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Elaboration of Electrophilic Carbon-Heteroatom Bond Forming Reactions Using Organozinc Reagents

von

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aus

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ERKLÄRUNG

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Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

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(Simon Graßl)

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"Der Beginn aller Wissenschaften ist das
Erstaunen, dass die Dinge sind, wie sie sind"

Aristoteles

List of Publications

First Author

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

ii. S. Graßl, C. Hamze, T. J. Koller, P. Knochel, *Chem. Eur. J.* **2019**, 25, 3752–3755.

iii. S. Graßl, Y.-H. Chen, C. Hamze, C. P. Tüllmann, P. Knochel, *Org. Lett.* **2019**, 21, 494–497.

iv. S. Graßl, J. Singer, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 335–338.

v. S. Graßl, P. Knochel, *Org. Lett.* **2020**, DOI: 10.1021/acs.orglett.0c00297.

Co-Author

vi. S. Bouarfa, S. Graßl, M. Ivanova, T. Langlais, G. Bentabed-Ababsa, F. Lassagne, W. Erb, T. Roisnel, V. Dorcet, P. Knochel, F. Mongin, Eur. J. Org. Chem. **2019**, 20, 3244–3258

vii. K. Schwärzer, C. P. Tüllmann, S. Graßl, B. Górski, C. E. Brocklehurst, P. Knochel, *Org. Lett.* **2020**, DOI: 10.1021/acs.orglett.0c00238.

Review

viii. F. H. Lutter, S. Graßl, L. Grokenberger, M. S. Hofmayer, Y.-H. Chen, P. Knochel, *ChemCatChem* **2019**, *11*, 5188–5197.

Table of Contents

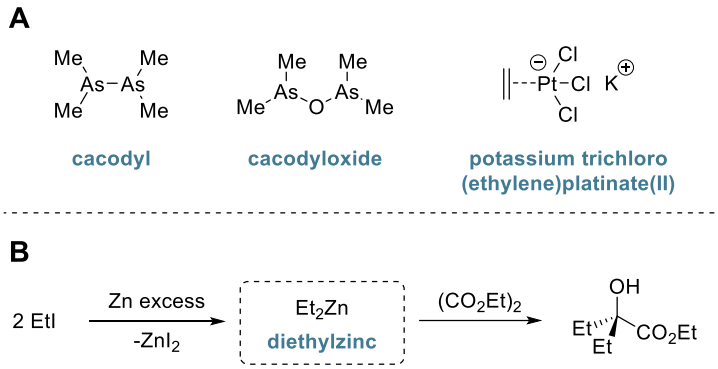
Abbreviations

acac	acetylacetonate
Ar	undefined aryl substituent
ATR	attenuated total reflection
aq. sat.	aqueous, saturated
Boc	tert-butyloxycarbonyl
BPO	benzoyl peroxide
calc.	calculated
conc.	concentrated
d	doublet (NMR)
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMPU	N,N'-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
EDC	1-[3-(dimethylamino)propyl]-3-ethylcarbodimide hydrochloride
EI	electron ionization (MS)
equiv	equivalents
ESI	electrospray ionization (MS)
FG	functional group
GC	gas chromatography
HOBt	1-hydroxylbenzotriazole
HRMS	high resolution mass spectroscopy
IR	infrared
LAH	Lithium aluminium hydride
LDA	lithium diisopropylamide
M	mol/L
Met	Metal
m.p.	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidone
n.d.	not determined
OPiv	pivalate (OCOtBu)
OTf	Triflate (trifluoromethanesulfonate)
Pht	Phthalimide
ppm	parts per million
q	quartet (NMR)
R	undefined organic substituent
r.t.	room temperature
s	singulet (NMR)
t	Triplet (NMR)
TBAF	tetra-*N*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofurane
TMCD	(*R*,*R*)-tetramethylcyclohexanediamine
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethan-1,2-diamin
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
TP	typical procedure
UV	ultraviolet

A. Introduction

1. Overview – Organometallic Chemistry

Synthetic organic chemistry targets the construction and alteration of carbon based chemical compounds. Therein, keeping the right balance between selectivity and chemical reactivity is one of the most important challenges. This applies especially for organometallic compounds, which contain at least one chemical bond between a metal or metalloid and carbon.[1] This sensitive harmony between selectivity and reactivity of an organometallic has a long history, reaching back to the first half of the 19th century, when this chapter of organic chemistry was opened with the discovery of cacodyl ($(Me_2As)_2$) and cacodyl oxide ($Me_2AsOAsMe_2$) by Cadet[2], and later potassium trichloro(ethylene)platinate(II) by Zeise[3] (Scheme 1A). These reagents, however, suffered from low stability and significant toxicity and thus found no further application in organic synthesis. Later, Frankland discovered the first organozinc species with the development of diethylzinc (Et_2Zn, Scheme 1B).[4] This highly pyrophoric liquid, which reacts violently with air or oxygen, proved to be a reasonable nucleophile adding readily to ethyl oxalate, producing the tertiary alcohol.[5] Nevertheless, drawn back by its difficult and dangerous handling, these reagents attracted only little attention.



Scheme 1. A. Structures of cacodyl ($(Me_2As)_2$), cacodyl oxide ($Me_2AsOAsMe_2$) and potassium trichloro(ethene)platinate(II); **B.** Frankland's preparation of diethylzinc and its addition to ethyl oxalate.[2,3,4,5]

1 M. H. Crabtree, *The Organometallic Chemistry of the Transition Metals* (5th ed.), John Wiley and Sons, New York, **2009**.

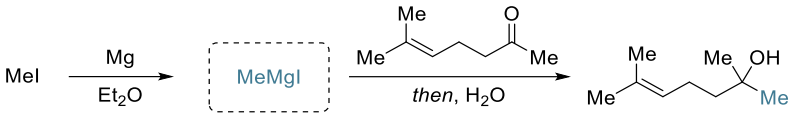
2 a) D. Seyferth, *Organometallics* **2001**, *20*, 1488–1498; b) L. C. Cadet de Gassicourt, "Suite d'Experiences nouvelles sur l'Encre sympathique de M. Hellot qui peuvent servir a` l'analyse du Cobolt; et Histoire d′une liqueur fumante, tire de l'Arsenic" *Memoires de Mathematique et de Physique. Presentes a` l'Academie Royale des Sciences par diverse Savans et lus dans ses Assembles.* Tome Troisieme, MDCCLX, **1760**. These results were communicated to the Royal Academy of Sciences in 1757, reported on favorably by two academicians, Bourdelin and Lassone, in January 1758, and finally published in 1760.

3 W. C. Zeise, *Ann. Phys. (Berl.)* **1831**, *97*, 497–541.

4 E. Frankland, *Justus Liebigs Ann. Chem.* **1849**, *71*, 171–213.

5 E. Frankland, *Justus Liebigs Ann. Chem.* **1863**, *126*, 109–113.

A substantial milestone was set by Grignard at the beginning of the 20th century with the preparation of methylmagnesium chloride as the first stabilized organomagnesium reagent.[6] He established the use of coordinative solvents, such as diethyl ether, which break through coordination the highly aggregated organometallic clusters and lead to more reactive but stable monomeric organometallic species.[7] These Grignard reagents showed excellent behaviour in addition reactions to aldehydes, ketones and carbon dioxide, leading to secondary alcohols, tertiary alcohols and carboxylic acids, respectively (Scheme 2).[8] The reactions smoothly proceeded at room temperature and under atmospheric pressure. This provided the first rapid and highly versatile method for the synthesis of numerous organic compounds of different types, using organometallic reagents.



Scheme 2. Preparation of MeMgI and addition to a ketone, leading to the corresponding tertiary alcohol.[9]

In the following years, the synthesis of such reagents has been further investigated and optimized.[10] This resulted in a wide range of main-group or transition metal based organometallics, which have been successfully applied as nucleophiles in various organic syntheses.[8] Based on these discoveries it was found, that the reactivity of organometallic reagents can be fine-tuned by the choice of the metal. Reagents with a strongly polarized carbon-metal bond (high ionic character), like carbon-lithium and carbon-magnesium bonds are closely connected to a high reactivity towards electrophiles accompanied by low chemical selectivity and often lowered stability. However, reagents with more covalent carbon-metal bonds, such as carbon-copper or carbon-boron bonds show a reversed behaviour. In general, the reactivity of an organometallic species depends on the character of the carbon-metal bond: the more ionic, the more reactive. Thus, the lower the electronegativity of the metal the more reactive is the corresponding organometallic (Figure 1).[8]

6 V. Grignard, *C. R. Acad. Sci*. **1900**, 130, 1322–1324.
7 F. W. Walker, E. C. Ashby, *J. Am. Chem. Soc.* **1969**, *91*, 3845–3850.
8 a) H. G. Richey, *Grignard reagents: new developments*, Wiley, **2000**; b) G. S. Silverman, P. E. Rakita, *Handbook of Grignard Reagents*, Taylor & Francis, **1996**; c) B. J. Wakefield, *Organomagnesium Methods in Organic Chemistry*, Elsevier Science, **1995**.
9 P. Barbier, *Compt. Rend.* **1899**, *128*, 110–112.
10 P. Knochel, *Handbook of Functionalized Organometallics, Vol. 1 and 2*, Wiley-VCH, Weinheim, **2005**.

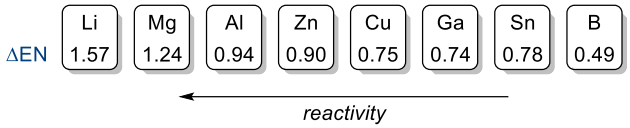


Figure 1. Electronegativity difference of selected metals relative to carbon (Pauling electronegativity scale).[11]

In modern synthetic organic chemistry, organometallics play an important role in numerous methodologies and the synthesis of complex molecules. Their well tuneable reactivity and selectivity as well as their broad and ready availability made them an indispensable tool for the preparation of pharmaceutical and agrochemical molecules.[12]

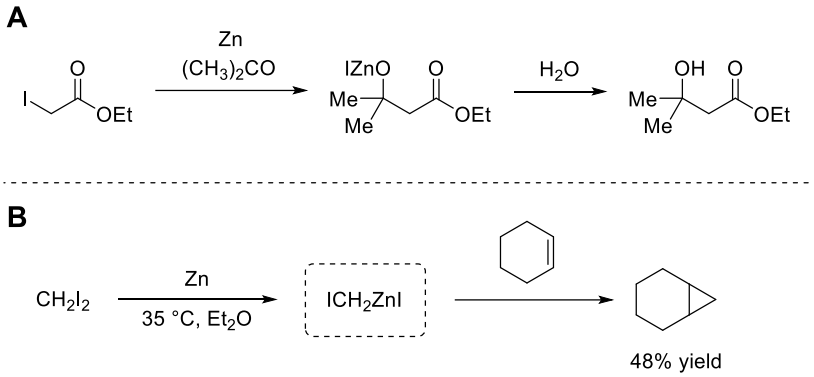
One outstanding class of organometallics, despite not yet fully included in industrial applications, are organozinc reagents. Their history, preparation, and their potential in organic synthesis will be discussed in the following.

[11] A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *39*, 4414–4435.
[12] K. C. Nicolaou, J. S. Chen, *in Classics in Total Synthesis III*, Wiley-VCH Verlag GmbH, **2011**.

2. Organozinc Chemistry

2.1 Overview

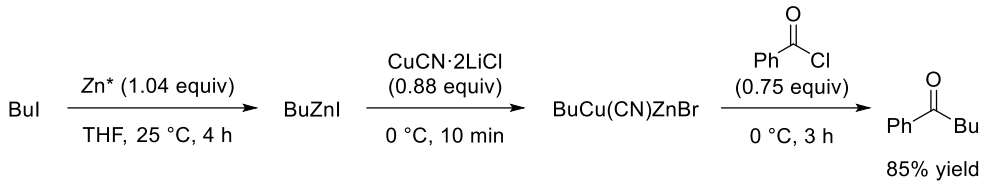
Organozinc reagents play an important role in modern organic chemistry and have proved to be valuable synthetic tools in carbon-carbon bond formation reactions. Their chemistry dates back to 1849, when Frankland discovered diethylzinc as the first organozinc reagent (Scheme 1B).[4] Although their potential as nucleophiles using the polarized carbon-metal bond was quickly recognized, Grignard's discovery of the organomagnesium species in 1900 was dedicated most attention at that time.[8] Nevertheless, a few important reactions using organozinc chemistry, such as the Reformatsky reaction[13] (Scheme 3A) or the Simmons-Smith[14] cyclopropanation (Scheme 3B), have been developed in the meanwhile.



Scheme 3. A. Reformatsky reaction – zinc insertion into carbon-iodine bond of α-iodo ethyl acetate, providing, after addition to acetone, the corresponding tertiary alcohol.[13] **B.** Simmons-Smith cyclopropanation using diiodomethane and elementary zinc (activated with copper or sonication).[14]

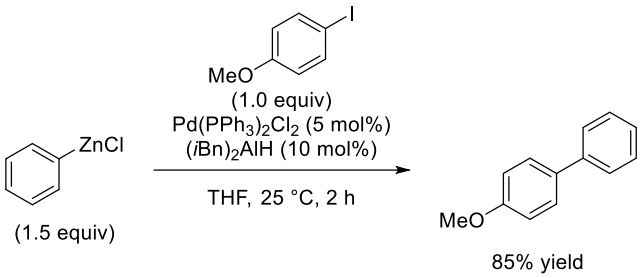
It was only after several decades that the full potential of organozinc reagents was discovered.[10] Compared to other organometallics, organozinc reagents have a very high compatibility with a large number of sensitive functional groups. Unfortunately, this results in a low reactivity towards electrophiles, which makes a broad synthetic application difficult. However, the presence of empty p-orbitals of suitable energy allows fast and smooth transmetalations to many other transition metals, such as copper.

[13] S. Reformatsky, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210–1211.
[14] H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323–5324.



Scheme 4. Preparation of BuZnI via oxidative insertion of activated zinc into the carbon-iodine bond, transmetalation with CuCN·2LiCl and subsequent acylation using benzoyl chloride.[15]

In the case of a transmetalation with CuCN·2LiCl, the resulting reagents are thermodynamically more stable (more covalent carbon-copper bond). However, they are also more reactive due to the presence of nucleophilic, non-binding d-electrons, which interact with the electrophile in an oxidative process and mediate the formation of the new carbon-carbon bonds, such as an acylation (Scheme 4).[10] This extraordinary ability of committing transmetalation gained new importance when the power of palladium-catalyzed cross-coupling reactions was recognized in the 1960s due to the findings of Heck.[16] With the help of palladium complexes, an efficient way of forming C-C bonds between less reactive organic aryl halides and various carbon nucleophiles was found. By now, these palladium-catalyzed cross-coupling reactions (especially using organozinc and organoboron reagents) have become powerful and indispensable tools in organic synthesis (Scheme 5).[17] This rewarded Richard F. Heck, Ei-ichi Negishi and Akira Suzuki with the Nobel Prize in Chemistry in 2010 for their work on this new type of C-C bond formation.



Scheme 5. Selected example of a Negishi cross coupling reaction.[18]

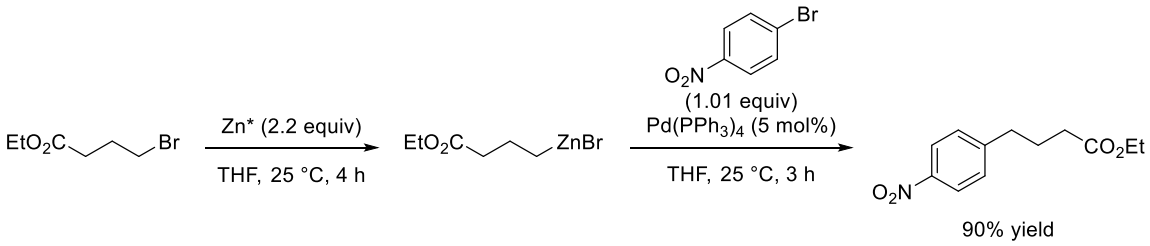
[15] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2392–2394.
[16] K. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972** *87*, 2320–2322.
[17] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; b) J. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530; c) N. Miyaura, A. Suzuki, *Chem. Rev.***1995**, *95*, 2457–2483.
[18] E.-i. Negishi, A. O. King, N. Okukado *J. Org. Chem.* **1977**, *42*, 1821–1823.

2.2 Preparation of Organozinc Compounds

The choice of method for the preparation of an organozinc reagent depends on the nature of the starting substrate. However, the most common approaches utilize organic halides, but also direct C-H activation or transmetalation from other organometallics are possible. The method of preparation can also depend on the presence of certain functional groups.

2.2.1 Oxidative Insertion

The most common approach for the direct synthesis of organozinc reagents is the insertion of zinc powder into organic halides. In many cases, however, expensive organic iodides must be used and elevated reaction temperatures are required.[1,19] To overcome these disadvantages, Rieke and co-workers developed a procedure to activate metal atoms by reduction of the corresponding metal salt with lithium naphthalide. Thus, functionalized organozinc reagents from less reactive aryl or alkyl bromides can be obtained, using this highly active zinc (Zn*) produced by reduction of $ZnCl_2$ (Scheme 6).[20] Therefore, starting from ethyl 4-bromobutyrate, the corresponding organozinc bromide was obtained using Rieke zinc. A subsequent palladium-catalyzed cross-coupling with 1-bromo-4-nitrobenzene, led to the desired ethyl 4-(4-nitrophenyl)butanoate in 90% yield over two steps.



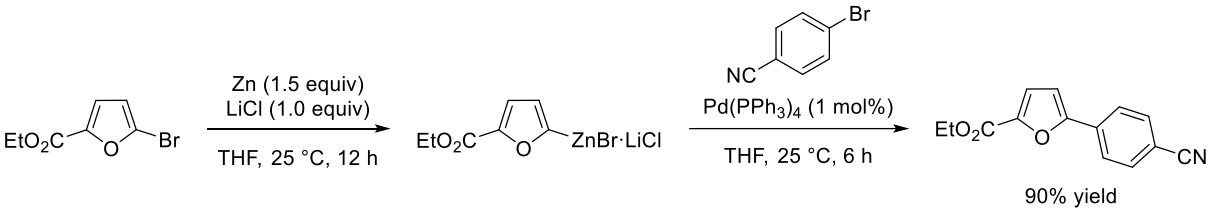
Scheme 6. Oxidative zinc insertion into a carbon-halide bond using highly activated Rieke zinc, and subsequent palladium-catalyzed cross-coupling.[20a]

This method of activation, however, produces a lot of sideproducts and proved to be inconvenient to use. Knochel and co-workers were able to utilize commercially available zinc powder as suitable reagent for the insertion into highly functionalized halides under mild

[19] P. Knochel, N. Millot, A. L. Rodriguez, in *Organic Reactions* 58, Wiley–VCH: Weinheim, Germany, **2004**, 417–759 c) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117–2188.

[20] a) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445–1453; b) R. D. Rieke, *Science* **1989**, *246*, 1260–1264; c) T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1983**, *48*, 4141–4143.

conditions in the presence of LiCl (Scheme 7).[21] This enabled the preparation of aromatic, heteroaromatic, alkylic and benzylic zinc reagents in the presence of a variety of functional groups such as esters, nitriles and aldehydes. Based on experimental, computational and analytical studies, the origin of this behaviour was revealed.[22] First, LiCl increases the solubility of the organometallic reagent in THF solution, which enables the regeneration of a free metal surface during the insertion reaction.[22] Thus, the heteroaromatic bromide was converted into the corresponding organozinc compound and subsequently exposed into a palladium-catalyzed cross-coupling to form the arylated product. [21a]



Scheme 7. Zinc insertion in the presence of LiCl, and subsequent palladium-catalyzed cross-coupling.[21a]

2.2.2 Halogen-Zinc Exchange

Starting from organic halides, an alternative approach to access organozinc reagents is the exchange reaction with another organozinc reagent. The halogen-metal exchange represents one of the most efficient methods for the preparation of functionalized organometallics. The reaction of an organic halide R^1–X with an organometallic R^2–Met produce a halogenate complex ($R^1R^2X^-$ Met^+).[23] Subsequent decomposition forms the most stable organometallic species, meaning it has the carbon skeleton with the lowest electron density and/or the highest ability to stabilize the excess negative charge (Scheme 8A). Therefore, the exchange reagent (R^2–Met) must be less stable than the organometallic species formed (R^1–Met). The speed of the halogen-zinc exchange can be catalyzed by the addition of a carboxylate such as Li(acac)[24]

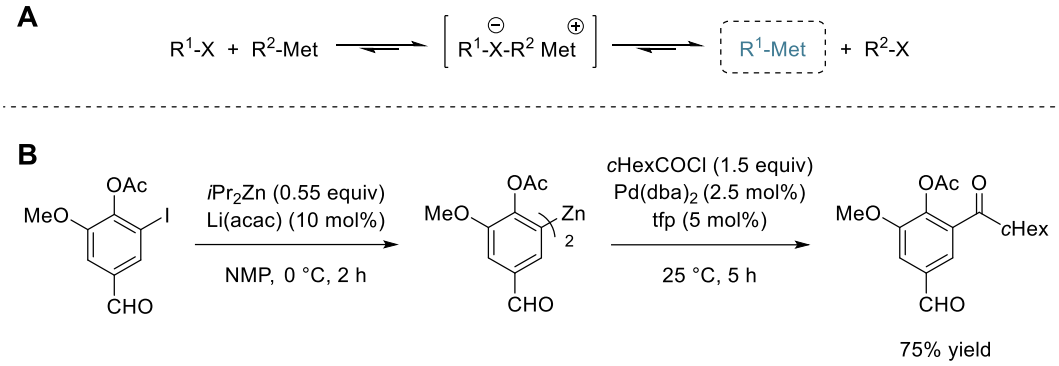
[21] a) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107–1110; b) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358–12359; c) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040–6044.

[22] a) J. E. Fleckenstein, K. Koszinowski, *Organometallics* **2011**, *30*, 5018–5026; b) C.-Y. Liu, X. Wang, T. Furuyama, S. Yasuike, A. Muranaka, K. Morokuma, M. Uchiyama, *Chem. Eur. J.* **2010**, *16*, 1780–1784; c) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771–779; d) C. Feng, D. W. Cunningham, Q. T. Easter, S. A. Blum, *J. Am. Chem. Soc.* **2016**, 138, 11156–; e) 11159A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159–162.

[23] H. J. Reich, A. W. Sanders, A. T. Fiedler, M. J. Bevan, *J. Am. Chem. Soc.* **2002**, *124*, 13386–13387.

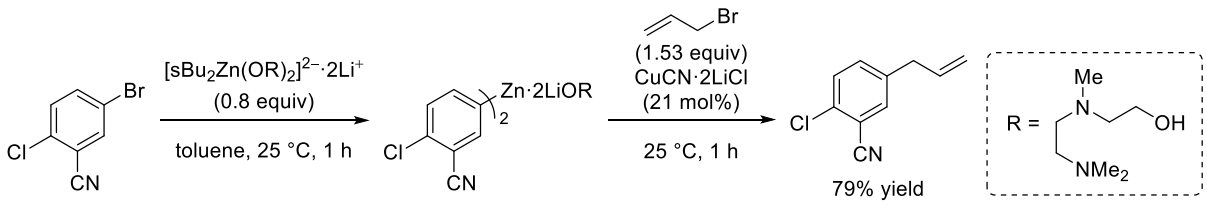
[24] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed* **2004**, *43*, 1017–1021.

or a lithium alcoholate[25]. Thus, the treatment of 4-formyl-2-iodo-6-methoxyphenyl acetate with *i*Pr$_2$Zn in NMP, accelerated by the addition of Li(acac) (10 mol%), led to the corresponding diarylzinc species. After acylation in the presence of tfp[26] (5 mol%) and Pd(dba)$_2$ (2.5 mol%), 2-(cyclohexanecarbonyl)-4-formyl-6-methoxyphenyl acetate is obtained in 75% yield (Scheme 8B).[24]



Scheme 8. A. General equation for the halogen-metal exchange; **B.** Li(acac)-catalyzed I/Zn-exchange for the preparation of polyfunctional diarylzinc species.[24]

The use of stronger electron donors, such as an alcoholate, allows for the performance of a Br/Zn exchange under mild conditions. Thus, treatment of 2-((2-(dimethylamino)ethyl)(methyl)amino)ethan-1-ol with Et$_2$Zn and *s*BuLi produces the dialkylzinc lithium alkoxide complex [*s*Bu$_2$Zn(OR)$_2$]$^{2-}$·2Li$^+$ in toluene.[25] Subsequent treatment of 5-bromo-2-chlorobenzonitrile with this diorganozinc complex (0.8 equiv) in toluene at 25 °C produces the corresponding diaryl zinc species within 1 h, which after allylation yields the desired product in 79% yield (Scheme 9).[25]

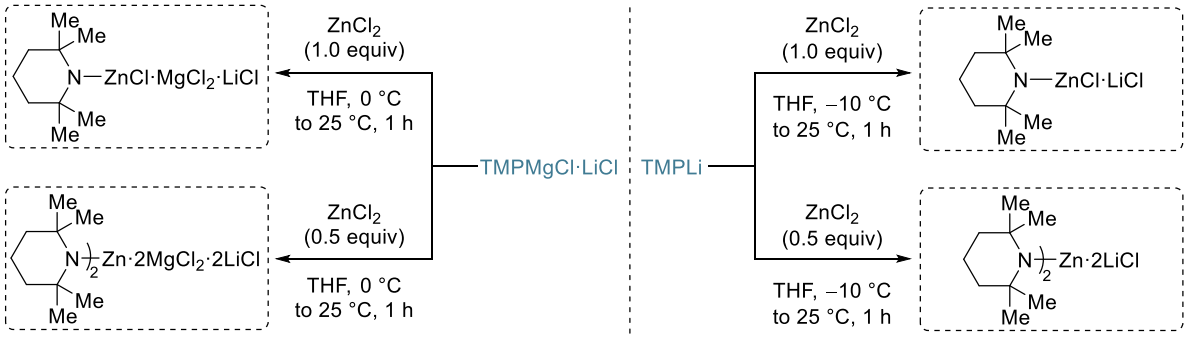


Scheme 9. Br/Zn exchange using the highly reactive alkoxide exchange reagent [*s*Bu$_2$Zn(OR)$_2$]2Li, leading to the corresponding diorganozinc species.[25]

[25] M. Balkenhohl, D. S. Ziegler, A. Desaintjean, L. J. Bole, A. R. Kennedy, E. Hevia, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 12898–12902.
[26] V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.

2.2.3 Directed Metalation

Another approach to access functionalized organometallics is the directed metalation with metal bases. Therein, thermodynamic and kinetic parameters have a strong influence on the speed of metalation as well as on the regioselectivity. The base selected for directional metalation (R^2–Met or $R^2{}_2N$–Met) must be stronger than the produced metalated species R^1–Met.[10] Traditionally, strong bases such as alkyllithium reagents and lithium amides (R^2NLi; e.g. LDA) are widely used for this purpose. However, due to their high reactivity and low tolerance to functional groups, organolithium reagents often suffer from undesired side reactions. Another serious disadvantage is their low stability in THF at ambient temperature, requiring often low temperatures of −78 to −100 °C.[27] A significant improvement, in this respect, was the development of the highly active mixed Mg/Li bases of the type $R^2{}_2NMgCl{\cdot}LiCl$, reported by Knochel and co-workers.[28] TMP based magnesium bases, such as TMPMgCl·LiCl, have been extensively used for the metalation of various substrates.[29] To elaborate TMP bases, that exhibit a higher tolerance towards functional groups, Knochel and co-workers developed the highly chemoselective TMP-derived bases $TMPZnCl{\cdot}MgCl_2{\cdot}LiCl$[30] $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[31], $TMPZnCl{\cdot}LiCl$[32] and $TMP_2Zn{\cdot}2LiCl$[30] for the metalation of sensitive aromatics and heterocycles under mild conditions (Scheme 10).



Scheme 10. Preparation of different TMP-zinc bases, starting from TMPMgCl·LiCl or TMPLi.[30,31,32]

[27] a) J. Skotnitzki, A. Kremsmair, P. Knochel, *Synthesis* **2020**, *52*, 189–196; b) G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596–2616; c) R. G. Jones, H. Gilman, *Organic Reactions* **2004**, *6*, 339–366.

[28] a) T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 1958–1961; b) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958–2961.

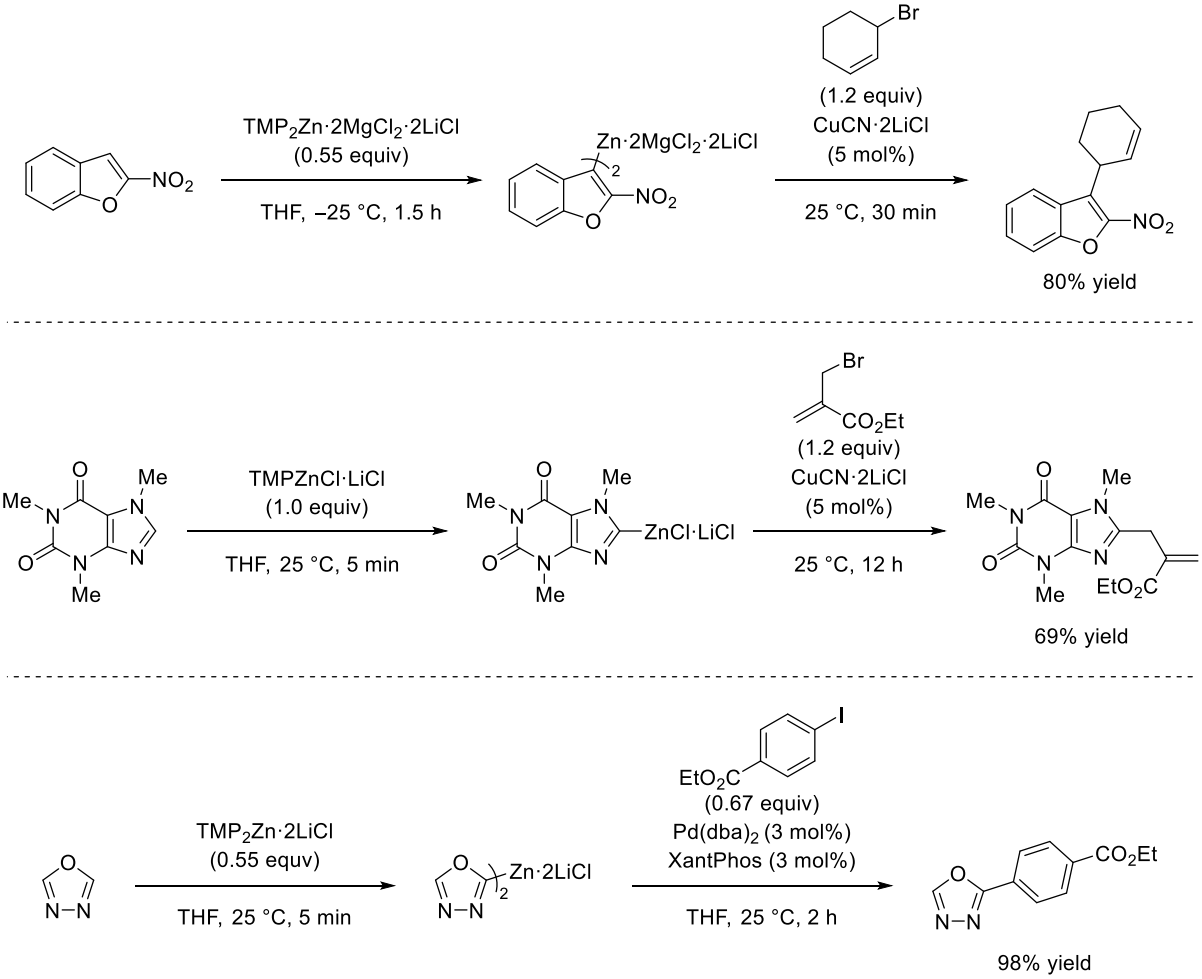
[29] a) T. Klatt, J. T. Markiewicz, C. Sämann, P. Knochel, *J. Org. Chem.* **2014**, *79*, 4253–4269; b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794–9824.

[30] K. Schwärzer, C. P. Tüllmann, S. Graßl, B. Górski, C. E. Brocklehurst, P. Knochel, *Org. Lett.* **2020**, DOI: 10.1021/acs.orglett.0c00238.

[31] M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837–1840.

[32] S. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685–7688.

Thus, 2-nitrobenzofuran is readily metalated using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$, providing after copper-catalyzed allylation the functionalized heteroarene in 80% yield (Scheme 11).[32] Also, caffeine and 1,3,4-oxadiazole are smoothly functionalized using TMPZnCl·LiCl and $TMP_2Zn{\cdot}2LiCl$, respectively, to afford after allylation or palladium-catalyzed cross-coupling the corresponding heteroarenes in 69–98% yield.[30,31]

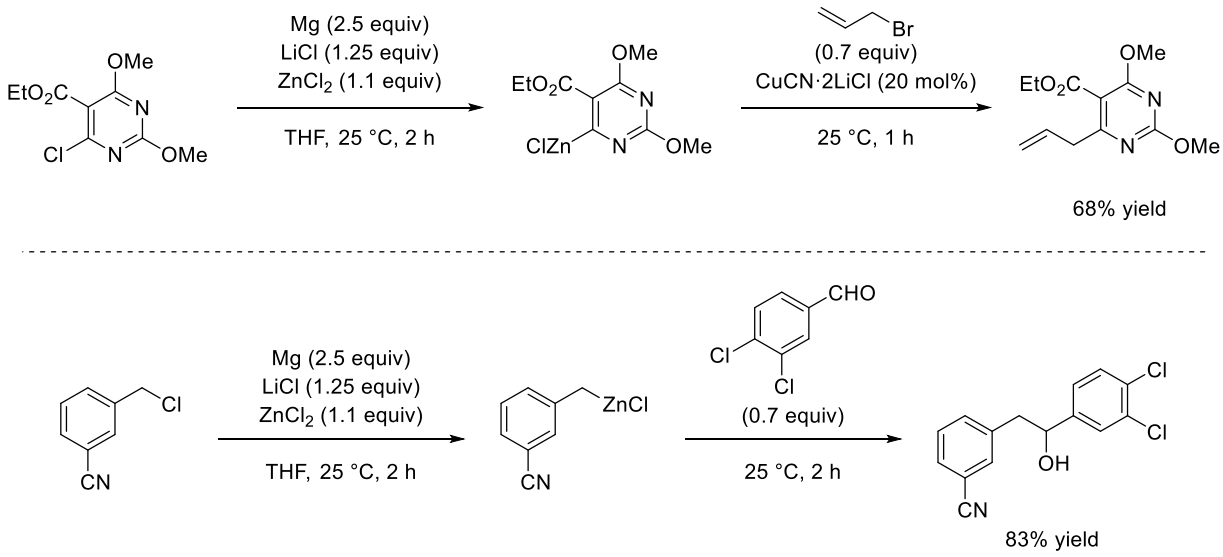


Scheme 11. Metalation of various heteroarenes using TMP-zinc bases.[30,31,32]

2.2.4 Transmetalation

Transmetalation reactions are key transformations in synthetic organic chemistry, as they allow the reactivity of organometallic reagents to be adjusted to the electrophile and avoid side reactions. The most common method of transmetalation is the treatment of an organometallic R^1–Met^1 with a metal salt Met^2–X_n, providing a new organometallic species R^1–Met^2. As mentioned for the directed metalation and the halogen/metal exchange, the driving force is the formation of the stronger carbon-metal bond, possessing the more covalent character.

Therefore, it is crucial for the process of transmetalation, that the C–Met^2 bond is energetically more favourable than the C–Met^1 bond. Since organozinc reagents are very stable, possesing a highly covalent C–Met bond, the transformation starting from various reactive organometallics, such as organolithium or organomagnesium reagents, is possible.[10] Therefore, most organomagnesium species can be transmetalated to the corresponding organozinc reagent by treatment with a suitable zinc-salt. To maintain the key advantage of organozincs, namely its functional group tolerance, Knochel and co-workers developed an oxidative magnesium insertion into aryl-halide bonds in the presence of $ZnCl_2$.[33] Using this method, various functional groups like esters or nitriles can be tolerated in this magnesium insertion, since the transmetalation proceeds faster than a possible attack of the formed organomagnesium reagent. The oxidative insertion of magnesium proceeds faster than the insertion of zinc. This allows to use rather unreactive halides with would not undergo a zinc insertion and thus drastically enlargens the scope of organozinc reagents. Thus, ethyl 4-chloro-2,6-dimethoxypyrimidine-5-carboxylate and 3-(chloromethyl)benzonitrile are smoothly converted to their organozinc species, allowing further functionalizations to give the corresponding functionalized compounds (Scheme 12).[33]



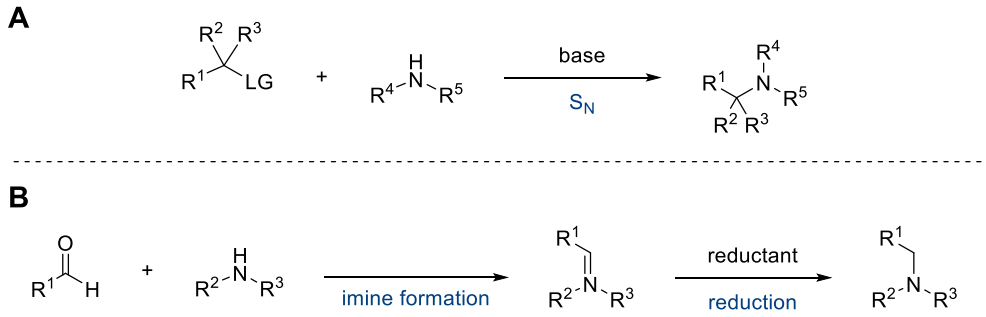
Scheme. 12. Preparation and subsequent trapping of organozinc reagents via oxidative magnesium insertion in the presence of $ZnCl_2$.[33]

[33] F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192–7202.

3. C-N Bond Forming reactions using Organometallic Reagents

3.1 Overview

The elaboration of carbon-heteroatom bonds is of one of the most important challenges in synthetic organic chemistry. Therein, the formation of carbon-nitrogen bonds is especially worth mentioning, since over 80% among the FDA approved pharmaceuticals contain at least one nitrogen atom.[34] Typically, such C-N bonds are formed by a nucleophilic attack (S_N-attack) of a nitrogen[35] on an electrophilic carbon (Scheme 13A) or via reductive amination[36] (Scheme 13B). These methods have found broad application in various organic synthetic processes, however, entail undesireable limitations, such as restricted tolerance towards functional groups or unselectivtity (*e.g.* overalkylation). Thus, over the last decades, various new methods to furnish carbon-nitrogen bonds have been developed. A few selected examples will be discussed in the following.

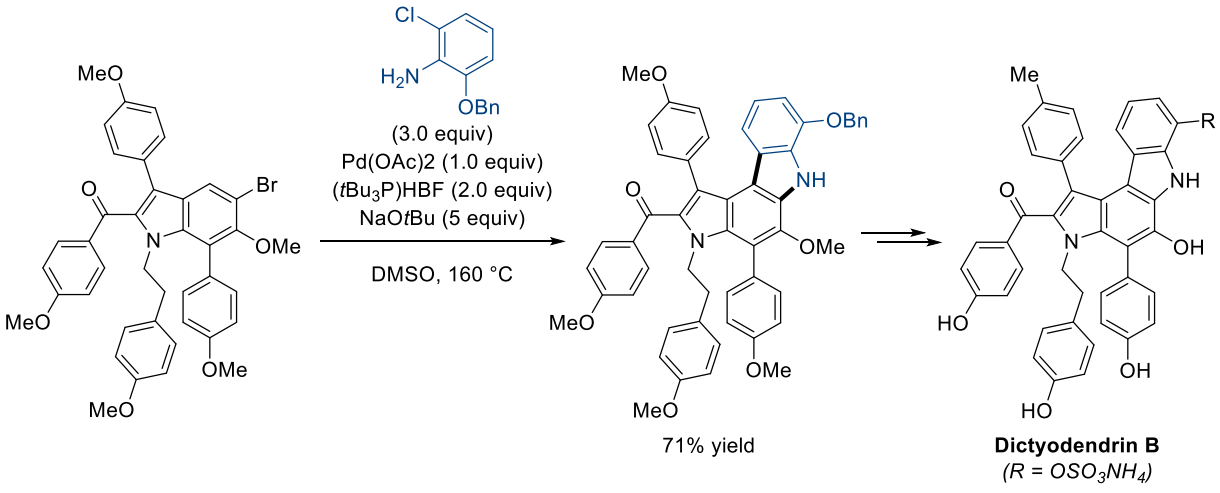


Scheme 13. A. General amination through a S_N-attack of an amine; **B.** General reductive amination procedure, using an aldehyde and a reducing agent, such as $NaBH_4$.[35,36]

[34] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.
[35] J. March "Advanced organic chemistry: reactions, mechanisms, and structure" John Wiley & Sons, Weinheim, **1992**.
[36] E. W. Baxter, A. B. Reitz, "Reductive aminations of carbonyl compounds with borohydride and borane reducing agents" *Organic reactions* **2004**, *59*, 1–714.

3.2 Nucleophilic Aminations Using Transition Metal Catalyst

After the discovery of palladium-catalyzed carbon-carbon cross-coupling reactions in the 1960s, the potential of these transformations for bond forming reactions in general has been revealed. Nowadays, one of the most common methods for the construction of carbon-nitrogen bonds is the transition metal catalyzed nucleophilic amination.[37] Most frequently palladium complexes are used for these transformation, as developed by Buchwald and Hartwig in 1994.[38] Although these haven't been the first examples of palladium-catalyzed C-N bond forming reactions,[39] the tremendous scope and utility of the Buchwald-Hartwig amination protocol led to the development of various optimized procedures and it has become one of the most powerful tools to construct carbon-nitrogen bonds. It combines the usage of easily available starting materials (amines and halides or pseudohalides) with an excellent orthogonality towards functional groups. This enabled applications in numerous syntheses of biologically active molecules.[37] One examples is the synthesis of the carbazole alkaloide dictyodendrine B, reported by Jia and co-workers.[40] Therein, the key-step to furnish the carbazole scaffold is achieved using a Buchwald-Hartwig type cross-coupling. Thus, the 5-bromoindole is aminated using a 2-chloro aniline derivative in the presence of a palladium-catalyst, providing after a subsequent oxidative ring closure the desired carbazole derivative in 71% yield (Scheme 14).



Scheme 14. Application of nucleophilic palladium-catalyzed amination in the synthesis of dictyodendrine B.[40]

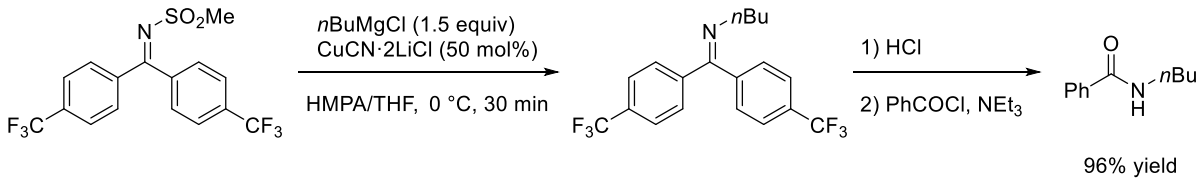
[37] P. Ruiz-Castillio, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649.
[38] a) F. Paul, J. Patt; J. F. Hartwig, *J. Am. Chem. Soc.* **1994**, *116*, 5969–5970; b) A. S. Guram, S. L. Buchwald *J. Am. Chem. Soc.* **1994**, *116*, 7901–7902.
[39] a) J. P. Genêt, M. Balabane, J. Bäckvall, J. E. Nyström, *Tetrahedron Lett.* **1983**, *24*, 2745–2748; b) J.-E. Báckvall, R. E. Nordberg, J.-E. Nyström, *J. Org. Chem.* **1981**, *46*, 3479–3483.
[40] J. Liang, W. Hu, P. Tao, Y. Jia, *J. Org. Chem.* **2013**, *78*, 5810–8515.

3.3 Electrophilic Aminations

These methods proved to be succesful in most cases, therefore representing an extremely valuable tool for synthetic chemistry. Nevertheless, all procedures mentioned so far, are based on a nucleophilic nitrogen source. Given the high electronegativity of nitrogen such a behaviour appears to be obvious, though limits the scope of all these reactions, since many amines have only limited nucleophilic character. This could either originate from aromatic residues, which delocalize the electron density of the nitrogen into the ring-system, or simply from sterical hinderance. These difficulties may be overcome with the aid of an "umpolung strategy", utilizing an electrophilic nitrogen source of type $[NR_2]^+$. There are different approaches to change the electronic character of a nitrogen atom, of which the usage of nitrenoid intermediates for C-N bond forming reactions is rather less explored.[41] The following chapter will focus on various examples of transition-metal catalyzed reactions using an electrophilic nitrogen source containing a weak N-X bond (X is an equally or more electronegative atom than nitrogen) and an organometallic species.

3.3.1 Early Examples

The first example of a transition metal catalyzed electrophilic amination of an organometallic species was reported by Narasaka in 1997.[42] *O*-Methylsulfonyloximes were utilized as electrophilic nitrogen source, which after treatment with an alkyl Grignard reagent in the presence of a copper-catalyst reacted to the corresponding substituted imine. After hydrolysis and benzoylation the desired amide was obtained in 96% yield (Scheme 15). This method was succesful for primary as well as for secondary and tertiary magnesium reagents. The presence of the copper catalyst proved to be essential for this transformation, as without this transition metal, no product formation was observed.



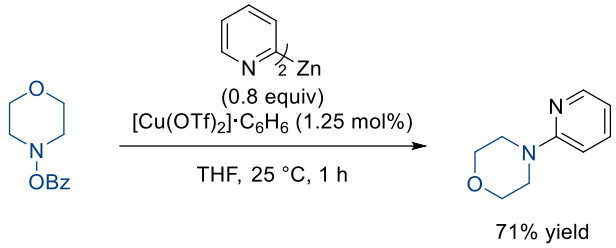
Scheme 15. Electrophilic amination of alkyl Grignard reagents in the presence of a copper-catalyst, using *O*-methylsulfonyloximes.[42]

[41] a) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417–424; b) P. Mueller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905–2920; c) I. D. G. Watson, A. K. Yudin, *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 906–917.

[42] T. Hironori, Y. Hayashi, K. Narasaka, *Chem. Lett.* **1997**, *26*, 317–318.

3.3.2 Electrophilic Aminations Using *N*-Hydroxylamine Benzoates

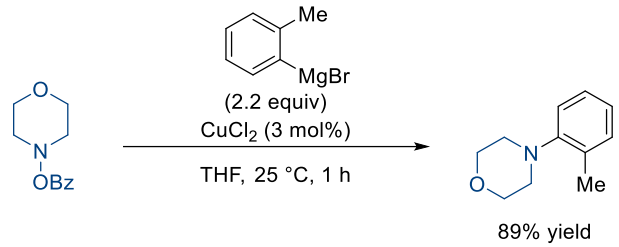
A frequently used electrophilic nitrogen source are *N*-hydroxylamine benzoates, which have been introduced by Johnson and co-workers.[43] Similar to the oximes mentioned above, the electronegativity difference between nitrogen and oxygen leads to a positively polarized nitrogen atom. In addition to this electronic umpolung on the nitrogen atom, the N-O bond is rather weak and OCOPh an excellent leaving group. This combination enabled a smooth transformation with various diorganozinc reagents in the presence of a copper-catalyst. Thus, dipyridylzinc (0.6 equiv) is readily aminated using morpholino benzoate and $[Cu(OTf)]_2 \cdot C_6H_6$ (1.25 mol%) under mild conditions (25 °C, 1 h), providing the 4-(pyridin-2-yl)morpholine in 71% yield (Scheme 16).[43]



Scheme 16. Copper-catalyzed electrophilic amination of diarylzincs using *N*-hydroxylamine benzoates.[43]

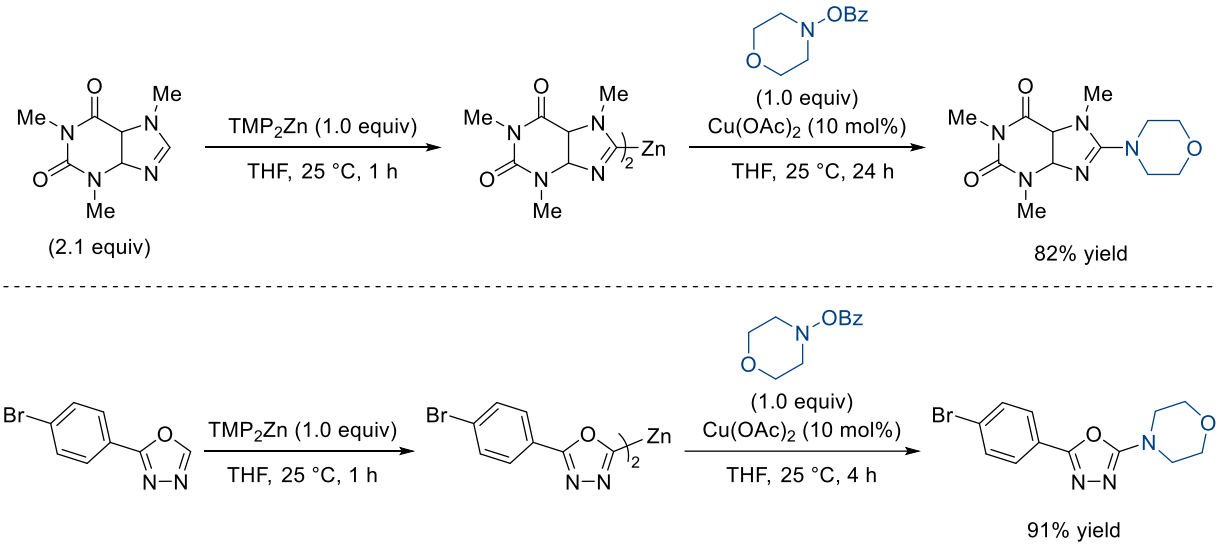
The scope and the mechanism of this transformation was further investiagted in the following years.[44] Due to the usage of a mild organozinc species, various functional groups, such as esters were tolerated. However, the limited scope of diorganozinc reagents as well as of polyfunctionalized hydroxylamine benzoates still represented major drawbacks. Later, this method was extended to secondary hydroxylamine benzoates and Grignard reagents (Scheme 17).[44,45] Interstingly, the attack of the Grignard reagent at the carbonyl position of the benzoate was easily suppressed by employing a slow addition of the metallic species.

[43] a) A. M. Berman, J. S. Johnson, *J. Org. Chem.* **2005**, *70*, 364–366; b) A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 5680–5681.
[44] M. Campbell, J. S. Johnson, *Org. Lett.* **2007**, *9*, 1521–1524.
[45] A. M. Berman, J. S. Johnson, *J. Org. Chem.* **2006**, *71*, 219–224.



Scheme 17. Electrophilic amination of Grignard reagents in the presence of a copper-catalyst.[44]

To enhance the scope of suitable nucleophiles, Wang and co workers showed that using a slightly alterated procedure, highly functionalized aryl and heteroaryl diorganozinc reagents obtained from directed metalation with TMP_2Zn can engage in electrophilic amination.[46] Therefore, various heterocyclic scaffolds, such as caffeine or 1,3,4-oxadiazole have been metalated using the bis-base TMP_2Zn (0.6 equiv, 25 °C) and subsequently aminated using morpholino benzoate in the presence of $Cu(OAc)_2$ (10 mol%) affording the corresponding aminated products in 82–91% yield (Scheme 18).[46]

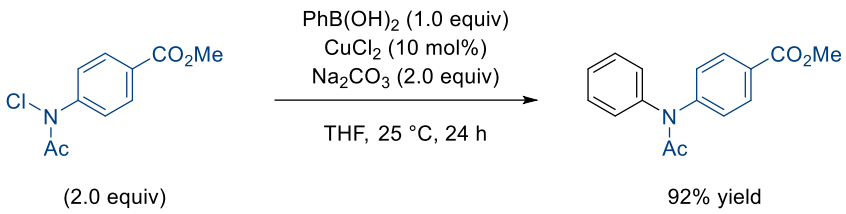


Scheme 18. Metalation of caffeine and substituted 1,3,4-oxadiazole using TMP_2Zn and subsequent electrophilic amination using morpholino benzoate.[46]

[46] S. L. McDonald, C. E. Hendrick, Q. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 4667–4670.

3.3.3 Electrophilic Aminations Using *N*-Chloroamines

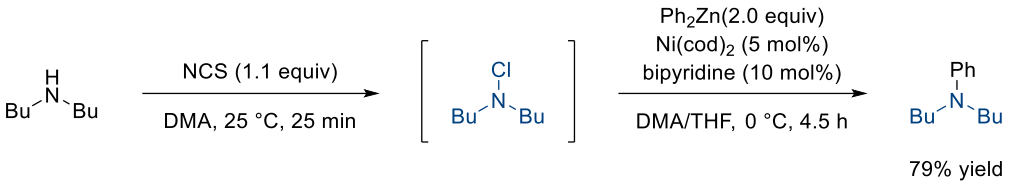
Another widely used source of electrophilic nitrogen are *N*-chloroamines. In the past, these rather labile substrates have been used to generate aminyl radicals, which then undergo for example cyclization reactions.[47] These radical based reactions, however, lack of selectivity due to the high reactivity of the aminyl radicals. Nevertheless, the basic prerequisite for a transition metal-catalyzed electrophilic amination with an organometallic reagent is given. Although the electronegativity of chlorine and nitrogen is almost identical, the slight polarization engaged with the weak N-Cl bond and chloride as a good leaving group, provides a highly suitable precursor. Lei and co-workers showed the utility of *N*-chloroamines in the copper-catalyzed coupling with boronic acids.[48] A wide range of arylboronic acids was successfully amidated with acetylated aniline derivatives, providing the corresponding teriary amides in high yields (Scheme 19). Suprisingly, a radical mechanism was ruled out by experimental studies. The proposed mechanism is based on an oxidative insertion into the N-Cl bond followed by transmetalation with the boronic acid.



Scheme 19. Amidation of boronic acids using *N*-chloroamines in the presence of a copper-catalyst.[48]

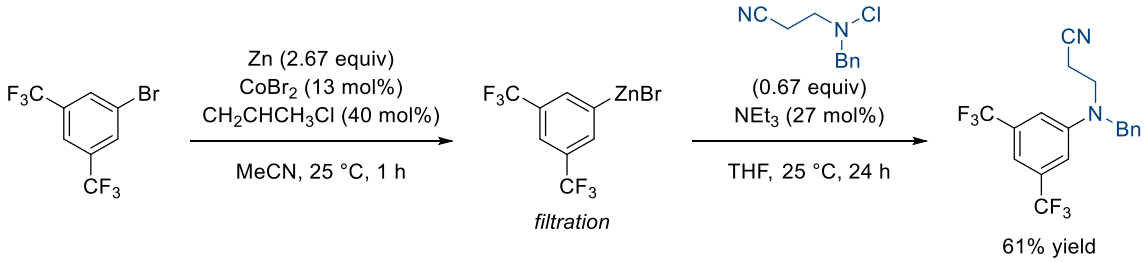
This method, however, was limited to acetylated substrates, therefore leading to amides only. Later, Jarvo and co-workers extended this method and developed a nickel-catalyzed cross-coupling between *N*-chloroamines and diphenylzinc.[49] Thus, the diarylzinc species (2.0 equiv) was readily aminated in the presence of $Ni(cod)_2$ (5.0 mol%) and bipyridine (10 mol%) using *N*-chloro dibutylamine, leading to the corresponding tertiary amine in 60% yield (Scheme 20). Remarkably, electron-donating as well as electron-withdrawing substituents were tolerated. This method was further extended to a one-pot procedure, generating the *N*-chloroamine in-situ using NCS (1.1 equiv).

[47] a) R. Göttlich, M. Noack, *Tetrahedron Lett.* **2001**, *42*, 7771–7774; b) L. Stella, *Angew. Chem. Int. Ed.* **1983**, *22*, 337–350.
[48] C. He, C. Chen, J. Cheng, C. Liu, W. Liu, Q. Li, A. Lei, *Angew. Chem. Int. Ed.* **2008** , *47* , 6414–6417.
[49] T. J. Barker, E. R. Jarvo, *J. Am. Chem. Soc.* **2009**, *131*, 15598–15599.



Scheme 20. In-situ generation of *N*-chloroamines and subsequent electrophilic amination of diorganozinc reagents in the presence of a nickel-catalyst.[49]

Another development of this protocol was reported by Gosmini and co-workers.[50] They showed, that this transformation is also efficiently achieved using a cobalt-catalyst. Interstingly, the cobalt-catalyst was used prior to generate the organozinc species by a radical cobalt-catalyzed insertion,[51] and then reused for the electrophilic amination reaction. Thus, 1-bromo-3,5-bis(trifluoromethyl)benzene was smoothly converted into the corresponding organozinc reagent using this $CoBr_2$-catalyzed insertion, and subsequently aminated with 3-(benzylchloroamino)propanenitrile, leading to the desired tertiary amine in 61% yield (Scheme 21).

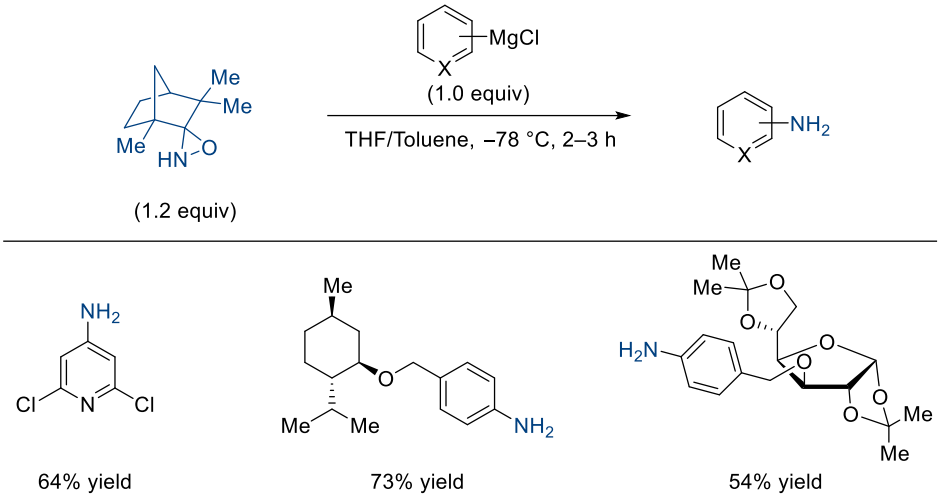


Scheme 21. Cobalt-catalyzed zinc insertion into a carbon-bromine bond and subsequent amination with a *N*-chloramine, reusing the cobalt-catalyst.[50]

[50] X. Qian, Z. Yu, A. Auffrant, C. Gosmini, *Chem. Eur. J.* **2013**, *19*, 6225–6229.
[51] a) H. Fillon, C. Gosmini, J. Perichon, *J. Am. Chem. Soc.* **2003**, *125*, 3867–3870; b) I. Kazmierski, C. Gosmini, J.-M. Paris, J. Perichon, *Tetrahedron Lett.* **2003**, *44*, 6417–6420.

3.3.4 Electrophilic Aminations Using other Nitrogen Sources

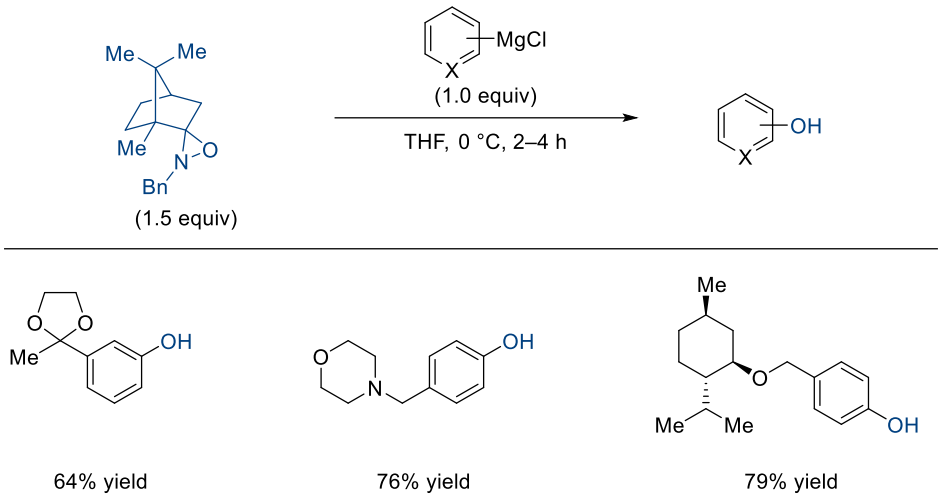
The basic idea of utilizing a polarized, weak nitrogen-heteroatom bond for electrophilic aminations has been further developed by Kürti and co-workers. So far, no direct synthesis of primary amines using an electrophilic amination has been developed. The difficulty presented by this task, is to find a suitable aminating agent, which can transfer the electrophilic nitrogen, yet will not undergo deprotonation by the basic organometallic species. The approach to overcome this undesired sidereaction, was to utilize a sterically hindered nitrogen source.[52] Thus, bulky NH-oxaziridines represent excellent electrophilic nitrogen transfer reagents, which after ring-opening provide the desired primary amines in excellent yields (Scheme 22).[53]



Scheme 22. Electrophilic amination of aryl and heteroaryl Grignard reagents using NH-oxaziridine, leading to primary aniline derivatives.[53]

This reaction utilizes aryl and heteroaryl Grignard reagents and proceeds smoothly without the presence of a transition metal. Remarkably, strained oxaziridines could also be used to prepare phenoles derivatives under similar conditions. For unprotected NH-oxaziridines, exclusively the attack on the nitrogen atom was observed. However, when attaching a sterically hindered group, such as a benzyl moiety, the attack on the nitrogen is blocked and a selective oxygenation of the magnesium reagent was observed (Scheme 23).[53]

[52] E. J. Corey, A. W. Gross, *J. Org. Chem.* **1985**, *50*, 5391–5393.
[53] a) H. Gao, Z. Zhou, D.-H. Kwon, J. Coombs, S. Jones, N. E. Behnke, D. H. Ess, L. Kürti, *Nat. Chem.* **2017**, *9*, 681–688; b) Z. Zhou, Z. Ma, N. E. Behnke, H. Gao, L. Kürti, *J. Am. Chem. Soc.* **2017**, *139*, 115–118.

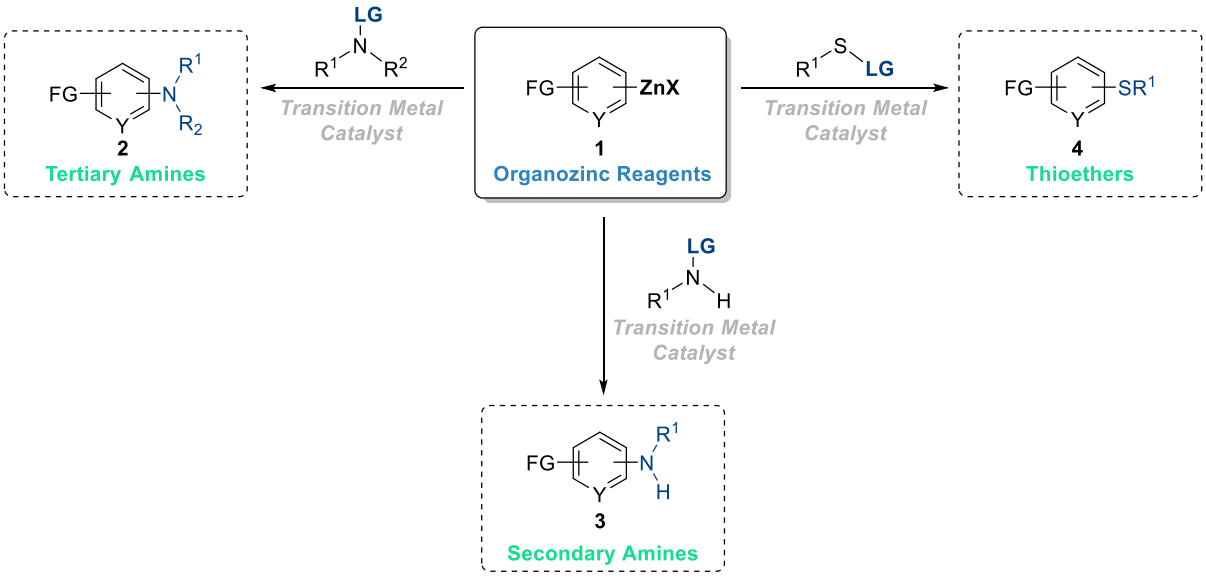


Scheme 23. Electrophilic oxygenation of arylmagnesium halides with *N*–benzyl oxaziridine.[53]

4. Objectives

The importance of carbon-heteratom bond forming reactions has been displayed above. However, most literature known procedures utilize nucleophilic sources of e.g. nitrogen or sulphur. As shown in previous procedures, the usage of a N/S–X bond, where X equals an even more electrophilic atom, can lead to electrophilic sources of e.g. nitrogen or sulphur. These react with suitable nucleophile to the desired products. We envisioned, that organozinc halides of type **1** would be especially attractive nucleophiles, since these organometallics are compatible with the presence of various functional groups. This high tolerance towards functional groups correlates with a low reactivity of organozinc reagents. Therefore, we anticipated, that a transition metal catalyst will be required for achieving the desired transformations.

Thus, we planned to elaborate the preparation of suitable electrophilic sources of nitrogen and sulphur, using a more electronegative leaving group. These will be tasked for their activity in transition metal-catalyzed reactions with various alkyl-, benzyl-, aryl- and hetereoarylzinc reagents **1**, aiming for tertiary amines **2**, secondary amines **3** or thioethers **4** (Scheme 24).



Scheme 24. Envisioned new procedures to construct carbon-heteroatom bonds using organozinc reagents and electrophilic nitrogen and sulphur sources in the presence of a transition metal catalyst.

B. Results and Discussion

1. Cobalt-Catalyzed Electrophilic Amination of Aryl- and Heteroaryl-Zinc Pivalates with *N*-Hydroxylamine Benzoates

1.1 Introduction

Functionalized aromatic amines are widely found in pharmaceuticals, natural products, and agricultural chemicals.[34,54] Thus, general aromatic C-N bond forming reactions are required. Over the past two decades, the development of palladium catalyzed Buchwald-Hartwig nucleophilic aminations[38,55] allowed a facile synthesis of aryl amines. However, these reactions usually require expensive catalysts and ligands. Moreover, elevated temperatures and stoichiometric amounts of base are often necessary. In 2004, Johnson reported an alternative electrophilic amination using diarylzinc reagents and *O*-benzoylhydroxylamine derivatives **5** to afford tertiary amines under mild conditions.[43,44,45] This amination[56] has been extended to organometallics derived from Mg,[45] Zn,[57] Al,[58] B,[59] Si[60] and Cu[61] using Cu or Ni as catalysts. Despite the impressive progress made, the use of air sensitive reagents, ligands or toxic Ni-catalysts still represent drawbacks. Recently, we reported a new class of highly functionalized organozinc reagents with enhanced air- and moisture-stability.[62] These reagents were used to

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55 a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50; b) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361.

56 a) C. E. Hendrick, Q. Wang, *J. Org. Chem.* **2017**, *82*, 839–847; b) J. J. Farndon, X. Ma, J. F. Bower, *J. Am. Chem. Soc.* **2017**, *139*, 14005–14008; c) M. Corpet, C. Gosmini, *Synthesis*, **2014**, *46*, 2258–2271; d) I. P. Beletskaya, A. V. Cheprakov, *Organometallics* **2012**, *31*, 7753–7808.

57 a) C. E. Hendrick, K. J. Bitting, S. Cho, Q. Wang, *J. Am. Chem. Soc.* **2017**, *139*, 11622–11628; b) S. L. McDonald, Q. Wang, *Chem. Commun.* **2014**, *50*, 2535–2538.

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59 a) R. P. Rucker, A. M. Whittaker, H. Dang, G. Lalic, *Angew. Chem. Int. Ed.* **2012**, *51*, 3953–3956; b) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2012**, *51*, 3642–3645; c) Q. Xiao, L. Tian, R. Tan, Y. Xia, D. Qiu, Y. Zhang, J. Wang, *Org. Lett.* **2012**, *14*, 4230–4233; d) C. He, C. Chen, J. Cheng, C. Liu, W. Liu, Q. Li, A. Lei, *Angew. Chem. Int. Ed.* **2008**, *47*, 6414–6417; e) Z. Zhang, Y. Yu, L. S. Liebeskind, *Org. Lett.* **2008**, *10*, 3005–3008.

60 a) Y. Miki, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2013**, *15*, 172–175; b) M. H. Nguyen, A. B. Smith, III *Org. Lett.* **2013**, *15*, 4872–4875.

61 a) N. Tezuka, K. Shimojo, K. Hirano, S. Komagawa, K. Yoshida, C. Wang, K. Miyamoto, T. Saito, R. Takita, M. Uchiyama, *J. Am. Chem. Soc.* **2016**, *138*, 9166–9171; b) M. T. Pirnot, Y.-M. Wang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 48–57.

62 a) M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10662–10665; b) S. M. Manolikakes, M. Ellwart, C. I. Stathakis, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 12289–12297; c) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald, P. Knochel, *Org. Lett.* **2013**, *15*, 5754–5757; d) C. I. Stathakis, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2013**, *15*, 1302–1305; e) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9428–9432; f) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205–9209.

improve the efficiency of cobalt-catalyzed Negishi cross-coupling[63] and were useful for biological active molecule syntheses[64] and high-throughput screenings[65]. Thus, we deveoped a cobalt-catalyzed electrophilic amination of organozinc pivalates with *O*-benzoylhydroxylamines. The reaction scope is especially broad, allowing the preparation of tertiary diarylalkylamines not available by copper- or nickel-catalyzed aminations. Also, the utility of this amination method was demonstrated by the synthesis of a potent clinical candidate for the treatment of tuberculosis.[66]

1.2 Reaction Optimization

Preliminary studies showed that phenylzinc pivalate (**1a**) is aminated with benzoylhydroxylmorpholine (**5a**) in the presence of various catalysts at room temperature (Table 1). ArZnCl·Mg(OPiv)$_2$·LiCl is abbreviated as ArZnOPiv for the sake of clarity.[67] When using iron(II) or copper(I) catalysts, the main product is the corresponding homodimer (e.g. biphenyl, Table 1, entries 1–3). Better results are obtained with Ni(II)-catalysts (entries 4–5). Interestingly, THF soluble $CoCl_2$·2LiCl proved to be the most effective catalyst and afforded *N*-phenylmorpholine (**2a**) in 93% isolated yield (entry 7). In this study, we also found that considerably more homodimer was generated using phenylzinc chloride compared to phenylzinc pivalate.[68] Further optimizations showed that 2.5% $CoCl_2$·2LiCl as well as 1.1 equiv of PhZnOPiv were sufficient to achieve a complete conversion.

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[64] a) Y.-H. Chen, M. Ellwart, G. Toupalas, Y. Ebe, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 4612–4616; b) Y.-H. Chen, C. P. Tüllmann, M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 9236–9239.

[65] T. J. Greshock, K. P. Moore, R. T. McClain, A. Bellomo, C. K. Chung, S. D. Dreher, P. S. Kutchukian, Z. Peng, I. W. Davies, P. Vachal, M. Ellwart, S. M. Manolikakes, P. Knochel, P. G. Nantermet, *Angew. Chem. Int. Ed.* **2016**, *55*, 13714–13718.

[66] K. Pethe, P. Bifani, J. Jang, S. Kang, S. Park, S. Ahn, J. Jiricek, J. Jung, H. K. Jeon, J. Cechetto, T. Christophe, H. Lee, M. Kempf, M. Jackson, A. J. Lenaerts, H. Pham, V. Jones, M. J. Seo, Y. M. Kim, M. Seo, J. J. Seo, D. Park, Y. Ko, I. Choi, R. Kim, S. Y. Kim, S. Lim, S.-A. Yim, J. Nam, H. Kang, H. Kwon, C.-T. Oh, Y. Cho, Y. Jang, J. Kim, A. Chua, B. H. Tan, M. B. Nanjundappa, S. P. S. Rao, W. S. Barnes, R. Wintjens, J. R. Walker, S. Alonso, S. Lee, J. Kim, S. Oh, T. Oh, U. Nehrbass, S.-J. Han, Z. No, J. Lee, P. Brodin, S.-N. Cho, K. Nam, J. Kim, *Nat. Med.* **2013**, *19*, 1157–1160.

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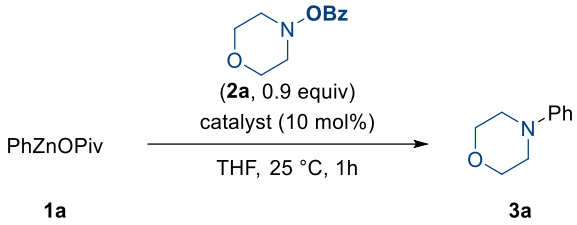
[68] For a detailed investigation, see experimental section.

Table 1: Catalyst screening for the electrophilic amination.



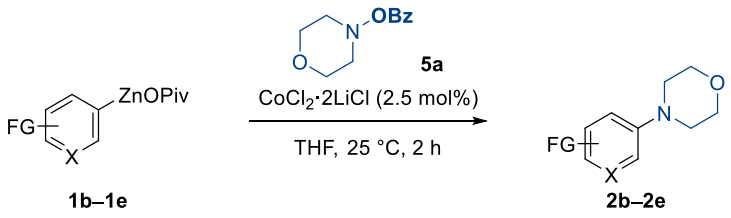
Entry	Catalyst	Yield (%)[a]
1	$Fe(acac)_2$	31
2	CuI	36
3	$Cu(OTf)_2$	40
4	$NiCl_2$	84
5	$NiCl_2(PPh_3)_2$	72
6	$Co(acac)_2$	61
7	$CoCl_2 \cdot 2LiCl$	98 (93)[b]

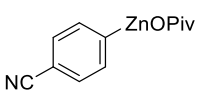
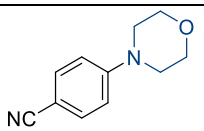
[a] GC yield using undecane as internal standard. [b] Isolated yield.

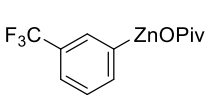
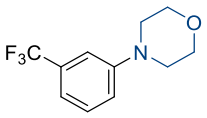
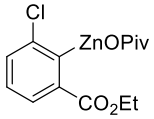
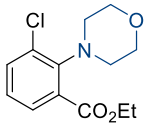
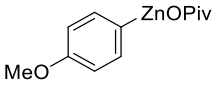
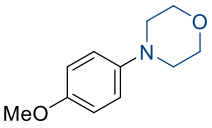
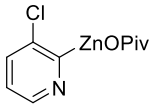
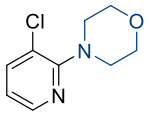
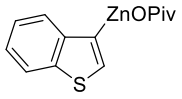
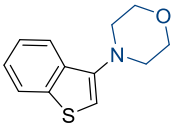
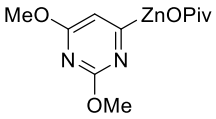
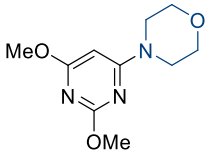
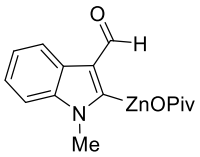
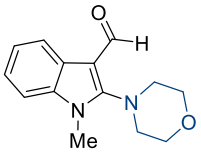
1.3 Scope and Limitations

Using *O*-benzoylhydroxylmorpholine (**5a**) as typical amination reagent, we have determinated the scope of the amination of organozinc pivalates (Table 2). We have noticed that both electron-rich, electron-poor or sterically hindered arylzinc pivalates **1b**–**1e** are aminated with benzoylhydroxylmorpholine (**5a**) smoothly to afford the desired products **2b**–**2e** in 81–97% yield (entries 1–4).

Table 2: The scope of organozinc pivalates for electrophilic amination.



Entry	(Hetero)arylzinc pivalate	Product[a]
1	 **1b**	 **2b**: 93%

2		**1c**		**2c**: 97%
3		**1d**		**2d**: 81%[b]
4		**1e**		**2e**: 96%
5		**1f**		**2f**: 95%[b]
6		**1g**		**2g**: 84%[c]
7		**1h**		**2h:** 91%[b]
8		**1i**		**2i**: 80%[b]

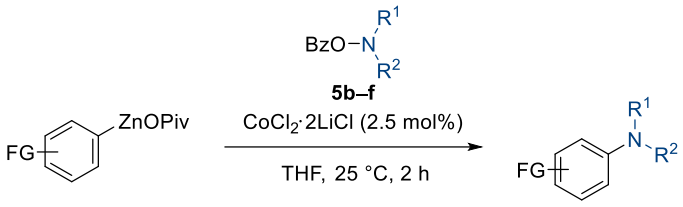
[a] Isolated yields of analytically pure products. [b] TMEDA (5 mol%) was added. [c] Reaction time = 12 h.

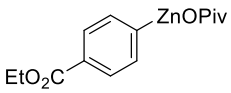
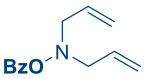
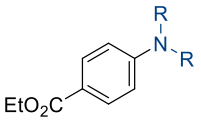
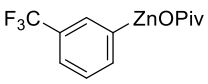
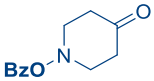
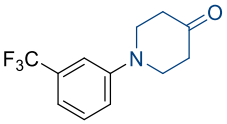
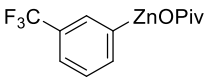
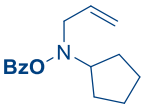
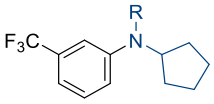
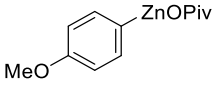
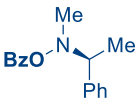
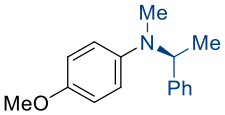
This electrophilic amination was extended to heteroarylzinc pivalates bearing a pyridine, benzylthiophene, pyrimidine and indole ring. Thus, heteroarylzinc pivalates **1f**–**1i** were aminated with **5a** in 80–95% yield (entries 5–8). Surprisingly, we observed that organozinc pivalates which were prepared via directed metallation using TMPMgCl·LiCl[28a] or TMPZnCl·LiCl[31], (TMP = 2,2,6,6-tetramethylpiperidyl) did not undergo the amination reaction. We assume that a strong coordination of TMP-base to the cobalt center deactivates

the catalyst.[69] Interestingly, the addition of 5% TMEDA (tetramethylethylenediamine) avoids this deactivation.

Encouraged by these results, we have extended the scope of this amination to various *O*-benzoylhydroxylamines **5b**–**5f** affording trisubstituted aniline derivatives **2j**–**2n** in 78–97% yield (Table 3, entries 1–5). Notably, the reaction is compatible with benzoylhydroxylpiperidone (**5c**) bearing a sensitive ketone function and acidic alpha-protons. The cleavage of the allyl group was realized under mild conditions, affording either the primary **6** or secondary aniline derivative **3a** in 91–93% yield (entries 1 and 3).[70]

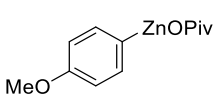
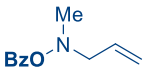
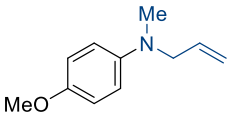
Table 3: Amination of arylzinc pivalates with various *O*-benzoylhydroxylamines of type **2**.



Entry	Organozinc pivalate 1	*N*-Hydroxylamine benzoate 5	Product 2[a]
1	 **1j**	 **5b**	 **2j**: R = allyl; 81% **6**: R = H; 91%
2	 **1c**	 **5c**	 **2k:** 81%
3	 **1c**	 **5d**	 **2l:** R = allyl; 78% **3a:** R = H; 93%
4	 **1e**	 **5e**	 **2m**: 97%

69 see experimental section.

