Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

Metalation and Amination of *N*-Heterocycles and the Halogen/Zinc Exchange of Aryl Halides

von

Moritz Balkenhohl

aus

Speyer

2019

ERKLÄRUNG

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Paul Knochel betreut.

EIDESSTATTLICHE VERSICHERUNG

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, 18.04.2019

……..……

(Moritz Balkenhohl)

Dissertation eingereicht am:	18.04.2019
1. Gutachter:	Prof. Dr. Paul Knochel
2. Gutachter:	Prof. Dr. Oliver Trapp
Mündliche Prüfung am:	27.05.2019

This work was carried out from June 2016 to May 2019 under the guidance of Prof. Dr. Paul Knochel at the Department of Chemistry of the Ludwig-Maximilians-Universität, Munich.

First I would like to thank Prof. Dr. Paul Knochel for giving me the great opportunity in doing my Ph.D. thesis in his group. His guidance and support has helped me a lot during the past three years and for this I am extremely grateful.

I would also like to express my gratitute to Prof. Dr. Oliver Trapp for agreeing to be second reviewer of my thesis, as well as Prof. Dr. Franz Bracher, Prof. Dr. Manfred Heuschmann, Prof. Dr. Konstantin Karaghiosoff and Dr. Henry Dube for their interest shown in this manuscript by accepting to be members of my defense committee. In addition, special thanks go to Prof. Dr. Hendrik Zipse for the collaborations in the past years, I enjoyed it a lot. Also, I would like to thank Prof. Dr. Konstantin Karaghiosoff for his endless motivation towards chemistry and that he was always willing to meet and to discuss chemistry, thank you so much! Thank you Prof. Dr. Eva Hevia for the nice collaboration on the halogen/zinc exchange!

Furthermore, I would like to thank Juri Skotnitzki, Ferdinand Lutter, Maximilian Hofmayer and Benjamin Heinz for careful correction of this manuscript.

Also, I would like to thank all past and present members of the Knochel group, it has been a great pleasure to work with you in the last three years. Especially I want to mention all former and current lab mates of F2.012, namely Dr. Sarah Fernandez, Dr. Alicia Castelló-Mico, Dr. Diana Haas, Dr. Johannes Nickel, Denise Cibu, Maximilian Hofmayer, Lucie Grokenberger, Ferdinand Lutter, Benjamin Heinz and Dr. Jie Li. It was a great pleasure working with you all!

Thank you Jeffrey and Diana for helping me to get started in the Knochel group! Benny, thank your for your help in the lab in the last year, I wish you a successful PhD and an amazing time in the Knochel group. Thank you Alex for the nice collaboration on the halogen/zinc exchange! Thanks Lucie for always being so cheerful and happy! Ferdi, I want to thank you for our nice chemistry discussions and the joy we share upon developing new chemistry. Max! Thanks a lot for the nice time in the last years as my lab partner, I couln't have asked for a better one, especially the similar taste in music always made things easy in the everyday lab life. Thank you Juri for being the way you are: always happy and always motivated - this attitude really keeps things going at all times! I will miss the "Malle" days and you as as well! Dear Doro, thank you for your help in the last year, it was invaluable to be able to rely on you, especially in the past few months, thank you so so much.

Moreover, I want to say thank you to my former students Benjamin Heinz, Bruno Salgues, Takahiro Hirai, Vasiliki Valsamidou, Tobias Lenz, Thomas Abegg, and Marian Ebeling for their excellent contributions during their internships. I would not have been able to finish off all this work in this time without you!

I would also like to thank Peter Dowling, Sophie Hansen, Dr. Vladimir Malakhov and Yulia Tsvik for their help organizing everyday life in the lab and the office, it was nice to be able to rely on your work! Also, the analytical team of the LMU did a really great job and I am grateful for their invaluable help.

I would like to thank my mother Iris, my siblings Jakob and Hannah, and especially my father, without whom I would never have found the passion and motivation towards chemistry which I feel today.

Finally, I thank Michelle, who has been guiding me outside of the chemistry life for the past eight years, and has always supported me in what I like doing most. You mean the world to me and I am looking forward to our future.

Parts of this Ph.D. Thesis have been published

A) Communications

1) "Transition-Metal-Free Amination of Pyridine-2-sulfonyl Chloride and Related *N*-Heterocycles Using Magnesium Amides"
M. Balkenhohl, C. François, D. Sustac Roman, P. Quinio, P. Knochel, *Org. Lett.* **2017**, *19*, 536–539.

2) "Zn-, Mg-, and Li-TMP Bases for the Successive Regioselective Metalations of the 1,5-Naphthyridine Scaffold (TMP = 2,2,6,6-Tetramethylpiperidyl)"
M. Balkenhohl, R. Greiner, I. S. Makarov, B. Heinz, K. Karaghiosoff, H. Zipse, P. Knochel, *Chem. Eur. J.* **2017**, *23*, 13046–13050.

3) "Regioselective Metalation and Functionalization of the Pyrazolo[1,5-*a*]pyridine Scaffold Using Mg- and Zn-TMP Bases"
M. Balkenhohl, B. Salgues, T. Hirai, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2018**, *20*, 3114–3118.

4) "Amination of Phosphorodiamidate-Substituted Pyridines and Related *N*-Heterocycles with Magnesium Amides"
M. Balkenhohl, B. Heinz, T. Abegg, P. Knochel, *Org. Lett.* **2018**, *20*, 8057–8060.

5) "Amination of 2-Pyridinesulfonic and 8-Quinolinesulfonic Acids with Magnesium Amides"
M. Balkenhohl, V. Valsamidou, P. Knochel, *Eur. J. Org. Chem.* **2019**,
DOI: 10.1002/ejoc.201900057.

6) "Lewis Acid Directed Regioselective Metalations of Pyridazine"
M. Balkenhohl, H. Jangra, T. Lenz, M. Ebeling, H. Zipse, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, DOI: 10.1002/anie.201903839.

7) "Preparation of Polyfunctional Arylzinc Organometallics in Toluene via Halogen/Zinc Exchange Reactions"
M. Balkenhohl, D. S. Ziegler, A. Desaintjean, L. J. Bole, A. R. Kennedy, E. Hevia, P. Knochel, **2019**, manuscript in preparation.

B) Review

1) "Regioselective C-H Activation of Substituted Pyridines and other Azines Using Mg- and Zn-TMP-Bases"
M. Balkenhohl, P. Knochel, *SynOpen* **2018**, *2*, 78–95.

Für Papa

Abbreviations

AcOH	acetic acid
An	anisyl
aq.	aqueous
Ar	undefined aryl substituent
ATR	attenuated total reflection
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
ca.	circa
calc.	calculated
CCDC	Cambridge Crystallographic Data Center
CDER	Center for Drug Evaluation and Research
d	doublet (NMR)
DABCO	1,4-diazabicyclo[2.2.2]octan
DABSO	1,4-diazabicyclo[2.2.2]octan-bis(sulfur dioxide)
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
E-X	electrophile
EI	electron ionization (MS)
e.g.	for example
equiv	equivalents
ESI	electrospray ionization (MS)
Et	ethyl
etc.	*et cetera*
FDA	U.S. Food and Drug Administration
FG	functional group
GC	gas chromatography
Het	undefined heteroaryl substituent
Hex	hexyl
HRMS	high resolution mass spectroscopy
i	*iso*
IR	infrared
J	coupling constant (NMR)
m	multiplet (NMR)

M	$mol \cdot L^{-1}$
Me	methyl
Met	metal
M.p.	melting point
MS	mass spectrometry
MTBE	methyl-*tert*-butylether
NMP	1-methylpyrrolidin-2-one
NMR	nuclear magnetic resonance
o	*ortho*
Ph	phenyl
Piv	pivaloyl
PMDTA	bis(2-dimethylaminoethyl)methylamin
ppm	parts per million
Pr	propyl
q	quartet (NMR)
R	undefined organic substituent
s	*sec*
s	singulet (NMR)
sat.	saturated
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	*tert*
t	triplett (NMR)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tf	trifluoromethanesulfonate
TLC	thin layer chromatography
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
Tol	tolyl
TP	typical procedure

TABLE OF CONTENTS

A. INTRODUCTION

1 Overview

In the year 2018, the United States Food and Drug Administration's Center for Drug Evaluation and Research (FDA, CDER) has approved as many as 59 novel drugs.[1] This is a record in the FDAs approvals since 1993, with the previous number lying at 53 drugs in the year 1996. Out of the estimated most potential blockbuster approvals for 2018, eight out of nine small molecule drugs contain a nitrogen heterocycle, showing the incredible value of heteroaromatic scaffolds in modern pharmaceutical chemistry. Baricitinib (Incyte/Eli Lilly, rheumatoid arthritis), apalutamide (Johnson & Johnson, prostate cancer), bictegravir (Gilead Sciences, HIV), and tezacaftor (Vertex Pharmaceuticals, cystic fibrosis) belong to the most promising aprovals of the year 2018 and contain numerous *N*-heterocycles such as a pyridine, an indole or a pyrazole (Figure 1).[1]

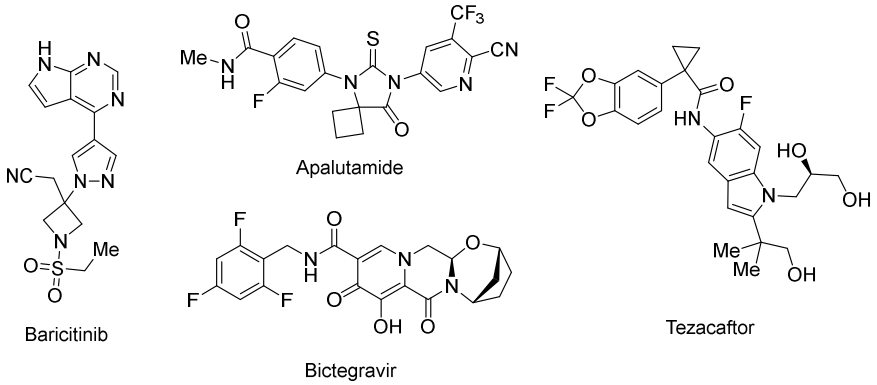


Figure 1: Selected potential blockbuster drugs approved by the FDA in 2018.[1]

However, not only these well established ring structures are represented, but also less investigated heterocycles, such as a 7*H*-pyrrolo[2,3-*d*]pyrimidine (baracitinib) or a pyrido[1,2-*a*]pyrazine (bictegravir) structure can be detected. This indicates that research in the field of nitrogen containing heterocycles is yet of utmost importance, and, that especially less common stuctures can lead to breakthroughs in modern medicinal chemistry.[2] A research field which allows the preparation and functionalization of various (hetero)aromatic scaffolds is organometallic chemistry. By being able to create a carbon-metal bond *via* various methods such as oxidative insertion, halogen/metal exchange, directed metalation or transmetalation, a plethora of functionalizations, including the formation of C-C and C-N bonds, have been made possible.[3] Therefore, it is evident, that making use of organometallic chemistry to conduct research towards the functionalization of challenging *N*-heterocycles and to develop novel organometallic transformations is of high interest.

---

[1] A. Mullard, *Nat. Rev. Drug Discovery* **2019**, *18*, 85–89.
[2] a) W. R. Pitt, D. M. Parry, B. G. Perry, C. R. Groom, *J. Med. Chem.* **2009**, *52*, 2952–2963; b) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.
[3] a) W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1–46; b) D. Seyferth, *Organometallics* **2006**, *25*, 2–24. c) *Handbook of Functionalized Organometallics Vol. 1 and 2* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.

2 Amination of Arenes and Heteroarenes

2.1 Transition-Metal-Catalyzed Amination

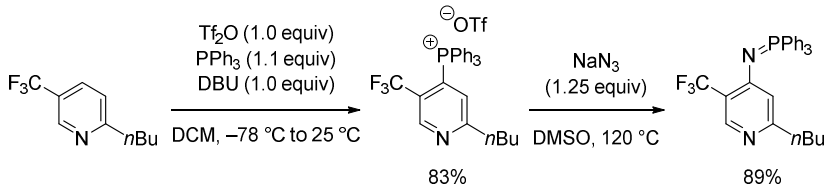
Transition-metal-catalyzed amination reactions have been pioneered by Ullman,[4] Migita,[5] Buchwald,[6] and Hartwig[7]. In 1901, Ullman reported the first copper mediated *ipso*-substitution of an aryl halide.[4] However, it was not until 1983, when Migita performed the first palladium-catalyzed amination reactions between aryl bromides and tin amides.[5] The first tin-free catalysis was developed independently by Buchwald and Hartwig in 1995, followed by several optimizations and reaction scope expansions by e.g. varying the reaction conditions, the palladium catalyst or the phosphine ligand.[6,7] This eventually made the Buchwald-Hartwig amination reaction one of the most versatile reactions for the construction of the C-N bond. However, transition-metal-catalysts are expensive and often toxic.[8] Therefore, the development of transition-metal-free alternatives for the formation of the carbon nitrogen bond is highly desirable.

2.2 Transition-Metal-Free Amination

Not only have transition-metal-catalyzed reactions made huge progress in the last decades, but also have there been several developments towards alternative, transition-metal-free coupling reactions.[9] Especially, the amination of *N*-heterocycles, including pyridines, has gained interest over the years. The main approach is the use of nucleophilic aromatic substitution reactions (S_NAr) between amines or amides and activated 2-functionalized pyridines, such as 2-halo, or 2-cyanopyridines.[10] Also, 2-pyridyl trifluoromethanesulfonates, dihydrothiazolopyridinium salts, or pyridine-*N*-oxides have been employed

[4] a) F. Ullmann, J. Bielecki, *Ber. Dtsch. Chem. Ges.* **1901**, 34, 2174–2185; b) J. Lindley, *Tetrahedron* **1984**, *40*, 1433–1456.
[5] K. Masanori, K. Masayuki, M. Toshihiko, *Chem. Lett.* **1983**, *12*, 927–928.
[6] a) A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1995**, *34*, 1348–1350; b) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805–818; c) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125–146; d) S. L. Buchwald, A. Muci, *Top. Curr. Chem.* **2002**, *219*, 133–209.
[7] a) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609–3612; b) J. F. Hartwig, *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067; c) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 852–860; d) J. Hartwig, *Pure Appl. Chem.* **1999**, *71*, 1417–1423.
[8] K. S. Egorova, V. P. Ananikov, *Angew. Chem. Int. Ed.* **2016**, *55*, 12150–12162.
[9] a) T. Hatakeyama, Y. Yoshimoto, S. K. Ghorai, M. Nakamura, *Org. Lett.* **2010**, *12*, 1516–1519; b) Q. Xiao, L. Tian, R. Tan, Y. Xia, D. Qiu, Y. Zhang, J. Wang, *Org. Lett.* **2012**, *14*, 4230–4233; c) C.-L. Sun, Z.-J. Shi, *Chem. Rev.* **2014**, *114*, 9219–9280; d) V. Tona, A. de la Torre, M. Padmanaban, S. Ruider, L. González, N. Maulide, *J. Am. Chem. Soc.* **2016**, *138*, 8348–8351; e) J. J. Farndon, X. Ma, J. F. Bower, *J. Am. Chem. Soc.* **2017**, *139*, 14005–14008.
[10] a) L. Pasumansky, A. R. Hernández, S. Gamsey, C. T. Goralski, B. Singaram, *Tetrahedron Lett.* **2004**, *45*, 6417–6420; b) J. M. Penney, *Tetrahedron Lett.* **2004**, *45*, 2667–2669; c) S. Narayan, T. Seelhammer, R. E. Gawley, *Tetrahedron Lett.* **2004**, *45*, 757–759; d) B. C. Hamper, E. Tesfu, *Synlett* **2007**, 2257–2261; e) J. L. Bolliger, C. M. Frech, *Tetrahedron* **2009**, *65*, 1180–1187; f) J. G. Kim, E. H. Yang, W. S. Youn, J. W. Choi, D.-C. Ha, J. D. Ha, *Tetrahedron Lett.* **2010**, *51*, 3886–3889; g) K. Walsh, H. F. Sneddon, C. J. Moody, *ChemSusChem* **2013**, *6*, 1455–1460.

as substrates.[11] A recent approach towards the amination of pyridines and other diazines is the reaction of heterocyclic phosphonium salts with sodium azide, leading to iminophosphoranes, which can be further functionalized, in good to excellent yields (Scheme 1).[12]

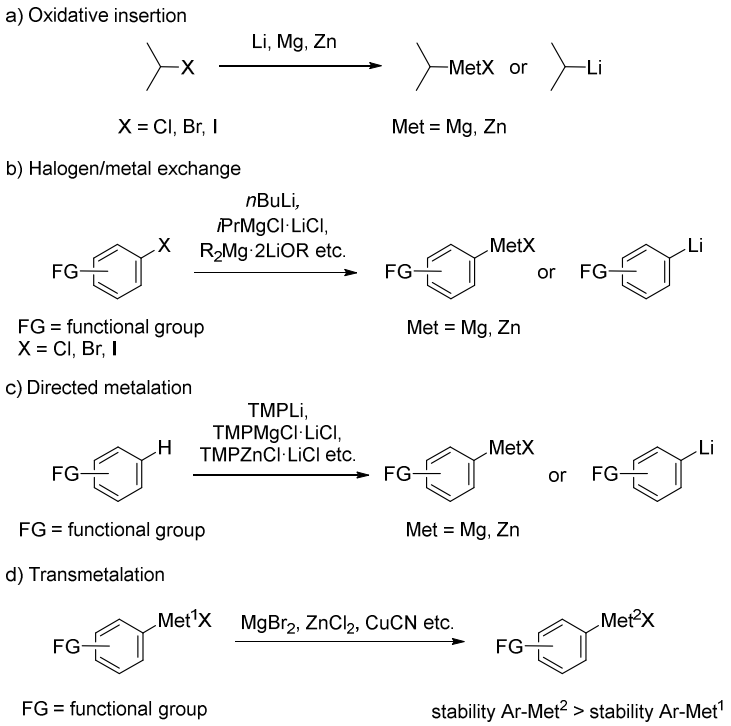


Scheme 1: Selected example for for the metal-free amination of heterocylic phosphonium salts using sodium azide.

3 Generation of Polyfunctional Organomagnesium, -Zinc, and -Lithium Reagents and their Use in Organic Synthesis

With the discovery of diethylzinc in 1848 and the Grignard reagent in 1901, the era of organometallic chemistry began.[13] Since then, a large variety of carbon-metal bond forming reactions were discovered and employed in carbon-carbon and carbon-heteroatom bond formation. The first major method to generate an organometallic species is the oxidative insertion of a metal into a carbon halogen bond (Scheme 2a).[13] The second major pathway is the halogen/metal exchange reaction, in which a thermodynamically less stable metal species reacts with an alkyl or aryl halide to form the more stable organometallic (Scheme 2b).[14] The third method is the directed metalation, in which a base abstracts ("metalates") a proton, giving rise to the desired metal species (Scheme 2c).[15] The final pathway is the transmetalation reaction in which an existing metal species reacts with a metal salt, forming a more covalent and thus stable carbon metal bond (Scheme 2d).[3b]

[11] a) S. Cacchi, A. Carangio, G. Fabrizi, L. Moro, P. Pace, *Synlett* **1997**, *12*, 1400–1402; b) J. Yin, B. Xiang, M. A. Huffman, C. E. Raab, I. W. Davies, *J. Org. Chem.* **2007**, *72*, 4554–4557; c) B. Poola, W. Choung, M. H. Nantz, *Tetrahedron* **2008**, *64*, 10798–10801.
[12] a) K. Murakami, S. Yamada, T. Kaneda, K. Itami, *Chem. Rev.* **2017**, *117*, 9302–9332; b) C. Patel, M. Mohnike, M. C. Hilton, A. McNally, *Org. Lett.* **2018**, *20*, 2607–2610.
[13] a) E. Frankland, *J. Chem. Soc.* **1848**, *2*, 263; b) V. Grignard, *Compt. Rend. Acad. Sci.* **1900**, *130*, 1322; c) V. Grignard, *Ann. Chim* **1901**, *24*, 433–490.
[14] a) G. Wittig, U. Pockels, H. Droge, *Chem. Ber.* **1938**, *71*, 1903–1912; b) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106–109; c) W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1–46; d) D. Seyferth, *Organometallics* **2006**, *25*, 2–24.
[15] a) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794–9824; b) T. Klatt, J. T. Markiewicz, C. Sämann, P. Knochel, *J. Org. Chem.* **2014**, *79*, 4253–4269; c) M. Balkenhohl, P. Knochel, *SynOpen* **2018**, *2*, 78–95.

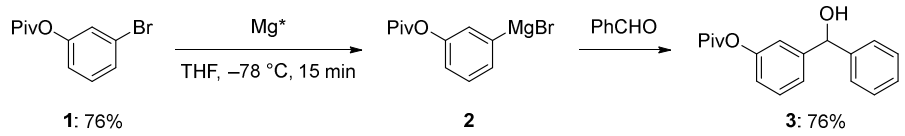


Scheme 2: The four pathways for the generation of polyfunctional organomagnesium, -zinc, and -lithium reagents.

3.1 Oxidative Insertion

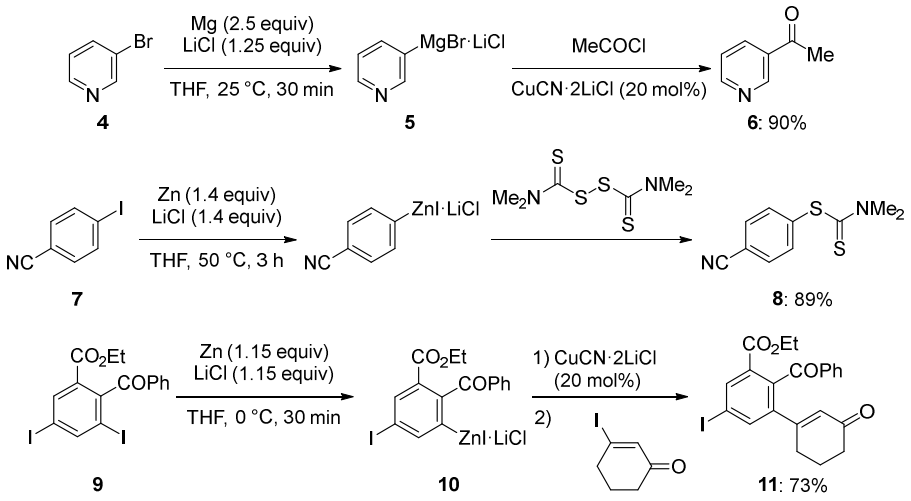
The oldest method for generating organometallic reagents is the oxidative insertion, pioneered by Frankland and Grignard.[13] A limiting factor for this transformation was the reactivity of the zerovalent metal. In the past centuries, chemists have developed several methods to improve the oxidative insertion reaction by activating the metal species.[16] Amongst others, grinding the metal, addition of activating substances such as iodine or dibromotetrachloroethane, the use of polar solvents or the addition of inorganic salts have all in all led to an improvement of the oxidative insertion reaction.[16] Major improvements have been made by Rieke, who prepared activated metals *via* reduction of metal salts with e.g. lithium or potassium.[17] With these activated metals it is possible to perform the oxidative insertion reaction in the presence of functional groups such as esters or nitriles, since the insertion step proceeds even at low temperatures. Bromoarene **1**, for example, reacts with Rieke magnesium (Mg*) to form the desired magnesium species **2**, which is quenched with benzaldehyde to yield the expected alcohol **3** in 76% yield (Scheme 3).[18]

[16] R. D. Rieke, *Acc. Chem. Res.* **1977**, *10*, 301–306.
[17] a) R. D. Rieke, *Science* **1989**, *246*, 1260–1264; b) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445–1453; c) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925–1956.
[18] J.-s. Lee, R. Velarde-Ortiz, A. Guijarro, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428–5430.



Scheme 3: Oxidative insertion of Rieke magnesium to an aryl bromide at low temperature.

Also, sonification of reaction mixtures facilitates the synthesis of organozinc reagents.[19] The addition of an inorganic salt such as LiCl leads to improved results in the formation of sensitive organometallic reagents, allowing the preparation of a wide variety of sensitive organomagnesium and zinc species.[20] The magnesium insertion to 3-bromopyridine (**4**) in the presence of lithium chloride proceeds smoothly, producing the magnesium species **5** which undergoes a copper mediated acylation reaction with acetyl chloride, giving ketone **6** in 90% yield.[20] Zinc insertion to 4-iodobenzonitrile (**7**) followed by quenching with tetramethylthiuram disulfide gives the dithiocarbamate **8** in 89% yield.[20] Interestingly, in the case of the di-iodo substituted arene **9**, the halogen which is positioned *ortho* to a directing group is favored regarding site selectivity for the insertion reaction. This phenomenon is known as the directed *ortho*-insertion (DoI).[20] The zinc species **10** prepared *via* directed *ortho*-insertion readily reacts with 3-iodocyclohexenone in the presence of CuCN·2LiCl (20 mol%) to give the substitution product **11** in 73% yield (Scheme 4).[20] Interstingly, the role of LiCl has also been investigated using fluorescence microscopy.[21]



Scheme 4: Preparation of various sensitive (hetero)arylzinc and -magnesium reagents *via* oxidative insertion.

[19] a) T. Kentaro, *Chem. Lett.* **1993**, *22*, 469–472; b) T. Kentaro, S. Yasuaki, S. Ken, *Chem. Lett.* **1994**, *23*, 2055–2058.

[20] a) R. Ikegami, A. Koresawa, T. Shibata, K. Takagi, *J. Org. Chem.* **2003**, *68*, 2195–2199; b) S. Huo, *Org. Lett.* **2003**, *5*, 423–425; c) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040–6044; d) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358–12359; e) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802–6806; f) T. D. Blümke, T. Klatt, K. Koszinowski, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9926–9930.

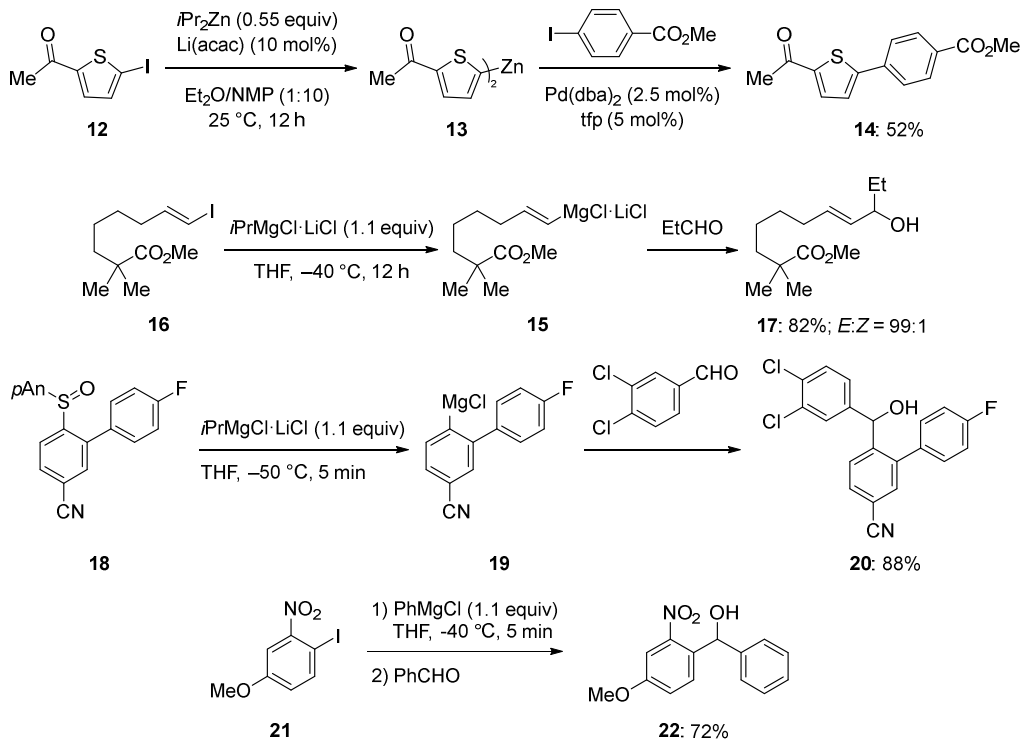
[21] a) C. Feng, D. W. Cunningham, Q. T. Easter, S. A. Blum, *J. Am. Chem. Soc.* **2016**, *138*, 11156–11159; b) C. Feng, Q. T. Easter, S. A. Blum, *Organometallics* **2017**, *36*, 2389–2396.

3.2 Halogen/Metal Exchange

The halogen/metal exchange, first discovered by Gilman and Wittig,[14] is a versatile reaction in the synthesis of organometallic reagents.[22] The driving force of the halogen/metal exchange reaction is the formation of a thermodynamically more stable metal species in comparison to the exchange reagent itself, with the stability of the organometallic species decreasing from C(sp) > $C(sp^2_{vinyl})$ > $C(sp^2_{aryl})$ > $C(sp^3_{primary})$ > $C(sp^3_{secondary})$ > $C(sp^3_{tertiary})$.[23] With the development of the turbo-Grignard *i*PrMgCl·LiCl in 2004, a wide range of functionalized magnesium organometallics were preparable due to the higher kinetic activity in comparison to the salt free predecessor *i*PrMgCl.[24] Almost simultaneously to the improved halogen/magensium exchange reagent, a Li(acac) catalyzed iodine/zinc exchange was reported.[25] Li(acac) leads to the formation of catalytic amounts of a more reactive zincate species, which reacts with various aryl iodides bearing sensitive functional groups such as ketones or aldehydes. For example, the iodothiophene **12** reacts with *i*Pr_2Zn (0.55 equiv) in the presence of Li(acac) (10 mol%) leading to the diarylzinc species **13**, which is subsequently submitted to a palladium catalyzed Negishi cross-coupling,[26] producing the arylated thiophene **14** in 52% yield. Using *i*PrMgCl·LiCl, not only (hetero)aryl, but also alkenyl halides undergo halogen/metal exchange reactions. The alkenyl magnesium species **15** formed by reaction of an alkenyl halide **16** with *i*PrMgCl·LiCl readily reacts with ethanal, providing alcohol **17** in 82% yield and excellent diastereoselectivity (*E*/*Z* = 99:1).[27] Furthermore, the turbo Grignard undergoes facile sulfoxide/magnesium exchange reactions. Thus, treatment of the sulfoxide **18** with *i*PrMgCl·LiCl (1.1 equiv) at –50 °C for 5 min results in the formation of the desired magnesium species **19**, which is quenched with a halogenated benzaldehyde, producing the alcohol **20** in 88% yield.[28] The preparation of organometallic reagents *via* oxidative insertion is challenging in the presence of nitro groups, since they are prone to undergo single electron transfer processes during the reaction.[29] However, when a nitro-substituted iodoanisole **21** is treated with the milder exchange reagent PhMgCl, a halogen/metal exchange proceeds rapidly at –40 °C, and the metal species can be quenched with benzaldehyde, leading to arene **22** in 72% yield (Scheme 5).[29]

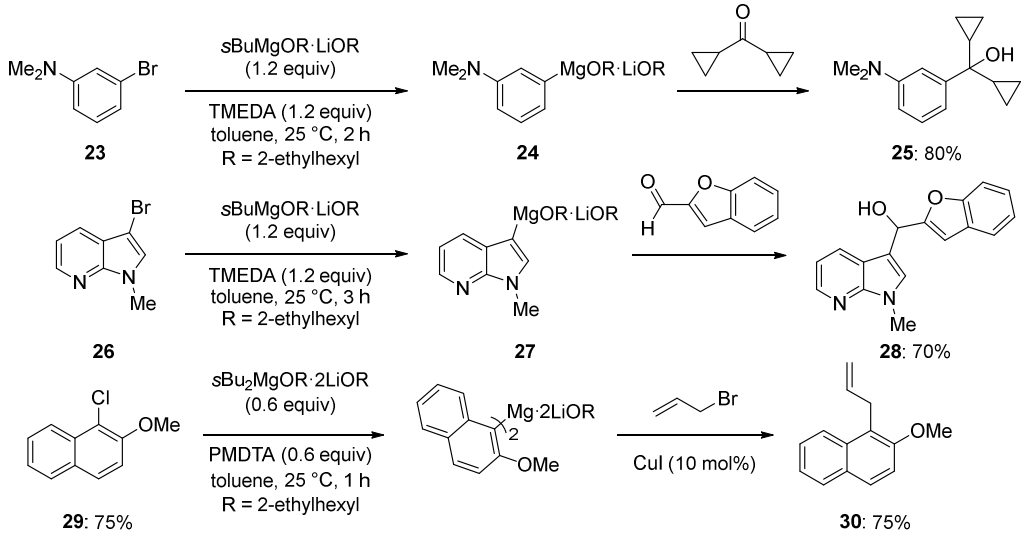
---

[22] a) W. F. Bailey, E. R. Punzalan, *J. Org. Chem.* **1990**, *55*, 5404–5406; b) E. Negishi, D. R. Swanson, C. J. Rousset, *J. Org. Chem.* **1990**, *55*, 5406–5409; c) C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983–3985; For reviews, see: d) D. Tilly, F. Chevallier, F. Mongin, P. C. Gros, *Chem. Rev.* **2014**, *114*, 1207-1257; e) R. Li-Yuan Bao, R. Zhao, L. Shi, *Chem. Commun.* **2015**, *51*, 6884–6900; f) D. S. Ziegler, B. Wei, P. Knochel, *Chem. Eur. J.* **2019**, *25*, 2695–2703.
[23] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733–738.
[24] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333–3336.
[25] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017–1021.
[26] a) A. O. King, N. Okukado, E.-i. Negishi, *J. Chem. Soc., Chem. Commun.* **1977**, 683; b) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540.
[27] H. Ren, A. Krasovskiy, P. Knochel, *Org. Lett.* **2004**, *6*, 4215–4217.
[28] C. B. Rauhut, L. Melzig, P. Knochel, *Org. Lett.* **2008**, *10*, 3891–3894.
[29] I. Sapountzis, P. Knochel, *Angew. Chem.* **2002**, *114*, 1680–1681.



Scheme 5: Various halogen/metal exchange reactions using *i*Pr$_2$Zn, *i*PrMgCl·LiCl, and PhMgCl.

Recently, a new class of exchange reagents has been developed, allowing not only a rapid bromine/magnesium, but also a chlorine/magnesium exchange, using lithium alkoxide complexed dialkylmagnesium reagents.[30] Additionally, these reagents are soluble in unpolar hydrocarbons and therefore enable the generation of highly reactive magnesium reagents in toluene. Electron rich 3-bromo-*N*,*N*-dimethylaniline (**23**) is converted into the corresponding magnesium species **24** using *s*BuMgOR·LiOR (R = 2-ethylhexyl, 1.2 equiv) in the presence of TMEDA at room temperature within



Scheme 6: The halogen/magnesium exchange on aryl bromides and chlorides in toluene.

[30] D. S. Ziegler, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 6701–6704.

3 h. This metal species **24** reacts with dicyclopropylketone to give **25** in 80% yield. Also the azaindole **26** is converted under similar conditions to the corresponding magnesium species **27**, which, upon quenching with 2-benzofurancarboxaldehyde, gives alcohol **28** in 70% yield. Finally, the dialkylmagnesium reagent sBu$_2$Mg·2LiOR (R = 2-ethylhexyl, 0.6 equiv) reacts with an electron rich aryl chloride **29** bearing a methoxy group in *ortho* position, to afford, after quenching with allyl bromide in the presence of CuI (10 mol%), the functionalized naphthalene **30** in 75% yield (Scheme 6).

3.3 Directed Metalation

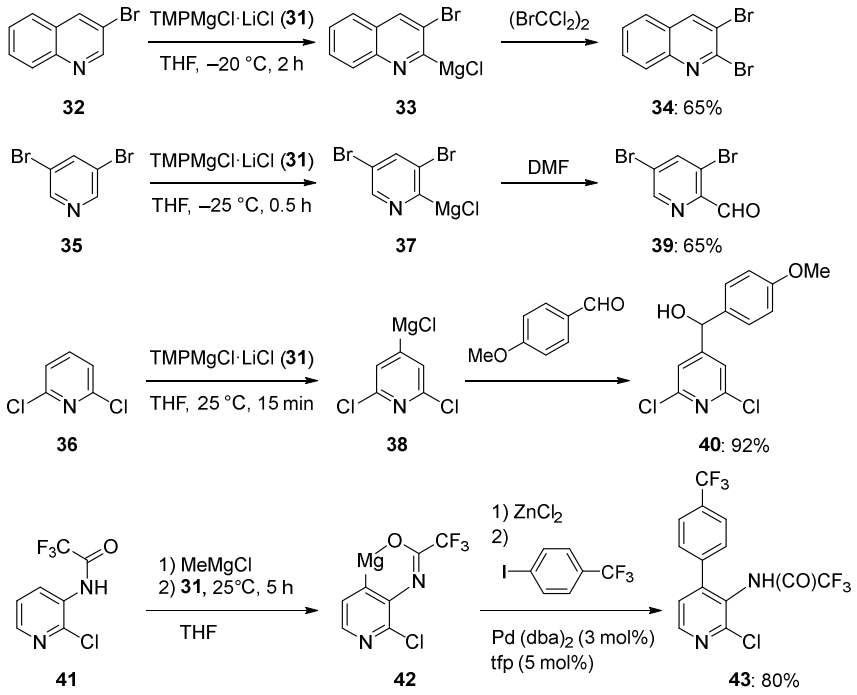
A possibility to generate a metal species without requiring a carbon-halogen bond (as in chapters 3.1 and 3.2) is the directed metalation.[15c] In this case, a base deprotonates ("metalates") a substrate, thus forming a carbon-metal bond. Initially discovered by Gilman[31] and Wittig[32], the directed metalation was pioneered by Snieckus,[33] Hauser,[34] Eaton[35] and Mulzer.[36] Lithium bases were employed as metalating reagents, which however only tolerate few functional groups and often led to degradation of the lithiated reagents. The use of metal amides firstly allowed the functionalization of sensitive arenes and heteroarenes. These early amide bases however tended to form aggregates and often reacted sluggishly, thus requiring a large excess of metalating reagent. A huge improvement was made when the metal amides of type TMPMgCl (TMP = 2,2,6,6-tetramethylpiperidyl) were mixed with one equivalent of lithium chloride, leading to TMPMgCl·LiCl (**31**).[37] Similarly as in the case of iPrMgCl·LiCl, the lithium chloride breaks up the aggregates and therefore provides a kinetically highly reactive base.[24] Furthermore, the use of lithium magnesiate or zincate bases pioneered by Mulvey, Mongin, Uchiyama, and Kondo has considerably broadened the scope of metalations for the functionalizations of (hetero)arenes.[38] In the case of TMP-Mg or -Zn metalations, magnesiated or zincated heterocycles are produced, which are compatible with a range of functional groups at moderate to low temperatures. In the case of the zincation of azines, ambient temperatures or elevated temperatures (up to 120 °C) can be used, offering considerable potential for industrial applications.[39]

---

[31] H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109–112.
[32] G. Wittig, G. Fuhrmann, *Ber. Dtsch. Chem. Ges.* **1940**, *73*, 1197–1218.
[33] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933.
[34] a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295–297; b) F. C. Frostick, C. R. Hauser, *J. Am. Chem. Soc.* **1949**, *71*, 1350–1352.
[35] P. E. Eaton, C. H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016–8018.
[36] a) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414–8416; b) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Liebigs Ann.* **1995**, 1441–1446; c) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Synthesis* **1995**, 1225–1227.
[37] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958–2961
[38] a) R. E. Mulvey, *Organometallics* **2006**, *25*, 1060–1075; b) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802–3824; c) R. E. Mulvey, *Acc. Chem. Res.* **2009**, *42*, 743–755; d) P. J. Harford, A. J. Peel, F. Chevallier, R. Takita, F. Mongin, M. Uchiyama, A. E. H. Wheatley, *Dalton Trans.* **2014**, *43*, 14181–14203; e) S. D. Robertson, M. Uzelac, R. E. Mulvey, *Chem. Rev.* **2019**, DOI: 10.1021/acs.chemrev.9b00047
[39] S. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705.

3.3.1 Magnesiation Using TMPMgCl·LiCl

Usually, magnesium amides of type R_2NMgX or $(R_2N)_2Mg$ are aggregated and relatively slow deprotonation reagents, partially because of their moderate solubility.[34,35] Mulzer pioneered the use of TMPMgCl for the magnesiation of an azine.[36] A more THF soluble and more active base was obtained by using TMPMgCl with LiCl (1 equiv). Thus, the mixing of TMP-H with *i*-PrMgCl·LiCl in THF (25 °C, 24 h) provides a ca. 1.4 M soluble base TMPMgCl·LiCl (**31**).[15,40] This base magnesiates a range of functionalized pyridines and quinolines under mild conditions. Since magnesium reagents are produced, there is no need for low temperatures as it is often the case with corresponding lithiations.[41] Thus, the magnesiation of 2-bromoquinoline (**32**) with TMPMgCl·LiCl (**31**) at –20 °C for 2 h provides the *ortho*-magnesiated product **33** (Scheme 7). After bromolysis, the dibromoquinoline **34** is obtained in 65% yield.[42] Pyridines bearing less sensitive functional groups like 3,5-dibromopyridine (**35**) or 2,6-dichloropyridine (**36**) are magnesiated at convenient temperatures (–25 °C or 25 °C) regioselectively providing the pyridylmagnesium derivatives **37** and **38**. Quenching with various electrophiles such as DMF or 4-methoxybenzaldehyde affords the polyfunctional pyridines **39** and **40** in 65–92% yield. The latter reaction can be readily scaled up to a 100 mmol-scale with no yield loss.[43] Aminopyridines are



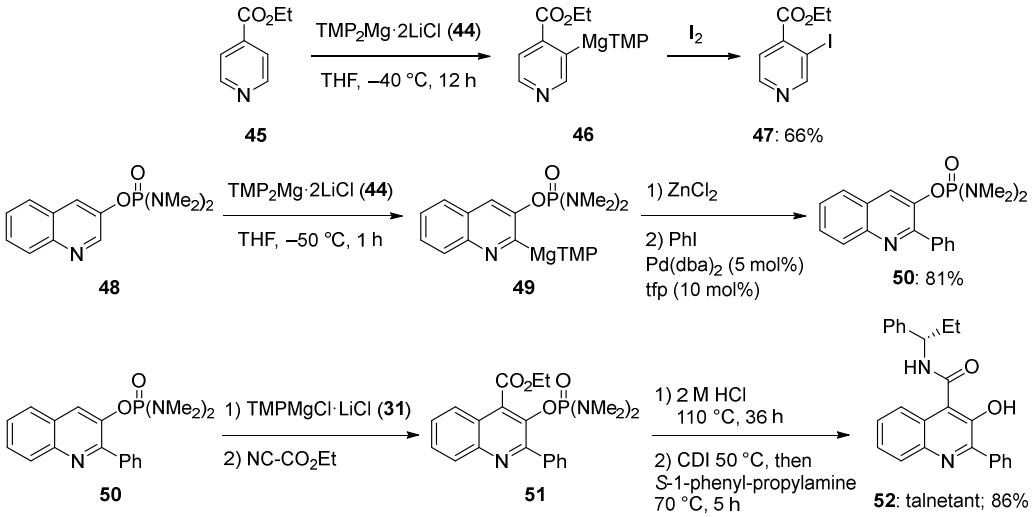
Scheme 7: Regioselective magnesiation of halogenoazines using TMPMgCl·LiCl.

[40] P. García-Álvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079–8081.
[41] a) G. W. Gribble, M. G. Saulnier, *Tetrahedron Lett.* **1980**, *21*, 4137–4140; b) J. Verbeek, L. Brandsma, *J. Org. Chem.* **1984**, *49*, 3857–3859; c) J. Verbeek, A. V. E. George, R. L. P. de Jong, L. Brandsma, *J. Chem. Soc., Chem. Commun.* **1984**, 257–258; d) A. I. Subota, O. O. Grygorenko, Y. B. Valter, M. A. Tairov, O. S. Artamonov, D. M. Volochnyuk, S. V. Ryabukhin, *Synlett* **2015**, *26*, 408–411.
[42] N. Boudet, J. R. Lachs, P. Knochel, *Org. Lett.* **2007**, *9*, 5525–5528.
[43] S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel, *Org. Process Res. Dev.* **2010**, *14*, 339–345.

converted to the corresponding trifluoroacetamides such as **41**. Deprotonation of the amide function with MeMgCl and ring-magnesiation with TMPMgCl·LiCl (**31**) furnishes the Grignard reagent **42**, which, after a transmetalation with $ZnCl_2$ and Negishi cross-coupling,[26] affords the 4-arylated pyridine **43** in 80% yield (Scheme 7).[44]

3.3.2 Magnesiation Using $TMP_2Mg·2LiCl$

Although TMPMgCl·LiCl (**31**) is a very powerful magnesiation reagent, in the case of substrates bearing weakly acidic or sterically hindered protons, the magnesiation is advantageously performed using $TMP_2Mg·2LiCl$ (**44**).[45] Often, the presence of sensitive functional groups, such as a carbethoxy group, requires low magnesiation temperatures, since higher temperatures lead to considerable side reactions. $TMP_2Mg·2LiCl$ (**44**), which is prepared in quantitative yield by treating TMPLi with **31**, can be stored at 25 °C for several hours. A degradation after several days is however observed. This base readily magnesiates 4-carbethoxypyridine (**45**) at –40 °C for 12 h leading to **46**, furnishing, after iodolysis, the iodopyridine **47** in 66% yield (Scheme 8).[45] The phosphordiamidate substituted pyridine **48** was magnesiated with **44**, yielding the magnesium reagent **49** (–50 °C, 1 h). After transmetalation with $ZnCl_2$ and Negishi cross-coupling using PhI, 5% $Pd(dba)_2$ and 10% P(*o*-furyl)$_3$ as catalyst,[46] the arylated quinoline **50** is obtained in 81% yield. Interestingly, the quinoline **50** can now be magnesiated with TMPMgCl·LiCl (**31**) at 25 °C within 1 h. The presence of the phenyl group at position 2 avoids nucleophilic additions to the quinoline ring and allows higher metalation temperatures (0 °C instead of –50 °C). Quenching with NC-CO_2Et produces the 2,3,4-trisubstituted quinoline **51** which is further converted to talnetant (**52**), an NK_3 receptor antagonist, in 86% yield (Scheme 8).[47]

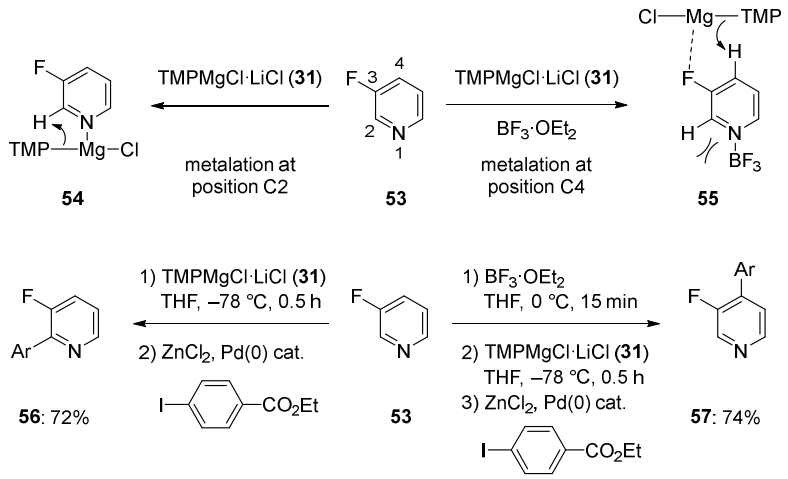


Scheme 8: Azine functionalization using $TMP_2Mg·2LiCl$ (**44**).

[44] G. Monzón, I. Tirotta, Y. Nishii, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 10624–10627.
[45] G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681–7684.
[46] V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
[47] C. J. Rohbogner, S. Wirth, P. Knochel, *Org. Lett.* **2010**, *12*, 1984–1987.

3.3.3 BF_3·OEt_2-Promoted Metalation

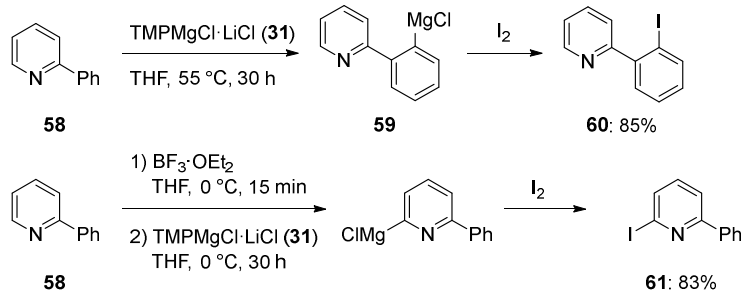
A typical mono-substituted pyridine, 3-fluoropyridine (**53**), can be metalated in two complementary positions (position C2 or position C4) with TMPMgCl·LiCl (**31**), either in the absence or in the presence of the strong Lewis acid BF_3·OEt_2. Preliminary experiments showed, that BF_3·OEt_2 does not react in an irreversible manner with TMPMgCl·LiCl (**31**) at tempeartures below –30 °C. Also, the 3-fluoro substituent considerably acidifies the adjacent positions C2 and C4 of **53**. The position of the metalation is determined by the nature of the complexation with the TMP-base.[48] Thus, by adding TMPMgCl·LiCl (**31**) to **53** a complexation of **31** to the heterocyclic *N*-atom takes place, leading to a complex of type **54**, which favors a metalation at position C2. On the other hand, in the presence of BF_3·OEt_2, this strong Lewis acid forms a complex with the *N*-atom of the pyridine ring and the base **31** may, if at all, only complex the fluorine substituent. This favors a metalation at position C4 (see **55**). Thus, the presence or absence of BF_3·OEt_2 allows the arylation of 3-fluoropyridine (**53**) either in position C2 or C4 leading to the expected products **56** and **57** (Scheme 9).[48] The exact nature of the organometallic species obtained after the metalation of **53** in the presence of BF_3·OEt_2 has been examined by ^{13}C-NMR-spectroscopy.[48,49]



Scheme 9: Regioselective metalation of 3-fluoropyridine **53** in the presence or absence of BF_3·OEt_2.

This regioselectivity switch is observed for a range of pyridines. An unexpected regioselectivity is observed in the case of 2-phenylpyridine (**58**). Thus, the treatment of **58** with TMPMgCl·LiCl (**31**) at 55 °C provides the magnesiated pyridine **59**. After iodolysis, the pyridine **60** is obtained in 85% yield. Alternatively, the treatment of **58** with BF_3·OEt_2, followed by TMPMgCl·LiCl (**31**), furnishes, after iodolysis, the 2,6-disubstituted pyridine **61** in 83% yield (Scheme 10).[48]

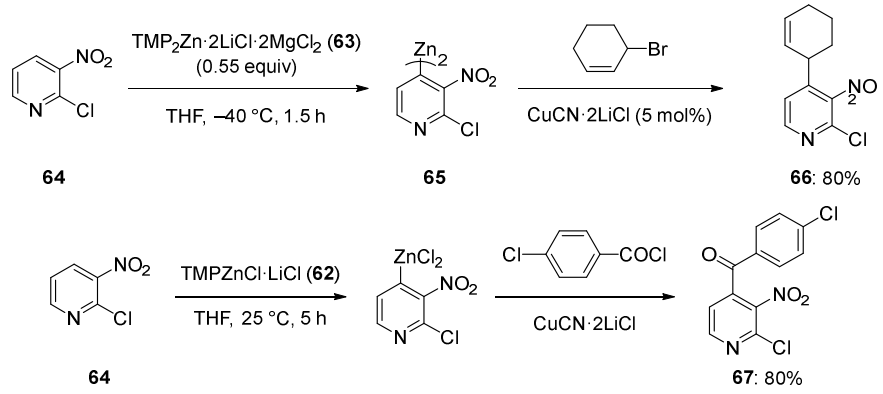
[48] M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451–5455.
[49] S. M. Manolikakes, M. Jaric, K. Karaghiosoff, P. Knochel, *Chem. Commun.* **2013**, *49*, 2124–2126.



Scheme 10: Regioselective metalation of 2-phenylpyridine (**58**) with or without $BF_3 \cdot OEt_2$.

3.3.4 Zincation of Pyridines and Related Azines Using TMPZnCl·LiCl and $TMP_2Zn \cdot 2LiCl \cdot 2MgCl_2$

The availability of kinetically active zinc amides further extends the scope of directed metalations of functionalized azines. Two complementary zinc bases TMPZnCl·LiCl (**62**) and $TMP_2Zn \cdot 2LiCl \cdot 2MgCl_2$ (**63**) are obtained from TMPLi and $ZnCl_2$ or TMPMgCl·LiCl (**31**) and $ZnCl_2$ (Scheme 11).[50,51] Since the carbon-zinc bond is much more covalent than the carbon-magnesium bond, electrophilic functional groups are much better tolerated in such zinc organometallics and the directed zincation of various functionalized pyridines is readily achieved. Furthermore, organozinc organometallics do not undergo electron-transfer reactions. Therefore, the electron-deficient nitro group is well tolerated in the zincation of nitro-substituted pyridines such as **64**. In this case, the zincation proceeds at –40 °C within 1.5 h, leading to the *bis*-pyridylzinc **65**. After a copper-catalyzed allylation with 3-bromocyclohexene, the trisubstituted pyridine **66** is obtained in 80% yield (Scheme 11).[51] Alternatively, the milder zinc base TMPZnCl·LiCl (**62**) is able to zincate **64** at 25 °C within 5 h and does not require low temperature metalations[50,51] leading to the acylated pyridine **67** in 77% yield on 50 mmol scale (Scheme 11).[52]

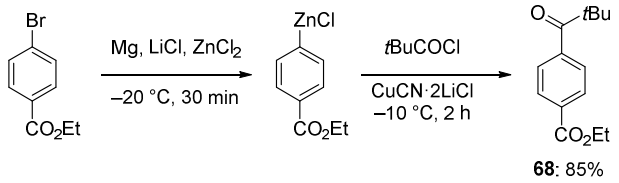


Scheme 11: Zincation of nitro-substituted pyridine **64** using TMPZnCl·LiCl (**62**) or $TMP_2Zn \cdot 2LiCl \cdot 2MgCl_2$ (**63**).

[50] M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837–1840.
[51] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685–7688.
[52] T. Bresser, G. Monzon, M. Mosrin, P. Knochel, *Org. Process Res. Dev.* **2010**, *14*, 1299–1303.

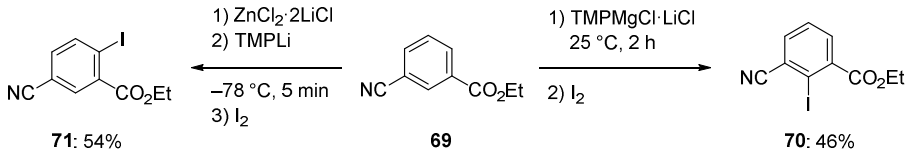
3.4 Transmetalation

When a magnesium or lithium organometallic species is treated with an inorganic salt such as $ZnCl_2$, the more stable carbon-metal bond forms. This so called transmetalation process was found to be useful in the preparation of sensitive reagents and also allows the metalation of certain scaffolds with new selectivities.[53] Additionally, the transmetalation process is used for e.g. allylation, acylation or cross-coupling reactions, in which the reactive organometallic is required to be either a copper or a zinc species.[15] Thus, in the presence of a zinc salt and lithium chloride, magnesium inserts to the carbon bromine bond of ethyl 4-bromobenzoate, and is then rapidly transmetalated to the more stable zinc species, which, after copper-mediated acylation with pivaloyl chloride, leads to the ketone **68** in 85% yield (Scheme 12).



Scheme 12: A magnesium insertion followed by an *in situ* transmetalation to zinc.

When arene **69** is treated with TMPMgCl·LiCl (**31**) the most acidic proton is deprotonated. After quenching of this metal species with iodine, arene **70** is obtained in 46% yield. However, performing the metalation with TMPLi in the presence of $ZnCl_2 \cdot 2LiCl$, the least sterically hindered site, adjacent to the more powerful ester directing group, is deprotonated and rapidly transmetalated to zinc. Due to the transmetalation process, unwanted side reactions, such as attack of the sensitive functional groups, are avoided, and the iodinated arene **71** is obtained in 54% yield (Scheme 13).

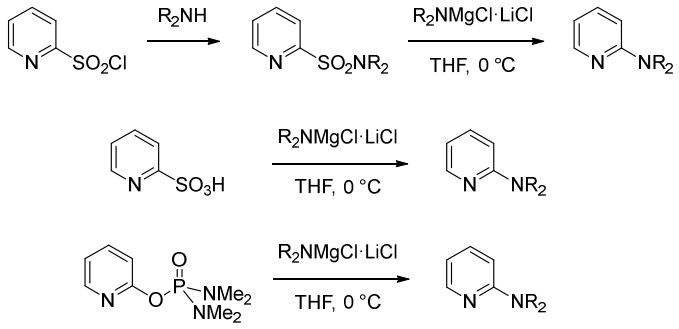


Scheme 13: Metalation of arene **69** using either TMPMgCl·LiCl or TMPLi in the presence of $ZnCl_2 \cdot 2LiCl$.

[53] a) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192–7202; b) A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928–7932.

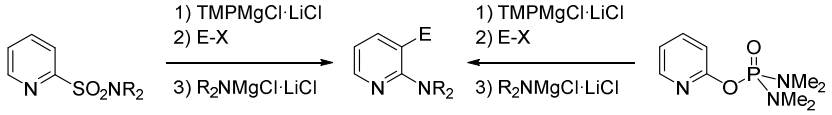
4 Objectives

Since the development of transition-metal-free amination reactions is highly desirable, the amination of several *N*-heterocycles using magnesium amides was to be tested. First, pyridine-2-sulfonyl chloride and the corresponding sulfonamide were investigated,[54] followed by the related sulfonic acids. Also, substituted 2-pyridones and related *N*-heterocycles were to be treated with magnesium amides (Scheme 14).



Scheme 14: Transition-metal-free amination reactions of pyridine-2-sulfonyl chlorides, sulfonic acids, and substituted 2-pyridones.

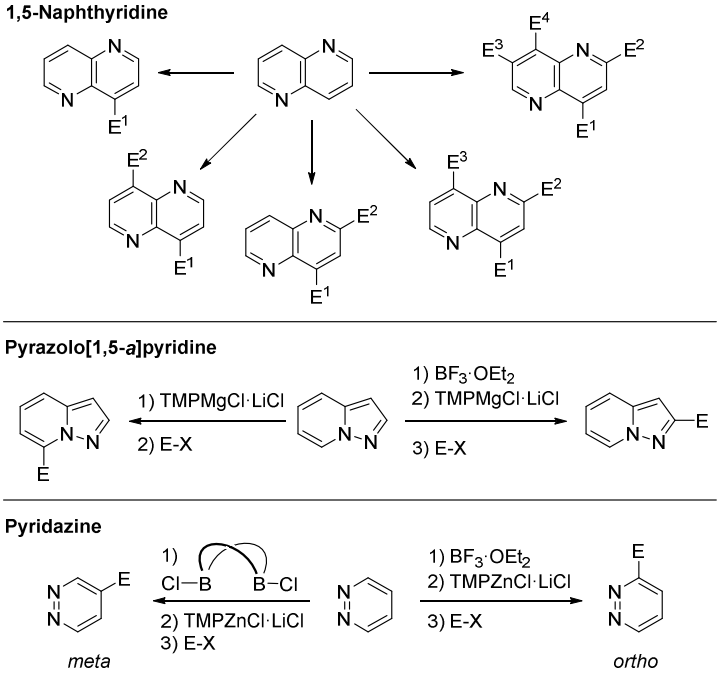
For pyridine-2-sulfonamides and substituted 2-pyridones, a directed *ortho*-metalation/amination sequence was envisioned, which would allow the facile preparation of 2,3-difunctionalized pyridines (Scheme 15).



Scheme 15: Directed *ortho*-metalation and subsequent amination of pyridine-2-sulfonamides and substituted 2-pyridones using magnesium amides.

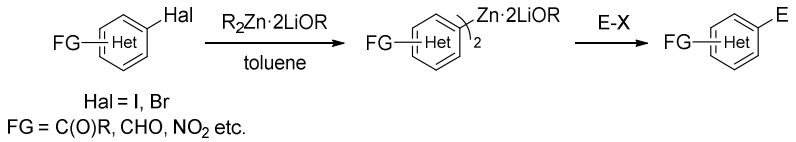
Another task was the metalation and functionalization of the heterocycles 1,5-naphthyridine,[55] pyrazolo[1,5-*a*]pyridine, and pyridazine using TMP-bases. The regioselectivity of the metalation was to be investigated and adjusted by choice of an appropriate Lewis acid. Especially in the case of pyridazine, it was envisioned, that the use of a bidentate boron Lewis acid might enable a directed metalation in the *meta* position (Scheme 16).

[54] This project was developed in cooperation with Dr. C. François, Dr. P. Quinio, and Dr. D. S. Roman. The project was commenced by M. Balkenhohl during his Master Thesis and finalized during the PhD studies, see: M. Balkenhohl, Master Thesis, **2016**, Julius-Maximilians-Universität Würzburg.
[55] This project was developed in cooperation with R. Greiner, see: R. Greiner, Dissertation, LMU München **2017**.



