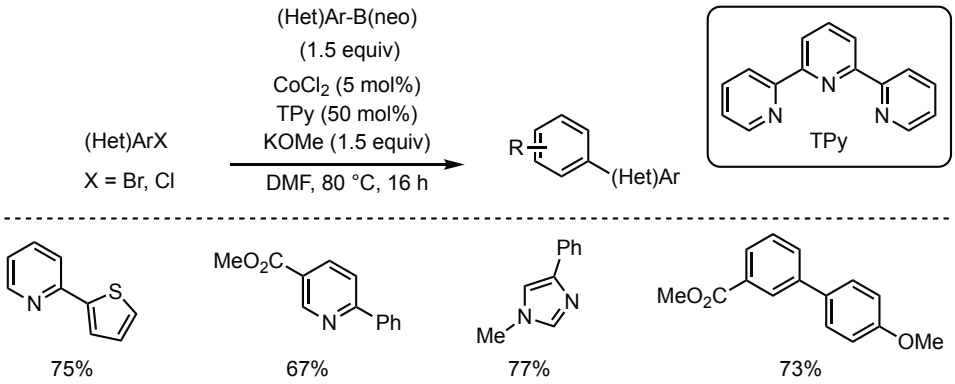
[13] a) G. Bringmann, C. Günther, M. Ochse, O. Schupp, S. Tasler in *Fortschritte der Chemie organischer Naturstoffe / Progress in the Chemistry of Organic Natural Products*, (eds.: W. Herz, H. Falk, G. W. Kirby, R. E. Moore), Springer Vienna, Vienna, **2001**, pp. 1–249; b) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470; c) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930.

[14] a) C. Gosmini, Y. Rollin, J. Y. Nédélec, J. Périchon, *J. Org. Chem.* **2000**, *65*, 6024–6026; b) H. Fillon, E. L. Gall, C. Gosmini, J. Périchon, *Tetrahedron Lett.* **2002**, *43*, 5941–5944; c) H. Fillon, C. Gosmini, J. Périchon, *J. Am. Chem. Soc.* **2003**, *125*, 3867–3870.

[15] J.-M. Bégouin, C. Gosmini, *J. Org. Chem.* **2009**, *74*, 3221–3224.

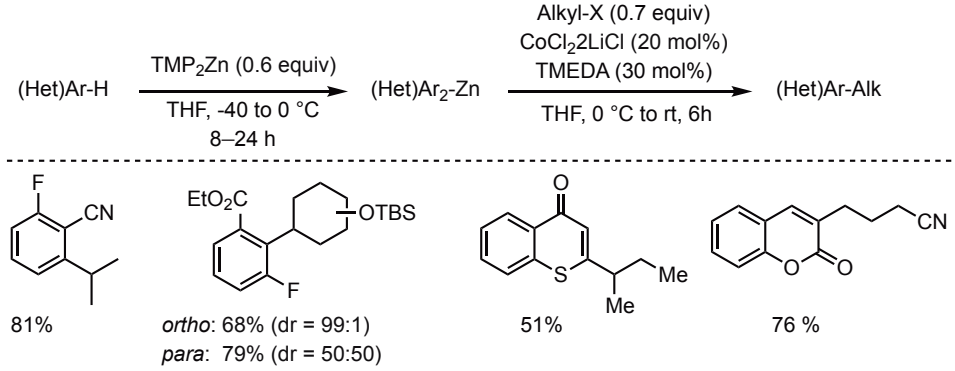
[16] D. Haas, J. M. Hammann, F. H. Lutter, P. Knochel, *Angew. Chem. Int. Ed.* **2016**, *55*, 3809–3812.

The same year a cobalt-catalyzed *Suzuki-Miyaura* cross-coupling was discovered by the group of *Chirik*.[17] The key to this transformation was the preparation of a new class of tetrahedral, high-spin bis(phosphino)pyridine cobalt(I) alkoxide and aryloxide complexes, which enabled the coupling of (benzo)furanylboronic esters with various aryl triflate electrophiles. *Duong et al.* could broaden the scope of the cobalt-catalyzed *Suzuki-Miyaura* coupling by a catalytic system comprising cobalt(II)/terpyridine and potassium methoxide.[18] Under these conditions a broad range of (hetero)aryl halides with (hetero)arylboronic esters could be coupled, leading to various (hetero)biaryl products (see Scheme 5).



Scheme 5 Cobalt-catalyzed cross-coupling of arylboronic esters and aryl halides.[18]

The formation of C(sp^2)-C(sp^3) centers can be hampered due to β-hydride elimination, therefore their preparation is often more challenging.[19] *Hammann et al.* reported a cobalt catalyzed cross-coupling of bisarylzinc reagents, generated by directed metalation using TMP_2Zn with primary and secondary alkyl halides, avoiding rearrangement of the secondary halides (see Scheme 6).[20]

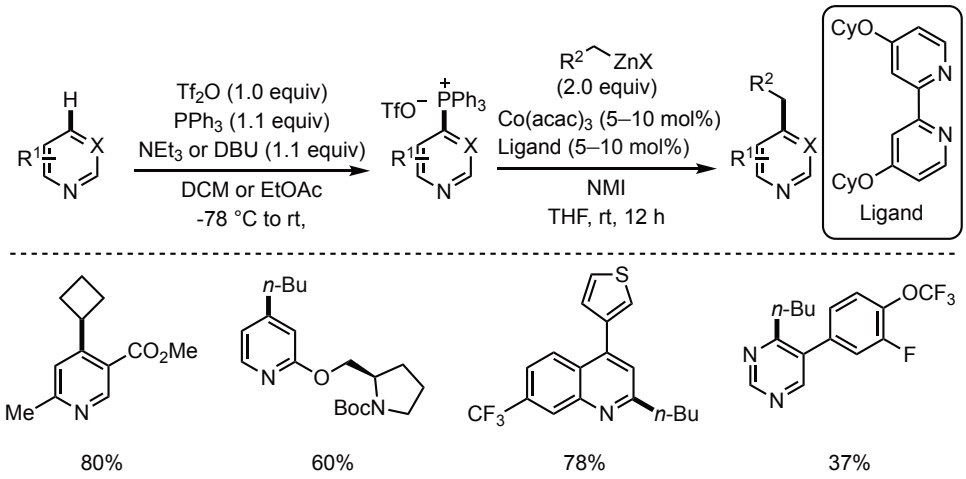


Scheme 6 Cobalt-catalyzed cross-coupling reaction of bis(heteo)arylzinc reagents with primary and secondary alkyl bromides and iodides.[20]

[17] J. M. Neely, M. J. Bezdek, P. J. Chirik, *ACS Cent. Sci.* **2016**, *2*, 935–942.
[18] H. A. Duong, W. Wu, Y.-Y. Teo, *Organometallics* **2017**, *36*, 4363–4366.
[19] a) M. Netherton, G. Fu, *Adv. Synth. Catal.* **2004**, *346*, 1525–1532; b) A. C. Frisch, M. Beller, *Angew. Chem. Int. Ed.* **2005**, *44*, 674–688; c) A. Rudolph, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 2656–2670; d) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492.
[20] J. M. Hammann, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 4478–4481.

The coupling of disubstituted cyclohexyl iodides in a diastereoselective manner was only possible for 1,2-substitution, 1,3-OTBS-substituted cyclohexyliodide led to a 1:1 mixture of the corresponding product.

A C(sp^3)-C(sp^2) cobalt-catalyzed coupling using alkylzinc reagents was developed by *Zhang et al.* in 2019 (see Scheme 7).[21] A catalytic system consisting of $Co(acac)_3$ and a cyclohexyloxy-substituted bipyridine ligand facilitated the coupling of *N*-heterocyclic phosphonium salts, which could be selectively installed in one step from C-H precursors, with alkylzinc reagents. Thus, alkylated *N*-heterocylces could be obtained in a two step procedure.



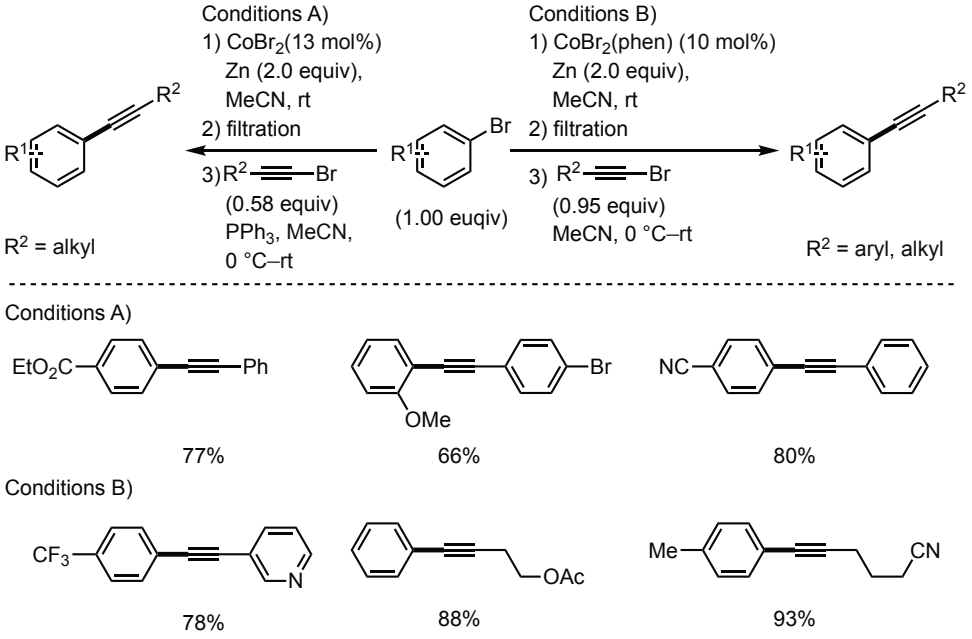
Scheme 7 Cobalt-catalyzed alkylation of *N*-heterocyclic phosphonium salts.[21]

Phenylacetylenes are important motifs in organic synthesis, especially for materials and in polymer science.[22] Therefore, the installation of the alkyne unit is of great interest. The group of *Gosmini* developed a cobalt-catalyzed C(sp^2)-C(sp) cross-coupling of *in situ* generated arylzinc reagents with alkynyl bromides (see Scheme 8).[23] The freshly prepared arylzinc reagent in combination with PPh_3, enabled the coupling with electron rich phenylalkynyl bromides. For the coupling of bromoalkynes bearing an alkyl group, $CoBr_2$(phen) was used as catalyst. Under these conditions bromo alkynes bearing aryl and alkyl moieties could be used.

[21] X. Zhang, A. McNally, *ACS Catal.* **2019**, *9*, 4862–4866.

[22] a) *The Chemistry of Triple-Bonded Functional Groups*, (eds.: S. Patai), John Wiley & Sons, Ltd, New York, **1994**; b) H. Hirakawa, *Angew. Chem. Int. Ed.* **2001**, *40*, 2574–2580; c) J. Liu, J. W. Y. Lam, B. Z. Tang, *Chem. Rev.* **2009**, *109*, 5799–5867.

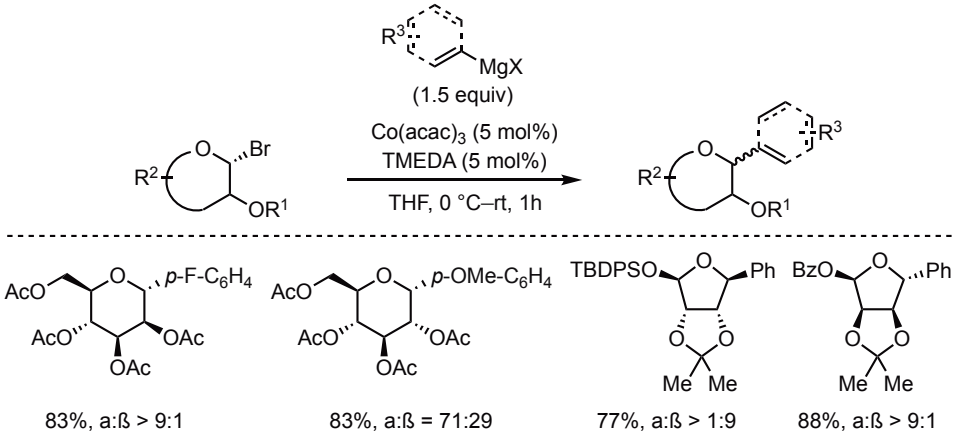
[23] M. Corpet, X.-Z. Bai, C. Gosmini, *Adv. Synth. Catal.* **2014**, *356*, 2937–2942.



Scheme 8 Cobalt-catalyzed cross-coupling of organozinc halides with bromoalkynes.[23]

3 Stereoselective Cobalt-Catalyzed Cross-Couplings

The access to diastereomerically or enantiomericmerically pure products is crucial for the synthesis of many natural products and pharmaceuticals.[3,24] Stereoselective reactions are still challenging and the use of cobalt-salts in those transformations is rare. *Cossy* and co-workers could apply cobalt-catalysis to the formation of anomeric C-C bonds in carbohydrate derivatives (see Scheme 9).[25] $Co(acac)_3$ and TMEDA enabled the diastereoselective cross-coupling



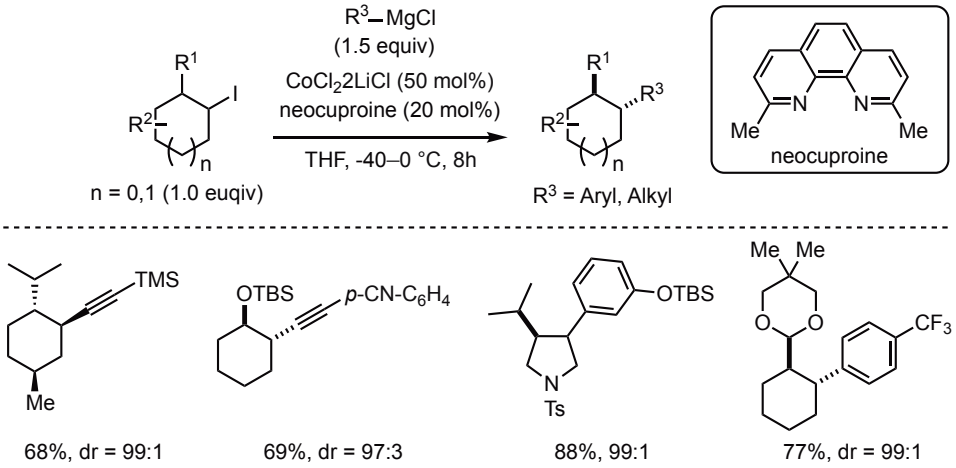
Scheme 9 Diastereoselective cobalt-catalyzed synthesis of C-aryl glycosides and furanosides.[25]

[24] a) V. Yeh, W. A. Szabo in *Applications of Transition Metal Catalysis in Drug Discovery and Development*, John Wiley & Sons, Ltd, Chichester, U.K., **2012**, pp. 165–213; b) *Stereoselective Synthesis of Drugs and Natural Products*, (eds.: V. Andrushko, N. Andrushko), John Wiley & Sons, Inc., Hoboken, **2013**.

[25] a) L. Nicolas, P. Angibaud, I. Stansfield, P. Bonnet, L. Meerpoel, S. Reymond, J. Cossy, *Angew. Chem. Int. Ed.* **2012**, *51*, 11101–11104; b) L. Nicolas, E. Izquierdo, P. Angibaud, I. Stansfield, L. Meerpoel, S. Reymond, J. Cossy, *J. Org. Chem.* **2013**, *78*, 11807–11814.

of 1-bromo glycosides and furanosides with several unsaturated magnesium reagents.[25] The transformation of bromo-mannose and galactose derivatives, proceeded in highly diastereoselective manner. Whereas, the coupling of bromo-galactose turned out to be more challenging, since only α/β ratios of only 75:25 could be reached. The high α-selectivity of this coupling is presumably induced by a radical pathway, including an anomeric radical intermediate, which was confirmed by a cyclization reaction with a radical clock precursor.[25a] Furthermore, under the same conditions diastereoselective cross-couplings of aryl and vinyl *Gringard* reagents with 1-halo furanosides were possible.[25b] In contrast to the coupling with 1-bromo glycosides the diastereoselectivity is only controlled by the substituent present at the C2 position, leading to the thermodynamically more stable 1,2-*trans* product.

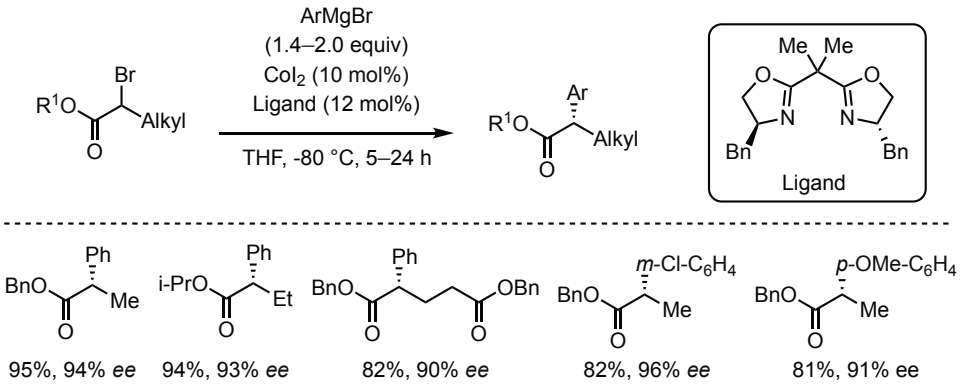
Another diastereoselective protocol utilizing 1,2-substituted systems was reported by *Hammann et al.*[26] A catalytic system comprising $CoCl_2$·LiCl and neocuproine enabled the coupling of various substituted cycloalkyl iodides with aryl and alkynyl *Grignard* reagents with high diastereoselectivity (see Scheme 10).



Scheme 10 Diastereoselective cobalt-mediated cross-couplings of cycloalkyl iodides with alknynyl or aryl *Grignard* reagents.[26]

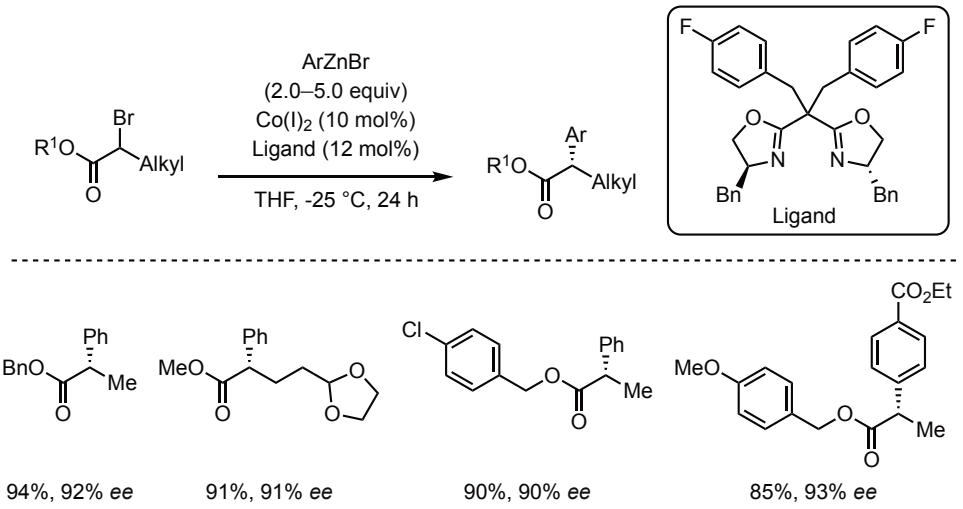
Remarkably, there also have been reported enantioselective protocols using cobalt-catalysis. The group of *Walsh* discovered a catalytic system, consisting of CoI_2 and a bisoxazoline-ligand, which enabled the asymmetric *Kumada* cross-coupling of racemic α-bromo esters with aryl magnesium reagents (see Scheme 11).[27] For this coupling not only the ligand had an effect on the enantioselectivity, but also the choice of the cobalt salt was crucial for the reaction outcome. For example using $CoCl_2$, led to a significantly decreased *ee* of 23%. Under these conditions

[26] J. M. Hammann, D. Haas, C.-P. Tüllmann, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2016**, *18*, 4778–4781.
[27] 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*, 17662–17668.



Scheme 11 Cobalt-bisoxazoline-catalyzed asymmetric *Kumada* cross-coupling of racemic α-bromo esters with aryl magnesium reagents.[27]

a variety of chiral α-aryl alkanoic esters in high enantioselectivity up to 97% *ee* was obtained, which were also transformed into α-arylcarboxylic acids and primary alcohols without significant loss of *ee*. Due to the reactivity of magnesium reagents toward carbonyl groups, the reaction temperature had to be held at -80 °C. To overcome this drawback and also to ensure a higher functional group tolerance, *Liu et al.* switched to arylzinc reagents (see Scheme 12).[28]



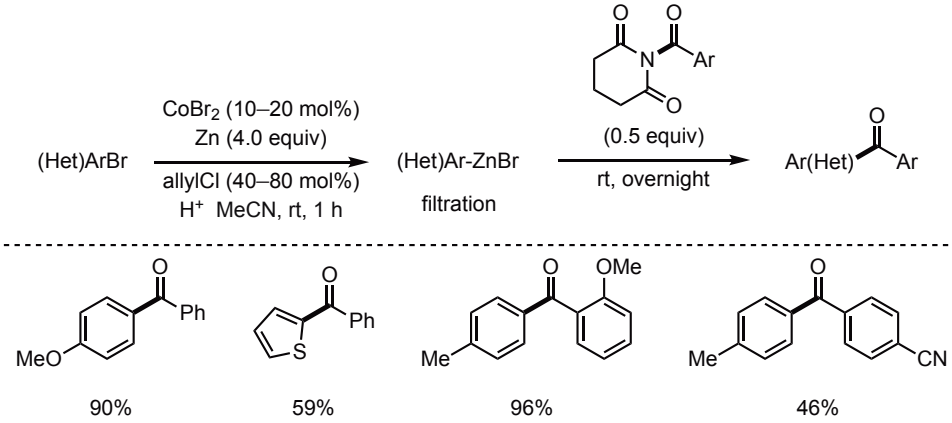
Scheme 12 Cobalt-catalyzed eantioselective *Negishi* cross-coupling of racemic α-bromo esters with arylzinc reagents.[28]

Thus, the reaction temperature could be increased to -25 °C . In addition ester functions in corresponding organometallic reagent could be tolerated. To gain insight into the mechanism, radical clock experiments were performed, which indicated the involvement of radical intermediates.

[28] F. Liu, J. Zhong, Y. Zhou, Z. Gao, P. J. Walsh, X. Wang, S. Ma, S. Hou, S. Liu, M. Wang, M. Wang, Q. Bian, *Chem. – Eur. J.* **2018**, *24*, 2059–2064.

4 Cobalt-Catalyzed Acylation Reactions

The formation of carbon-carbon bonds in the presence of carbonyl moieties using reactive organometallic reagents is often challenging due to a moderate chemoselectivity. Therefore, the usage of less reactive zinc reagents is beneficial.[29] For the synthesis of bisaryl ketones acylation reactions proved to be valuable tools.[29a,30] The group of *Gosmini* developed a range of cobalt catalyzed acylation reactions using aryl zinc reagents with various nucleophiles such as acid chlorides[31] and anhydrides.[32] Moreover, the formation of symmetrical diaryl ketones was discovered by a cross-coupling of *in situ* generated arylzinc bromides with ethyl chloroformate in the presence of $CoBr_2$(bipy) and zinc in acetonitrile.[33] Additionally, the *in situ* generated arylzinc reagents could be coupled with amides, without the need for a ligand, leading to several bis(hetero)aryl ketones in very high yields (see Scheme 13).[34]



Scheme 13 Cobalt-catalyzed diaryl ketone formation of amides with (hetero)arylzinc reagents.[34]

5 Cobalt-Catalyzed C-H Activation

Besides the classical cross-coupling between two polarized carbon bonds, cobalt-catalyzed C-C-bond formations by activation of unpolar C-H bonds are also available. A large number of cobalt-catalyzed C-H activations need high temperatures and proceed between activated C-H bonds and terminal double or triple bonds in the presence of organometallic reagents.[35] *Li et al.*

[29] a) R. Dieter, *Tetrahedron* **1999**, *55*, 4177–4236; b) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540–1552.

[30] D. S. Walter in *Comprehensive Organic Functional Group Transformations*, (eds.: A. R. Katritzky, O. Meth-Cohn, C. W. Rees), Elsevier Science, Oxford, **1995**, pp. 277–312.

[31] H. Fillon, C. Gosmini, J. Périchon, *Tetrahedron* **2003**, *59*, 8199–8202.

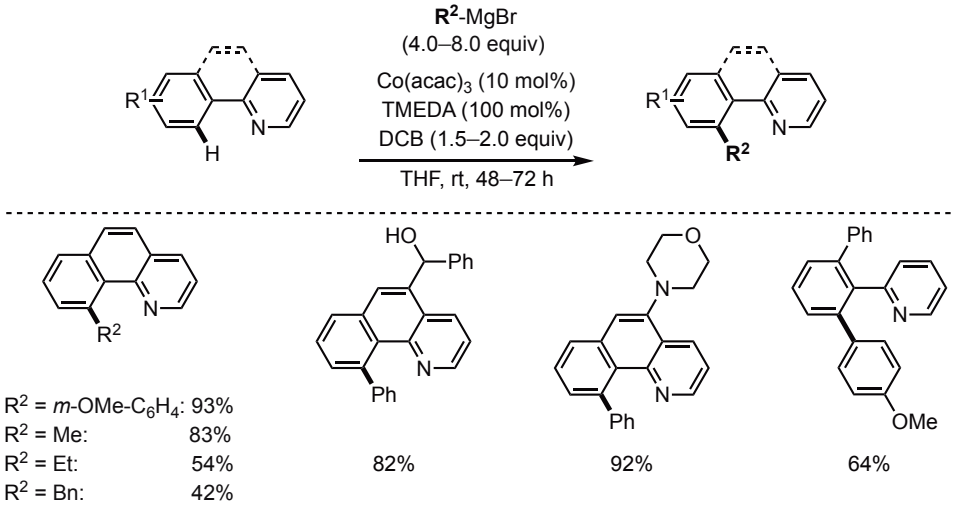
[32] I. Kazmierski, M. Bastienne, C. Gosmini, J.-M. Paris, J. Périchon, *J. Org. Chem.* **2004**, *69*, 936–942.

[33] A. Rérat, C. Michon, F. Agbossou-Niedercorn, C. Gosmini, *Eur. J. Org. Chem.* **2016**, *2016*, 4554–4560.

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

[35] a) K. Gao, P.-S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.* **2010**, *132*, 12249–12251; b) Z. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.* **2012**, *51*, 4698–4701; c) T. Yamakawa, N. Yoshikai, *Tetrahedron* **2013**, *69*, 4459–4465; d) K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2011**, *133*, 400–402; e) W. Xu, N. Yoshikai, *Angew. Chem. Int. Ed.* **2014**, *53*, 14166–14170; f) M. Moselage, J. Li, L. Ackermann, *ACS Catal.* **2016**, *6*, 498–525.

discovered a cobalt-catalyzed C-H activation protocol, by direct coupling of *Grignard* reagents with no need for high temperatures (see Scheme 14).[36] $Co(acac)_3$, TMEDA and DCB facilitate the highly regioselective coupling of aryl and primary alkyl magnesium reagents. However, the coupling of secondary *Grignard* reagents like *i*-PrMgBr led to a mixture of the branched and unbranched product with only 35% yield in total. The additional performance of radical trapping experiments, indicated a mechanism without the involvement of radical intermediates. As the addition of two equivalents of the free radical reagent TEMPO did not lead to an inhibition of the cross-coupling.

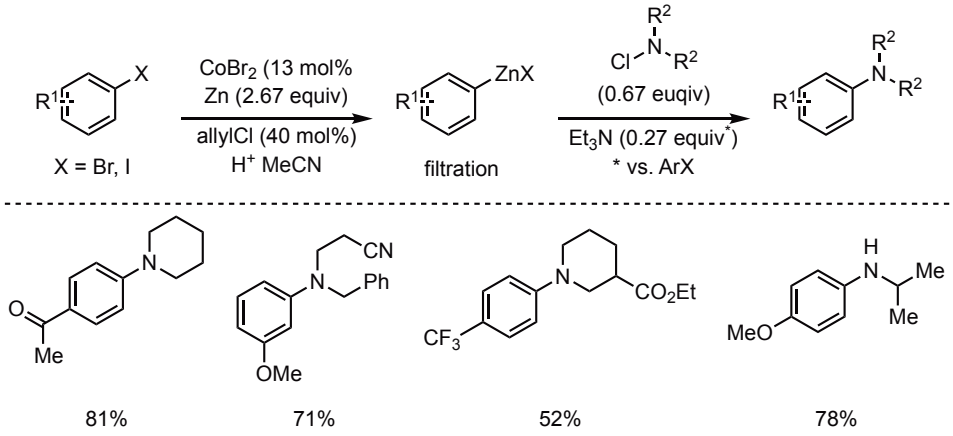


Scheme 14 Cobalt-catalyzed direct cross-coupling of C-H bonds with *Grignard* reagents.[36]

6 Cobalt-Catalyzed Carbon-Heteroatom Bond Forming Reactions

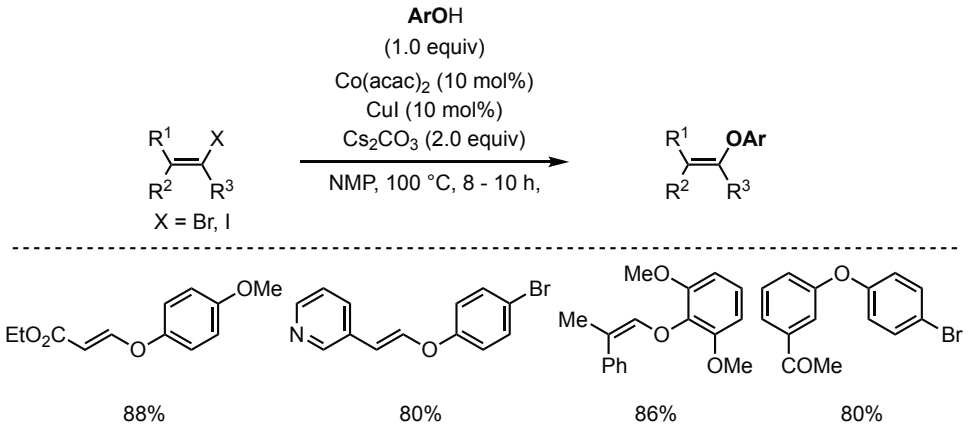
Apart from the construction of carbon-carbon bonds, cobalt catalysis was also applied to the formation of carbon-heretoatom bonds, such as C-O, C-S and C-N bonds. The group of *Gosmini* applied the under cobalt-catalysis generated arylzinc species in electrophilic aminations (see Scheme 15). The arylhalides were either reduced by zinc dust or electrochemically *via* a zinc anode and the corresponding arylzinc reagents could directly be coupled with *N*-chloroamines and required no supplementary addition of cobalt. This protocol allowed the use of secondary and tertiary *N*-chloramines, leading to various aminated aromatics, bearing sensitive functional groups, like esters, nitriles or ketones [37]

[36] B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2011**, *50*, 1109–1113.
[37] X. Qian, Z. Yu, A. Auffrant, C. Gosmini, *Chem. – Eur. J.* **2013**, *19*, 6225–6229.



Scheme 15 Cobalt catalyzed electrophilic amination of arylzinc reagents with *N*-chloramines.[37]

Moreover, cobalt catalysis facilitates the formation of carbon-oxygen bonds.[38] The cross-coupling of phenols with vinyl or aryl halides was enabled by a catalytic system consisting of $Co(acac)_2$ and CuI (see Scheme 16). This combination is crucial for the success of this coupling, in the

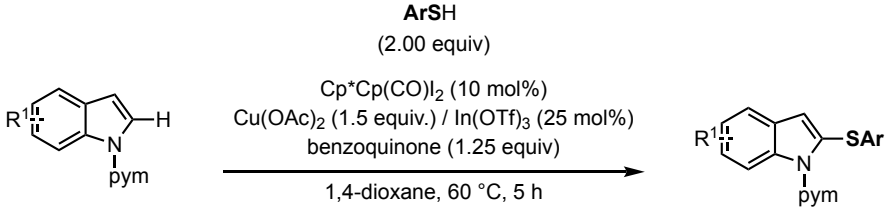


Scheme 16 Cobalt-catalyzed C(sp^2)-O cross-coupling.[38]

absence of one of those components, no product formation was observed. The authors propose a mechanism *via* an aryloxy-copper intermediate, which is then transmetalated to the Co(III) center with the vinyl halide, followed by the reductive elimination, leading to the product.

The homologue higher chalcogen such as thiols undergoes cobalt catalyzed cross-couplings as well. The group of *Glorius* reported in 2016 a dehydrogenative C-H thiolation of indoles (see Scheme 17).[39] Mechanistic studies indicated a pathway, starting with a C-H activation, thiolate transfer, followed by the reductive elimination. Similarly, to the previous reaction with the phenols, copper also plays an essential role in this formation, by forming an active copper-thiolate reagent.

[38] D. Kundu, M. Tripathy, P. Maity, B. C. Ranu, *Chem. – Eur. J.* **2015**, *21*, 8727–8732.
[39] T. Gensch, F. J. R. Klauck, F. Glorius, *Angew. Chem. Int. Ed* **2016**, *55*, 11287–11291.

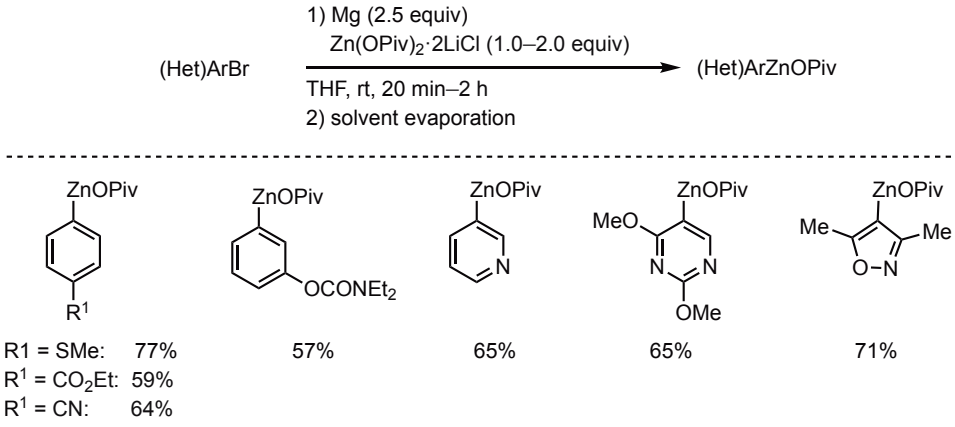


Scheme 17 Cobalt-catalyzed C-H thiolation through dehydrogenative cross-coupling.[39]

7 Preparation of Organozinc Reagents

Organozinc reagents belong to the first organometallic reagents and were discovered in 1848 by *Edward Frankland*.[40] By mixing ethyl iodide with granulated zinc in a sealed glass tube, ethyl zinc iodide and diethyl zinc were generated as a colorless liquid.

From there on a lot of progress has been made and organozinc reagents have found large application in many processes due to their high functional group tolerance combined with a high reactivity.[29,41] Nevertheless, organozinc compounds have one major drawback. They are often highly sensitive to moisture and air, which limits practical use in the laboratory and on an industrial scale. An approach for that problem was made by *Bernhardt et al.* by the synthesis of solid arylzinc pivalates of type $RZnOPiv \cdot MgX_2$.[42] These aryl zinc reagents are prepared from the corresponding bromides in a one pot synthesis using Mg and $Zn(OPiv)_2 \cdot 2LiCl$ (see Scheme 18).



Scheme 18 Preparation of solid functionalized arylzinc pivalates.[42]

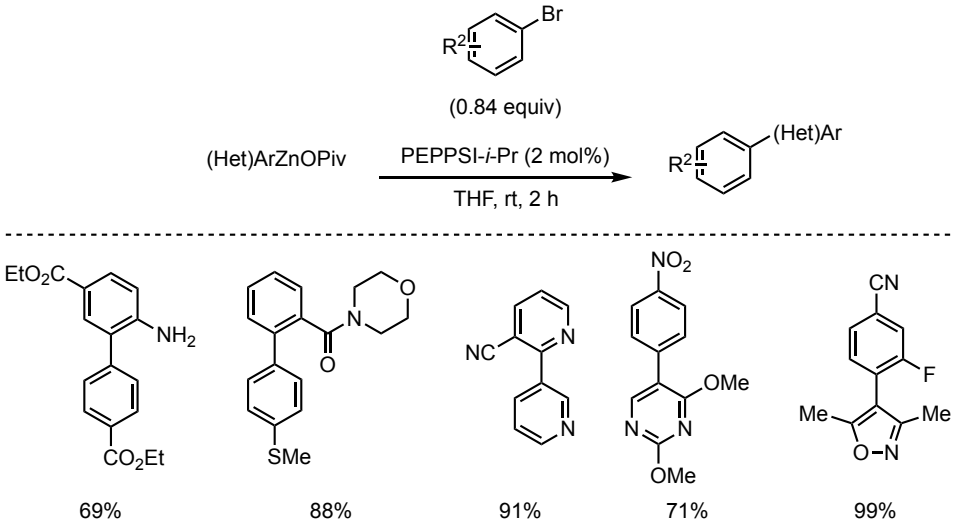
After solvent evaporation the aryl zinc pivalates are obtained as powders with enhanced air and moisture stability. The solid zinc reagents can be weighed under air, with no significant

[40] E. von Frankland, *Liebigs Ann. Chem.* **1849**, *71*, 171–213.

[41] a) T. Harada in *The Chemistry of Organozinc Compounds*, (Hrsg.: I. M. Zvi Rappoport), John Wiley & Sons, Ltd, Chichester, U.K., **2007**, Kap. 15, S. 685–711; b) P. Knochel, H. Leuser, L.-Z. Cong, S. Perrone, F. F. Kneisel in *Handbook of Functionalized Organometallics*, (ed.: P. Knochel), John Wiley & Sons, Ltd, New York, 2008, pp. 251–346; c) P. Knochel, M. I. Calaza, E. Hupe in *Metal-Catalyzed Cross-Coupling Reactions*, John Wiley & Sons, Ltd, New York, **2008**, pp. 619–670; d) A. D. Dilman, V. V. Levin, *Tetrahedron Lett.* **2016**, *57*, 3986–3992.

[42] S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205–9209.

loss of activity and can be stored under argon for more than a month. These arylzinc pivalates also underwent palladium-catalyzed *Negishi* cross-couplings in good to excellent yields (see Scheme 19).



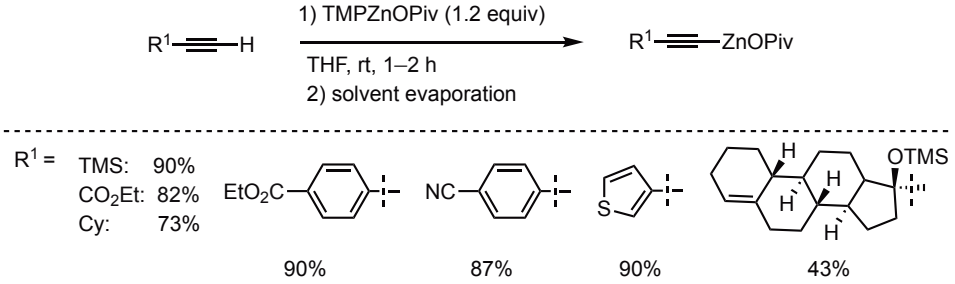
Scheme 19 Palladium-catalyzed *Negishi* cross-coupling of aromatic organozinc pivalates.[42]

A few years later the origin of this enhanced air and moisture stability could be discovered by X-ray crystallographic, NMR and ESI mass spectrometric studies. In fact, the proper writing of these organometallics would be $RZnCl{\cdot}Mg(OPiv)_2{\cdot}LiCl$ and the enhanced stability towards air was explained by the ability of $Mg(OPiv)_2$ to bind H_2O.[43] In the following years a broad range of unsaturated zinc pivalates have been explored and applied to cross-coupling and electrophilic quench reactions,[44] including alkynyl zinc pivalates.[45] *Knochel* and co-workers could generate alkynyl zinc pivalates from terminal alkynes by deprotonation with TMPZnOPiv, a TMP base, which directly introduces a ZnOPiv moiety. This class of unsaturated zinc pivalates showed a high tolerance towards air and moisture (see Scheme 20).

[43] A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey, C. Schnegelsberg, *Angew. Chem. Int. Ed* **2014**, *53*, 2706–2710.

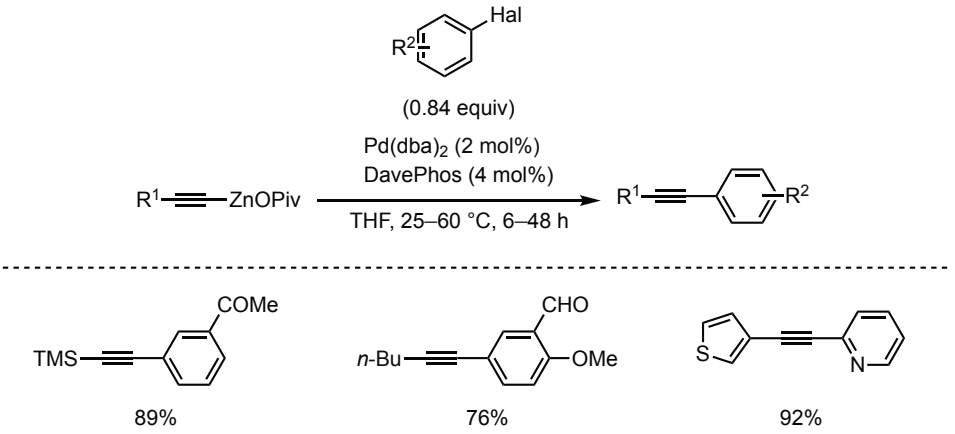
[44] a) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9428–9432; b)S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. – Eur. J.* **2014**, *20*, 12289–12297; c) M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10662–10665; d) Y. Chen, C. Tüllmann, M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 9236–9239; e) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754–5757; f) Y.-H. Chen, M. Ellwart, V. Malakhov, P. Knochel, *Synthesis* **2017**, *49*, 3215–3223.

[45] Y.-H. Chen, C. P. Tüllmann, M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 9236–9239.



Scheme 20 Preparation of functionalized solid alkynylzinc pivalates. The following yields of the zinc pivalates were determined after 4 h under air.[45]

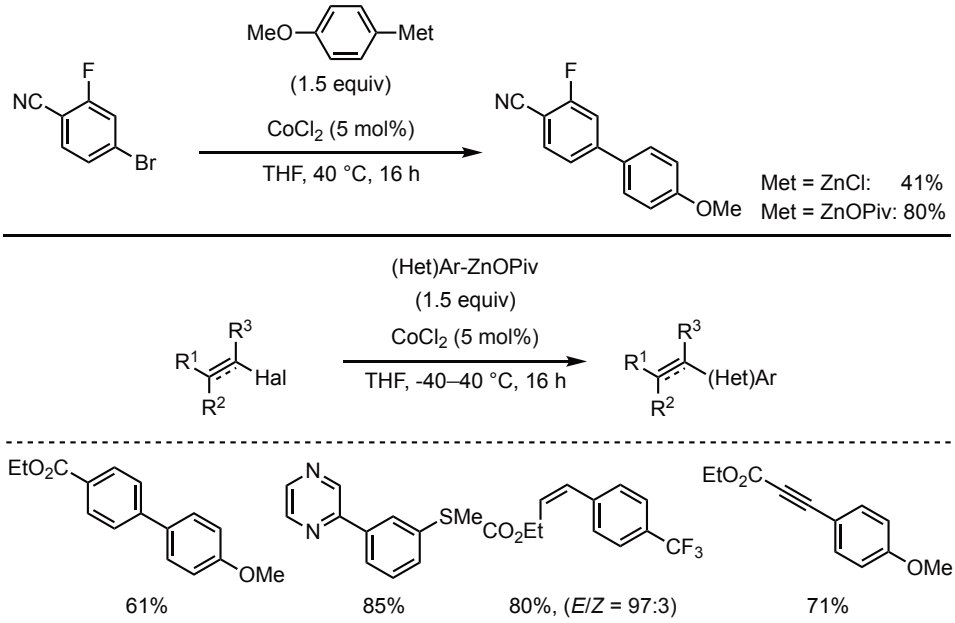
According to the aryl analogs the alkynyl zinc pivalates underwent palladium-catalyzed *Negishi*-type cross-couplings with various aryl halides, leading to functionalized alkynes (see Scheme 21).



Scheme 21 Palladium-catalyzed *Negishi* cross-coupling of alkynylzinc pivalates.[45]

8 Cobalt-Catalyzed Cross-Couplings using Organozinc Pivalates

The advantages of these solid organozinc compounds were used for cobalt-catalysis. *Hammann et al.* reported in 2017 a broadly applicable cobalt-catalyzed cross-coupling of functionalized bench-stable organozinc pivalates with unsaturated halides.[46] Using (4-methoxy-phenyl) zinc pivalate instead of the corresponding arylzinc chloride resulted in almost twice the amount of arylated product (see Scheme 22).

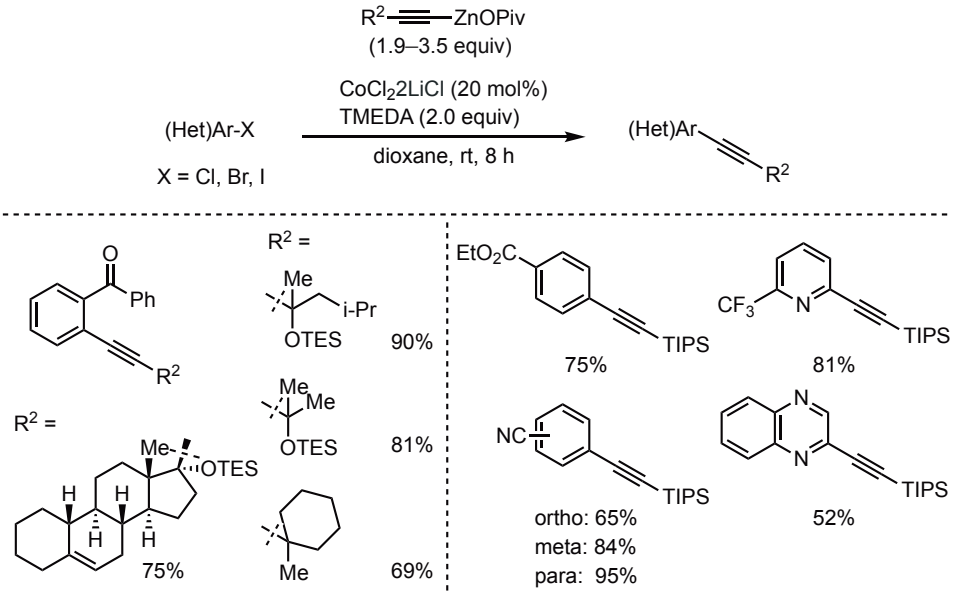


Scheme 22 Cobalt-catalyzed of functionalized organozinc pivalates unsaturated halides.[46]

The utilization of arylzinc pivalates made the additional use of ligands redundant. This protocol not only allows the coupling of aryl halides or heterocyclic halides, but also *cis*-alkene iodides, which proceed in a stereoselective manner and even alkynyl bromides were suitable coupling partners.

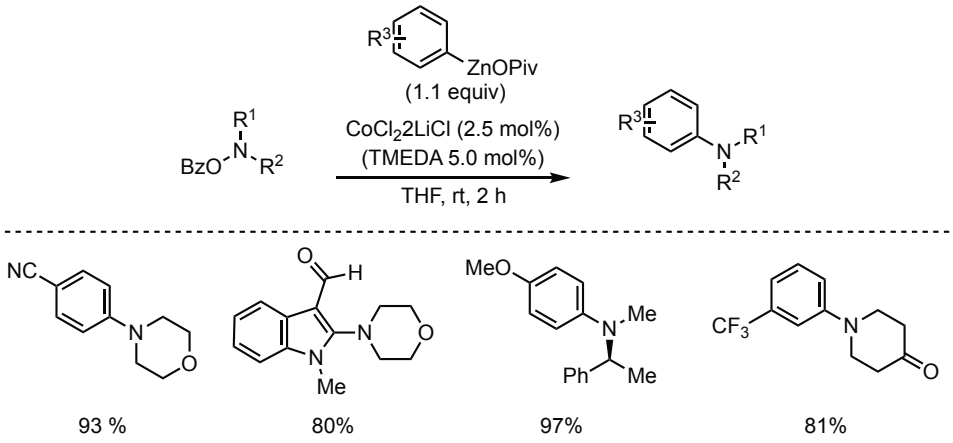
Furthermore, the previous developed alkynylzinc pivalates could also be used in cobalt-catalyzed C(sp)-C(sp)^2-couplings with (hetero)aryl halides as electrophilic coupling partners.[47] A catalytic system consisting of $CoCl_2 \cdot 2LiCl$ and TMEDA enabled the alkynylation of various *N*-heterocycles and aromatics (see Scheme 23). However, the reaction only allowed the coupling of bulky alkynylzinc pivalates.

[46] J. M. Hammann, F. H. Lutter, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 1082–1086.
[47] J. M. Hammann, L. Thomas, Y.-H. Chen, D. Haas, P. Knochel, *Org. Lett.* **2017**, *19*, 3847–3850.



Scheme 23 Cobalt-catalyzed cross couplings of alkynylzinc pivalates with (hetero)aryl and alkenyl halides.[47]

Apart from cobalt-catalyzed carbon-carbon bond formations, also cobalt-catalyzed amination reactions using organozinc pivalates have been discovered.[48] In 2018 *Chen et al.* reported a $CoCl_2 \cdot 2LiCl$ catalyzed electrophilic amination of *O*-benzoylhydroxylamines with various aryl and heteroarylzinc pivalates. Remarkably, under this protocol (hetero)aryl zinc pivalates generated by directed metalation with TMP-bases were suitable coupling partners. The key for the usage of this organometal reagents under cobalt catalysis, was the addition of TMEDA, presumably TMEDA prevents remaining TMP from a coordination with cobalt.



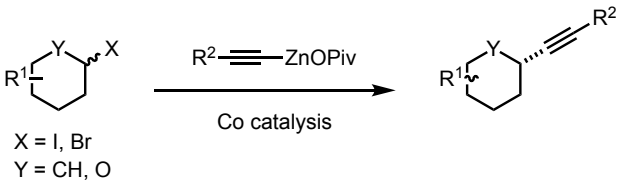
Scheme 24 Cobalt-catalyzed electrophilic amination of (hetero)arylzinc pivalates with *N*-hydroxylamine benzoates.[48]

[48] Y.-H. Chen, S. Graßl, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 1108–1111.

9 Objectives

Organozinc compounds with their unique combination of high tolerance of sensitive functional groups and high reactivity, are valuable organometallic reagents for transition-metal catalyzed cross-couplings.[29,41] Although they have found their way to cobalt-catalyzed cross-coupling reactions, there is still a lack of convenient transformations.[33] Therefore, the aim of this thesis was the development of new cobalt-catalyzed cross-coupling protocols, using zinc organometallics for the synthesis of new small molecules.

Alkynes play an important role in the synthesis of natural products and bioactive molecules, furthermore they are components in functional materials, like polymers, dyes and organic light-emitting diodes (OLEDs).[22,49] Thus, methods for the introduction of the alkynyl unit into organic molecules and especially stereoselective versions are highly desirable. Although stereoselective cobalt-catalyzed cross-couplings using *Grignard* reagents have been reported, no diastereoselective *Negishi*-type reactions are available. In addition, these protocols only gave satisfactory diastereoselectivities for 1,2-substituted systems.



Scheme 25 Cobalt-catalyzed diastereoselective C(sp)-C(sp^3) cross-coupling.

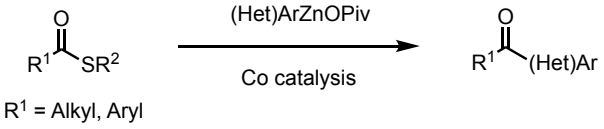
The carbonyl group is a central motif in organic chemistry and a convenient way for the construction of unsymmetrical ketones are acylation reactions.[29a,50] One protocol for the synthesis of functionalized ketones is the *Fukuyama*-coupling, using organothio ester and organozinc halides under palladium catalysis.[51] Due to the high price of palladium a cobalt-catalyzed acylation reaction using organothio esters and air and moisture stable arylzinc pivalates is therefore highly desirable.[52]

[49] a) S. Nakatsuji, K. Nakashima, S. Akiyama, H. Nakazumi, *Dyes and Pigments* **1994**, *24*, 37–57; b) M. Kivala, F. Diederich, *Acc. Chem. Res.* **2009**, *42*, 235–248.

[50] D. S. Walter in *Comprehensive Organic Functional Group Transformations*, (Hrsg.: A. R. Katritzky, O. Meth-Cohn, C. W. Rees), Elsevier Science, Oxford, **1995**, S. 277–312.

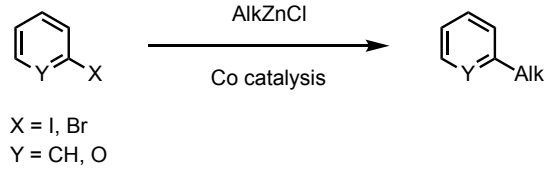
[51] H. Tokuyama, S. Yokoshima, T. Yamashita, T. Fukuyama, *Tetrahedron Lett.* **1998**, *39*, 3189 –3192.

[52] a) World market price for palladium:1,865.37€/ozt, 59.98 €/g, 6383 €/mol and for cobalt: 27,277.82 €/t, 0.027 €/g, 1.59 €/mol, from http://www.infomine.com/investment/metal-prices, retrieved 25. March **2020**; b) This project was developed in cooperation with Ferdinand H. Lutter, see F. H. Lutter, L. Grokenberger, M. S. Hofmayer, P. Knochel, *Chem. Sci.* **2019**, *10*, 8241–8245 and Ferdinand H. Lutter Dissertation, LMU Munich.