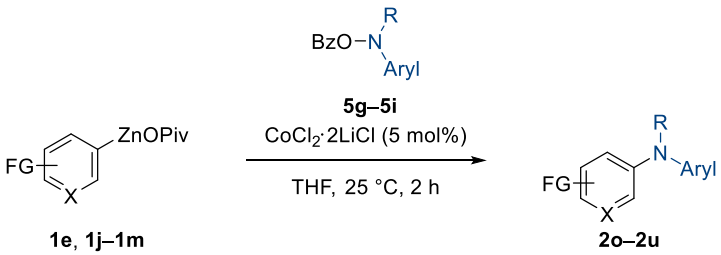
70 a) V. Cadierno, S. E. García-Garrido, J. Gimeno, N. Nebra, *Chem. Commun.* **2005**, 4086–4088; b) F. Garro-Helion, A. Merzouk, F. Guibé, *J. Org. Chem.* **1993**, *58*, 6109–6113.

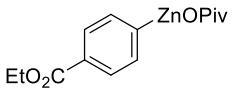
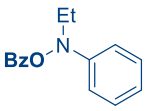
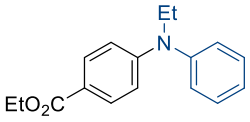
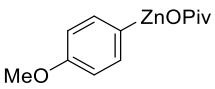
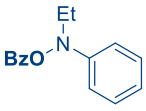
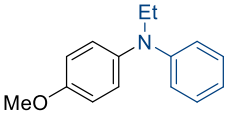
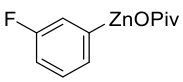
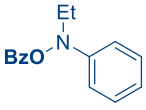
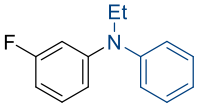
			
5	**1e**	**5f**	**2n**: 89%

[a] Isolated yields of analytically pure products.

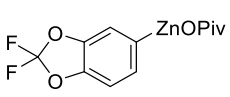
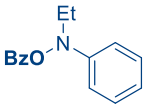
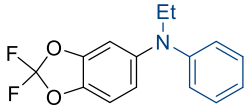
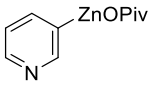
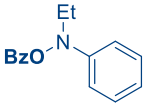
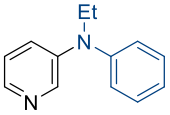
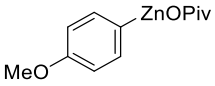
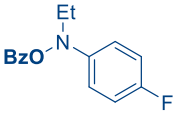
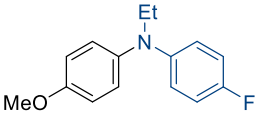
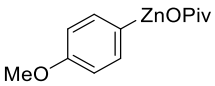
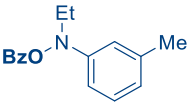
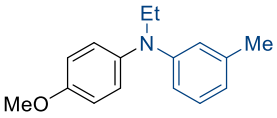
In contrast to previous electrophilic aminations, the reaction between arylzinc and benzoylhydroxylaniline derivatives proceeds also well. Thus, the amination of arylzinc pivalates **1e** and **1j**–**1m** with *O*-benzoylhydroxylaniline[71] **5g** led to the diarylamines **2o**–**2s** under standard conditions in 61–89% yield (Table 4, entries 1–5). Also anisylzinc pivalate (**1e**) underwent amination with the *O*-benzoyl hydroxylanilines **5h**–**5i** leading to diarylamines **2t**–**2u** in 68–78% yield (entries 6–7).

Table 4: Amination of arylzinc pivalates **1** with various *O*-benzoylhydroxylanilines **5**.



Entry	Organozinc pivalate of type 1	Electrophile 5	Product[a]
			
1	**1j**	**5g**	**2o**: 89%
			
2	**1e**	**5g**	**2p**: 79%
			
3	**1k**	**5g**	**2q**: 84%

[71] a) K. N. Hojczyk, P. Feng, C. Zhan, M. Y. Ngai, *Angew. Chem. Int. Ed.* **2014**, *53*, 14559–14563; b) D. A. Evans, H.-J. Song, K. R. Fandrick, *Org. Let.* **2006**, *8*, 3351–3354; c) S.-C. Hung, S. R. Thopate, F.-C. Chi, S.-W. Chang, J.-C. Lee, C.-C. Wang, Y.-S. Wen, *J. Am. Chem. Soc.* **2001**, *123*, 3153–3154; d) A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849–3862.

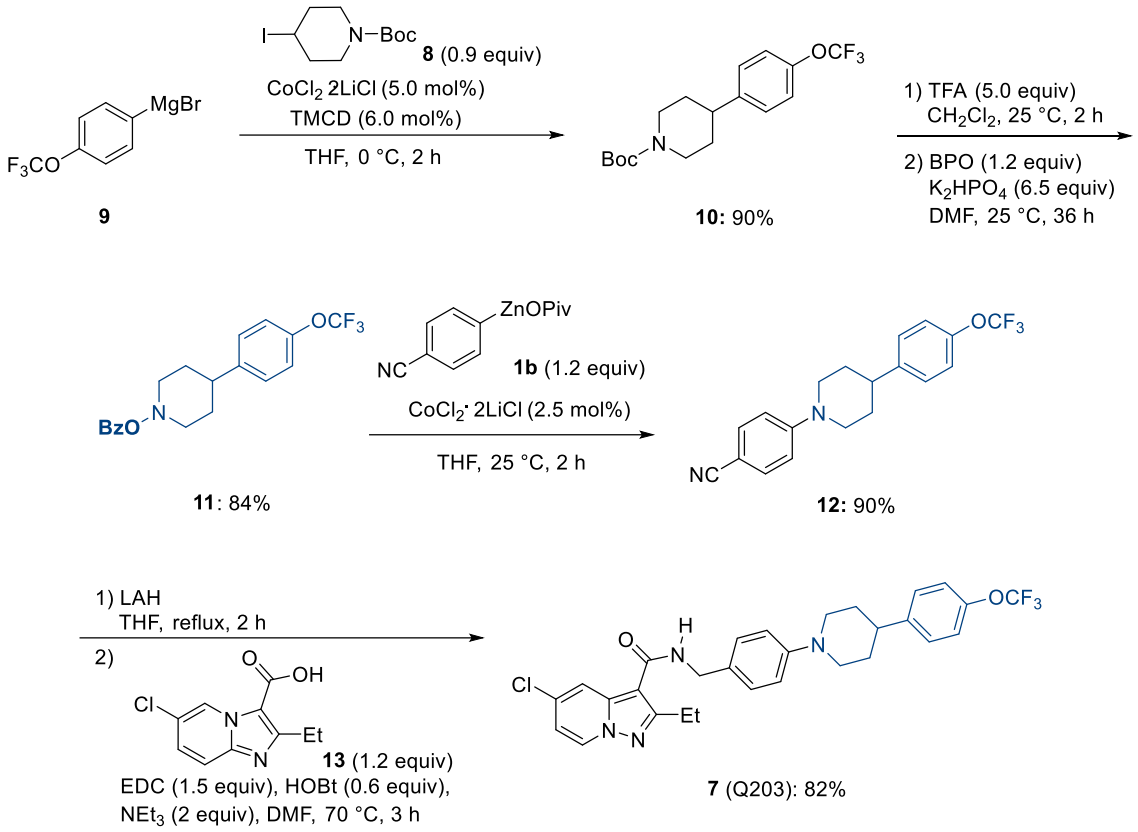
4		**1l**		**5g**		**2r**: 66%
5		**1m**		**5g**		**2s:** 61%[b]
6		**1e**		**5h**		**2t**: 78%
7		**1e**		**5i**		**2u:** 68%

[a] Isolated yields of analytically pure products. [b] **1m** (2.0 equiv); THF:NMP = 3:1; 12 h reaction time.

1.4 Synthesis of Q203

The synthetic utility of this electrophilic amination for the preparation of medicinally valuable molecules was demonstrated by a concise synthesis of the potential anti-tuberculosis drug candidate Q203 (**7**)[66] (Scheme 25). The synthesis began with a cobalt-catalyzed cross-coupling of commercial available 4-iodopiperidine (**8**) with Grignard reagent[72] **9** under conditions reported by Yorimitsu, Oshima[73] and Cossy[74] providing the piperidine **10** in 90% yield. The Boc-protecting group was removed using trifluoroacetic acid followed by oxidation with BPO to afford hydroxylamine **11** in 84% yield (2 steps). The key step in the construction of diarylpiperidine **7** was the electrophilic amination with 4-cyanophenylzinc pivalate (**1b**) in the presence of 2.5% $CoCl_2 \cdot 2LiCl$ generating piperidine **12** in 90% yield. With the core skeleton in hand, benzonitrile **12** was reduced with LAH (lithium aluminum hydride) and further coupled with acid **13** furnishing the amide Q203 (**7**) in 82% yield (6 steps, 56% overall yield).

[72] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802–6806.
[73] H. Ohmiya, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 1886–1889.
[74] L. Gonnard, A. Guérinot, J. Cossy, *Chem. Eur. J.* **2015**, *21*, 12797–12803.



Scheme 25. Synthesis of Q203 (**7**) with cobalt-catalyzed C-C and C-N bond forming reactions. TMCD= (*R*,*R*)-tetramethylcyclohexanediamine; BPO= benzoyl peroxide; EDC= 1-[3-(dimethylamino)propyl]-3-ethylcarbodimide hydrochloride; HOBt= 1-hydroxylbenzotriazole.

1.5 Summary

In summary, we have reported the first cobalt-catalyzed electrophilic amination with aryl- and heteroaryl-zinc pivalates and *O*-benzoylhydroxylamine derivatives under very mild conditions. The amination was further extended to *O*-benzoylhydroxylanilines which previously were not appropriate substrates using Cu-catalysis. Finally, the concise synthesis of Q203 (**7**) demonstrates the utility of our method.

2. Late Stage Functionalization of Secondary Amines via a Cobalt-Catalyzed Electrophilic Amination of Organozinc Reagents

2.1 Introduction

The formation of a carbon-nitrogen bond is one of the most important reactions for the elaboration of pharmaceuticals and agrochemicals.[75] Especially the late-stage functionalization[76] of secondary amines would be a valuable method for producing new biologically active compounds.[77] Palladium-catalyzed nucleophilic aminations have tremendously improved the performance of aryl and heteroaryl aminations.[37,78] However, electrophilic aminations pioneered by Johnson[43,44] are a valuable alternative, since cheaper and less toxic metal catalysts of Cu, Ru, Ni, Fe and Co may be used.[56a–b,57a,79] As described aboved, we developed a new cobalt-catalyzed electrophilic amination of organozinc pivalates[62a–f,64a,80] of type **1** with *N*-hydroxylamine benzoates **5** allowing the preparation of various functionalized amines of type **2** (Scheme 26).[81] The required *N*-hydroxylamine benzoates **5** have been prepared from the corresponding amines **14** using benzoylperoxide (BPO), as previously reported.[43,44] However, the scope of preparation of such *N*-hydroxylamine benzoates **5** is quite limited and considerably reduces the synthetic potential of these electrophilic aminations.

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75 a) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383–394; b) N. Schneider, D. M. Lowe, R. A. Sayle, M. A. Tarselli, G. A. Landrum, *J. Med. Chem.* **2016**, *59*, 4385–4402.

76 a) J. R. Clark, K. Feng, A. Sookezian, M. C. White, *Nat. Chem.* **2018**, *10*, 583–591; b) C. A. Kluttruff, M. Haile, J. Kraml, C. S. Tautermann, *ChemMedChem* **2018**, *13*, 983–987; c) M. Shang, M.-M. Wang, T. G. Saint-Denis, M.-H. Li, H.-X. Dai, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5317–5321; d) L. J. Durak, J. T. Payne, J. C. Lewis, *ACS Catal.* **2016**, *6*, 1451–1454; e) A. Sharma, J. Hartwig, *Nature* **2015**, *517*, 600–604; f) D. A. DiRocco, K. Dykstra, S. Krska, P. Vachal, D. V. Conway, M. Tudge, *Angew. Chem. Int. Ed.* **2014**, *53*, 4802–4806; Reviews: g) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546–576; h) T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.* **2016**, *45*, 2900–2936.

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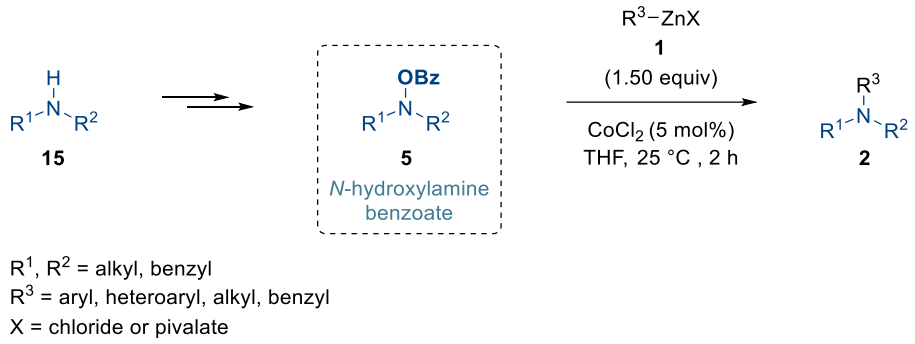
80 a) M. Ellwart, Y.-H. Chen, C. P. Tüllmann, V. Malakhov, P. Knochel, *Org. Synth.* **2018**, *95*, 127–141; j) Y.-H. Chen, M. Ellwart, V. Malakhov, P. Knochel, *Synthesis* **2017**, *49*, 3215–3223.

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



Scheme 26. Cobalt-catalyzed electrophilic amination using organozinc reagents **1** and *N*-hydroxylamine benzoates **5** leading to functionalized tertiary amines of type **2**.

Therefore, we developed a new method with a broad scope to prepare *N*-hydroxylamine benzoates **5** and demonstrate their utility for the performance of late-stage functionalizations of various amines including pharmaceuticals and peptides. Furthermore, we showed the efficiency of this method in the preparation of the two drugs gepirone[82] (**2v**) and penfluridol[83] (**15**).

2.2 Preparation of *N*-Hydroxylamine Benzoates

Preliminary experiments have shown, that the benzoyloxylation of a typical functionalized amine such as 1,4-piperidone (**14a**) provides the corresponding benzoyloxyamine **5c** in only 27% yield using BPO (Method A, Scheme 27). An alternative method using a dimethyldioxirane (DMDO)[84] oxidation and subsequent benzoylation with PhCOCl (BzCl) provides **5c** in 64% yield (Method B). Unfortunately, this reaction could not be easily scaled up. Several other oxidation methods were tested, but were neither selective, nor high yielding.[85] However, the oxidation method of O'Neil for preparing *N*-hydroxylamines **16** proved to be convenient and general.[86] According to this method, amine **14** was treated with acrylonitrile (MeOH, 55 °C, 12 h) providing a tertiary amine of type **17**. Its oxidation with

[82] P. A. J. Janssen, C. J. E. Niemegeers, K. H. L. Schellekens, F. M. Lenaerts, F. J. Verbruggen, J. M. Van Nueten, W. K. A. Schaper *Eur. J. Pharmacol.* **1970**, *11*, 139–154.

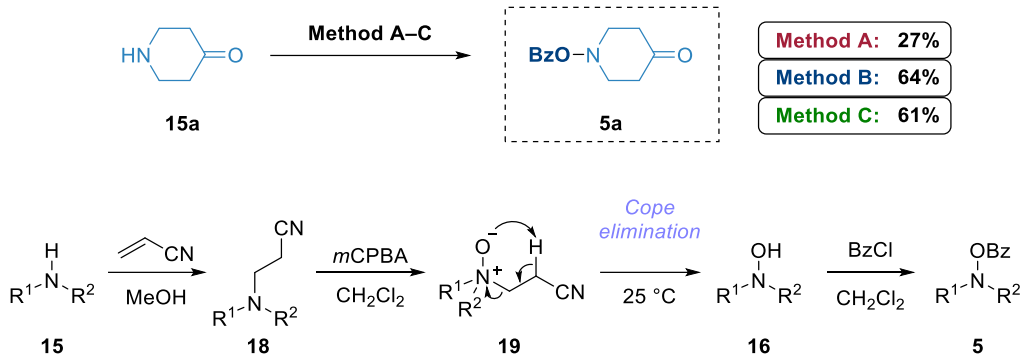
[83] J. P. Yevich, J. S. New, D. W. Smith, W. G. Lobeck, J. D. Catt, J. L. Minielli, M. S. Eison, D. P. Taylor, L. A. Riblet D. L. Temple Jr. *J. Med. Chem.* **1986**, *29*, 359–369.

[84] R. W. Murray, M. Singh, *Syn. Commun.* **1989**, *19*, 3509–3522.

[85] a) A. Banan, H. Valizadeh, A. Heydari, A. Moghimi, *Synlett* **2017**, *28*, 2315–2319; b) J. D. Fields, P. J. Kropp, *J. Org. Chem.* **2000**, *65*, 5937–5941; c) R. Bußmann, A. Heesing, *Chem. Ber.* **1987**, *120*, 1767–1781; d) W. W. Zajac, T. R. Walters, M. G. Darcy, *J. Org. Chem.* **1987**, *53*, 5856–5860; e) J. J. Yaouanc, G. Massf, G. Sturtz, *Synthesis* **1985**, *8*, 807–810.

[86] a) V. Matoušek, E. Pietrasiak, L. Sigrist, B. Czarniecki, A. Togni, *Eur. J. Org. Chem.* **2014**, *15*, 3087–3092; b) G. L. Ellis, I. A. O'Neil, V. E. Ramos, S. B. Kalindjian, A. P. Chorlton, D. J. Tapolczay, *Tetrahedron Lett.* **2007**, *48*, 1687–1690; c) I. A. O'Neil, E. Cleator, D. Tapolczay, *Tetrahedron Lett.* **2001**, *42*, 8247–8249.

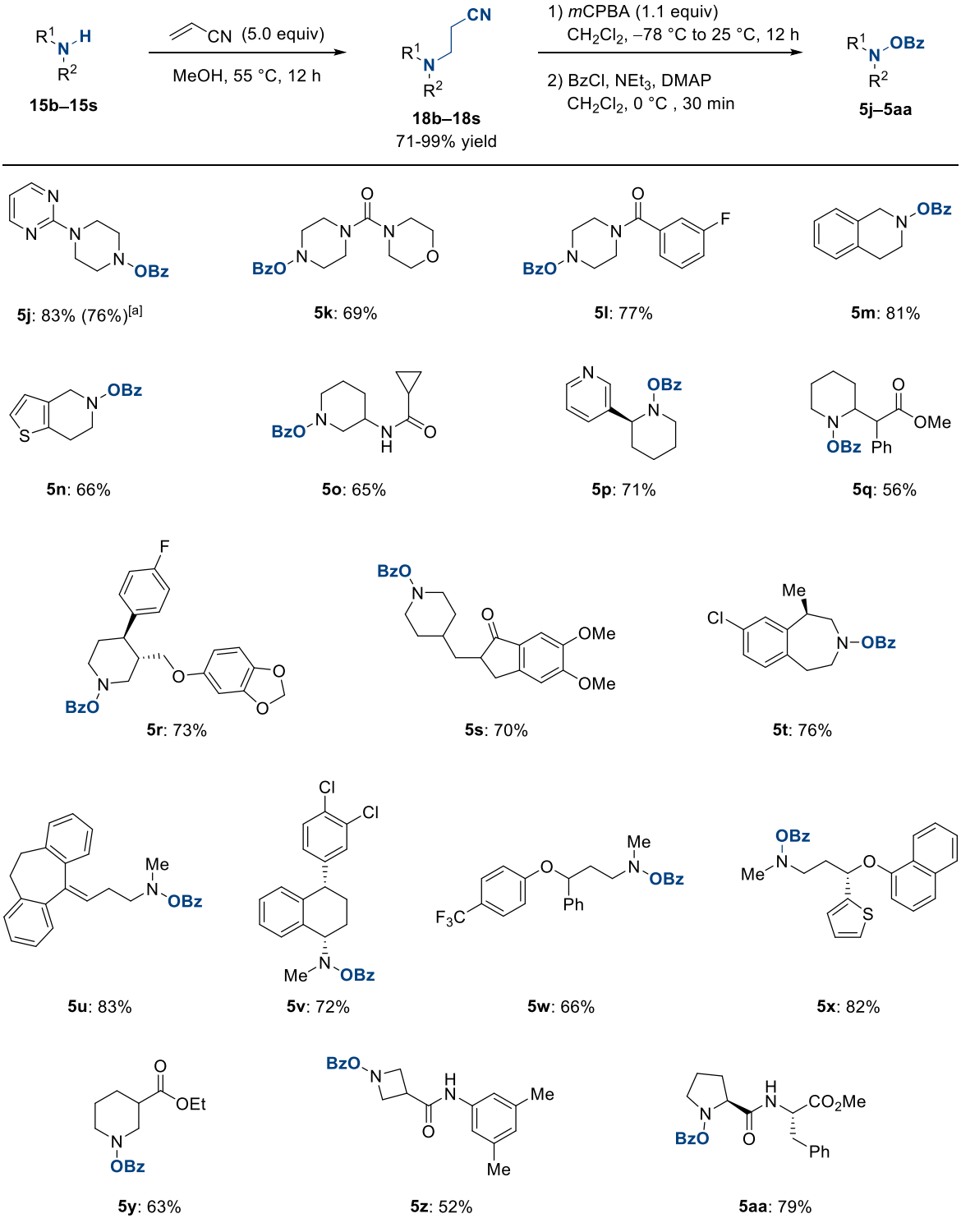
meta-chloroperbenzoic acid (*m*CPBA; CH_2Cl_2, −78 °C, 3 h) gives an amine *N*-oxide of type **18**, which underwent a Cope-elimination (25 °C, 9 h) affording *N*-hydroxylamines of type **16**.[86] Benzoylation with BzCl (NEt_3, DMAP, CH_2Cl_2, 0 °C, 0.5 h) furnished the desired hydroxylamine benzoates **5**. Applying this sequence to **14a** led to the desired product **5c** in an overall yield of 61% (Method C).



Scheme 27. Comparison of three preparations of *N*-hydroxylamine benzoate **5c** from amine **14a**. *Method A*: amine 4 (1.5 equiv), BPO (1.0 equiv), K_2HPO_4 (1.5 equiv), DMF, rt, 12 h; *Method B*: 1) amine 4 (1.0 equiv), DMDO (1.05 equiv), acetone, 0 °C, 1 h; 2) BzCl (1.2 equiv), NEt_3 (1.5 equiv), DMAP (1 mol%), CH_2Cl_2, 0 °C, 30 min; *Method C*: 1) amine 4, (1.0 equiv), acrylonitrile (5.0 equiv), MeOH, 55 °C, 12 h; 2) *m*CPBA (1.1 equiv), CH_2Cl_2, −78 °C to 25 °C, 12 h; 3) BzCl (1.2 equiv), NEt_3 (1.5 equiv), DMAP (1 mol%), CH_2Cl_2, 0 °C, 30 min.

This selective oxidation was performed on diverse amines **14b**–**14s** affording *via* the 2-cyanoethyl amines **17b**–**17s** the desired hydroxylamine benzoates in satisfactory overall yields (Scheme 28). In contrast to Method B, Method C allows a convenient scale-up. Thus, the preparation of the hydroxylamine benzoate **5j** derived from a piperazine (83% yield on 1 mmol scale) could readily be scaled-up (77% yield on 10 mmol scale; Scheme 28). Likewise, we have prepared the related piperazine and piperidine derived hydroxylamine benzoates **5k**–**5o** (65–81% yields). This method has been extended to biologically active amines, such as the alkaloid anabasine and the psychostimulant methylphenidate and led to the expected hydroxylamine benzoates **5p** and **5q** in 56–71% yields. Important drugs bearing cyclic secondary amines such as paroxetine (antidepressant), debenzylated donepezil (treatment of dementia) and lorcaserine (former morbid obesity medication) were smoothly converted to the desired products **5r**–**5t** in 73–76% yields. Also open-chain antidepressants like nortriptyline, sertraline, fluoxetine and duloxetine were predictably converted to the hydroxylamine esters **5u**–**5x** in 66–90% yields. Finally, amino acids and a peptide such as a nipecotic acid derivative, an azetidine derivate and

a dipeptide were chemoselectively converted to the corresponding hydroxylamines **5y**–**5aa** in 52–79% yields.



Scheme 28. Preparation of *N*-hydroxylamine benzoates **5**. All experiments were performed on a 1 mmol scale and the reported yields are isolated yields of analytically pure products; [a] 10 mmol scale.

2.3 Cobalt-Catalyzed Electrophilic Amination

Having in hand a general conversion of secondary amines **14** to the corresponding hydroxylamine benzoates **5**, we have shown their cross-coupling with polyfunctional organozinc chlorides[87] **1** providing a wide range of tertiary amines of type **2**. Thus, various aryl- and heteroaryl-zinc chlorides **1n**–**1q** underwent a cobalt-catalyzed electrophilic amination with cyclic hydroxylamine benzoates **5k**–**5n** in the presence of 5 mol% $CoCl_2$ (THF, 25 °C, 2 h) leading to polyfunctional tertiary amines **2w**–**2z** in 83–92% yields (Scheme 29). This amination was found to be compatible with several important functional groups (secondary and tertiary alcohols, primary and secondary amines, amides and epoxides).[88] For example, the reaction of 3-anisylzinc chloride (**1r**) with hydroxylamine ester **5o**, bearing an acidic amide proton proceeded smoothly in the presence of 5 mol% $CoCl_2$ affording the tertiary amine **2aa**. These electrophilic aminations complement the nucleophilic amination of Buchwald and Hartwig.[37,78] Thus, the melatonin receptor ligand **2aa** as well as the 517-β-hydroxysteroid dehydrogenase inhibitor **2w** have been prepared *via* the nucleophilic Pd-catalyzed amination in moderate yields (respectively 55%[89] and 37%[90]), whereas the present electrophilic amination produces these pharmaceutical targets in 89% and 77% yield. The robustness of this amination has been used for completing a late-stage functionalization of several alkaloids and pharmaceuticals bearing a secondary amine. Thus, the corresponding hydroxylamine benzoates **5p**–**5x** provided, after treatment with the organozinc chlorides **1s**–**1aa**, the desired functionalized pharmaceuticals or alkaloids **2bb**–**2jj** in 61–90% yields. Alkylzinc chlorides[91] such as **1bb** are also good reaction partners for this amination. Hence, zinc reagent **1bb** has been aminated with **5j** providing gepirone (**2v**), an antidepressant drug, in 82% yield.

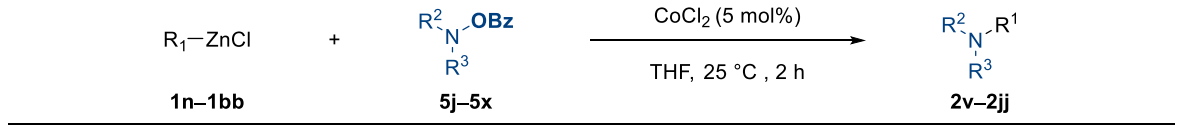
[87] A. D. Benischke, M. Ellwart, M. R. Becker, P. Knochel, *Synthesis* **2016**, *48*, 1101–1107.

[88] For a detailed study on the functional group tolerance of this cobalt catalyzed amination, see the experimental section. T. Gensch, M. Tenders, F. Glorius, *J. Org. Chem.* **2017**, *82*, 9154–9159.

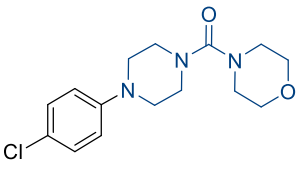
[89] J. U. Flanagan, G. J. Atwell, D. M. Heinrich, D. G. Brooke, S. Silvia, L. J. M. Rigoreau, E. Trivier, A. P. Turnbull, T. Raynahm, S. M. F. Jamieson, W. A. Denny, *Bioorg. Med. Chem.* **2014**, *22*, 967–977.

[90] G. Li, H. Zhou, Y. Jiang, H. Keim, S. W. Topiol, S. B. Poda, Y. Ren, G. Chandrasena, D. Doller, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1236–1242.

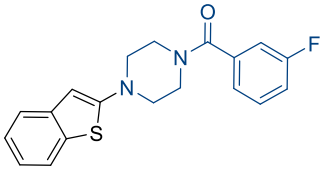
[91] A. Metzger, F. M. Piller, P. Knochel *Chem. Commun.* **2008**, *44*, 5824–5826.



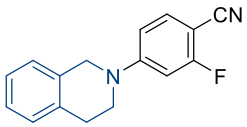
1n–1bb **5j–5x** **2v–2jj**



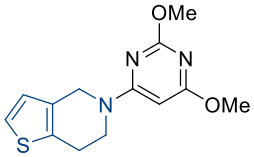
2w: 89%



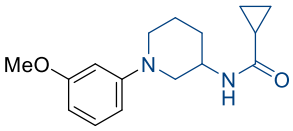
2x: 92%



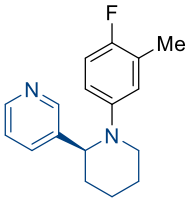
2y: 86%



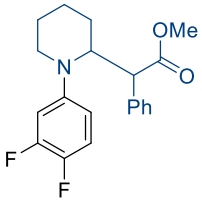
2z: 83%



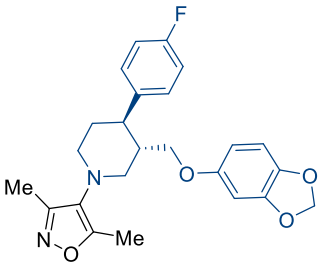
2aa: 77%



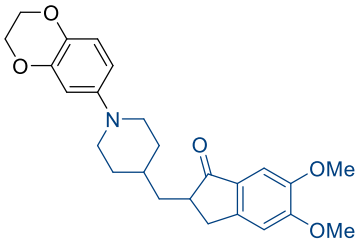
2bb: 78%



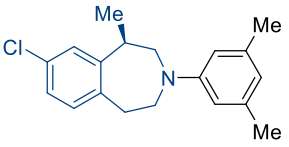
2cc: 81%



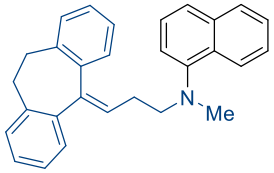
2dd: 64%



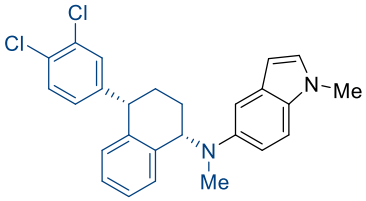
2ee: 74%



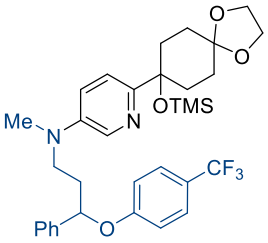
2ff: 78%



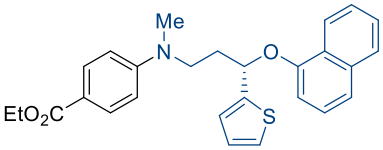
2gg: 90%



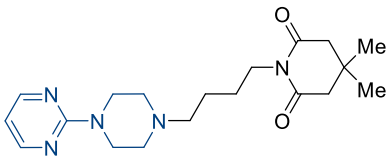
2hh: 64%



2ii: 61%



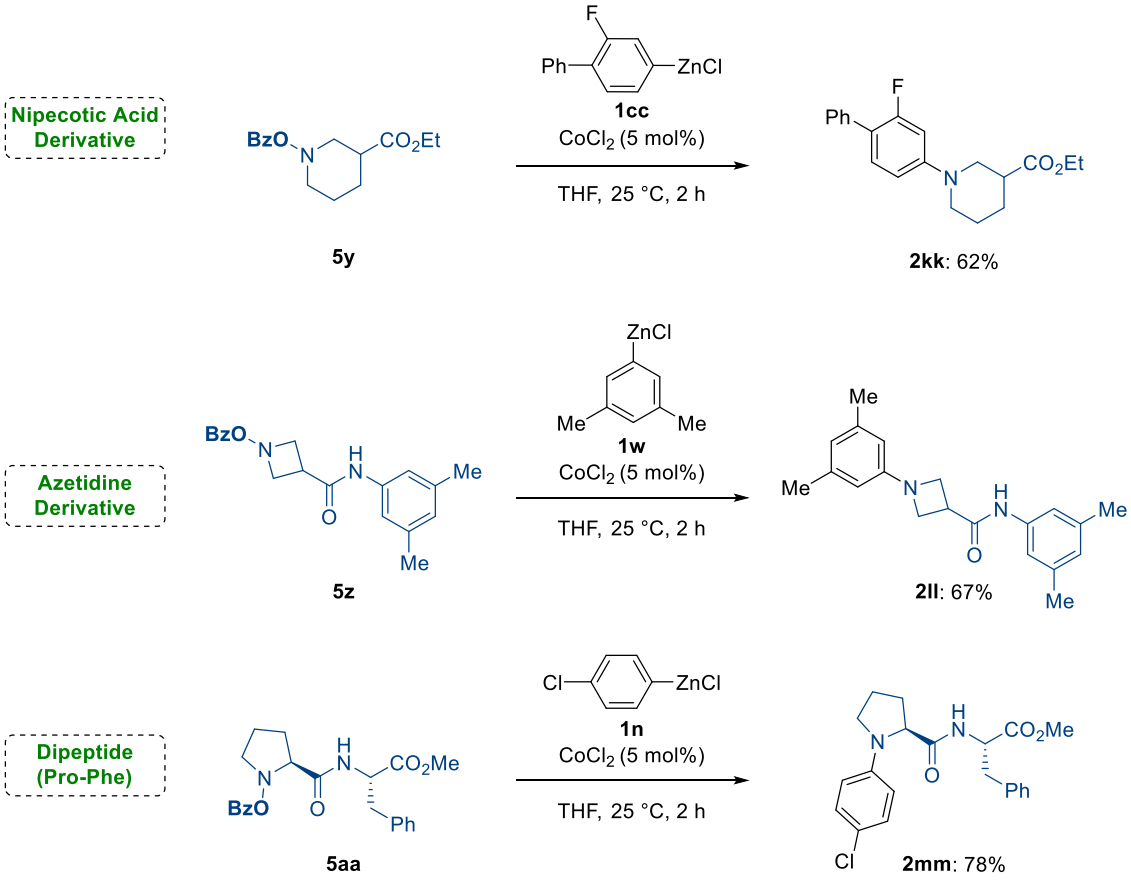
2jj: 87%



2v (gepirone): 82%

Scheme 29. Electrophilic amination of organozinc chlorides of type **1**. All experiments were performed on a 1 mmol scale and the reported yields are isolated yields of analytically pure products.

Encouraged by these results, we envisioned a late stage functionalization of amino-acids and peptides. Therefore, the hydroxylamine benzoates derived from two β-amino-acids **5y**–**5z** and dipeptide **5aa** underwent the expected amination with organozinc chlorides **1cc**, **1w** and **1n** leading to the arylated amino-acids **2kk**–**2ll** and peptide **2mm** in 62–78% yield (Scheme 30). As observed for benzoate **5o**, the amidic proton of **5z** and **5aa** did not disturb the desired amination.



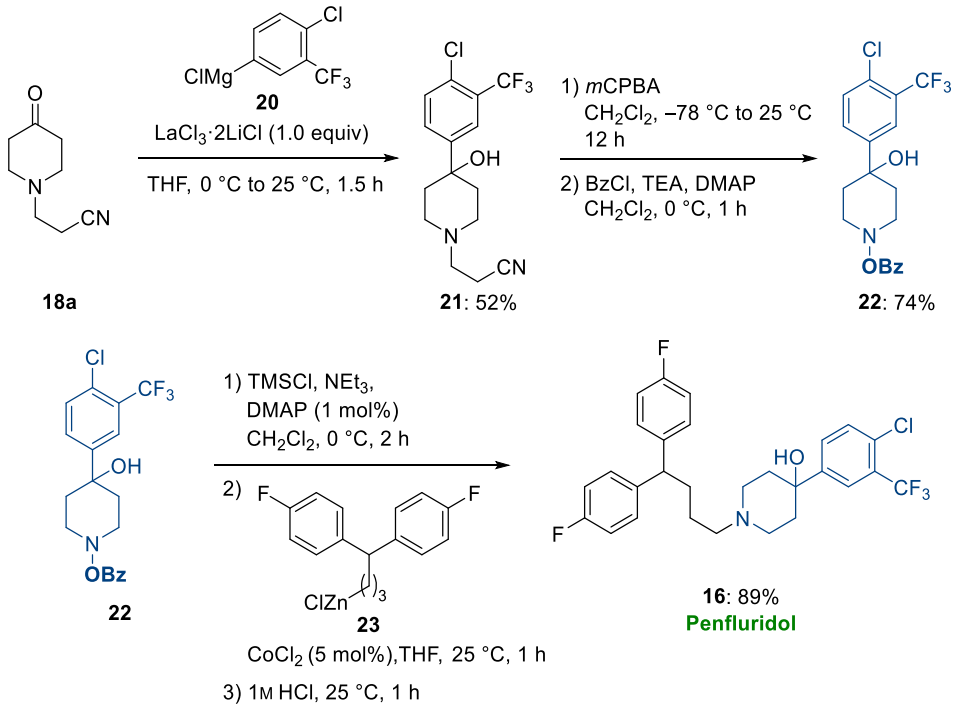
Scheme 30. Functionalization of amino-acids **5y**–**5z** and peptidic substrates **5aa**, using the cobalt-catalyzed amination of organozincs **1cc**, **1w** and **1n**.

2.4 Synthesis of Penfluridol (15)

To demonstrate the synthetic versatility of this amination, we have also performed a short synthesis of penfluridol (**15**), a highly potent antipsychotic (Scheme 31). Thus, the arylmagnesium chloride **19** underwent a $LaCl_3 \cdot 2LiCl$[92] mediated addition to the 2-cyanoethyl-piperidone (**17a**) (THF, 25 °C, 1.5 h) leading to the tertiary alcohol **20** in 52% yield. Without

[92] Krasovskiy, A.; Kopp, F.; Knochel P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497–500.

protection of the tertiary hydroxyl function, alcohol **20** was converted by the standard method to the hydroxylamine benzoate **21** in 74% yield. Protection of **21** with TMSCl followed by the cobalt-catalyzed amination, using the alkylzinc chloride **22** and desilylation (1M HCl, 25 °C, 1 h) produces penfluridol (**15**) in 89% yield.



Scheme 31. A new synthesis of penfluridol **15**.

2.5 Summary

In summary, we have reported a very general and functional group tolerating synthesis of hydroxylamine benzoates **5** and demonstrated their utility in the cobalt-catalyzed amination of various alkyl-, aryl- and heteroaryl-zinc chlorides leading for the first time to complex polyfunctional amines in a predictable way. We have shown that this method allows the late stage functionalization of various drugs including peptidic target substrates and can be readily used for the synthesis of complex target amines such as the pharmaceuticals penfluridol (**15**) and gepirone (**2v**).

3. Preparation of Tertiary Amines by Triple Functionalization of Tris-(2-cyanoethyl)amine Using a Cobalt-Catalyzed Electrophilic Amination of Organozinc Halides

3.1 Introduction

The formation of carbon-nitrogen bonds is a central challenge in the elaboration of pharmaceuticals und agrochemicals.[75] During the last decades, several new amine preparations have been developed.[93] Therein, the palladium-catalyzed nucleophilic aminations reported by Buchwald[55b] and Hartwig[55a] tremendously improved the scope of especially aryl and heteroaryl amine formations.[78] Lately, electrophilic aminations, pioneered by Narasaka[94] and Johnson[43,44], have proven to display a valuable alternative, since cheaper and less toxic catalysts derived from Cu, Ni, Co or Fe may be used.[95] These aminations utilize electrophilic nitrogen sources, such as organic azides[96], *N*-chloro amines[97] or *N*-hydroxylamine benzoates[98] in combination with various organometallic reagents as nucleophiles. As described above, we have developed a preparation of *N*-hydroxylamines via a Cope-elimination on amines bearing a 2-cyanoethyl moiety.[99] This method provided to be very robust, enabling the late stage functionalization of various polyfunctionalized amines.[76] Therefore, we have envisioned to use tris(2-cyanoethyl)amine (**23**) as a precursor for a triple electrophilic amination using three different organozinc reagents[19] of type **1**, providing tertiary amines of type **2** (Scheme 32). This would enable to construct a variety of tailored tertiary amines, bearing three chosen moieties.

[93] a) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247–9301; b) J. X. Qiao, P. Y. S. Lam, in Boronic Acids, 2nd ed.; Wiley-VCH: Weinheim, Germany, **2011**; 315–361.

[94] a) K. Narasaka, M. Kitamura, *Eur. J. Org. Chem.* **2005**, *2005*, 4505–4519; b) H. Tsutsui, Y. Hayashi, K. Narasaka, *Chem. Lett.* **1997**, *26*, 317–318.

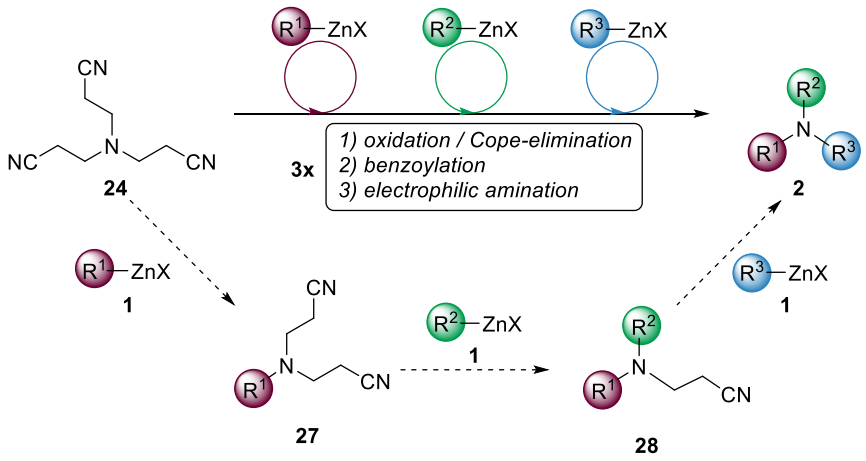
[95] a) Z. Zhou, L. Kürti, *Synlett* **2019**, *30*, 1525–1535; b) M. Corpet, C. Gosmini, *Synthesis* **2014**, *46*, 2258−2271.

[96] S. Graßl, J. Singer, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 335–338.

[97] X. Qian, Z. Yu, A. Auffrant, C. Gosmini, *Chem. Eur. J.* **2013**, *19*, 6225–6229.

[98] a) Hemric, B. N.; Chen, A.; Wang, Q. *J. Org. Chem.* **2019**, *84*, 1468–1488; b) Hendrick, C. E.; Bitting, K. J.; Cho, S.; Wang, Q. *J. Am. Chem. Soc.* **2017**, *139*, 11622−11628; d) Liu, J.; Wu, K.; Shen, T.; Liang, Y.; Zou, M.; Zhu, Y.; Li, X.; Li, X.; Jiao, N. *Chem. Eur. J.* **2017**, *23*, 563−567; e) Hendrick, C. E.; Wang, Q. *J. Org. Chem.* **2017**, *82*, 839−847; f) Dong, X.; Liu, Q.; Dong, Y.; Liu, H. *Chem. Eur. J.* **2017**, 23, 2481−2511.

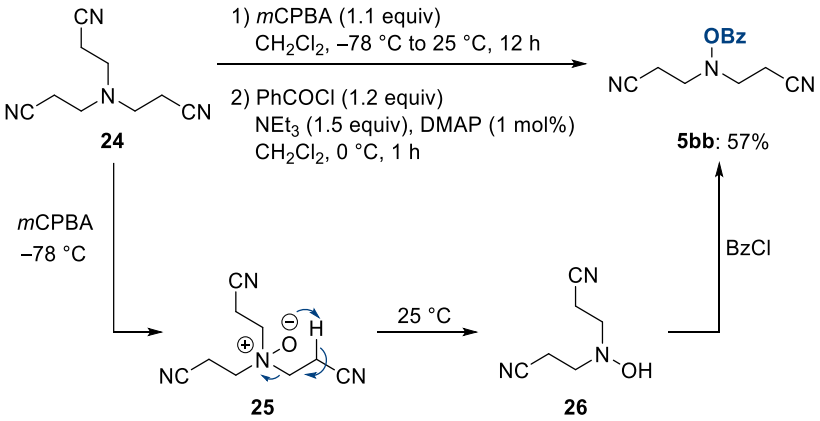
[99] S. Graßl, Y.-H. Chen, C. Hamze, C. P. Tüllmann, P. Knochel, *Org. Lett.* **2018**, *21*, 494–497.



Scheme 32. General approach to construct triple functionalized tertiary amines of type **2** starting from amine **1**.

3.2 First Functionalization of Tris(2-cyanoethyl)amine

Tris(2-cyanoethyl)amine (**23**) was treated with *m*CPBA (1.05 equiv) at −78 °C, to form the *N*-oxide **24**, which reacts at 25 °C to the corresponding hydroxylamine **25** (Scheme 33). After benzoylation using benzoyl chloride (1.2 equiv) and triethylamine (1.5 equiv), the *N*-hydroxylamine benzoate **5bb** was obtained in 57% yield. This benzoate **5bb** was submitted to a cobalt-catalyzed electrophilic amination with alkylzinc halides of type **1**.

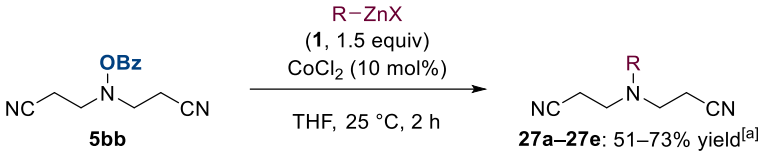


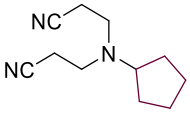
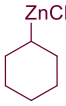
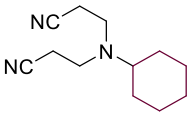
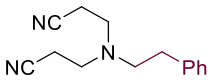
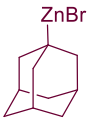
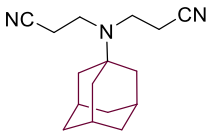
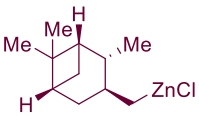
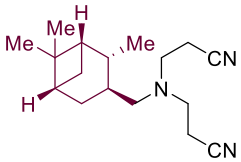
Scheme 33. Preparation of hydroxylamine benzoate **5bb** starting from amine **23** and proposed mechanistic pathway.

Thus, the amination of organometallics **1dd**–**1ff** provided after amination with benzoate **5bb** in the presence of $CoCl_2$ (10 mol%) the tertiary amines **26a**–**26c** in 61–73% yield (Table 5, entries 1–3). Remarkably, even the sterically hindered adamantylzinc bromide (**1gg**) was

readily aminated with hydroxylamine **5bb**, leading to amine **26d** in 51% yield (entry 4). Also, the pinene derived organometallic **1hh** provided after a cobalt-catalyzed amination with benzoate **5bb** the desired tertiary amine **26e** in 66% yield (entry 5). As reported in the literature, hydroxylamine benzoates derived from aromatic amines are not stable and undergo [3,3]-sigmatropic rearrangement of the OBz moiety to the aryl ring.[100] Therefore, only alkylzinc reagents were used for the first two functionalizations.

Table 5. Cobalt-catalyzed electrophilic amination of alkyl organozinc reagents **1dd**–**1hh** using *N*-hydroxylamine benzoates **5bb**, leading to tertiary amines of type **26**.



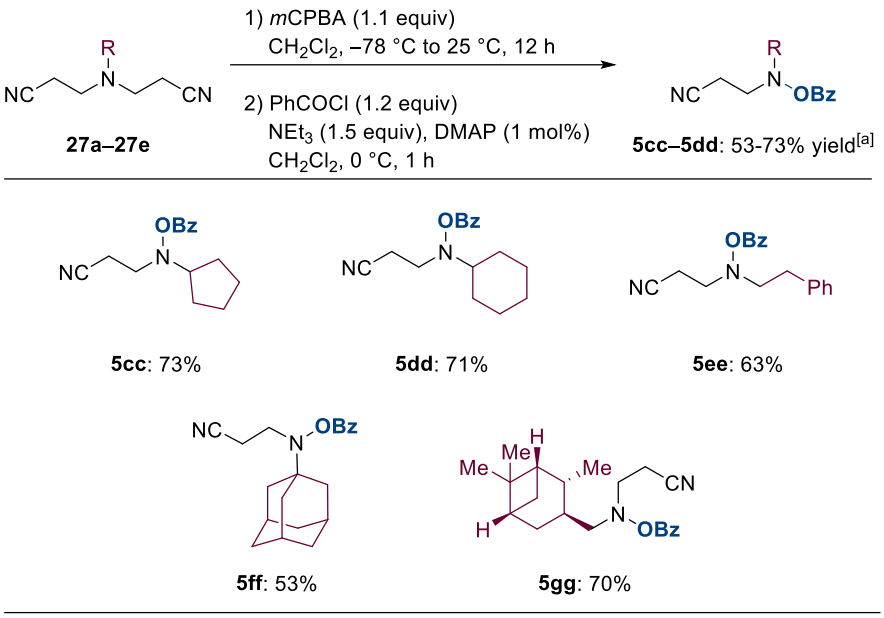
Entry	Organozinc reagent 1	Product 26[a]
		
1	**1dd**	**26a** : 65%
		
2	**1ee**	**26b**: 73%
		
3	**1ff**	**26c**: 61%
		
4	**1gg**	**26d**: 51%
		
5	**1hh**	**26e**: 66%

[a] All reported yields are isolated yields of analytically pure products.

[100] S. Ichikawa, S. Zhu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2018**, *57*, 8714–8718.

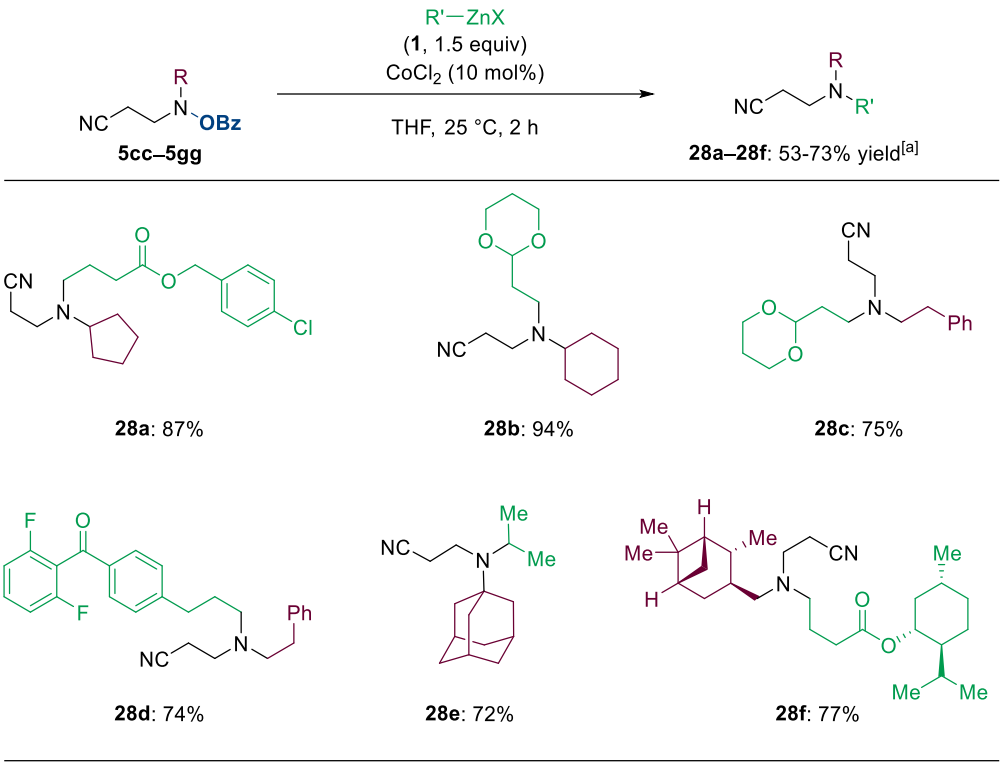
3.3 Second Functionalization of Tris(2-cyanoethyl)amine

Next, we applied the oxidation procedure to the alkylated tertiary amines of type **26**. As expected, a selective formation of the corresponding hydroxylamine was straightforward and after benzoylation provided the benzoates **5cc**–**5gg** in 53–73% yield (Scheme 34). Those have been coupled a second time, using various alkylzinc reagents of type **1**. Thus, treatment of cyclopentylamine benzoate **5cc** with polyfunctional organozinc reagent **1ii** in the presence of a cobalt-catalyst, led to the double functionalized amine **27a** in 87% yield (Scheme 35). Also, the benzoates **5dd**–**5ee** were smoothly alkylated using the functionalized organozinc reagents **1jj**–**1kk**, providing the tertiary amines **27b**–**27d** in 74–94% yield. Noteworthy, the sterically hindered *N*-hydroxylamine benzoate **5ff** was successfully reacted with isopropylzinc chloride (**1ll**), providing the bulky tertiary amine **27e** in 72% yield.[101] In addition, the pinene derived benzoate **5gg** was alkylated with the menthol derived organozinc reagent **1mm**, leading to the tertiary amine **27f** in 77% yield.



Scheme 34. Preparation of *N*-hydroxylamine benzoates of type **5** starting from amines of type **26**. [a] All reported yields are isolated yields of analytically pure products.

[101] K. Banert, M. Heck, A. Ihle, J. Kronawitt, T. Pester, T. Shoker, *J. Org. Chem.* **2018**, *9*, 5138–5148.

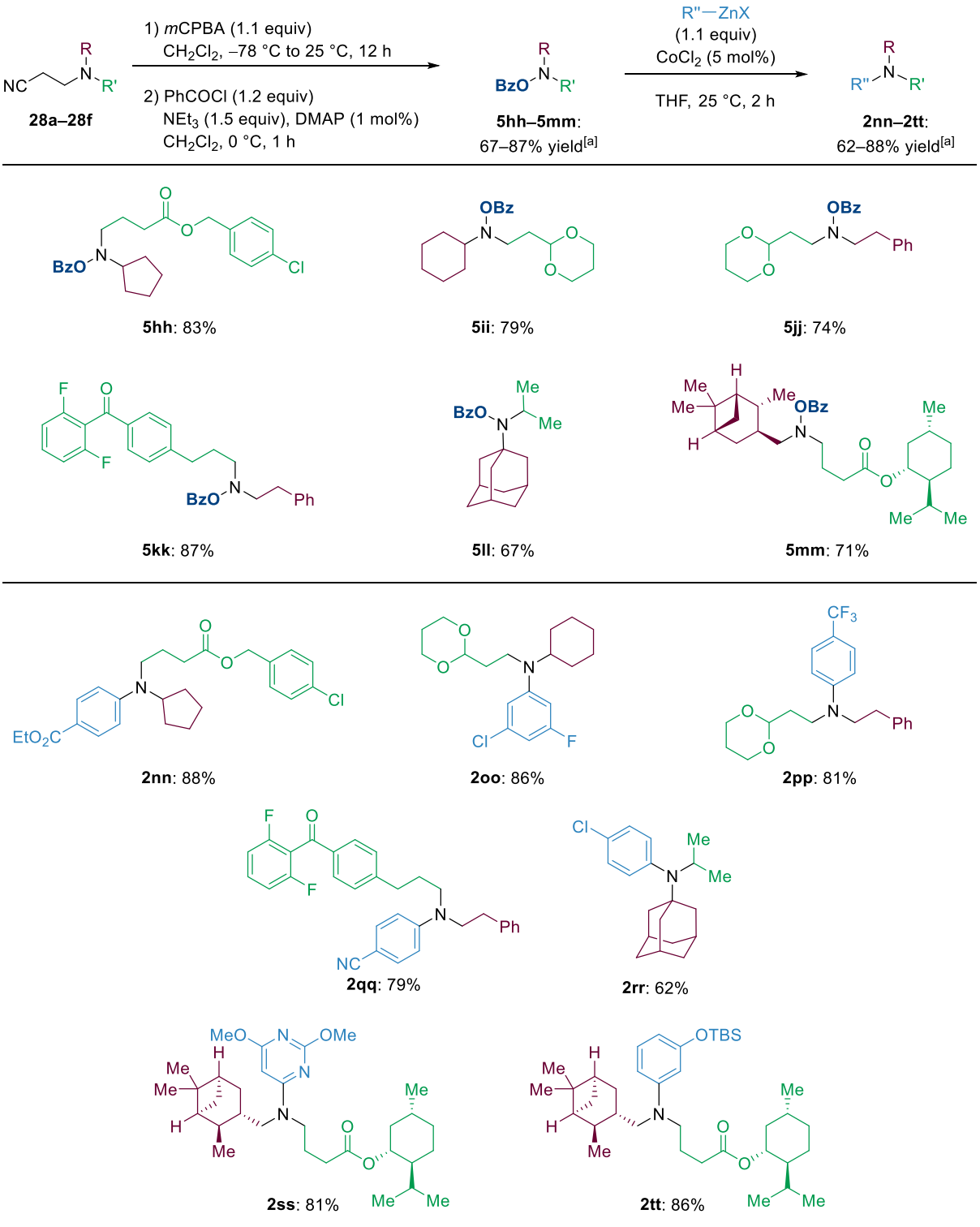


Scheme 35. Electrophilic amination of organozinc reagents of type **1** using benzoates of type **5** in the presence of $CoCl_2$. [a] All reported yields are isolated yields of analytically pure products.

3.4 Third Functionalization of Tris(2-cyanoethyl)amine

With these double alkylated amines of type **27** in hand, we focused on the last functionalization. Therefore, the amines of type **27** have been treated with *m*CPBA (1.05 equiv; −78 °C to 25 °C), followed by benzoylation, providing to the unsymmetrical hydroxylamine benzoates **5hh**–**5mm** in 67–87% yield (Scheme 36). These have been submitted to a cobalt-catalyzed electrophilic amination with various functionalized aryl- and heteroarylzinc reagents of type **1**. Thus, arylzinc chloride **1n** was aminated with hydroxylamine benzoate **5hh** in the presence of $CoCl_2$ (5 mol%), providing the triple functionalized tertiary amine **2nn** in 88% yield (Scheme 36). Also, benzoates **5ii**–**5kk** are readily arylated with organozinc chlorides **1nn**–**1pp**, leading to the corresponding aniline derivatives **2oo**–**2qq** in 79–86% yield. As expected, various functional groups, such as esters, nitriles and a diaryl acetate were tolerated by this transformation. Interestingly, adamantly hydroxylamine benzoate **5ll** smoothly reacted with 3-chlorophenylzinc chloride ( ), affording the corresponding amine **2rr** in 62% yield. Remarkably, the pinene-derived hydroxylamine benzoate (**5mm**) reacted in the presence of a

cobalt-catalyst with the aryl- and heteroarylzinc chlorides **1q** and **1qq** to give the arylated amines **2ss**–**2tt** in 81–86% yield.



Scheme 36. Preparation of *N*-hydroxylamine benzoates of type **5** starting from amines of type **27** and electrophilic amination of organozinc reagents of type **1** using benzoates of type **5** in the presence of $CoCl_2$. [a] All reported yields are isolated yields of analytically pure products.

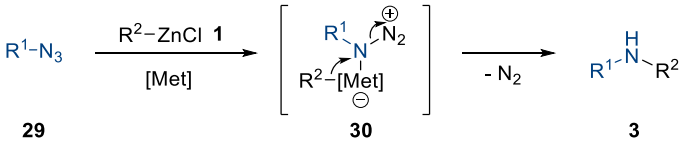
3.5 Summary

In summary, we have developed a procedure to construct triple alkylated or arylated tertiary amines, starting from commercially available tris(2-cyanoethyl)amine (**23**). This iterative method involves standard steps such as an oxidation (generating after a Cope-elimination a hydroxylamine), a benzoylation and a cobalt-catalyzed electrophilic amination of organozinc reagents of type **1**. Thus, various polyfunctionalized tertiary amines **2** have been prepared in good yields.

4. Iron-Mediated Electrophilic Amination of Organozinc Halides using Organic Azides Detailed Reaction Optimization

4.1 Introduction

The preparation of polyfunctional amines is central to organic synthesis.[102] Nucleophilic aminations[93] in which the amine plays the role of a nucleophile, such as the Buchwald-Hartwig amination[55a–b], have been widely used for the preparation of aryl and heteroaryl amines. In contrast, electrophilic aminations are much less developed. Pioneer work from Narasaka[94] and more recently from Johnson[43,44] have led to a number of electrophilic aminations using for example *N*-hydroxylamines derivatives as electrophilic aminating reagent.[95, 98] Recently, we have shown that the cobalt-catalyzed amination of organozinc halides and pivalates by *N*-hydroxylamine benzoates furnishes polyfunctional tertiary amines.[81, 99] In the search of electrophilic amination reactions leading to secondary amines, we have envisioned the use of organic azides of type **28** as electrophilic nitrogen sources.[103] In the early work of Trost[104] and others[105], such reactions have been performed using Grignard reagents. We envisioned, that organozinc halides of type **1** would be especially attractive, since these organometallics are compatible with the presence of various functional groups.[87] In general organozinc reagents are not very reactive, so that we anticipated, that transition metal catalysts (Met) may be required for achieving the desired amination *via* transition state **29**, leading to secondary amines of type **3** (Scheme 37).



Scheme 37. Tentative pathway for the electrophilic amination of organozinc halides **1** with organic azides **28** in the presence of a transition metal catalyst.

[102] A. Ricci; *Modern amination methods*. Wiley-VCH: Weinheim, Germany, **2008**.

[103] a) P. Starkov, T. F. Jamison, I. Marek, *Chem. Eur. J.* **2015**, *21*, 5278–5300; b) K. Shin, H. Kim, S. Chang, *Acc. Chem. Res.* **2015**, *48*, 1040–1052; c) E. Ciganek, in *Organic Reactions 72*, Wiley-VCH: Weinheim, Germany, **2009,** 1–366; d) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188–5240.

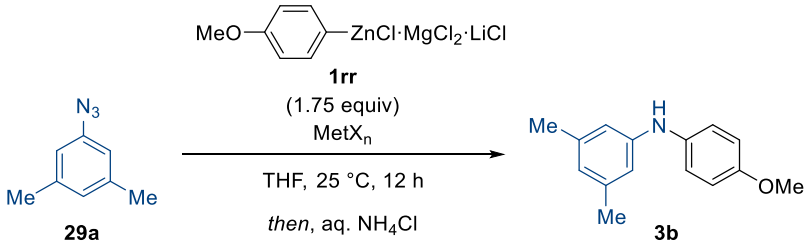
[104] B. M. Trost, W. H. Pearson, *J. Am. Chem. Soc.* **1983**, *105*, 1054–1056.

[105] a) B. V. S. Reddy, N. S. Reddy, Y. J. Reddy, Y. V. Reddy, *Tetrahedron Lett.* **2011**, *52*, 2547–2549; b) J. S. Yadav, B. V. S. Reddy, P. Borkar, P. J. Reddy, *Tetrahedron Lett.* **2009**, *50*, 6642–6645; c) J. S. Yadav, C. Madhuri, B. V. S. Reddy, G. S. K. K. Reddy, G. Sabitha, *Synth. Commun.* **2002**, *32*, 2771–2777; d) H. M. S. Kumar, B. V. S. Reddy, S. Anjaneyulu, J. S. Yadav, *Tetrahedron Lett.* **1999**, *40*, 8305–8306.

4.2 Reaction Optimization

In preliminary experiments we have treated aryl azide (**28a**) with 4-anisylzinc chloride (**1rr**), prepared from the corresponding Grignard reagent by transmetalation with $ZnCl_2$, in THF at 25 °C. In the absence of a transition metal catalyst, no amination was observed (Table 6, entry 1). Also, metallic salts derived from Cu(I), Cu(II), Cr(II), Cr(III), Ni(II), Pd(II) provided only traces of the secondary amine **3b** (entries 2–8). However, a Fe(II) or Fe(III)-catalysisgave valuable results, whereby $FeCl_3$ was more active than $FeCl_2$ (entries 9–10).[106] Varying the stoichiometry showed, that 0.5 equiv of $FeCl_3$ led to the best result, furnishing **3b** in 68% isolated yield (entry 11–12). Further optimization of the reaction conditions showed, that performing the amination at 50 °C led to complete conversion to **3b** within 1 h in 74% isolated yield (entry 11).

Table 6. Optimization of the electrophilic amination of organozinc halides **1** with organic azides **28**, leading to secondary amines of type **3**.



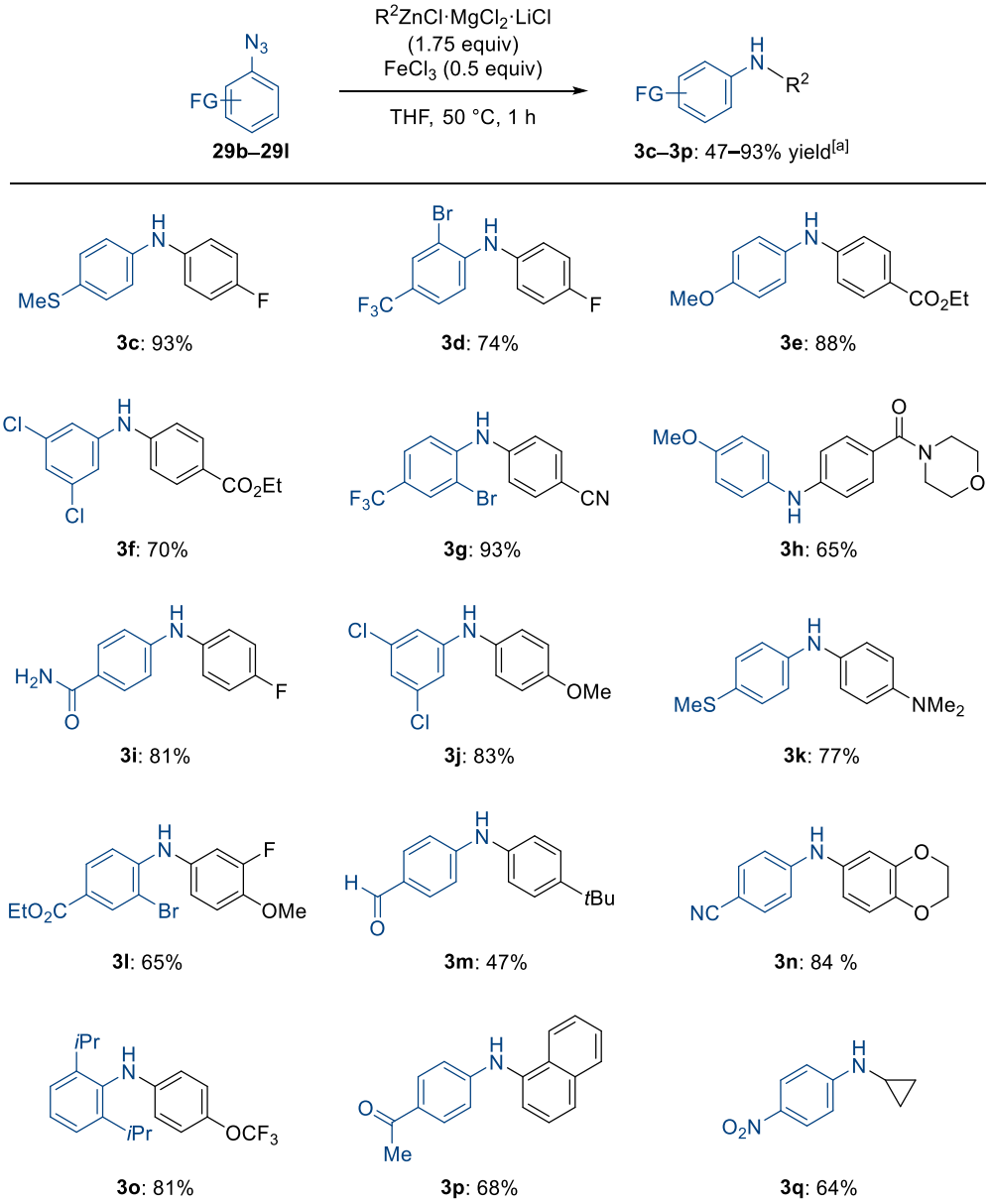
Entry	Catalyst (loading)	Yield [%]
1	-	0
2	CuCN·2LiCl (20 mol%)	<5%
3	$CuCl_2$ (20 mol%)	<5%
4	$CrCl_3$ (20 mol%)	<5%
5	$CoCl_2$ (20 mol%)	<5%
6	$CrCl_2$ (20 mol%)	<5%
7	$NiCl_2$ (20 mol%)	<5%
8	$PdCl_2$ (20 mol%)	<5%
9	$FeCl_2$ (20 mol%)	51[a]
10	$FeCl_3$ (20 mol%)	55[a]
11	$FeCl_3$ (50 mol%)	68[b] (74[b,c])
12	$FeCl_3$ (75 mol%)	32[a]

[a] GC-yield; [b] isolated yield; [c] 50 °C, 1 h.

[106] a) A. Fürstner, *ACS Cent. Sci.* **2016**, *2*, 778–789; b) I. Bauer, H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170–3387; c) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254.

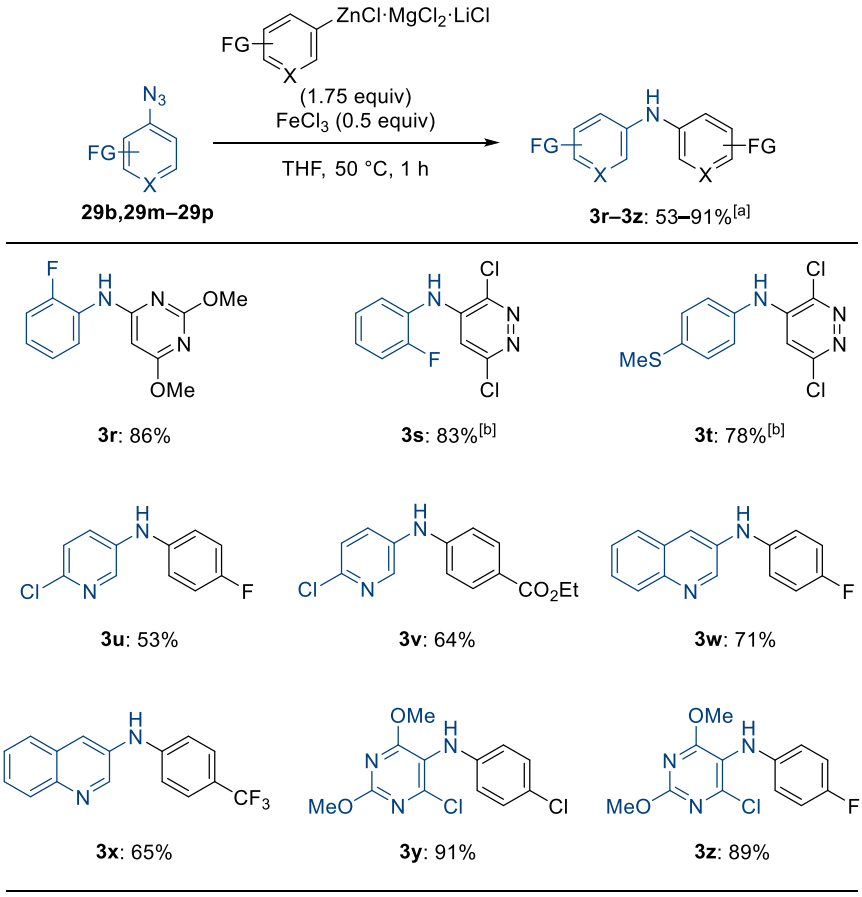
4.3 Scope and Limitations

These amination conditions were satisfactory for wide range of organic azides **28** as well as organozinc halides **1** (Scheme 38). Remarkably, arylzinc chlorides bearing electron-withdrawing groups, and therefore being less nucleophilic, still react under our standard conditions (50 °C, 1 h). Thus, various highly functionalized diarylamines (**3c**–**3i**), containing functional groups such as halides, esters, cyano, *N*-morpholino amides as well as a primary amide group ($CONH_2$), have been prepared in high yields (65–93% yield).



Scheme 38. Scope of functionalized aryl azides of type **28** and arylzinc halides of type **1** in the iron-mediated electrophilic amination procedure; [a] Isolated yields; R^1 = aryl, alkyl.

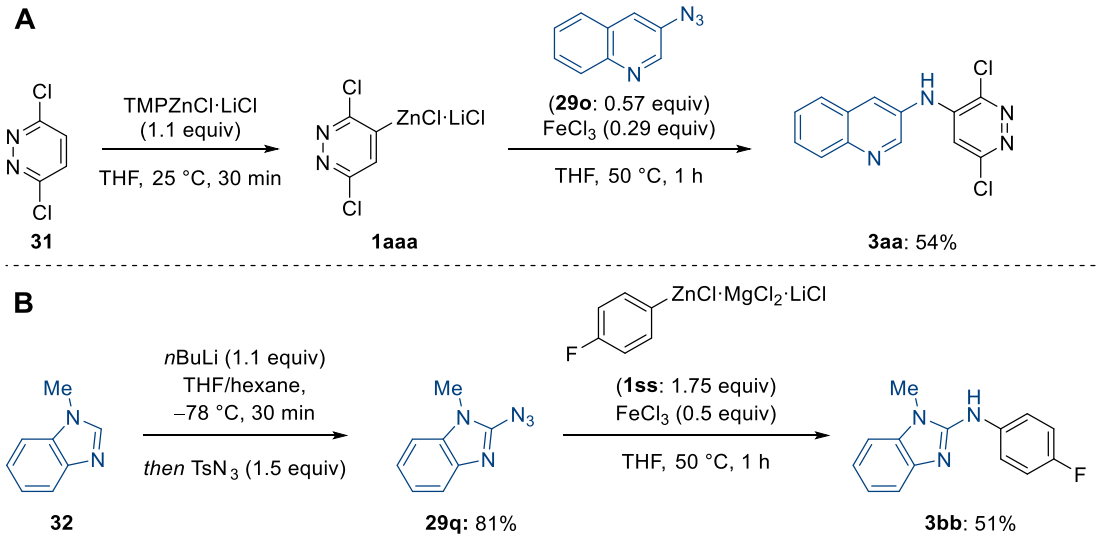
As expected electron-rich arylzinc reagents react smoothly under the described conditions, leading to diarylamines **3j**–**3p** bearing functional groups such as dimethylamino, OCF_3, formyl or acetyl (47–84% yield). Alkylzinc reagents also showed to be suitable substrates and cyclopropylzinc chloride (**1iii**) was aminated by 4-nitrophenylazide in 64% yield. Interestingly, no electron-transfer from the zinc reagent to the nitro group is observed.[107]



Scheme 39. Preparation of functionalized heteroaryl amines **3** using heterocyclic azides of type **28** and heteroarylzinc halides of type **1**; [a] Isolated yields; [b] The used organozinc chlorides do not contain $mgCl_2$.

The preparation of secondary amines bearing N-heterocyclic groups is of prime importance for pharmaceutical applications.[54] Therefore, heterocyclic zinc reagents **1q** and **1aaa** or heterocyclic azides **28n–28p** have been aminated according to this novel iron-mediated amination, leading to the heterocyclic amines **3r**–**3z** (53–91% yield, Scheme 39).

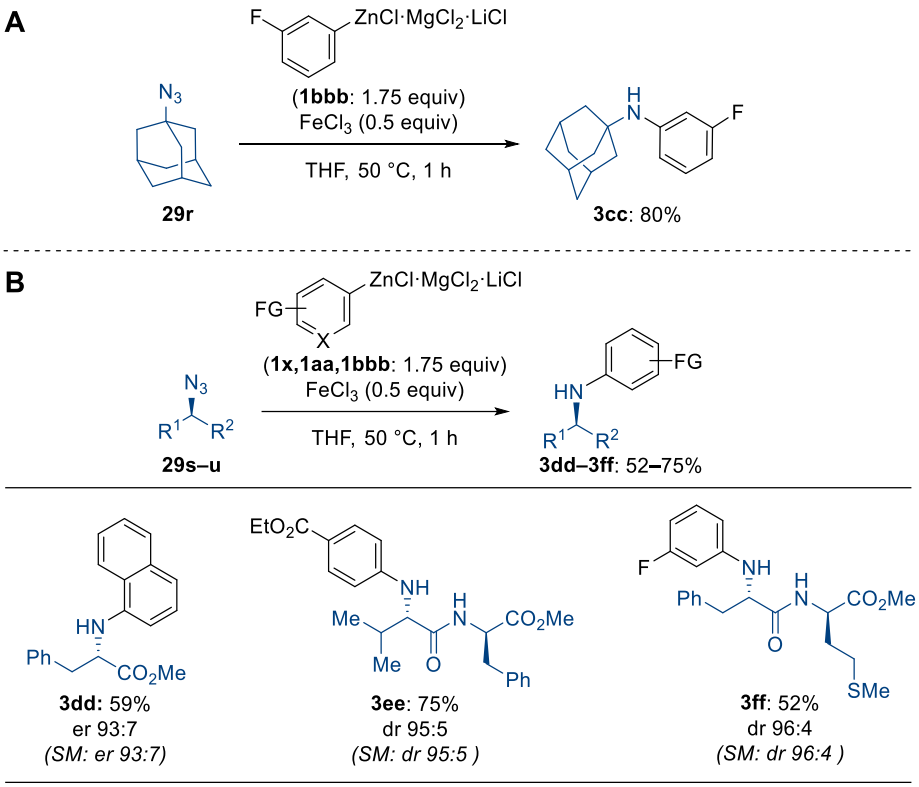
[107] I. Sapountzis, P. Knochel, *J. Am. Chem. Soc.* **2002**, *124*, 9390–9391.



Scheme 40. A: Metalation of 3,6-dichloropyridazine (**30**) and subsequent iron-mediated electrophilic amination. **B:** Generation of 2-azido-*N*-methyl benzimidazole (**28q**) and following amination providing amine **3bb**.

Interestingly, the required heterocyclic zinc reagents can be generated by the selective metalation of a heterocyclic precursor. Thus, 3,6-dichloropyridazine (**30**) was readily zincated with TMPZnCl·LiCl (TMP=2,2,6,6-tetramethylpiperidyl) at 25 °C for 30 min, leading to the heterocyclic zinc species **1aaa**, which then has been aminated with various aryl (Scheme 39, **3s**–**3t**) and heteroaryl (Scheme 40A, **3aa**) azides. Despite the presence of TMP–H, generated during the zincation, the amination proceeds without interference. Also, heterocyclic azides, such as *N*-methyl benzimidazole (**31**) have been generated according to Fujieda[108] *via* lithiation using *n*BuLi and subsequent trapping with TsN_3. Further reaction with arylzinc chloride **1ss** gave the desired secondary amine in 51% yield (Scheme 40B, **3bb**). Finally, alkyl azides including bulky azides like 1-adamantyl azide **28r** react smoothly with arylzinc derivatives such as 3-fluorophenylzinc chloride **1bbb**, leading to the adamantylamine **3cc** in 80% yield (Scheme 41A). This reaction was also extended to peptidic azides and azido esters (Scheme 41b, R^2 = OMe or NH–alkyl), which were arylated under standard conditions, providing the polyfunctional chiral amines **3dd**–**3ff** under full retention of configuration (Scheme 41B).

[108] S. Ohta, N. Tsuno, S. Nakamura, N. Taguchi, M. Yamashita, I. Kawasaki, M. Fujieda, *Heterocycles* **2000**, *53*, 1939–1955.

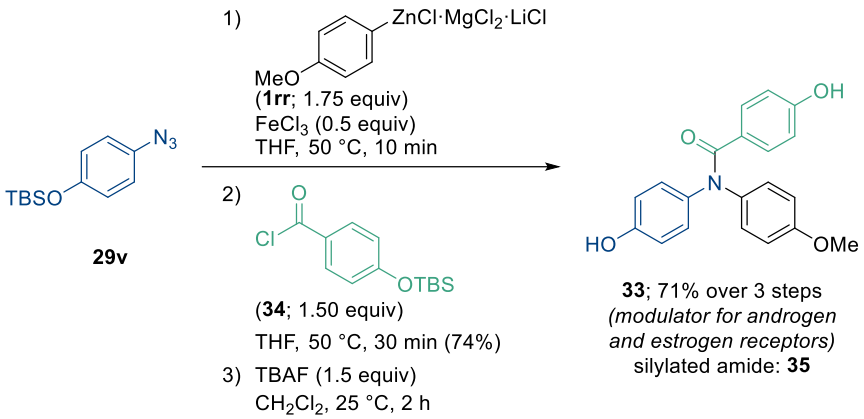


Scheme 41. A: Iron-mediated amination of organozinc chloride **1bbb** using the bulky alkyl azide 1-azidoadamantane (**28r**), leading to amine **3cc** in 80% isolated yield; **B:** Electrophilic amination of arylzinc halides **1x**, **1aa** and **1bbb** using α-azido ester **28s** and peptidic azides **28t**–**28u**, providing the arylated substrates in 52–75% isolated yields under full retention of configuration.