Scheme 16: Regioselective metalation and functionalization of 1,5-naphthyridine, pyrazolo[1,5-*a*]pyridine, and pyridazine using TMP-bases and boron Lewis acids.

A final objective was the development of a halogen/zinc exchange reaction using lithium alkoxide complexed dialkyl zinc reagents.[56] It was anticipated, that these reagents are suitable for the preparation of organometallic species in toluene (see chapter 3.2). Since zinc organometallics are very mild, sensitive functional groups such as ketones, aldehydes or nitro-groups should be tolerated by these novel exchange reagents (Scheme 17).



Scheme 17: The halogen/zinc exchange reaction using lithium alcoxide complexed dialkylzinc reagents.

[56] This project was developed in cooperation with Dr. D. S. Ziegler, and A. Desaintjean, see: A. Desaintjean, Dissertation, LMU München.

B. Results and Discussion

1 Transition-Metal-Free Amination of Pyridine-2-Sulfonyl Chloride and Related *N*-Heterocycles Using Magnesium Amides

1.1 Introduction

Aminopyridines and related aminated *N*-heterocycles are important targets for the pharmaceutical industry.[57] The amination of 2-halopyridines has been extensively studied using either Pd-, Ni-, Cu-, Co-, or Cr-catalysis, or a transition-metal-free substitution with various amines or lithium amides.[6,7,10,11,12,58] Most of the transition-metal-free aminations proceed at high temperatures, require long reaction times or highly basic lithium amides. Also, 2-halo, 2-cyano or 2-trifluoromethylsulfonylpyridines were often used as substrates. Additionally, pyridine sulfonamides have attracted attention due to their medical significance and as building blocks for the preparation of more complex pyridine derivatives.[59]

Herein, we describe a new amination procedure of chlorosulfonyl substituted *N*-heterocycles of type **72** or related sulfonamides of type **73** with magnesium amides of type **74** leading to the aminated pyridine derivatives of type **75** (Scheme 18). So far, only *ortho*-lithiation of (hetero)aryl sulfonamides and subsequent Suzuki-Miyaura cross-coupling or reaction with selected electrophiles has been reported.[60] Thus, to extend the utility of the amination method, the *ortho*-magnesiation[33,61] of sulfonamides of type **73** with TMPMgCl·LiCl[15,37] (TMP = 2,2,6,6-tetramethylpiperidyl) was investigated.[62]

---

[57] a) C. P. Huttrer, C. Djerassi, W. L. Beears, R. L. Mayer, C. R. Scholz, *J. Am. Chem. Soc.* **1946**, *68*, 1999–2002; b) T. Asano, I. Ikegaki, S. Satoh, Y. Suzuki, M. Shibuya, M. Takayasu, H. Hidaka, *J. Pharmacol. Exp. Ther.* **1987**, *241*, 1033–1040; c) S. Cacchi, A. Carangio, G. Fabrizi, L. Moro, P. Pace, *Synlett* **1997**, *12*, 1400–1402; d) L. B. Delvos, J.-M. Begouin, C. Gosmini, *Synlett* **2011**, *2011*, 2325–2328; e) S. Sedehizadeh, M. Keogh, P. Maddison, *Clin. Neuropharmacol.* **2012**, *35*, 191–200; f) S. P. Andrews, R. J. Cox, *J. Med. Chem.* **2016**, *59*, 2894–2917.

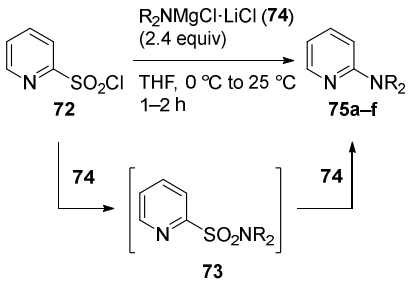
[58] a) K. Kamikawa, S. Sugimoto, M. Uemura, *J. Org. Chem.* **1998**, *63*, 8407–8410; b) G. Toma, K.-i. Fujita, R. Yamaguchi, *Eur. J. Org. Chem.* **2009**, 4586–4588; c) T. Mesganaw, A. L. Silberstein, S. D. Ramgren, N. F. F. Nathel, X. Hong, P. Liu, N. K. Garg, *Chem. Sci.* **2011**, *2*, 1766–1771; d) T. Tu, W. Fang, J. Jiang, *Chem. Commun.* **2011**, *47*, 12358–12360; e) M. Shang, S.-Z. Sun, H.-X. Dai, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 3354–3357; f) S. L. McDonald, C. E. Hendrick, Q. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 4667–4670; g) A. K. Steib, S. Fernandez, O. M. Kuzmina, M. Corpet, C. Gosmini, P. Knochel, *Synlett* **2015**, *26*, 1049–1054; h) X. Dong, Q. Liu, Y. Dong, H. Liu, *Chem. Eur. J.* **2017**, *23*, 2481–2511; i) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247–9301; j) Y. H. Chen, S. Graßl, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 1108–1111

[59] a) J. R. Colombe, J. R. DeBergh, S. L. Buchwald, *Org. Lett.* **2015**, *17*, 3170–3173; b) J. Drews, *Science* **2000**, *287*, 1960–1964; c) R. E. Olson, C. F. Albright, *Curr. Top. Med. Chem.* **2008**, *8*, 17–33; d) D. Sun, M. Wang, Z. Wang, *Curr. Top. Med. Chem.* **2011**, *11*, 1464–1475.

[60] a) C. Schneider, E. Broda, V. Snieckus, *Org. Lett.* **2011**, *13*, 3588–3591; b) F. Marsais, A. Cronnier, F. Trécourt, G. Quéquiner, *J. Org. Chem.* **1987**, *52*, 1133–1136; c) B. I. Alo, O. B. Familoni, F. Marsais, G. Quéguiner, *J. Heterocycl. Chem.* **1992**, *29*, 61–64; d) H. Watanabe, R. A. Schwarz, C. R. Hauser, J. Lewis, D. W. Slocum, *Can. J. Chem.* **1969**, *47*, 1543–1546; e) C. Lane, V. Snieckus, *Synlett* **2000**, 1294–1296.

[61] a) T. Rantanen, S. P. Singh, V. Snieckus, *Platin. Met. Rev.* **2013**, 57, 234; b) C. G. Hartung, V. Snieckus in *The Directed ortho Metalation Reaction – A Point of Departure for New Synthetic Aromatic Chemistry.* In *Modern Arene Chemistry*, Wiley-VCH, Weinheim, **2004**; pp 330–367.

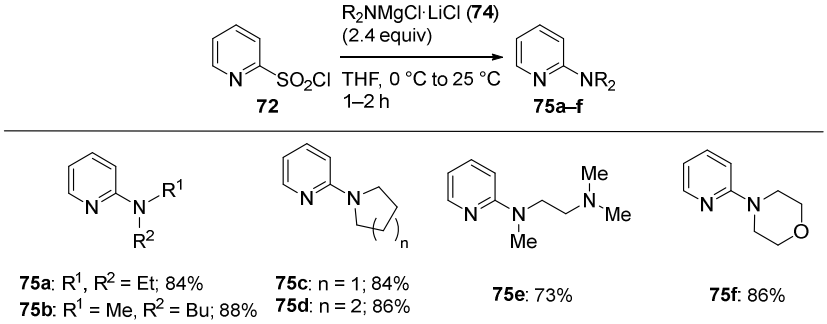
[62] The compounds **75a,c,d,f**, **77a–e**, **79a–d**, **81a–f**, **83b** were prepared by C. François and P. Quinio and will be shown for the sake of completeness. The analytical data can be found in the corresponding publication.



Scheme 18: Synthesis of 2-aminopyridines using magnesium amides (**74**).

1.2 Amination of Pyridine-2-sufonyl Chloride and the Directed *ortho*-Metalation of Pyridine-2-sulfonamides.

Thus, pyridine-2-sulfonyl chloride (**72**) was treated with $Et_2NMgCl \cdot LiCl$ (2.4 equiv) in THF at 0 °C and stirred for 2 h at 25 °C, leading to the 2-aminated pyridine **75a** in 84% yield. This amination was extended to various magnesium amides affording the corresponding 2-aminopyridines **75b–f** under similar conditions in 73–88% yield (Scheme 19).



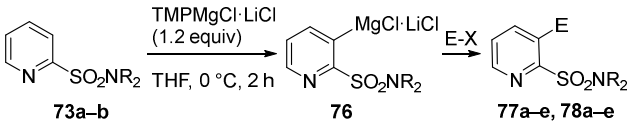
Scheme 19: Synthesis of 2-aminopyridines **75a–f** starting from pyridine-2-sulfonyl chloride (**72**) using magnesium amides (**74**).

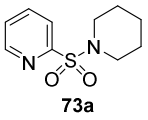
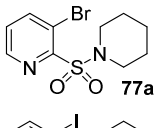
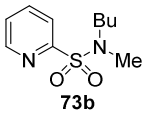
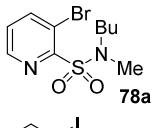
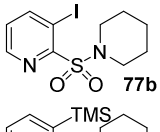
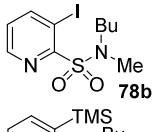
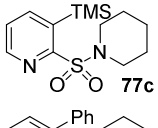
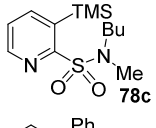
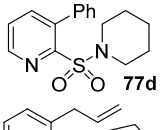
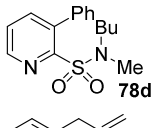
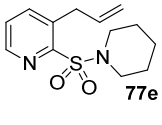
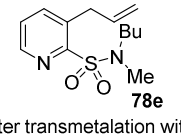
The pyridine sulfonamide **73a** was prepared from pyridine-2-sulfonyl chloride (**72**) and piperidine (3 equiv) in 81% yield. Subsequent reaction of **73a** with TMPMgCl·LiCl at 0 °C for 2 h lead to the corresponding 3-magnesiated sulfonamide of type **76** (Table 1). Quenching of this metalated species with various electrophiles such as $(BrCl_2C)_2$, I_2 or TMSCl furnished the expected products **77a–c** in 64–81% yield (entries 1–3). Arylation of the magnesium species of type **76** was achieved by transmetalation with $ZnCl_2$ and Negishi cross-coupling[26] with iodobenzene in the presence of 3 mol% $Pd(OAc)_2$ and 6 mol% SPhos[63] which gave the sulfonamide **77d** in 82% yield (entry 4). Transmetalation of the Grignard reagent of type **76** to the corresponding copper derivative using $CuCN \cdot 2LiCl$[64] and subsequent reaction with allyl bromide (–20 °C to 25 °C, 1 h) afforded the allylated sulfonamide **77e** in 90% yield (entry 5). Similarly, the pyridine sulfonamide **73b**, prepared from pyridine-2-sulfonyl chloride (**72**) and

[63] a) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696; b) G. Manolikakes, C. Muñoz Hernandez, M. A. Schade, A. Metzger, P. Knochel, *J. Org. Chem.* **2008**, *73*, 8422–8436.
[64] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390–2392.

the acyclic amine *N*-butylmethylamine in 86% yield, was magnesiated and subsequently quenched with several electrophiles leading to the 3-substituted sulfonamides **78a–e** in 73–92% yield (entries 6–10).

Table 1: *ortho*-Functionalization of sulfonamides **73a** and **73b** using TMPMgCl·LiCl.



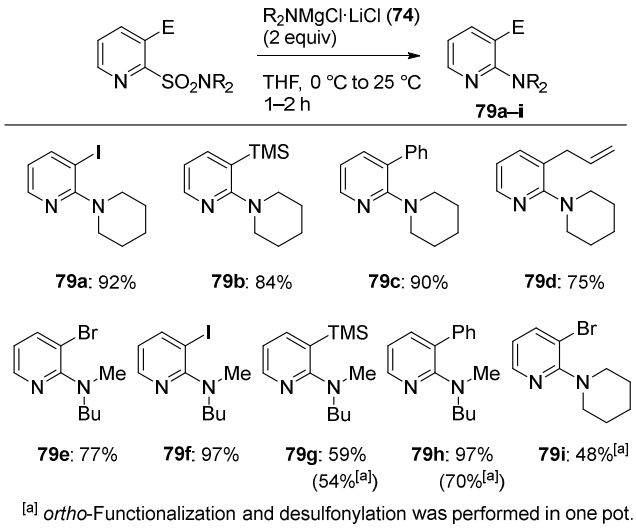
entry	reagent	electrophile	product	yield (%)[a]	entry	reagent	electrophile	product	yield (%)[a]
1	 **73a**	$(BrCl_2C)_2$	 **77a**	74	6	 **73b**	$(BrCl_2C)_2$	 **78a**	73
2	**73a**	I_2	 **77b**	81	7	**73b**	I_2	 **78b**	73
3	**73a**	TMSCl	 **77c**	64	8	**73b**	TMSCl	 **78c**	84
4	**73a**	PhI	 **77d**	82[b]	9	**73b**	PhI	 **78d**	85[b]
5	**73a**		 **77e**	90[c]	10	**73b**		 **78e**	92[c]

[a] Isolated yield. [b] The cross-coupling was performed with 3 mol% $Pd(OAc)_2$ and 6 mol% SPhos after transmetalation with a 1 M $ZnCl_2$ solution (1.2 equiv). [c] Allylation was performed after transmetalation with a 1 M CuCN·2LiCl solution (1.2 equiv).

1.3 Amination of *ortho*-Functionalized Pyridine- and Quinoline-Sulfonamides and Quinolinesulfonyl Chlorides

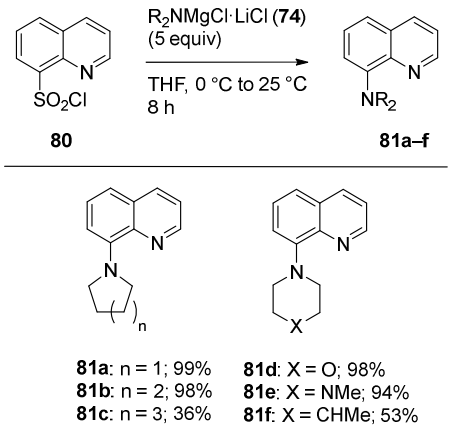
The substituted sulfonamides of type **77** and **78** were smoothly aminated with two different magnesium amides leading to the corresponding aminopyridines **79a–h** under standard conditions in up to 97% yield (Scheme 20).[65] A one-pot procedure involving first the magnesiation of **73a** or **73b** with TMPMgCl·LiCl, then a reaction with an electrophile (such as $(BrCl_2C)_2$, TMSCl or PhI) and subsequent amination with a magnesium amide gave the 2,3-disubstituted aminopyridines **79g–i** in 48–70% yield (Scheme 20).

[65] Amination of **78e** led to double-bond isomerization instead of clean formation of the desired aminated compound of type **79**.



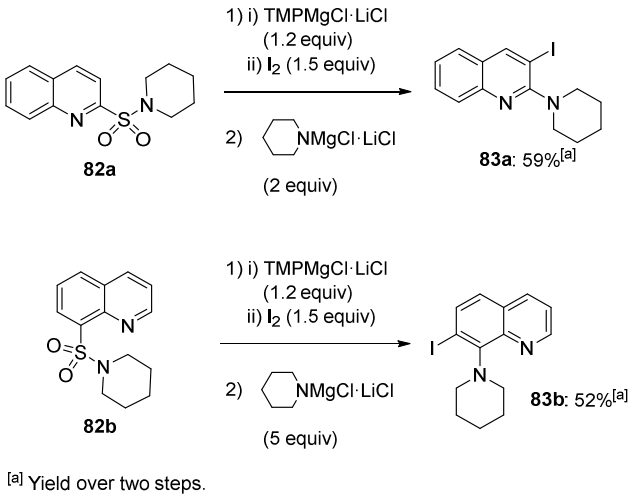
Scheme 20: Desulfonylation of sulfonamides of type **77** and **78** to give aminopyridines **79a–i**.

Additionally, the amination procedure was performed with commercially available 8-quinolinesulfonyl chloride (**80**). Interestingly, the magnesium amide of type **74** prepared from pyrrolidine (5 equiv) using *i*PrMgCl·LiCl (5 equiv) reacted with **80** to afford the aminated quinoline **81a** in 99% yield. Extension to further cyclic amides led to the corresponding amination products **81b–f** in 36–98% yield (Scheme 21).



Scheme 21: Synthesis of 8-aminoquinolines **81a–f** starting from 8-quinolinesulfonyl chloride (**80**).

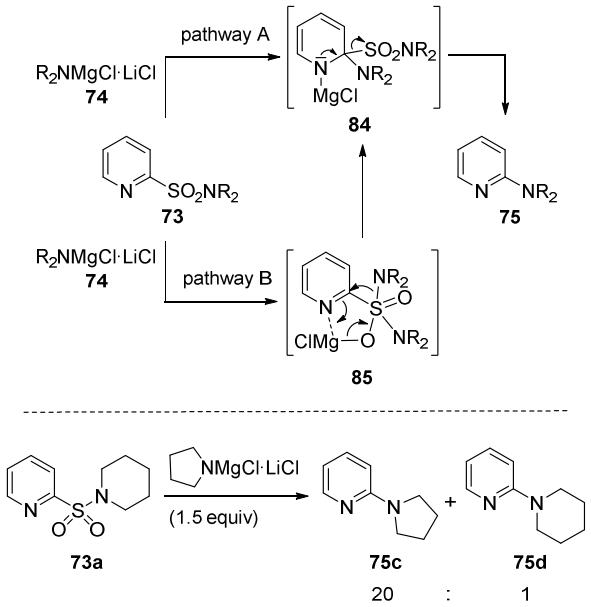
Furthermore, the *ortho*-metalation of the quinoline scaffold was investigated. Thus, the quinoline sulfonamides **82a**–**b** were readily magnesiated using TMPMgCl·LiCl and reacted with iodine. Subsequent reactions with the piperidine magnesium amide of type **74** afforded the 2,3- and 7,8-functionalized quinolines **83a**–**b** in 52–59% yield over two steps (Scheme 22).



Scheme 22: *ortho*-Functionalization and desulfonylation of quinoline sulfonamides **82a** and **82b**.

1.4 Mechanistic Investigations and Intramolecular Cyclization Reactions

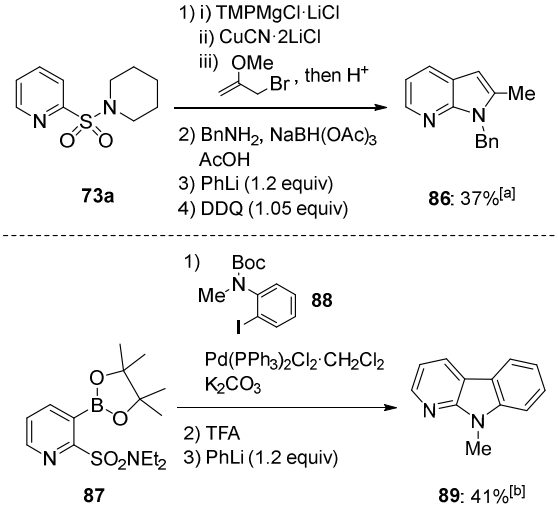
Also, the mechanism of this amination was briefly examined. Two mechanistic pathways can be postulated. The first mechanism involves an addition of the magnesium amide of type **74** to the pyridine core leading to the intermediate **84**, which, after elimination of R_2NSO_2MgCl, afforded the aminated pyridine **75** (S_NAr; pathway A; Scheme 23). Alternatively, a second mechanism may involve the addition of $R_2NMgCl{\cdot}LiCl$ (**74**) to the sulfonamide group providing intermediate **85**, which may undergo an intramolecular transfer of the amino moiety leading to intermediate **84** and finally to the aminopyridine **75** (pathway B, Scheme 23). Evidence for this second pathway was found when a pyridine-2-sulfonamide $PySO_2NR^1_2$ reacted with the magnesium amide $R^2_2NMgCl{\cdot}LiCl$ which led to mixtures of $PyNR^1_2$ and $PyNR^2_2$.



Scheme 23: Plausible mechanisms for the amination of pyridines using magnesium amides.

When for example sulfonamide **73a** reacted with the pyrrolidine magnesium amide of type **74** (1.5 equiv) the ratio between amines **75c** and **75d** was 20:1 (Scheme 23).[66] Notice, that the treatment of 1-naphthalenesulfonyl chloride with an excess of magnesium amide $R_2NMgCl \cdot LiCl$ only led to the formation of the corresponding sulfonamide, and no amination product was detected, showing the importance of the heterocyclic nitrogen atom present in intermediate **85** for this amination.

Finally, the amination method was extended to cyclization reactions. Thus, pyridine sulfonamide **73a** was magnesiated with TMPMgCl·LiCl and then transmetalated with CuCN·2LiCl. Subsequent reaction with 2-methoxyallyl bromide[67] followed by acidic enol ether cleavage gave the corresponding ketone in 94% yield. Subsequent reductive amination using benzylamine, sodium triacetoxyborohydride and acetic acid[68] afforded the desired pyridine sulfonamide in 73% yield. Deprotonation with phenyllithium (1.2 equiv) led to a lithium amide that underwent a smooth cyclization, which, after aromatization using DDQ (1.05 equiv), gave the azaindole **86** in 47% yield over two steps (Scheme 24). Also, sulfonamide **87** reacted with the Boc-protected iodoaniline **88** under Suzuki-Miyaura cross-coupling conditions.[60a,69] Subsequent deprotection using TFA gave the desired pyridine sulfonamide in 49% yield over two steps. Reaction with phenyllithium led to the aza-carbazole **89** in 84% yield (Scheme 24).



Scheme 24: Synthesis of heterocycles *via* cyclization reactions using phenyllithium.

[66] See the Experimental Part C for further details.
[67] R. M. Jacobson, R. A. Raths, McDonald, J. H. *J. Org. Chem.* **1977**, *42*, 2545–2549.
[68] A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849–3862.
[69] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; b) A. Suzuki, *J. Organomet. Chem.* **1999**, 576, 147–168.

2 Amination of 2-Pyridinesulfonic and 8-Quinolinesulfonic Acids with Magnesium Amides

2.1 Introduction

Aminated *N*-heterocycles and especially aminopyridines and -quinolines are important targets for the pharmaceutical industry.[57] Chloropyramine (**90**), for example, is an antihistaminic and the pyridine **91** is a CXCR3 Inhibitor.[70] The aminoquinoline primaquine (**92**) is commonly prescribed for the treatment of malaria,[71] and crenolanib (**93**) is currently being evaluated as a drug against various types of tumors (Figure 2).[72]

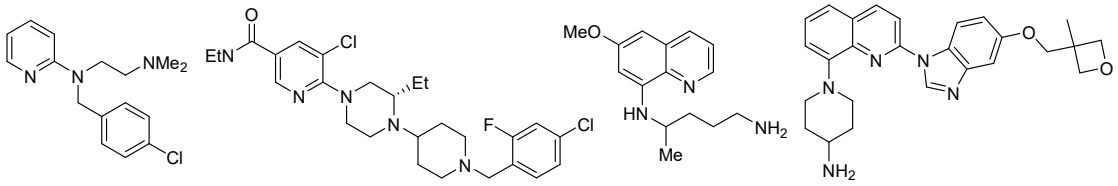


Figure 2: Various pharmaceutically active aminopyridines and -quinolines.

Thus, the development of C-N bond forming reactions is of high importance. So far, transition-metal-catalyzed methods using Ni-, Pd-, Cr-, Co-, or Cu-salts have been used for the formation of the C-N bond (Figure 3a).[6,7,58] However, transition-metals are expensive and often toxic.[8] Therefore, the development of transition-metal-free amination methods is highly desirable. So far, 2-halo, 2-mercapto and 2-cyanopyridines, and 2-pyridyl trifluoromethanesulfonate or pyridine *N*-oxides were found to be suitable substrates for this transformation (Figure 3b).[10,11,12] However, many of these methods require high temperatures or highly basic lithium amides. Transition-metal-free aminations of 2-pyridinesulfonyl chloride and related heterocycles using magnesium amides of type $R_2NMgCl \cdot LiCl$ are described in chapter 1. 2-Pyridinesulfonyl chloride, though, is a sensitive reagent which decomposes at 25 °C within several hours.[73] Albeit being commercially available, quinoline-8-sulfonyl chloride also decomposes at ambient temperature within three to five months. 2-Pyridine- or 8-quinolinesulfonic acids (**94** and **95**) are commercially available and stable reagents, which are formed upon decomposition

[70] a) J. R. Vaughan, G. W. Anderson, R. C. Clapp, J. H. Clark, J. P. English, K. L. Howard, H. W. Marson, L. H. Sutherland, J. J. Denton, *J. Org. Chem.* **1949**, *14*, 228–234; b) Y. Shao, G. N. Anilkumar, C. D. Carroll, G. Dong, J. W. Hall, D. W. Hobbs, Y. Jiang, C.-H. Jenh, S. H. Kim, J. A. Kozlowski, B. F. McGuinness, S. B. Rosenblum, I. Schulman, N.-Y. Shih, Y. Shu, M. K. C. Wong, W. Yu, L. G. Zawacki, Q. Zeng, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1527–1531.

[71] G. Mihaly, S. Ward, G. Edwards, D. Nicholl, M. Orme, A. Breckenridge, *Br. J. Clin. Pharmacol.***1985**, *19*, 745–750.

[72] M. C. Heinrich, D. Griffith, A. McKinley, J. Patterson, A. Presnell, A. Ramachandran, M. Debiec-Rychter, *Clin. Cancer Res.* **2012**, *18*, 4375–4384.

[73] A. Maślankiewicz, K. Marciniec, M. Pawlowski, P. Zajdel, *Heterocycles* **2007**, *71*, 1975–1990.

of the corresponding sulfonyl chloride. Herein, we report the amination of 2-pyridine- and 8-quinolinesulfonic acids using magnesium amides of type $R_2NMgCl \cdot LiCl$, leading to aminopyridines of type **96** and **97** and aminoquinolines of type **98** (Figure 3c).

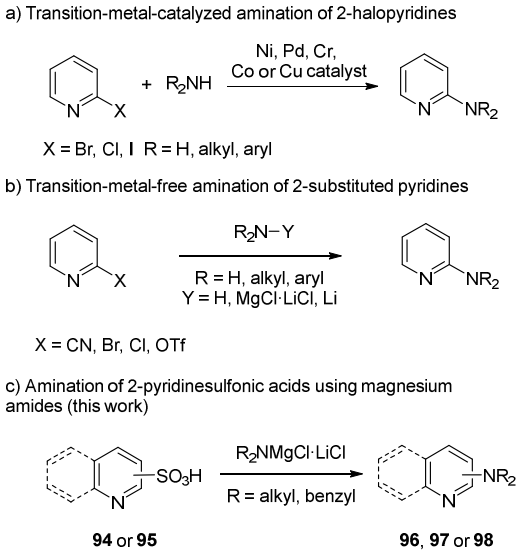
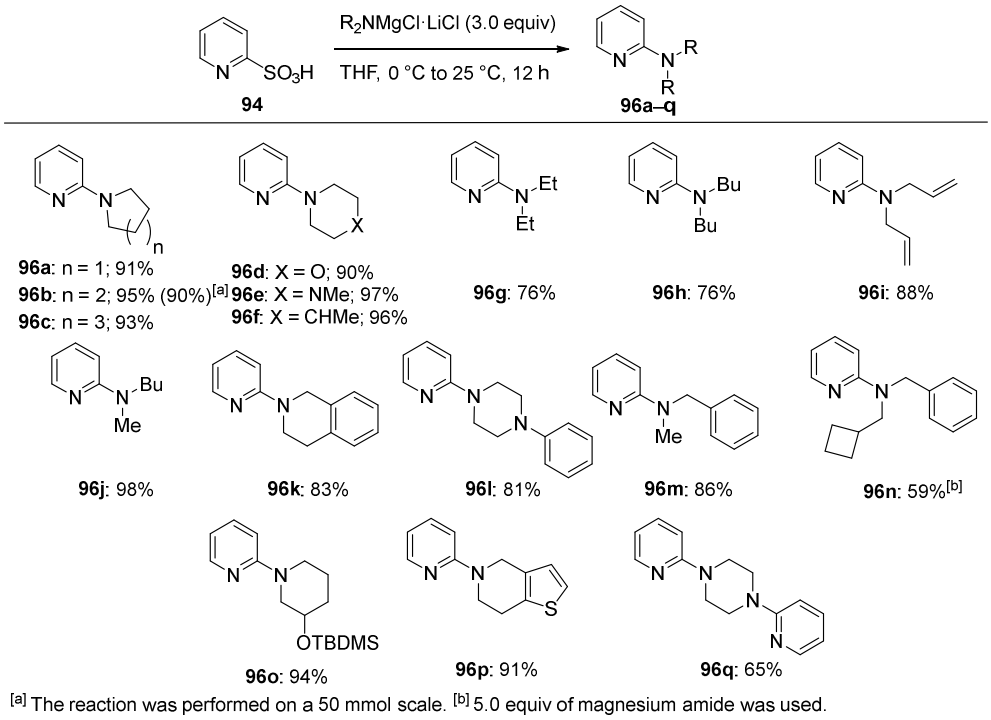


Figure 3: Various conditions for amination reactions, including the transition-metal-free amination of 2-pyridinesulfonic acids using magnesium amides.

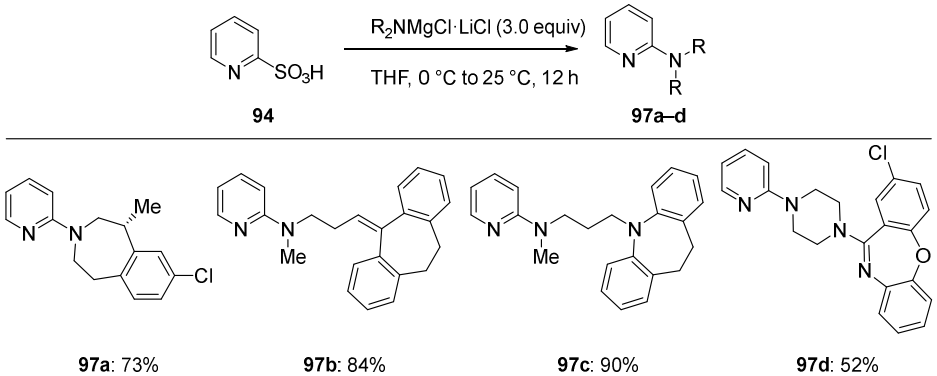
2.2 Amination of 2-Pyridinesulfonic Acid with Magnesium Amides

Thus, pyrrolidine (3.0 equiv) was dissolved in THF and treated with *i*PrMgCl·LiCl (3.0 equiv) at 0 °C. The resulting magnesium amide $R_2NMgCl \cdot LiCl$ was then added to a suspension of 2-pyridinesulfonic acid (**94**) in THF at 0 °C and stirred at 25 °C for 12 h. After workup, the aminopyridine **96a** was isolated in 91% yield (Scheme 25). Using less equivalents of magnesium amide led to a decrease in yield. Other cyclic amides derived from piperidine, azepane, morpholine, *N*-methylpiperazine, or 4-methylpiperidine gave aminopyridines **96b–f** in 90–97% yield. Additionally, the upscaling of the reaction was evaluated by preparing the aminopyridine **96b** on a 50 mmol scale in 90% yield. Symmetrical amides prepared from diethyl-, dibutyl-, or diallylamine yielded pyridines **96g–i** in 76–88% yield. The unsymmetrical amine *N*-butylmethylamine was also suitable for the amination reaction, leading to the aminopyridine **96j** in 98% yield. Other amines bearing e.g. a cyclobutane ring or a TBDMS-protected alcohol, produced the aminopyridines **96k–o** in 59–94% yield. Amines containing a heterocycle such as a pyridine or a thiophene gave the corresponding pyridines **96p–q** in 65–91% yield (Scheme 25).



Scheme 25: Amination of 2-pyridinesulfonic acid (**94**) using magnesium amides of type $R_2NMgCl \cdot LiCl$ leading to aminopyridines **96a–q**.

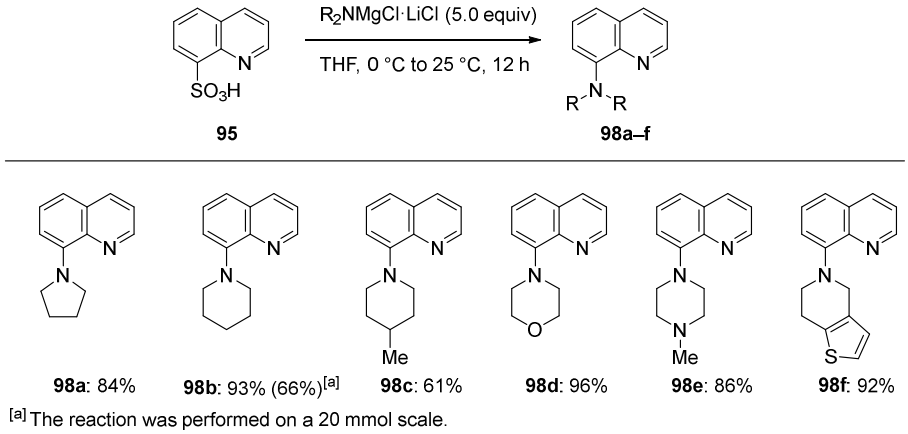
As an extension, several amines important in medicinal chemistry were employed in this amination protocol. Thus, lorcaserin hydrochloride hemihydrate was treated with an excess of *i*PrMgCl·LiCl in order to neutralize the hemihydrate and the HCl salt, which resulted in the formation of the respective magnesium amide. This amide readily reacted with 2-pyridinesulfonic acid (**94**), to give aminopyridine **97a** in 73% yield (Scheme 26). Also, the HCl salts of the amines nortriptyline and desipramine were neutralized and deprotonated using *i*PrMgCl·LiCl. The resulting amides were employed in the amination reaction, leading to pyridines **97b–c** in 84–90% yield. The antidepressant amoxapine gave the polycyclic heterocycle **97d** in 52% yield (Scheme 26).



Scheme 26: Amination of 2-pyridinesulfonic acid (**94**) using magnesium amides leading to aminopyridines **97a–d**.

2.3 Amination of Quinoline-8-sulfonic Acid with Magnesium Amides

Interestingly, 8-quinolinesulfonic acid (**95**) was also a suitable reagent for the amination reaction. Thus, when the amides (5.0 equiv) derived from several amines, including 4-methylpiperidine or *N*-methylpiperazine, were employed in the amination reaction, 8-aminoquinolines **98a–f** were obtained in 61–96% yield. The upscaling of this method was demonstrated upon the synthesis of aminoquinoline **98b** on a multi-gram scale in 66% yield (Scheme 27).



[a] The reaction was performed on a 20 mmol scale.

Scheme 27: Amination of 8-quinolinesulfonic acid (**95**) using magnesium amides, leading to aminoquinolines **98a–f**.

3 Amination of Phosphorodiamidate-Substituted Pyridines and Related *N*-Heterocycles with Magnesium Amides

3.1 Introduction

Aminated *N*-heterocycles play a major role in modern pharmaceutical chemistry.[57] Especially aminopyridines and -quinolines have shown to be of high importance. For example, tripelennamine and chlorothen are antihistamines, flupirtine is a non-opioid analgesic and chloroquine is used for the treatment of malaria (Figure 4).[74]

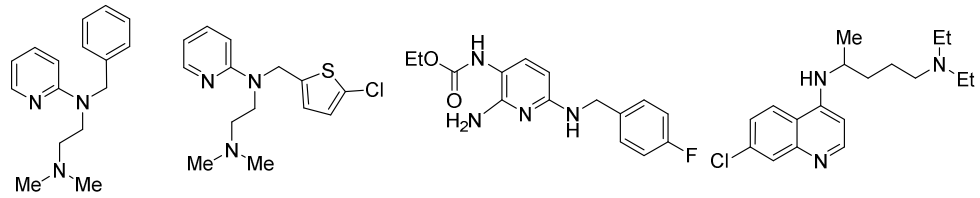


Figure 4: Biologically active aminopyridines tripelennamine, chlorothen, flupirtine, and chloroquine.

A range of heteroaryl amines have been prepared *via* nucleophilic aminations using transition metal catalysts of Pd, Ni, Cu, Co, and Cr.[6,7,58] The development of transition-metal-free amination methods is highly desirable.[8] So far, 2-halo-, 2-mercapto-, and 2-cyanopyridines, and 2-pyridyl trifluoromethanesulfonates or pyridine *N*-oxides were employed as electrophilic substrates for transition-metal-free amination reactions.[10,11,12] However, most of these methods require high temperatures or highly basic lithium amides. In chapter 1, it was demonstrated, that pyridine-2-sulfonyl chloride, which was prepared from 2-mercaptopyridine, readily undergoes an amination when being treated with a magnesium amide of type $R_2NMgCl{\cdot}LiCl$. However, pyridine-2-sulfonyl chloride is instable at room temperature,[73] and 2-mercaptopyridine has to be prepared from a halopyridine, making this procedure lengthy and inefficient.

On another hand, hydroxypyridines (pyridones) or hydroxyquinolines (quinolones) are readily available scaffolds, which are building blocks for the synthesis of several pharmaceuticals and natural products.[75]

---

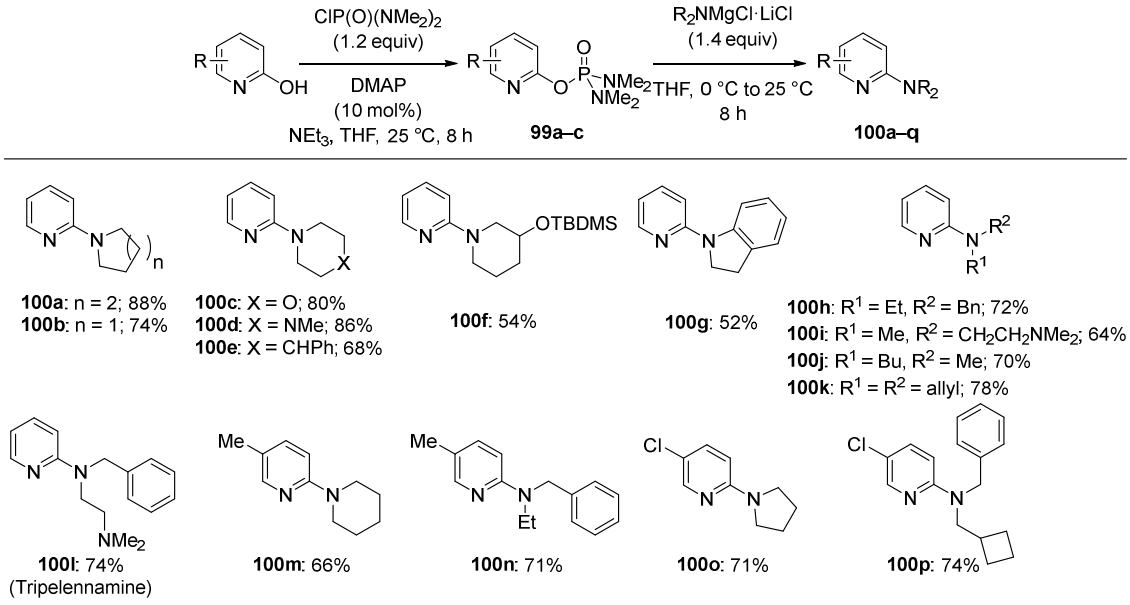
[74] a) R. E. Jensen, R. T. Pflaum, *J. Pharm. Sci.* **1964**, *53*, 835–837; b) R. Oishi, S. Shishido, M. Yamori, K. Saeki, *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1994**, *349*, 140–144; c) T. Sato, K. Suemaru, K. Matsunaga, S. Hamaoka, Y. Gomita, R. Oishi, *Jpn. J. Pharmacol.* **1996**, *71*, 81–84; d) P. R. Graves, J. J. Kwiek, P. Fadden, R. Ray, K. Hardeman, A. M. Coley, M. Foley, T. A. Haystead, J. *Mol. Pharmacol.* **2002**, *62*, 1364–1372; e) S. Harish, K. Bhuvana, G. Bengalorkar, T. Kumar, *J. Anaesthesiol. Clin. Pharmacol.* **2012**, *28*, 172–177.

[75] a) H. J. Jessen, K. Gademann, *Nat. Prod. Rep.* **2010**, *27*, 1168–1185; b) G. Yu, P. N. Praveen Rao, M. A. Chowdhury, K. R. A. Abdellatif, Y. Dong, D. Das, C. A. Velázquez, M. R. Suresh, E. E. Knaus, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2168–2173; c) S. Heeb, M. P. Fletcher, S. R. Chhabra, S. P. Diggle, P. Williams, Cámara, M. *FEMS Microbiol. Rev.* **2011**, *35*, 247–274; d) W. S. Hamama, M. Waly, I. El-Hawary, H. H. Zoorob, *Synth. Commun.* **2014**, *44*, 1730–1759; e) S. M. Geddis, L. Carro, J. T. Hodgkinson, D. R. Spring, *Eur. J. Org. Chem.*

They are readily converted to the corresponding phosphorodiamidates of type **99**, which are prone to undergo directed *ortho*-metalation (D*o*M), allowing the synthesis of 2,3-difunctionalized *N*-heterocycles.[47] Herein, we report, that the treatment of such phosphorodiamidate substituted pyridines with $R_2NMgCl \cdot LiCl$ leads to the desired aminated heterocycles in the absence of any transition-metal catalyst.

3.2 Amination of Phosphorodiamidate-Substituted Pyridines, Quinolines, and Quinoxalines

Thus, 2-pyridone was treated with $(Me_2N)_2P(O)Cl$ (1.2 equiv) in THF to give the phosphorodiamidate **99a** in 91% yield (Scheme 28). Other *N*-heterocyclic phosphorodiamidates were obtained using the same or a slightly modified procedure to give the substituted *N*-heterocycles **99b–i** in 56–94% yield.[47] Next, piperidine (1.4 equiv) was dissolved in THF, cooled to 0 °C, and treated with *i*PrMgCl·LiCl (1.4 equiv) to give the corresponding magnesium amide $R_2NMgCl \cdot LiCl$ within 30 min. This amide was added to a solution of **99a** in THF at 0 °C and stirred at 25 °C for 8 h. After workup, the desired aminated pyridine **100a** was isolated in 88% yield (Scheme 28). Other cyclic amines, such as pyrrolidine, morpholine, *N*-methyl piperazine, or 4-phenylpiperidine were also converted into the corresponding amide derivatives using *i*PrMgCl·LiCl and employed in the amination reaction, leading to aminated pyridines **100b–e** in 68–86% yield. Also, the more challenging TBDMS-protected 3-hydroxypiperidine and indoline were suitable substrates for the amination protocol, leading to aminopyridines **100f–g** in 52-54% yield.

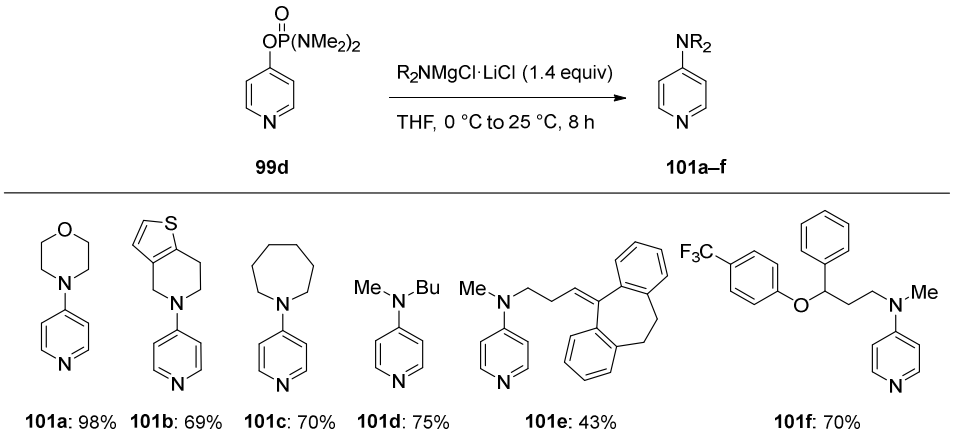


Scheme 28: Synthesis of pyridine-2-phosphorodiamidates of type **99** followed by the amination of **99** using magnesium amides $R_2NMgCl \cdot LiCl$, leading to aminopyridines of type **100**.

2016, 5799–5802; f) P. Shi, L. Wang, K. Chen, J. Wang, Zhu, J. *Org. Lett.* **2017**, *19*, 2418–2421; g) D. S. Ziegler, R. Greiner, H. Lumpe, L. Kqiku, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2017**, *19*, 5760–5763.

Acyclic amines were converted into the corresponding amides, which, after amination, resulted in the formation of the pyridines **100h–k** in 64–78% yield. When *N*'-benzyl-*N*,*N*-dimethylethylenediamine was used as substrate, the antihistaminic tripelennamine **100l** was obtained in 74% yield. Additionally, prefunctionalized pyridones were transformed into the corresponding phosphorodiamidates, leading, after amination, to pyridines **100m–p** in 66–74% yield (Scheme 28).

Amination at the C4-position of the pyridine ring is often difficult to achieve, mainly due to instability of the corresponding starting material. Thus, 4-bromopyridine is only stable when being stored as the corresponding HCl salt[76] and pyridine-4-sulfonyl chloride decomposes rapidly and is difficult to isolate.[73] However, 4-pyridone is a commercially available solid, which can be stored at 25 °C over months. Thus, after conversion of 4-pyridone to the corresponding phosphorodiamidate **99d**, several amines, including a mixed nitrogen sulfur heterocycle and azepane, were applied to the amination protocol, yielding the 4-aminopyridines **101a–d** in 69–98% yield (Scheme 29). The aminopyridines **101e–f** were isolated in 43–70% yield, by the reaction of the magnesium amides derived from the antidepressants nortriptyline and fluoxetine with **99d** (Scheme 29).

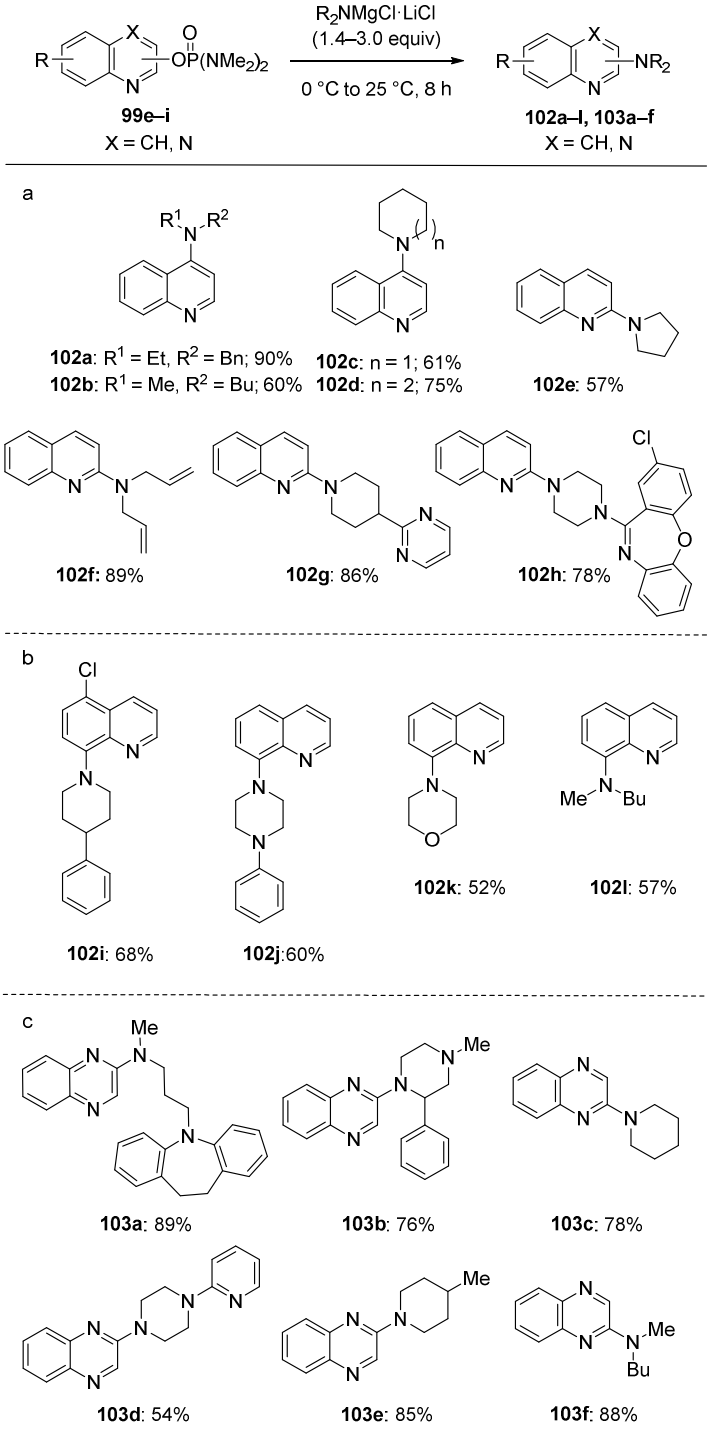


Scheme 29: Synthesis of 4-aminopyridines **101a–f** using magnesium amides $R_2NMgCl \cdot LiCl$.

Apart from the pyridine scaffold, also hydroxyquinolines and 2-hydroxyquinoxaline were aminated. Thus, 2-, 4-, and 8-hydroxyquinoline and 2-hydroxyquinoxaline were converted into the corresponding phosphorodiamidates **99e–i** and submitted to the standard amination protocol. The substituted 2- and 4-hydroxyquinolines were aminated using various amines including amoxapine, leading to quinolines **102a–h** in 57–90% yield (Scheme 30a). Interestingly, the phosphorodiamidate derived from 8-hydroxyquinoline or 5-chloro-8-hydroxyquinoline also underwent amination, yielding 8-aminoquinolines **102i–l** in 52–68% yield (Scheme 30b). Finally, the electron-rich quinoxaline derivative **99i** was treated with various magnesium amides, including the amides derived from

[76] J. P. Wibaut, J. Overhoff, H. Geldof, *Rec. Trav. Chim. Pays-Bas* **1935**, *54*, 807–812.

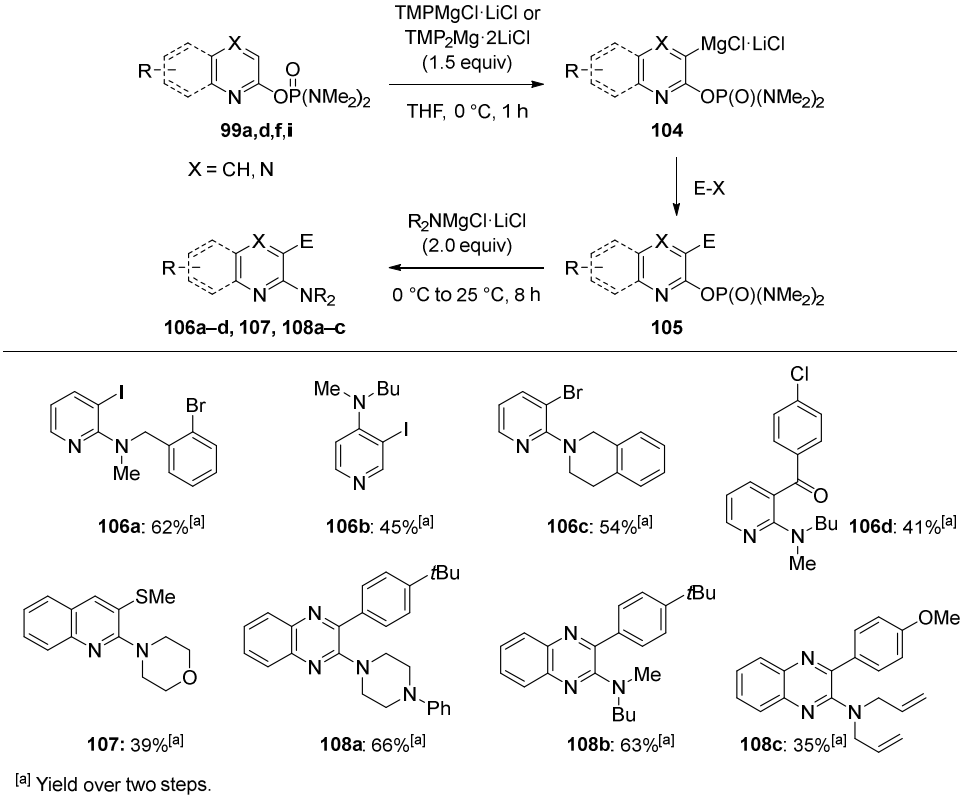
desipramine or the sterically demanding 1-methyl-3-phenyl-piperazine, and the quinoxalines **103a–f** were isolated in 54–89% yield (Scheme 30c).



Scheme 30: Synthesis of 2-, 4- and 8-aminoquinolines **102a–l** and 2-aminoquinoxalines **103a–f** using magnesium amides $R_2NMgCl \cdot LiCl$.

3.3 Directed *ortho*-Metalation and Amination of Various Phosphorodiamidate-Substituted *N*-Heterocycles

Since the phosphorodiamidate functional group is a strong directed metalation group (DMG),[33,61] it was possible to combine the amination with an *ortho*-functionalization. Thus, several phosphorodiamidate substituted *N*-heterocycles (**99a**,**d**,**f**,**i**) were treated with TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidyl)[15,37] or $TMP_2Mg·2LiCl$[15,45] in THF at 0 °C for 1 h. The formed magnesium species of type **104** was then either quenched with electrophiles (E-X) such as I_2 or $(BrCl_2C)_2$ or underwent Cu-catalyzed acylation reactions or Pd-catalyzed Negishi[26] cross-couplings after transmetalation to Zn.[77] The resulting functionalized heterocycles of type **105** were then aminated, leading to difunctionalized pyridines **106a–d**, quinoline **107**, and to quinoxalines **108a–c** in 35–66% yield over two steps (Scheme 31).



[a] Yield over two steps.

Scheme 31: Directed *ortho*-Metalation and Functionalization of Various Phosphorodiamidates, Followed by Amination with $R_2NMgCl·LiCl$.

[77] Transmetalation to the corresponding zinc organometallic was performed using a 1 M $ZnCl_2$ solution in THF. For more details see the Experimental Part C.

4 Zn-, Mg-, and Li-TMP Bases for the Successive Regioselective Metalations of the 1,5-Naphthyridine Scaffold

4.1 Introduction

Heterocyclic structures are ubiquitous in pharmaceutical and agrochemical research, and the discovery of new medicinal targets requires the functionalization of always less common heterocycles.[2,78] Naphthyridines certainly belong to the heterocycles of the future[79] and their functionalization *via* metalation is still in its infancy.[80] Especially 1,5-naphthyridines have been identified as suitable candidates for antimalarial,[81] antibacterial,[82] anti-Alzheimer,[83] antiparasitic,[84] or anticancer[85] drugs. Also, their applicability for OLED materials has been demonstrated.[86] Recently, it has reported, that various metallic TMP bases (TMP = 2,2,6,6-tetramethylpiperidyl) are powerful metalating reagents, and, that Lewis acids such as $BF_3{\cdot}OEt_2$ may enhance their metalation power and/or improve regioselective metalations.[15,48,49,87]

Herein, we report a convenient regioselective metalation and functionalization of the 1,5-naphthyridine scaffold (**109**) and show, that, by using a combination of Zn-, Mg-, and Li-TMP bases with or without

---

[78] a) S. Sharma, P. K. Sharma, N. Kumar, R. Dudhe, *Biomed. Pharmacother.* **2011**, *65*, 244–251; b) A. Gomtsyan, *Chem. Heterocycl. Compd.* **2012**, *48*, 7–10; c) P. Martins, J. Jesus, S. Santos, L. Raposo, C. Roma-Rodrigues, P. Baptista, A. Fernandes, *Molecules* **2015**, *20*, 16852–16891; d) R. Martín, M. Rodríguez Rivero, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 7079–7082.

[79] R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845–5859.

[80] a) E. A. Voight, H. Yin, S. V. Downing, S. A. Calad, H. Matsuhashi, I. Giordano, A. J. Hennessy, R. M. Goodman, J. L. Wood, *Org. Lett.* **2010**, *12*, 3422–3425; b) Z.-L. Shen, V. Dhayalan, A. D. Benischke, R. Greiner, K. Karaghiosoff, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2016**, *55*, 5332–5336.

[81] a) J. T. Adams, C. K. Bradsher, D. S. Breslow, S. T. Amore, C. R. Hauser, *J. Am. Chem. Soc.* **1946**, *68*, 1317–1319; b) D. J. McCaustland, C. C. Cheng, *J. Heterocycl. Chem.* **1970**, *7*, 467–473; c) E. F. Elslager, S. C. Perricone, D. F. Worth, *J. Heterocycl. Chem.* **1970**, *7*, 543–553; d) B. R. Lahue, S.-M. Lo, Z.-K. Wan, G. H. C. Woo, J. K. Snyder, *J. Org. Chem.* **2004**, *69*, 7171–7182.

[82] a) H. A. Ioannidou, A. Martin, A. Gollner, P. A. Koutentis, *J. Org. Chem.* **2011**, *76*, 5113–5122; b) A. K. Parhi, Y. Zhang, K. W. Saionz, P. Pradhan, M. Kaul, K. Trivedi, D. S. Pilch, E. J. LaVoie, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4968–4974.

[83] F. J. R. Rombouts, J.-I. Andrés, M. Ariza, J. M. Alonso, N. Austin, A. Bottelbergs, L. Chen, V. Chupakhin, E. Cleiren, K. Fierens, A. Fontana, X. Langlois, J. E. Leenaerts, J. Mariën, C. Martínez Lamenca, R. Salter, M. E. Schmidt, P. Te Riele, C. Wintmolders, A. A. Trabanco, W. Zhang, G. Macdonald, D. Moechars, *J. Med. Chem.* **2017**, *60*, 1272–1291.

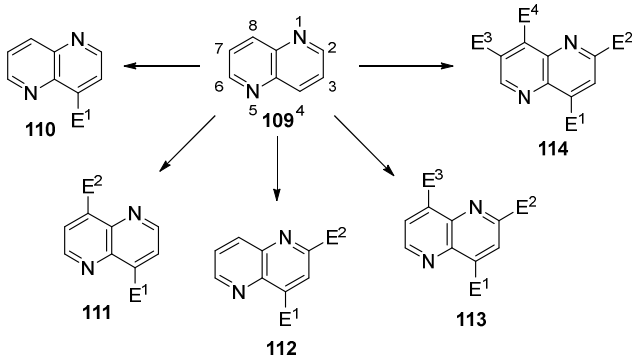
[84] K. T. Osman, J. Ye, Z. Shi, C. Toker, D. Lovato, R. S. Jumani, W. Zuercher, C. D. Huston, A. M. Edwards, M. Lautens, V. Santhakumar, R. Hui, *Bioorg. Med. Chem.* **2017**, *25*, 1672–1680.

[85] F. Gellibert, J. Woolven, M.-H. Fouchet, N. Mathews, H. Goodland, V. Lovegrove, A. Laroze, V.-L. Nguyen, S. Sautet, R. Wang, C. Janson, W. Smith, G. Krysa, V. Boullay, A.-C. de Gouville, S. Huet, D. Hartley, *J. Med. Chem.* **2004**, *47*, 4494–4506.

[86] a) S.-H. Liao, J.-R. Shiu, S.-W. Liu, S.-J. Yeh, Y.-H. Chen, C.-T. Chen, T. J. Chow, C.-I. Wu, *J. Am. Chem. Soc.* **2009**, *131*, 763–777; b) C.-T. Chien, J.-R. Shiu, C.-P. Chang, Y.-S. Hon, D.-F. Huang, P.-T. Chou, C.-Y. Liu, T. J. Chow, *J. Chin. Chem. Soc.* **2012**, *59*, 357–364; c) K.-Y. Wang, C. Chen, J.-F. Liu, Q. Wang, J. Chang, H.-J. Zhu, C. Li, *Org. Biomol. Chem.* **2012**, *10*, 6693–6704; d) H. Wei, Z. Zhao, C. Wei, G. Yu, Z. Liu, B. Zhang, J. Bian, Z. Bian, C. Huang, *Adv. Funct. Mater.* **2016**, *26*, 2085–2096.

[87] a) M. Jaric, B. A. Haag, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2011**, *13*, 2306–2309; b) T. Klatt, D. S. Roman, T. León, P. Knochel, *Org. Lett.* **2014**, *16*, 1232–1235.

$BF_3 \cdot OEt_2$, it is possible to regioselectively metalate the 1,5-naphthyridine scaffold providing mono-, di-, tri-, or tetra- substituted naphthyridines of type **110–114** (Scheme 32).[55,88]



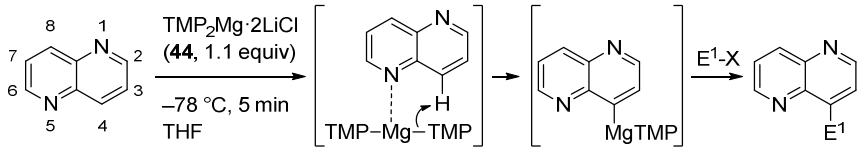
Scheme 32: Regioselective functionalization of the 1,5-naphthyridine scaffold (**109**) using Zn-, Mg-, and Li-TMP bases.