Scheme 26 Cobalt-catalyzed *Fukuyama*-type reaction.

Whereas many cobalt-catalyzed cross-couplings for the formation of $C(sp^3)$-$C(sp^2)$ centers focus on the use of unsaturated metallic reagents with alkyl electrophiles, the use of alkyl organometallics is rare, especially the use of alkylzinc reagents.[9] A general method for the coupling of alkylzinc reagents with aryl halides under cobalt catalysis is higly appreciated and also the use of secondary cyclohexyl zinc species for the alkylation of arylhalides in a diastereoselective manner would be desirable.[53]



Scheme 27 Cobalt-catalyzed cross-coupling of alkylzinc reagents.

[53] This project was developed in cooperation with Ferdinand H. Lutter, see F. H. Lutter, L. Grokenberger, P. Spieß, J. M. Hammann, K. Karaghiosoff, P. Knochel, *Angewandte Chemie International Edition* **2020**, *59*, 5546–5550 and Ferdinand H. Lutter Dissertation, LMU Munich.

II RESULTS AND DISCUSSION

1 Cobalt-Catalyzed Diastereoselective Cross-Couplings between Alkynylzinc Pivalates and Functionalized Cyclic Iodides or Bromides

1.1 Introduction

Transition-metal catalyzed diastereoselective cross-couplings represent an excellent way for the stereoselective synthesis of organic molecules.[19c,54] Although palladium-salts have been employed for such stereoselective cross-couplings,[55] the use of alternative, less expensive, and less toxic transition-metals such as iron-salts[56] or cobalt-salts,[9,25,26,57] has recently attracted a lot of attention. In most cross-coupling reactions, organomagnesium reagents, including alkynylmagnesium halides, are the preferred nucleophiles.[26,55e,56e,57c,58] As already previously mentioned, the use of organozinc reagents can be advantageous for such cross-couplings because of the high tolerance of functional groups of these organometallics.[29b] Particularly, the use of organozinc pivalates of the type $RZnOPivMgX_2$[42,44] enables fast and efficient cobalt-catalyzed cross-couplings.[46] *Cheng et al.* reported that alkynylzinc pivalates are readily prepared from

[54] a) S. Chemler, D. Trauner, S. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568; b) D. A. Powell, T. Maki, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 510–511; c) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *Chem. Rev.* **2015**, *115*, 9587–9652.

[55] a) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; b) T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer, P. Knochel, *Nat. Chem.* **2010**, *2*, 125–130; c) T. Thaler, L.-N. Guo, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 2174–2177; d) S. Seel, T. Thaler, K. Takatsu, C. Zhang, H. Zipse, B. F. Straub, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2011**, *133*, 4774–4777; e) C. E. I. Knappke, A. Jacobi von Wangelin, *Chem. Soc. Rev.* **2011**, *40*, 4948–4962; f) L. Li, C.-Y. Wang, R. Huang, M. R. Biscoe, *Nat. Chem.* **2013**, *5*, 607–612.

[56] a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254; b) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500–1511; c) I. Bauer, H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170–3387; For diastereoselective reactions, see: d) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687; e) A. K. Steib, T. Thaler, K. Komeyama, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 3303–3307; f) L. Adak, S. Kawamura, G. Toma, T. Takenaka, K. Isozaki, H. Takaya, A. Orita, H. C. Li, T. K. M. Shing, M. Nakamura, *J. Am. Chem. Soc.* **2017**, *139*, 10693–10701.

[57] a) H. Ohmiya, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 1886–1889; b) H. Ohmiya, H. Yorimitsu, K. Oshima, *Org. Lett.* **2006**, *8*, 3093–3096; c) J. M. Hammann, A. K. Steib, P. Knochel, *Org. Lett.* **2014**, *16*, 6500–6503.

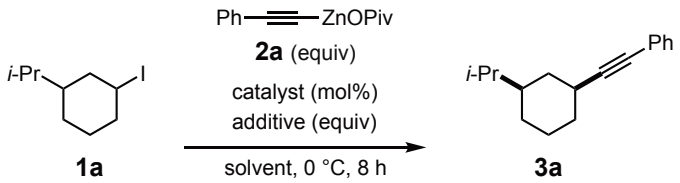
[58] a) T. Hatakeyama, Y. Okada, Y. Yoshimoto, M. Nakamura, *Angew. Chem. Int. Ed.* **2011**, *50*, 10973–10976; b) C. W. Cheung, P. Ren, X. Hu, *Org. Lett.* **2014**, *16*, 2566–2569; c) O. Vechorkin, A. Godinat, R. Scopelliti, X. Hu, *Angew. Chem. Int. Ed.* **2011**, *50*, 11777–11781.

the corresponding alkynes. After solvent evaporation, solid organozinc pivalates are obtained with enhanced air and moisture stability.[45] Also, these organozinc pivalates undergo convenient cobalt-catalyzed cross-couplings with aryl halides and heteroaryl halides.[47]

1.2 Design of the Procedure

In preliminary experiments, 3-isopropylcyclohexyl iodide (**1a**) was treated with 2-phenylethynyl-zinc pivalate (**2a**) at 0 °C under various conditions (see Table 1). First, some low-cost transition-metal salts were tested without any additive or in the presence of TMEDA.[47] However, $NiCl_2$,[58c,59] $MnCl_2$,[60] $FeCl_2$,[56e,58a, 58b] and $CuCl_2$[61] were unsuitable metal catalysts for this coupling (entries 1–8). However, using 20 mol% of $CoCl_2$ and TMEDA as an additive provided **3a** in 67% yield, but with a moderate diastereoselectivity (dr = 85:15, entry 10).

Table 1 Optimization of the reaction conditions for diastereoselective cross-coupling of 1,3-disubstituted cyclohexyl iodode **1a** with alkynylzinc pivalate **2a**.



Entry	Catalyst (Loading [mol%])	Ligand (Amount [equiv])	**2a** [equiv]	Solvent	Yield of **3a**[a] [%]	dr[a]
1	$NiCl_2$ (20)	–	1.5	THF	0	–
2	$NiCl_2$ (20)	TMEDA (2.0)	1.5	THF	0	–
3	$MnCl_2$ (20)	–	1.5	THF	0	–
4	$MnCl_2$ (20)	TMEDA (2.0)	1.5	THF	0	–
5	$FeCl_2$(20)	–	1.5	THF	0	–
6	$FeCl_2$(20)	TMEDA (2.0)	1.5	THF	0	–
7	$CuCl_2$(20)	–	1.5	THF	0	–
8	$CuCl_2$(20)	TMEDA (2.0)	1.5	THF	0	–
9	$CoCl_2$ (20)	–	1.5	THF	5	80:20
10	$CoCl_2$ (20)	TMEDA (2.0)	1.5	THF	67	85:15
11	$CoBr_2$ (20)	TMEDA (2.0)	1.5	THF	11	85:15

[59] a) H. Gong, M. R. Gagné, *J. Am. Chem. Soc.* **2008**, *130*, 12177–12183; b) J. Caeiro, J. Pérez Sestelo, L. A. Sarandeses, *Chem. – Eur. J.* **2008**, *14*, 741–746; c) G. Xu, X. Li, H. Sun, *J. Organomet. Chem.* **2011**, *696*, 3011–3014.

[60] G. Cahiez, C. Duplais, J. Buendia, *Angew. Chem.* **2009**, *121*, 6859–6862.

[61] S. Thapa, B. Shrestha, S. K. Gurung, R. Giri, *Org. Biomol. Chem.* **2015**, *13*, 4816–4827.

Entry	Catalyst (Loading [mol%])	Ligand (Amount [equiv])	**2a** [equiv]	Solvent	Yield of **3a**[a] [%]	dr[a]
12	$CoCl_2$·2LiCl (20)	TMEDA (2.0)	1.5	THF	62	85:15
13	$CoCl_2$ (20)	bipy[b] (2.0)	1.5	THF	2	n.d
14	$CoCl_2$ (20)	neocuproine (2.0)	1.5	THF	38	88:12
15	**$CoCl_2$ (20)**	**Me_4DACH[c] (2.0)**	**1.5**	**THF**	**86 (78)[d]**	**92:8**
16	$CoCl_2$ (20)	Me_4DACH (2.0)	1.5	THF	85[e]	92:8
17	$CoCl_2$ (5)	Me_4DACH (2.0)	1.5	THF	43	92:8
18	$CoCl_2$ (10)	Me_4DACH (2.0)	1.5	THF	58	92:8
19	$CoCl_2$ (30)	Me_4DACH (2.0)	1.5	THF	83	92:8
20	$CoCl_2$ (20)	Me_4DACH (0.5)	1.5	THF	63	92:8
22	$CoCl_2$ (20)	Me_4DACH (1.0)	1.5	THF	63	92:8
23	$CoCl_2$ (20)	Me_4DACH (1.5)	1.5	THF	75	92:8
24	$CoCl_2$ (20)	Me_4DACH (2.0)	1.5	dioxane	86	92:8
25	$CoCl_2$ (20)	Me_4DACH (2.0)	1.5	DME	82	92:8
26	$CoCl_2$ (20)	Me_4DACH (2.0)	1.5	*t*-BuOMe	79	91:9
27	$CoCl_2$ (20)	Me_4DACH (2.0)	1.5	NMP	12	92:8
28	$CoCl_2$ (20)	Me_4DACH (2.0)	1.5	DMPU	15	89:11
29	$CoCl_2$ (20)	Me_4DACH (2.0)	1.5	2-MeTHF	83	91:9
30	$CoCl_2$ (20)	Me_4DACH (2.0)	1.2	THF	76	92:8
31	$CoCl_2$ (20)	Me_4DACH (2.0)	1.8	THF	78	92:8
32	$CoCl_2$ (20)	Me_4DACH (2.0)	2.0	THF	19	92:8
33	$CoCl_2$ (20)	Me_4DACH (2.0)	1.5	THF	56[f]	92:8

[a] Determined by GC analysis. Tetradecane ($C_{14}H_{30}$) was used as internal standard. Reactions were performed on a 0.5 mmol scale. Only the major diastereomer is shown.[b] 2,2'-Bipyridine. [c] *trans-N,N,N',N'*-Tetramethylcyclohexane-1,2-diamine. [d] Isolated yield of analytically pure product. [e] $CoCl_2$ (99.99% purity) was used.[f] The reaction was performed at rt.

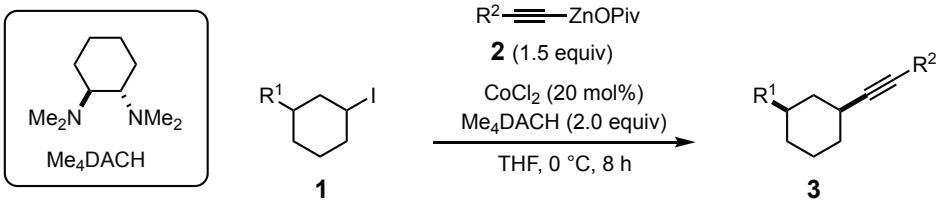
Other cobalt sources, such as $CoBr_2$ or $CoCl_2$·2LiCl, did not have beneficial effects (entries 11–12). The diastereoselectivity was improved by screening various *N*-heterocyclic ligands (entries 13–15). Clearly, *trans-N,N,N',N'*-tetramethylcyclohexane-1,2-diamine (Me_4DACH) gave the best results (entry 15). At this point, it was verified that no other traces of metal contaminations

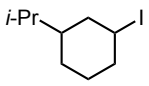
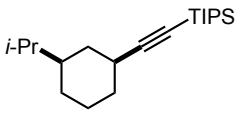
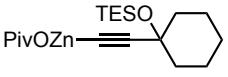
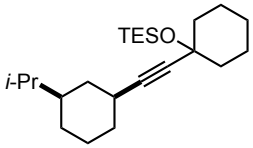
are responsible for this catalysis. Thus, using $CoCl_2$ (99.99% purity) led to **3a** in 85% yield (dr = 92:8, entry 16). With a decrease of the catalyst loading the yield of the coupling product **3a** significantly drops (entries 17–18). Also, a higher catalyst loading did not improve the reaction outcome (entry 19). Furthermore, it was shown that less than 2.0 equivalents of Me_4DACH lead to significantly lower formation of product **3a** (entries 20–23). Varying the solvent system and the amount of the organometallic reagent **2a** did not improve the reaction outcome (entries 24–32).

1.3 Cobalt-Catalyzed Diastereoselective Cross-Couplings of 1,3-Disubstituted Cyclohexyl Iodides

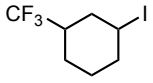
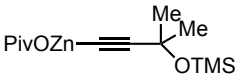
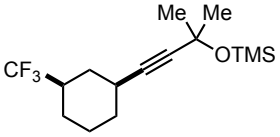
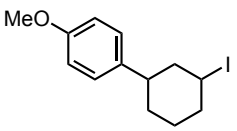
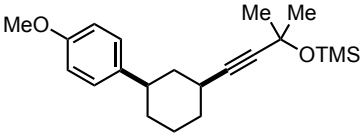
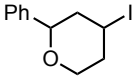
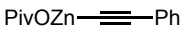
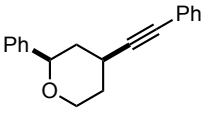
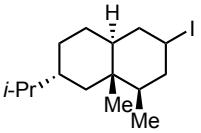
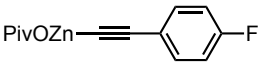
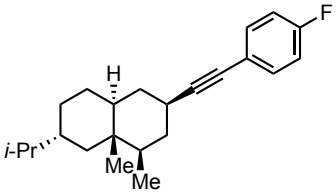
With these optimized reaction conditions in hand, a range of coupling reactions of various alkynylzinc pivalates of type **2** with 1,3-substituted cyclic alkyl iodides of type **1** was performed, furnishing the thermodynamically favored *cis*-isomer **3** (see Table 2).[62] The coupling of **1a** with bulky alkynes, such as zinc pivalates **2b** or **2c**, resulted in the corresponding coupling products (**3b** or **3c**) in 91%–95% yield and high diastereoselectivity (dr = 95:5–98:2, entries 1–2).

Table 2 Cross-coupling of 1,3-disubstituted cyclic (hetero)alkyl halides (**1**) with various alkynylzinc pivalates (**2**).



Entry	Electrophile **1** (dr)	Zinc reagent PivOZn-R **2**	Product **3**: yield[a] (dr)
1	 **1a** (99:1)	 **2b**	 **3b**: 95% (95:5)
2	**1a** (99:1)	 **2c**	 **3c**: 91% (98:2)

[62] The stereochemistry of **3a** and **3b** was confirmed by literature NMR data. See T. Thaler, L.-N. Guo, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 2174–2177.

Entry	Electrophile **1** (dr)	Zinc reagent PivOZn-R **2**	Product **3**: yield[a] (dr)
3	 **1b** (99:1)	 **2d**	 **3d**: 62% (90:10)
4	 **1c** (99:1)	**2d**	 **3e**: 78% (98:2)
5	 **1d** (99:1)	 **2a**	 **3f**: 76% (93:7)
6	 **1e** (85:15)	 **2e**	 **3g**: 60% (94:6)

[a] Isolated yield of analytically pure product. The diastereoselectivity (dr) was determined by GC analysis from the crude mixture.

Also, the propargylic alcohol derivative **2d** was successfully coupled with cyclic iodides bearing a trifluoromethyl **1b** and an aryl group **1c**, providing **3d** and **3e** in 62%–78% yield, respectively, with a diastereomeric ratio of up to 98:2 (entries 3–4). The pyran derivative **3f** was obtained by coupling of the heterocyclic iodide **1d** with **2a** in 76% yield and diastereomeric ratio of 93:7 (entry 5).

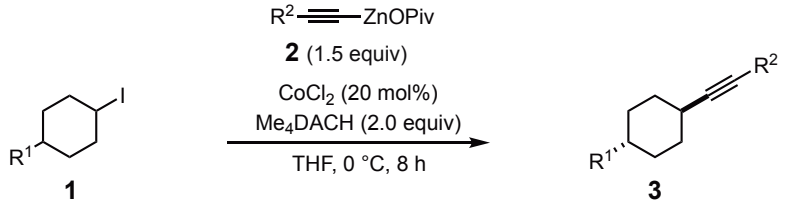
Remarkably, the cross-coupling of iodide **1e**, derived from the natural product (+)-nootkatone,[63] proceeded smoothly with alkynylzinc pivalate **2e**, furnishing **3g** in 60% yield (dr = 96:4, entry 6).

[63] X. Mu, Y. Shibata, Y. Makida, G. C. Fu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5821–5824.

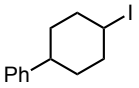
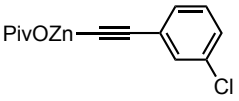
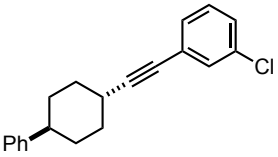
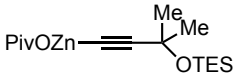
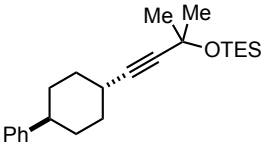
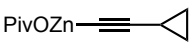
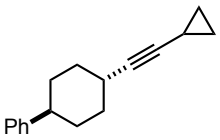
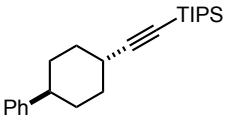
1.4 Cobalt-Catalyzed Diastereoselective Cross-Couplings of 1,4-Disubstituted Cyclohexyl Halides

Furthermore, this cobalt-catalyzed cross-coupling was applied to 1,4-disubstituted cyclohexyl halides, leading to the corresponding *trans*-coupling products (see Table 3).[64] Thus, 4-phenyl cyclohexyl iodide (**1f**) reacted smoothly with various alkynylzinc pivalates (**2f**, **2g**, **2h**, **2b**), resulting in the products **3h**–**3k** in 68%–96% yield (dr = 90:10–99:1, entries 1–4).

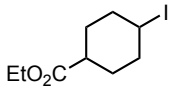
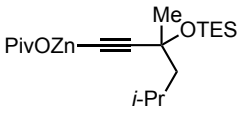
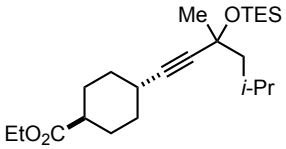
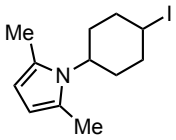
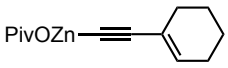
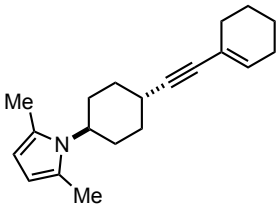
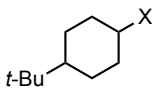
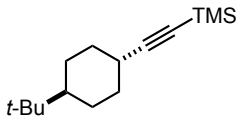
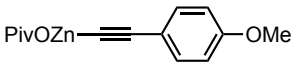
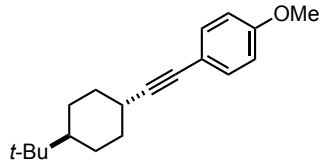
Table 3 Cross-coupling of 1,4-disubstituted cyclohexyl halides (**1**) with various alkynylzinc pivalates (**2**).



1 **3**

Entry	Electrophile **1** (dr)	Zinc reagent PivOZn-R **2**	Product **3**: yield[a] (dr)
			
1	**1f** (92:8)	**2f**	**3h**: 68% (90:10)
			
2	**1f** (92:8)	**2g**	**3i**: 95% (99:1)
			
3	**1f** (92:8)	**2h**	**3j**: 71% (95:5)
			
4	**1f** (92:8)	**2b**	**3k**: 96% (98:2)

[64] The stereochemistry of the product **3o** was determined by crystal structure analysis, see appendix.

Entry	Electrophile **1** (dr)	Zinc reagent PivOZn-R **2**	Product **3**: yield[a]
			
5	**1g** (68:32)	**2i**	**3l**: 71% (90:10)
			
6	**1h** (90:10)	**2j**	**3m**: 83% (95:5)
			
7	**1i**: X = Br (99:1)	**2k**	**3n**: 71% (90:10)
8	**1j**: X = I (99:1)	**2k**	**3n**: 84% (90:10)
			
9	**1j** (99:1)	**2l**	**3o**: 73% (94:6)

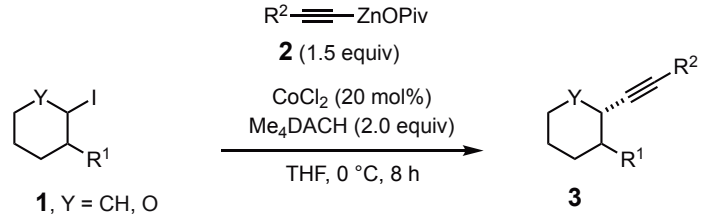
[a] Isolated yield of analytically pure product. The diastereoselectivity (dr) was determined by GC analysis from the crude mixture.

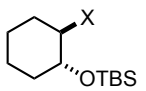
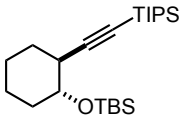
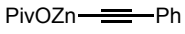
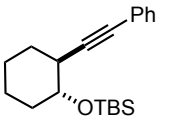
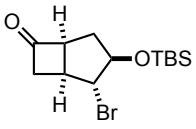
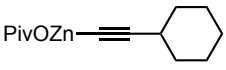
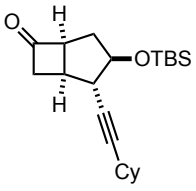
Also, an ester function was tolerated in this cross-coupling reaction and the iodoester **1g** was converted to the *trans*-alkyne **3l** in 71% yield (dr = 90:10, entry 5). Furthermore, pyrrole derivative **1h** was coupled with **2j**, furnishing the *trans*-pyrrole-substituted cyclohexane derivative **3m** in 83% yield and a dr of 95:5 (entry 6). 4-(*tert*-Butyl)cyclohexyl bromide (**1i**) reacts readily with the silylated alkynylzinc pivalate **2k**, leading to the *trans*-1,4-cyclohexane derivative **3n** (71%, dr = 90:10, entry 7). Also, the corresponding cyclohexyl iodide **1j** undergoes such couplings with alkynylzinc pivalates **2k** and **2l**, providing the products **3n** and **3o** in 73%–84% yields and a diastereoselectivity up to 94:6 (entries 8–9).

1.5 Cobalt-Catalyzed Diastereoselective Cross-Couplings of 1,2-Disubstituted Cyclic (Hetero)alkyl Halides

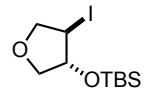
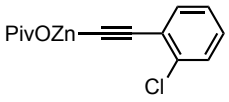
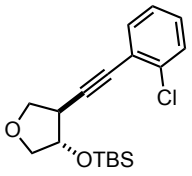
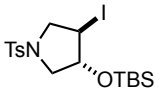
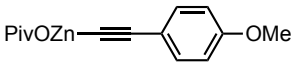
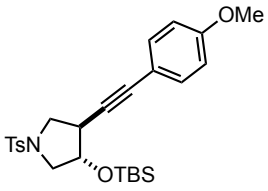
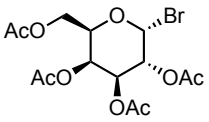
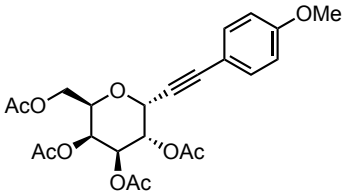
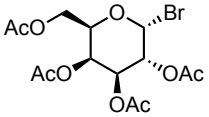
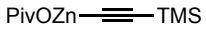
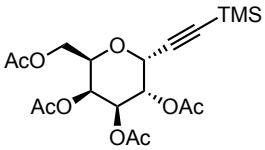
Moreover, this cross-coupling was performed with 1,2-substituted cyclic halides and bromo-glycosides (see Table 4).[56f,25a] TBS-protected iodo- or bromohydrins **1k** and **1l** were successfully coupled with alkynylzinc pivalate **2b**, leading to the thermodynamically preferred *trans*-substituted product **3p** in 60%–78% yield (dr = 99:1, entry 1).[65] Similarly, iodohydrin **1k** reacted with **2a** to give the *trans*-1,2- disubstituted cyclohexane derivative **3q** in 72% yield (dr = 94:6, entry 3). Bicyclic bromide **1m** bearing a ketone moiety was converted to the alkynylated product **3r** in 62% yield (dr = 99:1, entry 4).

Table 4 Cross-coupling of 1,2-disubstituted cyclic (hetero)alkyl halides (**1**) with various alkynylzinc pivalates (**2**)



Entry	Electrophile **1** (dr)	Zinc reagent PivOZn-R **2**	Product **3a**: yield[a] (dr)
			
1	**1k**: X = I (99:1)	**2b**	**3p**: 77%[b] (99:1)
2	**1l**: X = Br (99:1)	**2b**	**3p**: 60% (99:1)
			
3	**1k** (99:1)	**2a**	**3q**: 72% (96:4)
			
4	**1m** (99:1)	**2m**	**3r**: 62% (99:1)

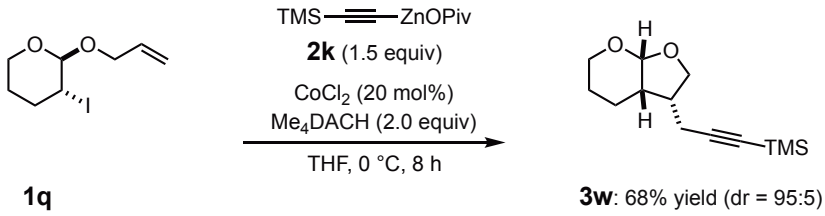
[65] The stereochemistry of **3p** was confirmed by literature NMR data. See J. M. Hammann, D. Haas, C.-P. Tüllmann, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2016**, *18*, 4778–4781.

Entry	Electrophile **1** (dr)	Zinc reagent PivOZn-R **2**	Product **3a**: yield[a]
5	 **1n** (99:1)	 **2n**	 **3s**: 63% (99:1)
6	 **1o** (99:1)	 **2l**	 **3t**: 75% (99:1)
7	 **1p** (99:1)	**2l**	 **3u**: 54% (94:6)
8	 **1p** (99:1)	 **2k**	 **3v**: 52% (95:5)

[a] Isolated yield of analytically pure product. The diastereoselectivity (dr) was determined by GC analysis from the crude mixture. [b] 5 mmol scale.

This cobalt-catalyzed cross-coupling was further extended to five-membered heterocyclic halohydrins **1n** and **1o** (entries 5–6). The coupling of the TBS-protected cyclic iodohydrin **1n** with alkynylzinc pivalate **2n** afforded the substituted tetrahydrofuran **3s** in 63% yield (dr = 99:1, entry 5). Coupling of the iodopyrrolidine derivative **1o** with **2l** afforded the *trans*-1,2-disubstituted heterocycle **3t** in 75% yield and high diastereoselectivity (dr = 99:1, entry 6). Remarkably, this diastereoselective cross-coupling could also be performed using the bromo-glycoside **1p**. Thus, galactose derivative **1p** was successfully cross-coupled under cobalt catalysis with alkynylzinc pivalates **2l** and **2k**, furnishing the α-C-glycosides **3u** and **3v** in 52%–54% yields and high α/β-selectivity (α/β = 94:6–95:5, entries 7–8). The stereochemical outcome of these

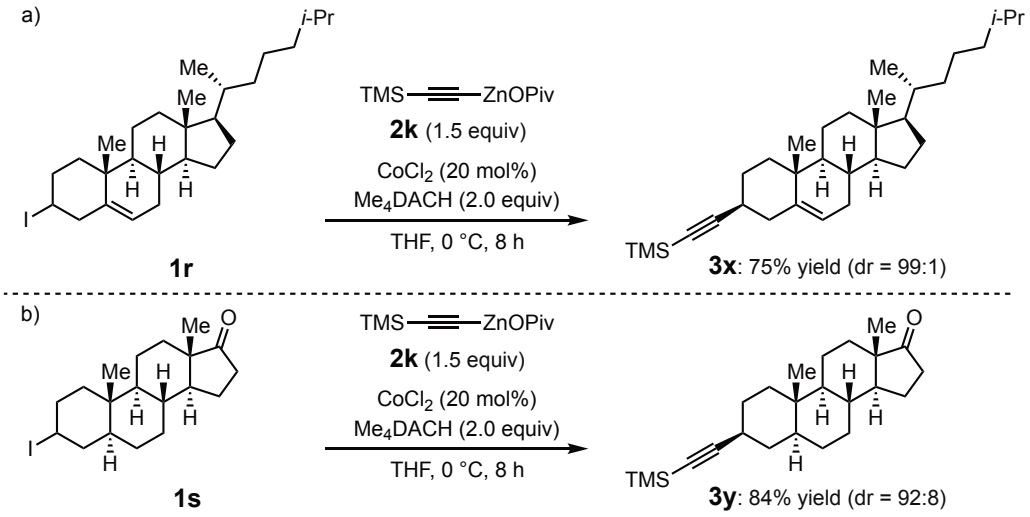
cobalt-catalyzed cross-couplings with bromo-glycosides could be explained with the formation of an anomeric α-radical intermediate.[9b,25a,66] The reaction between the allyl-protected iodohydrin **1q** and the alkynylzinc pivalate **2k** led to the bicyclic product **3w** in 68% yield (dr = 95:5; see Scheme 28).[67] This result indicates a radical pathway for this cross-coupling.



Scheme 28 Diastereoselective cyclization of iodide **1q** with alkynylzinc pivalate **2k**.

1.6 Cobalt-Catalyzed Diastereoselective Cross-Couplings with Steroid Derivatives

Finally, silylated alkynylzinc reagent **2k** was coupled with steroid derivatives (see Scheme 29). The iodinated cholesteryl derivative (**1r**) was succesfully cross-coupled with **2k** leading to the alkynylated steroid derivative **3x** in 75% yield (dr = 98:2, see Scheme 29 a).[68] Remarkably, the use of an iodo-epiandrosterone derivative **1s** containing a ketone moiety also proceeded smoothly in 84% yield affording steroid **3y** (see Scheme 29 b).



Scheme 29 Diastereoselective cross-coupling of steroid derivatives **1r** and **1s** with alkynylzinc pivalate **2k**

[66] a) R. M. Adlington, J. E. Baldwin, A. Basak, R. P. Kozyrod, *J. Chem. Soc., Chem. Commun.* **1983**, 944–945; b) J. Dupuis, B. Giese, D. Rüegge, H. Fischer, H.-G. Korth, R. Sustmann, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 896–898; c) H. Abe, S. Shuto, A. Matsuda, *J. Am. Chem. Soc.* **2001**, *123*, 11870–11882; d) G. Li, D.-C. Xiong, X.-S. Ye, *Synlett* **2011**, *2011*, 2410–2414; e) K. Wakabayashi, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2001**, *123*, 5374–5375; f) K. O. T. Tsuji, H. Yorimitsu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4137–4139.

[67] The stereochemistry of **3w** was determined by NOESY-NMR spectroscopy. See Appendix.

[68] The stereochemistry of **3x** was determined by crystal structure analysis. See Appendix.

2 Cobalt-Catalyzed Acylation-Reactions of (Hetero)arylzinc Pivalates with Thiopyridyl Ester Derivatives

2.1 Introduction

The carbonyl group is a central functionality in organic chemistry and the performance of acylation reactions employing organometallic reagents represents a general access to various ketones.[29a,69] A major drawback of these reactions is the moderate chemoselectivity or the use of expensive catalysts.[29a,69] Acid chlorides are the most common acylation reagents.[29a,31,69,70] However, their preparation requires harsh conditions, thus lowering the functional group tolerance. In contrast, the use of thioesters is a valuable alternative since *Fukuyama* showed in his pioneering work that these acylating reagents react readily with organozinc halides in the presence of a palladium catalyst.[51] Additionally, *Seki*,[71] *Rovis*,[72] *Fleischer*,[73] and others[74] showed that these reactions can be performed using various transition-metal catalysts. Recently, the *knochel* group has shown that organozinc pivalates (RZnOPiv) are an attractive class of zinc organometallics due to their enhanced air- and moisture stability and their excellent compatibility with various transition-metal catalyzed transformations.[42,44,45,75] Especially, cobalt-catalyzed reactions have proven to be advantageous.[46,47,48,76]

2.2 Design of the Procedure

Although most thioesters are readily available from the corresponding acid chlorides and thiols, the thioesters were directly synthesized from caboxylic acids of type **4** using *Mukaiyama's* method[77] into the corresponding thioesters **5** under exceedingly mild and neutral conditions.

[69] D. A. Shirley, *Organic Reactions*, Wiley-VCH, Weinheim, **2011**.

[70] a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117–2188; b) C. K. Reddy, P. Knochel, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1700–1701; c) *Handbook of Functionalized Organometallics*, (Ed.: P. Knochel), Wiley- VCH, Weinheim, **2005**; d) S.-H. Kim, R. D. Rieke, *Tetrahedron Lett.* **2011**, *52*, 1523 –1526.

[71] T. Shimizu, M. Seki, *Tetrahedron Lett.* **2002**, *43*, 1039 –1042.

[72] Y. Zhang, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 15964–15965.

[73] P. H. Gehrtz, P. Kathe, I. Fleischer, *Chem. – Eur. J.* **2018**, *24*, 8774–8778.

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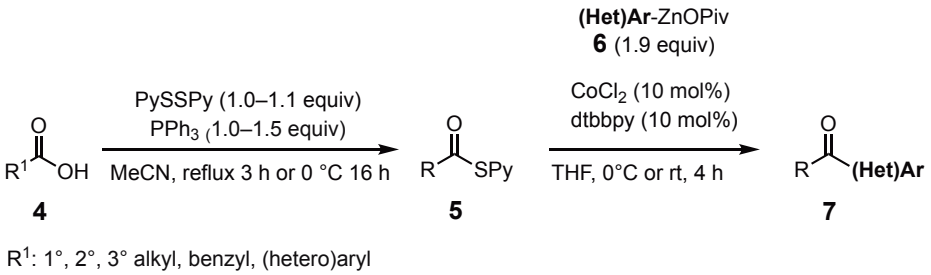
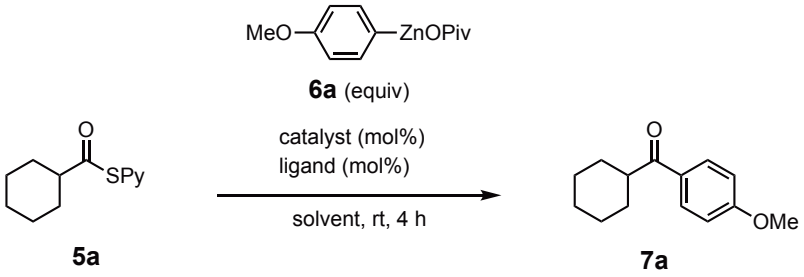


Scheme 30 Preparation of thiolpyridyl ester of type **5** from carboxylic acids **4** and cobalt-catalyzed acylation with organozinc pivalates **6**, affording ketones of type **7**.

In preliminary experiments, *S*-(pyridin-2-yl)-cyclohexanecarbothioate (**5a**) was treated with 4-(methoxyphenyl)zinc pivalate (**6a**) under various conditions (see Table 5). In the absence of a catalyst, ketone **7a** was obtained in only 9% yield (entry 1). Although palladium and nickel are well-known metal catalysts for the *Fukuyama* acylation, the use of cheaper[6e] and more abundant catalysts is highly desirable. Whereas, $MnCl_2$, $CrCl_2$, $FeCl_2$ or $CuCl_2$ gave unsatisfying results (entries 2–5), $CoCl_2$ proved to be an excellent catalyst for this transformation (entry 6). Its catalytic efficiency could be further improved by the addition of various ligands.

Table 5 Optimization of the reaction conditions for the acylation of thioester **5a** with arylzinc **6a**.



Entry	Catalyst (Loading [mol%])	Ligand (Amount [mol%])	Equivalents of **6a**	Solvent	Yield of **7a**[a] [%]
1	–	–	1.5	THF	9
2	$MnCl_2$ (10)	–	1.9	THF	traces
3	$CrCl_2$ (10)	–	1.9	THF	traces
4	$FeCl_2$ (10)	–	1.9	THF	50
5	$CuCl_2$ (10)	–	1.9	THF	29
6	$CoCl_2$ (10)	–	1.9	THF	67
7	$CoCl_2$ (10)	PPh_3 (20)	1.9	THF	63
8	$CoCl_2$ (10)	TMEDA (10)	1.9	THF	64
9	$CoCl_2$ (10)	neocuproine (10)	1.9	THF	49

Entry	Catalyst (Loading [mol%])	Ligand (Amount [mol%])	Equivalents of **6a**	Solvent	Yield of **7a**[a] [%]
10	$CoCl_2$ (10)	bipy[b] (10)	1.9	THF	71
11	**$CoCl_2$ (10)**	**dtbbpy[c]** (10)	**1.9**	**THF**	**90 (88)[d] (87)[e]**
12	$CoCl_2$[f] (10)	dtbbpy (10)	1.9	THF	86
13	$CoCl_2$ (5)	dtbbpy (5)	1.9	THF	81
14	$CoCl_2$ (20)	dtbbpy (20)	1.9	THF	92
15	$CoCl_2$ (10)	dtbbpy (10)	1.5	THF	85
16	$CoCl_2$ (10)	dtbbpy (10)	2.5	THF	87
17	$CoCl_2$ (10)	dtbbpy (10)	1.9	MeCN	89
18	$CoCl_2$ (10)	dtbbpy (10)	1.9	1,4-dioxane	90
19	$CoCl_2$ (10)	dtbbpy (10)	1.9	2-MeTHF	87
20	$CoCl_2$ (10)	dtbbpy (10)	1.9	THF	80[g]
21	$CoCl_2$ (10)	dtbbpy (10)	1.9	THF	80[h]
22	$CoBr_2$ (10)	dtbbpy (10)	1.9	THF	86
23	$Co(acac)_2$ (10)	dtbbpy (10)	1.9	THF	86
24	$Co(acac)_3$ (10)	dtbbpy (10)	1.9	THF	84
25	$CoCl_2$ (10)	dtbbpy (10)	1.9	THF	8[i]
26	$CoCl_2$ (10)	dtbbpy (10)	1.9	THF	53[j]

[a] Determined by GC analysis. Tetradecane ($C_{14}H_{30}$) was used as internal standard. Reactions were performed on a 0.25 mmol scale. [b] 2,2'-Bipyridine. [c] 4,4'-Di-*tert*-butyl-2,2'-dipyridyl.[d] isolated yield. [e] Reaction was performed on a 5 mmol scale. [f] $CoCl_2$ (99.99% purity) was used. [g] The corresponding zinc species with ZnCl was used. [h] The solid zinc pivalate **6a** was weighed out on the bench and added to the reaction mixture under air. [i] The corresponding thioethyl ester RC(O)SEt was used. [j] The corresponding thiophenyl ester RC(O)SPh was used.

After a short screening it became clear that 4,4'-di-*tert*-butyl-2,2'-dipyridyl (dtbbpy) gave the best results leading to the ketone **7a** in 88% isolated yield (entry 11). At this point, it was verified that no other metal contaminations are responsible for this catalysis. Thus, using $CoCl_2$ (99.99% purity) in combination with a new stirring bar and a reaction vessel.[78] led to **7a** in 86% yield (entry 12). Using half the amount of $CoCl_2$ led to a slightly reduced yield (entry 13)

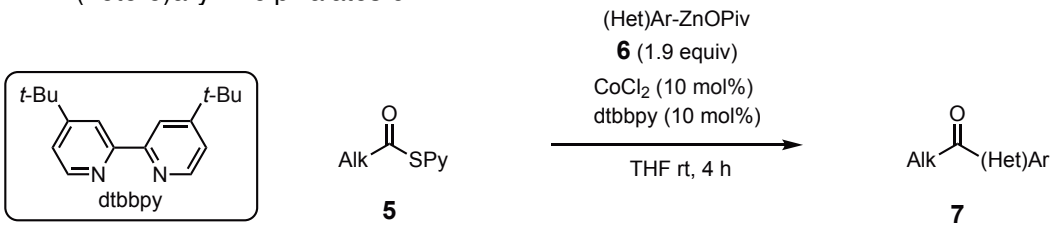
[78] E. O. Pentsak, D. B. Eremin, E. G. Gordeev, V. P. Ananikov, *ACS Catal.* **2019**, *9*, 3070–3081.

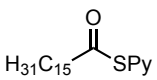
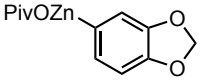
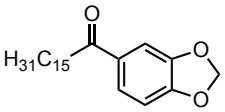
and a higher catalyst loading did not increase the yield significantly (entry 14). A variation of the equivalents of the zinc species (**6a**) resulted in a decrease of the product yield (entries 15–16). Variation of the reaction solvent did not improve the product formation, as MeCN, 1,4-dioxane and 2-MeTHF nearly gave similar yields of product **7a** (87-90% yield, entries 17–19). Also, $CoCl_2$ was superior to other cobalt sources like $CoBr_2$, $Co(acac)_2$ and $Co(acac)_3$ (entries 22–24). Furthermore, a screening revealed that RC(O)SPy thioesters are the preferable acylation reagents, since other thioesters of type RC(O)SEt or RC(O)SPh afforded the product **7a** in 8% or 53% yield (entries 25–26).

2.3 Cobalt-Catalyzed Acylation of Alkylthiopyridyl Esters

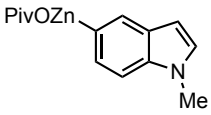
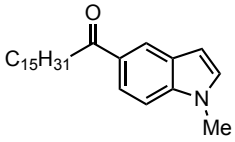
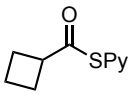
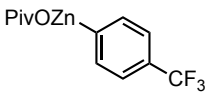
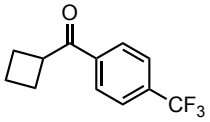
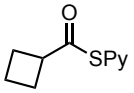
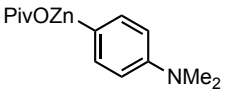
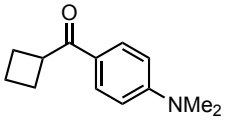
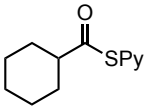
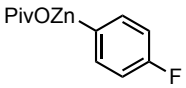
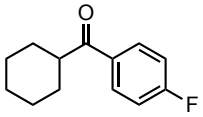
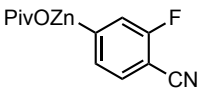
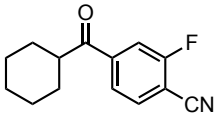
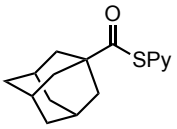
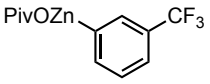
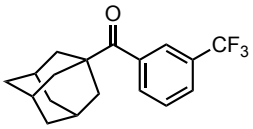
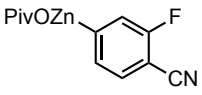
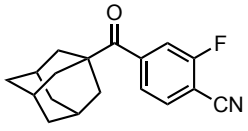
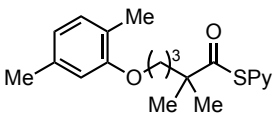
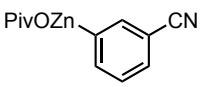
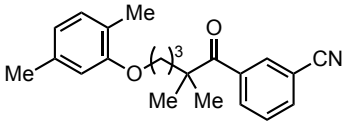
In a typical experiment palmitic acid (**4b**) was treated with 2,2'-dipyridyl disulfide (1.1 equiv) and PPh_3 (1.5 equiv) in acetonitrile (0.3 M) under reflux for 3 h. Purification using flash column chromatography afforded **5b** in 98% yield. The required zinc pivalate **6b** was prepared by treating 1-bromo-3,4-(methylene-dioxy)benzene **8** with Mg (1.2 equiv) and anhydrous LiCl (1.2 equiv) for 2 h at 0 °C leading to the corresponding arylmagnesium derivative (91% yield).[79] Transmetalation with $Zn(OPiv)_2$ (1.0 equiv) afforded the zinc organometallic **6b** in 93% yield.[79] The thioester **5b** reacted with 3,4-(methylene-dioxy)-1-phenylzinc pivalate (**6b**) in the presence of 10% $CoCl_2$ and 10% dtbbpy in THF (25 °C, 4 h) furnishing after standard workup and chromatographic purification the ketone **7b** in 90% yield (see Table 6, entry 1).

Table 6 Ketones of type **7** obtained by acylation of varios alkylthiopyridyl esters **5** with (hetero)arylzinc pivalates **6**.



Entry	Thiopyridyl ester **5**	Zinc reagent PivOZn-R **6**	Product **7**: yield[a]
1	 **5b**	 **6b**	 **7b**: 90%

[79] The yield was determined by iodometric titration, see: A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *2006*, 890–891.

Entry	Thiopyridyl ester **5**	Zinc reagent PivOZn-R **6**	Product **7**: yield[a]
			
2	**5b**	**6c**	**7c**: 74%
			
3	**5c**	**6d**	**7d**: 84%
			
4	**5c**	**6e**	**7e**: 95%
			
5	**5a**	**6f**	**7f**: 60%
			
6	**5a**	**6g**	**7g**: 79%
			
7	**5d**	**6h**	**7h**: 61%
			
8	**5d**	**6g**	**7i**: 81%
			
9	**5e**	**6i**	**7j**: 72%

Entry	Thiopyridyl ester **5**	Zinc reagent PivOZn-R **6**	Product **7**: yield[a]
10	**5e**	**6j**	**7k**: 78%

[a] Reactions were performed on a 0.5 mmol scale. Isolated yield of analytically pure product.

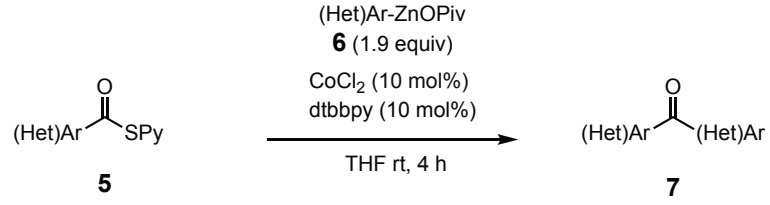
According to this procedure various ketones of type **7** were prepared. Hence, the heterocyclic indolylzinc pivalate (**6c**) was acylated with palmitic *S*-pyridyl thioate (**5b**) furnishing ketone **7c** in 74% yield (entry 2). Additionally, secondary thioesters derived from cyclobutane- (**4a**) and cyclohexanecarboxylic acid (**4a**) were employed to this acylation procedure leading to the corresponding ketones **7d**–**7g** in 60–95% yield (entries 3–6). Tertiary *S*-pyridyl thioesters **5d** and **5e** derived from 1-adamantanecarboxylic acid (**4d**) and the lipid regulating drug gemfibrozil.[80] **4e** reacted smoothly with various functionalized arylzinc pivalates affording acylation products **7h**–**7k** in 61– 81% yield (entries 7–10).

2.4 Cobalt-Catalyzed Acylation of (Hetero)arylthiopyridyl Esters

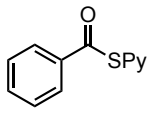
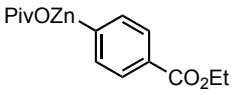
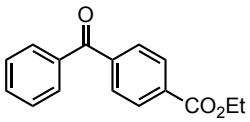
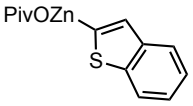
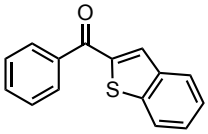
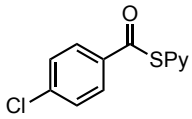
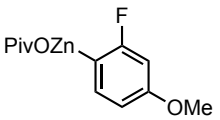
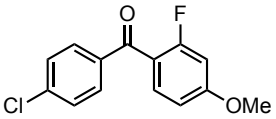
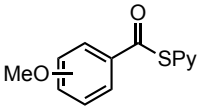
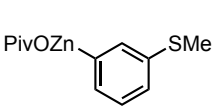
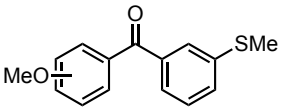
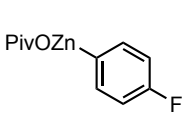
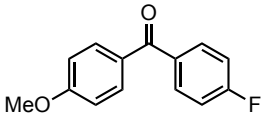
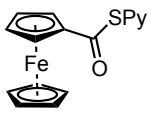
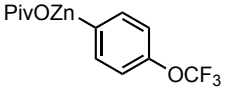
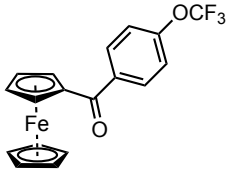
Furthermore, this acylation reaction was extended to aryl- and heteroaryl-*S*-pyridyl thioesters (Table 6). Thus, (4-(ethoxycarbonyl)-phenyl)-zinc pivalate (**6k**) prepared *via* I/Mg- exchange using *i*-PrMgCl·LiCl followed by transmetalation with $Zn(OPiv)_2$[75c] was readily acylated with *S*-pyridyl thioester **5f** affording the benzophenone derivative **7l** in 71% yield (entry 1). Also, 2-benzothiophenylzinc pivalate (**6l**) generated *via* directed metalation of benzothiophene using TMPMgCl·LiCl and subsequent transmetalation with $Zn(OPiv)_2$[75c] underwent a cobalt catalyzed acylation reaction with **5f** leading to the ketone **7m** in 68% yield (entry 2). Various substituted aryl thioesters (**5g**, **5h**) and ferrocenyl (**5i**) derivatives reacted successfully with functionalized (hetero)arylzinc pivalates affording the diaryl ketones **7n**–**7r** in 81–96% yield (entries 3–7).

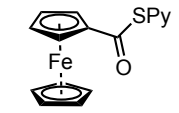
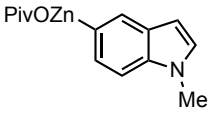
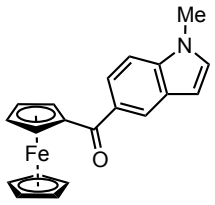
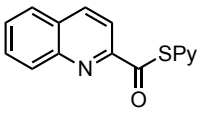
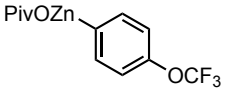
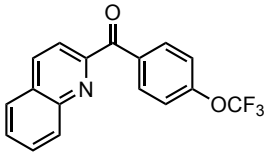
[80] P. A. Todd and A. Ward, *Drugs*, **1988**, *36*, 314–339.

Table 7 Ketones of type **7** obtained by acylation of (hetero)aryl thiopyridyl esters **5** with (hetero)arylzinc pivalates **6**.



5 **7**

Entry	Thiopyridyl ester **5**	Zinc reagent PivOZn-R **6**	Product **7**: yield[a]
			
1	**5f**	**6k**	**7l**: 71%
			
2	**5f**	**6l**	**7m**: 68%[b]
			
3	**5g**	**6m**	**7n**: 92%
			
4	*para*: **5h**	**6n**	*para*: **7o**: 96%
	ortho: **5h**'	**6n**	*ortho*: **7o**': 71%
			
5	**5h**	**6f**	**7p**: 86%
			
6	**5i**	**6o**	**7q**: 81%

Entry	Thiopyridyl ester **5**	Zinc reagent PivOZn-R **6**	Product **7**: yield[a]
7	 **5i**	 **6c**	 **7r**: 84%
8	 **5j**	 **6o**	 **7s**: 68%

[a] Reactions were performed on a 0.5 mmol scale. Isolated yield of analytically pure product. [b] TMEDA was used instead of dtbbpy.

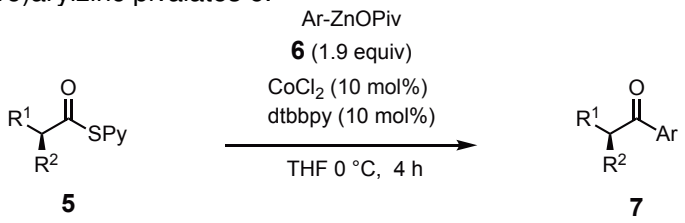
Additionally, 4-trifluoro-methoxyphenylzinc pivalate (**6o**) was acylated using quinoline thioester **5j** furnishing ketone **7s** in 68% yield (entry 8). Unfortunately, *ortho*-functionalized arylzinc pivalates, like (2-(trifluoromethyl)phenyl)zinc pivalate or (2-cyanophenyl)zinc pivalate did not gave satisfactory results. Also, several electron poor *N*-heterocyclic organozinc pivalates, like isoxazol-, pyridazine- and pyrimidine derivatives were unsuitable zinc-reagents in this acylation procedure.

2.5 Cobalt-Catalyzed Acylation of α-chiral Thiopyridyl Esters

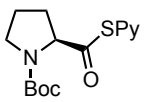
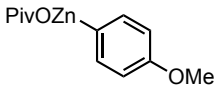
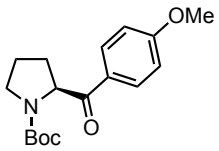
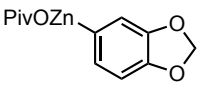
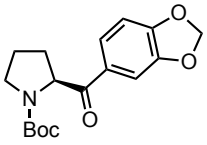
The synthesis of α-chiral ketones is of great interest[51,72,74c,74f,81] but often challenging under basic conditions due to epimerization. Also, reactions under pH-neutral conditions have been reported by *Liebeskind et al.* for the synthesis of highly enantiopure peptidyl ketones.[82]

Also, the applicability of this cobalt-catalyzed acylation to the synthesis of optically enriched α-chiral ketones was tested. Using α-chiral *S*-pyridyl thioesters at 0 °C afforded several α-chiral ketones with high stereoretention (Table 8). Thus, *S*-pyridyl thioester **5k** prepared from *N*-Boc protected (*S*)-proline was treated with arylzinc reagents **6a** and **6b** leading to the corresponding α-chiral ketones (**7t**–**7u**) in 72–82% yield and >99% *ee* (entries 1 and 2). Furthermore, thioester **5l** derived from enantiopure (*S*)-ibuprofen reacted smoothly with the functionalized arylzinc pivalates **6p** and **6n** in 71–89% yield and 94–97% *ee* (entries 3–4).

Table 8 Preparation of α-chiral ketones of type **7** obtained by acylation of thiopyridyl esters **5** with (hetero)arylzinc pivalates **6**.