4.4 Preparation of an Androgen/Estrogen Receptor Modultor and Antrafenine

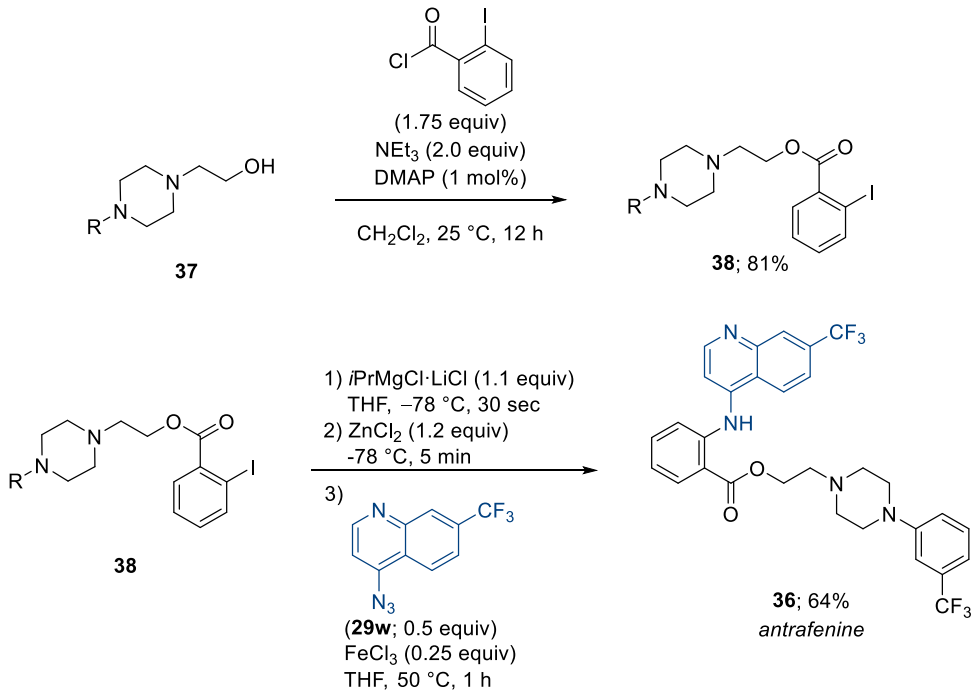
As an application, we have prepared two amine derivatives of pharmaceutical relevance. The first target was the amide **32**, a modulator for androgen and estrogen receptors, reported by Dalton.[109] Thus, the treatment of aryl azide **28v** with *p*-anisylzinc chloride (**1rr**) in the presence of 50 mol% $FeCl_3$ (50 °C, 10 min) led to an intermediate amine, which then was directly acylated using acid chloride **33**, providing the protected amide **34** in 74% yield (Scheme 42). After desilylation (TBAF) the desired product **32** was obtained in 71% overall yield.

[109] J. T. Dalton (Pearl Cohen), US 2007/0265296A1, **2007**.



Scheme 42. Preparation of androgen and estrogen receptor modulator **32** using the iron-mediated electrophilic amination; TBAF = tetrabutylammoniumfluoride.

In a second application, we have prepared the pain relief drug antrafenine (**35**, Scheme 43). Starting from amino-alcohol **36**, after acylation the iodide **37** was obtained in 81% yield. Following, a very fast iodine-magnesium exchange using *i*PrMgCl·LiCl (–78 °C, 30 sec) and subsequent transmetalation using $ZnCl_2$ provided the corresponding organozinc chloride. This is submitted to an electrophilic amination with heterocyclic azide **28w**, leading to antrafenine (**11**) in 64% yield.



Scheme 43. Preparation of the pain relief drug antrafenine **35**, using the iron-mediated electrophilic amination; R = 3-CF_3-C_6H_5.

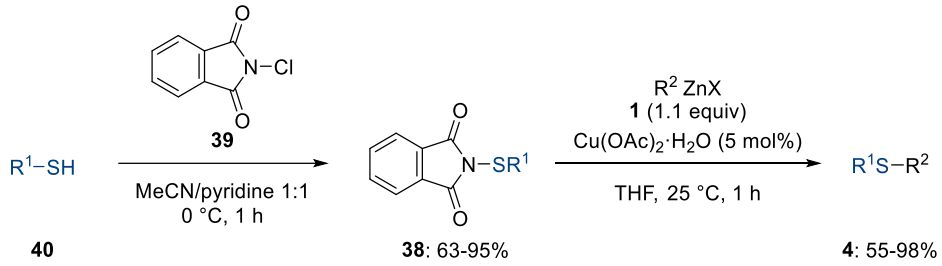
4.5 Summary

In summary, we have developed a general electrophilic amination of polyfunctional organozinc halides **1** with organic azides **28**, mediated by $FeCl_3$ (0.5 equiv). The reactions are generally complete within 1 h at 50 °C, providing highly functionalized secondary amines **3**. As mechanistic guideline we used a transition state of type **29** (Scheme 1). Iron-salts seem to have a unique ability to trigger efficiently this amination.

5. Copper-Catalyzed Electrophilic Thiolation of Organozinc Halides Using *N*-Thiophthalimides Leading to Polyfunctional Thioethers

5.1 Introduction

Thioethers are very common functional group in bioactive molecules[110] and the synthesis of the sulphur linkage led to the development of numerous methodologies.[111] Thus, Cu-catalyzed nucleophilic thiolations using aryl halides and organic thiols have been reported.[112] Also, electrophilic thiolations involving electrophilic sulfur-reagents of type RS–X (X = SR, halogeno, *N*-succimidyl and arylsulfonyl) with various organometallics have found growing interest.[113] In this respect, the use of polyfunctional organozinc reagents[87] is of special interest, since they are readily prepared and tolerate a broad range of functional groups like an ester, a nitrile or an aldehyde.



Scheme 44. General preparation of *N*-thiophthalimides **38** and their reaction with organozinc reagents **1** to provide thioethers of type **4**.

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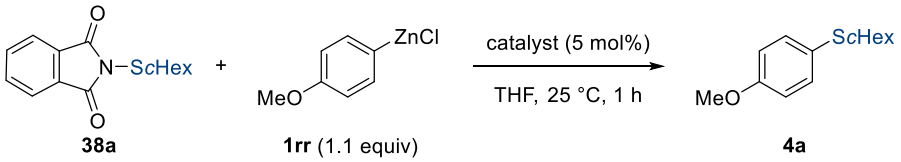
[113] a) Cheng, Y.; Liu, X.; Dong, Z.-B. *Eur. J. Org. Chem.* **2018**, *6*, 815–820; b) B.-X. Du, Z.-J. Quan, X.-Y. Da, Z. Zhang, X.-C. Wang *Adv. Synth. Catal.* **2015**, *357*, 1270–1276; c) Y. Zhang, Y. Li, X. Zhang, X. Jiang *Chem. Commun.* **2015**, *51*, 941–944; d) Y. Li, J. Pu, X. Jiang *Org. Lett.* **2014**, *16*, 2692–2695; e) J. T. Reeves, K. Camara, Z. S. Han, Y. Xu, L. Lee, C. A. Busacca, C. H. Senanayake *Org. Lett.* **2014**, *16*, 1196–1199; f) M. I. Yonova, C. A. Osborne, N. S. Morrissette, E. R. Jarvo *J. Org. Chem.* **2014**, *79*, 1947–1953; g) H. Liu, X. Jiang **2013**, *8*, 2546–2563; h) C. Savarin, J. Srogl, L. S. Liebeskind *Org. Lett.* **2002**, *4*, 4309–4312.

Thus, we developed a convenient preparation of polyfunctional thioesters of type **4** by the reaction of functionalized aryl, heteroaryl, alkyl or benzylic organozinc halides **1** with *N*-thiophthalimides **38**. These *N*-thiophthalimides were conveniently prepared by an optimized literature procedure based on the methods published by Liebeskind[113h] and Chen[114], involving the reaction of commercial *N*-chlorophthalimide **39** with various organic thiols of type **40** (Scheme 44).

5.2 Reaction Opimization

In preliminary experiments, we have examined the effect of a transition metal catalyst on the formation of thioether **1a**. Therefore, 4-anisylzinc chloride (**1rr**) was treated with *N*-(cyclohexylthio)phthalimide (**38a**; 25 °C, 1 h). In the absence of a catalyst, a yield of only 49% of **1a** was obtained (Table 7, entry 1). Catalysis with $FeCl_2$, $CrCl_2$, $Fe(acac)_3$, $CoCl_2$, $NiCl_2$ and $MnCl_2$ (5%) increased this yield up to 72% (entries 2–7). By testing various copper salts such as $CuBr_2$, CuBr, $CuCl_2$, Cu(OAc) and CuCN·2LiCl, we have further increased the yield up to 88% (entries 8–12). However, CuCl and $Cu(OAc)_2{\cdot}H_2O$ were found to give the best results (93–95% yield, entries 13–14).

Table 7. Catalyst screening for the electrophilic thiolation of zinc organometallic **1rr**.



Entry	Catalyst	Yield [%][a]
1	-	49
2	$FeCl_2$	54
3	$CrCl_2$	60
4	$Fe(acac)_3$	63
5	$CoCl_2$	64
6	NiCl	71
7	$MnCl_2$	72
8	$CuBr_2$	74
9	CuBr	79
10	$CuCl_2$	82

[114] J. Qiu, D. Wu, P. G. Karmaker, H. Yin, F.-X. Chen *Org. Lett.* **2018**, *20*, 1600–1603.

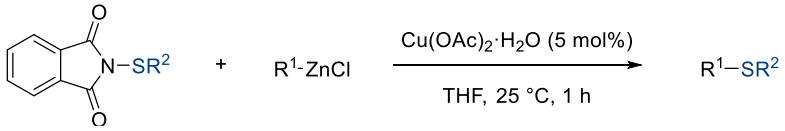
11	Cu(OAc)	88
12	CuCN·2LiCl	88
13	CuCl	93
14	Cu(OAc)·H_2O	95[b]

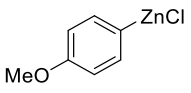
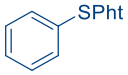
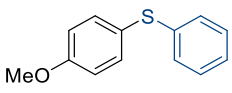
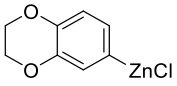
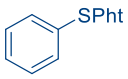
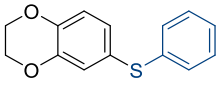
[a] GC yield using undecane as internal standard [b] Isolated yields of analytically pure products

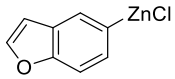
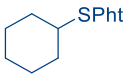
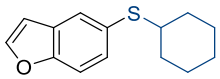
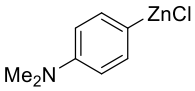
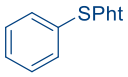
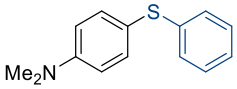
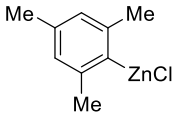
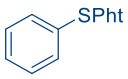
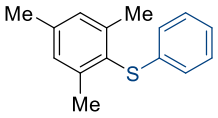
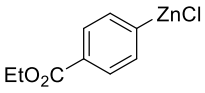
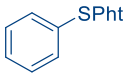
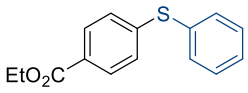
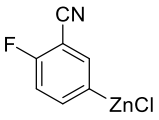
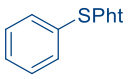
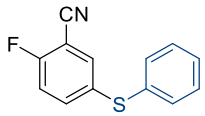
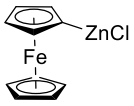
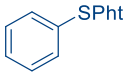
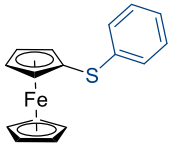
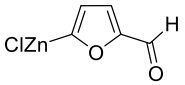
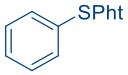
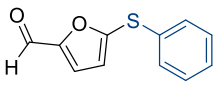
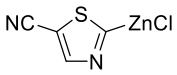
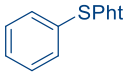
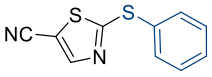
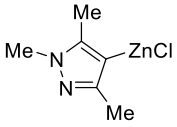
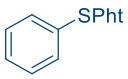
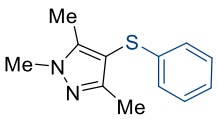
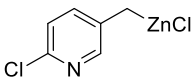
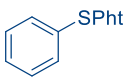
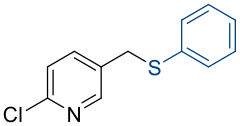
5.3 Scope and Limitations

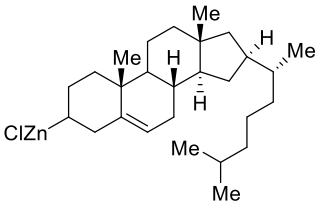
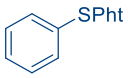
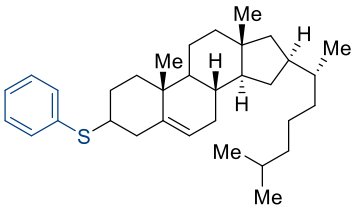
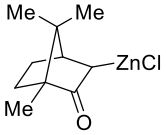
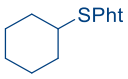
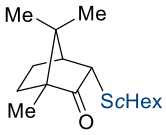
With this optimized procedure, we have examined the scope of organozinc reagents **1**. Thus, the reaction of electron-rich (**1v**, **1rr**, **1vv** , **1ccc** and **1ddd**) as well as electron-poor arylzinc chlorides (**1p** and **1aa**) with *N*-thiophthalimide **38a** or **38b** using 5% $Cu(OAc)_2·H_2O$ provided the desired thioethers **4b**–**4h** in 86–99% yield (Table 8, entries 1–7). Moreover, ferrocenylzinc chloride (**1eee**) was coupled with thiophthalimide **38b**, furnishing the ferrocenyl thioether **4i** in 90% yield (entry 8). Also heteroarylzinc halides **1fff**–**1hhh** underwent an electrophilic thiolation giving the thioethers **4j**–**4l** in 71–94% yield (entries 9–11). Furthermore, alkyl and benzylic zinc halides **1iii**–**1kkk** were successfully coupled with *N*-(phenylthio)phthalimide (**38b**) and *N*-(cyclohexylthio)-phthalimide (**38a**), furnishing the thioethers **4m**–**4o** (entries 12–14). Noteworthy, sensitive functional groups such as nitriles, esters, aldehydes and ketones were tolerated (entries 6, 7, 9, 10 and 14). Also, sterically hindered nucleophiles such as zinc organometallics **1ddd** and **1hhh** gave the desired thioethers **4d** and **4l** in 94–99% yield (entry 5 and 11).

Table 8. Thioethers of type **4** via a copper-catalyzed thiolation of organozinc reagents of type **1** with *N*-thiophthalimides of type **38**.



Entry	Organozinc reagent 1	*N*-Thiophthalimide 38[a]	Product of type 4 [b]
1			
	1rr	**38b**	**4b**: 98%
2			
	1v	**38b**	**4c**: 98%

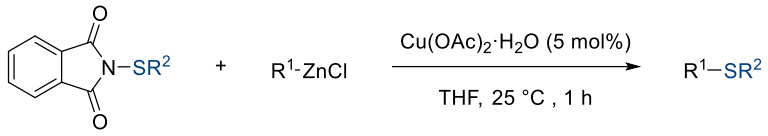
3			
	1ccc	**38a**	**4d**: 90%
4			
	1vv	**38b**	**4e**: 86%
5			
	1ddd	**38b**	**4f**: 99%
6			
	1aa	**38b**	**4g**: 98%
7			
	1p	**38b**	**4h**: 95%
8			
	1eee	**38b**	**4i**: 90%
9			
	1fff	**38b**	**4j**: 89%
10			
	1ggg	**38b**	**4k**: 71%
11			
	1hhh	**38b**	**4l**: 94%
12			
	1iii	**38b**	**4m**: 97%

13			
	1jjj	**38b**	**4n**: 96% (d.r. 71:29)
14			
	1kkk	**38a**	**4o**: 98% (d.r. 97:3)

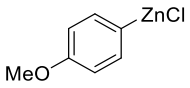
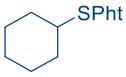
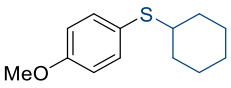
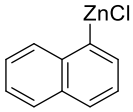
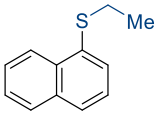
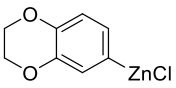
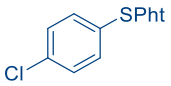
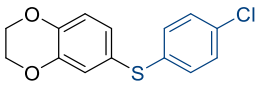
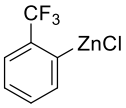
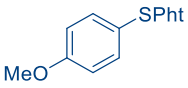
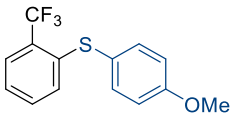
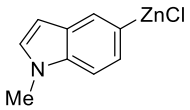
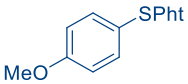
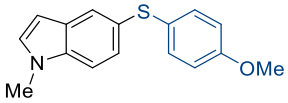
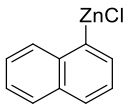
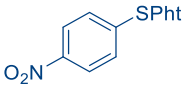
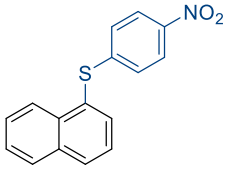
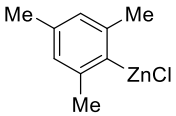
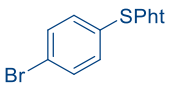
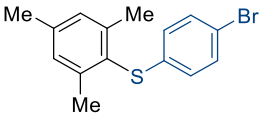
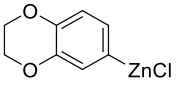
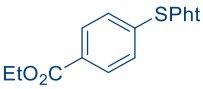
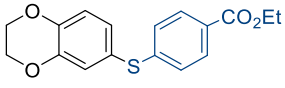
[a] Pht = phthalimide; [b] Isolated yields of analytically pure products.

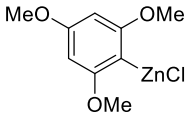
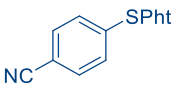
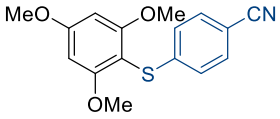
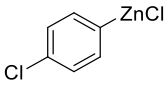
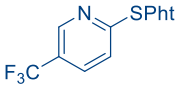
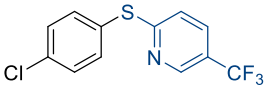
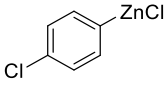
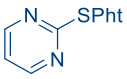
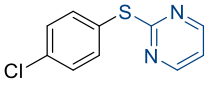
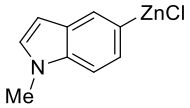
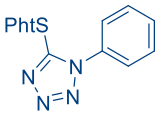
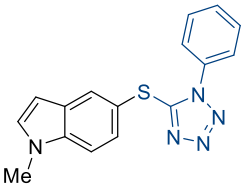
Next, we have investigated the scope of polyfunctional thiophthalimides of type **38**. We have found that both, alkyl and (hetero)aryl thiophthalimides gave excellent results. Therefore, the alkyl thiophthalimides **38a** and **38c** were coupled with arylzinc chlorides **1x** and **1rr** affording thioethers **4a** and **4p** in 71–95% yield (Table 9, entries 1–2). Also various functionalized aryl- and heteroaryl thiophthalimides have been prepared according to the method described above (Scheme 44) and subsequently coupled to form the corresponding thioether of type **1**. Thus, the copper-catalyzed thiolation of organozinc reagents , **1v**–**1y**, **1rr**, **1lll**, **1ddd**, **1mmm** and thiophthalimides **38d**–**38l** led to the expected thiolation products **4p**–**4z** in 55–97% yield (entries 3–12). Electron-rich as well as electron-poor aryl and heteroaryl derivatives can be used for this thiolation. Furthermore, sensitive functional groups such as esters and nitriles attached to the *N*-thiophthalimide were tolerated (entries 8–9). Noteworthy, even highly reactive nitro groups are tolerated with only slightly reduced yields. Thus, the reaction of thiophthalimide **38f** with organozinc chloride **1x** provided thioether **4s** in 55% yield (entry 6).

Table 9. Electrophile scope of electrophilic thioether formation using various *N*-thiophthalimides of type **38**.



38 | **1** (1.1 equiv) | **4**

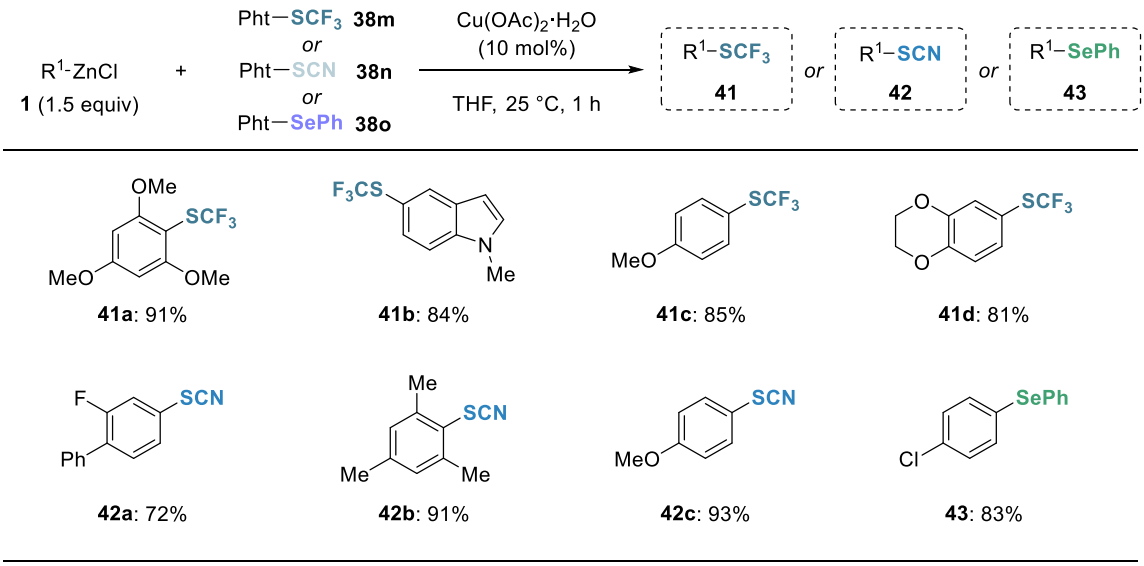
Entry	Zinc reagent 2	Pht–SR 3[a]	Product of type 1[b]
1			
	1rr	**38a**	**4a**: 95%
2			
	1x	**38c**	**4p**: 71%
3			
	1v	**38d**	**4q**: 94%
4			
	1lll	**38e**	**4r**: 97%
5			
	1y	**38e**	**4s**: 96%
6			
	1x	**38f**	**4t**: 55%
7			
	1ddd	**38g**	**4u**: 89%
8			
	1v	**38h**	**4v**: 70%

9			
	1mmm	**38i**	**4w**: 90%
10			
		38j	**4x**: 94%
11			
		38k	**4y**: 85%
12			
	1y	**38l**	**4z**: 81%

[a] Pht = phthalimide; [b] Isolated yields of analytically pure products.

Interestingly, this method was further extended to the introduction of a trifluoromethylthio (SCF_3), a thiocyanate (SCN) as well as a phenylselenyl (SePh) moiety. SCF_3 groups are important bioisosteres to alter the biological activity of drugs, what entails the requirement of elaborated methods for their introduction.[115] Therefore, commercially available *N*-(trifluoromethylthio) phthalimide **38m** was treated with arylzinc halides of type **1** in the presence of 10% $Cu(OAc)_2 \cdot H_2O$ to give the corresponding trifluoromethylthiolated products (**41a**–**41c**) in 78–91% yield (Scheme 45). Next, we have extended the scope to thiocyanates. As expected, the reaction of *N*-thiophthalimide **38n** with arylzinc chlorides of type **1** provided arylthiocyanates **42a**–**42c** in 72–93% yield (Scheme 45). Due to the lower reactivity of these thiophthalimides (**38m**–**38n**), 10% $Cu(OAc)_2 \cdot H_2O$ was necessary. Additionally, we have extended this method to the preparation of selenium compounds. Thus, selenophthalimide (**43**) was treated with 4-chlorophenylzinc chloride (**2s**) to give selenoether **43** in 83% yield (Scheme 45).

[115] a) M. Horvat, M. Jereb, J. Iskra *Eur. J. Org. Chem.* **2018**, 3837–3843; b) S. Barata-Vallejo, S. Bonesi, A. Postigo *Org. Biomol. Chem.* **2016**, *14*, 7150–7182; c) K. Zhang, X. Xu, F. Qing *Chin. J. Org. Chem.* **2015**, *35*, 556–569; d) X. H. Xu, K. Matsuzaki, N. Shibata *Chem. Rev.* **2015**, *115*, 731–764; e) A. B. Durr, G. Yin, I. Kalvet, F. Napoly, F. Schoenebeck *Chem. Sci.* **2016**, *7*, 1076–1081; f) G. Yin, I. Kalvet, U. Englert, F. Schoenebeck *J. Am. Chem. Soc.* **2015**, *137*, 4164–4172; g) S. Alazet, L. Zimmer, T. Billard *Chem. Eur. J.* **2014**, *20*, 8589–8593; h) G. Landelle, A. Panossian, F. R. Leroux *Curr. Top. Med. Chem.* **2014**, *14*, 941–951; i) K. Kang, C. Xu, Q. Shen *Org. Chem. Front.* **2014**, *1*, 294–297; j) J. H. Clark, C. W. Jones, A. P. Kybett, M. A. McClinton, J. M. Miller, D. Bishop, R. J. Blade *J. Fluor. Chem.* **1990**, *48*, 249–253.

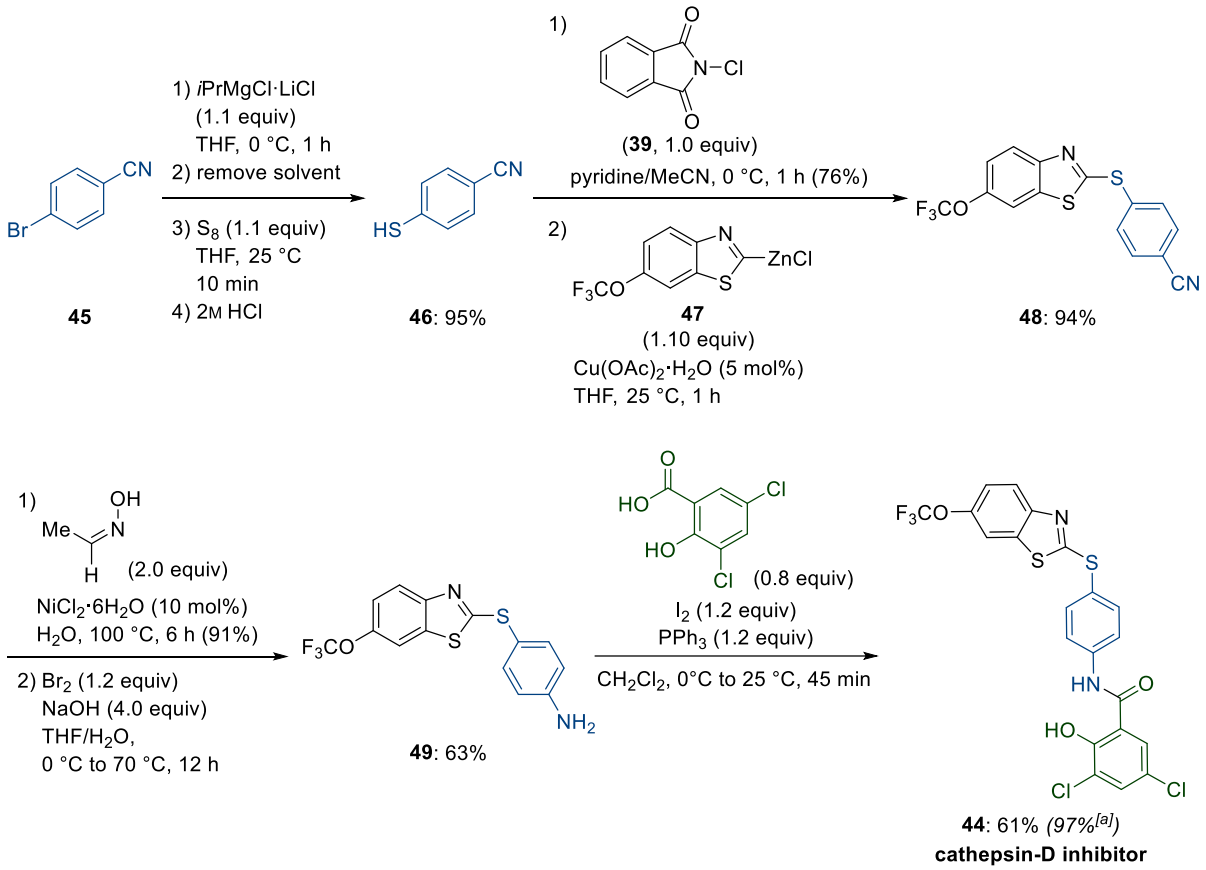


Scheme 45. Preparation of SCF_3, SCN and SePh substituted aryl and heteroaryl derivatives *via* a copper-catalyzed thiolation of arylzinc chlorides.

5.4 Synthesis of a Cathespin-D Inhibitor

To show the utility of this method, we have applied this methodology to a short synthesis of the bioactive cathepsin-D inhibitor **44**[116] starting from 4-bromobenzonitrile **45** (Scheme 46). Thus, the conversion of **45** to the corresponding Grignard reagent was achieved with turbo-Grignard (*i*PrMgCl·LiCl)[72], leading after thiolation with elementary sulphur to the thiol **46** in 95% yield.[11] In this procedure, it was important to remove *i*PrBr under *vacuum* after the Br/Mg-exchange step. Using the above described procedure, thiol **46** was converted to the corresponding *N*-thiophthalimide in 76% yield. A subsequent copper-catalyzed thiolation with heteroarylzinc chloride **47** afforded the desired thioether **48** in 94% yield. Next, the nitrile functionality was hydrolysed using acetaldoxime and $NiCl_2{\cdot}6H_2O$ to provide an intermediate amide in 91% yield.[117] The corresponding aniline derivative **49** was obtained *via* a Hofmann rearrangement (Br_2, NaOH) in 63% yield.[118] Finally, using an iodine/triphenylphosphine-mediated amidation, the desired target **44** was obtained in 61% yield (97% based on recovered starting material).[119]

[116] J. Dumas, D. Brittelli, J. Chen, B. Dixon, H. Hatoum-Mokdad, G. König, R. Sibley, J. Witowsky, S. Wong *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2531–2536.
[117] X. Ma, Y. He, P. Wang, M. Lu *Appl. Organomet. Chem.* **2012**, *26*, 377–382.
[118] J. B. Lambert, D. Stec III *Org. Magn. Reson.* **1984**, *22*, 301–307.
[119] S. Wangngae, C. Duangkamol, M. Pattarawarapan, W. Phakhodee *RSC Adv.* **2015**, *5*, 25789–25793.



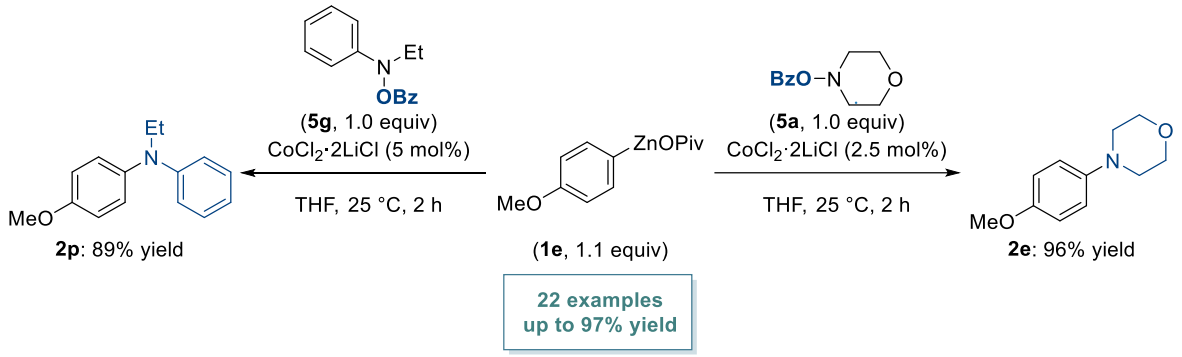
Scheme 46. Synthesis of bioactive cathepsin-D inhibitor **44**; [a] Yield based on recovered starting material.

5.5 Summary

In summary, we have developed a new preparation of thioethers (**4**) from *N*-thiophthalimides **38** *via* a $Cu(OAc)_2 \cdot H_2O$-catalyzed thiolation of organozinc halides **1**. This method has a broad scope, tolerating various reactive functional groups including aldehydes and nitro groups. An extension to the introduction of SCF_3, SCN and SePh groups was also achieved. The utility of the method was shown in a short synthesis of a bioactive cathepsin-D inhibitor **44**.

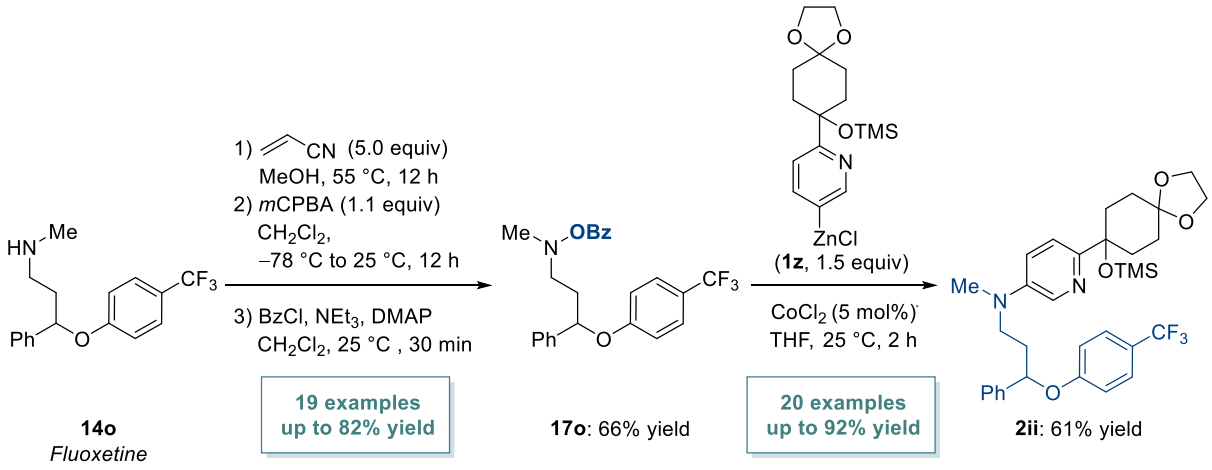
6. Summary

We have devolped various methods to construct either carbon-nitrogen or carbon-sulphur bonds, using organozinc reagents and electrophilic heteroatom sources. In our first approach we aminated aryl- and heteroarylzinc pivalates **1** with *N*-hydroxylamine benzoates **5** at 25 °C within 2–4 h in the presence of 2.5–5% $CoCl_2 \cdot 2LiCl$, furnishing the corresponding tertiary arylated or heteroarylated amines **2** in good yields (Scheme 47). This electrophilic amination provides also an access to diarylamines and aryl(heteroaryl)amines **2**. A new tuberculosis drug candidate (Q203, **7**) was prepared in 6 steps and 56% overall yield using this cobalt-catalyzed amination as the key step.



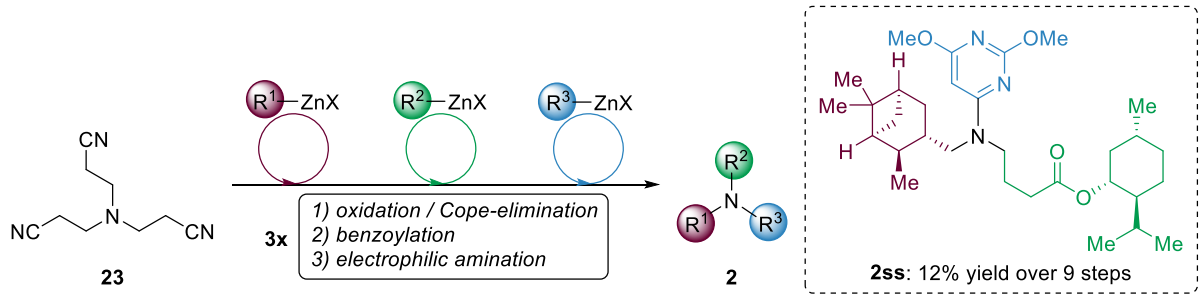
Scheme 47. Electrophilic amination of aryl- and heteroarylzinc pivalates **1** using *N*-hydroxylamine benzoates **5** leading to functionalized tertiary amines **2** (22 examples with up to 97% yield).

Next, to enhace this method, we developed a general preparation of polyfunctional hydroxylamine benzoates **5** from the corresponding secondary amines **14**. This convenient synthesis allows the set-up of a late-stage functionalization of various secondary amines including pharmaceuticals and peptidic derivatives. Thus, a cross-coupling of hydroxylamine benzoates **5** with various alkyl-, aryl- and heteroaryl-zinc chlorides in the presence of 5 mol% $CoCl_2$ (25 °C, 2 h) provides a range of polyfunctional tertiary amines **2** in good yields (Scheme 48). This method has been used to prepare the two drugs penfluridol **15** and gepirone **2v**.



Scheme 48. General preparation of *N*-hydroxylamine benzoates **5** from complex secondary amines **14** and usage in a cobalt-catalyzed electrophilic amination of organozinc chlorides **1**, leading to polyfunctional tertary amines **2** (exemplified on fluoxetine).

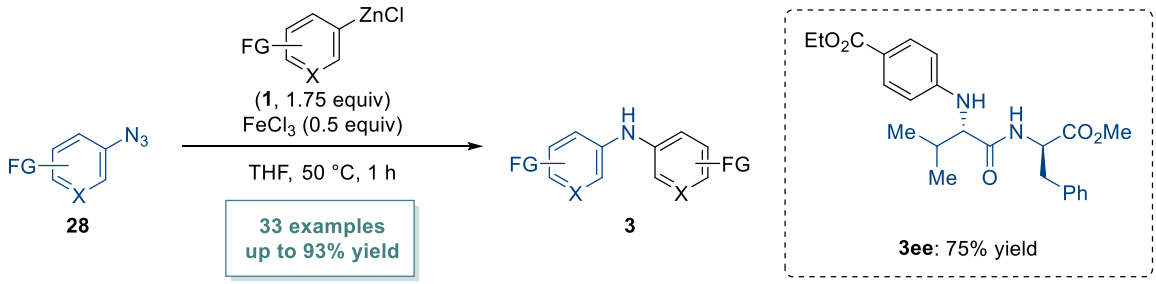
This preparation of hydroxylamines was further developed and applied to a stepwise process to construct triple alkylated or arylated tertiary amines **2**, starting from commercially available tris(2-cyanoethyl)amine **23** using a sequence of a selective oxidation (formation of *N*-oxide followed by a Cope-elimination) leading to a hydroxylamine, a benzoylation and a cobalt-catalyzed electrophilic amination with organozinc halides **1**. Various polyfunctionalized tertiary amines **2** have been prepared in good yields using this method (Scheme 49).



Scheme 49. Iterative sequence to furnish tertiary amines **2** using three different organozinc reagents of type **1** and tris(2-cyanoethyl)amine (**23**) as nitrogen source.

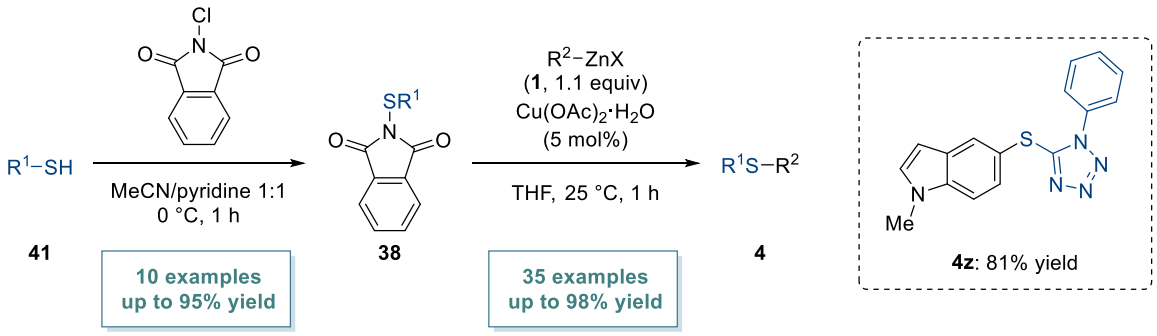
Since the previous described electrophilic amination is limited to the formation of tertiary amines **2**, we developed a complementary procedure to obtain secondary amines **3**. Therefore, a wide range of alkyl-, aryl- and heteroarylzinc halides **1** have been aminated with highly functionalized alkyl, aryl and heterocyclic azides **28** (Scheme 50). The reaction proceeds smoothly at 50 °C within 1 h in the presence of $FeCl_3$ (0.5 equiv) to furnish the corresponding secondary amines **3** in good yields. This method was extended to peptidic azides, providing the

arylated substrates under full retention configuration. To demonstrate the utility of this reaction, we prepared two amine derivatives of pharmaceutical relevance using this iron-mediated electrophilic amination as the key step.



Scheme 50. Electrophlic amination of a wide range of alkyl-, aryl- and heteroarylzinc halides **1** with alkyl, aryl and heterocyclic azides **28** in the presence of $FeCl_3$ (50%), providing highly functionalized secondary amines **3**.

Last, we developed an electrophilic thiolation of (hetero)aryl, benzylic and alkyl zinc halides **1** with *N*-thiophthalimides **38**. The reaction proceeds at 25 °C within 1 h in the presence of $Cu(OAc)_2 \cdot H_2O$ (5–10 mol%) to furnish the corresponding polyfunctionalized thioethers **4** in good yields (Scheme 51). This electrophilic thiolation was extended to the introduction of trifluoromethylthio (SCF_3), thiocyanate (SCN) and selenophenyl (SePh) groups. The utility of this method was shown in a seven step synthesis of a potent cathepsin D inhibitor **44** in 34% overall yield.



Scheme 51. General preparation of *N*-thiophthalimides **38** and their reaction with organozinc reagents **1** to provide thioethers of type **4**.

C. Experimental Section

1. General Considerations

All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over molecular sieves. AcOEt was purchased from Sigma-Aldrich with a purity of 99% and used without distillation or drying prior to use. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by 1H-NMR (25 °C) and capillary GC.

1.1 Solvents

Solvents were dried according to standard procedures by distillation over drying agents and stored under argon.

CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2.

EtOH was treated with phthalic anhydride (25 g/L) and sodium, heated to reflux for 6 h and distilled.

Et_2O was predried over CaH_2 and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

Pyridine was dried over KOH and distilled.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and then stored over molecular sieves.

Solvents for column chromatography were distilled prior to use.

1.2 Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated.

***i*PrMgCl·LiCl** solution in THF was obtained from Albermale.

***n*BuLi** solution in hexane was obtained from Albermale.

Zinc dust (> 98%) was obtained from Sigma Aldrich.

Preparation of $Zn(OPiv)_2$

Pivalic acid (20.4 g, 22.6 mL, 200 mmol, 1.90 equiv) was placed in a dry and argon-flushed 500 mL three-necked round-bottom flask, equipped with a magnetic stirring bar, a septum and a pressure equalizer, and was dissolved in dry THF (120 mL). The mixture was cooled to 0 °C, and a solution of Et_2Zn (13.0 g, 10.8 mL, 105 mmol, 1.00 equiv) in dry THF (120 mL) was cannulated to it over a period of 30 min under vigorous stirring. Then, the ice-bath was removed and stirring continued at 25 °C for one additional hour at which point bubbling was ceased (a thick slurry was formed). The solvent was removed *in vacuo* and the solid residue was dried for at least 4 h. $Zn(OPiv)_2$ was received in quantitative yield, as a puffy amorphous white solid.

Preparation of TMPMgCl·LiCl[120]

In a dry and argon flushed Schlenk-flask TMPH (14.8 g, 105 mmol, 1.05 equiv) was added to *i*PrMgCl·LiCl (71.4 mL, 100 mmol, 1.40 M in THF, 1.00 equiv) at 25 °C and the mixture was stirred overnight at 40 °C. The freshly prepared TMPMgCl·LiCl was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

Preparation of $TMPZnCl{\cdot}Mg(OPiv)_2{\cdot}LiCl$[62d]

A dry and argon flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar, was charged with a solution of TMPMgCl·LiCl (87.7 mL, 100 mmol, 1.00 equiv) and cooled at 0 °C. Then, solid $Zn(OPiv)_2$ (28.1 g, 105 mmol, 1.05 equiv, dried *in vacuo* at 400 °C prior to use) was added in one portion and the mixture was allowed to slowly warm up to 25 °C over ca. 1.5 h. Then THF (ca. 10–20 mL) was added to give $TMPZnCl{\cdot}Mg(OPiv)_2{\cdot}LiCl$ as a bright yellow solution. The freshly prepared $TMPZnCl{\cdot}Mg(OPiv)_2{\cdot}LiCl$ was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

Preparation of $CoCl_2{\cdot}2LiCl$ (1.0 M)

A dry and argon-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and a rubber septum, was charged with anhydrous LiCl (140 mmol, 5.94 g, 2.00 equiv) and heated to 150 °C under high vacuum for 5 h. After cooling to 25 °C under vacuum, anhydrous $CoCl_2$

[120] W. Lin, **O. Ba**ron, P. Knochel, *Org. Let.* 2006, *8*, 5673–5676.

(70.0 mmol, 9.09 g, 1.00 equiv) was added under argon. The Schlenk-flask was further heated to 130 °C for 3 h under high vacuum, cooled to 25 °C and charged with dry THF (70 mL). The mixture was vigorously stirred until all solids were dissolved (ca. 8 h). The reagent $CoCl_2 \cdot 2LiCl$ (1 M in THF) is obtained as a dark blue solution.

1.3 Content Determination of Organometallic Reagents

Titration of Organozinc Reagents Using Iodine

Accurately weighted aliquots of the iodine (50 mg, 0.20 mmol) were dissolved in dry THF (2 mL). To the resulting solution the organozinc reagent was added till complete disappearance of the dark brown colour of iodine. Thus, the concentration of the active species (in mmol/mL) is determined and thereof the yield of the zinc reagent.[121]

Organolithium reagents were titrated against isopropanol using 1,10-phenanthroline as indicator in THF.[122]

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

1.4 Chromatography

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

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

- Seebach's stain: Phosphomolybdic acid (2.5 g), $Ce(SO_4)_2$ (1.0 g), conc. H_2SO_4 (6 mL), H_2O (94 mL).
- $KMnO_4$ stain: $KMnO_4$ (3.0 g), K_2CO_3 (20 g), 5% NaOH solution (5 mL), water (300 mL).

[121] A. Krasovskiy, P. Knochel *Synthesis* **2006**, *5*, 890–891.
[122] H.-S. Lin, A. Paquette, *Synth. Commun.* **1994**, *24*, 2503–2506.

1.5 Analytical Data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 Sand BRUKER AMX 600 instruments in CDCl3 or C6D6 and chemical shifts are reported in parts per million (ppm) relative to the residual solvent peak. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Mass spectroscopy: High resolution (HR-MS) electron impact ionization (EI) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. EI was conducted with an electron energy of 70 eV. Electrospray ionization (ESI) spectra were recorded on a FINNIGAN LTQ FTICR instrument. GCs were recorded on machines of the types Hewlett-Packard 6890 or 5890 Series II (Hewlett Packard, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm; film thickness: 0.25 μm).

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX59343 instrument. For detection a SMITHS DETECTION DuraSamplIR II Diamond ATR sensor was used. The absorption bands are reported in wavenumbers (cm^{-1}). **Melting points (m.p.)** were determined on a BÜCHI B-540 apparatus and are uncorrected.

2. Typical Procedures

2.1 TP1 : Typical Procedure for the Preparation of the Organozinc Pivalates by Halogen-Magnesium Exchange and Subsequent Transmetalation with $Zn(OPiv)_2$

A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the aromatic substrate (5.00 mmol, 1.00 equiv) and dry THF (15 mL). The reaction mixture was put to the appropriate temperature, before *i*PrMgCl·LiCl (4.30 mL, 1.28 M, 5.50 mmol, 1.10 equiv) was added dropwise. The progress of the halogen-magnesium exchange was monitored by GC-analysis of reaction aliquots quenched with aq. sat. NH_4Cl solution and/or I_2. Upon completion of the exchange, solid $Zn(OPiv)_2$ (1.61 g, 6.00 mmol, 1.2 equiv) was added in one portion at 0 °C and the mixture was allowed to slowly warm up to 25 °C. After stirring at ambient temperature for 15 min, the solvent was carefully removed *in vacuo*. The dried material was titrated using iodine solution (1 M in THF) in order to determine its actual content in zinc species and the yield of the reaction.

2.2 TP2: Typical Procedure for the Preparation of the Organozinc Chlorides by Halogen-Magnesium Exchange and Subsequent Transmetalation with $ZnCl_2$

A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the aryl halide (5.00 mmol, 1.00 equiv) and dissolved in dry THF (15 mL). The reaction mixture was set to the appropriate temperature, before *i*PrMgCl·LiCl (4.30 mL, 1.28 M, 5.50 mmol, 1.10 equiv) was added dropwise. The progress of the halogen-magnesium exchange was monitored by GC-analysis of reaction aliquots quenched with aq. sat. NH_4Cl solution and/or I_2. Upon completion of the exchange, $ZnCl_2$ (1 M in THF, 6.00 mL, 6.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C and the mixture was allowed to slowly warm up to 25 °C. After stirring at ambient temperature for 15 min, the mixture was titrated using iodine in order to determine its actual content in zinc species and the yield of the reaction.[123]

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

2.3 TP3: Typical Procedure for the Preparation of the Organozinc Pivalates by Magnesium Insertion and Subsequent Transmetalation with $Zn(OPiv)_2$

A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with magnesium turnings (304 mg, 12.5 mmol, 2.50 equiv), LiCl (318 mg, 7.50 mmol, 1.50 equiv) and THF (15 mL). The aromatic halide (5.00 mmol, 1.00 equiv) was added dropwise. If necessary, the Schlenk-flask was placed in a water bath for cooling during the initial heat evolution of the insertion reaction. The progress of the insertion reaction was monitored by GC-analysis of reaction aliquots quenched with aq. sat. NH_4Cl solution and/or I_2. Upon completion of the insertion, solid $Zn(OPiv)_2$ (1.61 g, 6.00 mmol, 1.20 equiv) was added in one portion. After stirring at ambient temperature for 15 min, the solvent was carefully removed *in vacuo*. The dried material was titrated using iodine solution (1 M in THF) in order to determine its actual content in zinc species and the yield of the reaction.

2.4 TP4: Typical Procedure for the Preparation of the Organozinc Chlorides by Magnesium Insertion and Subsequent Transmetalation with $ZnCl_2$

In a dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) were suspended in dry THF (5 mL). The alkyl or aryl halide (2.50 mmol, 1.00 equiv) was added in one portion and magnesium turnings was activated by gentle heating. After the exothermic reaction started, the reaction mixture was cooled to 25 °C and stirred overnight. Upon completion of the insertion, a solution of $ZnCl_2$ (1.00 M, 3.00 mL, 3.00 mmol, 1.20 equiv) in dry THF was added at 0℃ and the mixture was allowed to slowly warm up to rt. After stirring at ambient temperature for 15 min, the mixture was titrated using iodine in order to determine its actual content in zinc species and the yield of the reaction.[72]

2.5 TP5: Typical Procedure for the Preparation of the Organozinc Chlorides by Magnesium Insertion in the Presence of $ZnCl_2$

A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv), with anhydrous $ZnCl_2$ (409 mg, 3.00 mmol, 1.20 equiv), magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) and suspended in dry THF (5 mL). The aryl halide (2.50 mmol, 1.00 equiv) was added in one portion and the magnesium activated by gentle heating. After the exothermic reaction started, the reaction mixture was cooled to 25 °C and stirred for the indicated time. Upon completion

of the insertion the mixture was titrated using iodine in order to determine its actual content in zinc species and the yield of the reaction.[91]

2.6 TP6: Typical Procedure for the Preparation of the Organozinc halides by Zinc Insertion

A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with anhydrous LiCl (127 mg, 3.00 mmol, 1.20 equiv) and zinc dust (245 mg, 3.75 mmol, 1.50 equiv) and suspended in dry THF (5 mL). Zinc was activated with 1,2-dibromoethane (5 drops) and TMSCl (5 drops). Then, the aryl halide (2.50 mmol, 1.00 equiv) was added in one portion and the reaction mixture was stirred at the appropriate temperature for the indicated time. Upon completion of the insertion the mixture was filtered through a syringe filter and titrated using iodine in order to determine its actual content in zinc species and the yield of the reaction.[21a]

2.7 TP7: Typical Procedure for the Preparation of the Organozinc Pivalates via Direct Metalation Using TMPMgCl·LiCl and Subsequent Transmetalation with $Zn(OPiv)_2$

A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the aromatic substrate (3.00 mmol, 1.00 equiv) and dry THF (9 mL). The reaction mixture was put to the appropriate temperature, before TMPMgCl·LiCl (2.70 mL, 1.23 M, 3.30 mmol, 1.10 equiv) was added dropwise. The progress of the deprotonation was monitored by GC-analysis of reaction aliquots quenched with I_2. Upon completion of the metalation, solid $Zn(OPiv)_2$ (963 mg, 3.60 mmol, 1.20 equiv) was added in one portion and the mixture was allowed to slowly warm up to 25 °C. After stirring at ambient temperature for 15 min, the solvent was carefully removed *in vacuo*. The dried material was titrated using iodine in order to determine its actual content in zinc species and the yield of the metalation.

2.8 TP8: Typical Procedure for the Preparation of the Organozinc Pivalates via Direct Metalation Using TMPZnCl·$Mg(OPiv)_2$·LiCl

A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the aromatic substrate (3.00 mmol, 1.00 equiv) and dry THF (9 mL). The reaction mixture was put to the appropriate temperature, before TMPZnCl·$Mg(OPiv)_2$·LiCl (2.84 mL,

1.16 M, 3.30 mmol, 1.10 equiv) was added dropwise. The progress of the deprotonation was monitored by GC-analysis of reaction aliquots quenched with I_2. Upon completion of the metalation, the solvent was carefully removed *in vacuo*. The dried material was titrated using iodine solution (1 M in THF) in order to determine its actual content in zinc species and the yield of the metalation.

2.9 TP9: Typical Procedure for the Preparation of *N*-Hydroxylamine Benzoate Derivatives of Type 5 using Benzoyl Peroxide

A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with K_2HPO_4 (1.31 g, 7.50 mmol, 1.50 equiv) and anhydrous benzoyl peroxide (1.21 g, 5.00 mmol, 1.00 equiv). The mixture was suspended in DMF (20 mL) and amine (6.00 mmol, 1.20 equiv) was added slowly. The reaction mixture was stirred at room temperature and checked by thin layer chromatography analysis. Upon full consumption of benzoyl peroxide, the reaction was quenched with sat. aqueous NH_4Cl solution (30 mL). The organic layer was removed and the aqueous phase was extracted from EtOAc (3 x 15 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ solution (15 mL), brine (15 mL) and subsequent dried over $mgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the desired products.

2.10 TP10: Typical Procedure for the 1,4-Addition of Acrylonitrile to Secondary Amines

A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with sodium metal (23 mg, 1.00 mmol, 1.00 equiv) and dissolved in dry MeOH (2 mL). In another dry and argon flushed flask equipped with a magnetic stirring bar and a septum, amine hydrochloride **14** (1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (2 mL) and added to the previously prepared sodium methoxide solution. To the resulting solution, acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added and the reaction mixture was stirred at 55 °C overnight. The solvent was evaporated and the resulting crude purified by flash column chromatography to afford the desired product of type **17**.[86a]

In the case of non-hydrochloride amine starting materials, the addition of sodium methoxide is not necessary and can be overleaped.

2.11 TP11: Typical Procedure for the Preparation of *N*-Hydroxylamine Derivatives of Type 16 by Oxidation and Cope-Elimination

A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with 1,4-addition product **17** (1.00 mmol, 1.00 equiv) and dissolved in dry CH_2Cl_2 (2 mL). The solution was cooled to −78 °C and *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was added slowly as a solution in dry CH_2Cl_2 (2 mL). The mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography to afford the desired product.[86a]

2.12 TP12: Typical Procedure for the Electrophilic Amination of Organozinc Pivalates with *N*-Hydroxylamine Derivatives

A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with *N*-hydroxylamine benzoate derivative **5** (0.50 mmol, 1.00 equiv) and THF (2 mL). To the mixture $CoCl_2 \cdot 2LiCl$ (13–25 µmol, 2.5–5.0 mol%) was added as a 1 M solution in THF. Then, presolved organozinc pivalate **1** (0.55 mmol, 1.10 equiv) in THF was added dropwise. The solution was stirred for 2 h at room temperature and the reaction progress checked by thin layer chromatography. Upon completion of starting material (approximately less than 2 h) the reaction was quenched with sat. aqueous NH_4Cl solution (1 mL). The mixture was extracted from EtOAc (3 x 15 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ solution (15 mL), brine (15 mL) and subsequent dried over $mgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the expected products.

2.13 TP13: Typical Procedure for the Electrophilic Amination of Organozinc Chlorides with *N*-Hydroxylamine Derivatives

A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with *N*-hydroxylamine derivative **5** (0.50 mmol, 1.00 equiv) and THF (2 mL). To the mixture pre-dried $CoCl_2$ (3–6 mg, 5.0–10 mol%) was added. Then, organozinc chloride **1** (0.75 mmol, 1.50 equiv) in THF was added dropwise. The solution was stirred for 2 h at 25 °C and the reaction progress checked by thin layer chromatography. Upon completion of starting material (approximately less than 2 h) the reaction was quenched with sat. aqueous NH_4Cl solution (1 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ solution (15 mL), brine (15 mL) and subsequent dried over $mgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the expected products.

2.14 TP14: Typical Procedure for the Electrophilic Amination by Reacting the Organozinc Chlorides with the Azides

In a dry and argon flushed flask equipped with a magnetic stirring bar and a septum the azide (0.50 mmol, 1.0 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then the organozinc chloride (0.875 mmol, 1.75 equiv) were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was finally purified by flash column chromatography.

2.15 TP 15: General Preparation of *N*-thiophthalimides from Their Corresponding Thiol Using *N*-Chlorophthalimide

A dry and argon flushed round bottom flask equipped with a magnetic stirring bar and a septum was charged with *N*-chlorophthalimide (908 mg, 5.00 mmol, 1.00 equiv), dry MeCN (2.6 mL) and pyridine (2.1 mL). The thiol (5.00 mmol, 1.00 equiv) in dry MeCN (2.6 mL) and dry pyridine (2.1 mL) was added dropwise at 0 °C over a period of 30 min and the resulting mixture was stirred for additional 30 min. After removal of most MeCN *in vacuo*, water (20 mL) was added dropwise at 0 °C over 10 min and stirred for a further period of 10 min. Filtration of the resulting suspension and washing of the filtrate with ice cold MeOH (3 × 5 mL) provide the corresponding *N*-thiophthalimide **50** in good yield.

2.16 TP 16: Preparation of Thioethers *via* a $Cu(OAc)_2 \cdot H_2O$ Catalyzed Electrophilic Thiolation of Organozinc Reagents

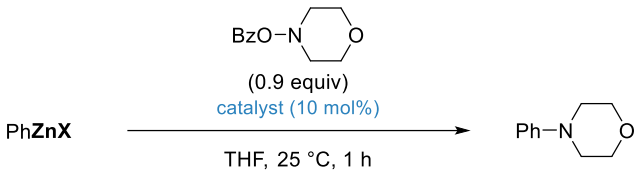
A dry and argon flushed reaction tube equipped with a magnetic stirring bar and a septum was charged with the selected *N*-thiophthalimide **40** (0.50 mmol, 1.00 equiv), $Cu(OAc)_2.H_2O$ (5 mg, 25 μmol, 5.00 mol%) and dry THF (1 mL). The selected organometallic zinc reagent **1** (0.55 mmol, 1.10 equiv) was added dropwise. The reaction mixture was stirred for 1 h at 25 °C and then quenched with *aq. sat.* NH_4Cl. The aqueous phase was extracted with EtOAc (3×30 mL). The combined organic phases were dried over $mgSO_4$ and concentrated *in vacuo*. The crude product was further purified by flash column chromatography on silica gel to provide the desired thioether **4**.

3. Cobalt-Catalyzed Electrophilic Amination of Aryl- and Heteroaryl-Zinc Pivalates with *N*-Hydroxylamine Benzoates

3.1 Comparison of PhZnCl and PhZnOPiv

In order to study the advantage of using organozinc pivalates for cobalt-catalyzed amination, phenylzinc chloride in the presence of $mgCl_2$ and phenylzinc pivalate were used with copper(II) or cobalt(II) as catalysts (Scheme 10). We have noticed that phenylzinc pivalate provided 10–15% more product under both catalysts. The pivalate reduced the amount of homodimer (biphenyl) formation in both cases.

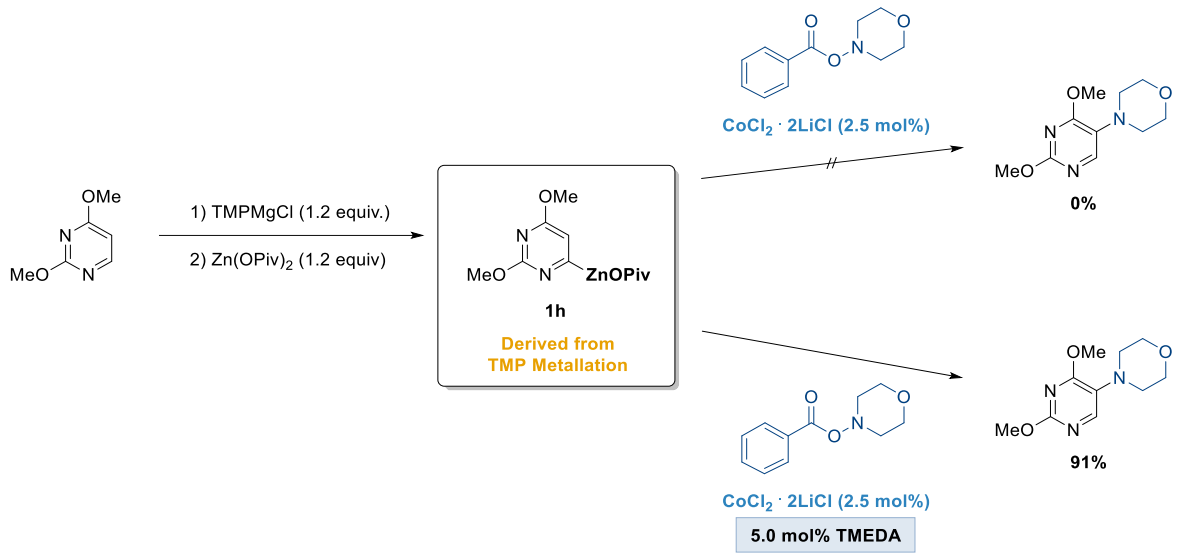
Table 10. Comparison between $PhZnCl \cdot MgCl_2$ and $PhZnCl \cdot Mg(OPiv)_2$ with copper or cobalt catalyst.



PhZnX	catalyst	Product [%]
$PhZnCl \cdot MgCl_2$	$Cu(OTf)_2$	29
$PhZnCl \cdot Mg(OPiv)_2$	$Cu(OTf)_2$	40
$PhZnCl \cdot MgCl_2$	$CoCl_2 \cdot LiCl$	87
$PhZnCl \cdot Mg(OPiv)_2$	$CoCl_2 \cdot LiCl$	98

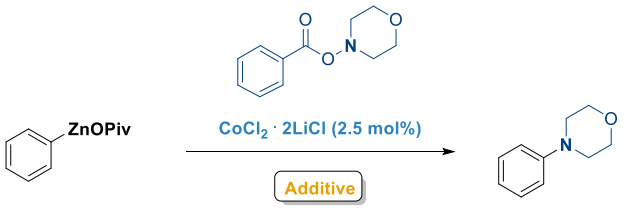
3.2 Investigation of the Effect of TMPH on the Reactivity of Organozinc Pivalate Reagents Derived by Directed Metalation Using TMP-Bases

We have observed, that organozinc pivalates prepared by directed metalation using TMP bases do not undergo the described electrophilic amination, but lead to an undefined mixture of products. However, the addition of 5.0 mol% tetramethylethylenediamine (TMEDA) is sufficient enough to restore the reactivity in the amination procedure (Scheme 52). TMEDA most likely acts as a ligand for the cobalt catalyst and we assume that this metal-ligand coordination protects the catalyst toward desactivation.



Scheme 52. Electrophilic amination of TMP metalation derived organozinc reagent **1h** with and without 5.0 mol% of TMEDA

Further, we performed the reaction of phenylzinc pivalate with *O*-benzoyl hydroxylamine **5a** in the presence of various additives. We observed, that the addition of 4.00 equiv of TMPH do not harm the reaction. Thus, residual TMPH seems not to be the origin for the reduced reactivity. However, the addition of 0.5 equiv TMPMgCl·LiCl also lead to a catalyst desactivation (Scheme 53). In summary, TMEDA coordination to the cobalt centre protects the catalyst if TMPMgCl·LiCl is used to generate the organozinc pivalate.



Entry	Additive	Yield [%]
1	without	98
2	10 mol% TMPH	98
3	4 equiv. TMPH	98
4	0.5 equiv. TMPMgCl	0

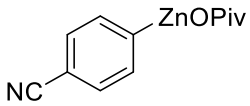
Scheme 53. Background reaction for clarifying the origin of the hindered reactivity.

3.3 Preparation of Organozinc Pivalates

Phenylzinc Pivalate (1a)

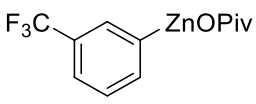
A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with phenylmagnesium chloride (3.21 mL, 1.56 M, 5.00 mmol, 1.00 equiv). Solid $Zn(OPiv)_2$ (1.61 g, 6.00 mmol, 1.20 equiv) was added in one portion while the temperature was maintained at 20 °C with a water bath. After stirring at ambient temperature for 15 min, the solvent was carefully removed *in vacuo* to afford phenylzinc pivalate (**1a**) (3.81 g) as a white solid. Titration with iodine gave 1.26 mmol/g concentration of active zinc species, corresponding to 96% yield.

(4-Cyanophenyl)zinc Pivalate (1b)



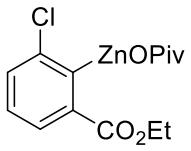
According to **TP1** 4-bromobenzonitrile (910 mg, 5.00 mmol) was dissolved in dry THF (15 mL) and *i*PrMgCl·LiCl (4.30 mL, 1.28 M, 5.50 mmol) was added. After stirring for 12 h at 0 °C solid $Zn(OPiv)_2$ (1.61 g, 6.00 mmol) was added and after evaporation of the solvent the arylzinc pivalate **1b** (2.69 g) was obtained as a yellowish solid. Titration with iodine gave 1.34 mmol/g concentration of active zinc species, corresponding to 72% yield.

(4-(Trifluoromethyl)phenyl)zinc Pivalate (1c)



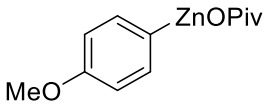
According to **TP1** 1-bromo-3-(trifluoromethyl)benzene (563 mg, 2.50 mmol) was dissolved in dry THF (7.5 mL) and *i*PrMgCl·LiCl (2.15 mL, 1.28 M, 2.75 mmol) was added. After stirring for 4 h at 25 °C solid $Zn(OPiv)_2$ (803 mg, 3.00 mmol) was added and after evaporation of the solvent the arylzinc pivalate **1c** (2.25 g) was obtained as a yellowish solid. Titration with iodine gave 1.01 mmol/g concentration of active zinc species, corresponding to 91% yield.

(2-(Ethoxycarbonyl)-6-chlorophenyl)zinc Pivalate (1d)



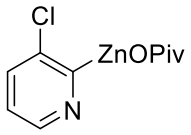
According to **TP7**, ethyl 3-chlorobenzoate (554 mg, 3.00 mmol) in dry THF (9 mL) was treated with TMPMgCl·LiCl (2.68 mL, 1.23 M, 3.30 mmol) for 6 h at 0 °C. After transmetalation with solid $Zn(OPiv)_2$ (963 mg, 3.60 mmol) and careful evaporation of the solvent the arylzinc pivalate **1d** (2.33 g) was obtained as a pale orange solid. Titration with iodine gave 1.20 mmol/g concentration of active zinc species, corresponding to 93% yield.

(4-Methoxyphenyl)zinc Pivalate (1e)



According to **TP1** 1-iodo-4-methoxybenzene (1.17 g, 5.00 mmol) was dissolved in dry THF (15 mL) and *i*PrMgCl·LiCl (4.30 mL, 1.28 M, 5.50 mmol) was added. After stirring for 30 min at 0 °C solid $Zn(OPiv)_2$ (1.61 g, 6.00 mmol) was added and after evaporation of the solvent the arylzinc pivalate **1e** (4.22 g) was obtained as a white solid. Titration with iodine gave 1.09 mmol/g concentration of active zinc species, corresponding to 92% yield.

(3-Chloropyridin-2-yl)zinc Pivalate (1f)

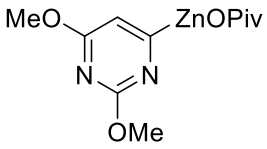


According to **TP7** 3-chloro-2-iodopyridine (837 mg, 3.00 mmol) was dissolved in dry THF (15 mL) and treated with TMPMgCl·LiCl (2.68 mL, 1.23 M, 3.30 mmol) for 6 h at 0 °C. After transmetalation with solid $Zn(OPiv)_2$ (963 mg, 3.60 mmol) and careful evaporation of the solvent heteroarylzinc pivalate **1f** (4.83 g) was obtained as a brownish solid. Titration with iodine gave 0.89 mmol/g concentration of active zinc species, corresponding to 86% yield.

Benzo[*b*]thiophen-3-ylzinc Pivalate (1g)

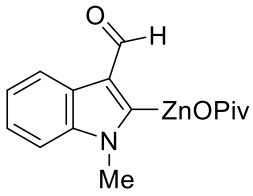
According to **TP3** 3-bromobenzo[*b*]thiophene (1.07 g, 5.00 mmol) was added to mixture of magnesium turnings (304 mg, 12.5 mmol), LiCl (318 mg, 7.50 mmol) and dry THF (15 mL). After stirring for 3 h at 25 °C solid $Zn(OPiv)_2$ (1.61 g, 6.00 mmol) was added and after evaporation of the solvent the arylzinc pivalate **1g** (4.89 g) was obtained as a yellow solid. Titration with iodine gave 0.93 mmol/g concentration of active zinc species, corresponding to 93% yield.

(2,6-Dimethoxypyrimidin-4-yl)zinc Pivalate (1h)



According to **TP7**, 2,6-dimethoxypyrimidine (420 mg, 3.00 mmol) in dry THF (9 mL) was treated with TMPMgCl·LiCl (2.68 mL, 1.23 M, 3.30 mmol) for 30 min at 25 °C. After transmetalation with solid $Zn(OPiv)_2$ (963 mg, 3.60 mmol) and careful evaporation of the solvent the heteroarylzinc pivalate **1h** (2.18 g) was obtained as a brown solid. Titration with iodine gave 1.17 mmol/g concentration of active zinc species, corresponding to 85% yield.

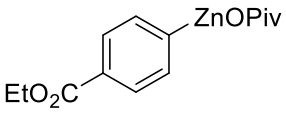
(3-Formyl-1-methyl-1*H*-indol-2-yl)zinc Pivalate (1i)



According to **TP8** 1-methyl-1*H*-indole-3-carbaldehyde (318 mg, 2.00 mmol) in dry THF (6 mL) reacted with TMPZnCl·$Mg(OPiv)_2$·LiCl (1.90 mL, 1.16 M, 2.20 mmol) at 25 °C and stirred at this temperature for 30 min. After solvent removal *in vacuo* heteroarylzinc pivalate

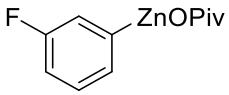
1i (2.06 g) was obtained as a yellow solid. Titration with iodine gave 0.85 mmol/g concentration of active zinc species, corresponding to 88% yield.

(4-(Ethoxycarbonyl)phenyl)zinc Pivalate (1j)



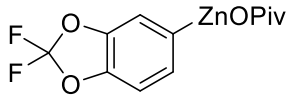
According to **TP1** ethyl 4-iodobenzoate (1.38 g, 5.00 mmol) was dissolved in dry THF (15 mL) and *i*PrMgCl·LiCl (4.30 mL, 1.28 M, 5.50 mmol) was added. After stirring for 30 min at -30 °C solid $Zn(OPiv)_2$ (1.61 g, 6.00 mmol) was added and after evaporation of the solvent the arylzinc pivalate **1j** (3.77 g) was obtained as a yellowish solid. Titration with iodine gave 1.22 mmol/g concentration of active zinc species, corresponding to 92% yield.

(3-Fluorophenyl)zinc Pivalate (1k)



According to **TP1** 1-fluoro-3-iodobenzene (1.11 g, 5.00 mmol) was dissolved in 15 mL of dry THF and *i*PrMgCl·LiCl (4.30 mL, 1.28 M, 5.50 mmol) was added. After stirring for 30 min at -30 °C solid $Zn(OPiv)_2$ (1.61 g, 6.00 mmol) was added and after evaporation of the solvent the arylzinc pivalate **1k** (3.73 g) was obtained as a pale grey solid. Titration with iodine gave 1.26 mmol/g concentration of active zinc species, corresponding to 94% yield.

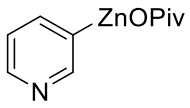
(2,2-Difluorobenzo[*d*][1,3]dioxol-5-yl)zinc Pivalate (1l)



According to **TP1** 5-bromo-2,2-difluorobenzo[*d*][1,3]dioxole (1.19 g, 5.00 mmol) was dissolved in dry THF (15 mL) and *i*PrMgCl·LiCl (4.30 mL, 1.28 M, 5.50 mmol) was added. After stirring for 5 h at room temperature, solid $Zn(OPiv)_2$ (1.61 g, 6.00 mmol) was added and after evaporation of the solvent the arylzinc pivalate **1l** (4.13 g) was obtained as a pale grey

solid. Titration with iodine gave 0.98 mmol/g concentration of active zinc species, corresponding to 81% yield.

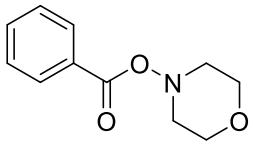
(Pyridin-3-yl)zinc Pivalate (1m)



According to **TP1** 3-bromopyridine (790 mg, 5.00 mmol) was dissolved in dry THF (15 mL) and *i*PrMgCl·LiCl (4.30 mL, 1.28 M, 5.50 mmol) was added. After stirring for 4 h at room temperature, solid $Zn(OPiv)_2$ (1.61 g, 6.00 mmol) was added and after evaporation of the solvent the arylzinc pivalate **1m** (3.78 g) was obtained as a pale grey solid. Titration with iodine gave 1.19 mmol/g concentration of active zinc species, corresponding to 90% yield.

3.4 Preparation of *N*-Hydroxylamine Benzoate Derivatives

4-Benzoyloxy-morpholine (5a)



According to **TP9** dry benzoyl peroxide (1.21 g, 5.00 mmol) and K_2HPO_4 (1.31 g, 7.50 mmol) were suspended in dry DMF (20 mL). Morpholine (523 mg, 6.00 mmol) was slowly added and the resulting mixture was stirred for 3 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 1:1) afforded the title compound as a pale white solid (623 mg, 3.05 mmol, 61%).

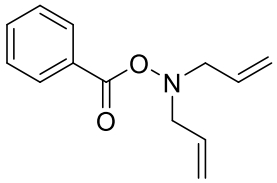
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03–7.98 (m, 2H), 7.60–7.54 (m, 1H), 7.47–7.41 (m, 2H), 4.03–3.82 (m, 4H), 3.45 (d, *J* = 10.0 Hz, 2H), 3.10–2.99 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.6, 133.2, 129.4 (2C), 129.1, 128.5 (2C), 65.9 (2C), 57.0 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3334, 3322, 3312, 2958, 2932, 2902, 2862, 1738, 1636, 1602, 1578, 1538, 1490, 1452, 1436, 1378, 1308, 1292, 1256, 1248, 1178, 1168, 1156, 1102, 1084, 1066, 1048, 1024, 1008, 858, 804, 708, 694, 678.

m.p. (°C): 65.7–69.8.

***N*,*N*-Diallyl-*O*-benzoylhydroxylamine (5b)**



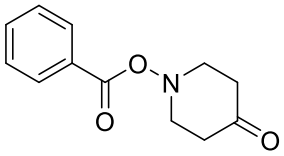
According to **TP9** dry benzoyl peroxide (1.21 g, 5.00 mmol) and K_2HPO_4 (1.31 g, 7.50 mmol) were suspended in dry DMF (20 mL). Diallylamine (583 mg, 6.00 mmol) was slowly added and the resulting mixture stirred for 6 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 4:1) afforded the title compound as a yellow oil (684 mg, 3.15 mmol, 63%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.00–7.91 (m, 2H), 7.50 (tt, *J* = 7.5, 1.9 Hz, 1H), 7.38 (dd, *J* = 8.4, 7.1 Hz, 2H), 5.98 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 2H), 5.23 (dq, *J* = 17.2, 1.5 Hz, 2H), 5.14 (dq, *J* = 10.3, 1.2 Hz, 2H), 3.62 (dt, *J* = 6.8, 1.3 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.2, 132.9, 132.5 (2C), 129.3 (2C), 129.1, 128.3 (2C), 119.4 (2C), 61.6 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3080, 2984, 2838, 1738, 1646, 1602, 1450, 1436, 1416, 1314, 1280, 1238, 1176, 1082, 1062, 1024, 988, 922, 860, 818, 798, 706, 686.

4-Oxopiperidin-1-yl Benzoate (5c)



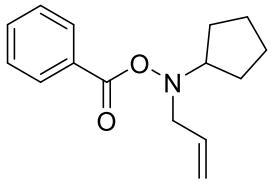
According to **TP9** dry benzoyl peroxide (1.21 g, 5.00 mmol) and K_2HPO_4 (1.31 g, 7.50 mmol) were suspended in dry DMF (20 mL). Piperidin-4-one (595 mg, 6.00 mmol) was slowly added and the resulting mixture stirred for 48 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 1:1) afforded the title compound as a colourless oil (307 mg, 1.40 mmol, 28%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05–8.00 (m, 2H), 7.63–7.58 (tt, *J* = 7.5, 1.3 Hz 1H), 7.5–7.44 (m, 2H), 3.57 (s, 4H), 2.71 (t, *J* = 6.3 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 206.1, 164.6, 133.5, 129.5 (2C), 128.8 128.6 (2C), 55.4 (2C), 38.6 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972, 2846, 1716, 1600, 1450, 1412, 1366, 1348, 1314, 1274, 1242, 1212, 1178, 1148, 1110, 1082, 1060, 1024, 998, 870, 764, 706, 688, 668.