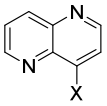
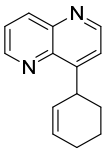
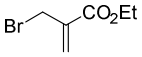
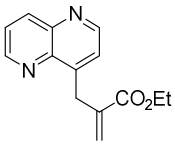
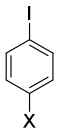
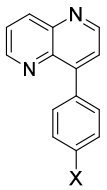
4.2 Metalation and Functionalization of 1,5-Naphthyridine in Positions C2, C4 and C8.

Thus, it was found that the precomplexation[89]of **109** with the magnesium amide $TMP_2Mg \cdot 2LiCl$ (**44**; 1.1 equiv)[45] at –78 °C in THF induces a magnesiation at position C4 within 5 min leading to the magnesiated heterocycle **115**, which, after quenching with several electrophiles (E^1-X), leads to 4-substituted 1,5-naphthyridines of type **110** (Table 2). When the magnesium species **115** was treated with iodine and 1,2-dibromotetrachloroethane, the 4-halo-1,5-naphthyridines **110a–b** were isolated in 49–62% yield (entries 1–2). Transmetalation of **115** with $ZnCl_2$ and subsequent acylation with pivaloyl chloride in the presence of 2 mol% $Pd(PPh_3)_4$ gave the 4-acyl-1,5-naphthyridine **110c** in 63% yield (entry 3). Transmetalation of **115** to the corresponding copper derivative using $CuCN \cdot 2LiCl$[64] and reaction with 3-bromocyclohexene or ethyl 2-(bromomethyl)acrylate[90] provided the allylated 1,5-naphthyridines **110d–e** in 53–60% yield (entries 4–5). Arylation of the magnesium species **115** was performed by transmetalation with $ZnCl_2$ and Negishi cross-coupling[26] with electron rich, neutral, and poor aryl iodides in the presence of either 3 mol% $Pd(dba)_2$ and 6 mol% tfp (tri(2-furyl)phosphine)[46] or 5 mol% $Pd(PPh_3)_4$ leading to 1,5-naphthyridines **110f–h** in 48–75% yield (entries 6–8).

[88] The compounds **110a–e**,**g**,**h**, **111a**,**d–g** and **112a–e** were prepared by R. Greiner and will be shown for the sake of completeness. See: R. Greiner, Dissertation, LMU München 2017. The analytical data can be found in the corresponding publication.
[89] M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206–2225.
[90] J. Villieras, M. Rambaud, *Org. Synth.* **1988**, *66*, 220.

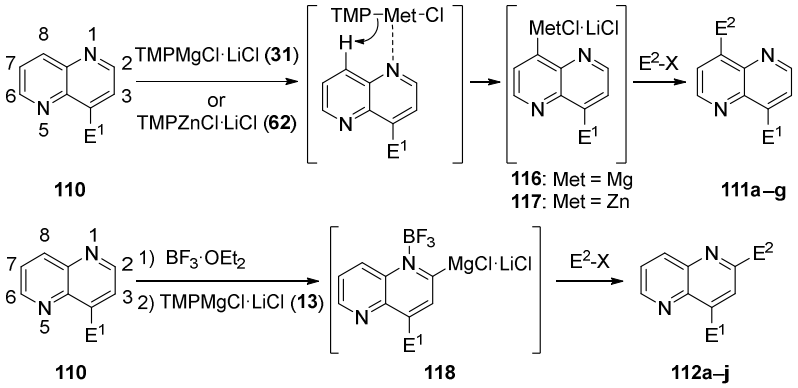
Table 2: Metalation and functionalization of 1,5-naphthyridine (**109**) in the C4 position using $TMP_2Mg \cdot 2LiCl$ (**44**).



entry	electrophile	product	yield[a]
1	I_2		**110a**: X = I; 62%
2	$(BrCCl_2)_2$		**110b**: X = Br; 49%
3	*t*BuCOCl		**110c**: X = CO*t*Bu; 63%[b]
4			**110d**: 60%[c]
5			**110e**: 53%[c]
6	 X = H		**110f**: X = H; 63%[d]
7	X = OMe		**110g**: X = OMe; 75%[d]
8	X = CN		**110h**: X = CN; 48%[e]

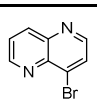
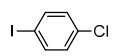
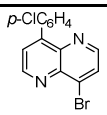
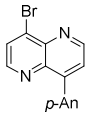
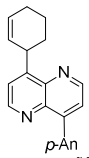
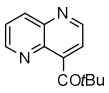
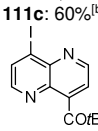
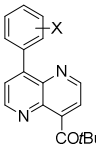
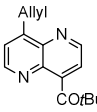
[a] Isolated yield. [b] 2 mol% $Pd(PPh_3)_4$ after transmetalation with a 1 M $ZnCl_2$ solution was used [c] A 1 M CuCN·2LiCl solution was used for transmetalation. [d] 3 mol% $Pd(OAc)_2$ and 6 mol% SPhos after transmetalation with a 1 M $ZnCl_2$ solution was used. [e] 5 mol% $Pd(PPh_3)_4$ after transmetalation with a 1 M $ZnCl_2$ solution was used.

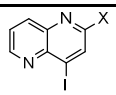
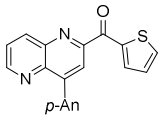
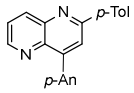
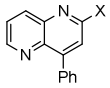
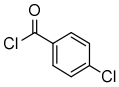
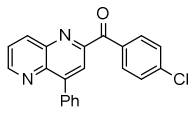
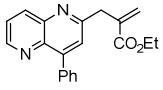
The presence of a substituent E^1 in the naphthyridine **110** at position C4 prevents further complexation of a metallic amide at N5 and favors the precomplexation of TMPMgCl·LiCl (**31**)[15,37] or TMPZnCl·LiCl (**62**)[15,50] at N1. This favors a directed magnesiation (or zincation) at C8, providing, after quenching with several electrophiles (E^2-X), the regioselectively defined 4,8-substituted 1,5-naphthyridines of type **111**. Alternatively, the naphthyridine **110** can be treated with $BF_3 \cdot OEt_2$ which has two consequences: (1) BF_3 hampers a metalation at position C8, since no efficient complexation of the magnesium base (**31**) is possible; (2) the BF_3-complexation dramatically enhances the acidity at C2. This results in a regioselective magnesiation at C2 using TMPMgCl·LiCl (**31**). After quenching with an electrophile (E^2-X), 2,4-disubstituted 1,5-naphthyridines of type **112** are obtained (Scheme 33). Thus, the naphthyridine **110b** was metalated with TMPMgCl·LiCl (**31**, 1.2 equiv, –40 °C, 1 h) to give the magnesiated species **116**. Reaction of **116** after transmetalation to zinc with 1-chloro-4-iodobenzene under standard Negishi cross-coupling conditions[26] resulted in the formation of the biaryl **111a** in 59%



Scheme 33: Metalation and functionalization of 4-substituted 1,5-naphthyridines (**110**) using TMPMgCl·LiCl (**31**) or TMPZnCl·LiCl (**62**).

Table 3: Metalation and functionalization of 1,5-naphthyridines of type **110** in the C8- and C2-position using TMPMgCl·LiCl (**31**) or TMPZnCl·LiCl (**62**).

entry	substrate	electrophile	product, yield[a]
			
1	**110b**		**111a**: 59%[b][c]
		$(BrCCl_2)_2$	
2	**110g**: *p*-An = *p*-C_6H_4OMe		**111b**: 60%[b]
3	**110g**		
			111c: 60%[b][d]
4		I_2	
	110c		**111d**: 71%[e]
			
5	**110c**	X = *p*-CF_3	**111e**: X = *p*-CF_3; 98%[c][e]
6	**110c**	X = *m*-CO*i*Pr	**111f**: X = *m*-CO*i*Pr; 97%[c][e]
7	**110c**		
			111g: 80%[d][e]

entry	substrate	electrophile	product, yield[a]
			
8	**110a**	I_2	**112a**: X = I; 74%[f]
9	**110a**	$(BrCCl_2)_2$	**112b**: X = Br; 72%[f]
10	**110a**	PhCOCl	**112c**: X = COPh; 53%[d][f]
11			
	110g		**112d**: 70%[d][f]
12	**110g**	*p*-Tol-I	
		p-Tol = *p*-C_6H_4Me	**112e**: 56%[c][f]
			
13	**110f**	I_2	**112f**: X = I; 58%[f]
14	**110f**	$(BrCCl_2)_2$	**112g**: X = Br; 89%[f]
15	**110f**	$MeSSO_2Me$	**112h**: X = SMe; 52%[f]
16	**110f**		
			112i: 59%[d][f]
17	**110f**		
			112j: 63%[d][f]

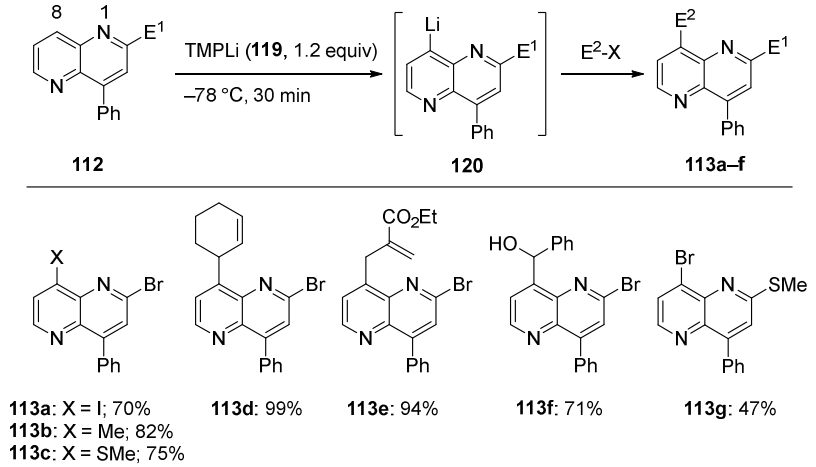
[a] Isolated yield. [b] TMPMgCl·LiCl (1.3 equiv, –40 °C, 1 h) was used. [c] 4 mol% $Pd(dba)_2$ and 8 mol% tfp after transmetalation with a 1 M $ZnCl_2$ solution was used. [d] A 1 M CuCN·2LiCl solution was used for transmetalation. [e] TMPZnCl·LiCl (1.5 equiv, 25 °C, 1 h) was used. [f] BF_3·OEt_2 (1.1 equiv, 0 °C, 10 min) and TMPMgCl·LiCl (1.2 equiv, –40 °C, 1 h) were used.

yield (Table 3, entry 1). Magnesiation of naphthyridine **110g** and quenching with 1,2-dibromotetrachloroethane gave the 8-bromo-naphthyridine **111b** in 60% yield (entry 2). Allylation of the magnesium species **116** with 3-bromocyclohexene after transmetalation to copper afforded naphthyridine **111c** in 60% yield (entry 3). Zincation of naphthyridine **110c** with TMPZnCl·LiCl[15,50] (**62**, 1.5 equiv, 25 °C, 1 h) led to the formation of the heteroarylzinc halide **117**, which was iodolyzed to give the 4,8-disubstituted naphthyridine **111d** in 71% yield (entry 4). Cross-coupling of **117** with 1-iodo-4-trifluoromethylbenzene or 1-(3-iodophenyl)-2-methylpropan-1-one yielded naphthyridines **111e–f** in 97–98% yield (entries 5–6). Allylation of **117** with allyl bromide gave naphthyridine **111g** in 80% yield (entry 7). A regioselectivity switch was possible as mentioned above by adding $BF_3 \cdot OEt_2$ followed by TMPMgCl·LiCl (**31**).[15,37] Both reagents are compatible with each other at temperatures below –40 °C.[48] Thus, the 1,5-naphthyridines **110a**,**g** and **110f** were treated with $BF_3 \cdot OEt_2$ (1.1 equiv, 0 °C, 10 min) followed by TMPMgCl·LiCl (**31**, 1.2 equiv, –40 °C, 1 h) providing the corresponding magnesium species **118** (Scheme 33). Subsequent acylation or halogenation provided 2,4-substituted 1,5-naphthyridines **112a–c** in 53–74% yield (entries 8–10). Applying a similar metalation protocol on the naphthyridine **110g** furnished after acylation or cross-coupling the expected naphthyridines **112d-e** in 56-70% yield (entries 11-12). Finally, 4-phenyl-1,5-naphthyridine (**110f**) was submitted to the standard metalation protocol and subsequent reaction with various electrophiles including *S*-methyl methanethiosulfonate gave naphthyridines **112f–j** in 52–89% yield (entries 13–17).

4.3 Metalation of Functionalized 1,5-Naphthyridines in Positions C7 and C8

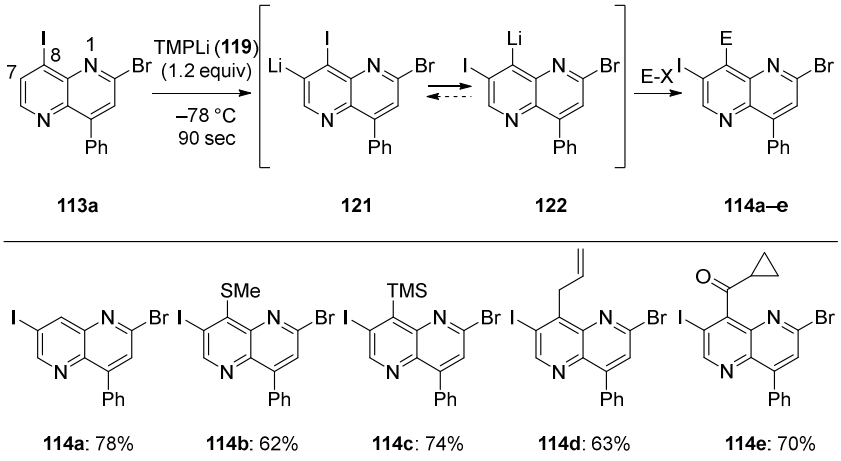
A third functionalization of 2,4-disubstituted 1,5-naphthyridines of type **112** was not possible using TMPMgCl·LiCl (**31**) or $TMP_2Mg \cdot 2LiCl$ (**44**), presumably due to a too weak precomplexation of these sterically hindered Mg-bases and a too low kinetic basicity. However, the stronger lithium amide TMPLi (**119**)[91] readily complexes N1 and lithiates the closest C-H bond at C8. Thus, the treatment of **112g** with TMPLi (1.2 equiv, –78 °C, 30 min) afforded the 8-lithionaphthyridine of type **120** which was trapped by several electrophiles including methyl iodide and benzaldehyde providing 2,4,8-trifunctionalized naphthyridines **113a–f** in 70–99% yield. Addition of TMPLi to **112h** followed by 1,2-dibromotetrachloroethane gave the bromonaphthyridine **113g** in 47% yield (Scheme 34).

[91] a) C. L. Kissel, B. Rickborn, *J. Org. Chem.* **1972**, *37*, 2060–2063; b) R. A. Olofson, C. M. Dougherty, *J. Am. Chem. Soc.* **1973**, *95*, 582–584; c) M. Uzelac, A. R. Kennedy, E. Hevia, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2016**, *55*, 13147–13150.



Scheme 34: Metalation and functionalization of 2,4-functionalized 1,5-naphthyridines (**112**) in the C8 position using TMPLi (**119**).

A fourth functionalization was achieved using a lithium-mediated "halogen dance" rearrangement.[92] Thus, the reaction of the trifunctionalized naphthyridine **113a** with TMPLi (1.2 equiv, –78 °C, 90 sec) followed by quenching with water gave the corresponding regioisomer **114a** in 78% yield (Scheme 35). The formation of **114a** was explained by a lithiation at position C7 leading to the lithium intermediate **121** followed by a very fast "halogen dance" providing the more stable C8-lithiated naphthyridine (**122**). Reaction of **122** with various electrophiles (E-X) gave the 2,4,7,8-tetrasubstituted 1,5-naphthyridines **114b–e** in 62–74% yield. This iodine migration was also proven by an X-ray structure of **114b** (Scheme 35).[93]



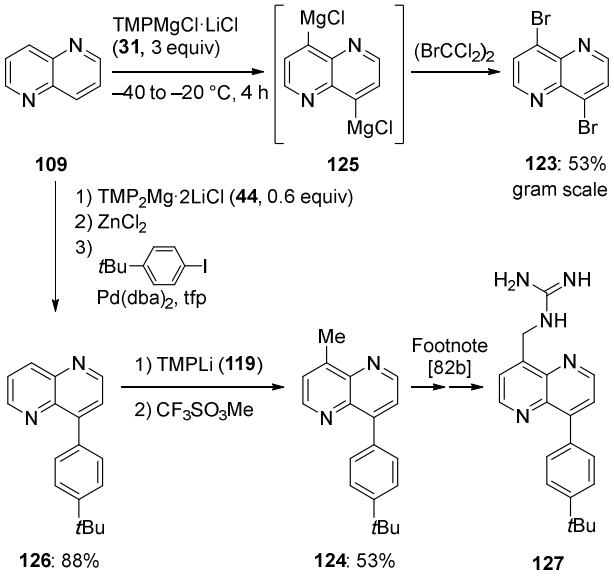
Scheme 35: Performance of the "halogen dance" rearrangement leading to 2,4,7,8-tetrafunctionalized 1,5-naphthyridines **114a–e**.

[92] a) M. Mallet, G. Quéguiner, *Tetrahedron* **1979**, *35*, 1625–1631; b) M. Mallet, G. Quénguiner, *Tetrahedron* **1982**, *38*, 3035–3042; c) G. W. Gribble, M. G. Saulnier, *Tetrahedron Lett.* **1980**, *21*, 4137–4140; d) J. Clayden, in *Organolithiums: selectivity for synthesis*, Elsevier, Oxford, **2002**, pp. 63–66.

[93] CCDC 1559514 (**114b**) contains the supplementary crystallographic data for this chapter. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

4.4 Preparation of Precursors for OLED Materials and an Antibacterial Drug Candidate

To demonstrate the utility of these naphthyridine functionalizations, a precursor for OLED materials **123**[86c] as well as a precursor for an antibacterial drug candidate **124**[82a] were prepared. Thus, 1,5-naphthyridine (**109**) was treated with TMPMgCl·LiCl (**31**, 3 equiv, –40 to –20 °C, 4 h) affording the 4,8-dimagnesiated naphthyridine **125**,[94] which was subsequently quenched with 1,2-dibromotetrachloroethane to give the desired dibrominated naphthyridine **123** in 53% yield on gram scale. Additionally, the reaction of 1,5-naphthyridine (**109**) with $TMP_2Mg·2LiCl$ (**44**, 0.6 equiv) and subsequent transmetalation with $ZnCl_2$ followed by Negishi cross-coupling[16] with 1-iodo-4-*tert*-butylbenzene yielded the substituted naphthyridine **126** in 88% yield. Subsequent directed lithiation using TMPLi (**119**) and quenching with methyl trifluoromethanesulfonate gave the naphthyridine **124** in 53% yield (Scheme 36).



Scheme 36: Synthesis of key step naphthyridines **123** and **124** for the synthesis of OLED materials and an antibacterial reagent **127**.

[94] After iodolysis and GC-analysis (at 4 h, –20 °C) the ratio between the di-iodo and mono-iodo naphthyridine was 6:1.

5 Regioselective Metalation and Functionalization of the Pyrazolo[1,5-*a*]pyridine Scaffold Using Mg- and Zn-TMP Bases

5.1 Introduction

N-heterocycles are important scaffolds in pharmaceutical and agrochemical research.[2,78] Whereas common *N*-heterocycles, such as pyridines, quinolines, or pyrimidines have been studied thoroughly, the functionalization of less conventional heterocycles is still in its infancy and the metalation of such unusual scaffolds is mainly unexplored. For example, pyrazolo[1,5-*a*]pyridines (**128**–**132**) have recently attracted much attention due to their multiple biologic activities and pharmaceutical applications.[95] Pyrazolo[1,5-*a*]pyridine **129** is a dopamine D3 antagonist,[95e] **130** is a PI3 kinase inhibitor,[95i] and **131** and **132** act as EP_1- and diuretic adenosine A1 antagonists, making them suitable candidates for the treatment of schizophrenia, cancer, or Parkinson's disease (Figure 5).[95b,c,k]

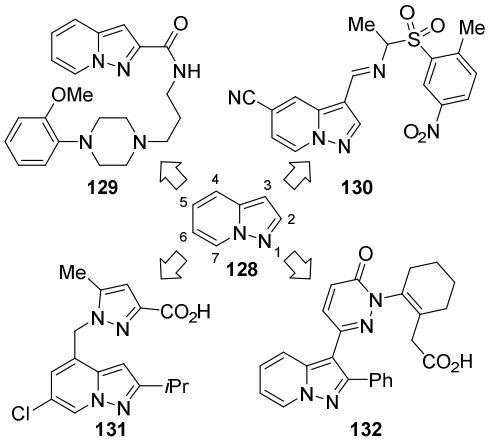


Figure 5: Biologically active derivatives of the pyrazolo[1,5-*a*]pyridine scaffold.

[95] a) J. Bondo Hansen, J. Weis, P. D. Suzdak, K. Eskesen, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 695–698; b) A. Akahane, H. Katayama, T. Mitsunaga, T. Kato, T. Kinoshita, Y. Kita, T. Kusunoki, T. Terai, K. Yoshida, Y. Shiokawa, *J. Med. Chem.* **1999**, *42*, 779–783; c) S. Kuroda, A. Akahane, H. Itani, S. Nishimura, K. Durkin, T. Kinoshita, Y. Tenda, K. Sakane, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1979–1984; d) S. Löber, H. Hübner, P. Gmeiner, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 97–102; e) L. Bettinetti, K. Schlotter, H. Hübner, P. Gmeiner, *J. Med. Chem.* **2002**, *45*, 4594–4597; f) S. Löber, H. Hübner, P. Gmeiner, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2377–2380; g) B. A. Johns, K. S. Gudmundsson, E. M. Turner, S. H. Allen, V. A. Samano, J. A. Ray, G. A. Freeman, F. L. Boyd, C. J. Sexton, D. W. Selleseth, K. L. Creech, K. R. Moniri, *Bioorg. Med. Chem.* **2005**, *13*, 2397–2411; h) K. L. Stevens, D. K. Jung, M. J. Alberti, J. G. Badiang, G. E. Peckham, J. M. Veal, M. Cheung, P. A. Harris, S. D. Chamberlain, M. R. Peel, *Org. Lett.* **2005**, *7*, 4753–4756; i) J. D. Kendall, P. D. O'Connor, A. J. Marshall, R. Frédérick, E. S. Marshall, C. L. Lill, W.-J. Lee, S. Kolekar, M. Chao, A. Malik, S. Yu, C. Chaussade, C. Buchanan, G. W. mRewcastle, B. C. Baguley, J. U. Flanagan, S. M. F. Jamieson, W. A. Denny, P. R. Shepherd, *Bioorg. Med. Chem.* **2012**, *20*, 69–85; j) J. G. Kettle, S. Brown, C. Crafter, B. R. Davies, P. Dudley, G. Fairley, P. Faulder, S. Fillery, H. Greenwood, J. Hawkins, M. James, K. Johnson, C. D. Lane, M. Pass, J. H. Pink, H. Plant, S. Cosulich, C. *J. Med. Chem.* **2012**, *55*, 1261–1273; k) K. Umei, Y. Nishigaya, A. Kondo, K. Tatani, N. Tanaka, Y. Kohno, S. Seto, *Bioorg. Med. Chem.* **2017**, *25*, 2635–2642.

The direct functionalization of the pyrazolo[1,5-*a*]pyridine scaffold is not well studied,[95h,96] and especially the regioselective functionalization of the C2 position is difficult to achieve.[97] Recently, a range of TMP-Mg and TMP-Zn bases (TMP = 2,2,6,6-tetramethylpiperidyl) have been developed, which have proven to be very active metalating reagents, tolerating various functional groups, as well as sensitive heterocyclic structures.[15,37,50] Furthermore, these Mg- and Zn-bases are compatible at low temperatures with strong Lewis acids, such as $BF_3 \cdot OEt_2$ or $MgCl_2$.[48,49,87] This combination (frustrated Lewis pair)[98] greatly enhances the functionalization scope of such bases and allows to achieve new metalation patterns.[48,49,87] Herein, the straightforward functionalization of the pyrazolo[1,5-*a*]pyridine scaffold **128** using a combination of Mg- or Zn-TMP bases and $BF_3 \cdot OEt_2$ is reported.

5.2 Metalation and Functionalization of Pyrazolo[1,5-*a*]pyridine in the Presence or Absence of the Lewis Acid $BF_3 \cdot OEt_2$

Thus, pyrazolo[1,5-*a*]pyridine (**128**) was treated with TMPMgCl·LiCl (1.2 equiv) for 15 min at –78 °C[99] in THF, which results in the coordination of the TMP-base to the nitrogen atom N1, inducing a magnesiation in the C7-position. This led to the magnesium species of type **133**, which, after quenching with iodine or dibromotetrachloroethane, gave the halogenated pyrazolo[1,5-*a*]pyridines **134a**–**b** in 69–93% yield (Table 4, entries 1–2). Reaction of the magnesium intermediate **133** with *S*-methyl methanethiosulfonate gave the thiolated pyrazolo[1,5-*a*]pyridine **134c** in 46% yield (entry 3). After transmetalation of **133** to the corresponding copper species using a CuCN·2LiCl[64] solution in THF, quenching with 3-bromocyclohexene or ethyl 2-(bromomethyl)acrylate[90] gave the allylated products **134d**–**e** in 73–86% yield (entries 4–5). Such heterocyclic copper derivatives also reacted with several acid chlorides such as 2-chloro-, 2-iodo-, or 4-chlorobenzoyl chloride to give the acylated pyrazolo[1,5-*a*]pyridines **134f**–**h** in 53–70% yield (entries 6–8). Reaction of **133** with DABSO (DABSO = DABCO-bis(sulfur dioxide)),[100] followed by sulfuryl chloride and piperidine, gave the sulfonamide **134i** in 55% yield (entry 9). After transmetalation of the magnesium species **133** to zinc

[96] For the synthesis of pyrazolo[1,5-*a*]pyridines see: a) T. Tsuchiya, H. Sashida, *J. Chem. Soc., Chem. Commun.* **1980**, 1109–1110; b) J. Valenciano, A. M. Cuadro, J. J. Vaquero, J. Alvarez-Builla, R. Palmeiro, O. Castaño, *J. Org. Chem.* **1999**, *64*, 9001–9010; c) A. Nuñez, A. G. de Viedma, V. Martínez-Barrasa, C. Burgos, J. Alvarez-Builla, *Synlett* **2002**, 1093–1096; d) B. A. Johns, K. S. Gudmundsson, E. M. Turner, S. H. Allen, D. K. Jung, C. J. Sexton, F. L. Boyd, M. R. Peel, *Tetrahedron* **2003**, *59*, 9001–9011; e) H.-C. Wu, L.-C. Hwang, M.-J. Wu, *Org. Biomol. Chem.* **2011**, *9*, 670–672; f) D. C. Mohan, C. Ravi, S. N. Rao, S. Adimurthy, *Org. Biomol. Chem.* **2015**, *13*, 3556–3560; g) C. Ravi, D. Chandra Mohan, N. Naresh Kumar Reddy, S. Adimurthy, *RSC Advances* **2015**, *5*, 42961–42964; h) C. Ravi, A. Qayum, D. Chandra Mohan, S. K. Singh, S. Adimurthy, *Eur. J. Med. Chem.* **2017**, *126*, 277–285.

[97] a) J. J. Mousseau, A. Fortier, A. B. Charette, *Org. Lett.* **2010**, *12*, 516–519; b) J. J. Mousseau, J. A. Bull, C. L. Ladd, A. Fortier, D. Sustac Roman, A. B. Charette, *J. Org. Chem.* **2011**, *76*, 8243–8261.

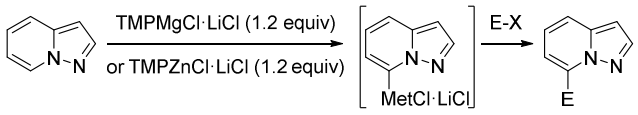
[98] D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2015**, *54*, 6400–6441.

[99] A temperature of –78°C has to be used, since temperatures higher than –60 °C led to decomposition of the magnesiated heterocycle.

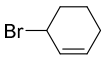
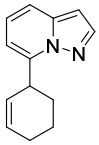
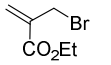
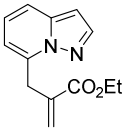
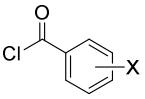
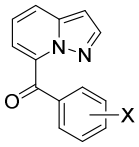
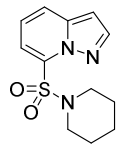
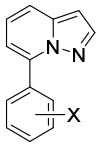
[100] H. Woolven, C. González-Rodríguez, I. Marco, A. L. Thompson, M. C. Willis, *Org. Lett.* **2011**, *13*, 4876–4878.

using $ZnCl_2$, a Negishi cross-coupling[26] catalyzed by $Pd(dba)_2$ (3 mol%, dba = dibenzylideneacetone) and tfp (6 mol%, tfp = tri-2-furylphosphine)[46] with 4-iodotoluene was performed, leading to the arylated pyrazolo[1,5-*a*]pyridine **134j** in 69% yield (entry 10). Reaction of this zinc species with other aryl iodides such as ethyl 3- or 4-iodobenzoate gave unsatisfactory results (yields below 20%). However, when the metalation was performed with TMPZnCl·LiCl (1.2 equiv) at 0 °C for 15 min, followed by standard Negishi cross-coupling conditions, the desired cross-coupling products **134k–l** were obtained in 74–97% yield (entries 11–12). Apparently, the absence of magnesium salts had a significant influence on the reaction outcome of the corresponding cross-coupling reactions.

Table 4: Metalation and functionalization of the pyrazolo[1,5-*a*]pyridine scaffold (**128**) using TMPMgCl·LiCl and TMPZnCl·LiCl.



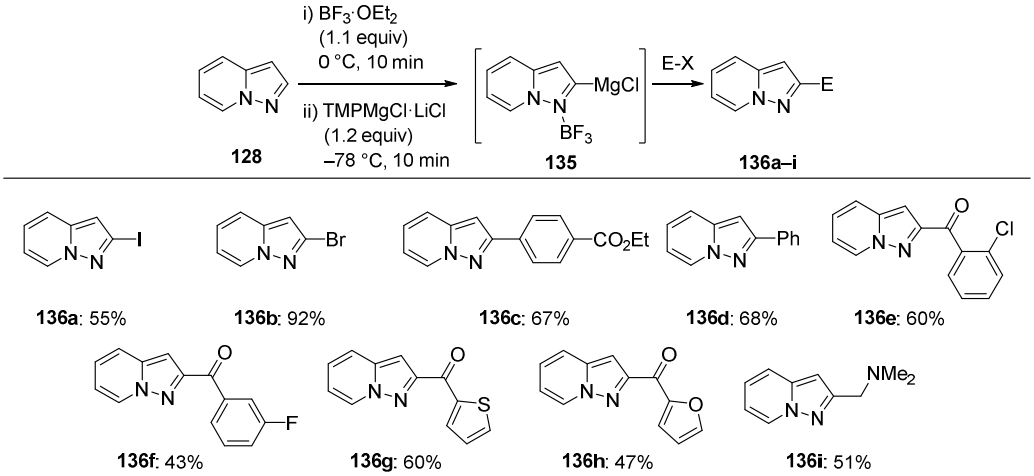
128 **133**, Met = Mg, Zn **134a–l**

entry	electrophile	product	yield
1	I_2		**134a**: X = I; 69%[a]
2	$(BrCCl_2)_2$		**134b**: X = Br; 93%[a]
3	$MeSSO_2Me$		**134c**: X = SMe; 46%[a]
4			**134d**: 86%[a],[b]
5			**134e**: 73%[a],[b]
6			**134f**: X = *o*-Cl; 53%[a],[b]
7			**134g**: X = *o*-I; 67%[a],[b]
8			**134h**: X = *p*-Cl; 70%[a],[b]
9	DABSO SO_2Cl_2 piperidine		**134i**: 55%[a]
10			**134j**: X = *p*-Me; 69%[a],[c]
11			**134k**: X = *p*-CO_2Et; 97%[d]
12			**134l**: X = *m*-OMe; 74%[d]

[a] TMPMgCl·LiCl (1.2 equiv, –78 °C, 15 min) was used. [b] A 1 M CuCN·2LiCl solution was used for transmetalation. [c] 3 mol% $Pd(dba)_2$ and 6 mol% tfp after a transmetalation with a 1 M $ZnCl_2$ solution was used. [d] TMPZnCl·LiCl (1.2 equiv, 0 °C, 15 min), 3 mol% $Pd(dba)_2$ and 6 mol% tfp were used.

When pyrazolo[1,5-*a*]pyridine (**128**) was treated with $BF_3{\cdot}OEt_2$ prior to the addition of the TMP-base, a switch of the metalation regioselectivity was observed. Presumably, BF_3 coordinates to the nitrogen atom N1, which results in (1) blocking the coordination site for TMPMgCl·LiCl and (2) an enhancement

of the acidity at the C2 position. This leads to a regioselective magnesiation at C2 using TMPMgCl·LiCl. Thus, $BF_3·OEt_2$ was added to **128** at 0 °C for 10 min, followed by TMPMgCl·LiCl (1.2 equiv) at –78 °C, leading to the tentative magnesium species **135** after 10 min (Scheme 37). Reaction of **135** with iodine or dibromotetrachloroethane led to the C2 halogenated pyrazolo[1,5-*a*]pyridines **136a–b** in 55–92% yield. Palladium-catalyzed Negishi cross-couplings of **135** after transmetalation with $ZnCl_2$ and reaction with ethyl 4-iodobenzoate or iodobenzene gave the arylated *N*-heterocycles **136c–d** in 67–68% yield. Copper-catalyzed acylation reactions with various acid chlorides, including 3-fluorobenzoyl chloride and 2-thiophenecarbonyl chloride, gave the acylated pyrazolo[1,5-*a*]pyridines **136e–h** in 43–60% yield. Reaction of **135** with Tietze's reagent[101] yielded the aminomethylated *N*-heterocycle **136i** in 51% yield (Scheme 37).

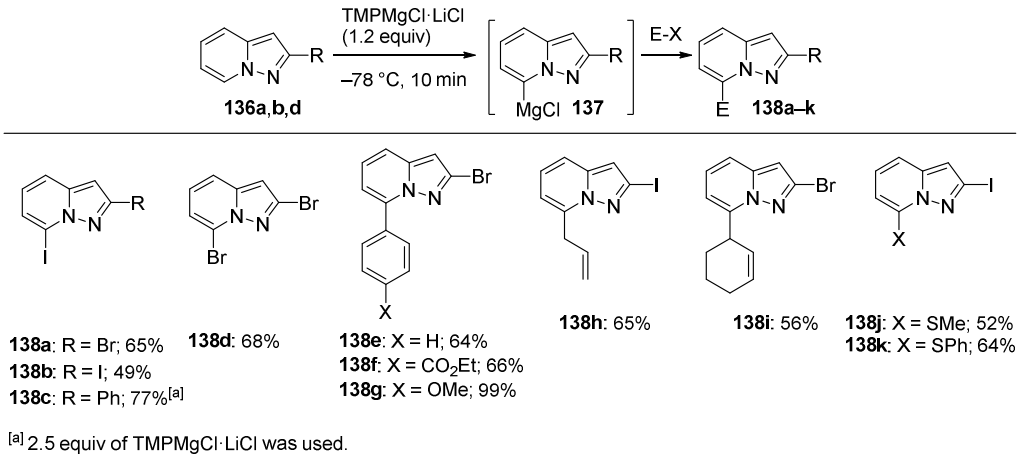


Scheme 37: Metalation and functionalization of pyrazolo[1,5-*a*]pyridine (**128**) in the C2 position using $BF_3·OEt_2$ and TMPMgCl·LiCl.

5.3 Metalation of Prefunctionalized Pyrazolo[1,5-*a*]pyridines

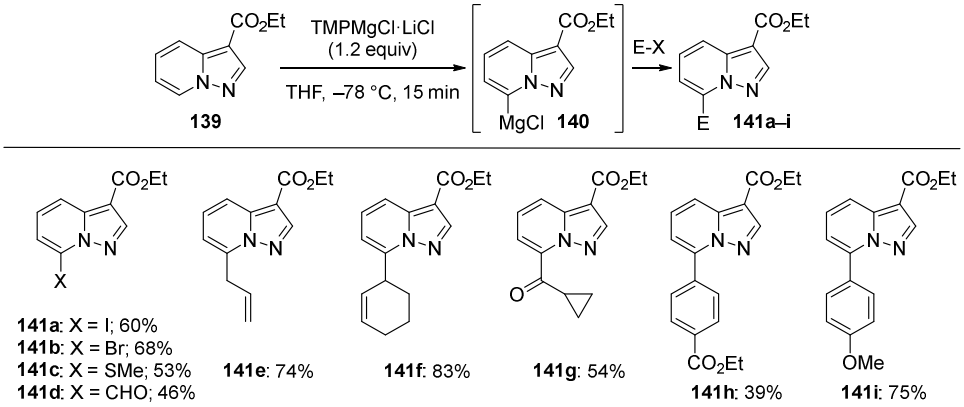
Pyrazolo[1,5-*a*]pyridines were also functionalized in the C7 position using TMPMgCl·LiCl in the presence of a previously introduced substituent in position C2. Thus, several C2 functionalized pyrazolo[1,5-*a*]pyridines were treated with TMPMgCl·LiCl (1.2 equiv), leading to the magnesium species of type **137** (Scheme 38). Halogenation of **137** gave the expected products **138a–d** in 49–77% yield. Interestingly, the metalation of 2-phenylpyrazolo[1,5-*a*]pyridine required 2.5 equivalents of the TMP-base to achieve full conversion. Palladium-catalyzed Negishi cross-couplings with various aryl halides or copper-mediated allylation reactions with allyl bromide or 3-bromocyclohexene gave the difunctionalized *N*-heterocycles **138e–i** in 56–99% yield. Thiolation was achieved by quenching **137** with *S*-methyl methanethiosulfonate or *S*-phenyl benzenethiosulfonate, producing the thioethers **138j–k** in 52–64% yield (Scheme 38).

[101] a) G. Kinast, L.-F. Tietze, *Angew. Chem. Int. Ed.* **1976**, *15*, 239–240; b) V. Werner, M. Ellwart, A. J. Wagner, P. Knochel, *Org. Lett.* **2015**, *17*, 2026–2029.



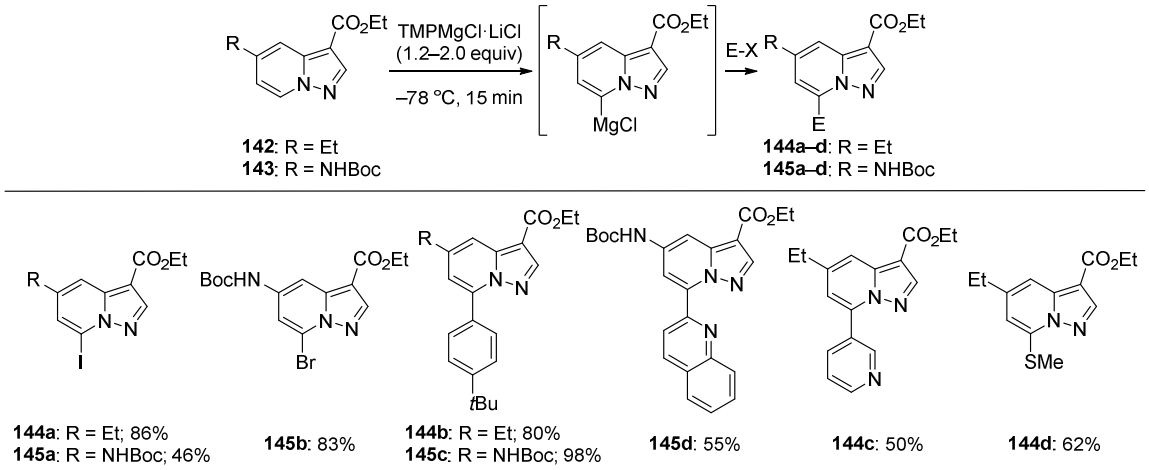
Scheme 38: Metalation and functionalization of various substituted pyrazolo[1,5-*a*]pyridines using TMPMgCl·LiCl.

Pyrazolo[1,5-*a*]pyridines bearing an ester functionality in the C3 position also underwent a metalation using TMPMgCl·LiCl, allowing facile functionalization of the C7 position. Thus, magnesiation of **139** with TMPMgCl·LiCl (1.2 equiv) led to the metalated species **140**. The reaction of **140** with several electrophiles, including *N*-formylmorpholine and cyclopropane carbonyl chloride gave the 3,7-bisfunctionalized pyrazolo[1,5-*a*]pyridines **141a–i** in 39–83% yield (Scheme 39).



Scheme 39: Metalation and functionalization of pyrazolo[1,5-*a*]pyridine **139** bearing an ester functionality in position C3.

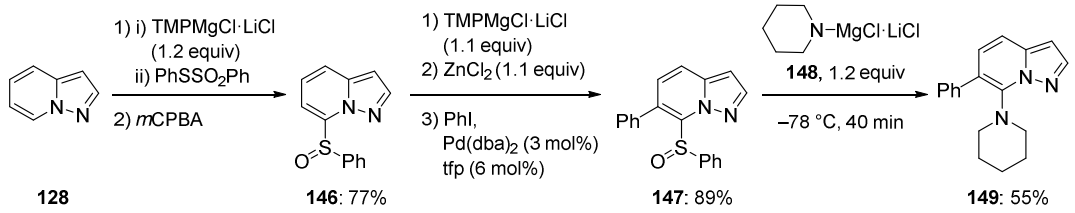
Additionally, ethyl or NHBoc substituted pyrazolo[1,5-*a*]pyridines at the C5-position bearing an ester at C3 (**142** and **143**) did not influence the metalation selectivity, leading to 3,5,7-trifunctionalized pyrazolo[1,5-*a*]pyridines of type **144** and **145** (Scheme 40). In the case of **143**, 2.0 equivalents of TMPMgCl·LiCl were required for a complete magnesiation due to a carbamate functionality deprotonation. Reaction of the corresponding magnesium species with several electrophiles, including 2-bromoquinoline and 3-iodopyridine gave the trifunctionalized pyrazolo[1,5-*a*]pyridines **144a–d** and **145a–d** in 46–98% yield (Scheme 40).



Scheme 40: Metalation and functionalization of substituted pyrazolo[1,5-*a*]pyridines bearing a substituent in position C3 and C5.

5.4 Sulfoxide Directed *ortho*-Metalation and Amination Using a Magnesium Amide

Sulfoxides have shown to be excellent directed metalation groups (DMGs) and are also prone to undergo sulfoxide/magnesium exchange reactions, making them versatile intermediates in heteroarene functionalization.[102] Thus, pyrazolo[1,5*a*]pyridine (**128**) was magnesiated under standard conditions and then quenched with *S*-phenyl benzenethiosulfonate. The resulting thioether was then oxidized using *m*CPBA (1.1 equiv) to give the sulfoxide **146** in 77% yield over two steps (Scheme 41). Subsequent directed *ortho*-metalation[33,61] using TMPMgCl·LiCl (1.1 equiv) at –30 °C for 15 min, followed by Negishi cross-coupling with iodobenzene gave the *ortho*-arylated pyrazolo[1,5-*a*]pyridine **147** in 89% yield. Surprisingly, a sulfoxide/magnesium exchange was not possible using *i*PrMgCl·LiCl.[103] However, a new transition-metal-free amination of a heteroaryl sulfoxide was achieved. Thus, **147** was treated with 1.2 equiv of piperidyl magnesium amide **148** at –78 °C and, after 40 min reaction time, the 6,7-difunctionalized pyrazolo[1,5-*a*]pyridine **149** was isolated in 55% yield (Scheme 41).



Scheme 41: Directed *ortho*-metalation of a sulfoxide-substituted pyrazolo[1,5-*a*]pyridine using TMPMgCl·LiCl, followed by a transition-metal-free amination reaction.

[102] a) L. Melzig, C. B. Rauhut, N. Naredi-Rainer, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 5362–5372; b) N. M. Barl, E. Sansiaume-Dagousset, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 10093–10096; c) C. Sämann, E. Coya, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 1430–1434.

[103] When pyrazolo[1,5-*a*]pyridine sulfoxides were treated with *i*PrMgCl·LiCl at –78 °C the corresponding *iso*propylated heterocycles were isolated in low yield (below 35%).

6 Lewis Acid Directed Regioselective Metalations of Pyridazine

6.1 Introduction

N-Heterocycles are invaluable scaffolds in pharmaceutical and material research.[2,78] Whereas the functionalization of pyridines is well established, other diazines such as pyrimidines and pyrazines are much less investigated and the regioselective functionalization of the pyridazine scaffold (**150**) is still in its infancy.[50,104] Pyridazines are especially important *N*-heterocycles since they are present in various pharmaceuticals and agrochemicals.[105] Also, they play the role of bioisosteres of pyridines and may therefore be important in drug design.[106] Although a metalation of pyridazine (**150**) using TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl) in the presence of $ZnCl_2$·TMEDA (TMEDA = tetramethylethylenediamine) has been reported by Mongin, the *ortho*-regioselectivity was only 83%.[104b] Earlier metalations were found to proceed in moderate yields (16–32%).[104a] Kondo has shown, that a *meta*-functionalization of **150** could be achieved using an excess of a bulky Schwesinger base.[107] Previously, it has been reported that magnesium and zinc organometallics are compatible with strong Lewis acids including BF_3·OEt_2.[48,49,87] These frustrated Lewis pairs[98] proved to be exceptional reagents for the regioselective metalation of various *N*-heterocycles.[87] So far, directed *ortho*-metalations (D*o*M) of *N*-heterocycles have been the privileged method for performing regioselective metalations.[33,61] *Meta*-metalations of arenes have been achieved using mixed alkali-metal-mediated metalations in which the second metal sodium plays a pivotal role in the stability of the formed organometallic species.[108] Remote lithiations are also feasible on sterically hindered silylated arenes.[109] That Lewis acids strongly acidify the protons of pyridazine (**150**) was demonstrated by calculations,[110] showing that the ease of deprotonation may increase by mono-complexation (see **151**) and further by a bis-complexation as shown in **152** (Scheme 42). These calculations led us to examine the metalation of **150** using mono- or bidentate Lewis

---

[104] a) N. Ple, A. Turck, K. Couture, G. Queguiner, *J. Org. Chem.* **1995**, *60*, 3781–3786; b) A. Seggio, F. Chevallier, M. Vaultier, F. Mongin, *J. Org. Chem.* **2007**, *72*, 6602–6605; c) J.-M. L'Helgoual'ch, G. Bentabed-Ababsa, F. Chevallier, M. Yonehara, M. Uchiyama, A. Derdour, F. Mongin, *Chem. Commun.* **2008**, 5375–5377; d) S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256–7260.

[105] a) J. P. Chambon, J. Brochard, A. Hallot, M. Heaulme, R. Brodin, R. Roncucci, K. Biziere, *J. Pharmacol. Exp. Ther.* **1985**, *233*, 836–844; b) A. Perio, J. P. Chambon, R. Calassi, M. Heaulme, K. Biziere, *J. Pharmacol. Exp. Ther.* **1986**, *239*, 542–547; c) M. Asif, *Curr. Med. Chem.* **2012**, *19*, 2984–2991; d) H. Abou-Hamdan, L. Désaubry, *J. Org. Chem.* **2018**, *83*, 2954–2958.

[106] a) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591; b) C. G. Wermuth, *MedChemComm* **2011**, *2*, 935–941.

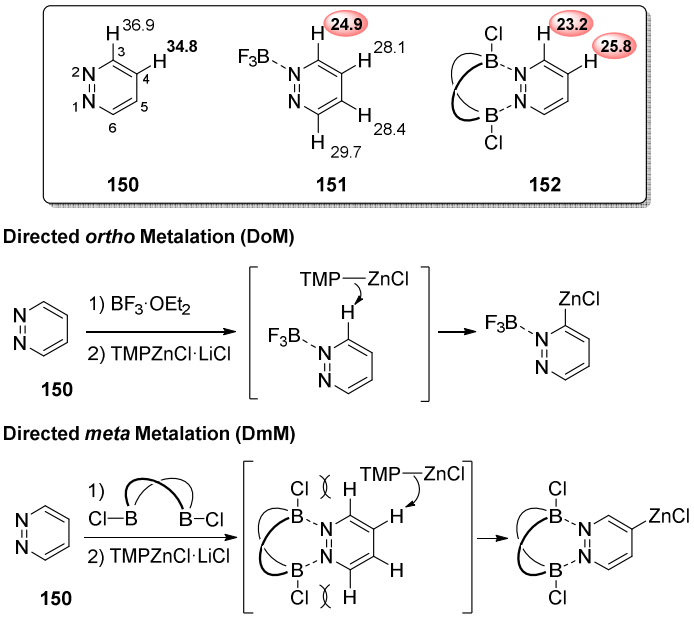
[107] a) T. Imahori, Y. Kondo, *J. Am. Chem. Soc.* **2003**, *125*, 8082–8083; b) T. Imahori, K. Suzawa, Y. Kondo, *Heterocycles* **2008**, *76*, 1057–1060.

[108] a) P. C. Andrikopoulos, D. R. Armstrong, D. V. Graham, E. Hevia, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, C. Talmard, *Angew. Chem. Int. Ed.* **2005**, *44*, 3459–3462; b) D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2006**, *45*, 3775–3778; c) A. J. Martínez-Martínez, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, *Science* **2014**, *346*, 834–837.

[109] a) M. Schlosser, C. Heiss, E. Marzi, R. Scopelliti, *Eur. J. Org. Chem.* **2006**, 4398–4404; b) A. B. Bellan, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 1838–1841.

[110] For further details, see the Experimental Part C.

acids. Herein, we wish to report, that the appropriate choice of a Lewis acid considerably facilitates a metalation and, combined with steric effects, allows the regioselective metalation of the pyridazine scaffold (**150**) either in position C3 or in position C4 (Scheme 42).

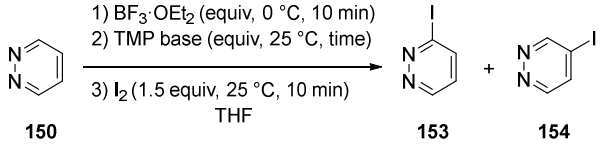


Scheme 42: Calculated pK_a values of pyridazine (**150**), the pyridazine-BF_3 adduct (**151**), and a bidentate Lewis acid-pyridazine adduct (**152**) and the directed *ortho*- and *meta*-metalation of pyridazine (**150**) using TMPZnCl·LiCl.

6.2 Directed *ortho*- and *meta*-Metalation and Functionalization of Pyridazine Using BF_3·OEt_2

Thus, the metalation of pyridazine (**150**) with TMPMgCl·LiCl (**31**)[15,37] in THF in the absence or presence of BF_3·OEt_2 was examined. In both cases, the yield was low and a good regioselectivity for this metalation could only be achieved in the presence of the Lewis acid (Table 5, entries 1–2). Higher yields were obtained, using the more covalent metal amide TMPZnCl·LiCl (**62**, entries 3–6).[15,50] A low regioselectivity of the zincation was observed in the absence of BF_3·OEt_2 (entry 3). However, in the presence of BF_3·OEt_2 (1.1 equiv), a room temperature metalation of **150** proceeds within 2 h reaction time (entry 4). A crude NMR-determination showed a 96:4 ratio between 3-iodopyridazine (**153**) and 4-iodopyridazine (**154**). By using 1.5 equiv of TMPZnCl·LiCl (**62**) and extending the reaction time to 6 h a maximum conversion and excellent regioselectivity (**153**:**154** = 97:3) was obtained, leading, after iodolysis, to pure 3-iodopyridazine (**153**) in 57% isolated yield.

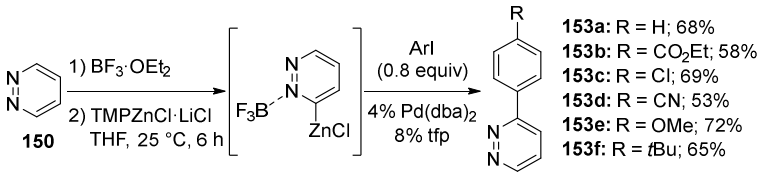
Table 5: Optimization of the reaction conditions for the directed *ortho*-metalation of pyridazine (**150**).



entry	TMP base	BF_3·OEt_2	Time [h]	yield[a]	ratio (**153**:**154**)[b]
1	TMPMgCl·LiCl (**31**)[c] (1.05 equiv)	-	0.25	12%	32:68
2	TMPMgCl·LiCl (**31**)[c] (1.05 equiv)	1.1 equiv	0.25	1%	96:4
3	TMPZnCl·LiCl (**62**) (1.10 equiv)	-	2	45%	60:40
4	TMPZnCl·LiCl (**62**) (1.30 equiv)	1.1 equiv	2	45%	96:4
5	TMPZnCl·LiCl (**62**) (1.30 equiv)	1.1 equiv	6	64%	n.d.
6	TMPZnCl·LiCl (**62**) (1.50 equiv)	1.1 equiv	6	72% (57%)[d]	97:3

[a] NMR yield using trimethoxybenzene as standard. [b] Determined by NMR analysis. [c] The reaction was run at –78 °C. [d] Isolated yield of **154**.

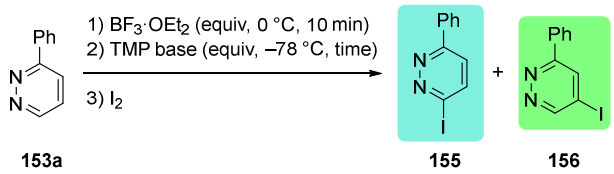
Further functionalizations were performed and an arylation using palladium-catalyzed Negishi cross-couplings[26] with various electron-rich and -poor aryl iodides, provided the 3-arylated pyridazines **153a–f** in 53–72% yield (Scheme 43).



Scheme 43: BF_3·OEt_2 mediated *ortho*-zincation and arylation of pyridazine (**150**).

In order to expand the scope of such metalations, 3-phenylpyridazine (**153a**, prepared according to Scheme 43) was treated with various metalation conditions (Table 6). The very strong and kinetically active base TMPLi (**119**, 0.95 equiv) led to an almost completely regioselective lithiation at position C6 (**155**:**156** ratio = 96:4), providing, after iodolysis and isolation, the pure iodopyridazine **155** in 72% yield (Table 6, entry 1).

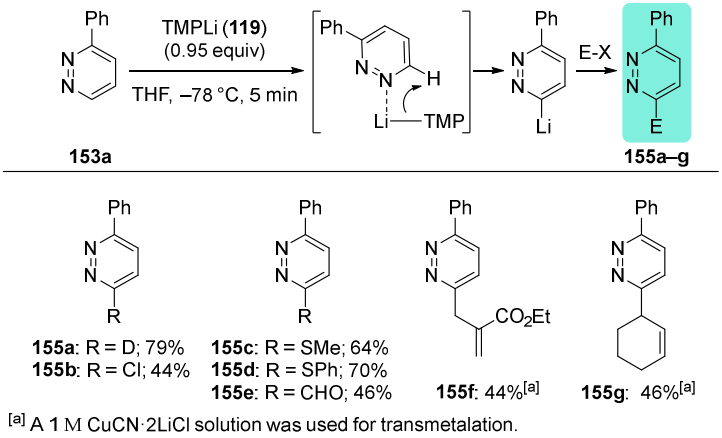
Table 6: Optimization of the reaction conditions for the directed *ortho*- and *meta*- metalation of 3-phenylpyridazine (**153a**).



entry	TMP base (equiv)	$BF_3 \cdot OEt_2$	time	yield	ratio (**155**:**156**)[a]
1	TMPLi (**119**) (0.95 equiv)	-	5 min	72%[b]	96:4
2	TMPMgCl·LiCl (**31**) (1.1 equiv)	1.1 equiv	20 min	65%[c]	44:56
3	TMPMgCl·LiCl (**31**) (2.0 equiv)	1.1 equiv	20 min	82%[c] (58%)[b]	27:73
4	TMPMgCl·LiCl (**31**) (3.0 equiv)	1.1 equiv	20 min	45%[c]	26:74

[a] Determined by NMR analysis. [b] Isolated yield of the main regioisomer. [c] NMR yield using trimethoxybenzene as standard.

These conditions were used for further reactions of the metal species with D_2O, $(Cl_3C)_2$, $MeSSO_2Me$, $PhSSO_2Ph$, and *N*-formylmorpholine, as well as allylic bromides, to give various 2,6-disubstituted pyridazines **155a–g** in 44–79% yield (Scheme 44).

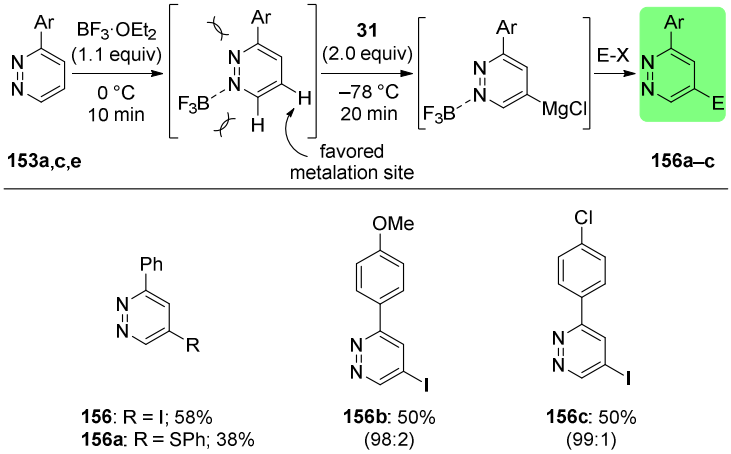


[a] A 1 M CuCN·2LiCl solution was used for transmetalation.

Scheme 44: Directed *ortho*- metalation of 3-phenylpyridazine (**153a**) using TMPLi (**119**).

Alternatively, using TMPMgCl·LiCl (**31**, 1.1 equiv) in the presence of $BF_3 \cdot OEt_2$ (1.1 equiv) led to an unselective deprotonation. In this case, after iodolysis, a 44:56 ratio between the iodides **155** and **156** was obtained (Table 6, entry 2). Interestingly, increasing the amount of **31** (2.0 equiv) led to an improved regioselectivity of 27:73 (Table 6, entry 3). This result may be explained by assuming that 1.0 equiv of **31** is used up to activate the heterocycle in addition to $BF_3 \cdot OEt_2$, also playing the role of a Lewis acid, whereas the second equivalent acts as deprotonating agent. Further increase of the amount of **31** did not improve this regioselectivity (entry 4). This enhanced selectivity proved to be sufficient for preparative applications. Thus, the treatment of various 2-arylpyridazines (**153a**,**c**,**e**) with

TMPMgCl·LiCl (**31**) in the presence of $BF_3 \cdot OEt_2$ led, after iodolysis or thiolation, to the regiomerically pure products **156** and **156a** in 38–58% yield. Interestingly, replacing the 2-phenyl substituent of **153a** with a *para*-anisyl or *para*-chlorophenyl substituent, led, with the same base system, to an almost perfectly regioselective metalation (regioisomeric ratio = 98:2 (**156b**) and 99:1 (**156c**)). After iodolysis, the pyridazines **156b** and **156c** were obtained in 50% yield (Scheme 45). To confirm the regioselectivity of the reaction, a crystal structure ob **156c** was obtained.[111]



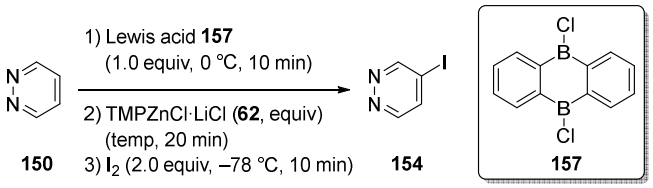
Scheme 45: Directed *meta*-metalation of 3-arylpyridazines **153a**,**c**,**e** using $BF_3 \cdot OEt_2$ and TMPMgCl·LiCl (**31**).

[111] CCDC 1906337 (**156c**), CCDC 1906338 (**155c**), CCDC 1906339 (**153a**), and CCDC 1906340 (**151**) contain the supplementary crystallographic data for this chapter. These data are provided free of charge by The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

6.3 Directed *meta*-Metalation of Pyridazine Using a Bidentate Lewis Acid

These results led us to examine further possibilities for a Lewis acid directed *meta*-metalation. After several experiments, we chose the bidentate diboroanthracene **157**, first reported by Kaufmann.[112] Thus, mixing equimolar amounts of **157** and **150** at 0 °C led to a yellow solution, indicating the formation of a 1:1 complex. The structure of this complex **158** was confirmed by NMR studies.[113] Treatment of **158** with TMPZnCl·LiCl (**62**) at 0 °C led to the formation of the zincated pyridazine **159**, which, after iodolysis, exclusively gave 4-iodopyridazine **154** in 40% yield (Table 7, entry 1).

Table 7: Optimization of the reaction conditions for the Lewis acid directed *meta*-metalation of pyridazine (**150**).