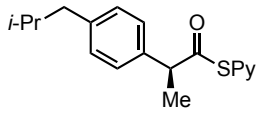
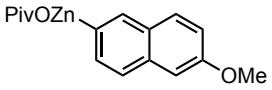
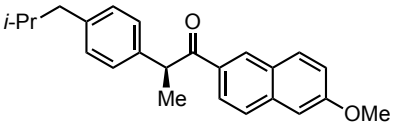
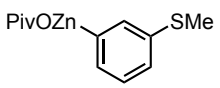
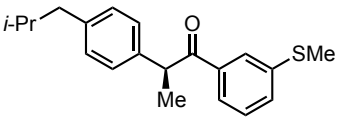
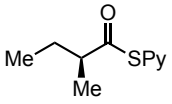
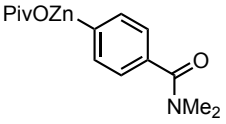
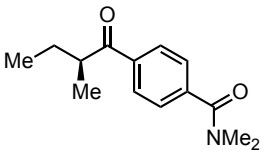
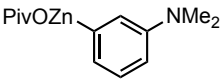
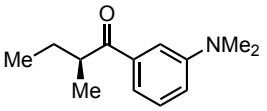


5 **7**

Entry	Thiopyridyl ester **5** (*ee*)	Zinc reagent PivOZn-R **6**	Product **7**: yield[a]
1	 **5k** (>99%)	 **6a**	 **7t**: 72%, >99% *ee*
2	**5k**	 **6b**	 **7u**: 82%, >99% *ee*

[81] a)G. T. Crisp, T. P. Bubner, *Synth. Commun.* **1990**, *20*, 1665–1670, b)G. Cahiez, E. Metais, *Tetrahedron Lett.* **1995**, *36*, 6449 –6452, c)T. Fukuyama, H. Tokuyama, *Aldrichimica Acta* **2004**, *37*, 101–110, d) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc.* **2013**, *135*, 7442–7445, e) R. Oost, A. Misale, N. Maulide, *Angew. Chem. Int. Ed.* **2016**, *55*, 4587–4590.

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

Entry	Thiopyridyl ester **5** (*ee*)	Zinc reagent PivOZn-R **6**	Product **7**: yield[b]
			
3	**5l** (98%)	**6p**	**7v**: 89%, 97% *ee*
			
4	**5l**	**6n**	**7w**: 71%, 94% *ee*
			
5	**5m** (98%)	**6q**	**7x**: 69%, >95% *ee*
			
6	**5m**	**6r**	**7y**: 84%, 98% *ee*

[a] Reactions were performed on a 0.5 mmol scale. Isolated yield of analytically pure product.

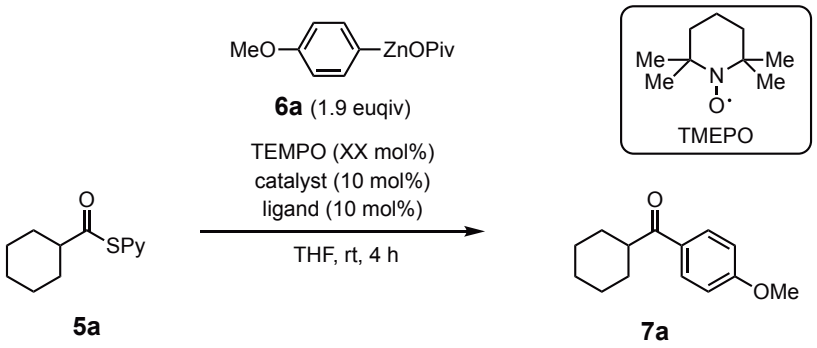
Also, arylzinc pivalates**6q** and **6r** bearing an amide or dimethylamino functionality were acylated using optically pure *S*-(pyridin-2-yl)-(*S*)-2-methylbutanethioate (**5m**) furnishing the α-chiral ketones **7x** and **7y** in 69–84% yield and 95–98% *ee* (entries 5–6).

2.6 Mechanistic Experiments

To gain insights into the reaction mechanism, radical trapping experiments were carried out. Thus, to a standard acylation setup of the developed protocol using *S*-pyridyl thioester **5a** with arylzinc and organozinc pivalate **6a**, various amounts of the radical trapping agent 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) were added (see Table 9). With 10% of the trapping reagent a decrease of the yield by 19% was observed for the acylation product **7a** (entry 2). To ensure, that TEMPO does not react with the arylzinc species, **6a** was stirred with equimolar amounts of TEMPO. Iodolysis of the reaction mixture after 4 h led to 99% of iodinated **6a**, determined using GC-analysis with an internal standard ($C_{14}H_{30}$). However, using 1.5 equivalents

of TEMPO the product formation is almost completely suppressed, affording **7a** on only 6% yield. This may indicate the involvement of radical intermediates within this acylation reaction. Performing the reaction with a Co(I) catalyst led to only a small decrease in yield of product **7a** compared to the corresponding Co(II) catalyst system, this result also supports a radical mechanism (entries (5–6).

Table 9 Optimization of the reaction conditions for the acylation of thioester **5a** with arylzinc **6a**.

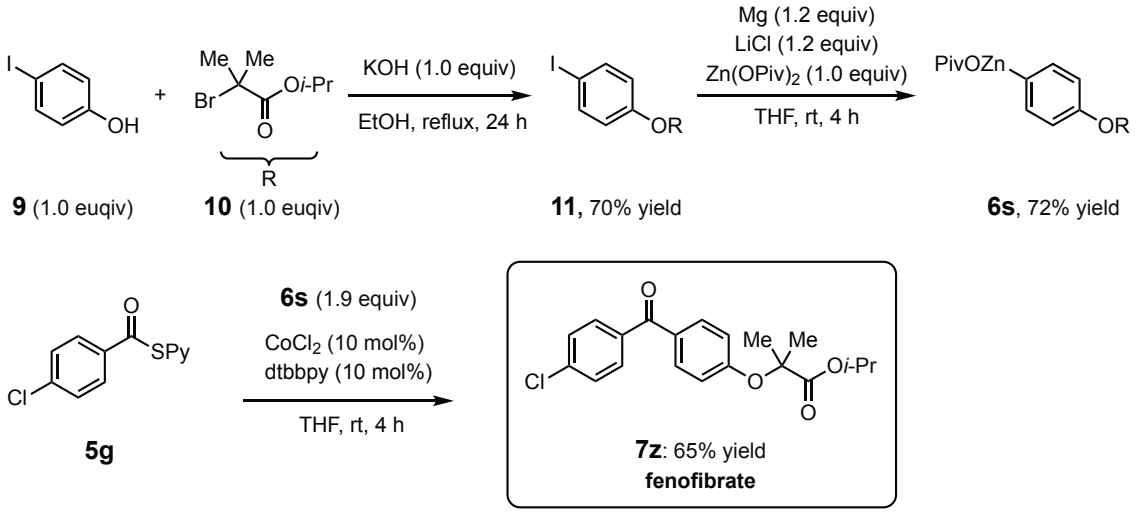


Entry	Catalyst	Ligand	TEMPO [mol%]	Yield of **7a**[a] [%]
1	$CoCl_2$	dtbbpy	0	90
2	$CoCl_2$	dtbbpy	10	71
3	$CoCl_2$	dtbbpy	150	6
4	Co powder	dtbbpy	0	2
5	$CoCl(PPh_3)_3$	-	0	64
6	$CoCl_2(PPh_3)_3$	-	0	73

[a] Determined by GC analysis. Tetradecane ($C_{14}H_{30}$) was used as internal standard. Reactions were performed on a 0.25 mmol scale.

2.7 Synthesis of the Antilipidemic Drug Fenofibrate

The utility of this acylation was demonstrated in the synthesis of the antilipidemic drug fenofibrate[83] (**7z**, Scheme 31). Alkylation of 4-iodophenol (**9**) with isopropyl 2-bromo-2-methyl-propanoate (**10**) affords the corresponding iodoaryl ether **11** in 70% yield. **11** was treated with Mg, LiCl and $Zn(OPiv)_2$ generating the arylzinc pivalate **6s** in 72% yield (see Scheme 31).[42] Using the new cobalt-catalyzed acylation procedure, fenofibrate (**7z**) was obtained in 65% yield.



Scheme 31 Synthesis of fenofibrate (**7z**) using the cobalt-catalyzed acylation.

[83] K. F. C. G. M. Keating, *Drugs* **2007**, *67*, 121–153.

3 Cobalt-Catalyzed Cross-Couplings of Functionalized Alkylzinc Reagents with (Hetero)aryl Halides

3.1 Introduction

The transition-metal catalyzed construction of new C-C bonds is of utmost importance in modern organic chemistry and finds wide application in academic and industrial processes.[84] Especially, *Negishi* cross-couplings are among the most versatile methods for the formation of carbon-carbon bonds to create highly functionalized scaffolds. Albeit, various examples of palladium- [29b,85] or nickel-catalyzed[29b,85e,86] C(sp^2)-C(sp^3) cross-couplings using alkylzinc reagents have been reported, the search for cheaper and more abundant alternative catalytic systems is highly desirable. As already mentioned above, cobalt-salts have been found to display several beneficial characteristics.[9,76c,87] In comparison to palladium, cobalt is a fairly cheap metal and for many transformations no sophisticated ligands are required for an efficient catalysis.[55a,b,87] Cobalt salts are especially well suited catalysts for various types of reactions utilizing organozinc reagents as nucleophilic coupling partners[55a,b,87] including acylations,[31,32,34,88] cross-coupling reactions[12,16,20,21,23,28,34,46,47,76,89]or aminations.[37,48,90]

3.2 Design of the Procedure

In a preliminary experiment, 6-chloronicotinonitrile (**12a**) was treated with (2-(1,3-dioxan-2-yl) ethyl)zinc chloride (**13a**) under various conditions (see Table 10). In the absence of a catalyst, the desired coupling product **14a** could not be detected. Various metal halides such as $MnCl_2$, $CuCl_2$, $FeCl_2$ or $CrCl_2$ were tested. However, no catalytic activity was observed for this cross-coupling (entries 2–5). As expected, $NiCl_2$ was able to catalyze the reaction leading to **14a** in 51% yield

[84] *Modern Drug Synthesis*, (eds. J. J. Li, D. S. Johnson), John Wiley & Sons, Ltd New York, **2010**.

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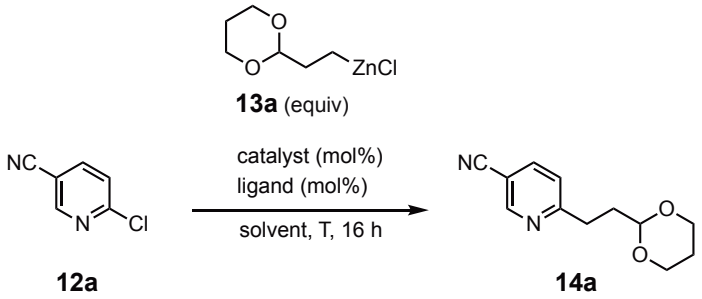
(entry 6). However, $CoCl_2$ also proved to be a suitable catalyst for this transformation affording the desired alkylated heterocycle **14a** in 52% yield (entry 7). Various ligands were tested to further improve the reaction outcome (entries 8–11). Thus, using the unsubstituted 2,2'-bipyridine led to the best coupling yield of 66% (entry 8). Increasing the amount of ligand furnished **14a** in 75% isolated yield (entry 12).

Table 10 Optimization of the reaction conditions for the cross-coupling of **12a** with alkylzinc reagent **13a**.



Entry	Catalyst (Loading [mol%])	Ligand (Amount [mol%])	Equiv of **13a**	Solvent	T [°C]	Yield of **14a**[a] [%]
1	–	–	1.5	THF	0	0
2	$MnCl_2$ (10)	–	1.5	THF	0	0
3	$CuCl_2$ (10)	–	1.5	THF	0	0
4	$FeCl_2$(10)	–	1.5	THF	0	0
5	$CrCl_2$(10)	–	1.5	THF	0	0
6	$NiCl_2$ (10)	–	1.5	THF	0	51
7	$CoCl_2$ (10)	–	1.5	THF	0	52
8	$CoCl_2$ (10)	bipy[b] (10)	1.5	THF	0	66
9	$CoCl_2$(10)	dtbbpy[c] (10)	1.5	THF	0	63
10	$CoCl_2$(10)	neocuproine (10)	1.5	THF	0	65
11	$CoCl_2$(10)	TMEDA (10)	1.5	THF	0	39
12	**$CoCl_2$ (10)**	**bipy (20)**	**1.5**	**THF**	**0**	**80 (75)[e]**
13	$CoCl_2$ (10)[f]	bipy (10)	1.5	THF	0	82
14	$CoBr_2$ (10)	bipy (20)	1.5	THF	0	78
15	$Co(acac)_2$ (10)	bipy (20)	1.5	THF	0	79
16	$Co(acac)_3$ (10)	bipy (20)	1.5	THF	0	71
17	$CoCl_2$ (2.5)	bipy (5)	1.5	THF	0	51
18	$CoCl_2$ (5.0)	bipy (10)	1.5	THF	0	73

Entry	Catalyst (Loading [mol%])	Ligand (Amount [mol%])	Equiv of **13a**	Solvent	T [°C]	Yield of **14a**[a] [%]
19	$CoCl_2$ (20)	bipy (40)	1.5	THF	0	12
20	$CoCl_2$ (10)	bipy (20)	1.2	THF	0	62
21	$CoCl_2$ (10)	bipy (20)	1.7	THF	0	81
22	$CoCl_2$ (10)	bipy (20)	1.5	toluol	0	56
23	$CoCl_2$ (10)	bipy (20)	1.5	MeCN	0	79
24	$CoCl_2$ (10)	bipy (20)	1.5	Et_2O	0	79
25	$CoCl_2$ (10)	bipy (20)	1.5	*t*-BuOMe	0	76
26	$CoCl_2$ (10)	bipy (20)	1.5	THF	-10	65
27	$CoCl_2$ (10)	bipy (20)	1.5	THF	25	65

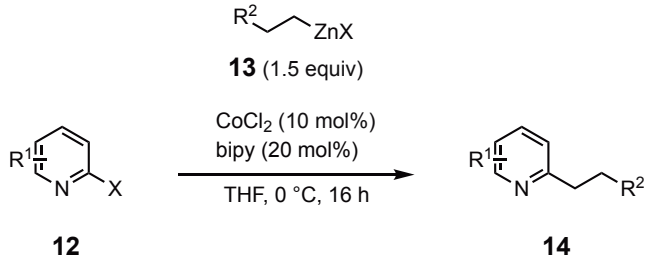
[a] Determined by GC analysis. Tetradecane ($C_{14}H_{30}$) was used as internal standard. Reactions were performed on a 0.25 mmol scale. [b] 2,2'-Bipyridine. [c] 4,4'-Di-*tert*-butyl-2,2'-dipyridyl. [d] 20 mol% of bipy was used.[e] Isolated yield of the reaction performed on a 1.00 mmol scale. [f] $CoCl_2$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

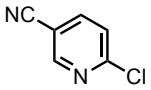
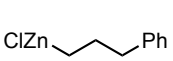
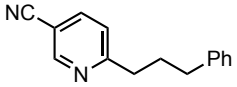
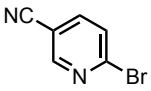
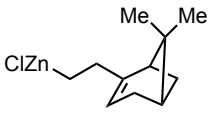
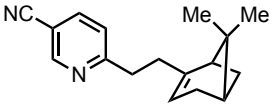
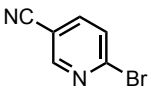
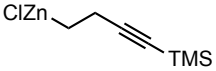
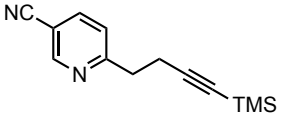
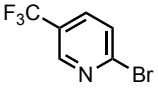
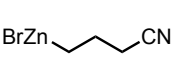
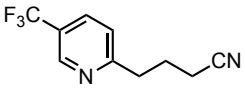
At this point it was verified that no other metal contaminants are responsible for this catalysis. Using $CoCl_2$ (99.99% purity) in combination with a new stirring bar[78] and reaction vessel afforded the pyridine derivative **14a** in 82% yield (entry 13). Variation of the cobalt-species (entries 14–16), catalyst loading (entries 17–19), the amounts of metal species (entries 20–21), reaction solvent (22–25) and the reaction temperature (26–27) did not further improve the yield.

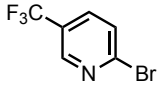
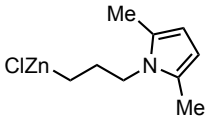
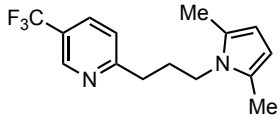
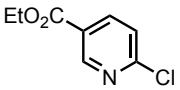
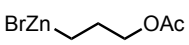
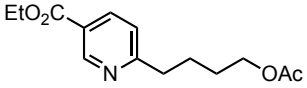
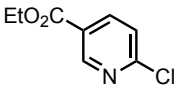
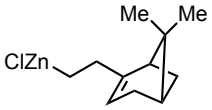
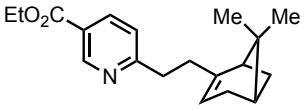
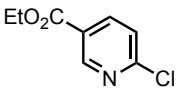
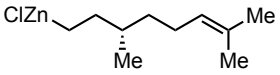
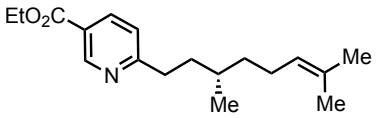
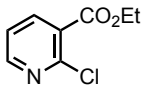
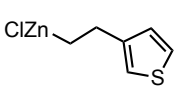
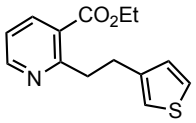
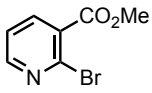
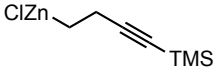
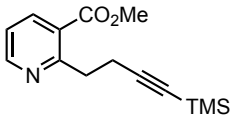
3.3 Cobalt-Catalyzed Cross-Couplings of functionalized Alkylzinc Reagents with Heteroaryl Halides

With these results in hand the scope of this cross-coupling reaction was examined. *N*-hetero-cyclic halides of type **12** were coupled with various functionalized alkylzinc reagents of type **13** (see Table 11). Thus, the reaction of **12a** with (3-phenylpropyl)zinc chloride (**13b**) afforded **14b** in 73% yield (entry 1). Also, the corresponding bromopyridine **12b** was coupled with zinc species **13c**, derived from natural product (1*R*)-(–)-nopol and **13d** bearig a TMS-protected alkyne group led to the coupling products **14c** and **14d** in 62–75% yield (entries 2–3). Several alkylzinc reagents bearing various functional groups were excellent substrates for this cross-coupling.

Table 11 Pyridines of type **14** obtained by cross-coupling of various substituted halopyridines **12** with primary alkylzinc reagents **13**.



Entry	Electrophile **12**	Zinc reagent AlkylZnX **13**	Product **14**: yield[a]
			
1	**12a**	**13b**	**14b**: 73%
			
2	**12b**	**13c**	**14c**: 75%
			
3	**12b**	**13d**	**14d**: 62%
			
4	**12b**	**13e**	**14e**: 87%[b]

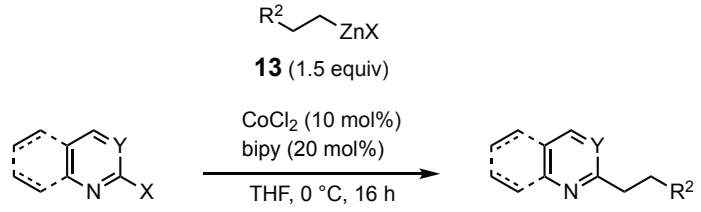
Entry	Electrophile **12**	Zinc reagent AlkylZnX **13**	Product **14**: yield[a]
			
5	**12c**	**13f**	**14f**: 87%
			
6	**12d**	**13g**	**14g**: 66%[b]
			
7	**12d**	**13c**	**14h**: 76%
			
8	**12d**	**13h**	**14i**: 83%
			
9	**12e**	**13i**	**14j**: 78%
			
10	**12f**	**13d**	**14k**: 83%

[a] Reactions were performed on a 0.5 mmol scale. Isolated yield of analytically pure product. [b] 20% $CoCl_2$, 40% dtbbpy and 1.9 equiv of the corresponding alkylzinc reagent were used.

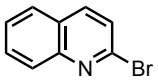
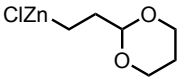
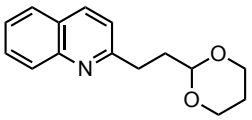
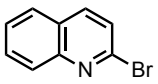
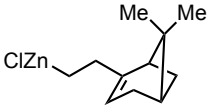
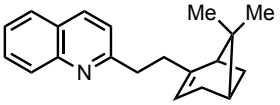
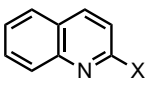
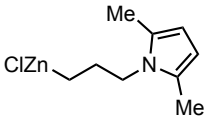
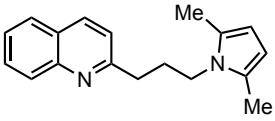
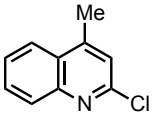
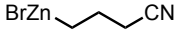
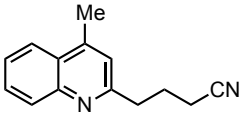
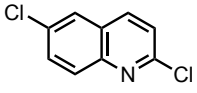
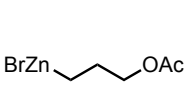
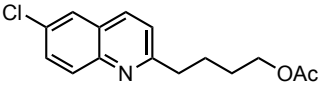
Zinc organometallics containing a nitrile group (**13e**), a pyrrole protected amine (**13f**) or an acetate group (**13g**) were successful substrates in this reaction, furnishing the alkylated pyridines **14e**–**14g** in 66–87% yield (entries 4–6). The reactions of zinc species **13c** and zinc species dervived from (*S*)-citronellol (**13h**) with ethyl 6-chloronicotinate (**12d**) afforded **14h** and **14i** in 76–83% yield (entries 7–8). Also, using 2-halonicotinic esters **12e** and **12g** in combination with zinc reagents bearing a thiophene (**13i**) or an alkyne moiety (**13d**) coupled smoothly leading to **14j** and **14k** in 78–83% yield (9–10).

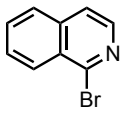
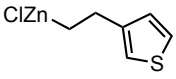
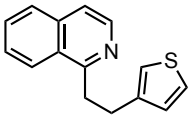
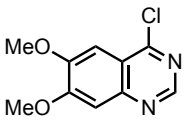
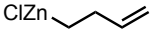
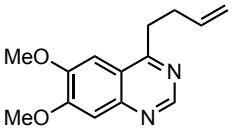
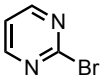
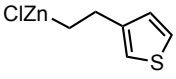
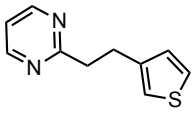
Furthermore, other *N*-heterocyclic halides were suitable electrophiles in this coupling (see Table 12). The reaction of 2-bromoquinoline (**12h**) with zinc species **13a**, **13c** and **13f** lead to quinoline derivatives **14l**, **14m** and **14n** 75–95%yield (entries 1–3). **14n** could also be synthesized starting from the corresponding chloride **12i** in 82% yield (entry 4). Methyl- and chloro-substituted 2-chloroquinolines **12j** and **12k** were alkylated with zinc species **13e** and **13g** affording the quinoline derivatives **14o** and **14p** in 70% and 58% yield (entries 5–6).

Table 12 Products of type **14** obtained by cross-coupling of various substituted *N*-heterocycles **12** with primary alkylzinc reagents **13**.



12 **14**

Entry	Electrophile **12**	Zinc reagent AlkylZnX **13**	Product **15**: yield[a]
1	 **12h**	 **13a**	 **14l**: 95%
2	 **12h**	 **13c**	 **14m**: 75%
3	 **12h**: X = Br	 **13f**	 **14n**: 85%
4	**12i**: X = Cl	**13f**	**14n**: 82%
5	 **12j**	 **13e**	 **14o**: 70%[b]
6	 **12k**	 **13g**	 **14p**: 58%[b]

Entry	Electrophile **12**	Zinc reagent AlkylZnX **13**	Product **14**: yield[a]
			
7	**12l**	**13i**	**14q**: 61%
			
8	**12m**	**13j**	**14r**: 60%
			
9	**12n**	**13i**	**14s**: 71%

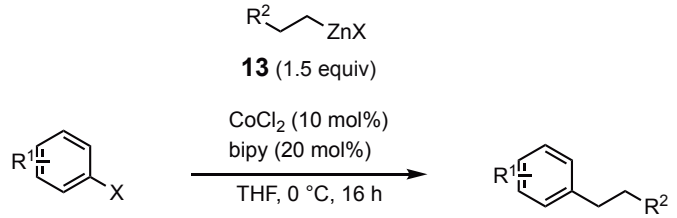
[a] Reactions were performed on a 0.5 mmol scale. Isolated yield of analytically pure product. [b] 20% $CoCl_2$, 40% dtbbpy and 1.9 equiv of the corresponding alkylzinc reagent were used.

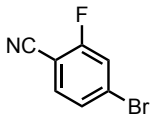
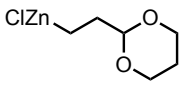
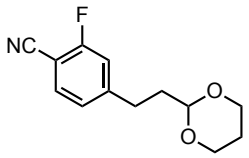
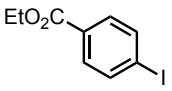
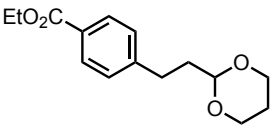
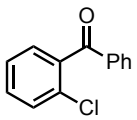
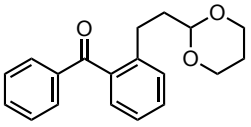
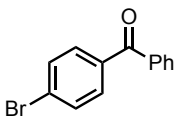
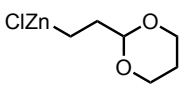
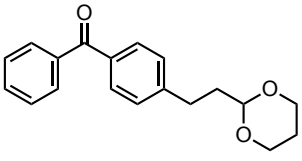
Moreover 2-bromoisoquinoline (**12l**) and (2-(thiophen-3-yl)ethyl)zinc chloride (**13i**) led to **14q** in 61% yield (entry 7). In addition, the coupling of (but-3-en-1-yl)zinc chloride(**13j**) and quinazoline **12m** afforded **14r** in 60% yield (entry 8). Pyrimidine **14s** was obtained in 71% yield by cross-coupling of 2-bomopyriminide (**12n**) and zinc species **13i** in 71% yield (entry 9). However, the reaction with less activated heterocyclic halides like 2-bromopyridine or 2-bromo-6-methoxypyridine led to poor coupling results.

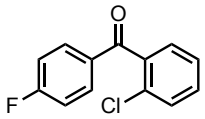
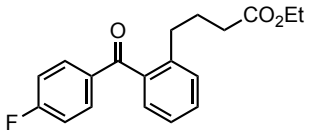
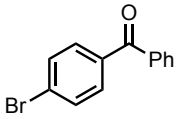
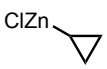
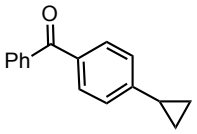
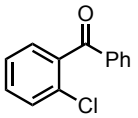
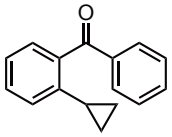
3.4 Cobalt-Catalyzed Cross-Couplings of functionalized Alkylzinc Reagents with Aryl Halides

Next, this cobalt catalyzed cross-coupling was extended to various electron-deficient aryl halides as electrophilic coupling partners (see Table 13). Thus, (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**13a**) was coupled with 4-bromo-2-fluorobenzonitrile (**12o**) and ethyl 4-iodobenzoate (**12p**) furnishing **14t**-**14u** in 66-82% yield (entries 1–2). Benzophenone was successfully alkylated in *ortho*- and *para*-position, respectively, starting from the corresponding halides **12q** and **12r**, leading to **14v** and **14w** in 70–85% yield (entries 3–4).

Table 13 Products of type **14** obtained by cross-coupling of various substituted aryl halides **12** with alkylzinc reagents **13**.



Entry	Electrophile **12**	Zinc reagent AlkylZnX **13**	Product **14**: yield[a]
1	 **12o**	 **13a**	 **14t**: 66%
2	 **12p**	**13a**	 **14u**: 82%[b]
3	 **12q**	**13a**	 **14x**: 70%
4	 **12r**	 **13a**	 **14v**: 85%

Entry	Electrophile **12**	Zinc reagent AlkylZnX **13**	Product **14**: yield[a]
			
5	**12s**	**13k**	**14w**: 73%[b]
			
6	**12r**	**13l**	**14y**: 70%[c]
			
7	**12q**	**13l**	**14z**: 71%[c]

[a] Reactions were performed on a 0.5 mmol scale. Isolated yield of analytically pure product. [b] 20% $CoCl_2$, 40% dtbbpy and 1.9 equiv of the corresponding alkylzinc reagent were used.

[c] Dtbbpy was used instead of bipy. The reaction was performed at rt.

The cross-coupling of zinc reagent **13k** containing an ester moiety with fluoro functionalized chlorobenzophenone **12s** led to **14y** in 73% yield (entry 5). Also, cyclopropylzinc chloride **13l** was used in this procedure, affording the benzophenones **14y** and **14z** in 70–71% yield (6-7).

3.5 Diastereoselective Cobalt-Catalyzed Cross-Couplings of functionalized Alkylzinc Reagents with Heteroaryl Halides

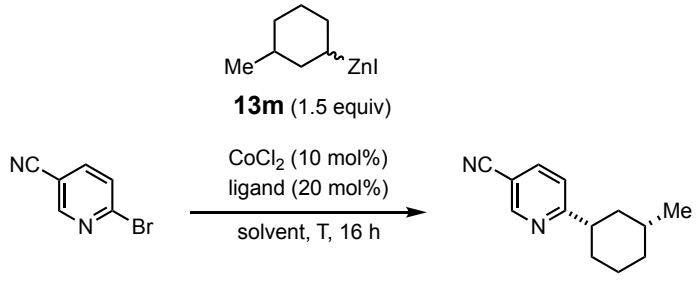
Encouraged by the results with the secondary cyclopropylzinc reagent **13l**, the cross-coupling of various substituted six-membered cycloalkylzinc reagents was examined. In the past, several diastereoselective Csp^3-Csp^2 *Negishi*-type cross-couplings using palladium[55b-d, 91] and nickel salts[92] have been reported. Also, a cobalt-catalyzed version applying bis-arylzinc reagents is

[91] a) P. Knochel, C. Diène, *Comptes Rendus Chimie* **2011**, *14*, 842 –850; b) R. J. Mycka, S. Duez, S. Bernhardt, J. Heppekausen, P. Knochel, F. F. Fleming, *J. Org. Chem.* **2012**, *77*, 7671–7676; c) K. Moriya, P. Knochel, *Org. Lett.* **2014**, *16*, 924–927.

[92] a) H. Gong, M. R. Gagné, *J. Am. Chem. Soc.* **2008**, *130*, 12177–12183; b) H. Gong, R. Sinisi, M. R. Gagné, *J. Am. Chem. Soc.* **2007**, *129*, 1908–1909.

known.[20] However, this methodology only allows the coupling of 1,2-substituted cycloalkyl iodides with (hetero)aryl zinc reagents in a diastereoselective manner. To overcome this limitation, the problem was approached by using substituted cycloalkylzinc species with heteroaryl halides as coupling partners. Previous studies have shown that the carbon-zinc bond is prone for epimerization in the presence of metal salts.[55b,c] Thus, a highly diastereoselective cross-coupling is only enabled by a fast transmetalation of the thermodynamically more stable alkylzinc species to the transition-metal catalyst.[55b] To evaluate the scope of a diastereoselective cross-coupling using substituted cyclohexylzinc reagents, 2-methylcyclo-hexylzinc iodide (**13m**) was coupled with 6-bromonicotinonitrile (**12b**) (see Table 14). A short screening revealed that a catalytic system of 10% $CoCl_2$ and 20% 4,4'-di-*tert*-butyl-2,2'-dipyridyl in acetonitrile led to the best yield and diastereomeric ratio (entry 7).

Table 14 Optimization of the reaction conditions for the cross-coupling of **12b** with alkylzinc reagent **13m**.



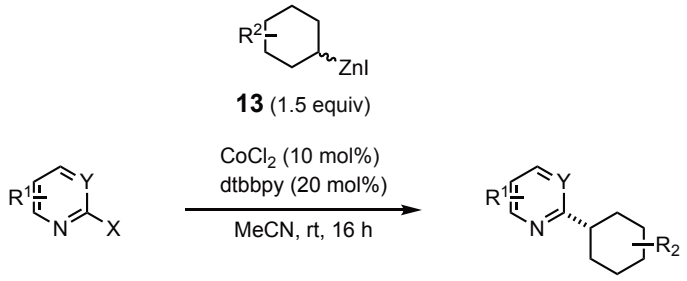
12b **14aa**

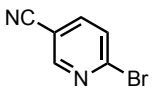
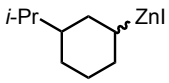
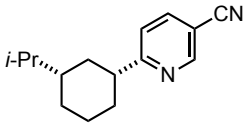
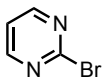
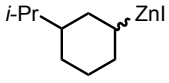
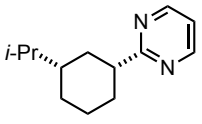
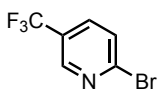
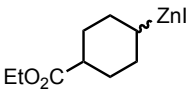
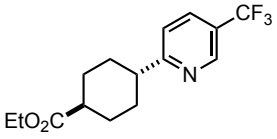
Entry	Ligand	T [°C]	Solvent	dr	Yield of **14aa**[a] [%]
1	-	rt	THF	40:60	13
2	neocuproine	rt	THF	69:31	6
3	bipy[b]	rt	THF	91:9	33
4	bipy	0	THF	91:9	24
5	dtbbpy[c]	rt	THF	90:10	28
6	bipy	rt	MeCN	79:21	81
7	**dtbbpy**	**rt**	**MeCN**	**91:9**	**85 (80)[d]**

[a] Determined by GC analysis. Tetradecane ($C_{14}H_{30}$) was used as internal standard. Reactions were performed on a 0.25 mmol scale.[b] 2,2'-Bipyridine. [c] 4,4'-Di-*tert*-butyl-2,2'-dipyridyl.[d] Isolated yield of analytically pure product.

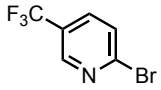
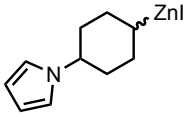
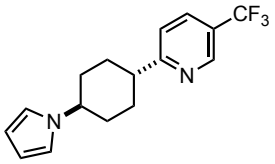
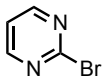
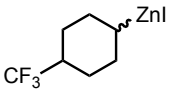
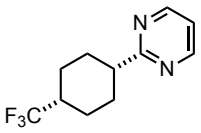
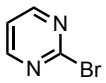
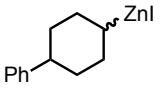
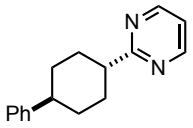
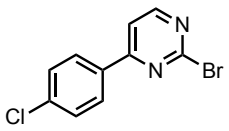
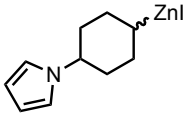
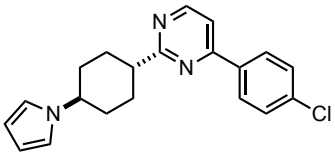
Hence, the coupling of various 1,3-, and 1,4-functionalized cycloalkylzinc reagent with *N*-heterocyclic bromides was examined (see Table 15). The reaction of bromide **12b** with 3-methylcyclohexylzinc iodide (**13m**) led to the thermodynamically more stable *cis*-1,3-disubstituted cyclohexane **14aa** in 80% yield and diastereoselectivity of 91:9 (see Table 15, entry 7). However, using the corresponding zinc reagent **13n** bearing the bulkier *iso*-propyl residue led to **14ab** in 63% yield and an improved diastereomeric ratio of 96:4 (see Table 15, entry 1). Additionally, this zinc reagent was coupled with pyrimidine **12t** furnishing **14ac** (52% yield, dr = 94:6[93]) (entry 2). Also, 1,4-substituted cyclohexylzinc reagents could be used in this protocol.

Table 15 Products of type **14** obtained by diastereoselective cross-coupling of various substituted pyridyl halides (**12**) with 1,3- and 1,4-substituted secondary alkylzinc reagents (**13**).



Entry	Electrophile **12**	Zinc reagent AlkylZnI **13**	Product **14**: yield[a] (dr)
			
1	**12b**	**13n**	**14ab**: 63% (96:4)
			
2	**12t**	**13n**	**14ac**: 52% (94:6)
			
3	**12c**	**13o**	**14ad**: 51% (80:20)

[93]The stereochemistry of **14ac** was determined by NOESY-NMR spectroscopy, see Appendix.

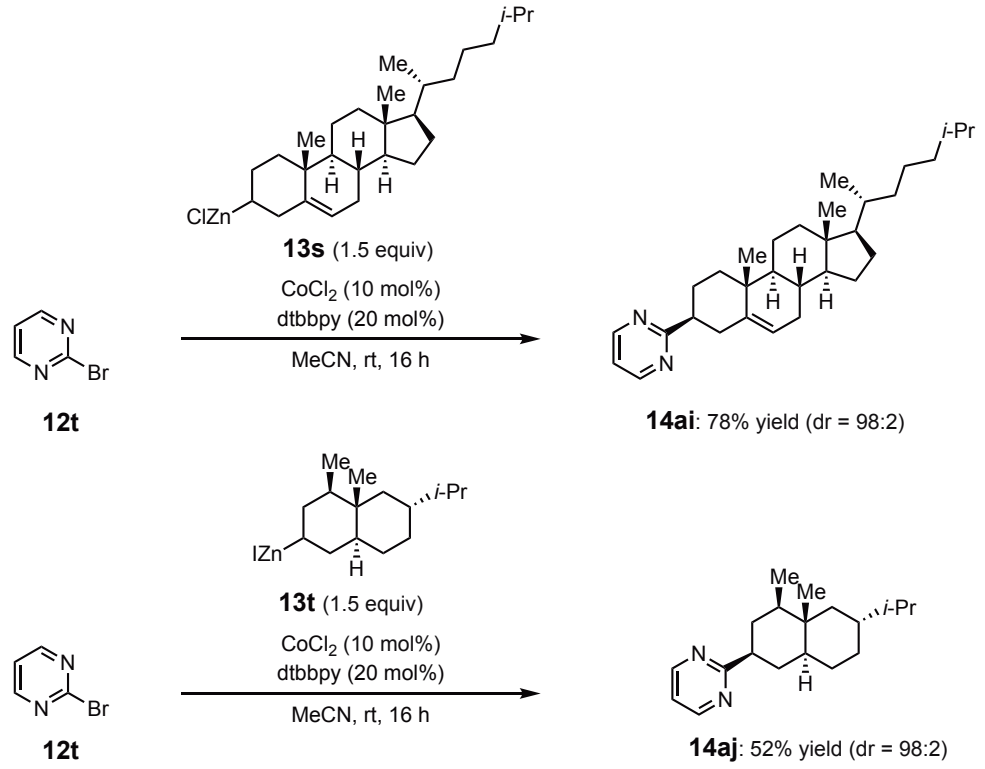
Entry	Electrophile **12**	Zinc reagent AlkylZnI **13**	Product **14**: yield[a]
			
4	**12c**	**13p**	**14ae**: 54% (98:2)
			
5	**12t**	**13q**	**14af**: 73% (98:2)
			
6	**12t**	**13r**	**14ag**: 67% (96:4)
			
7	**12u**	**13p**	**14ah**: 64% (91:1)

[a] Reactions were performed on a 0.5 mmol scale. Isolated yield of analytically pure product. The major diastereomer is shown. [b] 20% $CoCl_2$, 40% dtbbpy and 1.9 equiv of the corresponding alkylzinc reagent were used. [c] Dtbbpy was used instead of bipy. The reaction was performed at rt.

Thus, the cross-coupling of zinc reagents bearing an ester (**13o**) or a pyrrole (**13p**) substituent with trifluoromethylated bromopyridine **12c** led to the corresponding *trans*-1,4-bifunctionalized cyclohexanes **14ad** and **14ae** in 51-54% yield (dr = 80:20–98:2,[94] entries 3–4). Bromopyrimidine (**12t**) could also be coupled with 1,4-substituted cyclohexylzinc iodides **13q** and **13r** affording the functionalized cyclohecyl reagents **14af** and **14ag** in 54–73% yield and 96:4–98:2 dr (entries 5–6). Additionally, the 2-bromopyrimidine derivative **12u** was cross-coupled with zinc species **13p** leading to the polyfunctional pyrimidine **14ah** in 64% yield and 91:1 dr (entry 7).

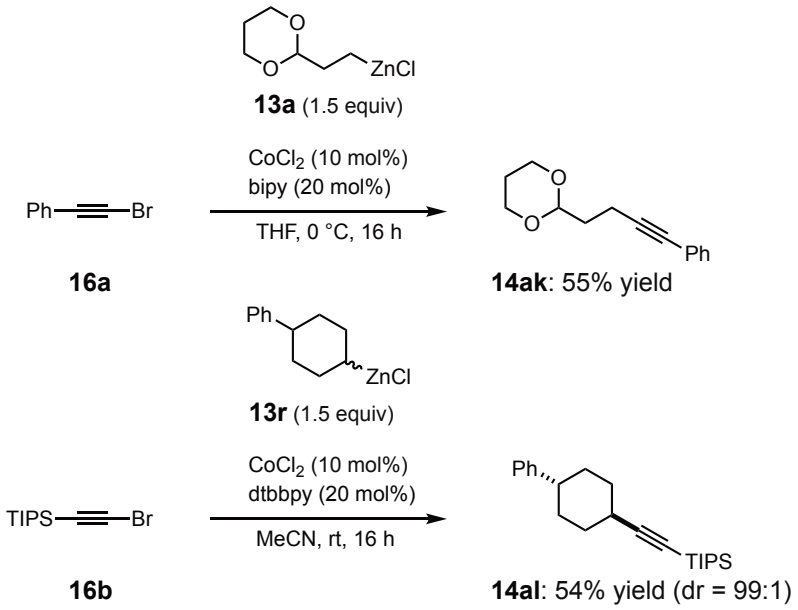
[94] The stereochemistry of **14ae** was determined by crystal structure analysis, see Appendix.

Remarkably, 2-bromopyrimidine (**12t**) could be coupled with complex alkylzinc reagents prepared from steroid and sesquiterpene derivatives (see Scheme 32). The reaction of cholesterylzinc chloride **13s** with 2-bromopyrimide (**12t**) furnished **14ai** in 78% yield and a diastereomeric ratio of 98:2. Also, the corresponding coupling using zinc reagent **13t** derived from a reduced nootkaton derivative proceeded in a highly diastereoselective fashion leading to **14aj** in 52% yield (dr = 98:2).



Scheme 32 Cobalt-catalyzed diastereoselective cross-coupling of **12t** with zinc organometallics **13s** and **13t** derived from cholesterol and nootkatone. The major diastereomers are shown.

Finally, this cobalt-catalyzed cross-coupling was further extended to alkynyl bromides (see Scheme 33). (Bromoethynyl)-benzene (**16a**) reacted smoothly with alkylzinc chloride **13a** affording the alkylated alkyne **14ak** in 55% yield. Interestingly, the coupling of the TIPS protected alkyne **16b** with the 1,4 phenyl substituted cyclohexylzinc reagent **13r** furnished the 1,4-*trans*-alkynylated cyclohexane derivative **14al** in 54% yield and dr = 99:1.



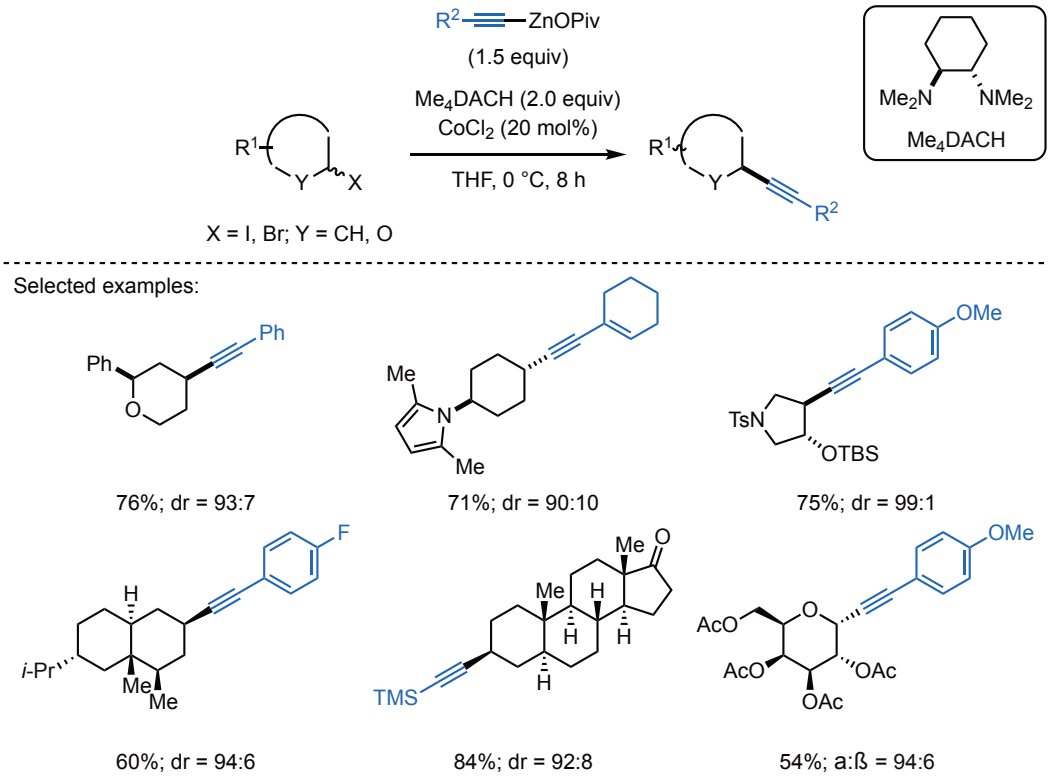
Scheme 33 Cobalt-catalyzed cross-coupling of alkynyl bromides with primary and secondary alkylzinc reagents.

To gain an insight into the reaction mechanism, radical-trapping experiments using 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) were performed. Previous studies and as we have seen in chapter 2.5 TEMPO is able to significantly inhibit cobalt-catalyzed reactions, which might indicate an involvement of radical intermediates within the course of this reaction.[25a] Thus, to a standard coupling setup of **12a** with **13a** 2.0 equivalents of TEMPO were added. However, the coupling product **14a** was obtained in comparable yield to the standard conditions, without the radical trapping agent. This indicates that this new cobalt-catalyzed cross-coupling might not proceed *via* radical intermediates.

4 Summary

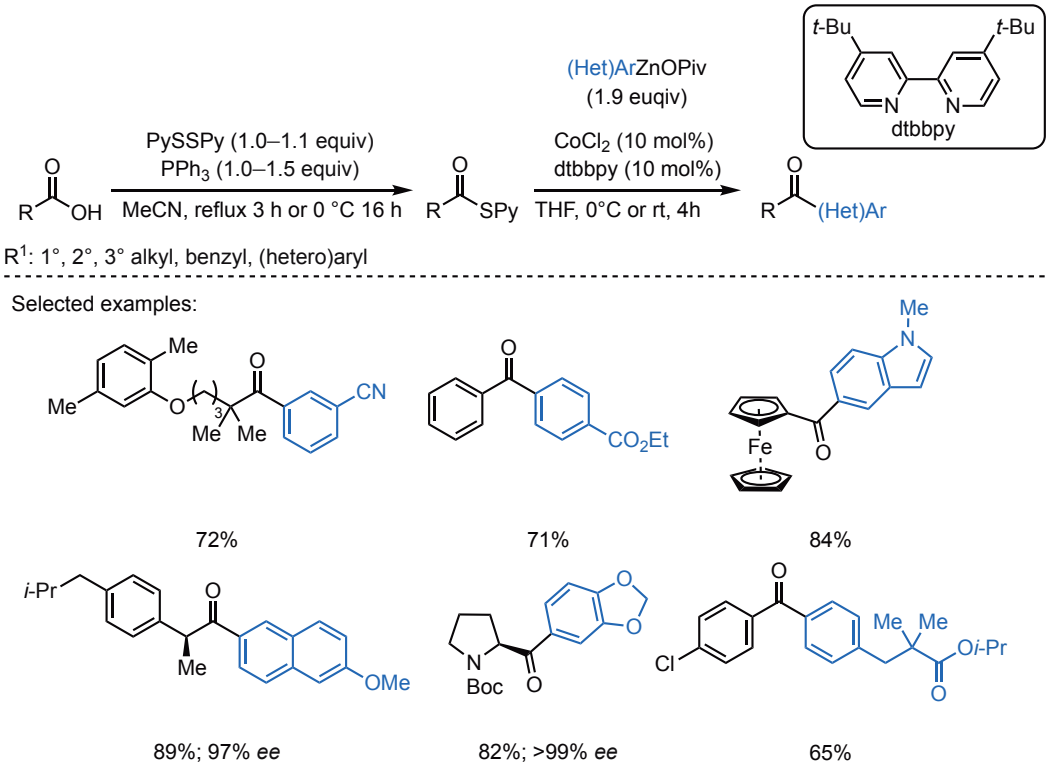
This work focused on the application of sp-, sp^2- and sp^3-hybridized organozinc reagents in cobalt-catalyzed carbon-carbon bond formation.

First, a broad range of bench stable alkynylzinc pivalates underwent cobalt-catalyzed cross-coupling reactions with 1,2- 1,3-, and 1,4-substituted five- and six-membered cyclic (hetero)alkyl halides with predictable diastereoselectivity. This protocol allowed the coupling of alkynes bearing silyl, alkyl and aryl moieties and was not limited to the use of bulky alkynes, in contrast to the prior developed C(sp)-C(sp^2) coupling. Several functional groups like silyl ethers, trifluoromethyl, ester, pyrrol, halides and even ketone moieties could be tolerated under these conditions. Additionally, alkynyl-substituted glycosides were prepared with excellent α-selectivity and also steroids could be alkynylated in high diastereoselectivity. Radical trapping experiments indicated an involvement of radicals during the course of the reaction.



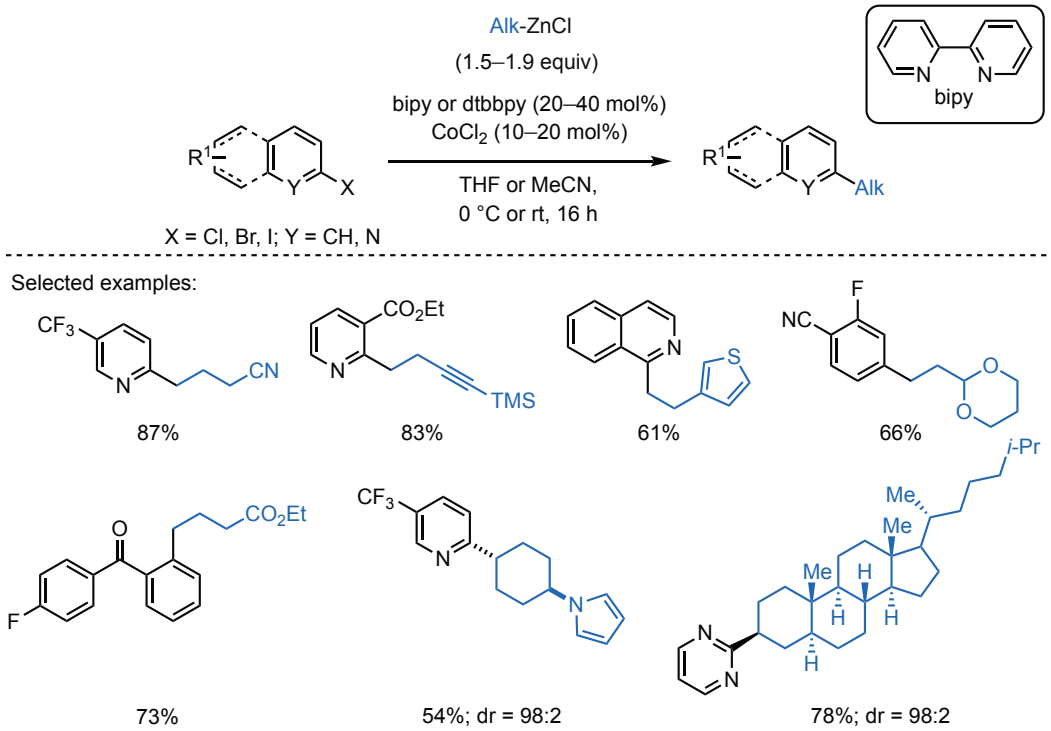
Scheme 34 Cobalt-catalyzed diastereoselective cross-coupling between alkynylzinc pivalates and functionalized cyclic iodides and bromides.

Moreover, a cobalt-catalyzed acylation procedure of primary, secondary and tertiary alkyl, benzyl and (hetero)aryl pyridyl thioesters with bench stable (hetero)arylzinc pivalates was developed. These thioesters were readily prepared from the corresponding carboxylic acids under mild conditions allowing their synthesis in the presence of various sensitive functional groups and stereocenters. Therefore, several α-chiral ketones could be prepared with high retention of configuration (94% to >99% *ee*). Furthermore, this protocol was applied to the synthesis of the antilipidemic drug fenofibrate. Due to a complete suppression of the acylation reaction using the radical trapping reagent TEMPO the mechanism proceeds propaply *via* radical intermediates.



Scheme 35 Cobalt-catalyzed acylation-reaction between (hetero)arylzinc pivalates and thiopyridyl ester derivatives.

Finally, a cobalt-catalyzed cross-coupling of various substituted primary and secondary alkylzinc reagents with aryl and heteroaryl halides was developed. Under these mild conditions a broad range of functional groups like trifluoromethyl, halides and also sensitive groups like nitrile, ester, and ketone moieties were tolerated. Couplings using 1,3- and 1,4-functionalized cyclohexylzinc reagents proceeded in a diastereoselective manner with a diastereomeric ratio up to 98:2. In addition, the coupling of secondary and primary alkylzinc reagents with alkynyl bromides was possible, providing the alkylated alkynes. Addition of TEMPO did not result in an inhibition of the reaction, therefore it can be assumed that the catalytic cycle does not involve radical formation.