_N_-Allyl-_O_-benzoyl-_N_-cyclopentylhydroxylamine (5d)



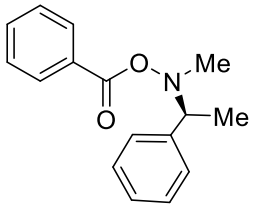
According to **TP9** dry benzoyl peroxide (1.21 g, 5.00 mmol) and K_2HPO_4 (1.31 g, 7.50 mmol) were suspended in dry DMF (20 mL). *N*-allylcyclopentanamine (751 mg, 6.00 mmol) was slowly added and the resulting mixture stirred for 6 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a colourless oil (920 mg, 3.75 mmol, 75%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.01–7.96 (m, 2H), 7.53 (tt, *J* = 7.6, 1.8 Hz 1H), 7.44–7.38 (m, 2H), 6.02 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.20 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.11 (dq, *J* = 10.2, 1.2 Hz, 1H), 3.72–3.54 (m, 2H), 3.47 (p, *J* = 7.5 Hz, 1H), 1.89–1.50 (m, 8H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.6, 133.0, 132.9, 129.4 (2C), 129.3, 128.4 (2C), 119.2, 68.3, 61.3, 29.8 (2C), 24.6 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2960, 2870, 1740, 1450, 1314, 1258, 1238, 1176, 1082, 1060, 1024, 992, 972, 922, 816, 798, 706, 688, 672.

(*S*)-*O*-Benzoyl-*N*-methyl-*N*-(1-phenylethyl)hydroxylamine (5e)



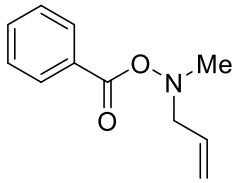
According to **TP9** dry benzoyl peroxide (1.21 g, 5.00 mmol) and K_2HPO_4 (1.31 g, 7.50 mmol) were suspended in dry DMF (20 mL). (*S*)-*N*-methyl-1-phenylethan-1-amine (811 mg, 6.00 mmol) was slowly added and the resulting mixture stirred for 3 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 3:2) afforded the title compound as a colourless oil (574 mg, 2.25 mmol, 45%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.97–7.86 (m, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.48–7.39 (m, 4H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.31–7.25 (m, 1H), 4.09 (q, *J* = 6.6 Hz, 1H), 2.83 (s, 3H), 1.54 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.2, 141.4, 132.9, 129.4 (2C), 128.6, 128.4 (2C), 128.4 (2C), 127.8 (2C), 127.7, 68.7, 44.4, 20.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 3032, 2980, 1740, 1700, 1684, 1602, 1494, 1452, 1372, 1314, 1248, 1192, 1176, 1080, 1060, 1024, 1004, 916, 868, 760, 702, 672.

_N_-Allyl-_O_-benzoyl-_N_-methylhydroxylamine (5f)



According to **TP9** dry benzoyl peroxide (1.21 g, 5.00 mmol) and K_2HPO_4 (1.31 g, 7.50 mmol) were suspended in dry DMF (20 mL). *N*-methylprop-2-en-1-amine (427 mg, 6.00 mmol) was slowly added and the resulting mixture stirred for 6 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 6:1) afforded the title compound as a brownish oil (717 mg, 3.75 mmol, 75%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94 (d, *J* = 8.5 Hz, 2H), 7.53–7.46 (m, 1H), 7.41–7.34 (m, 2H), 6.01–5.89 (m, 1H), 5.27–5.11 (m, 2H), 3.58 (d, *J* = 6.6 Hz, 2H), 2.84 (d, *J* = 1.6 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.0, 132.9, 132.4, 129.3 (2C), 128.3 (2C), 127.9, 119.3, 63.8, 46.1.

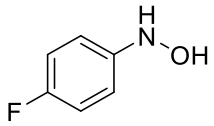
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3072, 2968, 2880, 1736, 1602, 1450, 1314, 1264, 1244, 1204, 1176, 1086, 1056, 1024, 994, 976, 926, 862, 814, 796, 706, 688, 678.

3.5 Preparation of *N*-Hydroxylaniline Derivatives

Additional Information

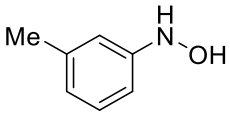
All *O*-hydroxylaniline derivatives of type **5** are not stable at room temperature and will decompose within minutes. Thus, all samples were dried at 0 °C *in vacuo* and instantly after solvent removal resolved in dry THF to obtain a stock solution of known concentration. In solution all prepared *N*-hydroxylaniline derivatives of type **5** are sufficiently stable at 0 °C (at least for 2 weeks).

N-(4-Fluorophenyl)hydroxylamine[71b]



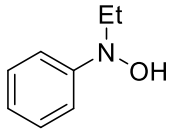
A flask equipped with a magnetic stirring bar and a septum was charged with NH_4Cl (1.07 g, 20.0 mmol, 1.00 equiv) and 1-fluoro-4-nitrobenzene (2.82 g, 20.0 mmol, 1.00 equiv). The mixture was suspended in water (50 mL) and zinc dust (1.44 g, 22.0 mmol, 1.10 equiv) was added slowly. The reaction mixture was stirred for 40 min at 70 °C and subsequent filtered through a glass frit. The filtrate was extracted from diethyl ether (3 x 35 mL) and the combined organic layers were dried over $mgSO_4$. Evaporation of the solvents *in vacuo* gave the crude product as brown solid. The title compound was used without further purification.

N-(*m*-Tolyl)hydroxylamine[71a]



A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with 5% rhodium on activated aluminium oxide (105 mg, 0.30 mol% Rh) and 1-methyl-3-nitrobenzene (686 mg, 5.00 mmol, 1.00 equiv). The mixture was suspended in dry THF (10 mL) and hydrazine monohydrate (300 mg, 6.0 mmol, 1.2 equiv) was added dropwise while maintaining the temperature below 0 °C. The reaction mixture was stirred for 20 min at 0 °C and subsequent filtered through kieselguhr. The filtrate was concentrated *in vacuo* to give the crude product as yellow solid. The title compound was used without further purification.

_N_-Ethyl-_N_-phenylhydroxylamine



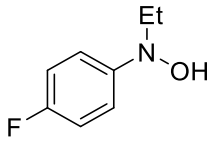
A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with *N*-phenylhydroxylamine (327 mg, 3.00 mmol, 1.00 equiv) and dissolved in dry methanol (10 mL). Acetaldehyde (264 mg, 6 mmol, 2.00 equiv) was added at 0 °C. The resulting mixture was stirred for 5 min at 0 °C and subsequent $NaBH_4$ (114 mg, 3.00 mmol, 1.00 equiv) was added. The suspension was stirred at 0 °C and checked by thin layer chromatography analysis. After full consumption of starting material (after 45 min) the reaction was quenched with sat. aqueous NH_4Cl solution (10 mL). The organic layer was removed and the aqueous phase was extracted from EtOAc (3 x 10 mL). The combined organic layers were dried over $mgSO_4$ and concentrated *in vacuo*. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a yellow oil (249 mg, 1.82 mmol, 61%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33–7.27 (m, 2H), 7.19–7.14 (m, 2H), 7.02 (tt, *J* = 7.2, 1.2 Hz, 1H), 6.84 (s, 1H), 3.32 (q, *J* = 7.0 Hz, 2H), 1.20 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 152.5, 128.7 (2C), 122.7, 117.4 (2C), 54.3, 11.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3240, 3064, 2974, 2938, 2874, 1596, 1488, 1452, 1378, 1222, 1128, 1076, 1058, 1030, 910, 756, 732, 692.

***N*-Ethyl-*N*-(4-fluorophenyl)hydroxylamine**



A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with crude *N*-(4-fluorophenyl)hydroxylamine (324 mg, 2.55 mmol, 1.00 equiv) and dissolved in dry methanol (10 mL). Acetaldehyde (225 mg, 5.10 mmol, 2.00 equiv) was added at 0 °C. The resulting mixture was stirred for 5 min at 0 °C and subsequent $NaBH_4$ (96 mg, 2.55 mmol, 1.00 equiv) was added. The suspension was stirred at 0 °C and checked by thin layer chromatography analysis. After full consumption of starting material (after 1 h) the reaction was quenched with sat. aqueous NH_4Cl solution (10 mL). The organic layer was removed and the aqueous phase was extracted from EtOAc (3 x 10 mL). The combined organic layers were dried over $mgSO_4$ and concentrated *in vacuo*. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a colourless oil (253 mg, 1.63 mmol, 64%).

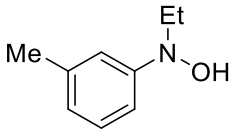
^{1}H-NMR (400 MHz, Acetone-*d*$_6$): δ / ppm = 7.95 (s, 1H), 7.17–7.11 (m, 2H), 7.03–6.97 (m, 2H), 3.29 (q, *J* = 7.0 Hz, 2H), 1.15 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, Acetone-*d*$_6$): δ / ppm = 157.65 (d, *J* = 236.9 Hz), 150.23 (d, *J* = 2.2 Hz), 117.68 (d, *J* = 7.7 Hz, 2C), 114.67 (d, *J* = 22.3 Hz, 2C), 53.24 , 10.79.

^{19}F NMR (377 MHz, Acetone-*d*$_6$): δ / ppm = -126.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2978, 2348, 2308, 2174, 1988, 1720, 1598, 1494, 1384, 1376, 1072, 756, 694.

_N_-Ethyl-_N_-(_m_-tolyl)hydroxylamine



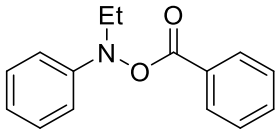
A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with crude *N*-(*m*-tolyl)hydroxylamine (554 mg, 4.50 mmol, 1.00 equiv) and dissolved in dry methanol (10 mL). Acetaldehyde (396 mg, 9.00 mmol, 2.00 equiv) was added at 0 °C. The resulting mixture was stirred for 5 min at 0 °C and subsequent $NaBH_4$ (170 mg, 4.50 mmol, 1.00 equiv) was added. The suspension was stirred at 0 °C and checked by thin layer chromatography analysis. After full consumption of starting material (after 1 h) the reaction mixture was quenched with sat. aqueous NH_4Cl solution (10 mL). The organic layer was removed and the aqueous phase was extracted from EtOAc (3 x 10 mL). The combined organic layers were dried over $mgSO_4$ and concentrated *in vacuo*. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 4:1) afforded the title compound as a colourless oil (447 mg, 2.88 mmol, 64%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.17 (t, *J* = 7.8 Hz, 1H), 7.02–6.90 (m, 2H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.12 (s, 1H), 3.32 (q, *J* = 7.0 Hz, 2H), 2.33 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 150.0, 138.7, 128.5, 125.0, 118.8, 115.1, 53.4, 21.6, 11.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2988, 1752, 1712, 1614, 1607, 1586, 1575, 1503 1489, 1454, 1338, 1276, 1251, 1203, 1120, 1103, 1081, 904, 819, 789, 768, 705, 627.

_O_-Benzoyl-_N_-ethyl-_N_-phenylhydroxylamine (5g)



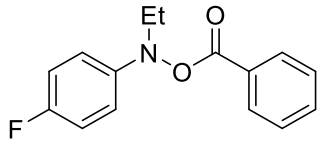
A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with *N*-ethyl-*N*-phenylhydroxylamine (249 mg, 1.82 mmol, 1.00 equiv) and dissolved in dry dichloromethane (10 mL). Triethylamine (184 mg, 1.82 mmol, 1.00 equiv) was added at 0 °C. The resulting mixture was stirred for 5 min at 0 °C and subsequent benzoyl chloride (256 mg, 1.82 mmol, 1.00 equiv) was added. The solution was stirred at 0 °C and checked by thin layer chromatography analysis. After full consumption of starting material (after 1.5 h) the reaction mixture was quenched with sat. aqueous NH_4Cl solution (10 mL). The organic layer was removed and the aqueous phase was extracted from EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (neutral alumina, isohexane/EtOAc = 9:1) afforded the title compound as a colourless oil (229 mg, 0.95 mmol, 52%).

^{1}H-NMR (400 MHz, Acetone-d_6): δ / ppm = 8.16–8.12 (m, 2H), 7.70 (tt, *J* = 7.0, 1.3 Hz 1H), 7.61–7.55 (m, 2H), 7.37–7.31 (m, 2H), 7.16–7.11 (m, 2H), 7.18 (tt, *J* = 7.5, 1.0 Hz, 1H), 3.65 (q, *J* = 7.0 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, Acetone-d_6): δ / ppm = 165.0, 151.4, 134.4, 130.3 (3C), 129.9 (2C), 129.8 (2C), 124.4, 118.4 (2C), 53.5, 11.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 2982, 2940, 1748, 1598, 1586, 1490, 1450, 1382, 1316, 1294, 1240, 1178, 1160, 1134, 1100, 1078, 1054, 1024, 1002, 862, 756, 708, 694, 672.

_O_-Benzoyl-_N_-ethyl-_N_-(4-fluorophenyl)hydroxylamine (5h)



A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with *N*-ethyl-*N*-(4-fluorophenyl)hydroxylamine (253 mg, 1.63 mmol, 1.00 equiv) and dissolved in dry dichloromethane (10 mL). Triethylamine (165 mg, 1.63 mmol, 1.00 equiv) was added at 0 °C. The resulting mixture was stirred for 5 min at 0 °C and subsequent benzoyl chloride (229 mg, 1.63 mmol, 1.00 equiv) was added. The solution was stirred at 0 °C and checked by thin layer chromatography analysis. After full consumption of starting material (after 1.5 h) the reaction was quenched with sat. aqueous NH_4Cl solution (10 mL). The organic layer was removed and the aqueous phase was extracted from EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (neutral alumina, isohexane/EtOAc = 9:1) afforded the title compound as a pale yellow oil (246 mg, 0.95 mmol, 58%).

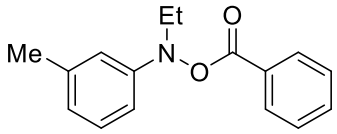
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.01–7.96 (m, 2H), 7.78 (tt, *J* = 7.6, 2.0 Hz, 1H), 7.61–7.54 (m, 2H), 6.92–6.86 (m, 2H), 6.66–6.61 (m, 2H), 3.10 (q, *J* = 6.4 Hz, 2H), 1.25 (t, *J* = 6.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.1, 162.5 (d, *J* = 251 Hz), 147.6, 133.4, 129.6 (2C), 129.1 (2C), 127.4, 119.5 (d, *J* = 8.5 Hz, 2C), 114.8 (d, *J* = 8.3 Hz, 2C), 48.0, 13.0.

^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = -125.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 2978, 1614, 1574, 1522, 1508, 1448, 1436, 1422, 1380, 1318, 1292, 1258, 1156, 1122, 976, 852, 790, 700.

_O_-Benzoyl-_N_-ethyl-_N_-(m-tolyl)hydroxylamine (5i)



A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with _N_-ethyl-_N_-(m-tolyl)hydroxylamine (447 mg, 2.88 mmol, 1.00 equiv) and dissolved in dry dichloromethane (10 mL). Triethylamine (291 mg, 2.88 mmol, 1.00 equiv) was added at 0 °C. The resulting mixture was stirred for 5 min at 0 °C and subsequent benzoyl chloride (405 mg, 2.88 mmol, 1.00 equiv) was added. The solution was stirred at 0 °C and checked by thin layer chromatography analysis. After full consumption of starting material (after 1.5 h) the reaction was quenched with sat. aqueous NH_4Cl solution (10 mL). The organic layer was removed and the aqueous phase was extracted from EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated _in vacuo_. Purification of the crude product by flash chromatography (neutral alumina, isohexane/EtOAc = 9.5:0.5) afforded the title compound as a yellow oil (398 mg, 1.56 mmol, 54%).

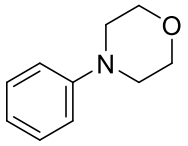
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15–8.10 (m, 2H), 7.62 (tt, _J_ = 7.5, 1.8 Hz, 1H), 7.52–7.47 (m, 2H), 7.23–7.17 (m, 1H), 7.01–6.96 (m, 2H), 6.91 (d, _J_ = 7.6 Hz, 1H), 3.61 (q, _J_ = 7.0 Hz, 2H), 2.33 (s, 3H), 1.26 (t, _J_ = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.0, 150.1, 138.8, 133.4, 129.7 (2C), 128.9, 128.8, 128.6 (2C), 125.1, 118.9, 115.2, 53.5, 21.7, 11.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 2936, 1742, 1700, 1624, 1616, 1602, 1576, 1560, 1518, 1488, 1450, 1408, 1378, 1316, 1286, 1242, 1204, 1178, 1166, 1128, 1104, 1080, 1056, 1024, 906, 818, 780, 728, 708, 672.

3.6 Preparation of Amination Products of type 2

4-Phenylmorpholine (2a)



According to **TP12** 4-benzoyloxy-morpholine (**5a**, 104 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) was added and subsequent phenylzinc pivalate (**1a**, 437 mg, 1.26 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a colourless oil (76 mg, 0.47 mmol, 93%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.30 (t, *J* = 7.9 Hz, 2H), 6.97–6.87 (m, 3H), 3.88 (t, *J* = 5.3 Hz, 4H), 3.17 (t, *J* = 4.9 Hz, 4H).

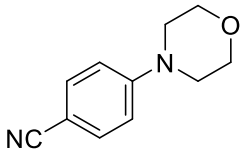
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.2, 129.2 (2C), 120.1, 115.8 (2C), 66.9 (2C), 49.4 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964, 2892, 2856, 2824, 1624, 1616, 1600, 1578, 1560, 1496, 1450, 1418, 1406, 1380, 1364, 1332, 1304, 1262, 1234, 1122, 1068, 926, 758, 740, 722, 692.

MS (EI, 70 eV): *m/z* (%) = 163 (56), 132 (21), 105 (100), 77 (54).

HRMS (EI): *m/z* calc. for [$C_{10}H_{13}NO$]: 163.0997; found 163.0992.

4-Morpholinobenzonitrile (2b)



According to **TP12** 4-benzoyloxy-morpholine (**5a**, 104 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) was added and subsequent (4-cyanophenyl)zinc pivalate (**1b**, 410 mg, 1.34 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (88 mg, 0.47 mmol, 93%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.57–7.45 (m, 2H), 6.89–6.82 (m, 2H), 3.84 (t, *J* = 5.3 Hz, 4H), 3.27 (t, *J* = 5.1 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 153.5, 133.5 (2C), 119.9, 114.1 (2C), 100.9, 66.5 (2C), 47.3 (2C).

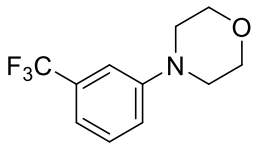
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2974, 2926, 2898, 2872, 2858, 2832, 2216, 1604, 1516, 1452, 1440, 1384, 1364, 1306, 1296, 1266, 1244, 1222, 1196, 1180, 1112, 1074, 1062, 1048, 1026, 1006, 926, 852, 834, 814, 782, 718, 680.

MS (EI, 70 eV): *m/z* (%) = 188 (49), 129 (100), 101 (33).

HRMS (EI): *m/z* calc. for [$C_{11}H_{12}N_2O$]: 188.0950; found 188.0944.

m.p. (°C): 120.8–121.4.

4-(3-(Trifluoromethyl)phenyl)morpholine (2c)



According to **TP12** 4-benzoyloxy-morpholine (**5a**, 104 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) was added and subsequent (4-(trifluoromethyl)phenyl)zinc pivalate (**1c**, 545 mg, 1.01 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (114 mg, 0.50 mmol, 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.39 (td, *J* = 8.1, 0.9 Hz, 1H), 7.16–7.12 (m, 2H), 7.08 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.87 (t, *J* = 4.8 Hz, 4H), 3.20 (t, *J* = 4.8 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.4, 131.5 (q, *J* = 31.8 Hz), 129.6, 124.3 (d, *J* = 272.4 Hz), 118.5, 116.2 (q, *J* = 3.8 Hz), 111.9 (q, *J* = 3.9 Hz), 66.7 (2C), 48.7 (2C).

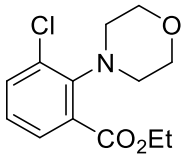
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3332, 1712, 1698, 1638, 1610, 1590, 1496, 1448, 1354, 1320, 1310, 1294, 1266, 1236, 1162, 1116, 1100, 1074, 994, 948, 860, 786, 728, 696.

MS (EI, 70 eV): *m/z* (%) = 231 (65), 173 (100), 145 (27), 57 (12).

HRMS (EI): *m/z* calc. for [$C_{11}H_{12}F_3NO$]: 231.0871; found 231.0865.

m.p. (°C): 55.1 - 58.8.

Ethyl 3-chloro-2-morpholinobenzoate (2d)



According to **TP12** 4-benzoyloxy-morpholine (**5a**, 104 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) and tetramethylethylenediamine (3.7 µL, 5.0 mol%) was added and subsequent (2-(ethoxycarbonyl)-6-chlorophenyl)zinc pivalate (**1d**, 458 mg, 1.20 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a yellowish oil (109 mg, 0.50 mmol, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.46 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.39 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.79 (t, *J* = 4.8 Hz, 4H), 3.16 (t, *J* = 4.8 Hz, 4H), 1.41 (t, *J* = 7.1 Hz, 3H).

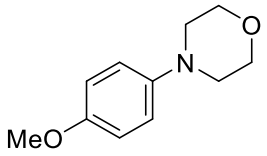
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 168.4, 146.4, 133.9, 133.0, 132.6, 128.2, 125.0, 67.8 (2C), 61.8, 50.4 (2C), 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2966, 2858, 2254, 1722, 1460, 1444, 1374, 1288, 1268, 1250, 1228, 1208, 1148, 1110, 1044, 940, 904, 724.

MS (EI, 70 eV): *m/z* (%) = 269 (26), 240 (68), 182 (100).

HRMS (EI): *m/z* calc. for [$C_{13}H_{16}ClNO_3$]: 269.0819; found 269.0822.

4-(4-Methoxyphenyl)morpholine (2e)



According to **TP12** 4-benzoyloxy-morpholine (**5a**, 104 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) was added and subsequent (4-methoxyphenyl)zinc pivalate (**1e**, 505 mg, 1..09 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (93 mg, 0.48 mmol, 96%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.94–6.84 (m, 4H), 3.87 (t, *J* = 4.8 Hz, 4H), 3.77 (s, 3H), 3.06 (t, *J* = 4.8 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.0, 145.5, 117.9 (2C), 114.5 (2C), 67.0, 55.6 (2C), 50.9 (2C).

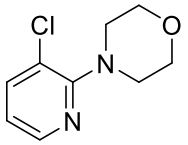
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972, 2908, 2888, 2854, 2836, 2816, 1724, 1674, 1512, 1464, 1452, 1424, 1382, 1364, 1330, 1292, 1264, 1244, 1228, 1214, 1184, 1172, 1152, 1118, 1068, 1052, 1028, 926, 860, 850, 816, 806, 796, 716, 702.

MS (EI, 70 eV): *m/z* (%) = 193 (71), 135 (100), 120 (59), 71 (14).

HRMS (EI): *m/z* calc. for [$C_{11}H_{15}NO_2$]: 193.1103; found 193.1088.

m.p. (°C): 61.9–65.2.

4-(3-Chloropyridin-2-yl)morpholine (2f)



According to **TP12** 4-benzoyloxy-morpholine (**5a**, 104 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) and tetramethylethylenediamine (3.7 µL, 5.0 mol%) was added and subsequent (3-chloropyridin-2-yl)zinc pivalate (**1f**, 618 mg, 0.89 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (98 mg, 0.50 mmol, 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.18 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.58 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.85 (dd, *J* = 7.7, 4.7 Hz, 1H), 3.85 (t, *J* = 4.6 Hz, 4H), 3.35 (t, *J* = 4.9 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.2, 145.9, 138.9, 122.7, 118.2, 66.9 (2C), 49.5 (2C).

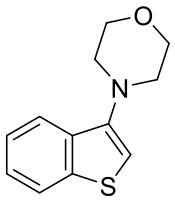
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2960, 2900, 2854, 1574, 1464, 1450, 1428, 1422, 1366, 1344, 1322, 1308, 1276, 1268, 1258, 1246, 1236, 1224, 1212, 1156, 1108, 1082, 1070, 1046, 1032, 940, 924, 908, 846, 798, 778, 760, 696.

MS (EI, 70 eV): *m/z* (%) = 198 (44), 140 (69), 23 (100).

HRMS (EI): *m/z* calc. for [$C_9H_{11}ClN_2O$]: 198.0560; found 198.0554.

m.p. (°C): 132.1–132.8.

4-(Benzo[*b*]thiophen-3-yl)morpholine (2g)



According to **TP12** 4-benzoyloxy-morpholine (**5a**, 104 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) was added and subsequent benzo[*b*]thiophen-3-ylzinc pivalate (**1g**, 591 mg, 0.93 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 12 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a yellowish oil (92 mg, 0.42 mmol, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.79 (ddd, *J* = 20.0, 6.7, 2.6 Hz, 2H), 7.41–7.33 (m, 2H), 6.64 (s, 1H), 3.95 (t, *J* = 4.8 Hz, 4H), 3.15 (t, *J* = 4.9 Hz, 4H).

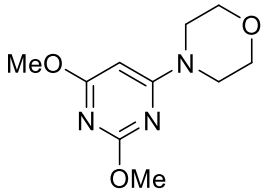
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 146.7, 139.4, 134.4, 124.7, 123.7, 123.4, 121.8, 107.3, 67.1 (2C), 52.9 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2918, 2890, 2854, 2822, 1520, 1450, 1430, 1368, 1356, 1282, 1260, 1190, 1116, 1020, 902, 760, 736.

MS (EI, 70 eV): *m/z* (%) = 219 (71), 161 (50), 111 (26), 57 (100).

HRMS (EI): *m/z* calc. for [$C_{12}H_{13}NOS$]: 219.0718; found 219.0706.

4-(2,6-Dimethoxypyrimidin-4-yl)morpholine (2h)



According to **TP12** 4-benzoyloxy-morpholine (**5a**, 104 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) and tetramethylethylenediamine (3.7 µL, 5.0 mol%) was added and subsequent (2,6-dimethoxypyrimidin-4-yl)zinc pivalate (**1h**, 470 mg, 1.17 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (102 mg, 0.46 mmol, 91%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.00 (s, 1H), 3.65 (s, 3H), 3.64 (s, 3H), 3.52–3.48 (t, *J* = 5.1 Hz, 4H), 3.29 (t, *J* = 5.3 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.5, 164.4, 163.8, 78.3, 65.5 (2C), 53.2, 52.6, 43.6 (2C).

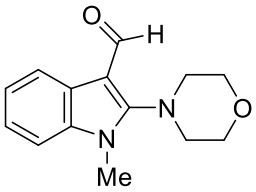
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2924, 2854, 1586, 1494, 1460, 1378, 1312, 1280, 1272, 1084, 910, 878, 840, 786, 686.

MS (EI, 70 eV): *m/z* (%) = 225 (94), 168 (100), 105 (84), 77 (26).

HRMS (EI): *m/z* calc. for [$C_{10}H_{15}N_3O_3$]: 225.1113; found 225.1110.

m.p. (°C): 184.3–190.1.

1-Methyl-2-morpholino-1*H*-indole-3-carbaldehyde (2i)



According to **TP12** 4-benzoyloxy-morpholine (**5a**, 104 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) and tetramethylethylenediamine (3.7 µL, 5.0 mol%) was added and subsequent (3-formyl-1-methyl-1*H*-indol-2-yl)zinc pivalate (**1i**, 647 mg, 0.85 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (99 mg, 0.40 mmol, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 10.33 (s, 1H), 8.30–8.24 (m, 1H), 7.31–7.21 (m, 3H), 3.91 (t, *J* = 4.4 Hz, 4H), 3.67 (s, 3H), 3.42 (t, *J* = 4.4 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 183.3, 154.9, 134.9, 125.2, 123.3, 123.0, 121.4, 109.3, 108.7, 67.4 (2C), 52.7 (2C), 29.9.

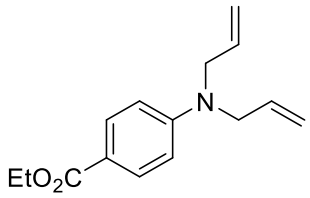
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964, 2890, 2852, 1634, 1610, 1580, 1526, 1470, 1444, 1414, 1394, 1362, 1326, 1310, 1264, 1250, 1114, 1068, 1040, 978, 864, 810, 750, 740.

MS (EI, 70 eV): *m/z* (%) = 244 (87), 227 (100), 158 (60).

HRMS (EI): *m/z* calc. for [$C_{14}H_{16}N_2O_2$]: 244.1212; found 244.1199.

m.p. (°C): 198.1–200.5.

Ethyl 4-(diallylamino)benzoate (2j)



According to **TP12** *N*,*N*-diallyl-*O*-benzoylhydroxylamine (**5b**, 109 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) was added and subsequent (4-(ethoxycarbonyl)phenyl)zinc pivalate (**1j**, 451 mg, 1.22 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (106 mg, 0.44 mmol, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.90–7.85 (m, 2H), 6.69–6.62 (m, 2H), 5.84 (ddt, *J* = 17.1, 9.9, 4.7 Hz, 2H), 5.22–5.11 (m, 4H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.97 (dt, *J* = 4.1, 1.7 Hz, 4H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.7, 151.7, 132.5 (2C), 131.1 (2C), 117.5, 116.2 (2C), 110.8 (2C), 59.9, 52.4 (2C), 14.3.

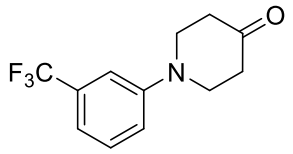
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2904, 1698, 1602, 1522, 1446, 1394, 1366, 1316, 1276, 1236, 1182, 1106, 1024, 990, 946, 920, 830, 770, 700.

MS (EI, 70 eV): *m/z* (%) = 245 (100), 218 (62), 200 (44), 130 (56).

HRMS (EI): *m/z* calc. for [$C_{15}H_{19}NO_2$]: 245.1416; found 245.1411.

m.p. (°C): 101.3–104.1.

1-(3-(Trifluoromethyl)phenyl)piperidin-4-one (2k)



According to **TP12** 4-oxopiperidin-1-yl benzoate (**5c**, 109 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) was added and subsequent (4-(trifluoromethyl)phenyl)zinc pivalate (**1c**, 545 mg, 1.01 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a yellow oil (106 mg, 0.44 mmol, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 (t, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 2.1 Hz, 1H), 7.04 (dd, *J* = 8.2, 2.1 Hz, 2H), 3.59 (t, *J* = 6.1 Hz, 4H), 2.51 (t, *J* = 6.1 Hz, 4H).

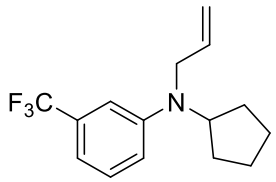
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 207.6, 149.3, 131.8 (q, *J* = 31.9 Hz), 130.0, 124.1 (q, *J* = 271.9 Hz), 118.5, 116.01 (q, *J* = 3.8 Hz), 111.89 (q, *J* = 3.9 Hz), 48.2 (2C), 40.5 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972, 2908, 2834, 1716, 1610, 1588, 1496, 1452, 1412, 1386, 1354, 1322, 1220, 1162, 1118, 1100, 1074, 1038, 994, 940, 858, 810, 784, 722, 696, 656.

MS (EI, 70 eV): *m/z* (%) = 243 (100), 200 (46), 173 (96), 145 (40).

HRMS (EI): *m/z* calc. for [$C_{12}H_{12}F_3NO$]: 243.0871; found 243.0865.

_N_-Allyl-_N_-cyclopentyl-3-(trifluoromethyl)aniline (2l)



According to **TP12** *N*-allyl-*O*-benzoyl-*N*-cyclopentylhydroxylamine (**5d**, 123 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) was added and subsequent (4-(trifluoromethyl)phenyl)zinc pivalate (**1c**, 545 mg, 1.01 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a colourless oil (105 mg, 0.39 mmol, 78%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.26 (s, 1H), 6.94 (s, 1H), 6.88 (dt, *J* = 8.7, 4.5 Hz, 2H), 5.88 (ddt, *J* = 17.2, 10.4, 4.1 Hz, 1H), 5.26–5.13 (m, 2H), 4.16 (h, *J* = 7.7, 7.1 Hz, 1H), 3.84 (dt, *J* = 4.3, 1.9 Hz, 2H), 2.05–1.90 (m, 2H), 1.82–1.46 (m, 6H).

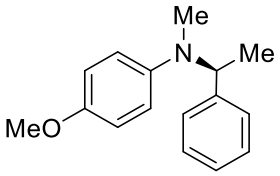
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 150.1, 135.4, 131.6 (q, *J* = 31.3 Hz), 129.4, 124.73 (q, *J* = 272.4 Hz), 116.3, 115.7, 112.54 (q, *J* = 3.9 Hz), 109.45 (q, *J* = 4.0 Hz), 59.4, 48.7, 29.4 (2C), 24.0 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2872, 1610, 1586, 1498, 1456, 1398, 1368, 1322, 1312, 1246, 1186, 1160, 1116, 1076, 1018, 988, 958, 918, 870, 850, 778, 736, 696, 662.

MS (EI, 70 eV): *m/z* (%) = 269 (42), 240 (100), 145 (38), 69 (17).

HRMS (EI): *m/z* calc. for [$C_{15}H_{18}F_3N$]: 269.1391; found 269.1389.

(*S*)-4-Methoxy-*N*-methyl-*N*-(1-phenylethyl)aniline (2m)



According to **TP12** (*S*)-*O*-benzoyl-*N*-methyl-*N*-(1-phenylethyl)hydroxylamine (**5e**, 128 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) was added and subsequent (4-methoxyphenyl)zinc pivalate (**1e**, 505 mg, 1.09 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (117 mg, 0.49 mmol, 97%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.36 (d, *J* = 4.3 Hz, 4H), 7.32–7.26 (m, 1H), 6.88 (s, 4H), 4.94 (q, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 2.64 (s, 3H), 1.53 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 128.3 (2C), 127.8, 127.1 (2C), 126.9, 116.3, 114.6 (4C), 114.2, 58.6, 55.7, 32.9, 16.2.

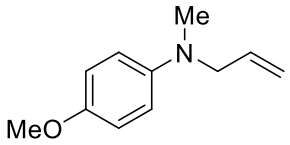
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972, 2936, 2834, 1686, 1510, 1464, 1450, 1372, 1244, 1180, 1110, 1038, 816, 784, 754, 702.

MS (EI, 70 eV): *m/z* (%) = 241 (100), 226 (83), 164 (15), 136 (56), 105 (74).

HRMS (EI): *m/z* calc. for [$C_{16}H_{19}NO$]: 241.1467; found 241.1460.

m.p. (°C): 110.9–111.4.

***N*-Allyl-4-methoxy-*N*-methylaniline (2n)**



According to **TP12** *N*-allyl-*O*-benzoyl-*N*-methylhydroxylamine (**5f**, 96 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (13 µL, 1.00 M, 2.5 mol%) was added and subsequent (4-methoxyphenyl)zinc pivalate (**1e**, 505 mg, 1.09 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a brownish oil (79 mg, 0.45 mmol, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.86–6.81 (m, 2H), 6.76–6.70 (m, 2H), 5.85 (ddt, *J* = 17.2, 10.2, 5.4 Hz, 1H), 5.24–5.11 (m, 2H), 3.85–3.82 (m, 2H), 3.76 (s, 3H), 2.86 (s, 3H).

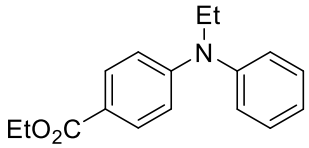
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.7, 144.5, 134.3, 116.6, 114.7 (2C) 114.7 (2C), 56.6, 55.8, 38.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936, 2910, 2832, 1678, 1664, 1512, 1464, 1454, 1442, 1296, 1276, 1244, 1210, 1182, 1040, 824, 814.

MS (EI, 70 eV): *m/z* (%) = 177 (100), 162 (40), 150 (55), 136 (56), 121 (12).

HRMS (EI): *m/z* calc. for [$C_{11}H_{15}NO$]: 177.1154; found 177.1150.

Ethyl 4-(ethyl(phenyl)amino)benzoate (2o)



According to **TP12** *O*-benzoyl-*N*-ethyl-*N*-phenylhydroxylamine (**5g**, 1.00 mL, 0.50 M, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (25 µL, 1.00 M, 5.0 mol%) was added and subsequent (4-(ethoxycarbonyl)phenyl)zinc pivalate (**1j**, 451 mg, 1.22 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (135 mg, 0.45 mmol, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.87 (dt, *J* = 9.1, 2.8 Hz, 2H), 7.46–7.40 (m, 2H), 7.28–7.20 (m, 3H), 6.73 (dt, *J* = 8.9, 2.0 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.83 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.8, 151.6, 146.0, 131.1 (2C), 129.9 (2C), 126.9 (2C), 125.6, 119.0, 113.6 (2C), 60.2, 46.7, 14.5, 12.5.

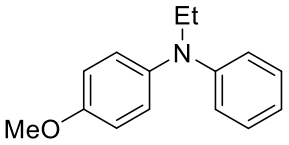
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2984, 2944, 2908, 2208, 1736, 1650, 1480, 1466, 1448, 1394, 1372, 1300, 1234, 1182, 1160, 1098, 1044, 1004, 938, 918, 846, 786.

MS (EI, 70 eV): *m/z* (%) = 269 (65), 254 (100), 167 (12).

HRMS (EI): *m/z* calc. for [$C_{17}H_{19}NO_2$]: 269.1416; found 269.1411.

m.p. (°C): 135.5–136.2.

_N_-Ethyl-4-methoxy-_N_-phenylaniline (2p)



According to **TP12** *O*-benzoyl-*N*-ethyl-*N*-phenylhydroxylamine (**5g**, 1.00 mL, 0.50 M, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (25 µL, 1.00 M, 5.0 mol%) was added and subsequent (4-methoxyphenyl)zinc pivalate (**1e**, 505 mg, 1.09 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (90 mg, 0.40 mmol, 79%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.20–7.14 (m, 2H), 7.11–7.06 (dt, *J* = 9.1, 2.6 Hz, 2H), 6.93–6.88 (dt, *J* = 8.8, 2.4 Hz, 2H), 6.76–6.71 (m, 3H), 3.82 (s, 3H), 3.70 (q, *J* = 7.1 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.5, 148.7, 140.3, 129.0 (2C), 127.7 (2C), 117.6, 115.3 (2C), 114.8 (2C), 55.5, 46.5, 12.6.

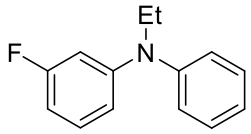
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930, 2872, 2364, 1738, 1598, 1508, 1500, 1466, 1444, 1372, 1268, 1240, 1100, 1040, 748, 732.

MS (EI, 70 eV): *m/z* (%) = 227 (73), 212 (100).

HRMS (EI): *m/z* calc. for [$C_{15}H_{17}NO$]: 227.1310; found 227.1299.

m.p. (°C): 105.2–107.1.

***N*-Ethyl-3-fluoro-*N*-phenylaniline (2q)**



According to **TP12** *O*-benzoyl-*N*-ethyl-*N*-phenylhydroxylamine (**5g**, 1.00 mL, 0.50 M, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (25 µL, 1.00 M, 5.0 mol%) was added and subsequent (3-fluorophenyl)zinc pivalate (**1k**, 437 mg, 1.26 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (90 mg, 0.42 mmol, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.30–7.24 (m, 2H), 7.09–7.01 (m, 4H), 6.52 (dd, *J* = 8.0, 2.6 Hz, 1H), 6.49–6.39 (m, 2H), 3.68 (q, *J* = 7.1 Hz, 2H), 1.15 (q, *J* = 7.6, 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.80 (d, *J* = 242.9 Hz), 149.72 (d, *J* = 10.3 Hz), 146.8, 130.01 (d, *J* = 10.1 Hz), 129.6 (2C), 124.7 (2C), 123.8, 112.7, 105.42 (d, *J* = 21.5 Hz), 104.01 (d, *J* = 25.1 Hz), 46.6, 12.6.

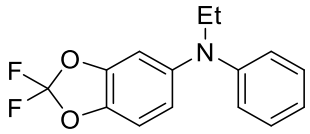
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1732, 1614, 1590, 1578, 1492, 1448, 1374, 1348, 1268, 1244, 1186, 1162, 1126, 1096, 1046, 996, 964, 904, 848, 834, 726, 702, 686.

MS (EI, 70 eV): *m/z* (%) = 215 (50), 200 (100).

HRMS (EI): *m/z* calc. for [$C_{14}H_{14}FN$]: 215.1110; found 215.1099.

m.p. (°C): 72.3–72.8.

_N_-Ethyl-2,2-difluoro-_N_-phenylbenzo[_d_][1,3]dioxol-5-amine (2r)



According to **TP12** *O*-benzoyl-*N*-ethyl-*N*-phenylhydroxylamine (**5g**, 1.00 mL, 0.50 M, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (25 µL, 1.00 M, 5.0 mol%) was added and subsequent (2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)zinc pivalate (**1l**, 561 mg, 0.98 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crzude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (91 mg, 0.33 mmol, 66%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.29–7.23 (m, 2H), 6.97–6.89 (m, 4H), 6.75 (d, *J* = 2.2 Hz, 1H), 6.70 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.72 (q, *J* = 7.1 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 147.7, 144.4, 138.8, 131.8 (t, *J* = 254.2 Hz), 129.4 (2C), 121.0, 119.8 (2C), 116.9, 109.7, 104.6, 46.9, 12.6.

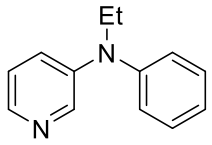
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3164, 3006, 2944, 2294, 2254, 1636, 1534, 1508, 1498, 1444, 1422, 1376, 1274, 1202, 1038, 984, 918, 886, 830, 782, 750.

MS (EI, 70 eV): *m/z* (%) = 277 (19), 262 (36), 151 (18).

HRMS (EI): *m/z* calc. for [$C_{15}H_{13}F_2NO_2$]: 277.0917; found 277.0911.

m.p. (°C): 180.2–182.8.

_N_-Ethyl-_N_-phenylpyridin-3-amine (2s)



According to **TP12** *O*-benzoyl-*N*-ethyl-*N*-phenylhydroxylamine (**5g**, 1.00 mL, 0.50 M, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (25 µL, 1.00 M, 5.0 mol%) was added and subsequent (pyridin-3-yl)zinc pivalate (**1m**, 462 mg, 1.19 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a brownish solid (31 mg, 0.16 mmol, 31%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.20 (d, *J* = 2.5 Hz, 1H), 8.02 (dd, *J* = 4.5, 1.4 Hz, 1H), 7.30–7.24 (m, 2H), 7.12–7.00 (m, 5H), 3.71 (q, *J* = 7.1 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 147.3, 146.6, 145.5, 144.2, 129.3 (2C), 124.8, 123.9, 123.5 (2C), 120.3, 43.1, 14.6.

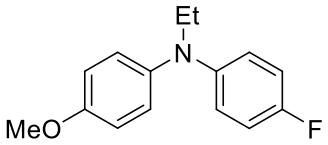
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2966, 2956, 2924, 2854, 1710, 1704, 1600, 1580, 1566, 1494, 1424, 1376, 1348, 1268, 1262, 1246, 1134, 1094, 1062, 794, 754, 710, 700.

MS (EI, 70 eV): *m/z* (%) = 198 (51), 183 (100), 105 (25), 77 (24).

HRMS (EI): *m/z* calc. for [$C_{13}H_{14}N_2$]: 198.1157; found 198.1160.

m.p. (°C): 117.2–120.1.

***N*-Ethyl-4-fluoro-*N*-(4-methoxyphenyl)aniline (2t)**



According to **TP12** *O*-benzoyl-*N*-ethyl-*N*-(4-fluorophenyl)hydroxylamine (**5h**, 1.00 mL, 0.50 M, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (25 µL, 1.00 M, 5.0 mol%) was added and subsequent (4-methoxyphenyl)zinc pivalate (**1e**, 505 mg, 1.09 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (96 mg, 0.39 mmol, 78%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.94–6.89 (m, 2H), 6.86–6.77 (m, 4H), 6.69–6.63 (m, 2H), 3.73 (s, 3H), 3.58 (q, *J* = 7.1 Hz, 2H), 1.10 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.6 (*J* = 237.6 Hz), 155.7, 145.1 (*J* = 2.2 Hz), 141.0, 125.6 (2C), 118.8 (d, *J* = 7.5 Hz, 2C), 115.7 (d, *J* = 22.5 Hz, 2C) , 114.8 (2C), 55.5, 46.8, 12.6.

^{19}F-NMR (377 MHz, $CDCl_3$) δ / ppm = -125.8.

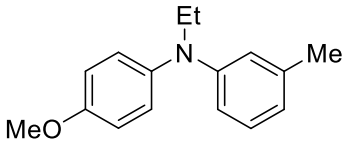
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2974, 2948, 2836, 1504, 1466, 1442, 1372, 1290, 1266, 1240, 1226, 1180, 1132, 1036, 820, 760.

MS (EI, 70 eV): *m/z* (%) = 245 (66), 230 (100), 202 (26), 122 (16).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}FNO$]: 245.1216; found 245.1208.

m.p. (°C): 122.2–125.8.

_N_-Ethyl-_N_-(4-methoxyphenyl)-3-methylaniline (2u)



According to **TP12** _O_-benzoyl-_N_-ethyl-_N_-(_m_-tolyl)hydroxylamine (**5i**, 1.00 mL, 0.50 M, 0.50 mmol) was dissolved in dry THF (2 mL). $CoCl_2 \cdot 2LiCl$ (25 µL, 1.00 M, 5.0 mol%) was added and subsequent (4-ethoxyphenyl)zinc pivalate (**1e**, 505 mg, 1.09 mmol/g, 0.55 mmol) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (82 mg, 0.34 mmol, 68%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.02–6.96 (m, 3H), 6.84–6.79 (m, 2H), 6.51–6.45 (m, 3H), 3.73 (s, 3H), 3.60 (q, _J_ = 7.1 Hz, 2H), 2.17 (s, 3H), 1.11 (t, _J_ = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.5, 148.8, 140.5, 138.8, 129.0, 127.7 (2C), 118.8, 116.2, 114.9 (2C), 112.7, 55.6, 46.6, 21.9, 12.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2935, 2882, 2371, 1741, 1599, 1515, 1510, 1501, 1498, 1467, 1454, 1382, 1278, 1235, 1160,, 1104, 1049, 760, 736.

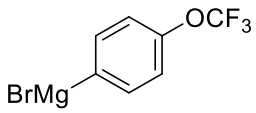
MS (EI, 70 eV): _m/z_ (%) = 241 (55), 226 (100).

HRMS (EI): _m/z_ calc. for [$C_{16}H_{19}NO$]: 241.1467; found 241.1462.

m.p. (°C): 115.3–118.2.

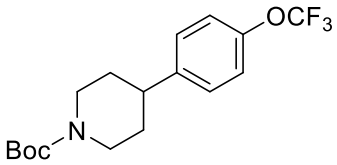
3.7 Synthesis of Tuberculosis Target Q203

(4-(Trifluoromethoxy)phenyl)magnesium Bromide (9)



A dry and argon-flushed Schlenk –flask was charged with magnesium turnings (111 mg, 4.57 mmol) and LiCl (5.0 mL, 0.50 M in THF, 2.5 mmol). 1-Bromo-4-(trifluoromethoxy)benzene (917 mg, 3.80 mmol) in THF (2.0 mL) was added in one portion at room temperature. The reaction mixture was stirred for 3 h to afford the title magnesium reagent in 0.64 M solution, corresponding to 94% yield.

Tert-butyl 4-(4-(trifluoromethoxy)phenyl)piperidine-1-carboxylate (10)



A dry and argon-flushed Schlenk-flask was charged with *N*-Boc-4-iodo-piperidine (**8**, 311 mg, 1.00 mmol) and THF (1 mL). $CoCl_2$•2LiCl (50 µL, 1.00 M in THF, 5.0 mol%) and (*R,R*)-tetramethylcyclohexanediamine (11 mg, 6.0 mol%) were added the solution. Grignard reagent **9** (1.88 mL, 0.64 M in THF 1.20 mmol) was then added dropwise at 0 °C and the resulting mixture was stirred for 1 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Purification via flash column chromatography (silica gel, isohexane/EtOAc = 8:1) afforded the title compound as a colourless oil (311 mg, 0.90 mmol, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.21 (dt, *J* = 8.8, 2.1 Hz, 2H), 7.17–7.13 (m, 2H), 4.24 (s, 2H), 2.80 (t, *J* = 12.5 Hz, 2H), 2.66 (tt, *J* = 12.2, 3.5 Hz, 1H), 1.81 (d, *J* = 13.3 Hz, 2H), 1.65–1.53 (m, 2H), 1.48 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.8, 147.6, 144.4, 128.0 (2C), 121.0 (2C), 120.3 (q, *J* = 100.1 Hz), 79.6, 44.3 (2C), 42.14, 33.2 (2C), 28.5 (3C).

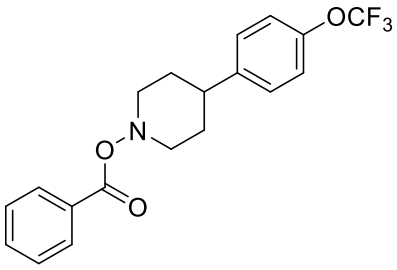
^{19}F-NMR (377 MHz, $CDCl_3$) δ / ppm = -57.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2938, 1692, 1510, 1480, 1468, 1446, 1424, 1394, 1366, 1322, 1260, 1230, 1164, 1124, 1016, 856, 840, 668.

MS (EI, 70 eV): *m/z* (%) = 345 (10), 289 (100), 245 (46), 127 (23).

HRMS (EI): *m/z* calc. for [$C_{17}H_{22}F_3NO_3$]: 345.1552; found 345.1545.

4-(4-(Trifluoromethoxy)phenyl)piperidin-1-yl benzoate (11)



In a dry and argon flushed flask, a solution of *N*-Boc-piperidine **10** (250 mg, 0.72 mmol) in dry CH_2Cl_2 (2.5 mL) was treated with trifluoroacetic acid (0.28 mL, 3.62 mmol) at room temperature and stirred for 2 h. The reaction mixture was quenched with sat. aqueous $NaHCO_3$ solution (2 mL) and extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4 and filtered, then the solvent was removed *in vacuo*. The crude product was used for next step without further purification. According to **TP9** dry benzoyl peroxide (280 mg, 0.86 mmol) and K_2HPO_4 (815 mg, 4.68 mmol, 5.40 equiv) were suspended in dry DMF (20 mL). The crude 4-(4-(trifluoromethoxy)phenyl)piperidine was slowly added and the resulting mixture stirred for 36 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 9:1) afforded the title compound as a pale white solid (220 mg, 0.72 mmol, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06–8.01 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 4.2 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 3.69 (d, *J* = 10.6 Hz, 2H), 2.91 (t, *J* = 10.5 Hz, 2H), 2.66 (t, *J* = 12.1 Hz, 1H), 2.14 (qd, *J* = 12.5, 2,1 Hz, 2H), 1.99 (d, *J* = 12.4 Hz, 2H).

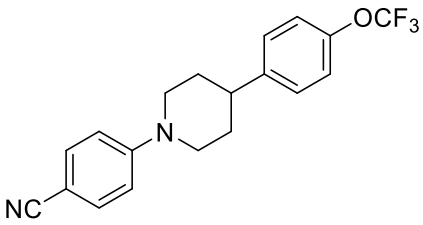
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.8, 147.7, 143.5, 133.1 (2C), 129.4 (2C), 128.4 (2C), 128.1 (2C), 121.1 (2C), 120.4 (q, *J* = 100.1 Hz), 57.3 (2C), 41.2, 32.8 (2C).

^{19}F-NMR (377 MHz, $CDCl_3$) δ / ppm = -57.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2948, 2926, 2838, 1730, 1512, 1450, 1316, 1280, 1262, 1220, 1200, 1192, 1166, 1090, 1068, 1016, 722, 710, 676.

m.p. (°C): 150.2–120.8.

4-(4-(4-(Trifluoromethoxy)phenyl)piperidin-1-yl)benzonitrile (12)



According to **TP12** 4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl benzoate **(11**, 220 mg, 0.72 mmol) was dissolved in dry THF (10 mL). $CoCl_2$·2LiCl (18 µL, 1.00 M, 5.0 mol%) was added and subsequent (4-cyanophenyl)zinc pivalate (**1b**, 642 mg, 1.34 mmol/g, 0.86 mmol, 1.20 equiv) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. Purification of the crude product by flash chromatography (silica gel, isohexane/EtOAc = 5:1) afforded the title compound as a pale white solid (225 mg, 0.65 mmol, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.50 (dt, *J* =8.9, 2.2 Hz, 2H), 7.24 (dt, *J* =8.4, 1.9 Hz, 2H), 7.19–7.14 (m, 2H), 6.91 (dt, *J* =8.9, 2.4 Hz, 2H), 3.99 (dp, *J* = 13.0, 1.9 Hz, 2H), 2.98 (td, *J* = 12.8, 2.6 Hz, 2H), 2.77 (tt, *J* = 12.2, 3.7 Hz, 1H), 2.01–1.93 (m, 2H), 1.79 (dtd, *J* = 13.2, 12.1, 3.9 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 153.3, 147.8, 144.0, 133.6 (2C), 129.4, 128.0 (2C), 121.1 (2C), 120.6 (q, *J* = 100.7 Hz), 114.5 (2C), 99.9, 48.3 (2C), 41.9, 32.7 (2C).

^{19}F-NMR (377 MHz, $CDCl_3$) δ / ppm = -57.9.

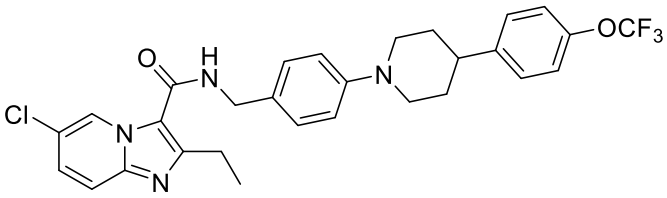
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2942, 2926, 2838, 2212, 1686, 1604, 1510, 1464, 1448, 1390, 1354, 1326, 1254, 1216, 1196, 1176, 1158, 1114, 1102, 1092, 1010, 920, 882, 848, 820, 780, 716, 684, 676.

MS (EI, 70 eV): *m/z* (%) = 345 (75), 184 (31), 157 (100), 102 (38).

HRMS (EI): *m/z* calc. for [$C_{19}H_{17}F_3N_2O$]: 346.1293; found 345.1211 [M-H^+].

m.p. (°C): 199.8–204.1.

6-Chloro-2-ethyl-*N*-(4-(4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide–Q203 (7)



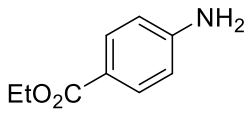
A solution of benzonitrile **12** (80 mg, 0.23 mmol, 1.00 equiv) in dry THF (2.5 mL) was treated with lithium aluminium hydride (35 mg, 0.93 mmol, 4.00 equiv) at room temperature. The resulting reaction mixture was reflux for 2 h. The reaction was cooled and quenched with sat. aqueous NH_4Cl solution (2 mL) followed by extraction with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4 and filtered, then the solvent was removed *in vacuo*. The crude product was dissolved in DMF (1 mL) followed by the addition of acid **13** (was prepared according to literature procedure; analytical data is consistent to literature)[124] (67 mg, 0.28 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodimide hydrochloride (EDC, 66 mg, 0.35 mmol), 1-hydroxylbenzotriazole (HOBt, 19 mg, 0.14 mmol) and triethylamine (60 µL, 0.46 mmol) at room temperature. The resulting solution was stirred at 70 °C for 2 h and cooled to room temperature. Water (5 mL) was added into the crude residue, the resulting solution was extracted with EtOAc (3 x 5 mL). The crude mixture was purified by flash column chromatography (silica gel, isohexane/EtOAc/methylene chloride = 1:1:1) to give Q203 as a pale white solid (103 mg, 0.19 mmol, 82% over two steps).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.55 (dd, *J* = 2.1, 0.8 Hz, 1H), 7.56 (dd, *J* = 9.5, 0.9 Hz, 1H), 7.34–7.29 (m, 4H), 7.27 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.07 (t, *J* = 5.7 Hz, 1H), 4.64 (d, *J* = 5.5 Hz, 2H), 3.92–3.72 (m, 2H), 2.99 (q, *J* = 7.6 Hz, 2H), 2.87 (d, *J* = 2.9 Hz, 2H), 2.70 (tt, *J* = 11.7, 4.1 Hz, 1H), 2.03–1.84 (m, 4H), 1.42 (t, *J* = 7.5 Hz, 3H).

[124] S. Kang, R. Y. Kim, M. J. Seo, S. Lee, Y. M. Kim, M. Seo, J. J. Seo, Y. Ko, I. Choi, J. Jang, *J. Med. Chem.* **2014**, *57*, 5293–5305.

3.8 Deprotection Procedures to Afford Primary and Secondary Amines

Ethyl 4-aminobenzoate (6)



To a solution of allylaniline **3j** (123 mg, 0.50 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) *N*,*N*-dimethylbarbituric acid (468 mg, 3.00 mmol, 6.00 equiv) and $Pd(PPh_3)_4$ (78 mg, 0.05 mmol, 10 mol%) were added. The reaction mixture was stirred at 40 °C for 24 h and checked by GC analysis. After full consumption of the starting material, the mixture was quenched with sat. aqueous NH_4Cl solution and extract with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and filtered, then the solvent was removed *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, isohexane/EtOAc = 1:1) to give the title compound as a colourless solid (75 mg, 0.46 mmol, 91%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.87–7.83 (m, 2H), 6.65–6.60 (m, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.20–3.97 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.8, 150.8, 131.5 (2C), 119.9, 113.8 (2C), 60.3, 14.4.

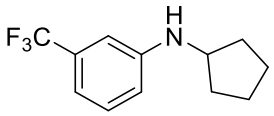
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2874, 1614, 1594, 1514, 1492, 1476, 1436, 1344, 1318, 1280, 1248, 1158, 1116, 1096, 1068, 1044, 1026, 992, 900, 856, 780, 696, 660.

MS (EI, 70 eV): *m/z* (%) = 165 (40), 137 (39), 120 (100), 92 (20).

HRMS (EI): *m/z* calc. for [$C_9H_{11}NO_2$]: 165.0790; found 165.0783.

m.p. (°C): 81.1–84.6.

_N_-Cyclopentyl-3-(trifluoromethyl)aniline (3a)



To a solution of allylaniline **2l** (135 mg, 0.50 mmol, 1.00 equiv) and ruthenium-catalyst (dichlorodi-μ-chlorobis[(1,2,3,6,7,8-η-2,7-dimethyl-2,6-octadiene-1,8-diyl]diruthenium(IV)) (7 mg, 0.01 mmol, 2.0 mol%) in water (5 mL) was stirred at 90 °C for 14 h. The reaction mixture was cooled to room temperature and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4 and filtered, then the solvent was removed *in vacuo*. The crude mixture was purified by flash column chromatography (silica gel, isohexane/EtOAc = 6:1) to give the title compound as a colourless oil (107 mg, 0.47 mmol, 93%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.27 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.75 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.89 (s, 1H), 3.87–3.80 (m, 1H), 2.13–2.03 (m, 2H), 1.83–1.63 (m, 4H), 1.56–1.46 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 148.1, 131.45 (q, *J* = 31.6 Hz), 129.5, 124.44 (q, *J* = 272.4 Hz), 116.0, 113.13 (q, *J* = 3.9 Hz), 109.13 (q, *J* = 3.9 Hz), 54.5, 33.4, 24.0.

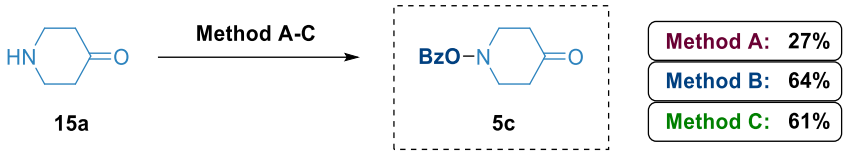
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3420, 3340, 3222, 2984, 2898, 1680, 1634, 1594, 1574, 1514, 1474, 1442, 1392, 1366, 1310, 1274, 1240, 1170, 1124, 1110, 1080, 1024, 908, 882, 846, 772, 732, 700.

MS (EI, 70 eV): *m/z* (%) = 229 (34), 200 (100), 161 (13).

HRMS (EI): *m/z* calc. for [$C_{12}H_{14}F_3N$]: 229.1078; found 229.1073.

4. Late Stage Functionalization of Secondary Amines via a Cobalt-Catalyzed Electrophilic Amination of Organozinc Reagents

4.1 Comparison of Hydoxylamine Benzoate Preparations



Method A: A dry and argon flushed flask equipped with a magnetic stirring bar and a septum was charged with K_2HPO_4 (1.31 g, 7.50 mmol, 1.50 equiv) and anhydrous benzoyl peroxide (1.21 g, 5.00 mmol, 1.00 equiv). The mixture was suspended in DMF (20 mL) and amine **32** (7.50 mmol, 1.50 equiv) was added slowly. The reaction mixture was stirred at room temperature and checked by thin layer chromatography analysis. Upon full consumption of benzoyl peroxide, the reaction was quenched with sat. aqueous NH_4Cl solution (30 mL). The organic layer was removed and the aqueous phase was extracted from EtOAc (3 x 15 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ solution (15 mL), brine (15 mL) and subsequent dried over $mgSO_4$. Evaporation of the solvents *in vacuo* and purification by flash column chromatography afforded the desired products.

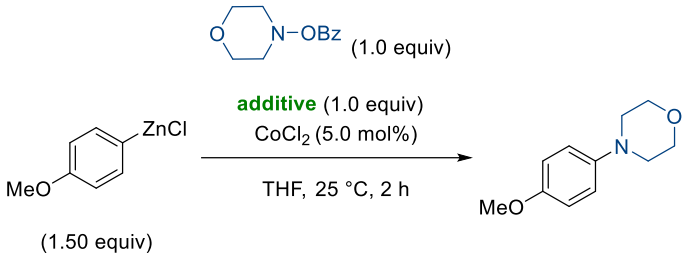
Method B[84]**:** In an argon flushed flask, amine **32** (1.00 mmol, 1.00 equiv) was dissolved in acetone (10 mL) and dimethyldioxirane (0.075 M, 14 mL, 1.05 mmol, 1.00 equiv) was added as a solution in acetone at 0 °C. The mixture was stirred at 0 °C for 30 min and then concentrated *in vacuo*. The resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.0 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography to afford the desired product.

Method C**:** 1) amine **32**, (1.0 equiv), acrylonitrile (5.0 equiv), MeOH, 55 °C, 12 h; 2) *m*CPBA (1.1 equiv), CH_2Cl_2, −78 °C to rt, 12 h; 3) BzCl (1.2 equiv), NEt_3 (1.5 equiv), DMAP (1 mol%), CH_2Cl_2, 0 °C, 30 min. *A detailed procedure is given in the following.*

4.2 Functional Group Tolerance Test

To investigate the functional group tolerance of the described amination procedure, we performed the amination according to **TP13** and added various additives (Table 11). Therefore, morpholino benzoate (**5a**, 42 mg, 0.20 mmol, 1.00 equiv) was reacted with 4-methoxyphenylzinc chloride (**1rr**, 0.50 M, 0.60 mL, 0.30 mmol, 1.50 equiv) under cobalt-catalysis ($CoCl_2$) in the presence of the given additive (0.20 mmol, 1.00 equiv).

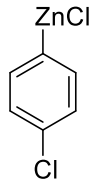
Table 11. Perforance of the cobalt-catalyzed electrophilic amination in the presence of various additives, to show its tolerance towards functional groups



Entry	Additive	Yield [%]
1	*none*	96%
2	1,1-diphenylethan-1-ol	90%
3	2,2,4,4-tetramethylpentan-3-ol	96%
4	3,5-dimethylaniline	96%
5	butylamine	56%
6	morpholine	96%
7	*N*-methylbenzamide	96%
8	7-oxabicyclo[4.1.0]heptane	81%
9	2-(4-bromophenyl)oxirane	96%

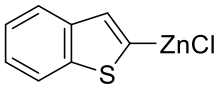
4.3 Preparation of Organozinc Chlorides

(4-Chlorophenyl)zinc Chloride ( )



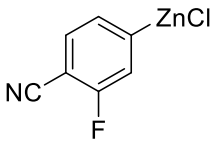
According to **TP4**, 1-bromo-4-chlorobenzene (479 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.29 mmol/mL active zinc species, corresponding to 98% yield.

Benzo[*b*]thiophen-2-ylzinc Chloride (1o)



According to **TP4**, 2-bromobenzo[*b*]thiophene (533 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.27 mmol/mL active zinc species, corresponding to 92% yield.

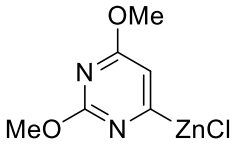
(4-Cyano-3-fluorophenyl)zinc Chloride (1p)



According to **TP2**, 2-fluoro-4-iodobenzonitrile (1.23 g, 5.00 mmol, 1.00 equiv) was dissolved in dry THF (5 mL) and *i*PrMgCl·LiCl (4.30 mL, 1.28 M, 5.50 mmol, 1.10 equiv) was added. After stirring for 2 h at −20 °C $ZnCl_2$ (1 M in THF, 6.0 mL, 6.00 mmol) was added. Titration

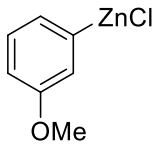
with iodine gave a concentration of 0.29 mmol/mL active zinc species, corresponding to 92% yield.

(2,6-Dimethoxypyrimidin-4-yl)zinc Chloride (1q)



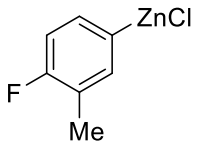
According to **TP4**, 4-bromo-2,6-dimethoxypyrimidine (549 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.28 mmol/mL active zinc species, corresponding to 96% yield.

(3-Methoxyphenyl)zinc Chloride (1r)



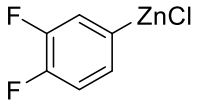
According to **TP4**, 1-bromo-3-methoxybenzene (468 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.29 mmol/mL active zinc species, corresponding to 99% yield.

(4-Fluoro-3-methylphenyl)zinc Chloride (1s)



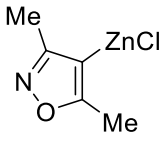
According to **TP4**, 4-bromo-1-fluoro-2-methylbenzene (473 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.28 mmol/mL active zinc species, corresponding to 96% yield.

(3,4-Difluorophenyl)zinc Chloride (1t)



According to **TP4**, 4-bromo-1,2-difluorobenzene (483 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.26 mmol/mL active zinc species, corresponding to 90% yield.

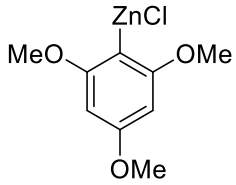
(3,5-dimethylisoxazol-4-yl)zinc Chloride (1u)



According to **TP4**, 4-bromo-3,5-dimethylisoxazole (440 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution

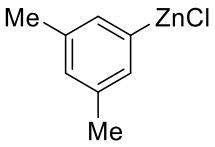
in THF at 0 °C. Titration with iodine gave a concentration of 0.26 mmol/mL active zinc species, corresponding to 88% yield.

(2,4,6-Trimethoxyphenyl)zinc Chloride (1v)



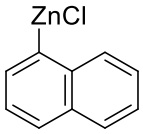
According to **TP4**, 2-bromo-1,3,5-trimethoxybenzene (618 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.26 mmol/mL active zinc species, corresponding to 89% yield.

(3,5-Dimethylphenyl)zinc Chloride (1w)



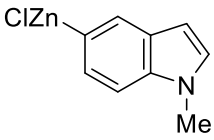
According to **TP4**, 1-bromo-3,5-dimethylbenzene (458 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.29 mmol/mL active zinc species, corresponding to 99% yield.

Naphthalen-1-ylzinc Chloride (1x)



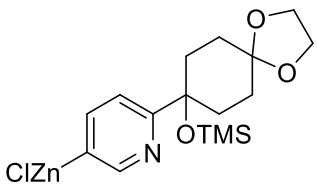
According to **TP4**, 1-bromonaphthalene (518 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.27 mmol/mL active zinc species, corresponding to 92% yield.

(1-Methyl-1*H*-indol-5-yl)zinc Chloride (1y)



According to **TP4**, 5-bromo-1-methyl-1*H*-indole (525 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.26 mmol/mL active zinc species, corresponding to 82% yield.

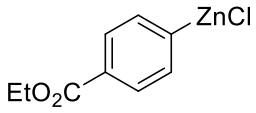
(6-(8-((Trimethylsilyl)oxy)-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)zinc chloride (1z)



According to **TP4**, 5-iodo-2-(8-((trimethylsilyl)oxy)-1,4-dioxaspiro[4.5]decan-8-yl)pyridine (1.08 g, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF

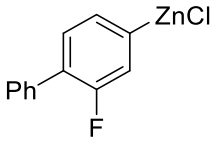
(5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.23 mmol/mL active zinc species, corresponding to 78% yield.

(4-(Ethoxycarbonyl)phenyl)zinc Chloride (1aa)



According to **TP2** ethyl 4-iodobenzoate (1.38 g, 5.00 mmol, 1.00 equiv) was dissolved in dry THF (5 mL) and *i*PrMgCl·LiCl (4.30 mL, 1.28 M, 5.50 mmol, 1.10 equiv) was added. After stirring for 30 min at -30 °C $ZnCl_2$ (1 M in THF, 6.0 mL, 6.00 mmol) was added. Titration with iodine gave a concentration of 0.30 mmol/mL active zinc species, corresponding to 95% yield.

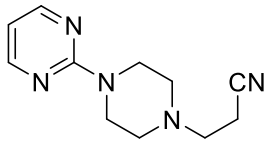
(2-fluoro-[1,1'-biphenyl]-4-yl)zinc Chloride (1cc)



According to **TP4**, 4-bromo-2-fluoro-1,1'-biphenyl (628 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.28 mmol/mL active zinc species, corresponding to 96% yield.

4.4 Preparation of 1,4-Addition Products of Type 17

3-(4-(Pyrimidin-2-yl)piperazin-1-yl)propanenitrile (17b)



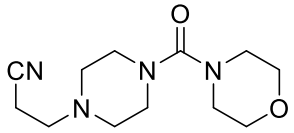
According to **TP10**, 2-(piperazin-1-yl)pyrimidine (**14b**, 164 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added. After stirring the mixture at 55 °C overnight the solvent was removed and the crude product purified by flash column chromatography (EtOAc:MeOH 9.5:0.5) to afford the title compound as a colourless oil (211 mg, 0.97 mmol, 97%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.24 (d, *J* = 4.7 Hz, 2H), 6.43 (t, *J* = 4.8 Hz, 1H), 3.85–3.70 (m, 4H), 2.67 (t, *J* = 7.0 Hz, 2H), 2.53–2.45 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 161.6, 157.7, 118.7, 110.0, 53.5, 52.6, 43.5, 16.0.

Analytical data according to literature.[125]

3-(4-(Morpholine-4-carbonyl)piperazin-1-yl)propanenitrile (17c)



According to **TP10**, morpholino(piperazin-1-yl)methanone (**14c**, 199 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added. After stirring the mixture at 55 °C overnight the solvent was removed and the crude product purified by flash column chromatography (EtOAc:MeOH 9.5:0.5) to afford the title compound as a colourless oil (235 mg, 0.93 mmol, 93%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.61 (q, *J* = 4.6 Hz, 2H), 3.20 (dt, *J* = 18.8, 4.8 Hz, 4H), 2.64 (q, *J* = 6.1 Hz, 1H), 2.45 (dq, *J* = 13.8, 4.6 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.5, 118.7, 66.5 (2C), 53.2, 52.3 (2C), 47.2 (2C), 46.4 (2C), 15.8.

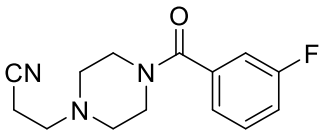
[125] K. Ishizumi, A. Kojima, F. Antoku *Chem. Pharm. Bull.* **1991**, *39*, 2288–2300.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2975, 2935, 2852, 2601, 2497, 1641, 1473, 1469, 1460, 1443, 1419, 1397, 1359, 1352, 1302, 1288, 1279, 1266, 1245, 1229, 1169, 1152, 1128, 1114, 1109, 1100, 1067, 1044, 1037, 1022, 996, 969, 931, 901, 871, 839, 785, 761.

MS (EI, 70 eV): *m/z* (%) = 252 (18), 166 (35), 114(100), 86 (38).

HRMS (EI): *m/z* calc. for [$C_{12}H_{20}N_4O_2$]: 252.1586; found 252.1583.

3-(4-(3-Fluorobenzoyl)piperazin-1-yl)propanenitrile (17d)



According to **TP10**, (3-fluorophenyl)(piperazin-1-yl)methanone (**14d**, 208 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added. After stirring the mixture at 55 °C overnight the solvent was removed and the crude product purified by flash column chromatography (EtOAc:MeOH 9.5:0.5) to afford the title compound as a colourless oil (256 mg, 0.98 mmol, 98%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.31 (t, *J* = 7.8, 5.5 Hz, 1H), 7.11–6.99 (m, 3H), 3.70 (s, 2H), 3.35 (s, 2H), 2.62 (t, *J* = 6.8 Hz, 2H), 2.55–2.32 (m, 7H).

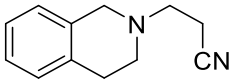
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 168.7 (d, *J* = 2.3 Hz), 162.4 (d, *J* = 248.0 Hz), 137.6 (d, *J* = 6.9 Hz), 130.4 (d, *J* = 8.0 Hz), 122.7 (d, *J* = 3.2 Hz), 118.7, 116.8 (d, *J* = 21.1 Hz), 114.26 (d, *J* = 22.7 Hz), 53.0, 52.8, 52.1, 47.4, 42.0, 15.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2931, 2822, 2819, 1626, 1583, 1490, 1461, 1439, 1426, 1370, 1354, 1300, 1280, 1267, 1213, 1139, 1133, 1096, 1021, 1000, 964, 940, 931, 880, 832, 795, 747, 710, 687.

MS (EI, 70 eV): *m/z* (%) = 261 (23), 166 (40), 123 (100), 95 (40).

HRMS (EI): *m/z* calc. for [$C_{14}H_{16}FN_3O$]: 261.1277; found 261.1273.

3-(3,4-dihydroisoquinolin-2(1H)-yl)propanenitrile (17e)



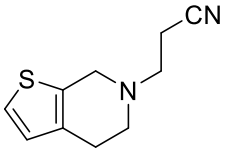
According to **TP10**, 1,2,3,4-tetrahydroisoquinoline (**14e**, 133 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added. After stirring the mixture at 55 °C overnight the solvent was removed and the crude product purified by flash column chromatography (EtOAc:MeOH 9.5:0.5) to afford the title compound as a colourless oil (180 mg, 0.97 mmol, 97%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.11–7.01 (m, 3H), 7.00–6.91 (m, 1H), 3.64 (s, 2H), 2.85 (t, *J* = 5.9 Hz, 2H), 2.81 (t, *J* = 7.1 Hz, 2H), 2.74 (t, *J* = 5.8 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 133.9, 133.9, 128.7, 126.6, 126.4, 125.8, 118.8, 55.4, 53.2, 50.6, 28.9, 16.3.

Analytical Data according to Literature[126]

3-(4,7-Dihydrothieno[2,3-*c*]pyridin-6(5*H*)-yl)propanenitrile (17f)



According to **TP10**, 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (**14f**, 139 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added. After stirring the mixture at 55 °C overnight the solvent was removed and the crude product purified by flash column chromatography (EtOAc:MeOH 9.5:0.5) to afford the title compound as a colourless oil (190 mg, 0.99 mmol, 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.12 (d, *J* = 5.1 Hz, 1H), 6.76 (d, *J* = 5.1 Hz, 1H), 3.67 (d, *J* = 1.7 Hz, 2H), 2.98–2.89 (m, 6H), 2.63 (t, *J* = 7.1 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 133.2, 132.9, 125.1, 123.0, 118.8, 52.7, 52.5, 50.6, 25.2, 16.5.

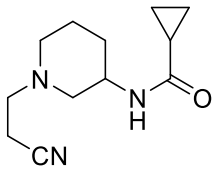
[126] H. Stamm, J. Hoenicke *Arch. Pharm.* **1974**, *5*, 340–348.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 2822, 1464, 1430, 1414, 1361, 1320, 1243, 1213, 1169, 1137, 1117, 1081, 1048, 1017, 987, 974, 903, 833, 775, 707, 668.

MS (EI, 70 eV): *m/z* (%) = 192 (5), 152 (78), 135 (78), 110 (100), 84 (14).

HRMS (EI): *m/z* calc. for [$C_{10}H_{12}N_2S$]: 192.0721; found 192.0714.

***N*-(1-(2-Cyanoethyl)piperidin-3-yl)cyclopropanecarboxamide (17g)**



According to **TP10**, *N*-(piperidin-3-yl)cyclopropanecarboxamide (**14g**, 168 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added. After stirring the mixture at 55 °C overnight the solvent was removed and the crude product purified by flash column chromatography (EtOAc:MeOH 9.5:0.5) to afford the title compound as a colourless oil (210 mg, 0.95 mmol, 95%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.59 (s, 1H), 3.96 (s, 1H), 2.64–2.39 (m, 6H), 2.37–2.23 (m, 2H), 1.64 (s, 1H), 1.47 (s, 3H), 1.34 (s, 1H), 0.80 (s, 2H), 0.60 (s, 2H).

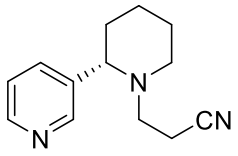
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.8, 118.9, 57.6, 53.1, 52.9, 45.1, 28.9, 22.2, 16.1, 14.5, 6.9 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2851, 2360, 2341, 1700, 1652, 1645, 1640, 1635, 1627, 1558, 1539, 1506, 1456, 1436, 1429, 1423, 1419, 1405, 1399, 1394, 1359, 1352, 1279, 1265, 1229, 1152, 1114, 1109, 1100, 1044, 1022, 995, 931, 901, 871, 838, 784, 761.

MS (EI, 70 eV): *m/z* (%) = 221 (11), 181 (56), 140 (100).

HRMS (EI): *m/z* calc. for [$C_{12}H_{19}N_3O$]: 221.1528; found 221.1521.

(*S*)-3-(2-(pyridin-3-yl)piperidin-1-yl)propanenitrile (17h)



According to **TP10**, anabasine (**14h**, 162 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added. After stirring the mixture at 55 °C overnight the solvent was removed and the crude product purified by flash column chromatography (EtOAc:MeOH 9.5:0.5) to afford the title compound as a colourless oil (213 mg, 0.99 mmol, 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.51–8.39 (m, 2H), 7.70 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.22 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.13–3.02 (m, 2H), 2.71–2.61 (m, 1H), 2.40–2.29 (m, 1H), 2.28–2.15 (m, 2H), 2.09 (td, *J* = 11.6, 3.0 Hz, 1H), 1.78–1.53 (m, 4H), 1.52–1.40 (m, 1H), 1.30 (qt, *J* = 12.5, 3.8 Hz, 1H).

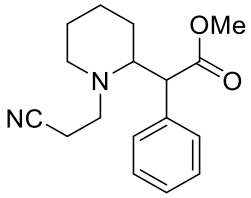
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.1, 148.9, 139.6, 135.0, 123.8, 118.8, 65.5, 52.9, 50.1, 36.7, 25.7, 24.6, 15.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3852, 3744, 2934, 2854, 2796, 2364, 2341, 1733, 1717, 1700, 1695, 1684, 1675, 1669, 1652, 1646, 1635, 1616, 1576, 1558, 1539, 1521, 1506, 1472, 1456, 1436, 1423, 1419, 1322, 1128, 1107, 1025, 984, 805, 760, 716.

MS (ESI, 70 eV): *m/z* (%) = 216 (100), 175 (5).

HRMS (ESI): *m/z* calc. for [$C_{13}H_{17}N_3$]: 215.1422; found 216.1491 [M+H].