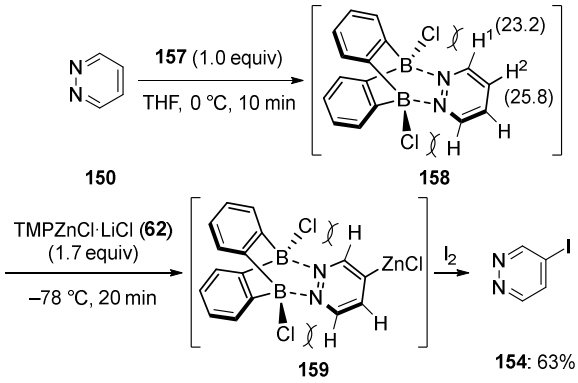


entry	equiv	temperature	yield[a]	ratio (meta:ortho)[b]
1	1.3	0 °C	40%[c]	99:1
2	1.3	–78 °C	52%	99:1
3	1.7	–78 °C	86% (63%)[c]	99:1
4	2.0	–78 °C	69%	99:1

[a] NMR yield using trimethoxybenzene as standard. [b] Determined by NMR analysis. [c] Isolated yield.

Lowering the temperature to –78 °C resulted in an increase in yield to 52% (entry 2). An additional screening of equivalents showed, that with 1.7 equiv of **62**, the optimal reaction conditions were achieved, leading to **154** in 63% isolated yield (Table **7**, entries 3–4, Scheme 46). According to the calculations,[114] H^1 is the most acidic proton ($pK_a(H^1)$=23.2). However, due to steric effects combined with a high acidity ($pK_a(H^2)$=25.8), exclusively H^2 is deprotonated.

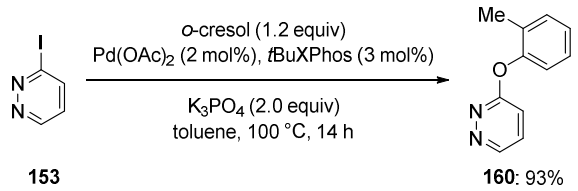
[112] W. Schacht, D. Kaufmann, *J. Organomet. Chem.* **1987**, *331*, 139–152.
[113] For further details, see the Experimental Part C and: S. N. Kessler, H. A. Wegner, *Org. Lett.* **2010**, *12*, 4062–4065.
[114] For further details, see the Experimental Part C.



Scheme 46: Directed *meta*-metalation and functionalization of pyridazine using the bidentate Lewis acid **157** and TMPZnCl·LiCl (**62**).

6.4 Preparation of the Herbicide Credazine

Finally, to prove the synthetic utility of these regioselective metalations, the herbicide credazine (**160**)[115] was prepared. Thus, 3-iodopyridazine (**150**) was dissolved in toluene and mixed with *o*-cresol (1.2 equiv), $Pd(OAc)_2$ (2 mol%), *t*BuXPhos (3 mol%) and potassium phosphate (2.0 equiv). After stirring at 100 °C for 14 h, credazine (**153**) was obtained in 93% yield (Scheme 47).



Scheme 47: Synthesis of the herbicide credazine (**160**) starting from 3-iodopyridazine (**153**).

[115] M. Nakagawa, M. Ando, *Agric. Biol. Chem.* **1977**, *41*, 1975-1984.

7 Preparation of Polyfunctional Arylzinc Organometallics in Toluene via Halogen/Zinc Exchange Reactions

7.1 Introduction

Organozinc reagents are key intermediates in organic synthesis since they tolerate most functional groups and readily participate in transition-metal-catalyzed C-C bond forming reactions.[116] Especially, aryl and heteroaryl zinc halides have been widely used organometallics for preparing complex organic molecules.[117] Organozinc compounds are generated by directed insertion of zinc powder to organic halides[17,20c-d,118] or by directed metalation using TMP-zinc bases (TMP = 2,2,6,6-tetramethylpiperidyl).[15,50] A halogen/zinc exchange is possible using mixed metal reagents of type R_3ZnLi or R_4ZnLi_2, leading to lithium organozincates.[119] Also, a Li(acac)-catalyzed I/Zn-exchange performed on aryl and heteroaryl iodides using pyrophoric and light sensitive *i*Pr_2Zn in NMP has been reported.[25] Unfortunately, the corresponding less expensive aryl or heteroaryl bromides do not react under these conditions. For preparing related organomagnesium species, the exchange reagent *i*PrMgCl·LiCl (*turbo*-Grignard) has been extensively used, since it allows high rates for the Br/Mg-exchange reaction.[24] This exchange can be further accelerated by replacing LiCl by a stronger donor, namely a lithium alkoxide (ROLi; R = 2-ethylhexyl).[30] Furthermore, this exchange could be performed in the industrially friendly solvent toluene. Herein, we report a new I/Zn and firstly, a Br/Zn exchange using a bimetallic exchange reagent of type *s*Bu_2Zn·2LiOR (**161**), which allows the generation of a wide range of polyfunctional aryl- and heteroarylzinc reagents.[56,120]

---

[116] a) E.-i. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340–348; b) P. Knochel, R. D. Singer, Chem. Rev. **1993**, *93*, 2117–2188; c) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, in *Preparation and Applications of Functionalized Organozinc Compounds. Organic Reactions. Vol. 58*, Wiley-VCH, Weinheim, **2004**, 417–759; d) E.-i. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738–6764; e) *Metal-Catalyzed Cross-Coupling Reactions, Second Edition* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2008**; f) Y.-H. Chen, M. Ellwart, V. Malakhov, P. Knochel, *Synthesis* **2017**, *49*, 3215–3223.

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

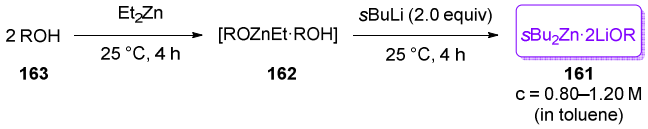
[118] C. Y. Liu, X. Wang, T. Furuyama, S. Yasuike, A. Muranaka, K. Morokuma, M. Uchiyama, *Chem. Eur. J.* **2010**, *16*, 1780–1784.

[119] a) M. Uchiyama, T. Furuyama, M. Kobayashi, Y. Matsumoto, K. Tanaka, *J. Am. Chem. Soc.* **2006**, *128*, 8404–8405; b) T. Furuyama, M. Yonehara, S. Arimoto, M. Kobayashi, Y. Matsumoto, M. Uchiyama, *Chem. Eur. J.* **2008**, *14*, 10348–10356; c) L. Melzig, C. R. Diène, C. J. Rohbogner, P. Knochel, *Org. Lett.* **2011**, *13*, 3174–3177; d) D. Tilly, F. Chevallier, F. Mongin, P. C. Gros, *Chem. Rev.* **2014**, *114*, 1207–1257.

[120] The compounds **166a**–**c**,**h**,**i**,**k**–**p**,**r** and **169a**,**b**,**e**–**k**,**r** were prepared by A. Desaintjean under the guidance of M. Balkenhohl and D.S. Ziegler and will be shown for the sake of completeness. See: A. Desaintjean, Dissertation, LMU München. The analytical data can be found in the corresponding publication.

7.2 The I/Zn Exchange of Aryl and Heteroaryl Iodides and Bromides

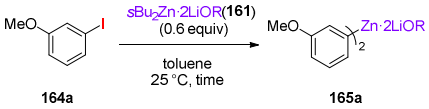
Thus, we have prepared several zinc alkoxides ROZnEt·ROH of type **162** by treating various alcohols (ROH, **163**) with Et_2Zn (25 °C, 4 h) in toluene.[121] These zinc alkoxides (**162**) further reacted with *s*BuLi (2.0 equiv, in cyclohexane) to produce the bimetallic reagent tentatively represented as *s*Bu_2Zn·2LiOR (**161**). Removal of the solvents and further redissolution in toluene provided a light yellow solution of **161** (c = 0.8–1.2 M in toluene; Scheme 48) which can be stored at 25 °C over months without significant loss of reactivity.

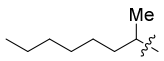
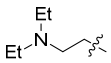
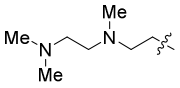


Scheme 48: Preparation of bimetallic exchange reagents of type **161**.

To our delight, the complex *s*Bu_2Zn·2LiOR (R = 2-octyl; **161a**) reacted with 3-iodoanisole (**164a**) in toluene[122] within 30 min at 25 °C, providing bis-anisylzinc (**165a**) in 23% yield, as determined by GC-analysis of reaction aliquots (Table 8, entry 1). The use of alcohols bearing *N*-coordination sites further improved the I/Zn exchange.[123] Thus, the complex **161b** (R = -$CH_2CH_2N(Et)_2$) led to the diarylzinc **165a** in 95% GC-yield (entry 2).

Table 8: Optimization of the reaction conditions for the I/Zn exchange using dialkylzinc reagents of type **161**.



entry	*s*Bu_2Zn·2LiOR (**161**)	time [min]	yield[a]
1	**161a**; R = 	30	23%
2	**161b**; R = 	30	95%
3	**161c**; R = 	30	99%
4	**161c**	1	99%

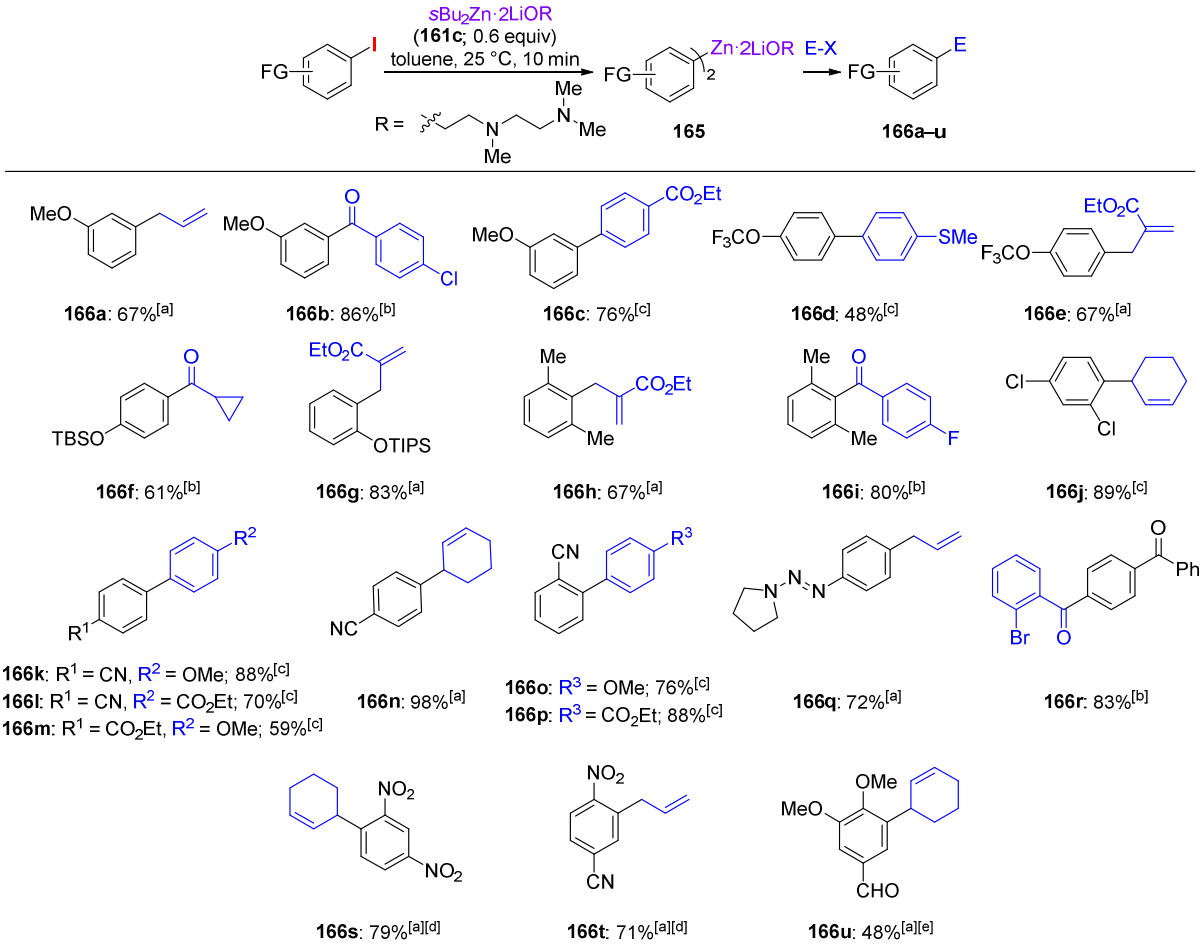
[a] Yield of **165a** determined by GC analysis of reaction aliquots quenched with water.

[121] a) R. L. Geerts, J. C. Huffman, K. G. Caulton, *Inorg. Chem.* **1986**, *25*, 1803–1805; b) S. C. Goel, M. Y. Chiang, W. E. Buhro, *Inorg. Chem.* **1990**, *29*, 4646–4652; c) K. Merz, S. Block, R. Schoenen, M. Driess, *Dalton Trans.* **2003**, 3365–3369.

[122] A solvent screening showed, that the halogen/zinc exchange can not only be performed in hydrocarbons such as toluene or hexane, but also in other industrially friendly ethereal solvents such as 2-methyl-THF or MTBE.

[123] D. Sälinger, R. Brückner, *Chem. Eur. J.* **2009**, *15*, 6688–6703.

An improvement was achieved by using an alcohol bearing a second *N*-coordination site. The new reagent **161c** (R = -$CH_2CH_2N(CH_3)CH_2CH_2N(CH_3)_2$) led to the formation of **165a** in 99% GC-yield (entry 3). In fact, after 1 min reaction time, the I/Zn exchange was already complete (entry 4).Thus, 3-iodoanisole (**164a**) reacted with *s*$Bu_2Zn{\cdot}2LiOR$ (**161c**) in toluene at 25 °C for 10 min, to produce the bis-anisylzinc reagent **165a**. Reaction of **165a** with allyl bromide in the presence of CuI (20 mol%) gave the allylated arene **166a** in 67% yield (Scheme 49). Transmetalation of **165a** to copper using CuI (0.6 equiv) followed by addition of 4-chlorobenzoyl chloride, gave the acylated anisole **166b** in 86% yield. When the zinc species **165a** was mixed with ethyl 4-iodobenzoate, $Pd(OAc)_2$ (3 mol%), and SPhos (6 mol%),[63a,124] a palladium-catalyzed Negishi cross-coupling[26] took place, leading to the biaryl **166c** in 76% yield. 4-Iodobenzotrifluoride underwent a smooth I/Zn exchange using **161c**, leading to the corresponding diarylzinc reagent **165b**.

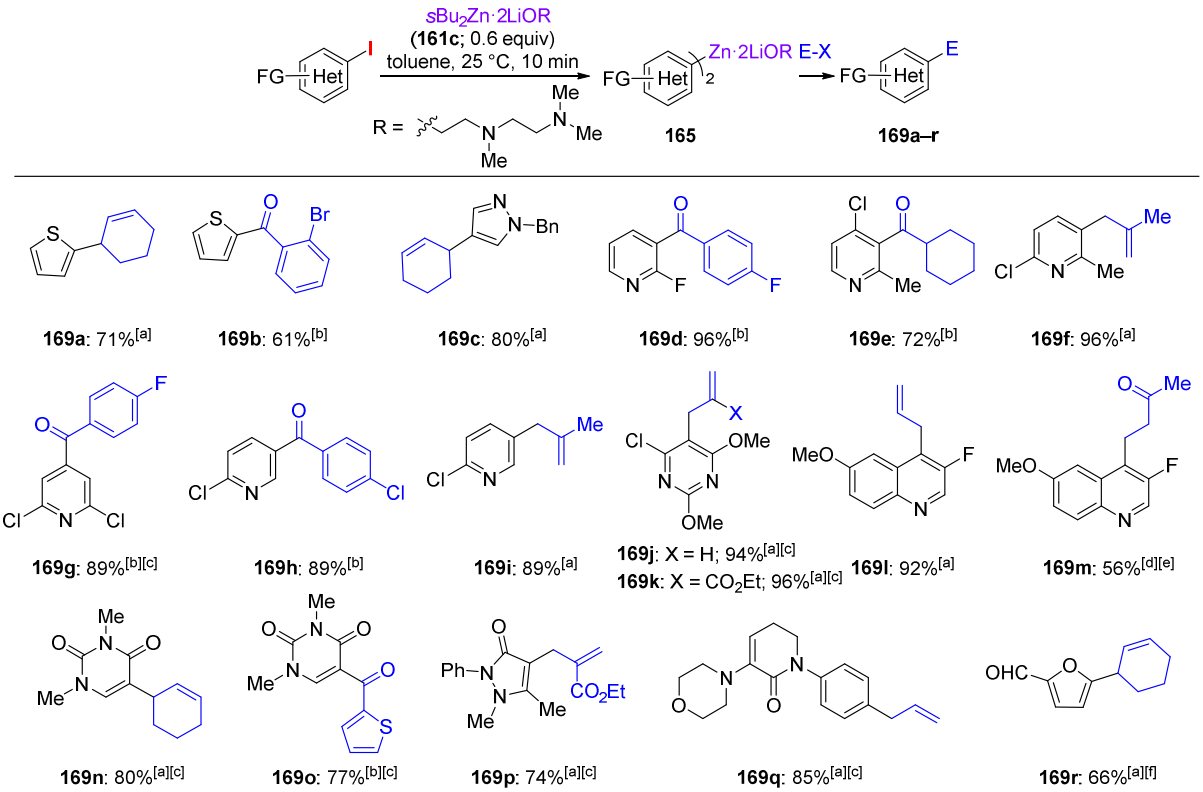


[a]CuI (20 mol%) was used. [b]CuI (0.6 equiv) was used. [c]$Pd(OAc)_2$ (3 mol%) and SPhos (6 mol%) was used. [d]$Tol_2Zn{\cdot}2LiOR$ (**167**, 0.6 equiv, –15 °C, 15 min) was used. [e]*t*$Bu_2Zn{\cdot}2LiOR$ (**168**, 0.8 equiv, 0 °C, 10 min) was used.

Scheme 49: Reaction of various aryl iodides with *s*$Bu_2Zn{\cdot}2LiOR$ (**161c**), followed by electrophilic functionalizations.

[124] R. A. Altman, S. L. Buchwald, *Nat. Protoc.* **2007**, *2*, 3115.

Reaction of **165b** with ethyl 2-(bromomethyl)acrylate or a palladium-catalyzed cross-coupling with 4-iodothioanisole gave functionalized arenes **166d–e** in 48–67% yield (Scheme 49). TBS- or TIPS-protected iodophenols were treated with **161c** and the resulting zinc organometallic was allylated or acylated, providing **166f–g** in 61–83% yield. The zinc reagent obtained from sterically demanding 2-iodo-1,3-dimethylbenzene was quenched with ethyl 2-(bromomethyl)acrylate and 4-fluorobenzoyl chloride to give the 2-substituted *m*-xylenes **166h–i** in 67–80% yield. Various electron-poor aryl iodides bearing ester or nitrile groups readily reacted with **161c** and quenching of the zinc reagent of type **165** with various electrophiles gave products **166j–p** in 59–98% yield. Exchange on an aryl iodide bearing a triazine moiety, followed by allylation, gave **166q** in 72% yield. Next, the diaryl zinc species generated from 4-iodobenzophenone was allylated, providing ketone **166r** in 83% yield. Finally, the I/Zn exchange could also be extended to nitro-substituted aryl iodides. In this case, $Tol_2Zn{\cdot}2LiOR$ (**167**) gave the best result.[125] Hence, the mild exchange reagent $Tol_2Zn{\cdot}2LiOR$ (**167**, R = -$CH_2CH_2N(CH_3)CH_2CH_2N(CH_3)_2$; Tol = *p*-tolyl) was prepared by mixing the akoxide **162c** with tolyllithium (2.0 equiv).[126]



[a]CuI (20 mol%) was used. [b]CuI (0.6 equiv) was used. [c]The reaction was run in THF. [d]Yield over two steps. [e]Reaction conditions: 1) CuI, methyl vinyl ketone, TMSCl 2) TBAF. [f]*t*Bu$_2$Zn·2LiOR (**168**, 0.8 equiv, 0 °C, 10 min) was used.

Scheme 50: Reaction of various heteroaryl iodides with *s*Bu$_2$Zn·2LiOR (**161c**), followed by electrophilic functionalizations.

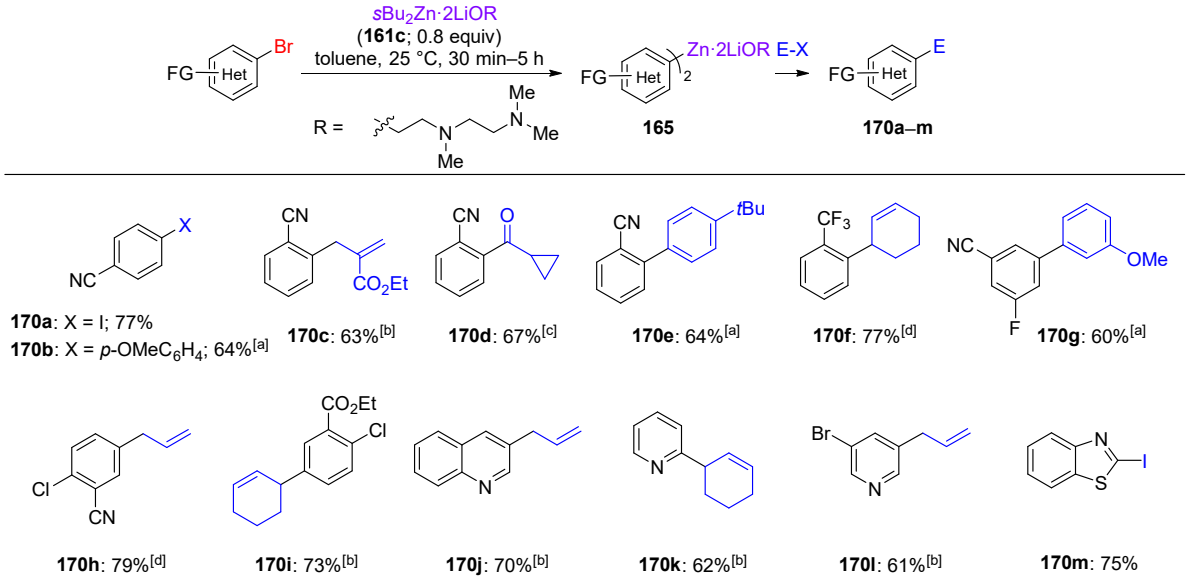
[125] When 2,4-dinitroiodobenzene was treated with **1c**, decomposition of the starting material was observed.
[126] Tolyllithium was prepared by a direct lithium insertion to 4-chlorotoluene, see: C. G. Screttas, B. R. Steele, M. Micha-Screttas, G. A. Heropoulos, *Org. Lett.* **2012**, *14*, 5680–5683.

Treatment of 2,4-dinitroiodobenzene or 3-iodo-4-nitrobenzonitrile with **167** (0.6 equiv) at –15 °C for 15 min, followed by a copper-mediated allylation reaction, afforded nitroarenes **166s–t** in 71–79% yield. For converting an iodo-benzaldehyde to the corresponding zinc species, a short screening showed, that the best exchange reagent was *t*Bu_2Zn·2LiOR (**168**). Thus, the alkoxide **162c** was treated with *t*BuLi (2.0 equiv) and the resulting less nucleophilic reagent *t*Bu_2Zn·2LiOR (**168**, R = -$CH_2CH_2N(CH_3)CH_2CH_2N(CH_3)_2$) was obtained as a 1 M solution in toluene. Reaction of 5-iodo-veratraldehyde with **168** (0.8 equiv, 0 °C, 10 min) afforded a diarylzinc organometallic of type **165**, which, after allylation, provided the vanillin derivative **166u** in 48% yield (Scheme 49).

Various aryl- and heteroaryl iodides reacted smoothly with **161c**, to give a range of functionalized bis-arylzinc organometallics. Thus, bis-thienylzinc either reacted with 3-bromocyclohexene or 2-bromobenzoyl chloride to provide **169a–b** in 61–71% yield (Scheme 50). Benzyl-protected 3-iodopyrazole reacted with **161c** to give, after allylation, **169c** in 80% yield. Also, various iodopyridines, -pyrimidines and -quinoline were converted into the corresponding zinc reagents using **161c** and quenched with several acid chlorides and allyl bromides, producing **169d–l** in 72–96% yield. The organometallic obtained from an iodoquinoline underwent a copper-mediated 1,4-addition to methyl vinyl ketone in the presence of TMSCl. Subsequent enol ether cleavage using TBAF (1.1 equiv, 25 °C, 1 h) gave ketone **169m** in 56% yield over two steps. Reaction of more complex iodinated *N*-heterocycles namely pyrazolone, uracil or 5,6-dihydropyridone gave the expected bis-zinc reagents of type **165**, which, after allylation or acylation provided **169n–q** in 74–85% yield.[127] 4-Iodofuraldehyde was treated with *t*Bu_2·2LiOR (**168**) and the resulting zinc reagent reacted with 3-bromocyclohexene in the presence of CuI to give the furfural derivative **169r** in 66% yield (Scheme 50).

The excellent reactivity of these bimetallic exchange reagents led us to examine the Br/Zn exchange reaction. Thus, treatment of 4-bromobenzonitrile with **161c** (0.8 equiv) at 25 °C for 5 h in toluene (1 M), provided the desired bis-arylzinc of type **165**, which, after quenching with iodine, gave 4-iodobenzonitrile (**170a**) in 77% yield (Scheme 51). Reaction of the same zinc reagent with 4-iodoanisole under palladium-catalysis gave the desired biaryl **170b** in 64% yield.[128] Allylation, acylation and cross-coupling of the zinc reagents obtained from 2-bromobenzonitrile and 2-bromobenzotrifluoride gave **170c–e** in 63–67% yield. Various bromoarenes bearing e.g. an ester functional group underwent a smooth Br/Zn exchange, which, after allylation or cross-coupling, produced the arenes **170f–i** in 60–79% yield. Additionally, bromopyridines and a bromoquinoline were treated with **161c**. Allylation of the resulting zinc reagents gave the functionalized heteroarenes **170j–l** in 61–70% yield. Finally, 2-bromobenzothiazole was mixed with **161c** and the obtained metal species reacted with iodine to give **170m** in 75% yield (Scheme 51).

[127] Due to poor solubility of the aryl iodides, the reactions leading to **169g**,**j**,**k**,**n–q** were performed in THF.
[128] Prior to the addition of the catalyst system and aryl iodide, TMSCl (0.8 equiv, 0 °C, 10 min) was added in order to quench the excess of alkoxide.



[a]$Pd(OAc)_2$ (3 mol%), SPhos (6 mol%) and TMSCl (0.8 equiv) were used. [b]CuI (20 mol%) was used. [c]CuI (0.6 equiv) was used. [d]A 1 M CuCN·2LiCl solution in THF (20 mol%) was used.

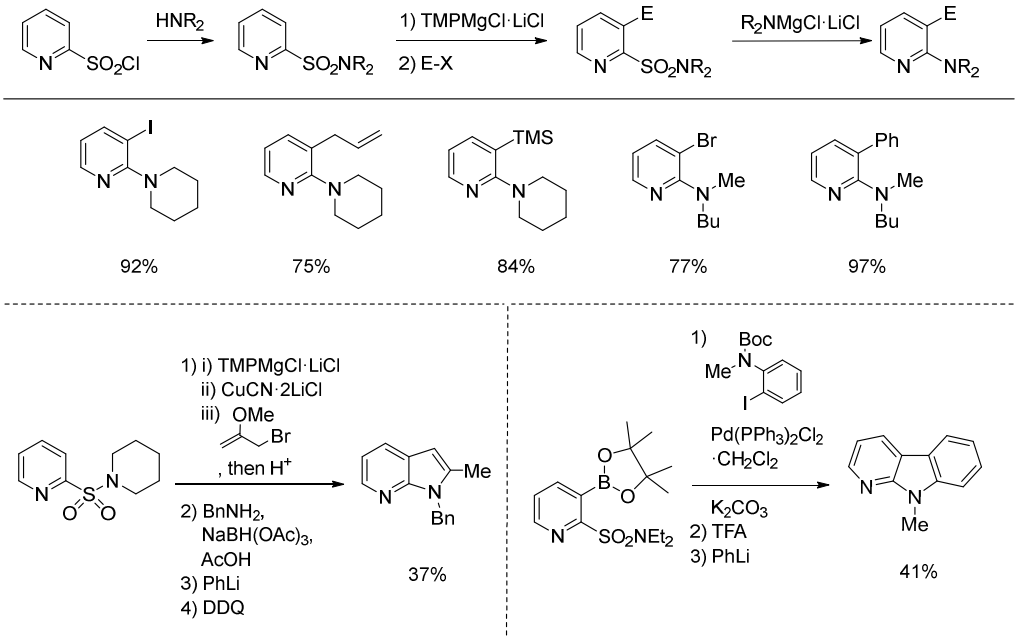
Scheme 51: Reaction of various aryl bromides with *s*Bu_2Zn·2LiOR (**161c**), followed by electrophilic functionalizations.

8 Summary

In this thesis, several challenges in the field of organometallic chemistry were addressed. First, alternative methodologies for the transition-metal-free amination of pyridines and related *N*-heterocycles, such as quinolines or quinoxalines were developed. Not only pyridine sulfonyl chlorides, but also sulfonic acids underwent a facile amination reaction using magnesium amides. Also, phosphorodiamidate-substituted *N*-heterocycles were readily aminated with magnesium amides, presenting a synthetic approach which does not require the use of 2-halo or 2-mercaptopyridines. Then, the regioselective metalation and functionalization of various complex *N*-heterocycles was investigated using Li-, Mg-, and Zn-TMP bases in the presence or absence of a Lewis acid, such as $BF_3 \cdot OEt_2$. First, the 1,5-naphthyridine scaffold was functionalized in up to four positions and a novel "halogen-dance" was disclosed. Pyrazolo[1,5-*a*]pyridines were metalated in up to three different positions with the help of the Lewis acid $BF_3 \cdot OEt_2$ or a previously introduced sulfoxide moiety. This sulfoxide was also aminated using a magnesium amide. Also, pyridazine underwent highly regioselective metalations, and the choice of the Lewis acid allowed either the functionalization in the *ortho* or the *meta* position. Finally, a lithium alkoxide complexed dialkylzinc reagent was developed for a solvent independent halogen/zinc exchange. These reagents of type $R_2Zn \cdot 2LiOR$ allowed not only the exchange of aryl iodides in solvents such as THF or toluene, but also the first bromine/zinc exchange using dialkylzinc reagents. Additionally, highly sensitive functional groups such as ketones, aldehydes or nitro groups were tolerated by these new reagents.

8.1 Transition-Metal-Free Amination of Pyridine-2-sulfonyl Chloride and Related *N*-Heterocycles Using Magnesium Amides

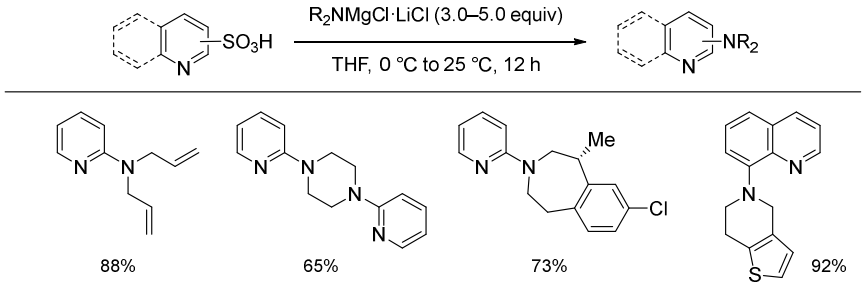
The transition-metal-free amination of pyridine-2-sulfonyl chloride and quinoline-8-sulfonyl chloride was described. Pyridine- and quinoline-sulfonamides, derived from the corresponding sulfonyl chlorides were also suitable candidates for this amination method. Since sulfonamides are good directed metalation groups (DMGs), an efficient *ortho*-metalation and functionalization was possible, which, after subsequent amination reaction, allowed the preparation of 2,3-difunctionalized pyridines and quinolines. Also, an aza-indole and an aza-carbazole were prepared *via* intramolecular cyclization reactions using phenyllithium (Scheme 52).



Scheme 52: Preparation of 2,3-difunctionalized pyridines, an aza-indole, and an aza-carbazole.

8.2 Amination of 2-Pyridinesulfonic and 8-Quinolinesulfonic Acids with Magnesium Amides

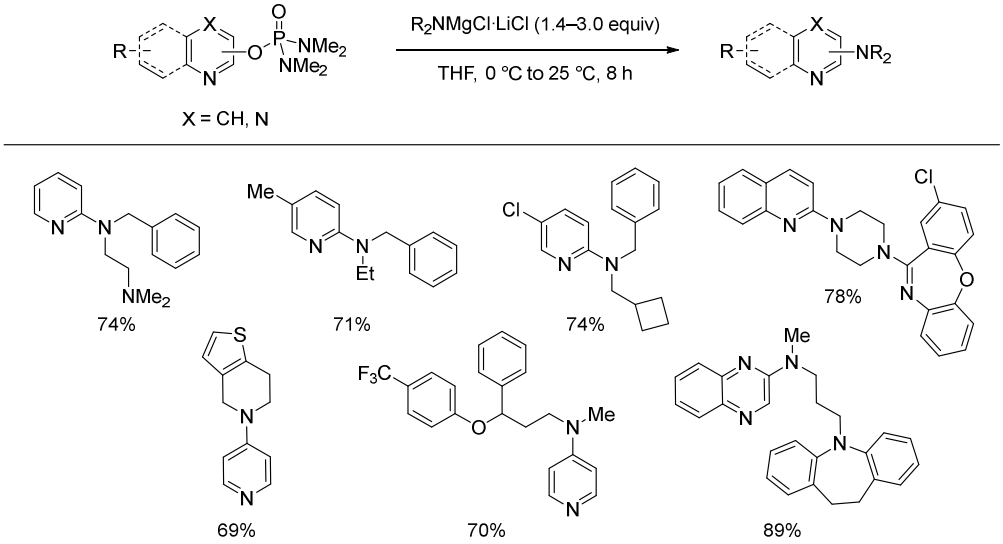
The amination of 2-pyridine- and 8-quinolinesulfonic acid was reported. Several amines, including pharmaceutically active substrates, were applicable to the reaction protocol, affording the respective 2-aminopyridines and 8-aminoquinolines. Also, this amination was readily scaled-up to a 50 mmol scale (Scheme 53).



Scheme 53: Amination of pyridine-2- and quinoline-8-sulfonic acids using magnesium amides.

8.3 Amination of Phosphorodiamidate-Substituted Pyridines and Related *N*-Heterocycles with Magnesium Amides

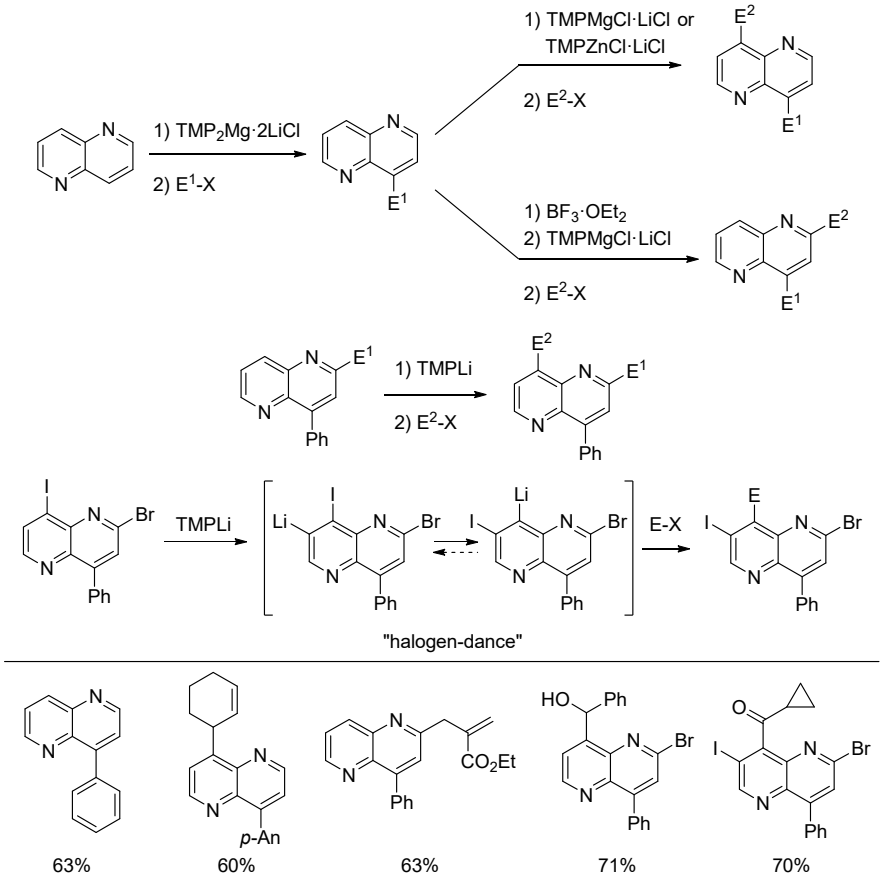
The amination of pyridones was performed by reaction of phosphorodiamidate-substituted pyridines with magnesium amides. Since pyridones are readily accessible reagents, it was not only possible to perform amination reactions with functionalized pyridines, but also the amination of the quinoxaline scaffold was achieved (Scheme 54). Similarly as in chapter 1, a directed *ortho*-metalation/amination sequence was performed.



Scheme 54: Amination of phosphorodiamidate-substituted pyridines, quinolines and quinoxalines using magnesium amides.

8.4 Zn-, Mg-, and Li-TMP Bases for the Successive Regioselective Metalations of the 1,5-Naphthyridine Scaffold

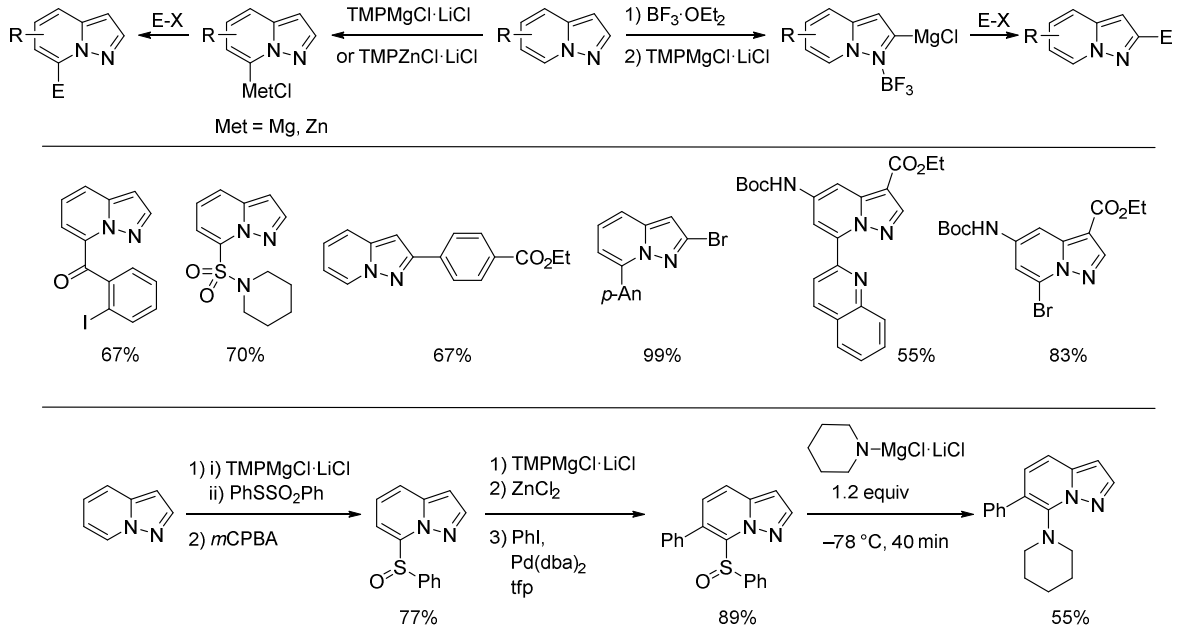
The 1,5-naphthyridine scaffold was regioselectively metalated in up to three positions using Zn-, Mg- and Li-TMP bases in the presence or absence of the Lewis acid $BF_3 \cdot OEt_2$, producing a range of functionalized 1,5-naphtyridines. A fourth substituent was introduced by a novel "halogen-dance" rearrangement, induced by a lithiation using TMPLi (Scheme 55). Additionally the synthesis of two key 1,5-naphthyridines, required for the synthesis of OLED materials and an anti-bacterial agent, was disclosed.



Scheme 55: Metalation and functionalization of the 1,5-naphthyridine skeleton using TMP-bases.

8.5 Regioselective Metalation and Functionalization of the Pyrazolo[1,5-*a*]pyridine Scaffold Using Mg- and Zn-TMP Bases

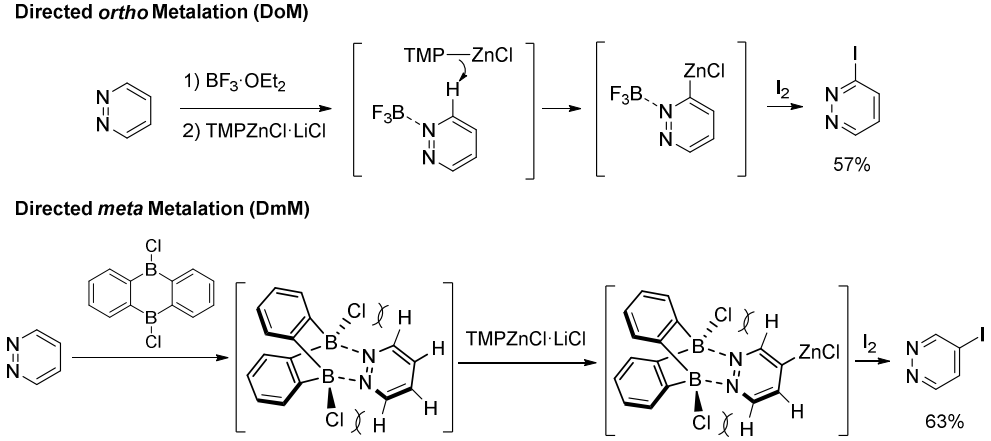
The regioselective metalation of the Pyrazolo[1,5-*a*]pyridine scaffold was investigated using Zn- and Mg-TMP bases. A switch in the selectivity of the metalation was observed, when the Lewis acid $BF_3 \cdot OEt_2$ was mixed with the *N*-heterocycle, prior to addition of the TMP-base, allowing the efficient functionalization of the C2-position. Pyrazolo[1,5-*a*]pyridines bearing various substituents, such as an ester or a carbamate, also underwent an efficient metalation and functionalization. Finally, the amination of a pyrazolo[1,5-*a*]pyridine sulfoxide was performed using a magnesium amide (Scheme 56).



Scheme 56: Metalation and functionalization of pyrazolo[1,5-*a*]pyridine using TMP-bases and the amination of a pyrazolo[1,5-*a*]pyridine sulfoxide using a magnesium amide.

8.6 Lewis Acid Directed Regioselective Metalations of Pyridazine

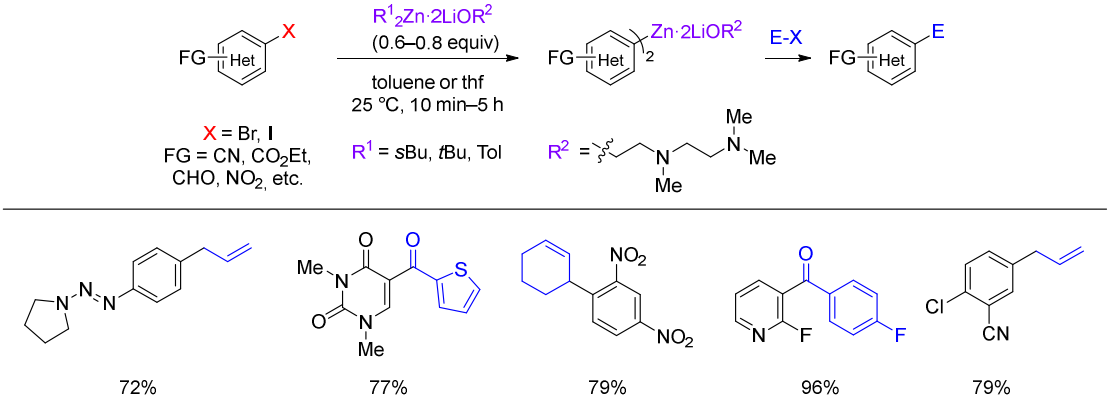
A highly regioselective Lewis acid directed *ortho*- and *meta*-metalation and functionalization of pyridazine was developed. The choice of the Lewis acid is key for the success and the regioselectivity of the reaction, allowing the first Lewis acid directed *meta*-metalation using a TMP-base. This unprecedented reactivity opens up new perspectives for the metalation of heterocycles using metal amide bases (Scheme 57).



Scheme 57: The directed *ortho*- and *meta*-metalation of pyridazine using TMPZnCl·LiCl and the appropriate Lewis acid.

8.7 Preparation of Polyfunctional Arylzinc Organometallics in Toluene via Halogen/Zinc Exchange Reactions

New bimetallic reagents of type $R_2Zn{\cdot}2LiOR$ for the I/Zn and Br/Zn exchange reaction have been developed. Due to the nature of the carbon zinc bond, several highly sensitive functional groups including triazines, ketones, aldehydes or nitro groups could be tolerated. Thus, quenching of the formed diarylzinc species with various electrophiles allowed the preparation of a plethora of functionalized arenes and heteroarenes. Additionally, the exchange could be performed in hydrocarbons such as toluene or hexane, and in ethereal solvents including THF, 2-methyl-THF or MTBE (Scheme 58).



Scheme 58: The halogen/zinc exchange using dialkylzinc reagents complexed with lithium alkoxides of type $R_2Zn{\cdot}2LiOR$.

C. EXPERIMENTAL PART

1 General Considerations

All reactions were carried out under argon or nitrogen atmosphere in glassware dried with a heat gun (650 °C) under high vacuum (<1 mbar). Syringes which were used to transfer anhydrous solvents or reagents were purged thrice with argon or nitrogen prior to use. Indicated yields are isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR (25 °C) and capillary GC. Unless otherwise indicated, all reagents were obtained from commercial sources. Optical rotation values were recorded on a PerkinElmer 241 or Anton Paar MCP 200 polarimeter. The specific rotation is calculated as follows:

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

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

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.
Et_2O was predried over CaH_2 and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.
DMF was distilled from CaH_2 and stored over molecular sieves (3 Å).
MeCN was distilled from CaH_2 and stored over molecular sieves (3 Å).
THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.
Solvents for column chromatography were distilled on a rotary evaporator prior to use.

1.2 Reagents

TMPLi: Tetramethylpiperidine (1.48 g, 10.5 mmol) was dissolved in THF (10 mL) and cooled to –40 °C. Then, *n*BuLi (4.14 mL, 10.0 mmol) was added dropwise and the reaction stirred at 0 °C for 30 min.

TMPMgCl·LiCl: A dry and argon-flushed 250-mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with freshly titrated *i*PrMgCl·LiCl (100 mL, 1.2 M in THF, 120 mmol). TMPH (17.8 g, 126 mmol, 1.05 equiv) was added dropwise at 25 °C. The reaction mixture was stirred at 25 °C until gas evolution ceased (ca. 24 h).[37]

$TMP_2Mg·2LiCl$: In an argon-flushed Schlenk flask equipped with a magnetic stirring bar, TMPH (4.24 g, 30 mmol) was dissolved in THF (30 mL). This solution was cooled to –40 °C and *n*BuLi (2.4 M in Hexane, 12.5 mL, 30 mmol) was added dropwise. After the addition was complete, the reaction mixture was warmed to 0 °C and stirred at this temperature for 30 min. Freshly titrated TMPMgCl·LiCl (1.0 M in THF, 30 mL, 30 mmol) was then added dropwise to the reaction mixture. The reaction mixture was stirred at 0 °C for 30 min, warmed to 25 °C, and stirred for 1 h. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved.[45]

TMPZnCl·LiCl: A dry and argon flushed 250 mL Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with TMPH (8.48 g, 60 mmol) and dissolved in THF (60 mL). This solution was cooled to –40 °C and *n*BuLi (2.4 M in hexane, 25 mL, 60 mmol) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm slowly to –10 °C for 1 h. $ZnCl_2$ (1.0 M in THF, 66 mL, 66 mmol) was added dropwise and the resulting solution stirred for 30 min at –10 °C and then for 30 min at 25 °C. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved.[50]

***i*PrMgCl·LiCl:** Magnesium turnings (2.67 g, 110 mmol) and anhydrous LiCl (4.66 g, 100 mmol) were placed in an argon-flushed flask and THF (50 mL) was added. A solution of *i*PrCl (9.13 mL, 100 mmol) in THF (50 mL) was slowly added at 25 °C. The reaction starts within a few minutes. After addition, the reaction mixture was stirred for 12 h at 25 °C. The grey solution of *i*PrMgCl·LiCl was cannulated to another flask under argon and removed in this way from excess of magnesium. A yield of ca. 95–98% of *i*PrMgCl·LiCl is obtained.[24]

***n*BuLi** solution was purchased from Albemarle (Hoechst, Germany).

***s*BuLi** solution in cyclohexane was purchased from Albemarle or Sigma Aldrich.

***t*BuLi** solution in pentane was purchased from Albemarle or Sigma Aldrich.

Et_2Zn: **Either** a Commerially available Et_2Zn (purchased from Sigma Aldrich, 15 wt.% (= 1.11 M) in toluene) was used **or** Et_2Zn (100 mmol) was dissolved in dry toluene (100 mL) and titrated against I_2 in a 0.5 M LiCl solution at 0 °C. Both Et_2Zn reagents were suitable for the performed reactions.

0.5 M LiCl solution: LiCl (5 mmol) was dried in vacuo using a heatgun (400 °C) for 10 minutes. After cooling to room tempetature, dry THF (10 mL) was added and the mixture stirred until the salt was dissolved completely.

CuCN·2LiCl: A CuCN·2LiCl solution (1.00 m) was prepared by drying CuCN (80.0 mmol, 7.17 g) and LiCl (160 mmol, 6.77 g) in a Schlenk-flask under vacuum at 140 °C for 12 h. After cooling, dry THF (80 mL) was added and stirring continued until the salts were dissolved.[64]

$ZnCl_2$: A $ZnCl_2$ solution (1.00 m) was prepared by drying $ZnCl_2$ (200 mmol, 27.3 g) in a Schlenk-flask under vacuum at 140 °C for 5 h. After cooling, dry THF (200 mL) was added and stirring continued until the salt was dissolved.

$BF_3{\cdot}OEt_2$ was distilled prior to use and stored under argon at 5 °C.

Pyridazine was distilled from CaH_2 prior to use and stored under argon at 5 °C.

2-((2-(Dimethylamino)ethyl)(methyl)amino)ethane-1-ol: The alcohol was distilled in vacuo from CaH_2 (29 mbar, 95 °C) and stored under argon in a Schlenk flask.

1.3 Chromatography

Flash column chromatography was performed using silica gel 60 (0.040–0.063 mm) from MERCK.

Thin layer chromatography was performed using SiO_2 pre-coated aluminum plates (Merck 60, F-254). The chromatograms were examined under 254 nm UV irradiation, by incubating the plates in an iodine chamber and/or by staining the TLC plate with a $KMnO_4$ solution followed by heating with a heat gun.

$KMnO_4$ solution: $KMnO_4$ (3.0 g), 5 drops of conc. H_2SO_4 in water (300 mL).

HPLC was performed on an Agilent Technologies 1200 Series using a Chromolit® SemiPrep RP-18e 100–10 mm column. The HPLC was run with a gradient of acetonitrile/water.

1.4 Content Determination of Organometallic Reagents

***i*PrMgCl·LiCl** was titrated with I_2 in THF.[129]

Organolithium (*n*BuLi, *t*BuLi, TolLi) reagents were titrated with menthol and 1,10-phenanthroline as indicator in THF.[130]

TMPMgCl·LiCl was titrated with benzoic acid and 4-(phenylazo)diphenylamine as indicator in THF.[37]

TMP_2Mg·2LiCl was titrated with benzoic acid and 4-(phenylazo)diphenylamine as indicator in THF.[45]

TMPZnCl·LiCl was titrated with benzoic acid and 4-(phenylazo)diphenylamine as indicator in THF.[50]

TMPLi was titrated with *N*-benzylbenzamide in THF.[131]

***s*BuLi** was titrated against *N*-benzylbenzamide in THF.[131]

1.5 Analytical Data

^{1}H-NMR and **^{13}C-NMR** spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as values in ppm relative to tetramethylsilane. $CDCl_3$ peaks were set to 7.26 ppm in ^{1}H NMR and 77.16 ppm in ^{13}C NMR experiments. The following abbreviations were used to characterize signal multiplicities: s

[129] P. Knochel, A. Krasovskiy, *Synthesis* **2006**, 890–891.
[130] a) H.-S. Lin, L. A. Paquette, *Synth. Commun.* **1994**, *24*, 2503–2506; b) S. C. Watson, J. F. Eastham, *J. Organomet. Chem.* **1967**, *9*, 165–168.
[131] A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.* **1997**, *542*, 281–283.

(singlet), d (doublet), dd (doublet of doublets),t (triplet),q (quartet), hept (heptett) as well as m (multiplet).

Mass spectroscopy: High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an ionization energy of 70 eV. For coupled gas chromatography/mass spectrometry, a HEWLETT-PACKARD HP 6890/MSD 5973 GC/MS system was used. Molecular fragments are reported starting at a relative intensity of 10–20%.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSampl*IR* II Diamond ATR sensor was used. The main absorption peaks are reported in cm^{-1}.

Melting points (m.p.) were determined on a BÜCHI B-540 melting point apparatus and are uncorrected.

2 Transition-Metal-Free Amination of Pyridine-2-sulfonyl Chloride and Related *N*-Heterocycles Using Magnesium Amides

2.1 Typical Procedures

Typical Procedure 1: Amination of pyridine-2-sulfonyl chloride (**72**) and 8-quinolinesulfonyl chloride (**80**)

*i*PrMgCl·LiCl (2.4–5 equiv) was added to a solution of amine (2.4–5 equiv) in THF (5 mL/mmol of sulfonyl chloride) at 0 °C. The solution was stirred for 15 min at 0 °C and then 15 min at 25 °C before being added to a suspension/solution of freshly prepared sulfonyl chloride (1 equiv) in THF (5 mL/mmol of sulfonyl chloride) at 0 °C. The reaction mixture was then stirred at 25 °C until completion. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. If the crude product needed purification, it was purified by flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 2: *ortho*-Functionalization of heteroaryl sulfonamides **73a–b** and **82a–b** using TMPMgCl·LiCl

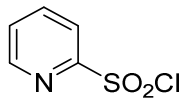
To a solution of the sulfonamide (1 equiv) in THF (5 mL/mmol of the sulfonamide) a solution of TMPMgCl·LiCl (1.2 equiv) was added at 0 °C. After completion of the metalation (2 h, 0 °C) which was checked *via* GC aliquots (hydrolysis and iodolysis), a solution of the electrophile (1.2–1.5 equiv) in THF (5 mL/mmol of sulfonamide) was added and the reaction mixture was allowed to warm slowly to 25 °C. The reaction mixture was stirred at 25 °C until completion, then quenched with water and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 3: Desulfonylation of *ortho*-substituted heteroaryl sulfonamides **77a–e**, **78a–d**, **A**, **B**.

To a solution of sulfonamide in THF (5 mL/mmol of sulfonamide) was added a solution of the corresponding magnesium amide of type **74** at 0 °C. The reaction was then stirred at 25 °C until completion. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. If the crude product needed purification, it was purified by flash chromatography on silica gel using the appropriate eluent.

2.2 Preparation of Compounds 72 to 89

Synthesis of pyridine-2-sulfonyl chloride (72)



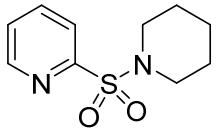
Adapted from a literature procedure,[132] 2-mercaptopyridine (1.11 g, 10.0 mmol) was dissolved in conc. sulfuric acid (28 mL) and cooled to –10°C in a dry ice / acetone bath. Then, NaOCl 13% (42 mL, 30 mmol) was added dropwise without letting the temperature rise above 0 °C. After completion of the addition, the reaction mixture was stirred for 30 min at 0°C. The reaction mixture was extracted with DCM (3 x 150 mL), washed with an aq. 10% Na_2SO_3 solution (200 mL) until decoloration and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo* yielding compound **72** (1.26 g, 7.09 mmol, 71%) as a colorless oil. The crude product **72** was used without purification in the next step.

The spectra matched those of the literature.[132]

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.81 – 8.79 (m, 1H), 8.11 – 8.05 (m, 2H), 7.72 – 7.68 (m, 1H).

[132] M. K. Nielsen, C. R. Ugaz, W. Li, A. G. Doyle, *J. Am. Chem. Soc.* **2015**, *137*, 9571–9574.

Synthesis of 2-(piperidin-1-ylsulfonyl)pyridine (73a)

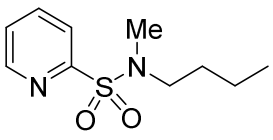


Piperidine (0.29 mL, 3.00 mmol) was added to a solution of sulfonyl chloride **72** (177 mg, 1.00 mmol) in DCM (3 mL) at 0 °C. After stirring at 25 °C for 12 h, the reaction mixture was quenched with water, extracted with DCM (3 x 10 mL) and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 6:4) to give **73a** (184 mg, 813 µmol, 81%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.73 – 8.67 (m, 1H), 7.95 - 7.86 (m, 2H), 7.47 (ddd, J = 6.8, 4.7, 1.9 Hz, 1H), 3.26 (t, 4H), 1.67 - 1.58 (m, 4H), 1.52 - 1.44 (m, 2H).

The spectra matched those of the literature.[60b]

Synthesis of *N*-butyl-*N*-methylpyridine-2-sulfonamide (73b)



N-Butylmethylamine (0.33 mL, 3.00 mmol) was added to a solution of sulfonyl chloride **72** (165 mg, 0.93 mmol) in DCM (3 mL) at 0 °C. After stirring at 25 °C for 12 h, the reaction mixture was quenched with water, extracted with DCM (3 x 10 mL) and dried over Na_2SO_4. After filtration, the solvent was

removed *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 7:3) to give **73b** (182 mg, 797 µmol, 86%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.68 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 7.96 - 7.84 (m, 2H), 7.46 (ddd, *J* = 7.3, 4.7, 1.6 Hz, 1H), 3.21 (t, *J* = 7.3 Hz, 2H), 2.90 (s, 3H), 1.57 - 1.46 (m, 2H), 1.39 - 1.27 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

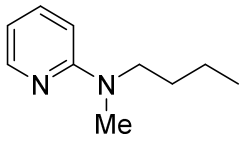
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.3, 150.0, 137.9, 126.5, 122.8, 50.7, 35.4, 30.0, 19.8, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3053, 2959, 2933, 2873, 1577, 1426, 1333, 1170, 1115, 927, 757.

MS (EI, 70 eV): *m/z* (%) = 185 (100), 121 (39), 79 (71).

HRMS (EI) for **$C_{10}H_{17}O_2N_2S$** (229.0966): 229.0988 (M^++H).

Synthesis of 2-(*N*-butylmethylamine)pyridine (75b)



The aminopyridine **75b** was prepared *via* **TP1** using pyridine-2-sulfonyl chloride (177 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.87 mL, 2.40 mmol) and *N*-butylmethylamine (0.28 mL, 2.40 mmol). After stirring at 25 °C for 2 h, the reaction mixture was quenched with water (15 mL), extracted with ethyl acetate (3 x 20 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **75b** (144 mg, 876 µmol, 88%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.39 (ddd, *J* = 8.8, 7.1, 2.0 Hz, 1H), 6.51 – 6.41 (m, 2H), 3.51 – 3.43 (m, 2H), 3.02 (s, 3H), 1.61 – 1.50 (m, 2H), 1.40 – 1.27 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

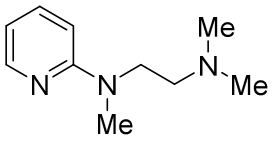
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.6, 148.0, 137.1, 111.1, 105.7, 50.0, 36.3, 29.4, 20.4., 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2970, 3950, 2880, 2860, 1590, 1550, 1500, 1460, 765, 730.

MS (EI, 70 eV): *m/z* (%) = 164 (18), 121 (100), 106 (13), 78 (19).

HRMS (EI) for **$C_{10}H_{16}N_2$** (164.1313): 164.1307 (M^+).

Synthesis of *N*^{1},*N*^{1},*N*^{2}-trimethyl-*N*^{2}-(pyridin-2-yl)ethane-1,2-diamine (75e)



The aminopyridine **75e** was prepared *via* **TP1** using pyridine-2-sulfonyl chloride (177 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.87 mL, 2.40 mmol) and *N,N,N'*-trimethyl-ethylenediamine (0.31 mL, 2.40 mmol). After stirring at 25 °C for 2 h, the reaction mixture was quenched with water (15 mL), extracted with ethyl acetate (3 x 20 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo*. The crude product was purified *via* column chromatography (DCM:MeOH = 7.5:2.5) to give **75e** (130 mg, 725 µmol, 74%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.12 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.39 (ddd, *J* = 8.6, 7.1, 2.0 Hz, 1H), 6.50 – 6.44 (m, 2H), 3.66 – 3.61 (m, 2H), 3.03 (s, 3H), 2.50 – 2.45 (m, 2H), 2.27 (s, 6H).