Scheme 36 Cobalt-catalyzed cross-coupling between functionalized alkylzinc reagents and (hetero)aryl halides.

III EXPERIMENTAL PART

1 General Considerations

Unless otherwise indicated, all reactions were carried out in flame-dried glassware under argon atmosphere using *Schlenk* technique with rubber septum and manetic stirring bars. Syringes used to transfer reagents and solvents were purged with argon prior to use.

1.1 Solvents

CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2 under nitrogen atmosphere.

DME was distilled under nitrogen atmosphere.

DMPU was distilled under nitrogen atmosphere.

dioxane was distilled from sodium benzophenone ketyl under nitrogen atmosphere.

***t*-BuOMe** was distilled from sodium benzophenone ketyl under nitrogen atmosphere.

NMP was distilled under nitrogen atmosphere.

MeCN was used from acros extra dry

MeTHF was used from acros extra dry

THF was used from acros extra dry over molecular sieves

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

1.2 Reagents

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.

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

$ZnCl_2$ solution in THF (1 M) was prepared by adding anhydrous THF to dry $ZnCl_2$ (40.8 g, 300 mmol), which was prior to use dried in a *Schlenk*-flask under high vacuum at 150 °C for 4 h. 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 under argon upon use.

$CoCl_2$·2LiCl solution in THF (1 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.

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

$Zn(OPiv)_2$ A dry, tared, 500 mL round-bottomed flask equipped with a magnetic stirring bar and a septum was charged with toluene (250 mL, 0.2 M). Pivalic acid (12.5 mL, 11.3 g, 110 mmol, 2.2 equiv) was added to form a colorless solution. Zinc oxide (4.07 g, 50 mmol, 1.0 equiv) was added in 1 g portions at 25 °C over 15 min to form a colorless suspension. The flask was equipped with a *Dean-Stark* apparatus (10 mL) wrapped in aluminum foil and topped with a reflux condenser (20 cm) and the suspension was stirred under nitrogen at reflux in an oil bath for 16 h. A viscous colorless suspension was obtained after 12 h. After cooling to 25 °C, the mixture was concentrated by rotary evaporation (50 °C/50 mmHg). The remaining pivalic acid and water were removed in vacuo from the reaction mixture using a vacuum line (0.1 mmHg) and a liquid nitrogen cold trap (1000 mL). The white solid was warmed to 100 °C in an oil bath and dried for at least 6 h. Zinc pivalate (13.1–13.2 g, 48.9–49.7 mmol, 98–99% yield), was obtained as a puffy amorphous white

[95] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333–3336

solid.[96]

EtMgBr A dry and argon-flushed 250 mL *Schlenk*-flask, equipped with a stirring bar and a septum, was charged with magnesium turnings (2.88 g, 120 mmol) in THF (90 mL). Bromoethane (10.8 g, 100 mmol) 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 1.03 M was determined.

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 aluminium plates covered with SiO_2 (Merk 60, F-254) and visulized either by UV detection, 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) or PMA stain (Molybdophosphoric acid 10 g in Ethanol 200 mL).

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 (δ) are reported in parts per million (ppm) relative to the residual solvent peak $CHCl_3$ (δ_H = 7.26, δ_C = 77.0) or DMSO-d_6 (δ_H = 2.50, δ_C = 39.5) (For the characterization of the observed signal multiplicities the following abbreviations were used: s(singulet), 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 concucted with an electron energy of 70 eV. Elektrospray ionization (ESI) was conducted with an IONMax ion-source equiped with an ESI head. It was performed with a voltage of 4 kV at the spray capillary tube, a heating filament temperature of 250 °C and a nitrogen flow of 25 units.

Gas Chromatography (GC) was performed with maschines 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 μ). For the combination of gas chromatography with mass

[96] M. Ellwart, Y.-H. Chen, V. Malakhov, P. Knochel, *Org. Synth* **2018**, *95*, 127–141

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/R II Diamond ATR sensor was used. The absorption bands ($\tilde{\nu}$) are reported in wave numbers (cm^{-1}).

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

Single Crystal X-Ray Diffraction Studies The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an *Oxford* Xcalibur 3 diffractometer equipped with a *Spellman* generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-Kα radiation (λ = 0.71071). Data collection and data reduction were performed with the *CrysAlisPro* software. Absorption correction using the 13 1415 multiscan method was applied. The structures were solved with SHELXS-97, refined with SHELXL-97 and finally checked using PLATON. Details for data collection and structure refinement are summarized in the appendix section.

Enantiomeric Excess (*ee*) of chiral products were determined *via* chiral HPLC analysis on a *Shimadzu Prominence* 20A HPLC system. For developing a chiral resolution method, different chiral normal phase columns (*Daicel Chemical Industries* Chiralcel OD-H, OJ, OB-H or Chiralpak AS-H, ADH) were tested with *n*-heptane and *i*-PrOH as mobile phase (isocratic) using a racemic mixture of the compound.

Optical Rotation were resorded on *Anton Paar* MCP 500 polarimeter. The specific rotation is calculated as follows:

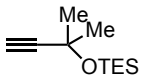
$$[\alpha]_{\lambda}^{\varphi} = \frac{[\alpha]\cdot 100}{c\cdot d}$$

Thereby, the wavelength λ is report ed in nm and the measuring temperature φ °C, α represents the recorded optical rotation, c the concentration of the analyte in 10 mg/mL and d the length of the cuvette in dm. Thus, the specific rotation is given in $10^{-1}\cdot deg\cdot cm^2\cdot g^{-1}$. Usage of the sodium D line (λ = 589 nm) is indicated by D instead of the wavelength in nm. The respective concentration as well as the solvent is reported at the relevant section of the experimental section.

2 Cobalt-Catalyzed Diastereoselective Cross-Couplings between Alkynylzinc Pivalates and Functionalized Cyclic Iodides or Bromides

2.1 Preparation of Starting Materials

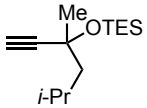
Triethyl((2-methylbut-3-yn-2-yl)oxy)silane (17)



Triethyl((2-methylbut-3-yn-2-yl)oxy)silane (**17**) was prepared according to literature procedure from 2-methylbut-3-yn-2-ol and chlorotriethylsilane.[97]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 2.39 (s, 1H), 1.49 (s, 6H), 0.94 (t, J = 7.9 Hz, 9H), 0.67 (q, J = 7.9 Hz, 6H).

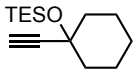
((3,5-Dimethylhex-1-yn-3-yl)oxy)triethylsilane (18)



((3,5-Dimethylhex-1-yn-3-yl)oxy)triethylsilane (**18**) was prepared according to literature procedure from 3,5-dimethylhex-1-yn-3-ol and chlorotriethylsilane.[97]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 2.40 (s, 1H), 1.92 (dh, J = 13.1, 6.5 Hz, 1H), 1.64 – 1.50 (m, 2H), 1.46 (s, 3H), 0.96 (t, J = 7.6 Hz, 15H), 0.68 (qd, J = 7.8, 2.1 Hz, 6H).

Triethyl((1-ethynylcyclohexyl)oxy)silane (19)

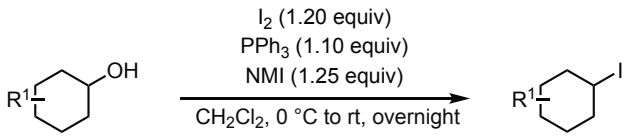


Triethyl((1-ethynylcyclohexyl)oxy)silane (**19**) was prepared from 1-ethynylcyclohexan-1-ol and chlorotriethylsilane according to literature procedure.[97]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 2.45 (s, 1H), 1.83 (dt, J = 10.4, 5.4 Hz, 2H), 1.71 – 1.07 (m, 8H), 0.97 (t, J = 7.9 Hz, 9H), 0.68 (q, J = 7.9 Hz, 6H).

[97] D. L. J. Clive, W. Yang, A. C. MacDonald, Z. Wang, M. Cantin, *J. Org. Chem.* **2001**, *66*, 1966–1983.

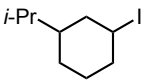
Preparation of Iodides TP1:



1

A dry round bottom flask equipped with a magnetic stirring bar was charged with I_2 (1.20 equiv) which was dissolved in CH_2Cl_2 (0.5 M) and cooled to 0 °C. PPh_3 (1.10 equiv) was carefully added at this temperature. The resulting suspension was stirred for 1.5 h. Then, *N*-methylimidazole (1.25 equiv) was added. After 10 min of stirring, the respective cyclohexanol (1.00 equiv) was added. The reaction mixture was stirred at this temperature for 4h, befor it was let warm to ambient temperature and stirred overnight.The reaction mixture was quenched with sat. aq. NaS_2O_3 solution. The phases were separated and the aq. layer was extracted 3x with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were evaporated and the crude product was subjected to column chromatography furnishing the analytically pure cyclohexyl iodide **1**.[98]

1-Iodo-3-isopropylcyclohexane (1a)



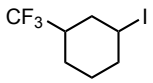
1-Iodo-3-isopropylcyclohexane (**1a**) was prepared according to **TP1** from 3-isopropylcyclohexan-1-ol (12.07 g, 85 mmol), which was prepared according to literature procedure[55b] and was obtained as a slightly pink oil (15.09 g, 60 mmol, 70% yield). The analytical data is in full consictency with the data reported in literature.[55c]

dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.93 (qt, *J* = 3.3, 2.0 Hz, 1H), 2.05 (ddtt, *J* = 14.5, 10.5, 3.5, 1.8 Hz, 2H), 1.81 – 1.58 (m, 4H), 1.53 – 1.38 (m, 2H), 1.29 (ddd, *J* = 14.4, 11.0, 3.4 Hz, 1H), 1.13 – 1.00 (m, 1H), 0.86 (d, *J* = 6.6, 6H).

[98] G. L. Lange, C. Gottardo, *Synth. Commun.* **1990**, *20*, 1473–1479.

1-Iodo-3-(trifluoromethyl)cyclohexane (1b)



1-Iodo-3-(trifluoromethyl)cyclohexane (**1t**) was prepared according to **TP1** from 3-(trifluoromethyl) cyclohexan-1-ol (1 g, 6.0 mmol) and was obtained as a colorless oil (533 mg, 1.9 mmol, 32% yield).

dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.89 (p, J = 3.6 Hz, 1H), 2.72 – 2.54 (m, 1H), 2.25 (dtt, J = 14.6, 3.5, 2.1 Hz, 1H), 1.99 – 1.92 (m, 1H), 1.75 (tq, J = 10.4, 3.7 Hz, 2H), 1.67 – 1.43 (m, 2H), 1.36 (qd, J = 12.6, 4.2 Hz, 2H).

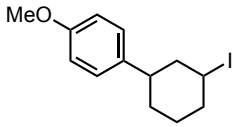
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 127.8 (q, J = 278.7 Hz), 39.4 – 38.3 (m), 35.54, 35.4 – 34.7 (m), 31.9, 24.6 (t, J = 2.8 Hz), 21.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951, 1431, 1392, 1339, 1287, 1259, 1248, 1212, 1166, 1105, 1094, 1075, 903.

MS (EI, 70 eV): *m/z* (%) = 151 (47), 131 (40), 127 (100), 111 (31), 109 (31), 103 (16).

HR-MS (EI, 70 eV): [$C_7H_{10}F_3$], calcd.: 151.0740; found: 151.0727 [M^+-I].

1-(3-Iodocyclohexyl)-4-methoxybenzene (1c)



A dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum, was charged with dry LiCl (168 mg, 4.0 mmol) and CuI (380 mg, 2.0 mmol) in THF (20 mL). The reaction mixure was cooled to 0 °C and 2-cyclohexenone (1.92 g, 20 mmol) and TMSCl (2.16 g, 20 mmol) were added and stirring was continued for 1 h. After cooling the reaction mixture to -78 °C (4-methoxyphenyl)magnesium bromide, which was preparred according to literature procedure,[26] was added drop wise over 15 min. The stirring was continued for 4 h, the reaction mixture was quenched with saturated aq. NH_4Cl solution (20 mL) and was allowed to warm to rt. Most of the solvents were removed under reduced pressure. The residue was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed several times with saturated aq. NH_4Cl solution until the aq. phase remained colorless. The solvent was removed on the rotary

evaporator and the crude product was treated with a mixture of EtOH and H_2O (1:1, 5 mL) and HCl (2 M, 3 mL) and was stirred at rt overnight. The reaction mixture was extracted with EtOAc (3 x 20 mL) and the combined organic phases were dried ($MgSO_4$). The solvent was removed *via* rotary evaporation to give 3-(4-methoxyphenyl)cyclohexanone as a colorless liquid and was used without further purification. $LiAH_4$ (230 mg, 6.1 mmol) was suspended in Et_2O (6 mL) and the suspension was heated to reflux for 1 h. After cooling to 0 °C, 3-(4-methoxyphenyl)cyclohexanone in Et_2O (1.6 mL) was added dropwise. The reaction mixture was heated to reflux for 12 h the suspension was cooled to 0 °C and carefully quenched *via* addition of aq. NaOH solution (1 M, 0.5 mL). Celite (2 g) and H_2O (1.5 mL) were added and the suspension was stirred for 2 h at rt and filtered. The precipitate was washed with Et_2O and the solvent was removed *via* rotary evaporation to give 3-(4-methoxyphenyl)cyclohexanole as a colorless liquid (2.62 g, 64%) and was used without further purification. Following **TP1** 1-(3-Iodocyclohexyl)-4-methoxybenzene (**1c**) was prepared from 3-(4-methoxyphenyl)cyclohexanole (2.62 g, 12.7 mmol). A colorless oil (2.28 g, 5.0 mmol, 39% yield) was obtained.

dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.22 – 7.02 (m, 2H), 6.92 – 6.69 (m, 2H), 3.79 (s, 3H), 3.10 (tt, J = 11.8, 3.4 Hz, 1H), 2.23 (dddd, J = 14.5, 5.3, 3.2, 2.0 Hz, 1H), 2.11 (dtt, J = 14.7, 3.4, 1.5 Hz, 1H), 2.02 – 1.83 (m, 2H), 1.80 – 1.61 (m, 2H), 1.61 – 1.38 (m, 2H), 0.92 – 0.79 (m, 1H).

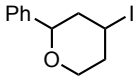
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 158.1, 138.3, 128.1, 113.9, 55.4, 43.9, 39.2, 36.5, 36.1, 33.8, 23.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932, 1610, 1512, 1464, 1443, 1295, 1262, 1245, 1178, 1148, 1107, 1036, 904, 851, 825.

MS (EI, 70 eV): *m/z* (%) = 316 (3), 254 (100), 188 (11), 184 (14), 169 (9), 134 (46), 128 (19), 127 (79), 121 (29).

HR-MS (EI, 70 eV): [$C_{13}H_{17}OI$], calcd.: 316.0324; found: 316.0320.

4-Iodo-2-phenyltetrahydro-2*H*-pyran (1d)

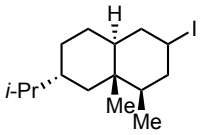


4-Iodo-2-phenyltetrahydro-2*H*-pyran (**1d**) was prepared according to literature procedure.[99]

dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.32 – 7.17 (m, 5H), 4.44 – 4.30 (m, 1H), 4.26 (dd, *J* = 11.1, 2.2 Hz, 1H), 3.95 (ddd, *J* = 11.8, 4.4, 2.5 Hz, 1H), 3.65 – 3.45 (m, 1H), 2.50 (ddt, *J* = 13.1, 3.8, 1.8 Hz, 1H), 2.38 – 2.10 (m, 3H).

(1*R*,4a*S*,7*R*,8a*S*)-3-Iodo-7-isopropyl-1,8a-dimethyldecahydronaphthalene (1e)[63]



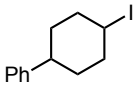
(+)-Nootkatone (20.0 mmol, 4.40 g) and Pd/C (10%, 700 mg) were suspended in EtOAc (35 mL) in a 250 mL round- bottom flask charged with a stirring bar. A H_2 balloon was attached to the flask was stirred for 72 h until full reduction of the olefinic double bonds was detected according to GC-MS and NMR analysis of a crude reaction aliquot. The reaction mixture was filtered through a short silica plug using EtOAc as eluent. After solvent evaporation the obtained pale yellow oil was dissolved in MeOH (50 mL), cooled to 0 °C, $NaBH_4$ was added portion wise and the reaction mixture was stirred overnight. The reaction mixture was quenched with HCl (1.0 M) and extracted with CH_2Cl_2. After solvent evaporation the crude product was purified by flash column chromatogrpahy using silica gel (9:1 hexanes/EtOAc), affording the corresponding alcohol as a colorless oil. (1*S*,2*S*,4*aS*,8*aS*)-6-iodo-2-isopropyl-1,8*a*-dimethyldecahydronaphthalene was prepared according to **TP1** from the corresponding alcohol and was obtained as pink oil (14.8 mmol, 4.95 g, 75% over 3 steps). The analytical data is in full consistency with the data reported in the literature.[63]

dr = 85:15.

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

[99] J. Yadav, B. S. Reddy, G. N. Kumar, T. Swamy, *Tetrahedron Lett.* **2007**, *48*, 2205–2208.

(4-Iodocyclohexyl)benzene (1f)

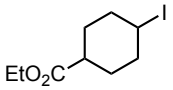


(4-Iodocyclohexyl)benzene (**1f**) was prepared accprding to **TP1** from 4-phenylcyclohexan-1-ol (3.5 g, 20 mmol) and was obtained as colorless crystals (34.81 g, 16.8 mmol, 84% yield). The analytical data is in full consictency with the data reported in literature.[63]

dr = 92:8.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.37 – 6.99 (m, 5H), 2.49 (m, 1H), 2.11 (ddt, *J* = 8.7, 7.0, 3.3 Hz, 2H), 1.96 (qd, *J* = 12.5, 3.2 Hz, 2H), 1.88 – 1.54 (m, 4H), 0.85 – 0.70 (m, 1H).

Ethyl 4-iodocyclohexane-1-carboxylate (1g)

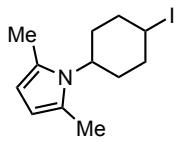


Ethyl 4-iodocyclohexane-1-carboxylate (**1g**) was prepared accroding to **TP1** from ethyl 4-hydroxy-cyclohexane-1-carboxylate (1.72 g, 10 mmol) and was obtained as a colorless oil (1 g, 3.5 mmol, 35% yield) was obtained. The analytical data is in full consictency with the data reported in literature.[91c]

dr = 68:32.

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

1-(4-Iodocyclohexyl)-2,5-dimethyl-1*H*-pyrrole (1h)



1-(4-Iodocyclohexyl)-2,5-dimethyl-1*H*-pyrrole (**1h**) was prepared according to **TP1** from 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)cyclohexan-1-ol (1.93 g, 10 mmol), which was prepared according to literature procedure[100] and was obtained as light red crystals (860 mg, 28%).

[100] H. Cho, R. Madden, B. Nisanci, B. Török, *Green Chem.* **2015**, *17*, 1088–1099.

dr = 90:10.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.76 (s, 2H), 4.88 (t, J = 3.2 Hz, 1H), 3.94 (tt, J = 12.7, 4.0 Hz, 1H), 2.53 (qd, J = 12.8, 3.4 Hz, 2H), 2.37 (s, 6H), 2.22 (dt, J = 15.1, 3.0 Hz, 2H), 1.86 – 1.63 (m, 4H).

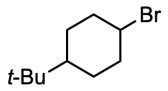
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 128.0, 106.4, 55.2, 36.5, 34.1, 28.1, 14.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2940, 2890, 2864, 2832, 1516, 1439, 1428, 1394, 1347, 1291, 1231, 1212, 1191, 1161, 1084, 1021, 944, 977, 904, 873, 821, 790.

MS (EI, 70 eV): *m/z* (%) = 303 (10), 254 (53), 176 (7), 128 (37), 127 (100), 96 (8), 94 (17), 79 (11).

HR-MS (EI, 70 eV): [$C_{12}H_{18}NI$], calcd.: 303.0484; found: 303.0478.

1-(*tert*-Butyl)-4-bromocyclohexane (1i)

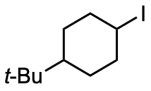


1-(*tert*-Butyl)-4-bromocyclohexane (**1i**) was preparedfrom 4-(*tert*-butyl)cyclohexan-1-ol according to literature procedure.[101]

dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.68 (p, J = 3.0 Hz, 1H), 2.19 – 2.07 (m, 2H), 1.75 (tdd, J = 14.6, 4.5, 3.1 Hz, 2H), 1.68 – 1.51 (m, 4H), 1.10 – 0.95 (m, 1H), 0.87 (d, J = 7.4 Hz, 9H).

1-(*tert*-Butyl)-4-iodocyclohexane (1j)



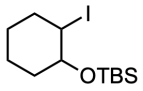
1-(*tert*-Butyl)-4-iodocyclohexane (**1j**) was prepared according to **TP1** from 4-(*tert*-butyl)cyclohexan-1-ol (12.8 g, 20 mmol) and was obtained as colorless crystals (2.48 mg, 47%). The analytical data is in full consictency with the data reported in literature.[63]

dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.88 (dd, J = 3.6, 2.2 Hz, 1H), 2.12 (dt, J = 13.9, 2.7 Hz, 2H), 1.70 – 1.43 (m, 7H), 1.06 (ddd, J = 11.3, 7.6, 3.5 Hz, 1H), 0.89 (s, 9H).

[101] Mundy, B P.; Stewart, C. A. *e-Eros*, **2008**, *Phosphorus(V) bromide*, 1

***tert*-Butyl((2-iodocyclohexyl)oxy)dimethylsilane (1k)**

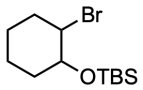


tert-Butyl((2-iodocyclohexyl)oxy)dimethylsilane (**1k**) was prepared from cylcohexene, *N*-iodosuccinimide and water, followed by TBS-protection, according to literature procedure.[102,97] The analytical data is in full consictency with the data reported in literature.[26]

dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.53 – 4.39 (m, 1H), 3.36 (s, 1H), 2.32 – 2.20 (m, 1H), 1.96 – 1.84 (m, 1H), 1.79 – 1.60 (m, 3H), 1.57 – 1.30 (m, 3H), 0.95 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H).

***tert*-Butyl((2-bromocyclohexyl)oxy)dimethylsilane (1l)**

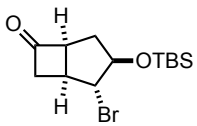


tert-Butyl((2-bromocyclohexyl)oxy)dimethylsilane (**1l**) was prepared according to literature procedure from cylcohexene, *N*-bromosuccinimide and water, followed by TBS-protection.[57c]

dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.90 (ddd, *J* = 9.6, 7.6, 4.1 Hz, 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).

(*trans*-2-bromo-3-((*tert*-butyldimethylsilyl)oxy)bicyclo[3.2.0]heptan-6-one (1m)



(*trans*)-3-Bromo-4-((*tert*-butyldimethylsilyl)oxy)bicyclo[3.2.0]heptan-6-one (2m) was prepared from (*trans*)-2-bromo-3-hydroxybicyclo[3.2.0]heptan-6-one, which was prepared according to literature procedure,[103] by TBS protection.[97]

[102] M Smietana, V Gouverneur, C Mioskowski, *Tetrahedron Letters* **2000**, *41*, 193–195
[103] J. M. Kelly, F. J. Leeper, *Tetrahedron Lett.* **2012**, *53*, 819–821.

dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.52 (d, *J* = 3.7 Hz, 1H), 4.21 (s, 1H), 3.78 (dddd, *J* = 10.2, 6.1, 1.9, 0.9 Hz, 1H), 3.35 – 3.20 (m, 1H), 3.19 – 3.13 (m, 2H), 2.48 (ddd, *J* = 13.6, 9.5, 3.8 Hz, 1H), 2.17 (dt, *J* = 14.0, 0.8 Hz, 1H), 0.85 (s, 9H), 0.08 (s, 2H), 0.06 (s, 3H).

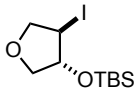
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 210.6, 82.29, 63.6, 58.4, 53.3, 39.1, 38.0, 25.7, 17.9, –4.9, –5.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928, 1781, 1471, 1253, 1165, 1074, 1026, 1017, 1005, 906, 871, 837, 825, 809, 777.

MS (EI, 70 eV): *m/z* (%) = 318 (4), 263 (67), 261 (51), 221 (97), 139 (79), 137 (76), 79 (56), 75 (100=, 73 (100), 57 (48), 55 (22).

HR-MS (EI, 70 eV): [$C_{13}H_{23}O_3BrSi$], calcd.: 318.0651; found: 318.0651.

tert-Butyl((4-iodotetrahydrofuran-3-yl)oxy)dimethylsilane (1n)

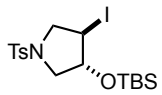


tert-Butyl((4-iodotetrahydrofuran-3-yl)oxy)dimethylsilane (**1n**) was prepared from 2,5-dihydrofuran, *N*-iodosuccinimide and water, followed by TBS-protection, according to literature procedure.[102,97] The analytical data is in full consictency with the data reported in literature.[57c]

dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.58 (dt, *J* = 4.42, 2.21 Hz, 1H), 4.17 – 4.36 (m, 2H), 3.97 – 4.10 (m, 2H), 3.66 (dd, *J* = 9.3, 2.1 Hz, 1H), 0.87 (s, 9H), 0.01 – 0.14 (m, 6H).

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



3-((*tert*-Butyldimethylsilyl)oxy)-4-iodo-1-tosylpyrrolidine (**1o**) was prepared from 1-tosyl-2,5-dihydro-1*H*-pyrrole, *N*-iodosuccinimide and water, followed by TBS-protection, according to literature produre .[102]

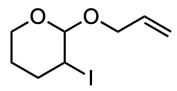
dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.70 (m, *J* = 8.3 Hz, 2H), 7.30 (m, *J* = 8.6 Hz, 2H), 4.34 (dt,

J = 4.7, 2.4 Hz, 1H), 3.77 – 3.96 (m, 3H), 3.63 -3.71 (m, 1H), 3.17 (dd, *J* = 10.2, 1.9 Hz, 1H), 2.40 (s, 3H), 0.73 (s, 9H), -0.08 -0.02 (m, 6H).

The ^{1}H-NMR spectra data are in agreement with literature.[57c]

2-(Allyloxy)-3-iodotetrahydro-2*H*-pyran (1q)

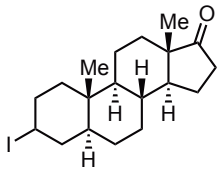


2-(Allyloxy)-3-iodotetrahydro-2*H*-pyran (**1q**) was prepared according to literature procedure from 3,4-dihydro-2*H*-pyran, *N*-iodosuccinimide and allyl alcohol.[104]

dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.87 (dddd, *J* = 16.9, 10.3, 6.1, 5.2 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.15 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.62 (d, *J* = 5.3 Hz, 1H), 4.20 (ddt, *J* = 12.9, 5.3, 1.5 Hz, 1H), 4.05 (ddd, *J* = 8.1, 5.3, 4.3 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.94 – 3.88 (m, 1H), 3.52 (ddd, *J* = 11.2, 7.4, 3.5 Hz, 1H), 2.32 (ddt, *J* = 14.9, 7.8, 4.1 Hz, 1H), 1.96 (dtd, *J* = 14.0, 8.3, 4.0 Hz, 1H), 1.71 (dtt, *J* = 14.2, 7.3, 3.8 Hz, 1H), 1.61 – 1.41 (m, 1H).

3-Iodo-epiandrosterone (1u)



3-Iodo epiandrosterone (**1u**) was prepared according to **TP1** from epiandrosterone (2.0 g, 7 mmol) and was obtained as colorless crystals (2.2 g, 79%). The analytical data is in full consictency with the data reported in literature.[105]

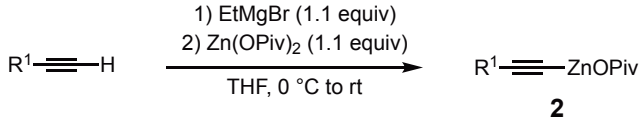
dr = 99:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.93 (p, *J* = 3.0 Hz, 1H), 2.43 (ddd, *J* = 19.2, 8.8, 1.1 Hz, 1H), 2.14 – 1.99 (m, 1H), 1.99 – 1.86 (m, 2H), 1.85 – 1.61 (m, 7H), 1.61 – 1.39 (m, 5H), 1.30 (dddd, *J* = 18.4, 13.6, 7.2, 2.9 Hz, 5H), 1.07 (qd, *J* = 12.2, 5.1 Hz, 1H), 0.85 (s, 3H), 0.81 (s, 3H).

[104] C. Ollivier, P. Renaud, *J. Am. Chem. Soc.* **2001**, *123*, 4717–4727.
[105] E. Keinan, M. Sahai, R. Shvily, *Synthesis* **1991**, *1991*, 641–643.

2.2 Cobalt-Catalyzed Diastereoselective Cross-Couplings between Alkynylzinc Pivalates and Functionalized Cycliclodides or Bromides

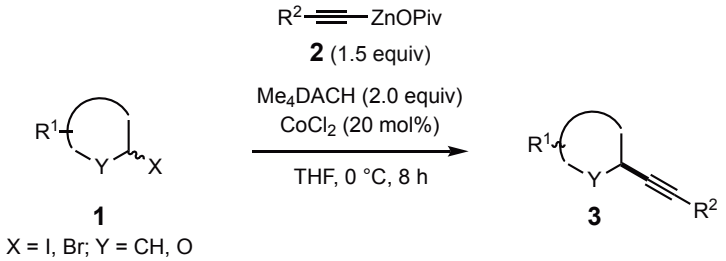
Preparation of alkynylzinc pivalates (TP2):



2

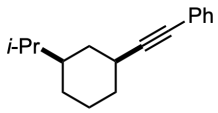
The corresponding alkyne (1.0 equiv, 1.0 mmol) and THF (0.5 mL) were added to a dry and argon-flushed 10 mL *Schlenk*-flask, equipped with a stirring bar and a septum. EtMgBr (1.1 equiv) was added dropwise at room temperature and stirred until a reaction aliquot quenched with I_2 in THF showed full conversion of the starting material determined by GC. Solid $Zn(OPiv)_2$ (1.1 equiv) was added in one portion at 0 °C and the reaction mixture was stirred at ambient temperature for 15 min.

Cobalt-catalyzed cross-coupling of alkynylzinc pivalates (TP3):



A dry and argon-flushed 10 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was charged with anhydrous $CoCl_2$ (0.1 mmol, 13 mg, 20 mol%, dried *in vacuo* at 400 °C prior to use), the respective halide (0.5 mmol, 1.0 equiv), THF (1.0 mL) and Me^4DACH (1 mmol, 0.19 mL, 2.0 equiv) were added. The reaction mixture was cooled to 0 °C with an ice bath and the THF solution of the appropriate alkynylzinc pivalate (0.6 M, 0.75 mmol, 1.5 equiv) was added dropwise. The reaction was stirred and monitored by GC-analysis (tetradecane, $C_{14}H_{30}$ was used as an internal standard). After 8 h, saturated aq. NH_4Cl solution (10 mL) was added, the phases were separated and the aq. 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.

cis-3-Isopropylcyclohexyl)ethynyl)benzene (3a)



Following **TP3** 1-iodo-3-isopropylcyclohexane (**1a**, 126 mg, 0.5 mmol, 1.0 equiv) was coupled with 2-phenylethynylzinc pivalate (**2a**, 1.0 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 88 mg, 0.39 mmol, 78%, dr = 92:8, colorless oil.

Purification: *i*-hexane.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.43 – 7.36 (m, 2H), 7.31 – 7.20 (m, 3H), 2.43 (tt, J = 11.4, 3.6 Hz, 1H), 2.12 – 1.95 (m, 2H), 1.81 (dq, J = 12.9, 3.3 Hz, 1H), 1.68 (ddq, J = 12.6, 3.5, 1.6 Hz, 1H), 1.47 (pd, J = 6.9, 4.7 Hz, 1H), 1.40 – 1.20 (m, 2H), 1.13 (tdd, J = 11.9, 9.8, 5.6 Hz, 2H), 0.97 (tdd, J = 11.9, 6.2, 3.7 Hz, 1H), 0.89 (d, J = 6.8 Hz, 6H).

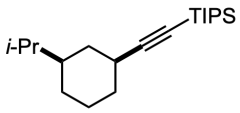
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 131.7, 128.3, 127.6, 124.2, 94.9, 80.0, 43.7, 36.6, 33.4, 33.0, 30.7, 29.1, 26.1, 19.9, 19.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928, 2858, 1701, 1598, 1490, 1460, 1443, 1385, 1367, 1331, 1308, 1263, 1176, 1069, 1026, 934, 911, 886, 869, 847.

MS (EI, 70 eV): *m/z* (%) = 226 (8), 211 (100), 155 (63), 141 (99), 129 (51), 128 (50), 115 (51).

HR-MS (EI, 70 eV): [$C_{17}H_{22}$], calcd.: 226.1722; found: 226.1714.

Triisopropyl(((_cis_)-3-isopropylcyclohexyl)ethynyl)silane (3b)



Following **TP3** 1-iodo-3-isopropylcyclohexane (**1a**, 126 mg, 0.5 mmol, 1.0 equiv) was coupled with triisopropylsilyl)ethynyl)zinc pivalate (**2b**, 1.0 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 145 mg, 0.48 mmol, 95%, dr = 95:5, colorless oil.

Purification: *i*-hexane.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 2.24 (ddt, J = 11.4, 7.0, 3.6 Hz, 1H), 2.04 – 1.91 (m, 2H), 1.83 – 1.71 (m, 1H), 1.71 – 1.60 (m, 1H), 1.50 – 1.36 (m, 1H), 1.31 – 1.13 (m, 2H), 1.13 – 0.95 (m, 24H), 0.87 (d, J = 1.9 Hz, 3H), 0.85 (d, J = 2.0 Hz, 3H).

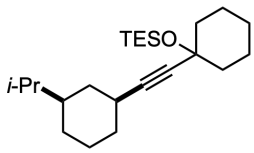
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 114.3, 78.7, 43.7, 36.8, 33.7, 33.0, 31.2, 29.0, 26.1, 19.9, 19.8, 18.8, 11.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2933, 2873, 1458, 1448, 1445, 1367, 1305, 1181, 1096, 1060, 1002, 867, 820, 739, 727, 723, 721.

MS (EI, 70 eV): *m/z* (%) = 306 (1), 263 (100), 221 (17), 207 (22), 193 (12), 179 (11), 151 (10), 73 (15), 59 (10).

HR-MS (EI, 70 eV): [$C_{20}H_{38}Si$], calcd.: 306.2743; found: 306.2732.

Triethyl((1-(((*cis*)-3-isopropylcyclohexyl)ethynyl)cyclohexyl)oxy)silane (3c)



Following **TP3** 1-iodo-3-isopropylcyclohexane (**1a**, 126 mg, 0.5 mmol, 1.0 equiv) was coupled with ((1-((triethylsilyl)oxy)cyclohexyl)ethynyl)zinc pivalate (**2c**, 1.0 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 165 mg, 0.46 mmol, 91%, dr = 98:2, colorless oil.

Purification: *i*-hexane.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 2.23 (ddq, J = 12.2, 7.0, 3.8 Hz, 1H), 1.98 – 1.85 (m, 2H), 1.84 – 1.70 (m, 3H), 1.70 – 1.38 (m, 9H), 1.35 – 1.17 (m, 3H), 1.11 – 1.02 (m, 2H), 0.96 (t, J = 7.9 Hz, 10H), 0.86 (d, J = 6.8 Hz, 6H), 0.67 (q, J = 7.9 Hz, 6H).

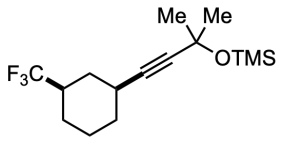
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 89.6, 83.9, 69.5, 43.7, 41.8, 36.6, 33.4, 33.0, 30.2, 29.1, 26.1, 25.6, 23.4, 19.8, 19.8, 7.3, 6.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2938, 2863, 2171, 1462, 1385, 1367, 1097, 1061, 1062, 1017, 995, 918, 882, 810, 667.

MS (EI, 70 eV): *m/z* (%) = 334 (22), 333 (92), 215 (57), 187 (53), 145 (69), 131 (52), 117 (48), 105 (42), 103 (92), 79 (43), 75 (100).

HR-MS (EI, 70 eV): [$C_{23}H_{42}OSi$], calcd.: 362.3005; found: 362.3001.

Trimethyl((2-methyl-4-((*cis*)-3-(trifluoromethyl)cyclohexyl)but-3-yn-2-yl)oxy)silane (3d)



Following **TP3** 1-iodo-3-(trifluoromethyl)cyclohexane (**1b**, 139 mg, 0.5 mmol, 1.0 equiv) was coupled with (3-methyl-3-((trimethylsilyl)oxy)but-1-yn-yl)zinc pivalate (**2d**, 1.0 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 95 mg, 0.31 mmol, 62%, dr = 90:10, orange oil.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 2.27 (tt, J = 11.9, 3.6 Hz, 1H), 2.14 (dtt, J = 12.9, 3.6, 1.6 Hz, 1H), 2.10 – 1.79 (m, 4H), 1.44 (s, 6H), 1.40 – 1.15 (m, 4H), 0.18 (s, 9H).

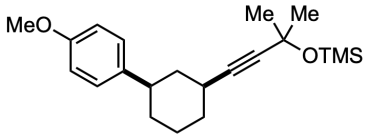
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 131.6 (q, J = 278.6 Hz), 128.8, 126.0, 123.3, 86.0, 85.6, 66.6, 42.0, 41.8 (q, J = 26.7 Hz) 41.5, 41.2, 33.5, 32.3, 31.4 (q, J = 2.5 Hz) , 28.7, 24.5, 24.3 (q, J = 2.6 Hz), 2.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2925, 1359, 1327, 1283, 1273, 1248, 1210, 1166, 1111, 1099, 1072, 1032, 902, 877, 838, 752, 686.

MS (EI, 70 eV): *m/z* (%) = 291 (100), 161 (16), 105 (51), 91 (38), 75 (53).

HR-MS (EI, 70 eV): [$C_{15}H_{25}F_3O_2Si$], calcd.: 291.1398; found: 291.1389 [M^+-CH_3].

((4-((*cis*)-3-(4-Methoxyphenyl)cyclohexyl)-2-methylbut-3-yn-2-yl)oxy)trimethylsilane (3e)



Following **TP3** 1-(3-iodocyclohexyl)-4-methoxybenzene (**1v**, 158 mg, 0.5 mmol, 1.0 equiv) was coupled with (3-methyl-3-((trimethylsilyl)oxy)but-1-yn-yl)zinc pivalate (**2d**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 134 mg, 0.39 mmol, 78%, dr = 98:2, colorless oil.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.15 – 7.10 (m, 2H), 6.88 – 6.82 (m, 2H), 3.79 (s, 3H), 2.44 (m, 2H), 2.10 (dtt, *J* = 12.9, 3.5, 1.8 Hz, 1H), 2.05 – 1.96 (m, 1H), 1.85 (tdd, *J* = 12.6, 5.4, 2.4 Hz, 3H), 1.44 (s, 9H), 0.18 (s, 9H).

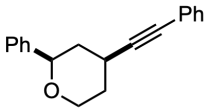
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 158.0, 139.1, 127.8, 113.9, 87.0, 85.3, 66.7, 55.4, 43.1, 40.8, 33.8, 33.6, 32.7, 30.2, 26.3, 2.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929, 2855, 1611, 1512, 1461, 1446, 1443, 1358, 1244, 1176, 1157, 1100, 1032, 914, 896, 839, 823, 753, 721, 686, 655.

MS (EI, 70 eV): *m/z* (%) = 254 (50), 239 (59), 223 (44), 211 (44), 179 (54), 155 (55), 121 (49), 121 (49), 91 (49), 91 (46), 75 (100).

HR-MS (EI, 70 eV): [$C_{21}H_{32}O_2Si$], calcd.: 344.2172; found: 344.2167.

***cis*-2-Phenyl-4-(phenylethynyl)tetrahydro-2*H*-pyran (3f)**



Following **TP3** 4-iodo-2-phenyltetrahydro-2*H*-pyran (**1d**, 144 mg, 0.5 mmol, 1.0 equiv) was coupled with 2-phenylethynylzinc pivalate (**2a**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 99 mg, 0.38 mmol, 76%, dr = 93:7, pale yellow oil.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.32 – 7.21 (m, 6H), 7.21 – 7.10 (m, 4H), 4.24 (dd, *J* = 11.4, 2.2 Hz, 1H), 4.09 (ddd, *J* = 11.7, 4.5, 1.7 Hz, 1H), 3.53 (td, *J* = 12.1, 2.4 Hz, 1H), 2.79 (tt, *J* = 11.9, 3.9 Hz, 1H), 2.10 (ddt, *J* = 13.3, 3.9, 2.0 Hz, 1H), 1.87 (ddq, *J* = 13.4, 4.1, 2.1 Hz, 1H), 1.83 – 1.74 (m, 1H), 1.68 (dt, *J* = 13.4, 11.6 Hz, 1H).

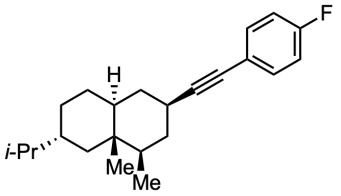
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 142.3, 131.7, 128.5, 128.3, 127.9, 127.7, 126.0, 123.6, 92.3, 81.0, 79.4, 68.0, 40.1, 32.4, 28.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2930, 2856, 1730, 1731, 1601, 1492, 1451, 1372, 1240, 117, 1091, 1068, 1026, 970, 939, 899, 859, 836, 807, 777, 757.

MS (EI, 70 eV): *m/z* (%) = 262 (42), 218 (40), 185 (28), 141 (37), 128 (100), 115 (64), 91 (28), 77 (32).

HR-MS (EI, 70 eV): [$C_{19}H_{18}O$], calcd.: 262.1358; found: 262.1353.

(1*R*,3*S*,4a*R*,7*R*,8a*S*)-3-((4-Fluorophenyl)ethynyl)-7-isopropyl-1,8a dimethyldecahydro naphthalene (3g)



Following **TP3** (1*R*,3*R*,4a*S*,7*R*,8a*S*)-3-iodo-7-isopropyl-1,8a dimethyldecahydronaphthalene (**1e**, 174 mg, 0.5 mmol, 1.0 equiv) was coupled with ((4-fluorophenyl)ethynyl)zinc pivalate (**2e**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 98 mg, 0.30 mmol, 60%, dr = 94:6, colorless oil.

Purification: *i*-hexane.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.50 (dd, *J* = 7.5, 5.8 Hz, 2H), 7.06 – 6.97 (m, 2H), 2.44 (p, *J* = 8.0 Hz, 2H), 1.77 (dt, *J* = 12.6, 7.8 Hz, 2H), 1.72 – 1.57 (m, 4H), 1.51 – 1.13 (m, 10H), 0.90 (d, *J* = 6.1 Hz, 4H), 0.87 (d, *J* = 2.2 Hz, 6H), 0.86 (s, 2H), 0.74 – 0.65 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 163.2 (d, *J* = 162.1) 161.2, 91.6, 83.3, 46.6, 39.9, 37.3, 35.7, 34.9, 32.3, 28.7, 28.4, 28.0, 22.9, 18.9, 15.8.

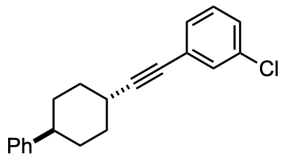
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953, 2925, 2858, 1601, 1506, 1463, 1441, 1384, 1367, 1231, 1155, 1091, 1014, 905, 834, 816.

MS (EI, 70 eV): *m/z* (%) = 326 (36), 201 (50), 188 (80), 173 (90), 159 (100), 146 (91), 133 (45), 95 (49).

HR-MS (EI, 70 eV): [$C_{23}H_{31}F$], calcd.: 326.2410; found: 326.2403.

Optical rotation: $[\alpha]_\lambda^\varphi$ = 33.8 (c = 0.81, $CHCl_3$).

1-Chloro-3-(((*trans*)-4-phenylcyclohexyl)ethynyl)benzene (3h)



Following **TP3** (4-iodocyclohexyl)benzene (**1f**, 143 mg, 0.5 mmol, 1.0 equiv) was coupled with ((3-chlorophenyl)ethynyl)zinc pivalate (**2f**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 100 mg, 0.34 mmol, 68%, dr = 90:10, colorless crystals.

Purification: *i*-hexane.

m.p.: 67.2 – 68.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.32 (d, J = 1.8 Hz, 1H), 7.27 – 7.09 (m, 8H), 2.55 – 2.35 (m, 2H), 2.10 (dd, J = 13.4, 3.6 Hz, 2H), 1.94 – 1.83 (m, 2H), 1.48 (ttd, J = 25.5, 13.0, 3.2 Hz, 4H).

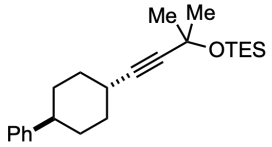
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 147.1, 134.1, 131.7, 129.9, 129.5, 128.5, 127.9, 126.9, 126.2, 125.8, 95.7, 79.22, 43.6, 33.7, 33.4, 30.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3018, 2932, 2857, 1704, 1592, 1560, 1493, 1475, 1448, 1214, 1092, 1077, 1028, 961, 882, 812.

MS (EI, 70 eV): *m/z* (%) = 268 (9), 266 (27), 164 (16), 156 (14), 153 (9), 130 (11), 129 (100), 128 (13), 115 (16), 91 (11).

HR-MS (EI, 70 eV): [$C_{20}H_{19}Cl$], calcd.: 294.1175; found: 294.1170.

Triethyl((2-methyl-4-((*trans*)-4-phenylcyclohexyl)but-3-yn-2-yl)oxy)silane (3i)



Following **TP3** (4-iodocyclohexyl)benzene (**1f**, 139 mg, 0.5 mmol, 1.0 equiv) was coupled with (3-methyl-3-((triethylsilyl)oxy)but-1-yn-1-yl)zinc pivalate (**2g**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 169 mg, 0.48 mmol, 95%, dr = 99:1, colorless oil.

Purification: *i*-hexane.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.26 – 7.17 (m, *J* = 7.4, 6.9 Hz, 2H), 7.12 (d, *J* = 7.4 Hz, 3H), 2.43 (tt, *J* = 11.7, 3.5 Hz, 1H), 2.28 – 2.14 (m, 1H), 2.06 – 1.94 (m, 2H), 1.84 (d, *J* = 11.0 Hz, 2H), 1.50 – 1.30 (m, 10H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.61 (q, *J* = 7.9 Hz, 6H).

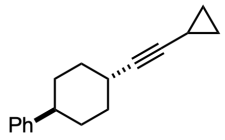
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 147.3, 128.5, 126.9, 126.2, 86.5, 85.5, 66.3, 43.7, 33.8, 33.6, 33.4, 29.5, 7.2, 6.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2931, 2873, 1494, 1448, 1376, 1357, 1300, 1242, 1157, 1096, 1034, 1011, 975, 907, 894, 789, 740, 725, 697.

MS (EI, 70 eV): *m/z* (%) = 327 (18), 209 (19), 196 (45), 156(50), 155 (25), 129 (26), 115 (39), 103 (43), 94 (24), 91 (60), 79 (100), 75 (46).

HR-MS (EI, 70 eV): [$C_{22}H_{33}OSi$], calcd.: 341.2306; found: 341.2294 [M^+-Me].

((*trans*)-4-(Cyclopropylethynyl)cyclohexyl)benzene(3j)



Following **TP3** (4-iodocyclohexyl)benzene (**1f**, 139 mg, 0.5 mmol, 1.0 equiv) was coupled with (cyclopropylethynyl)zinc pivalate (**2h**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 80 mg, 0.36 mmol, 71%, dr = 95:5, colorless crystals.

Purification: *i*-hexane.

m.p.: 70.8 – 72.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.40 – 7.30 (m, 2H), 7.25 (d, *J* = 7.3 Hz, 3H), 2.54 (ddd, *J* = 11.6, 8.2, 3.4 Hz, 1H), 2.29 (td, *J* = 11.5, 3.7 Hz, 1H), 2.20 – 2.08 (m, 2H), 2.02 – 1.88 (m, 2H), 1.67 – 1.41 (m, 4H), 1.37 – 1.22 (m, 1H), 0.79 (dt, *J* = 8.0, 3.2 Hz, 2H), 0.69 (dt, *J* = 5.2, 3.1 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 147.3, 128.5, 126.9, 126.1, 83.1, 80.0, 43.7, 33.9, 33.8, 29.6, 8.3, -0.3.

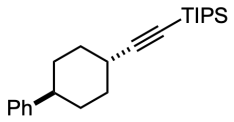
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928, 1699, 1490, 1447, 1023, 976, 888, 814.

MS (EI, 70 eV): *m/z* (%) = 223 (2), 196 (16), 195 (21), 181 (33), 167 (36), 156 (17), 155 (24), 117

(17), 115 (33), 91 (46), 79 (100).

HR-MS (EI, 70 eV): [$C_{17}H_{19}$], calcd.: 223.1492; found: 223.1479 [M^+-Me].

Triisopropyl(((*trans*)-4-phenylcyclohexyl)ethynyl)silane (3k)



Following **TP3** (4-iodocyclohexyl)benzene (**1f**, 139 mg, 0.5 mmol, 1.0 equiv) was coupled with triisopropylsilyl)ethynyl)zinc pivalate (**2b**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 163 mg, 0.48 mmol, 96%, dr = 98:2, colorless oil.

Purification: *i*-hexane.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.28 – 7.17 (m, 2H), 7.12 (d, J = 7.3 Hz, 3H), 2.44 (tt, J = 11.7, 3.5 Hz, 1H), 2.26 (tt, J = 11.7, 3.7 Hz, 1H), 2.06 (dd, J = 13.4, 3.6 Hz, 2H), 1.84 (dd, J = 12.0, 3.1 Hz, 2H), 1.56 – 1.30 (m, 6H), 1.00 (d, J = 5.1 Hz, 19H).

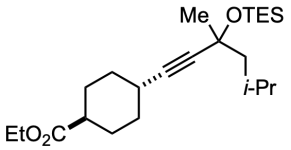
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 147.3, 128.5, 127.0, 126.9, 126.2, 113.7, 79.3, 43.7, 33.8, 33.7, 30.5, 18.8, 11.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929, 2890, 2862, 2175, 1462, 1449, 1444, 1072, 1017, 995, 882, 753, 697, 685, 670, 657.

MS (EI, 70 eV): *m/z* (%) = 298 (23), 297 (100), 156 (27), 155 (28), 141 (21), 131 (41), 117 (34), 115 (34), 91 (43), 75 (31).

HR-MS (EI, 70 eV): [$C_{20}H_{29}Si$], calcd.: 297.2044; found: 297.2033 [M^+-*i*-Pr].

Ethyl (*trans*)-4-(3,5-dimethyl-3-((triethylsilyl)oxy)hex-1-yn-1-yl)cyclohexane-1-carboxylate (3l)



Following **TP3** ethyl 4-iodocyclohexane-1-carboxylate (**1g**, 141 mg, 0.5 mmol, 1.0 equiv) was coupled with (3,5-dimethyl-3-((triethylsilyl)oxy)hex-1-yn-1-yl)zinc pivalate (**2i**, 0.75 mmol,

1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 139 mg, 0.35 mmol, 71%, dr = 90:10, yellow oil.

Purification: *i*-hexane:ethyl acetate = 97:3.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.11 (q, J = 7.1 Hz, 2H), 2.24 (tdt, J = 11.2, 7.9, 3.3 Hz, 2H), 2.03 – 1.94 (m, 4H), 1.93 – 1.81 (m, 1H), 1.58 – 1.32 (m, 9H), 1.24 (t, J = 7.1 Hz, 3H), 0.99 – 0.91 (m, 15H), 0.65 (dtd, J = 8.4, 7.4, 1.3 Hz, 6H).

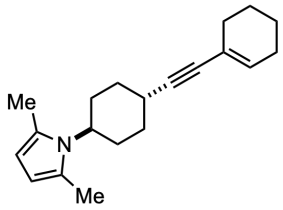
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 175.9, 86.9, 85.4, 69.2, 60.4, 54.1, 42.5, 32.2, 31.9, 31.9, 29.1, 28.3, 25.0, 24.7, 24.6, 14.4, 7.2, 6.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2950, 2873, 1733, 1450, 1414, 1367, 1300, 1378, 1162, 1136, 1072, 1039, 1022, 970, 740, 724, 671.

MS (EI, 70 eV): *m/z* (%) = 365 (44), 337 (70), 188 (13), 173 (69), 1313 (50), 117 (40), 103 (97), 75 (100).

HR-MS (EI, 70 eV): [$C_{22}H_{39}O_3Si$], calcd.: 379.2674; found: 379.2662 [M^+-Me].

1-((*trans*)-4-(Cyclohex-1-en-1-ylethynyl)cyclohexyl)-2,5-dimethyl-1*H*-pyrrole (3m)



Following **TP3** 1-(4-iodocyclohexyl)-2,5-dimethyl-1*H*-pyrrole (**1h**, 152 mg, 0.5 mmol, 1.0 equiv) was coupled with (cyclohex-1-en-1-ylethynyl)zinc pivalate (**2j**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 117 mg, 0.42 mmol, 83%, dr = 95:5, pale yellow oil.

Purification: *i*-hexane:ethyl acetate = 97:3.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 6.04 (tt, J = 3.8, 1.7 Hz, 1H), 5.73 (s, 2H), 3.92 (tt, J = 12.0, 4.0 Hz, 1H), 2.45 – 2.32 (m, 1H), 2.28 (s, 6H), 2.19 – 2.05 (m, 6H), 2.01 – 1.86 (m, 4H), 1.69 – 1.46 (m, 6H).

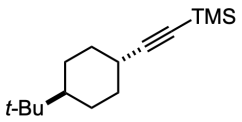
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 133.8, 127.9, 120.9, 106.4, 90.4, 82.4, 55.6, 33.5, 31.7, 29.7, 29.7, 25.7, 22.5, 21.7, 14.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928, 2858, 1517, 1444, 1396, 1349, 1292, 1237, 1212, 1189, 1166, 1135, 1086, 1019, 988, 978, 917, 899, 839, 815, 799, 786, 780.