Methyl 2-(1-(2-cyanoethyl)piperidin-2-yl)-2-phenylacetate (17i)



According to **TP10**, methylphenidate hydrochloride (**14i**, 270 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and added to a solution of sodium metal (23 mg, 1.00 mmol, 1.00 equiv). Then, acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added and the resulting mixture was stirred at 55 °C overnight. The solvent was removed and the crude product purified by flash column chromatography (EtOAc:MeOH 9.5:0.5) to afford the title compound as a colourless oil (258 mg, 0.90 mmol, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.35–7.29 (m, 2H), 7.28–7.18 (m, 3H), 4.01 (d, *J* = 11.7 Hz, 1H), 3.62 (s, 3H), 3.28–3.21 (m, 1H), 3.15–3.06 (m, 1H), 2.97–2.82 (m, 2H), 2.68–2.59 (m, 1H), 2.49–2.31 (m, 2H), 1.50–1.22 (m, 5H), 0.9 (d, *J* = 13.3 Hz, 1H).

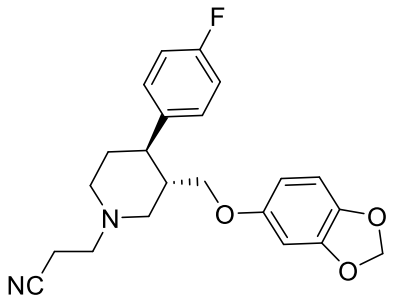
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 174.1, 136.6, 128.8 (2C), 128.5 (2C), 127.6, 119.3, 60.7, 52.7, 52.1, 50.0, 47.7, 20.9, 20.5, 20.0, 18.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2947, 2919, 2854, 2358, 2339, 1733, 1723, 1717, 1700, 1695, 1684, 1652, 1635, 1558, 1539, 1521, 1506, 1496, 1472, 1456, 1448, 1436, 1433, 1419, 1346, 1285, 1201, 1188, 1163, 1155, 1146, 1125, 1013, 994, 869, 781, 729, 695.

MS (ESI, 70 eV): *m/z* (%) = 287 (100), 246 (14), 137 (46).

HRMS (ESI): *m/z* calc. for [$C_{17}H_{22}N_2O_2$]: 286.1681; found 287.1753 [M+H].

3-((3*S*,4*R*)-3-((Benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidin-1-yl) propanenitrile (17j)



According to **TP10**, paroxetine hydrochloride (**14j**, 366 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and added to a solution of sodium metal (23 mg, 1.00 mmol, 1.00 equiv). Then, acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added and the resulting mixture was stirred at 55 °C overnight. The solvent was removed and the crude product purified by flash column chromatography (hexane:EtOAc 1:1) to afford the title compound as a colourless oil (371 mg, 0.97 mmol, 97%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.18–7.12 (m, 2H), 7.00–6.96 (m, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.13 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.88 (s, 2H), 3.57 (dd, *J* = 9.3, 2.7 Hz, 1H), 3.44 (dd, *J* = 9.4, 6.8 Hz, 1H), 3.23 (d, *J* = 9.7 Hz, 1H), 3.02 (d, *J* = 10.8 Hz, 1H), 2.83–2.74 (m, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 2.46 (td, *J* = 11.0, 5.1 Hz, 1H), 2.24–2.13 (m, 3H), 1.91–1.81 (m, 2H).

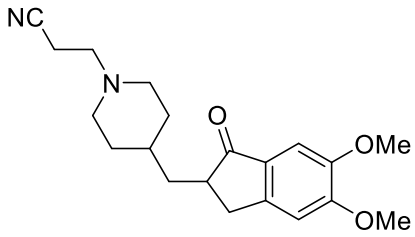
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.6 (d, *J* = 244.5 Hz), 154.3, 148.2, 141.6, 139.3, 128.8, 118.8, 115.5 (d, *J* = 21.1 Hz), 107.9, 105.5 (d, *J* = 9.0 Hz), 101.1, 101.1, 101.0, 97.9 (d, *J* = 9.2 Hz), 69.4, 57.1, 53.7, 53.6, 43.8, 42.0, 34.1, 16.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2938, 2933, 2919, 2900, 2815, 2774, 2249, 1631, 1604, 1509, 1502, 1487, 1467, 1378, 1351, 1269, 1242, 1221, 1182, 1159, 1136, 1102, 1090, 1060, 1036, 1015, 974, 932, 832, 817, 783, 762, 731.

MS (EI, 70 eV): *m/z* (%) = 382 (51), 342 (54), 329 (28), 245 (100), 204 (39), 192 (50), 171 (24), 109 (49), 97 (98), 58 (78).

HRMS (EI): *m/z* calc. for [$C_{22}H_{23}FN_2O_3$]: 382.1693; found 382.1687.

3-(4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)piperidin-1-yl)propanenitrile (17k)



According to **TP10**, 5,6-dimethoxy-2-(piperidin-4-ylmethyl)-2,3-dihydro-1*H*-inden-1-one (**14k**, 289 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and added to a solution of sodium metal (23 mg, 1.00 mmol, 1.00 equiv). Then, acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added and the resulting mixture was stirred at 55 °C overnight. The solvent was removed and the crude product purified by flash column chromatography (pure EtOAc) to afford the title compound as a colourless oil (300 mg, 0.87 mmol, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.17 (s, 1H), 6.86 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.25 (dd, *J* = 17.5, 8.1 Hz, 1H), 2.95–2.86 (m, 2H), 2.75–2.65 (m, 4H), 2.51 (t, *J* = 7.2 Hz, 2H), 2.13–2.03 (m, 2H), 1.91 (ddd, *J* = 13.1, 7.9, 4.4 Hz, 1H), 1.81–1.68 (m, 2H), 1.62–1.45 (m, 2H), 1.40–1.19 (m, 2H).

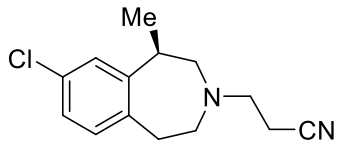
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 203.1, 154.7, 149.9, 144.6, 127.5, 118.3, 109.5, 108.8, 56.4, 55.9, 53.5, 53.5, 50.3, 45.4, 34.1, 33.4, 32.1, 30.9, 30.8, 16.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921, 1686, 1649, 1606, 1590, 1500, 1462, 1316, 1269, 1246, 1214, 1125, 1032, 969.

MS (EI, 70 eV): *m/z* (%) = 342 (72), 288 (54), 226 (23), 136 (100), 98 (45), 58 (23).

HRMS (EI): *m/z* calc. for [$C_{20}H_{26}N_2O_3$]: 342.4390; found 342.4394.

(*R*)-3-(8-Chloro-1-methyl-1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepin-3-yl)propanenitrile (17l)



According to **TP10**, lorcaserin hydrochloride (**14l**, 232 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and added to a solution of sodium metal (23 mg, 1.00 mmol, 1.00 equiv). Then, acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added and the resulting mixture was stirred at 55 °C overnight. The solvent was removed and the crude product purified by flash column chromatography (hexane:EtOAc 3:1) to afford the title compound as a colourless oil (239 mg, 0.96 mmol, 96%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.13 (d, *J* = 2.2 Hz, 1H), 7.09 (dd, *J* = 7.9, 2.2 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 3.11 (p, *J* = 7.4 Hz, 1H), 3.00–2.77 (m, 5H), 2.73 (d, *J* = 12.2 Hz, 1H), 2.57–2.42 (m, 4H), 1.35 (d, *J* = 7.3 Hz, 3H).

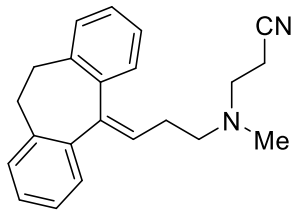
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 147.0, 139.3, 132.0, 130.7, 126.3, 126.0, 118.9, 61.4, 54.6, 54.5, 38.8, 35.8, 18.2, 15.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2936, 2932, 2917, 2891, 2883, 2879, 2814, 2782, 2779, 2245, 1594, 1569, 1488, 1466, 1452, 1435, 1402, 1369, 1359, 1341, 1330, 1311, 1283, 1265, 1187, 1176, 1151, 1123, 1114, 1106, 1058, 1048, 1028, 1004, 975, 952, 934, 895, 877, 842, 818, 772.

MS (EI, 70 eV): *m/z* (%) = 248 (1), 208 (100), 115 (27).

HRMS (EI): *m/z* calc. for [$C_{14}H_{17}ClN_2$]: 248.1080; found 248.1076.

3-((3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl)(methyl)amino) propanenitrile (17m)



According to **TP10**, nortiptyline hydrochloride (**14m**, 300 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and added to a solution of sodium metal (23 mg, 1.00 mmol, 1.00 equiv). Then, acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added and the resulting mixture was stirred at 55 °C overnight. The solvent was removed and the crude product purified by flash column chromatography (hexane:EtOAc 1:3) to afford the title compound as a colourless oil (313 mg, 0.99 mmol, 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.30–7.27 (m, 1H), 7.23–7.12 (m, 6H), 7.06–7.03 (m, 1H), 5.86 (t, *J* = 7.4 Hz, 1H), 3.41 (s, 1H), 3.31 (s, 1H), 2.97 (s, 1H), 2.79 (s, 1H), 2.66 (t, *J* = 7.1 Hz, 2H), 2.49 (q, *J* = 6.2, 5.7 Hz, 2H), 2.41–2.35 (m, 2H), 2.29 (q, *J* = 7.4 Hz, 2H), 2.20 (s, 3H).

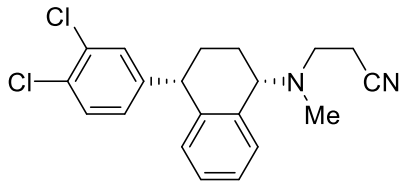
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 143.9, 141.1, 140.0, 139.3, 137.0, 130.0, 128.8, 128.6, 128.1, 128.1, 127.5, 127.1, 126.0, 125.8, 56.7, 52.5, 41.4, 33.8, 32.0, 27.2, 18.7, 15.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 3015, 2943, 2938, 2934, 2927, 2923, 2918, 2849, 2843, 2832, 2798, 2795, 2248, 1485, 1464, 1452, 1443, 1427, 1373, 1360, 1333, 1306, 1279, 1246, 1220, 1181, 1142, 1126, 1097, 1052, 1038, 948, 923, 893, 861, 777, 768, 756, 743, 719.

MS (EI, 70 eV): *m/z* (%) = 316 (1), 218 (13), 202 (22), 97 (100).

HRMS (EI): *m/z* calc. for [$C_{22}H_{24}N_2$]: 316.1939; found 316.1931.

3-(((1*S*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)(methyl)amino) propanenitrile (17n)



According to **TP10**, sertraline hydrochloride (**14n**, 343 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and added to a solution of sodium metal (23 mg, 1.00 mmol, 1.00 equiv). Then, acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added and the resulting mixture was stirred at 55 °C overnight. The solvent was removed and the crude product purified by flash column chromatography (hexane:EtOAc 1:4) to afford the title compound as a colourless oil (352 mg, 0.98 mmol, 98%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.86 (d, *J* = 7.8 Hz, 1H), 7.34–7.27 (m, 2H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.13–7.09 (m, 1H), 6.91 (dt, *J* = 7.7, 0.9 Hz, 1H), 6.80 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.15 (dd, *J* = 5.8, 3.3 Hz, 1H), 3.94 (dd, *J* = 10.2, 5.8 Hz, 1H), 2.80 (hept, *J* = 6.5, 6.0 Hz, 2H), 2.55 (t, *J* = 6.7 Hz, 2H), 2.31 (s, 3H), 2.21–2.10 (m, 1H), 2.06–1.98 (m, 1H), 1.74–1.57 (m, 2H).

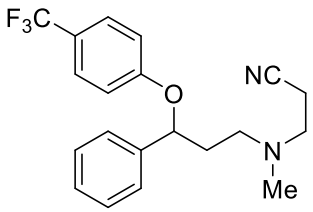
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 147.3, 138.4, 138.0, 132.2, 130.7, 130.3, 130.0, 130.0, 128.6, 128.2, 127.3, 127.2, 118.9, 62.7, 49.2, 43.4, 36.8, 30.0, 17.7, 16.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2939, 2862, 2799, 2248, 1586, 1559, 1485, 1466, 1450, 1427, 1418, 1390, 1357, 1336, 1317, 1271, 1254, 1201, 1154, 1131, 1069, 1062, 1043, 1028, 993, 941, 911, 882, 849, 828, 784, 763, 739, 712, 686, 678.

MS (EI, 70 eV): *m/z* (%) = 358 (3), 318 (41), 275 (100), 202 (14), 159 (90), 129 (64), 91 (22), 44 (51).

HRMS (EI): *m/z* calc. for [$C_{20}H_{20}Cl_2N_2$]: 358.1002; found 358.1004.

3-(Methyl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)propanenitrile (17o)



According to **TP10**, fluoxetine hydrochloride (**14o**, 346 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and added to a solution of sodium metal (23 mg, 1.00 mmol, 1.00 equiv). Then, acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added and the resulting mixture was stirred at 55 °C overnight. The solvent was removed and the crude product purified by flash column chromatography (hexane:EtOAc 1:2) to afford the title compound as a colourless oil (355 mg, 0.98 mmol, 98%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.43 (d, *J* = 8.7 Hz, 2H), 7.38–7.32 (m, 4H), 7.29–7.25 (m, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.39 (dd, *J* = 8.4, 4.8 Hz, 1H), 2.76–2.59 (m, 2H), 2.46 (dt, *J* = 27.5, 6.5 Hz, 3H), 2.29 (s, 3H), 2.21–2.13 (m, 1H), 2.02–1.94 (m, 1H).

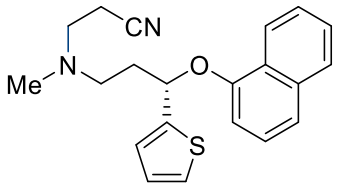
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.5, 141.0, 128.88–128.65 (m), 127.96–127.74 (m), 126.8 (q, *J* = 3.3 Hz), 126.06–125.85 (m), 126.0, 125.9, 124.4 (q, *J* = 271.1 Hz), 122.8 (q, *J* = 32.7 Hz), 118.9, 115.8, 115.7, 77.8, 77.7, 53.0, 52.8, 41.6, 36.4, 16.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2955, 2944, 2941, 2933, 2926, 2850, 2840, 2807, 2803, 2781, 1613, 1589, 1516, 1494, 1466, 1454, 1423, 1357, 1324, 1310, 1250, 1205, 1177, 1160, 1109, 1067, 1049, 1028, 1009, 999, 951, 917, 836, 814, 760, 701.z

MS (EI, 70 eV): *m/z* (%) = 362 (2), 218 (8), 97 (100), 58 (10), 44 (15).

HRMS (EI): *m/z* calc. for [$C_{20}H_{21}F_3N_2O$]: 362.1598; found 362.1598.

(*S*)-3-(Methyl(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)amino)propanenitrile (17p)



According to **TP10**, duloxetine hydrochloride (**14p**, 334 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and added to a solution of sodium metal (23 mg, 1.00 mmol, 1.00 equiv). Then, acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added and the resulting mixture was stirred at 55 °C overnight. The solvent was removed and the crude product purified by flash column chromatography (EtOAc:MeOH 9.5:0.5) to afford the title compound as a colourless oil (347 mg, 0.99 mmol, 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.41–8.34 (m, 1H), 7.81 (dt, *J* = 7.9, 2.8 Hz, 1H), 7.56–7.48 (m, 2H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.24 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.14 (dd, *J* = 3.5, 1.2 Hz, 1H), 7.00–6.92 (m, 2H), 5.89 (dd, *J* = 7.9, 5.3 Hz, 1H), 2.70 (hept, *J* = 6.4 Hz, 3H), 2.65–2.56 (m, 1H), 2.51–2.38 (m, 3H), 2.33 (s, 3H), 2.27–2.17 (m, 1H).

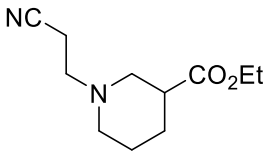
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 153.3, 145.1, 134.6, 127.6, 126.6, 126.3, 126.1, 125.9, 125.3, 125.0, 124.8, 122.0, 120.6, 118.9, 107.1, 73.9, 53.1, 53.0, 41.7, 36.7, 16.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2806, 1626, 1595, 1576, 1505, 1460, 1395, 1372, 1319, 1263, 1233, 1155, 1093, 1063, 1017, 974, 907, 788, 770, 726.

MS (ESI, 70 eV): *m/z* (%) = 351 (100), 299 (8), 97 (48).

HRMS (ESI): *m/z* calc. for [$C_{21}H_{22}N_2OS$]: 350.1453; found 351.1522 [M+H].

Ethyl 1-(2-cyanoethyl)piperidine-3-carboxylate (17q)



According to **TP10**, ethyl piperidine-3-carboxylate (**14q**, 157 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and added to a solution of sodium metal (23 mg, 1.00 mmol, 1.00 equiv). Then, acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added and the resulting mixture was stirred at 55 °C overnight. The solvent was removed and the crude product purified by flash column chromatography (EtOAc:MeOH 9.5:0.5) to afford the title compound as a colourless oil (200 mg, 0.95 mmol, 95%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.12 (q, *J* = 7.1 Hz, 1H), 2.95–2.88 (m, 1H), 2.76–2.65 (m, 1H), 2.60–2.46 (m, 2H), 2.30 (t, *J* = 10.4 Hz, 1H), 2.13 (td, *J* = 10.7, 3.1 Hz, 1H), 1.96–1.87 (m, 1H), 1.78–1.69 (m, 1H), 1.63–1.40 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 2H).

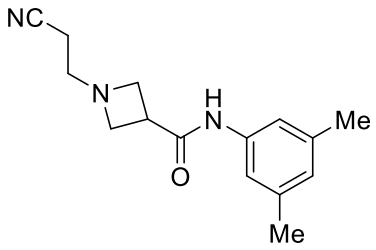
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.8, 118.8, 60.5, 54.9, 53.7, 53.3, 41.7, 26.6, 24.4, 15.9, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2943, 2813, 1725, 1469, 1447, 1370, 1307, 1235, 1217, 1214, 1182, 1153, 1135, 1103, 1032, 859.

MS (ESI, 70 eV): *m/z* (%) = 210 (15), 170 (100), 137 (24), 96 (31), 53 (39).

HRMS (EI): m/z calc. for [$C_{11}H_{18}N_2O_2$]: 210.1368; found 210.1361.

1-(2-cyanoethyl)-*N*-(3,5-dimethylphenyl)azetidine-3-carboxamide (17r)



According to **TP10**, *N*-(3,5-dimethylphenyl)azetidine-3-carboxamide (**14r**, 204 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL)and added to a solution of sodium metal (23 mg, 1.00 mmol, 1.00 equiv). Then, acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added and the resulting mixture was stirred at 55 °C overnight. The solvent was removed and the crude product purified by flash column chromatography (pure EtOAc) to afford the title compound as a colourless oil (196 mg, 0.76 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.19 (s, 1H), 7.21 (s, 2H), 6.76 (s, 1H), 3.54 (p, *J* = 7.0 Hz, 4H), 3.17 (ddd, *J* = 7.5, 5.1, 2.4 Hz, 1H), 2.76 (t, *J* = 6.6 Hz, 2H), 2.42 (t, *J* = 6.6 Hz, 2H), 2.29 (s, 6H).

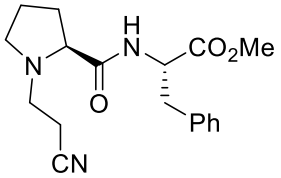
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.0, 139.2, 138.5 (2C), 138.1, 126.1, 125.9, 118.7, 118.0 (2C), 51.9, 43.9 (2C), 21.4, 18.3 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3292, 2946, 2915, 2831, 1679, 1610, 1598, 1530, 1459, 1454, 1449, 1426, 1310, 1193, 1129, 1037, 844, 690.

MS (EI, 70 eV): *m/z* (%) = 257 (3), 137 (8), 120 (100), 105 (10).

HRMS (EI): *m/z* calc. for [$C_{15}H_{19}N_3O$]: 257.3370; found 257.3373.

Methyl (2-cyanoethyl)-*L*-prolyl-*L*-phenylalaninate (17s)



According to **TP10**, methyl *L*-prolyl-*L*-phenylalaninate (**14s**, 276 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and acrylonitrile (0.33 mL, 265 mg, 5.00 mmol, 5.00 equiv) was added. After stirring the mixture at 55 °C overnight the solvent was removed and the crude product purified by flash column chromatography (pure EtOAc) to afford the title compound as a colourless oil (300 mg, 0.91 mmol, 91%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.66 (d, *J* = 8.6 Hz, 1H), 7.32–7.26 (m, 2H), 7.26–7.21 (m, 1H), 7.19–7.15 (m, 2H), 4.79 (td, *J* = 8.7, 5.2 Hz, 1H), 3.76 (s, 3H), 3.25 (dd, *J* = 14.0, 5.2 Hz, 1H), 3.19 (t, *J* = 7.1 Hz, 1H), 3.06 (dd, *J* = 9.7, 4.1 Hz, 2H), 2.96 (ddd, *J* = 12.4, 8.1, 6.7 Hz, 1H), 2.72 (dt, *J* = 12.4, 6.1 Hz, 1H), 2.57–2.40 (m, 2H), 2.33 (ddd, *J* = 10.1, 8.6, 6.2 Hz, 1H), 2.08 (dtd, *J* = 12.6, 10.0, 7.7 Hz, 1H), 1.78–1.68 (m, 1H), 1.66–1.45 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 174.0, 172.0, 136.4, 129.2 (2C), 128.5 (2C), 127.0, 118.7, 67.3, 53.8, 52.7, 52.4, 50.7, 37.4, 30.5, 24.2, 18.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 1741, 1668, 1506, 1455, 1436, 1360, 1215, 1200, 1177, 1128, 1030, 988, 746, 701.

MS (EI, 70 eV): *m/z* (%) = 329 (1), 262 (5), 123 (100), 91 (21), 51 (21).

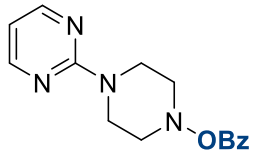
HRMS (EI): *m/z* calc. for [$C_{18}H_{23}N_3O_3$]: 329.1739; found 329.1745.

4.5 Preparation of *N*-Hydroxylamine Derivatives of Type 2

Additional Information

Most *N*-hydroxylamine derivatives of type **2** decompose prior to their melting points. Thus, no melting point was detected.

4-(Pyrimidin-2-yl)piperazin-1-yl benzoate (5j)



According to **TP11** 3-(4-(pyrimidin-2-yl)piperazin-1-yl)propanenitrile (**17b**, 217 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 3:1) to afford the desired product a pale white solid (230 mg, 0.81 mmol, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.33 (d, *J* = 4.7 Hz, 1H), 8.04–8.00 (m, 1H), 7.60–7.54 (m, 1H), 7.47–7.42 (m, 1H), 6.54 (t, *J* = 4.8 Hz, 1H), 4.65 (d, *J* = 13.3 Hz, 1H), 3.63–3.46 (m, 2H), 3.01 (s, 1H).

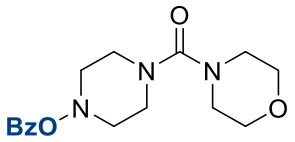
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.7, 161.4, 157.8 (2C), 133.2, 129.5 (2C), 129.2, 128.5 (2C), 110.4, 55.9 (2C), 42.2 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2931, 2824, 2812, 1613, 1582, 1497, 1453, 1364, 1354, 1304, 1240, 1262, 1219, 1143, 1159, 1096, 1021, 1010, 964, 940, 931, 883, 852, 791, 751, 720, 657.

MS (EI, 70 eV): *m/z* (%) = 284 (3), 163 (32), 122 (29), 105 (100), 77 (14).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}N_4O_2$]: 284.1273; found 284.1266.

4-(Morpholine-4-carbonyl)piperazin-1-yl benzoate (5k)



According to **TP11** 3-(4-(morpholine-4-carbonyl)piperazin-1-yl)propanenitrile (**17c**, 252 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 4:1) to afford the desired product a pale white solid (179 mg, 0.56 mmol, 56%).

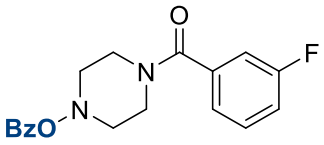
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.97 (dd, *J* = 38.1, 7.8 Hz, 2H), 7.54 (dt, *J* = 27.9, 7.5 Hz, 1H), 7.40 (dt, *J* = 18.0, 7.7 Hz, 2H), 3.75 (dt, *J* = 49.1, 5.4 Hz, 2H), 3.63 (p, *J* = 6.3, 5.7 Hz, 6H), 3.40 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.23 (tt, *J* = 10.1, 4.6 Hz, 6H), 2.92 (t, *J* = 10.6 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.3 (2C), 161.7 (2C), 133.3 (2C), 129.4 (2C), 129.0 (2C), 128.5 (2C), 66.6 (2C), 55.8 (2C), 47.3 (2C), 45.0 (2C).

NMR spectroscopy indicated the presence of rotamers. Therefore, 2 sets of carbon signals are observed.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2964, 2923, 2853, 1766, 1736, 1691, 1641, 1600, 1460, 1450, 1411, 1362, 1310, 1238, 1178, 1113, 1083, 1063, 1031, 1018, 1002, 919, 880, 789, 728, 708.

4-(3-Fluorobenzoyl)piperazin-1-yl benzoate (5l)



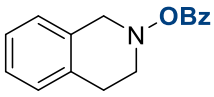
According to **TP11** 3-(4-(3-fluorobenzoyl)piperazin-1-yl)propanenitrile (**17d**, 261 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 6:1) to afford the desired product a pale white solid (213 mg, 0.65 mmol, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.96 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.45–7.32 (m, 3H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.15–7.05 (m, 2H), 4.54 (s, 1H), 3.74 (s, 1H), 3.47 (s, 4H), 2.95 (s, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 168.8 (d, *J* = 2.3 Hz), 164.4, 162.5 (d, *J* = 248.6 Hz), 137.1 (d, *J* = 6.9 Hz), 133.4, 130.5 (d, *J* = 8.0 Hz), 129.4, 128.8, 128.5, 122.7 (d, *J* = 3.2 Hz), 117.1 (d, *J* = 21.1 Hz), 114.40 (d, *J* = 22.8 Hz), 56.0, 55.7, 45.8, 40.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 1614, 1573, 1496, 1451, 1421, 1416, 1372, 1351, 1304, 1288, 1261, 1215, 1126, 1121, 1096, 1020, 1005, 942, 935, 881, 710, 687.

3,4-Dihydroisoquinolin-2(1*H*)-yl benzoate (5m)



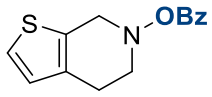
According to **TP11** 3-(3,4-dihydroisoquinolin-2(1*H*)-yl)propanenitrile (**17e**, 186 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 4:1) to afford the desired product a pale white solid (220 mg, 0.78 mmol, 78%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.00 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.23–7.12 (m, 3H), 7.06 (d, *J* = 6.4 Hz, 1H), 4.43 (s, 0H), 3.55 (s, 2H), 3.12 (t, *J* = 6.0 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.9, 133.2, 132.9, 132.3, 129.5 (2C), 129.3, 128.5 (2C), 128.4, 126.9, 126.8, 126.3, 58.1, 53.4, 26.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 2953, 2854, 1733, 1703, 1699, 1682, 1632, 1626, 1598, 1580, 1490, 1448, 1427, 1364, 1313, 1249, 1232, 1191, 1173, 1159, 1117, 1100, 1083, 1068, 1059, 1037, 1022, 1010, 1002, 996, 983, 961, 942, 923, 888, 878, 865, 841, 811, 795, 765, 759, 740, 705, 685, 680, 673, 660.

4,7-Dihydrothieno[2,3-*c*]pyridin-6(5*H*)-yl benzoate (5n)



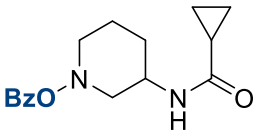
According to **TP11**, 3-(4,7-dihydrothieno[2,3-*c*]pyridin-6(5*H*)-yl)propanenitrile (**17f**, 192 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 9:1) to afford the desired product a pale white solid (220 mg, 0.85 mmol, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.00–7.97 (m, 2H), 7.59–7.53 (m, 1H), 7.43 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.15 (d, *J* = 5.1 Hz, 1H), 6.76 (d, *J* = 5.1 Hz, 1H), 4.60–4.10 (m, 0H), 3.57 (t, *J* = 6.0 Hz, 2H), 3.11 (t, *J* = 6.0 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 133.2, 132.3, 131.1, 129.5, 129.2, 128.5, 125.3, 123.5, 55.6, 53.1, 22.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2927, 2924, 2847, 1736, 1450, 1434, 1315, 1285, 1241, 1213, 1176, 1164, 1088, 1065, 1046, 1019, 996, 833, 804, 744, 706, 686, 678, 665.

3-(Cyclopropanecarboxamido)piperidin-1-yl benzoate (5o)



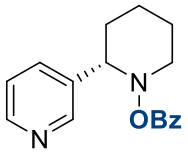
According to **TP11** *N*-(1-(2-cyanoethyl)piperidin-3-yl)cyclopropanecarboxamide (**17g**, 286 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (pure EtOAc 1:1) to afford the desired product a pale white solid (161 mg, 0.56 mmol, 56%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.00–7.92 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 6.97 (s, 1H), 4.39 (d, *J* = 32.0 Hz, 1H), 3.41 (d, *J* = 43.0 Hz, 1H), 3.09–2.66 (m, 2H), 2.06–1.90 (m, 1H), 1.78 (tt, *J* = 16.1, 12.0, 4.5 Hz, 1H), 1.61–1.36 (m, 1H), 1.24 (d, *J* = 5.5 Hz, 1H), 0.96–0.90 (m, 2H), 0.75–0.67 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.0, 165.0, 133.3, 129.4 (2C), 129.0, 128.5 (2C), 60.7, 56.8, 45.9, 29.4, 28.1, 21.0, 14.7, 7.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3290, 2947, 1736, 1639, 1545, 1451, 1402, 1249, 1232, 1201, 1176, 1100, 1083, 1065, 1034, 1024, 984, 948, 923, 904, 853, 828, 709, 686, 676, 659.

(*S*)-2-(Pyridin-3-yl)piperidin-1-yl benzoate (5p)



According to **TP11** (*S*)-3-(2-(pyridin-3-yl)piperidin-1-yl)propanenitrile (**17h**, 215 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 1:1) to afford the desired product a pale white solid (423 mg, 0.86 mmol, 86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.61 (d, *J* = 1.9 Hz, 1H), 8.42 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.87 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.66 (d, *J* = 7.3 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.20 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.91 (d, *J* = 10.7 Hz, 1H), 3.81–3.72 (m, 1H), 2.88 (t, *J* = 10.0 Hz, 1H), 2.10–1.78 (m, 5H), 1.56–1.40 (m, 1H).

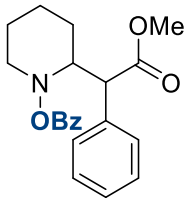
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.7, 148.7, 148.6, 138.0, 134.5, 132.9, 129.1 (2C), 129.0, 128.3 (2C), 123.7, 69.5, 58.1, 35.6, 25.4, 24.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2941, 2856, 1735, 1600, 1593, 1577, 1480, 1450, 1442, 1426, 1365, 1321, 1313, 1268, 1242, 1176, 1081, 1059, 1025, 1006, 933, 869, 804, 781, 707, 687, 674.

MS (EI, 70 eV): *m/z* (%) = 282 (9), 160 (16), 105 (100).

HRMS (EI): *m/z* calc. for [$C_{17}H_{18}N_2O_2$]: 282.1368; found 282.1370.

2-(2-Methoxy-2-oxo-1-phenylethyl)piperidin-1-yl benzoate (5q)



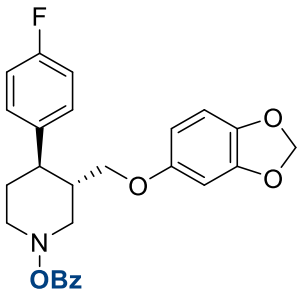
According to **TP11** methyl 2-(1-(2-cyanoethyl)piperidin-2-yl)-2-phenylacetate (**17i**, 286 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 4:1) to afford the desired product a pale white solid (216 mg, 0.61 mmol, 61%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (d, *J* = 8.2 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.39–7.22 (m, 5H), 3.83–2.78 (m, 7H), 1.93–1.51 (m, 3H), 1.45–1.13 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 174.1, 164.6, 136.0, 133.1, 129.6 (3C), 128.9 (2C), 128.6 (2C), 128.4 (2C), 127.6, 67.5, 58.0, 55.8, 51.6, 29.5, 25.2, 23.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2946, 2856, 1734, 1713, 1600, 1583, 1496, 1491, 1450, 1433, 1350, 1314, 1289, 1264, 1242, 1218, 1198, 1176, 1169, 1152, 1128, 1080, 1055, 1023, 1006, 1001, 973, 966, 940, 919, 897, 875, 864, 842, 791, 776, 731, 707, 699, 687, 674.

(3*S*,4*R*)-3-((Benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidin-1-yl benzoate (5r)



According to **TP11** 3-((3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidin-1-yl)propanenitrile (**17j**, 382 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 2:1) to afford the desired product a pale white solid (400 mg, 0.89 mmol, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04 (d, *J* = 7.7 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.22–7.14 (m, 2H), 6.99 (t, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 6.14 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.88 (s, 2H), 3.86 (dd, *J* = 10.4, 1.9 Hz, 1H), 3.71 (d, *J* = 9.5 Hz, 1H), 3.61 (dd, *J* = 9.4, 2.8 Hz, 1H), 3.51 (dd, *J* = 9.4, 5.9 Hz, 1H), 2.95 (dt, *J* = 35.3, 11.0 Hz, 2H), 2.68 (t, *J* = 11.8 Hz, 1H), 2.51 (s, 1H), 2.20 (q, *J* = 12.8 Hz, 1H), 2.00 (d, *J* = 13.9 Hz, 1H).

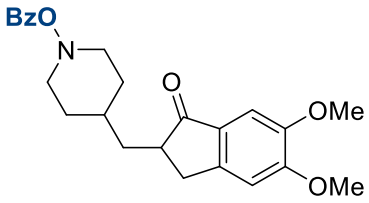
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.8, 161.7 (d, *J* = 244.9 Hz), 154.2, 148.2, 141.7, 138.4, 133.1, 129.5 (4C), 128.86 (d, *J* = 7.3 Hz), 128.4, 115.6 (d, *J* = 21.1 Hz), 107.9, 107.8, 105.5 (d, *J* = 6.5 Hz), 101.1 (d, *J* = 4.8 Hz), 101.1, 98.0 (d, *J* = 6.3 Hz), 68.9, 60.2, 57.3, 42.9, 42.1, 32.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 1735, 1509, 1502, 1487, 1468, 1450, 1261, 1240, 1224, 1183, 1159, 1086, 1059, 1037, 1025, 936, 908, 830, 783, 732, 729, 709.

MS (EI, 70 eV): *m/z* (%) = 449 (3), 327 (28), 188 (32), 147 (10), 138 (69), 105 (100), 77 (48), 44 (51).

HRMS (EI): *m/z* calc. for [$C_{26}H_{24}FNO_5$]: 449.1639; found 49.1631.

4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)methyl)piperidin-1-yl benzoate (5s)



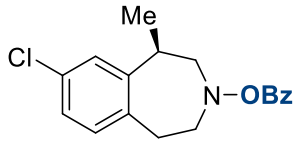
According to **TP11**, 3-(4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)piperidin-1-yl)propanenitrile (**17k**, 342 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 1:1) to afford the desired product a pale white solid (287 mg, 0.70 mmol, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07–7.91 (m, 2H), 7.55–7.46 (m, 1H), 7.42–7.33 (m, 2H), 7.11 (s, 1H), 6.80 (s, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.53 (d, *J* = 9.1 Hz, 2H), 3.21 (dd, *J* = 17.5, 8.1 Hz, 1H), 2.77–2.61 (m, 4H), 1.89–1.78 (m, 2H), 1.66–1.55 (m, 3H), 1.35–1.17 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 207.5, 164.8, 155.6, 149.5, 148.7, 133.4, 129.5, 129.4, 129.2, 128.4, 107.3, 104.4, 57.1, 56.3, 56.1, 45.4, 38.2, 33.6, 33.5, 31.9, 31.3, 29.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2911, 1626, 1639, 1616, 1591, 1515, 1509, 1502, 1487, 1432, 1269, 1246, 1224, 1121, 1038, 869.

(*R*)-8-Chloro-1-methyl-1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepin-3-yl benzoate (5t)



According to **TP11** (*R*)-3-(8-chloro-1-methyl-1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepin-3-yl)propanenitrile (**17l**, 249 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 7:1) to afford the desired product a pale white solid (268 mg, 0.85 mmol, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.02 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.19 (s, 1H), 7.13 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 3.85–3.15 (m, 2H), 2.85 (s, 1H), 1.43 (d, *J* = 7.3 Hz, 2H).

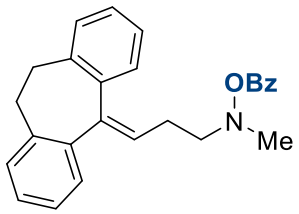
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.4, 146.3, 138.9, 133.1, 132.5, 130.6, 129.4 (4C), 129.4, 128.5 (2C), 126.3, 57.8, 31.6 (2C), 18.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2963, 2841, 1736, 1597, 1569, 1450, 1404, 1382, 1370, 1314, 1241, 1176, 1083, 1065, 1058, 1049, 1024, 1009, 947, 878, 819, 707.

MS (EI, 70 eV): *m/z* (%) = 315 (1), 122 (10), 105 (100), 77 (19).

HRMS (EI): *m/z* calc. for [$C_{18}H_{18}ClNO_2$]: 315.1026; found 315.1024.

_O_-Benzoyl-_N_-(3-(10,11-dihydro-5_H_-dibenzo[_a,d_][7]annulen-5-ylidene)propyl)-_N_-methylhydroxylamine (5u)



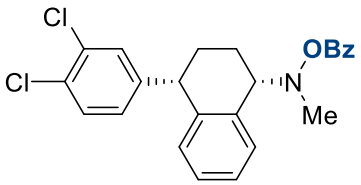
According to **TP11** 3-((3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl) (methyl)amino)propanenitrile (**17m**, 316 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 4:1) to afford the desired product a pale white solid (345 mg, 0.90 mmol, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.93 (d, *J* = 8.4 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.32–7.28 (m, 1H), 7.20–7.09 (m, 6H), 7.05 (dd, *J* = 6.9, 2.1 Hz, 1H), 5.98 (t, *J* = 7.5 Hz, 1H), 3.47–3.23 (m, 2H), 3.17–2.95 (m, 3H), 2.91 (s, 3H), 2.75 (d, *J* = 14.1 Hz, 1H), 2.53 (q, *J* = 6.5 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.1, 144.4, 141.0, 139.9, 139.3, 137.1, 133.0, 130.0, 129.4 (2C), 129.3, 128.6, 128.4 (2C), 128.1, 128.1, 127.5, 127.1, 126.0, 125.8, 60.8, 47.0, 33.8, 32.0, 27.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2918, 2236, 1731, 1601, 1485, 1450, 1441, 1429, 1362, 1314, 1258, 1246, 1195, 1175, 1160, 1080, 1060, 1024, 1002, 907, 869, 859, 815, 801, 776, 769, 755, 726, 706, 686, 669.

_O_-Benzoyl-_N_-((1_S_,4_S_)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-_N_-methylhydroxylamine (5v)



According to **TP11** 3-(((1*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)(methyl)amino)propanenitrile (**17n**, 359 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 9:1) to afford the desired product a pale white solid (307 mg, 0.72 mmol, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91 (d, *J* = 7.2 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.27 (d, *J* = 0.8 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.89 (t, *J* = 9.4 Hz, 2H), 4.25 (t, *J* = 6.0 Hz, 1H), 4.15 (t, *J* = 5.3 Hz, 1H), 3.00 (s, 2H), 2.32–2.25 (m, 1H), 2.22–2.15 (m, 2H), 2.06–1.99 (m, 1H).

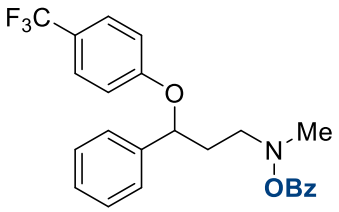
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.7, 147.4, 138.5, 135.8, 133.0, 132.2, 130.7, 130.6, 130.2 (2C), 130.0, 129.5, 129.4, 129.4 (2C), 128.5, 128.4, 127.7, 126.7, 65.4, 44.1, 42.7, 29.2, 20.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2948, 2944, 2861, 1739, 1601, 1584, 1489, 1467, 1450, 1396, 1352, 1314, 1258, 1247, 1209, 1174, 1131, 1087, 1076, 1058, 1024, 908, 878, 819, 782, 760, 740, 707, 686, 678.

MS (EI, 70 eV): *m/z* (%) = 425 (1), 275 (30), 158 (21), 105 (100).

HRMS (EI): *m/z* calc. for [$C_{24}H_{21}Cl_2NO_2$]: 425.0949; found 425.0948.

_O_-Benzoyl-_N_-methyl-_N_-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)hydroxylamine (5w)



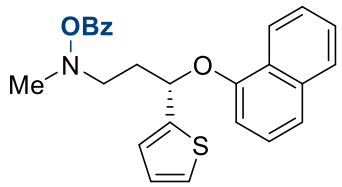
According to **TP11** 3-(methyl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino) propanenitrile (**17o**, 362 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 7:1) to afford the desired product a pale white solid (283 mg, 0.66 mmol, 66%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.00 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.34–7.28 (m, 3H), 7.24 (t, *J* = 7.0 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 5.49 (d, *J* = 8.4 Hz, 1H), 3.22–3.16 (m, 1H), 3.14–3.06 (m, 1H), 2.90 (s, 2H), 2.32–2.21 (m, 1H), 2.15–2.06 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.3, 160.5, 140.8, 133.2, 129.4 (4C), 129.1, 128.8 (2C), 128.5 (2C), 127.8 , 126.7 (2C), 124.4 (q, J = 271.1 Hz), 122.8 (q, J = 32.7 Hz), 115.8 (2C), 77.8, 57.2, 47.4, 36.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 2964, 2851, 1738, 1614, 1585, 1516, 1494, 1451, 1424, 1324, 1245, 1200, 1176, 1159, 1109, 1081, 1066, 1024, 1009, 962, 868, 835, 810, 757, 708, 701, 687, 668.

_O_-Benzoyl-_N_-((1_R_,2_S_)-1-((_tert_-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-_N_-methylhydroxylamine (5x)



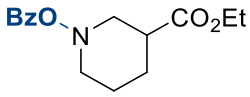
According to **TP11** 3-(((1*R*,2*S*)-1-((*tert*-butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)(methyl)amino)propanenitrile (**17p**, 261 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 4:1) to afford the desired product a pale white solid (340 mg, 0.85 mmol, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.47–8.39 (m, 1H), 8.07 (d, *J* = 7.5 Hz, 2H), 7.82 (dt, *J* = 7.7, 2.6 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.58–7.41 (m, 5H), 7.34–7.27 (m, 1H), 7.23 (d, *J* = 4.7 Hz, 1H), 7.13 (d, *J* = 3.2 Hz, 1H), 7.00–6.93 (m, 2H), 3.29 (hept, *J* = 7.3 Hz, 2H), 2.95 (s, 3H), 2.70–2.58 (m, 1H), 2.46–2.35 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.3, 153.3, 144.9, 134.6, 133.2, 129.5 (2C), 129.2, 128.5 (2C), 127.6, 126.7, 126.4, 126.1, 125.9, 125.3, 124.9, 124.9, 122.1, 120.7, 107.2, 74.1, 57.4, 47.5, 36.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057, 1735, 1595, 1578, 1506, 1461, 1449, 1396, 1315, 1260, 1235, 1176, 1092, 1080, 1057, 1024, 1018, 907, 790, 770, 728, 722, 707, 702, 686, 665.

Ethyl 1-(benzoyloxy)piperidine-3-carboxylate (5y)



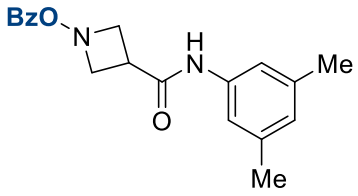
Then, according to **TP11**, ethyl 1-(2-cyanoethyl)piperidine-3-carboxylate (**17q**, 210 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 4:1) to afford the desired product a yellowish oil (175 mg, 0.63 mmol, 63%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04–7.86 (m, 2H), 7.59–7.51 (m, 1H), 7.48–7.35 (m, 2H), 4.14 (q, *J* = 7.3 Hz, 2H), 3.84–2.64 (m, 5H), 2.09–1.37 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.7, 164.6, 133.1, 129.4 (2C), 128.4 (2C), 127.6, 60.7, 58.3, 56.7, 41.5, 26.2, 23.6, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2952, 2839, 1728, 1601, 1476, 1450, 1378, 1313, 1244, 1234, 1177, 1147, 1133, 1084, 1063, 1044, 1025, 1012, 911, 854, 802, 794, 729, 707, 687, 674.

3-((3,5-dimethylphenyl)carbamoyl)azetidin-1-yl benzoate (5z)



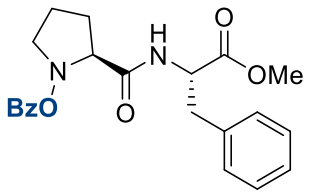
According to **TP11** 1-(2-cyanoethyl)-N-(3,5-dimethylphenyl)azetidine-3-carboxamide (**17r**, 257 mg, 1.00 mmol, 1.00 equiv) and K_2CO_3 (207 mg, 1.5 mmol, 1.50 equiv) was suspended in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 4:1) to afford the desired product a pale white solid (169 mg, 0.52 mmol, 52%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.16 (s, 1H), 7.96–7.90 (m, 2H), 7.53–7.47 (m, 1H), 7.40–7.34 (m, 2H), 7.16 (s, 2H), 6.68 (s, 1H), 4.09 (d, *J* = 7.9 Hz, 4H), 3.36 (p, *J* = 8.1 Hz, 1H), 2.19 (d, *J* = 3.7 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 168.2, 165.3, 138.7 (2C), 133.4, 129.7, 129.5 (2C), 128.5 (2C), 128.0, 126.3, 117.7 (2C), 61.8 (2C), 45.0, 21.4 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3309, 2917, 1732, 1686, 1612, 1600, 1546, 1461, 1450, 1433, 1315, 1246, 1177, 1082, 1061, 1025, 842, 708, 689.

(*S*)-2-(((*S*)-1-Methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidin-1-yl benzoate (5aa)



According to **TP11** methyl N^2-(*tert*-butoxycarbonyl)-N^6-(2-cyanoethyl)-N^6-ethyl-*L*-lysylglycinate (**17s**, 399 mg, 1.00 mmol, 1.00 equiv) and K_2CO_3 (207 mg, 1.5 mmol, 1.50 equiv) was suspended in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 1:1) to afford the desired product a pale white solid (273 mg, 0.69 mmol, 69%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.17 (d, *J* = 8.3 Hz, 1H), 8.14–7.94 (m, 2H), 7.65–7.55 (m, 1H), 7.46 (dtd, *J* = 14.1, 7.6, 7.1, 1.7 Hz, 2H), 7.32–7.18 (m, 4H), 7.18–7.13 (m, 1H), 4.95–4.76 (m, 1H), 4.07–3.97 (m, 1H), 3.87 (dd, *J* = 9.9, 6.6 Hz, 0.5H), 3.62 (d, *J* = 66.4 Hz, 3H), 3.45–2.96 (m, 3H), 2.81 (tt, *J* = 8.6, 2.5 Hz, 1H), 2.35–2.24 (m, 0.5H), 2.03–1.67 (m, 3H).

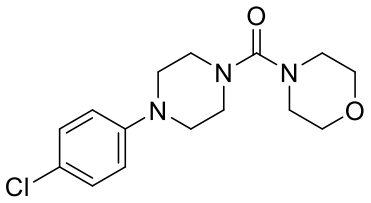
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.5, 171.3, 165.7, 135.9, 133.4, 130.2, 129.6 (2C), 129.2 (2C), 128.6 (2C), 128.5 (2C), 127.1, 69.9, 61.9, 53.2, 52.4, 38.1, 34.0, 22.1.

NMR spectroscopy indicated the presence of rotamers. Therefore, 2 sets of proton and carbon signals are observed.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2948, 1738, 1677, 1626, 1602, 1519, 1497, 1450, 1436, 1315, 1248, 1217, 1176, 1157, 1083, 1064, 1025, 711, 703, 688.

4.6 Preparation of Amination Products of Type 2

(4-(4-Chlorophenyl)piperazin-1-yl)(morpholino)methanone (2w)



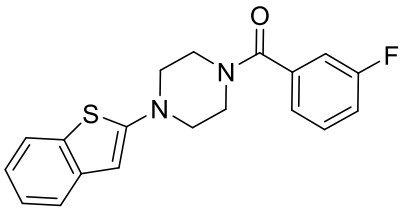
According to **TP13** 4-(morpholine-4-carbonyl)piperazin-1-yl benzoate (**5k**, 160 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (4-chlorophenyl)zinc chloride (, 2.6 mL, 0.29 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 9:1) afforded the title compound as a colourless oil (138mg, 0.45 mmol, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.21 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 3.75–3.65 (m, 4H), 3.46–3.38 (m, 4H), 3.31 (t, *J* = 4.7 Hz, 4H), 3.17–3.08 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.7, 149.8, 129.1 (2C), 125.2, 117.7 (2C), 66.7 (2C), 49.3 (2C), 47.3 (2C), 46.6 (2C).

Analytical data according to literature[89]

(4-(benzo[*b*]thiophen-2-yl)piperazin-1-yl)(3-fluorophenyl)methanone (2x)



According to **TP13** 4-(3-fluorobenzoyl)piperazin-1-yl benzoate (**5l**, 164 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent benzo[*b*]thiophen-2-ylzinc chloride (**1o**, 2.8 mL, 0.27 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:1) afforded the title compound as a colourless oil (47 mg, 0.46 mmol, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.64 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.48–7.41 (m, 1H), 7.31–7.26 (m, 1H), 7.24 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.22–7.13 (m, 3H), 6.30 (s, 1H), 4.12–3.11 (m, 8H).

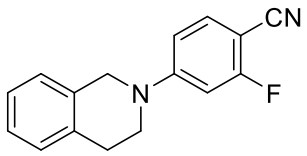
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.0, 162.6 (d, *J* = 248.6 Hz), 156.8, 140.1, 137.3 (d, *J* = 6.9 Hz), 133.0, 130.5 (d, *J* = 8.0 Hz), 124.7, 122.8 (d, *J* = 3.2 Hz), 122.0, 121.7, 121.3, 117.1 (d, *J* = 21.1 Hz), 114.48 (d, *J* = 22.8 Hz), 101.0, 51.1 (2C), 46.9, 41.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066, 1713, 1637, 1634, 1613, 1583, 1566, 1535, 1489, 1458, 1439, 1384, 1304, 1285, 1266, 1254, 1231, 1210, 1199, 1157, 1130, 1067, 1010, 941, 821, 793, 777, 747, 724.

MS (EI, 70 eV): *m/z* (%) = 340 (90), 215 (69), 160 (100), 95 (57).

HRMS (EI): *m/z* calc. for [$C_{19}H_{17}FN_2OS$]: 340.1064; found 340.1073.

4-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-fluorobenzonitrile (2y)



According to **TP13** 3,4-dihydroisoquinolin-2(1*H*)-yl benzoate (**5k**, 127 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (4-cyano-3-fluorophenyl)zinc chloride (**1p**, 2.6 mL, 0.29 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 9:1) afforded the title compound as a colourless oil (108 mg, 0.43 mmol, 86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.42 (dd, *J* = 8.9, 7.7 Hz, 1H), 7.26–7.16 (m, 3H), 6.64 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.56 (dd, *J* = 13.1, 2.5 Hz, 1H), 4.49 (s, 2H), 3.62 (t, *J* = 5.9 Hz, 2H), 3.00 (t, *J* = 5.9 Hz, 2H).

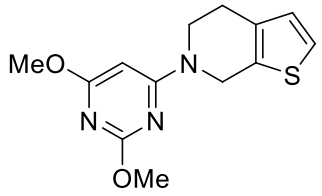
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm =164.91 (d, *J* = 253.9 Hz), 154.08 (d, *J* = 11.1 Hz), 134.8, 133.9, 132.9, 128.1, 127.2, 126.60 (d, *J* = 26.0 Hz), 115.7, 108.5, 99.32 (d, *J* = 3.9 Hz), 99.08 (d, *J* = 3.7 Hz), 87.32 (d, *J* = 16.2 Hz), 48.7, 44.7, 28.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3073, 2234, 1708, 1655, 1651, 1602, 1584, 1578, 1498, 1473, 1460, 1422, 1406, 1331, 1310, 1296, 1257, 1225, 1168, 1159, 1117, 1063, 879, 831, 818, 775, 746, 702.

MS (EI, 70 eV): *m/z* (%) = 252 (76), 147 (10), 120 (15), 104 (100), 78 (21).

HRMS (EI): *m/z* calc. for [$C_{16}H_{13}FN_2$]: 252.1063; found 252.1061.

6-(2,6-Dimethoxypyrimidin-4-yl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (2z)



According to **TP13** 4,7-dihydrothieno[2,3-c]pyridin-6(5*H*)-yl benzoate (**5n**, 130 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (2,6-dimethoxypyrimidin-4-yl)zinc chloride (**1q**, 2.7 mL, 0.28 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 9:1) afforded the title compound as a colourless oil (98 mg, 0.35 mmol, 71%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.86 (s, 1H), 7.13 (d, *J* = 5.1 Hz, 1H), 6.79 (d, *J* = 5.1 Hz, 1H), 4.17 (d, *J* = 1.7 Hz, 2H), 4.06 (s, 3H), 3.96 (s, 3H), 3.41 (t, *J* = 5.7 Hz, 2H), 2.94 (t, *J* = 5.8 Hz, 2H).

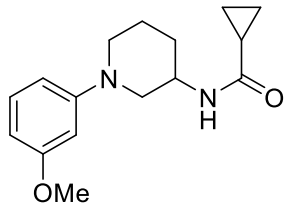
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.9, 160.7, 146.5, 133.3, 132.9, 128.2, 124.9, 123.1, 54.8, 54.3, 50.5, 48.6, 25.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 1740, 1595, 1562, 1479, 1468, 1456, 1409, 1380, 1278, 1243, 1211, 1080, 1055, 1014, 790, 699.

MS (EI, 70 eV): *m/z* (%) =277 (80), 247 (71), 138 (57), 109 (100), 81 (31), 56 (25).

HRMS (EI): *m/z* calc. for [$C_{13}H_{15}N_3O_2S$]: 277.0885; found 277.0882.

***N*-(1-(3-Methoxyphenyl)piperidin-3-yl)cyclopropanecarboxamide (2aa)**



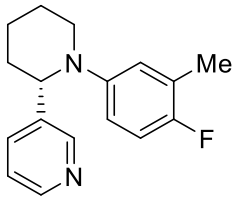
According to **TP13** 3-(cyclopropanecarboxamido)piperidin-1-yl benzoate (**5o**, 144 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (3-methoxyphenyl)zinc chloride (**1r**, 2.6 mL, 0.29 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 2:1) afforded the title compound as a colourless oil (106 mg, 0.39 mmol, 77%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.16 (t, *J* = 8.2 Hz, 1H), 6.60–6.54 (m, 1H), 6.49 (t, *J* = 2.2 Hz, 1H), 6.43 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.13 (d, *J* = 7.5 Hz, 1H), 4.25–4.16 (m, 1H), 3.79 (s, 3H), 3.30–3.19 (m, 2H), 3.12–2.99 (m, 2H), 1.88–1.59 (m, 4H), 1.40–1.30 (m, 1H), 1.00–0.94 (m, 2H), 0.72 (dq, *J* = 7.2, 3.9 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.8, 160.6, 153.2, 129.8, 109.9, 104.8, 103.5, 55.2, 55.2, 50.3, 45.0, 29.4, 22.3, 14.9, 7.2 (2C).

Analytical data according to literature[90]

(*S*)-3-(1-(4-Fluoro-3-methylphenyl)piperidin-2-yl)pyridine (2bb)



According to **TP13** (*S*)-2-(pyridin-3-yl)piperidin-1-yl benzoate (**5p**, 141 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (4-fluoro-3-methylphenyl)zinc chloride (**1s**, 2.7 mL, 0.28 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc:CH_2Cl_2 1:1:1) afforded the title compound as a colourless oil (105 mg, 0.39 mmol, 78%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.47 (d, *J* = 2.3 Hz, 1H), 8.33 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.54 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.09 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.77 (dd, *J* = 7.0, 2.6 Hz, 1H), 6.73–6.65 (m, 2H), 4.07 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.33 (dtd, *J* = 12.0, 3.9, 1.5 Hz, 1H), 2.91–2.82 (m, 1H), 2.11 (d, *J* = 2.0 Hz, 3H), 1.96–1.88 (m, 1H), 1.86–1.66 (m, 4H), 1.59–1.45 (m, 1H).

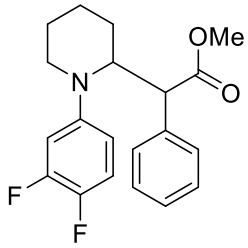
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.0 (d, *J* = 240.2 Hz), 149.2, 148.0 (d, *J* = 2.9 Hz), 147.8, 139.8, 135.0, 126.0 (d, *J* = 5.0 Hz), 124.8 (d, *J* = 18.1 Hz), 123.3, 121.3 (d, *J* = 7.8 Hz), 114.8 (d, *J* = 23.0 Hz), 61.9, 56.2, 35.9, 26.3, 23.9, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932, 2856, 1576, 1499, 1479, 1449, 1441, 1423, 1372, 1326, 1284, 1264, 1252, 1224, 1203, 1184, 1173, 1147, 1120, 1103, 1063, 1057, 1023, 995, 956, 893, 880, 845, 838, 809, 758, 715.

MS (EI, 70 eV): *m/z* (%) = 270 (48), 193 (12), 192 (100), 136 (14), 109 (22), 83 (18), 57 (36), 43 (54).

HRMS (EI): *m/z* calc. for [$C_{17}H_{19}FN_2$]: 270.1532; found 270.1530.

Methyl 2-(1-(3,4-Difluorophenyl)piperidin-2-yl)-2-phenylacetate (2cc)



According to **TP13** 2-(2-methoxy-2-oxo-1-phenylethyl)piperidin-1-yl benzoate (**5q**, 177 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (3,4-difluorophenyl)zinc chloride (**1t**, 2.9 mL, 0.26 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 4:1) afforded the title compound as a colourless oil (140 mg, 0.41 mmol, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.41–7.37 (m, 2H), 7.31–7.25 (m, 2H), 7.25–7.22 (m, 1H), 6.93 (q, *J* = 9.3 Hz, 1H), 6.75 (ddd, *J* = 13.8, 6.9, 3.0 Hz, 1H), 6.66–6.60 (m, 1H), 4.36 (dd, *J* = 11.5, 3.9 Hz, 1H), 4.26 (d, *J* = 11.5 Hz, 1H), 3.39 (s, 3H), 3.38–3.27 (m, 2H), 1.71–1.31 (m, 6H).

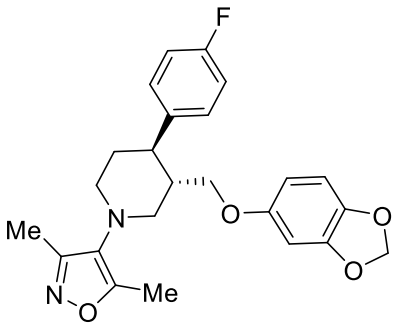
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.2, 150.5 (dd, *J* = 244.3, 13.2 Hz), 147.8 (dd, *J* = 8.0, 2.1 Hz), 143.2 (dd, *J* = 238.5, 13.0 Hz), 136.3, 128.9 (2C), 128.6 (2C), 127.8, 117.0 (dd, *J* = 17.5, 1.8 Hz), 111.7 (dd, *J* = 5.3, 2.9 Hz), 105.4 (d, *J* = 20.2 Hz), 60.8, 51.9, 51.2, 42.7, 24.0, 23.3, 19.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2946, 2939, 1732, 1628, 1598, 1514, 1497, 1454, 1445, 1434, 1392, 1354, 1317, 1274, 1223, 1210, 1195, 1186, 1156, 1126, 1109, 1022, 1010, 964, 873, 832, 824, 799, 775, 733, 703, 696.

MS (EI, 70 eV): *m/z* (%) = 345 (1), 225 (11), 196 (100), 178 (95), 91 (90).

HRMS (EI): *m/z* calc. for [$C_{20}H_{21}F_2NO_2$]: 345.1540; found 345.1547.

4-((3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidin-1-yl)-3,5-dimethylisoxazole (2dd)



According to **TP13** (3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl) piperidin-1-yl benzoate (**5r**, 225 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (3,5-dimethylisoxazol-4-yl)zinc chloride (**1u**, 2.9 mL, 0.26 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 3:1) afforded the title compound as a colourless oil (136 mg, 0.32 mmol, 64%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.23–7.19 (m, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.33 (d, *J* = 2.5 Hz, 1H), 6.12 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.87 (s, 2H), 3.59 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.49–3.45 (m, 1H), 3.35 (dd, *J* = 11.3, 3.1 Hz, 2H), 3.10–3.00 (m, 2H), 2.96 (t, *J* = 11.0 Hz, 1H), 2.53 (td, *J* = 11.6, 4.3 Hz, 1H), 2.41 (s, 3H), 2.28 (s, 3H), 1.96–1.85 (m, 2H).

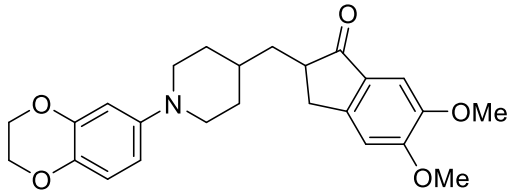
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.6 (d, *J* = 244.6 Hz), 160.7, 158.3, 154.2, 148.2, 141.6, 139.4 (d, *J* = 3.1 Hz), 128.8, 128.0, 115.5 (d, *J* = 21.1 Hz, 2C), 107.9, 107.8, 105.5 (d, *J* = 9.2 Hz), 101.1, 97.9 (d, *J* = 9.4 Hz), 69.3, 56.2, 52.9, 43.9, 42.9, 35.2, 11.7 (d, *J* = 5.0 Hz), 10.6 (d, *J* = 3.8 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2919, 1631, 1604, 1509, 1502, 1486, 1467, 1451, 1422, 1389, 1283, 1269, 1242, 1214, 1180, 1159, 1135, 1101, 1099, 1090, 1036, 1015, 951, 937, 922, 911, 832, 816, 798, 784, 765, 731.

MS (EI, 70 eV): *m/z* (%) = 424 (100), 383 (11), 342 (48), 287 (58), 220 (21), 190 (29), 139 (70), 109 (60), 96 (24), 56 (39), 44 (52), 43 (79).

HRMS (EI): *m/z* calc. for [$C_{24}H_{25}FN_2O_4$]: 424.1798; found 424.1796.

2-((1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)piperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (2ee)



According to **TP13** 4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)piperidin-1-yl benzoate (**5s**, 205 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)zinc chloride (**1v**, 2.9 mL, 0.26 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:1) afforded the title compound as a colourless oil (157 mg, 0.37 mmol, 74%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.12 (s, 1H), 6.80 (s, 1H), 6.73–6.68 (m, 1H), 6.49–6.44 (m, 2H), 4.19–4.15 (m, 2H), 4.15–4.12 (m, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.51–3.41 (m, 2H), 3.25–3.15 (m, 1H), 2.72–2.63 (m, 2H), 2.62–2.52 (m, 2H), 1.93–1.84 (m, 1H), 1.82–1.70 (m, 2H), 1.61–1.19 (m, 4H).

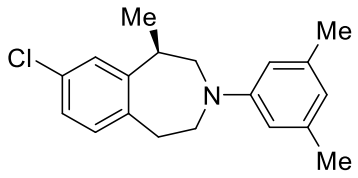
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 207.9, 155.5, 149.5, 148.9, 143.6, 133.5, 130.1, 128.4, 117.3, 111.3, 107.4, 106.4, 104.4, 64.6, 64.3, 56.2, 56.1, 51.4, 45.3, 38.7, 34.2, 33.4, 32.9, 31.7, 29.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921, 2851, 2360, 2335, 1697, 1691, 1598, 1578, 1502, 1496, 1453, 1313, 1283, 1264, 1244, 1222, 1211, 1173, 1153, 1123, 1068, 1038, 961, 912, 890, 854, 794, 715.

MS (EI, 70 eV): *m/z* (%) = 423 (15), 288 (47), 191 (100), 135 (31), 97 (21), 55 (16).

HRMS (EI): *m/z* calc. for [$C_{25}H_{29}NO_5$]: 423.2046; found 423.2046.

(*R*)-8-Chloro-3-(3,5-dimethylphenyl)-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2ff)



According to **TP13** (*R*)-8-chloro-1-methyl-1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepin-3-yl benzoate (**5t**, 158 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (3,5-dimethylphenyl)zinc chloride (**1w**, 2.6 mL, 0.29 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 4:1) afforded the title compound as a colourless oil (118 mg, 0.40 mmol, 79%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.15 (d, *J* = 1.9 Hz, 1H), 7.07 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.47 (s, 2H), 6.42 (s, 1H), 3.74–3.61 (m, 1H), 3.36–3.26 (m, 2H), 3.09–2.94 (m, 1H), 2.28 (s, 4H), 1.36 (d, *J* = 6.5 Hz, 2H).

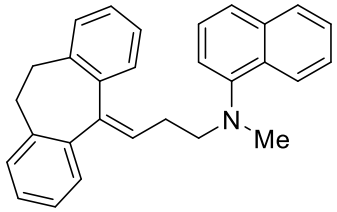
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.9, 146.9, 138.9 (2C), 138.6, 132.0, 131.1, 127.2, 125.9, 119.4, 112.1 (2C), 55.8, 49.9, 39.2, 35.1, 21.8, 18.9 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2960, 2916, 1593, 1568, 1478, 1475, 1463, 1389, 1372, 1360, 1265, 1194, 1175, 1155, 1101, 1038, 1000, 953, 931, 909, 886, 813, 730, 688, 662.

MS (EI, 70 eV): *m/z* (%) = 229 (100), 234 (60), 115 (49).

HRMS (EI): *m/z* calc. for [$C_{19}H_{22}ClN$]: 299.1441; found 229.1434.

***N*-(3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl)-*N*-methylnaphthalen-1-amine (2gg)**



According to **TP13** *O*-benzoyl-*N*-(3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl)-*N*-methylhydroxylamine (**5u**, 192 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent naphthalen-1-ylzinc chloride (**1x**, 2.8 mL, 0.27 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 9:1) afforded the title compound as a yellowish oil (175 mg, 0.45 mmol, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.27 (d, *J* = 7.7 Hz, 1H), 7.89–7.80 (m, 1H), 7.60–7.45 (m, 3H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.32–7.27 (m, 1H), 7.23 (d, *J* = 4.2 Hz, 2H), 7.20–7.03 (m, 6H), 5.98 (t, *J* = 7.6 Hz, 1H), 3.48–3.17 (m, 4H), 2.99 (s, 1H), 2.85 (s, 3H), 2.80 (s, 1H), 2.50 (q, *J* = 7.5 Hz, 2H).

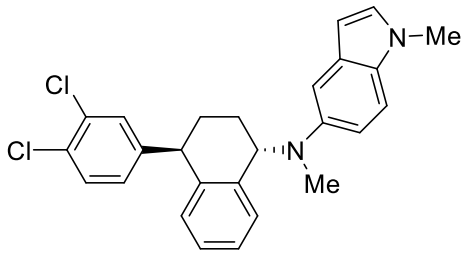
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 150.1, 143.9, 141.3, 140.1, 139.4, 137.1, 134.9, 130.0, 129.5, 129.1, 128.6, 128.3, 128.2, 128.0, 127.4, 127.0, 126.0, 125.8, 125.7, 125.2, 124.0, 123.2, 123.1, 115.6, 57.0, 42.2, 33.8, 32.0, 27.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3432, 1725, 1481, 1451, 1368, 1316, 1284, 1258, 1212, 1178, 1132, 1114, 1088, 1066, 1046, 1034, 1019, 976, 908, 831, 731, 709, 664.

MS (EI, 70 eV): *m/z* (%) = 389 (1), 170 (100).

HRMS (EI): *m/z* calc. for [$C_{29}H_{27}N$]: 389.2143; found 389.2144.

_N_-((1_S_,4_R_)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-_N_,1-dimethyl-1_H_-indol-5-amine (2hh)



According to **TP13** *O*-benzoyl-*N*-((1*S*,4*R*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen -1-yl)-*N*-methylhydroxylamine (**5v**, 213 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (1-methyl-1*H*-indol-5-yl)zinc chloride (**1y**, 2.9 mL, 0.26 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 10:1) afforded the title compound as a white solid (139 mg, 0.32 mmol, 64%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.70 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.33–7.25 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.17 (dd, *J* = 13.4, 1.6 Hz, 2H), 7.08–7.00 (m, 2H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.90 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.39 (d, *J* = 2.9 Hz, 1H), 5.07 (dd, *J* = 10.3, 5.8 Hz, 1H), 4.25–4.19 (m, 1H), 3.79 (s, 3H), 2.76 (s, 3H), 2.27 (tdd, *J* = 12.9, 5.7, 2.8 Hz, 1H), 2.06–1.97 (m, 1H), 1.95–1.83 (m, 1H), 1.81–1.70 (m, 1H).

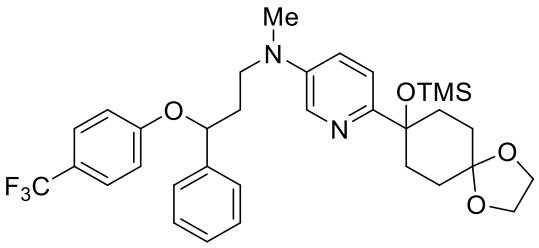
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 147.6, 145.1, 139.3, 138.2, 132.2, 131.3, 130.8, 130.5, 130.0, 129.9, 129.3, 129.1, 128.2, 128.1, 127.2, 127.1, 112.7, 109.7, 105.6, 100.0, 61.0, 43.6, 33.7, 32.9, 30.6, 19.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936, 2865, 1621, 1569, 1489, 1466, 1448, 1420, 1386, 1316, 1268, 1247, 1217, 1131, 1113, 1085, 1029, 975, 907, 881, 826, 784, 729, 678.

MS (EI, 70 eV): *m/z* (%) = 343 (18), 159 (100), 131 (13), 43 (20).

HRMS (EI): *m/z* calc. for [$C_{26}H_{24}Cl_2N_2$]: 434.1317; found 434.1308.

_N_-Methyl-_N_-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)-6-(8-((trimethylsilyl)oxy)-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-amine (2ii)



According to **TP13** *O*-benzoyl-*N*-methyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy) propyl)hydroxylamine (**5w**, 215 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (6-(8-((trimethylsilyl)oxy)-1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)zinc chloride (**1z**, 3.3 mL, 0.23 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 3:1) afforded the title compound as a colourless oil (188 mg, 0.31 mmol, 61%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (d, *J* = 3.0 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.35–7.31 (m, 2H), 7.30–7.25 (m, 4H), 6.92 (dd, *J* = 8.8, 3.1 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.18 (dd, *J* = 8.9, 3.9 Hz, 1H), 4.00–3.92 (m, 4H), 3.61–3.54 (m, 2H), 2.94 (s, 3H), 2.25–2.10 (m, 4H), 2.10–2.03 (m, 2H), 1.99 (t, *J* = 11.8 Hz, 2H), 1.69–1.63 (m, 2H), -0.11 (s, 9H).

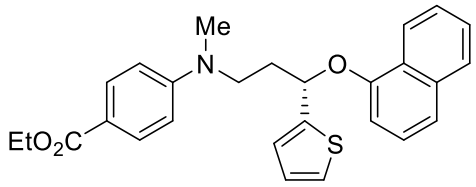
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.3–160.2 (m), 152.6, 143.5, 140.5, 132.4, 129.0–128.8 (m), 128.0, 126.8 (q, *J* = 3.4 Hz), 124.3 (q, *J* = 271.2 Hz), 123.0 (q, *J* = 32.7 Hz), 120.8 (d, *J* = 6.1 Hz, 2C), 119.1, 115.7 (4C), 108.9, 77.9, 77.8, 75.7, 64.2, 64.1, 48.7, 38.2, 38.2, 35.7, 35.7, 35.6, 31.0, 1.9 (3C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2880, 1614, 1591, 1555, 1516, 1497, 1452, 1371, 1323, 1246, 1210, 1177, 1158, 1107, 1067, 1052, 1037, 1010, 944, 937, 908, 862, 834, 753, 701.

MS (EI, 70 eV): *m/z* (%) = 614 (1), 600 (11), 525 (12), 438 (20), 362 (21), 297 (15), 276 (43), 173 (17), 162 (44), 101 (29), 75 (100).

HRMS (EI): *m/z* calc. for [$C_{33}H_{41}F_3N_2O_4Si$]: 614.2788; found 614.2796.

(*S*)-4-Chloro-*N*-methyl-*N*-(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)aniline (2jj)



According to **TP13** (*S*)-*O*-benzoyl-*N*-methyl-*N*-(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)hydroxylamine (**5x**, 209 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent 4-chlorophenylzinc chloride (**1aa**, 2.6 mL, 0.29 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:1) afforded the title compound as a white solid (149 mg, 0.44 mmol, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.45–8.39 (m, 1H), 7.89 (d, *J* = 8.9 Hz, 2H), 7.87–7.81 (m, 1H), 7.60–7.51 (m, 2H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.24 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.08 (d, *J* = 3.5 Hz, 1H), 6.96 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.68 (d, *J* = 9.0 Hz, 2H), 5.72 (d, *J* = 3.8 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.73 (t, *J* = 7.2 Hz, 2H), 3.01 (s, 3H), 2.58–2.37 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

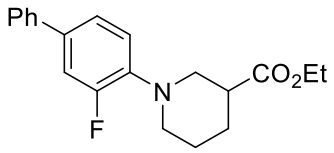
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.0, 153.0, 152.0, 144.5, 134.7, 131.4 (2C), 127.7, 126.7, 126.5, 126.0 (2C), 125.7, 125.5, 125.0, 124.8, 121.9, 120.9, 117.6, 110.8, 106.9, 73.9, 60.2, 48.9, 38.7, 36.2, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2973, 1697, 1605, 1523, 1462, 1366, 1279, 1236, 1184, 1106, 1094, 1017, 830, 790, 770.

MS (EI, 70 eV): *m/z* (%) = 445 (5), 301 (8), 192 (100), 164 (13).

HRMS (EI): *m/z* calc. for [$C_{27}H_{27}NO_3S$]: 445.1712; found 448.1700.

Ethyl 1-(3-fluoro-[1,1'-biphenyl]-4-yl)piperidine-3-carboxylate (2kk)



According to **TP13** ethyl 1-(benzoyloxy)piperidine-3-carboxylate (**5y**, 139 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (3-fluoro-[1,1'-biphenyl]-4-yl)zinc chloride (**1cc**, 2.6 mL, 0.29 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 4:1) afforded the title compound as a colourless oil (102 mg, 0.31 mmol, 62%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.57 (dt, *J* = 8.1, 1.5 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.39–7.32 (m, 2H), 6.82 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.75 (dd, *J* = 14.1, 2.5 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.81 (ddd, *J* = 12.6, 3.6, 1.7 Hz, 1H), 3.62–3.53 (m, 1H), 3.17 (dd, *J* = 12.6, 9.8 Hz, 1H), 3.00–2.90 (m, 1H), 2.76–2.67 (m, 1H), 2.13–2.06 (m, 1H), 1.90–1.80 (m, 1H), 1.80–1.68 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H).

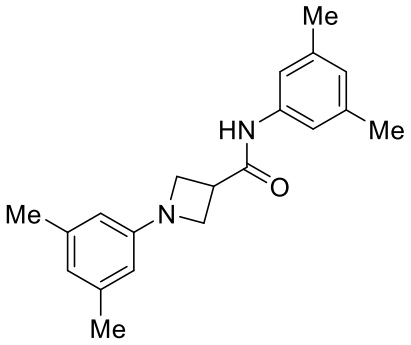
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.7, 160.61 (d, *J* = 245.9 Hz), 151.96 (d, *J* = 10.1 Hz), 136.06 (d, *J* = 1.5 Hz), 130.90 (d, *J* = 5.5 Hz), 128.67 (d, *J* = 3.0 Hz), 128.4, 126.8, 119.17 (d, *J* = 13.8 Hz), 111.9, 103.43 (d, *J* = 26.8 Hz), 60.7, 51.4, 49.1, 41.1, 26.9, 23.9, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2939, 2819, 2354, 2335, 1723, 1623, 1555, 1517, 1487, 1387, 1308, 1237, 1170, 1136, 1112, 1036, 978, 857, 829, 762, 697.

MS (EI, 70 eV): *m/z* (%) = 327 (100), 298 (99), 282 (15), 254 (61), 26 (59), 214 (42), 199 (98), 170 (90), 151 (14), 99 (10), 55 (12).

HRMS (EI): *m/z* calc. for [$C_{20}H_{22}FNO_2$]: 327.1635; found 327.1630.

_N_,1-bis(3,5-dimethylphenyl)azetidine-3-carboxamide (2ll)



According to **TP13** 3-((3,5-dimethylphenyl)carbamoyl)azetidin-1-yl benzoate (**5aa**, 162 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (3,5-dimethylphenyl)zinc chloride (**1w**, 2.6 mL, 0.29 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 4:1) afforded the title compound as a colourless oil (103 mg, 0.34 mmol, 67%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.77 (s, 1H), 7.10 (s, 2H), 6.69 (s, 1H), 6.41 (s, 1H), 6.09 (s, 2H), 3.97 (dd, *J* = 6.5, 2.1 Hz, 4H), 3.32 (ddd, *J* = 7.5, 5.5, 1.8 Hz, 1H), 2.21 (s, 6H), 2.20 (s, 6H).

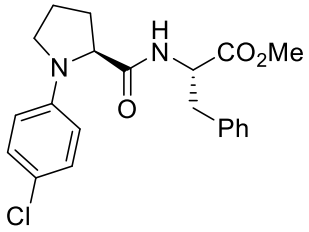
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.9, 151.7, 138.8 (2C), 137.6 (2C), 126.2, 120.7, 117.7 (2C), 110.0 (2C), 55.1 (2C), 37.1, 29.7, 21.5 (2C), 21.4 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3262, 2920, 2850, 1650, 1615, 1599, 1540, 1482, 1463, 1444, 1438, 1432, 1397, 1377, 1361, 1302, 1218, 1152, 1038, 908, 843, 817, 730, 724, 717, 712, 704, 686.

MS (EI, 70 eV): *m/z* (%) = 308 (13), 203 (61), 120 (100), 105 (43), 83 (66).

HRMS (EI): *m/z* calc. for [$C_{20}H_{24}N_2O$]: 308.1889; found 308.1882.

Methyl (4-chlorophenyl)-*L*-prolyl-*L*-phenylalaninate (2mm)



According to **TP13** (*S*)-2-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidin-1-yl benzoate (**5aa**, 185 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent 4-chlorophenylzinc chloride (, 2.6 mL, 0.29 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 4:1) afforded the title compound as a colourless oil (153 mg, 0.40 mmol, 79%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.31–7.23 (m, 3H), 7.21–7.15 (m, 2H), 7.11–7.05 (m, 2H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.55–6.49 (m, 2H), 4.86 (td, *J* = 7.9, 5.4 Hz, 1H), 3.91 (dd, *J* = 9.7, 2.1 Hz, 1H), 3.69 (s, 3H), 3.45 (t, *J* = 8.0 Hz, 1H), 3.26 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.12 (ddd, *J* = 10.9, 8.9, 6.1 Hz, 1H), 2.99 (dd, *J* = 14.0, 7.8 Hz, 1H), 2.24–2.12 (m, 1H), 2.10–2.02 (m, 1H), 1.96–1.87 (m, 1H), 1.66–1.52 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.4, 171.5, 145.9, 135.9, 129.0 (2C), 129.0 (2C), 128.6 (2C), 127.2, 123.2, 114.3 (2C), 64.5, 52.6, 52.4, 49.6, 37.5, 31.3, 23.9.