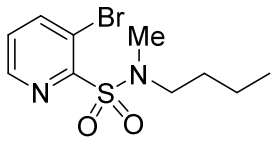
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.6, 148.1, 137.1, 111.5, 105.6, 56.6, 48.4, 45.9, 36.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2970, 3950, 2880, 2860, 1590, 1550, 1500, 1460, 765, 730.

MS (EI, 70 eV): *m/z* (%) = 179 (6), 121 (75), 109 (14), 108 (13), 77 (21), 71 (25), 58 (100).

HRMS (EI) for $C_{10}H_{17}N_3$ (179.1422): 179.1418 (M^+).

Synthesis of 3-bromo-*N*-butyl-*N*-methylpyridine-2-sulfonamide (78a)



The pyridine sulfonamide **78a** was prepared *via* **TP2** using **73b** (205 mg, 898 µmol), TMPMgCl·LiCl (1.19 mL, 1.08 mmol) and 1,2-dibromotetrachloroethane (351 mg, 1.08 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8:2) to give **78a** (202 mg, 658 µmol, 73%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.48 (dd, *J* = 4.6, 1.4 Hz, 1H), 8.07 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.30 (dd, *J* = 8.1, 4.6 Hz, 1H), 3.40 (t, *J* = 7.3 Hz, 2H), 3.09 (s, 3H), 1.67 - 1.59 (m, 2H), 1.44 - 1.34 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.8, 146.5, 143.7, 126.9, 118.4, 51.7, 36.4, 30.4, 19.8, 13.9.

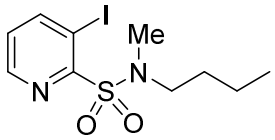
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2934, 2872, 1558, 1460, 1433, 1395, 1338, 1213, 1163, 1137, 1019, 771.

MS (EI, 70 eV): *m/z* (%) = 263 (33), 199 (10), 158 (36), 86 (100).

HRMS (EI) for $C_7H_8BrO_2N_2S$ (262.9490): 262.9329 (M^+-C_3H_7).

M.p. (°C): 69 – 70.

Synthesis of *N*-butyl-3-iodo-*N*-methylpyridine-2-sulfonamide (78b)



The pyridine sulfonamide **78b** was prepared *via* **TP2** using **73b** (272 mg, 1.19 mmol), TMPMgCl·LiCl (1.57 mL, 1.43 mmol) and iodine (453 mg, 1.79 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8:2) to give **78b** (251 mg, 865 µmol, 73%) as an off-white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.49 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.35 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.12 (dd, *J* = 8.0, 4.6 Hz, 1H), 3.38 (t, *J* = 7.2 Hz, 2H), 3.07 (s, 3H), 1.67 - 1.56 (m, 2H), 1.44 - 1.32 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.6, 150.5, 147.0, 126.6, 89.1, 51.7, 36.4, 30.3, 19.8, 13.8.

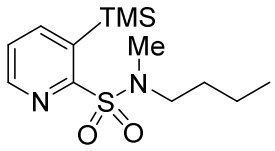
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2933, 2872, 1553, 1460, 1388, 1333, 1165, 1131, 766.

MS (EI, 70 eV): *m/z* (%) = 310 (73), 247 (34), 219 (40), 205 (53), 204 (83), 86 (100), 43 (90).

HRMS (EI) for **$C_7H_8IO_2N_2S$** (310.9351): 310.9349 (M^+-C_3H_7).

M.p. (°C): 71 – 73.

Synthesis of *N*-butyl-*N*-methyl-3-(trimethylsilyl)pyridine-2-sulfonamide (78c)



The pyridine sulfonamide **78c** was prepared *via* **TP2** using **73b** (228 mg, 1.00 mmol), TMPMgCl·LiCl (1.32 mL, 1.20 mmol) and trimethylsilyl chloride (0.16 mL, 1.3 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8.5:1.5) to give **78c** (251 mg, 835 µmol, 84%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.54 (dd, *J* = 4.6, 1.8 Hz, 1H), 8.05 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.37 (dd, *J* = 7.6, 4.6 Hz, 1H), 3.30 (t, *J* = 7.2 Hz, 2H), 2.99 (s, 3H), 1.61 - 1.52 (m, 2H), 1.43 - 1.32 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.43 (s, 9H).

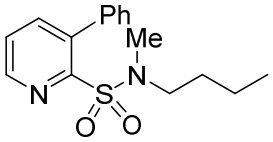
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.2, 148.7, 145.2, 135.3, 125.2, 51.4, 36.2, 30.3, 19.9, 13.9, 0.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2935, 2874, 1564, 1548, 1371, 1330, 1168, 1125, 844, 775.

MS (EI, 70 eV): *m/z* (%) = 286 (15), 285 (79), 257 (19), 193 (19), 165 (45), 152 (31), 151 (74), 150 (100), 136 (25), 86 (66).

HRMS (EI) for **$C_{13}H_{23}O_2N_2SSi$** (299.1250): 299.1242 (M^+-H).

Synthesis of *N*-butyl-*N*-methyl-3-phenylpyridine-2-sulfonamide (78d)



The pyridine sulfonamide **78d** was prepared *via* **TP2** using **73b** (228 mg, 1.00 mmol) and TMPMgCl·LiCl (1.32 mL, 1.20 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (1.20 mL, 1.20 mmol) was added at 0 °C and the reaction was stirred at this temperature for 30 min. Then, iodobenzene (0.11 mL, 1.00 mmol), SPhos (16.0 mg, 40.0 µmol) and $Pd(OAc)_2$ (4.50 mg, 20.0 µmol) were added and the reaction stirred at 25 °C for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8.5:1.5) to give **78d** (259 mg, 851 µmol, 85%) as a light yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.55 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.75 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.54 - 7.38 (m, 6H), 3.31 (t, *J* = 7.2 Hz, 2H), 3.00 (s, 3H), 1.61 - 1.50 (m, 2H), 1.40 - 1.27 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.5, 147.0, 141.0, 137.8, 137.0, 129.5, 128.5, 128.2, 125.7, 51.5, 36.2, 30.4, 19.8, 13.9.

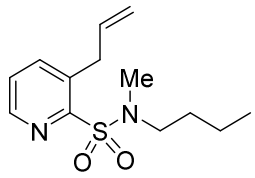
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2934, 2872, 1444, 1334, 1161, 722.

MS (EI, 70 eV): *m/z* (%) = 261 (14), 197 (27), 156 (17), 155 (98), 154 (100), 127 (40), 86 (69).

HRMS (EI) for **$C_{16}H_{20}N_2O_2S$** (305.1323): 305.1279 (M^++H).

M.p. (°C): 100 – 102.

Synthesis of 3-allyl-*N*-butyl-*N*-methylpyridine-2-sulfonamide (78e)



The pyridine sulfonamide **78e** was prepared *via* **TP2** using **73b** (228 mg, 1.00 mmol) and TMPMgCl·LiCl (1.65 mL, 1.50 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (1.50 mL, 1.50 mmol) was added at –20°C and the reaction stirred at this temperature for 30 min. Then, allyl bromide (0.13 mL, 1.50 mmol) was added and the reaction was stirred at 25 °C for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8.5:1.5) to give **78e** (246 mg, 917 µmol, 92%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.38 (dd, *J* = 4.6, 1.6 Hz, 1H), 7.75 - 7.69 (m, 1H), 7.36 (dd, *J* = 7.8, 4.6 Hz, 1H), 6.08 - 5.93 (m, 1H), 5.22 - 5.11 (m, 2H), 3.84 (d, *J* = 6.8 Hz, 2H), 3.40 (t, *J* = 7.3 Hz, 2H), 3.07 (s, 3H), 1.67 - 1.55 (m, 2H), 1.46 - 1.33 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

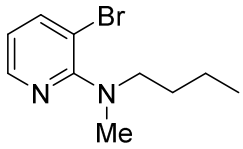
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.9, 145.9, 140.0, 135.5, 135.4, 126.1, 117.8, 51.7, 36.4, 35.5, 30.4, 19.9, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2934, 2873, 1640, 1563, 1450, 1416, 1333, 1160, 723.

MS (EI, 70 eV): *m/z* (%) = 225 (18), 161 (9), 133 (18), 118 (100), 86 (47).

HRMS (EI) for **$C_{13}H_{20}N_2O_2S$** (268.1245): 268.1235 (M^+).

Synthesis of 3-bromo-*N*-butyl-*N*-methylpyridine-2-amine (79e)



The aminopyridine **79e** was prepared *via* **TP3** using **78a** (76.8 mg, 0.25 mmol), *N*-butylmethylamine (60.0 µL, 0.50 mmol) and *i*PrMgCl·LiCl (0.30 mL, 0.50 mmol). The reaction was complete after 2 h at 25 °C. After work-up, compound **79e** (47.0 mg, 193 µmol, 77%) was isolated as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.18 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.74 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.67 (dd, *J* = 7.7, 4.7 Hz, 1H), 3.33 - 3.26 (m, 2H), 2.94 (s, 3H), 1.68 - 1.58 (m, 2H), 1. - 1.27 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

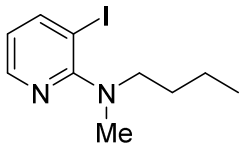
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.3, 146.1, 142.5, 117.3, 111.5, 53.8, 39.1, 30.0, 20.3, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2930, 2861, 1577, 1477, 1434, 1407, 1011, 780.

MS (EI, 70 eV): *m/z* (%) = 198 (16), 99 (15), 85 (55), 71 (73), 57 (100).

HRMS (ESI) for **$C_{10}H_{16}BrN_2$** (243.0497): 243.0493 (M^++H).

Synthesis of *N*-butyl-3-iodo-*N*-methylpyridine-2-amine (79f)



The aminopyridine **79f** was prepared *via* **TP3** using **78b** (88.0 mg, 248 µmol), *N*-butylmethylamine (59.0 µL, 497 µmol) and *i*PrMgCl·LiCl (0.30 mL, 497 µmol). The reaction was complete after 2 h at 25 °C. After work-up, compound **79f** (70.0 mg, 241 µmol, 97%) was isolated as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 (dd, *J* = 4.7, 1.7 Hz, 1H), 8.02 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.55 (dd, *J* = 7.6, 4.7 Hz, 1H), 3.25 - 3.18 (m, 2H), 2.88 (s, 3H), 1.65 - 1.56 (m, 2H), 1.38 - 1.27 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).

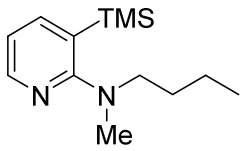
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.3, 149.2, 146.9, 118.3, 87.1, 54.6, 40.0, 29.9, 20.4, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2930, 2861, 1570, 1466, 1438, 1400, 1000, 723.

MS (EI, 70 eV): *m/z* (%) = 290 (14), 248 (10), 247 (100), 119 (14), 86 (16), 78 (12), 57 (11).

HRMS (EI) for **$C_{10}H_{15}IN_2$** (290.0280): 290.0293 (M^+).

Synthesis of *N*-butyl-*N*-methyl-3-(trimethylsilyl)pyridine-2-amine (79g)



The aminopyridine **79g** was prepared *via* **TP3** using **78c** (179 mg, 596 µmol), *N*-butylmethylamine (0.14 mL, 1.19 mmol) and *i*PrMgCl·LiCl (0.72 mL, 1.19 mmol). The reaction was complete after 2 h at 25 °C. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 10:0.5) to give **79g** (105 mg, 359 µmol, 59%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.31 (dd, *J* = 4.8, 2.1 Hz, 1H), 7.73 (dd, *J* = 7.2, 2.1 Hz, 1H), 6.89 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.12 - 3.05 (m, 2H), 2.73 (s, 3H), 1.55 - 1.45 (m, 2H), 1.34 - 1.23 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.30 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.4, 148.7, 145.2, 127.9, 118.2, 55.4, 42.4, 30.0, 20.8, 14.2, 0.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2932, 2863, 1560, 1427, 1392, 1247, 837, 732.

MS (EI, 70 eV): *m/z* (%) = 193 (11), 97 (22), 85 (38), 71 (52), 43 (100).

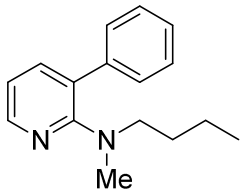
HRMS (ESI) for **$C_{13}H_{25}N_2Si$** (237.1787): 237.1783 (M^++H).

One-pot procedure:

The aminopyridine **79g** was prepared *via* **TP2** using **73b** (228 mg, 1.00 mmol), TMPMgCl·LiCl (0.96 mL, 1.20 mmol) and trimethylsilyl chloride (0.16 mL, 1.30 mmol). The reaction was stirred at 25 °C for 12 h. Then the reaction mixture was cooled to 0 °C and the magnesium amide prepared from *N*-butylmethylamine (0.36 mL, 3.00 mmol) and *i*PrMgCl·LiCl (1.91 mL, 3.00 mmol) was added

dropwise. The reaction was complete after 4 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 10:0.8) to give **79g** (163 mg, 542 µmol, 54%) as a yellow oil.

Synthesis of *N*-butyl-*N*-methyl-3-phenylpyridine-2-amine (79h)



The aminopyridine **79h** was prepared *via* **TP3** using **78d** (80.0 mg, 263 µmol), *N*-butylmethylamine (57.0 µL, 479 µmol) and *i*PrMgCl·LiCl (0.29 mL, 479 µmol). The reaction was complete after 2 h at 25 °C. After work-up, compound **79h** (61 mg, 254 µmol, 97%) was isolated as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.19 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.48 - 7.43 (m, 2H), 7.43 - 7.36 (m, 3H), 7.32 - 7.27 (m, 1H), 6.79 (dd, *J* = 7.3, 4.8 Hz, 1H), 3.07 - 3.01 (m, 2H), 2.71 (s, 3H), 1.44 - 1.34 (m, 2H), 1.15 - 1.04 (m, 2H), 0.78 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.1, 146.2, 141.2, 139.8, 128.7, 128.2, 126.9, 125.9, 115.1, 52.7, 38.9, 29.5, 20.3, 14.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3055, 2958, 2930, 2861, 1584, 1559, 1481, 1446, 1400.

MS (EI, 70 eV): *m/z* (%) = 240 (23), 239 (22), 198 (14), 197 (100), 183 (15), 127 (13).

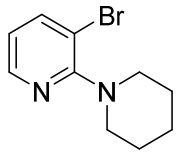
HRMS (EI) for **$C_{16}H_{20}N_2$** (240.1626): 240.1622 (M^+).

One-pot procedure:

The aminopyridine **79h** was prepared *via* **TP2** using **73b** (228 mg, 1.00 mmol) and TMPMgCl·LiCl (0.96 mL, 1.20 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (1.20 mL, 1.20 mmol) was added at 0 °C and the reaction mixture stirred at this temperature for 30 min. Then, iodobenzene (0.11 mL, 1.00 mmol), SPhos (16.0 mg, 40.0 µmol) and $Pd(OAc)_2$ (4.50 mg, 20.0 µmol) were added and the reaction stirred at 25 °C for 12 h. Then, the reaction mixture was cooled to 0 °C and the magnesium amide prepared from *N*-butylmethylamine (0.48 mL, 4.00 mmol) and *i*PrMgCl·LiCl (2.54 mL, 4.00 mmol) was added dropwise. The reaction was complete after 3 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 10:1) to give **79h** (167 mg, 695 µmol, 70%) as a yellow oil.

Synthesis of 3-bromo-2-(piperidin-1-yl)pyridine (79i)

One-pot procedure:



The aminopyridine **79i** was prepared *via* **TP2** using **73a** (134 mg, 0.59 mmol), TMPMgCl·LiCl (0.69 mL, 0.71 mmol) and 1,2-dibromotetrachloroethane (230 mg, 0.71 mmol). The reaction was stirred at 25 °C for 12 h. Then the reaction mixture was cooled to 0 °C and the magnesium amide prepared from piperidine (0.18 mL, 1.77 mmol) and *i*PrMgCl·LiCl (1.50 mL, 1.77 mmol) was added dropwise. The reaction was complete after 3 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **79i** (68 mg, 222 µmol, 48%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ / ppm = 8.21 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.75 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.72 (dd, *J* = 7.5, 4.8 Hz, 1H), 3.27 - 3.23 (m, 4H), 1.76 - 1.69 (m, 4H), 1.66 - 1.59 (m, 2H).

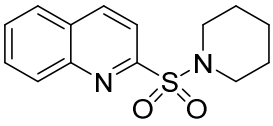
^{13}C NMR (75 MHz, $CDCl_3$): δ / ppm = 160.8, 146.5, 142.2, 118.1, 113.4, 51.1, 26.1, 24.6.

IR (Diamond-ATR, neat): υ / cm^{-1} = 2931, 1574, 1437, 1428, 1373, 1239, 1105, 1008, 932, 780.

MS (EI, 70 eV): m/z (%) = 242 (78), 213/211 (100), 161 (75), 84 (54).

HRMS (ESI) for **$C_{10}H_{14}{}^{79}BrN_2$** (241.0340): 241.0335 (M^++H).

Synthesis of 2-(Piperidin-1-ylsulfonyl)quinoline (82a)



Adapted from a literature procedure,[133] *n*BuMgCl (0.89 mL, 0.80 mmol) was dissolved in THF (2 mL) and cooled to 0 °C. Then, *n*BuLi (0.65 mL, 1.60 mmol) was added dropwise and the mixture stirred at this temperature for 15 min. Then a solution of 2-bromoquinoline (416 mg, 2.00 mmol) in THF (4 mL) was added at –10 °C and the reaction mixture stirred at this temperature for 2 h. Then, SO_2Cl_2 (0.24 mL, 3.00 mmol) in hexane (2 mL) was added at –10 °C and the reaction mixture stirred for 10 min. Piperidine (1.00 mL, 10.0 mmol) was added and the reaction mixture stirred at 0 °C for 30 min. The reaction was quenched with water (20 mL), extracted with ethyl acetate (3 x 50 mL) and dried over Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8.5:1.5) to give **82a** (325 mg, 1.18 mmol, 59%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.36 (d, *J* = 8.7 Hz, 1H), 8.21 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.91 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.82 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.68 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 3.45 - 3.36 (m, 4H), 1.71 - 1.60 (m, 4H), 1.56 - 1.46 (m, 2H).

[133] T. Emura, H. Yoshino, K. Tachibana, T. Shiraishi, A. Honma, A. Mizutani, T. Muraoka, *Synlett* **2011**, 1117–1120.

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.8, 147.3, 138.4, 130.9, 130.4, 128.9, 128.8, 127.9, 119.0, 47.8, 25.6, 23.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2939, 2854, 1582, 1497, 1334, 1323, 1174, 719, 637.

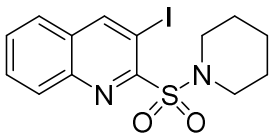
MS (EI, 70 eV): *m/z* (%) = 156 (27), 130 (16), 129 (82), 128 (40), 101 (14), 84 (100).

HRMS (EI) for **$C_{14}H_{15}N_2O_2S$** (275.0854): 275.0870 (M^+-H).

M.p. (°C): 144–145.

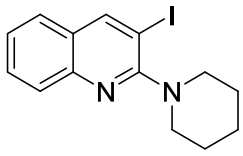
Synthesis of 3-iodo-2-(piperidin-1-yl)quinoline (83a)

Synthesis of 3-iodo-2-(piperidin-1-ylsulfonyl)quinoline (**A**)



The quinoline sulfonamide **A** was prepared *via* **TP2** using **82a** (88.0 mg, 318 µmol), TMPMgCl·LiCl (0.38 mL, 414 µmol) and iodine (121 mg, 477 µmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 7:3) to give **A** (85 mg) as a yellow oil. The compound contained 5% impurities which could not be removed *via* column chromatography. It was used as is in the next step (synthesis of compound **83a**).

Synthesis of 3-iodo-2-(piperidin-1-yl)quinoline (**83a**)



The aminoquinoline **83a** was prepared *via* **TP3** using **A** (85 mg, 234 µmol), piperidine (50.0 µL, 468 µmol) and *i*PrMgCl·LiCl (0.30 mL, 468 µmol). The reaction was complete after 2 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **83a** (63.0 mg, 186 µmol, 59% over two steps) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.54 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.64 - 7.54 (m, 2H), 7.35 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 3.38 - 3.29 (m, 4H), 1.84 - 1.75 (m, 4H), 1.71 - 1.62 (m, 2H).

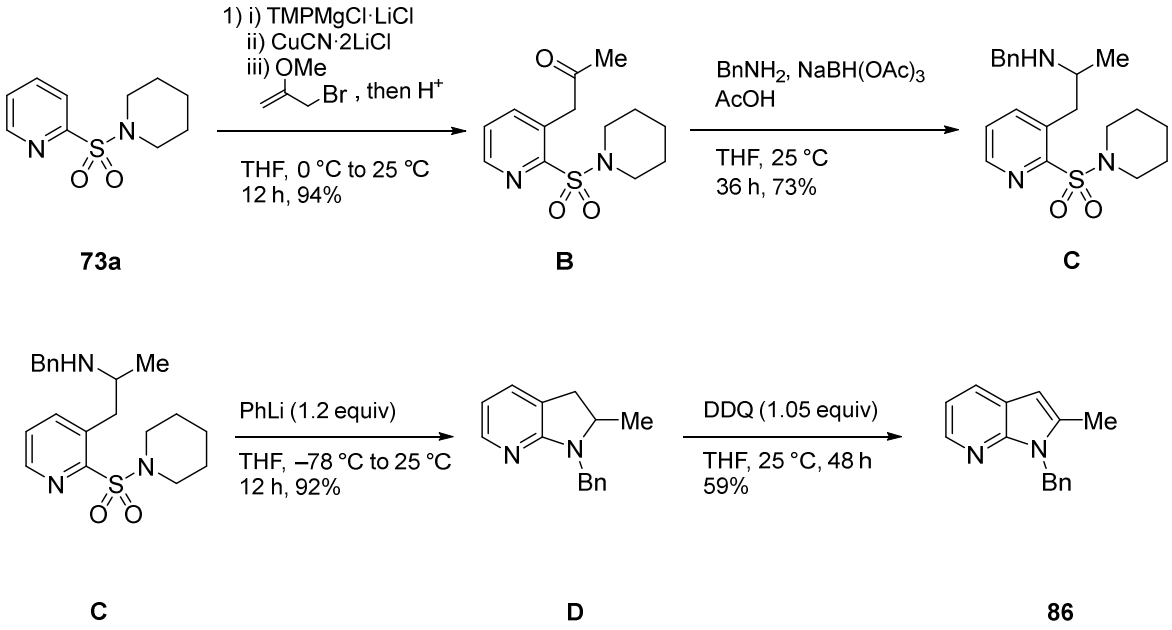
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.8, 148.8, 146.6, 129.9, 127.8, 126.8, 126.3, 124.8, 88.5, 52.1, 25.9, 24.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3054, 2932, 1612, 1582, 1448, 1408, 1371, 1233, 752.

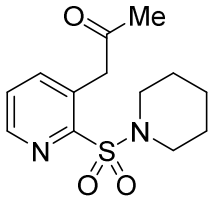
MS (EI, 70 eV): *m/z* (%) = 338 (100), 309 (83), 295 (38), 255 (62), 211 (70), 129 (44), 128 (90), 84 (43).

HRMS (EI) for **$C_{14}H_{15}IN_2$** (338.0280): 338.0279 (M^+).

Synthesis of compound 86



Synthesis of 1-(2-(piperidin-1-ylsulfonyl)pyridin-3-yl)propan-2-one (B)



The pyridine sulfonamide **B** was prepared *via* **TP2** using **73a** (2.02 g, 8.94 mmol) and TMPMgCl·LiCl (11.2 mL, 13.4 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (13.4 mL, 13.4 mmol) was added at –20°C and the reaction stirred at this temperature for 30 min. Then, 2-methoxyallyl bromide[67] (2.70 g, 17.9 mmol) was added dropwise and the reaction stirred at 25 °C for 12 h. Then, according to a literature procedure[9] a 1 M aq. oxalic acid solution (18 mL) was added and the reaction stirred for 30 minutes at 25 °C. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 6:4) to give **B** (2.38 g, 8.44 mmol, 94%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.49 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.40 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.14 (s, 2H), 3.50 - 3.42 (m, 4H), 2.32 (s, 3H), 1.69 - 1.55 (m, 6H).

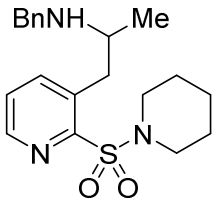
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 204.5, 157.2, 147.2, 142.0, 130.0, 126.0, 48.1, 46.3, 30.3, 26.0, 24.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} =2942, 2858, 2256, 1724, 1563, 1331, 1321, 1164, 726.

MS (EI, 70 eV): *m/z* (%) = 162 (20), 134 (53), 93 (28), 84 (100), 83 (15), 43 (17).

HRMS (EI) for **$C_{16}H_{19}N_2$** (283.1116): 283.1100 (M^++1H).

Synthesis of N-benzyl-1-(2-(piperidin-1-ylsulfonyl)pyridin-3-yl)propan-2-amine (C)



Adapted from a literature procedure,[68] compound **B** (1.41 g, 5.00 mmol) was dissolved in THF (25 mL) and benzylamine (0.66 mL, 6.00 mmol), $NaBH(OAc)_3$ (1.48 g, 7.00 mmol) and glacial acetic acid (0.29 mL, 5.00 mmol) were added subsequently. The reaction mixture was then stirred for 36 h at 25 °C. The reaction mixture was quenched with 2 M aq. NaOH (10 mL), extracted with ethyl acetate (3 x 50 mL) and dried over Na_2SO_4. After filtration, the crude product was purified *via* column chromatography (DCM:methanol:triethylamine = 95:5:1) to give **C** (1.30 g, 3.63 mmol, 73%) as a colorless oil.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.48 (dd, *J* = 4.6, 1.7 Hz, 1H), 7.77 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.39 (dd, *J* = 7.8, 4.6 Hz, 1H), 7.35 - 7.24 (m, 5H), 3.93 (d, *J* = 13.2 Hz, 1H), 3.80 (d, *J* = 13.2 Hz, 1H), 3.59 - 3.52 (m, 4H), 3.32 (dd, *J* = 13.6, 6.9 Hz, 1H), 3.21 (sept, *J* = 6.4 Hz, 1H), 3.05 (dd, *J* = 13.6, 6.3 Hz, 1H), 1.76 - 1.70 (m, 4H), 1.70 - 1.63 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 3H).

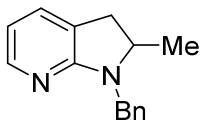
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 157.6, 146.1, 141.4, 140.8, 135.4, 128.4, 128.2, 126.9, 125.6, 53.6, 51.4, 48.2, 39.4, 26.1, 24.2, 20.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3027, 2940, 2858, 1560, 1450, 1331, 1319, 1165, 724.

MS (EI, 70 eV): *m/z* (%) = 134 (74), 93 (9), 91 (100).

HRMS (EI) for **$C_{19}H_{24}O_2N_3S$** (258.1595): 258.1565 (M^+-CH_3).

Synthesis of 1-benzyl-2-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (D)



Compound **C** (996 mg, 2.78 mmol) was dissolved in THF (15 mL) and cooled to –78 °C. Then, phenyl lithium (1.50 mL, 3.34 mmol) was added dropwise and the reaction mixture slowly warmed to 25 °C over 12 h. After hydrolysis (5 mL), the reaction mixture was extracted with ethyl acetate (3 x 50 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **D** (571 mg, 2.55 mmol, 92%) as a colorless oil:

.

^{1}H-NMR (800 MHz, $CDCl_3$): δ / ppm = 7.90 - 7.88 (m, 1H), 7.32 - 7.27 (m, 4H), 7.24 - 7.22 (m, 1H), 7.15 (dq, *J* = 6.9, 1.4 Hz, 1H), 6.43 (dd, *J* = 7.0, 5.3 Hz, 1H), 4.92 (d, *J* = 15.6 Hz, 1H), 4.36 (d, *J* = 15.6 Hz, 1H), 3.76 - 3.71 (m, 1H), 3.11 (ddt, 1H), 2.56 (ddt, *J* = 16.2, 7.9, 1.3 Hz, 1H), 1.23 (d, *J* = 6.2 Hz, 3H).

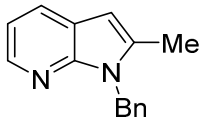
^{13}C-NMR (201 MHz, $CDCl_3$): δ / ppm = 162.9, 146.0, 138.5, 130.8, 128.5, 128.1, 127.1, 122.2, 112.3, 55.7, 46.4, 34.8, 20.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 3031, 2966, 2936, 2846, 2360, 1610, 1579, 1494, 1486, 1444, 1358, 769, 699.

MS (EI, 70 eV): *m/z* (%) = 224 (58), 223 (13), 209 (51), 147 (10), 92 (14), 91 (100), 65 (15).

HRMS (EI) for **$C_{15}H_{16}N_2$** (224.1313): 224.1310 (M^+).

Synthesis of 1-benzyl-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (86)



Compound **D** (22 mg, 100 µmol) was dissolved in THF (2 mL) and DDQ (25 mg, 110 µmol) was added at 25 °C. The reaction mixture was then stirred for two days at the same temperature. Full conversion was observed *via* GC-MS. The reaction mixture was then diluted with water (2 mL), extracted with dichloromethane (3 x 10 mL) and dried over Na_2SO_4. After filtration, the crude product was purified *via* column chromatography (*iso*hexane: ethyl acetate = 9:1) to give **86** (13 mg, 59 µmol, 59%) as a colorless solid.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.25 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.82 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.27 - 7.23 (m, 2H), 7.23 - 7.19 (m, 1H), 7.06 - 7.02 (m, 3H), 6.25 (q, *J* = 1.1 Hz, 1H), 5.53 (s, 2H), 2.35 (d, *J* = 1.2 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 148.8, 141.9, 138.2, 137.7, 128.8, 127.3, 127.3, 126.6, 120.7, 116.0, 98.5, 44.9, 13.3.

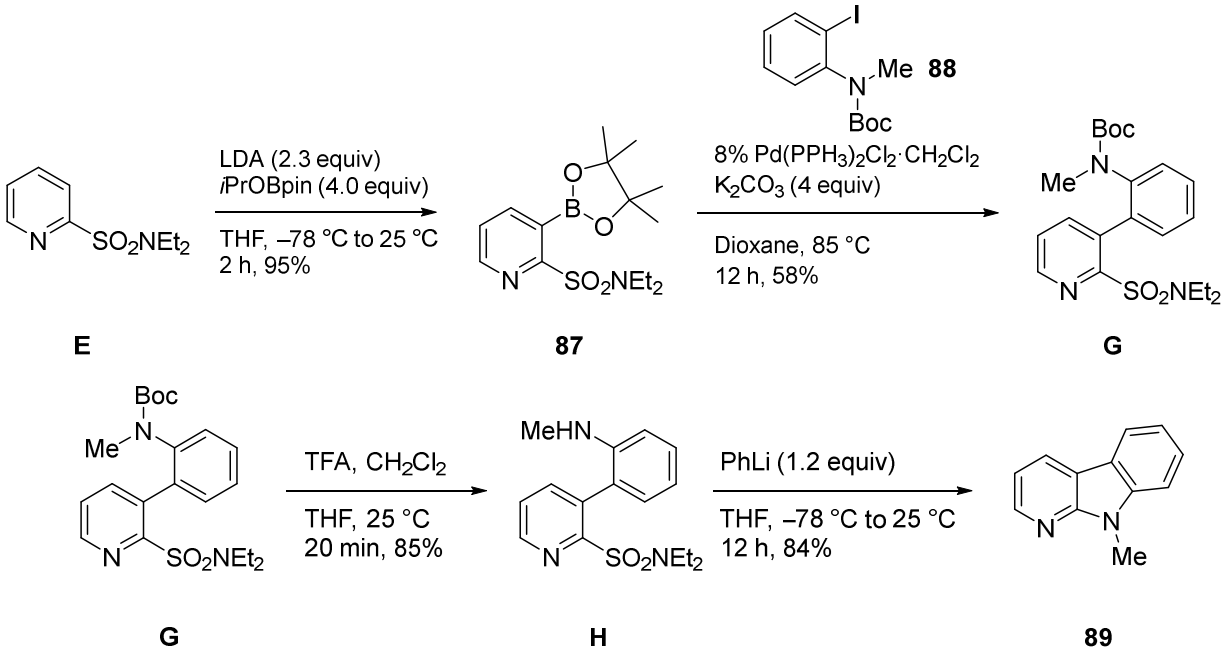
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057, 3027, 2923, 2854, 1592, 1549, 1434, 1311, 730.

MS (EI, 70 eV): *m/z* (%) = 223 (17), 222 (100), 221 (78), 207 (45), 91 (79), 57 (22), 43 (57).

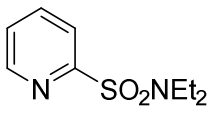
HRMS (EI) for **$C_{15}H_{14}N_2$** (222.1157): 222.1153 (M^+).

M.p. (°C): 111-112.

Synthesis of compounds 87–89



Synthesis of *N*,*N*-diethylpyridine-2-sulfonamide (E)

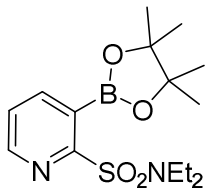


Diethylamine (11.6 mL, 112 mmol) was added to a solution of sulfonyl chloride **72** (6.62 g, 37.3 mmol) in DCM (50 mL) at 0 °C. After stirring at 25 °C for 12 h, the reaction mixture was quenched with water, extracted with DCM (3 x 100 mL) and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 6:4) to give **E** (6.74 g, 31.5 mmol, 84%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.67 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 7.95 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.87 (td, *J* = 7.7, 1.7 Hz, 1H), 7.45 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 3.40 (q, *J* = 7.2 Hz, 4H), 1.14 (t, *J* = 7.2 Hz, 6H).

The spectra matched those of the literature.[60b]

Synthesis of N,N-diethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-sulfonamide (87)

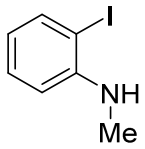


According to a literature procedure[60a] diisopropylamine (4.92 mL, 35.0 mmol) was dissolved in THF (35 mL) and cooled to 0 °C. Then, *n*BuLi (14.8 mL, 38.5 mmol) was added dropwise and the reaction stirred for 30 min at the same temperature. In a separate flask, **F** (2.14 g, 10.0 mmol) was dissolved in THF (50 mL) and cooled to –78 °C. The freshly prepared solution of LDA was added dropwise and the reaction stirred for 60 min at the same temperature. Then, *i*PrOBpin was added dropwise and the mixture stirred for five minutes. Then, the cold bath was removed and the reaction stirred at 25 °C for 12 h. The reaction was quenched with a sat. NH_4Cl solution (50 mL) extracted with ethyl acetate (3 x 100 mL) and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 6:4) to give **16** (3.28 g, 9,64 mmol, 96%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.65 (dd, *J* = 4.7, 1.8 Hz, 1H), 7.86 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.39 (dd, *J* = 7.6, 4.7 Hz, 1H), 3.41 (q, *J* = 7.1 Hz, 4H), 1.41 (s, 12H), 1.14 (t, *J* = 7.1 Hz, 6H).

The spectra matched those of the literature[60a]

Synthesis of 2-iodo-*N*-methylaniline (F)



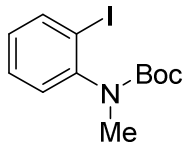
Adapted from a literature procedure,[134] 2-iodoaniline (8.67 g, 40.0 mmol) was dissolved in THF (50 mL) and cooled to –78 °C. Then, MeLi (47.1 mL, 40.0 mmol) was added dropwise over 30 min. After stirring at the same temperature for 30 min, methyl iodide (3.25 mL, 52.0 mmol) was added dropwise over 5 min and the reaction mixture stirred for 1 h. After warming to 25 °C and stirring for 1 h, the reaction mixture was quenched with sat. NH_4Cl solution (50 mL), extracted with ethyl acetate (3 x 100 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 10:0.3) to give **F** (6.00 g, 25.8 mmol, 65%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.67 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.25 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 6.57 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.46 (td, *J* = 7.5, 1.5 Hz, 1H), 4.21 (s, 1H), 2.89 (s, 3H).

The spectra matched those of the literature.[134]

[134] B. Yao, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2012**, *51*, 12311–12315.

Synthesis of 2-iodo-*N*-boc-*N*-methylaniline (88)



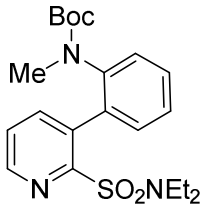
Hexamethyldisilazane (5.93 mL, 28.3 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. Then, *n*BuLi (10.9 mL, 27.0 mmol) was added dropwise and the reaction stirred for 30 min at the same temperature. In a separate flask, **F** (6.00 g, 25.8 mmol) was dissolved in THF (50 mL) and cooled to –78 °C. The freshly prepared solution of LiHMDS was added dropwise and the reaction stirred for 30 min. Then, Boc_2O (16.6 mL, 77.4 mmol) was added dropwise and the reaction stirred for 10 min. Then the cold bath was removed and the reaction stirred at 25 °C for 12 h. The reaction was quenched with sat. NH_4Cl (25 mL) and water (25 mL), extracted with ethyl acetate (3 x 100 mL) and dried over Na_2SO_4. After filtration, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 10:0.5) to give **88** (7.87 g, 23.6 mmol, 92%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.85 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.34 (td, *J* = 7.6, 1.4 Hz, 1H), 7.20 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.97 (td, *J* = 7.7, 1.7 Hz, 1H), 3.13 (s, 3H), 1.54 (s, 3H), 1.35 (s, 9H).

The spectra matched those of the literature.[135]

[135] Y. Yasui, H. Kamisaki, T. Ishida, Y. Takemoto, *Tetrahedron* **2010**, *66*, 1980–1989.

Synthesis of *tert*-butyl (2-(2-(*N*,*N*-diethylsulfamoyl)pyridin-3-yl)phenyl)(methyl) carbamate (G)



Adapted from a literature procedure,[60a] **87** (340 mg, 1.00 mmol) was dissolved in degassed dioxane (10 mL). Then $Pd(PPh_3)_2Cl_2 \cdot CH_2Cl_2$ (65 mg, 80 µmol). K_2CO_3 (552 mg, 4.00 mmol), and **88** (334 mg, 1.00°mmol) were added at 25 °C and the reaction stirred for 14 h. The reaction mixture was then quenched with water (15 mL), extracted with ethyl acetate (3 x 50 mL) and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 85:15) to give **G** (244 mg, 582 µmol, 58%) as a light yellow oil.

^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ / ppm = 8.64 (b, 1H), 7.81 (b, 1H), 7.63 (b, 1H), 7.51 - 7.38 (m, 2H), 7.38 - 7.25 (m, 2H), 3.60 - 3.32 (m, 4H), 3.00 - 2.68 (s, 3H), 1.39 (s, 9H), 1.17 (s, 6H).

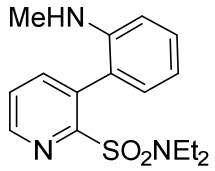
^{13}C-NMR (101 MHz, $(CD_3)_2CO$): δ / ppm = 157.4, 155.6, 155.3, 148.6, 142.6, 142.2, 141.8, 136.6, 135.7, 134.9, 132.1, 129.9, 129.3, 129.0, 127.1, 127.1, 126.3, 80.1, 45.2, 37.4, 36.5, 28.4, 15.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2978, 2435, 1694, 1497, 1456, 1439, 1363, 1330, 1153, 1124, 754.

MS (EI, 70 eV): *m/z* (%) = 184 (13), 183 (100), 182 (12), 181 (19), 72 (11), 57 (18).

HRMS (EI) for **$C_{21}H_{29}N_3O_4S$** (419.1879): 419.1869 (M^+).

Synthesis of N,N-diethyl-3-(2-(methylamino)phenyl)pyridine-2-sulfonamide (H)



The pyridine sulfonamide **G** (210 mg, 657 µmol) was dissolved in dichloromethane (4 mL). Then trifluoroacetic acid (1.5 mL, 1.95 mmol) was added dropwise at 25 °C and the reaction mixture stirred for 20 min. After removal of the solvents in *vacuo* the crude product was dissolved in water (10 mL) and dichloromethane (10 mL). After phase separation, the aqueous phase was extracted with dichloromethane (2 x 10 mL). The organic phases were combined and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 7:3) to give **H** (136 mg, 426 µmol, 85%) as an off-white solid.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.60 (dd, *J* = 4.7, 1.8 Hz, 1H), 7.72 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.49 (dd, *J* = 7.7, 4.7 Hz, 1H), 7.32 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H), 7.03 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.80 (td, *J* = 7.4, 1.2 Hz, 1H), 6.75 (dd, *J* = 8.3, 1.1 Hz, 1H), 3.33 (q, *J* = 7.2 Hz, 4H), 2.79 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 157.8, 147.7, 146.9, 142.4, 134.5, 130.4, 130.0, 126.3, 122.9, 116.9, 110.7, 44.0, 31.1, 15.4.

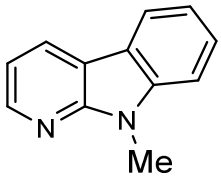
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3047, 2976, 2936, 2815, 1605, 1581, 1512, 1330, 1159, 1022, 705.

MS (EI, 70 eV): *m/z* (%) = 184 (13), 183 (100), 182 (12), 181 (19), 71 (11), 57 (18).

HRMS (EI) for **$C_{16}H_{21}N_3O_2S$** (319.1354): 319.1359 (M^+).

M.p. (°C): 87–88.

Synthesis of 9-methyl-9*H*-pyrido[2,3-*b*]indole (89)



The pyridine sulfonamide **H** (71 mg, 222 µmol) was dissolved in THF (3 mL) and cooled to –78 °C. Then, phenyl lithium (0.13 mL, 266 µmol) was added dropwise and the reaction mixture slowly warmed to 25 °C over 12 h. After hydrolysis (5 mL), the reaction mixture was extracted with ethyl acetate (3 x 10 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 8:2) to give **89** (34 mg, 187 µmol, 84%) as a colorless oil.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.51 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.32 (dd, *J* = 7.6, 1.6 Hz, 1H), 8.08 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.55 (ddd, *J* = 8.3, 7.1, 1.1 Hz, 1H), 7.47 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.29 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 7.17 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.98 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 151.9, 146.1, 140.4, 128.2, 126.9, 121.1, 120.5, 119.9, 116.1, 115.0, 109.2, 27.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3051, 2929, 1627, 1589, 1571, 1472, 1403, 1243, 772.

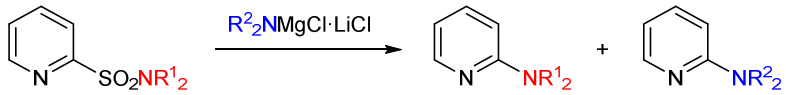
MS (EI, 70 eV): *m/z* (%) = 182 (100), 127 (12), 91 (11).

HRMS (EI) for **$C_{12}H_{10}N_2$** (182.0844): 182.0842 (M^+).

2.3 Mechanistic Insights

1 Investigation of the Sulfonamide Substitution Mechanism

Pyridine-2-sulfonamides of type $PySO_2NR^1_2$ reacted with magnesium amides of type $R^2_2NMgCl \cdot LiCl$ which led to mixtures of $PyNR^1_2$ and $PyNR^2_2$ (Scheme 59).



Scheme 59: Reaction of a pyridine sulfonamide $PySO_2NR^1_2$ with a magnesium amide $R^2_2NMgCl \cdot LiCl$.

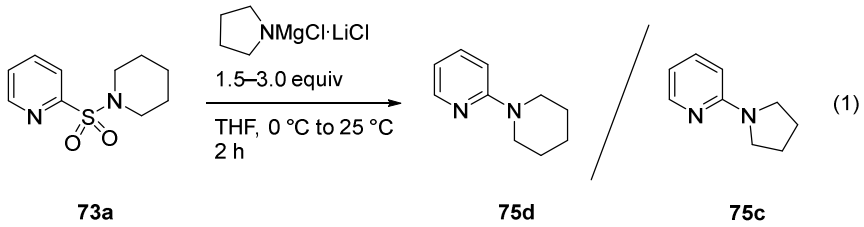
Typical procedure for the above described mechanistic experiments and results

*i*PrMgCl·LiCl (1.5 – 3.0 equiv) was added to a solution of amine (1.5 – 3.0 equiv) in THF (5 mL/mmol of sulfonamide) at 0 °C. The solution was stirred for 15 min at 0 °C and then 15 min at 25 °C before being added to a solution of sulfonamide (1.0 equiv) in THF (5 mL/mmol of sulfonamide) at 0 °C. The reaction mixture was then stirred at 0 °C for 15 min and 105 min at 25 °C. GC aliquots (hydrolysis) were taken at this point. After another 60 min the reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*.

The minimum amount of magnesium amide equivalents used was set to 1.5 equiv, to assure complete conversion in 2 h reaction time.

Competition experiments (1) to (4) were performed according to the typical procedure.

Experiment (1)



Sulfonamide **73a** (751 mg, 3.32 mmol) was dissolved in THF (10 mL). For each run, 3 mL of sulfonamide solution was used and diluted with additional THF (2 mL). This resulted in 996 µmol sulfonamide per reaction in 5 mL THF. The pyrrolidine magnesium amide was prepared according to the typical procedure. The exact amounts can be found in Table **9**.

Table 9: Amount of reagents used for mechanistic experiment (1)

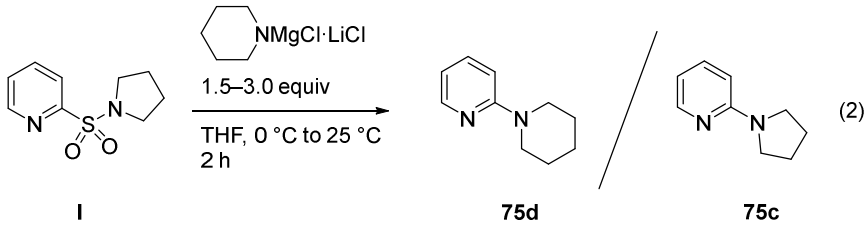
Entry	Amide base eq.	*i*PrMgCl·LiCl (1.66 m)	Pyrrolidine	THF
1	1.5	0.90 mL, 1.49 mmol	0.12 mL	3.75 mL
2	2.0	1.20 mL, 1.99 mmol	0.16 mL	5.00 mL
3	3.0	1.80 mL, 2.99 mmol	0.25 mL	7.50 mL

GC Analysis led to the results in Table **10**.

Table 10: Results from mechanistic experiment (1).

Entry	Amide base eq.	Ratio (**75d / 75c**)
1	1.5	1:20
2	2.0	1:34
3	3.0	1:50

Experiment (2)



Sulfonamide **I** (760 mg, 3.58 mmol) was dissolved in THF (10 mL). For each run, 3 mL of sulfonamide solution was used and diluted with additional THF (2 mL). This resulted in 1.07 mmol sulfonamide per reaction in 5 mL THF. The piperidine magnesium amide was prepared according to the typical procedure. The exact amounts can be found in Table **11**.

Table 11: Amount of reagents used for mechanistic experiment (2).

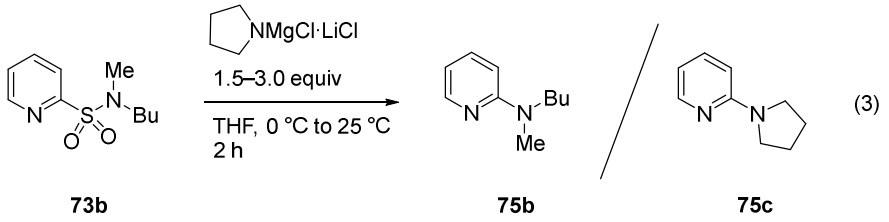
Entry	Amide base eq.	*i*PrMgCl·LiCl (1.66 m)	Piperidine	THF
1	1.5	0.97 mL, 1.61 mmol	0.16 mL	3.75 mL
2	2.0	1.29 mL, 2.15 mmol	0.21 mL	5.00 mL
3	3.0	1.94 mL, 3.22 mmol	0.32 mL	7.50 mL

GC Analysis lead to the results in Table 12.

Table 12: Results from mechanistic experiment (2).

Entry	Amide base eq.	Ratio (**75d / 75c**)
1	1.5	15:1
2	2.0	34:1
3	3.0	56:1

Experiment (3)



73b **75b** **75c**

For the first two experiments (Table 13, entries 1–2) sulfonamide **73b** (916 mg, 4.01 mmol) was dissolved in THF (10 mL). For each run, 3 mL of sulfonamide solution was used and diluted with additional THF (2 mL). This resulted in 1.20 mmol sulfonamide per reaction in 5 mL THF. For the third experiment (Table 13, entry 3) 113 mg (495 µmol) sulfonamide was used. The pyrrolidine magnesium amide was prepared according to the typical procedure. The exact amounts can be found in Table 13.

Table 13: Amount of reagents used for mechanistic experiment (3).

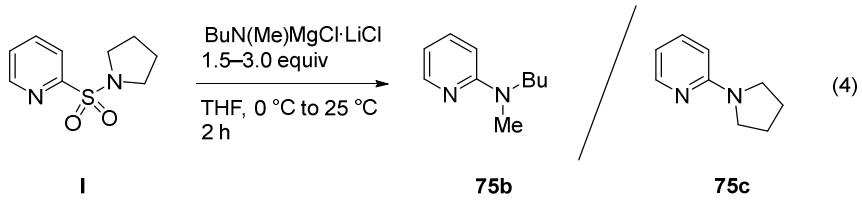
Entry	Amide base eq.	*i*PrMgCl·LiCl (1.66 m)	pyrrolidine	THF
1	1.5	1.09 mL, 1.80 mmol	0.15 mL	4.50 mL
2	2.0	1.45 mL, 2.40 mmol	0.20 mL	6.00 mL
3	3.0	895 µL, 1.48 mmol	122 µL	3.70 mL

GC Analysis lead to the results in Table 14.

Table 14: Results from mechanistic experiment (3).

Entry	Amide base eq.	Ratio (**75b / 75c**)
1	1.5	1:36
2	2.0	1:60
3	3.0	1:216

Experiment (4)



I **75b** **75c**

Sulfonamide **I** (862 mg, 4.06 mmol) was dissolved in THF (10 mL). For each run, 3 mL of sulfonamide solution was used and diluted with additional THF (3 mL). This resulted in 1.22 mmol sulfonamide per reaction in 6 mL THF. The *N*-butylmethylamine magnesium amide was prepared according the typical procedure. The exact amounts can be found in Table 15.

Table 15: Amount of reagents used for mechanistic experiment (4).

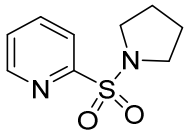
Entry	Amide base eq.	*i*PrMgCl·LiCl (1.66 M)	*N*-Butylmethylamine	THF
1	1.5	1.16 mL, 1.83 mmol	0.22 mL	4.50 mL
2	2.0	1.55 mL, 2.44 mmol	0.29 mL	6.00 mL
3	3.0	2.33 mL, 3.65 mmol	0.433 mL	9.60 mL

GC Analysis lead to the results in Table 16.

Table 16: Results from mechanistic experiment (4).

Entry	Amide base eq.	Ratio (**75b / 75c**)
1	1.5	7.5:1
2	2.0	8.7:1
3	3.0	18.4:1

Synthesis of 2-(Pyrrolidin-1-ylsulfonyl)pyridine (I)



Pyrrolidine (0.95 mL, 11.6 mmol) was added to a solution of sulfonyl chloride **1** (686 mg, 3.86 mmol) in DCM (10 mL) at 0 °C. After stirring at 25 °C for 12 h, the reaction mixture was quenched with water, extracted with DCM (3 x 20 mL) and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 7:3) to give **I** (793 mg, 3.74 mmol, 97%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.71 - 8.66 (m, 1H), 7.99 - 7.93 (m, 1H), 7.89 (td, J = 7.7, 1.8 Hz, 1H), 7.48 (ddd, J = 7.5, 4.7, 1.3 Hz, 1H), 3.53 - 3.42 (m, 4H), 1.87 - 1.79 (m, 4H).

The spectra matched those of the literature.[60b]

3 Amination of 2-Pyridinesulfonic Acid and 8-Quinolinesulfonic Acid with Magnesium Amides

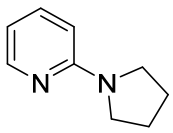
3.1 Typical Procedure

Amination of 2-pyridinesulfonic- and 8-quinolinesulfonic acids (94 or 95) using magnesium amides of type $R_2NMgCl \cdot LiCl$ (TP4)

*i*PrMgCl·LiCl (3.0–5.0 mmol) was added to a solution of the amine (3.0–5.0 mmol) in THF (5 mL/mmol of sulfonic acid) at 0 °C. The solution was stirred for 15 min at 0 °C and 15 min at 25 °C before being added to a suspension of the sulfonic acid (1 mmol) in THF (5 mL/mmol sulfonic acid) at 0 °C. The reaction mixture was stirred at 25 °C until completion. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. If the crude product needed purification, it was purified by flash chromatography on silica gel using the appropriate eluent.

3.2 Preparation of Compounds 96 to 98

Synthesis of 2-(pyrrolidin-1-yl)pyridine (96a)



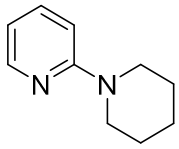
The aminopyridine **7a** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and pyrrolidine (0.25 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **96a** (135 mg, 0.91 mmol, 91%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (ddd, J = 5.0, 1.9, 0.9 Hz, 1H), 7.42 (ddd, J = 8.5, 7.1, 2.0 Hz, 1H), 6.50 (ddd, J = 7.1, 5.0, 0.9 Hz, 1H), 6.35 (dt, J = 8.6, 1.0 Hz, 1H), 3.50 - 3.39 (m, 4H), 2.04 - 1.97 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 157.5, 148.3, 137.0, 111.2, 106.6, 46.8, 25.7.

The spectra matched those of the literature.[10a]

Synthesis of 2-(piperidin-1-yl)pyridine (96b)



The aminopyridine **96b** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and piperidine (0.30 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **96b** (154 mg, 0.95 mmol, 95%) as a yellow oil.

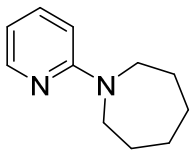
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.17 (ddd, *J* = 4.9, 2.1, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 6.64 (dd, *J* = 8.6, 1.0 Hz, 1H), 6.55 (ddd, *J* = 7.1, 4.9, 0.9 Hz, 1H), 3.58 - 3.47 (m, 4H), 1.65 (td, *J* = 3.5, 1.7 Hz, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 159.9, 148.1, 137.4, 112.5, 107.2, 46.5, 25.7, 24.9.

The spectra matched those of the literature.[10a]

Reaction on 50 mmol scale:

The aminopyridine **96b** was prepared *via* TP4 using 2-pyridinesulfonic acid (7.96 g, 50.0 mmol), *i*PrMgCl·LiCl (95.9 mL, 150 mmol) and piperidine (14.9 mL, 150 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (200 mL), extracted with ethyl acetate (3 x 200 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **96b** (7.29 g, 44.9 mmol, 90%) as a yellow oil.

Synthesis of 1-(pyridin-2-yl)azepane (96c)

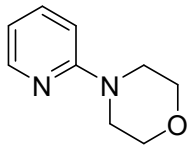


The aminopyridine **96c** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and azepane (0.34 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **96c** (164 mg, 0.93 mmol, 93%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.17 - 8.10 (m, 1H), 7.40 (ddd, *J* = 8.4, 7.2, 2.0 Hz, 1H), 6.51 - 6.44 (m, 2H), 3.65 - 3.58 (m, 4H), 1.81 - 1.75 (m, 4H), 1.55 (dt, *J* = 5.8, 2.7 Hz, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 158.4, 148.2, 137.2, 111.0, 105.5, 47.6, 28.0, 27.4.

The spectra matched those of the literature.[10a]

Synthesis of 4-(pyridin-2-yl)morpholine (96d)

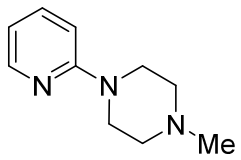


The aminopyridine **96d** was prepared *via* TP4 using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and morpholine (0.27 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **96d** (148 mg, 0.90 mmol, 90%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.21 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.50 (ddd, *J* = 8.6, 7.2, 2.0 Hz, 1H), 6.70 - 6.60 (m, 2H), 3.88 - 3.80 (m, 4H), 3.54 - 3.46 (m, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 159.7, 148.1, 137.7, 114.0, 107.1, 66.9, 45.8.

The spectra matched those of the literature.[10a]

Synthesis of 1-methyl-4-(pyridin-2-yl)piperazine (96e)

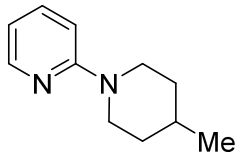


The aminopyridine **96e** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and 1-methylpiperazine (0.34 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **96e** (171 mg, 0.97 mmol, 97%) as a light brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.19 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.47 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 6.68 - 6.58 (m, 2H), 3.59 - 3.53 (m, 4H), 2.55 - 2.50 (m, 4H), 2.35 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 159.7, 148.1, 137.6, 113.4, 107.2, 55.1, 46.4, 45.3.

The spectra matched those of the literature.[58b]

Synthesis of 2-(4-methylpiperidin-1-yl)pyridine (96f)

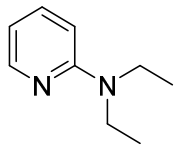


The aminopyridine **96f** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and 4-methylpiperidine (0.36 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **96f** (170 mg, 0.96 mmol, 96%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 6.64 (dt, *J* = 8.6, 0.9 Hz, 1H), 6.54 (ddd, *J* = 7.1, 4.9, 0.9 Hz, 1H), 4.29 - 4.20 (m, 2H), 2.87 - 2.74 (m, 2H), 1.77 - 1.67 (m, 2H), 1.67 - 1.54 (m, 1H), 1.30 - 1.16 (m, 2H), 0.96 (d, *J* = 6.6 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 159.8, 148.1, 137.4, 112.5, 107.3, 45.8, 33.9, 31.3, 22.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2950, 2922, 1593, 1483, 1464, 1438, 1314, 1237, 972, 770.

MS (EI, 70 eV): m/z = 176 (80), 161, (51), 133 (100), 119, (43), 107 (31), 106 (33).
HRMS (EI) for $\mathbf{C_{11}H_{16}N_2}$ (176.1313): 176.1307 (M^+).

Synthesis of *N*,*N*-diethylpyridin-2-amine (96g)

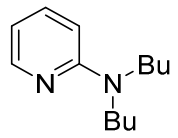


The aminopyridine **96g** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and diethylamine (0.31 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **96g** (114 mg, 0.76 mmol, 76%) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.40 (ddd, *J* = 9.0, 7.1, 2.0 Hz, 1H), 6.52 - 6.42 (m, 2H), 3.51 (q, *J* = 7.1 Hz, 4H), 1.18 (t, *J* = 7.1 Hz, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 157.6, 148.2, 137.2, 110.9, 105.6, 42.5, 13.1.

The spectra matched those of the literature.[10a]

Synthesis of *N*,*N*-dibutylpyridin-2-amine (96h)



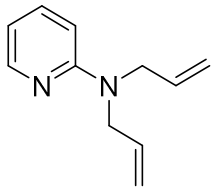
The aminopyridine **96h** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.77 mL, 3.00 mmol) and dibutylamine (0.51 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **96h** (157 mg, 0.76 mmol, 76%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.12 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.37 (ddd, *J* = 8.9, 7.0, 2.0 Hz, 1H), 6.48 - 6.39 (m, 2H), 3.46 - 3.39 (m, 4H), 1.63 - 1.53 (m, 4H), 1.35 (dq, *J* = 14.7, 7.4 Hz, 4H), 0.95 (t, *J* = 7.3 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 158.1, 148.2, 137.0, 110.8, 105.6, 48.5, 30.0, 20.5, 14.2.

The spectra matched those of the literature.[136]

Synthesis of *N*,*N*-diallylpyridin-2-amine (96i)

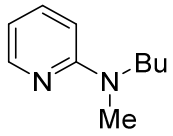


The aminopyridine **96i** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and diallylamine (0.37 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **96i** (153 mg, 0.88 mmol, 88%) as a light brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.40 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 6.53 (ddd, *J* = 7.1, 5.0, 0.9 Hz, 1H), 6.47 (dt, *J* = 8.7, 0.9 Hz, 1H), 5.93 - 5.80 (m, 2H), 5.16 (dq, *J* = 7.2, 1.7 Hz, 2H), 5.13 (t, *J* = 1.6 Hz, 2H), 4.11 (dt, *J* = 5.1, 1.7 Hz, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 158.2, 148.1, 137.3, 134.2, 116.2, 111.9, 106.2, 50.2.