MS (EI, 70 eV): *m/z* (%) = 282 (21), 281 (93), 266 (81), 129 (39), 128 (31), 115 (46), 94 (91), 91 (100).

HR-MS (EI, 70 eV): [$C_{20}H_{27}N$], calcd.: 281.2143; found: 281.2138.

(((*trans*)-4-(*tert*-Butyl)cyclohexyl)ethynyl)trimethylsilane (3n)



Following **TP3** 1-(*tert*-butyl)-4-bromocyclohexane (**1i**: 109 mg, 0.5 mmol, 1.0 equiv), or 1-(*tert*-butyl)-4-iodocyclohexane (**1j**: 133 mg, 0.5 mmol, 1.0 equiv was coupled with ((4-methoxyphenyl) ethynyl)zinc pivalate (**2k**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: starting from **1i**: 99 mg, 0.42 mmol, 84%, dr = 90:10, colorless oil.

Isolated yield: starting from **1j**: 84 mg, 0.36 mmol, 71%, dr = 90:10, colorless oil

Purification: *i*-hexane

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 2.14 (tt, *J* = 12.0, 3.7 Hz, 1H), 2.06 – 1.96 (m, 2H), 1.75 (ddd, *J* = 9.1, 4.6, 2.6 Hz, 2H), 1.42 – 1.22 (m, 2H), 1.04 – 0.88 (m, 3H), 0.82 (s, 9H), 0.14 (s, 9H).

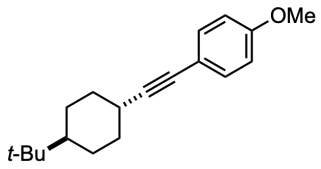
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 112.2, 83.2, 47.4, 33.7, 32.5, 30.9, 27.6, 27.0, 0.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2941, 2858, 1365, 1248, 1211, 862, 837, 758, 696, 665.

MS (EI, 70 eV): *m/z* (%) = 236 (1), 221 (49), 147 (39), 119 (39), 105 (20), 91 (18), 73 (100), 41 (20).

HR-MS (EI, 70 eV): [$C_{15}H_{28}Si$], calcd.: 236.1960; found: 236.1953.

1-(((*trans*)-4-(*tert*-Butyl)cyclohexyl)ethynyl)-4-methoxybenzene (3o)



Following **TP3** 1-(*tert*-butyl)-4-iodocyclohexane (**1j**, 133 mg, 0.5 mmol, 1.0 equiv) was coupled with ((4-methoxyphenyl) ethynyl)zinc pivalate (**2l**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 99 mg, 0.37 mmol, 73%, dr = 94:6, colorless crystals.

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

m.p.: 83.6 – 85.4 °C. **^{1}H-NMR (400 MHz, $CDCl_3$, ppm):** δ = 7.39 – 7.28 (m, 2H), 6.85 – 6.73 (m, 2H), 3.79 (s, 3H), 2.32 (tt, *J* = 12.0, 3.7 Hz, 1H), 2.17 – 2.03 (m, 2H), 1.87 – 1.72 (m, 2H), 1.47 – 1.34 (m, 2H), 1.14 – 0.94 (m, 3H), 0.85 (s, 9H).

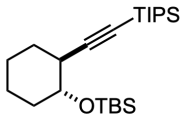
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 159.1, 133.0, 116.3, 113.9, 93.2, 79.8, 55.4, 47.5, 33.9, 32.6, 30.6, 27.6, 27.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2937, 2858, 1605, 1509, 1466, 1441, 1364, 1287, 1245, 1364, 1287, 1245, 1181, 1172, 1031, 904, 831.

MS (EI, 70 eV): *m/z* (%) = 270 (18), 160 (100), 159 (64), 145 (25), 134 (24), 129 (38).

HR-MS (EI, 70 eV): [$C_{19}H_{26}O$], calcd.: 270.1984; found: 270.1980.

***tert*-Butyldimethyl(((*trans*)-2-((triisopropylsilyl)ethynyl)cyclohexyl)oxy)silane (3p)**



Following **TP3** *tert*-butyl((2-bromocyclohexyl)oxy)dimethylsilane (**1l**, 146 mg 0.5 mmol, 1.0 equiv) was coupled with triisopropylsilyl)ethynyl)zinc pivalate (**2b**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Large scale experiment:

A dry and argon-flushed 50 mL *Schlenk*-tube, equipped with a stirring bar and a septum, was

charged with anhydrous $CoCl_2$ (1.0 mmol, 130 mg, 20 mol%), *tert*-butyl((2-iodocyclohexyl)oxy) dimethylsilane (**1k**, 1.70 g, 5.0 mmol, 1.0 equiv), THF (10 mL), and **20** (10 mmol, 1.9 mL, 2.0 equiv) were added. The reaction mixture was cooled to 0 °C with an ice bath and the THF solution of triisopropylsilyl)ethynyl)zinc pivalate (**2b**, 0.58 M, 7.5 mmol, 1.5 equiv), prepared according to *TP2* was added dropwise. The reaction was stirred and monitored by GC-analysis (tetradecane, $C_{14}H_{30}$ was used as an internal standard). After 8 h, saturated aq. NH_4Cl solution (100 mL) was added, the phases were separated and the aq. phase was extracted with EtOAc (3 x 200 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 **3p**.

Isolated yield: starting from **1k**: 1.54 g, 3.85 mmol, 77%; dr = 99:1, colorless oil.

Isolated yield: starting from **1l**: 118 mg 0.30 mmol, 60%; dr = 99:1, colorless oil.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 3.77 – 3.63 (m, 1H), 2.44 (td, J = 6.8, 4.2 Hz, 1H), 2.03 – 1.83 (m, 1H), 1.77 – 1.59 (m, 2H), 1.53 – 1.41 (m, 1H), 1.31 (tdd, J = 16.4, 11.7, 6.2 Hz, 4H), 1.06 (d, J = 4.7 Hz, 21H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

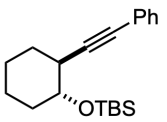
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 114.3, 78.7, 43.7, 36.8, 33.8, 33.0, 31.2, 29.0, 26.1, 19.9, 19.8, 18.8, 11.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932, 2890, 2861, 1694, 1471, 1462, 1360, 1250, 1157, 1104, 1064, 1022, 1005, 996, 943, 919, 70, 834, 811, 773, 689, 668.

MS (EI, 70 eV): *m/z* (%) = 296 (19), 295 (100), 269 (35), 253 (87), 225 (18), 211 (12).

HR-MS (EI, 70 eV): [$C_{23}H_{45}OSi_2$], calcd.: 393.3014; found: 393.2999 [M^+-Me].

***tert*-Butyldimethyl(((*trans*)-2-(phenylethynyl)cyclohexyl)oxy)silane (3q)**



Following **TP3** *tert*-butyl((2-iodocyclohexyl)oxy)dimethylsilane (**1k**, 170 mg, 0.5 mmol, 1.0 equiv) was coupled with 2-phenylethynylzinc pivalate (**2a**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 113 mg, 0.36 mmol, 72%, dr = 96:4, yellow oil.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.42 – 7.35 (m, 2H), 7.32 – 7.23 (m, 3H), 3.67 (td, *J* = 8.0, 3.5 Hz, 1H), 2.52 (td, *J* = 8.8, 3.8 Hz, 1H), 2.15 – 2.01 (m, 1H), 1.93 (ddd, J = 9.9, 6.0, 3.1 Hz, 1H), 1.70 (ddt, *J* = 16.7, 11.0, 6.3 Hz, 2H), 1.48 (ddd, *J* = 13.3, 9.7, 3.7 Hz, 1H), 1.31 (ddd, *J* = 18.8, 14.6, 9.6 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).

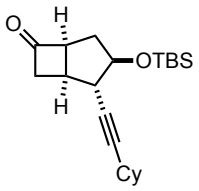
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 131.7, 128.3, 127.6, 124.3, 93.2, 81.7, 73.3, 38.5, 34.4, 30.5, 26.0, 24.3, 23.5, 18.3, -4.4, -4.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928, 2855, 1490, 1471, 1461, 1442, 1360, 1248, 1130, 1098, 1060, 1039, 1039, 1022, 1005, 937, 875, 833, 814, 773, 753, 689.

MS (EI, 70 eV): *m/z* (%) = 257 (100), 183 (89), 181 (48), 159 (25), 141 (56), 115 (22), 75 (95), 73 (20).

HR-MS (EI, 70 eV): [$C_{20}H_{29}OSI$], calcd.: 313.1993; found: 313.1982 [M^+-Me].

4-((*tert*-Butyldimethylsilyl)oxy)-3-(cyclohexylethynyl)bicyclo[3.2.0]heptan-6-one (3r)



Following **TP3** (3-bromo-4-((*tert*-butyldimethylsilyl)oxy)bicyclo[3.2.0]heptan-6-one (**1w**, 159 mg, 0.5 mmol, 1.0 equiv) was coupled with (cyclohexylethynyl)zinc pivalate (**2m**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 107 mg, 0.31 mmol, 62%, dr = 99:1, yellow oil.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 4.34 – 4.29 (m, 1H), 3.67 (ddt, *J* = 9.3, 7.7, 2.0 Hz, 1H), 3.19 – 3.01 (m, 2H), 2.98 – 2.88 (m, 1H), 2.82 (dd, *J* = 2.1, 1.0 Hz, 1H), 2.31 (s, 1H), 2.25 – 2.05 (m, 2H), 1.78 – 1.46 (m, 5H), 1.43 – 1.18 (m, 5H), 0.83 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 212.8, 88.0, 81.3, 80.8, 63.6, 52.5, 45.1, 39.9, 36.5, 33.0, 29.1, 26.0, 25.7, 24.9, 17.9, -4.9.

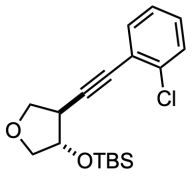
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928, 2855, 1779, 1471, 1463, 1449, 1362, 1255, 1215, 1179, 1093,

1070, 1027, 1005, 963, 937, 903, 835, 812, 774.

MS (EI, 70 eV): *m/z* (%) = 289 (49), 189 (15), 155 (16), 129 (32), 91 (37), 75 (100), 73 (52).

HR-MS (EI, 70 eV): [$C_{20}H_{31}O_2Si$], calcd.: 331.2099; found: 331.2084 [M^+-Me].

***tert*-Butyl(((*trans*)-4-((2-chlorophenyl)ethynyl)tetrahydrofuran-3-yl)oxy)dimethylsilane (3s)**



Following **TP3** *tert*-butyl((4-iodotetrahydrofuran-3-yl)oxy)dimethylsilane (**1n**, 164 mg, 0.5 mmol, 1.0 equiv) was coupled with ((2-chlorophenyl)ethynyl)zinc pivalate (**2n**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 106 mg, 0.32 mmol, 63%, dr = 99:1, yellow oil.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.27 (dd, J = 7.2, 2.2 Hz, 1H), 7.23 (dd, J = 7.9, 1.5 Hz, 1H), 7.11 – 7.00 (m, 2H), 4.39 (dt, J = 5.0, 3.1 Hz, 1H), 4.08 (dd, J = 8.2, 7.0 Hz, 1H), 3.91 (dd, J = 9.2, 4.9 Hz, 1H), 3.74 (dd, J = 8.3, 5.4 Hz, 1H), 3.56 (dd, J = 9.2, 2.9 Hz, 1H), 2.97 (ddd, J = 7.0, 5.4, 3.2 Hz, 1H), 0.76 (s, 9H), 0.00 (s, 3H), –0.02 (s, 3H).

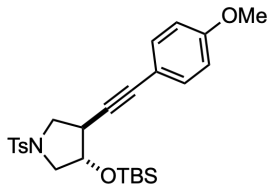
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 136.0, 133.3, 129.3, 129.1, 126.5, 123.2, 94.1, 80.1, 78.8, 75.4, 72.5, 41.4, 25.9, 18.2, -4.5, -4.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2950, 2928, 2855, 1694, 1472, 1436, 1361, 1251, 1202, 1101, 1063, 1033, 1004, 940, 907, 862, 834, 831, 811, 777, 752, 722.

MS (EI, 70 eV): *m/z* (%) = 279 (18), 162 (12), 148 (12), 139 (31), 118 (8), 117 (100), 75 (40), 73 (31), 59 (8).

HR-MS (EI, 70 eV): [$C_{18}H_{24}ClO_2Si$], calcd.: 335.1240; found: 335.1237 [M^+-H].

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



Following **TP3** 3-((*tert*-butyldimethylsilyl)oxy)-4-iodo-1-tosylpyrrolidine (**1o**, 241 mg, 0.5 mmol, 1.0 equiv) was coupled with ((4-methoxyphenyl)ethynyl)zinc pivalate (**2l**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 182 mg, 0.38 mmol, 75%, dr = 99:1, colorless crystals.

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

m.p.: 87.3 – 89.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.73 (d, J = 8.3 Hz, 2H), 7.30 – 7.25 (m, 3H), 7.20 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 4.34 – 4.21 (m, 1H), 3.80 (s, 3H), 3.73 – 3.55 (m, 2H), 3.45 (dd, J = 9.5, 4.9 Hz, 1H), 3.24 – 3.12 (m, 1H), 2.89 (dt, J = 6.9, 4.6 Hz, 1H), 2.35 (s, 3H), 0.80 (s, 10H), 0.04 (s, 3H), 0.02 (s, 3H).

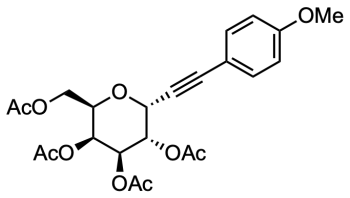
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 159.6, 143.6, 133.90 133.1, 129.8, 127.7, 114.9, 113.95, 85.5, 83.7, 76.2, 55.4, 54.7, 51.6, 39.5, 25.7, 21.6, 18.0, -4.6, -4.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953, 2932, 2858, 1606, 1508, 1471, 1460, 1441, 1380, 1343, 1322, 1290, 1247, 1231, 1209, 1175, 1156, 1091, 1053, 1032, 1016, 1003, 955, 939, 914, 835, 816, 800, 776.

MS (EI, 70 eV): *m/z* (%) = 439 (30), 429 (73), 428 (100), 428 (100), 428 (97), 428 (92), 428 (93), 428 (76), 428 (83), 428 (88), 428 (89), 298 (43), 91 (23), 73 (31).

HR-MS (EI, 70 eV): [$C_{26}H_{35}NO_4SSi$], calcd.: 485.2056; found: 485.2037.

(1-(4-Methoxyphenyl)ethynyl)-2,3,4,6-tetra-O-acetyl-α-*D*-galactopyranose (3u)



Following **TP3** 1-bromo-2,3,4,6-tetra-O-Acetyl-α-*D*-galactopyranose (**1p**, 205 mg, 0.5 mmol, 1.0 equiv) was coupled with ((4-methoxyphenyl)ethynyl)zinc pivalate (**2l**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 125 mg, 0.27 mmol, 54%, α/β = 94:6, yellow oil.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.50 – 7.37 (m, 2H), 6.95 – 6.76 (m, 2H), 5.50 (dd, *J* = 3.4, 1.3 Hz, 1H), 5.42 (dd, *J* = 10.5, 3.3 Hz, 1H), 5.29 (d, *J* = 5.8 Hz, 1H), 5.24 (dd, *J* = 10.5, 5.8 Hz, 1H), 4.48 (td, *J* = 6.7, 1.3 Hz, 1H), 4.24 – 4.04 (m, 2H), 3.83 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 170.6, 170.4, 170.4, 170.3, 160.4, 133.7, 114.2, 113.7, 89.9, 80.3, 69.6, 69.0, 68.0, 67.3, 66.8, 61.8, 55.5, 21.0, 20.9, 20.9, 20.8.

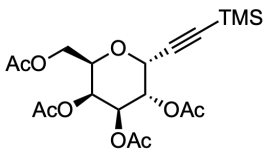
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3018, 1747, 1606, 1510, 1370, 1212, 1054, 834.

MS (EI, 70 eV): *m/z* (%) = 269 (21), 240 (37), 227 (100), 203 (11), 187 (13), 161 (16), 159 (30), 139 (11), 135 (15), 97 (21), 43 (28).

HR-MS (EI, 70 eV): [$C_{23}H_{26}O_{10}$], calcd.: 462.1526; found: 462.1519.

Optical rotation: $[\alpha]_\lambda^\varphi$ = 157.7 (c = 0.35, $CHCl_3$).

(1-(Trimethylsilyl)ethynyl)-2,3,4,6-tetra-O-acetyl-α-*D*-galactopyranose (3v)



Following **TP3** 1-bromo-2,3,4,6-tetra-O-Acetyl-α-*D*-galactopyranose (**1p**, 205 mg, 0.5 mmol, 1.0 equiv) was coupled with (trimethylsilyl)ethynyl)zinc pivalate (**2k**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 111 mg, 0.26 mmol, 52%, α/β = 95:5, yellow oil.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.45 (dd, *J* = 3.4, 1.3 Hz, 1H), 5.29 (dd, *J* = 10.5, 3.3 Hz, 1H), 5.12 (dd, *J* = 10.5, 5.9 Hz, 1H), 5.06 (d, *J* = 5.9 Hz, 1H), 4.36 (td, *J* = 6.6, 1.3 Hz, 1H), 4.13 (dd, *J* = 11.3, 6.5 Hz, 1H), 4.04 (dd, *J* = 11.3, 6.7 Hz, 1H).2.11 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 0.20 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 170.5, 170.3, 170.2, 170.1, 97.9, 96.0, 69.5, 68.8, 67.8, 66.9, 66.4, 61.7, 20.9, 20.8, 20.8, 20.8, -0.2.

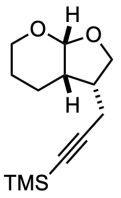
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962, 1745, 1431, 1369, 1220, 1121, 1091, 1057, 950, 908, 844, 761.

MS (EI, 70 eV): *m/z* (%) = 139 (10), 115 (10), 97 (17), 44 (12), 43 (100).

HR-MS (EI, 70 eV): [$C_{19}H_{28}O_9Si$], calcd.: 428.1503; found: 428.1491.

Optical rotation: $[\alpha]_\lambda^\varphi$ = 161.4 (c = 0.57, $CHCl_3$)

Hexahydro-4*H*-furo[2,3-*b*]pyran-3-yl)prop-1-yn-1-yl)trimethylsilane (3w)



Following **TP3** 2-(allyloxy)-3-iodotetrahydro-2*H*-pyran (**1q**, 134 mg, 0.5 mmol, 1.0 equiv) was coupled with (trimethylsilyl)ethynyl)zinc pivalate (**2k**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 91 mg, 0.34 mmol, 68%, dr = 95:5, colorless solid.

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.24 (d, *J* = 3.5 Hz, H), 3.83 (t, *J* = 8.1 Hz, H), 3.67 (tdd, *J* = 10.9, 2.6, 0.6 Hz, 1H), 3.57 – 3.35 (m, 2H), 2.17 (dqd, *J* = 9.5, 8.0, 6.1 Hz, 1H), 2.02 – 1.84 (m, 2H), 1.65 (dtd, *J* = 10.1, 6.2, 3.6 Hz, 1H), 1.37 – 1.15 (m, 2H), 1.14 – 0.91 (m, 2H), 0.20 (s, H).

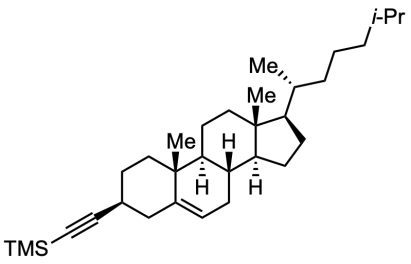
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 105.6, 102.1, 85.2, 69.4, 60.9, 40.3, 36.9, 23.4, 19.4, 18.5, 0.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3018, 2948, 2173, 1770, 1405, 1250, 1214, 1147, 1097, 1018, 945, 899, 843.

MS (EI, 70 eV): *m/z* (%) = 209 (10), 139 (16), 125 (100), 97 (29), 91 (27), 79 (25), 75 (35), 73 (31).

HR-MS (EI, 70 eV): [$C_{13}H_{21}O_2Si$], calcd.: 237.1316; found: 237.1305 [M^+-H].

(3β)-3-(Trimethylsilyl(ethynyl))cholest-5-ene (3x)



Following **TP3** 3-iodo cholest-5-ene (**1r**, 248 mg, 0.5 mmol, 1.0 equiv) was coupled with (trimethylsilyl)ethynyl)zinc pivalate (**2k**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 175 mg, 0.38 mmol, 75%, dr = 98:2, colorless crystals.

Purification: *i*-hexane.

m.p.: 132.8 – 134.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 5.31 (dt, *J* = 5.5, 1.9 Hz, 1H), 2.39 – 2.13 (m, 3H), 2.07 – 1.90 (m, 2H), 1.89 – 1.73 (m, 4H), 1.69 – 0.94 (m, 21H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.86 (dd, *J* = 6.6, 1.9 Hz, 7H), 0.66 (s, 3H), 0.14 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 141.5, 120.9, 111.6, 83.8, 56.9, 56.3, 50.3, 42.4, 39.9, 39.7, 39.1, 39.0, 36.9, 36.3, 35.9, 32.2, 32.0, 31.9, 29.9, 29.3, 28.4, 28.2, 24.4, 24.0, 23.0, 22.2, 21.0, 19.51, 18.9, 12.0, 0.4.

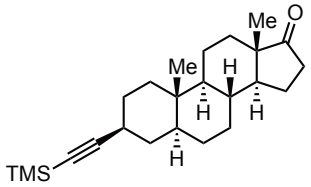
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932, 2864, 2848, 1466, 1436, 1374, 1247, 837, 802, 758.

MS (EI, 70 eV): *m/z* (%) = 466 (21), 281 (39), 225 (58), 209 (23), 207 (100), 145 (15), 95 (14), 91 (17), 73 (54).

HR-MS (EI, 70 eV): [$C_{32}H_{54}Si$], calcd.: 466.3995; found: 466.3983.

Optical rotation: $[\alpha]_\lambda^\varphi$ = 9.4 (c = 1.04, $CHCl_3$)

(3β)-3-(Trimethylsilyl(ethynyl))epiandrosterone (3y)



Following **TP3** 3-iodo epiandrosterone (**1s**, 248 mg, 0.5 mmol, 1.0 equiv) was coupled with (trimethylsilyl)ethynyl)zinc pivalate (**2k**, 0.75 mmol, 1.5 equiv) prepared according to **TP2**. The solution was stirred for 8 h and was worked-up as usual.

Isolated yield: 156 mg, 0.42 mmol, 84%, dr = 93:7, orange crystals.

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

m.p.: 115.9 – 118.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 2.51 – 2.33 (m, 1H), 2.23 (tt, *J* = 12.3, 4.1 Hz, 1H), 2.03 (dt, *J* = 19.0, 9.0 Hz, 1H), 1.96 – 1.84 (m, 1H), 1.83 – 1.70 (m, 3H), 1.71 – 1.58 (m, 2H), 1.49 (dddd, *J* = 17.8, 15.9, 8.1, 3.5 Hz, 4H), 1.42 – 1.14 (m, 6H), 1.09 – 0.97 (m, 1H), 0.97 – 0.87 (m, 2H), 0.82 (s, 3H), 0.80 (s, 3H), 0.67 (ddd, *J* = 12.0, 10.3, 3.9 Hz, 1H), 0.11 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 221.28, 111.77, 83.25, 54.54, 51.55, 47.87, 46.39, 38.07, 35.91, 35.84, 35.32, 35.11, 31.64, 30.98, 30.93, 28.77, 28.33, 21.84, 20.28, 13.90, 12.36, 0.39.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2928, 2847, 2168, 1736, 1448, 1374, 1244, 1199, 1057, 1022, 1007, 900, 831, 758.

MS (EI, 70 eV): *m/z* (%) = 371 (16), 370 (40), 356 (36), 355 (100), 142 (10), 142 (10), 73 (39).

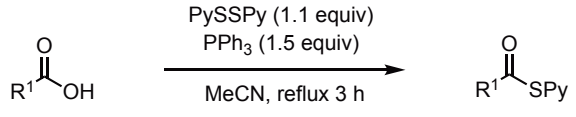
HR-MS (EI, 70 eV): [$C_{32}H_{54}Si$], calcd.: 370.2692; found: 370.2668.

Optical rotation: $[\alpha]_\lambda^\varphi$ = 80.2 (c = 1.01, $CHCl_3$)

3 Cobalt-Catalyzed Acylation-Reactions of (Hetero)arylzinc Pivalates with Thiopyridyl Ester Derivatives

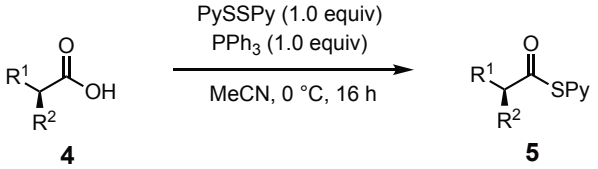
3.1 Preparation of Starting Materials

Preparation of thiopyridyl esters TP4:[77a]



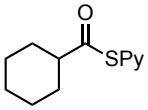
The corresponding carboxylic acid **4** (1.0 equiv), PPh_3 (1.5 equiv) and 2,2'-dipyridyl disulfide (1.1 equiv) were added to a round bottom flask equipped with a magnetic stirring bar. The mixture was dissolved in MeCN (0.3 M) and heated to reflux for 3 h. After solvent evaporation, the resulting thiopyridyl ester was purified by column chromatography (SiO_2, *i*-hexane/ethyl acetate) yielding the pure thioester **5**.

Preparation of α-chiral-thiopyridyl esters (TP5):



The corresponding α-chiral-carboxylic acid **4** (1.0 equiv), PPh_3 (1.0 equiv) and 2,2'-dipyridyl disulfide (1.0 equiv) were added to a round bottom flask equipped with a magnetic stirring bar. The mixture was dissolved in MeCN (0.3 M), cooled to 0 °C and stirred for 16 h. After solvent evaporation, the resulting substrate was purified by column chromatography (SiO_2, *i*-hexane/ethyl acetate) yielding the corresponding thioester **5**..

***S*-(Pyridin-2-yl) cyclohexanecarbothioate (5a)**

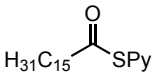


S-(Pyridin-2-yl) cyclohexanecarbothioate (**5a**) was prepared according to **TP4** from

cyclohexanecarboxylic acid (**4a**, 2.21 g, 10.00 mmol) and was obtained as a yellow solid (1.68 g, 7.60 mmol, 76% yield). The analytical data is in full consistency with the data reported in the literature.[106]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.61 (dd, *J* = 5.2, 1.9 Hz, 1H), 7.71 (tt, *J* = 7.7, 1.4 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.17 (m, 1H), 2.62 (tt, *J* = 11.4, 3.5 Hz, 1H), 2.08 – 1.96 (m, 2H), 1.81 (dt, *J* = 12.8, 3.4 Hz, 2H), 1.67 (dt, *J* = 12.6, 3.6 Hz, 1H), 1.53 (qd, *J* = 12.0, 3.3 Hz, 2H), 1.40 – 1.12 (m, 3H).

***S*-(Pyridin-2-yl) hexadecanethioate (5b)**



S-(Pyridin-2-yl) hexadecanethioate (**5b**) was prepared according to **TP4** from palmitic acid (**4b**, 512 mg, 2.00 mmol) and was obtained as a yellow powder (684 mg, 1.96 mmol, 98% yield).

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

m.p.: 62.0 – 63.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.66 – 8.58 (m, 1H), 7.73 (td, *J* = 7.7, 1.9 Hz, 1H), 7.61 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.33 – 7.26 (m, 1H), 2.69 (t, *J* = 7.5 Hz, 2H), 1.72 (p, *J* = 7.5 Hz, 2H), 1.25 (s, 24H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.8, 151.8, 150.5, 137.2, 130.3, 123.6, 44.4, 32.1, 29.9, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.1, 25.6, 22.9, 14.3.

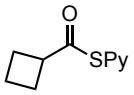
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2916, 2848, 1796, 1739, 1696, 1571, 1472, 1463, 1446, 1421, 1382, 1124, 1107, 1092, 1061, 1049, 981, 945, 905, 762, 718.

MS (EI, 70 eV): *m/z* (%) = 239 (9), 112 (32), 111 (100), 98 (16), 57 (11), 43 (25).

HR-MS (EI, 70 eV): [$C_{21}H_{35}NOS$], calcd.: 349.2439; found: 349.2432.

[106] B. Neises, W. Steglich, T. Van Ree, S. *Afr. J. Chem.* **1981**, *34*, 58-59.

***S*-Pyridin-2-yl) cyclobutanecarbothioate (5c)**



S-(Pyridin-2-yl) cyclobutanecarbothioate (**5c**) was prepared according to **TP4** from cyclobutanecarboxylic acid (**4c**, 200 mg, 2.00 mmol) and was obtained as a yellow oil (305 mg, 1.58 mmol, 79%).

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.66 – 8.50 (m, 1H), 7.67 (td, *J* = 7.7, 1.9 Hz, 1H), 7.55 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.24 – 7.18 (m, 1H), 3.43 (pd, *J* = 8.5, 1.0 Hz, 1H), 2.45 – 2.27 (m, 2H), 2.20 (dtdd, *J* = 12.6, 8.3, 4.2, 2.3 Hz, 2H), 2.02 – 1.72 (m, 2H).

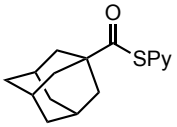
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 198.4, 151.6, 150.4, 137.1, 130.2, 123.4, 47.0, 26.0, 18.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2986, 2944, 1698, 1572, 1562, 1448, 1420, 1334, 1280, 1245, 1186, 1139, 1105, 1059, 1046, 988, 956, 885, 813, 763, 722, 677.

MS (EI, 70 eV): *m/z* (%) = 258 (36), 211 (19), 136 (9) 135 (100), 77 (11).

HR-MS (EI, 70 eV): [$C_{10}H_{12}NOS$], calcd.: 194.0634; found: 194.0634 [M^++H].

***S*-(Pyridin-2-yl)-adamantane-1-carbothioate (5d)**



S-(Pyridin-2-yl)-adamantane-1-carbothioate (**5d**) was prepared according to **TP4** from adamantane-1-carboxylic acid (**4d**, 360 mg, 2.00 mmol) and was obtained as a pale yellow powder (464 mg, 1.70 mmol, 85% yield).

Purification: *i*-hexane:ethyl acetate = 9:1 to 8:2.

m.p.: 73.2 – 75.6 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.62 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.71 (td, *J* = 7.7, 1.9 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.17 (m, 1H), 2.09 (p, *J* = 3.1 Hz, 3H), 2.00 (d, *J* = 3.0 Hz, 6H),

1.83 – 1.63 (m, 6H).

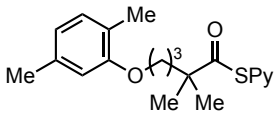
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 203.5, 152.0, 150.5, 137.0, 131.1, 123.4, 49.6, 39.3, 36.5, 28.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2909, 2848, 1689, 1572, 1562, 1449, 1421, 1342, 1280, 1250, 1188, 1138, 1116, 1102, 1084, 1045, 986, 946, 918, 822, 795, 760, 742, 724, 671.

MS (EI, 70 eV): *m/z* (%) = 273 (2), 244 (6), 136 (8), 135 (100), 93 (8), 79 (9).

HR-MS (EI, 70 eV): [$C_{16}H_{19}NOS$], calcd.: 273.1187; found: 273.1176.

***S*-pyridin-2-yl) 3-(2,5-dimethylphenoxy)-2,2-dimethylpropanethioate (5e)**



S-(Pyridin-2-yl) 3-(2,5-dimethylphenoxy)-2,2-dimethylpropanethioate (**5e**) was prepared according to **TP4** from 3-(2,5-dimethylphenoxy)-2,2-dimethylpropanoic acid (**4e**, 444 mg, 2.00 mmol) and was obtained as a yellow oil (617 mg, 1.96 mmol, 98% yield).

Purification: *i*-hexane:ethyl acetate = 9:1 to 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.64 (ddd, J = 4.8, 2.0, 0.8 Hz, 1H), 7.73 (td, J = 7.7, 2.0 Hz, 1H), 7.53 (dt, J = 8.0, 1.0 Hz, 1H), 7.29 (ddd, J = 7.6, 4.8, 1.1 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.69 – 6.64 (m, 1H), 6.61 (d, J = 1.5 Hz, 1H), 3.95 (t, J = 5.4 Hz, 2H), 2.31 (s, 3H), 2.19 (s, 3H), 1.91 – 1.79 (m, 4H), 1.36 (s, 6H).

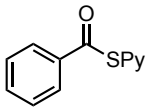
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 203.6, 157.0, 151.9, 150.6, 137.1, 136.6, 131.0, 130.4, 123.7, 123.5, 120.8, 112.0, 67.8, 50.6, 37.6, 25.4, 25.0, 21.6, 16.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2966, 2922, 1693, 1614, 1583, 1573, 1563, 1509, 1448, 1419, 1389, 1366, 1285, 1263, 1156, 1129, 1044, 1000, 988, 931, 906, 803, 764, 724.

MS (EI, 70 eV): *m/z* (%) = 258 (36), 211 (19), 136 (9) 135 (100), 77 (11).

HR-MS (EI, 70 eV): [$C_{20}H_{25}NO_2S$], calcd.: 344.1679; found: 344.1678 [M^++H].

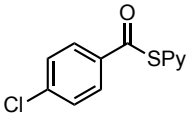
_S_-(Pyridin-2-yl) benzothioate (5f)



_S_-(Pyridin-2-yl) benzothioate (**5f**) was prepared according to **TP4** from 4-chlorobenzoic acid (**4f**, 1.22 g, 10.0 mmol) and was obtained as a yellow solid (1.81 g, 8.40 mmol, 84% yield). The analytical data was in full consistency with the data reported in the literature.[107]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.72 – 8.62 (m, 1H), 8.08 – 7.97 (m, 2H), 7.79 (td, J = 7.7, 1.9 Hz, 1H), 7.73 (dt, J = 8.0, 1.0 Hz, 1H), 7.67 – 7.56 (m, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.33 (ddt, J = 7.1, 4.8, 1.0 Hz, 1H).

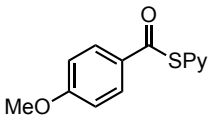
_S_-(Pyridin-2-yl) 4-chlorobenzothioate (5g)



_S_-(Pyridin-2-yl) 4-chlorobenzothioate (**5g**) was prepared according to **TP4** from 4-chlorobenzoic acid (**4f**, 1.55 g, 10.0 mmol) and was obtained as a yellow needles (1.64 g, 6.60 mmol, 66% yield). The analytical data was in full consistency with the data reported in the literature.[108]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.68 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 8.03 – 7.92 (m, 2H), 7.79 (td, J = 7.7, 1.9 Hz, 1H), 7.71 (dt, J = 7.9, 1.0 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.34 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H).

_S_-Pyridin-2-yl) 4-methoxybenzothioate (5h)



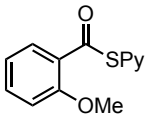
_S_-(Pyridin-2-yl) 4-methoxybenzothioate (**5h**) was prepared according to **TP4** from 4-methoxybenzoic acid (**4h**, 304 mg, 2.00 mmol) and was obtained as a yellow solid

[107] C. M. Lemon, E. Karnas, M. G. Bawendi, D. G. Nocera, *Inorg. Chem.* **2013**, *52*, 10394–10406.
[108] M. Ociepa, O. Baka, J. Narodowiec, D. Gryko, *Adv. Synth. Catal.* **2017**, *359*, 3560–3565.

(338 mg, 1.38 mmol, 69% yield). The analytical data was in full consistency with the data reported in the literature.[109]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.59 (ddt, J = 3.6, 2.6, 1.4 Hz, 1H), 7.93 (dd, J = 9.0, 2.2 Hz, 2H), 7.77 – 7.59 (m, 2H), 7.25 (dtd, J = 6.8, 3.2, 1.6 Hz, 1H), 6.89 (dd, J = 9.1, 2.6 Hz, 2H), 3.81 (s, 3H).

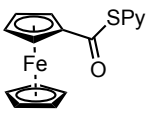
***S*-Pyridin-2-yl) 2-methoxybenzothioate (5h')**



S-(Pyridin-2-yl) 2-methoxybenzothioatewas (**5h**') prepared according to **TP4** from 2-methoxybenzoic acid (**4h'**, 304 mg, 2.00 mmol) and was obtained as a yellow oil (470 mg, 1.92 mmol, 96% yield). The analytical data was in full consistency with the data reported in the literature.[110]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.74 – 8.58 (m, 1H), 7.86 (dd, J = 8.0, 1.7 Hz, 1H), 7.80 – 7.70 (m, 2H), 7.51 (ddd, J = 7.9, 7.0, 1.8 Hz, 1H), 7.30 (ddd, J = 6.7, 4.8, 1.9 Hz, 1H), 7.07 – 6.98 (m, 2H), 3.96 (s, 3H).

***S*-(Pyridin-2-yl) ferrocenecarbothioate(5n)**



S-(Pyridin-2-yl) ferrocene (**5n**) prepared according to **TP4** from ferrocene monocarboxylic acid (**4i**, 460 mg, 2.00 mmol) and was obtained as red crystals (588 mg, 1.22 mmol, 91% yield).

Purification: *i*-hexane:ethyl acetate = 9:1 to 8:2.

m.p.: 84.6 – 86.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.64 (d, J = 5.1 Hz, 1H), 7.75 (d, J = 6.5 Hz, 2H), 7.28 (dd, J = 11.8, 5.0 Hz, 1H), 4.94 (s, 2H), 4.55 (s, 2H), 4.31 (s, 5H).

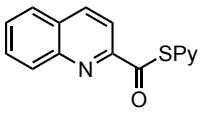
[109] S. H. H. Zaidi, K. Muthukumaran, S.-i. Tamaru, J. S. Lindsey, *J. Org. Chem.* **2004**, *69*, 8356–8365.
[110] M. Ociepa, O. Baka, J. Narodowiec, D. Gryko, *Adv. Synth. Catal.* **2017**, *359*, 3560–3565.

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 190.9, 152.4, 150.4, 150.3, 137.0, 130.4, 123.3, 123.3, 123.3, 78.8, 72.4, 72.4, 71.0, 70.8, 69.4, 69.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2923, 1652, 1570, 1446, 1422, 1369, 1239, 1121, 1106, 1045, 1024, 1002, 986, 942, 837, 810, 762, 721, 693.

MS (EI, 70 eV): *m/z* (%) = 2923, 1652, 1570, 1446, 1422, 1369, 1239, 1121, 1106, 1045, 1024, 1002, 986, 942, 837, 810, 762, 721, 693.

***S*-(Pyridin-2-yl) quinoline-2-carbothioate (5o)**



S-(Pyridin-2-yl) quinoline-2-carbothioate (**5o**) was prepared according to **TP4** from quinoline-2-carboxylic acid (**4j**, 856 mg, 5.00 mmol) and was obtained as yellow crystals (998 mg, 3.75 mmol, 75%).

Purification: *i*-hexane:ethyl acetate = 9:1 to 8:2.

m.p.: 142.8 – 144.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.80 – 8.70 (m, 1H), 8.38 – 8.25 (m, 2H), 8.03 (d, J = 8.4 Hz, 1H), 7.90 (dd, J = 8.2, 1.4 Hz, 1H), 7.87 – 7.73 (m, 3H), 7.69 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.35 (ddd, J = 7.3, 4.8, 1.4 Hz, 1H).

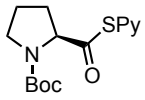
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 192.1, 152.5, 151.1, 150.6, 147.9, 137.8, 137.4, 131.0, 130.7, 130.6, 130.5, 129.2, 127.9, 123.7, 117.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2926, 1682, 1668, 1572, 1561, 1502, 1461, 1448, 1419, 1378, 1305, 1279, 1263, 1227, 1206, 1142, 1108, 1082, 1046, 988, 964, 912, 834, 792, 763, 738, 722,702.

MS (EI, 70 eV): *m/z* (%) = 266 (3), 238 (19), 237 (40), 206 (40), 205 (23).

HR-MS (EI, 70 eV): [$C_{15}H_{10}N_2OS$], calcd.: 266.0514; found: 266.0509.

***tert*-Butyl (*S*)-2-((pyridin-2-ylthio)carbonyl)pyrrolidine-1-carboxylate (5k)**



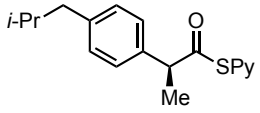
tert-Butyl (*S*)-2-((pyridin-2-ylthio)carbonyl)pyrrolidine-1-carboxylate (**5k**) was prepared according to **TP5** from (*tert*-butoxycarbonyl)-*L*-proline (**4k**, 2.15 g, 10.0 mmol) and was obtained as a yellow solid (2.24 g, 7.3 mmol, 73% yield). The analytical data is in full consistency with the data reported in the literature.[77c]

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.61 (dd, *J* = 5.0, 2.0 Hz, 0.6 H), 8.60 – 8.56 (m, 0.4 H), 7.72 (qd, *J* = 7.1, 6.5, 1.9 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 0.4 H), 7.55 (d, *J* = 7.9 Hz, 0.6 H), 7.26 (td, *J* = 9.7, 8.7, 5.0 Hz, 1.1 H), 4.57 (dd, *J* = 8.3, 3.4 Hz, 0.4 H), 4.44 (dd, *J* = 8.8, 3.8 Hz, 0.6 H), 3.54 (dtdd, *J* = 37.3, 18.1, 9.0, 6.1 Hz, 2H), 2.36 – 1.99 (m, 3H), 1.91 (pd, *J* = 7.6, 3.8 Hz, 1H), 1.48 (d, *J* = 7.1 Hz, 9H).

Optical rotation: $[\alpha]_\lambda^\varphi$ = -118 (c = 1.17, $CHCl_3$).

Chiral HPLC: >99% *ee*, AD-H column, *i*-PrOH:heptane = 5:95, 1.5 mL/min, 30 °C.

***S*-(Pyridin-2-yl) (*S*)-2-(4-isobutylphenyl)propanethioate (5l)**



(*S*)-2-(4-Isobutylphenyl)propanethioate (**5l**) was prepared according to **TP5** from (*S*)-2-(4-isobutylphenyl)- propanoic acid (**4l**, 412 mg, 2.00 mmol) and was obtained as a yellow oil (574 mg, 1.96 mmol, 96% yield).

Purification: *i*-hexane:ethyl acetate = 9:1 to 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.80 (t, *J* = 1.8 Hz, 1H), 7.69 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.34 (ddd, *J* = 7.8, 2.0, 1.1 Hz, 1H), 7.32 – 7.23 (m, 1H), 7.20 – 7.14 (m, 2H), 7.09 – 7.02 (m, 2H), 4.01 (q, *J* = 7.1 Hz, 1H), 2.47 (d, *J* = 7.1 Hz, 2H), 1.86 (dp, *J* = 13.6, 6.8 Hz, 1H), 1.60 (d, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 198.5, 151.8, 150.2, 141.3, 137.1, 136.2, 130.1, 129.6, 127.9, 123.4, 54.2, 45.1, 30.2, 22.4, 18.4.

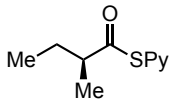
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2928, 2868, 1706, 1573, 1563, 1511, 1448, 1420, 1368, 1240, 1217, 1183, 1168, 1140, 121, 1097, 1084, 1066, 1045, 998, 988, 930, 847, 802, 763, 738, 724, 663.

MS (ESI, 70 eV): [$C_{18}H_{22}NOS$], calcd.: 300.1417; found: 300.1416 [M^++H].

Optical rotation: $[\alpha]_\lambda^\varphi$ = 104 (c = 1.24 $CHCl_3$).

Chiral HPLC: 98% *ee*, OD-H column, *i*-PrOH:heptane = 10:90, 1.0 mL/min, 30 °C.

***S*-(Pyridin-2-yl) (*S*)-2-methylbutanethioate (5m)**



S-(Pyridin-2-yl) (S)-2-methylbutanethioate (**5m**) was prepared according to **TP5** from (*S*)-2-methylbutanoic acid (**4m**, 510 mg, 5 mmol) and was obtained as a yellow oil (950 mg, 4.87 mmol, 97% yield).

Purification: *i*-hexane:ethyl acetate = 9:1 to 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.61 (ddd, *J* = 5.1, 1.8, 0.9 Hz, 1H), 7.72 (td, *J* = 7.7, 1.9 Hz, 1H), 7.60 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.26 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H), 2.70 (h, *J* = 6.9 Hz, 1H), 1.82 (dt, *J* = 13.7, 7.2 Hz, 1H), 1.54 (tt, *J* = 14.4, 7.1 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 200.8, 151.8, 150.4, 137.1, 130.3, 123.5, 50.6, 27.2, 17.1, 11.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2968, 2934, 2877, 1702, 1573, 15622, 1448, 1418, 1380, 1260, 1201, 1139, 1118, 1084, 1045, 987, 967, 939, 829, 807, 762, 732, 719, 669, 670.

MS (EI, 70 eV): *m/z* (%) = 196 (2), 166 (15), 139 (18), 134 (65), 112 (91), 111 (100), 67 (26).

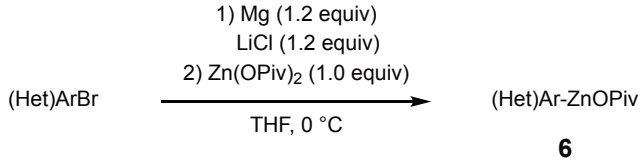
HR-MS (EI, 70 eV): [$C_{10}H_{14}NOS$], calcd.: 196.0791; found: 196.0789 [M^++H].

Optical rotation: $[\alpha]_\lambda^\varphi$ = 19 (c = 1.20 $CHCl_3$).

Chiral HPLC: 98% *ee*, OD-H column, *i*-PrOH:heptane = 2:98, 1.0 mL/min, 30 °C.

3.2 Cobalt-Catalyzed Acylation-Reactions of (Hetero)arylzinc Pivalates with Organic Thiopyridylester Derivatives

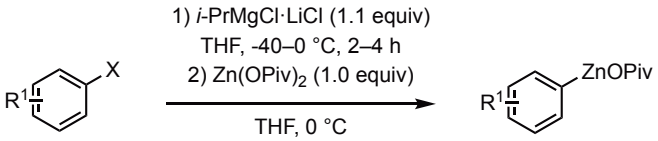
Preparation of arylzinc pivalates by magnesium insertion (TP6):



6

Magnesium turnings (1.2 equiv), dry LiCl (1.2 equiv) and dry THF (1.0 M) solution relating to the aryl bromide) were added to a dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum. The tube was charged with the aromatic bromide (1.0 equiv). For controlling the following initial heat evolution of the insertion reaction, the *Schlenk*-tube was placed in an ice bath for cooling. To monitor the progress of the insertion reaction, reaction aliquots quenched with iodine and were analyzed as water-quenched samples by GC-analysis. When the insertion was completed, solid $Zn(OPiv)_2$ (1.0 equiv) was added in one portion at 0 °C and stirred at ambient temperature for 15 min.

Preparation of arylzinc pivalates by halogen/magnesium exchange (TP7):

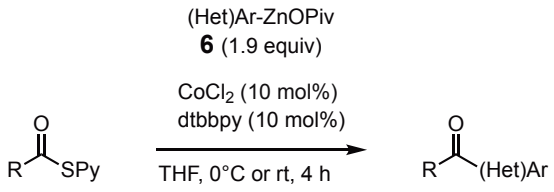


X = Br, I

6

A dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum was charged with the corresponding aryl halide (1.0 mmol) in THF (0.5 M) Then, after stirring for 5 min at ambient temperature, the resulting solution was cooled to the appropiate tepmperature, *i*-PrMgCl (1.1 mmol, 1.1 equiv) was added dropwise. GC-analysis was used to monitor the progress of the halogen-magnesium exchange, by analysis of reaction aliquots quenched with I_2. After the reaction was completed $Zn(OPiv)_2$ (1.0 equiv) was added in one portion and the mixture was slowly warmed to rt.

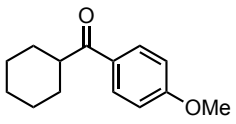
Cobalt-catalyzed acylation of arylzinc pivalates with thiopyridyl esters TP8:



5 **7**

A dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum was charged with $CoCl_2$ (6.5 mg, 0.05 mmol, 0.10 equiv, dried *in vacuo* at 400 °C prior to use). Then, the ligand 4,4'-di-*tert*-butyl-2,2'- dipyridyl (13.0 mg, 0.05 mmol, 0.10 equiv) and the corresponding thiopyridyl ester (**5**, 0.5 mmol, 1.0 equiv) were added to the *Schlenk*-tube. The resulting mixture was dissolved in dry THF (1 mL). Then, the organozinc pivalate, synthesized *via* **TP6** or **TP7** (**6**, 0.95 mmol, 1.9 equiv) was added and stirring was continued for 4 h, at 25 °C. For products **7t**-**7y** the reaction was carried out at 0 °C. The reaction conversion was monitored by GC-analysis of water-quenched reaction aliquots ($C_{14}H_{30}$ was used as an internal standard). Upon consumption of the starting material, sat. aq. NH_4Cl solution (10 mL) was added, the phases were separated and the aq. phase was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the residue was subjected to column chromatographical purification (pentane/ethyl acetate) on silica yielding the corresponding title compound **7**.

Cyclohexyl(4-methoxyphenyl)methanone (7a)



Following **TP8** *S*-(pyridin-2-yl) cyclohexanecarbothioate (**5a**, 111 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-(methoxy)phenylzinc pivalate (**6a**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 96 mg, 0.44 mmol, 88%, colorless crystals.

Purification: pentane:ethyl acetate = 99:1.

m.p.: 64.2 – 66.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.94 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H), 3.22 (tt, J = 11.5, 3.2 Hz, 1H), 1.85 (tdd, J = 11.7, 6.2, 3.0 Hz, 4H), 1.73 (dddt, J = 12.8, 5.0, 3.3, 1.7 Hz, 1H), 1.57 – 1.38 (m, 3H), 1.36 – 1.19 (m, 2H).

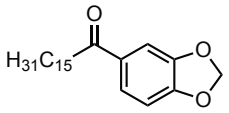
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 202.6, 163.3, 130.6, 129.4, 113.8, 55.6, 45.4, 29.7, 26.1, 26.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3065, 3019, 2973, 2944, 2916, 2846, 1639, 1628, 1594, 1573, 1504, 1499, 1466, 1454, 1442, 1416, 1405, 1302, 1296, 1284, 1256, 1224, 1182, 1175, 1148, 1116, 1094, 1064, 1028, 1013, 967, 959, 949, 928, 856, 842, 828, 815, 789, 763, 682.

MS (EI, 70 eV): *m/z* (%) = 2923, 2851, 1658, 1598, 1571, 1505, 1458, 1420, 1370, 1334, 1313, 1299, 1251, 1208, 1163, 1133, 1103, 1025, 972, 896, 844, 825, 791, 770, 742, 687.

HR-MS (EI, 70 eV): [$C_{14}H_{18}O_2$], calcd.: 218.1307; found: 218.1302.

1-(Benzo[*d*][1,3]dioxol-5-yl)hexadecan-1-one (7b)



Following **TP8** *S*-(pyridin-2-yl) hexadecanethioate (**5b**, 175 mg, 0.50 mmol, 1.0 equiv) was coupled with (benzo[*d*][1,3]dioxol-5-yl)zinc pivalate (**6b**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 162 mg, 0.45 mmol, 90%, white solid.

Purification: pentane:ethyl acetate = 100:2.

m.p.: 73.5 – 75.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.56 (dd, J = 8.2, 1.7 Hz, 1H), 7.44 (d, J = 1.7 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.04 (s, 2H), 2.87 (t, J = 7.5 Hz, 2H), 1.70 (p, J = 7.4 Hz, 2H), 1.25 (s, 26H), 0.88 (t, J = 6.7 Hz, 3H).

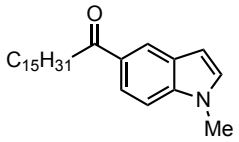
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 198.9, 151.7, 148.3, 132.1, 124.4, 108.1, 108.0, 101.9, 38.6, 32.1, 29.9, 29.8, 29.8, 29.8, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 24.8, 22.9, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961, 2952, 2914, 2868, 2847, 2774, 1675, 1604, 1497, 1488, 1472, 1462, 1444, 1418, 1373, 1359, 1285, 1279, 1263, 1258, 1250, 1200, 1110, 1092, 1051, 1004, 990, 940, 900, 889, 824, 811, 805, 780, 757, 742, 730, 719, 655.

MS (EI, 70 eV): *m/z* (%) = 281 (21), 225 (8), 209 (8), 208 (10), 207 (84), 191 (16), 165 (10), 164 (100), 149 (57), 121 (12), 44 (7).

HR-MS (EI, 70 eV): [$C_{23}H_{36}O_3$], calcd.: 360.2664; found: 360.2662.

1-(1-Methyl-1*H*-indol-5-yl)hexadecan-1-one (7c)



Following **TP8** *S*-(pyridin-2-yl) hexadecanethioate (**5b**, 175 mg, 0.50 mmol, 1.0 equiv) was coupled with ((1-methyl-1*H*-indol-5-yl)zinc pivalate (**6c**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 137 mg, 0.37 mmol, 74%, pale yellow crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 71.6 – 73.5 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.31 (d, *J* = 1.6 Hz, 1H), 7.91 (dd,*J* = 8.7, 1.7 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.11 (d, *J* = 3.2 Hz, 1H), 6.61 (d, *J* = 3.1 Hz, 1H), 3.82 (s, 3H), 3.03 (t, *J* = 7.5 Hz, 2H), 1.77 (p, *J* = 7.5 Hz, 2H), 1.26 (s, 18H), 0.88 (t, *J* = 6.7 Hz, 3H).

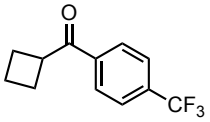
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 200.9, 139.2, 130.4, 129.4, 128.0, 122.9, 121.9, 109.2, 103.1, 38.7, 33.2, 32.1, 29.8, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 25.1, 22.9, 14.3.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2948, 2920, 2848, 1657, 1606, 1556, 1513, 1464, 1450, 1212, 1412, 1368, 1343, 1309, 1297, 1264, 1249, 1229, 1163, 1145, 1090, 968, 821, 803, 780, 766, 733, 724.