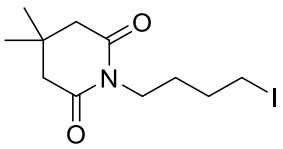
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2950, 1738, 1657, 1598, 1493, 1435, 1357, 1337, 1213, 1175, 1157, 1124, 1095, 1031, 977, 907, 809, 729, 699.

MS (EI, 70 eV): *m/z* (%) = 386 (13), 180 (100), 138 (34), 111 (23), 91 (16).

HRMS (EI): *m/z* calc. for [$C_{21}H_{23}ClN_2O_3$]: 386.1397; found 386.1392.

4.7 Synthesis of Gepirone (3p)

1-(4-Iodobutyl)-4,4-dimethylpiperidine-2,6-dione



1-(4-iodobutyl)-4,4-dimethylpiperidine-2,6-dione was prepared according to a literature procedure.[127]

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.80 (d, *J* = 7.4 Hz, 2H), 3.20 (t, *J* = 6.9 Hz, 2H), 2.51 (s, 4H), 1.88–1.78 (m, 2H), 1.64 (p, *J* = 7.3 Hz, 2H), 1.09 (s, 6H).

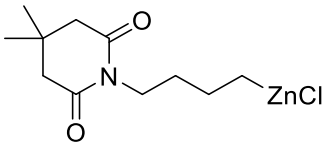
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 171.9, 46.4, 38.2, 31.0, 29.2, 29.0, 27.7, 5.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2929, 2870, 1722, 1666, 1468, 1453, 1432, 1392, 1349, 1332, 1275, 1268, 1256, 1214, 1181, 1122, 1020, 933, 818, 734.

MS (EI, 70 eV): *m/z* (%) = 323 (1), 196 (100), 154 (23), 126 (24), 83 (60), 55 (40).

HRMS (EI): *m/z* calc. for [$C_{11}H_{18}INO_2$]: 163.0997; found 163.0992.

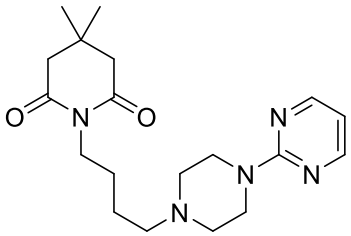
(4-(4,4-Dimethyl-2,6-dioxopiperidin-1-yl)butyl)zinc chloride (1bb)



According to **TP5**, 1-(4-Iodobutyl)-4,4-dimethylpiperidine-2,6-dione (618 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv), anhydrous $ZnCl_2$ (409 mg, 3.00 mmol, 1.20 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight. Titration with iodine gave a concentration of 0.24 mmol/mL active zinc species, corresponding to 82% yield.

[127] E. Ofori, X. Y. Zhu, J. R. Etukala, B. A. Bricker, S. Y. Ablordeppey **2016**, *24*, 5730–5740.

4,4-Dimethyl-1-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)butyl)piperidine-2,6-dione (Gepirone) (2v)



According to **TP13** 4-(pyrimidin-2-yl)piperazin-1-yl benzoate (**5j**, 142 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(6 mg, 50 µmol, 10.0 mol%) was added and subsequent (4-(4,4-dimethyl-2,6-dioxopiperidin-1-yl)butyl)zinc chloride (**1o**, 3.13 mL, 0.24 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (pure EtOAc) afforded the title compound as a yellowish liquid (147 mg, 0.41 mmol, 82%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.20 (d, *J* = 4.7 Hz, 2H), 6.42 (t, *J* = 4.7 Hz, 1H), 3.91 (s, 4H), 3.69 (t, *J* = 7.1 Hz, 2H), 2.68–2.47 (m, 6H), 2.42 (s, 4H), 1.64–1.41 (m, 4H), 0.97 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.1, 161.4, 157.8, 110.4, 58.0, 52.6, 46.4, 38.7, 29.2, 27.7, 25.7, 23.0.

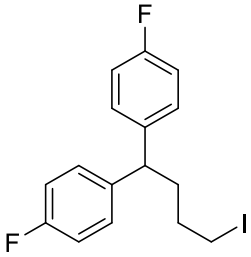
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2931, 2870, 1722, 1668, 1584, 1547, 1511, 1495, 1469, 1446, 1392, 1357, 1307, 1290, 1273, 1260, 1219, 1208, 1130, 983, 955, 798, 731.

MS (EI, 70 eV): *m/z* (%) = 359 (30), 21 (61), 177 (100), 122 (65).

HRMS (EI): *m/z* calc. for [$C_{19}H_{29}N_5O_2$]: 359.2321; found 359.2326.

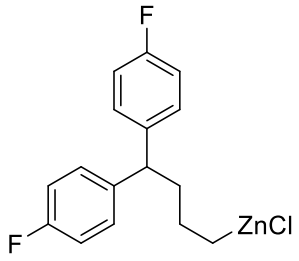
4.8 Synthesis of Penfluridol

4,4'-(4-Iodobutane-1,1-diyl)bis(fluorobenzene)



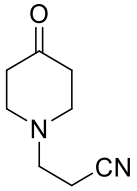
4,4'-(4-Iodobutane-1,1-diyl)bis(fluorobenzene) was prepared according to a literature procedure. The analytical data was consistent with the literature.[128]

(4,4-Bis(4-fluorophenyl)butyl)zinc chloride (22)



According to **TP5**, 4,4'-(4-iodobutane-1,1-diyl)bis(fluorobenzene) (931 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv), anhydrous $ZnCl_2$ (409 mg, 3.00 mmol, 1.20 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight. Titration with iodine gave a concentration of 0.27 mmol/mL active zinc species, corresponding to 92% yield.

3-(4-Oxopiperidin-1-yl)propanenitrile (17a)



According to **TP10**, piperidin-4-one hydrochloride (272 mg, 2.00 mmol, 1.00 equiv) was dissolved in dry MeOH (5 mL) and added to a solution of sodium metal (46 mg, 2.00 mmol, 1.00 equiv). Then, acrylonitrile (0.66 mL, 530 mg, 10.0 mmol, 5.00 equiv) was added and the resulting mixture was stirred at 55 °C overnight. The solvent was removed and the crude product purified by flash column chromatography (hexane:EtOAc 1:1) to afford the title compound as a colourless oil (332 mg, 1.52 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 2.82 (td, *J* = 6.5, 2.9 Hz, 6H), 2.56 (t, *J* = 6.8 Hz, 2H), 2.48 (t, *J* = 6.2 Hz, 4H).

[128] M. Saito, N. Tsuji, Y. Kobayashi, Y. Takemoto *Org. Lett.* **2015**, *17*, 3000–3003.

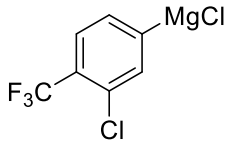
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 208.0, 118.5, 52.7, 52.5, 41.1, 16.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2960, 2817, 2246, 1715, 1475, 1418, 1378, 1355, 1336, 1280, 1234, 1195, 1135, 1093, 1049, 1013, 748.

MS (EI, 70 eV): *m/z* (%) = 112 (100), 84 (16).

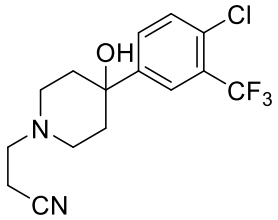
HRMS (EI): *m/z* calc. for [$C_8H_{12}N_2O$]: 152.0950; found 112.0757 [M-CH_2CN].

(3-Chloro-4-(trifluoromethyl)phenyl)magnsium Chloride (19)



According to **TP4** *(without the last step of transmetalation using $ZnCl_2$)*, 4-bromo-2-chloro-1-(trifluoromethyl)benzene (649 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight. Titration with iodine gave a concentration of 0.47 mmol/mL active magnesium species, corresponding to 96% yield.

3-(4-(4-Chloro-3-(trifluoromethyl)phenyl)-4-hydroxypiperidin-1-yl)propanenitrile (20)



A dry and argon flushed Schlenk-flask equipped with a septum and a magnetic stirring bar was charged with $LaCl_3 \cdot 2LiCl$ (0.33 M; 6.10 mL, 2.00 mmol, 1.00 equiv) as a solution in dry THF. 3-(4-oxopiperidin-1-yl)propanenitrile (437 mg, 2.00 mmol, 1.00 equiv) was added and the resulting mixture was stirred for 1 h at rt. The reaction mixture was cooled to 0 °C and (3-chloro-4-(trifluoromethyl)phenyl)magnesium chloride (**19**, 0.56 M, 3.8 mL, 2.10 mmol, 1.05 equiv) was added dropwise. The reaction mixture was stirred at 25 °C for 1.5 h and then quenched with sat. aqueous NH_4Cl (2 mL). The aqueous layer was extracted with EtOAc

(3×10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexane:EtOAc 1:2) to afford the titel compound as white solid (346 mg, 1.04 mmol, 52%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.85 (d, *J* = 2.3 Hz, 1H), 7.59 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 2.84–2.79 (m, 2H), 2.77 (t, *J* = 7.0 Hz, 2H), 2.61–2.53 (m, 4H), 2.12 (td, *J* = 13.2, 4.6 Hz, 2H), 1.73 (dq, *J* = 14.4, 2.9 Hz, 2H).

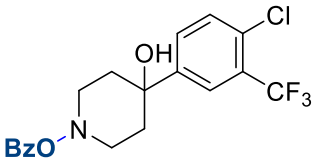
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 147.3, 131.4, 130.9, 129.2, 128.22 (q, *J* = 31.1 Hz), 124.07 (q, *J* = 5.3 Hz, 2C), 122.89 (q, *J* = 273.3 Hz), 118.8, 70.9, 53.4, 48.8 (2C), 38.3, 16.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3436, 2946, 2827, 2824, 2249, 1481, 1471, 1409, 1377, 1349, 1315, 1269, 1257, 1215, 1175, 1124, 1113, 1047, 1032, 1009, 969, 940, 908, 833, 771, 730, 664, 654.

MS (EI, 70 eV): *m/z* (%) = 332 (4), 292 (100), 274 (43), 201 (22), 179 (18), 109 (12), 56 (17), 42 (64).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}ClF_3N_2O$]: 332.0903; found 332.0911.

4-(4-Chloro-3-(trifluoromethyl)phenyl)-4-hydroxypiperidin-1-yl benzoate (21)



According to **TP11** 3-(4-(4-chloro-3-(trifluoromethyl)phenyl)-4-hydroxypiperidin-1-yl)propanenitrile (**20**, 333 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were

washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 1:1) to afford the desired product a pale white solid (148 mg, 0.74 mmol, 74%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.89 (d, *J* = 2.3 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 3.59–3.25 (m, 3H), 2.53–2.42 (m, 2H), 1.96–1.59 (m, 4H).

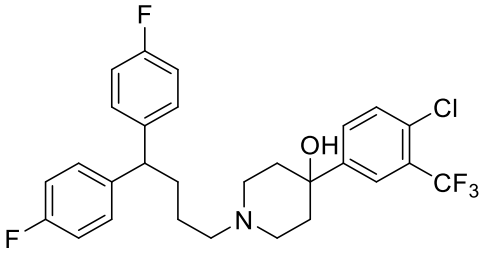
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.8, 146.4, 133.2, 131.6, 131.2, 129.4 (2C), 129.2, 129.0, 128.5 (2C), 128.2 (d, *J* = 31.1 Hz, 2C), 124.1 (q, *J* = 5.4 Hz, 2C), 122.8 (d, *J* = 273.4 Hz), 70.2, 52.3, 38.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3436, 1725, 1605, 1481, 1451, 1410, 1368, 1316, 1284, 1258, 1212, 1178, 1132, 1114, 1088, 1066, 1046, 1034, 1019, 975, 908, 831, 731, 709, 664.

MS (EI, 70 eV): *m/z* (%) =382 (1), 257 (100), 202 (26), 153 (14).

HRMS (EI): *m/z* calc. for [$C_{19}H_{17}ClF_3NO_3$]: 399.0849; found 382.0818 [M-OH].

1-(4,4-Bis(4-fluorophenyl)butyl)-4-(4-chloro-3-(trifluoromethyl)phenyl)piperidin-4-ol (Penfluridol) (15)



In a dry and argon flushed flask, 4-(4-chloro-3-(trifluoromethyl)phenyl)-4-hydroxypiperidin-1-yl benzoate (**21**, 200 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) followed by the addition of triethylamine (0.11 mL, 0.75 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 2.0 mol%) and trimethylsilyl chloride (65 mg, 0.60 mmol, 1.20 equiv) at 0 °C. The mixture was stirred for 2 h at 0 °C and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. Evaporation of the solvent afforded the crude 4-(4-chloro-3-(trifluoromethyl)phenyl)-4-((trimethylsilyl) oxy)piperidin-1-yl benzoate.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.09–7.95 (m, 2H), 7.82 (d, *J* = 2.1 Hz, 1H), 7.60–7.41 (m, 5H), 3.48 (dd, *J* = 8.5, 5.0 Hz, 2H), 3.28 (t, *J* = 11.2 Hz, 2H), 2.32 (td, *J* = 13.1, 4.0 Hz, 2H), 2.09 (d, *J* = 13.5 Hz, 2H), -0.02 (s, 9H).

Then, according to **TP13**, the 4-(4-chloro-3-(trifluoromethyl)phenyl)-4-((trimethylsilyl) oxy)piperidin-1-yl benzoate was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (4,4-bis(4-fluorophenyl)butyl)zinc chloride (**12**, 2.78 mL, 0.27 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. The crude 1-(4,4-Bis(4-fluorophenyl)butyl)-4-(4-chloro-3-(trifluoromethyl)phenyl)-4-((trimethylsilyl)oxy)piperidine was dissolved in dry THF and aqueous 1 M hCl (2 mL) was added. The mixture was stirred for 1 h at rt. The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. Purification of the crude product by flash chromatography (hexane:EtOAc 1:1) afforded the title compound as a colourless oil (233 mg, 0.45 mmol, 89%)

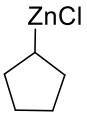
Analytical data according to literature[129]

[129] G. Chen, h. Xia, Y. Cai, D. Ma, J. Yuan, C. Yuan *Bioorg. Med. Chem Lett.* **2011**, *21*, 234–239.

5. Preparation of Tertiary Amines by Triple Functionalization of Tris-(2-cyanoethyl)amine Using a Cobalt-Catalyzed Electrophilic Amination of Organozinc Halides

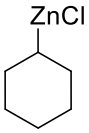
5.1 Preparation of Organozinc Chlorides

Cyclopentylzinc chloride (1dd)



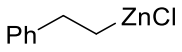
According to **TP4**, bromocyclopentan (373 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.29 mmol/mL active zinc species, corresponding to 98% yield.

Cyclohexylzinc chloride (1ee)



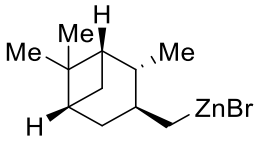
According to **TP4**, bromocyclohexyl (408 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.27 mmol/mL active zinc species, corresponding to 88% yield.

Phenethylzinc chloride (1ff)



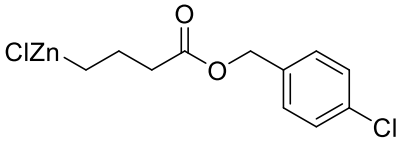
According to **TP4**, (2-bromoethyl)benzene (463 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.28 mmol/mL active zinc species, corresponding to 92% yield.

(((1*S*,2*S*,3*S*,5*R*)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-yl)methyl)zinc chloride (1hh)



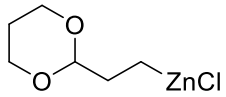
According to **TP6**, (1S,2S,3S,5R)-3-(bromomethyl)-2,6,6-trimethylbicyclo[3.1.1]heptane (578 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and activated zinc dust (245 mg, 3.75 mmol, 1.50 equiv) in dry THF (5 mL). The mixture was stirred at 50 °C overnight. Titration with iodine gave a concentration of 0.32 mmol/mL active zinc species, corresponding to 67% yield.

(4-((4-Chlorobenzyl)oxy)-4-oxobutyl)zinc chloride (1ii)



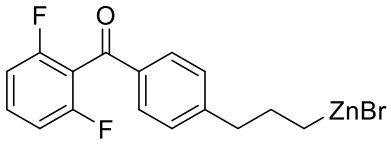
According to **TP6**, 4-chlorobenzyl 4-bromobutanoate (738 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and activated zinc dust (245 mg, 3.75 mmol, 1.50 equiv) in dry THF (5 mL). The mixture was stirred at 50 °C overnight. Titration with iodine gave a concentration of 0.40 mmol/mL active zinc species, corresponding to 84% yield.

(2-(1,3-Dioxan-2-yl)ethyl) (1jj)



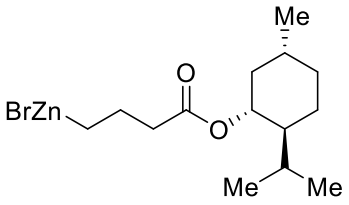
According to **TP6**, 2-(2-bromoethyl)-1,3-dioxane (488 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and activated zinc dust (245 mg, 3.75 mmol, 1.50 equiv) in dry THF (5 mL). The mixture was stirred at 50 °C overnight. Titration with iodine gave a concentration of 0.45 mmol/mL active zinc species, corresponding to 95% yield.

(3-(4-(2,6-Difluorobenzoyl)phenyl)propyl)zinc chloride (1kk)



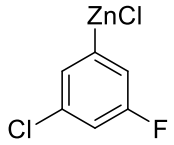
According to **TP6**, (4-(3-bromopropyl)phenyl)(2,6-difluorophenyl)methanone (848 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and activated zinc dust (245 mg, 3.75 mmol, 1.50 equiv) in dry THF (5 mL). The mixture was stirred at 50 °C overnight. Titration with iodine gave a concentration of 0.41 mmol/mL active zinc species, corresponding to 86% yield.

(4-(((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)-4-oxobutyl)zinc chloride (1mm)



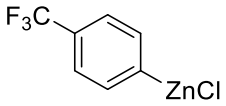
According to **TP6**, (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 4-bromobutanoate (763 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and activated zinc dust (245 mg, 3.75 mmol, 1.50 equiv) in dry THF (5 mL). The mixture was stirred at 50 °C overnight. Titration with iodine gave a concentration of 0.43 mmol/mL active zinc species, corresponding to 90% yield.

(3-Chloro-5-fluorophenyl)zinc chloride (1nn)



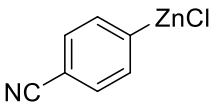
According to **TP4**, 1-bromo-3-chloro-5-fluorobenzene (524 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.27 mmol/mL active zinc species, corresponding to 92% yield.

(4-(Trifluoromethyl)phenyl)zinc chloride (1oo)



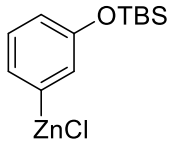
According to **TP2**, 1-bromo-4-(trifluoromethyl)benzene (563 mg, 2.50 mmol) was dissolved in dry THF (7.5 mL) and *i*PrMgCl·LiCl (2.15 mL, 1.28 M, 2.75 mmol) was added. After stirring for 4 h at 25 °C $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.29 mmol/mL active zinc species, corresponding to 96% yield.

(4-Cyanophenyl)zinc chloride (1pp)



According to **TP2**, 4-iodobenzonitrile (1.15 g, 5.00 mmol, 1.00 equiv) was dissolved in dry THF (5 mL) and *i*PrMgCl·LiCl (4.30 mL, 1.28 M, 5.50 mmol, 1.10 equiv) was added. After stirring for 2 h at 0 °C $ZnCl_2$ (1 M in THF, 6.0 mL, 6.00 mmol) was added. Titration with iodine gave a concentration of 0.25 mmol/mL active zinc species, corresponding to 81% yield.

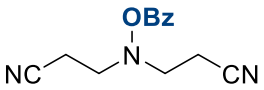
(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)zinc chloride (1qq)



According to **TP4**, (3-bromophenoxy)(*tert*-butyl)dimethylsilane (718 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.26 mmol/mL active zinc species, corresponding to 88% yield.

5.2 Preparation of *N*-Hydroxylamine Derivatives

3,3'-((Benzoyloxy)azanediyl)dipropanenitrile (5bb)



According to **TP11** 3,3',3''-nitrilotripropanenitrile (**23**, 217 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 2:1) to afford the desired product a pale white solid (139 mg, 0.57 mmol, 57%).

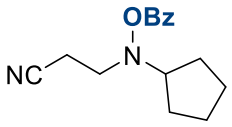
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.99–7.83 (m, 2H), 7.58–7.48 (m, 1H), 7.39 (dt, *J* = 20.7, 7.9 Hz, 2H), 3.32 (t, *J* = 6.7 Hz, 4H), 2.62 (td, *J* = 6.8, 1.9 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.1, 134.0, 129.8 (2C), 128.8 (2C), 128.0, 117.6 (2C), 54.6 (2C), 16.1 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1771, 1600, 1493, 1454, 1316, 1294, 1229, 1204, 1151, 1075, 1038, 1016, 1002, 977, 933, 914, 797, 781, 767, 700, 691.

HRMS (EI): *m/z* calc. for [$C_{13}H_{15}N_3O_2$]: 243.1008; found 243.1001.

3-((Benzoyloxy)(cyclopentyl)amino)propanenitrile (5cc)



According to **TP11** 3,3'-(cyclopentylazanediyl)dipropanenitrile (**26a**, 191 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 3:1) to afford the desired product a pale white solid (189 mg, 0.73 mmol, 73%).

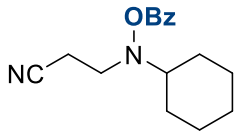
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06–7.86 (m, 2H), 7.67–7.52 (m, 1H), 7.50–7.35 (m, 2H), 3.48 (p, *J* = 7.3 Hz, 1H), 3.30 (t, *J* = 7.2 Hz, 2H), 2.65 (td, *J* = 7.2, 4.1 Hz, 2H), 1.85 (tdd, *J* = 9.3, 4.2, 2.5 Hz, 2H), 1.79–1.51 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.8, 133.5, 129.7 (2C), 128.6 (2C), 127.8, 118.1, 69.1, 53.4, 29.9 (2C), 24.5 (2C), 16.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961, 2871, 2251, 1742, 1601, 1575, 1473, 1451, 1423, 1358, 1315, 1282, 1276, 1238, 1177, 1103, 1080, 1061, 1024, 1002, 903, 885, 862, 804, 744, 709, 687, 674.

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}N_2O_2$]: 258.1368; found 258.1362.

3-((Benzoyloxy)(cyclohexyl)amino)propanenitrile (5dd)



According to **TP11** 3,3'-(cyclohexylazanediyl)dipropanenitrile (**26b**, 205 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 3:1) to afford the desired product a pale white solid (193 mg, 0.71 mmol, 71%).

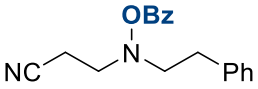
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05–7.89 (m, 2H), 7.59 (dddd, *J* = 14.2, 8.0, 2.5, 1.2 Hz, 1H), 7.50–7.38 (m, 2H), 3.36 (t, *J* = 7.2 Hz, 2H), 2.94 (tt, *J* = 10.8, 3.6 Hz, 1H), 2.64 (td, *J* = 7.2, 4.5 Hz, 2H), 2.03–1.92 (m, 2H), 1.86–1.77 (m, 2H), 1.70–1.59 (m, 1H), 1.42–1.06 (m, 5H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.6, 133.5, 129.7 (2C), 128.6 (2C), 127.8, 118.1, 66.0, 50.6, 29.0, 25.7 (2C), 25.0 (2C), 16.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2934, 2857, 2251, 1742, 1601, 1451, 1422, 1372, 1349, 1315, 1238, 1194, 1177, 1159, 1079, 1063, 1022, 1002, 913, 895, 866, 852, 826, 802, 780, 731, 707, 687, 674.

HRMS (EI): *m/z* calc. for [$C_{16}H_{20}N_2O_2$]: 272.1525; found 272.1529.

3-((Benzoyloxy)(phenethyl)amino)propanenitrile (5ee)



According to **TP11** 3,3'-(phenethylazanediyl)dipropanenitrile (**26c**, 227 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 3:1) to afford the desired product a pale white solid (185 mg, 0.63 mmol, 63%).

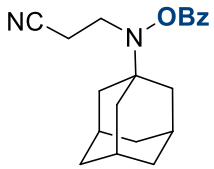
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05–7.86 (m, 2H), 7.64–7.55 (m, 1H), 7.52–7.38 (m, 2H), 7.30–7.24 (m, 2H), 7.23–7.15 (m, 3H), 3.43–3.23 (m, 4H), 3.01–2.87 (m, 2H), 2.69 (td, *J* = 7.1, 5.7 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.4, 138.4, 134.8, 133.7 (2C), 129.9 (2C), 129.7 (2C), 128.6 (2C), 127.8, 126.6, 117.8, 61.0, 54.6, 33.4, 16.0

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3028, 2923, 2851, 1742, 1602, 1575, 1496, 1452, 1424, 1362, 1315, 1283, 1238, 1178, 1117, 1100, 1088, 1079, 1060, 1044, 1022, 1002, 883, 802, 743, 708, 699, 673.

HRMS (EI): *m/z* calc. for [$C_{18}H_{18}N_2O_2$]: 294.1368; found 294.1363.

3-(((3*s*,5*s*,7*s*)-adamantan-1-yl)(benzoyloxy)amino)propanenitrile (5ff)



According to **TP11**, 3,3'-(((3*s*,5*s*,7*s*)-adamantan-1-yl)azanediyl)dipropanenitrile (**26d**, 257 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 3:1) to afford the desired product a pale white solid (172 mg, 0.53 mmol, 53%).

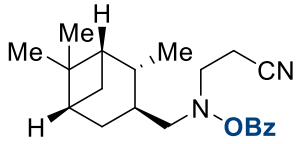
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.11–8.01 (m, 2H), 7.66–7.55 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 3.35 (t, *J* = 7.3 Hz, 2H), 2.61 (t, *J* = 7.3 Hz, 2H), 2.19–2.08 (m, 3H), 1.84 (d, *J* = 3.0 Hz, 6H), 1.76–1.57 (m, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.1, 133.5, 129.7 (2C), 128.7 (2C), 128.5, 118.4, 61.2, 46.3, 38.2 (3C), 36.4 (3C), 29.2 (3C), 17.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3018, 1642, 1622, 1595, 1482, 1476, 1434, 1395, 1301, 1261, 1221, 1189, 1135, 1122, 1050, 1060, 1021, 1001, 879, 812, 734, 718, 694, 667.

HRMS (EI): *m/z* calc. for [$C_{20}H_{24}N_2O_2$]: 324.1838; found 324.1830.

3-((Benzoyloxy)(((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)amino)propanenitrile (5gg)



According to **TP11** 3,3'-((((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)azanediyl)dipropanenitrile (**26e**, 273 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (pure EtOAc 2:1) to afford the desired product a pale white solid (238 mg, 0.670 mmol, 70%).

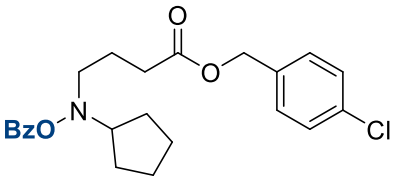
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04–7.88 (m, 2H), 7.62–7.54 (m, 1H), 7.49–7.40 (m, 2H), 3.41–3.27 (m, 2H), 3.10 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.87 (dd, *J* = 12.4, 9.7 Hz, 1H), 2.73–2.65 (m, 2H), 2.30 (dtd, *J* = 9.8, 6.2, 2.1 Hz, 1H), 2.19 (dddd, *J* = 12.1, 10.0, 3.6, 1.9 Hz, 1H), 1.94–1.82 (m, 2H), 1.81–1.67 (m, 3H), 1.16 (s, 3H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.91 (s, 3H), 0.72 (d, *J* = 9.7 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.2, 133.5, 129.6 (2C), 128.6 (2C), 127.7, 118.1, 69.1, 54.6, 47.8, 41.5, 41.4, 38.8, 34.4, 33.9, 33.5, 27.9, 23.0, 21.7, 15.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2903, 2870, 1744, 1472, 1451, 1423, 1385, 1374, 1367, 1315, 1239, 1177, 1101, 1084, 1056, 1024, 1002, 906, 862, 801, 735, 707, 687, 673, 657.

HRMS (EI): *m/z* calc. for [$C_{21}H_{28}N_2O_2$]: 340.2151; found 340.2155.

4-Chlorobenzyl 4-((benzoyloxy)(cyclopentyl)amino)butanoate (5hh)



According to **TP11** 4-chlorobenzyl 4-((2-cyanoethyl)(cyclopentyl)amino)butanoate (**27a**, 349 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 4:1) to afford the desired product a pale white solid (345 mg, 0.83 mmol, 83%).

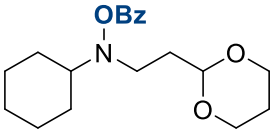
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05–7.88 (m, 2H), 7.61–7.52 (m, 1H), 7.48–7.37 (m, 2H), 7.32–7.24 (m, 4H), 5.06 (d, *J* = 2.0 Hz, 2H), 3.82–3.71 (m, 1H), 3.41 (td, *J* = 7.4, 2.4 Hz, 1H), 3.01 (t, *J* = 7.0 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 1.94–1.76 (m, 5H), 1.74–1.52 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.2, 165.9, 133.1, 129.8, 129.6, 129.6, 129.2, 128.7, 128.5, 127.7, 69.2, 68.0, 65.3, 57.0, 31.6, 29.9, 25.6, 24.5, 22.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2869, 1740, 1682, 1601, 1574, 1450, 1425, 1412, 1355, 1314, 1282, 1239, 1176, 1116, 1101, 1080, 1061, 1023, 1002, 861, 850, 833, 775, 744, 708, 686, 674.

HRMS (EI): *m/z* calc. for [$C_{23}H_{26}ClNO_4$]: 415.1550; found 415.1559.

_N_-(2-(1,3-dioxan-2-yl)ethyl)-_O_-benzoyl-_N_-cyclohexylhydroxylamine (5ii)



According to **TP11** 3-((2-(1,3-dioxan-2-yl)ethyl)(cyclohexyl)amino)propanenitrile (**27b**, 266 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 3:1) to afford the desired product a pale white solid (263 mg, 0.79 mmol, 79%).

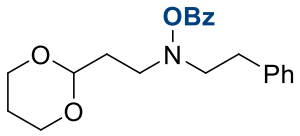
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.02–7.86 (m, 2H), 7.56–7.48 (m, 1H), 7.44–7.30 (m, 2H), 4.67 (t, *J* = 5.1 Hz, 1H), 4.05–3.98 (m, 2H), 3.70 (ddt, *J* = 12.3, 10.3, 2.4 Hz, 2H), 3.13 (dd, *J* = 8.5, 6.4 Hz, 2H), 2.85 (tt, *J* = 11.0, 3.5 Hz, 1H), 2.08–1.88 (m, 3H), 1.84 (ddd, *J* = 9.9, 7.9, 4.0 Hz, 2H), 1.75 (dt, *J* = 12.6, 3.2 Hz, 2H), 1.65–1.53 (m, 1H), 1.42–1.05 (m, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.9, 133.1, 129.6 (2C), 129.2, 128.5 (2C), 100.7, 66.9 (2C), 65.8, 50.0, 32.5, 29.1 (2C), 25.9, 25.8, 25.2 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933, 2854, 1742, 1602, 1575, 1469, 1451, 1428, 1407, 1377, 1315, 1284, 1239, 1195, 1177, 1140, 1081, 1059, 1024, 998, 974, 967, 938, 927, 907, 893, 856, 824, 745, 734, 709, 688, 674.

HRMS (EI): *m/z* calc. for [$C_{19}H_{27}NO_4$]: 333.1940; found 333.1947.

_N_-(2-(1,3-Dioxan-2-yl)ethyl)-_O_-benzoyl-_N_-phenethylhydroxylamine (5jj)



According to **TP11** 3-((2-(1,3-dioxan-2-yl)ethyl)(phenethyl)amino)propanenitrile (**27c**, 288 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 3:1) to afford the desired product a pale white solid (263 mg, 0.74 mmol, 74%).

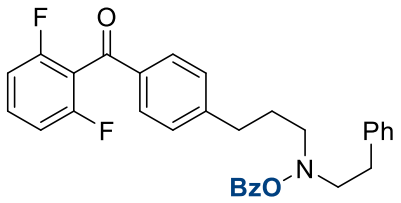
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04–7.98 (m, 2H), 7.60–7.54 (m, 1H), 7.47–7.41 (m, 2H), 7.25–7.14 (m, 5H), 4.71 (t, *J* = 5.1 Hz, 1H), 4.11–4.02 (m, 2H), 3.81–3.70 (m, 2H), 3.30–3.22 (m, 2H), 3.16 (dd, *J* = 8.2, 6.6 Hz, 2H), 2.96–2.88 (m, 2H), 2.10–1.97 (m, 2H), 1.91 (ddd, *J* = 10.2, 7.9, 4.1 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.6, 139.3, 133.1, 129.6 (2C), 128.7 (2C), 128.5 (2C), 128.4 (2C), 126.2, 100.4, 66.9 (2C), 61.2, 54.4, 33.4, 32.4, 25.8, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 3028, 2961, 2854, 1740, 1602, 1584, 1496, 1470, 1451, 1429, 1409, 1378, 1315, 1241, 1176, 1139, 1092, 1080, 1058, 1024, 1001, 972, 940, 926, 893, 854, 747, 709, 700, 673.

HRMS (EI): *m/z* calc. for [$C_{21}H_{25}NO_4$]: 355.1784; found 355.1795.

(4-(3-((Benzoyloxy)(phenethyl)amino)propyl)phenyl)(2,6-difluorophenyl)methanone (5kk)



According to **TP11** 3-((3-(4-(2,6-difluorobenzoyl)phenyl)propyl)(phenethyl)amino) propanenitrile (**27d**, 433 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 4:1) to afford the desired product a pale white solid (435 mg, 0.87 mmol, 87%).

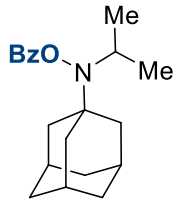
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04–8.00 (m, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.61–7.56 (m, 1H), 7.49–7.39 (m, 3H), 7.29–7.23 (m, 4H), 7.23–7.14 (m, 3H), 7.03–6.95 (m, 2H), 3.28–3.19 (m, 2H), 3.03 (t, *J* = 7.1 Hz, 2H), 2.97–2.89 (m, 2H), 2.82 (t, *J* = 7.7 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 188.6, 165.8, 159.8 (dd, *J* = 251.5, 7.7 Hz), 149.1, 139.3, 134.9, 133.3, 131.9 (t, *J* = 9.8 Hz),130.1, 129.7, 129.1, 129.0, 128.8, 128.6, 128.6, 126.4, 117.27 (t, *J* = 22.0 Hz), 112.2–111.8 (m), 61.5, 59.0, 33.7, 28.3, 21.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 3030, 2955, 2866, 1739, 1713, 1672, 1622, 1604, 1589, 1496, 1464, 1452, 1416, 1361, 1312, 1277, 1243, 1235, 1222, 1177, 1146, 1090, 1063, 1024, 1005, 930, 911, 853, 791, 750, 729, 708, 700, 670.

HRMS (EI): *m/z* calc. for [$C_{31}H_{27}FNO_3$]: 499.1959; found 499.1967.

_N_-((3_s_,5_s_,7_s_)-adamantan-1-yl)-_O_-benzoyl-_N_-isopropylhydroxylamine (5ll)



According to **TP11** 3-(((3*s*,5*s*,7*s*)-adamantan-1-yl)(isopropyl)amino)propanenitrile (**27e**, 246 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 4:1) to afford the desired product a pale white solid (210 mg, 0.67 mmol, 67%).

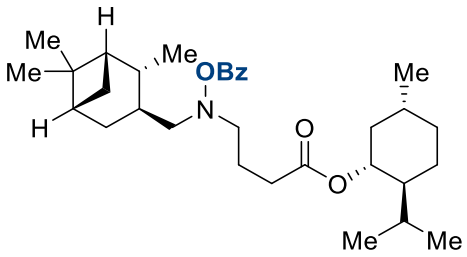
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.11–8.06 (m, 2H), 7.67–7.53 (m, 1H), 7.50–7.44 (m, 2H), 3.67 (p, *J* = 6.5 Hz, 1H), 2.15–2.06 (m, 3H), 1.96–1.83 (m, 6H), 1.70–1.59 (m, 6H), 1.26–1.14 (m, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.6, 132.9, 129.6, 129.6 (2C), 128.5 (2C), 61.2, 50.7, 39.7 (3C), 36.6 (3C), 29.5 (3C), 24.2, 19.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2906, 2846, 1739, 1699, 1600, 1583, 1448, 1381, 1361, 1344, 1311, 1274, 1259, 1240, 1190, 1177, 1130, 1120, 1081, 1061, 1044, 1020, 977, 970, 939, 906, 876, 860, 819, 801, 707, 686, 672.

HRMS (EI): *m/z* calc. for [$C_{20}H_{27}NO_2$]: 313.2042; found 313.2050.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 4-((benzoyloxy)(((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)amino)butanoate (5mm)



According to **TP11** (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 4-((2-cyanoethyl)(((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)amino)butanoate (**27f**, 445 mg, 1.00 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C. Then, *m*CPBA (190 mg, 1.10 mmol, 1.10 equiv) was slowly added as a solution in dry CH_2Cl_2 (2 mL) and the resulting mixture was stirred at −78 °C for 1 h. Following, the cooling bath was removed and the mixture stirred at 25 °C overnight. The solvent was removed and the acid by-product removed by filtration through a silica plug. After solvent removal, the resulting *N*-hydroxylamine was dissolved in CH_2Cl_2 (4 mL) followed by the addition of triethylamine (0.21 mL, 1.50 mmol, 1.50 equiv), DMAP (1 mg, 0.01 mmol, 1.00 mol%) and benzoyl chloride (168 mg, 1.20 mmol, 1.20 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and quenched with sat. aqueous NH_4Cl solution (2 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution (2 mL), brine (2 mL), and dried over Na_2SO_4. The crude mixture was purified with flash column chromatography (hexane:EtOAc 4:1) to afford the desired product a pale white solid (363 mg, 0.71 mmol, 71%).

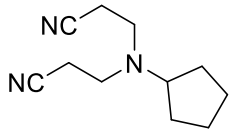
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05–7.86 (m, 2H), 7.61–7.50 (m, 1H), 7.49–7.35 (m, 2H), 4.66 (td, *J* = 10.9, 4.3 Hz, 1H), 3.12–2.95 (m, 4H), 2.81 (t, *J* = 11.3 Hz, 1H), 2.53–2.43 (m, 2H), 2.34–2.14 (m, 2H), 2.00–1.80 (m, 8H), 1.79–1.70 (m, 2H), 1.65 (ddd, *J* = 13.0, 6.1, 2.3 Hz, 4H), 1.54–1.39 (m, 1H), 1.33 (ddt, *J* = 12.2, 10.7, 3.1 Hz, 1H), 1.16 (s, 3H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.92 (s, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.72 (d, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.1, 165.3, 133.0, 129.4 (2C), 128.5 (2C), 127.6, 74.1, 69.3, 58.4, 47.9, 46.9, 41.6, 41.5, 40.9, 38.9, 34.4, 34.2, 33.9, 33.5, 31.9, 31.4, 28.0, 26.2, 23.4, 23.1, 22.2, 22.0, 21.7, 20.8, 16.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2926, 2869, 1744, 1727, 1602, 1576, 1469, 1451, 1385, 1370, 1345, 1314, 1239, 1176, 1152, 1134, 1099, 1083, 1057, 1039, 1024, 1010, 985, 966, 935, 912, 843, 824, 802, 744, 707, 687, 673.

5.3 Preparation of Amination Products

3,3'-(Cyclopentylazanediyl)dipropanenitrile (26a)



According to **TP13** 3,3'-((benzoyloxy)azanediyl)dipropanenitrile (**5bb**, 122 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent cyclopentylzinczinc chloride (**1dd**, 2.6 mL, 0.29 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:3) afforded the title compound as a colourless oil (62 mg, 0.33 mmol, 65%).

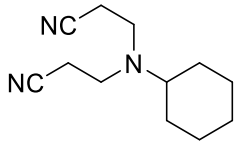
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.06 (p, *J* = 8.6, 8.1 Hz, 1H), 2.89 (t, *J* = 6.9 Hz, 4H), 2.46 (t, *J* = 6.9 Hz, 3H), 1.87–1.76 (m, 2H), 1.74–1.62 (m, 1H), 1.61–1.48 (m, 1H), 1.44–1.30 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 118.9 (2C), 63.4, 47.9 (2C), 29.9 (2C), 23.8 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2868, 2247, 1463, 1453, 1421, 1362, 1338, 1312, 1265, 1238, 1130, 1085, 1040, 1023, 966, 945, 757.

HRMS (EI): *m/z* calc. for [$C_{11}H_{17}N_3$]: 191.1422; found 191.1425.

3,3'-(Cyclohexylazanediyl)dipropanenitrile (26b)



According to **TP13** 3,3'-((benzoyloxy)azanediyl)dipropanenitrile (**5bb**, 122 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent cyclohexylzinc chloride (**1ee**, 2.8 mL, 0.27 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:3) afforded the title compound as a colourless oil (75 mg, 0.37 mmol, 73%).

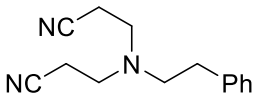
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 2.81 (t, *J* = 6.8 Hz, 4H), 2.42 (t, *J* = 6.8 Hz, 4H), 2.40–2.35 (m, 1H), 1.76 (ddt, *J* = 10.7, 8.1, 4.9 Hz, 4H), 1.64–1.57 (m, 1H), 1.27–0.98 (m, 5H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 118.9 (2C), 60.4, 46.8 (2C), 29.4 (2C), 26.0, 25.9 (2C), 19.2 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2995, 2247, 1432, 1442, 2, 1355, 1321, 1305, 1287, 1230, 1070, 1065, 955, 760.

HRMS (EI): *m/z* calc. for [$C_{12}H_{19}N_3$]: 205.1579; found 205.1586.

3,3'-(Phenethylazanediyl)dipropanenitrile (26c)



According to **TP13** 3,3'-((benzoyloxy)azanediyl)dipropanenitrile (**5bb**, 122 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent phenethylzinc chloride (**1ff**, 2.7 mL, 0.28 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:3) afforded the title compound as a colourless oil (69 mg, 0.31 mmol, 61%).

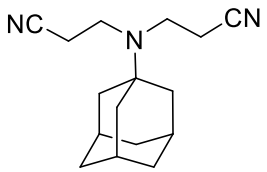
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.33–7.27 (m, 2H), 7.25–7.18 (m, 3H), 2.90 (t, *J* = 6.8 Hz, 4H), 2.85–2.73 (m, 4H), 2.41 (t, *J* = 6.8 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm =139.4, 128.8 (2C), 128.6 (2C), 126.5, 118.7 (2C), 55.7, 49.9 (2C), 34.3, 17.2 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 3028, 2930, 2849, 2248, 1626, 1602, 1584, 1495, 1465, 1454, 1420, 1362, 1336, 1242, 1180, 1128, 1080, 1030, 966, 910, 825, 748, 700.

HRMS (EI): *m/z* calc. for [$C_{14}H_{17}N_3$]: 227.1422; found 227.1422.

3,3'-(((3*s*,5*s*,7*s*)-adamantan-1-yl)azanediyl)dipropanenitrile (26d)



According to **TP13** 3,3'-((benzoyloxy)azanediyl)dipropanenitrile (**5bb**, 122 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent ((3*s*,5*s*,7*s*)-adamantan-1-yl)zinc chloride (**1gg**, 2.7 mL, 0.28 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:3) afforded the title compound as a white solid (66 mg, 0.26 mmol, 51%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 2.88 (t, *J* = 7.1 Hz, 4H), 2.39 (t, *J* = 7.1 Hz, 4H), 2.07–2.00 (m, 3H), 1.59 (t, *J* = 3.7 Hz, 9H), 1.57–1.48 (m, 3H).

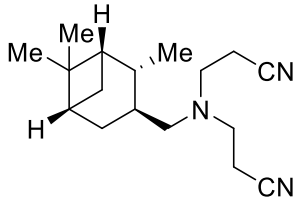
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 118.9 (2C), 55.7, 45.4 (2C), 40.0 (3C), 36.4 (3C), 29.4 (3C), 20.8 (2C)l.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2906, 2847, 1740, 1600, 1583, 1448, 1381, 1361, 1344, 1311, 1273, 1257, 1240, 1190, 1176, 1130, 1120, 1081, 1061, 1044, 1020, 977, 954, 939, 907, 876, 860, 818, 801, 771, 747, 707, 686, 672.

HRMS (EI): *m/z* calc. for [$C_{16}H_{23}N_3$]: 257.1892; found 257.1899.

m.p.: 46 °C

3,3'-((((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)azanediyl)dipropanenitrile (26e)



According to **TP13** 3,3'-((benzoyloxy)azanediyl)dipropanenitrile (**5bb**, 122 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)zinc chloride (**1hh**, 2.3 mL, 0.32 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:3) afforded the title compound as a colourless oil (90 mg, 0.33 mmol, 66%).

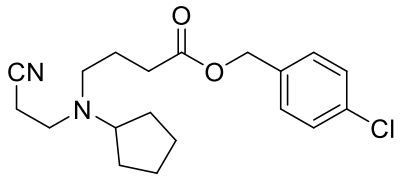
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 2.89–2.75 (m, 4H), 2.51–2.35 (m, 5H), 2.29–2.19 (m, 2H), 2.14–2.04 (m, 1H), 1.92–1.84 (m, 1H), 1.78–1.66 (m, 2H), 1.54–1.39 (m, 2H), 1.13 (s, 3H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.94 (s, 3H), 0.62 (d, *J* = 9.7 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 118.6 (2C), 64.1, 49.7 (2C), 47.9, 41.6, 41.6, 38.9, 34.3, 33.8, 33.2, 27.9, 23.1, 22.0, 16.7 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932, 2856, 2249, 2197, 1742, 1621, 1601, 1584, 1464, 1450, 1421, 1372, 1350, 1315, 1239, 1194, 1177, 1162, 1137, 1080, 1063, 1023, 1002, 894, 866, 825, 802, 780, 746, 709, 687, 674.

HRMS (EI): *m/z* calc. for [$C_{17}H_{27}N_3$]: 273.2205; found 273.2212.

4-Chlorobenzyl 4-((2-cyanoethyl)(cyclopentyl)amino)butanoate (27a)



According to **TP13** 3-((benzoyloxy)(cyclopentyl)amino)propanenitrile (**5cc**, 129 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (4-((4-chlorobenzyl)oxy)-4-oxobutyl)zinc bromide (**1ii**, 1.9 mL, 0.40 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 2:1) afforded the title compound as a colourless oil (152 mg, 0.44 mmol, 81%).

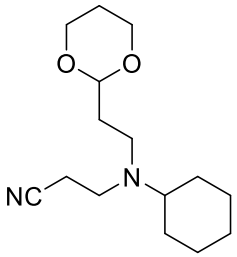
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.35–7.27 (m, 4H), 5.07 (s, 2H), 3.04–2.93 (m, 1H), 2.82 (t, *J* = 7.1 Hz, 2H), 2.50 (dd, *J* = 7.9, 6.4 Hz, 2H), 2.39 (td, *J* = 7.1, 3.6 Hz, 4H), 1.79–1.70 (m, 2H), 1.69–1.58 (m, 2H), 1.56–1.45 (m, 2H), 1.37–1.24 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.3, 134.5, 134.2, 129.8 (2C), 128.8 (2C), 119.2, 65.4, 63.1, 50.5, 47.3, 31.6, 29.7 (2C), 23.9 (2C), 22.6, 16.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2868, 2247, 1732, 1695, 1621, 1600, 1493, 1463, 1452, 1417, 1412, 1378, 1355, 1316, 1255, 1212, 1161, 1122, 1091, 1015, 971, 944, 838, 805.

HRMS (EI): *m/z* calc. for [$C_{19}H_{25}ClN_2O_2$]: 348.1605; found 348.1613.

3-((2-(1,3-Dioxan-2-yl)ethyl)(cyclohexyl)amino)propanenitrile (27b)



According to **TP13** 3-((benzoyloxy)(cyclohexyl)amino)propanenitrile (**5dd**, 136 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (2-(1,3-dioxan-2-yl)ethyl)zinc chloride (**1jj**, 1.7 mL, 0.45 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:1) afforded the title compound as a colourless oil (125 mg, 0.47 mmol, 94%).

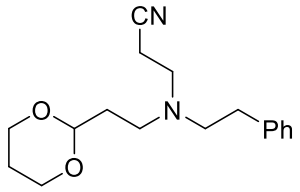
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.66 (t, *J* = 5.3 Hz, 1H), 4.03 (ddt, *J* = 10.5, 5.0, 1.4 Hz, 2H), 3.78–3.70 (m, 2H), 2.66 (t, *J* = 6.7 Hz, 2H), 2.52 (t, *J* = 6.9 Hz, 2H), 2.35 (t, *J* = 6.7 Hz, 2H), 2.01 (dtt, *J* = 15.8, 12.5, 5.0 Hz, 1H), 1.79–1.68 (m, 4H), 1.63 (td, *J* = 6.9, 5.3 Hz, 2H), 1.59–1.50 (m, 1H), 1.37–1.25 (m, 2H), 1.20–1.09 (m, 4H), 1.08–0.93 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 119.4, 100.4, 66.8, 59.4, 46.2, 44.8, 34.3, 29.0, 26.2, 26.1, 25.9, 18.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2963, 2926, 2850, 1469, 1458, 1451, 1432, 1405, 1380, 1336, 1290, 1283, 1273, 1251, 1240, 1222, 1169, 1155, 1132, 1108, 1090, 1073, 1046, 1025, 1007, 994, 973, 958, 925, 902, 894, 888, 859, 845, 826, 752.

HRMS (EI): *m/z* calc. for [$C_{15}H_{26}N_2O_2$]: 266.1994; found 266.1999.

3-((2-(1,3-Dioxan-2-yl)ethyl)(phenethyl)amino)propanenitrile (27c)



According to **TP13** 3-((benzoyloxy)(phenethyl)amino)propanenitrile (**5ee**, 147 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (2-(1,3-dioxan-2-yl)ethyl)zinc bromide (**1jj**, 1,7 mL, 0.45 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:1) afforded the title compound as a colourless oil (108 mg, 0.38 mmol, 75%).

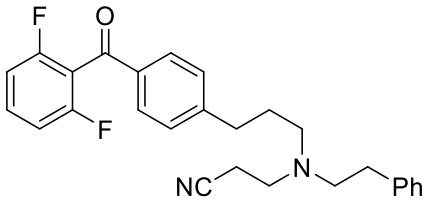
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.31–7.26 (m, 2H), 7.23–7.17 (m, 3H), 4.56 (t, *J* = 5.3 Hz, 1H), 4.07 (ddt, *J* = 10.5, 5.1, 1.4 Hz, 2H), 3.74 (ddt, *J* = 12.3, 10.3, 2.0 Hz, 2H), 2.79 (t, *J* = 6.9 Hz, 2H), 2.76–2.67 (m, 4H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.40 (t, *J* = 6.8 Hz, 2H), 2.12–1.98 (m, 1H), 1.70 (td, *J* = 7.0, 5.3 Hz, 2H), 1.36–1.24 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 140.2, 128.9 (2C), 128.4 (2C), 126.1, 119.2, 100.4, 66.9 (2C), 55.8, 49.9, 48.1, 34.0, 32.9, 25.9, 16.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2851, 2247, 1624, 1604, 1496, 1462, 1454, 1429, 1407, 1379, 1286, 1238, 1218, 1202, 1135, 1088, 1048, 1031, 1006, 974, 961, 930, 892, 853, 748, 700.

HRMS (EI): *m/z* calc. for [$C_{17}H_{24}N_2O_2$]: 288.1838; found 288.1842.

3-((3-(4-(2,6-Difluorobenzoyl)phenyl)propyl)(phenethyl)amino)propanenitrile (27d)



According to **TP13** 3-((benzoyloxy)(phenethyl)amino)propanenitrile (**5ee**, 147 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and (3-(4-(2,6-difluorobenzoyl)phenyl)propyl)zinc bromide (**1kk**, 1.8 mL, 0.41 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 2:1) afforded the title compound as a yellowish oil(160 mg, 0.37 mmol, 74%).

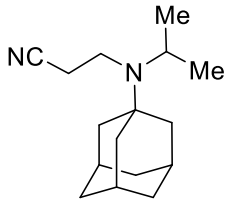
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.71 (d, *J* = 8.1 Hz, 2H), 7.36 (tt, *J* = 8.5, 6.4 Hz, 1H), 7.24–7.16 (m, 4H), 7.15–7.08 (m, 3H), 6.96–6.89 (m, 2H), 2.75 (t, *J* = 6.8 Hz, 2H), 2.65 (s, 4H), 2.61 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.46 (t, *J* = 7.0 Hz, 2H), 2.29 (t, *J* = 6.8 Hz, 2H), 1.76–1.66 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 188.6, 159.8 (dd, *J* = 251.4, 7.7 Hz, 2C), 149.5, 140.1, 134.8, 131.8 (t, *J* = 9.8 Hz), 130.0 (2C), 128.9 (2C), 128.8 (2C), 128.5 (2C), 126.2, 119.1, 117.2 (t, *J* = 22.0 Hz), 112.3–111.5 (m, 2C), 55.6, 53.0, 49.6, 33.9, 33.4, 28.7, 16.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2938, 1712, 1670, 1622, 1604, 1589, 1496, 1464, 1416, 1362, 1311, 1277, 1234, 1183, 1145, 1080, 1030, 1004, 930, 852, 790, 748, 724, 699.

HRMS (EI): *m/z* calc. for [$C_{27}H_{26}F_2N_2O$]: 432.2013; found 432.2018.

3-(((3*s*,5*s*,7*s*)-adamantan-1-yl)(isopropyl)amino)propanenitrile (27e)



According to **TP13** 3-(((3*s*,5*s*,7*s*)-adamantan-1-yl)(benzoyloxy)amino)propanenitrile (**5ff**, 162 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent isopropylzinc chloride (**1ll**, 1.4 mL, 0.52 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:1) afforded the title compound as a colourless oil (89 mg, 0.36 mmol, 72%).

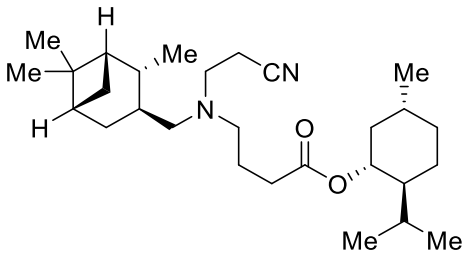
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.44–3.33 (m, 1H), 2.91–2.83 (m, 2H), 2.31–2.24 (m, 2H), 2.00 (s, 3H), 1.64–1.48 (m, 12H), 0.94 (d, *J* = 6.6 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 119.3, 55.7, 44.7, 41.5 (3C), 37.4, 36.6 (3C), 29.7 (3C), 23.2 (2C), 22.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2924, 2869, 1729, 1596, 1557, 1466, 1456, 1402, 1384, 1370, 1333, 1314, 1284, 1265, 1241, 1175, 1153, 1134, 1123, 1107, 1097, 1076, 1039, 1013, 984, 964, 938, 919, 801, 710.

HRMS (EI): *m/z* calc. for [$C_{16}H_{26}N_2$]: 246.2096; found 246.2101.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 4-((2-cyanoethyl)(((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)amino)butanoate (27f)



According to **TP13** 3-((benzoyloxy)(((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)amino)propanenitrile (**5gg**, 170 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (4-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-4-oxobutyl)zinc bromide (**1mm**, 1.7 mL, 0.43 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 2:1) afforded the title compound as a colourless oil (171 mg, 0.39 mmol, 77%).

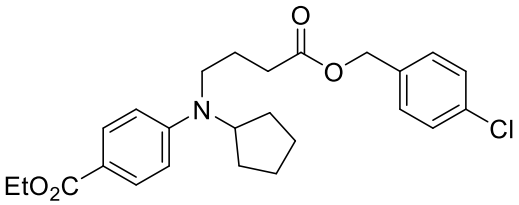
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.58 (qt, *J* = 7.0, 2.6 Hz, 1H), 2.90–2.75 (m, 2H), 2.73–2.65 (m, 4H), 2.53–2.42 (m, 2H), 2.39 (t, *J* = 7.1 Hz, 2H), 2.08–1.73 (m, 8H), 1.72–1.38 (m, 9H), 1.38–1.26 (m, 2H), 1.00 (d, *J* = 6.8 Hz, 6H), 0.94 (s, 3H), 0.91 (dd, *J* = 6.8, 1.5 Hz, 3H), 0.89–0.85 (m, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.7, 118.0, 76.2, 57.0, 53.7, 52.3, 47.0, 45.1, 40.3, 40.0, 39.5, 39.4, 38.3, 34.3, 33.0, 31.3, 31.3, 30.4, 26.3, 24.7, 24.6, 24.4, 24.3, 22.0, 19.1, 19.0, 17.6, 15.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2870, 1727, 1456, 1420, 1385, 1370, 1345, 1328, 1298, 1252, 1178, 1151, 1133, 1119, 1097, 1081, 1059, 1039, 1010, 984, 966, 939, 914, 844.

HRMS (EI): *m/z* calc. for [$C_{28}H_{48}N_2O_2$]: 444.3716; found 444.3722.

Ethyl 4-((4-((4-chlorobenzyl)oxy)-4-oxobutyl)(cyclopentyl)amino)benzoate (2nn)



According to **TP13** 4-chlorobenzyl 4-((benzoyloxy)(cyclopentyl)amino)butanoate (**5hh**, 208 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (4-(ethoxycarbonyl)phenyl)zinc chloride (**1aa**, 2.5 mL, 0.30 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:1) afforded the title compound as a colourless oil (195 mg, 0.44 mmol, 88%).

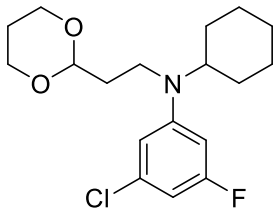
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.87 (d, *J* = 9.1 Hz, 2H), 7.39–7.24 (m, 4H), 6.71 (d, *J* = 9.2 Hz, 2H), 5.10 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.11 (p, *J* = 9.0, 8.5 Hz, 1H), 3.29–3.19 (m, 2H), 2.42 (t, *J* = 7.0 Hz, 2H), 2.02–1.85 (m, 4H), 1.78–1.65 (m, 2H), 1.65–1.56 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.8, 166.9, 152.4, 134.3, 131.3, 129.8 (2C), 128.8 (2C), 127.2 (2C), 117.3, 111.6 (2C), 65.6, 60.1, 59.7, 44.8, 31.4, 29.2 (2C), 23.8, 23.4 (2C), 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 2854, 1736, 1688, 1667, 1462, 1453, 1417, 1371, 1347, 1317, 1241, 1219, 1165, 1145, 1095, 1072, 1046, 1020, 987, 906, 892, 869, 844, 825, 725, 681.

HRMS (EI): *m/z* calc. for [$C_{25}H_{30}ClNO_4$]: 443.1863; found 443.1869.

***N*-(2-(1,3-Dioxan-2-yl)ethyl)-3-chloro-*N*-cyclohexyl-5-fluoroaniline (2oo)**



According to **TP13** *N*-(2-(1,3-dioxan-2-yl)ethyl)-*O*-benzoyl-*N*-cyclohexylhydroxylamine (**5ii**, 167 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (3-chloro-5-fluorophenyl)zinc chloride (**1nn**, 2.8 mL, 0.27 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 1:1) afforded the title compound as a white solid (179 mg, 0.43 mmol, 86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.49 (t, *J* = 2.2 Hz, 1H), 6.38–6.26 (m, 2H), 4.59 (t, *J* = 4.8 Hz, 1H), 4.12 (ddd, *J* = 12.0, 5.0, 1.4 Hz, 2H), 3.76 (ddt, *J* = 12.3, 10.4, 2.4 Hz, 2H), 3.44 (tt, *J* = 11.4, 3.4 Hz, 1H), 3.38–3.24 (m, 2H), 2.22–2.02 (m, 1H), 1.93–1.78 (m, 6H), 1.78–1.60 (m, 1H), 1.54–1.25 (m, 5H), 1.21–1.07 (m, 1H).

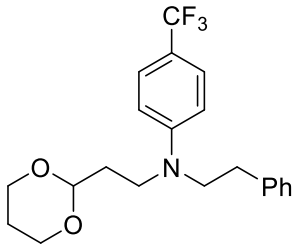
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.1 (d, *J* = 243.1 Hz), 150.6 (d, *J* = 12.0 Hz), 135.5 (d, *J* = 14.4 Hz), 108.2 (d, *J* = 2.3 Hz), 102.9 (d, *J* = 25.8 Hz), 100.5, 97.7 (d, *J* = 26.3 Hz), 67.0 (2C), 57.8, 39.6, 34.6, 30.6 (2C), 26.2(2C), 25.8, 25.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2967, 2927, 2860, 2843, 1611, 1594, 1574, 1564, 1486, 1474, 1455, 1448, 1434, 1406, 1364, 1340, 1274, 1257, 1240, 1200, 1172, 1142, 1131, 1100 , 1033, 1003, 995, 978, 951, 922, 888, 861, 848, 834, 813, 778, 760, 734, 677.

HRMS (EI): *m/z* calc. for [$C_{18}H_{25}ClFNO_2$]: 341.1558; found 341.1563.

m.p.: 62.5 °C

_N_-(2-(1,3-Dioxan-2-yl)ethyl)-_N_-phenethyl-4-(trifluoromethyl)aniline (2pp)



According to **TP13** *N*-(2-(1,3-dioxan-2-yl)ethyl)-*O*-benzoyl-*N*-phenethylhydroxylamine (**5jj**, 178 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (4-(trifluoromethyl)phenyl)zinc chloride (**1oo**, 2.6 mL, 0.29 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 2:1) afforded the title compound as a colourless oil (154 mg, 0.41 mmol, 81%).

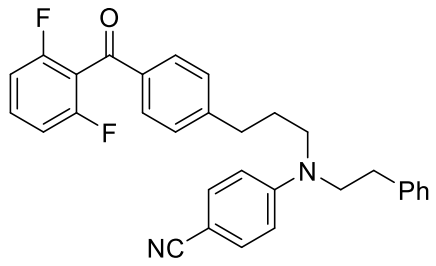
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 (d, *J* = 8.8 Hz, 2H), 7.27–7.20 (m, 2H), 7.18–7.10 (m, 3H), 6.69–6.62 (m, 2H), 4.46 (t, *J* = 4.9 Hz, 1H), 4.03 (ddt, *J* = 10.5, 5.0, 1.4 Hz, 2H), 3.65 (ddt, *J* = 12.3, 10.5, 2.4 Hz, 2H), 3.50–3.41 (m, 2H), 3.34 (t, *J* = 7.4 Hz, 2H), 2.78 (dd, *J* = 9.0, 6.7 Hz, 2H), 2.09–1.93 (m, 1H), 1.82–1.74 (m, 2H), 1.26 (dtt, *J* = 13.5, 2.7, 1.4 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.7, 139.1, 129.3, 128.8, 128.7, 126.7 (d, *J* = 3.7 Hz), 126.5, 125.2 (d, *J* = 270.1 Hz), 117.1 (q, *J* = 32.7 Hz), 110.8, 100.2, 66.9, 52.5, 45.7, 33.2, 32.6, 25.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2872, 1733, 1697, 1601, 1519, 1493, 1479, 1462, 1452, 1432, 1403, 1386, 1365, 1314, 1271, 1170, 1104, 1016, 958, 829, 805, 769, 746, 700, 674, 653.

HRMS (EI): *m/z* calc. for [$C_{21}H_{24}F_3NO_2$]: 379.1759; found 379.1768.

4-((3-(4-(2,6-Difluorobenzoyl)phenyl)propyl)(phenethyl)amino)benzonitrile (2qq)



According to **TP13** (4-(3-((benzoyloxy)(phenethyl)amino)propyl)phenyl)(2,6-difluorophenyl)methanone (**5kk**, 250 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (4-cyanophenyl)zinc chloride (**1vv**, 3.0 mL, 0.25 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 3:1) afforded the title compound as a colourless oil (190 mg, 0.40 mmol, 79%).

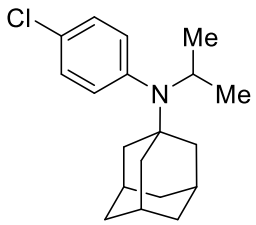
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.90 (d, *J* = 8.2 Hz, 2H), 7.59–7.51 (m, 3H), 7.37 (ddt, *J* = 11.5, 8.8, 7.0 Hz, 5H), 7.26–7.21 (m, 2H), 7.15–7.07 (m, 2H), 6.70–6.65 (m, 2H), 3.72–3.54 (m, 2H), 3.41–3.25 (m, 2H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 2.04–1.88 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 188.5, 159.8 (dd, *J* = 251.5, 7.6 Hz, 2C), 150.1, 148.2, 138.6, 135.1, 133.8 (2C), 132.9, 131.9 (t, *J* = 9.9 Hz), 130.1 (2C), 128.8 (2C), 128.7 (2C), 128.7 (2C), 126.7, 117.1 (t, *J* = 21.9 Hz), 112.1–111.8 (m, 2C), 111.2 (2C), 97.2, 52.7, 50.4, 33.3, 33.2, 27.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932, 2211, 1670, 1622, 1602, 1519, 1496, 1463, 1405, 1360, 1311, 1294, 1277, 1234, 1202, 1174, 1145, 1117, 1004, 967, 930, 815, 790, 748, 724, 699.

HRMS (EI): *m/z* calc. for [$C_{31}H_{26}F_2N_2O$]: 480.2013; found 480.2023.

(3*s*,5*s*,7*s*)-*N*-(4-chlorophenyl)-*N*-isopropyladamantan-1-amine (2rr)



According to **TP13** *N*-((3*s*,5*s*,7*s*)-adamantan-1-yl)-*O*-benzoyl-*N*-isopropylhydroxylamine (**5ll**, 157 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent naphthalen-1-ylzinc chloride (, 2.8 mL, 0.27 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 9:1) afforded the title compound as a colourless oil (94 mg, 0.31 mmol, 62%).

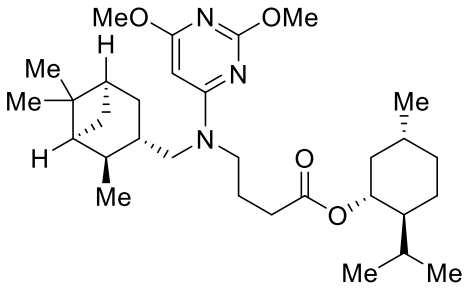
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.33–7.17 (m, 2H), 6.90–6.79 (m, 2H), 3.84 (p, *J* = 6.8 Hz, 1H), 2.17–1.97 (m, 9H), 1.73–1.62 (m, 6H), 1.24 (d, *J* = 6.8 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.9, 129.4 (2C), 127.6, 119.3 (2C), 60.5, 47.3, 40.7 (3C), 36.3 (3C), 29.7 (3C), 22.4 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2950, 1738, 1657, 1598, 1493, 1435, 1357, 1337, 1213, 1175, 1157, 1124, 1095, 1031, 977, 907, 809, 729, 699.

HRMS (EI): *m/z* calc. for [$C_{19}H_{26}ClN$]: 303.1754; found 303.1749.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 4-((2,6-dimethoxypyrimidin-4-yl) (((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)amino)butanoate (2ss)



According to **TP13** (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 4-((benzoyloxy) (((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)amino)butanoate (**5mm**, 256 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (2,6-dimethoxypyrimidin-4-yl)zinczinc chloride (**1q**, 2.7 mL, 0.28 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 4:1) afforded the title compound as a colourless oil (215 mg, 0.41 mmol, 81%).

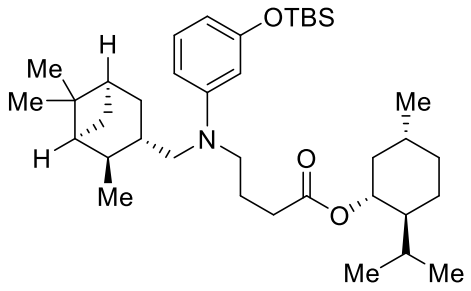
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.89 (s, 1H), 4.64 (td, *J* = 10.8, 4.3 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.10 (dd, *J* = 12.5, 5.3 Hz, 1H), 2.96 (dd, *J* = 7.9, 6.4 Hz, 2H), 2.66 (dd, *J* = 12.5, 9.6 Hz, 1H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.28–2.20 (m, 1H), 2.01–1.89 (m, 2H), 1.89–1.76 (m, 2H), 1.74–1.57 (m, 7H), 1.58–1.40 (m, 2H), 1.37–1.28 (m, 1H), 1.14 (s, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.89–0.84 (m, 12H), 0.72 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.1, 167.1, 161.2, 152.7, 126.1, 74.0, 62.9, 54.7, 53.8, 53.0, 48.0, 47.0, 41.6, 41.4, 40.9, 38.9, 34.2, 34.1, 33.6, 32.9, 31.9, 31.4, 27.9, 26.3, 23.4, 23.1, 23.0, 22.0, 21.8, 20.8, 16.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951, 2924, 2869, 1729, 1596, 1557, 1466, 1456, 1402, 1384, 1370, 1333, 1314, 1284, 1265, 1241, 1175, 1153, 1134, 1123, 1107, 1097, 1076, 1039, 1013, 984, 964, 938, 919, 844, 801, 764, 733, 710.

HRMS (EI): *m/z* calc. for [$C_{31}H_{51}N_3O_4$]: 529.3880; found 529.3888.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 4-((3-((*tert*-butyldimethylsilyl)oxy)phenyl) (((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)amino)butanoate (2tt)



According to **TP13** (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 4-((benzoyloxy) (((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)methyl)amino)butanoate (**5mm**, 256 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (2 mL). Predried $CoCl_2$·(3 mg, 25 µmol, 5.00 mol%) was added and subsequent (3-((*tert*-butyldimethylsilyl)oxy)phenyl)zinc chloride (**1qq**, 2.9 mL, 0.26 M, 0.75 mmol, 1.50 equiv) was added dropwise and the resulting mixture was stirred for 2 h at rt. Purification of the crude product by flash chromatography (hexane:EtOAc 4:1) afforded the title compound as a colourless oil (257 mg, 0.43 mmol, 86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.84 (t, *J* = 8.1 Hz, 1H), 6.03 (t, *J* = 2.3 Hz, 1H), 5.97 (ddd, *J* = 7.9, 2.2, 0.7 Hz, 1H), 4.51 (d, *J* = 4.4 Hz, 1H), 3.27–3.13 (m, 2H), 3.08 (dd, *J* = 14.3, 6.8 Hz, 1H), 2.94 (dt, *J* = 14.2, 7.2 Hz, 1H), 2.17–2.07 (m, 4H), 2.06–1.95 (m, 1H), 1.87 (dddd, *J* = 13.1, 9.7, 3.3, 1.9 Hz, 1H), 1.79 (dtd, *J* = 11.9, 3.8, 1.7 Hz, 1H), 1.75–1.43 (m, 10H), 1.29 (dddd, *J* = 11.8, 9.2, 6.2, 3.8 Hz, 3H), 1.18 (ddt, *J* = 12.5, 10.9, 3.2 Hz, 1H), 0.98 (s, 3H), 0.89–0.81(m, 1H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.78 (s, 9H), 0.77 (s, 3H), 0.70 (dd, *J* = 6.8, 3.6 Hz, 6H), 0.56 (d, *J* = 7.0 Hz, 3H), -0.00 (d, *J* = 1.7 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.8, 156.7, 149.4, 129.7, 107.9, 106.3, 104.8, 74.2, 61.0, 51.5, 48.3, 47.0, 41.7, 41.6, 41.0, 38.8, 34.3, 34.0, 33.9, 32.4, 32.0, 31.4, 28.0, 26.3, 25.8 (3C), 23.4, 23.0, 22.1, 22.1, 22.0, 20.8, 18.3, 16.3, -4.3, -4.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2953, 2928, 2859, 1729, 1601, 1573, 1496, 1471, 1462, 1456, 1386, 1368, 1252, 1231, 1193, 1172, 1159, 1126, 1096, 1081, 1037, 1004, 984, 963, 953, 909, 834, 780, 757, 732, 690, 664.

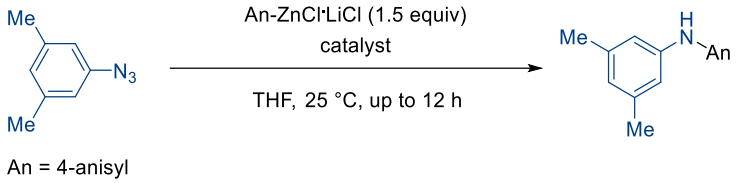
HRMS (EI): *m/z* calc. for [$C_{37}H_{63}NO_3Si$]: 597.4577; found 597.4588.

6. Iron-Mediated Electrophilic Amination of Organozinc Halides using Organic Azides Detailed Reaction Optimization

6.1 Reaction Optimization

The optimization of the conditions was performed according to the described procedure for amine **3b**, altering the conditions as described in the following (Table 12).

Table 12. Detailed reaction optimization.



An = 4-anisyl

Entry	Catalyst (loading)	Other alteration	GC-yield [%]
1	-	-	0
2	CuCN·2LiCl (20 mol%)	-	< 5
3	$CuCl_2$ (20 mol%)	-	< 5
4	$NiCl_2$ (20 mol%)	-	< 5
5	$CoCl_2$ (20 mol%)	-	< 5
6	$CrCl_2$ (20 mol%)	-	< 5
7	$CrCl_3$ (20 mol%)	-	< 5
8	$MnCl_2$ (20 mol%)	-	< 5
9	$PdCl_2$ (20 mol%)	-	< 5
10	$FeCl_2$ (20 mol%)	-	48
11	$FeBr_2$ (20 mol%)	-	45
12	$Fe(acac)_2$ (20 mol%)	-	38
13	$Fe(OAc)_2$ (20 mol%)	-	46
14	$Fe(acac)_3$ (20 mol%)	-	47
15	$Fe(DBM)_3$ (20 mol%)	-	48
16	$Fe(OTf)_3$ (20 mol%)	-	40
17	$FeBr_3$ (20 mol%)	-	46
18	$FeCl_3$ (20 mol%)	-	49
19	$FeCl_3$ (15 mol%)	-	39
20	$FeCl_3$ (10 mol%)	-	32
21	$FeCl_3$ (5 mol%)	-	16
22	$FeCl_3$ (20 mol%)	Azide:AnZnCl = 1.5:1.0	27
23	$FeCl_3$ (20 mol%)	Inverse addition (Organozinc/Azide)	46
24	$FeCl_3$ (20 mol%)	Inverse addition (Organozinc/Azide) + 45 °C, 1 h	50

25	$FeCl_3$ (20 mol%)	45 °C, 1 h	59
26	$FeCl_3$ (33 mol%)	45 °C, 1 h	60
27	$FeCl_3$ (50 mol%)	45 °C, 1 h	69
28	$FeCl_3$ (75 mol%)	45 °C, 1 h	27
29	$FeCl_3$ (1.0 equiv)	45 °C, 1 h	25
30	$FeCl_3$ (20 mol%)	AnZnCl (1.1 equiv); 45 °C, 1 h	61
31	$FeCl_3$ (50 mol%)	AnZnCl (1.75 equiv); 45 °C, 1 h	79
32	$FeCl_3$ (50 mol%)	AnZnCl (2.0 equiv); 45 °C, 1 h	80
33	$FeCl_3$ (42 mol%)	AnZnCl (1.25 equiv); 45 °C, 1 h	54
34	$FeCl_3$ (35 mol%)	AnZnCl (1.05 equiv); 45 °C, 1 h	37
35	$FeCl_3$ (75 mol%)	AnZnCl (2.25 equiv); 45 °C, 1 h	59
36	$FeCl_3$ (1.00 equiv)	AnZnCl (3.0 equiv); 45 °C, 1 h	58

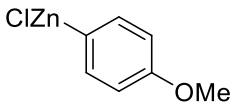
Furthermore, solvent mixture of type THF/solvent 1:1 have been tested (solvent = DMF, DMSO, DCE, DMPU, NMP, DME, toluene). However, all mixture led to decreased amounts of product yield.

Higher amounts of $FeCl_2$ (e.g. 50%) also always provided less good yields than equal amounts of $FeCl_3$. Over 50% the same decrease in yield as for $FeCl_3$ was observed.

We assume, that the decrease of product formation with higher amounts of iron originates from the concurring dimerization reaction. The described reaction is very fast (usually done within 5 min) and is in most cases faster than the transition metal catalyzed homo-dimerization of the organozinc reagent. However, if the amount of $FeCl_3$ is too high, dimerization overpowers the desired transformation. We also assume that higher amounts of $FeCl_3$ lead to decomposition of the azide.

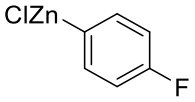
6.2 Preparation of the Organozinc Chlorides

(4-Methoxyphenyl)zinc chloride (1rr)



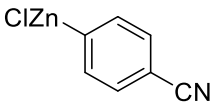
According to **TP4**, 1-bromo-4-methoxybenzene (468 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The reaction mixture was stirred at 25 °C overnight and then a solution of $ZnCl_2$ (1.00 M, 3.00 mL, 3.00 mmol, 1.20 equiv) in dry THF was added at 0 ℃. After warming up slowly and stirring at 25 °C for 15 min, the titration using iodine gave a concentration of 0.29 mmol/mL active zinc species, corresponding to 98% yield.

(4-Fluorophenyl)zinc chloride (1ss)



According to **TP4**, 1-bromo-4-fluorobenzene (438 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The reaction mixture was stirred at 25 °C overnight and then a solution of $ZnCl_2$ (1.00 M, 3.00 mL, 3.00 mmol, 1.20 equiv) in dry THF was added at 0 ℃. After warming up slowly and stirring at 25 °C for 15 min, the titration using iodine gave a concentration of 0.27 mmol/mL active zinc species, corresponding to 92% yield.

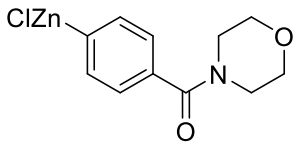
(4-Cyanophenyl)zinc chloride (1tt)



According to **TP2**, 4-iodobenzonitrile (1.15 g, 5.00 mmol, 1.00 equiv) was dissolved in dry THF (10 mL) and *i*PrMgCl·LiCl (1.28 M, 4.30 mL, 5.50 mmol, 1.10 equiv) was added dropwise at 0 ℃. The reaction mixture was stirred at the set temperature for 1 h and then a solution of $ZnCl_2$ (1.00 M, 6.00 mL, 6.00 mmol, 1.20 equiv) in dry THF was added at 0 ℃. After

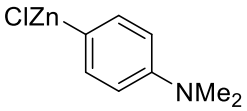
warming up slowly and stirring at 25 °C for 15 min, the titration using iodine gave a concentration of 0.20 mmol/mL active zinc species, corresponding to 81% yield.

(4-(Morpholine-4-carbonyl)phenyl)zinc chloride (1uu)



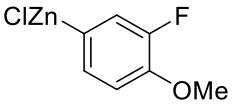
According to **TP2**, (4-iodophenyl)(morpholino)methanone (1.59 g, 5.00 mmol, 1.00 equiv) was dissolved in dry THF (5 mL) and *i*PrMgCl·LiCl (1.28 M, 4.30 mL, 5.50 mmol, 1.10 equiv) was added dropwise at 0 ℃. The reaction mixture was stirred at the set temperature for 2 h and then a solution of $ZnCl_2$ (1.00 M, 6.00 mL, 6.00 mmol, 1.20 equiv) in dry THF was added at 0 ℃. After warming up slowly and stirring at 25 °C for 15 min, the titration using iodine gave a concentration of 0.20 mmol/mL active zinc species, corresponding to 81% yield.