The spectra matched those of the literature.[137]

Synthesis of *N*-butyl-*N*-methylpyridin-2-amine (96j)



The aminopyridine **96j** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and *N*-methylbutylamine (0.36 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3

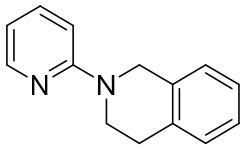
[136] M.-T. Chen, D. A. Vicic, M. L. Turner, O. Navarro, *Organometallics* **2011**, *30*, 5052–5056.
[137] O. Navarro, N. Marion, J. Mei, S. P. Nolan, *Chem. Eur. J.* **2006**, *12*, 5142–5148.

x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **96j** (161 mg, 0.98 mmol, 98%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (ddd, *J* = 5.0, 2.1, 0.9 Hz, 1H), 7.41 (ddd, *J* = 8.8, 7.0, 2.0 Hz, 1H), 6.52 - 6.44 (m, 2H), 3.53 - 3.45 (m, 2H), 3.04 (s, 3H), 1.63 - 1.52 (m, 2H), 1.35 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 158.8, 148.1, 137.1, 111.1, 105.8, 50.1, 36.4, 29.5, 20.4, 14.2.

The spectra matched those of the literature.[11c]

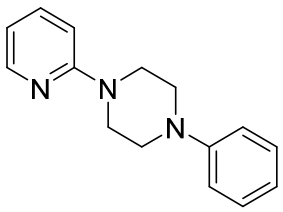
Synthesis of 2-(pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline (96k)



The aminopyridine **96k** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.38 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **96k** (175 mg, 0.83 mmol, 83%) as a light yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.50 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 7.24 - 7.15 (m, 4H), 6.68 (dt, *J* = 8.7, 1.0 Hz, 1H), 6.60 (ddd, *J* = 7.1, 5.0, 0.9 Hz, 1H), 4.71 (s, 2H), 3.85 (t, *J* = 5.9 Hz, 2H), 2.98 (t, *J* = 5.8 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 158.8, 148.1, 137.6, 135.5, 134.5, 128.5, 126.7, 126.5, 126.3, 112.6, 106.8, 47.3, 42.7, 29.2.
The spectra matched those of the literature.[58b]

Synthesis of 1-phenyl-4-(pyridin-2-yl)piperazine (96l)

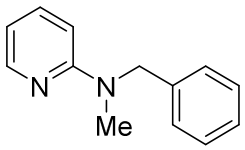


The aminopyridine **96l** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and 1-phenylpiperazine (0.46 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 8:2) to give **96l** (193 mg, 0.81 mmol, 81%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.51 (ddd, *J* = 8.8, 7.0, 2.0 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.02 - 6.97 (m, 2H), 6.89 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 6.69 - 6.63 (m, 1H), 3.75 - 3.67 (m, 4H), 3.35 - 3.26 (m, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 159.6, 151.4, 148.1, 137.7, 129.3, 120.2, 116.5, 113.7, 107.4, 49.3, 45.5.

The spectra matched those of the literature.[58d]

Synthesis of *N*-benzyl-*N*-methylpyridin-2-amine (96m)

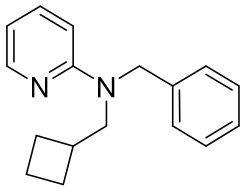


The aminopyridine **96m** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and *N*-benzylmethylamine (0.39 mL, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 10:0.5:0.1) to give **96m** (170 mg, 0.86 mmol, 86%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.19 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 7.34 - 7.28 (m, 2H), 7.26 - 7.19 (m, 3H), 6.56 (ddd, *J* = 7.1, 4.9, 0.9 Hz, 1H), 6.51 (dt, *J* = 8.6, 0.9 Hz, 1H), 4.81 (s, 2H), 3.07 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 159.1, 148.1, 138.9, 137.4, 128.7, 127.2, 127.0, 112.0, 105.8, 53.4, 36.3.

The spectra matched those of the literature.[58b]

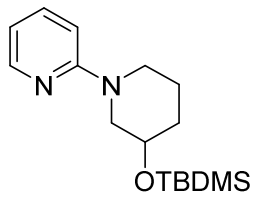
Synthesis of 2-(piperidin-1-yl)pyridine (96n)



The aminopyridine **96n** was prepared *via* **TP4** using 2-pyridinesulfonic acid (54 mg, 0.34 mmol), *i*PrMgCl·LiCl (1.09 mL, 1.71 mmol) and *N*-benzyl-1-cyclobutylmethanamine (300 mg, 1.71 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 10:0.2:0.1) to give **96n** (50 mg, 0.20 mmol, 59%) as a colorless oil.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 8.16 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.37 (ddd, *J* = 8.9, 7.0, 2.0 Hz, 1H), 7.32 - 7.27 (m, 2H), 7.24 - 7.18 (m, 3H), 6.52 (ddd, *J* = 7.0, 5.0, 0.9 Hz, 1H), 6.42 (dt, *J* = 8.7, 0.9 Hz, 1H), 4.77 (s, 2H), 3.60 (d, *J* = 7.1 Hz, 2H), 2.76 - 2.66 (m, 1H), 2.06 - 1.98 (m, 2H), 1.90 - 1.71 (m, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 158.7, 148.1, 139.2, 137.2, 128.6, 126.9, 126.8, 111.7, 106.1, 53.9, 52.0, 34.7, 27.1, 18.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972, 2934, 1594, 1559, 1488, 1452, 1436, 1366, 768, 729, 696.
MS (EI, 70 eV): m/z = 252 (27), 197 (34), 183 (62), 133 (33), 91 (100), 78 (17), 43 (64).
HRMS (EI) for **$C_{17}H_{20}N_2$** (252.1626): 252.1622 (M^+).

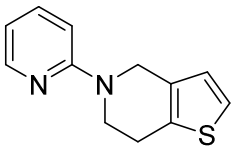
Synthesis of 2-(3-(*tert*-butyldimethylsilyl)piperidin-1-yl)pyridine (96o)



The aminopyridine **96o** was prepared *via* **TP4** using 2-pyridinesulfonic acid (159 mg, 1.00 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and 3-((*tert*-butyldimethylsilyl)oxy)piperidine (650 mg, 3.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **96o** (274 mg, 0.94 mmol, 94%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.16 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 6.63 (dt, *J* = 8.7, 1.0 Hz, 1H), 6.55 (ddd, *J* = 7.1, 4.9, 0.9 Hz, 1H), 4.16 - 4.04 (m, 2H), 3.70 (tt, *J* = 8.8, 4.2 Hz, 1H), 2.95 - 2.77 (m, 2H), 2.02 - 1.94 (m, 1H), 1.84 - 1.76 (m, 1H), 1.61 - 1.44 (m, 2H), 0.89 (s, 9H), 0.09 (d, *J* = 2.7 Hz, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 159.5, 148.2, 137.5, 112.6, 107.1, 67.7, 53.1, 45.4, 34.6, 26.0, 23.2, 18.3, -4.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930, 2857, 1596, 1484, 1438, 1242, 1097, 975, 859, 836, 771.
MS (EI, 70 eV): m/z = 236 (20), 235 (100), 161 (22), 160 (15), 159 (16), 121 (20).
HRMS (EI) for **$C_{16}H_{28}ON_2Si$** (292.1971): 292.1964 (M^+).

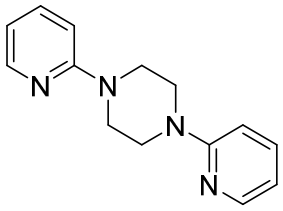
Synthesis of 5-(pyridin-2-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (96p)



The aminopyridine **96p** was prepared *via* **TP4** using 2-pyridinesulfonic acid (168 mg, 1.06 mmol), *i*PrMgCl·LiCl (2.01 mL, 3.18 mmol) and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (441 mg, 3.18 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **96p** (208 mg, 0.96 mmol, 91%) as a light yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.21 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.50 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 7.15 - 7.10 (m, 1H), 6.86 (d, *J* = 5.1 Hz, 1H), 6.70 (dt, *J* = 8.6, 0.9 Hz, 1H), 6.61 (ddd, *J* = 7.1, 4.9, 0.9 Hz, 1H), 4.60 (t, *J* = 1.7 Hz, 2H), 3.99 (t, *J* = 5.6 Hz, 2H), 3.00 - 2.94 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 159.1, 148.1, 137.6, 134.0, 133.1, 125.3, 123.0, 113.0, 107.1, 45.9, 43.0, 25.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3098, 3066, 3004, 2904, 2841, 1589, 1560, 1478, 1434, 1308, 1237, 986, 979, 769.
MS (EI, 70 eV): m/z = 216 (100), 215 (15), 199 (19), 187 (16), 121 (10), 110 (70), 79 (38), 78 (18).
HRMS (EI) for **$C_{12}H_{12}N_2S$** (216.0721): 216.0715 (M^+).
M.p. (°C): 149-150.

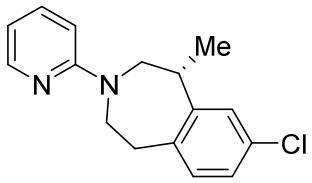
Synthesis of 1,4-di(pyridin-2-yl)piperazine (96q)



The aminopyridine **96q** was prepared *via* **TP4** using 2-pyridinesulfonic acid (80 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.95 mL, 1.50 mmol) and 1-(2-pyridyl)piperazine (0.23 mL, 1.50 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 5:5:0.1) to give **96q** (78 mg, 0.326 mmol, 65%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.21 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 2H), 7.49 (ddd, *J* = 8.6, 7.1, 2.0 Hz, 2H), 6.68 (dt, *J* = 8.6, 0.9 Hz, 2H), 6.64 (ddd, *J* = 7.1, 4.9, 0.9 Hz, 2H), 3.68 (s, 8H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 159.5, 148.1, 137.6, 113.6, 107.3, 45.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3098, 3067, 2888, 2848, 1592, 1559, 1482, 1467, 1438, 1382, 1309, 1238, 1162, 977, 954, 769, 728.
MS (EI, 70 eV): m/z = 240 (15), 146 (33), 133 (73), 120 (17), 107 (100), 83 (28), 79 (57), 57 (50), 43 (42).
HRMS (EI) for **$C_{14}H_{16}N_4$** (240.1375): 240.1361 (M^+).
M.p. (°C): 133–135.

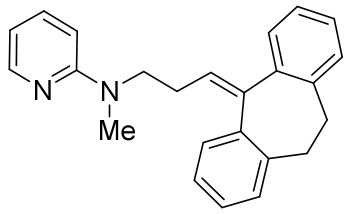
Synthesis of (*R*)-8-chloro-1-methyl-3-(pyridin-2-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*] azepine (97a)



The aminopyridine **97a** was prepared *via* **TP4** using 2-pyridinesulfonic acid (80 mg, 0.50 mmol), *i*PrMgCl·LiCl (2.40 mL, 3.75 mmol) and lorcaserine hydrochloride hemihydrate (362 mg, 1.50 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **97a** (100 mg, 0.367 mmol, 73%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.17 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.44 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 7.15 (d, *J* = 2.1 Hz, 1H), 7.10 - 7.01 (m, 2H), 6.59 (dt, *J* = 8.7, 0.9 Hz, 1H), 6.53 (ddd, *J* = 7.1, 4.9, 0.8 Hz, 1H), 4.00 - 3.88 (m, 2H), 3.69 - 3.59 (m, 2H), 3.24 (pd, *J* = 7.4, 3.2 Hz, 1H), 3.10 (ddd, *J* = 15.1, 9.2, 2.9 Hz, 1H), 2.95 (ddd, *J* = 15.1, 6.8, 2.8 Hz, 1H), 1.32 (d, *J* = 7.2 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 158.5, 148.2, 146.8, 138.3, 137.5, 132.2, 131.6, 127.9, 126.0, 112.0, 106.2, 52.0, 47.3, 40.3, 35.3, 18.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3093, 3004, 2962, 2926, 2848, 1592, 1558, 1478, 1439, 1429, 1240, 1228, 949, 814, 765, 728.
MS (EI, 70 eV): m/z = 272 (18), 257 (9), 119 (12), 115 (16), 107 (100), 78 (11).
HRMS (EI) for **$C_{16}H_{17}ClN_2$** (272.1080): 272.1075 (M^+).
Optical rotation: α_D^{20}= 15.5 (c 1.10, CH_2Cl_2).

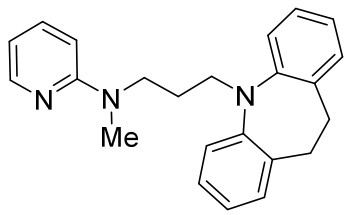
Synthesis of *N*-(3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl)-*N*-methylpyridin-2-amine (97b)



The aminopyridine **97b** was prepared *via* TP4 using 2-pyridinesulfonic acid (80 mg, 0.50 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and nortriptyline hydrochloride (450 mg, 1.50 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **97b** (143 mg, 0.42 mmol, 84%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.19 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.39 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 7.33 - 7.26 (m, 1H), 7.28 - 7.19 (m, 2H), 7.23 - 7.13 (m, 4H), 7.11 - 7.04 (m, 1H), 6.54 (ddd, *J* = 7.1, 5.0, 0.9 Hz, 1H), 6.34 (dt, *J* = 8.6, 0.9 Hz, 1H), 5.96 (t, *J* = 7.7 Hz, 1H), 3.68 - 3.59 (m, 2H), 3.47 - 3.27 (m, 2H), 3.08 - 2.95 (m, 4H), 2.80 (s, 1H), 2.47 (q, *J* = 7.5 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 158.5, 148.0, 144.6, 141.2, 140.0, 139.5, 137.1, 137.1, 130.1, 128.6, 128.4, 128.3, 128.1, 127.5, 127.2, 126.1, 125.9, 111.4, 105.7, 50.0, 36.5, 33.9, 32.1, 27.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2918, 1596, 1558, 1498, 1422, 1321, 767, 756.
MS (EI, 70 eV): m/z = 340 (2), 202 (4), 122 (8), 121 (100), 94 (7), 78 (6).
HRMS (EI) for **$C_{24}H_{24}N_2$** (340.1939): 340.1941 (M^+).

Synthesis of *N*-(3-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)propyl)-*N*-methylpyridin-2-amine (97c)

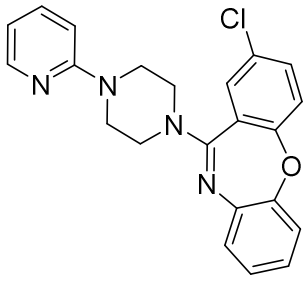


The aminopyridine **97c** was prepared *via* **TP4** using 2-pyridinesulfonic acid (80 mg, 0.50 mmol), *i*PrMgCl·LiCl (1.92 mL, 3.00 mmol) and desipramine hydrochloride (454 mg, 1.50 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and

the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **97c** (154 mg, 0.45 mmol, 90%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.12 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.30 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 7.19 - 7.12 (m, 4H), 7.12 - 7.07 (m, 2H), 6.99 - 6.91 (m, 2H), 6.48 (ddd, *J* = 7.1, 5.0, 0.9 Hz, 1H), 6.23 (dt, *J* = 8.7, 1.0 Hz, 1H), 3.82 (t, *J* = 6.6 Hz, 2H), 3.59 - 3.51 (m, 2H), 3.23 (s, 4H), 2.96 (s, 3H), 1.94 - 1.83 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 158.6, 148.2, 148.0, 137.1, 134.3, 130.0, 126.5, 122.6, 120.0, 111.3, 105.6, 48.2, 48.1, 36.4, 32.3, 25.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3011, 2917, 2842, 1594, 1495, 1485, 1421, 1319, 1289, 1244, 1226, 1110, 981, 910, 766, 749.
MS (EI, 70 eV): m/z = 343 (42), 235 (65), 234 (42), 208 (48), 195 (36), 194 (44), 193 (59), 149 (39), 135 (36), 122 (100), 121 (38), 93 (75), 78 (32).
HRMS (EI) for **$C_{23}H_{25}N_3$** (343.2048): 343.2045 (M^+).

Synthesis of 2-chloro-11-(4-(pyridin-2-yl)piperazin-1-yl)dibenzo[*b*,*f*][1,4]oxazepine (97d)



The aminopyridine **97d** was prepared *via* a slightly modified **TP4** using 2-pyridinesulfonic acid (13 mg, 79.6 µmol), *i*PrMgCl·LiCl (0.15 mL, 1.50 mmol) and amoxapine (75 mL, 239 µmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **97d** (16 mg, 41 µmol, 52%) as a light yellow oil.

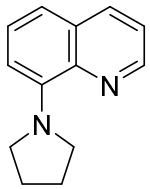
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = δ 8.22 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.54 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 7.41 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.37 (d, *J* = 2.6 Hz, 1H), 7.23 - 7.16 (m, 2H), 7.13 - 7.07 (m, 2H), 7.04 - 6.98 (m, 1H), 6.75 - 6.66 (m, 2H), 3.67 (s, 8H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): δ 159.5, 159.1, 152.0, 147.6, 140.1, 138.1, 132.8, 130.5, 129.2, 127.3, 126.0, 125.1, 124.9, 122.9, 120.3, 114.0, 107.8, 47.3, 45.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3065, 3002, 2923, 2849, 1588, 1558, 1478, 1471, 1436, 1236, 1020, 980, 772, 733.

MS (EI, 70 eV): m/z = 390 (27), 271 (27), 257 (48), 193 (36), 146 (100), 145 (46), 133 (85), 119 (25), 57 (25).

HRMS (EI) for **$C_{22}H_{19}ClN_4O$** (390.1247): 390.1249 (M^+).

Synthesis of 8-(pyrrolidin-1-yl)quinoline (98a)



The aminopyridine **98a** was prepared *via* **TP4** using 8-quinolinesulfonic acid (209 mg, 1.00 mmol), *i*PrMgCl·LiCl (3.20 mL, 5.00 mmol) and pyrrolidine (0.41 mL, 5.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **98a** (167 mg, 0.84 mmol, 84%) as a light-brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.76 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.04 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.31 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 3.78 - 3.69 (m, 4H), 2.08 - 1.99 (m, 4H).

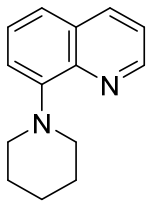
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 147.6, 146.2, 141.6, 135.9, 130.0, 127.1, 120.8, 116.7, 111.0, 52.1, 25.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2965, 2870, 1562, 1504, 1471, 1460, 1426, 1393, 1354, 1328, 1108, 814, 787, 742.

MS (EI, 70 eV): m/z = 198 (49), 197 (26), 170 (17), 169 (48), 156 (53), 155 (32), 129 (100), 128 (17).

HRMS (EI) for **$C_{13}H_{14}N_2$** (198.1157): 198.1151 (M^+).

Synthesis of 8-(piperidin-1-yl)quinoline (98b)



The aminopyridine **98b** was prepared *via* **TP4** using 8-quinolinesulfonic acid (209 mg, 1.00 mmol), *i*PrMgCl·LiCl (3.20 mL, 5.00 mmol) and piperidine (0.50 mL, 5.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **98b** (198 mg, 0.93 mmol, 93%) as a yellow oil.

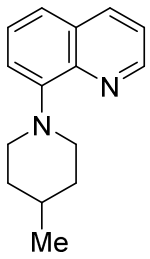
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.89 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.46 - 7.37 (m, 2H), 7.35 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.15 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.35 - 3.29 (m, 4H), 1.91 (p, *J* = 5.6 Hz, 4H), 1.70 - 1.63 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 151.0, 148.3, 143.1, 136.5, 129.8, 126.8, 121.3, 120.8, 116.2, 53.9, 26.4, 24.8.

The spectra matched those of **81b**.

Reaction on 20 mmol scale:

The aminopyridine **98b** was prepared *via* TP4 using 8-quinolinesulfonic acid (3.98 g, 20.0 mmol), *i*PrMgCl·LiCl (94.0 mL, 100.0 mmol) and piperidine (9.90 mL, 100.0 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (100 mL), extracted with ethyl acetate (3 x 100 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **98b** (2.82 g, 13.3 mmol, 66%) as a yellow oil.

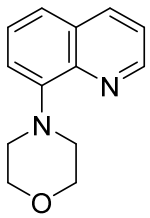
Synthesis of 8-(4-methylpiperidin-1-yl)quinoline (98c)



The aminopyridine **98c** was prepared *via* **TP4** using 8-quinolinesulfonic acid (209 mg, 1.00 mmol), *i*PrMgCl·LiCl (3.20 mL, 5.00 mmol) and 4-methylpiperidine (0.60 mL, 5.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **98c** (138 mg, 0.61 mmol, 61%) as a light-yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.89 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.45 - 7.37 (m, 2H), 7.35 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.15 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.96 - 3.87 (m, 2H), 2.74 (td, *J* = 11.5, 2.7 Hz, 2H), 1.79 (dp, *J* = 7.7, 3.0, 2.6 Hz, 2H), 1.70 (qd, *J* = 12.4, 11.8, 3.7 Hz, 2H), 1.60 (dddd, *J* = 10.9, 8.5, 6.3, 3.4 Hz, 1H), 1.04 (d, *J* = 6.3 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 150.7, 148.3, 143.1, 136.5, 129.7, 126.8, 121.2, 120.8, 116.2, 53.2, 34.6, 31.2, 22.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2947, 2923, 2360, 1566, 1450, 1469, 1455, 1389, 1368, 1238, 1104, 825, 792.
MS (EI, 70 eV): m/z = 226 (47), 183 (51), 169 (57), 157 (31), 156 (35), 155 (43), 143 (59), 129 (100).
HRMS (EI) for **$C_{15}H_{18}N_2$** (226.1470): 226.1462 (M^+).

Synthesis of 4-(quinolin-8-yl)morpholine (98d)

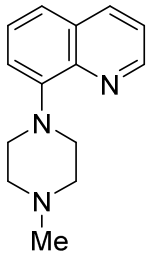


The aminopyridine **98d** was prepared *via* **TP4** using 8-quinolinesulfonic acid (209 mg, 1.00 mmol), *i*PrMgCl·LiCl (3.20 mL, 5.00 mmol) and morpholine (0.44 mL, 5.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL)

and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **98d** (205 mg, 0.957 mmol, 96%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.88 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.47 - 7.44 (m, 2H), 7.38 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.14 (dd, *J* = 5.0, 3.9 Hz, 1H), 4.08 - 4.02 (m, 4H), 3.47 - 3.38 (m, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 149.4, 148.4, 142.8, 136.7, 129.8, 126.8, 122.0, 121.1, 115.9, 67.4, 52.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972, 2933, 1594, 1489, 1437, 768, 729, 696.
MS (EI, 70 eV): m/z = 214 (16), 196 (27), 195 (27), 183 (25), 169 (29), 168 (44), 156 (20), 155 (35), 129 (100).
HRMS (EI) for **$C_{13}H_{14}ON_2$** (214.1106): 214.1099 (M^+).

Synthesis of 8-(4-methylpiperazin-1-yl)quinoline (98e)

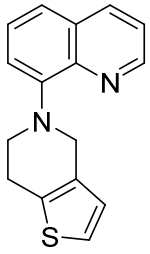


The aminopyridine **98e** was prepared *via* **TP4** using 8-quinolinesulfonic acid (209 mg, 1.00 mmol), *i*PrMgCl·LiCl (3.20 mL, 5.00 mmol) and 1-methylpiperazine (0.56 mL, 5.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **98b** (196 mg, 0.86 mmol, 86%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.88 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.47 - 7.39 (m, 2H), 7.36 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.15 (dd, *J* = 6.3, 2.7 Hz, 1H), 3.46 (s, 4H), 2.79 (t, *J* = 5.0 Hz, 4H), 2.42 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 149.6, 148.3, 142.9, 136.6, 129.7, 126.8, 121.7, 120.9, 116.1, 55.4, 52.2, 46.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936, 2795, 1567, 1500, 1470, 1448, 1389, 1373, 1308, 1289, 1246, 1150, 1109, 1029, 1011, 825, 793.
MS (EI, 70 eV): m/z = 227 (38), 183 (25), 170 (17), 169 (14), 157 (100), 155 (15), 144 (20), 129 (34), 128 (11).

HRMS (EI) for $C_{14}H_{17}N_3$ (227.1422): 227.1416 (M^+).

Synthesis of 5-(quinolin-8-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (98f)



The aminopyridine **98f** was prepared *via* **TP4** using 8-quinolinesulfonic acid (209 mg, 1.00 mmol), *i*PrMgCl·LiCl (3.20 mL, 5.00 mmol) and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (681 mg, 5.00 mmol). After stirring at 25 °C for 12 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* to give **98f** (246 mg, 0.92 mmol, 92%) as a light brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.91 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.11 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.45 - 7.41 (m, 2H), 7.38 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.19 (dd, *J* = 6.1, 2.8 Hz, 1H), 7.14 (dd, *J* = 5.1, 0.8 Hz, 1H), 6.85 (d, *J* = 5.1 Hz, 1H), 4.56 - 4.51 (m, 2H), 3.90 (t, *J* = 5.6 Hz, 2H), 3.06 (td, *J* = 5.7, 2.8 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 148.9, 148.4, 143.1, 136.5, 134.1, 133.8, 129.7, 126.7, 125.2, 122.7, 121.6, 121.0, 116.9, 51.6, 50.8, 25.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3034, 3007, 2917, 2812, 2774, 2708, 2213, 1660, 1567, 1498, 1470, 1388, 1325, 1225, 1103, 1045, 907.

MS (EI, 70 eV): m/z = 267 (17), 266 (100), 265 (23), 248 (24), 233 (11), 155 (48), 144 (75), 129 (92), 102 (15).

HRMS (EI) for $C_{16}H_{14}N_2S$ (266.0878): 266.0874 (M^+).

4 Amination of Phosphorodiamidate-Substituted Pyridines and Related *N*-Heterocycles with Magnesium Amides

4.1 Typical Procedures

Typical Procedure 5: Synthesis of phosphorodiamidates **99a–i** starting from the corresponding pyridones, quinolones, and 2-hydroxy-quinoxaline.

According to a literature procedure,[47] the hydroxy-substituted heterocycles (20.0 mmol) were dissolved in THF (20 mL) and 4-dimethylaminopyridine (DMAP, 244 mg, 2.00 mmol) was added to the solution/suspension. Then, Cl-P(O)(NMe_2)$_2$ (3.9 mL, 24.0 mmol) and triethylamine (3.33 mL, 24.0 mmol) were added and the reaction stirred at 25 °C for 12 h. The reaction mixture was quenched with brine (20 mL), extracted with ethyl acetate (3 x 50 mL). The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. If the crude product needed purification, it was purified by flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 6: Amination of phosphorodiamidate substituted heterocycles (**99a–i**) using magnesium amides of type $R_2NMgCl \cdot LiCl$

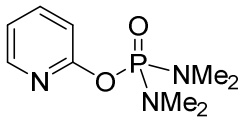
*i*PrMgCl·LiCl (1.4–3.0 equiv) was added to a solution of amine (1.4–3.0 equiv) in THF (5 mL/mmol of phosphorodiamidate substituted heterocycle) at 0 °C. The solution was stirred for 15 min at 0 °C and then 15 min at 25 °C before being added to a suspension/solution of the freshly prepared substrates **99a–i** (1 equiv) in THF (5 mL/mmol substrates **99a–i**) at 0 °C. The reaction mixture was then stirred at 25 °C until completion. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. If the crude product needed purification, it was purified by flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 7: Directed *ortho*-metalation and functionalization of substituted *N*-heterocycles of type **99** using TMPMgCl·LiCl.

To a solution of substituted *N*-heterocycle of type **99** in THF (5 mL/mmol substituted *N*-heterocycle) was added dropwise a solution of TMPMgCl·LiCl (1.5 equiv) at 0 °C. After full metalation (1 h, checked *via* TLC analysis of iodolyzed reaction aliquots), a solution of the corresponding electrophile in THF (2 mL/mmol substituted *N*-heterocycle) was added dropwise and the reaction slowly warmed to 25 °C and stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (20 mL/mmol substituted *N*-heterocycle) and extracted with ethyl acetate (3 x 50 mL/mmol substituted *N*-heterocycle). The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. If the crude product needed purification, it was purified *via* flash chromatography on silica gel using the appropriate eluent.

4.2 Preparation of Compounds 99 to 108

Synthesis of pyridin-2-yl *N*,*N*,*N'*,*N'*-tetramethyldiamidophosphate (99a)

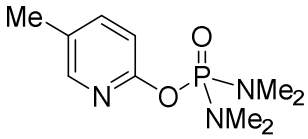


Phosphorodiamidate **99a** was prepared *via* **TP5** using 2-hydroxypyridine (1.90 g, 20.0 mmol), bis(*N*,*N*-dimethylamino)phosphoryl chloride (3.90 mL, 24.0 mmol), DMAP (244 mg, 2.00 mmol) and triethylamine (3.34 mL, 24 mmol). After workup, the crude product was isolated without further purification to give pyridin-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate **99a** (4.18 g, 18.2 mmol, 91%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.26 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.67 (ddd, *J* = 8.5, 7.3, 2.0 Hz, 1H), 7.13 - 7.08 (m, 1H), 7.06 (dd, *J* = 7.2, 4.9 Hz, 1H), 2.73 (d, *J* = 10.3 Hz, 12H).

The spectra matched those of the literature.[47]

Synthesis of 5-methylpyridin-2-yl *N*,*N*,*N'*,*N'*-tetramethyldiamidophosphate (99b)



Phosphorodiamidate **99b** was prepared *via* **TP5** using 5-methylpyridin-2-ol (1.09 g, 10.0 mmol), bis(*N*,*N*-dimethylamino)phosphoryl chloride (1.95 mL, 12.0 mmol), DMAP (122 mg, 1.00 mmol) and triethylamine (1.67 mL, 12 mmol). After workup, the crude product was isolated without further purification to give 5-methylpyridin-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate **99b** (1.36 g, 5.59 mmol, 56%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.10 - 8.05 (m, 1H), 7.51 - 7.45 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 2.73 (d, *J* = 10.3 Hz, 12H), 2.27 (s, 3H).

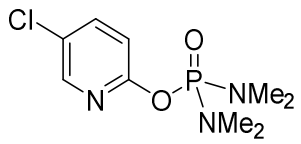
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.5, 156.4, 148.0, 140.4, 129.6, 113.5, 113.5, 36.9, 36.8, 17.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3421, 2962, 2900, 1560, 1580, 1478, 1378, 1304, 1242, 1204, 988, 914, 764.

MS (EI, 70 eV): 200 (21), 199 (50), 156 (86), 111 (24), 109 (100), 107 (67), 92 (42), 65 (24), 44 (65), 42 (27).

HRMS (EI) for **$C_8H_{12}N_2O_2P$** (199.0636): 199.0630 (M^+-(NMe_2))

Synthesis of 5-chloropyridin-2-yl *N*,*N*,*N'*,*N'*-tetramethyldiamidophosphate (99c)



Phosphorodiamidate **99c** was prepared *via* **TP5** using 5-chloropyridin-2-ol (1.30 g, 10.0 mmol), bis(*N*,*N*-dimethylamino)phosphoryl chloride (1.95 mL, 12.0 mmol), DMAP (122 mg, 1.00 mmol) and triethylamine (1.67 mL, 12 mmol). After workup, the crude product was isolated without further purification to give 5-chloropyridin-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate **99c** (2.24 g, 8.50 mmol, 85%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 - 8.20 (m, 1H), 7.66 - 7.62 (m, 1H), 7.09 (dt, *J* = 8.7, 0.8 Hz, 1H), 2.73 (d, *J* = 10.4 Hz, 12H).

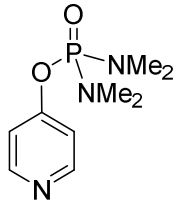
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.8, 156.8, 146.8, 139.4, 127.8, 127.8, 115.1, 115.0, 36.8, 36.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3457, 2931, 2812, 1678, 1579, 1461, 1371, 1305, 1253, 1218, 1113, 992, 914, 786, 760.

MS (EI, 70 eV): 219 (30), 176 (40), 129 (38), 127 (39), 112 (38), 44 (69), 43 (100).

HRMS (EI) for **$C_9H_{15}ClN_3O_2P$** (263.0590): 263.0582 (M^+)

Synthesis of pyridin-4-yl *N*,*N*,*N'*,*N'*-tetramethyldiamidophosphate (99d)

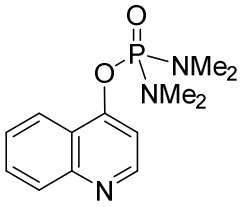


Phosphorodiamidate **99d** was prepared *via* **TP5** using 4-hydroxypyridine (951 mg, 10.0 mmol), bis(*N*,*N*-dimethylamino)phosphoryl chloride (1.95 mL, 12.0 mmol), DMAP (122 mg, 1.00 mmol) and triethylamine (1.67 mL, 12 mmol). After workup, the crude product was isolated without further purification to give pyridin-4-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate **99d** (2.05 g, 8.94 mmol, 89%) as a red oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.51 - 8.47 (m, 2H), 7.16 - 7.13 (m, 2H), 2.70 (d, *J* = 10.2 Hz, 12H).

The spectra matched those of the literature.[47]

Synthesis of quinolin-4-yl *N*,*N*,*N'*,*N'*-tetramethyldiamidophosphate (99e)

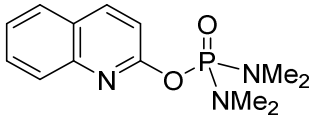


Phosphorodiamidate **99e** was prepared *via* **TP5** using 4-hydroxyquinoline (1.45 g, 10.0 mmol), bis(*N*,*N*-dimethylamino)phosphoryl chloride (1.95 mL, 12.0 mmol), DMAP (122 mg, 1.00 mmol) and triethylamine (1.67 mL, 12 mmol). After workup, the crude product was isolated without further purification to give quinolin-4-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate **99e** (2.37 g, 8.49 mmol, 85%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.79 (dd, *J* = 5.1, 1.6 Hz, 1H), 8.09 (dddd, *J* = 17.5, 8.5, 1.9, 1.0 Hz, 2H), 7.71 (ddt, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.54 (ddt, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.49 (dt, *J* = 5.1, 1.3 Hz, 1H), 2.77 (dd, *J* = 10.2, 1.7 Hz, 12H).

The spectra matched those of the literature.[47]

Synthesis of quinolin-2-yl *N*,*N*,*N'*,*N'*-tetramethyldiamidophosphate (99f)

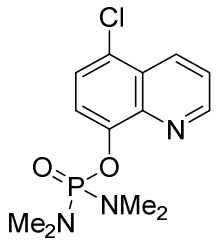


Phosphorodiamidate **99f** was prepared similarly to **TP5** using 2-hydroxyquinoline (1.45 g, 10.0 mmol), bis(*N*,*N*-dimethylamino)phosphoryl chloride (1.95 mL, 12.0 mmol), DMAP (122 mg, 1.00 mmol) and triethylamine (1.67 mL, 12 mmol). After stirring at 50 °C for 48 h, the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 50 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 2:8) to give **99f** (2.54 g, 9.09 mmol, 91%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.64-7.69 (m, 1H), 7.45-7.49 (m, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 2.80 (d, *J* = 10.4 Hz, 12H).

The spectra matched those of the literature.[47]

Synthesis of 5-chloroquinolin-8-yl *N*,*N*,*N'*,*N'*-tetramethyldiamidophosphate (99g)



Phosphorodiamidate **99g** was prepared *via* **TP5** using 5-chloroquinolin-8-ol (1.80 g, 10.0 mmol), bis(*N*,*N*-dimethylamino)phosphoryl chloride (1.95 mL, 12.0 mmol), DMAP (122 mg, 1.00 mmol) and triethylamine (1.67 mL, 12 mmol). After workup, the crude product was isolated without further purification to give 5-chloroquinolin-8-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate **99g** (2.95 g, 9.40 mmol, 94%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.93 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.49 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.60 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 8.6, 4.1 Hz, 1H), 2.78 (d, *J* = 10.2 Hz, 12H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 150.5, 146.7, 146.7, 142.0, 142.0, 132.9, 127.3,

126.4, 126.4, 126.3, 126.3, 122.2, 119.3, 119.2, 36.8, 36.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3457, 2926, 2811, 1589, 1495, 1464, 1383, 1357,

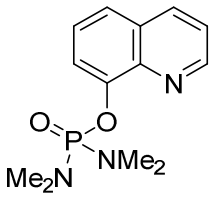
1296, 1216, 1066, 985, 852, 757, 672.

MS (EI, 70 eV): 271 (33), 269 (100), 206 (24), 179 (52), 177 (22), 150 (23), 44

(50), 42 (20).

HRMS (EI) for **$C_{13}H_{17}O_2N_3ClP$** (313.0747): 313.0744.

Synthesis of quinolin-8-yl *N,N,N',N'*-tetramethyldiamidophosphate (99h)



Phosphorodiamidate **99h** was prepared *via* **TP5** using 8-hydroxyquinoline (1.80 g, 10.0 mmol), bis(*N*,*N*-dimethylamino)phosphoryl chloride (1.95 mL, 12.0 mmol), DMAP (122 mg, 1.00 mmol) and triethylamine (1.67 mL, 12 mmol). After workup, the crude product was isolated without further purification to give quinolin-8-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate **99h** (2.43 g, 8.70 mmol, 87%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.92 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.68 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.58 (dt, *J* = 8.3, 1.2 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.40 (dd, *J* = 8.3, 4.1 Hz, 1H), 2.82 (d, *J* = 10.2 Hz, 12H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 150.0, 149.9, 136.3, 129.7, 126.8, 123.7, 121.6, 119.6, 119.5, 118.0, 37.0, 36.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3392, 2929, 2853, 2809, 1632, 1595, 1570, 1499, 1470, 1311, 1201, 1171, 1091, 993, 914, 823, 762.

MS (EI, 70 eV): 235 (100), 192 (36), 172 (19), 157 (29), 145 (43), 143 (27).

HRMS (EI) for **$C_{11}H_{12}N_2O_2P$** (235.0636): 235.0629 (M^+-(NMe_2))

M.p. (°C): 67–69.

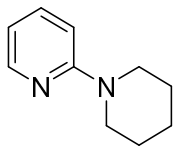
Synthesis of quinoxalin-2-yl *N*,*N*,*N'*,*N'*-tetramethyldiamidophosphate (99i)

Phosphorodiamidate **99i** was prepared *via* **TP5** using 2-hydroxyquinoxaline (1.46 g, 10.0 mmol), bis(*N*,*N*-dimethylamino)phosphoryl chloride (1.95 mL, 12.0 mmol), DMAP (122 mg, 1.00 mmol) and triethylamine (1.67 mL, 12 mmol). After workup, the crude product was isolated without further purification to give quinoxalin-2-yl *N*,*N*,*N*',*N*'-tetramethyldiamidophosphate **99i** (2.57 g, 9.17 mmol, 92%) as a red oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.69 (d, *J* = 0.7 Hz, 1H), 8.08 - 8.04 (m, 1H), 7.94 - 7.89 (m, 1H), 7.73 - 7.64 (m, 2H), 2.82 (d, *J* = 10.5 Hz, 12H).

The spectra matched those of the literature.[47]

Synthesis of 2-(piperidin-1-yl)pyridine (100a)



The aminopyridine **100a** was prepared *via* **TP6** using **99a** (112 mg, 0.49 mmol), *i*PrMgCl·LiCl (0.44 mL, 0.70 mmol) and piperidine (0.07 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **100a** (70 mg, 0.43 mmol, 88%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.16 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.46 - 7.39 (m, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 6.54 (dd, *J* = 7.1, 4.9 Hz, 1H), 3.56 - 3.43 (m, 4H), 1.63 (d, *J* = 3.1 Hz, 6H).

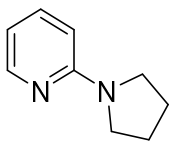
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 159.8, 148.0, 137.4, 112.5, 107.2, 46.4, 25.6, 24.8.

The spectra matched those of the literature.[10a]

Reaction on 1 mmol scale:

The aminopyridine **100a** was prepared *via* **TP6** using **99a** (229 mg, 1.00 mmol), *i*PrMgCl·LiCl (0.88 mL, 1.40 mmol) and piperidine (0.14 mL, 1.40 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (40 mL), extracted with ethyl acetate (3 x 50 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **100a** (129 mg, 0.795 mmol, 80%) as a colorless oil.

Synthesis of 2-(pyrrolidin-1-yl)pyridine (100b)



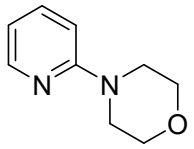
The aminopyridine **100b** was prepared *via* **TP6** using **99a** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and pyrrolidine (0.055 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 8:2) to give **100b** (55 mg, 0.37 mmol, 74%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.14 (ddd, *J* = 5.1, 2.0, 0.9 Hz, 1H), 7.41 (ddd, *J* = 8.8, 7.1, 2.0 Hz, 1H), 6.49 (ddd, *J* = 7.1, 5.1, 1.0 Hz, 1H), 6.38 - 6.29 (m, 1H), 3.48 - 3.40 (m, 4H), 2.02 - 1.95 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 157.4, 148.3, 137.0, 111.1, 106.6, 46.7, 25.7.

The spectra matched those of the literature.[10a]

Synthesis of 4-(pyridin-2-yl)morpholine (100c)



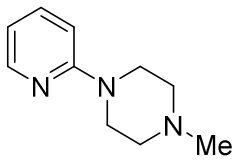
The aminopyridine **100c** was prepared *via* **TP6** using **99a** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and morpholine (0.065 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 8:2) to give **100c** (65 mg, 0.40 mmol, 80%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.19 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.48 (m, 1H), 6.68 - 6.59 (m, 2H), 3.83 - 3.78 (m, 4H), 3.50 - 3.45 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 159.7, 148.1, 137.6, 113.9, 107.0, 66.9, 45.7.

The spectra matched those of the literature.[10a]

Synthesis of 1-methyl-4-(pyridin-2-yl)piperazine (100d)



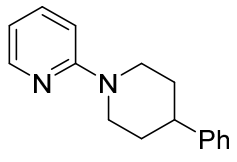
The aminopyridine **100d** was prepared *via* **TP6** using **99a** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and 4-methylpiperazine (70 mg, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (dichloromethane:methanol = 9:1) to give **100d** (76 mg, 0.43 mmol, 86%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.20-8.18 (m, 1H), 7.50-7.45 (m, 1H), 6.68 - 6.58 (m, 2H), 3.64 - 3.54 (t, *J* = 5.0 Hz, 4H), 2.61 - 2.52 (t, *J* = 5.0 Hz, 4H), 2.37 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 159.6, 148.1, 137.6, 113.6, 107.3, 55.0, 46.2, 45.2.

The spectra matched those of the literature.[58b]

Synthesis of 2-(4-phenylpiperidin-1-yl)pyridine (100e)



The aminopyridine **100e** was prepared *via* **TP6** using **99a** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and 4-phenylpiperidine (113 mg, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via*

column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **100e** (82 mg, 0.34 mmol, 68%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.24 - 8.22 (m, 1H), 7.51 - 7.47 (m, 1H), 7.35 - 7.31 (m, 2H), 7.27 - 7.21 (m, 3H), 6.74 - 6.71 (m, 1H), 6.63 - 6.60 (m, 1H), 4.49 - 4.44 (m, 2H), 2.94 (td, *J* = 12.8, 2.7 Hz, 2H), 2.77 (tt, *J* = 12.2, 3.7 Hz, 1H), 2.00 - 1.94 (m, 2H), 1.85-1.75 (m, 2H).

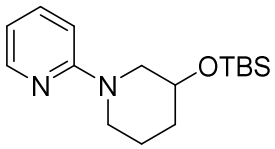
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.6, 148.1, 146.1, 137.6, 128.6, 126.9, 126.4, 112.9, 107.4, 46.3, 43.0, 33.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1593, 1482, 1437, 1224, 699.

MS (EI, 70 eV): m/z = 238 (28), 223 (48), 182 (19), 169 (51), 133 (100), 119 (44), 107 (20).

HRMS (EI) for **$C_{16}H_{18}N_2$** (238.1470): 238.1464 (M^+)

Synthesis of 2-(3-((*tert*-butyldimethylsilyl)oxy)piperidin-1-yl)pyridine (100f)



The aminopyridine **100f** was prepared *via* **TP6** using **99a** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and 3-((*tert*-butyldimethylsilyl)oxy)piperidine (149 mg, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 99:1) to give **100f** (79 mg, 0.27 mmol, 54%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.17 - 8.15 (m, 1H), 7.46 - 7.41 (m, 1H), 6.64 - 6.62 (m, 1H), 6.57 - 6.53 (m, 1H), 4.15 - 4.06 (m, 2H), 3.74 - 3.67 (m, 1H), 2.92 - 2.86 (m, 1H), 2.81 (dd, *J* = 12.5, 9.2 Hz, 1H), 1.99 - 1.95 (m, 1H), 1.83 - 77 (m, 1H), 1.57 - 1.44 (m, 2H), 0.89 (s, 9H), 0.09 (d, *J* = 2.7 Hz, 6H).

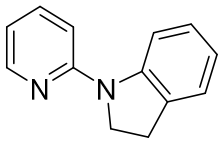
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.5, 148.2, 137.5, 112.6, 107.1, 67.7, 53.1, 45.3, 34.6, 26.0, 23.2, 18.3, -4.50.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 2856, 1595, 1492, 1437, 1241, 1096, 858, 835, 771.

MS (EI, 70 eV): m/z = 235 (100), 161 (33), 121 (19), 75 (19).

HRMS (EI) for **$C_{16}H_{28}N_2OSi$** (292.1971): 292.1972 (M^+)

Synthesis of 1-(pyridin-2-yl)indoline (100g)



The aminopyridine **100g** was prepared *via* **TP6** using **99a** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and indoline (0.08 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 10:0.5) to give **100g** (51 mg, 0.26 mmol, 52%) as an orange solid.

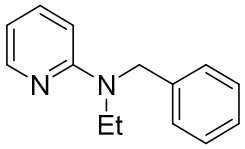
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.35 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 8.17 - 8.12 (m, 1H), 7.60 (ddd, *J* = 8.5, 7.2, 2.0 Hz, 1H), 7.22 - 7.15 (m, 2H), 6.88 (td, *J* = 7.4, 1.1 Hz, 1H), 6.85 - 6.75 (m, 2H), 4.07 (t, *J* = 8.6 Hz, 2H), 3.26 - 3.17 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ (ppm): 155.3, 147.7, 144.9, 137.7, 131.6, 127.4, 124.8, 120.8, 114.5, 113.4, 109.0, 49.7, 27.9.

The spectra matched those of the literature.[138]

[138] N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2001**, *123,* 10935–10941.

Synthesis of *N*-benzyl-*N*-ethylpyridin-2-amine (100h)



The aminopyridine **100h** was prepared *via* **TP6** using **99a** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and *N*-ethyl-*N*-benzylamine (0.11 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 95:5) to give **100h** (77 mg, 0.36 mmol, 72%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.21 - 8.18 (m, 1H), 7.41 - 7.36 (m, 1H), 7.34 - 7.21 (m, 5H), 6.55 - 6.51 (m, 1H), 6.46 - 6.44 (m, 1H). 4.75 (s, 2H), 3.59 (q, *J* = 7.0 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H).

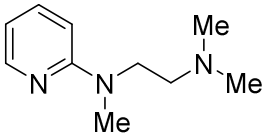
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.2, 148.2, 139.2, 137.3, 128.6, 127.0, 126.9, 111.7, 105.9, 51.0, 42.8, 12.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1593, 1489, 1432, 1360, 767, 727, 695.

MS (EI, 70 eV): m/z = 212 (15), 183 (90), 121 (100), 91 (37).

HRMS (EI) for **$C_{15}H_{17}N_2$** (212.1313): 212.1304 (M^+).

Synthesis of *N*,*N*,*N*'-trimethyl-*N*'-(pyridin-2-yl)ethane-1,2-diamine (100i)



The aminopyridine **100i** was prepared *via* **TP6** using **99a** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and *N*,*N*,*N*'-trimethylethylenediamine (0.093 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x

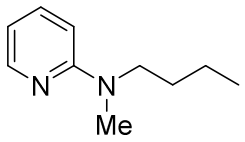
30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (dichloromethane:methanol = 8:2) to give **100i** (57 mg, 0.32 mmol, 64%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.13 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.40 (ddd, *J* = 8.8, 7.1, 2.0 Hz, 1H), 6.52 - 6.44 (m, 2H), 3.72 - 3.60 (m, 2H), 3.04 (s, 3H), 2.55 - 2.48 (m, 2H), 2.30 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.6, 148.1, 137.2, 111.5, 105.7, 56.4, 48.3, 45.8, 36.7.

The spectra matched those of **75e**.

Synthesis of *N*-butyl-*N*-methylpyridin-2-amine (100j)



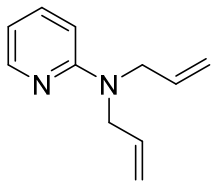
The aminopyridine **100j** was prepared *via* **TP6** using **99a** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and *N*-methylbutane-1-amine (0.09 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **100j** (57 mg, 0.35 mmol, 70%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.41 (ddd, *J* = 8.6, 7.1, 2.0 Hz, 1H), 6.52 - 6.44 (m, 2H), 3.53 - 3.45 (m, 2H), 3.04 (s, 3H), 1.62 - 1.52 (m, 2H), 1.41 - 1.29 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.7, 148.1, 137.1, 111.1, 105.8, 50.1, 36.4, 29.5, 20.4, 14.2.

The spectra matched those of **75b**.

Synthesis of *N*,*N*-diallylpyridin-2-amine (100k)



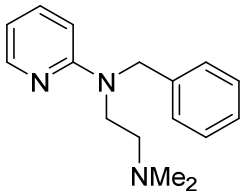
The aminopyridine **100k** was prepared *via* **TP6** using **99a** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and diallylamine (0.084 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **100k** (68 mg, 0.39 mmol, 78%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.40 (ddd, *J* = 8.8, 7.1, 2.0 Hz, 1H), 6.53 (ddd, *J* = 7.0, 5.0, 0.9 Hz, 1H), 6.47 (dt, *J* = 8.6, 1.0 Hz, 1H), 5.93 - 5.79 (m, 2H), 5.21 - 5.09 (m, 4H), 4.11 (dt, *J* = 5.1, 1.7 Hz, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.1, 148.0, 137.3, 134.1, 116.1, 111.9, 106.2, 50.2.

The spectra matched those of the literature.[137]

Synthesis of *N*-benzyl-*N*',*N*'-dimethyl-*N*-(pyridin-2-yl)ethane-1,2-diamine (Tripelen-namine) (100l)



The aminopyridine **100l** was prepared *via* **TP6** using **99a** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and *N*-benzyl-*N*',*N*'-dimethylethane-1,2-diamine (0.14 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (dichloromethane:methanol = 9:1) to give **100l** (94 mg, 0.37 mmol, 74%) as a yellow oil.

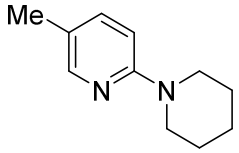
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.17 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.38 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.25 - 7.21 (m, 3H), 6.54 (ddd, *J* = 7.1, 5.0, 0.9 Hz, 1H), 6.46 (dt, *J* = 8.5, 0.9 Hz, 1H), 4.78 (s, 2H), 3.71 - 3.63 (m, 2H), 2.57 - 2.48 (m, 2H), 2.27 (s, 6H).p

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.3, 148.2, 139.0, 137.3, 128.6, 127.0, 127.0, 111.9, 105.8, 56.9, 52.0, 46.7, 45.9.

The spectra matched those of the literature.[139]

[139] M. H. S. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. Watson, J. M. Williams, *J. Am. Chem. Soc.* **2009**, *131*, 1766–1774.

Synthesis of 5-methyl-2-(piperidin-1-yl)pyridine (100m)



The aminopyridine **100m** was prepared *via* **TP6** using **99b** (122 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and piperidine (0.07 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 95:5) to give **100m** (58 mg, 0.33 mmol, 66%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.00 (dt, *J* = 2.5, 0.8 Hz, 1H), 7.29 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.60 (d, *J* = 8.7 Hz, 1H), 3.47 (dd, *J* = 5.5, 3.4 Hz, 4H), 2.18 (s, 3H), 1.70 - 1.56 (m, 6H).

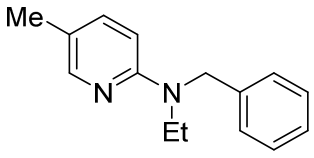
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.1, 147.1, 138.8, 121.6, 107.5, 47.1, 25.6, 24.8, 17.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2931, 2851, 1609, 1494, 1394, 1247, 1130, 1025, 932, 808.

MS (EI, 70 eV): m/z = 176 (83), 147 (100), 133 (55), 120 (66), 93 (46).

HRMS (EI) for **$C_{11}H_{16}N_2$** (176.1313): 176.1311 (M^+).

Synthesis of *N*-benzyl-*N*-ethyl-5-methylpyridin-2-amine (100n)



The aminopyridine **100n** was prepared *via* **TP6** using **99b** (122 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and *N*-benzyl-*N*-ethylamine (0.105 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL)

and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 99:1) to give **100n** (80 mg, 0.353 mmol, 71%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.01 - 8.00 (m, 1H), 7.32 - 7.27 (m, 2H), 7.25 - 7.21 (m, 4H), 6.39 (dd, *J* = 8.6, 0.8 Hz, 1H), 4.72 (s, 2H), 3.57 (q, *J* = 7.0 Hz, 2H), 2.17 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H).

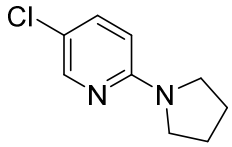
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.6, 147.8, 139.5, 138.4, 128.6, 127.0, 126.8, 120.3, 105.6, 51.2, 43.0, 17.4, 12.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1608, 1497, 1451, 1407, 1358, 804, 730, 704.

MS (EI, 70 eV): m/z = 226 (16), 197 (98), 135 (100), 92 (23).

HRMS (EI) for **$C_{15}H_{18}N_2$** (226.1470): 226.1459 (M^+).

Synthesis of 5-chloro-2-(pyrrolidin-1-yl)pyridine (100o)



The aminopyridine **100o** was prepared *via* **TP6** using **99c** (131 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and pyrrolidine (0.055 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 99:1) to give **100o** (70 mg, 0.358 mmol, 71%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 (d, *J* = 2.3 Hz, 1H), 7.36 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.28 (d, *J* = 9.0 Hz, 1H), 3.46 - 3.35 (m, 4H), 2.04 - 1.98 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 155.8, 146.6, 136.8, 118.2, 107.2, 47.0, 25.7.

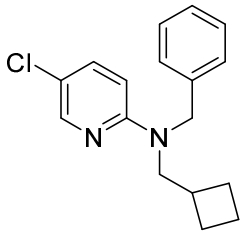
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2973, 1599, 1518, 1461, 1417, 1238, 1162, 1107, 991, 947, 808.

MS (EI, 70 eV): m/z = 182 (57), 181 (25), 155 (37), 154 (36), 153 (100), 141 (20), 112 (24), 70 (34).

HRMS (EI) for **$C_9H_{11}ClN_2$** (182.0611): 182.0602 (M^+).

M.p. (°C): 82-83.

Synthesis of *N*-benzyl-5-chloro-*N*-(cyclobutylmethyl)pyridin-2-amine (100p)



The aminopyridine **100p** was prepared *via* **TP6** using **99c** (131 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and *N*-benzyl-*N*-cyclobutylmethanamine (122 mg, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 95:5) to give **100p** (106 mg, 0.37 mmol, 74%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 (dd, *J* = 2.7, 0.7 Hz, 1H), 7.35 (tt, *J* = 7.5, 1.5 Hz, 3H), 7.31 - 7.27 (m, 1H), 7.24 - 7.19 (m, 2H), 6.39 (dd, *J* = 9.1, 0.7 Hz, 1H), 4.78 (s, 2H), 3.63 (d, *J* = 7.1 Hz, 2H), 2.81 - 2.67 (m, 1H), 2.13 - 2.01 (m, 2H), 2.00 - 1.73 (m, 4H).

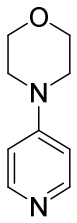
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.9, 146.3, 138.6, 136.8, 128.6, 127.0, 126.7, 118.6, 106.7, 54.2, 52.3, 34.6, 27.0, 18.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2931, 2860, 1590, 1490, 1407, 1364, 804, 729, 696.

MS (EI, 70 eV): m/z = 286 (7), 244 (18), 231 (18), 217 (30), 167 (33), 112 (14), 91 (100).

HRMS (EI) for **$C_{17}H_{19}ClN_2$** (286.1237): 286.1237 (M^+).

Synthesis of 4-(pyridin-4-yl)morpholine (101a)



The aminopyridine **101a** was prepared *via* **TP6** using **99d** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and morpholine (0.065 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (ethyl acetate) to give **101a** (81 mg, 0.49 mmol, 98%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.29 (d, *J* = 6.7 Hz, 2H), 6.71 - 6.58 (m, 2H), 3.87 - 3.77 (m, 4H), 3.33 - 3.21 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 155.3, 150.3, 108.3, 66.5, 46.2.

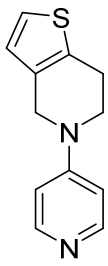
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1597, 1247, 1123, 934, 668.

MS (EI, 70 eV): m/z = 164 (100), 133 (17), 106 (92), 78 (35).

HRMS (EI) for **$C_9H_{12}N_2O$** (164.0945): 164.0950 (M^+).

M.p. (°C): 101–103.

Synthesis of 5-(pyridin-4-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (101b)



The aminopyridine **101b** was prepared *via* **TP6** using **99d** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (0.085 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (dichloromethane:methanol = 95:5) to give **101b** (75 mg, 0.347 mmol, 69%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.30 - 8.27 (m, 2H), 7.15 (d, *J* = 5.1 Hz.1H), 6.84 (d, *J* = 5.1 Hz, 1H), 6.72 - 6.71 (m, 2H), 4.42 (s, 2H), 3.73 (t, *J* = 5.7 Hz, 2H), 2.98 (t, *J* = 5.6 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.4, 150.3, 133.5, 132.2, 125.1, 123.6, 108.2, 46.7, 44.2, 24.9.

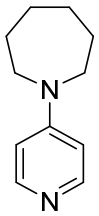
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2912, 2844, 1658, 1642, 1591, 1537, 1591, 1508, 1404, 1332, 1236, 1166, 986, 924, 831, 802, 716.

MS (EI, 70 eV): m/z = 216 (21), 135 (12), 110 (100), 84 (10).

HRMS (EI) for **$C_{12}H_{12}N_2S$** (216.0721): 216.0716 (M^+).

M.p. (°C): 90–92.

Synthesis of 1-(pyridin-4-yl)azepane (101c)



The aminopyridine **101c** was prepared *via* **TP6** using **99d** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and azepane (0.08 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (ethyl acetate) to give **101c** (62 mg, 0.352 mmol, 70%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 - 8.16 (m, 2H), 6.49 - 6.47 (m, 2H), 3.49 - 3.41 (m, 4H), 1.80-1.75 (m, 4H), 1.56-1.53 (m, 4H).

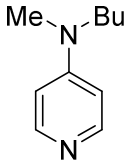
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 153.3, 150.0, 106.3, 48.7, 27.2, 27.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 1598, 1515, 1409, 1370, 1228, 1003, 988, 905, 802.

MS (EI, 70 eV): m/z = 176 (88), 147 (100), 133 (54), 121 (37), 78 (28).

HRMS (EI) for **$C_{11}H_{16}N_2$** (176.1313): 176.1307 (M^+).

Synthesis of *N*-butyl-*N*-methylpyridin-4-amine (101d)



The aminopyridine **101c** was prepared *via* **TP6** using **99d** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and *N*-methylbutane-1-amine (0.095 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL)

and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (dichloromethane:methanol = 9:1) to give **101d** (62 mg, 0.38 mmol, 75%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.21 - 8.10 (m, 2H), 6.51 - 6.41 (m, 2H), 3.36 - 3.28 (m, 2H), 2.96 (s, 3H), 1.63 - 1.49 (m, 2H), 1.33 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 153.8, 148.8, 106.5, 51.5, 37.7, 28.9, 20.3, 14.0.

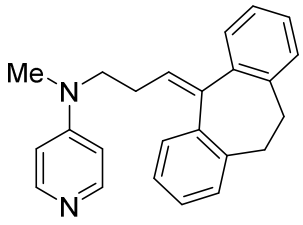
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2927, 2872, 1644, 1593, 1515, 1463, 1390,

1225, 1208, 985, 929, 800.

MS (EI, 70 eV): m/z = 164 (11), 121 (100), 94 (13).

HRMS (EI) for **C10H16N2** (164.1313): 164.1306 (M^+).

Synthesis of 4-(nortriptyline-*N*-yl)pyridine (101e)



The aminopyridine **101e** was prepared *via* **TP6** using **99d** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.92 mL, 1.40 mmol) and nortriptyline hydrochloride (210 mg, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (ethyl acetate) to give **101e** (73 mg, 0.214 mmol, 43%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.12 - 8.09 (m, 2H), 7.25 - 7.22 (m, 3H), 7.16 - 7.12 (m, 3H), 7.08 - 7.03 (m, 2H), 6.27 - 6.24 (m, 2H), 5.87 (t, *J* = 7.7 Hz, 1H), 3.37 - 3.27 (m, 4H), 3.00 - 2.96 (m, 1H), 2.90 (s, 3H), 2.79 - 2.72 (m, 1H), 2.46 - 2.34 (m, 2H).