MS (EI, 70 eV): *m/z* (%) = 130 (14), 158 (72), 173 (100), 174 (14), 369 (11).

HR-MS (EI, 70 eV): [$C_{25}H_{39}N$], calcd.: 369.3032; found: 369.3037.

Cyclobutyl(4-(trifluoromethyl)phenyl)methanone (7d)



Following **TP8** *S*-(pyridin-2-yl) cyclobutanecarbothioate (**5c**, 97 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-(trifluoromethyl)phenyl)zinc pivalate (**6d**, 0.95 mmol, 1.9 equiv) prepared

according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 96 mg, 0.42 mmol, 84% yield, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.99 (dt, J = 8.1, 1.0 Hz, 2H), 7.74 – 7.68 (m, 2H), 4.13 – 3.93 (m, 1H), 2.50 – 2.26 (m, 4H), 2.18 – 2.05 (m, 1H), 1.99 – 1.86 (m, 1H).

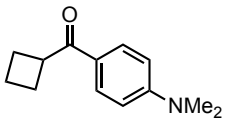
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 199.9, 138.3, 134.2 (q, J = 32.6 Hz), 128.6 , 125.7 (q, J = 3.8 Hz), 123.6 (q, J = 272.7 Hz), 42.4, 24.97, 18.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2951, 1674, 1510, 1410, 1322, 1252, 1227, 1212, 1166, 1125, 1108, 1065, 1015, 967, 949, 922, 893, 856, 842, 783, 774, 762, 731, 684, 671

MS (EI, 70 eV): *m/z* (%) = 227 (1), 174 (8), 173 (11), 173 (100), 145 (25).

HR-MS (EI, 70 eV): [$C_{12}H_{11}F_3O$], calcd.: 228.0762; found: 228.0758.

Cyclobutyl(4-(dimethylamino)phenyl)methanone (7e)



Following **TP8** *S*-(pyridin-2-yl) cyclobutanecarbothioate (**5c**, 97 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-(dimethylamino)phenyl)zinc pivalate (**6e**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 97 mg, 0.48 mmol, 95% yield, white solid.

Purification: pentane:ethyl acetate = 95:5.

m.p.: 75.2 – 77.0 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.82 – 7.71 (m, 2H), 6.67 – 6.57 (m, 2H), 3.88 (pd, J = 8.6, 1.1 Hz, 1H), 2.98 (s, 6H), 2.42 – 2.27 (m, 2H), 2.18 (dddd, J = 12.4, 10.6, 8.8, 3.9 Hz, 2H), 2.08 – 1.91 (m, 1H), 1.81 (ddddd, J = 14.6, 9.2, 7.9, 4.0, 1.1 Hz, 1H).

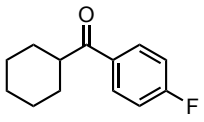
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 199.4, 153.0, 130.4, 111.0, 110.9, 41.7, 40.3, 25.3, 18.2.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959, 1667, 1622, 1478, 1387, 1261, 1195, 1167, 1025, 909, 856, 819.

MS (EI, 70 eV): *m/z* (%) = 203 (16), 148 (100), 44 (12), 42 (39).

HR-MS (EI, 70 eV): [13 xH$_{17}$NO], calcd.: 203.1310; found: 203.1305.

Cyclohexyl(4-fluorophenyl)methanone (7f)



Following **TP8** *S*-(pyridin-2-yl) cyclohexanecarbothioate (**5a**, 111 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-fluorophenyl)zinc pivalate (**6f**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 62 mg, 0.30 mmol, 60%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, CDCl$_3$, ppm): δ = 8.07 – 7.85 (m, 2H), 7.21 – 7.03 (m, 2H), 3.21 (tt, *J* = 11.4, 3.2 Hz, 1H), 1.95 – 1.79 (m, 4H), 1.74 (dtt, *J* = 13.0, 3.5, 1.8 Hz, 1H), 1.58 – 1.16 (m, 5H).

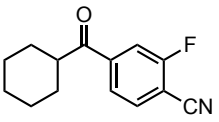
^{13}C-NMR (100 MHz, CDCl$_3$, ppm): δ = 202.4, 165.7 (d, *J* = 254.0 Hz), 132.8 (d, *J* = 3.0 Hz), 131.0 (d, *J* = 9.2 Hz), 115.8 (d, *J* = 21.7 Hz), 45.7, 29.6, 26.1, 26.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068, 2929, 2853, 1678, 1596, 1505, 1463, 1450, 1409, 1371, 1332, 1312, 1295, 1289, 1249, 1233, 1205, 1176, 1154, 1134, 1102, 1027, 1012, 974, 893, 860, 841, 824, 806, 800, 776, 738, 675.

MS (EI, 70 eV): *m/z* (%) = 206 (9), 151 (21), 138 (9), 124 (8), 123 (100), 95 (8).

HR-MS (EI, 70 eV): [C$_{13}$H$_{15}$FO], calcd.: 206.1107; found: 206.1101.

4-(Cyclohexanecarbonyl)-2-fluorobenzonitrile (7g)



Following **TP8** *S*-(pyridin-2-yl) cyclohexanecarbothioate (**5a**, 111 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-cyano-3-fluorophenyl)zinc pivalate (**6g**, 0.95 mmol, 1.9 equiv) prepared according to **TP7** from the corresponding bromide at -20 °C in 2 h. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 91 mg, 0.39 mmol, 79%, colorless crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 54.4 – 56.2 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.85 – 7.68 (m, 3H), 3.16 (tt, J = 11.3, 3.1 Hz, 1H), 1.86 (dp, J = 9.5, 3.4 Hz, 4H), 1.75 (dddd, J = 11.5, 5.2, 3.3, 1.7 Hz, 1H), 1.58 – 1.16 (m, 5H).

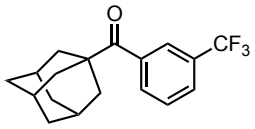
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 201.2 (d, J = 1.6 Hz), 163.4 (d, J = 261.1 Hz), 142.2 (d, J = 6.1 Hz), 134.1, 124.3 (d, J = 3.7 Hz), 116.1 (d, J = 20.5 Hz), 113.4, 105.2 (d, J = 15.9 Hz), 46.2, 29.2, 25.9, 25.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3076, 2930, 2855, 2239, 1686, 1618, 1567, 1495, 1463, 1450, 1421, 1415, 1373, 1331, 1313, 1299, 1290, 1274, 1253, 1230, 1192, 1157, 1133, 1120, 1103, 996, 988, 921, 908, 901, 873, 836, 797, 772, 734, 706.

MS (EI, 70 eV): *m/z* (%) = 231 (43), 225 (8), 216 (9), 213 (18), 190 (31), 189 (12), 188 (12), 177 (10), 176 (100), 165 (7), 164 (26), 163 (26), 158 (7), 148 (86), 121 (59), 129 (10), 105 (24), 100 (21), 83 (16), 77 (9), 68 (8), 67 (11), 55 (27).

HR-MS (EI, 70 eV): [$C_{14}H_{14}FNO$], calcd.: 231.1059; found: 231.1054.

(Adamantan-1-yl)(3-(trifluoromethyl)phenyl)methanone (7h)



Following **TP8** *S*-(pyridin-2-yl)-adamantane-1-carbothioate (**5d**, 137 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-(trifluoromethyl)phenyl) zinc pivalate (**6h**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 94 mg, 0.31 mmol, 61%, white solid.

Purification: pentane:ethyl acetate = 98:2.

m.p.: 63.6 – 65.3 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.76 (d, J = 2.0 Hz, 1H), 7.70 (t, J = 8.4 Hz, 2H), 7.52 (t, J = 7.8 Hz, 1H), 2.09 (q, J = 3.1 Hz, 3H), 1.99 (d, J = 2.9 Hz, 6H), 1.82 – 1.68 (m, 6H).

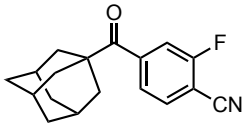
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 209.0, 140.3, 131.7 – 129.7 (m), 130.4 (d, J = 1.4 Hz), 128.7, 126.9 (q, J = 3.7 Hz), 124.1 (q, J = 3.9 Hz), 123.9 (q, J = 272.5 Hz), 47.1, 39.1, 36.5, 28.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2943, 2914, 2854, 1661, 1605, 1453, 1329, 1309, 1261, 1225, 1184, 1162, 1119, 1102, 1071, 998, 922, 808, 778, 762, 734, 695, 659.

MS (EI, 70 eV): *m/z* (%) = 308 (1), 136 (12), 135 (100), 93 (12), 79 (12).

HR-MS (EI, 70 eV): [$C_{18}H_{19}F_3O$], calcd.: 308.1388; found: 308.1382.

4-(Adamantane-1-carbonyl)-2-fluorobenzonitrile (7i)



Following **TP8** *S*-(pyridin-2-yl)-adamantane-1-carbothioate (**5d**, 137 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-cyano-3-fluorophenyl)zinc pivalate (**6g**, 0.95 mmol, 1.9 equiv) prepared according to **TP7** from the corresponding bromide at -20 °C in 2 h. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 114 mg, 0.41 mmol, 81%, colorless crystals.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 103.9 -105.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.66 (dd, J = 7.9, 6.2 Hz, 1H), 7.31 (ddd, J = 21.5, 8.5, 1.4 Hz, 2H), 2.07 (q, J = 3.1 Hz, 3H), 1.93 (d, J = 3.0 Hz, 6H), 1.81 – 1.65 (m, 6H).

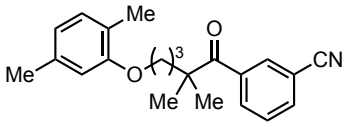
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 207.6 (d, J = 1.4 Hz), 162.6 (d, J = 261.2 Hz), 146.3 (d, J = 6.2 Hz), 133.5, 123.2 (d, J = 3.9 Hz), 115.1 (d, J = 20.9 Hz), 113.4, 102.8 (d, J = 15.6 Hz), 47.2, 38.8, 36.3, 27.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3053, 2930, 2901, 2858, 2849, 2673, 2652, 2241, 1682, 1620, 1561, 1497, 1451, 1413, 1344, 1323, 1297, 1276, 1269, 1252, 1225, 1209, 1191, 1179, 1171, 1106, 1099, 1003, 968, 938, 902, 884, 879, 851, 819, 793, 764, 751, 732, 718, 677, 661.

MS (EI, 70 eV): *m/z* (%) = 136 (11), 135 (100), 107 (14), 93 (16), 79 (13).

HR-MS (EI, 70 eV): [$C_{18}H_{18}FNO$], calcd.: 283.1372; found: 283.1266.

3-(5-(2,5-Dimethylphenoxy)-2,2-dimethylpentanoyl)benzonitrile (7j)



Following **TP8** *S*-(pyridin-2-yl) 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanethioate (**5e**, 172 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-cyanophenyl)zinc pivalate (**6i**, 0.95 mmol, 1.9 equiv) prepared according to **TP7** from the corresponding iodide at -20 °C in 2 h. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 110 mg, 0.33 mmol, 66%, yellow oil.

Purification: pentane:ethyl acetate = 95:5.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.97 (d, *J* = 1.8 Hz, 1H), 7.92 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.74 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.66 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.60 – 6.54 (m, 1H), 3.90 (t, *J* = 6.0 Hz, 2H), 2.29 (s, 3H), 2.13 (s, 3H), 2.02 – 1.91 (m, 2H), 1.80 – 1.67 (m, 2H), 1.37 (s, 6H).

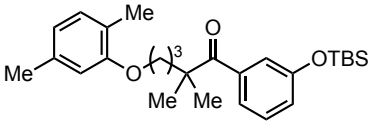
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 206.7, 156.8, 139.8, 136.6, 134.2, 131.8, 131.4, 130.4, 129.3, 123.4, 120.9, 118.2, 112.8, 111.8, 67.5, 47.9, 37.4, 26.0, 25.1, 21.5, 16.0.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2922, 2230, 1677, 1677, 1583, 1508, 1470, 1414, 1388, 1309, 1284, 1262, 1223, 1156, 1128, 1043, 1017, 999, 844, 803, 752, 683.

MS (EI, 70 eV): *m/z* (%) = 335 (4), 214 (100), 144 (13), 130 (26), 122 (17), 102 (10), 83 (12), 55 (15).

HR-MS (EI, 70 eV): [$C_{22}H_{25}NO_2$], calcd.: 335.1885; found: 335.1888.

1-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)-5-(2,5-dimethylphenoxy)-2,2-dimethylpentan-1-one (7k)



Following **TP8** *S*-(pyridin-2-yl) 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanethioate (**5e**, 172 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-((*tert*-butyldimethylsilyl)oxy)phenyl)zinc pivalate (**6j**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution

was stirred for 4 h and was worked-up as usual.

Isolated yield: 158 mg, 0.36 mmol, 78%, pale yellow oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.13 – 6.99 (m, 2H), 6.93 (t, J = 2.0 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 6.73 (ddd, J = 7.8, 2.5, 1.3 Hz, 1H), 6.44 (dd, J = 7.6, 1.5 Hz, 1H), 6.37 (d, J = 1.5 Hz, 1H), 3.68 (t, J = 6.1 Hz, 2H), 2.09 (s, 3H), 1.94 (s, 3H), 1.79 – 1.68 (m, 2H), 1.59 – 1.48 (m, 2H), 1.14 (s, 6H), 0.78 (s, 9H), 0.00 (s, 6H).

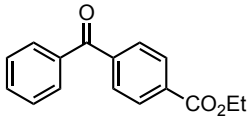
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 208.6, 156.9, 155.4, 140.3, 136.4, 130.3, 129.2, 123.5, 122.7, 120.7, 120.5, 119.3, 111.8, 67.8, 47.7, 37.5, 26.2, 25.7, 25.1, 21.4, 18.2, 15.8, -4.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953, 2927, 1672, 1594, 1576, 1508, 1470, 1421, 1388, 1362, 1251, 1183, 1156, 1129, 1044, 1000, 913, 834, 800, 779, 759, 685.

MS (EI, 70 eV): *m/z* (%) = 320 (23), 319 (100), 235 (32), 83 (8), 73 (14).

HR-MS (EI, 70 eV): [$C_{27}H_{40}O_3Si$], calcd.: 440.2747; found: 440.2751.

Ethyl 4-benzoylbenzoate (7l)



Following **TP8** *S*-(pyridin-2-yl) benzothioate (**5f**, 108 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-(ethoxycarbonyl)phenyl)zinc pivalate (**6k**, 0.95 mmol, 1.9 equiv) prepared according to **TP7** from the corresponding iodide at -40 °C in 2 h. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 90mg, 0.35mmol, 71% yield, colorless crystals.

Purification: pentane:ethyl acetate = 95:5.

m.p.: 93.6 – 95.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = .20 – 8.11 (m, 2H), 7.82 (ddd, J = 14.6, 7.6, 1.8 Hz, 4H), 7.66 – 7.57 (m, 1H), 7.50 (dd, J = 8.4, 7.1 Hz, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.2, 166.0, 141.3, 137.1, 133.7, 133.1, 130.3, 129.9,

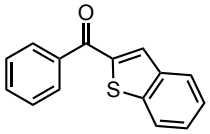
129.6, 128.6, 61.6, 14.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2979, 1704, 1660, 1604, 1480, 1446, 1399, 1367, 1266, 1179, 1102, 1019, 1004, 937, 925, 845, 752, 712, 695, 656.

MS (EI, 70 eV): *m/z* (%) = 177 (28), 105 (100), 149 (59), 152 (39), 181 (59), 209 (59), 226 (30), 254 (35).

HR-MS (EI, 70 eV): [$C_{16}H_{14}O_3$], calcd.: 254.0943; found: 254.0939.

Benzo[*b*]thiophen-2-yl(phenyl)methanone (7m)



Following **TP8**, using TMEDA (10 mol%, 0.05 mmol, 6 mg) as ligand, *S*-(pyridin-2-yl) benzothioate (**5f**, 108 mg, 0.50 mmol, 1.0 equiv) was coupled with (benzo[*b*]thiophen-2-yl)zinc pivalate (**6l**, 0.95 mmol, 1.9 equiv) prepared by directed metalation from benzo[*b*]thiophen and TMPMgCl (1.0 equiv) at 0 °C for 3 h, followed by transmetalation with $Zn(OPiv)_2$ (1.0 equiv) The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 81 mg, 0.34 mmol, 68%, orange oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.96 – 7.85 (m, 5H), 7.68 – 7.60 (m, 1H), 7.54 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.49 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H).

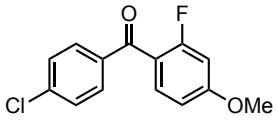
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 189.8, 143.2, 142.8, 139.2, 138.0, 132.6, 132.4, 129.4, 128.7, 127.6, 126.2, 125.2, 123.1.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1631, 1593, 1576, 1509, 1455, 1444, 1425, 1314, 1285, 1245, 1187, 1175, 1157, 1114, 1066, 1025, 880, 869, 833, 790, 746, 731, 708, 701, 664.

MS (EI, 70 eV): *m/z* (%) = 238 (100), 23 (11), 210 (10), 161 (97), 133 (16), 105 (40), 89 (23), 77 (31).

HR-MS (EI, 70 eV): [$C_{15}H_{10}OS$], calcd.: 238.0452; found: 238.0454.

(4-Chlorophenyl)(2-fluoro-4-methoxyphenyl)methanone (7n)



Following **TP8** *S*-(pyridin-2-yl) 4-chlorobenzothioate (**5g**, 125 mg, 0.50 mmol, 1.0 equiv) was coupled with (2-fluoro-4-methoxyphenyl)zinc pivalate (**6m**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 121 mg, 0.46, 92%, colorless oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.74 (dd, J = 8.5, 1.6 Hz, 2H), 7.57 (t, J = 8.4 Hz, 1H), 7.46 – 7.40 (m, 2H), 6.80 (dd, J = 8.6, 2.4 Hz, 1H), 6.66 (dd, J = 12.0, 2.4 Hz, 1H), 3.88 (s, 3H).

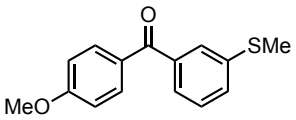
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 191.5 (d, J = 1.0 Hz), 164.2 (d, J = 11.3 Hz), 163.1, 161.9 (d, J = 254.1 Hz), 139.2, 136.7, 132.7 (d, J = 4.4 Hz), 130.9 (d, J = 1.7 Hz), 128.6, 118.9 (d, J = 13.6 Hz), 101.9 (d, J = 25.7 Hz), 55.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1671, 1588, 1570, 1560, 1544, 1446, 1426, 1340, 1282, 1235, 1218, 1154, 1116, 1069, 1054, 986, 916, 885, 791, 58, 733, 690.

MS (EI, 70 eV): *m/z* (%) = 139 (16), 153 (100), 154 (9), 187 (9), 220 (11), 264 (25), 266 (8).

HR-MS (EI, 70 eV): [$C_{14}H_{10}ClFO_2$], calcd.: 264.0353; found: 264.0351.

(4-Methoxyphenyl)(3-(methylthio)phenyl)methanone (7o)



Following **TP8** *S*-(pyridin-2-yl) 4-methoxybenzothioate (**5p**, 123 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-(methylthio)phenylzinc pivalate (**6n**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 123 mg, 0.48 mmol, 96%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.89 – 7.77 (m, 2H), 7.62 (t, *J* = 1.7 Hz, 1H), 7.55 – 7.30 (m, 3H), 7.05 – 6.88 (m, 2H), 3.89 (s, 3H), 2.52 (s, 3H).

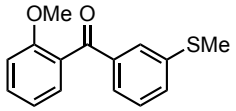
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 195.3, 163.5, 139.3, 139.0, 132.7, 130.1, 129.8, 128.6, 127.1, 126.5, 113.7, 55.7, 15.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2916, 2847, 1650, 1597, 1567, 1507, 1419, 1315, 1282, 1256, 1175, 1154, 1026, 842, 756, 710.

MS (EI, 70 eV): *m/z* (%) = 258 (36), 211 (19), 136 (9) 135 (100), 77 (11).

HR-MS (EI, 70 eV): [$C_{15}H_{14}O_2S$], calcd.: 258.0715; found: 258.0709.

(2-Methoxyphenyl)(3-(methylthio)phenyl)methanone (7o')



Following **TP8** *S*-(pyridin-2-yl) 2-methoxybenzothioate (**5p**', 123 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-(methylthio)phenylzinc pivalate (**6n**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 91 mg, 0.35 mmol, 71%, colorless oil.

Purification: pentane:ethyl acetate = 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.74 (t, *J* = 1.8 Hz, 1H), 7.54 – 7.40 (m, 3H), 7.39 – 7.29 (m, 2H), 7.04 (td, *J* = 7.4, 0.9 Hz, 1H), 6.99 (dd, *J* = 8.5, 0.9 Hz, 1H), 3.73 (s, 3H), 2.50 (s, 3H).

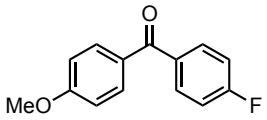
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.2, 157.5, 139.3, 138.5, 132.2, 130.9, 129.8, 128.7, 128.7, 127.0, 127.0, 120.7, 111.6, 55.7, 15.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2920, 2836, 1659, 1597, 1581, 1567, 1486, 1462, 1434, 1413, 1294, 1241, 1180, 1154, 1111, 1077, 1047, 1020, 994, 973, 959, 949, 936, 889, 809, 750, 716, 672.

MS (EI, 70 eV): *m/z* (%) = 258 (32), 211 (43), 138 (23), 135 (100), 121 (58), 79 (26), 77 (38)

HR-MS (EI, 70 eV): [$C_{15}H_{14}O_2S$], calcd.: 258.0715; found: 258.0707.

(4-Fluorophenyl)(4-methoxyphenyl)methanone (7p)



Following **TP8** *S*-(pyridin-2-yl) 4-methoxybenzothioate (**5p**, 123 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-fluorophenyl)zinc pivalate (**6f**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 99 mg, 0.43 mmol, 86% yield, white solid.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 97.1 – 98.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.80 (dt, *J* = 8.7, 2.7 Hz, 4H), 7.15 (t, *J* = 8.6 Hz, 2H), 7.03 – 6.92 (m, 2H), 3.89 (s, 3H).

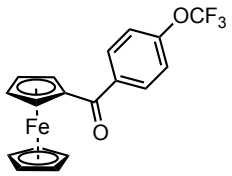
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 194.3, 165.2 (d, *J* = 253.2 Hz), 163.4, 134.6 (d, *J* = 3.1 Hz), 132.6, 132.4 (d, *J* = 9.1 Hz), 130.1, 115.5 (d, *J* = 21.8 Hz), 113.8, 55.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ =3065, 3019, 2973, 2944, 2916, 2846, 1639, 1628, 1594, 1573, 1504, 1499, 1466, 1454, 1442, 1416, 1405, 1302, 1296, 1284, 1256, 1224, 1182, 1175, 1148, 1116, 1094, 1064, 1028, 1013, 967, 959, 949, 928, 856, 842, 828, 815, 789, 763, 682.

MS (EI, 70 eV): *m/z* (%) = 231 (7), 230 (43), 199 (13), 136 (9), 135 (100), 123 (16), 77 (9).

HR-MS (EI, 70 eV): [$C_{14}H_{11}FO_2$], calcd.: 230.0743; found: 230.0737.

Ferrocenyl-(4-(trifluoromethoxy)phenyl)methanone (7q)



Following **TP8** *S*-(pyridin-2-yl) ferrocenecarbothioate (**5i**, 162 mg, 0.50 mmol, 1.0 equiv) was coupled with 4-(trifluoromethoxy)phenyl)zinc pivalate (**6o**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 151 mg, 0.40 mmol, 81%, red solid.

Purification: pentane:ethyl acetate = 9:1.

m.p.: 38.2 – 40.1 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.03 – 7.91 (m, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 4.89 (t, *J* = 1.9 Hz, 2H), 4.62 (t,*J* = 2.0 Hz, 2H), 4.21 (s, 5H).

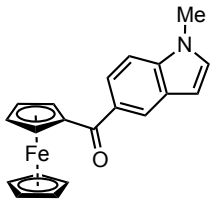
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 197.7, 153.8 – 150.2 (m), 138.2, 130.1, 120.5 (q, *J* = 258.3 Hz), 120.4, 77.9, 73.0, 71.6, 70.4.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2924, 1627, 1598, 1447, 1251, 1213, 1152, 1104, 1054, 1027, 1014, 1002, 968, 951, 923, 852, 822, 767, 713.

MS (EI, 70 eV): *m/z* (%) = 375 (20), 374 (100), 372 (6), 212 (7), 185 (9), 139 (24).

HR-MS (EI, 70 eV): [$C_{18}H_{13}F_3FeO_2$], calcd.: 374.0217; found: 374.0214.

Ferrocenyl-(4-(trifluoromethoxy)phenyl)methanone (7r)



Following **TP8** *S*-(pyridin-2-yl) ferrocenecarbothioate (**5i**, 162 mg, 0.50 mmol, 1.0 equiv) was coupled with ((1- methyl-1 *H*-indol-5-yl)zinc pivalate (**6c**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield:144 mg, 0.42, 84%, red oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.32 (d, *J* = 1.8 Hz, 1H), 7.87 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.14 (d, *J* = 3.1 Hz, 1H), 6.62 (d, *J* = 3.1 Hz, 1H), 4.98 (t, *J* = 2.0 Hz, 2H), 4.56 (t, *J* = 2.0 Hz, 2H), 4.21 (s, 5H), 3.85 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 199.1, 138.6, 131.6, 130.3, 127.7, 122.7, 122.5, 109.0, 102.7, 79.5, 72.0, 71.9, 70.3, 33.2.

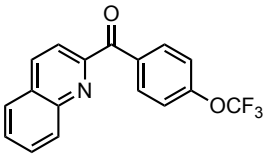
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3093, 2920, 1624, 1597, 1564, 1511, 1489, 1441, 1416, 1373, 1337, 1305, 1286, 1267, 1242, 1210, 1149, 1135, 1098, 1081, 1044, 1025, 1000, 900, 841, 818, 776,

753, 736, 722.

MS (EI, 70 eV): *m/z* (%) = 344 (23), 343 (100), 341 (7), 194 (9), 130 (9).

HR-MS (EI, 70 eV): [$C_{20}H_{17}FeNO$], 343.0660, found: 343.0659.

Quinolin-2-yl(4-(trifluoromethoxy)phenyl)methanone (7s)



Following **TP8** *S*-(pyridin-2-yl) quinoline-2-carbothioate (**5j**, 133 mg, 0.50 mmol, 1.0 equiv) was coupled with 4- (trifluoromethoxy)phenyl)zinc pivalate (**6o**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

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

Purification: pentane:ethyl acetate = 99:1

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.41 – 8.33 (m, 3H), 8.20 (dq, *J* = 8.6, 0.9 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.93 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.81 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.69 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.35 (dq, *J* = 9.1, 1.1 Hz, 2H).

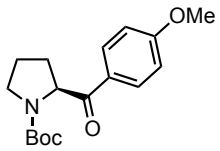
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 192.1, 154.2, 152.8, 152.7, 146.8, 137.5, 134.5, 133.7, 130.7, 130.4, 129.2, 128.9, 127.8, 121.9 – 119.1 (m, 2C)

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 1662, 1605, 1587, 1508, 1309, 1295, 1202, 1140, 1112, 967, 957, 920, 850, 835, 794, 769, 743, 669.

MS (EI, 70 eV): *m/z* (%) = 95, (12), 189 (100), 189 (29), 191 (15), 204 (42), 232 (17), 288 (69), 289 (53), 316 (28), 317 (30).

HR-MS (EI, 70 eV): [$C_{17}H_{10}F_3NO_2$], calcd.: 317.0664, found: 317.0660.

***tert*-Butyl (S)-2-(4-methoxybenzoyl)pyrrolidine-1-carboxylate (7t)**



Following **TP8** tert-butyl (*S*)-2-((pyridin-2-ylthio)carbonyl)pyrrolidine-1-carboxylate (**5k**, 154 mg, 0.50 mmol, 1.0 equiv) was coupled with ((4-methoxyphenyl)zinc pivalate (**6a**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 110 mg, 0.36 mmol, 72%, pale yellow crystals.

Purification: pentane:ethyl acetate = 8:2 to 6:4.

m.p.: 124.8–126.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): (mixture of rotamers) δ = 8.06 – 7.85 (m, 2H), 7.04 – 6.82 (m, 2H), 5.29 (dd, *J* = 9.3, 2.9 Hz, 0H), 5.15 (dd, *J* = 8.8, 3.8 Hz, 1H), 3.87 (s, 2H), 3.85 (s, 1H), 3.71 – 3.58 (m, 1H), 3.54 (dt, *J* = 10.6, 6.6 Hz, 1H), 3.46 (dt, *J* = 10.3, 7.3 Hz, 0H), 2.41 – 2.18 (m, 1H), 1.91 (ttd, *J* = 15.0, 7.2, 3.5 Hz, 3H), 1.46 (s, 3H), 1.25 (s, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): (mixture of rotamers) δ = 197.5, 197.0, 163.7, 163.6, 154.6, 154.0, 130.9, 130.6, 128.3, 128.1, 114.0, 113.9, 79.8, 79.7, 61.1, 60.9, 55.6, 55.6, 46.9, 46.7, 31.1, 30.1, 28.6, 28.3, 24.3, 23.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2972, 1680, 1597, 1574, 1510, 1477, 1455, 1391, 1363, 1307, 1254, 1228, 1158, 1115, 1080, 1025, 1010, 988, 918, 880, 838, 809, 771, 688.

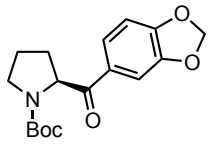
MS (EI, 70 eV): *m/z* (%) = 170 (34), 125 (81), 114 (89), 77 (13), 70 (100), 57 (67), 41 (14).

HR-MS (EI, 70 eV): [$C_{17}H_{23}NO_4$], 305.1627, found: 305.1624.305.1627, found: 305.1624.

Optical rotation: $[\alpha]_{\lambda}^{\varphi}$ = -23 (c = 1.02 $CHCl_3$).

Chiral HPLC: 99% *ee*, OJ-H column, *i*-PrOH:heptane = 5:95, 1.0 mL/min, 30 °C.

***tert*-Butyl (*S*)-2-(benzo[d][1,3]dioxole-5-carbonyl)pyrrolidine-1-carboxylate (7u)**



Following **TP8** *tert*-butyl 2-((pyridin-2-ylthio)carbonyl)pyrrolidine-1-carboxylate (**5k**, 154 mg, 0.50 mmol, 1.0 equiv) was coupled with (benzo[*d*][1,3]dioxol-5-yl)zinc pivalate (**6b**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 130 mg, 0.41 mmol, 82%, brown oil.

Purification: pentane:ethyl acetate = 8:2.

^{1}H-NMR (400 MHz, DMSO-d_6, ppm): (mixture of rotamers) δ = 7.66 (ddd, *J* = 8.2, 2.8, 1.7 Hz, 1H), 7.49 (t, *J* = 1.9 Hz, 1H), 7.06 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.15 (s, 2H), 5.25 (ddd, *J* = 10.8, 9.0, 3.8 Hz, 1H), 3.39 (dddd, *J* = 14.2, 11.8, 7.3, 4.6 Hz, 2H), 2.37 – 2.23 (m, 1H), 1.91 – 1.63 (m, 4H), 1.38 (s, 4H), 1.17 (s, 6H).

^{13}C-NMR (100 MHz, DMSO-d_6, ppm): (mixture of rotamers)δ = 197.3, 196.5, 153.8, 153.4, 152.1, 148.4, 129.7, 129.5, 125.2, 125.0, 108.7, 108.7, 108.2, 108.0, 102.6, 102.6, 79.0, 78.8, 61.0, 61.0, 47.0, 46.9, 31.0, 30.1, 28.6, 28.3, 27.5, 24.3, 23.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2974, 1682, 1614, 1605, 1505, 1488, 1442, 1392, 1364, 1245, 1160, 1120, 1108, 1097, 1034, 1000, 973, 927, 910, 884, 856, 807, 772, 740, 718.

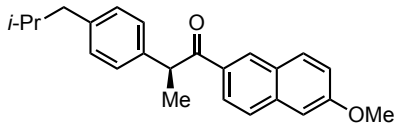
MS (EI, 70 eV): *m/z* (%) = 319 (4), 246 (11), 170 (48), 149 (100), 121 (18), 70 (75), 58 (23), 57 (48), 43 (53).

HR-MS (EI, 70 eV): [$C_{17}H_{21}NO_5$], 319.1420, found: 319.1411.

Optical rotation: $[\alpha]_\lambda^\varphi$ = -29 (c = 0,4 $CHCl_3$).

Chiral HPLC: 98% *ee*, OJ-H column, *i*-PrOH:heptane = 1:99, 1.0 mL/min, 30 °C.

(*S*)-2-(4-Isobutylphenyl)-1-(6-methoxynaphthalen-2-yl)propan-1-one (7v)



Following **TP8** *S*-(pyridin-2-yl) (S)-2-(4-isobutylphenyl)propanethioate (**5l**, 150 mg, 0.50 mmol, 1.0 equiv) was coupled with (6-methoxynaphthalen-2-yl)zinc pivalate (**6p**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 144 mg, 0.42 mmol, 89%, white solid.

Purification: pentane:ethyl acetate = 95:5 to 9:1.

m.p.: 70.1 – 72.8 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.34 (d, *J* = 1.7 Hz, 1H), 7.92 (dd, J = 8.7, 1.8 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.20 – 7.13 (m, 2H), 7.07 (dd, J = 8.9, 2.5 Hz, 1H), 7.01 (d, *J* = 2.6 Hz, 1H), 7.00 – 6.96 (m, 2H), 4.72 (q, *J* = 6.8 Hz, 1H), 3.83 (s, 3H), 2.31 (d, *J* = 7.2 Hz, 2H), 1.71 (dp, *J* = 13.5, 6.7 Hz, 1H), 1.49 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 200.4, 159.8, 140.4, 139.1, 137.2, 132.0, 131.3, 130.4, 129.8, 127.9, 127.6, 127.1, 125.5, 119.7, 105.7, 77.1, 55.5, 47.4, 5.1, 30.3, 22.5, 22.5, 19.8.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2954, 2923, 1670, 1622, 1508, 1480, 1458, 1438, 1389, 1369, 1337, 1271, 1264, 1231, 1200, 1167, 1150, 1061, 1024, 945, 911, 901, 893, 864, 856, 849, 830, 817, 801, 776, 770, 762, 738, 698.

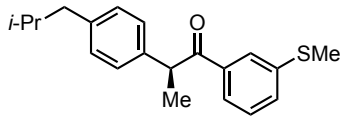
MS (EI, 70 eV): *m/z* (%) = 142 (7), 157 (13), 185 (100), 186 (13), 346 (1).

HR-MS (EI, 70 eV): [$C_{24}H_{26}O_2$], 346.1933, found: 346.1927.

Optical rotation: $[\alpha]_\lambda^\varphi$ = -89 (c = 1.02 $CHCl_3$).

Chiral HPLC: 98% *ee*, OD-H column, *i*-PrOH:heptane = 2:98, 1.0 mL/min, 30 °C.

(*S*)-2-(4-*iso*-Butylphenyl)-1-(3-(methylthio)phenyl)propan-1-one (7w)



Following **TP8** *S*-(pyridin-2-yl) 2-(4-isobutylphenyl)propanethioate (**5l**, 150 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-(methylthio)phenylzinc pivalate (**6n**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 110 mg, 0.35 mmol, 71%, colorless oil

Purification: pentane:ethyl acetate = 98:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.80 (t, *J* = 1.8 Hz, 1H), 7.69 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.34 (ddd, *J* = 7.8, 2.0, 1.1 Hz, 1H), 7.32 – 7.23 (m, 1H), 7.20 – 7.14 (m, 2H), 7.09 – 7.02 (m, 2H), 4.61 (q, *J* = 6.9 Hz, 1H), 2.45 (s, 3H), 2.40 (d, *J* = 7.2 Hz, 2H), 1.80 (dp, *J* = 13.6, 6.8 Hz, 1H), 1.51 (d, *J* = 6.9 Hz, 3H), 0.86 (dd, *J* = 6.6, 0.8 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 200.1, 140.4, 139.4, 138.5, 137.1, 130.6, 129.8, 128.7, 127.4, 126.1, 125.4, 47.7, 45.0, 30.2, 22.4, 22.4, 19.5, 15.6.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957, 2926, 1682, 1584, 1569, 1509, 1465, 1453, 1415, 1384, 1373, 1333, 1215, 1080, 1061, 1014, 960, 882, 848, 795, 747, 686, 667.

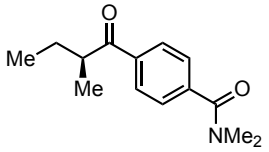
MS (EI, 70 eV): *m/z* (%) = 312 (4), 161 (35), 152 (9), 151 (100), 123 (10).

HR-MS (EI, 70 eV): [$C_{20}H_{24}OS$], 312. 1548, found: 312.2539.

Optical rotation: $[\alpha]_{\lambda}^{\varphi} = 107$ (c = 0.53 $CHCl_3$).

Chiral HPLC: 98% *ee*, OD-H column, *i*-PrOH:heptane = 2:98, 1.0 mL/min, 30 °C.

(/kuS)-*N*,*N*-Dimethyl-4-(2-methylbutanoyl)benzamide (7x)



Following **TP8** *S*-(pyridin-2-yl) (*S*)-2-methylbutanethioate (**5m**, 98 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-(dimethylcarbamoyl)phenyl)zinc pivalate (**6q**, 0.95 mmol, 1.9 equiv) prepared

according to **TP7** from the corresponding iodide at 0 °C in 2 h. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 80 mg, 0.34 mmol, 69%, yellow oil.

Purification: pentane:ethyl acetate = 6:4, 5% NEt_3

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 8.03 – 7.94 (m, 2H), 7.54 – 7.47 (m, 2H), 3.38 (h, *J* = 6.7 Hz, 1H), 3.13 (s, 3H), 2.96 (s, 3H), 1.82 (dqd, J = 13.8, 7.4, 6.3 Hz, 1H), 1.49 (ddd, *J* = 14.0, 7.6, 6.8 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 203.9, 170.6, 140.4, 137.4, 128.4, 127.3, 42.3, 26.6, 16.6, 11.7.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2963, 2933, 2363, 1684, 1636, 1508, 1458, 1396, 1266, 1219, 1081, 1015, 971, 861, 839, 709, 699.

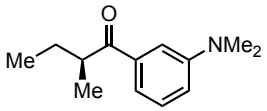
MS (EI, 70 eV): *m/z* (%) = 233 (7), 189 (5), 177 (11), 176 (100), 120 (6), 104 (11).

HR-MS (EI, 70 eV): [$C_{14}H_{19}NO_2$], 233.1416, found: 233.1407.

Optical rotation: $[\alpha]_\lambda^\varphi$ = 13 (c = 0.1 $CHCl_3$).

Chiral HPLC: 98% *ee*, AD-H column, *i*-PrOH:heptane = 1:99, 2.0 mL/min, 30 °C.

(*S*)-1-(3-(Dimethylamino)phenyl)-2-methylbutan-1-one (7y)



Following **TP8** *S*-(pyridin-2-yl) 2-(4-isobutylphenyl)propanethioate (**5m**, 150 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-(dimethylamino)phenyl)zinc pivalate (**6r**, 0.95 mmol, 1.9 equiv) prepared according to **TP6** from the corresponding bromide. The solution was stirred for 4 h and was worked-up as usual.

Isolated yield: 110 mg, 0.35 mmol, 71%, colorless oil.

Purification:pentane:ethyl acetate = 98:2.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.35 – 7.15 (m, 3H), 6.86 (ddd, *J* = 8.0, 2.6, 1.3 Hz, 1H), 3.34 (h, *J* = 6.7 Hz, 1H), 2.94 (s, 6H), 1.78 (ddd, *J* = 13.9, 7.5, 6.5 Hz, 1H), 1.52 – 1.37 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 205.3, 150.7, 137.6, 129.1, 116.8, 116.5, 111.5, 42.2, 40.6, 39.4, 35.3, 26.8, 17.0, 11.9.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2965, 2932, 2874, 1677, 1597, 1574, 1496, 1460, 1434, 1353, 1261, 1213, 1146, 1062, 986, 943, 865, 773, 7421, 682.

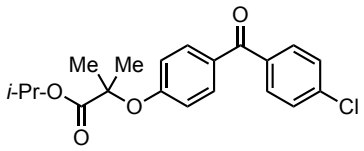
MS (EI, 70 eV): *m/z* (%) = 205 (77), 149 (12), 148 (74), 137 (22), 136 (14), 121 (38), 120 (100), 77 (15).

HR-MS (EI, 70 eV): [$C_{13}H_{19}NO$], 205.1467, found: 205.1460..

Optical rotation: $[\alpha]_\lambda^\varphi$ = 41 (c = 1.05 $CHCl_3$).

Chiral HPLC: 98% *ee*, OD-H column, *i*-PrOH:heptane = 1:99, 1.0 mL/min, 30 °C.

Fenofibrate (7z)



KOH (560 mg, 1.0 equiv, 10 mmol) was added to a solution of 4-iodophenol (**9**, 2.2 g, 10 mmol, 1.0 equiv) in EtOH (20 mL) at 0 °C. After 30 min, isopropyl 2-bromo-2-methylpropanoate (**10**, 2.09 g, 10 mmol, 1.0 equiv) was added and the mixture was refluxed for 16 h. After solvent evaporation the product was subjected to column chromatographical purification with *i*-hexane/EtOAc (98:2) as eluent. Isopropyl 2-(4-iodophenoxy)-2- methylpropanoate (**11**) was obtained as a yellow oil (2.44 g, 7 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.57 – 7.44 (m, 2H), 6.71 – 6.51 (m, 2H), 5.17 – 4.95 (m, 1H), 1.57 (s, 7H), 1.21 (d, *J* = 6.3 Hz, 6H).

Magnesium turnings (1.2 equiv), dry LiCl (1.2 equiv), $Zn(OPiv)_2$ (1.0 equiv) and dry THF (0.5 M) were added to a dry and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum. The tube was charged with isopropyl 2-(4-iodophenoxy)-2-methylpropanoate (**11**, 1.0 equiv) at rt. To monitor the progress of the insertion reaction, reaction aliquots were quenched with iodine and analyzed by GC-analysis. The insertion was completed within 4 h and the concentration was determined by titration with iodine, yielding (4-((1-isopropoxy- 2-methyl-1-oxopropan-2-yl)oxy)phenylzinc pivalate **6s** in 70%. A dry

and argon flushed *Schlenk*-tube equipped with a magnetic stirring bar and a septum was charged with $CoCl_2$ (3.2 mg, 0.025 mmol, 0.10 equiv, dried in vacuo at 400 °C prior to use). Then, the ligand 4,4'-di-*tert*-butyl-2,2'- dipyridyl (6.5 mg, 0.25 mmol, 0.10 equiv) and *S*-(pyridin-2-yl) 4-chlorobenzothioate (**5g**, 63 mg, 0.25 mmol, 1.0 equiv) added to the *Schlenk*-tube. The resulting mixture was dissolved in dry THF (0.5 mL). Then, (4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)phenylzinc pivalate (**6s** , 0.48 mmol, 1.9 equiv) was added and stirring was continued for 4 h, at 25 °C. Upon consumption of the starting material, satured aq. NH_4Cl solution (10 mL) was added, the phases were separated and the aq. phase was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were evaporated and the residue was subjected to column chromatographical purification.

Isolated yield: 59 mg, 0.16 mmol, 64% yield, colorless solid.

Purification: pentane:ethyl acetate = 90:10.

m.p.: 65.6 – 67.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.75 – 7.71 (m, 2H), 7.71 – 7.66 (m, 2H), 7.50 – 7.41 (m, 2H), 6.91 – 6.82 (m, 2H), 5.08 (h, *J* = 6.3 Hz, 1H), 1.66 (s, 6H), 1.20 (d, *J* = 6.2 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 194.3, 173.1, 159.7, 138.4, 136.4, 132.0, 131.2, 130.2, 128.5, 117.2, 79.4, 69.4, 25.4, 21.5.

FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2983, 2932, 1728, 1653, 1898, 1496, 1466, 1384, 1285, 1242, 1173, 1143, 4401, 1090, 1014, 972, 926, 898, 843, 825, 762, 740, 682, 655.

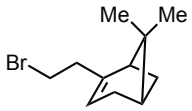
MS (EI, 70 eV): *m/z* (%) = 121 (100), 138 (78), 140 26), 197 (70), 232 (66), 234 (21), 273 (65), 275 (26), 360 (5).

HR-MS (EI, 70 eV): [$C_{20}H_{21}ClO_4$], 360.1128, found: 360.1125.

4 Cobalt-Catalyzed Cross-Coupling of functionalized Alkylzinc Reagents with (Hetero)aryl Halides

4.1 Preparation of Starting Materials

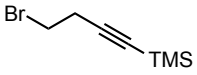
2-(2-Bromoethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene[111]



The title compound was prepared according to literature procedure from (1*R*)-(-)-nopol (6.7 mL, 40 mmol) affording (1*R*,5*S*)-2-(2-bromoethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene as pale yellow oil (8.25 g, 36.0 mmol, 90 %). The analytical data is in full consistency with the data reported in the literature.[111]

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

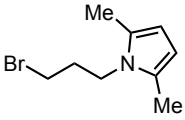
(4-Bromobut-1-yn-1-yl)trimethylsilane[112]



The title compound was prepared according to literature procedure from (4-(trimethylsilyl)-3-butyn-1-ol (3.00 g, 21 mmol), affording (4-bromobut-1-yn-1-yl)trimethylsilane as a colorless liquid (3.10 g, 16.0 mmol, 76%). The analytical data is in full consistency with the data reported in the literature.[112]

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

1-(3-Bromopropyl)-2,5-dimethyl-1*H*-pyrrole[113]

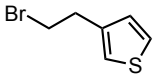


[111] B. Akgun, D. G. Hall, *Angewandte Chemie International Edition* **2016**, *55*, 3909–3913.
[112] H. M. Wisniewska, E. C. Swift, E. R. Jarvo, *Journal of the American Chemical Society* **2013**, *135*, 9083–9090.
[113] S. P. Bruekelman, S. E. Leach, G. D. Meakins, M. D. Tirel, *J. Chem. Soc., Perkin Trans. 1* **1984**, 2801–2807.

The title compound was prepared according to literature procedure from 3-bromopropylammonium bromide (5.00 g, 22.8 mmol) affording 1-(3-bromopropyl)-2,5-dimethyl-1*H*-pyrrole as a yellow oil (2.50 g, 11.6 mmol, 54%). The analytical data is in full consistency with the data reported in the literature.[113]

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

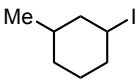
3-(2-Bromoethyl)thiophene[114]



The title compound was prepared according to literature procedure from 2-(thiophen-3-yl)ethan-1-ol (2.56 g, 20 mmol), affording 3-(2-bromoethyl)thiophene as a colorless liquid (2.75 g,14.4 mmol, 72%). The analytical data is infull consistency with data reported in the literature.[114]

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

1-Iodo-3-methylcyclohexane

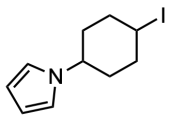


1-Iodo-3-methylcyclohexane was prepared according to **TP1** from 3-methylcyclohexanol (4.56 g, 40 mmol) and was obtained as a pale pink oil (6.05 g, 27 mmol, 68% yield). The analytical data is in full consistency with the data reported in the literature.[115]

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

[114] P. Taranekar, A. Baba, T. M. Fulghum, R. Advincula, *Macromolecules* **2005**, *38*, 3679–3687.
[115] X. Mu, Y. Shibata, Y. Makida, G. C. Fu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5821–5824.

1-(4-Iodocyclohexyl)-1*H*-pyrrole (21)



1-(4-Iodocyclohexyl)-1*H*-pyrrole was prepared according to **TP1** from 4-(1*H*-pyrrol-1-yl)cyclohexan-1-ol (6.6 g, 40.0 mmol), which was prepared according to literature procedure[116] from 4-aminocyclohexan-1-ol. 1-(4- iodocyclohexyl)-1*H*-pyrrole and was obtained as colorless crystals (6.08 g, 22.1 mmol, 55% yield).

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

m.p.: 51.0 – 52.7 °C.

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

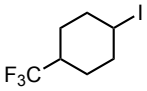
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 118.6, 107.8, 57.6, 35.8, 33.2, 30.6.

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

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

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

1-Iodo-4-(trifluoromethyl)cyclohexane (22)



1-Iodo-4-(trifluoromethyl)cyclohexane was prepared according to **TP1** from ethyl 4-(trifluoromethyl) cyclohexan-1-ol (1.00 g, 6.00 mmol) and was obtained as a colorless oil (750 mg, 2.74 mmol, 46% yield). The analytical data is in full consistency with the data reported in the literature.[115]

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

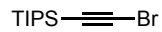
[116] N. B. Kumar, O. A. Mukhina, A. G. Kutateladze, *J. Am. Chem. Soc.* **2013**, *135*, 9608–9611.

(Bromoethynyl)benzene (23)

The title compound was prepared according to literature procedure from ethynylbenzene (306 mg, 3.00 mmol), affording (bromoethynyl)benzene as a pale yellow liquid (467 mg, 2.58 mmol, 86%).[117]

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

(Bromoethynyl)triisopropylsilane (24)

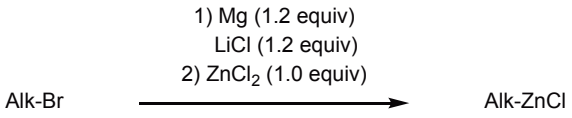


The title compound was prepared according to literature procedure from ethynyltriisopropylsilane (546 mg, 3.00 mmol), affording (bromoethynyl)triisopropylsilane as a colorless oil (734 mg, 2.80 mmol, 93%). [117]

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

4.2 Cobalt-Catalyzed Cross-Coupling of functionalized Alkylzinc Reagents with (Hetero)aryl Halides

Preparation of alkylzinc chlorides by magnesium insertion (TP9)

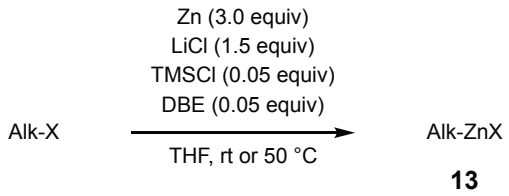


13

Dry LiCl (1.2 equiv) was placed in a dry and argon flushed 50 mL *Schlenk*-tube equipped with a magnetic stirring bar, a septum and was dried over 5 min at 300 °C under high vacuum (0.1 mbar). Magnesium turnings (1.2 equiv) were added followed by dry THF (1.0 M solution relating to the aryl halide) and the respective alkyl bromide (1.0 equiv). After the exothermic reaction started, the mixture was cooled with an ice bath. To monitor the progress of the insertion reaction, reaction aliquots quenched with iodine were analyzed as water-quenched samples by GC-analysis. When the insertion was completed, the concentration of the magnesium reagents was determined *via* titration of a small aliquot with I_2 (50 mg in 2 mL THF). A $ZnCl_2$ solution (1.00 M in THF, 1.0 equiv) was added at 0 °C and stirred at ambient temperature for 15 min affording the corresponding alkylzinc chloride **13**.[118]

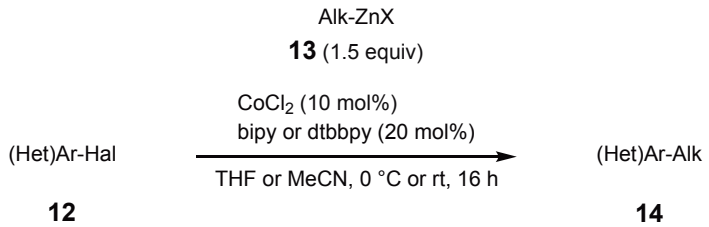
[117] Y. Ping, K. Wang, Q. Pan, Z. Ding, Z. Zhou, Y. Guo, W. Kong, *ACS Catalysis* **2019**, *9*, 7335–7342.
[118] F. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802–6806.

Preparation of alkylzinc halides by zinc insertion (TP10)[55c]



Dry LiCl (1.5 equiv) was placed in a dry and argon flushed 25 mL *Schlenk*-tube equipped with a magnetic stirring bar and a septum, was dried over 5 min at 300 °C under high vacuum (0.1 mbar). Zn powder (3.0 equiv) was added under argon and the heterogeneous mixture of Zn and LiCl was dried one more time at 300 °C for 5 min under high vacuum. The reaction flask was evacuated and refilled with argon three times. THF (0.5 M solution relating to the alkyl iodide) and 1,2-dibromoethane (0.05 equiv) were added. The mixture was then gently heated in order to activate the Zn surface. TMSCl (0.05 equiv) was added and the reaction mixture was again gently heated. The respective primary alkyl bromide or cyclohexyl iodide (1.0 equiv) was added neat at rt in one portion. The resulting reaction mixture was stirred until full consumption of the alkyl halide, in case of the primary alkyl bromides the insertion reaction was stirred at 50 °C. To monitor the progress of the insertion reaction, reaction aliquots quenched with iodine and quenched with sat. aq. NH_4Cl were analyzed by GC-analysis. When the insertion was completed the solution was then filtered from the remaining Zn powder *via* syringe filter (30 mm with 0.45 μm glass fiber membrane) and transferred to a dry argon flushed *Schlenk*-tube. The concentrations of all cyclohexylzinc reagents were determined *via* titration of a small aliquot with I_2 (50 mg in 2 mL THF).

Cobalt-catalyzed acylation of arylzinc pivalates with thiopyridyl esters (TP11)



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

A) For primary alkylzinc species:

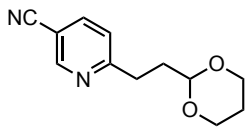
Bipyridine (17 mg, 0.1 mmol, 20 mol%) the respective (hetero)aryl halide (**12**, 0.5 mmol, 1.0 equiv) and dry THF (1.0 mL) were added. The reaction mixture was cooled to 0 °C with an ice bath and a solution of the appropriate alkylzinc halide (**13**, 0.75 mmol, 1.5 equiv) was added *via* syringe.