(4-(Dimethylamino)phenyl)zinc chloride (1vv)



According to **TP4**, 4-bromo-*N*,*N*-dimethylaniline (553 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The reaction mixture was stirred at 25 °C overnight and then a solution of $ZnCl_2$ (1.00 M, 3.00 mL, 3.00 mmol, 1.20 equiv) in dry THF was added at 0 ℃. After warming up slowly and stirring at 25 °C for 15 min, the titration using iodine gave a concentration of 0.26 mmol/mL active zinc species, corresponding to 88% yield.

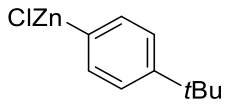
(3-Fluoro-4-methoxyphenyl)zinc chloride (1ww)



According to **TP4**, 4-bromo-2-fluoro-1-methoxybenzene (512 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The reaction mixture was stirred

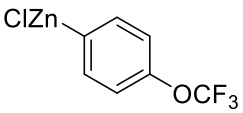
at 25 °C overnight and then a solution of $ZnCl_2$ (1.00 M, 3.00 mL, 3.00 mmol, 1.20 equiv) in dry THF was added at 0 ℃. After warming up slowly and stirring at 25 °C for 15 min, the titration using iodine gave a concentration of 0.27 mmol/mL active zinc species, corresponding to 92% yield.

(4-(*t*-Butyl)phenyl)zinc chloride (1xx)



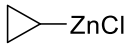
According to **TP4**, 1-bromo-4-(*t*-butyl)benzene (585 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The reaction mixture was stirred at 25 °C overnight and then a solution of $ZnCl_2$ (1.00 M, 3.00 mL, 3.00 mmol, 1.20 equiv) in dry THF was added at 0 ℃. After warming up slowly and stirring at 25 °C for 15 min, the titration using iodine gave a concentration of 0.28 mmol/mL active zinc species, corresponding to 95% yield.

(4-(Trifluoromethoxy)phenyl)zinc chloride (1yy)



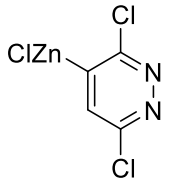
According to **TP4**, 1-bromo-4-(trifluoromethoxy)benzene (603 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The reaction mixture was stirred at 25 °C overnight and then a solution of $ZnCl_2$ (1.00 M, 3.00 mL, 3.00 mmol, 1.20 equiv) in dry THF was added at 0 ℃. After warming up slowly and stirring at 25 °C for 15 min, the titration using iodine gave a concentration of 0.26 mmol/mL active zinc species, corresponding to 88% yield.

Cyclopropylzinc chloride (1zz)



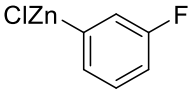
According to **TP4**, bromocyclopropane (302 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The reaction mixture was stirred at 25 °C overnight and then a solution of $ZnCl_2$ (1.00 M, 3.00 mL, 3.00 mmol, 1.20 equiv) in dry THF was added at 0 ℃. After warming up slowly and stirring at 25 °C for 15 min, the titration using iodine gave a concentration of 0.28 mmol/mL active zinc species, corresponding to 95% yield.

(3,6-Dichloropyridazin-4-yl)zinc chloride (1aaa)



In a dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum 3,6-dichloropyridazine (447 mg, 3.00 mmol, 1.00 equiv) was dissolved in dry THF (6 mL) and then a solution of TMPZnCl·LiCl (0.50 M, 6.6 mL, 3.30 mmol, 1.10 equiv) in dry THF was added dropwise. The reaction mixture was stirred at 25 °C for 30 min. the titration using iodine gave a concentration of 0.18 mmol/mL active zinc species, corresponding to 76% yield.[31]

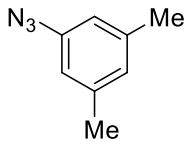
(3-Fluorophenyl)zinc chloride (1bbb)



According to **TP4**, 1-bromo-3-fluorobenzene (438 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The reaction mixture was stirred at 25 °C overnight and then a solution of $ZnCl_2$ (1.00 M, 3.00 mL, 3.00 mmol, 1.20 equiv) in dry THF was added at 0 ℃. After warming up slowly and stirring at 25 °C for 15 min, the titration using iodine gave a concentration of 0.27 mmol/mL active zinc species, corresponding to 92% yield.

6.3 Preparation of the Azides

1-Azido-3,5-dimethylbenzene (28a)

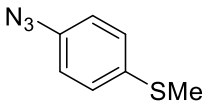


1-Azido-3,5-dimethylbenzene was prepared according to a literature known procedure.[130]

^{1}H MR (400 MHz, $CDCl_3$): δ / ppm = 6.79 (s, 1H), 6.66 (s, 2H), 2.32 (s, 6H).

Analytical data equivalent to literature.[131]

(4-Azidophenyl)(methyl)sulfane (28b)

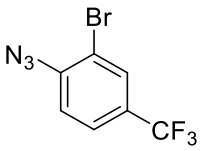


(4-Azidophenyl)(methyl)sulfane was prepared according to a literature known procedure.[130]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.31–7.25 (m, 1H), 7.01–6.95 (m, 1H), 2.50 (s, 1H).

Analytical data equivalent to literature.[131]

1-Azido-2-bromo-4-(trifluoromethyl)benzene (28c)

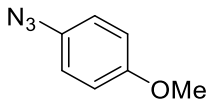


1-Azido-2-bromo-4-(trifluoromethyl)benzene was prepared according to a literature known procedure.[130]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.64–7.58 (m, 1H), 7.31 (d, *J* = 1.9 Hz, 1H), 7.22–7.15 (m, 1H).

[130] B.-Y. Ryu, T. Emrick, *Angew. Chem. Int Ed.* **2010**, *49*, 9644–9647.
[131] F. Shi, J. P. Waldo, Y. Chen, R. C. Larock, *Org. Lett.* **2008**, *10*, 2409–2412.

1-Azido-4-methoxybenzene (28d)

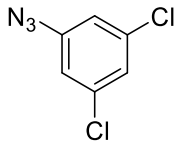


1-Azido-4-methoxybenzene was prepared according to a literature known procedure.[130]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 6.99–6.94 (m, 2H), 6.94–6.84 (m, 2H), 3.80 (s, 3H).

Analytical data equivalent to literature.[132]

1-Azido-3,5-dichlorobenzene (28e)

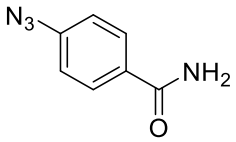


1-Azido-3,5-dichlorobenzene was prepared according to a literature known procedure.[130]

^{1}H MR (400 MHz, $CDCl_3$): δ / ppm = 7.13 (t, *J* = 1.8 Hz, 1H), 6.92 (d, *J* = 1.8 Hz, 2H).

Analytical data equivalent to literature.[133]

4-Azidobenzamide (28f)



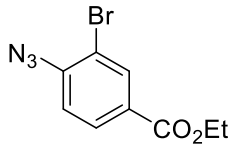
4-Azidobenzamide was prepared according to a literature known procedure.[130]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88–7.77 (m, 2H), 7.14–7.05 (m, 2H), 5.98 (s, 1H), 5.62 (s, 1H).

Analytical data equivalent to literature.[134]

[132] Y. Li, L.-X. Gao, F.-S Han, *Chem. Eur. J.* **2010**, *16*, 7969–7972.
[133] T. Meguro, N. Terashima, H. Ito, Y. Koike, I. Kii, S. Yoshida, T. Hosoya, *Chem. Commun.* **2018**, *54*, 7904–7907.
[134] K. D. Grimes, A. Gupte, C. C. Aldrich, *Synthesis* **2010**, *9*, 1441–1448.

Ethyl 4-azido-3-bromobenzoate (28g)

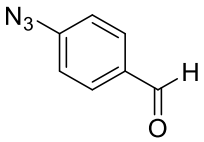


Ethyl 4-azido-3-bromobenzoate was prepared according to a literature known procedure.[130]

^{1}H MR (400 MHz, $CDCl_3$): δ / ppm = 8.23 (d, *J* = 1.9 Hz, 1H), 8.02 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

Analytical data equivalent to literature.[135]

4-Azidobenzaldehyde (28h)

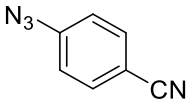


4-Azidobenzaldehyde was prepared according to a literature known procedure.[130]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 9.94 (s, 1H), 7.91–7.84 (m, 2H), 7.19–7.11 (m, 2H).

Analytical data equivalent to literature.[131]

4-Azidobenzonitrile (28i)



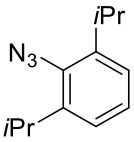
4-Azidobenzonitrile was prepared according to a literature known procedure.[130]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.69–7.60 (m, 2H), 7.13–7.08 (m, 2H).

Analytical data equivalent to literature.[131]

[135] C.-Y. Liu, P. Knochel, *J. Org. Chem.* **2007**, *72*, 7106–7115.

2-Azido-1,3-diisopropylbenzene (28j)

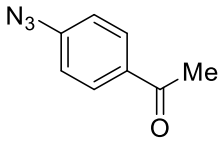


2-Azido-1,3-diisopropylbenzene was prepared according to a literature known procedure.[130]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.21 (dd, *J* = 8.8, 6.3 Hz, 1H), 7.15 (d, *J* = 6.8 Hz, 2H), 3.43–3.32 (m, 2H), 1.28 (d, *J* = 6.9 Hz, 12H).

Analytical data equivalent to literature.[136]

1-(4-Azidophenyl)ethan-1-one (28k)

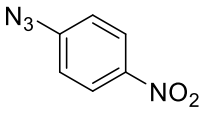


1-(4-Azidophenyl)ethan-1-one was prepared according to a literature known procedure.[130]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.92 (d, *J* = 8.2 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 2.54 (s, 3H).

Analytical data equivalent to literature.[131]

1-Azido-4-nitrobenzene (28l)



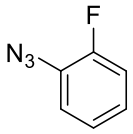
1-Azido-4-nitrobenzene was prepared according to a literature known procedure.[130]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 8.29–8.19 (m, 2H), 7.18–7.07 (m, 2H).

Analytical data equivalent to literature.[131]

[136] G. Guisado-Barrios, J. Bouffard, B. Donnadieu, G. Bertrand, *Angew. Chem. Int. Ed.* **2010**, *49*, 4759–4762.

1-Azido-2-fluorobenzene (28m)

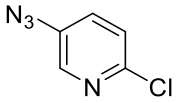


1-Azido-2-fluorobenzene was prepared according to a literature known procedure.[130]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.16–7.03 (m, 4H).

Analytical data equivalent to literature [137]

5-Azido-2-chloropyridine (28n)

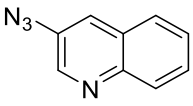


5-Azido-2-chloropyridine was prepared according to a literature known procedure.[130]

^{1}H MR (400 MHz, $CDCl_3$): δ / ppm = 8.13 (t, *J* = 1.8 Hz, 1H), 7.32 (d, *J* = 1.9 Hz, 2H).

Analytical data equivalent to literature.[138]

3-Azidoquinoline (28o)



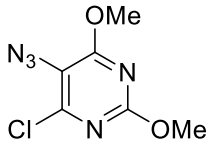
3-Azidoquinoline was prepared according to a literature known procedure.[130]

^{1}H MR (400 MHz, $CDCl_3$): δ / ppm = 8.62 (d, *J* = 2.6 Hz, 1H), 8.09 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.80–7.73 (m, 2H), 7.67 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H).

Analytical data equivalent to literature.[139]

[137] I. Birkenfelder, J. Gurke, L. Grubert, S. Hecht, B. M. Schmidt, *Chem. Asian J.* **2017**, *12*, 3156–3161.
[138] T. L. Seidl, D. R. Stuart, *J. Org. Chem.* **2017**, *82*, 11765–11771.
[139] F. R. Bou-Hamdan, F. Levesque, A. G. O'Brien, P. H. Seeberger, *Beilstein J. Org. Chem.* **2011**, *7*, 1124–1129.

5-Azido-4-chloro-2,6-dimethoxypyrimidine (28p)

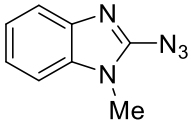


5-Azido-4-chloro-2,6-dimethoxypyrimidine was prepared according to a literature known procedure.[108]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 4.09 (s, 3H), 3.98 (s, 3H).

Analytical data equivalent to literature.[140]

2-Azido-1-methyl-1*H*-benzo[*d*]imidazole (28q)



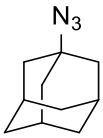
2-Azido-1-methyl-1*H*-benzo[*d*]imidazole was prepared according to a literature known procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.71–7.51 (m, 1H), 7.32–7.13 (m, 3H), 3.59 (s, 3H).

Analytical data equivalent to literature.[141]

[140] N. Ple, A. Turck, K. Couture, G. Queguiner, *Synthesis* **1996**, *7*, 838–842.
[141] D. Zornik, R. M. Meudtner, T. El Malah, C. M. Thiele, S. Hecht, *Chem. Eur. J.* **2011**, *17*, 1473–1484.

1-Adamantylazide (28r)

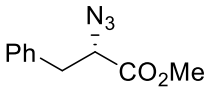


1-Adamantylazide was prepared according to a literature known procedure.[130]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 2.15 (p, *J* = 3.3 Hz, 3H), 1.80 (d, *J* = 2.9 Hz, 6H), 1.72–1.59 (m, 6H).

Analytical Data equivalent to literature[142]

Methyl (*S*)-2-azido-3-phenylpropanoate (28s)



Methyl (*S*)-2-azido-3-phenylpropanoate was prepared according to a literature known procedure.[143]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.40–7.23 (m, 5H), 4.10 (dd, *J* = 8.8, 5.4 Hz, 1H), 3.81 (s, 3H), 3.21 (dd, *J* = 14.0, 5.4 Hz, 1H), 3.04 (dd, *J* = 13.9, 8.8 Hz, 1H).

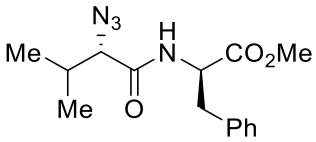
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 170.5, 135.9, 129.2 (2C), 128.7 (2C), 127.3, 63.3, 52.7, 37.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3031, 2955, 2106, 1741, 1604, 1497, 1455, 1436, 1356, 1259, 1203, 1172, 1112, 1081, 1015, 928, 905, 828, 748, 698, 672.

e.r. (determined by chiral-HPLC) = 92:8.

[142] S.-K. Chen, W-Q. Ma, Z.-B. Yan, F.-M. Zhang, S.-H. Wang, Y.-Q. Tu, X.-M. Zhang, J.-M. Tian, *J. Am. Chem. Soc.* **2018**, *140*, 10099–10103.
[143] E. D. Goddard-Borger, R. V. Stick, *Org. Lett.* **2007**, *9*, 3797–3800.

Methyl ((*S*)-2-azido-3-methylbutanoyl)-*D*-phenylalaninate (28t)



Methyl ((*S*)-2-azido-3-methylbutanoyl)-D-phenylalaninate was prepared according to a literature known procedure.[143]

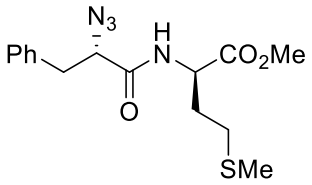
^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.26–7.14 (m, 3H), 7.10–6.98 (m, 2H), 6.64 (d, *J* = 8.3 Hz, 1H), 4.83 (ddd, *J* = 8.4, 7.1, 5.6 Hz, 1H), 3.72 (d, *J* = 4.3 Hz, 1H), 3.67 (s, 3H), 3.12–2.95 (m, 2H), 2.21 (td, *J* = 6.8, 4.3 Hz, 1H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.70 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 171.65, 168.62, 135.57, 129.11 (2C), 128.68 (2C), 127.24, 70.47, 52.92, 52.47, 38.10, 31.95, 19.53, 16.68.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3352, 2971, 2092, 1736, 1650, 1525, 1493, 1461, 1452, 1443, 1431, 1383, 1372, 1352, 1323, 1288, 1256, 1240, 1223, 1202, 1181, 1160, 1141, 1118, 1105, 1077, 1030, 994, 966, 949, 937, 892, 849, 816, 793, 763, 756, 740, 700, 682.

d.r. (determined by NMR) = 95:5.

Methyl ((*S*)-2-azido-3-phenylpropanoyl)-*D*-methioninate (28u)



Methyl ((*S*)-2-azido-3-phenylpropanoyl)-*D*-methioninate was prepared according to a literature known procedure.[143]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32–7.16 (m, 5H), 6.80 (d, *J* = 8.1 Hz, 1H), 4.60 (td, *J* = 7.7, 4.9 Hz, 1H), 4.22 (dd, *J* = 7.3, 4.2 Hz, 1H), 3.68 (s, 3H), 3.24 (dd, *J* = 14.1, 4.2 Hz, 1H), 3.04 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.18 (dt, *J* = 7.8, 6.3 Hz, 2H), 2.04–1.98 (m, 1H), 1.98 (d, *J* = 1.9 Hz, 3H), 1.83 (dd, *J* = 8.4, 7.2 Hz, 1H).

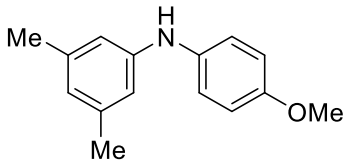
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 171.8, 168.2, 135.7, 129.6 (2C), 128.7 (2C), 127.4, 65.2, 52.7, 51.4, 38.2, 31.3, 29.6, 15.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3410, 3336, 3005, 2958, 2920, 2851, 2115, 1746, 1710, 1537, 1526, 1498, 1436, 1422, 1360, 1220, 1092, 1031, 991, 902, 786, 748, 702.

d.r. (determined by NMR) = 96:4.

6.4 Electrophilic Amination Reactions using Organic Azides

N-(4-Methoxyphenyl)-3,5-dimethylaniline (3b)



According to **TP14**, 1-azido-3,5-dimethylbenzene (**28a**, 74 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-methoxyphenyl)zinc chloride (**1rr**, 0.29 M, 3.0 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9:1) to yield the titel compound as brownish solid (84 mg, 0.37 mmol, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.18–7.06 (m, 2H), 6.98–6.86 (m, 2H), 6.63–6.59 (m, 2H), 6.57 (dt, *J* = 1.8, 1.0 Hz, 1H), 5.47 (s, 1H), 3.86 (s, 3H), 2.31 (d, *J* = 0.8 Hz, 6H).

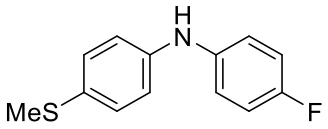
^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 155.1, 145.2, 139.1, 135.9, 122.3 (2C), 121.5 (2C), 114.6 (2C), 113.5 (2C), 55.6, 21.5 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3614, 3526, 3004, 2919, 2364, 1748, 1710, 1601, 1540, 1510, 1420, 1359, 1220, 1092, 902.

HRMS (EI): *m/z* calc. for [$C_{15}H_{17}NO$]: 227.1310; found 227.1304.

m.p.: 74.1 - 75.6 °C

4-Fluoro-*N*-(4-(methylthio)phenyl)aniline (3c)



According to **TP14**, (4-azidophenyl)(methyl)sulfane (**28b**, 83 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-fluorophenyl)zinc chloride (**1ss**, 0.27 M, 3.2 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9.5:0.5) to yield the titel compound as yellowish oil (108 mg, 0.465 mmol, 93%).

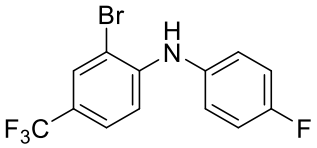
^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.31–7.23 (m, 2H), 7.08–6.99 (m, 4H), 6.97–6.91 (m, 2H), 5.61 (s, 1H), 2.49 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 158.1 (d, *J* = 240.2 Hz), 142.2, 138.8 (d, *J* = 2.4 Hz), 130.1, 128.6, 120.5 (d, *J* = 7.8 Hz), 117.6, 116.0 (d, *J* = 22.5 Hz), 18.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3357, 3003, 2922, 1748, 1708, 1652, 1595, 1508, 1493, 1436, 1421, 1359, 1316, 1219, 1184, 1156, 1092, 969, 902, 819, 776, 709

HRMS (EI): *m/z* calc. for [$C_{13}H_{12}FNS$]: 233.0674; found 233.0667.

2-Bromo-*N*-(4-fluorophenyl)-4-(trifluoromethyl)aniline (3d)



According to **TP14**, 1-azido-2-bromo-4-(trifluoromethyl)benzene (**28c**, 133 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then ((4-fluoro)phenyl)zinc chloride (**1ss**, 0.27 M, 3.2 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9.5:0.5) to yield the titel compound as yellowish oil (124 mg, 0.370 mmol, 74%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.6 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.2–7.1 (m, 3H), 7.1–7.1 (m, 2H), 6.9 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.2 (s, 1H).

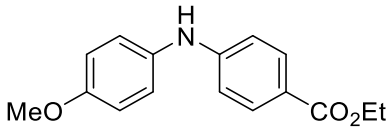
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.8 (d, *J* = 244.1 Hz), 143.0, 136.0, 133.3, 130.8 (q, *J* = 32.5 Hz), 124.6 (d, *J* = 8.2 Hz, 2C), 123.7 (q, *J* = 272.5 Hz), 116.6 (d, *J* = 22.7 Hz, 2C), 116.3 (q, *J* = 3.8 Hz), 114.0, 110.2 (q, *J* = 3.9 Hz).

^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = -62.90, -117.50 (tt, *J* = 8.6, 4.8 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3404, 1714, 1583, 1506, 1430, 1398, 1331, 1299, 1275, 1224, 1210, 1167, 1120, 1078, 1023, 937, 909, 867, 830, 806, 787, 754, 734, 712, 685.

HRMS (EI): *m/z* calc. for [$C_{13}H_8BrF_4N$]: 332.9776; found 332.9769.

Ethyl 4-((4'-methoxyphenyl)amino)benzoate (3e)



According to **TP14**, 1-azido-4-methoxybenzene (**28d**, 75 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-(ethoxycarbonyl)phenyl)zinc chloride (**1aa**, 0.22 M, 4.0 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9:1) to yield the titel compound as yellowish oil (119 mg, 0.440 mmol, 88%).

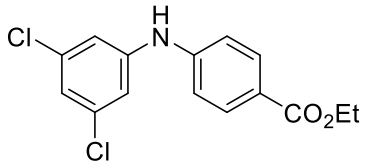
^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91–7.84 (m, 2H), 7.17–7.09 (m, 2H), 6.93–6.86 (m, 2H), 6.85–6.76 (m, 2H), 5.94 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 166.7, 156.4, 149.7, 133.5, 131.5 (2C), 124.3 (2C), 120.3, 114.7 (2C), 113.2 (2C), 60.4, 55.6, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3349, 3002, 1705, 1602, 1510, 1464, 1456, 1442, 1429, 1362, 1310, 1275, 1252, 1221, 1172, 1104, 1033, 837, 814, 772, 699.

HRMS (EI): *m/z* calc. for [$C_{16}H_{17}NO_3$]: 271.1208; found 271.1203.

Ethyl 4-((3,5-dichlorophenyl)amino)benzoate (3f)



According to **TP14**, 1-azido-3,5-dichlorobenzene (**28e**, 94 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-(ethoxycarbonyl)phenyl)zinc chloride (**1aa**, 0.22 M, 4.0 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9:1) to yield the titel compound as yellowish oil (109 mg, 0.35 mmol, 70%).

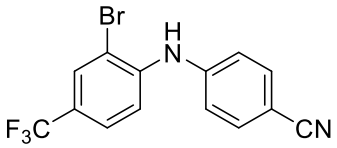
^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03–7.93 (m, 2H), 7.08–7.02 (m, 2H), 7.00 (d, *J* = 1.8 Hz, 2H), 6.97 (t, *J* = 1.8 Hz, 1H), 6.05 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 166.2, 145.7, 143.6, 135.8 (2C), 131.5 (2C), 122.0, 116.7 (2C), 116.6 (2C), 113.2, 60.8, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3004, 2919, 1748, 1710, 1584, 1539, 1434, 1419, 1359, 1276, 1220, 1177, 1092, 957, 902, 786, 772.

HRMS (EI): *m/z* calc. for [$C_{15}H_{13}Cl_2NO_2$]: 309.0323; found 309.0317.

4-((2-Bromo-4-(trifluoromethyl)phenyl)amino)benzonitrile (3g)



According to **TP14**, 1-azido-2-bromo-4-(trifluoromethyl)benzene (**28c**, 133 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-cyanophenyl)zinc chloride (**1tt**, 0.2 M, 4.4 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9:1) to yield the titel compound as white solid (159 mg, 0.465 mmol, 93%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.71 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.63–7.55 (m, 3H), 7.13 (dq, *J* = 9.2, 2.3 Hz, 3H), 6.43 (s, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 145.4, 139.4, 134.1, 134.0 (2C), 131.4, 130.9 (q, *J* = 33.0 Hz), 123.5 (d, *J* = 272.6 Hz), 119.9 (q, *J* = 3.8 Hz), 119.2, 118.1, 117.5 (2C), 115.1 (q, *J* = 3.8 Hz), 104.7.

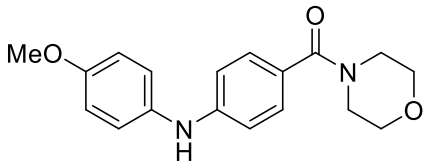
^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = -62.82.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3342, 2222, 1610, 1591, 1525, 1504, 1429, 1407, 1331, 1320, 1301, 1279, 1244, 1223, 1176, 1137, 1116, 1079, 1027, 974, 935, 890, 854, 838, 811, 758, 710, 687.

HRMS (EI): *m/z* calc. for [$C_{14}H_8BrF_3N_2$]: 339.9823; found 339.9816.

m.p.: 128.7-130.1 °C

(4-((4-Methoxyphenyl)amino)phenyl)(morpholino)methanone (3h)



According to **TP14**, 1-azido-4-methoxybenzene (**28d**, 75 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-(morpholine-4-carbonyl)phenyl)zinc chloride (**1uu**, 0.20 M, 4.4 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 4:1) to yield the titel compound as brownish solid (102 mg, 0.325 mmol, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.3 (dd, *J* = 9.1, 2.4 Hz, 2H), 7.1–7.1 (m, 2H), 6.9–6.8 (m, 4H), 5.9 (s, 1H), 3.8 (s, 3H), 3.8–3.6 (m, 8H).

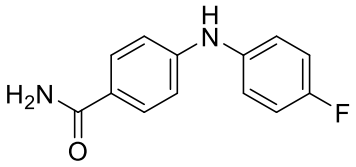
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.9, 156.1, 147.5, 134.3, 129.4 (2C), 124.9, 123.6 (2C), 114.8 (2C), 114.0 (2C), 67.0 (4C), 55.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3293, 3190, 3095, 3030, 3002, 2953, 2929, 2848, 2832, 1643, 1627, 1613, 1602, 1578, 1521, 1505, 1456, 1439, 1421, 1371, 1364, 1328, 1304, 1296, 1271, 1252, 1219, 1174, 1157, 1104, 1065, 1030, 1014, 1004, 959, 946, 933, 895, 846, 828, 811, 768, 759, 728, 710, 694.

HRMS (EI): *m/z* calc. for [$C_{18}H_{20}N_2O_3$]: 312.1474; found 312.1467.

m.p.: 125.1-127.3 °C

4-((4-Fluorophenyl)amino)benzamide (3i)



According to **TP14**, 4-azidobenzamide (**28f**, 81 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-fluorophenyl)zinc chloride (**1ss**, 0,27 M, 3.2 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9.5:0.5) to yield the titel compound as white solid (93 mg, 0.41 mmol, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.7–7.7 (m, 2H), 7.1 (ddt, *J* = 8.2, 5.7, 2.8 Hz, 2H), 7.1–7.0 (m, 2H), 6.9–6.9 (m, 2H), 5.9 (s, 1H), 5.7 (s, 2H).

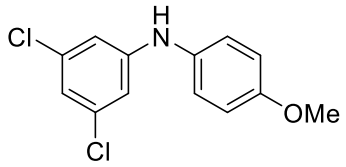
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 168.8, 159.1 (d, *J* = 242.7 Hz), 148.0, 136.8, 129.3, 123.9, 123.1 (d, *J* = 8.0 Hz), 116.3 (d, *J* = 22.6 Hz), 114.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3416, 3333, 3163, 2919, 1698, 1645, 1607, 1597, 1574, 1521, 1506, 1456, 1429, 1391, 1336, 1312, 1298, 1240, 1211, 1193, 1156, 1149, 1132, 1126, 1099, 1010, 970, 850, 820, 802, 780, 684.

HRMS (EI): *m/z* calc. for [$C_{13}H_{11}FN_2O$]: 230.0855; found 230.0848.

m.p.: 167.1-168.4 °C

3,5-Dichloro-*N*-(4-methoxyphenyl)aniline (3j)



According to **TP14**, 1-azido-3,5-dichlorobenzene (**28e**, 94 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-methoxyphenyl)zinc chloride (**1rr**, 0.29 M, 3.0 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9:1) to yield the titel compound as yellowish oil (111 mg, 0.415 mmol, 83%).

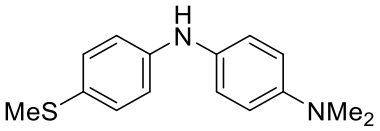
^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.08 (d, *J* = 8.4 Hz, 2H), 6.94–6.88 (m, 2H), 6.76 (s, 1H), 6.69 (d, *J* = 1.9 Hz, 2H), 3.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 156.7, 147.7, 135.6 (2C), 133.2, 124.5 (C), 118.8 (2C), 114.9 (2C), 112.8, 55.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3396, 3366, 1706, 1588, 1572, 1510, 1449, 1361, 1316, 1298, 1281, 1245, 1224, 1180, 1110, 1094, 1034, 987, 955, 824, 800, 765, 672, 660.

HRMS (EI): *m/z* calc. for [$C_{13}H_{11}Cl_2NO$]: 267.0218; found 267.0212.

N^1,N^1-Dimethyl-N^4-(4-(methylthio)phenyl)benzene-1,4-diamine (3k)



According to **TP14**, (4-azidophenyl)(methyl)sulfane (**28b**, 83 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-(dimethylamino)phenyl)zinc chloride (**1vv**, 0.26 M, 3.4 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9:1) to yield the titel compound as yellowish oil (99 mg, 0.39 mmol, 77%).

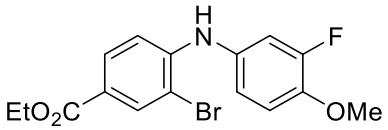
^{1}H-NMR (400 MHz, Acetone-d_6): δ / ppm = 7.2–7.1 (m, 2H), 7.1–7.0 (m, 2H), 7.0 (s, 1H), 6.9–6.8 (m, 2H), 6.8–6.7 (m, 2H), 2.9 (s, 6H), 2.4 (s, 3H).

^{13}C-NMR (101 MHz, Acetone-d_6): δ / ppm = 147.1, 145.4, 132.5 (2C), 125.0, 122.4 (2C), 115.0 (2C), 113.8 (2C), 40.4 (2C), 17.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3407, 3004, 2962, 2918, 1749, 1709, 1597, 1519, 1495, 1421, 1359, 1311, 1220, 1165, 1092, 946, 903, 819.

HRMS (EI): *m/z* calc. for [$C_{15}H_{18}N_2S$]: 258.1191; found 258.1187.

Ethyl 3-bromo-4-((3-fluoro-4-methoxyphenyl)amino)benzoate (3l)



According to **TP14**, ethyl 4-azido-3-bromobenzoate (**28g**, 135 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (3-fluoro-4-methoxyphenyl)zinc chloride (**1ww**, 0.27 M, 3.2 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9:1) to yield the titel compound as yellowish oil (118 mg, 0.325 mmol, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.2 (d, *J* = 2.0 Hz, 1H), 7.8 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.0–6.9 (m, 4H), 6.3 (s, 1H), 4.3 (q, *J* = 7.1 Hz, 2H), 3.9 (s, 3H), 1.4 (t, *J* = 7.1 Hz, 3H).

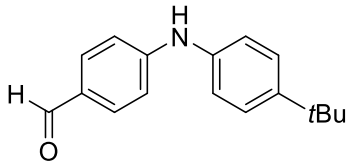
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.4, 152.6 (d, *J* = 247.5 Hz), 146.2, 145.2 (d, *J* = 10.7 Hz), 134.5, 132.8 (d, *J* = 8.6 Hz), 130.2, 121.6, 119.7 (d, *J* = 3.4 Hz), 114.2 (d, *J* = 2.9 Hz), 112.5 (d, *J* = 19.9 Hz), 112.2, 109.3, 60.8, 56.6, 14.4.

^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = -132.42 (dd, *J* = 12.0, 7.3 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3388, 2979, 2936, 2840, 1702, 1699, 1596, 1564, 1510, 1463, 1442, 1391, 1366, 1298, 1263, 1217, 1184, 1174, 1159, 1107, 1024, 972, 873, 828, 808, 760, 718, 703, 654.

HRMS (EI): *m/z* calc. for [$C_{16}H_{14}BrNO_4$]: 367.2024; found 367.0212.

4-((4-(*tert*-Butyl)phenyl)amino)benzaldehyde (3m)



According to **TP14**, 4-azidobenzaldehyde (**28h**, 74 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-(*t*-butyl)phenyl)zinc chloride (**1xx**, 0.28 M, 3.1 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9.5:0.5) to yield the titel compound as brownish solid (60 mg, 0.24 mmol, 47%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.8 (s, 1H), 7.8–7.7 (m, 2H), 7.4 (dd, *J* = 9.0, 2.5 Hz, 2H), 7.2–7.1 (m, 2H), 7.0–7.0 (m, 2H), 6.3 (s, 1H), 1.3 (s, 9H).

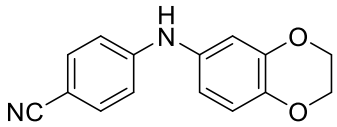
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.5, 150.4, 147.2, 137.3, 132.2 (2C), 128.1, 126.4 (2C), 121.5 (2C), 114.1, 34.5, 31.4 (3C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3523, 3410, 3351, 3005, 2965, 1748, 1708, 1652, 1592, 1525, 1421, 1360, 1308, 1270, 1221, 1164, 1110, 1092, 903, 829, 788.

HRMS (EI): *m/z* calc. for [$C_{17}H_{19}NO$]: 253.1467; found 253.1461.

m.p.: 129.6-132.4 °C

4-((2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)benzonitrile (3n)



According to **TP14**, 4-azidobenzonitrile (**28i**, 72 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)zinc chloride (**1v**, 0.28 M, 3.1 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9:1) to yield the titel compound as yellowish oil (106 mg, 0.420 mmol, 84%).

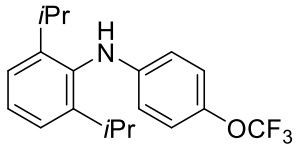
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.45–7.40 (m, 2H), 6.87–6.80 (m, 3H), 6.72 (d, *J* = 2.5 Hz, 1H), 6.65 (dd, *J* = 8.6, 2.6 Hz, 1H), 5.98 (s, 1H), 4.26 (s, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.2, 144.1, 140.9, 133.8, 133.4, 120.3, 118.0, 116.4, 114.1, 112.1, 100.5, 64.6, 64.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3337, 2980, 2930, 2876, 2212, 1705, 1599, 1504, 1458, 1440, 1408, 1382, 1339, 1297, 1278, 1258, 1240, 1204, 1171, 1121, 1105, 1065, 1049, 962, 923, 887, 826, 782, 736, 666.

HRMS (EI): *m/z* calc. for [$C_{15}H_{12}N_2O_2$]: 252.0899; found 252.0892.

2,6-Diisopropyl-*N*-(4-(trifluoromethoxy)phenyl)aniline (3o)



According to **TP14**, 2-azido-1,3-diisopropylbenzene (**28j**, 102 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then ((4-trifluoromethoxy)phenyl)zinc chloride (**1yy**, 0.26 M, 3.4 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9.5:0.5) to yield the titel compound as yellowish oil (137 mg, 0.405 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34–7.27 (m, 1H), 7.24–7.20 (m, 2H), 6.98 (dt, *J* = 8.0, 1.0 Hz, 2H), 6.45–6.40 (m, 2H), 5.16 (s, 1H), 3.15 (p, *J* = 6.9 Hz, 2H), 1.14 (d, *J* = 6.9 Hz, 12H).

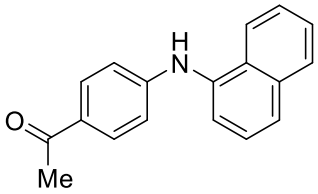
^{13}C NMR (101 MHz, $CDCl_3$): δ / ppm = 147.6 (2C), 146.9, 140.7, 134.7, 127.6, 124.0 (2C), 122.4 (2C), 120.7 (q, *J* = 255.3 Hz), 113.2 (2C), 28.2 (2C), 23.9 (4C).

^{19}F NMR (377 MHz, , $CDCl_3$): δ / ppm = -58.40.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3004, 2966, 2926, 1748, 1711, 1510, 1421, 1359, 1259, 1220, 1092, 902, 837, 787, 669.

HRMS (EI): *m/z* calc. for [$C_{19}H_{22}F_3NO$]: 337.1653; found 337.1645.

1-(4-(Naphthalen-1-ylamino)phenyl)ethan-1-one (3p)



According to **TP14**, 1-(4-azidophenyl)ethan-1-one (**28k**, 81 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then naphthalen-1-ylzinc chloride (**1x**, 0.27 M, 3.2 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9:1) to yield the titel compound as yellowish oil (89 mg, 0.34 mmol, 68%).

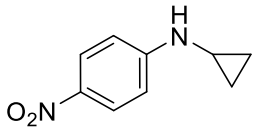
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.0–7.9 (m, 1H), 7.9–7.9 (m, 1H), 7.9–7.8 (m, 2H), 7.8–7.7 (m, 1H), 7.6–7.4 (m, 4H), 6.9–6.8 (m, 2H), 6.3 (s, 1H), 2.5 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.5, 150.4, 136.2, 134.7, 130.7 (2C), 128.6, 126.5, 126.3, 126.3, 125.9, 125.8, 125.7, 122.3, 120.7, 114.1 (2C), 26.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3349, 3055, 2924, 1659, 1626, 1595, 1574, 1523, 1437, 1417, 1397, 1359, 1324, 1308, 1276, 1178, 1075, 1018, 957, 832, 778.

HRMS (EI): *m/z* calc. for [$C_{18}H_{15}NO$]: 261.1154; found 261.1136.

***N*-Cyclopropyl-4-nitroaniline (3q)**



According to **TP14**, 1-azido-4-nitrobenzene (**28l**, 82 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then cyclopropylzinc chloride (**1zz**, 0.28 M, 3.1 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9.5:0.5) to yield the titel compound as yellowish solid (57 mg, 0.32 mmol, 64%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.1–8.0 (m, 2H), 6.8–6.7 (m, 2H), 4.9 (s, 1H), 2.5 (ttd, *J* = 6.7, 3.6, 1.5 Hz, 1H), 0.9–0.8 (m, 2H), 0.6–0.5 (m, 2H).

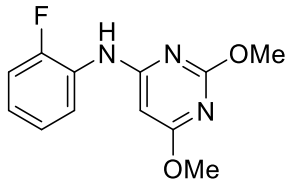
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.0 (2C), 138.5, 126.2 (2C), 111.7, 24.8, 7.8 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3389, 2921, 1698, 1595, 1558, 1516, 1506, 1494, 1466, 1343, 1319, 1298, 1283, 1260, 1194, 1180, 1172, 1109, 1058, 1048, 1028, 994, 978, 950, 902, 864, 852, 834, 812, 751, 696.

HRMS (EI): *m/z* calc. for [$C_9H_{10}N_2O_2$]: 178.0742; found 178.0735.

m.p.: 121.8-123.0 °C

***N*-(2-Fluorophenyl)-2,6-dimethoxypyrimidin-4-amine (3r)**



According to **TP14**, 1-azido-2-fluorobenzene (**28m**, 69 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (2,6-dimethoxypyrimidin-4-yl)zinc chloride (**1q**, 0.22 M, 4.0 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 4:1) to yield the titel compound as yellowish oil (107 mg, 0.430 mmol, 86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.21 (s, 1H), 7.12–6.96 (m, 3H), 6.88–6.78 (m, 1H), 5.53 (d, *J* = 2.9 Hz, 1H), 4.04 (s, 3H), 3.98 (s, 3H).

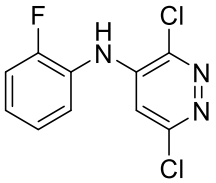
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.7, 160.4, 152.7 (d, *J* = 241.2 Hz), 146.8, 131.9 (d, *J* = 11.0 Hz), 124.5 (d, *J* = 3.6 Hz), 120.5 (d, *J* = 7.2 Hz), 119.1, 115.6 (d, *J* = 3.4 Hz), 115.5 (d, *J* = 24.5 Hz), 54.9, 54.4.

^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = -124.44 (dq, *J* = 8.5, 4.2 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3422, 2991, 2953, 1619, 1606, 1574, 1510, 1478, 1457, 1398, 1375, 1308, 1286, 1246, 1207, 1185, 1154, 1099, 1072, 1054, 1034, 1011, 961, 937, 878, 801, 779, 743, 712.

HRMS (EI): *m/z* calc. for [$C_{12}H_{12}FN_3O_2$]: 249.0914; found 249.0907.

3,6-Dichloro-*N*-(2-fluorophenyl)pyridazin-4-amine (3s)



According to **TP14**, 1-azido-2-fluorobenzene (**28m**, 69 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (3,6-dichloropyridazin-4-yl)zinc chloride (**1aaa**, 0.18 M, 4.9 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 4:1) to yield the titel compound as yellowish oil (107 mg, 0.415 mmol, 83%).

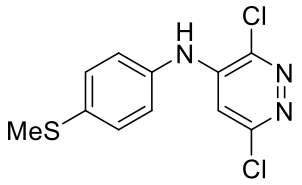
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.4–7.2 (m, 4H), 6.8 (d, *J* = 1.6 Hz, 1H), 6.6 (s, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.3 (d, *J* = 249.4 Hz), 155.8, 144.6, 141.8, 128.7 (d, *J* = 7.7 Hz), 125.6, 125.3 (d, *J* = 4.0 Hz), 124.0 (d, *J* = 12.0 Hz), 117.2 (d, *J* = 19.3 Hz), 107.6 (d, *J* = 1.5 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3196, 3059, 1568, 1531, 1501, 1449, 1376, 1350, 1304, 1262, 1204, 1131, 1113, 1103, 1080, 1054, 1030, 969, 948, 879, 859, 780, 750, 733, 707, 654.

HRMS (EI): *m/z* calc. for [$C_{10}H_6Cl_2FN_3$]: 256.9923; found 256.9917.

3,6-Dichloro-*N*-(4-(methylthio)phenyl)pyridazin-4-amine (3t)



According to **TP14**, (4-azidophenyl)(methyl)sulfane (**28b**, 83 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (3,6-dichloropyridazin-4-yl)zinc chloride (**1aaa**, 0.18 M, 4.9 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 4:1) to yield the titel compound as yellowish oil (112 mg, 0.390 mmol, 78%).

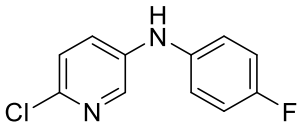
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.4–7.3 (m, 2H), 7.2–7.1 (m, 2H), 6.8 (s, 1H), 6.7 (s, 1H), 2.5 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 155.8, 144.4, 142.6, 138.3, 132.8, 127.9 (2C), 125.0 (2C), 106.9, 15.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3524, 3004, 1748, 1708, 1652, 1646, 1558, 1498, 1421, 1359, 1293, 1221, 1126, 1109, 1092, 966, 903, 825.

HRMS (EI): *m/z* calc. for [$C_{11}H_9Cl_2N_3S$]: 284.9894; found 284.9888.

6-Chloro-*N*-(4-fluorophenyl)pyridin-3-amine (3u)



According to **TP14**, 5-azido-2-chloropyridine (**28n**, 77 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-fluorophenyl)zinc chloride (**1ss**, 0.27 M, 3.2 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 4:1) to yield the titel compound as brownish soild (59 mg, 0.27 mmol, 53%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.0 (d, *J* = 2.9 Hz, 1H), 7.2 (dd, *J* = 8.6, 3.0 Hz, 1H), 7.1 (d, *J* = 8.6 Hz, 1H), 7.0–6.9 (m, 4H), 5.8 (s, 1H).

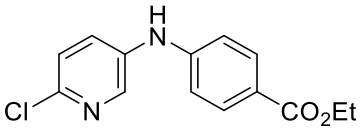
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.8 (d, *J* = 242.3 Hz), 141.6, 140.0, 138.0, 137.2, 125.5, 124.3, 121.7 (d, *J* = 8.0 Hz, 2C), 116.4 (d, *J* = 22.6 Hz, 2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3273, 3218, 3180, 3050, 1614, 1584, 1529, 1504, 1476, 1463, 1429, 1416, 1365, 1337, 1294, 1283, 1229, 1208, 1158, 1145, 1107, 1099, 1015, 899, 816, 801, 774, 724, 715, 686.

HRMS (EI): *m/z* calc. for [$C_{11}H_8ClFN_2$]: 222.0360; found 222.0353.

m.p.: 124.1-126.3 °C

Ethyl 4-((6-chloropyridin-3-yl)amino)benzoate (3v)



According to **TP14**, 5-azido-2-chloropyridine (**28n**, 77 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-(ethoxycarbonyl)phenyl)zinc chloride (**1aa**, 0.22 M, 4.0 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 4:1) to yield the titel compound as yellowish oil (89 mg, 0.32 mmol, 64%).

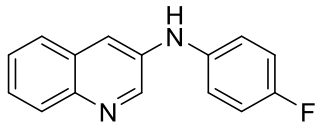
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.2 (d, *J* = 2.8 Hz, 1H), 8.0–7.9 (m, 2H), 7.5 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.3 (d, *J* = 8.6 Hz, 1H), 7.1–7.0 (m, 2H), 6.6 (s, 1H), 4.4 (q, *J* = 7.1 Hz, 2H), 1.4 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.4, 146.5, 144.0, 141.1, 137.3, 131.6 (2C), 129.2, 124.5, 122.9, 115.3 (2C), 60.8, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3342, 3003, 2917, 1748, 1708, 1609, 1581, 1523, 1463, 1421, 1392, 1360, 1334, 1311, 1274, 1220, 1176, 1142, 1106, 1018, 903, 838, 770, 734, 711, 694.

HRMS (EI): *m/z* calc. for [$C_{14}H_{13}ClN_2O_2$]: 276.0666; found 276.0659.

***N*-(4-Fluorophenyl)quinolin-3-amine (3w)**



According to **TP14**, 3-azidoquinoline (**28o**, 85 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-fluorophenyl)zinc chloride (**1ss**, 0.27 M, 3.2 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 4:1) to yield the titel compound as yellowish oil (85 mg, 0.36 mmol, 71%).

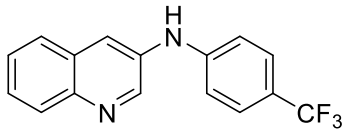
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.64 (d, *J* = 2.8 Hz, 1H), 8.02–7.97 (m, 1H), 7.61 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.58–7.54 (m, 1H), 7.48–7.42 (m, 2H), 7.19–7.13 (m, 2H), 7.09–7.04 (m, 2H), 6.08 (s, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.8 (d, *J* = 241.9 Hz), 144.6, 143.9, 143.5, 130.2, 129.1, 129.0, 127.3, 126.9, 126.5 (d, *J* = 2.9 Hz), 123.2, 121.5 (d, *J* = 8.0 Hz, 2C), 116.5 (d, *J* = 22.6 Hz, 2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3005, 2918, 1748, 1711, 1607, 1599, 1576, 1542, 1490, 1418, 1358, 1334, 1286, 1220, 1166, 1127, 1092, 1070, 901, 786, 755, 701.

HRMS (EI): *m/z* calc. for [$C_{15}H_{11}FN_2$]: 238.0906; found 238.0898.

***N*-(4-(Trifluoromethyl)phenyl)quinolin-3-amine (3x)**



According to **TP14**, 3-azidoquinoline (**28o**, 85 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-(trifluoromethyl)phenyl)zinc chloride (**1oo**, 0.23 M, 3.8 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 4:1) to yield the titel compound as yellowish solid (94 mg, 0.33 mmol, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.9 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.7 (d, *J* = 2.6 Hz, 1H), 7.6 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.4 (dddd, *J* = 23.1, 8.2, 6.9, 1.5 Hz, 2H), 7.3 (t, *J* = 7.9 Hz, 1H), 7.3 (d, *J* = 2.0 Hz, 1H), 7.2 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.2–7.1 (m, 1H).

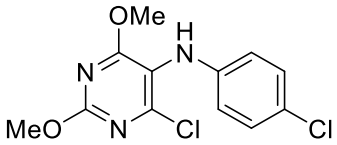
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 145.3, 142.9, 135.9, 132.1 (q, *J* = 32.2 Hz), 130.2, 129.0, 127.4, 127.3, 126.7, 124.0 (q, *J* = 272.5 Hz), 120.4, 119.0, 118.2 (q, *J* = 3.9 Hz, 2C), 114.1 (q, *J* = 3.9 Hz, 2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3207, 3140, 3111, 3044, 3008, 2921, 2852, 1615, 1600, 1567, 1543, 1497, 1468, 1426, 1397, 1380, 1367, 1352, 1327, 1304, 1280, 1250, 1220, 1185, 1160, 1153, 1140, 1122, 1104, 1097, 1009, 978, 952, 916, 885, 853, 828, 805, 781, 772, 750, 710, 682.

HRMS (EI): *m/z* calc. for [$C_{16}H_{11}F_3N_2$]: 288.0874; found 288.0865.

m.p.: 124.2-125.9 °C

4-Chloro-*N*-(4-chlorophenyl)-2,6-dimethoxypyrimidin-5-amine (3y)



According to **TP14**, 5-azido-4-chloro-2,6-dimethoxypyrimidine (**28p**, 108 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-chlorophenyl)zinc chloride (, 0.29 M, 3.0 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 4:1) to yield the titel compound as yellowish oil (137 mg, 0.455 mmol, 91%).

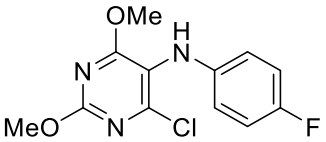
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.2–7.1 (m, 2H), 6.6–6.5 (m, 2H), 5.2 (s, 1H), 4.0 (s, 3H), 4.0 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 160.8, 156.8, 142.8, 129.0 (2C), 124.7, 115.9 (2C), 114.5, 55.6, 55.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3379, 2953, 1709, 1599, 1542, 1493, 1484, 1466, 1394, 1376, 1336, 1301, 1287, 1246, 1222, 1188, 1118, 1086, 1029, 1007, 963, 943, 861, 817, 779, 721, 667.

HRMS (EI): *m/z* calc. for [$C_{12}H_{11}Cl_2N_3O_2$]: 299.0228; found 299.0221.

4-Chloro-*N*-(4-fluorophenyl)-2,6-dimethoxypyrimidin-5-amine (3z)



According to **TP14**, 5-azido-4-chloro-2,6-dimethoxypyrimidine (**28p**, 108 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-fluorophenyl)zinc chloride (**1ss**, 0.27 M, 3.2 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 4:1) to yield the titel compound as yellowish solid (126 mg, 0.445 mmol, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.0–6.8 (m, 2H), 6.6–6.5 (m, 2H), 5.2 (s, 1H), 4.0 (s, 3H), 4.0 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.2, 160.5, 157.3 (d, *J* = 238.1 Hz), 156.1, 140.2, 116.2 (d, *J* = 7.7 Hz, 2C), 115.7 (d, *J* = 22.7 Hz, 2C), 115.4, 55.6, 55.2.

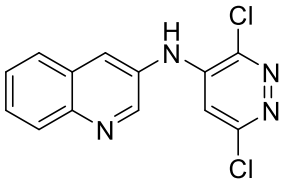
^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = -133.11 (tt, *J* = 7.6, 3.4 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3408, 2957, 2919, 1590, 1543, 1506, 1490, 1478, 1462, 1404, 1370, 1331, 1298, 1286, 1263, 1246, 1223, 1206, 1190, 1153, 1102, 1083, 1021, 940, 874, 860, 834, 825, 806, 791, 764, 748, 727, 706, 698.

HRMS (EI): *m/z* calc. for [$C_{12}H_{11}ClFN_3O_2$]: 283.0524; found 283.0517.

m.p.: 173.9-175.2 °C

***N*-(3,6-Dichloropyridazin-4-yl)quinolin-3-amine (3aa)**



According to **TP14**, 3-azidoquinoline (**28o**, 85 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (3,6-dichloropyridazin-4-yl)zinc chloride (**1aaa**, 0.18 M, 4.9 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 4:1) to yield the titel compound as yellowish oil (79 mg, 0.27 mmol, 54%).

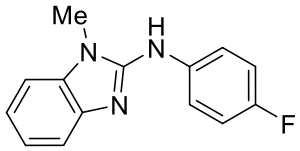
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.8 (d, *J* = 2.6 Hz, 1H), 8.1–8.1 (m, 2H), 7.8 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.7 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.6 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.6 (s, 1H), 6.9 (s, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 155.8, 147.5, 146.6, 144.8, 142.6, 130.1, 130.0, 130.0, 129.4, 128.0, 127.9, 127.6, 107.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3325, 3276, 3064, 3043, 1712, 1602, 1574, 1557, 1496, 1481, 1470, 1456, 1424, 1393, 1371, 1348, 1332, 1288, 1230, 1216, 1210, 1200, 1144, 1124, 1105, 1075, 1048, 1017, 987, 959, 924, 914, 906, 863, 846, 786, 776, 764, 750, 734.

HRMS (EI): *m/z* calc. for [$C_{13}H_8Cl_2N_4$]: 290.0126; found 290.0120.

_N_-(4-Fluorophenyl)-1-methyl-1_H_-benzo[_d_]imidazol-2-amine (3bb)



According to **TP14**, 2-azido-1-methyl-1*H*-benzo[*d*]imidazole (**28q**, 87 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-fluorophenyl)zinc chloride (**1ss**, 0.27 M, 3.2 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 2:1) to yield the titel compound as white solid (62 mg, 0.255 mmol, 51%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.51–7.44 (m, 1H), 7.38–7.30 (m, 2H), 7.14–7.04 (m, 3H), 6.98–6.89 (m, 2H), 3.49 (s, 3H).

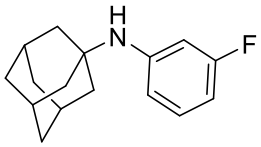
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.6 (d, *J* = 241.4 Hz), 150.4, 134.4, 121.8 (2C), 120.8 (2C), 120.36 (d, *J* = 7.7 Hz, 2C), 117.3, 115.91 (d, *J* = 22.6 Hz, 2C), 107.8, 29.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3422, 2992, 2953, 1619, 1606, 1574, 1510, 1478, 1456, 1398, 1374, 1308, 1285, 1246, 1207, 1185, 1154, 1099, 1072, 1054, 1034, 1011, 961, 937, 920, 878, 801, 779, 742, 712.

HRMS (EI): *m/z* calc. for [$C_{14}H_{12}FN_3$]: 241.1015; found 241.1021.

m.p.: 90.1-93.5 °C

(1*s*,3*s*)-*N*-(3-Fluorophenyl)adamantan-1-amine (3cc)



According to **TP14**, (1*s*,3*s*)-1-azidoadamantane (**28r**, 89 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (3-fluorophenyl)zinc chloride (**1bbb**, 0.27 M, 3.2 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction wxas stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 9.5:0.5) to yield the titel compound as brownish solid (98 mg, 0.40 mmol, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.10–7.00 (m, 1H), 6.53–6.46 (m, 2H), 6.46–6.36 (m, 1H), 2.12 (p, *J* = 3.3 Hz, 4H), 1.90 (d, *J* = 2.9 Hz, 6H), 1.76–1.62 (m, 7H).

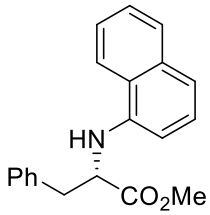
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.5 (d, *J* = 242.4 Hz), 129.8 (d, *J* = 10.2 Hz, 2C), 113.4, 104.6 (d, *J* = 20.2 Hz), 104.2 (d, *J* = 25.0 Hz), 52.3, 43.1 (3C), 36.4 (3C), 29.7 (3C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3418, 2904, 2849, 2088, 1618, 1582, 1509, 1490, 1480, 1450, 1436, 1422, 1412, 1356, 1340, 1305, 1286, 1273, 1259, 1240, 1210, 1186, 1174, 1146, 1125, 1096, 1059, 1040, 1006, 987, 980, 965, 935, 919, 906, 864, 826, 812, 779, 752, 681.

HRMS (EI): *m/z* calc. for [$C_{16}H_{20}FN$]: 245.1580; found 245.1573.

m.p.: 83.9-85.7 °C

Methyl naphthalen-1-yl-*L*-phenylalaninate (3dd)



According to **TP14**, methyl 2-azido-3-phenylpropanoate (**28s**, 103 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then naphthalen-1-ylzinc chloride (**1x**, 0.27 M, 3.2 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 3:1) to yield the titel compound as colourless oil (90 mg, 0.30 mmol, 59%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = .8–7.6 (m, 2H), 7.4–7.2 (m, 7H), 7.1–7.1 (m, 2H), 6.5 (dd, *J* = 7.3, 1.4 Hz, 1H), 4.5 (t, *J* = 6.1 Hz, 1H), 3.6 (s, 3H), 3.2 (qd, *J* = 13.6, 6.0 Hz, 2H).

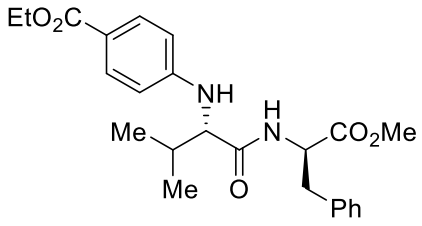
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 173.7, 141.5, 136.3, 134.4, 129.4 (2C), 128.6, 128.6 (2C), 127.1, 126.4, 125.9, 125.0, 123.8, 120.1, 118.5, 105.2, 57.7, 52.2, 38.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3397, 2920, 1595, 1576, 1506, 1438, 1423, 1386, 1313, 1216, 1183, 1155, 1094, 968, 816, 777, 708.

HRMS (EI): *m/z* calc. for [$C_{20}H_{19}NO_2$]: 305.1416; found 305.1418.

e.r. = 93:7 *(determined by chiral HPLC)*

Ethyl 4-(((*S*)-1-(((*R*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)benzoate (3ee)



According to **TP14**, methyl (2-azido-3-methylbutanoyl)-*D*-phenylalaninate (**28t**, 152 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-(ethoxycarbonyl)phenyl)zinc chloride (**1aa**, 0.22 M, 4.0 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 3:1) to yield the titel compound as colourless oil (160 mg, 0.375 mmol, 75%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.9–7.8 (m, 2H), 7.2–7.2 (m, 3H), 7.1–7.0 (m, 2H), 6.8 (d, *J* = 8.1 Hz, 1H), 6.6–6.5 (m, 2H), 4.9 (td, *J* = 7.8, 5.5 Hz, 1H), 4.5 (d, *J* = 5.8 Hz, 1H), 4.3 (q, *J* = 7.1 Hz, 2H), 3.6–3.6 (m, 1H), 3.6 (s, 3H), 3.2 (dd, *J* = 14.1, 5.5 Hz, 1H), 3.0 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.2 (d, *J* = 5.1 Hz, 0H), 1.3 (t, *J* = 7.1 Hz, 3H), 1.0–0.9 (m, 3H), 0.9 (d, *J* = 6.9 Hz, 3H).

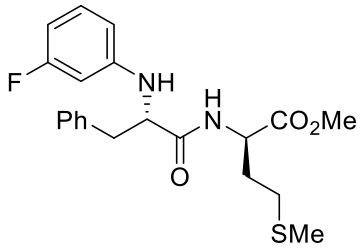
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.1, 171.6, 166.7, 151.1, 135.9, 131.4 (2C), 129.1 (2C), 128.6 (2C), 127.1, 120.3, 112.7 (2C), 64.1, 60.4, 53.0, 52.4, 37.8, 31.2, 19.4, 17.8, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3329, 3065, 3031, 2962, 2874, 1742, 1681, 1658, 1652, 1604, 1523, 1498, 1465, 1456, 1444, 1437, 1422, 1391, 1367, 1336, 1314, 1271, 1213, 1173, 1105, 1043, 1020, 910, 839, 771, 730, 698.

HRMS (EI): *m/z* calc. for [$C_{24}H_{30}N_2O_5$]: 426.2155; found 426.2161.

d.r. = 95:5 *(determined by NMR)*

Methyl (3-fluorophenyl)-*L*-phenylalanyl-*D*-methioninate (3ff)



According to **TP14**, methyl (2-azido-3-phenylpropanoyl)-*D*-methioninate (**28u**, 168 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (3-fluorophenyl)zinc chloride (**1bbb**, 0.27 M, 3.2 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 3:1) to yield the titel compound as colourless oil (105 mg, 0.26 mmol, 52%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.4–7.3 (m, 3H), 7.2–7.2 (m, 2H), 7.1 (ddd, *J* = 14.8, 8.9, 7.3 Hz, 2H), 6.5–6.4 (m, 1H), 6.3 (ddd, *J* = 8.1, 2.3, 0.8 Hz, 1H), 6.3 (dt, *J* = 11.2, 2.3 Hz, 1H), 4.7 (td, *J* = 7.9, 5.0 Hz, 1H), 4.0–4.0 (m, 2H), 3.7 (s, 3H), 3.3 (dd, *J* = 14.1, 4.3 Hz, 1H), 3.1 (dd, *J* = 14.1, 7.4 Hz, 1H), 2.4 (dd, *J* = 7.9, 6.9 Hz, 2H), 2.2–2.1 (m, 0H), 2.0 (s, 3H), 2.0–1.8 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 172.4, 171.7, 163.8 (d, *J* = 244.1 Hz), 148.2 (d, *J* = 10.4 Hz), 136.1, 130.4 (d, *J* = 10.0 Hz), 129.1 (2C), 129.0 (2C), 127.4, 110.0, 106.1 (d, *J* = 21.4 Hz), 101.3 (d, *J* = 25.4 Hz), 60.1, 52.5, 51.4, 38.5, 31.2, 29.9, 15.4.

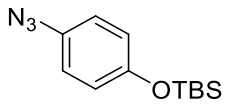
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3409, 3004, 1748, 1710, 1621, 1497, 1421, 1359, 1220, 1178, 1152, 1092, 1000, 903, 832, 765, 702, 685.

HRMS (EI): *m/z* calc. for [$C_{21}H_{25}FN_2O_3S$]: 404.1570; found 404.1578.

d.r. = 96:4 *(determined by NMR)*

6.5 Preparation of Androgen/Estrogen Modulator 32

(4-Azidophenoxy)(*tert*-butyl)dimethylsilane (28v)

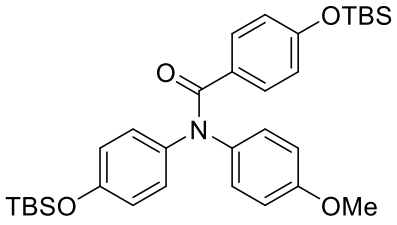


(4-Azidophenoxy)trimethylsilane was prepared according to a literature known procedure.[144]

^{1}H NMR (400 MHz, $CDCl_3$): δ / ppm = 6.90 (d, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 1H), 0.99 (s, 6H), 0.20 (s, 4H).

Analytical Data equivalent to literture[145]

4-((*tert*-Butyldimethylsilyl)oxy)-*N*-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-*N*-(4-methoxyphenyl)benzamide (34)



According to **TP14**, (4-azidophenoxy)trimethylsilane (**28v**, 125 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then (4-methoxyphenyl)zinc chloride (**1dd**, 0.29 M, 3.0 mL, 0.875 mmol, 1.75 equiv) in dry THF were added in one portion, respectively. The reaction was stirred at 50 ℃ for 10 min and subsequently 4-((*tert*-butyldimethylsilyl)oxy)benzoyl chloride (203 mg, 0.75 mmol, 1.50 equiv) was added. After stirring for additional 50 min, the reaction mixture was quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The crude product was purified by flash column chromatography (hexanes:EtOAc 4:1) to yield **34** as yellowish oil (209 mg, 0.370 mmol, 74%).

[144] M. I. Mangione, R. A. Spanevello, M. B. Anzardi, *RSC Adv.* **2017**, *7*, 47681–47688.
[145] S. Montanari, L. Scalvini, M. Bartolini, F. Belluti, S. Gobbi, V. Andrisano, A. Ligresti, V. Di Marzo, S. Rivara, M. Mor, A. Bisi, A. Rampa *J. Med. Chem.* **2016**, *59*, 6387–6406.

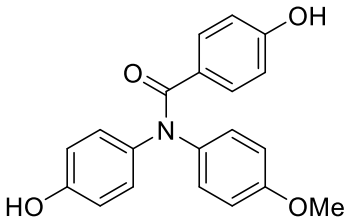
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37–7.32 (m, 2H), 7.03 (dd, *J* = 32.0, 8.4 Hz, 4H), 6.84–6.70 (m, 4H), 6.69–6.63 (m, 2H), 3.76 (s, 3H), 0.97 (s, 9H), 0.95 (s, 9H), 0.18 (s, 6H), 0.16 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.3, 157.6, 157.2, 153.7, 137.9, 137.3, 131.1 (2C), 129.1, 128.3 (4C), 120.4 (2C), 119.4 (2C), 114.3 (2C), 55.4, 25.7 (3C), 25.6 (3C), 18.2 (2C), -4.4 (4C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3409, 3004, 1748, 1710, 1621, 1497, 1421, 1359, 1220, 1178, 1152, 1092, 1000, 903, 832, 765, 702, 685.

HRMS (EI): *m/z* calc. for [C_{32} $H_{45}NO_4Si_4$]: 563.8850; found 563.8856.

4-Hydroxy-*N*-(4-hydroxyphenyl)-*N*-(4-methoxyphenyl)benzamide (32)



Amide **10** (209 mg, 0.37 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and treated with TBAF (145 mg, 0.56 mmol, 1.5 equiv) for 2 h at r.t.. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (hexanes:EtOAc 1:1) to give amide **32** as a yellowish oil (119 mg, 0.36 mmol, 96%).

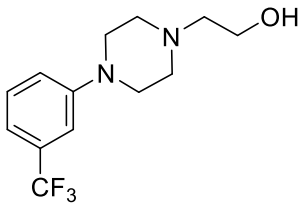
^{1}H-NMR (400 MHz, DMSO-d^6): δ / ppm = 8.77 (s, 1H), 8.56 (s, 1H), 7.95–7.83 (m, 2H), 7.28–7.21 (m, 2H), 7.21–7.15 (m, 2H), 6.94 (d, *J* = 7.5 Hz, 2H), 6.85 (d, *J* = 7.6 Hz, 2H), 6.82–6.79 (m, 2H). 2.62 (s, 3H).

^{13}C-NMR (101 MHz, DMSO-d^6): δ / ppm = 169.9, 159.1, 157.5, 155.9, 138.0, 136.4, 131.3 (2C), 129.1, 116.0 (2C), 114.8 (2C), 114.6 (2C), 55.7.

Analytical Data equivalent to literature.[109]

6.6 Preparation of Antrafenine (35)

2-(4-(3-(Trifluoromethyl)phenyl)piperazin-1-yl)ethan-1-ol (36)

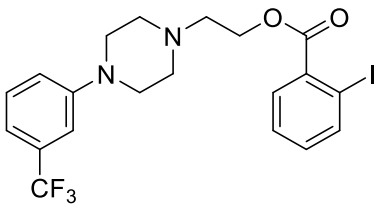


2-(4-(3-(Trifluoromethyl)phenyl)piperazin-1-yl)ethan-1-ol (**36**) was prepared according to a literature known procedure. (Literture/Patent: X. Zou, Y. Cai, Q. Li, H. Zhang, CN 106866582 A, Jun 20, 2017)

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.3 (t, *J* = 8.0 Hz, 1H), 7.1 (t, *J* = 2.0 Hz, 1H), 7.1–7.0 (m, 2H), 3.7–3.6 (m, 2H), 3.3–3.2 (m, 4H), 3.1–2.9 (m, 1H), 2.7–2.6 (m, 4H), 2.6 (t, *J* = 5.4 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.3, 131.4 (q, *J* = 31.7 Hz), 129.6, 124.3 (q, *J* = 272.4 Hz), 118.7, 115.9 (q, *J* = 3.8 Hz), 112.2 (q, *J* = 3.9 Hz), 59.4, 57.8, 52.7 (2C), 48.7 (2C).

2-(4-(3-(Trifluoromethyl)phenyl)piperazin-1-yl)ethyl 2-iodobenzoate (37)



In a dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum 2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethan-1-ol (**36**, 686 mg, 2.50 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (5 mL) and NEt_3 (0.70 mL, 5.00 mmol, 2.00 equiv) and DMAP (3 mg, 0,03 mmol, 1 mol%) were added. After the dropwise addition of 2-iodobenzoyl chloride (1.17 g, 4.38 mmol, 1.75 equiv), the reaction mixture was stirred at 25 °C for 12 h, quenched with H_2O and extracted with CH_2Cl_2 (3 × 20 mL). The combined org. layers were washed with sat. $NaHCO_3$, brine and dried over $NaSO_4$. The purification by flash column chromatography (hexanes:EtOAc 1:3) gave 2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl 2-iodobenzoate (**37**) as yellowish solid (1.21 g, 2.03 mmol, 81%).

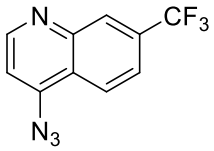
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.0 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.8 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.4 (td, *J* = 7.6, 1.2 Hz, 1H), 7.3 (t, *J* = 8.0 Hz, 1H), 7.2 (td, *J* = 7.7, 1.8 Hz, 1H), 7.1 (d, *J* = 2.1 Hz, 1H), 7.1–7.0 (m, 2H), 4.5 (t, *J* = 5.8 Hz, 2H), 3.3–3.2 (m, 4H), 2.8 (t, *J* = 5.8 Hz, 2H), 2.8–2.7 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.6, 151.3, 141.3, 135.2, 132.7, 131.4 (q, *J* = 31.7 Hz), 130.9, 129.6, 128.0, 124.3 (q, *J* = 272.5 Hz), 118.7, 115.8 (q, *J* = 3.8 Hz), 112.1 (q, *J* = 3.9 Hz), 94.1, 62.8, 56.5, 53.2 (2C), 48.7 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3409, 3004, 1748, 1710, 1621, 1497, 1421, 1359, 1220, 1178, 1152, 1092, 1000, 903, 832, 765, 702, 685.

HRMS (EI): *m/z* calc. for [$C_{20}H_{20}F_3IN_2O_2$]: 504.0522; found 504.0527.

4-Azido-7-(trifluoromethyl)quinoline (28w)



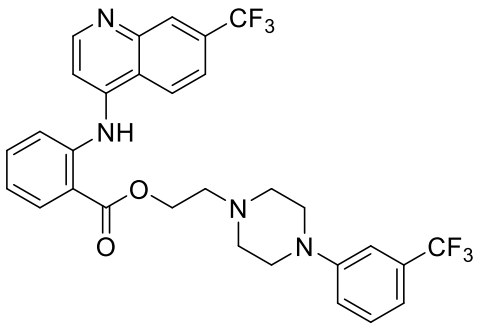
4-Azido-7-(trifluoromethyl)quinoline was prepared according to a literature known procedure.[146]

^{1}H-NMR (60 MHz, DMSO-d_6): δ / ppm = 8.93 (d, *J* = 6 Hz, 1H), 8.38 (d, *J* = 2 Hz, 1H), 8.20 (d, *J* = 8 Hz, 1H), 7.70 (q, *J* = 2 and 8 Hz, 1H), 7.23 (d, *J* = 6 Hz, 1H).

Analytical Data equivalent to literture

[146] S. Kamiya, S. Sueyoshi, M. Miyahara, K. Yanagimachi, T. Nakashima, *Chem. Pharm. Bull.* **1980**, 28, 1485–1490.

Antrafenine (35)



According to **TP2**, 2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl 2-iodobenzoate (**37**) (504 mg, 1.00 mmol, 2.00 equiv) was dissolved in dry THF (15 mL) and *i*PrMgCl·LiCl (1.28 M, 0.98 mL, 1.25 mmol, 1.25 equiv) was added dropwise at –78 °C. Subsequently, a solution of $ZnCl_2$ (1.00 M, 1.3 mL, 1.30 mmol, 1.20 equiv) in dry THF was added at −78 °C. Then in a separate flask (according to **TP14**), 4-azido-7-(trifluoromethyl)quinoline (**28w**), 119 mg, 0.50 mmol, 1.00 equiv) was dissolved in dry THF (1 mL). First anhydrous $FeCl_3$ (41 mg, 0.25 mmol, 0.50 equiv) and then the earlier prepared organozinc reagent were added in one portion, respectively. The reaction was stirred at 50 °C for 1 h and subsequently quenched with sat. aqueous NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined org. layers were washed with sat. $NaHCO_3$ solution (5 mL), brine (5 mL), and dried over Na_2SO_4. The final purification by flash column chromatography (hexanes:EtOAc 1:1) gave antrafenine (**11**) as solid (188 mg, 0.32 mmol, 64%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 10.9 (s, 1H), 9.0 (d, *J* = 5.2 Hz, 1H), 8.6 (s, 1H), 8.5 (d, *J* = 8.8 Hz, 1H), 8.3 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.9 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.7 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 7.7 (d, *J* = 5.2 Hz, 1H), 7.5 (t, *J* = 8.0 Hz, 1H), 7.3 (t, *J* = 2.1 Hz, 1H), 7.3–7.3 (m, 2H), 7.2 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.8 (t, *J* = 5.7 Hz, 2H), 3.4 (dd, *J* = 6.5, 3.6 Hz, 4H), 3.1 (t, *J* = 5.8 Hz, 2H), 3.0 (dd, *J* = 6.1, 3.9 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 168.3, 152.0, 151.3, 148.5, 145.1, 143.9, 134.2, 131.9, 131.3 (q, *J* = 31.6 Hz), 131.2 (q, *J* = 32.7 Hz), 129.5, 128.4, 127.7 (q, *J* = 4.2 Hz), 124.4 (d, *J* = 272.5 Hz), 124.0 (d, *J* = 272.5 Hz), 123.3, 122.3, 121.5, 121.5 (q, *J* = 2.9 Hz), 120.3, 119.9, 118.6, 117.5, 115.8 (q, *J* = 3.8 Hz), 112.0 (q, *J* = 3.9 Hz), 106.2, 62.8, 56.4, 53.1 (2C), 48.6 (2C).

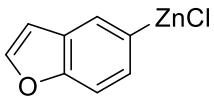
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3299, 3260, 2954, 2829, 1712, 1684, 1607, 1582, 1571, 1530, 1498, 1452, 1421, 1380, 1360, 1319, 1269, 1245, 1222, 1198, 1182, 1157, 1118, 1090, 1075, 992, 954, 919, 904, 877, 864, 832, 785, 750, 740, 730, 696, 683.

HRMS (EI): *m/z* calc. for [$C_{30}H_{26}F_6N_4O_2$]: 588.5544; found 588.5539.

7. Copper-Catalyzed Electrophilic Thiolation of Organozinc Halides Using *N*-Thiophthalimides Leading to Polyfunctional Thioethers

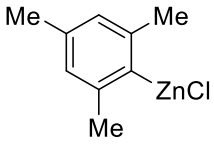
7.1 Preparation of Organozinc Reagents

Benzofuran-5-ylzinc chloride (1ccc)



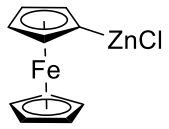
According to **TP4**, 5-bromobenzofuran (493 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.30 mmol/mL active zinc species, corresponding to 98% yield.

Mesitylzinc chloride (1ddd)



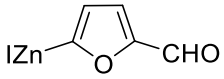
According to **TP4**, 2-bromo-1,3,5-trimethylbenzene (498 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.28 mmol/mL active zinc species, corresponding to 92% yield.

Ferrocenyl zinc chloride (1eee)



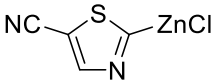
According to **TP4**, bromoferrocene (662 g, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.21 mmol/mL active zinc species, corresponding to 69% yield.

(5-Formylfuran-2-yl)zinc iodide (1fff)



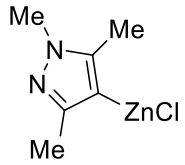
According to **TP6**, 5-iodofuran-2-carbaldehyde (555 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (127 mg, 3.00 mmol, 1.20 equiv) and activated zinc dust (245 mg, 3.75 mmol, 1.50 equiv) in dry THF (5 mL). The mixture reaction was stirred at 25 °C for 12 h. Titration with iodine gave a concentration of 0.33 mmol/mL active zinc species, corresponding to 69% yield.

(5-Cyanothiazol-2-yl)zinc chloride (1ggg)



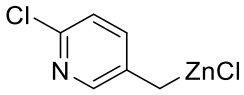
According to **TP2**, 2-bromothiazole-5-carbonitrile (945 mg, 5.00 mmol, 1.00 equiv) was dissolved in dry THF (5 mL) and *i*PrMgCl·LiCl (4.30 mL, 1.28 M, 5.50 mmol, 1.10 equiv) was added. After stirring for 2 h at −40 °C $ZnCl_2$ (1 M in THF, 6.0 mL, 6.00 mmol) was added. Titration with iodine gave a concentration of 0.33 mmol/mL active zinc species, corresponding to 99% yield.

(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)zinc Chloride (1hhh)



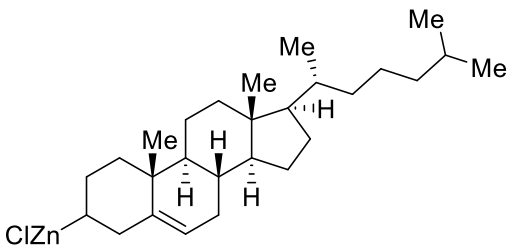
According to **TP4**, 4-bromo-1,3,5-trimethyl-1*H*-pyrazole (7n) (1.89 g, 10.0 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.18 mmol/mL corresponding to a yield of 40%.

((6-Chloropyridin-3-yl)methyl)zinc chloride (1iii)



According to **TP6**, 2-chloro-5-(chloromethyl)pyridine (405 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (127 mg, 3.00 mmol, 1.20 equiv) and activated zinc dust (245 mg, 3.75 mmol, 1.50 equiv) in dry THF (5 mL). The mixture reaction was stirred at 25 °C for 12 h. Titration with iodine gave a concentration of 0.45 mmol/mL active zinc species, corresponding to 94% yield.

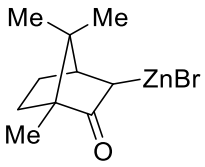
Cholest-5-ene-3-ylzinc chloride (1jjj)



According to **TP4**, 3*α*-bromocholest-5-ene (1.12 g, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C

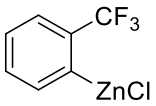
overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.13 mmol/mL active zinc species, corresponding to 43% yield.

((1*S*,4*S*)-4,7,7-Trimethyl-3-oxobicyclo[2.2.1]heptan-2-yl)zinc bromide (1kkk)



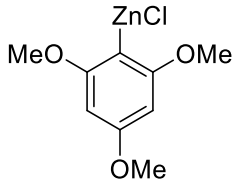
According to **TP6**, (1*S*,4*S*)-3-bromo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (578 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (127 mg, 3.00 mmol, 1.20 equiv) and activated zinc dust (245 mg, 3.75 mmol, 1.50 equiv) in dry THF (5 mL). The mixture reaction was stirred at 25 °C for 12 h. Titration with iodine gave a concentration of 0.33 mmol/mL active zinc species, corresponding to 69% yield.