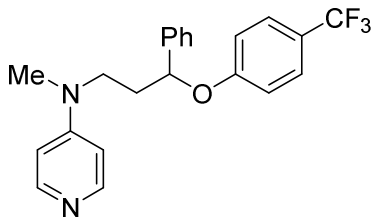
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 153.2, 149.8, 145.8, 140.8, 139.8, 139.6, 137.2, 130.3, 128.5, 128.2, 128.1, 127.9, 127.4, 127.0, 126.2, 126.1, 106.5, 51.2, 37.7, 33.9, 32.1, 26.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2914, 1597, 1517, 1391, 1229, 987, 804, 777, 756.

MS (EI, 70 eV): m/z = 340 (2), 122 (9), 121 (100).

HRMS (EI) for **$C_{24}H_{24}N_2$** (340.1939): 340.1935 (M^+).

Synthesis of 4-(fluoxetin-*N*-yl)pyridine (101f)



The aminopyridine **101f** was prepared *via* **TP6** using **99d** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.92 mL, 1.40 mmol) and fluoxetine hydrochloride (243 mg, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (ethyl acetate) to give **101f** (137 mg, 0.355 mmol, 70%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.17 - 8.16 (m, 2H), 7.46 - 7.44 (m, 2H), 7.37 - 7.27 (m, 5H), 6.91 - 6.89 (m, 2H), 6.46 - 6.44 (m, 2H), 5.17 (dd, *J* = 8.3, 4.4 Hz, 1H), 3.65 - 3.53 (m, 2H), 2.95 (s, 3H), 2.26 - 2.12 (m, 2H).

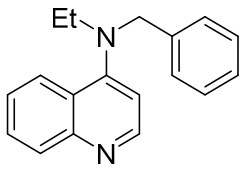
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.3, 153.4, 150.0, 140.4, 129.1, 128.3, 127.0, 125.7, 123.5, 123.2, 123.1, 115.8, 106.7, 48.0, 37.8, 36.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2917, 1598, 1539, 1517, 1326, 1248, 1110, 1067, 988, 836, 805, 701.

MS (EI, 70 eV): m/z = 387 (3), 122 (10), 121 (100).

HRMS (EI) for **$C_{22}H_{21}N_2F_3O$** (386.1606): 386.1599 (M^+).

Synthesis of *N*-benzyl-*N*-ethylquinolin-4-amine (102a)



The aminopyridine **102a** was prepared *via* **TP6** using **99e** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and *N*-benzyl-*N*-ethylamine (0.105 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (ethyl acetate) to give **102a** (118 mg, 0.45 mmol, 90%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.67 (d, *J* = 5.1 Hz, 1H), 8.15 (ddd, *J* = 8.5, 1.5, 0.6 Hz, 1H), 8.05 (ddd, *J* = 8.4, 1.4, 0.6 Hz, 1H), 7.65 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.45 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.35 - 7.31 (m, 5H), 6.83 (d, *J* = 5.1 Hz, 1H), 4.52 (s, 2H), 3.35 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).

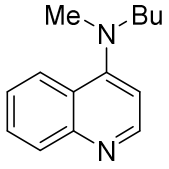
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 155.7, 150.5, 137.9, 130.1, 129.1, 128.7, 128.5, 128.3, 127.9, 127.4, 125.2, 124.0, 110.7, 56.8, 46.8, 12.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1599, 1505, 1424, 1398, 1297, 768, 737.

MS (EI, 70 eV): m/z = 262 (41), 247 (84), 91 (100).

HRMS (EI) for **$C_{18}H_{18}N_2$** (262.1470): 262.1468 (M^+).

Synthesis of *N*-butyl-*N*-methylquinolin-4-amine (102b)



The aminopyridine **102b** was prepared *via* **TP6** using **99e** (115 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and *N*-methylbutane-1-amine (0.095 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (ethyl acetate) to give **102b** (64 mg, 0.30 mmol, 60%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.65 (d, *J* = 5.1 Hz, 1H), 8.06 - 7.99 (m, 2H), 7.62 (ddd, *J* = 8.3, 6.8, 1.5 Hz, 1H), 7.44 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 6.78 (d, *J* = 5.1 Hz, 1H), 3.30 - 3.23 (m, 2H), 2.98 (s, 3H), 1.77 - 1.65 (m, 2H), 1.34 (h, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

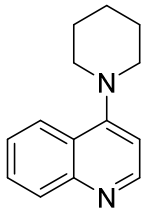
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.7, 150.5, 149.9, 129.9, 128.9, 124.7, 124.4, 123.6, 108.4, 56.0, 40.8, 29.7, 20.3, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3364, 2955, 2928, 2860, 1573, 1508, 1395, 1300, 1044, 925, 766.

MS (EI, 70 eV): m/z = 214 (20), 171 (100), 170 (21), 85 (17), 71 (25), 57 (39), 55 (16), 41 (16).

HRMS (EI) for **$C_{14}H_{18}N_2$** (214.1470): 214.1469 (M^+).

Synthesis of 4-(piperidin-1-yl)quinoline (102c)



The aminopyridine **102c** was prepared *via* **TP6** using **99e** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and piperidine (0.07 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (ethyl acetate) to give **102c** (65 mg, 0.306 mmol, 61%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.70 (d, *J* = 5.0 Hz, 1H), 8.07 - 7.97 (m, 2H), 7.64 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.46 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 6.81 (d, *J* = 5.0 Hz, 1H), 3.23 - 3.15 (m, 4H), 1.90 - 1.80 (m, 4H), 1.74 - 1.65 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.2, 150.9, 149.6, 130.0, 129.0, 125.1, 124.1, 123.9, 108.7, 53.8, 26.2, 24.6.

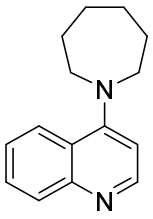
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933, 2851, 2810, 1738, 1577, 1567, 1505, 1423, 1395, 1295, 1243, 1221, 1115, 1101, 1007, 920, 829, 766.

MS (EI, 70 eV): m/z = 212 (45), 211 (100), 155 (22), 128 (11).

HRMS (EI) for **$C_{14}H_{15}N_2$** (211.1241): 211.1228 (M^+-H).

M.p. (°C): 83–86.

Synthesis of 4-(azepan-1-yl)quinoline (102d)



The aminopyridine **102d** was prepared *via* **TP6** using **99e** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and azepane (0.07 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (ethyl acetate) to give **102d** (87 mg, 0.384 mmol, 75%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.60 (d, *J* = 5.3 Hz, 1H), 8.06 (dd, *J* = 8.6, 1.4 Hz, 1H), 8.00 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.63 - 7.58 (m, 1H), 7.42-7.38 (m, 1H), 6.77 (d, *J* = 5.3 Hz, 1H), 3.54 - 3.51 (m, 4H), 1.95 - 1.90 (m, 4H), 1.78 - 1.75 (m, 4H).

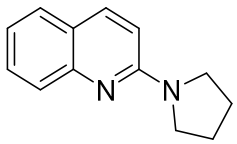
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.9, 150.4, 150.2, 129.9, 128.8, 124.9, 124.1, 123.3, 107.3, 54.5, 28.7, 27.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2924, 1567, 1507, 1429, 1397, 1300, 902, 763.

MS (EI, 70 eV): m/z = 226 (100), 197 (73), 183 (63), 169 (64), 155 (45).

HRMS (EI) for $C_{15}H_{18}N_2$ (226.1470): 226.1464 (M^+).

Synthesis of 2-(pyrrolidin-1-yl)quinoline (102e)



The aminopyridine **102e** was prepared *via* **TP6** using **99f** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and pyrrolidine (0.07 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (pentane:ethyl acetate = 8:2) to give **102e** (78 mg, 0.393 mmol, 78%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.82 (d, *J* = 9.0 Hz, 1H), 7.73 (dd, *J* = 8.5, 3.1 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 6.71-6.68 (m, 1H), 3.61 (s, 4H), 2.03 (s, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 155.9, 148.7, 137.0, 129.4, 127.5, 126.2, 122.7, 121.3, 110.3, 46.9, 25.6.

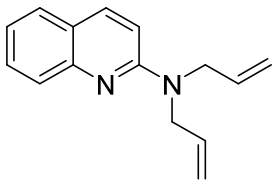
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1607, 1513, 1482, 1430, 1402, 810.

MS (EI, 70 eV): m/z = 198 (50), 169 (100), 129 (30), 71 (22), 57 (33), 43 (84).

HRMS (EI) for **$C_{13}H_{24}N_2$** (198.1157): 198.1153 (M^+).

M.p. (°C): 89–90.

Synthesis of *N*,*N*-diallylquinolin-2-amine (102f)



The aminopyridine **102f** was prepared *via* **TP6** using **99f** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and diallylamine (0.085 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (pentane:ethyl acetate = 99:1) to give **102f** (100 mg, 0.446 mmol, 89%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.84 (dd, *J* = 9.1, 0.8 Hz, 1H), 7.71 - 7.68 (m, 1H), 7.58 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.54-7.50 (m, 1H), 7.21-7.17 (m, 1H), 6.81 (d, *J* = 9.1 Hz, 1H), 5.98-5.89 (m, 2H), 5.24 - 5.16 (m, 4H), 4.28-4.26 (m, 4H).

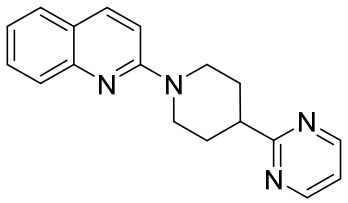
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.6, 148.2, 137.3, 134.3, 129.5, 127.3, 122.9, 121.9, 116.5, 109.6, 50.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1618, 1606, 1507, 1487, 1432, 1398, 1236, 809, 754.

MS (EI, 70 eV): m/z = 209 (11), 183 (100), 169 (37), 128 (47).

HRMS (EI) for **$C_{15}H_{15}N_2$** (223.1235): 223.1227 (M^+-H).

Synthesis of 2-(4-(pyrimidin-2-yl)piperidin-1-yl)quinoline (102g)



The aminopyridine **102g** was prepared *via* **TP6** using **99f** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and 4-(pyrimidin-2-yl)piperidine (0.11 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (pentane:ethyl acetate = 8:2) to give **102g** (126 mg, 0.434 mmol, 86%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.35 (d, *J* = 4.7 Hz, 2H), 7.92 (dd, *J* = 9.2, 0.8 Hz, 1H), 7.75 - 7.72 (m, 1H), 7.62 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.57 - 7.53 (m, 1H), 7.26 - 7.22 (m, 1H), 7.03 (d, *J* = 9.1 Hz, 1H), 6.53 (t, *J* = 4.7 Hz, 1H), 4.01 - 3.98 (m, 4H), 3.86 - 3.84 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.9, 157.9, 157.6, 148.0, 137.7, 129.7, 127.4, 126.8, 123.3, 122.7, 110.3, 109.8, 45.1, 43.7.

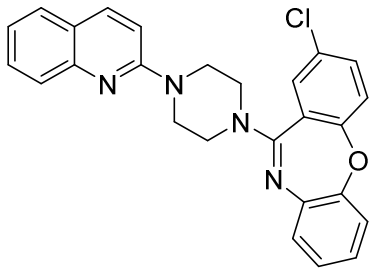
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1618, 1605, 1585, 1548, 1505, 1430, 1232, 981.

MS (EI, 70 eV): m/z = 291 (24), 183 (21), 169 (25), 157 (100), 147 (29), 128 (35), 80 (16).

HRMS (EI) for **$C_{18}H_{19}N_4$** (291.1610): 291.1453 (M^+-H).

M.p. (°C): 147–149.

Synthesis of 2-(amoxapin-*N*-yl)quinoline (102h)



The aminopyridine **102h** was prepared *via* **TP6** using **99f** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and amoxapine (220 mg, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **102h** (172 mg, 0.39 mmol, 78%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94 (dd, *J* = 9.2, 0.7 Hz, 1H), 7.74 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.58 - 7.54 (m, 1H), 7.43 - 7.40 (m, 2H), 7.28 - 7.24 (m, 1H), 7.22 - 7.18 (m, 2H), 7.13-7.09 (m, 2H), 7.05 - 6.99 (m, 2H), 3.88 (s, 4H), 3.69 (s, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.5, 159.2, 157.6, 152.0, 147.8, 140.2, 137.8, 132.8, 130.5, 129.8, 129.2, 127.4, 127.2, 126.9, 126.0, 125.1, 124.9, 123.5, 122.9, 122.9, 120.3, 109.9, 47.5, 45.3.

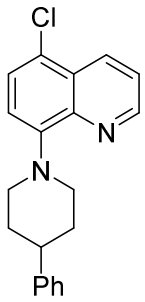
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1600, 1586, 1557, 1505, 1450, 1429, 1394, 1229, 906, 726, 727.

MS (EI, 70 eV): m/z = 440 (17), 271 (31), 257 (25), 228 (21), 196 (86), 183 (100), 169 (69), 157 (49), 128 (76).

HRMS (EI) for **$C_{26}H_{21}ClN_4O$** (440.1404): 440.1384 (M^+).

M.p. (°C): 104–106.

Synthesis of 5-chloro-8-(4-phenylpiperidin-1-yl)quinoline (102i)



The aminopyridine **102i** was prepared *via* **TP6** using **99g** (156 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.99 mL, 1.50 mmol) and 4-phenylpiperidine (242 mg, 1.50 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (pentane:ethyl acetate = 99:1) to give **102i** (109 mg, 0.338 mmol, 68%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.96 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.55 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.49 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.35 (d, *J* = 4.3 Hz, 4H), 7.25 - 7.22 (m, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 4.10 - 4.05 (m, 2H), 2.91 - 2.84 (m, 2H), 2.74 (tt, *J* = 12.2, 3.7 Hz, 1H), 2.31 - 2.21 (m, 2H), 2.05 - 1.99 (m, 2H).

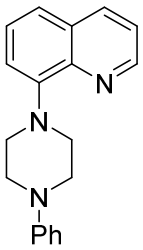
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.8, 148.7, 146.5, 143.5, 133.4, 128.6, 127.3, 127.1, 126.7, 126.3, 124.0, 121.6, 116.1, 53.6, 43.1, 33.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2357, 2006, 1496, 1389, 1219, 1008, 696.

MS (EI, 70 eV): m/z = 322 (25), 266 (20), 203 (70), 189 (60), 163 (100), 128 (39).

HRMS (EI) for **$C_{20}H_{19}ClN_2$** (322.1237): 322.1233 (M^+).

Synthesis of 8-(4-phenylpiperazin-1-yl)quinoline (102j)



The aminopyridine **102j** was prepared *via* **TP6** using **99h** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.99 mL, 1.50 mmol) and 4-phenylpiperazine (0.23 mL, 1.50 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **102j** (88 mg, 0.30 mmol, 60%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.93 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.48 - 7.47 (m, 2H), 7.39 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.35 - 7.30 (m, 2H), 7.21 (dd, *J* = 5.8, 3.1 Hz, 1H), 7.08 - 7.04 (m, 2H), 6.93 - 6.89 (m, 1H), 3.64 - 3.53 (m, 8H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.6, 149.3, 148.3, 142.8, 136.6, 129.7, 129.2, 126.8, 121.9, 121.0, 119.8, 116.3, 116.1, 52.2, 49.5.

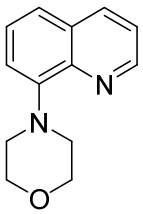
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1598, 1499, 1469, 1445, 1382, 1329, 1228, 1115, 1021, 937, 906, 824, 789, 755, 725, 689

MS (EI, 70 eV): m/z = 183 (19), 169 (23), 157 (100), 155 (32), 144 (21), 129 (67), 104 (40), 77 (33)

HRMS (EI) for **$C_{19}H_{19}N_3$** (289.1579): 289.1565 (M^+).

M.p. (°C): 125–127.

Synthesis of 4-(quinolin-8-yl)morpholine (102k)



The aminopyridine **102k** was prepared *via* **TP6** using **99h** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.99 mL, 1.50 mmol) and morpholine (0.135 mL, 1.50 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **102k** (56 mg, 0.261 mmol, 52%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.87 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.11-8.09 (m, 1H), 7.44-7.42 (m, 2H), 7.36 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.12 (dd, *J* = 5.1, 3.8 Hz, 1H), 4.07 - 4.01 (m, 4H), 3.43 - 3.39 (m, 4H).

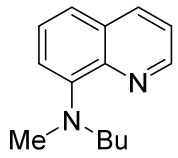
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.3, 148.3, 142.7, 136.6, 129.7, 126.8, 122.0, 121.0, 115.8, 67.3, 52.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2813, 1567, 1499, 1469, 1443, 1387, 1373, 1264, 1239, 1114, 1105, 1067, 1032, 1021, 921, 861, 824, 788, 752, 703.

MS (EI, 70 eV): m/z = 195 (12), 183 (16), 169 (24), 168 (25), 157 (15), 156 (21), 155 (39), 129 (100), 102 (14).

HRMS (EI) for **$C_{13}H_{14}N_2O$** (214.1106): 214.1093 (M^+).

Synthesis of *N*-butyl-*N*-methylquinolin-8-amine (102l)



The aminopyridine **102l** was prepared *via* **TP6** using **99h** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.99 mL, 1.50 mmol) and *N*-butyl-*N*-methylamine (0.18 mL, 1.50 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **102l** (62 mg, 0.29 mmol, 57%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.86 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.07-8.05 (m, 1H), 7.40 (t, *J* = 7.7, 1H), 7.34 - 7.31 (m, 2H), 7.09 (dd, *J* = 7.4, 1.4 Hz, 1H), 3.57 - 3.53 (m, 2H), 3.04 (s, 3H), 1.63 - 1.56 (m, 2H), 1.27 (h, *J* = 7.4 Hz, 2H), 0.86 (t, *J* = 7.4 Hz, 3H).

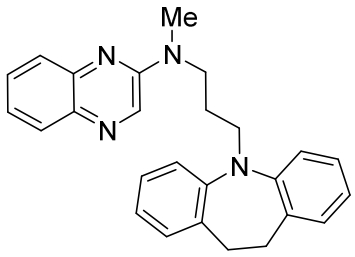
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.8, 147.6, 143.0, 136.3, 129.7, 126.6, 120.8, 120.3, 116.5, 56.2, 41.3, 28.8, 20.6, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 1564, 1500, 1469, 1388, 1361, 1310, 1095, 1062, 924, 821, 804, 787, 746

MS (EI, 70 eV): m/z = 171 (100), 157 (31), 156 (27), 155 (21), 129 (44).

HRMS (EI) for **$C_{14}H_{18}N_2$** (214.1470): 214.1456 (M^+).

Synthesis of 2-(protriptylin-*N*-yl)quinoline (103a)



The aminopyridine **103a** was prepared *via* **TP6** using **99i** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.66 mL, 1.00 mmol) and protriptyline hydrochloride (0.18 mL, 1.50 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **103a** (175 mg, 0.445 mmol, 89%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.30 (s, 1H), 7.85-7.82 (m, 1H), 7.61-7.58 (m, 1H), 7.55-7.51 (m, 1H), 7.35-7.31 (m, 1H), 7.15 - 7.11 (m, 4H), 7.09-7.07 (m, 2H), 6.96 - 6.92 (m, 2H), 3.85 (t, *J* = 6.5 Hz, 2H), 3.71 (t, *J* = 6.5 Hz, 2H), 3.22 (s, 4H), 3.11 (s, 3H), 2.01-1.93 (m, 2H).

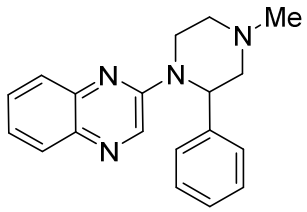
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.8, 148.1, 142.1, 136.4, 135.1, 134.3, 130.1, 130.0, 128.7, 126.6, 126.4, 124.0, 122.8, 119.9, 48.1, 48.0, 36.3, 32.3, 25.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2917, 2357, 1580, 1546, 1486, 758, 668.

MS (EI, 70 eV): m/z = 394 (25), 208 (19), 193 (23), 173 (100), 144 (90).

HRMS (EI) for **$C_{26}H_{26}N_4$** (394.2157): 394.2152 (M^+).

Synthesis of 2-(4-methyl-2-phenylpiperazin-1-yl)quinoxaline (103b)



The aminopyridine **103b** was prepared *via* **TP6** using **99i** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and 2-phenyl-4-methylpiperazine (123 mg, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 8:2) to give **103b** (116 mg, 0.381 mmol, 76%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.52 (s, 1H), 7.87 - 7.85 (m, 1H), 7.69 - 7.66 (m, 1H), 7.59 - 7.55 (m, 1H), 7.45 - 7.42 (m, 2H), 7.40-7.36 (m, 1H), 7.32 - 7.27 (m, 2H), 7.24 - 7.20 (m, 1H), 5.77 (s, 1H), 4.49 - 4.45 (m, 1H), 3.55 - 3.48 (m, 1H), 3.39 (dt, *J* = 11.8, 2.0 Hz, 1H), 2.97 - 2.93 (m, 1H), 2.61 (dd, *J* = 11.8, 4.3 Hz, 1H), 2.33 (s, 3H), 2.28 (td, *J* = 11.5, 3.5 Hz, 1H).

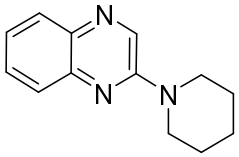
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.9, 141.7, 140.0, 136.8, 135.4, 130.1, 128.7, 128.6, 127.3, 127.1, 126.5, 124.6, 58.7, 55.1, 54.1, 46.6, 41.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057, 2936, 2844, 2791, 1673, 1576, 1547, 1433, 1299, 1022, 931, 857, 757, 696.

MS (EI, 70 eV): m/z = 304 (22), 234 (100), 159 (58), 146 (91), 130 (28), 104 (22), 71 (40), 43 (30).

HRMS (EI) for **$C_{19}H_{20}N_4$** (304.1688): 304.1684 (M^+).

Synthesis of 2-(piperidin-1-yl)quinoxaline (103c)



The aminopyridine **103c** was prepared *via* **TP6** using **99i** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and piperidine (0.07 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 8:2) to give **103c** (83 mg, 0.39 mmol, 78%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.58 (s, 1H), 7.85 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.71 - 7.65 (m, 1H), 7.55 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.36 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 3.78 (dd, *J* = 5.3, 3.1 Hz, 4H), 1.75 - 1.67 (m, 6H).

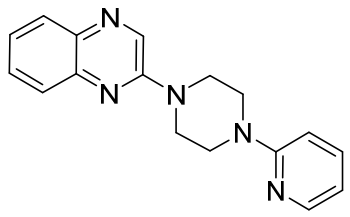
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 152.5, 142.0, 136.5, 136.2, 130.0, 128.7, 126.4, 124.4, 45.9, 25.8, 24.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3054, 2933, 2851, 1684, 1576, 1549, 1492, 1434, 1279, 1227, 1128, 1017, 973, 930, 758..

MS (EI, 70 eV): m/z = 213 (100), 212 (22), 184 (71), 170 (28), 158 (40), 157 (27), 145 (22), 130 (60), 129 (22), 102 (21), 84 (22), 44 (24).

HRMS (EI) for **$C_{13}H_{15}N_3$** (213.1266): 213.1261 (M^+).

Synthesis of 2-(4-(pyridin-2-yl)piperazin-1-yl)quinoxaline (103d)



The aminopyridine **103d** was prepared *via* **TP6** using **99i** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and 4-(pyridine-2-yl)piperazine (0.11 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 8:2) to give **103d** (79 mg, 0.271 mmol, 54%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.62 (s, 1H), 8.24-8.22 (m, 1H), 7.91-7.89 (m, 1H), 7.72-7.70 (m, 1H), 7.61-7.57 (m, 1H), 7.55-7.50 (m, 1H), 7.43-7.39 (m, 1H), 6.72-6.69 (m, 1H), 6.68 - 6.66 (m, 1H), 3.95 - 3.92 (m, 4H), 3.76 - 3.73 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.3, 152.4, 148.2, 141.7, 137.8, 137.1, 135.8, 130.3, 128.9, 126.7, 125.1, 113.9, 107.3, 45.0, 44.5.

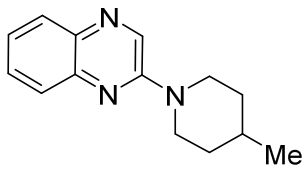
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1590, 1577, 1550, 1478, 1431, 1241, 1225, 979, 942, 759, 731.

MS (EI, 70 eV): m/z = 291 (25), 207 (40), 184 (45), 170 (45), 158 (32), 146 (46), 145 (78), 133 (100), 129 (37), 121 (32), 119 (60), 107 (71), 78 (40).

HRMS (EI) for **$C_{17}H_{17}N_5$** (291.1484): 291.1482 (M^+).

M.p. (°C): 136–139.

Synthesis of 2-(4-methylpiperazin-1-yl)quinoxaline (103e)



The aminopyridine **103e** was prepared *via* **TP6** using **99i** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and 4-methylpiperidine (0.08 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **103e** (97 mg, 0.427 mmol, 85%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.58 (s, 1H), 7.85 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.66 (ddd, *J* = 8.4, 1.4, 0.6 Hz, 1H), 7.55 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.36 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 4.57 - 4.51 (m, 2H), 3.00 (ddd, *J* = 13.3, 12.2, 2.7 Hz, 2H), 1.83 - 1.77 (m, 2H), 1.75 - 1.64 (m, 1H), 1.3 - 1.23 (m, 2H), 0.99 (d, *J* = 6.5 Hz, 3H).

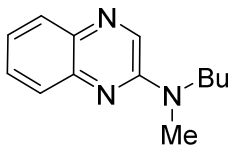
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 152.6, 142.1, 136.6, 136.2, 130.1, 128.7, 126.5, 124.5, 45.4, 34.0, 31.3, 22.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1578, 1551, 1441, 1308, 1226, 1133, 928, 758.

MS (EI, 70 eV): m/z = 227 (100), 158 (76), 130 (46), 103 (25).

HRMS (EI) for **$C_{14}H_{17}N_3$** (227.1422): 227.1416 (M^+).

Synthesis of *N*-butyl-*N*-methylquinoxalin-2-amine (103f)



The aminopyridine **103f** was prepared *via* **TP6** using **99i** (140 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.46 mL, 0.70 mmol) and *N*-methylbutane-1-amine (0.085 mL, 0.70 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 8:2) to give **103f** (95 mg, 0.44 mmol, 88%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.47 (s, 1H), 7.85 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.67 (ddd, *J* = 8.4, 1.5, 0.6 Hz, 1H), 7.54 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.33 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 3.69 - 3.61 (m, 2H), 3.23 (s, 3H), 1.66 (tt, *J* = 8.8, 6.8 Hz, 2H), 1.39 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 152.0, 142.2, 136.3, 135.3, 130.0, 128.7, 126.3, 123.9, 49.9, 36.2, 29.8, 20.3, 14.0.

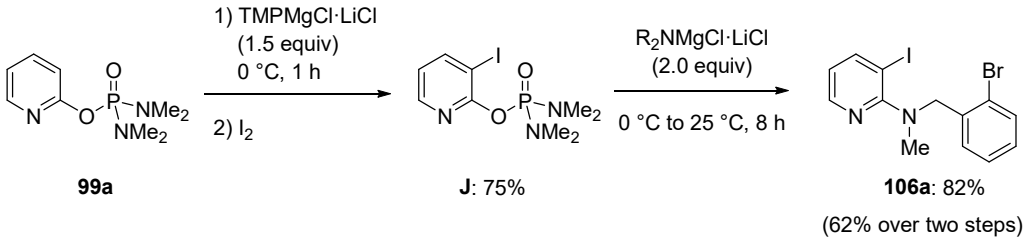
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3054, 2933, 2851, 1684, 1576, 1549, 1492, 1434, 1279, 1227, 1128, 1017, 973, 930, 758.

MS (EI, 70 eV): m/z = 213 (100), 212 (22), 184 (71), 170 (28), 158 (40), 157 (27), 145 (22), 130 (60), 129 (22), 102 (21), 84 (22), 44 (24).

HRMS (EI) for **$C_{13}H_{17}N_3$** (215.1422): 215.1416 (M^+).

Directed *ortho*-Metalation and Functionalization of Various Phosphorodiamidates, Followed by the Transition-Metal-Free Amination using Magnesium Amides: Synthesis of Aminated *N*-heterocycles 106a–d, 107, 108a–c

Synthesis of *N*-(2-bromobenzyl)-3-iodo-*N*-methylpyridin-2-amine (106a)



Synthesis of **J**

Phosphorodiamidate **J** was prepared *via* **TP7** using **99a** (1.14 g, 5.00 mmol), TMPMgCl·LiCl (5.80 mL, 7.50 mmol) and iodine (2.02 g, 8.00 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (ethyl acetate) to give **J** (1.33 g, 3.75 mmol, 75%) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.09 (ddd, *J* = 7.7, 1.8, 1.1 Hz, 1H), 6.80 (dd, *J* = 7.7, 4.8 Hz, 1H), 2.79 (d, *J* = 10.6 Hz, 12H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.7, 157.6, 149.1, 147.6, 121.0, 81.8, 81.8, 37.0, 37.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2925, 2851, 2809, 1570, 1414, 1300, 1214, 1067, 989, 908, 779, 748, 671.

MS (EI, 70 eV): 356 (100), 310 (30), 135 (15).

HRMS (EI) for **$C_9H_{16}O_2N_3IP$** (356.0019): 356.0021 (M^+).

Synthesis of 106a

The aminopyridine **106a** was prepared *via* **TP6** using **J** (1.03 mg, 2.91 mmol), *i*PrMgCl·LiCl (3.72 mL, 5.82 mmol) and 1-(2-bromophenyl)-*N*-methylmethanamine (0.86 mL, 5.82 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 99:1) to give **106a** (961 mg, 2.38 mmol, 82%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.27 (dd, *J* = 4.7, 1.7 Hz, 1H), 8.08 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.64-7.62 (m, 1H), 7.55 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.32 (td, *J* = 7.5, 1.3 Hz, 1H), 7.15 - 7.10 (m, 1H), 6.63 (dd, *J* = 7.7, 4.7 Hz, 1H), 4.53 (s, 2H), 2.91 (s, 3H).

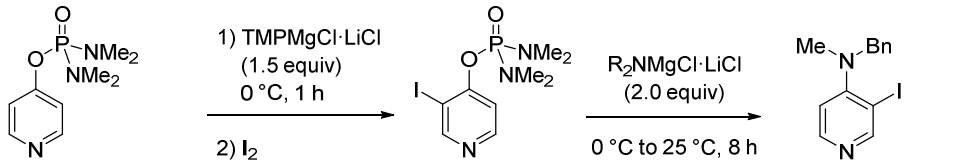
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.8, 149.4, 147.0, 137.7, 132.8, 130.0, 128.4, 127.3, 123.8, 118.9, 86.5, 58.4, 40.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2920, 1566, 1439, 1402, 1002, 746.

MS (EI, 70 eV): m/z = 402 (21), 474 (23), 323 (77), 307 (47), 233 (100), 195 (50), 169 (27), 90 (36) 57 (30).

HRMS (EI) for **$C_{13}H_{12}BrIN_2$** (401.9229): 401.9224 (M^+).

Synthesis of *N*-benzyl-3-iodo-*N*-methylpyridin-4-amine (106b)



99d **K**: 58% **106b**: 78% (45% over two steps)

Synthesis of **K**

Phosphorodiamidate **K** was prepared *via* **TP7** using **99d** (458 g, 2.00 mmol), TMPMgCl·LiCl (2.46 mL, 3.00 mmol) and iodine (761 mg, 3.00 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (ethyl acetate + 1% triethylamine) to give **K** (412 mg, 1.16 mmol, 58%) as an orange solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.82 (dd, *J* = 1.2, 0.4 Hz, 1H), 8.38 (d, *J* = 5.5 Hz, 1H), 7.49 (ddd, *J* = 5.6, 0.8, 0.4 Hz, 1H), 2.74 (d, *J* = 10.3 Hz, 12H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.6, 158.2, 158.1, 150.9, 115.2, 115.1, 87.6, 87.5, 36.9, 36.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3450, 2930, 2361, 1649, 1563, 1466, 1396, 1289, 1259, 1217, 1170,992, 904, 840, 750, 683.

MS (EI, 70 eV): 268 (24), 228 (95), 221 (56), 205 (13), 204 (12), 177 (37), 142 (23), 135 (72), 128 (13), 127 (100), 92 (11).

HRMS (EI) for **$C_9H_{15}O_2N_3IP$** (354.9947): 354.9941 (M^+).

M.p. (°C): 83–84.

Synthesis of 106b

The aminopyridine **106b** was prepared *via* **TP6** using **K** (226 mg, 0.70 mmol), *i*PrMgCl·LiCl (0.91 mL, 1.40 mmol) and *N*-benzylmethylamine (0.18 mL, 1.40 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 10:0.5) to give **106b** (176 mg, 0.55 mmol, 78%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.83 (s, 1H), 8.32 (d, *J* = 5.5 Hz, 1H), 7.38 - 7.27 (m, 5H), 6.84 (d, *J* = 5.5 Hz, 1H), 4.39 (s, 2H), 2.77 (s, 3H).

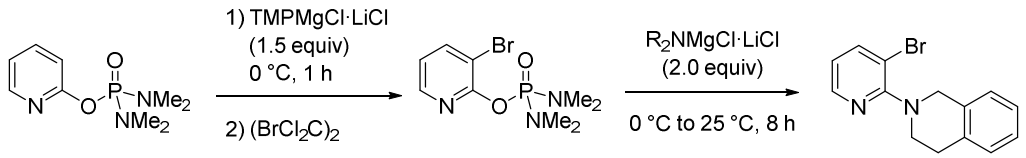
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.2, 159.3, 149.5, 137.1, 128.6, 128.3, 127.6, 116.1, 90.8, 59.1, 40.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3026, 2854, 2358, 1570, 1494, 1477, 1451, 1395, 1361, 1288, 1106, 1009, 944, 733, 697.

MS (EI, 70 eV): m/z = 198 (14), 197 (100), 195 (19), 182 (20), 181 (11), 91 (26).

HRMS (EI) for **$C_{13}H_{12}N_2I$** (323.0051): 323.0039 (M^+).

Synthesis of 2-(3-bromopyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline (106c)



99a → **L**: 62% → **106c**: 87% (54% over two steps)

Synthesis of **L**

Phosphorodiamidate **L** was prepared *via* **TP7** using **99a** (229 g, 1.00 mmol), TMPMgCl·LiCl (1.33 mL, 1.50 mmol) and dibromotetrachloroethane (488 mg, 1.50 mmol). The reaction was complete after 12 h.

After work-up, the crude product was purified *via* column chromatography (ethyl acetate + 1% triethylamine) to give **L** (192 mg, 0.62 mmol, 62%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.20 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.87 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 6.94 (dd, *J* = 7.7, 4.8 Hz, 1H), 2.78 (d, *J* = 10.6 Hz, 12H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 155.3, 155.3, 146.7, 142.8, 120.9, 109.3, 109.3, 36.9, 36.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2925, 2851, 2810, 1577, 1424, 1302, 1230, 1068, 1027, 997, 913, 782, 756, 673.

MS (EI, 70 eV): 310 (100), 308 (92), 265 (20), 176 (25), 135 (47).

HRMS (EI) for **$C_9H_{16}O_2N_3BrP$** (308.0158): 308.0157 (M^+).

Synthesis of 106c

The aminopyridine **106c** was prepared *via* **TP6** using **L** (170 mg, 0.55 mmol), *i*PrMgCl·LiCl (0.72 mL, 1.10 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.14 mL, 1.10 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 10:0.3) to give **106c** (138 mg, 0.48 mmol, 87%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.26 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.82 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.20 - 7.14 (m, 4H), 6.78 (dd, *J* = 7.7, 4.7 Hz, 1H), 4.55 (s, 2H), 3.64 (t, *J* = 5.8 Hz, 2H), 3.11 (t, *J* = 5.8 Hz, 2H).

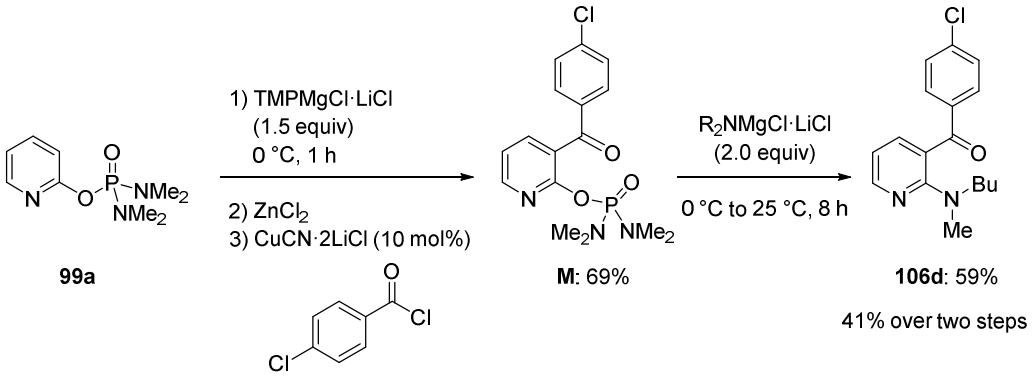
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.6, 146.3, 142.6, 134.8, 134.7, 129.0, 126.9, 126.4, 126.0, 118.3, 112.4, 51.3, 48.7, 29.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3049, 2922, 2830, 2350, 1667, 1574, 1431, 1375, 1230, 1113, 1010, 933, 784, 746.

MS (EI, 70 eV): m/z (%) = 288 (100).

HRMS (EI) for **$C_{14}H_{13}N_2Br$** (288.0262): 288.0253 (M^+).

Synthesis of (2-(butyl(methyl)amino)pyridin-3-yl)(4-chlorophenyl)methanone (106d)



Synthesis of **M**

Phosphorodiamidate **N** was prepared *via* **TP7** using **99a** (229 g, 1.00 mmol) and TMPMgCl·LiCl (1.33 mL, 1.50 mmol). After the metalation was complete, a 1 M $ZnCl_2$ solution in THF (1.60 mL, 1.60 mmol) was added at -40 °C. After stirring for 15 min, a 1 M CuCN·2LiCl solution in THF (0.10 mL, 0.10 mmol) was added. After 10 min, 4-chlorobenzoyl chloride (0.19 mL, 1.50 mmol) was added and the reaction stirred for 12 h at 25 °C. After work-up, the crude product was purified *via* column chromatography (ethyl acetate + 1% triethylamine) to give **M** (254 mg, 0.69 mmol, 69%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.46 (ddd, *J* = 4.9, 2.1, 0.8 Hz, 1H), 7.82 (ddt, *J* = 10.8, 7.6, 0.9 Hz, 3H), 7.50 - 7.44 (m, 2H), 7.22 (ddd, *J* = 7.5, 5.0, 0.7 Hz, 1H), 2.51 (dd, *J* = 10.6, 0.8 Hz, 12H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 192.8, 155.4, 155.4, 150.6, 140.3, 140.0, 135.3, 131.4, 129.1, 124.1, 124.0, 119.9, 36.5, 36.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930, 2811, 2357, 2231, 1165, 1586, 1422, 1303, 1216, 1090. 990. 935, 896, 763, 725.

MS (EI, 70 eV): 325 (31), 324 (79), 323 (53), 280 (70), 260 (47), 231 (40), 202 (32), 139 (38), 122 (32), 44 (100).

HRMS (EI) for **$C_{16}H_{19}N_3ClP$** (367.0853): 367.0846 (M^+).

Synthesis of 106d

The aminopyridine **106d** was prepared *via* **TP6** using **M** (210 mg, 0.57 mmol), *i*PrMgCl·LiCl (0.74 mL, 1.14 mmol) and *N*-methylbutane-1-amine (0.14 mL, 1.14 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 10:0.5) to give **106d** (102 mg, 0.33 mmol, 59%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.29 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.81 - 7.75 (m, 2H), 7.57 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.47 - 7.40 (m, 2H), 6.66 (dd, *J* = 7.5, 4.8 Hz, 1H), 3.49 - 3.41 (m, 2H), 2.75 (s, 3H), 1.57 - 1.45 (m, 2H), 1.30 - 1.18 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 194.5, 158.2, 149.7, 140.3, 139.7, 135.8, 131.4, 129.0, 119.0, 111.8, 52.0, 39.5, 29.4, 20.2, 14.0.

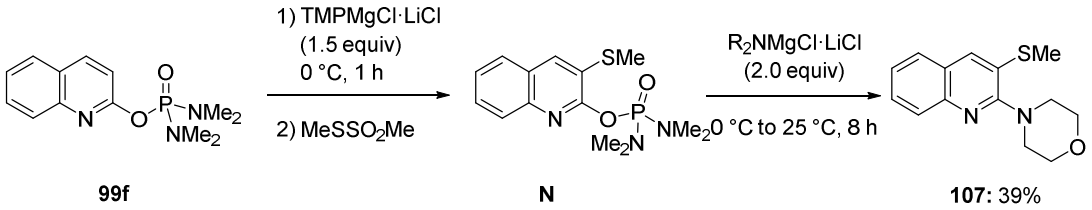
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 2927, 2870, 2357. 1650, 1581, 1543, 1500, 1406, 1287, 1243, 1222, 1088, 1013, 914, 845, 752.

MS (EI, 70 eV): m/z (%) = 302 (25), 273 (17), 261 (26), 260 (16), 259 (92), 127 (27), 125 (100), 110 (12).

HRMS (EI) for **$C_{17}H_{19}ON_2Cl$** (302.1186): 302.1179 (M^+).

M.p. (°C): 95–96.

Synthesis of 4-(3-(methylthio)quinolin-2-yl)morpholine (107)



Synthesis of **N**

Phosphorodiamidate **N** was prepared *via* **TP7** using **99f** (215 g, 0.77 mmol) and TMPMgCl·LiCl (0.76 mL, 1.16 mmol) and *S*-methyl methanethiosulfonate (0.145 mL, 1.54 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (ethyl acetate + 1% triethylamine) to give **N** (169 mg, 0.518 mmol, 67%) as a yellow oil. The product contained 5% impurities and was used as is in the next step.

Synthesis of 107

The aminopyridine **107** was prepared *via* **TP6** using **N** (169 mg, 0.519 mmol), *i*PrMgCl·LiCl (0.68 mL, 1.04 mmol) and morpholine (0.09 mL, 1.04 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (pentane:ethyl acetate = 95:5) to give **107** (78 mg, 0.30 mmol, 39%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.89 - 7.85 (m, 1H), 7.68 (s, 1H), 7.65 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.57-7.52 (m, 1H), 7.40-7.36 (m, 1H), 3.93 - 3.91 (m, 4H), 3.43 - 3.41 (m, 4H), 2.53 (s, 3H).

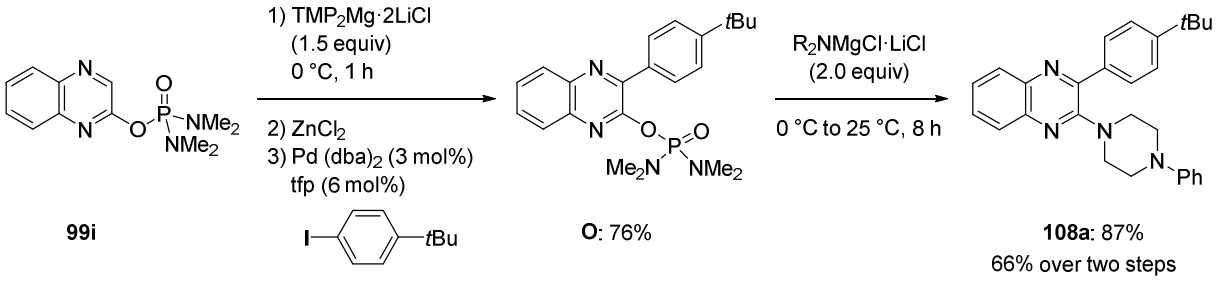
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.2, 144.5, 131.3, 128.5, 128.3, 127.8, 126.2, 126.0, 125.1, 67.1, 50.4, 15.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2848, 1577, 1448, 1405, 1364, 1256, 1228, 1203, 1111, 942, 877, 841, 779, 753, 730, 708.

MS (EI, 70 eV): m/z (%) = 245 (100), 215 (12), 201 (25), 187 (41), 160 (10), 129 (14).

HRMS (EI) for **$C_{14}H_{16}N_2OS$** (260.0983): 260.0979 (M^+).

Synthesis of 2-(4-(*tert*-butyl)phenyl)-3-(4-phenylpiperazin-1-yl)quinoxaline (108a)



Synthesis of **O**

Phosphorodiamidate **O** was prepared *via* **TP7** using **99i** (561 mg, 2.00 mmol) and $TMP_2Mg·2LiCl$ (5.40 mL, 3.00 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (3.00 mL, 3.00 mmol) was added dropwise at -40 °C and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (57 mg, 0.10 mmol), tfp (47 mg, 0.20 mol) and 4-*tert*-butyliodobenzene (425 mL, 2.40 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 2:8) to give **O** (626 mg, 1.52 mmol, 76%) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.11 - 8.08 (m, 1H), 7.94 - 7.91 (m, 3H), 7.71 - 7.64 (m, 2H), 7.54 - 7.51 (m, 2H), 2.75 (d, *J* = 10.6 Hz, 12H), 1.36 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 153.2, 150.6, 150.5, 147.6, 147.5, 140.4, 139.7, 133.1, 130.0, 129.5, 129.1, 128.5, 127.9, 125.4, 36.9, 36.9, 34.9, 31.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933, 1570, 1460, 1402, 1337, 1300, 1268, 1227, 1210, 1171, 1135, 1124, 1067, 984, 926, 852, 833, 795, 761, 693

MS (EI, 70 eV): 368 (12), 276 (65), 263 (51), 219 (100), 146 (45), 144 (82), 135 (41), 44 (82)

HRMS (EI) for **$C_{22}H_{30}N_4O_2P$** (413.2106): 413.2081 (M^++H).

Synthesis of 108a

The aminopyridine **108a** was prepared *via* **TP6** using **O** (200 mg, 0.49 mmol), *i*PrMgCl·LiCl (0.59 mL, 0.89 mmol) and *4*-phenylpiperazine (0.14 mL, 0.89 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (pentane:ethyl acetate = 99:1) to give **108a** (179 mg, 0.424 mmol, 87%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.00 - 7.95 (m, 3H), 7.86-7.84 (m, 1H), 7.64-7.59 (m, 1H), 7.53 - 7.49 (m, 3H), 7.31 - 7.27 (m, 2H), 6.96 - 6.92 (m, 2H), 6.90-6.86 (m, 1H), 3.49 - 3.46 (m, 4H), 3.24 - 3.21 (m, 4H), 1.37 (s, 9H).

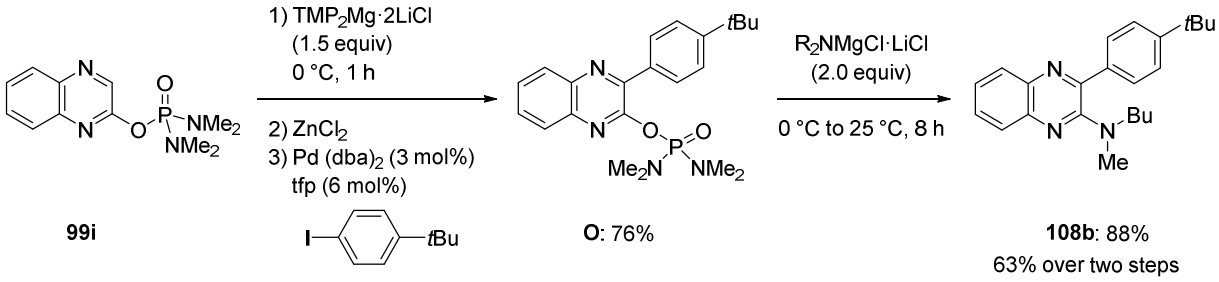
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.3, 152.8, 151.4, 148.6, 140.3, 138.9, 136.7, 129.6, 129.3, 128.9, 127.7, 127.1, 126.6, 125.9, 120.1, 116.3, 53.6, 48.8, 35.0, 31.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2961, 1599, 1502, 1417, 1375, 1270, 1231, 1214, 1002, 946, 910, 757, 734.

MS (EI, 70 eV): m/z (%) = 422 (34), 290 (21), 234 (100), 145 (78), 132 (92), 104 (28), 57 (34).

HRMS (EI) for **$C_{28}H_{30}N_4$** (422.2470): 422.2464 (M^+).

Synthesis of *N*-butyl-3-(4-(*tert*-butyl)phenyl)-*N*-methylquinoxalin-2-amine (108b)



Synthesis of **O**

Phosphorodiamidate **O** was prepared *via* **TP7** using **99i** (561 mg, 2.00 mmol) and $TMP_2Mg·2LiCl$ (5.40 mL, 3.00 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (3.00 mL, 3.00 mmol) was added dropwise at -40 °C and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (57 mg, 0.10 mmol), tfp (47 mg, 0.20 mol) and 4-*tert*-butyliodobenzene (425 mL, 2.40 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 2:8) to give **O** (626 mg, 1.52 mmol, 76%) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.11 - 8.08 (m, 1H), 7.94 - 7.91 (m, 3H), 7.71 - 7.64 (m, 2H), 7.54 - 7.51 (m, 2H), 2.75 (d, *J* = 10.6 Hz, 12H), 1.36 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 153.2, 150.6, 150.5, 147.6, 147.5, 140.4, 139.7, 133.1, 130.0, 129.5, 129.1, 128.5, 127.9, 125.4, 36.9, 36.9, 34.9, 31.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933, 1570, 1460, 1402, 1337, 1300, 1268, 1227, 1210, 1171, 1135, 1124, 1067, 984, 926, 852, 833, 795, 761, 693

MS (EI, 70 eV): 368 (12), 276 (65), 263 (51), 219 (100), 146 (45), 144 (82), 135 (41), 44 (82)

HRMS (EI) for **$C_{22}H_{30}N_4O_2P$** (413.2106): 413.2081 (M^++H).

Synthesis of 108b

The aminopyridine **108b** was prepared *via* **TP6** using **O** (208 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.65 mL, 1.00 mmol) and *N*-methylbutan-1-amine (0.12 mL, 1.00 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 10:0.3) to give **108b** (153 mg, 0.44 mmol, 88%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94 (ddd, *J* = 8.2, 1.5, 0.6 Hz, 1H), 7.82 - 7.78 (m, 1H), 7.78 - 7.73 (m, 2H), 7.56 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.52 - 7.47 (m, 2H), 7.42 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 3.26 - 3.18 (m, 2H), 2.89 (s, 3H), 1.54 - 1.44 (m, 2H), 1.36 (s, 9H), 1.10 (h, *J* = 7.4 Hz, 2H), 0.79 (t, *J* = 7.4 Hz, 3H).

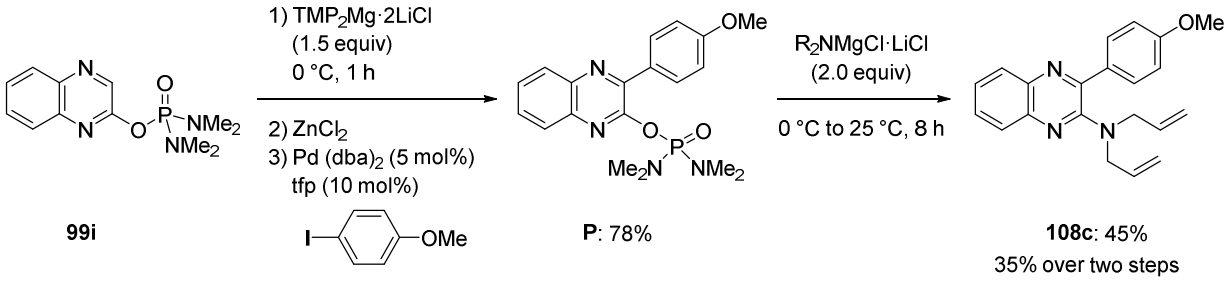
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.5, 152.1, 148.3, 140.4, 138.0, 137.5, 129.4, 128.7, 127.5, 126.5, 125.8, 125.4, 52.6, 38.6, 34.9, 31.4, 29.4, 20.3, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2958, 2865, 2357, 1543, 1460, 1398, 1260, 1133, 1119, 1003, 907, 839, 756, 729.

MS (EI, 70 eV): m/z (%) = 347 (68), 346 (100), 304 (18), 290 (18), 248 (93), 57 (18).

HRMS (EI) for **$C_{23}H_{28}N_3$** (346.2289): 346.2277 (M^+).

Synthesis of *N*,*N*-diallyl-3-(4-methoxyphenyl)quinoxalin-2-amine (108c)



Synthesis of **P**

Phosphorodiamidate **P** was prepared *via* **TP7** using **99i** (639 mg, 2.28 mmol) and $TMP_2Mg·2LiCl$ (6.16 mL, 3.42 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (3.42 mL, 3.42 mmol) was added dropwise at -40 °C and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ 66 mg, 0.114 mmol), tfp (52 mg, 0.228 mol) and 4-methoxyiodobenzene (641 mg, 2.74 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 1:9) to give **P** (667 mg, 1.73 mmol, 78%) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.09 - 8.06 (m, 1H), 8.01 - 7.97 (m, 2H), 7.93 - 7.89 (m, 1H), 7.69 - 7.63 (m, 2H), 7.04 - 7.00 (m, 2H), 3.88 (s, 3H), 2.77 (d, *J* = 10.7 Hz, 12H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.1, 150.5, 150.5, 147.1, 147.0, 140.5, 139.5, 131.4, 129.8, 128.9, 128.5, 128.4, 127.9, 113.9, 55.5, 37.0, 36.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932, 1605, 1400, 1341, 1292, 1239, 1204, 1176, 998, 837, 811, 763.

MS (EI, 70 eV): 252 (59), 250 (100), 236 (21), 224 (31), 219 (33), 57 (28), 44 (30).

HRMS (EI) for **$C_{19}H_{23}N_4O_3P$** (386.1508): 386.1498 (M^+).

Synthesis of 108c

The aminopyridine **108c** was prepared *via* **TP6** using **P** (195 mg, 0.50 mmol), *i*PrMgCl·LiCl (0.65 mL, 1.00 mmol) and diallylamine (0.13 mL, 1.00 mmol). After stirring at 25 °C for 8 h, the reaction mixture was quenched with water (20 mL), extracted with ethyl acetate (3 x 30 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (pentane:ethyl acetate = 99:1) to give **108c** (75 mg, 0.226 mmol, 45%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.96 - 7.93 (m, 1H), 7.89 - 7.85 (m, 2H), 7.81 - 7.78 (m, 1H), 7.60 - 7.55 (m, 1H), 7.48 - 7.44 (m, 1H), 7.03 - 6.99 (m, 2H), 5.84 - 5.74 (m, 2H), 5.15 - 5.12 (m, 2H), 5.10 - 5.09 (m, 2H), 3.90 (d, *J* = 6.3, 4H), 3.88 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.5, 153.8, 148.2, 140.2, 138.5, 134.5, 132.4, 129.5, 129.3, 128.6, 126.9, 126.1, 118.2, 114.3, 55.5, 52.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1607, 1543, 1513, 1406, 1280, 1248, 1208, 1174, 1030, 923, 837, 760.

MS (EI, 70 eV): m/z (%) = 331 (15), 290 (100), 276 (54), 235 (21), 57 (24), 43 (38).

HRMS (EI) for **$C_{21}H_{21}N_{30}$** (331.1685): 331.1678 (M^+).

5 Zn-, Mg-, and Li-TMP Bases for the Successive Regioselective Metalations of the 1,5-Naphthyridine Scaffold

5.1 Typical Procedures

Typical Procedure 8: Metalation and functionalization of 1,5-naphthyridine (**109**) in the C4 position using $TMP_2Mg \cdot 2LiCl$.

To a solution of 1,5-naphthyridine in THF (5 mL/mmol 1,5-naphthyridine) was added dropwise a solution of $TMP_2Mg \cdot 2LiCl$ (1.1 equiv) at –78 °C. After full metalation (5 min, checked *via* GC / GC-MS) the solution was cannulated dropwise to a solution of the electrophile in THF (5 mL/mmol 1,5-naphthyridine) which was precooled to –78 °C. After warming to 25 °C the reaction mixture was stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL/mmol 1,5-naphthyridine) and extracted with ethyl acetate (3 x 50 mL/mmol 1,5-naphthyridine). The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. If the crude product needed purification, it was purified *via* flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 9: Metalation and functionalization of **110b** and **110g** in the C8 position using TMPMgCl·LiCl

1,5-Naphthyridines **110b** and **110g** were dissolved in THF (5 mL/mmol 1,5-naphthyridine) and cooled to –40 °C. Then, TMPMgCl·LiCl (1.2 equiv) was added and the reaction stirred until full metalation was observed (1 h, checked *via* GC / GC-MS). Then, a solution of the electrophile in THF (5 mL/mmol 1,5-naphthyridine) was added dropwise and the reaction stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL/mmol 1,5-naphthyridine) and extracted with ethyl acetate (3 x 50 mL/mmol 1,5-naphthyridine). The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. If the crude product needed purification, it was purified *via* flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 10: Metalation and functionalization of **110c** in the C8 position using TMPZnCl·LiCl

1,5-Naphthyridine **110c** was dissolved in THF (5 mL/mmol 1,5-naphthyridine), TMPZnCl·LiCl (1.5 equiv) added dropwise and the reaction stirred until full metalation was observed (1 h, checked *via* GC / GC-MS). Then, a solution of the electrophile in THF (5 mL/mmol 1,5-naphthyridine) was added

dropwise and the reaction stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL/mmol 1,5-naphthyridine) and extracted with ethyl acetate (3 x 50 mL/mmol 1,5-naphthyridine). The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. If the crude product needed purification, it was purified *via* flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 11: Metalation and functionalization of **110a**, **110g**, and **110f** in the C2 position using $BF_3 \cdot OEt_2$ and TMPMgCl·LiCl

1,5-Naphthyridines **110a**, **110g**, and **110f** were dissolved in THF (5 mL/mmol 1,5-naphthyridine) and cooled to 0 °C. Then, $BF_3 \cdot OEt_2$ (1.1 equiv) was added dropwise and the reaction mixture stirred for 10 min. After cooling to –40 °C, TMPMgCl·LiCl (1.2 equiv) was added and the reaction stirred until full metalation was observed (1 h, checked *via* GC / GC-MS). Then, a solution of the electrophile in THF (5 mL/mmol 1,5-naphthyridine) was added dropwise and the reaction stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL/mmol 1,5-naphthyridine) and extracted with ethyl acetate (3 x 50 mL/mmol 1,5-naphthyridine). The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. If the crude product needed purification, it was purified *via* flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 12: Metalation and functionalization of **112g** and **112h** in the C8 position using TMPLi

1,5-Naphthyridines **112g** and **112h** were dissolved in THF (5 mL/mmol 1,5-naphthyridine) and cooled to –78 °C. Then, TMPLi (1.1 equiv) was added dropwise and the reaction mixture stirred until full metalation was observed (30 min, checked *via* GC / GC-MS). Then, a solution of the electrophile in THF (5 mL/mmol 1,5-naphthyridine) was added dropwise and the reaction stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL/mmol 1,5-naphthyridine) and extracted with ethyl acetate (3 x 50 mL/mmol 1,5-naphthyridine). The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. If the crude product needed purification, it was purified by flash chromatography on silica gel using the appropriate eluent.

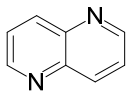
Typical Procedure 13: Metalation and functionalization of **113a** in the C7 position using TMPLi

1,5-Naphthyridine **113a** was dissolved in THF (5 mL/mmol 1,5-naphthyridine) and cooled to –78 °C. Then, TMPLi (1.2 equiv) was added dropwise and the reaction mixture stirred until full metalation was observed (90 sec, checked *via* GC / GC-MS). Then, a solution of the electrophile in THF (5 mL/mmol 1,5-naphthyridine) was added dropwise and the reaction stirred until completion. The

reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL/mmol 1,5-naphthyridine) and extracted with ethyl acetate (3 x 50 mL/mmol 1,5-naphthyridine). The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. If the crude product needed purification, it was purified *via* flash chromatography on silica gel using the appropriate eluent.

5.2 Preparation of Compounds 109 to 126

Synthesis of 1,5-naphthyridine (109)

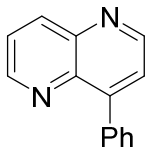


Adapted from a literature procedure,[140] 3-aminopyridine (5.00 g, 53.1 mmol) was dissolved in dioxane (30 mL) and water (30 mL). Then, glycerine (15.5 mL, 212 mmol) was added, followed by slow addition of conc. H_2SO_4 (55 mL) at 0 °C. After addition of iodine (4.04 g, 15.9 mmol), the reaction mixture was stirred at 150 °C for 15 h. After cooling to room temperature, the mixture was basified using a 50% aq. NaOH solution (250 mL). After addition of an aq. sat. $Na_2S_2O_3$ solution (150 mL) and filtration over celite, the reaction mixture was diluted with water (500 mL), extracted with diethyl ether (3 x 500 mL) and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 7:3:0.1) to give **109** (3.78 g, 29.1 mmol, 55%) as an off-white solid.