B) For secondary alkylzinc species:

4,4'-Di-*tert*-butyl-2,2'-bipyridine (27 mg, 0.10 mol, 20 mol%), the respective (hetero)aryl halide (**12**, 0.5 mmol, 1.0 equiv) and dry MeCN (1.0 mL) were added (for the synthesis of **14y** and **14z** the reaction was performed in THF). The appropriate alkylzinc halide (**13**, 0.75 mmol, 1.5 equiv) was added *via* syringe at rt.

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

6-(2-(1,3-Dioxan-2-yl)ethyl)nicotinonitrile (14a)



Following **TP11-A** 6-chloronicotinonitrile (**12v**, 138 mg, 1.00 mmol, 1.0 equiv) was coupled with (2-(1,3-dioxan-2- yl)ethyl)zinc chloride (**13a**, 1.50 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

Purification: pentane:ethyl acetate = 7:3.

m.p.: 100.1 – 102.7 °C.

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

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

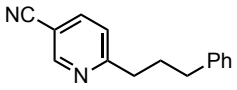
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2966, 2934, 2865, 227, 1979, 1596, 156, 1492, 1474, 1453, 1424, 1381, 1318, 1290, 1266, 1241, 1191, 1138, 1121, 1070, 1040, 1029, 998, 952, 943, 926, 888, 865, 856,

834, 758, 668.

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

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

6-(3-Phenylpropyl)nicotinonitrile (14b)



Following **TP11-A** 6-chloronicotinonitrile (**12a**, 69 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-phenylpropyl)zinc chloride (**13b**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

m.p.: 62.3 – 64.1 °C.

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

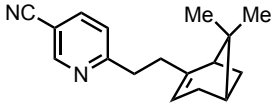
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 166.8, 152.3, 141.6, 139.4, 128.6, 128.6, 126.1, 123.0, 117.1, 107.3, 38.2, 35.5, 30.9.

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

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

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

6-(2-((1*R*,4*R*)-5,5-Dimethylbicyclo[2.1.1]hex-2-en-2-yl)ethyl)nicotinonitrile (14c)



Following **TP11-A** 6-bromonicotinonitrile (**12b**, 92 mg, 0.50 mmol, 1.0 equiv) was coupled

with (2-((1*R*,4*R*)-5,5- dimethylbicyclo[2.1.1]hex-2-en-2-yl)ethyl)zinc chloride (**13c**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

m.p.: 34.2 – 35.8 °C.

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

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

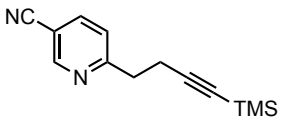
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2975 , 2925, 2834, 2231, 1595, 1554, 1482, 1447, 1382, 1364, 1338, 1304, 1264, 1202, 1119, 1098, 1025, 1003, 936, 886, 862, 838, 806, 725.

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

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

Optical rotation: $[\alpha]_\lambda^\varphi$ = -34(c = 0.83 $CHCl_3$).

6-(4-(Trimethylsilyl)but-3-yn-1-yl)nicotinonitrile (14d)



Following **TP11-A** 6-bromonicotinonitrile (**12b**, 92 mg 0.50 mmol, 1.0 equiv) was coupled with (4-(trimethylsilyl)but-3-yn- 1-yl)zinc chloride (**13d**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

m.p.: 70.0 – 71.2 °C.

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

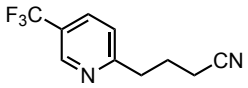
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 164.6, 152.3, 139.2, 123.5, 117.0, 107.8, 105.3, 86.4, 37.4, 19.7, 0.1.

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

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

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

4-(5-(Trifluoromethyl)pyridin-2-yl)butanenitrile (14e)



Following **TP11-A** using $CoCl_2$ (13 mg, 0.1 mmol, 20 mol%) and bipyridine (31 mg, 0.2 mmol, 40 mol%), 2-bromo-5- (trifluoromethyl)pyridine (**12c**, 113 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-cyanopropyl)zinc bromide (**13e**, 0.95 mmol, 1.9 equiv) prepared according to **TP10** from the corresponding bromide.

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

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

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

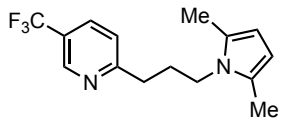
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 8.9 – 8.7 (m, 1H), 7.9 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.3 (d, *J* = 8.1 Hz, 1H), 3.0 (t, *J* = 7.4 Hz, 2H), 2.4 (t, *J* = 7.1 Hz, 2H), 2.2 (p, *J* = 7.2 Hz, 2H).

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

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

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

2-(3-(2,5-Dimethyl-1*H*-pyrrol-1-yl)propyl)-5-(trifluoromethyl)pyridine (14f)



Following **TP11-A** 2-bromo-5-(trifluoromethyl)pyridine (**12c**, 113 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-(2,5- dimethyl-1*H*-pyrrol-1-yl)propyl)zinc chloride (**13f**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

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

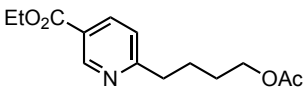
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 164.8, 146.1 (q, *J* = 4.1 Hz), 133.7 (q, *J* = 3.5 Hz), 127.4, 124.5 (q, *J* = 33.0 Hz), 123.6 (q, *J* = 272.0 Hz), 122.6, 105.3, 43.0, 35.2, 30.1, 12.5.

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

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

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

Ethyl 6-(4-acetoxybutyl)nicotinate (14g)



Following **TP11-A** using $CoCl_2$ (13 mg, 0.1 mmol, 20 mo%) and bipyridine (31 mg, 0.2 mmol, 40 mol%), ethyl 6- chloronicotinate (**12d**, 93 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-acetoxybutyl)zinc bromide (**13g**, 0.95 mmol, 1.9 equiv) prepared according to **TP10** from the corresponding bromide.

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

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

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 9.13 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.20 (dd, *J* = 8.1, 2.2 Hz,

1H), 7.25 – 7.20 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.08 (t, *J* = 6.5 Hz, 2H), 2.96 – 2.83 (m, 2H), 2.03 (s, 3H), 1.89 – 1.77 (m, 2H), 1.76 – 1.63 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H).

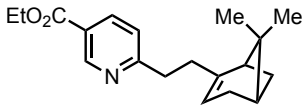
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 171.3, 166.3, 165.6, 150.7, 137.6, 124.1, 122.5, 64.3, 6.4, 38.1, 28.4, 26.1, 21.2, 14.4.

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

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

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

Ethyl 6-(2-((1*R*,4*R*)-5,5-dimethylbicyclo[2.1.1]hex-2-en-2-yl)ethyl)nicotinate (14h)



Following **TP11-A** ethyl 6-chloronicotinate (**12d**, 93 mg, 0.50 mmol, 1.0 equiv) was coupled with (2-((1*R*,4*R*)-5,5- dimethylbicyclo[2.1.1]hex-2-en-2-yl)ethyl)zinc chloride (**13c**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

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

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

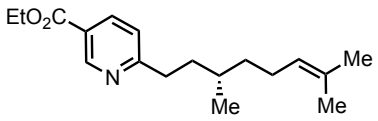
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982, 2913, 2831, 1678, 1619, 1600, 1563, 1504, 1468, 1427, 1381, 1364, 1312, 1319, 1264, 1220, 1140, 1115, 1082, 1016, 954, 886, 869, 824, 782, 753.

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

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

Optical rotation: $[\alpha]_{\lambda}^{\varphi}$ = - 23 (c = 1.35 $CHCl_3$).

Ethyl (*S*)-6-(3,7-dimethyloct-6-en-1-yl)nicotinate (14i)



Following **TP11-A** ethyl 6-chloronicotinate (**12d**, 93 mg, 0.50 mmol, 1.0 equiv) was coupled with (*S*)-(3,7-dimethyloct-6- en-1-yl)zinc chloride (**12w**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

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

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

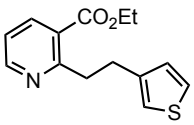
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961, 1719, 1598, 1568, 1462, 1380, 1368, 1276, 1173, 1112, 1027, 972, 856, 773, 736.

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

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

Optical rotation: $[\alpha]_{\lambda}^{\varphi}$ = 5 (c = 0.75 $CHCl_3$).

Ethyl 2-(2-(thiophen-3-yl)ethyl)nicotinate (14j)



Following **TP11-A** ethyl 2-chloronicotinate (**12e**, 93 mg, 0.50 mmol, 1.0 equiv) was coupled with (2-(thiophen-3- yl)ethyl)zinc chloride (**12x**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from

the corresponding bromide.

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

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

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

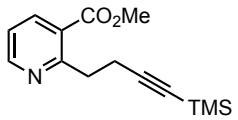
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 165.9, 161.7, 150.6, 141.6, 139.8, 128.4, 126.4, 125.3, 121.5, 120.7, 61.7, 30.4, 27.1, 14.3.

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

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

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

Methyl 2-(4-(trimethylsilyl)but-3-yn-1-yl)nicotinate (14k)



Following **TP11-A** methyl 2-chloronicotinate (**12y**, 93 mg, 0.50 mmol, 1.0 equiv) was coupled with with (4- (trimethylsilyl)but-3-yn-1-yl)zinc chloride (**13d**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

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

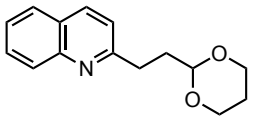
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 167.0, 161.2, 152.0, 138.6, 125.7, 121.3, 106.6, 85.0, 52.5, 35.6, 19.8, 0.2.

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

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

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

2-(2-(1,3-Dioxan-2-yl)ethyl)quinoline (14l)



Following **TP11-A** 2-bromoquinoline (**12h**, 104 mg, 0.50 mmol, 1.0 equiv) was coupled with (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**13a**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

m.p.: 54.8 – 56.7 °C.

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

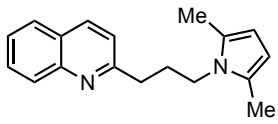
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 162.0, 148.0, 136.3, 129.4, 129.0, 127.5, 126.8, 125.8, 121.6, 101.6, 67.0, 34.8, 33.5, 25.9.

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

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

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

2-(3-(2,5-Dimethyl-1*H*-pyrrol-1-yl)propyl)quinoline (14n)



Following **TP11-A** 2-bromoquinoline (**12h**, 104 mg, 0.50 mmol, 1.0 equiv) or 2-chloroquinoline (**12i**, 82 mg, 0.50 mmol, 1.0 equiv) were coupled with (3-(2,5-dimethyl-1*H*-pyrrol-1-yl)propyl)zinc chloride (**13f**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

Isolated yield: using 2-bromoquinoline 112 mg, 0.42 mmol, 85%, yellow oil, using 2-chloroquinoline 108 mg, 0.41 mmol, 82%, yellow oil.

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

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

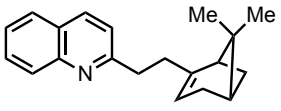
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 161.1, 136.8, 129.8, 128.5, 127.6, 127.4, 126.8, 126.1, 121.2, 121.2, 105.1, 43.2, 35.9, 30.3, 12.5.

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

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

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

2-(2-((1*R*,4*R*)-5,5-Dimethylbicyclo[2.1.1]hex-2-en-2-yl)ethyl)quinoline (14m)



Following **TP11-A** 2-bromoquinoline (**12h**, 104 mg, 0.50 mmol, 1.0 equiv) was coupled with (2-((1*R*,4*R*)-5,5- dimethylbicyclo[2.1.1]hex-2-en-2-yl)ethyl)zinc chloride (**13c**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

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

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

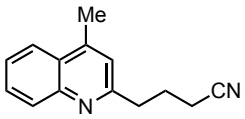
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2914.5, 1601.4, 1503.9, 1427.4, 1364.6, 1219.8, 904.6, 830.1, 731.6.

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

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

Optical rotation: $[\alpha]_\lambda^\varphi$ = - 37 (c = 1.36 $CHCl_3$).

4-(4-Methylquinolin-2-yl)butanenitrile (14o)



Following **TP11-A** using $CoCl_2$ (13 mg, 0.1 mmol, 20 mol%) and bipyridine (**12j** , 31 mg, 0.2 mmol, 40 mol%), 2-chloro-4-methylquinoline (89 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-cyanopro-pyl)zinc bromide (**13e**, 0.9 mmol, 1.9 equiv) prepared according to **TP10** from the corresponding bromide.

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

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

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

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

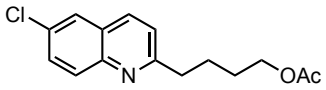
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2931, 2246, 1602, 1562, 1508, 1448, 1412, 1380, 1346, 1159, 1123,

1026, 953, 878, 865, 757.

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

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

4-(6-Chloroquinolin-2-yl)butyl acetate (14p)



Following **TP11-A** using $CoCl_2$ (13 mg, 0.1 mmol, 20 mol%) and bipyridine (31 mg, 0.2 mmol, 40 mol%), 2,6- dichloroquinoline (**12k**, 99 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-acetoxy-butyl)zinc bromide (**13g**, 0.95 mmol, 1.9 equiv) prepared according to **TP10** from the corresponding bromide.

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

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

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

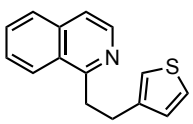
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 171.3, 162.7, 146.3, 135.6, 131.6, 130.5, 130.4, 127.4, 126.3, 122.3, 64.4, 38.7, 28.5, 26.3, 2.1.

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

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

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

1-(2-(thiophen-3-yl)ethyl)isoquinoline (14q)



Following **TP11-A** 1-bromoisoquinoline (**12l**, 104 mg, 0.50 mmol, 1.0 equiv) was coupled with (2-(thiophen-3-yl)ethyl)zinc chloride (**13i**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from

the corresponding bromide.

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

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

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

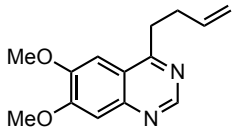
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 160.9, 136.8, 131.2, 128.4, 128.0, 128.0, 127.7, 127.0, 125.8, 125.8, 125.6, 120.9, 120.4, 35.6, 30.2.

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

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

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

4-(But-3-en-1-yl)-6,7-dimethoxyquinazoline (14r)



Following **TP11-A** 4-chloro-6,7-dimethoxyquinazoline (**12m**, 112 mg, 0.50 mmol, 1.0 equiv) was coupled with but-3-en-1-ylzinc chloride (**13j**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

m.p.: 66.9 – 69.1 °C.

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

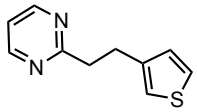
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 167.3, 156.2, 152.6, 150.6, 147.6, 137.3, 119.7, 115.9, 107.0, 101.9, 56.7, 56.4, 33.8, 32.5.

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

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

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

2-(2-(Thiophen-3-yl)ethyl)pyrimidine (14s)



Following **TP11-A** 2-bromopyrimidine (**12n**, 80 mg, 0.50 mmol, 1.0 equiv) was coupled with (2-(thiophen-3-yl)ethyl)zinc chloride (**13i** 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

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

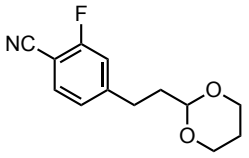
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 170.1, 157.1, 141.4, 128.3, 125.6, 120.8, 118.9, 39.9, 29.0.

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

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

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

4-(2-(1,3-Dioxan-2-yl)ethyl)-2-fluorobenzonitrile (14t)



Following **TP11-A** 4-bromo-2-fluorobenzonitrile (**12o**, 100 mg, 0.50 mmol, 1.0 quiv) was coupled with (2-(1,3-dioxan-2- yl)ethyl)zinc chloride (**13a**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

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

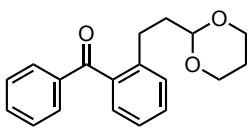
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 163.3 (d, *J* = 258.6 Hz), 151.0 (d, *J* = 7.7 Hz), 133.4, 125.1 (d, *J* = 3.2 Hz), 116.5 (d, *J* = 19.0 Hz), 114.4, 100.8 , 98.9 (d, *J* = 15.5 Hz), 67.0 , 35.8 , 30.2, 30.2, 25.8.

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

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

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

(2-(2-(1,3-Dioxan-2-yl)ethyl)phenyl)(phenyl)methanone (14x)



Following **TP11-A** (2-chlorophenyl)(phenyl)methanone (**12q**, 108 mg, 0.50 mmol, 1.0 equiv) was coupled with (2-(1,3- dioxan-2-yl)ethyl)zinc chloride (**13a**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

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

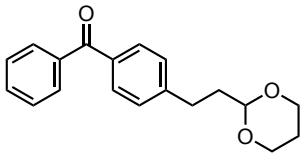
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 198.4, 140.9, 138.5, 137.8, 133.1, 130.4, 130.2, 128.7, 128.4, 125.3, 101.39, 66.8, 36.7, 27.6, 25.8.

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

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

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

(4-(2-(1,3-Dioxan-2-yl)ethyl)phenyl)(phenyl)methanone (14v)



Following **TP11-A** (4-bromophenyl)(phenyl)methanone (**12r**,131 mg, 0.50 mmol, 1.0 equiv) was coupled with (2-(1,3- dioxan-2-yl)ethyl)zinc chloride (**13a**, 0.75 mmol, 1.5 equiv) prepared according to **TP9** from the corresponding bromide.

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

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

m.p.: 68.6 – 70.5 °C.

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

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.6, 147.1, 138.0, 135.4, 132.3, 130.5, 130.1, 128.5,

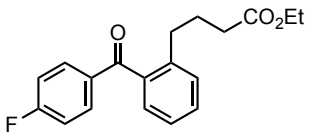
128.3, 101.3, 67.0, 36.4, 30.3, 25.9.

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

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

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

Ethyl 4-(2-(4-fluorobenzoyl)phenyl)butanoate (14w)



Following **TP11-A** using $CoCl_2$ (13 mg, 0.1 mmol, 20 mol%) and bipyridine (31 mg, 0.2 mmol, 40 mol%), (2- chlorophenyl)(4-fluorophenyl)methanone (**12s**, 117 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-ethoxy-4- oxobutyl)zinc bromide (**13u**,0.95 mmol, 1.9 equiv) prepared according to **TP10** from the corresponding bromide.

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

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

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

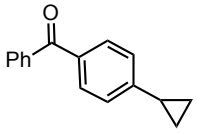
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.99, 173.42, 165.98 (d, *J* = 255.4 Hz), 140.66, 138.32, 134.25 (d, *J* = 2.9 Hz), 132.97 (d, *J* = 9.3 Hz), 130.51 (d, *J* = 7.9 Hz), 128.59, 125.66, 115.87, 115.65, 60.41, 33.92, 32.55, 26.86, 14.34.

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

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

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

(4-Cyclopropylphenyl)(phenyl)methanone (14y)



Following **TP11-B** (4-bromophenyl)(phenyl)methanone (**12r**, 131 mg, 0.50 mmol, 1.0 equiv) was coupled with cyclopropylzinc chloride (**13l**, 0.75 mmol, 1.5 equiv) in THF prepared according to **TP9** from the corresponding bromide.

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

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

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

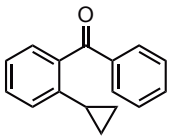
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 196.4, 149.9, 138.1, 134.8, 132.2, 130.5, 130.0, 128.3, 125.3, 15.8, 10.5.

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

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

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

(4-Chlorophenyl)(2-cyclopropylphenyl)methanone (14z)



Following **TP11-B** (2-chlorophenyl)(4-chlorophenyl)methanone (**12q**, 126 mg, 0.50 mmol, 1.0 equiv) was coupled with cyclopropylzinc chloride (**13l**, 0.75 mmol, 1.5 equiv) in THF prepared according to **TP9** from the corresponding bromide.

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

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

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

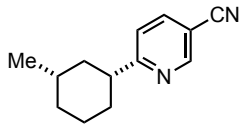
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 197.8, 142.1, 139.8, 139.4, 136.3, 131.6, 130.6, 128.9, 127.9, 125.4, 125.4, 13.8, 9.2.

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

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

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

6-(3-Methylcyclohexyl)nicotinonitrile (14aa)



Following **TP11-B** 6-bromonicotinonitrile (**12b**, 91 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-methylcyclohexyl)zinc iodide (**13m**, 0.75 mmol, 1.5 equiv) prepared according to **TP10** from the corresponding iodide.

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

Purification: pentane:ethyl acetate = 95:5.

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

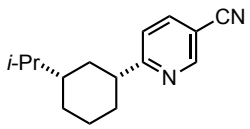
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 170.9, 152.1, 139.6, 121.4, 117.2, 107.2, 46.9, 41.0, 34.6, 32.8, 32.2, 26.2, 22.8.

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

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

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

6-(3-Isopropylcyclohexyl)nicotinonitrile (14ab)



Following **TP11-B** 6-bromonicotinonitrile (**12b**, 91 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-isopropylcyclohexyl)zinc iodide (**13n**, 0.75 mmol, 1.5 equiv) prepared according to **TP10** from the corresponding iodide.

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

Purification: pentane:ethyl acetate = 95:5.

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

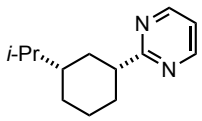
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 171.0, 152.0, 139.5, 121.4, 117.1, 107.1, 47.1, 43.9, 35.9, 33.0, 32.4, 29.1, 26.3, 19.8, 19.7.

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

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

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

2-(3-Isopropylcyclohexyl)pyrimidine (14ac)



Following **TP11-B** 2-bromopyrimidine (**12n**, 80 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-isopropylcyclohexyl)zinc iodide (**13n**, 0.75 mmol, 1.5 equiv) prepared according to **TP10** from the corresponding iodide.

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

Purification: pentane:ethyl acetate = 95:5.

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

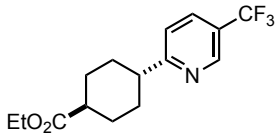
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.9, 157.1, 118.6, 48.0, 44.0, 35.4, 33.1, 32.0, 29.3, 26.4, 19.9, 19.9.

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

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

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

Ethyl-4-(5-(trifluoromethyl)pyridin-2-yl)cyclohexane-1-carboxylate (14ad)



Following **TP11-B** 2-bromo-5-(trifluoromethyl)pyridine (**12c**, 113 mg, 0.50 mmol, 1.0 equiv) was coupled with (4- (ethoxycarbonyl)cyclohexyl)zinc iodide (**13o**, 0.75 mmol, 1.5 equiv) prepared according to **TP10** from the corresponding iodide.

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

Purification: pentane:ethyl acetate = 9:1.

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

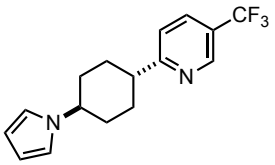
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 175.9, 169.5 (d, *J* = 1.8 Hz), 146.3 (q, *J* = 4.1 Hz), 133.7 (q, *J* = 3.5 Hz)124.5 (q, *J* = 32.9 Hz), 123.8 (q, *J* = 272.0 Hz), 121.1, 60.4, 45.7, 42.9, 31.7, 28.9, 14.4.

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

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

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

2-(4-(1*H*-Pyrrol-1-yl)cyclohexyl)-5-(trifluoromethyl)pyridine (14ae)



Following **TP11-B** 2-bromo-5-(trifluoromethyl)pyridine (**12c**, 113 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-(1*H*- pyrrol-1-yl)cyclohexyl)zinc iodide (**13p**, 0.75 mmol, 1.5 equiv) prepared according to **TP10** from the corresponding iodide.

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

Purification: pentane:ethyl acetate = 9:1.

m.p.: 130.8 – 132.4 °C.

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

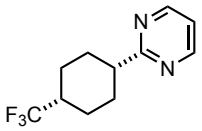
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 169.0 (d, *J* = 1.5 Hz), 146.4 (q, *J* = 4.1 Hz), 133.8 (q, *J* = 3.6 Hz), 123.8 (q, *J* = 272.0 Hz), 124.6 (q, *J* = 32.9 Hz), 121.2, 118.6, 107.8, 58.1, 45.5, 34.3, 31.7.

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

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

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

2-(4-(Trifluoromethyl)cyclohexyl)pyrimidine (14af)



Following **TP11-B** 2-bromopyrimidine (**12n**, 80 mg, 0.50 mmol, 1.0 equiv) was coupled with (3-(trifluoromethyl)cyclohexyl)zinc iodide (**13q**, 0.75 mmol, 1.5 equiv) prepared according to **TP10** from the corresponding iodide.

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

Purification: pentane:ethyl acetate = 9:1.

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

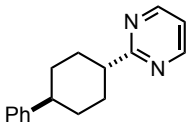
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.5, 157.1, 147.4, 128.5, 127.0, 126.1, 118.7, 47.2, 43.9, 34.0, 32.2.

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

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

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

2-(4-Phenylcyclohexyl)pyrimidine (14ag)



Following **TP11-B** 2-bromopyrimidine (**12n**, 80 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-phenylcyclohexyl)zinc iodide (**13r**, 0.75 mmol, 1.5 equiv) prepared according to **TP10** from the corresponding iodide.

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

Purification: pentane:ethyl acetate = 9:1.

m.p.: 117.8 – 119.1 °C.

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

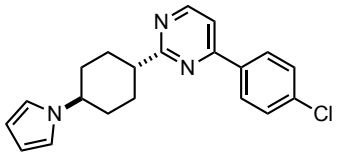
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.5, 157.1, 147.4, 128.5, 127.0, 126.1, 118.7, 47.2, 43.9, 34.0, 32.2.

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

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

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

2-(4-(1*H*-Pyrrol-1-yl)cyclohexyl)-4-(4-chlorophenyl)pyrimidine(14ah)



Following **TP11-B** 2-bromo-4-(4-chlorophenyl)pyrimidine (**12z**, 135 mg, 0.50 mmol, 1.0 equiv) was coupled with (4-(1*H*-pyrrol-1-yl)cyclohexyl)zinc iodide (**13p**, 0.75 mmol, 1.5 equiv) prepared according to **TP10** from the corresponding iodide.

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

Purification: pentane:ethyl acetate = 8:2.

m.p.: 104.0 – 105.7 °C.

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

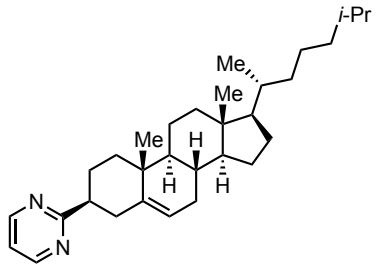
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 174.2, 162.2, 158.0, 137.2, 135.8, 129.3, 128.7, 118.5, 113.8, 108.3, 58.1, 46.6, 34.4, 31.2.

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

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

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

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



Following **TP11-B** 2-bromopyrimidine (**12n**, 80 mg, 0.50 mmol, 1.0 equiv) was coupled with ((8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)- 2,3,4,7,8,9,10,11,12, 13,14,15,16,17- tetradecahydro-1*H*-cyclopenta[/kua]phenanthren-3-yl)zinc chloride (**13s**, 0.75 mmol, 1.5 equiv) prepared according to **TP10** from the corresponding chloride.

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

Purification: pentane:ethyl acetate = 95:5.

m.p.: 125.2 – 127.0 °C.

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

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

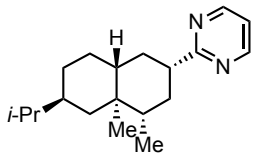
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2937, 2867, 1572, 1561, 1463, 1427, 1382, 1375, 1333, 1167, 1062, 1024, 960, 833, 797, 670.

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

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

Optical rotation: $[\alpha]_\lambda^\varphi$ = 104 (c = 0.98 $CHCl_3$).

2-((2*S*,4*R*,4*aS*,6*R*)-6-Isopropyl-4,4a-dimethyldecahydronaphthalen-2-yl)pyrimidine (14aj)



Following **TP11-B** 2-bromopyrimidine (**12n**, 80 mg, 0.5 mmol, 1.0 equiv) was coupled with ((4*R*,4*aS*, 6*R*)-6-isopropyl- 4,4*a*-dimethyldecahydronaphthalen-2-yl)zinc iodide (**13t**, 0.75 mmol, 1.5 equiv) prepared according to **TP10** from the corresponding iodide.

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

Purification: pentane:ethyl acetate = 9:1.

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

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

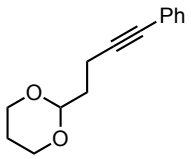
FT-IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2917, 2857, 1571, 1558, 1464, 1422, 1384, 1366, 1119, 963, 890, 780, 668.

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

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

Optical rotation: $[\alpha]_\lambda^\varphi$ = 22 (c = 0.87 $CHCl_3$).

2-(4-Phenylbut-3-yn-1-yl)-1,3-dioxane (14ak)



Following **TP11-B** (bromoethynyl)benzene (**24**, 91 mg, 0.50 mmol, 1.0 equiv) was coupled with (2-(1,3-dioxan-2- yl)ethyl)zinc chloride (0.75 mmol, 1.5 equiv) prepared according to **TP10** from

the corresponding bromide.

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

Purification: pentane:ethyl acetate = 9:1.

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

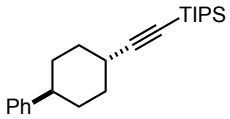
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ = 131.7, 128.3, 127.7, 124.0, 101.0, 89.5, 80.8, 67.1, 34.3, 26.0, 14.4.

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

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

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

Triisopropyl((4-phenylcyclohexyl)ethynyl)silane (14al)



Following **TP11-B** (bromoethynyl)triisopropylsilane (**23**, 131 mg, 0.50 mmol, 1.0 equiv) was coupled with (4- phenylcyclohexyl)zinc iodide (0.75 mmol, 1.5 equiv) prepared according to **TP10** from the corresponding iodide.

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

Purification: pentane.

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

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

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

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

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

IV APPENDIX

1 References

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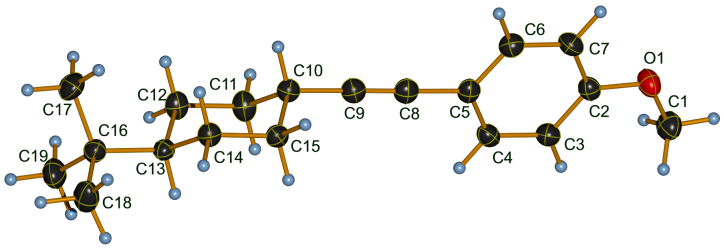
2 Single Crystal X-Ray Diffraction Studies

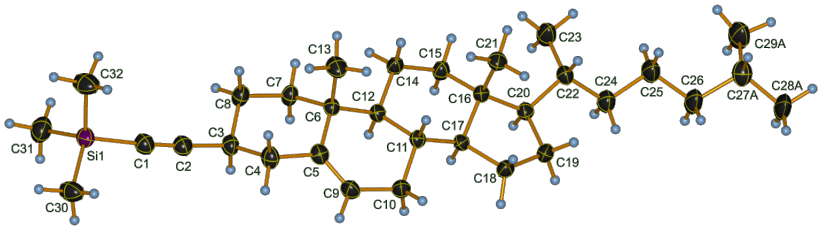
(1-(((*trans*)-4-(*tert*-Butyl)cyclohexyl)ethynyl)-4-methoxybenzene (3o)



3o	
Empirical formula	$C_{19}H_{26}O$
Formula mass	270.40
T[K]	138(2)
Crystal size [mm]	0.47 x 0.20 x 0.18
Crystal description	colorless rod
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	9.8412(4)
b [Å]	24.2551(7)
c [Å]	7.2296(3)
α [°]	90
β [°]	111.080(4)
γ [°]	90
V [Å^3]	1610.21(11)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.115
μ [mm-1]	0.066
F(000)	592
θ range [°]	4.14 – 25.68
Index ranges	-13 $\leq$ h $\leq$ 14
	-34 $\leq$ k $\leq$ 34
	-10 $\leq$ l $\leq$ 10
Reflns. collected	17161

Reflns. obsd.	3640
Reflns. unique	4889
	(Rint = 0.0418)
R1, wR_2 (2σ data)	0.0459, 0.1071
R1, wR_2 (all data)	0.0673, 0.1197
GOOF on F^2	1.039
Peak/hole [e Å^{-3}]	0.275 / -0.173

(3β)-3-(trimethylsilyl(ethynyl))cholest-5-ene (3x)

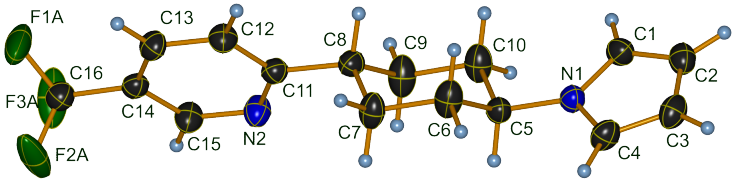


3x

Empirical formula	$C_{32}H_{54}Si$
Formula mass	466.84
T[K]	143(2)
Crystal size [mm]	0.49 x 0.20 x 0.09
Crystal description	colorless rod
Crystal system	monoclinic
Space group	*P*21
a [Å]	14.7063(6)
b [Å]	6.1180(2)
c [Å]	17.3324(6)
α [°]	90
β [°]	103.688(4)
γ [°]	90
V [Å^3]	1515.16(10)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.023
μ [mm-1]	0.094

F(000)	520
θ range [°]	4.16 – 25.24
Index ranges	-21 $\leq$ h $\leq$ 21
	-8 $\leq$ k $\leq$ 8
	-24 $\leq$ l $\leq$ 24
Reflns. collected	16324
Reflns. obsd.	6106
Reflns. unique	8150
	(Rint = 0.0418)
R1, wR_2 (2σ data)	0.0531, 0.1084
R1, wR_2 (all data)	0.0806, 0.1236
GOOF on F^2	1.018
Peak/hole [e $Å^{-3}$]	0.350 / -0.179

2-(4-(1*H*-Pyrrol-1-yl)cyclohexyl)-5-(trifluoromethyl)pyridine (14ae)



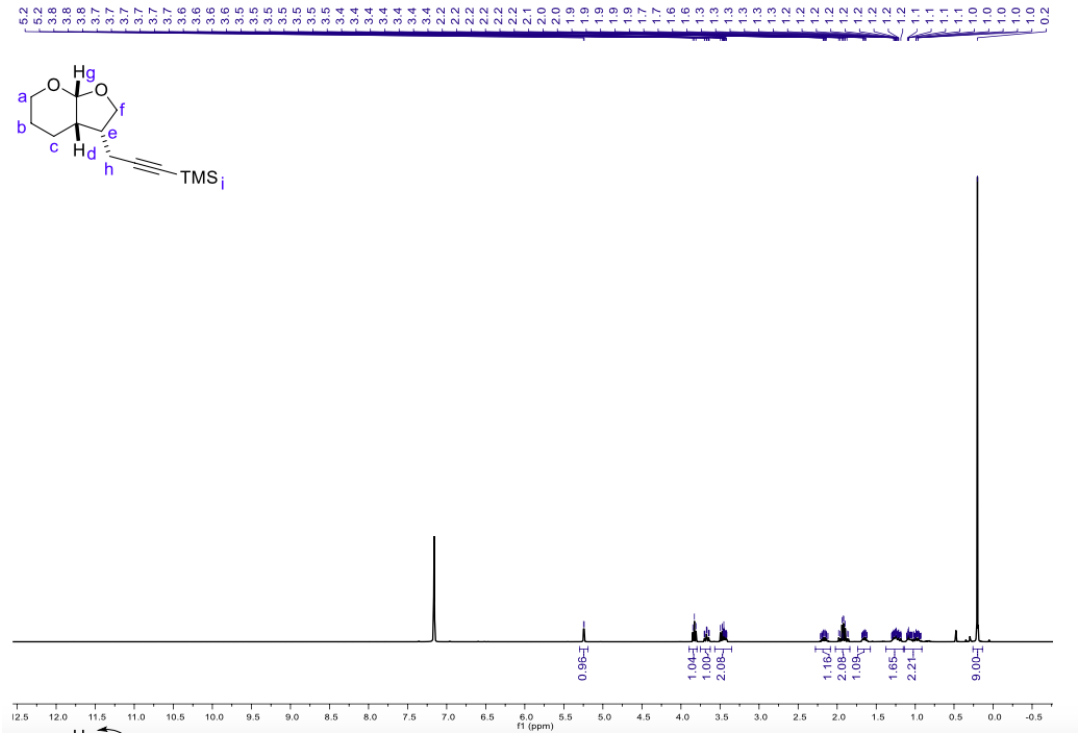
14ae	
Empirical formula	$C_{16}H_{17}F_3N_2$
Formula mass	294.32
T[K]	132(2)
Crystal size [mm]	0.25 x 0.20 x 0.03
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*-1
a [Å]	9.3100(9)
b [Å]	9.3232(11)
c [Å]	9.3565(9)
α [°]	66.006(10)
β [°]	72.336(9)
γ [°]	76.892(9)
V [Å^3]	701.97(14)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.392
μ [mm-1]	0.111
F(000)	308
θ range [°]	2.31 – 25.24
Index ranges	-11 $\leq$ h $\leq$ 11
	-11 $\leq$ k $\leq$ 11
	-11 $\leq$ l $\leq$ 10

Reflns. collected	4530
Reflns. obsd.	1669
Reflns. unique	2670
	(Rint = 0.0288)
R1, wR_2 (2σ data)	0.0548, 0.0923
R1, wR_2 (all data)	0.1003, 0.1093
GOOF on F^2	1.028
Peak/hole [e $Å^{-3}$]	0.193 / -0.211

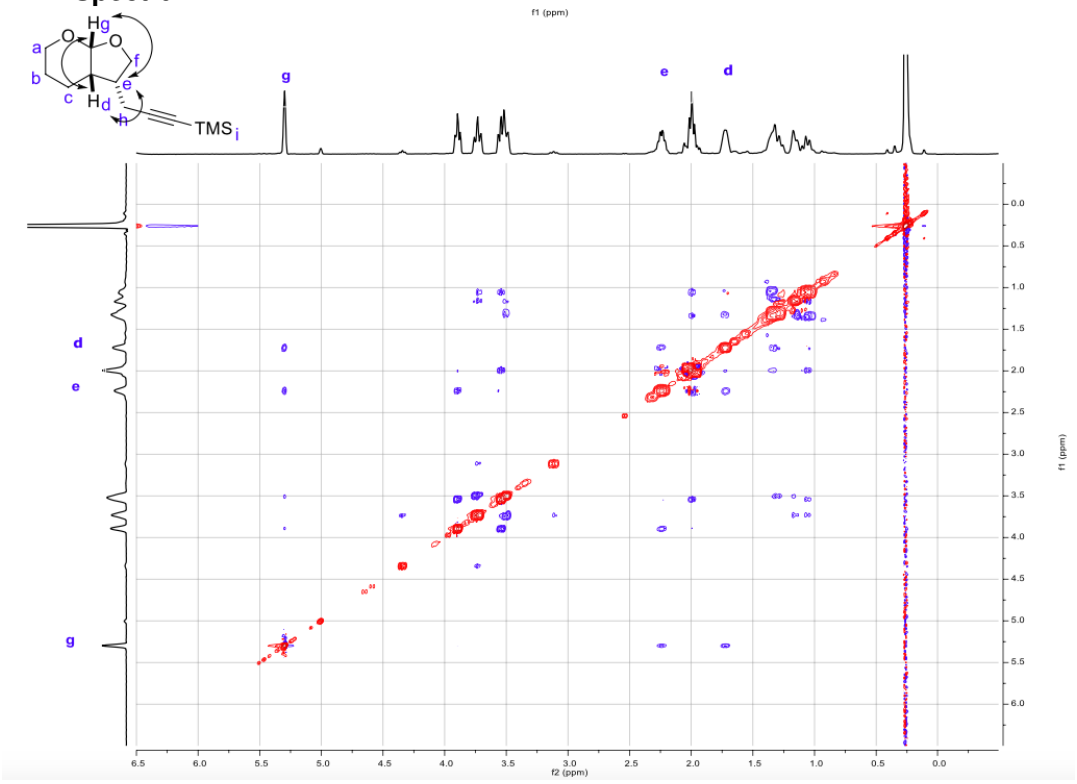
3 Additional NMR Data

Compound 3w

^{1}H-NMR Spectrum

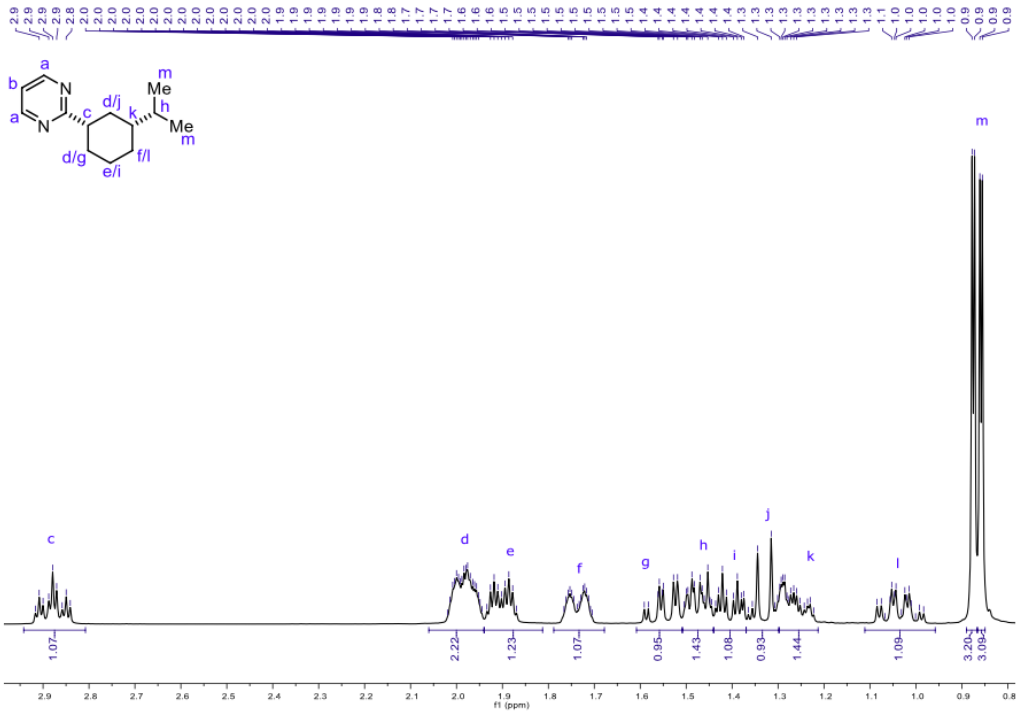


NMR Spectrum

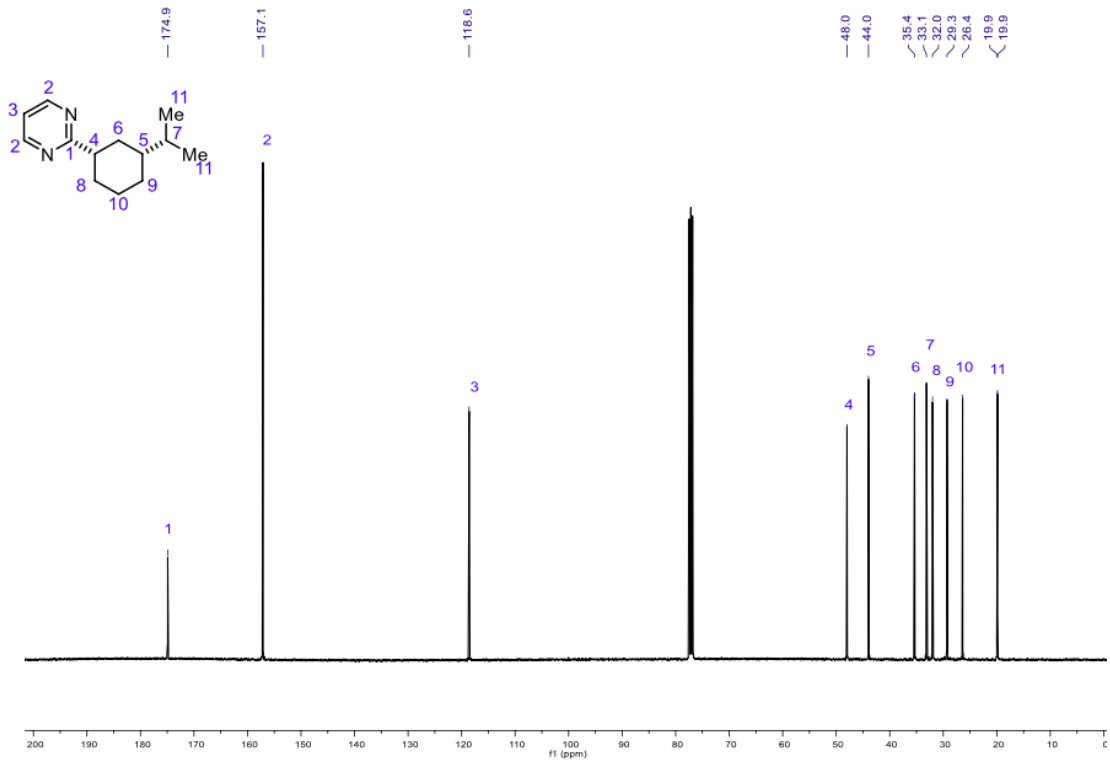


Compound 14ac

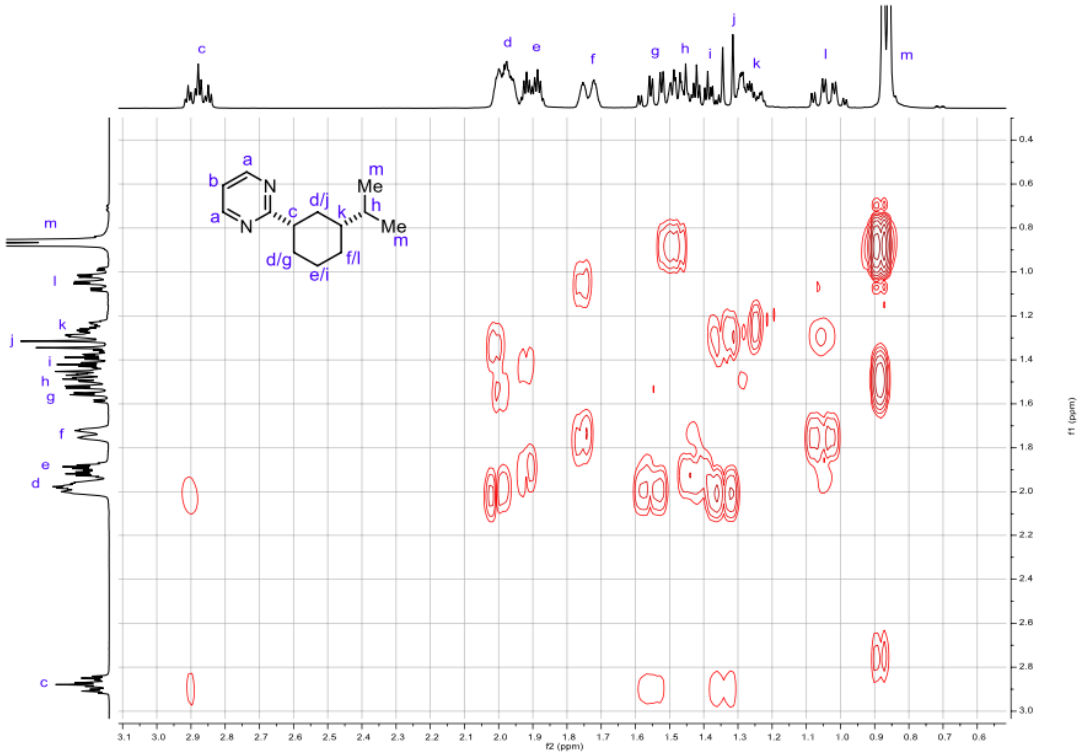
^{1}H-NMR Spectrum



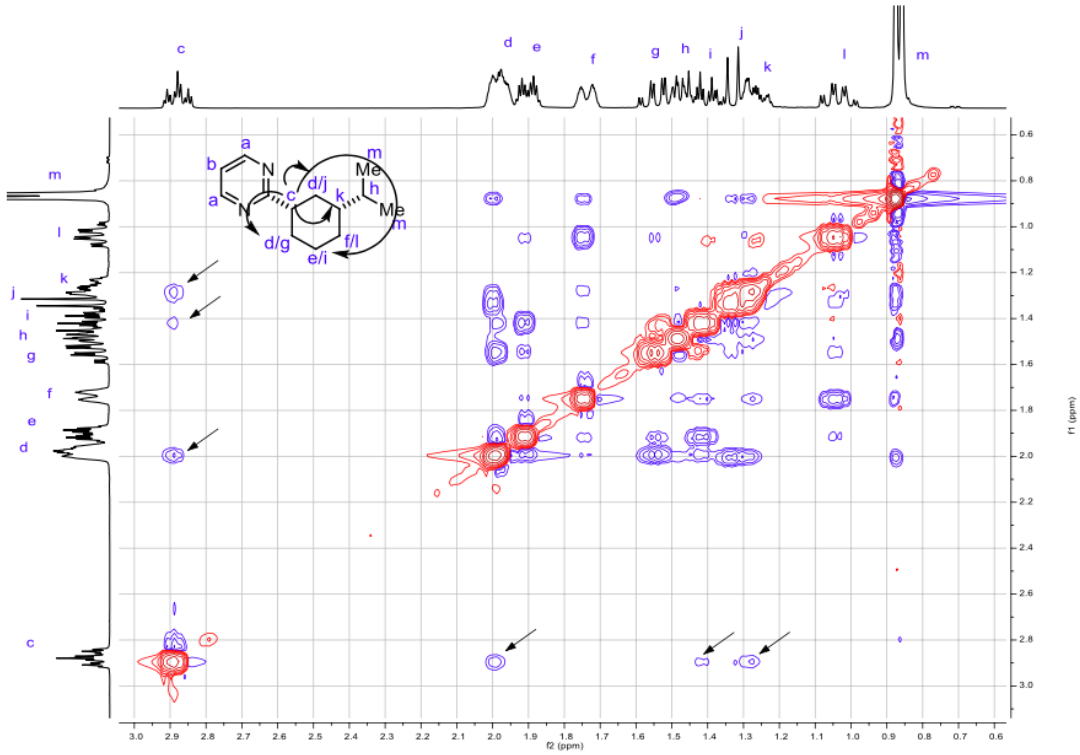
^{13}C-NMR Spectrum



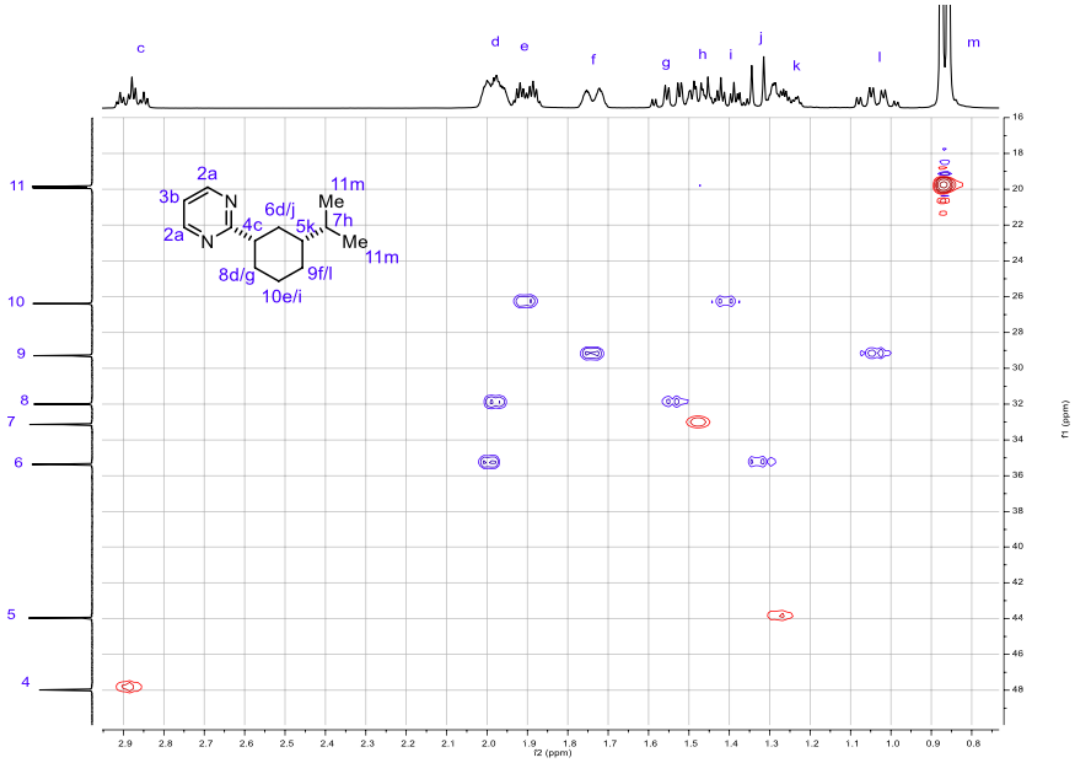
COSY-NMR Spectrum



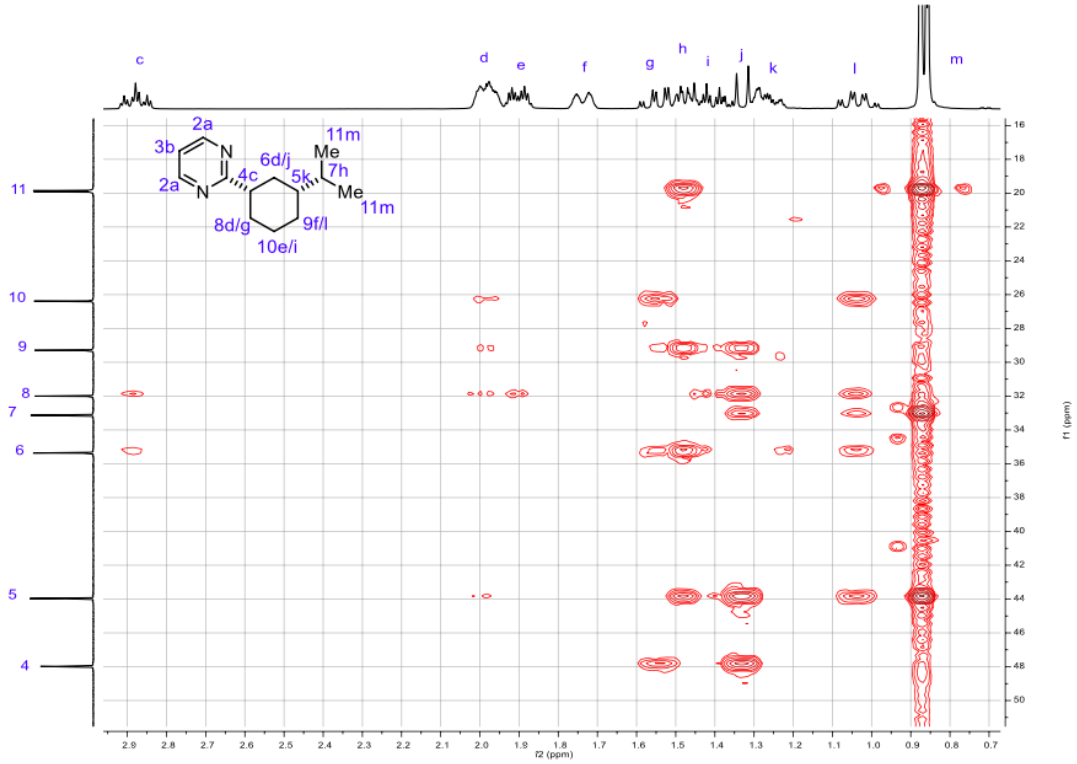
NOESY-NMR Spectrum



HSQC-NMR Spectrum



HMBC-NMR Spectrum

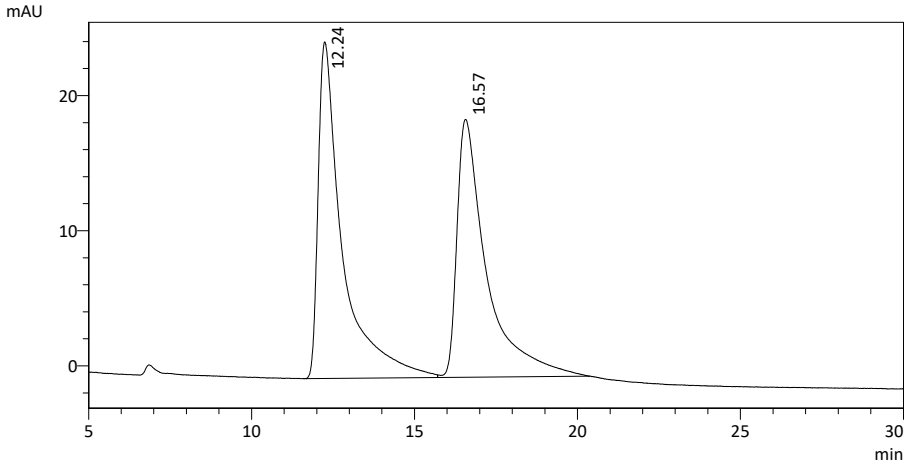


4 Chiral HPLC Analysis

tert-Butyl (*R/S*)-2-((pyridin-2-ylthio)carbonyl)pyrrolidine-1-carboxylate (5k)