(2-(Trifluoromethyl)phenyl)zinc chloride (1lll)



According to **TP4**, 1-bromo-2-(trifluoromethyl)benzene (563 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.43 mmol/mL active zinc species, corresponding to 99% yield.

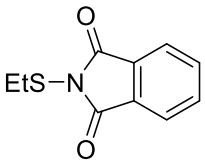
(2,4,6-Trimethoxyphenyl)zinc chloride (1mmm)



According to **TP4**, 2-bromo-1,3,5-trimethoxybenzene (618 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.26 mmol/mL active zinc species, corresponding to 85% yield.

7.2 Preparation of *N*-Thiophthalimides

N-(Ethylthio)phthalimide (38c)[147]



A dry and argon flushed reaction tube equipped with a magnetic stirring bar and a septum was charged with ethanethiol (311 mg, 5.00 mmol, 1.00 equiv), dry trimethylamine (76 mg, 0.75 mmol, 0.15 equiv) and dry CH_2Cl_2 (5 mL). Sulfuryl chloride (675 mg, 5.00 mmol, 1.00 equiv) in dry CH_2Cl_2 (1 mL) was added dropwise at 0 °C. After 15 min at 0 °C the solution was allowed to warm up to 25 °C while stirring for additional 30 min. The resulting solution was transferred dropwise *via* cannula to a solution of phthalimide (736 mg, 5.00 mmol, 1.00 equiv) and dry triethylamine (657 mg, 6.50 mmol, 1.30 equiv) in dry CH_2Cl_2 (5 mL) at 0 °C and subsequently stirred for 1 h at r.t.. The mixture was poured into ice cold water (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried with anhydrous mg_2SO_4. Evaporation of the solvents *in vacuo* and purification by recrystallization (EtOH) afforded the title compound as colourless needles (436 mg, 2.16 mmol, 43%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.93 (dd, J = 5.5, 3.1 Hz, 2H), 7.78 (dd, J = 5.5, 3.1 Hz, 2H), 2.92 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.6 (2C), 134.6 (2C), 132.0 (2C), 123.9 (2C), 32.7, 13.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1783, 1736, 1711, 1606, 1465, 1456, 1448, 1407, 1366, 1357, 1340, 1307, 1285, 1279, 1261, 1253, 1222, 1168, 1052, 1031, 1008, 895, 866, 854, 800, 793, 755, 710, 695, 687, 669, 660.

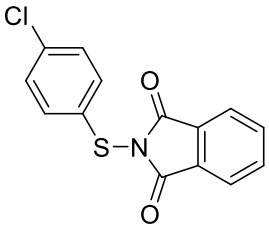
MS (EI, 70 eV): *m/z* (%) = 207 (6), 148 (100), 129 (75), 103 (37), 76 (40), 60 (25), 50(15).

HRMS (EI): *m/z* calc. for [$C_{10}H_9NO_2S$]: 207.0345; found 207.0346.

m. p. (°C): 117.1–119.4

[147] H. M. Gillis, L. Greene, A. Thompson, *Synlett* **2009**, 112−116.

***N*-((4-Chlorophenyl)thio)phthalimide (38d)[148]**



A dry and argon flushed round bottom flask equipped with a magnetic stirring bar and a septum was charged with 4-chlorobenzenethiol (723 mg, 5.00 mmol, 1.00 equiv), *N*-chlorophthalimide (908 mg, 5.00 mmol, 1.00 equiv) and dry toluene (30 mL). Dry triethylamine (506 mg, 5.00 mmol, 1.00 equiv) in dry toluene (20 mL) was added dropwise over 30 min and the reaction mixture was stirred for 12 h. After addition of Et_2O (30 mL) the resulting suspension was filtered and the filtrate was washed with Et_2O (3 x 10 mL). After removal of the solvents *in vacuo* the crude product was purified via flash column chromatography on silica gel (silica-gel, *iso*-hexane: EtOAc = 4:1). For complete removal of phthalimide the resulting powder was added to pyridine (2.5 mL) and water (10 mL) and was slowly added at 0 °C. Filtration of the resulting suspension and washing of the filtrate with ice cold MeOH (3 × 5 mL) afforded title compound as a white powder (182 mg, 0.63 mmol, 13 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.93 (dd, J = 5.5, 3.1 Hz, 2H), 7.79 (dd, J = 5.5, 3.1 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.6 (2C), 135.9, 134.8 (2C), 133.3 (2C), 132.9 (2C), 131.9, 129.5 (2C), 124.1 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} =1780, 1729, 1707, 1609, 1570, 1469, 1465, 1458, 1388, 1361, 1345, 1286, 1277, 1264, 1223, 1170, 1166, 1108, 1091, 1077, 1051, 1045, 1012, 970, 867, 833, 824, 801, 746, 712, 704, 695, 686.

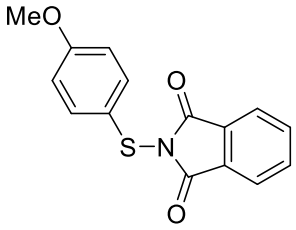
MS (EI, 70 eV): *m/z* (%) = 289 (40), 286 (40), 147 (100), 144 (60), 108 (60), 104 (61), 76 (59), 50 (26).

HRMS (EI): *m/z* calc. for [$C_{14}H_8ClNO_2S$]: 288.9964; found 288.9960.

m. p. (°C): 187.5–188.1.

[148] C. Savarin, J. Srogl L. S. Liebeskind, *Org. Lett.* **2002**, *4*, 4309−4312.

_N_-((4-Methoxyphenyl)thio)phthalimide (38e)[149]



A dry and argon flushed round bottom flask equipped with a magnetic stirring bar and a septum was charged with 4-methoxybenzenethiol (736 mg, 5.25 mmol, 1.05 equiv), phthalimide (736 mg, 5.00 mmol, 1.00 equiv), dry MeCN (3.3 mL) and dry pyridine (4.2 mL). Bromine (675 mg, 5.00 mmol, 1.00 equiv) in dry MeCN (2.6 mL) was added dropwise at 0 °C over a period of 1 h and the resulting mixture was stirred for additional 30 min. Water (20 mL) was then added dropwise at 0 °C over 30 min and strirred for a further period of 20 min. Filtration of the resulting suspension and washing of the filtrate with ice cold MeOH (3 × 5 mL) afforded title compound as a yellow powder (1.11 g, 3.69 mmol, 74%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.89 (dd, J = 5.5, 3.1 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.74 (dd, J = 5.5, 3.0 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.9 (2C), 161.5, 136.7 (2C), 134.5 (2C), 132.1 (2C), 125.4, 123.9 (2C), 114.7 (2C), 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2846, 1778, 1729, 1705, 1651, 1608, 1588, 1566, 1492, 1478, 1466, 1447, 1408, 1375, 1362, 1345, 1299, 1276, 1264, 1252, 1223, 1192, 1171, 1165, 1104, 1089, 1047, 1026, 1007, 968, 962, 867, 848, 831, 800, 718, 712, 695, 686.

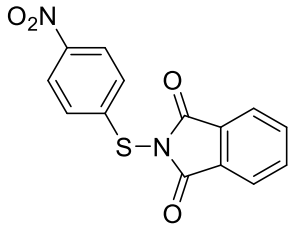
MS (EI, 70 eV): *m/z* (%) = 258 (28), 147 (100), 140 (39), 104 (47), 97 (22), 76 (43), 69 (10), 57 (15), 50 (22), 43 (22).

HRMS (EI): *m/z* calc. for [$C_{15}H_{11}NO_3S$]: 285.0460; found 285.0454.

m. p. (°C): 208.3–210.8.

[149] S. E. Denmark, E. Hartmann, D. J. P. Kornfilt, H. Wang, *Nat. Chem.* **2014**, *6*, 1056−1064.

***N*-((4-Nitrophenyl)thio)phthalimide (38f)**



According to **TP15**, 4-nitrothiophenol (776 mg, 5.00 mmol, 1.00 equiv) was added dropwise at 0 °C to the solution of *N*-chlorophthalimide (908 mg, 5.00 mmol, 1.00 equiv). The title compound was obtained as a powder (1.15 g, 3.80 mmol, 76%) including 10% of phthalimide impurity. The reagent was used for the following reactions without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.16 (d, *J* = 8.9 Hz, 2H), 8.01 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.87 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.40 (d, *J* = 8.9 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.0 (2C), 144.7, 135.3 (2C), 131.7 (2C), 126.4 (2C), 125.8, 124.6 (2C), 124.5 (2C).

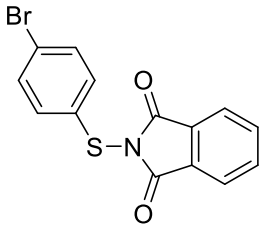
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1787, 1744, 1716, 1599, 1578, 1511, 1475, 1468, 1359, 1339, 1317, 1288, 1273, 1263, 1220, 1183, 1171, 1117, 1106, 1087, 1053, 1035, 1006, 949, 866, 854, 842, 826, 816, 789, 738, 726, 709, 695, 680.

MS (EI, 70 eV): *m/z* (%) = 300 (17), 323 (18), 292 (38), 279 (33), 223 (14), 147 (66), 104 (37), 76 (40), 50 (15).

HRMS (EI): *m/z* calc. for [$C_{14}H_8N_2O_4S$]: 300.0205; found 300.0208.

m. p. (°C): 162.0–162.9.

_N_-((4-Bromophenol)thio)phthalimide (38g)



According to **TP15**, 4-bromothiophenol (945 mg, 5.00 mmol, 1.00 equiv) was added dropwise at 0 °C to the solution of *N*-chlorophthalimide (908 mg, 5.00 mmol, 1.00 equiv). The title compound was obtained as a white powder (1.35 g, 4.00 mmol, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.93 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.52–7.42 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.6 (2C), 134.9, 134.0 (2C), 132.8 (2C), 132.5 (2C), 131.9 (2C), 124.2 (2C), 124.0.

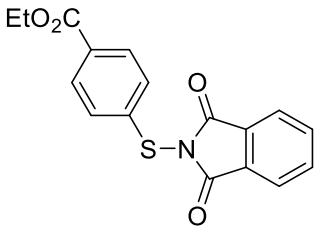
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1782, 1739, 1731, 1706, 1605, 1563, 1466, 1383, 1359, 1342, 1308, 1279, 1262, 1222, 1173, 1150, 1108, 1089, 1080, 1067, 1051, 1007, 867, 833, 811, 794, 730, 711, 695, 684.

MS (EI, 70 eV): *m/z* (%) = 332 (32), 254 (43), 149 (100), 140 (39), 104 (47), 97 (22), 76 (43), 69 (10), 57 (15), 50 (22), 43 (22).

HRMS (EI): *m/z* calc. for [$C_{14}H_8BrNO_2S$]: 332.9459; found 332.9455.

m. p. (°C): 123.6–125.3.

***N*-((Ethyl 4-benzoate)thio)phthalimide (38h)**



According to **TP15**, ethyl 4-mercaptobenzoate (841 mg, 4.60 mmol, 1.00 equiv) was added dropwise at 0 °C to the solution of *N*-chlorophthalimide (908 mg, 5.00 mmol, 1.00 equiv). The title compound was obtained as a white powder (924 mg, 2.80 mmol, 61%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.93-7.89 (m, 4H), 7.77 (dd, J = 5.5, 3.1 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.4 (2C), 165.8, 141.3, 135.0 (2C), 131.9 (2C), 130.4 (2C), 130.0 (2C), 126.6 (2C), 124.4, 61.2, 14.3.

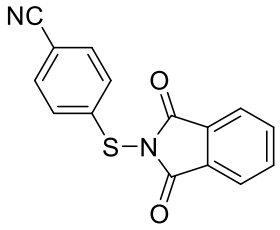
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2985, 1788, 1743, 1716, 1698, 1608, 1592, 1564, 1493, 1476, 1465, 1444, 1402, 1367, 1345, 1309, 1292, 1273, 1238, 1184, 1175, 1167, 1126, 1120, 1108, 1084, 1036, 1024, 1010, 978, 964, 902, 866, 851, 790, 759, 710, 686.

MS (EI, 70 eV): *m/z* (%) = 327 (28), 254 (43), 149 (100), 140 (39), 104 (47), 97 (22), 76 (43), 69 (10), 57 (15), 50 (22), 43 (22).

HRMS (EI): *m/z* calc. for [$C_{17}H_{13}NO_4S$]: 327.0565; found 327.0562

m. p. (°C): 148.8–150.6.

4-((1,3-Dioxoisoindolin-2-yl)thio)benzonitrile (38i)



According to **TP15**, 4-mercaptobenzonitrile (11, 676 mg, 5.00 mmol, 1.00 equiv) was added dropwise at 0 °C to the solution of *N*-chlorophthalimide (908 mg, 5.00 mmol, 1.00 equiv). The title compound was obtained as a beige powder (1.06 mg, 3.80 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.93 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.88–7.72 (m, 2H), 7.59–7.45 (m, 2H), 7.39–7.26 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.1 (2C), 142.3, 135.3 (2C), 132.9 (2C), 131.7 (2C), 126.5 (2C), 124.5 (2C), 118.2, 111.3.

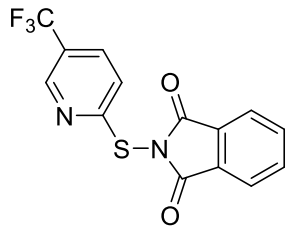
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2228, 1790, 1740, 1713, 1590, 1485, 1466, 1345, 1276, 1221, 1080, 1030, 1014, 862, 822, 797, 714, 697, 686.

MS (EI, 70 eV): *m/z* (%) = 280 (29), 268 (50), 146 (59), 104 (47), 76 (52), 42 (100).

HRMS (EI): *m/z* calc. for [$C_{15}H_8N_2O_2S$]: 280.0306; found 280.0294.

m. p. (°C): 151.2–151.9.

***N*-((5-(Trifluoromethyl)pyridin-2-yl)thio)phthalimide (38j)**



According to **TP15**, 5-(trifluoromethyl)pyridine-2-thiol (895 mg, 5.00 mmol, 1.00equiv), was added dropwise at 0 °C to the solution of *N*-chlorophthalimide (908 mg, 5.00 mmol, 1.00 equiv). The title compound was obtained as a white powder (1.49 g, 4.59 mmol, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.55 (s, 1H), 8.02 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.86 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.2 (2C), 161.0 (q, *J* = 1.4 Hz), 146.8 (q, *J* = 4.2 Hz), 135.0 (2C), 133.8 (q, *J* = 3.4 Hz), 132.1 (2C), 124.3 (2C), 124.1 (q, *J* = 33.4 Hz), 123.3 (q, *J* = 272.1 Hz), 117.6.

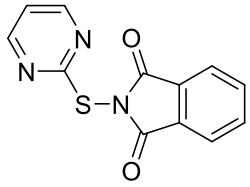
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3065, 1788, 1749, 1722, 1699, 1597, 1563, 1541, 1467, 1380, 1356, 1337, 1321, 1297, 1279, 1267, 1250, 1222, 1175, 1168, 1142, 1111, 1073, 1041, 1007, 978, 962, 934, 891, 868, 835, 792, 743, 708, 696, 689.

MS (EI, 70 eV): *m/z* (%) = 356 (100), 324 (17), 323 (18), 292 (38), 279 (33), 223 (14), 147 (66), 104 (37), 76 (40), 50 (15).

HRMS (EI): *m/z* calc. for [$C_{14}H_7F_3NO_2S$]: 324.0180; found 324.0166

m. p. (°C): 155.6–157.1.

***N*-((2-Pyrimidine)thio)phthalimide (38k)**



According to **TP15**, 2-mercaptopyrimidine (561 mg, 5.00 mmol, 1.00 equiv) was added dropwise at 0 °C to the solution of *N*-chlorophthalimide (908 mg, 5.00 mmol, 1.00 equiv). The title compound was obtained as a white powder (907 mg, 3.50 mmol, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.47 (d, J = 4.8 Hz, 2H), 8.01 (dd, J = 5.5, 3.0 Hz, 2H), 7.84 (dd, J = 5.5, 3.1 Hz, 2H), 7.02 (t, J = 4.9 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 167.4 (2C), 157.9, 134.8 (2C), 132.3 (2C), 124.3 (2C), 123.6 (2C), 118.2.

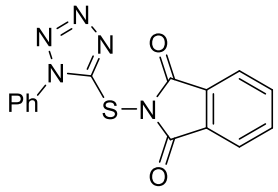
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3191, 3060, 1787, 1773, 1746, 1720, 1626, 1603, 1553, 1463, 1381, 1364, 1346, 1308, 1286, 1266, 1190, 1166, 1145, 1108, 1089, 1071, 1051, 991, 983, 973, 903, 867, 811, 799, 769, 747, 715, 696, 689, 669.

MS (EI, 70 eV): *m/z* (%) = 257 (32), 147 (100), 140 (39), 104 (47), 97 (22), 76 (43), 69 (10), 57 (15), 50 (22), 43 (22).

HRMS (EI): *m/z* calc. for [$C_{12}H_7N_3O_2S$]: 257.0259; found 257.0261

m. p. (°C): 115.2–116.7.

***N*-2-((1-Phenyl-1*H*-tetrazol-5-yl)thio)phthalimide (38l)**



According to **TP15**, 1-phenyl-1*H*-tetrazole-5-thiol (766 mg, 4.30 mmol, 1.00 equiv) was added dropwise at 0 °C to the solution of *N*-chlorophthalimide (781 mg, 4.30 mmol, 1.00 equiv). The title compound was obtained as a white powder (966 mg, 3.00 mmol, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.99 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.84 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.64–7.52 (m, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 165.9 (2C), 135.3, 131.9 (2C), 130.8 (2C), 130.3 (2C), 130.1, 124.8 (2C), 124.4, 123.4 (2C).

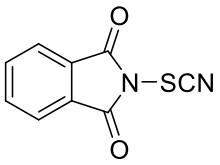
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1791, 1749, 1723, 1593, 1499, 1465, 1425, 1417, 1408, 1399, 1387, 1365, 1345, 1293, 1281, 1269, 1260, 1222, 1167, 1154, 1089, 1074, 1054, 1029, 1013, 1001, 973, 913, 865, 797, 792, 765, 760, 708, 697, 693, 684.

MS (EI, 70 eV): *m/z* (%) = 147 (100), 104 (37), 76 (40), 50 (15).

HRMS (EI): *m/z* calc. for [$C_{15}H_9N_5O_2S$]: 323.0477; found 323.0475

m. p. (°C): 164.4–164.9.

***N*-(Thiocyanato)phthalimide (38n)**



To a solution of *N*-chlorophthalimide (1.82 g, 10.0 mmol, 1.00 equiv) in dry acetonitrile (40 mL) under argon was added cuprous thiocyanate (1.46 g, 12.0 mmol, 1.20 equiv) in one portion. The dark brown reaction mixture was stirred at 25 °C for 2 h. The resulting suspension was concentrated *in vacuo*. The resulting residues were dissolved and washed with CH_2Cl_2/hexane (3:1, 2 x 40 mL) and filtered through a layer of celite. Filtrate was concentrated *in vacuo* to provide the title compound as a white solid (1.60 g, 7.80 mmol, 80%) and 20% of

a phthalimide impurity. The reagent was stored in the dark at -25°C, and used for the following reactions without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 (dd, J = 5.6, 3.1 Hz, 2H), 7.89 (dd, J = 5.6, 3.1 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.6 (2C), 135.7 (2C), 131.5 (2C), 124.9 (2C), 109.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2161, 1792, 1747, 1714, 1604, 1467, 1347, 1272, 1258, 1167, 1031, 866, 805, 793, 711, 696, 686, 666.

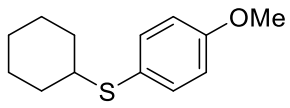
MS (EI, 70 eV): *m/z* (%) = 203 (38), 148 (100), 138 (60), 104 (62), 76 (55), 50 (20).

HRMS (EI): *m/z* calc. for [$C_9H_4N_2O_2S$]: 203.9993; found 203.9990.

m. p. (°C): 104.1–106.6.

7.3 Preparation of Thioethers

Cyclohexyl(4-methoxyphenyl)sulfane (4a)



According to **TP16**, *N*-(cyclohexylthio)phthalimide (**38a**, 131 mg, 0.50 mmol, 1.00 equiv) was reacted with (4-methoxyphenyl)zinc chloride (**1rr**, 1.53 mL, 0.36 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 95:5) afforded the title compound as a yellow oil (98 mg, 0.44 mmol, 95%). (4-methoxyphenyl)zinc chloride

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.39 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 3.09–2.72 (m, 1H), 1.98–1.88 (m, 2H), 1.82–1.69 (m, 2H), 1.66–1.51 (m, 1H), 1.39–1.15 (m, 5H).

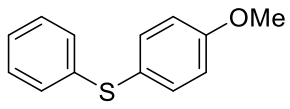
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.2, 135.5 (2C), 124.8, 114.2 (2C), 55.2, 47.8 (2C), 33.3 (2C), 26.0, 25.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 2850, 2834, 1590, 1570, 1491, 1461, 1447, 1296, 1283, 1261, 1241, 1200, 1178, 1170, 1102, 1096, 1031, 1008, 997, 887, 825, 806, 798, 739, 726.

MS (EI, 70 eV): *m/z* (%) = 222 (21), 140 (100), 125 (32).

HRMS (EI): *m/z* calc. for [$C_{13}H_{18}OS$]: 222.1078; found 222.1071.

(4-Methoxyphenyl)(phenyl)sulfane (4b)



According to **TP16**, *N*-(phenylthio)phthalimide (**38b**, 128 mg, 0.50 mmol, 1.00 equiv) was reacted with (4-methoxyphenyl)zinc chloride (**1rr**, 1.53 mL, 0.36 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 9:1) afforded the title compound as a white powder (106 mg, 0.49 mmol, 98%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.47 (d, J = 8.8 Hz, 2H), 7.32–7.15 (m, 5H), 6.95 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H).

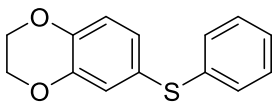
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.9, 138.7, 135.4 (2C), 129.0 (2C), 128.2 (2C), 125.8, 124.3, 115.0 (2C), 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2996, 2969, 2944, 2840, 1588, 1580, 1570, 1491, 1475, 1458, 1435, 1403, 1285, 1245, 1180, 1174, 1153, 1106, 1099, 1077, 1071, 1028, 1006, 996, 982, 966, 941, 896, 835, 812, 797, 732, 689.

MS (EI, 70 eV): *m/z* (%) = 216 (100), 200 (60), 171 (20), 129 (21), 96 (13), 77 (44), 51 (35).

HRMS (EI): *m/z* calc. for [$C_{13}H_{12}OS$]: 216.0609; found 216.0610.

6-(Phenylthio)-2,3-dihydrobenzo[*b*][1,4]dioxine (4c)



According to **TP16**, *N*-(phenylthio)phthalimide (**38b**, 128 mg, 0.50 mmol, 1.00 equiv) was reacted with (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)zinc chloride (**1v**, 1.34 mL, 0.41 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 9.5:0.5) afforded the title compound as a colourless oil (110 mg, 0.45 mmol, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.19–7.11 (m, 4H), 7.10–7.03 (m, 1H), 6.89 (d, *J* = 2.1 Hz, 1H), 6.84 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 4.18–4.10 (m, 4H).

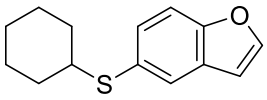
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.0, 143.8, 137.8, 129.1 (2C), 129.0 (2C), 126.5, 126.2, 125.8, 122.1, 118.2, 64.4, 64.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2977, 2928, 2877, 1577, 1488, 1477, 1456, 1438, 1408, 1299, 1279, 1248, 1193, 1121, 1062, 1048, 1023, 998, 931, 895, 871, 808, 737, 688.

MS (EI, 70 eV): *m/z* (%) = 244 (100), 187 (30), 160 (45), 134 (14), 115 (15), 79 (20), 51 (19).

HRMS (EI): *m/z* calc. for [$C_{14}H_{12}O_2S$]: 244.0558; found 244.0560.

5-(Cyclohexylthio)benzofuran (4d)



According to **TP16**, *N*-(cyclohexylthio)phthalimide (**38a**, 131 mg, 0.50 mmol, 1.00 equiv) was reacted with benzofuran-5-ylzinc chloride (**1ccc**, 1.83 mL, 0.30 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 99:1) afforded the title compound as a colourless oil (101 mg, 0.43 mmol, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.71 (d, J = 1.7 Hz, 1H), 7.62 (d, J = 2.2 Hz, 1H), 7.46–7.35 (m, 2H), 3.00 (tt, J = 10.6, 3.6 Hz, 1H), 2.04–1.88 (m, 2H), 1.84–1.68 (m, 2H), 1.67–1.51 (m, 1H), 1.46–1.12 (m, 5H).

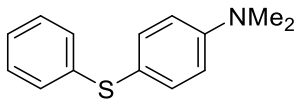
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 154.4, 145.6, 130.2, 128.1, 127.9, 126.7, 111.6, 106.3, 48.0, 33.3 (2C), 26.1, 25.8 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2925, 2850, 1651, 1445, 1386, 1324, 1257, 1243, 1200, 1170, 1130, 1108, 1030, 997, 915, 885, 874, 807, 775, 764, 732, 693.

MS (EI, 70 eV): *m/z* (%) = 232 (22), 150 (100), 121 (36).

HRMS (EI): *m/z* calc. for [$C_{14}H_{16}OS$]: 232.0922; found 232.0916.

***N*,*N*-Dimethyl-4-(phenylthio)aniline (4e)**



According to **TP16**, *N*-(phenylthio)phthalimide (**38b**, 128 mg, 0.50 mmol, 1.00 equiv) was reacted with (4-(dimethylamino)phenyl)zinc chloride (**1vv**, 1.90 mL, 0.29 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 9:1) afforded the title compound as a yellow powder (97 mg, 0.42 mmol, 85%).

1H-NMR (400 MHz, CDCl3): δ / ppm = 7.48 (d, *J* = 8.8 Hz, 2H), 7.28 (dd, *J* = 8.0, 7.0 Hz, 2H), 7.22 - 7.11 (m, 3H), 6.78 (d, *J* = 8.8 Hz, 2H), 3.05 (s, 6H).

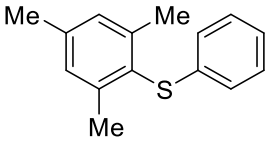
13C-NMR (100 MHz, CDCl3): *δ* / ppm = 150.6, 140.3, 136.1 (2C), 128.7 (2C), 126.8 (2C), 124.9 (2C), 117.3, 112.9 (2C), 40.3 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3053, 2925, 2851, 2809, 1886, 1592, 1582, 1571, 1546, 1508, 1477, 1443, 1436, 1425, 1367, 1328, 1315, 1298, 1290, 1257, 1228, 1194, 1183, 1171, 1131, 1101, 1082, 1065, 1024, 996, 945, 935, 874, 834, 809, 764, 738, 712, 691.

MS (EI, 70 eV): *m/z* (%) = 229 (100), 213 (32), 196 (52), 184 (43), 152 (30), 136 (27), 109 (17), 77 (13).

HRMS (EI): *m/z* calc. for [$C_{14}H_{15}NS$]: 229.0925; found 229.0919.

Mesityl(phenyl)sulfane (4f)



According to **TP16**, *N*-(phenylthio)phthalimide (**38b**, 128 mg, 0.50 mmol, 1.00 equiv) was reacted with mesitylzinc chloride (**1ddd**, 1.96 mL, 0.28 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane) afforded the title compound as a colourless oil (112 mg, 0.49 mmol, 98%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.21 (t, J = 7.7 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 7.06 (s, 2H), 6.98 (d, J = 8.0 Hz, 2H), 2.44 (s, 6H), 2.37 (s, 3H).

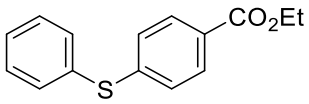
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.7 (2C), 139.2, 138.3, 129.3 (2C), 128.8 (2C), 126.9, 125.4 (2C), 124.4, 21.7 (2C), 21.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057, 2948, 2917, 2850, 1601, 1581, 1477, 1462, 1438, 1374, 1327, 1297, 1176, 1155, 1085, 1069, 1060, 1031, 1023, 1013, 998, 953, 895, 849, 735, 719, 695, 688.

MS (EI, 70 eV): *m/z* (%) = 228 (100), 213 (10), 198 (14), 180 (16), 165 (18), 150 (48), 135 (14), 119 (11), 91 (16).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}S$]: 228.0973; found 228.0965.

Ethyl 4-(phenylthio)benzoate (4g)



According to **TP16**, *N*-(phenylthio)phthalimide (**38b**, 128 mg, 0.50 mmol, 1.00 equiv) was reacted with (4-(ethoxycarbonyl)phenyl)zinc chloride (**1aa**, 1.83 mL, 0.30 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 97.5:2.5) afforded the title compound as a colourless oil (127 mg, 0.49 mmol, 98%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91 (d, J = 8.5 Hz, 2H), 7.53–7.43 (m, 2H), 7.42–7.33 (m, 3H), 7.21 (d, J = 8.6 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H).

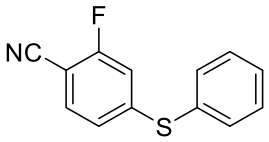
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.1, 144.0, 133.5 (2C), 132.4, 130.0 (2C), 129.5 (2C), 128.5, 127.8, 127.5 (2C), 60.8, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2978, 1709, 1674, 1592, 1581, 1562, 1488, 1475, 1464, 1439, 1399, 1366, 1308, 1267, 1176, 1103, 1082, 1068, 1014, 1000, 846, 759, 746, 704, 688.

MS (EI, 70 eV): *m/z* (%) = 258 (78), 230 (40), 213 (100), 198 (14), 184 (97), 152 (20).

HRMS (EI): *m/z* calc. for [$C_{15}H_{14}O_2S$]: 258.0715; found 258.0707.

2-Fluoro-5-(phenylthio)benzonitrile (4h)



According to **TP16**, *N*-(phenylthio)phthalimide (**38b**, 128 mg, 0.50 mmol, 1.00 equiv) was reacted with (4-cyano-3-fluorophenyl)zinc chloride (**1p**, 1.90 mL, 0.29 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 95:5) afforded the title compound as a white solid (105 mg, 0.46 mmol, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.51–7.43 (m, 2H), 7.41–7.34 (m, 5H), 7.13 (t, *J* = 8.6 Hz, 1H).

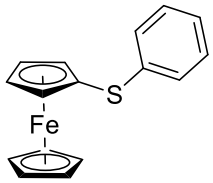
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.7 (d, *J* = 259.6 Hz), 136.2 (d, *J* = 8.1 Hz), 134.4 (d, J = 3.8 Hz), 133.9, 133.0, 132.4 (2C), 129.7 (2C), 128.5, 117.1 (d, *J* = 20.3 Hz), 113.3, 102.3 (d, *J* = 16.2 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3103, 3052, 2235, 1967, 1889, 1820, 1752, 1638, 1601, 1581, 1574, 1527, 1487, 1476, 1461, 1440, 1406, 1398, 1385, 1333, 1307, 1297, 1289, 1282, 1268, 1244, 1192, 1177, 1171, 1156, 1119, 1104, 1092, 1076, 1067, 1023, 1000, 946, 919, 879, 861, 847, 819, 758, 749, 704, 691, 657, 652.

MS (EI, 70 eV): *m/z* (%) = 229 (100), 208 (24), 202 (22).

HRMS (EI): *m/z* calc. for [$C_{13}H_8FNS$]: 229.0361; found 229.0355.

Ferrocene thiophenyl (4i)



According to **TP16**, *N*-(phenylthio)phthalimide (**38b**, 128 mg, 0.50 mmol, 1.00 equiv) was reacted with ferrocenylzinc chloride (**1eee**, 2.62 mL, 0.21 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (100% hexane) afforded the title compound as an orange oil (129 mg, 0.44 mmol, 88%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.22–7.14 (m, 2H), 7.10–7.02 (m, 3H), 4.41 (t, *J* = 1.9 Hz, 2H), 4.35 (t, *J* = 1.9 Hz, 2H), 4.28 (s, 5H).

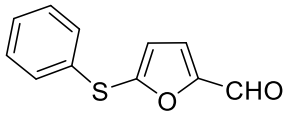
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 140.8, 128.6 (2C), 125.8 (2C), 124.8, 75.5, 75.0 (2C), 70.2 (2C), 69.7 (5C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921, 2852, 1577, 1569, 1475, 1454, 1434, 1409, 1387, 1362, 1347, 1195, 1170, 1152, 1106, 1071, 1060, 1053, 1023, 1016, 999, 890, 842, 826, 818, 743, 692.

MS (EI, 70 eV): *m/z* (%) = 294 (75), 228 (14), 171 (30), 141 (19), 121 (100), 95 (13), 77 (20), 56 (42).

HRMS (EI): *m/z* calc. for $[C_{16}H_{14}FeS]$: 294.0166; found 294.0162.

5-(Phenylthio)furan-2-carbaldehyde (4j)



According to **TP16**, *N*-(phenylthio)phthalimide (**38b**, 128 mg, 0.50 mmol, 1.00 equiv) was reacted with (5-formylfuran-2-yl)zinc iodide (**1fff**, 1.67 mL, 0.33 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 85:15) afforded the title compound as a yellow oil (85 mg, 0.42 mmol, 83%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.43 (s, 1H), 7.30–7.23 (m, 2H), 7.23–7.14 (m, 3H), 7.08 (d, J = 3.6 Hz, 1H), 6.44 (d, J = 3.6 Hz, 1H).

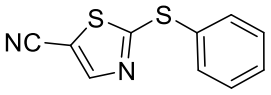
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 177.0, 154.5, 153.8, 131.7, 131.0 (2C), 129.5 (2C), 128.3, 122.0, 117.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3136, 2819, 1668, 1614, 1581, 1561, 1475, 1450, 1440, 1392, 1375, 1344, 1265, 1210, 1189, 1155, 1114, 1081, 1069, 1018, 999, 959, 933, 803, 760, 737, 687, 658.

MS (EI, 70 eV): *m/z* (%) = 204 (78), 175 (33), 147 (100), 115 (28), 121 (11), 115 (28), 103 (14).

HRMS (EI): *m/z* calc. for [$C_{11}H_8O_2S$]: 204.0245; found 204.0237.

2-(Phenylthio)thiazole-5-carbonitrile (4k)



According to **TP16**, *N*-(phenylthio)phthalimide (**38b**, 128 mg, 0.50 mmol, 1.00 equiv) was reacted with (5-cyanothiazol-2-yl)zinc chloride (**1ggg**, 1.67 mL, 0.33 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 4:1) afforded the title compound as a yellow solid (58 mg, 0.27 mmol, 71%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (s, 1H), 7.73–7.68 (m, 2H), 7.61–7.49 (m, 3H).

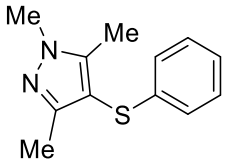
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 177.0, 152.4, 135.4 (2C), 131.4, 130.6 (2C), 128.6, 111.5, 105.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3098, 3051, 2218, 1896, 1767, 1575, 1496, 1473, 1440, 1358, 1334, 1310, 1285, 1274, 1206, 1182, 1167, 1159, 1143, 1132, 1067, 1046, 1024, 1000, 993, 974, 929, 886, 850, 759, 746, 702, 686, 676.

MS (EI, 70 eV): *m/z* (%) = 217 (100), 140 (14), 83 (10).

HRMS (EI): *m/z* calc. for [$C_{10}H_5N_2S_2$]: 216.9894; found 216.9888.

1,3,5-Trimethyl-4-(phenylthio)-1*H*-pyrazole (4l)



According to **TP16** *N*-(phenylthio)phthalimide (**38b**, 128 mg, 0.50 mmol, 1.00 equiv) was reacted with (1,3,5-trimethyl-1*H*-pyrazol-4-yl)zinc chloride (**1hhh**, 3.06 mL, 0.18 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 7:3) afforded the title compound as a yellow oil (103 mg, 0.47 mmol, 94%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.17 (t, J = 7.7 Hz, 2H), 7.04 (t, J = 7.4 Hz, 1H), 6.96 (d, J = 7.1 Hz, 2H), 3.77 (s, 3H), 2.23 (s, 3H), 2.19 (s, 3H).

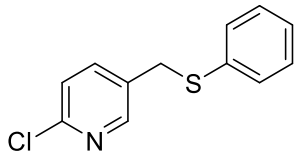
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 151.5, 143.7, 138.6, 128.6 (2C), 125.0 (2C), 124.6, 103.4, 36.5, 11.7, 9.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3055, 2941, 2922, 1770, 1734, 1726, 1581, 1531, 1492, 1477, 1438, 1423, 1411, 1382, 1365, 1327, 1300, 1274, 1193, 1155, 1106, 1082, 1069, 1037, 1023, 997, 985, 965, 897, 833, 737, 719, 689, 674.

MS (EI, 70 eV): *m/z* (%) = 218 (100), 203 (12), 190 (28), 185 (32), 170 (10), 158 (14), 144 (12), 56 (10).

HRMS (EI): *m/z* calc. for [$C_{12}H_{14}N_2S$]: 218.0878; found 218.0870.

2-Chloro-5-((phenylthio)methyl)pyridine (4m)



According to **TP16**, *N*-(phenylthio)phthalimide (**38b**, 128 mg, 0.50 mmol) was reacted with ((6-chloropyridin-3-yl)methyl)zinc chloride (**1iii**, 1.00 mL, 0.55 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 95:5) afforded the title compound as a colourless oil (108 mg, 0.49 mmol, 97%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 (d, J = 2.5 Hz, 1H), 7.49 (dd, J = 8.2, 2.5 Hz, 1H), 7.33–7.14 (m, 6H), 3.98 (s, 2H).

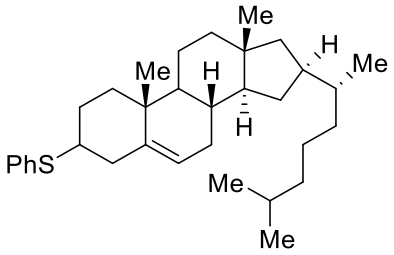
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 150.0, 149.4, 138.9, 134.2, 132.5, 131.0 (2C), 129.0 (2C), 127.2, 123.9, 35.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3073, 3050, 2923, 1583, 1563, 1480, 1458, 1438, 1378, 1286, 1256, 1209, 1132, 1102, 1087, 1067, 1022, 1000, 930, 871, 831, 820, 737, 689, 667.

MS (EI, 70 eV): *m/z* (%) = 235 (16), 126 (100), 90 (15).

HRMS (EI): *m/z* calc. for [$C_{12}H_{10}ClNS$]: 235.0222; found 235.0213.

3-(Phenylthio)-cholest-5-ene (4n)



According to **TP16**, *N*-(phenylthio)phthalimide (**38b**, 128 mg, 0.50 mmol, 1.00 equiv) was reacted with cholest-5-ene-3-ylzinc chloride (**1jjj**, 4.23 mL, 0.13 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane) afforded the diastereomeres 3*α*-(phenylthio)-cholest-5-ene (1nα) (49 mg, 0.10 mmol) and 3*β*-(phenylthio)-cholest-5-ene (1nβ) (185 mg, 0.39 mmol) as white powders which combined gives a yield of 98% (*d.r.* 21:79).

3*α*-(Phenylthio)-cholest-5-ene (1n*α*)

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.38 (d, *J* = 7.1 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 5.34 (dd, *J* = 4.9, 2.4 Hz, 1H), 3.69–3.62 (m, 1H), 2.76 (d, *J* = 14.6 Hz, 1H), 2.19 (dt, *J* = 14.8, 2.4 Hz, 1H), 2.07–1.78 (m, 4H), 1.80–0.93 (m, 22H), 1.02 (s, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.6, 3H) 0.87 (d, *J* = 6.6 Hz, 3H), 0.68 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 138.8, 136.3, 131.4 (2C), 128.8 (2C), 126.3, 122.5, 56.7, 56.11, 49.9, 46.6, 42.3, 39.7, 39.5, 37.2, 37.1, 36.2, 35.8, 33.8, 31.8, 31.8, 28.3, 28.0, 26.3, 24.3, 23.9, 22.8, 22.6, 20.7, 19.3, 18.7, 11.8.

IR (Diamond-ATR, neat): 2958, 2932, 2898, 2866, 2847, 1586, 1481, 1462, 1444, 1438, 1374, 1363, 1322, 1156, 1093, 1026, 1008, 983, 959, 887, 823, 799, 774, 732, 700, 689.

MS (EI, 70 eV): *m/z* (%) = 478 (36), 369 (100), 247 (26), 161 (27), 145 (41), 110 (37), 107 (36), 95 (53), 81 (55), 57 (40), 43 (40).

HRMS (EI): *m/z* calc. for [$C_{33}H_{50}S$]: 478.3633; found 478.3627.

3*β*-(Phenylthio)-cholest-5-ene (1n*β*)

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.39 (d, *J* = 7.0 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 5.31 (dd, *J* = 5.5, 2.4 Hz, 1H), 3.09–2.96 (m, 1H), 2.32 (d, *J* = 8.2 Hz, 2H),

2.09–1.73 (m, 5H), 1.69–0.93 (m, 21H), 0.99 (s, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.6, 3H) 0.86 (d, J = 6.6 Hz, 3H), 0.68 (s, 3H).

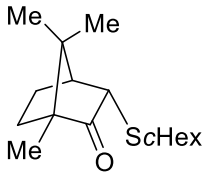
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 141.6, 134.8, 131.7 (2C), 128.7 (2C), 126.6, 121.1, 56.8, 56.1, 50.3, 47.3, 42.3, 39.7, 39.6, 39.5, 36.8, 36.2, 35.8, 31.8, 29.5, 28.2, 28.0, 24.2, 23.8, 22.8, 22.5, 20.9, 19.3, 18.7, 11.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2933, 2900, 2866, 2847, 1586, 1481, 1462, 1438, 1381, 1374, 1364, 1331, 1321, 1292, 1252, 1192, 1156, 1092, 1070, 1026, 1008, 983, 958, 955, 913, 887, 823, 799, 732, 700, 689.

MS (EI, 70 eV): *m/z* (%) = 478 (7), 369 (100), 161 (12), 147 (12), 109 (11), 95 (16), 81 (12), 55 (11), 43 (11).

HRMS (EI): *m/z* calc. for [$C_{33}H_{50}S$]: 478.3633; found 478.3632.

(1*S*,3*S*,4*S*)-3-(Cyclohexylthio)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4o)



According to **TP16**, *N*-(cyclohexylthio)phthalimide (**38a**, 131 mg, 0.50 mmol, 1.00 equiv) was reacted with ((1*S*,4*S*)-4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptan-2-yl)zinc bromide (**1kkk**, 1.67 mL, 0.33 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 99:1) afforded the title compound as a colourless oil (130 mg, 0.44 mmol, 97:3 d.r., 98%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 3.49 (dd, J = 4.7, 1.9 Hz, 1H), 2.88 (tt, J = 14.3, 5.5 Hz, 1H), 2.14 (t, J = 4.4 Hz, 1H), 2.07–1.86 (m, 3H), 1.82–1.54 (m, 5H), 1.46–1.14 (m, 6H), 1.00 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H).

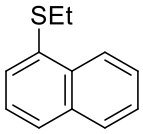
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 217.5, 58.3, 51.1, 48.8, 46.0, 44.1, 33.9, 33.7, 30.6, 26.0, 26.0, 25.7, 21.4, 19.6, 19.4, 9.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2960, 2926, 2851, 1740, 1592, 1492, 1446, 1391, 1375, 1338, 1320, 1298, 1263, 1244, 1208, 1178, 1152, 1104, 1037, 1001, 955, 919, 885, 860,831, 818, 780, 745.

MS (EI, 70 eV): *m/z* (%) = 266 (12), 155 (94), 152 (100), 137 (30), 124 (83), 108 (64), 83 (41), 73 (66).

HRMS (EI): *m/z* calc. for [$C_{16}H_{26}OS$]: 266.1704; found 266.1697.

Ethyl(naphthalen-1-yl)sulfane (4p)



According to **TP16**, *N*-(ethylthio)phthalimide (**38c**, 104 mg, 0.50 mmol, 1.00 equiv) was reacted with naphthalen-1-ylzinc chloride (**1x**, 2.04 mL, 0.27 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 95:5) afforded the title compound as a yellow oil (59.0 mg, 0.32 mmol, 71%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.42 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 7.4 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.60–7.48 (m, 3H), 7.42 (t, J = 15.4 Hz, 1H), 3.02 (q, J = 7.3 Hz, 2H), 1.34 (t, J = 7.4 Hz, 3H).

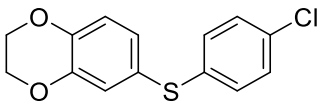
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 134.0, 133.9, 133.0, 128.7, 127.8, 127.1, 126.4, 126.3, 125.7, 125.2, 28.3, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3052, 2966, 2923, 2867, 1589, 1563, 1501, 1446, 1381, 1331, 1258, 1202, 1163, 1142, 1068, 1052, 1023, 975, 854, 825, 798, 785, 767, 665.

MS (EI, 70 eV): *m/z* (%) = 188 (100), 175 (32), 153 (52), 125 (43), 89 (40), 63 (25).

HRMS (EI): *m/z* calc. for [$C_{12}H_{12}S$]: 188.0660; found 188.0658.

6-((4-Chlorophenyl)thio)-2,3-dihydrobenzo[*b*][1,4]dioxine (4q)



According to **TP16**, *N*-((4-chlorophenyl)thio)phthalimide (**38d**, 128 mg, 0.50 mmol, 1.00 equiv) was reacted with (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)zinc chloride (**1v**, 1.34 mL, 0.41 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 95:5) afforded the title compound as a yellow oil (120 mg, 0.43 mmol, 94%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.24–7.19 (m, 2H), 7.16–7.11 (m, 2H), 6.97 (d, *J* = 2.1 Hz, 1H), 6.93 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.30–4.23 (m, 4H).

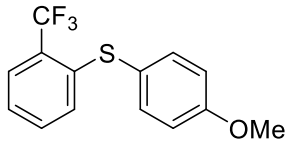
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 144.1, 136.5, 132.0, 130.1 (2C), 129.1 (2C), 126.7, 125.2, 122.2, 118.3, 64.4, 64.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2977, 2928, 2879, 1599, 1576, 1489, 1473, 1457, 1409, 1389, 1362, 1300, 1279, 1248, 1194, 1144, 1122, 1091, 1082, 1063, 1049, 1009, 932, 896, 872, 808, 767, 742, 713, 687, 664.

MS (EI, 70 eV): *m/z* (%) = 278 (100), 187 (75), 159 (20), 115 (15), 79 (25), 51 (24).

HRMS (EI): *m/z* calc. for $[C_{14}H_{11}ClO_2S]$: 278.0168; found 278.0170.

(4-Methoxyphenyl)(2-(trifluoromethyl)phenyl)sulfane (4r)



According to **TP16**, *N*-((4-methoxyphenyl)thio)phthalimide (**38e**, 143 mg, 0.50 mmol, 1.00 equiv) was reacted with (2-(trifluoromethyl)phenyl)zinc chloride (**1lll**, 1.16 mL, 0.43 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 95:5) afforded the title compound as an oil (138 mg, 0.49 mmol, 97%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.63 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H).

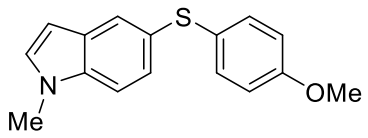
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.5, 138.1, 135.7 (2C), 130.8, 128.5, 126.4 (q, J = 30.7 Hz), 125.5 (q, J = 5.7 Hz), 124.3, 124.0, 121.4 (d, J = 27.0 Hz), 114.3 (2C), 54.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2921, 2852, 1591, 1572, 1493, 1466, 1458, 1446, 1435, 1407, 1312, 1300, 1292, 1257, 1251, 1169, 1159, 1112, 1103, 1098, 1090, 1031, 954, 875, 822, 799, 766, 729, 714, 706, 696.

MS (EI, 70 eV): *m/z* (%) = 284 (100), 268 (43), 171 (44), 139 (29), 95 (26), 69 (30).

HRMS (EI): *m/z* calc. for [$C_{14}H_{11}F_3S$]: 284.0483; found 284.0485.

5-((4-Methoxyphenyl)thio)-1-methyl-1*H*-indole (4s)



According to **TP16**, *N*-((4-methoxyphenyl)thio)phthalimide (**38e**, 143 mg, 0.50 mmol, 1.00 equiv) was reacted with (1-methyl-1*H*-indol-5-yl)zinc chloride (**1y**, 2.88 mL, 0.26 M in THF, 0.75 mmol, 1.50 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 4:1) afforded the title compound as a white powder (126 mg, 0.47 mmol, 96%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.63–7.60 (m, 1H), 7.28–7.13 (m, 4H), 6.94 (d, *J* = 3.2 Hz, 1H), 6.74–6.67 (m, 2H), 6.33 (d, *J* = 3.1 Hz, 1H), 3.66 (d, *J* = 3.9 Hz, 6H).

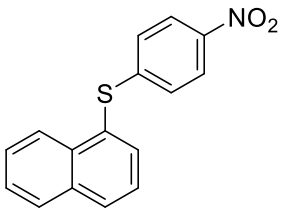
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 158.6, 136.2, 131.8 (2C), 129.8, 129.3, 129.2, 126.2, 125.3, 114.7 (2C), 110.2, 101.0, 55.4, 33.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2921, 2854, 2832, 1588, 1567, 1507, 1489, 1469, 1447, 1437, 1421, 1403, 1375, 1328, 1296, 1286, 1273, 1269, 1239, 1199, 1180, 1170, 1149, 1103, 1076, 1026, 910, 886, 865, 853, 832, 823, 792, 765, 756, 732, 719.

MS (EI, 70 eV): *m/z* (%) = 269 (100), 253 (37), 226 (19), 210 (16), 127 (27), 102(23), 63 (52).

HRMS (EI): *m/z* calc. for [$C_{16}H_{15}NOS$]: 269.0874; found 269.0878.

Naphthalen-1-yl(4-nitrophenyl)sulfane (4t)



According to **TP16**, *N*-((4-nitrophenyl)thio)phthalimide (**38f**, 180 mg, 0.50 mmol, 1.00 equiv) was reacted with naphthalen-1-ylzinc chloride (**1x**, 2.78 mL, 0.27 M in THF, 0.75 mmol, 1.50 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 95:5) afforded the title compound as a yellow powder (77 mg, 0.28 mmol, 55%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.27–8.22 (m, 1H), 8.05–7.97 (m, 3H), 7.93 (m, 2H), 7.55 (td, *J* = 7.8, 1.4 Hz, 3H), 7.07–7.02 (m, 2H).

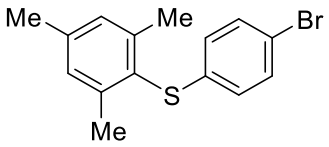
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 148.7, 145.2, 135.9 (2C), 134.7, 134.3, 131.7, 129.1, 128.0, 127.1, 126.8, 126.2, 126.0, 125.6, 124.2 (2C).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3102, 3054, 2921, 2851, 1732, 1590, 1573, 1500, 1474, 1422, 1398, 1375, 1363, 1332, 1254, 1212, 1200, 1175, 1163, 1140, 1107, 1086, 1056, 1019, 1007, 974, 954, 924, 866, 852, 840, 820, 800, 769, 738, 681, 667.

MS (EI, 70 eV): *m/z* (%) = 281 (80), 234 (65), 202 (35), 159 (12), 115 (100), 76 (30), 50 (35).

HRMS (EI): *m/z* calc. for [$C_{16}H_{11}NO_2S$]: 281.0510; found 281.0510.

(4-Bromophenyl)(mesityl)sulfane (4u)



According to **TP16**, *N*-((4-bromophenol)thio)phthalimide (**38g**, 167 mg, 0.50 mmol, 1.00 equiv) was reacted with mesitylzinc chloride (**1ccc**, 1.96 mL, 0.28 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 99:1) afforded the title compound as a white powder (134 mg, 0.44 mmol, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.27 (d, J = 8.3 Hz, 2H), 7.01 (s, 2H), 6.77 (d, J = 8.6 Hz, 2H), 2.36 (s, 6H), 2.32 (s, 3H).

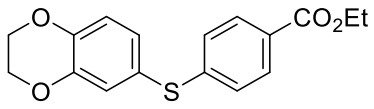
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.8 (2C), 139.8, 137.9, 132.0 (2C), 129.6 (2C), 127.1 (2C), 126.5, 118.0, 21.8 (2C), 21.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2950, 2918, 2851, 1895, 1739, 1600, 1557, 1470, 1435, 1385, 1372, 1295, 1177, 1110, 1086, 1067, 1055, 1032, 1004, 951, 891, 856, 835, 811, 727, 717, 693.

MS (EI, 70 eV): *m/z* (%) = 306 (100), 228 (32), 212 (52), 195 (43), 179 (30), 150 (27), 119 (17), 91 (13), 65(12).

HRMS (EI): *m/z* calc. for [$C_{15}H_{15}BrS$]: 306.0078; found 306.0075.

Ethyl 4-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)thio)benzoate (4v)



According to **TP16**, *N*-((ethyl 4-benzoate)thio)phthalimide (**38h**, 165 mg, 0.50 mmol, 1.00 equiv) was reacted with (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)zinc chloride (**1v**, 1.83 mL, 0.41 M in THF, 0.75 mmol, 1.50 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 9:1) afforded the title compound as a colourless oil (111 mg, 0.35 mmol, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94–7.87 (m, 2H), 7.17–7.13 (m, 2H), 7.08 (d, *J* = 2.2 Hz, 1H), 7.03 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.33–4.28 (m, 4H), 1.39 (t, *J* = 7.1 Hz, 3H).

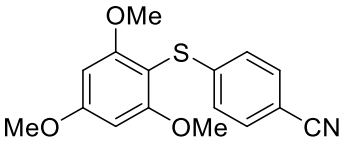
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 166.3, 145.6, 144.7, 144.2, 130.0 (2C), 128.2, 127.2, 126.3 (2C), 123.7, 122.8, 118.5, 64.4, 64.2, 60.9, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2933, 2880, 2359, 1709, 1592, 1577, 1562, 1487, 1460, 1409, 1399, 1366, 1301, 1270, 1250, 1196, 1177, 1121, 1105, 1081, 1064, 1050, 1015, 932, 897, 873, 846, 811, 759, 746, 731, 689.

MS (EI, 70 eV): *m/z* (%) = 316 (100), 288 (76), 215 (52), 138 (43), 76 (30).

HRMS (EI): *m/z* calc. for $[C_{17}H_{16}O_4S]$: 316.0769; found 316.0768.

4-((2,4,6-Trimethoxyphenyl)thio)benzonitrile (4w)



According to **TP16**, 4-((1,3-dioxoisoindolin-2-yl)thio)benzonitrile (**38i**, 165 mg, 0.50 mmol, 1.00 equiv) was reacted with (2,4,6-trimethoxyphenyl)zinc chloride (**1mmm**, 1.83 mL, 0.41 M in THF, 0.75 mmol, 1.50 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 9:1) afforded the title compound as a yellow oil (111 mg, 0.35 mmol, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 6.16 (s, 2H), 3.81 (s, 3H), 3.73 (s, 6H).

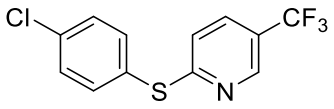
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 163.7, 162.4, 146.6, 132.0 (2C), 125.2 (2C), 119.4, 107.1, 95.9, 91.2, 56.3, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1577, 1492, 1458, 1322, 1301, 1282, 1247, 1126, 1069, 1058, 930, 903, 866, 839, 809, 724.

MS (EI, 70 eV): *m/z* (%) = 301 (100), 258 (32), 226 (29), 141 (40), 69 (46).

HRMS (EI): *m/z* calc. for [$C_{16}H_{15}NO_3S$]: 301.0773; found 301.0776.

2-((4-Chlorophenyl)thio)-5-(trifluoromethyl)pyridine (4x)



According to **TP16**, *N*-((5-(trifluoromethyl)pyridin-2-yl)thio)phthalimide (**38j**, 163 mg, 0.50 mmol, 1.00 equiv) was reacted with (4-chlorophenyl)zinc chloride (, 1.90 mL, 0.29 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 99:1) afforded the title compound as a colourless oil (119 mg, 0.41 mmol, 94%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.64 (s, 1H), 7.67 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 1H).

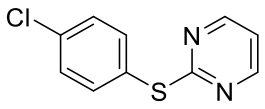
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 165.9, 146.7 (q, *J* = 4.2 Hz), 136.9 (2C), 136.5, 133.7 (q, *J* = 3.4 Hz), 130.3 (2C), 127.8, 126.4 (q, *J* = 271.9 Hz), 123.0 (q, *J* = 33.3 Hz), 120.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2925, 1630, 1593, 1573, 1558, 1477, 1462, 1390, 1379, 1322, 1245, 1164, 1125, 1112, 1091, 1073, 1013, 1008, 972, 938, 820, 790, 745, 714, 703.

MS (EI, 70 eV): *m/z* (%) = 288 (100), 126 (13), 108 (15), 75 (12).

HRMS (EI): *m/z* calc. for [$C_{12}H_7ClF_3NS$]: 288.9940; found 288.9945.

2-((4-Chlorophenyl)thio)pyrimidine (4y)



According to **TP16**, *N*-((2-pyrimidine)thio)phthalimide (**38k**, 129 mg, 0.50 mmol, 1.00 equiv) was reacted with (4-chlorophenyl)zinc chloride (, 1.90 mL, 0.29 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 9:1) afforded the title compound as a colourless oil (86 mg, 0.39 mmol, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.40 (d, J = 4.8 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 6.90 (t, J = 4.8 Hz, 1H).

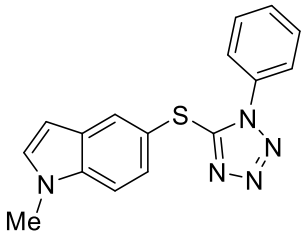
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 172.4, 157.7 (2C), 136.6 (2C), 135.3, 129.6, 127.9 (2C), 117.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3030, 2924, 2852, 1728, 1559, 1546, 1475, 1440, 1426, 1374, 1258, 1202, 1181, 1171, 1092, 1082, 1013, 981, 941, 818, 799, 770, 744, 702, 689.

MS (EI, 70 eV): *m/z* (%) = 222 (100), 187 (15), 169 (14), 143 (25), 108 (60), 75 (27), 53 (20).

HRMS (EI): *m/z* calc. for [$C_{10}H_7ClN_2S$]: 222.0018; found 222.0015.

1-Methyl-5-((1-phenyl-1*H*-tetrazol-5-yl)thio)-1*H*-indole (4z)



According to **TP16**, 2-((1-phenyl-1*H*-tetrazol-5-yl)thio)phthalimide (**38l**, 163 mg, 0.50 mmol, 1.00 equiv) was reacted with (1-methyl-1*H*-indol-5-yl)zinc chloride (**1y**, 2.12 mL, 0.26 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 4:1) afforded the title compound as a white powder (110 mg, 0.360 mmol, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.88 (s, 1H), 7.66–7.51 (m, 5H), 7.43 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.10 (d, *J* = 3.1 Hz, 1H), 6.49 (d, *J* = 3.0 Hz, 1H), 3.81 (s, 3H).

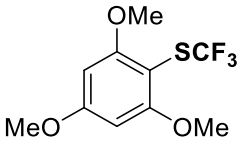
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 137.5, 134.5, 134.0, 130.4, 130.3, 129.8 (2C), 129.6, 128.6, 127.9, 124.5 (2C), 123.7, 115.1, 110.9, 101.8, 33.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2914, 1773, 1733, 1604, 1594, 1509, 1496, 1476, 1442, 1422, 1405, 1382, 1337, 1308, 1279, 1243, 1231, 1203, 1154, 1111, 1084, 1072, 1064, 1053, 1013, 972, 913, 908, 875, 863, 835, 802, 776, 753, 733, 715, 696, 691, 682.

MS (EI, 70 eV): *m/z* (%) = 162 (100), 136 (27), 109 (17), 77 (13).

HRMS (EI): *m/z* calc. for [$C_{16}H_{13}N_5S$]: 307.0892; found 307.0895.

(Trifluoromethyl)(2,4,6-trimethoxyphenyl)sulfane (41a)



According to **TP16**, 2-((trifluoromethyl)thio)phthalimide (124 mg, 0.50 mmol, 1.00 equiv) was reacted with (2,4,6-trimethoxyphenyl)zinc chloride (**1mmm**, 2.88 mL, 0.26 M in THF, 0.75 mmol, 1.5 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 9:1) afforded the title compound as a yellow oil (83.2 mg, 0.310 mmol, 91%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm 6.15 (s, 2H), 3.80 (s, 6H), 3.78 (s, 3H).

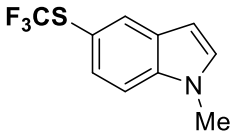
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.6 (2C), 163.6 (2C), 160.6, 157.6, 129.6 (q, J = 310.6 Hz), 56.4 (2C), 55.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2973, 2945, 2843, 1758, 1728, 1580, 1469, 1464, 1455, 1438, 1411, 1336, 1274, 1226, 1206, 1188, 1165, 1148, 1102, 1083, 1040, 1024, 952, 915, 867, 806, 787, 752, 713, 681, 664.

MS (EI, 70 eV): *m/z* (%) = 268 (100), 199 (80), 184 (30), 171 (40), 155 (12), 141 (15), 125 (20), 69 (60).

HRMS (EI): *m/z* calc. for [$C_{10}H_{11}F_3O_3S$]: 268.0381; found 268.0378.

1-Methyl-5-((trifluoromethyl)thio)-1*H*-indole (41b)



According to **TP16**, 2-((trifluoromethyl)thio)phthalimide (124 mg, 0.50 mmol, 1.00 equiv) was reacted with (1-methyl-1*H*-indol-5-yl)zinc chloride (**1y**, 2.88 mL, 0.29 M in THF, 0.75 mmol, 1.50 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 4:1) afforded the title compound as a yellow powder (107 mg, 0.47 mmol, 93%).

1H-NMR (400 MHz, CDCl3): δ / ppm = 7.97 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.12 (d, *J* = 3.1 Hz, 1H), 6.55 (d, *J* = 3.0 Hz, 1H), 3.81 (s, 3H).

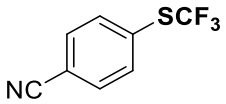
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 137.7, 130.6, 130.5, 130.1 (q, *J* = 308.1 Hz) 129.5, 129.3, 113.6 (q, *J* = 2.0 Hz), 110.2, 101.7, 33.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2918, 2850, 1727, 1709, 1694, 1615, 1605, 1582, 1511, 1474, 1441, 1423, 1376, 1361, 1331, 1279, 1244, 1146, 1123, 1110, 1091, 1063, 1009, 909, 901, 890, 798, 777, 759, 749, 728, 718.

MS (EI, 70 eV): *m/z* (%) = 231 (40), 162 (70), 118 (20), 69 (100).

HRMS (EI): *m/z* calc. for [$C_{10}H_8F_3NS$]: 231.0330; found 231.0333.

4-((Trifluoromethyl)thio)benzonitrile (41c)



According to **TP16**, 2-((trifluoromethyl)thio)phthalimide (124 mg, 0.50 mmol, 1.00 equiv) was reacted with (4-cyanophenyl)zinc chloride (**1tt**, 1.53 mL, 0.25 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 99:1) afforded the title compound as a colourless oil (86 mg, 0.43 mmol, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.79 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H).

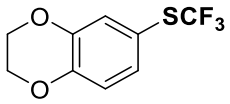
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 136.0 (2C), 132.9 (2C), 130.6, 129.04 (d, J = 311.7 Hz), 117.7, 114.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3092, 2230, 1926, 1594, 1487, 1403, 1396, 1305, 1276, 1259, 1187, 1160, 1119, 1084, 1018, 970, 961, 835, 780, 756, 728, 718.

MS (EI, 70 eV): *m/z* (%) = 203 (52), 134 (100), 90 (23), 69 (61).

HRMS (EI): *m/z* calc. for [$C_8H_4F_3NS$]: 203.0017; found 203.0013.

6-((Trifluoromethyl)thio)-2,3-dihydrobenzo[*b*][1,4]dioxine (41d)



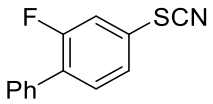
According to **TP16**, 2-((trifluoromethyl)thio)phthalimide (124 mg, 0.50 mmol, 1.00 equiv) was reacted with (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)zinc chloride (**1v**, 1.53 mL, 0.36 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 99:1) afforded the title compound as a yellow powder (95 mg, 0.41 mmol, 85%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.93–6.86 (m, 2H), 6.77 (d, J = 8.2 Hz, 1H), 4.19 (s, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 143.6, 142.8, 134.1, 131.4, 127.9 (q, J = 314.8 Hz), 119.7, 117.4, 115.4, 64.4 (2C).

Analytical data according to literature[115i]

2-Fluoro-4-thiocyanato-1,1'-biphenyl (42a)



According to **TP16**, *N*-(thiocyanato)phthalimide (141 mg, 0.50 mmol, 1.00 equiv) was reacted with (2-fluoro-[1,1'-biphenyl]-4-yl)zinc chloride (**1cc**,2.68 mL, 0.28 M in THF, 0.75 mmol, 1.50 equiv) in the presence of $Cu(OAc)_2.H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 95:5) afforded the title compound as a yellow oil (83 mg, 0.36 mmol, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.58–7.44 (m, 6H), 7.40 (ddd, *J* = 10.0, 6.2, 2.0 Hz, 2H).

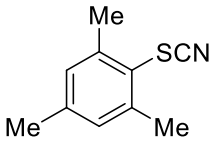
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.9 (d, *J* = 253.7 Hz), 134.1, 132.3 (d, *J* = 4.1 Hz), 130.7 (d, *J* = 13.6 Hz), 128.9 (d, *J* = 3.0 Hz), 128.7 (2C), 128.6 (2C), 125.8 (d, *J* = 3.9 Hz), 124.5 (d, *J* = 8.5 Hz), 117.8 (d, *J* = 26.7 Hz), 109.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 2360, 2158, 1606, 1581, 1558, 1506, 1477, 1447, 1400, 1285, 1267, 1212, 1132, 1083, 1076, 1009, 884, 858, 821, 764, 716, 696, 668, 662.

MS (EI, 70 eV): *m/z* (%) = 229 (100), 202 (10), 170 (46).

HRMS (EI): *m/z* calc. for [$C_{13}H_8FNS$]: 229.0361; found 229.0367.

1,3,5-Trimethyl-2-thiocyanatobenzene (42b)



According to **TP16**, *N*-(thiocyanato)phthalimide (141 mg, 0.50 mmol, 1.00 equiv) was reacted with mesitylzinc chloride (**1ddd**, 2.68 mL, 0.28 M in THF, 0.75 mmol, 1.50 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 95:5) afforded the title compound as a yellow powder (81 mg, 0.46 mmol, 91%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.01 (s, 2H), 2.56 (s, 6H), 2.30 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 142.8 (2C), 141.6, 130.2 (2C), 119.2, 111.0, 22.0 (2C), 21.2.

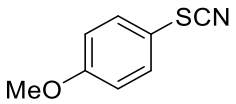
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 2952, 2919, 2851, 2147, 1761, 1599, 1451, 1435, 1377, 1299, 1278, 1251, 1180, 1031, 954, 867, 850, 809, 715, 676.

MS (EI, 70 eV): *m/z* (%) = 177 (100), 162 (22), 144 (72), 115 (38), 91 (55), 69 (17), 51 (34).

HRMS (EI): *m/z* calc. for [$C_{10}H_{11}NS$]: 177.0612; found 177.0615.

m. p. (°C): 62.

1-Methoxy-4-thiocyanatobenzene (42**c)**



According to **TP16**, *N*-(thiocyanato)phthalimide (141 mg, 0.50 mmol, 1.00 equiv) was reacted with (4-methoxyphenyl)zinc chloride (, 2.08 mL, 0.36 M in THF, 0.75 mmol, 1.50 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 95:5) afforded the title compound as a yellow oil (76.8 mg, 0.465 mmol, 93%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.50 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 3.83 (s, 3H).

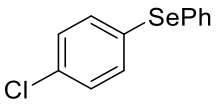
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 161.4, 134.0 (2C), 116.0 (2C), 113.9, 111.8, 55.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3092, 3072, 3019, 2946, 2927, 2840, 2153, 1899, 1589, 1571, 1493, 1460, 1443, 1407, 1295, 1275, 1249, 1181, 1174, 1107, 1087, 1021, 961, 954, 952, 942, 824, 796, 782, 713, 676.

MS (EI, 70 eV): *m/z* (%) = 165 (100), 139 (15), 122 (70), 92 (18), 69 (50), 50 (22).

HRMS (EI): *m/z* calc. for [C_8H_7NOS]: 165.0248; found 165.0245.

(4-Chlorophenyl)(phenyl)selane (43**)**



According to **TP16**, *N*-(selenophenyl)phthalimide (151 mg, 0.50 mmol, 1.00 equiv) was reacted with (4-chlorophenyl)zinc chloride (, 2.08 mL, 0.36 m in THF, 0.75 mmol, 1.50 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 95:5) afforded the title compound as a white solid (76.8 mg, 0.47 mmol, 93%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.42–7.36 (m, 1H), 7.32–7.28 (m, 1H), 7.24–7.18 (m, 2H), 7.18–7.14 (m, 1H).

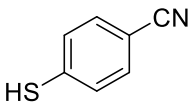
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 134.1 (2C), 133.5, 133.2 (2C), 130.6, 129.6, 129.5 (4C), 127.7.

Analytical data according to literature[150]

[150] S. Saba, J. Rafique, A. L. Braga *Adv. Synth. Catal.* **2015**, *357*, 1446–1452.

7.4 Synthesis of Cathepsin-D Inhibitor 9

4-Mercaptobenzonitrile (46)

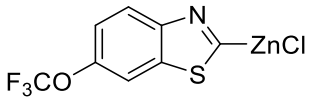


In a dry and argon flushed flask, 4-bromobenzonitrile (**45**) (4.56 g, 25.0 mmol, 1.00 equiv) was dissolved in dry THF (25 mL) and cooled to 0 °C. Then, *i*PrMgCl·LiCl (24 mL, 27.5 mmol, 1.10 equiv) was added dropwise to the reaction mixture. The solution was stirred for 2 h at 0 °C and then all volatiles were removed *in vacuo*. After re-dissolving in dry THF, elementary sulphur (882 mg, 27.5 mmol, 1.10 equiv) was added in one portion and the resulting mixture was stirred for 1 h at 0 °C. Afterwards, 2M HCl (50 mL) were added and the organic layer removed. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers washed with brine (50 mL), dried over $mgSO_4$ and the solvent removed *in vacuo* to afford the titel compound 11 as yellow oil (3.21 g, 23.8 mmol, 95%). The crude product was analytically pure (determined by NMR) and used without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.49 (d, J = 8.4 Hz, 1H), 7.34–7.29 (m, 1H), 3.67 (s, 1H).

Analytical data according to literature[151]

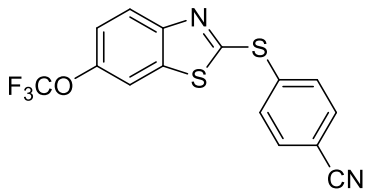
(6-(Trifluoromethoxy)benzo[*d*]thiazol-2-yl)zinc chloride (47)



According to **TP2**, 2-bromo-6-(trifluoromethoxy)benzo[*d*]thiazole (745 mg, 2.50 mmol, 1.00 equiv) was added to a suspension of anhydrous LiCl (159 mg, 3.75 mmol, 1.50 equiv) and magnesium turnings (122 mg, 5.00 mmol, 2.00 equiv) in dry THF (5 mL). The mixture was stirred at 25 °C overnight and then $ZnCl_2$ (1 M in THF, 3.0 mL, 3.00 mmol, 1.20 equiv) was added as a solution in THF at 0 °C. Titration with iodine gave a concentration of 0.32 mmol/mL corresponding to a yield of 75%.

[151] D. L. Orsi, B. J. Easley, A. M. R. A. Altman *Org. Lett.* **2017**, *19*, 1570–1573.

4-((6-(Trifluoromethoxy)benzo[*d*]thiazol-2-yl)thio)benzonitrile (48)



According to **TP16**, 4-((1,3-dioxoisoindolin-2-yl)thio)benzonitrile (**47**, 140 mg, 0.50 mmol, 1.00 equiv) was reacted with (6-(trifluoromethoxy)benzo[*d*]thiazol-2-yl)zinc chloride (12, 1.72 mL, 0.32 M in THF, 0.55 mmol, 1.10 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$. Purification by flash column chromatography on silica gel (hexane:EtOAc 4:1) afforded the title compound as a white powder (166 mg, 0.47 mmol, 94%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.93 (d, J = 8.9 Hz, 1H), 7.82–7.69 (m, 4H), 7.63 (dd, J = 2.3, 1.1 Hz, 1H), 7.34 (ddd, J = 8.9, 2.5, 1.0 Hz, 1H).

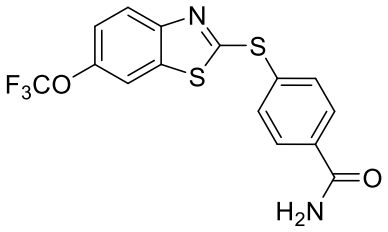
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 165.5, 151.9, 146.5, 136.7, 133.7 (2C), 133.2 (2C), 123.4, 120.5, 120.5 (q, J = 257.8 Hz), 117.9, 113.8, 113.8, 113.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2359, 2231, 1604, 1592, 1485, 1467, 1443, 1407, 1310, 1250, 1217, 1193, 1164, 1121, 1062, 1013, 995, 944, 876, 862, 831, 814, 683, 668.

MS (EI, 70 eV): *m/z* (%) = 351 (16), 102 (11), 69 (100).

HRMS (EI): *m/z* calc. for $[C_{15}H_7F_3N_2OS_2]$: 351.9952; found 351.9950.

4-((6-(Trifluoromethoxy)benzo[*d*]thiazol-2-yl)thio)benzamide



To a 25 mL round-bottom flask equipped with stirring bar were added 4-((6-(trifluoromethoxy)benzo[*d*]thiazol-2-yl)thio)benzonitrile (883 mg, 2.50 mmol, 1.00 equiv), acetaldoxime (296 mg, 5.00 mmol, 2.00 equiv), nickel(II) chloride hexahydrate (59 mg, 0.25 mmol, 10.0 mol%) and H_2O (10 mL). The mixture was heated to reflux for 6 h. After cooling to r.t., the solution was directly evaporated to dryness and the residue was purified by flash column chromatography on silica gel (hexane:EtOAc 4:1) to give 4-((6-(trifluoromethoxy)benzo[*d*]thiazol-2-yl)thio)benzamide as a white solid (843 mg, 2.23 mmol, 91%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.88–7.79 (m, 3H), 7.77–7.70 (m, 2H), 7.51 (dd, *J* = 2.2, 1.1 Hz, 1H), 7.24 (ddd, *J* = 8.8, 2.4, 0.9 Hz, 1H), 5.82 (d, *J* = 168.6 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.3, 167.9, 152.1, 146.1, 136.4, 134.9, 134.6 (2C), 134.3, 128.8 (2C), 123.0, 120.4 (q, *J* = 257.7 Hz), 120.3, 113.7.

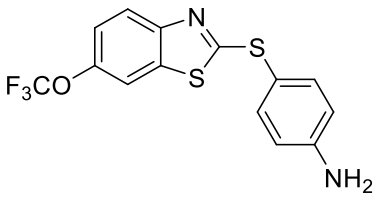
^{19}F NMR (377 MHz, $CDCl_3$): δ / ppm = -58.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2359, 2231, 1604, 1592, 1485, 1467, 1443, 1407, 1310, 1250, 1217, 1193, 1164, 1121, 1062, 1013, 995, 944, 876, 862, 831, 814, 683, 668.

MS (EI, 70 eV): *m/z* (%) = 370 (100), 217 (10), 152 (11), 120 (17), 69 (80).

HRMS (EI): *m/z* calc. for [$C_{15}H_9F_3N_2O_2S_2$]: 370.0058; found 370.0053.

4-((6-(Trifluoromethoxy)benzo[*d*]thiazol-2-yl)thio)aniline (49)



To a stirred solution of KOH (126 mg, 2.25 mmol, 5.00 equiv) in H_2O (2 mL) was added bromine (30 µL, 0.54 mmol, 1.20 equiv) at 0 °C. The mixture was stirred at 0 °C for 30 min. Then, 4-((6-(trifluoromethoxy)benzo[*d*]thiazol-2-yl)thio)benzamide (168 mg, 0.45 mmol, 1.00 equiv) was added dropwise as a solution in THF (2 mL). The resulting mixture was stirred for 2.5 h at 70 °C and subsequently extracted with CH_2Cl_2 (3 x 10 mL), dried over $mgSO_4$ and the solvent removed *in vacuo*. Purification by flash column chromatography on silica gel afforded the title compound as white solid (97 mg, 0.28 mmol, 63%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 (d, J = 8.9 Hz, 1H), 7.44–7.39 (m, 3H), 7.19–7.14 (m, 1H), 6.71–6.65 (m, 2H), 3.98 (s, 2H).

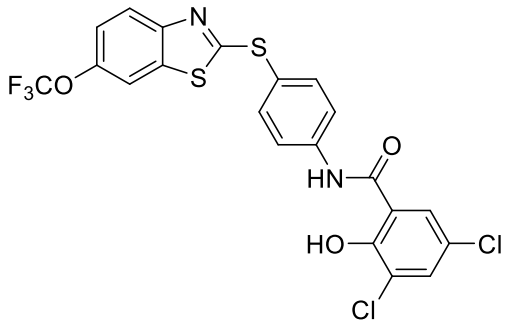
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 175.1, 152.9, 149.3, 145.4, 137.7, 136.1, 122.2, 120.5 (q, J = 257.3 Hz) 119.9, 116.1, 116.0, 113.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3003, 2358, 2341, 1748, 1709, 1433, 1420, 1359, 1220, 1092, 973, 902, 785, 668.

MS (EI, 70 eV): *m/z* (%) = 342 (100), 217 (10), 124 (30), 92 (12), 69 (76).

HRMS (EI): *m/z* calc. for [$C_{14}H_9F_3N_2OS_2$]: 342.0108; found 342.0105.

3,5-Dichloro-2-hydroxy-*N*-(4-((6-(trifluoromethoxy)benzo[*d*]thiazol-2-yl)thio)phenyl)benzamide (44)



To a stirred solution of iodine (61 mg, 0.24 mmol, 1.20 equiv) in dry CH_2Cl_2 (2 mL) was added with one portion of PPh_3 (63 mg, 0.24 mmol, 1.20 equiv) at 0 °C. 4-((6-(trifluoromethoxy) benzo[*d*]thiazol-2-yl)thio)aniline (**49**, 82 mg, 0.24 mmol, 1.20 equiv) was added under continuously stirring over 5 min. Subsequently, the resulting mixture was treated with 3,5-dichloro-2-hydroxybenzoic acid (41 mg, 0.20 mmol, 1.00 equiv) and stirred for 5 min, followed by addition of triethylamine (56 µL, 0.40 mmol, 2.00 equiv). After the solution was allowed to warm up to 25 °C and stirred for 10 min, the crude mixture was concentrated under reduced pressure then purified by flash column chromatography on silica gel(hexane:EtOAc 4:1) to give the title compound (64 mg, 0.12 mmol, 61% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 10.46 (s, 1H), 8.01 (d, J = 2.5 Hz, 1H), 7.74–7.68 (m, 4H), 7.68–7.62 (m, 3H), 7.54–7.50 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ / ppm = 167.6, 165.2, 155.5, 148.1, 146.6 (q, J = 257.9 Hz), 138.0, 135.3, 132.3, 131.3, 130.1, 126.8, 123.8, 122.2 (2C), 121.5, 120.8, 119.5, 118.2 (2C), 117.4, 113.9.

Analytical data according to literature[116]