SHIMADZU
LabSolutions

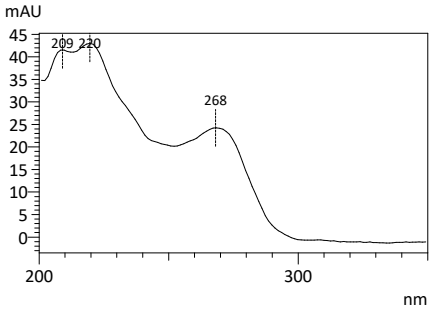
Method File : AD-H_H95_30min.lcm
Date Processed : 03/04/2019 09:07:51



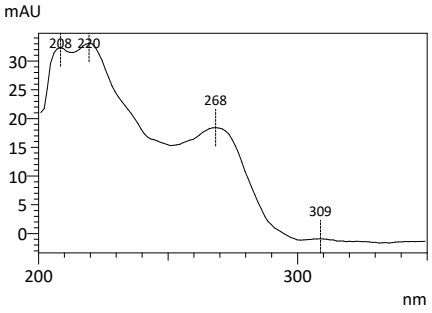
PDA Ch2 268nm

Peak#	Ret. Time	Area	Height	Area%
1	12.24	1282884	24914	51.6
2	16.57	1201484	19082	48.4
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 12.245 min



UV Spectrum
Peak#: 2
Retention Time: 16.565 min

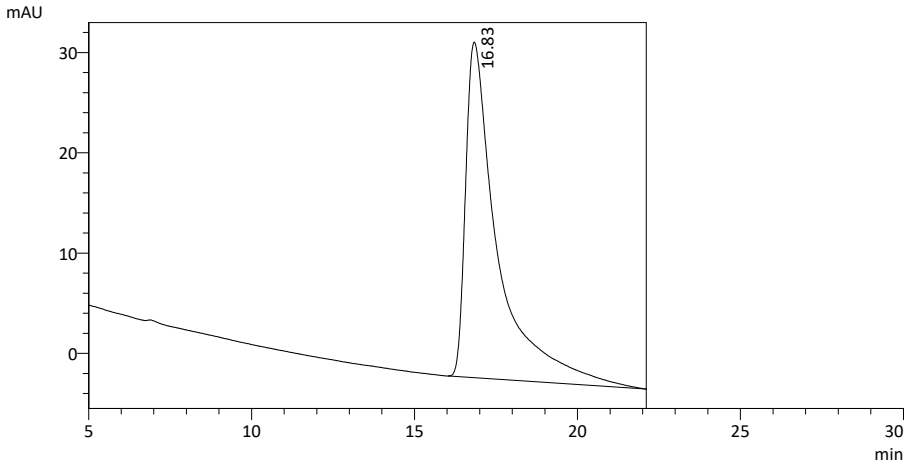


C:\LabSolutions\Data\Lucie\Methods\AD column\heptane-iPrOH\LG-Proline-sm-95-AD-H-rAC004.lcd

tert-Butyl (*S*)-2-((pyridin-2-ylthio)carbonyl)pyrrolidine-1-carboxylate (5k)

SHIMADZU
LabSolutions

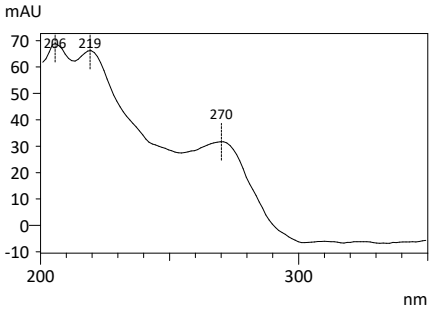
Method File : AD-H_H95_30min.lcm
Date Processed : 03/04/2019 08:25:14



PDA Ch2 267nm

Peak#	Ret. Time	Area	Height	Area%
1	16.83	2292279	33483	100.0
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 16.833 min



UV Spectrum

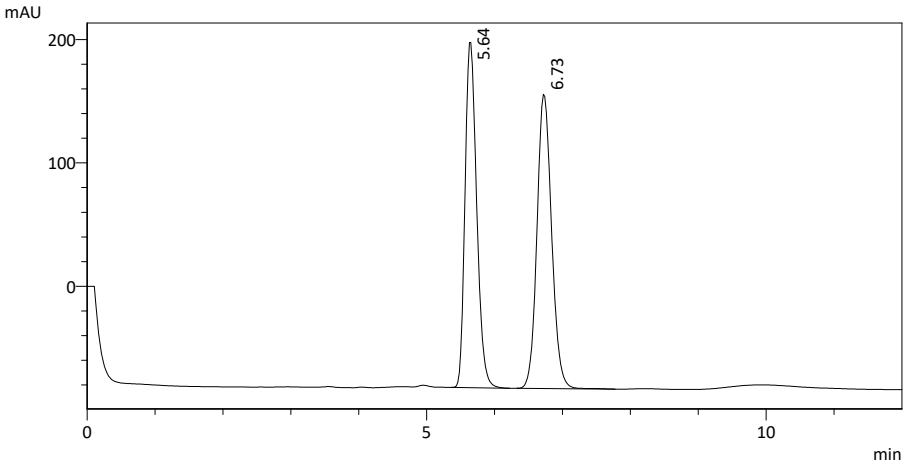
C:\LabSolutions\Data\Lucie\Methods\AD column\heptane-iPrOH\LG-Proline-sm-95-AD-H-rAC003.lcd

S-(Pyridin-2-yl) (*R/S*)-2-(4-isobutylphenyl)propanethioate (5l)

SHIMADZU
LabSolutions

S-(pyridin-2-yl) (R/S)-2-(4-isobutylphenyl)propanethioate (1l)

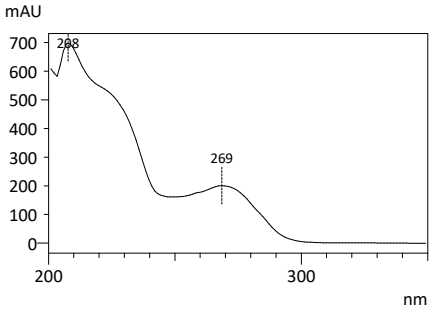
Method File : OD-H_90_10_run.lcm
Date Processed : 13/03/2019 12:54:18



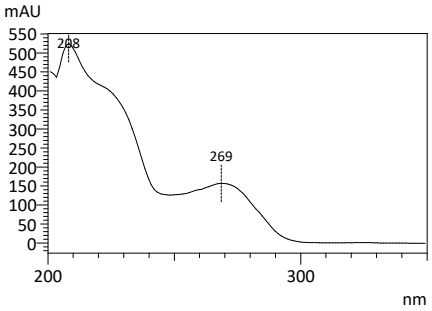
PDA Ch2 268nm

Peak#	Ret. Time	Area	Height	Area%
1	5.64	3345973	279898	48.4
2	6.73	3571156	238609	51.6
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 5.643 min



UV Spectrum
Peak#: 2
Retention Time: 6.727 min

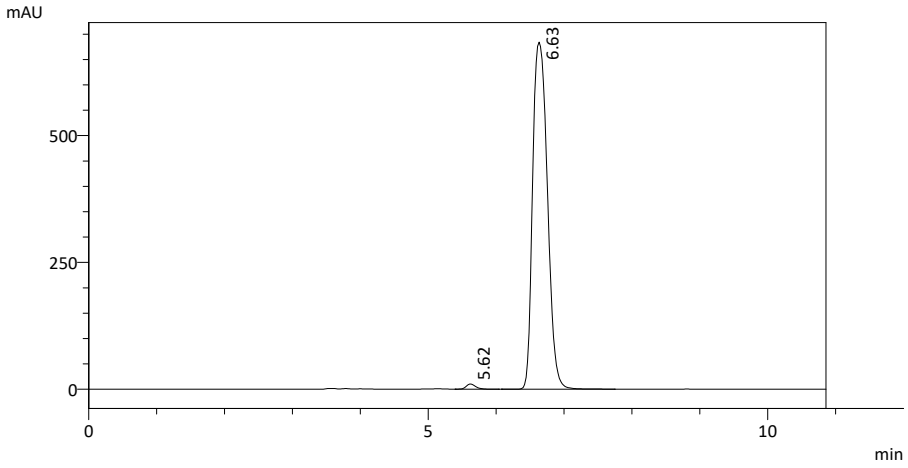


C:\LabSolutions\Data\Lucie\Methods\LG-S,R-Ibuprofen-Rac1.lcd

S-(Pyridin-2-yl) (*S*)-2-(4-isobutylphenyl)propanethioate (5l)

SHIMADZU
LabSolutions

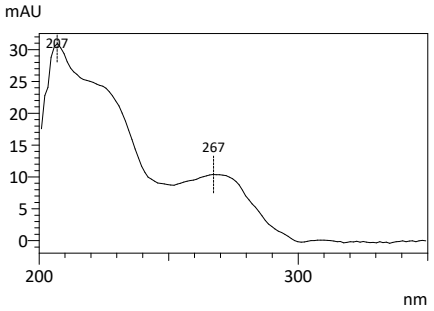
Method File : OD-H_90_10_run.lcm
Date Processed : 13/03/2019 14:03:08



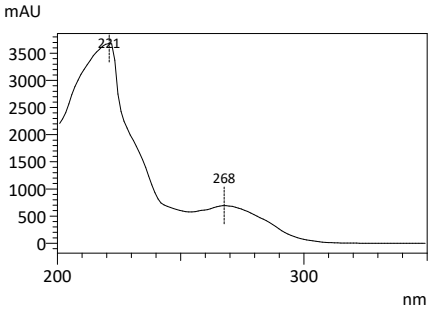
PDA Ch2 268nm

Peak#	Ret. Time	Area	Height	Area%
1	5.62	98756	10149	0.9
2	6.63	10337718	684373	99.1
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 5.625 min



UV Spectrum
Peak#: 2
Retention Time: 6.634 min



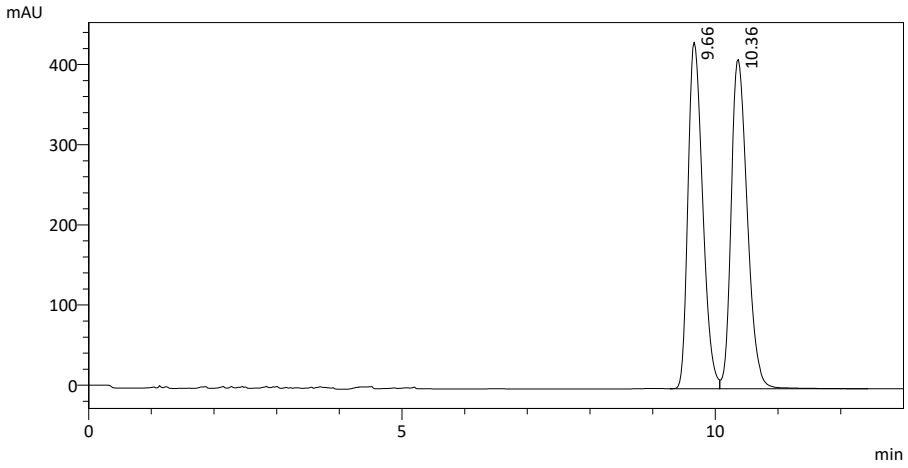
C:\LabSolutions\Data\Lucie\Methods\LG-S-Ibuprofen-Enan-NEwmix2.lcd

S-(Pyridin-2-yl) (*R/S*)-2-methylbutanethioate5m

SHIMADZU
LabSolutions

S-(pyridin-2-yl) (R/S)-2-methylbutanethioate (1m)

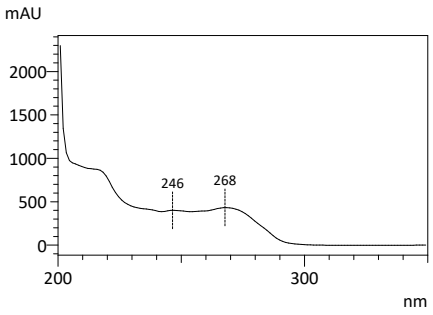
Method File : OD-H_98_2_run.lcm
Date Processed : 30/01/2019 14:37:29



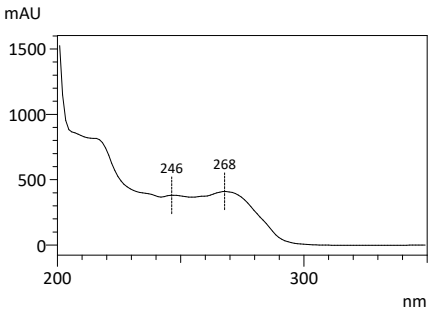
PDA Ch2 268nm

Peak#	Ret. Time	Area	Height	Area%
1	9.66	7082537	432518	49.0
2	10.36	7374118	410870	51.0
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 9.663 min



UV Spectrum
Peak#: 2
Retention Time: 10.362 min



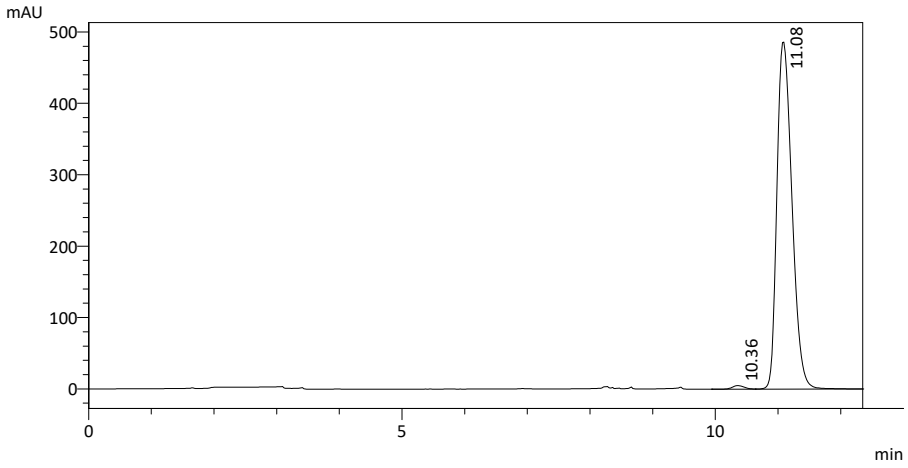
C:\LabSolutions\Data\Lucie\Methods\LG-2-methylbutSM-Rac-98ODH3.lcd

S-(Pyridin-2-yl) (*S*)-2-methylbutanethioate (5m)

SHIMADZU
LabSolutions

S-(pyridin-2-yl) (S)-2-methylbutanethioate (1m)

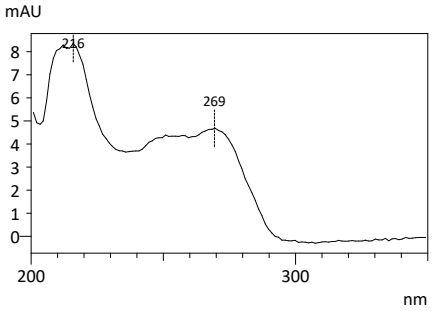
Method File : OD-H_98_2_run.lcm
Date Processed : 30/01/2019 14:51:03



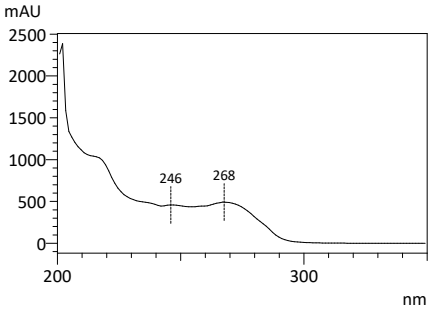
PDA Ch2 268nm

Peak#	Ret. Time	Area	Height	Area%
1	10.36	67843	5002	0.8
2	11.08	8089331	486237	99.2
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 10.363 min



UV Spectrum
Peak#: 2
Retention Time: 11.084 min

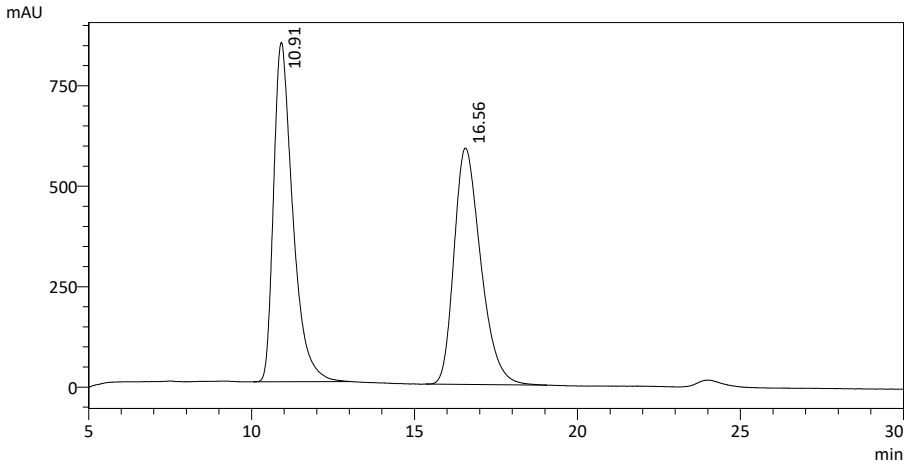


C:\LabSolutions\Data\Lucie\Methods\LG-2-methylbutSM-Enan-98ODH4.lcd

tert-Butyl (*R/S*)-2-(4-methoxybenzoyl)pyrrolidine-1-carboxylate (7t)

SHIMADZU LabSolutions

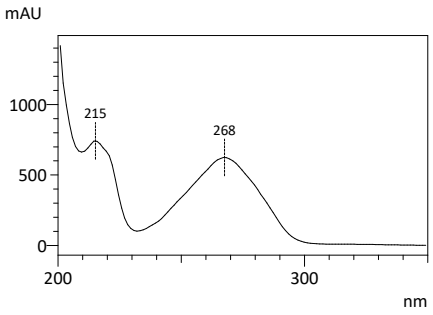
Method File : OJ-H_H95_30min.lcm
Date Processed : 13/03/2019 13:24:18



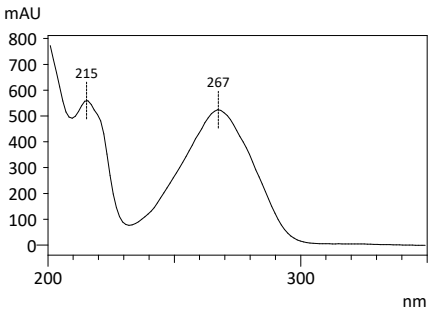
PDA Ch2 205nm

Peak#	Ret. Time	Area	Height	Area%
1	10.91	34590934	845603	50.8
2	16.56	33536738	588075	49.2
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 10.912 min



UV Spectrum
Peak#: 2
Retention Time: 16.560 min

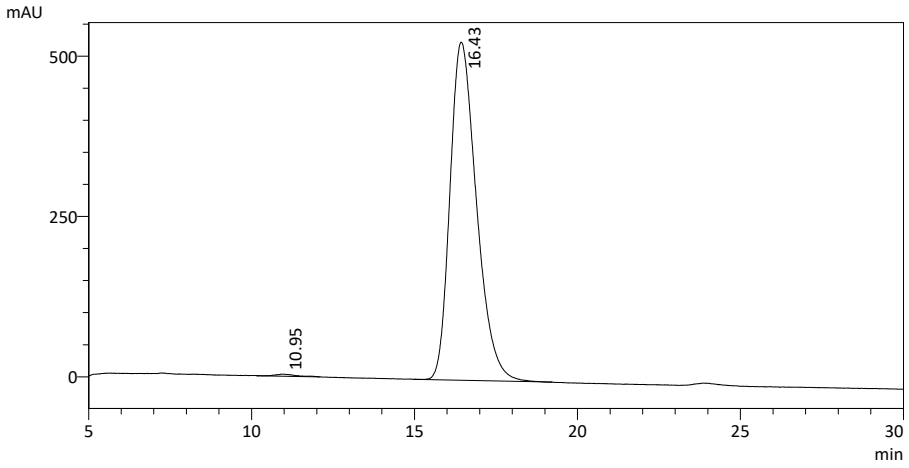


C:\LabSolutions\Data\Max H\Runs\prolin\CN60-eerein\3\mhcn55racoj95rac.lcd

tert-Butyl (*S*)-2-(4-methoxybenzoyl)pyrrolidine-1-carboxylate (7t)

SHIMADZU
LabSolutions

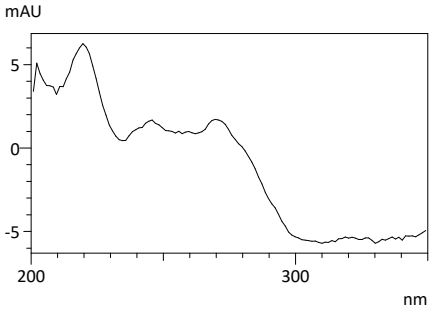
Method File : OJ-H_H95_30min.lcm
Date Processed : 20/04/2018 11:43:56



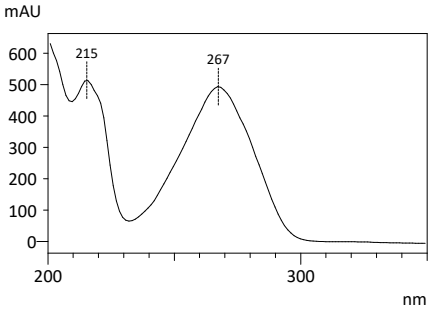
PDA Ch2 205nm

Peak#	Ret. Time	Area	Height	Area%
1	10.95	144744	3265	0.5
2	16.43	29893047	527759	99.5
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 10.947 min



UV Spectrum
Peak#: 2
Retention Time: 16.429 min

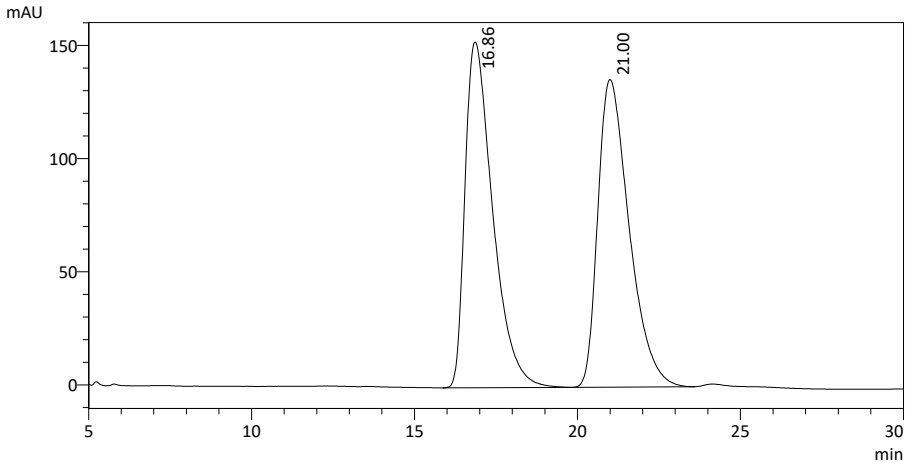


C:\LabSolutions\Data\Max H\Runs\prolin\CN60-eerein\2\mhcn60oj95rac.lcd

tert-Butyl (*R/S*)-2-(benzo[*d*][1,3]dioxole-5-carbonyl)pyrrolidine-1-carboxylate (7u)

SHIMADZU
LabSolutions

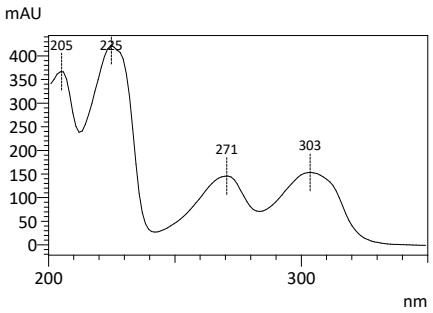
Method File : OJ_99_1.lcm
Date Processed : 16/01/2019 08:25:36



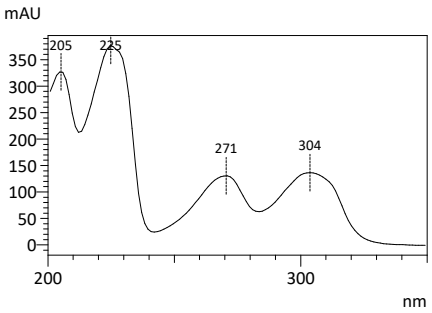
PDA Ch2 303nm

Peak#	Ret. Time	Area	Height	Area%
1	16.86	9027923	152766	49.9
2	21.00	9081683	135945	50.1
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 16.859 min



UV Spectrum
Peak#: 2
Retention Time: 20.998 min

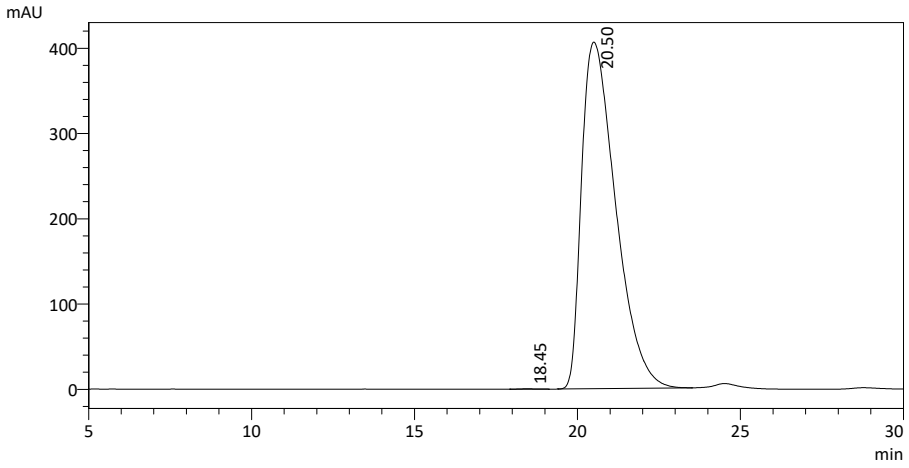


C:\LabSolutions\Data\Lucie\Methods\LG226B-Rac-98% OJ1.lcd

tert-Butyl (*S*)-2-(benzo[*d*][1,3]dioxole-5-carbonyl)pyrrolidine-1-carboxylate (7u)

SHIMADZU
LabSolutions

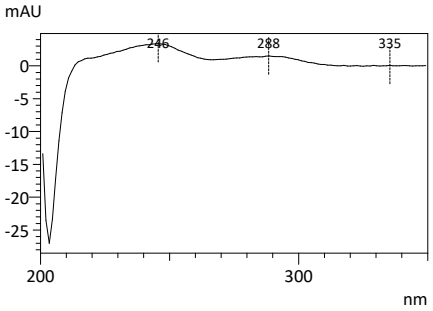
Method File : OJ_99_1.lcm
Date Processed : 16/01/2019 14:11:10



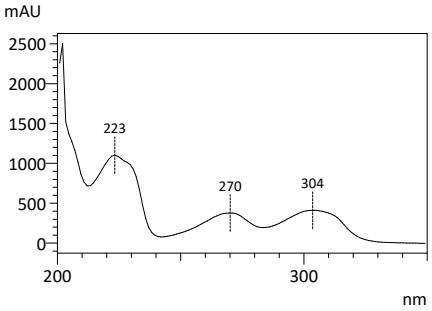
PDA Ch2 303nm

Peak#	Ret. Time	Area	Height	Area%
1	18.45	15261	456	0.1
2	20.50	29617587	406667	99.9
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 18.446 min



UV Spectrum
Peak#: 2
Retention Time: 20.503 min

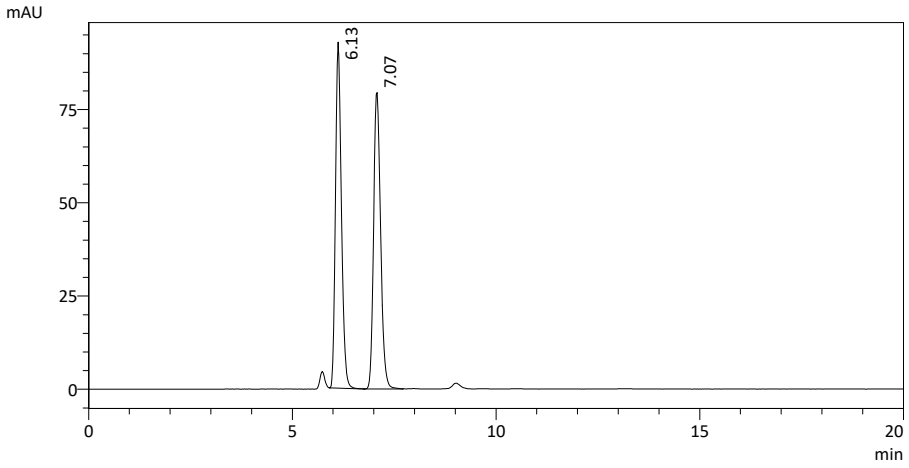


C:\LabSolutions\Data\Lucie\Methods\LG226A-Enan98% OJ-Isolated1.lcd

(*R/S*)-2-(4-*iso*-Butylphenyl)-1-(6-methoxynaphthalen-2-yl)propan-1-one (7v)

SHIMADZU
LabSolutions

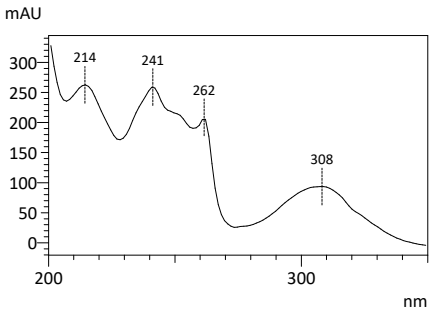
Method File : OD-H_98_2_run.lcm
Date Processed : 24/01/2019 11:29:28



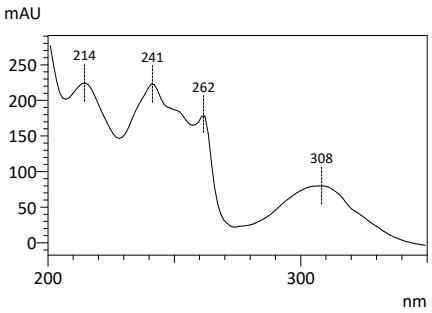
PDA Ch2 308nm

Peak#	Ret. Time	Area	Height	Area%
1	6.13	940487	92827	49.8
2	7.07	948746	79468	50.2
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 6.125 min



UV Spectrum
Peak#: 2
Retention Time: 7.074 min

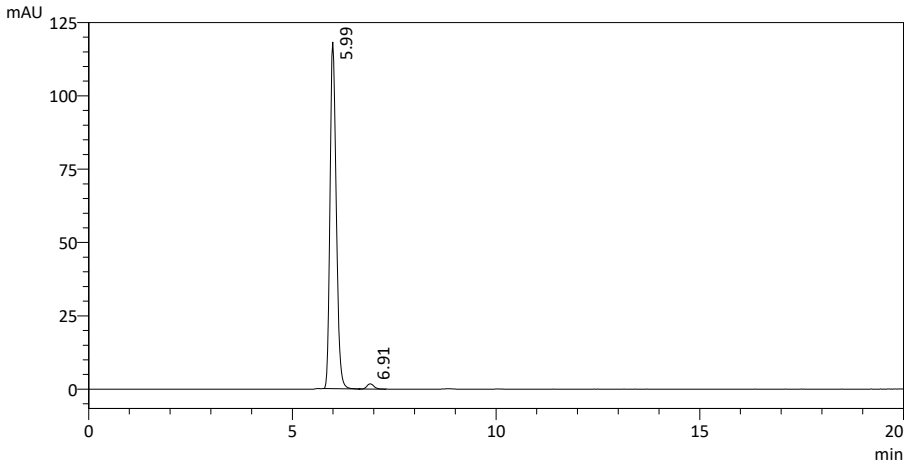


C:\LabSolutions\Data\Lucie\Methods\LG-OMe.98ODH-RacLG186-2.lcd

(*S*)-2-(4-*iso*-Butylphenyl)-1-(6-methoxynaphthalen-2-yl)propan-1-one (7v)

SHIMADZU
LabSolutions

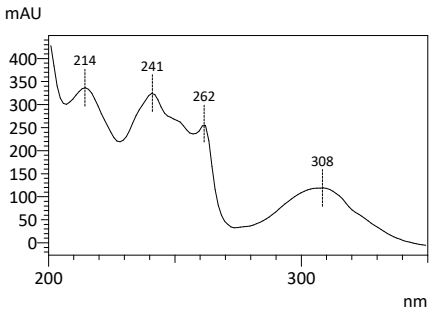
Method File : OD-H_98_2_run.lcm
Date Processed : 24/01/2019 13:00:50



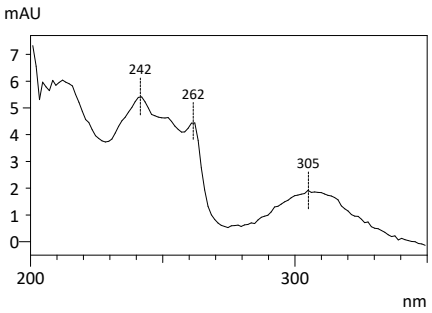
PDA Ch2 308nm

Peak#	Ret. Time	Area	Height	Area%
1	5.99	1260220	118202	98.3
2	6.91	21578	1804	1.7
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 5.994 min



UV Spectrum
Peak#: 2
Retention Time: 6.913 min

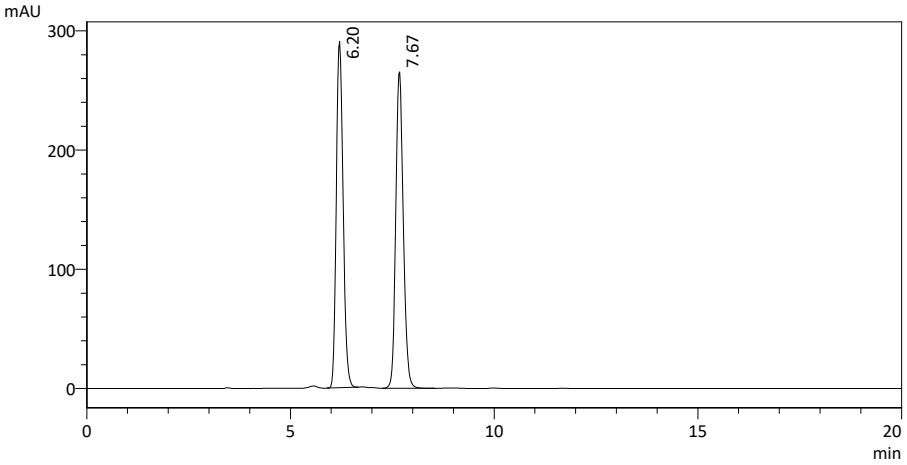


C:\LabSolutions\Data\Lucie\Methods\LG-OMe.98ODH-Enan-Fr-neu1.lcd

(*R/S*)-2-(4-iso-Butylphenyl)-1-(3-(methylthio)phenyl)propan-1-one (7w)

SHIMADZU
LabSolutions

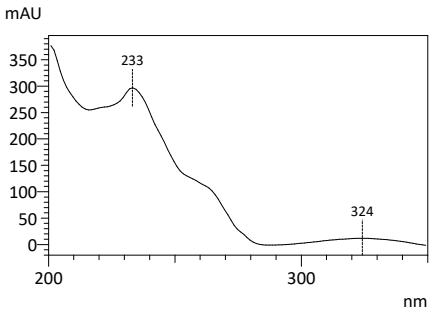
Method File : OD-H_98_2_run.lcm
Date Processed : 24/01/2019 10:04:22



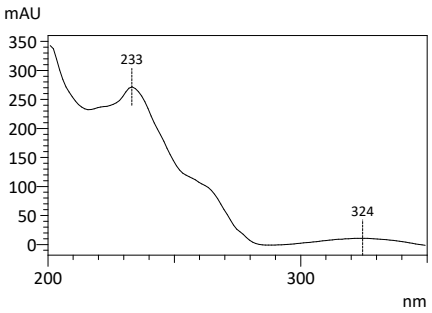
PDA Ch2 233nm

Peak#	Ret. Time	Area	Height	Area%
1	6.20	3372405	290642	49.7
2	7.67	3419067	265543	50.3
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 6.203 min



UV Spectrum
Peak#: 2
Retention Time: 7.672 min

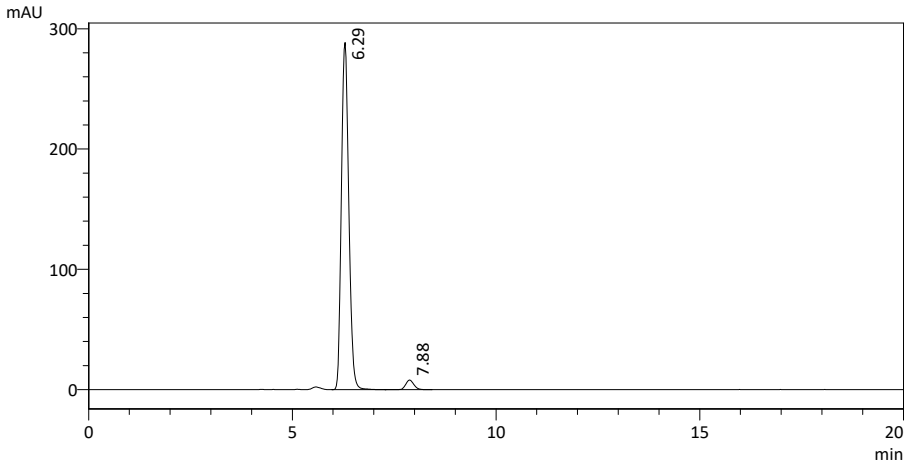


C:\LabSolutions\Data\Lucie\Methods\LG-SMe.99ODH-Enan-Fr163.lcd

(*S*)-2-(4-iso-Butylphenyl)-1-(3-(methylthio)phenyl)propan-1-one (7w)

SHIMADZU
LabSolutions

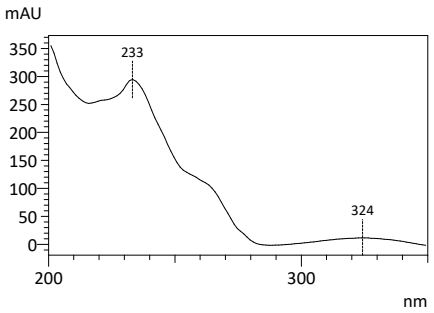
Method File : OD-H_98_2_run.lcm
Date Processed : 24/01/2019 10:28:05



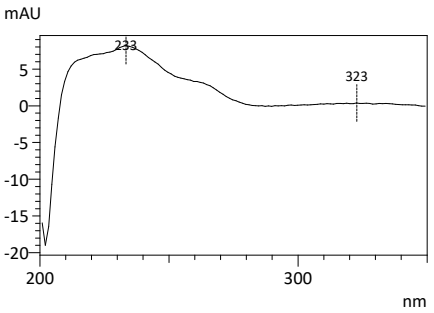
PDA Ch2 233nm

Peak#	Ret. Time	Area	Height	Area%
1	6.29	3644451	288696	97.0
2	7.88	111762	8053	3.0
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 6.289 min



UV Spectrum
Peak#: 2
Retention Time: 7.877 min

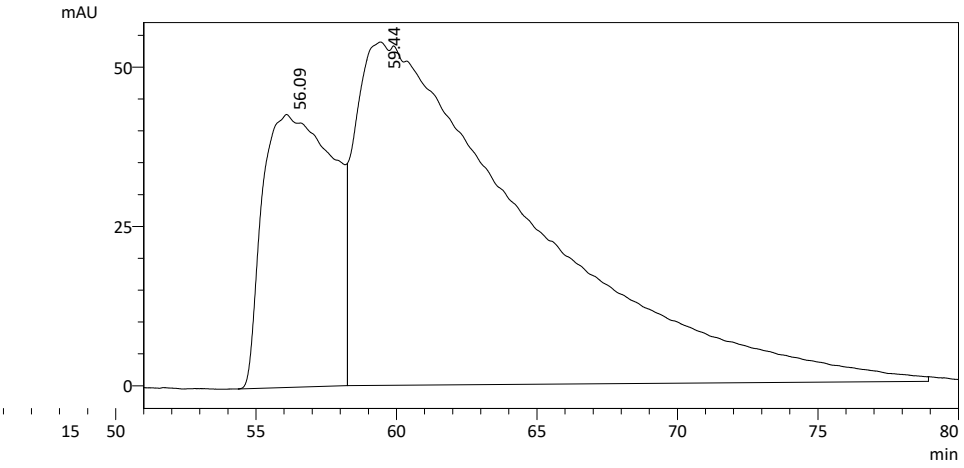


C:\LabSolutions\Data\Lucie\Methods\LG-SMe.99ODH-Enan-Fr16-richtig1.lcd

(*R/S*)-*N,N*-Dimethyl-4-(2-methylbutanoyl)benzamide (7x)

SHIMADZU
LabSolutions

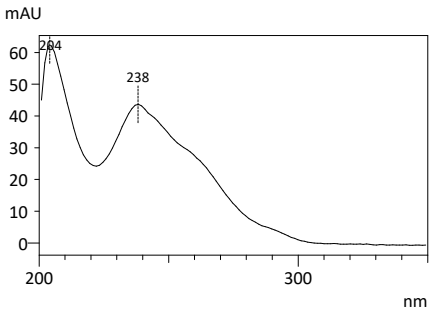
Method File : AD-H_H99.0_80min-2min-mL.lcm
Date Processed : 15/02/2019 15:06:04



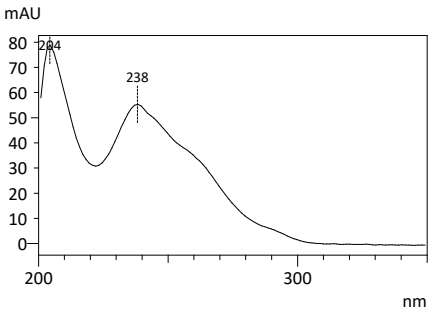
PDA Ch2 238nm

Peak#	Ret. Time	Area	Height	Area%
1	56.09	7545482	42833	24.3
2	59.44	23532946	53869	75.7
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 56.086 min



UV Spectrum
Peak#: 2
Retention Time: 59.443 min

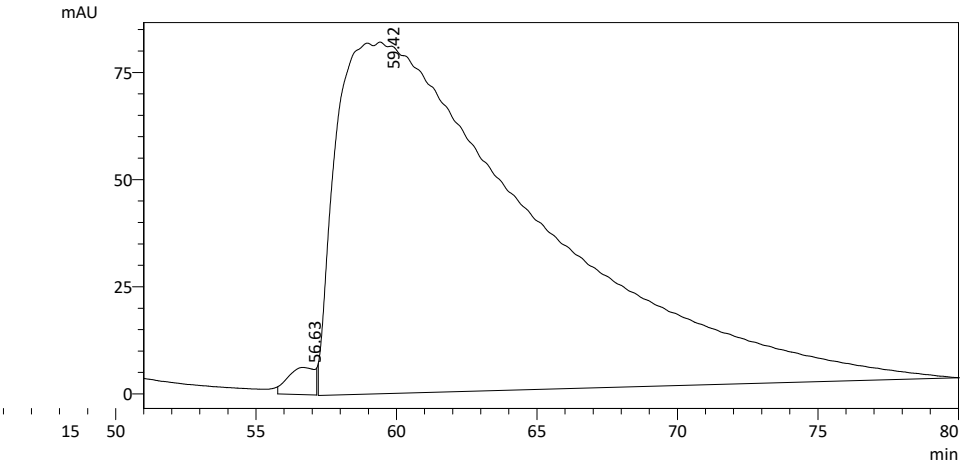


C:\LabSolutions\Data\Lucie\Methods\AD column\heptane-iPrOH\LG245B-Rac-AD-H-99-2Flow.lcd

(*S*)-*N*,*N*-Dimethyl-4-(2-methylbutanoyl)benzamide (7x)

SHIMADZU
LabSolutions

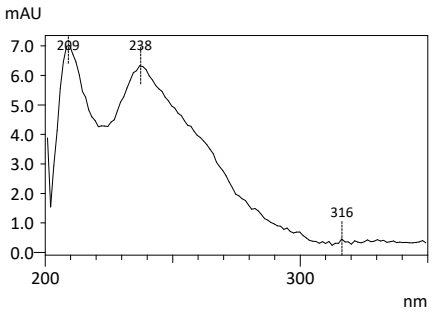
Method File : AD-H_H99.0_80min-2min-mL.lcm
Date Processed : 15/02/2019 15:23:38



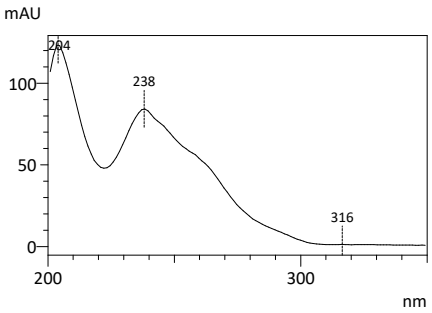
PDA Ch2 238nm

Peak#	Ret. Time	Area	Height	Area%
1	56.63	416671	6326	1.0
2	59.42	41146287	82083	99.0
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 56.629 min



UV Spectrum
Peak#: 2
Retention Time: 59.421 min

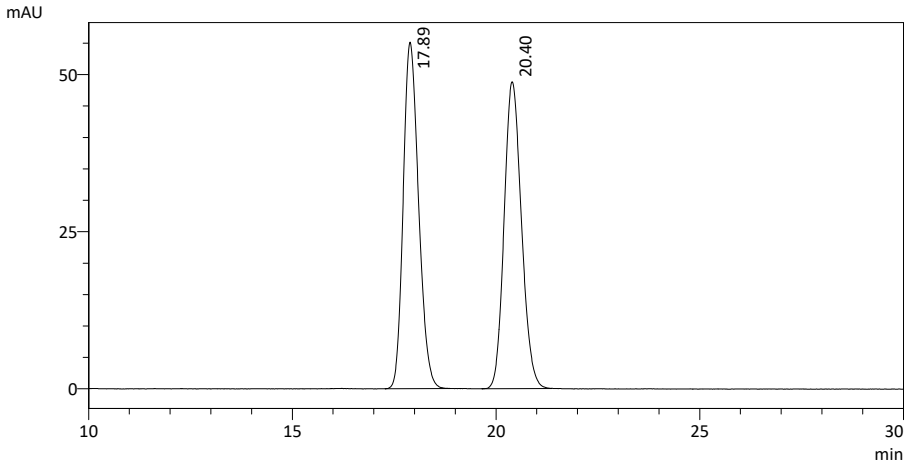


C:\LabSolutions\Data\Lucie\Methods\AD column\heptane-iPrOH\LG245A-Enan-AD-H-99-2Flow.lcd

(*R/S*)-1-(3-(Dimethylamino)phenyl)-2-methylbutan-1-one (7y)

SHIMADZU
LabSolutions

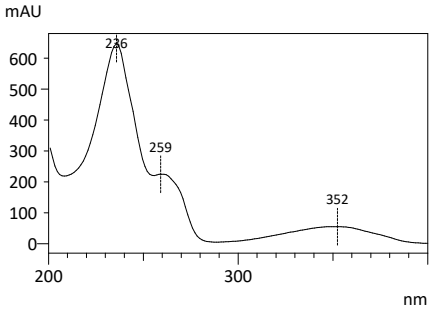
Method File : OD-H_H99.0_60min.lcm
Date Processed : 13/02/2019 14:58:44



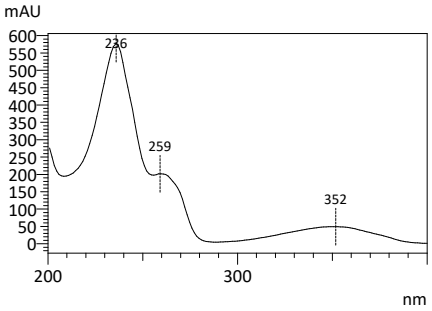
PDA Ch2 352nm

Peak#	Ret. Time	Area	Height	Area%
1	17.89	1445365	55158	50.0
2	20.40	1445361	48838	50.0
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 17.890 min



UV Spectrum
Peak#: 2
Retention Time: 20.398 min

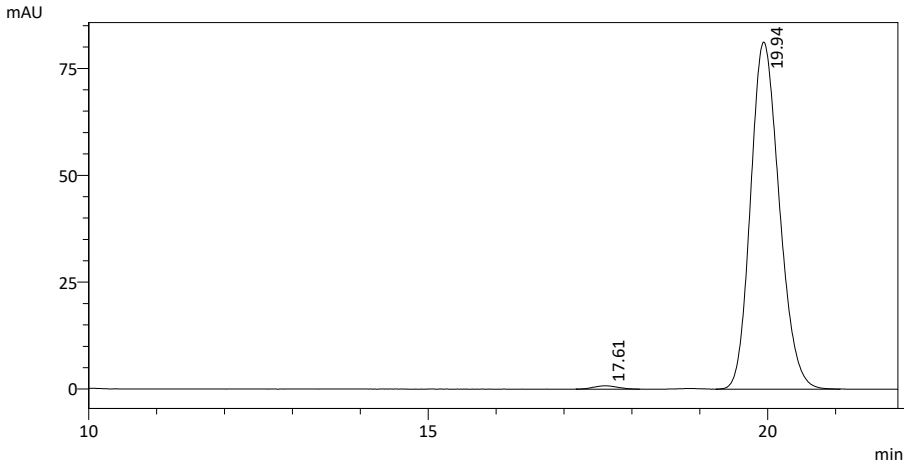


C:\LabSolutions\Data\Lucie\Methods\OD column\heptane-iPrOH\LG249D-Rac-OD-H-99.lcd

(*S*)-1-(3-(Dimethylamino)phenyl)-2-methylbutan-1-one (7y)

SHIMADZU
LabSolutions

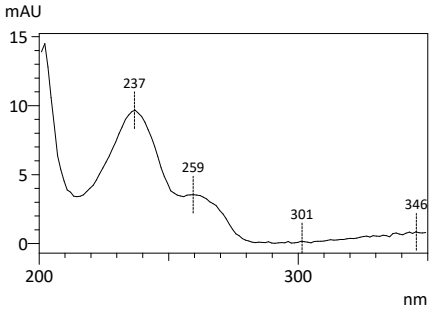
Method File : OD-H_H99.0_60min.lcm
Date Processed : 14/02/2019 07:48:51



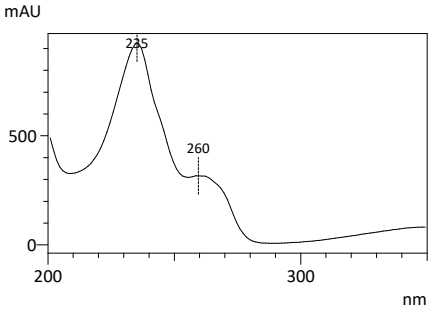
PDA Ch2 353nm

Peak#	Ret. Time	Area	Height	Area%
1	17.61	19705	797	0.8
2	19.94	2384952	81203	99.2
Total				100.0

UV Spectrum
Peak#: 1
Retention Time: 17.610 min



UV Spectrum
Peak#: 2
Retention Time: 19.943 min



C:\LabSolutions\Data\Lucie\Methods\OD column\heptane-iPrOH\LG249C-Enan-OD-H-99.lcd