The spectra matched those of the literature.[81d]

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.99 (dd, *J* = 4.1, 1.6 Hz, 2H), 8.42 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.65 (dd, *J* = 8.5, 4.1 Hz, 2H).

Synthesis of 4-phenyl-1,5-naphthyridine (110f)



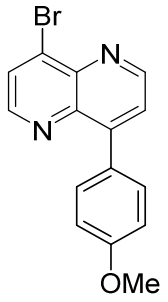
1,5-Naphthyridine **110f** was prepared *via* **TP8** using **109** (650 mg, 5.00 mmol), and $TMP_2Mg{\cdot}2LiCl$ (8.75 mL, 5.50 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (5.50 mL, 5.50 mmol) was added and the reaction stirred at the same temperature for 20 min. Then, iodobenzene (0.56 mL, 5.00 mmol), $Pd(dba)_2$ (86 mg, 150 µmol), and tfp (70 mg, 300 µmol) was added and the reaction slowly warmed to 25 °C over 12 h. After work-up, the crude product was purified *via* column

[140] K. C. Chunavala, S. Adimurthy, *Synth. Commun.* **2011**, *41*, 1843–1851.

chromatography (*iso*hexane:ethyl acetate = 6:4) to give **110f** (648 mg, 3.14 mmol, 63%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.04 - 9.00 (m, 2H), 8.47 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.81 - 7.75 (m, 2H), 7.68 - 7.63 (m, 2H), 7.58 - 7.46 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.1, 151.0, 148.7, 144.6, 142.1, 137.8, 136.8, 130.6, 128.9, 128.4, 124.3, 124.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm-1 = 3078, 3022, 2356, 2322, 1611, 1589, 1572, 1489, 1456, 1394, 1272, 1244, 876, 797, 699.
MS (EI, 70 eV): m/z (%) = 206 (40), 200 (100), 103 (6).
HRMS (EI) for **$C_{14}H_{10}N_2$** (206.0844): 206.0843 (M^+).
M.p. (°C): 75–76.

Synthesis of 4-bromo-8-(4-methoxyphenyl)-1,5-naphthyridine (111b)

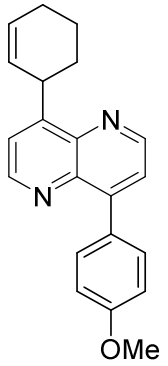


1,5-Naphthyridine **111b** was prepared *via* **TP9** using **110g** (31 mg, 0.13 mmol), TMPMgCl·LiCl (0.14 mL, 0.17 mmol), and dibromotetrachloroethane (85 mg, 0.26 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **111b** (25 mg, 79 µmol, 60%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.08 (d, *J* = 4.5 Hz, 1H), 8.75 (d, *J* = 4.6 Hz, 1H), 7.98 (d, *J* = 4.5 Hz, 1H), 7.77 - 7.71 (m, 2H), 7.68 (d, *J* = 4.5 Hz, 1H), 7.10 - 7.04 (m, 2H), 3.89 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.6, 151.6, 150.1, 148.9, 143.1, 142.6, 136.6, 132.1, 128.7, 128.1, 124.8, 114.1, 55.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3003, 2958, 2930, 2835, 1604, 1582, 1514, 1479, 1248, 1181, 1028, 835, 726.
MS (EI, 70 eV): m/z (%) = 316 (46), 315 (95), 314 (51), 313 (100), 301 (41), 285 (46), 283 (45), 272 (48), 270 (50), 207 (53), 192 (57), 191 (66).
HRMS (EI) for **$C_{15}H_{10}BrN_2O$** (312.9977): 312.9971 (M^+-1H).

M.p. (°C): 160–163.

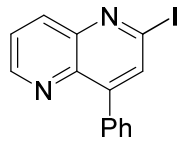
Synthesis of 4-(cyclohex-2-en-1-yl)-8-(4-methoxyphenyl)-1,5-naphthyridine (111c)



1,5-Naphthyridine **111c** was prepared *via* **TP9** using **110g** (93 mg, 0.39 mmol) and TMPMgCl·LiCl (0.40 mL, 0.51 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.51 mL, 0.51 mmol) was added and the reaction stirred at the same temperature for 20 min. Then, 3-bromocyclohexene (0.07 mL, 0.59 mmol) was added and the reaction slowly warmed to 25 °C over 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **111c** (74 mg, 234 µmol, 60%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.98 (d, *J* = 4.4 Hz, 1H), 8.92 (d, *J* = 4.4 Hz, 1H), 7.78 - 7.71 (m, 2H), 7.59 (d, *J* = 4.4 Hz, 1H), 7.50 (d, *J* = 4.5 Hz, 1H), 7.09 - 7.03 (m, 2H), 6.10 - 6.03 (m, 1H), 5.79 (dq, *J* = 10.1, 2.4 Hz, 1H), 4.94 - 4.87 (m, 1H), 3.88 (s, 3H), 2.34 - 2.24 (m, 1H), 2.21 - 2.12 (m, 2H), 1.83 - 1.70 (m, 2H), 1.70 - 1.61 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.2, 154.3, 150.5, 149.6, 148.4, 143.2, 141.9, 132.0, 129.8, 129.6, 129.1, 123.6, 122.4, 113.9, 55.5, 35.2, 30.8, 25.3, 21.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3016, 1928, 1858, 1835, 1607, 1583, 1496, 1248, 1175, 1036, 906, 824, 726.
MS (EI, 70 eV): m/z (%) = 316 (76). 315 (78), 287 (100), 275 (62), 243 (47), 230 (54), 217 (44).
HRMS (EI) for **$C_{21}H_{20}N_2O$** (316.1576): 316.1571 (M^+).
M.p. (°C): 129–131.

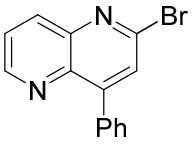
Synthesis of 2-iodo-4-phenyl-1,5-naphthyridine (112f)



1,5-Naphthyridine **112f** was prepared *via* **TP11** using **110f** (492 mg, 2.38 mmol), $BF_3 \cdot OEt_2$ (0.34 mL, 2.62 mmol), TMPMgCl·LiCl (2.10 mL, 2.86 mmol), and iodine (1.21 g, 4.77 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethyl amine = 9/2/0.1) and recrystallized from ethyl acetate / hexane to give **112f** (459 mg, 1.38 mmol, 58%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.01 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.38 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.98 (s, 1H), 7.76 - 7.72 (m, 2H), 7.64 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.56 - 7.47 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.1, 149.9, 146.0, 141.5, 137.0, 135.2, 135.0, 130.6, 129.4, 128.5, 124.9, 119.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3028, 2972, 2932, 1569, 1466, 1332, 1167, 1020, 862, 761, 705, 696.
MS (EI, 70 eV): m/z (%) =332 (94), 206 (23), 204 (23), 102 (27), 44 (26), 43 (29).
HRMS (EI) for **$C_{14}H_9N_2I$** (331.9810): 331.9800 (M).
M.p. (°C): 141–142.

Synthesis of 2-bromo-4-phenyl-1,5-naphthyridine (112g)



1,5-Naphthyridine **112g** was prepared *via* **TP11** using **110f** (103 mg, 0.50 mmol), $BF_3 \cdot OEt_2$ (0.07 mL, 0.55 mmol), TMPMgCl·LiCl (0.50 mL, 0.60 mmol), and 1,2-dibromotetrachloroethane (326 mg, 1.00 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8.5:1.5), recrystallized from hexane and hot filtered to give **112g** (127 mg, 445 µmol, 89%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.02 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.38 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.80 - 7.72 (m, 3H), 7.66 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.58 - 7.48 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.1, 151.1, 145.1, 142.5, 141.3, 136.9, 135.4, 130.6, 129.5, 128.7, 128.6, 125.1.

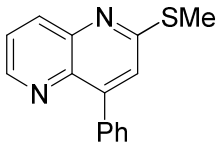
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 3044, 2360, 1565, 1546, 1479, 1303, 1133, 796, 695.

MS (EI, 70 eV): m/z (%) = 286 (47), 285 (100), 284 (47), 283 (100), 204 (27), 203 (35), 202 (17)102 (24), 43 (12).

HRMS (EI) for **$C_{14}H_8N_2Br$** (282.9871): 282.9854 (M^+-H).

M.p. (°C): 123–124.

Synthesis of 2-(methylthio)-4-phenyl-1,5-naphthyridine (112h)



1,5-Naphthyridine **112h** was prepared *via* **TP11** using **110f** (52 mg, 0.25 mmol), $BF_3{\cdot}OEt_2$ (35 µL, 275 µmol), TMPMgCl·LiCl (0.97 mL, 1.20 mmol), and S-methyl methanethiosulfonate (0.08 mL, 375 µmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 10:1:0.1) to give **112h** (33 mg, 131 µmol, 52%) as a light yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.86 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.28 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.73 (dd, *J* = 7.1, 1.5 Hz, 2H), 7.57 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.54 - 7.45 (m, 4H), 2.74 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.9, 149.0, 147.6, 144.7, 140.9, 136.6, 136.0, 130.4, 128.9, 128.4, 124.3, 123.7, 13.3.

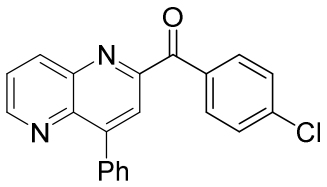
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 2924, 2365, 1585, 1543, 1480, 1321, 1137, 1092, 879, 794, 696.

MS (EI, 70 eV): m/z (%) = 253 (21), 252 (100), 251 (56), 219 (12), 218 (22), 206 (26), 205 (45), 43 (18).

HRMS (EI) for **$C_{15}H_{12}N_2S$** (252.0721): 252.0716 (M^+).

M.p (°C): 107–108.

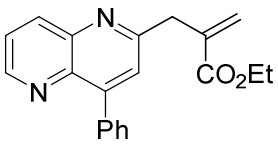
Synthesis of (4-chlorophenyl)(4-phenyl-1,5-naphthyridin-2-yl)methanone (112i)



1,5-Naphthyridine **112i** was prepared *via* **TP11** using **110f** (103 mg, 0.50 mmol), $BF_3 \cdot OEt_2$ (0.07 mL, 0.55 mmol), and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.60 mL, 0.60 mmol) was added and the reaction stirred at the same temperature for 20 min. Then, 4-chlorobenzoyl chloride (0.10 mL, 0.75 mmol) was added, and the reaction slowly warmed to 25 °C over 12 h. After work-up (the extraction was performed 6 times) the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8.5:1.5) and recrystallized from ethyl acetate / hexane to give **112i** (102 mg, 296 µmol, 59%) as an off-white solid.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 9.12 (dd, *J* = 4.0, 1.8 Hz, 1H), 8.53 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.36 (s, 1H), 8.24 (d, *J* = 8.6 Hz, 2H), 7.87 - 7.82 (m, 2H), 7.73 (dd, *J* = 8.6, 4.3 Hz, 1H), 7.59 - 7.54 (m, 2H), 7.55 - 7.49 (m, 3H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 192.0, 154.7, 152.8, 149.9, 143.2, 142.5, 140.0, 138.7, 136.4, 134.4, 133.0, 130.7, 129.3, 128.7, 128.5, 125.0, 124.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063, 1662, 1585, 1486, 1255, 1091, 796, 695.
MS (EI, 70 eV): m/z (%) = 346 (29), 345 (37), 344 (89), 343 (71), 317 (38), 316 (48), 315 (100), 309 (20), 267 (18), 204 (13), 141 (14), 139 (40), 111 (34), 44 (13).
HRMS (EI) for **$C_{21}H_{13}ON_2Cl$** (344.0716): 344.0707 (M^+).
M.p. (°C): 153–154.

Synthesis of ethyl 2-((4-phenyl-1,5-naphthyridin-2-yl)methyl)acrylate (112j)

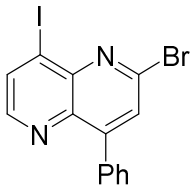


1,5-Naphthyridine **112j** was prepared *via* **TP11** using **110f** (206 mg, 1.00 mmol), $BF_3 \cdot OEt_2$ (0.14 mL, 1.10 mmol), and TMPMgCl·LiCl (0.97 mL, 1.20 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (1.20 mL, 1.20 mmol) was added and the reaction stirred at the same temperature for 20 min. Then, ethyl 2-(bromomethyl)acrylate (0.21 mL, 1.50 mmol) was added and the

reaction slowly warmed to 25 °C over 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 7:3) to give **112j** (202 mg, 630 µmol, 63%) as a light yellow oil.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.62 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.23 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.82 - 7.78 (m, 2H), 7.47 (s, 1H), 7.32 - 7.26 (m, 2H), 7.24 - 7.18 (m, 1H), 6.87 (dd, *J* = 8.5, 4.1 Hz, 1H), 6.38 - 6.35 (m, 1H), 5.50 - 5.46 (m, 1H), 4.04 (dd, *J* = 1.3, 0.6 Hz, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 0.87 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, C_6D_6): δ / ppm = 166.6, 160.7, 150.0, 148.7, 144.6, 141.6, 139.1, 137.6, 137.2, 131.3, 128.6, 128.2, 127.0, 124.8, 124.0, 60.7, 41.7, 14.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057, 2980, 2926, 2357, 1892, 1711, 1590, 1483, 1323, 1207, 1181,1136, 1026, 945, 797, 696.
MS (EI, 70 eV): m/z (%) = 318 (24), 289 (20), 246 (37), 245 (100), 244 (16), 243 (34), 123 (25).
HRMS (EI) for **$C_{20}H_{18}N_2O_2$** (318.1368): 318.1362 (M^+).

Synthesis of 2-bromo-8-iodo-4-phenyl-1,5-naphthyridine (113a)

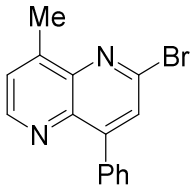


1,5-Naphthyridine **113a** was prepared *via* **TP12** using **112g** (107 mg, 375 µmol), TMPLi (0.75 mL, 0.45 mmol), and iodine (143 mg, 0.56 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.5:0.5) to give **113a** (108 mg, 263 µmol, 70%) as a light-yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.51 (d, *J* = 4.5 Hz, 1H), 8.25 (d, *J* = 4.5 Hz, 1H), 7.79 (s, 1H), 7.74 - 7.68 (m, 2H), 7.58 - 7.48 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.8, 150.5, 145.2, 143.5, 141.2, 135.9, 135.2, 130.6, 129.9, 129.6, 128.5, 114.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 1559, 1535, 1468, 1443, 1311, 1116, 1054, 989, 852, 751, 695, 638, 616.
MS (EI, 70 eV): m/z (%) = 412 (50), 411 (100), 410 (56), 409 (96), 204 (18), 203 (39), 165 (11), 164 (12).
HRMS (EI) for **$C_{14}H_7BrIN_2$** (408.8837): 409.8879 (M^+-H).

M.p. (°C): 132–133.

Synthesis of 2-bromo-8-methyl-4-phenyl-1,5-naphthyridine (113b)



1,5-Naphthyridine **113b** was prepared *via* **TP12** using **112g** (71 mg, 0.25 mmol), TMPLi (0.50 mL, 0.30 mmol), and methyl iodide (23 µL, 375 µmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **113b** (61 mg, 204 µmol, 82%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.84 (d, *J* = 4.3 Hz, 1H), 7.75 - 7.71 (m, 3H), 7.55 - 7.48 (m, 4H), 2.83 (d, *J* = 0.9 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.3, 150.7, 146.7, 145.2, 141.3, 141.0, 136.0, 130.6, 129.3, 128.6, 128.5, 125.4, 17.8.

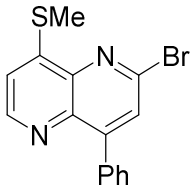
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2967, 2911, 1549, 1498, 1394, 1294, 1064, 835, 754, 740, 699, 670.

MS (EI, 70 eV): m/z (%) = 300 (36), 299 (98), 298 (44), 297 (100), 219 (23), 218 (31), 217 (14), 216 (14), 190 (13), 110 (17), 109 (13), 108 (13).

HRMS (EI) for **$C_{15}H_{10}BrN_2$** (297.0033): 297.0027 (M^+-H).

M.p (°C): 137–138.

Synthesis of 2-bromo-8-(methylthio)-4-phenyl-1,5-naphthyridine (113c)



1,5-Naphthyridine **113c** was prepared *via* **TP12** using **112g** (71 mg, 0.25 mmol), TMPLi (0.50 mL, 0.30 mmol), and S-methyl methanethiosulfonate (36 µL, 375 µmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **113c** (62 mg, 187 µmol, 75%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.78 (d, *J* = 4.8 Hz, 1H), 7.77 (s, 1H), 7.75 - 7.70 (m, 2H), 7.55 - 7.45 (m, 3H), 7.30 (d, *J* = 4.8 Hz, 1H), 2.56 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.9, 151.4, 150.0, 142.9, 141.0, 140.0, 135.8, 130.6, 129.4, 129.4, 128.5, 117.9, 13.9.

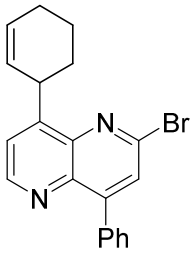
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3051, 2986, 2920, 2854, 2236, 1563, 1538, 1474, 1433, 855, 784, 696.

MS (EI, 70 eV): m/z (%) = 333 (19), 332 (100), 331 (85), 330 (93), 328 (67), 298 (26), 296 (26), 285 (24), 283 (20), 218 (34).

HRMS (EI) for **$C_{15}H_{12}BrN_2S$** (330.9899): 330.9904 (M^++H).

M.p (°C): 164–166.

Synthesis of 2-bromo-8-(cyclohex-2-en-1-yl)-4-phenyl-1,5-naphthyridine (113d)



1,5-Naphthyridine **113d** was prepared *via* **TP12** using **112g** (71 mg, 0.25 mmol), and TMPLi (0.50 mL, 0.30 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.30 mL, 0.30 mmol) was added and the reaction stirred at the same temperature for 20 min. Then, 3-bromocyclohexene (43 µL, 375 µmol) was added and the reaction slowly warmed to 25 °C over 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 10:0.3:0.1) to give **113d** (90 mg, 246 µmol, 99%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.91 (d, *J* = 4.4 Hz, 1H), 7.76 - 7.70 (m, 3H), 7.56 - 7.45 (m, 4H), 6.11 - 6.03 (m, 1H), 5.75 (dq, *J* = 10.1, 2.4 Hz, 1H), 4.85 - 4.77 (m, 1H), 2.33 - 2.23 (m, 1H), 2.21 - 2.13 (m, 2H), 1.83 - 1.68 (m, 2H), 1.68 - 1.58 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 153.9, 151.4, 150.9, 143.8, 141.2, 141.1, 136.1, 130.5, 130.0, 129.2, 128.6, 128.5, 128.4, 123.3, 35.1, 30.9, 25.2, 20.9.

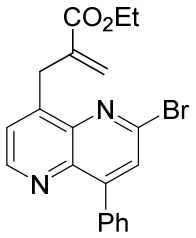
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3021, 2929, 1547, 1484, 1317, 1122, 855, 765, 697.

MS (EI, 70 eV): m/z (%) = 367 (22), 366 (98), 365 (50), 364 (100), 363 (37), 337 (25), 335 (25), 325 (21), 323 (29), 309 (20), 286 (21), 285 (82), 255 (23).

HRMS (EI) for **$C_{20}H_{17}BrN_2$** (364.0575): 364.0567 (M^+).

M.p (°C): 103–104.

Synthesis of ethyl 2-((6-bromo-8-phenyl-1,5-naphthyridin-4-yl)methyl)acrylate (113e)



1,5-Naphthyridine **113e** was prepared *via* **TP12** using **112g** (71 mg, 0.25 mmol), and TMPLi (0.50 mL, 0.30 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.30 mL, 0.30 mmol) was added and the reaction stirred at the same temperature for 20 min. Then, 3-bromocyclohexene (60 µL, 375 µmol) was added and the reaction slowly warmed to 25 °C over 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 10:0.3:0.1) and HPLC (acetonitrile/water gradient) to give **113e** (94 mg, 236 µmol, 94%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.88 (d, *J* = 4.4 Hz, 1H), 7.78 - 7.67 (m, 3H), 7.57 - 7.45 (m, 4H), 6.40 (d, *J* = 1.3 Hz, 1H), 5.79 (q, *J* = 1.3 Hz, 1H), 4.33 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

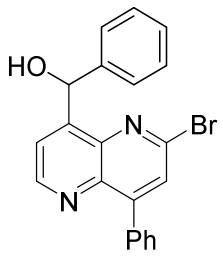
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.8, 151.4, 150.8, 147.2, 144.2, 141.4, 141.2, 138.2, 135.9, 130.5, 129.3, 128.7, 128.5, 128.5, 124.5, 61.1, 32.8, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3055, 2980, 2927, 1712, 1631, 1547, 1484, 1311, 1134, 1121, 1026, 765, 696.

MS (EI, 70 eV): m/z (%) = 396 (4), 369 (13), 167 (13), 326 (17), 325 (98), 324 (15), 321 (15), 244 (14), 243 (38), 242 (38), 241 (12), 122 (11).

HRMS (EI) for **$C_{20}H_{17}BrN_2O_2$** (396.0473): 396.0466 (M^+).

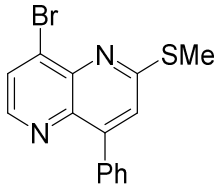
Synthesis of 2-bromo-8-(methylthio)-4-phenyl-1,5-naphthyridine (113f)



1,5-Naphthyridine **113f** was prepared *via* **TP12** using **112g** (71 mg, 0.25 mmol), TMPLi (0.50 mL, 0.30 mmol), and benzaldehyde (38 µL, 375 µmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **113f** (69 mg, 176 µmol, 71%) as a light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.93 (d, *J* = 4.4 Hz, 1H), 7.76 (s, 1H), 7.72 - 7.68 (m, 2H), 7.58 - 7.49 (m, 6H), 7.41 - 7.34 (m, 2H), 7.32 - 7.27 (m, 1H), 6.63 (s, 1H), 4.74 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.7, 151.1, 149.3, 143.0, 141.9, 141.2, 141.0, 135.4, 130.4, 129.4, 128.6, 128.5, 128.4, 127.8, 126.9, 122.2, 73.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3365, 3061, 2360, 1549, 1485, 1309, 1058, 765, 727, 698.
MS (EI, 70 eV): m/z (%) = 393 (27), 392 (100), 391 (77), 390 (99), 389 (47), 315 (20), 313 (19), 287 (18), 286 (17), 285 (35), 284 (22), 283 (22), 206 (29), 205 (36), 147 (16), 77 (20).
HRMS (EI) for **$C_{21}H_{15}BrN_2O$** (390.0368): 390.0372 (M^+).

Synthesis of 8-bromo-2-(methylthio)-4-phenyl-1,5-naphthyridine (113g)



1,5-Naphthyridine **113g** was prepared *via* **TP12** using **112h** (39 mg, 154 µmol), TMPLi (0.32 mL, 185 µmol), and 1,2-dibromotetrachloroethane (76 mg, 232 µmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9.5:0.5:0.1) to give **113g** (24 mg, 73 µmol, 47%) as a light yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.59 (d, *J* = 4.6 Hz, 1H), 7.89 (d, *J* = 4.6 Hz, 1H), 7.72 - 7.66 (m, 2H), 7.55 - 7.46 (m, 4H), 2.80 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.0, 148.0, 147.9, 142.1, 141.6, 136.2, 134.8, 130.3, 128.9, 128.3, 128.0, 124.6, 13.4.

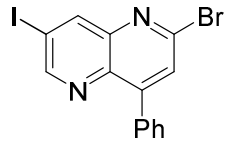
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3050, 2922, 2358, 1941, 1588, 1574, 1532, 1476, 1349, 1120, 878, 756, 692.

MS (EI, 70 eV): m/z (%) = 333 (21), 332 (100), 330 (91), 329 (48), 298 (15), 287 (24), 285 (26), 284 (16), 283 (21), 204 (16), 203 (21), 177 (16), 44 (25), 43 (24).

HRMS (EI) for **$C_{15}H_{11}BrN_2S$** (329.9826): 329.9813 (M^+).

M.p (°C): 164–166.

Synthesis of 2-bromo-7-iodo-4-phenyl-1,5-naphthyridine (114a)



1,5-Naphthyridine **114a** was prepared *via* **TP13** using **113a** (41 mg, 0.10 mmol), TMPLi (0.20 mL, 0.12 mmol), and H_2O (0.9 mL, 5.00 mmol). The reaction was complete after 2 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9.5:0.5:0.1) to give **114a** (32 mg, 78 µmol, 78%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.12 (d, *J* = 2.0 Hz, 1H), 8.77 (d, *J* = 2.1 Hz, 1H), 7.78 (s, 1H), 7.74 - 7.69 (m, 2H), 7.57 - 7.51 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.4, 151.3, 145.5, 144.7, 143.3, 139.8, 134.9, 130.5, 129.7, 129.1, 128.6, 94.8.

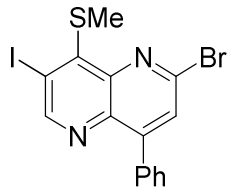
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 2236, 1560, 1537, 1463, 1442, 1295, 1100, 971, 895, 885, 838, 763, 717, 694.

MS (EI, 70 eV): m/z (%) = 412 (8), 411 (21), 410 (9), 409 (21), 281 (28), 225 (27), 209 (13), 208 (13), 207 (100), 203 (16), 191 (18).

HRMS (EI) for **$C_{14}H_7N_2BrI$** (408.8837): 408.8834 (M^+-H).

M.p. (°C): 136–137.

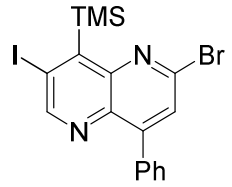
Synthesis of 2-bromo-7-iodo-8-(methylthio)-4-phenyl-1,5-naphthyridine (114b)



1,5-Naphthyridine **114b** was prepared *via* **TP13** using **113a** (55 mg, 134 µmol), TMPLi (0.27 mL, 160 µmol), and S-methyl methanethiosulfonate (20 µL, 200 µmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9.8:0.2:0.1) to give **114b** (38 mg, 83 µmol, 62%) as a light yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.08 (s, 1H), 7.76 (s, 1H), 7.70 - 7.64 (m, 2H), 7.55 - 7.49 (m, 3H), 3.02 (d, *J* = 0.6 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 156.6, 152.2, 152.2, 144.4, 140.8, 140.8, 135.4, 130.5, 129.6, 129.0, 128.5, 101.9, 21.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 2925, 2853, 2362, 1558, 1533, 1458, 1403, 1376, 1309, 1094, 876, 785, 758, 692.
MS (EI, 70 eV): m/z (%) = 458 (42), 456 (36), 330 (25), 329 (100), 285 (29), 283 (34), 85 (20), 71 (30), 57 (51), 44 (34), 43 (68).
HRMS (EI) for **$C_{15}H_{10}BrIN_2S$** (455.8793): 455.8789 (M^+).
M.p (°C): 169–170.

Synthesis of 2-bromo-7-iodo-8-(trimethylsilyl)-4-phenyl-1,5-naphthyridine (114c)



1,5-Naphthyridine **114c** was prepared *via* **TP13** using **113a** (41 mg, 0.10 mmol), TMPLi (0.20 mL, 0.12 mmol), and trimethylsilyl chloride (30 µL, 0.30 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 10:0.1:0.1) to give **114c** (36 mg, 74 µmol, 74%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.19 (s, 1H), 7.71 (s, 1H), 7.69 - 7.65 (m, 2H), 7.55 - 7.48 (m, 3H), 0.64 (s, 9H).

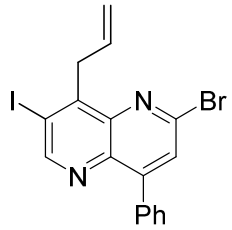
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.9, 155.6, 151.6, 149.9, 139.8, 139.0, 135.6, 130.5, 129.4, 128.5, 128.3, 104.6, 3.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2952, 2895, 1580, 1562, 1537, 1466, 1316, 1247, 1170, 1084, 997, 876, 848, 768, 695.

MS (EI, 70 eV): m/z (%) = 480 (2), 470 (21), 469 (199), 468 (20), 467 (100), 357 (24), 355 (24), 343 (32), 245 (21), 207 (15).

HRMS (EI) for **$C_{17}H_{15}N_2BrISi$** (480.9233): 480.9227 (M^+-H).

Synthesis of 8-allyl-2-bromo-7-iodo-4-phenyl-1,5-naphthyridine (114d)



1,5-Naphthyridine **114d** was prepared *via* **TP13** using **113a** (39 mg, 95 µmol), and TMPLi (190 µL, 114 µmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (114 µL, 114 µmol) was added and the reaction stirred at the same temperature for 20 min. Then, allyl bromide (15 µL, 143 µmol) was added and the reaction slowly warmed to 25 °C over 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 10:0.2:0.1) to give **114d** (27 mg, 60 µmol, 63%) as a yellow oil.

^{1}H-NMR (400 MHz, C_6D_6): δ / ppm = 8.94 (s, 1H), 7.50 - 7.43 (m, 2H), 7.37 (s, 1H), 7.26 - 7.17 (m, 3H), 6.05 - 5.92 (m, 1H), 5.25 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.04 (dq, *J* = 10.1, 1.5 Hz, 1H), 4.07 (dt, *J* = 6.5, 1.5 Hz, 2H).

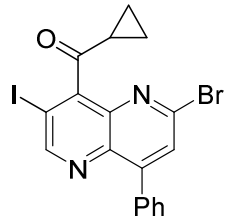
^{13}C-NMR (101 MHz, C_6D_6): δ / ppm = 157.3, 151.5, 150.6, 144.3, 142.2, 140.4, 135.7, 133.7, 131.1, 129.2, 128.8, 128.3, 117.6, 101.6, 39.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 2979, 1635, 1562, 1538, 1470, 1318, 1304, 1185, 1168, 1094, 1049, 920, 879, 830, 765, 695, 617.

MS (EI, 70 eV): m/z (%) = 452 (100), 450 (79), 437 (91), 434 (82), 322 (16), 243 (22), 241 (24).

HRMS (EI) for **$C_{17}H_{12}N_2BrI$** (449.9229): 449.9222 (M^+).

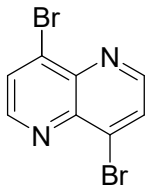
Synthesis of 2-bromo-8-(cyclopropanecarbonyl)-7-iodo-4-phenyl-1,5-naphthyridine (114e)



1,5-Naphthyridine **114f** was prepared *via* **TP13** using **113a** (62 mg, 0.15 mmol), and TMPLi (0.30 mL, 0.18 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.18 mL, 0.18 mmol) was added and the reaction stirred at the same temperature for 20 min. Then, cyclopropanecarbonyl chloride (30 µL, 225 µmol) was added and the reaction slowly warmed to 25 °C over 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9.5:0.5:0.1) to give **114f** (50 mg, 104 µmol, 70%) as a light yellow oil.

^{1}H-NMR (599 MHz, $CDCl_3$): δ / ppm = 9.20 (s, 1H), 7.80 (s, 1H), 7.73 - 7.68 (m, 2H), 7.56 - 7.51 (m, 3H), 2.36 - 2.30 (m, 1H), 1.60 - 1.56 (m, 2H), 1.28 - 1.23 (m, 2H).
^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 204.2, 157.1, 153.0, 150.9, 143.0, 141.9, 140.0, 134.6, 130.3, 129.6, 129.4, 128.5, 91.0, 22.7, 13.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3010, 2925, 1696, 1562, 1537, 1469, 1371, 1204, 1093, 982, 765, 730, 697.
MS (EI, 70 eV): m/z (%) = 453 (18), 452 (96), 451 (25), 450 (100), 399 (20), 216 (18), 203 (31), 176 (19), 69 (29), 41 (43).
HRMS (EI) for **$C_{18}H_{12}BrIN_2O$** (477.9178): 477.9167 (M^+).

Synthesis of 4,8-dibromo-1,5-naphthyridine (123)

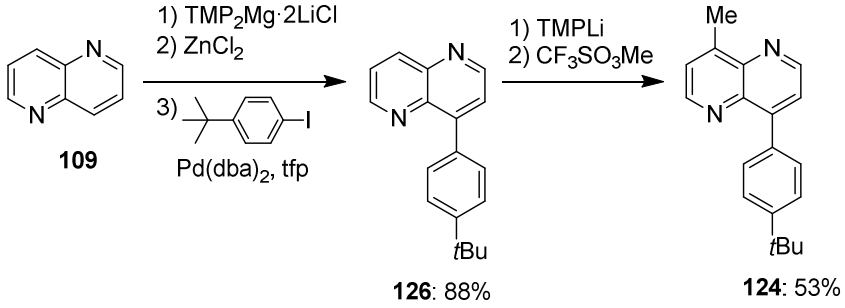


1,5-Naphthyridine (**109**, 1.04 g, 8.00 mmol) was dissolved in THF (40 mL) and cooled to -40 °C. Then, TMPMgCl·LiCl (20.5 mL, 24.0 mmol) was added and the reaction mixture stirred for 4 h whilst warming to -20 °C slowly. After adding a solution of 1,2-dibromotetrachloroethane (10.4 g, 32.0 mmol) in THF (40 mL), the reaction was slowly warmed to 25 °C and stirred for 12 h. After work-up, the crude

product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **123** (1.23 g, 4.27 mmol, 53%) as an off-white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.85 (d, *J* = 4.6 Hz, 2H), 8.06 (d, *J* = 4.6 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.3, 142.9, 136.9, 129.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 3019, 1576, 1474, 1456, 1376, 1264, 1180, 1041, 866, 711.
MS (EI, 70 eV): m/z (%) = 290 (48), 288 (100), 286 (53), 209 (46), 207 (47), 128 (17), 100 (15).
HRMS (EI) for **$C_8H_4N_2Br_2$** (285.8741): 285.8736 (M^+).
M.p. (°C): Compound sublimes at 220 °C followed by degradation.

Synthesis of 4-(4-(*tert*-butyl)phenyl)-8-methyl-1,5-naphthyridine (124)



Synthesis of 4-(4-(*tert*-butyl)phenyl)-1,5-naphthyridine (**126**)

1,5-Naphthyridine **109** (1.04 g, 8.00 mmol) was dissolved in THF (40 mL), cooled to -78 °C, and $TMP_2Mg·2LiCl$ (7.62 mL, 4.80 mmol) was added dropwise. After the metalation was complete (5 min, checked *via* GC / GC-MS), a 1.0 M $ZnCl_2$ solution in THF (4.80 mL, 4.80 mmol) was added and the reaction stirred at the same temperature for 20 min. Then, 4-*tert*-butyliodobenzene (1.14 mL, 6.40 mmol), $Pd(dba)_2$ (138 mg, 240 µmol), and tfp (111 mg, 480 µmol) was added and the reaction slowly warmed to 25 °C over 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **126** (1.11 g, 4.23 mmol, 88%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.03 (dd, *J* = 4.1, 1.8 Hz, 1H), 9.00 (d, *J* = 4.5 Hz, 1H), 8.46 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.78 - 7.73 (m, 2H), 7.68 - 7.62 (m, 2H), 7.60 - 7.54 (m, 2H), 1.40 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.8, 151.0, 150.7, 148.3, 144.5, 142.1, 137.7, 133.7, 130.2, 125.4, 124.1, 34.8, 31.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3015, 2962, 2903, 2868, 1611, 1582, 1492, 1404, 1363, 1268, 1106, 866, 834, 822, 792, 662.

MS (EI, 70 eV): m/z (%) = 262 (139, 261 (19), 247 (43), 232 (15), 231 (16), 218 (22), 206 (14), 205 (100).
HRMS (EI) for **$C_{18}H_{17}N_2$** (261.1392): 261.1385 (M^+-H).
M.p. (°C): 146-148.

Synthesis of 4-(4-(*tert*-butyl)phenyl)-8-methyl-1,5-naphthyridine (124)

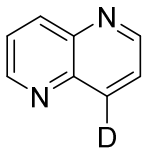
1,5-Naphthyridine **126** (100 mg, 0.38 mmol) was dissolved in THF (3 mL) and cooled to –78 °C. After addition of TMPLi (0.63 mL, 0.40 mmol) and stirring for 10 min, methyl trifluoromethanesulfonate (0.06 mL, 0.57 mmol) was added dropwise. After stirring at the same temperature for one hour, the solvent was removed rapidly from the reaction mixture and the crude 'wet loaded' on a pre packed column by dissolving in DCM. Elution in *iso*hexane:ethyl acetate:triethylamine = 9:1:0.1 gave **124** (56 mg, 0.20 mmol, 53%) as an off-white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.00 (d, *J* = 4.4 Hz, 1H), 8.87 (d, *J* = 4.2 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 4.4 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 4.3 Hz, 1H), 2.88 (s, 3H), 1.39 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.7, 150.5, 149.7, 148.7, 147.1, 144.5, 141.7, 134.3, 130.4, 125.5, 124.6, 124.2, 34.9, 31.5, 18.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3017, 2957, 2930, 2903, 2860, 1581, 1500, 1472, 1462, 1396, 1363, 1240, 1097, 1075, 1063, 864, 832, 772, 669.
MS (EI, 70 eV): m/z (%) = 276 (19), 175 (58), 261 (40), 259 (11), 245 (21), 232 (12), 231 (12), 220 (15), 219 (100), 218 (12), 207 (18), 116 (19).
HRMS (EI) for **$C_{19}H_{19}N_2$** (275.1548): 275.1545 (M^+-H).
M.p. (°C): 141–143.

5.3 Regioselectivity Investigations

To confirm the regioselectivity for each metalation (Typical Procedure **TP8–13**), the resulting metal species of type **115**, **116**, **117**, **120** and **122** were quenched with D_2O / THF solutions and the obtained deuterium-incorporated products analyzed *via* ^1H NMR spectroscopy. The measured spectra were also compared with the respective starting material spectra.

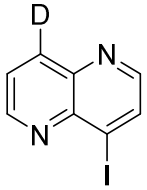
Synthesis of 1,5-naphthyridine-4-*d*



1,5-Naphthyridine-4-*d* was prepared *via* **TP8** using **109** (130 mg, 1.00 mmol) and $TMP_2Mg{\cdot}2LiCl$ (1.75 mL, 1.10 mmol). The metalated species was then slowly cannulated into a solution of D_2O (0.1 mL, 5.56 mmol) in THF (2 mL), warmed to room temperature and stirred for 1 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give 1,5-Naphthyridine-4-*d* (60 mg, 458 µmol, 46%) as an off-white solid. NMR-spectroscopy revealed an incorporation of deuterium at position C4 with a ^2H:^1H ratio of 89:11.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.98 (d, *J* = 4.2 Hz, 2H), 8.40 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.67-7.61 (m, 2H).

Synthesis of 4-iodo-1,5-naphthyridine-8-*d*

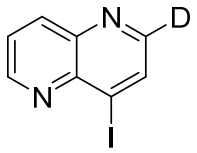


4-Iodo-1,5-naphthyridine-8-*d* was prepared *via* **TP9** using **110a** (139 mg, 0.50 mmol) and $TMPMgCl{\cdot}LiCl$ (0.52 mL, 0.60 mmol). Then, a solution of D_2O (0.05 mL, 2.78 mmol) in THF (2 mL) was added dropwise and the reaction mixture warmed to room temperature and stirred for 1 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give 4-iodo-1,5-naphthyridine-8-*d* (100 mg, 389 µmol, 78%) as an

off-white solid. NMR-spectroscopy revealed an incorporation of deuterium at position C8 with a $^{2}H:^{1}H$ ratio of 63:37.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.06 (d, *J* = 4.2 Hz, 1 H), 8.53 (d, *J* = 4.5 Hz, 1 H), 8.28 (d, *J* = 4.5 Hz, 1H), 7.70 (dd, *J* = 8.4, 4.2 Hz, 1 H).

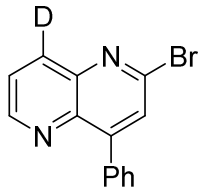
Synthesis of 4-iodo-1,5-naphthyridine-2-*d*



4-Iodo-1,5-naphthyridine-2-*d* was prepared *via* **TP11** using **110a** (128 mg, 0.50 mmol), $BF_3{\cdot}OEt_2$ (0.07 mL, 0.55 mmol) and TMPMgCl·LiCl (0.52 mL, 0.60 mmol). Then, a solution of D_2O (0.05 mL, 2.78 mmol) in THF (2 mL) was added dropwise and the reaction mixture warmed to room temperature and stirred for 1 h. After work-up, the crude product was purified *via* column chromatography (ethyl acetate) to give 4-iodo-1,5-naphthyridine-2-*d* (86 mg, 334 µmol, 67%) as an off-white solid. NMR-spectroscopy revealed an incorporation of deuterium at position C2 with a $^{2}H:^{1}H$ ratio of 76:24.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.05 (dd, *J* = 4.2 Hz, 1.6 Hz, 1 H), 8.35 (dd, *J* = 8.5 Hz, 1.6 Hz, 1 H), 8.29-8.24 (m, 1H), 7.69 (dd, *J* = 8.5 Hz, 4.2 Hz, 1 H).

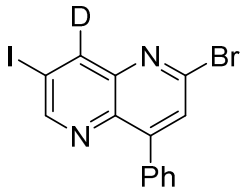
Synthesis of 2-bromo-4-phenyl-1,5-naphthyridine-8-*d*



2-Bromo-4-phenyl-1,5-naphthyridine-8-*d* was prepared *via* **TP12** using **112g** (57 mg, 0.20 mmol), and TMPLi (0.40 mL, 0.24 mmol). Then, a solution of D_2O (0.05 mL, 2.78 mmol) in THF (2 mL) was added dropwise and the reaction mixture warmed to room temperature and stirred for 1 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 1:1) to give 2-bromo-4-phenyl-1,5-naphthyridine-8-*d* (45 mg, 157 µmol, 79%) as a colorless solid. NMR-spectroscopy revealed an incorporation of deuterium at position C2 with a ^2H:^1H ratio of 98:12.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.01 (d, *J* = 4.1 Hz, 1H), 7.79 - 7.73 (m, 3H), 7.66 (d, *J* = 4.2 Hz, 1H), 7.58 - 7.48 (m, 3H).

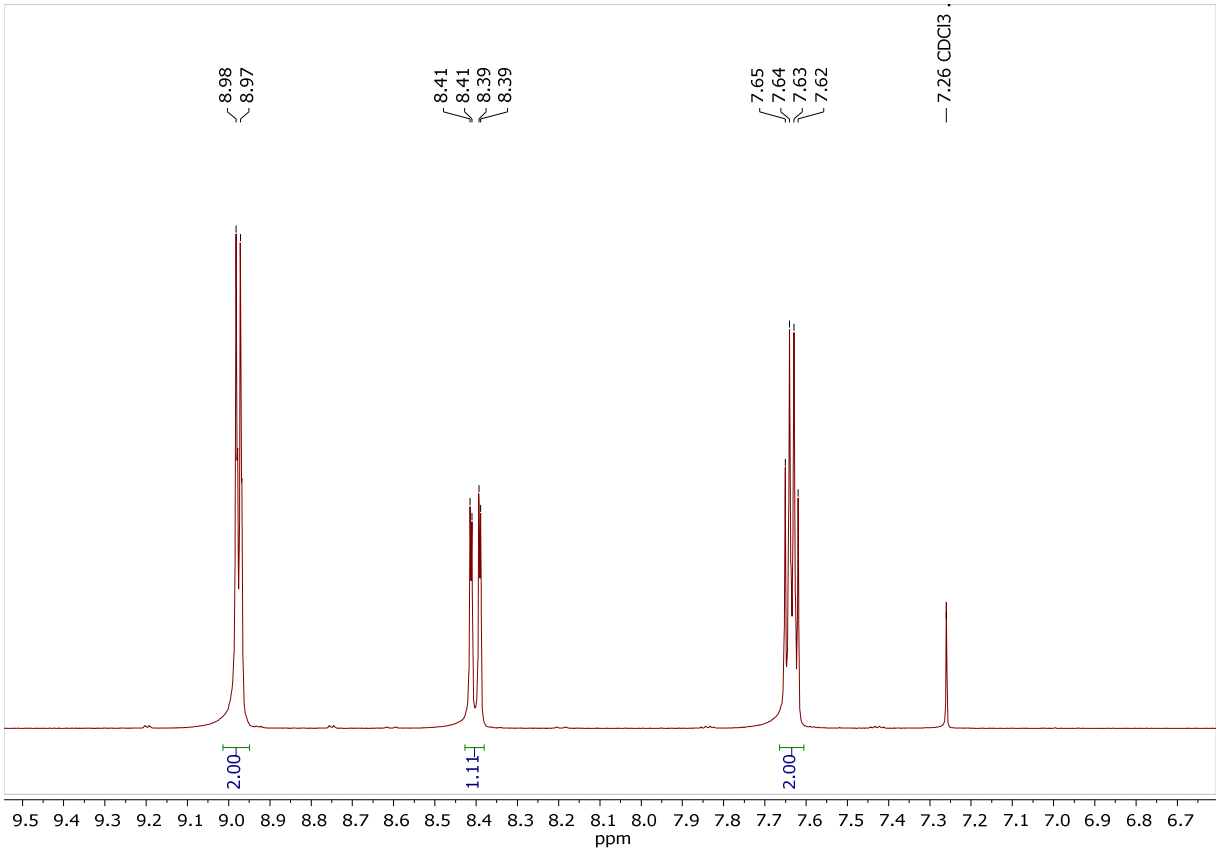
Synthesis of 2-bromo-7-iodo-4-phenyl-1,5-naphthyridine-8-*d*



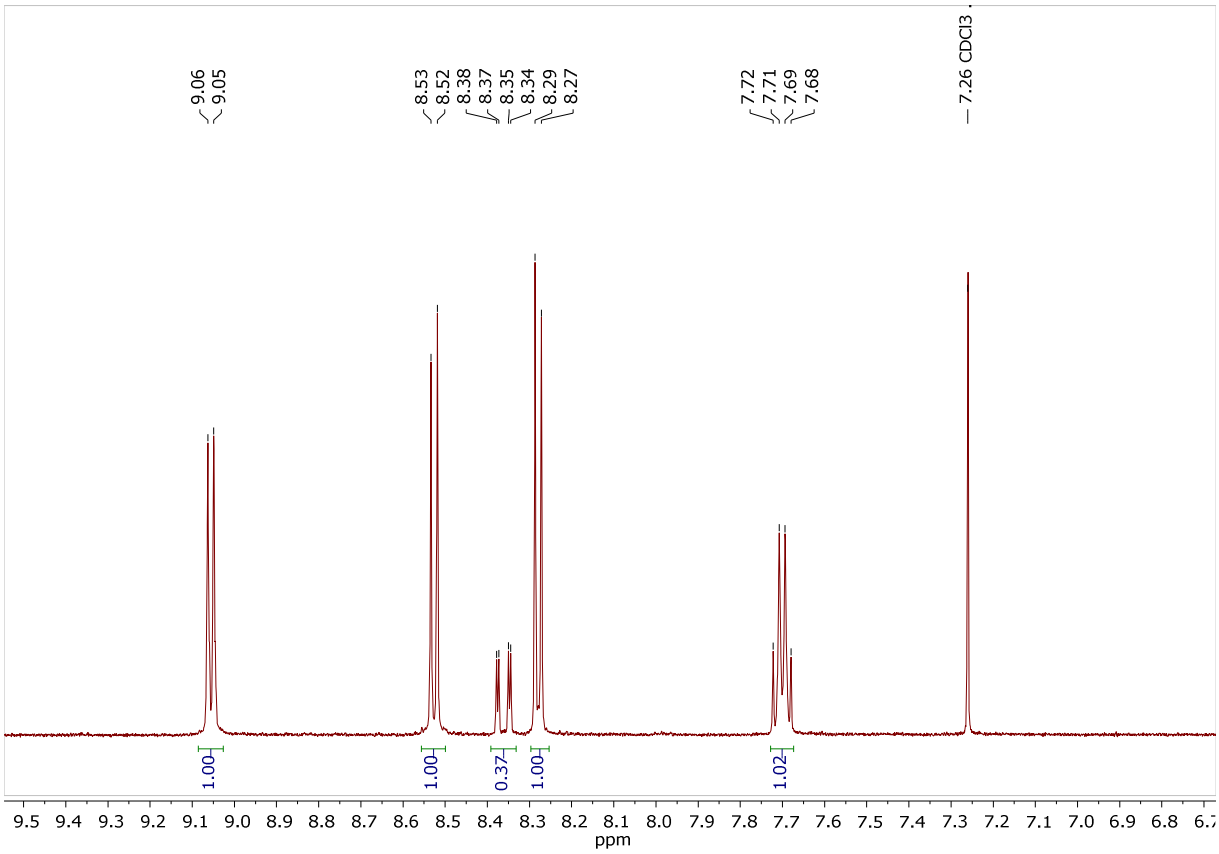
2-bromo-7-iodo-4-phenyl-1,5-naphthyridine-8-*d* was prepared *via* **TP13** using **113a** (41 mg, 0.10 mmol), and TMPLi (0.20 mL, 0.12 mmol). Then, a solution of D_2O (0.05 mL, 2.78 mmol) in THF (2 mL) was added dropwise and the reaction mixture warmed to room temperature and stirred for 1 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9.5:0.5:0.1) to give 2-bromo-7-iodo-4-phenyl-1,5-naphthyridine-8-*d* (25 mg, 61 µmol, 61%) as a colorless solid. NMR-spectroscopy revealed an incorporation of deuterium at position C2 with a ^2H:^1H ratio of 95:05.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.12 (s, 1H), 7.78 (s, 1H), 7.75 - 7.69 (m, 2H), 7.57 - 7.49 (m, 3H).

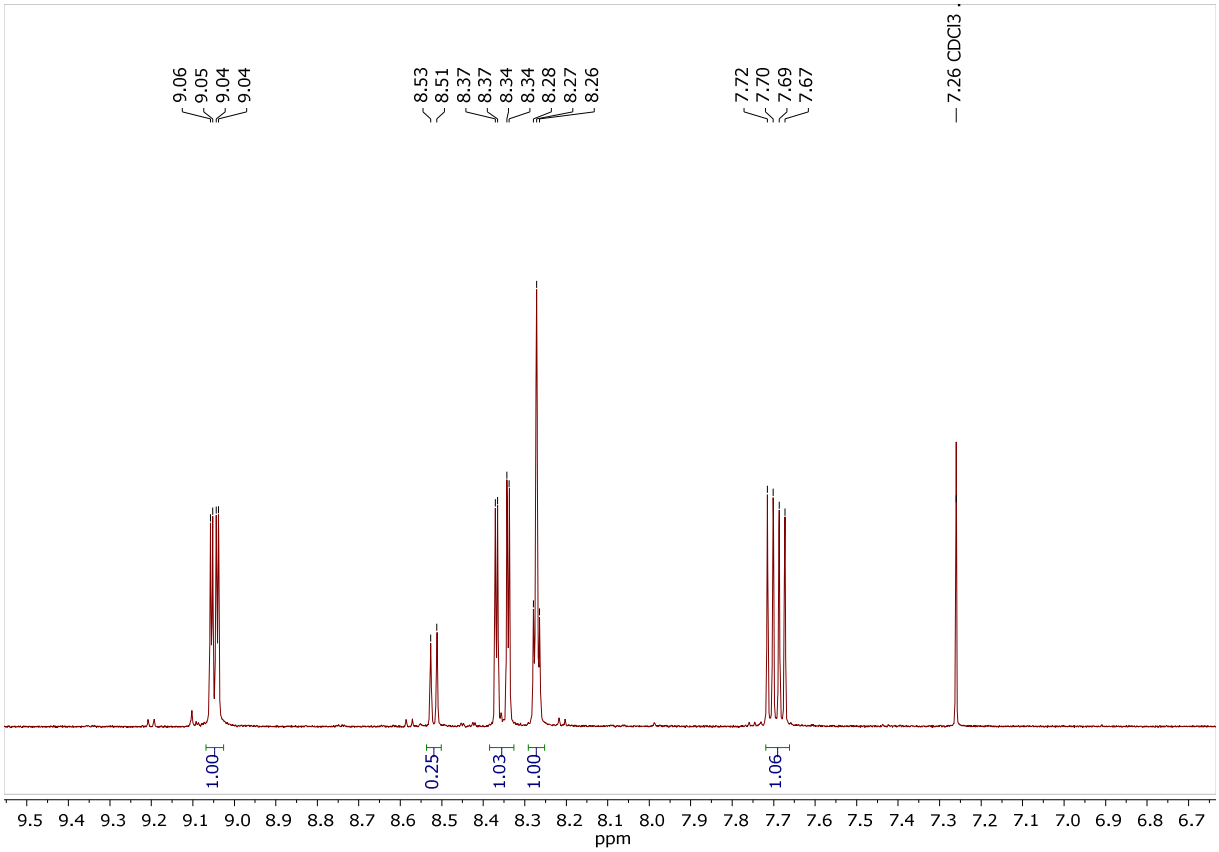
^{1}H NMR spectrum of 1,5-naphthyridine-4-*d*



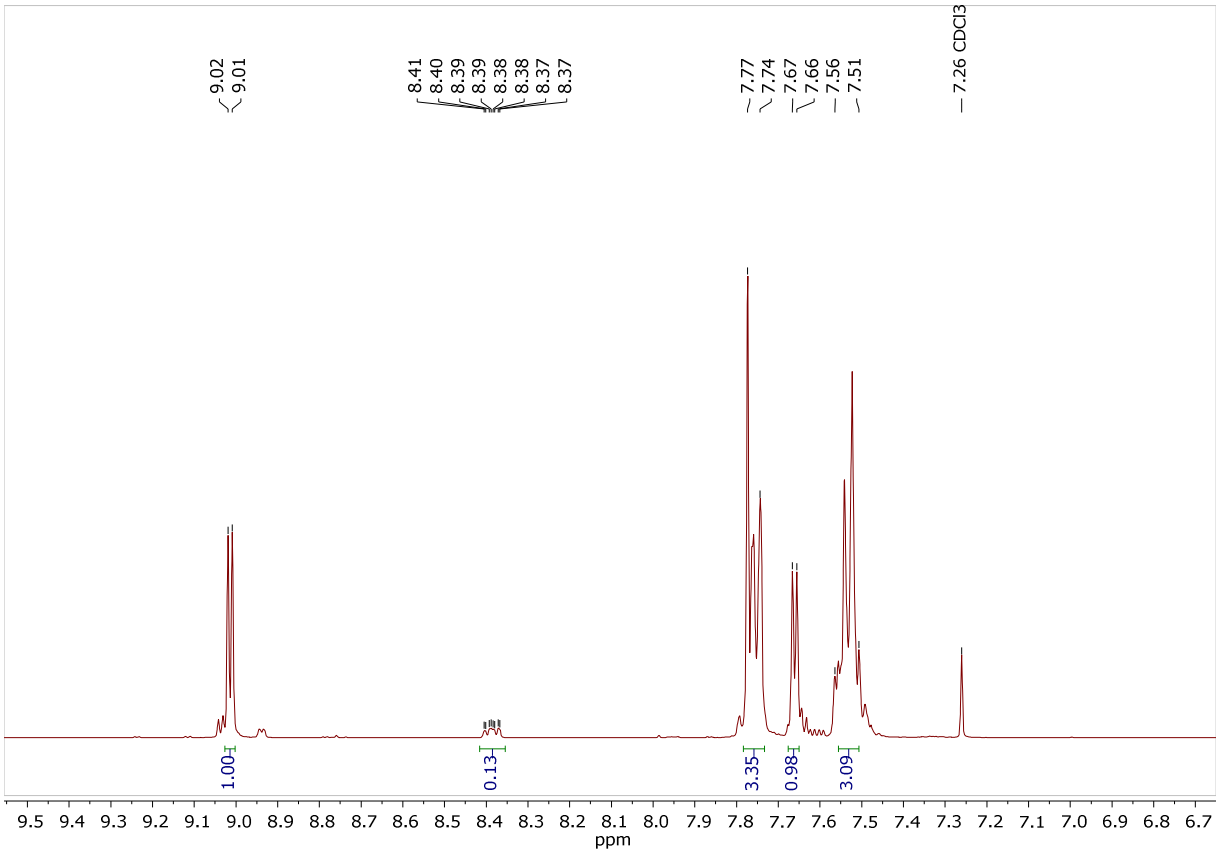
^{1}H NMR spectrum of 4-iodo-1,5-naphthyridine-8-*d*



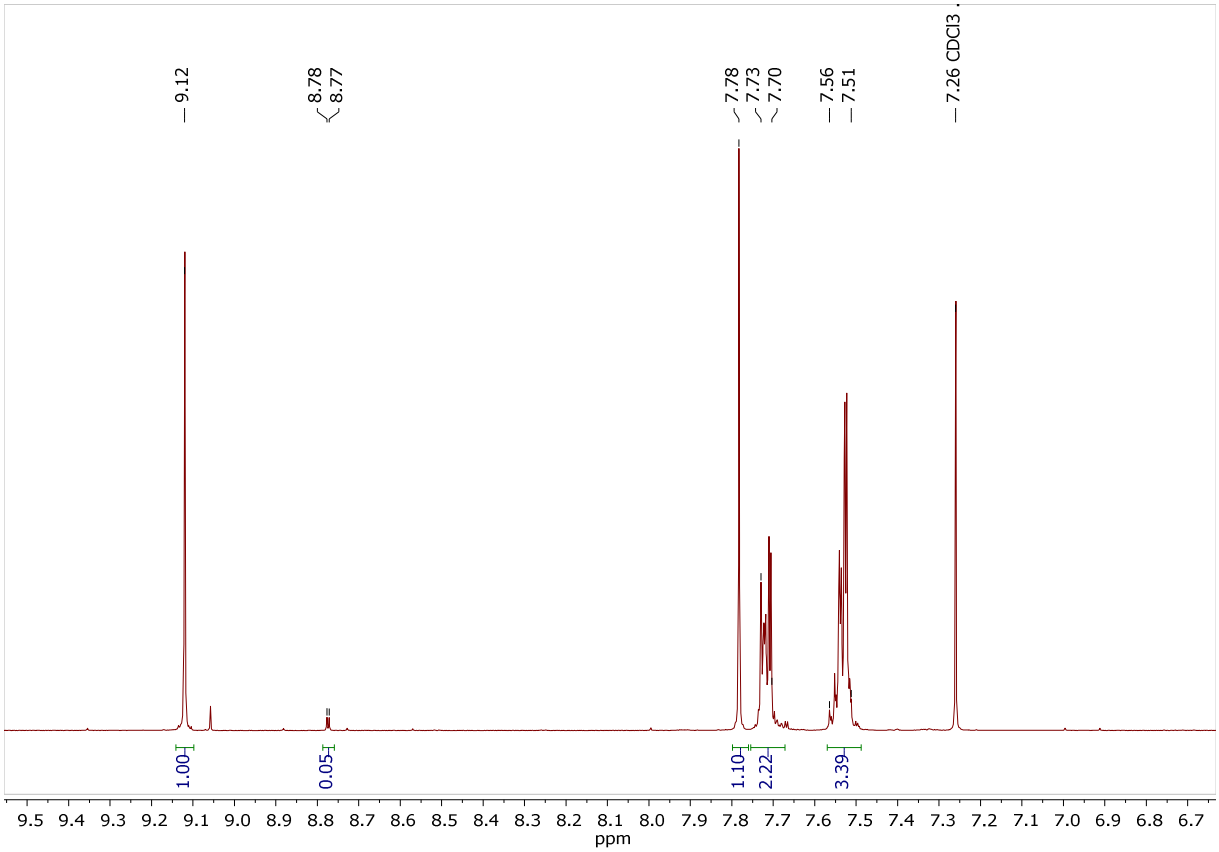
[1]H NMR spectrum of 4-iodo-1,5-naphthyridine-2-*d*



[1]H NMR spectrum of 2-bromo-4-phenyl-1,5-naphthyridine-8-*d*



^{1}H NMR spectrum of 2-bromo-7-iodo-4-phenyl-1,5-naphthyridine-8-*d*



6 Regioselective Metalation and Functionalization of the Pyrazolo[1,5-*a*]pyridine Scaffold using Mg- and Zn-TMP Bases

6.1 Typical Procedures

Typical Procedure 14: Metalation and functionalization of pyrazolo[1,5-*a*]pyridine (**128**) in the C7 position using TMPMgCl·LiCl (inverse addition).

To a solution of pyrazolo[1,5-*a*]pyridine **128,** in THF (5 mL/mmol pyrazolo[1,5-*a*]pyridine) was added dropwise a solution of TMPMgCl·LiCl (1.2 equiv) at –78 °C. After full metalation (15 min, checked *via* GC / GC-MS), the solution was canulated dropwise to a precooled solution of the corresponding electrophile in THF at –78 °C (5 mL/mmol pyrazolo[1,5-*a*]pyridine) and the reaction slowly warmed to 25 °C and stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL/mmol pyrazolo[1,5-*a*]pyridine) and extracted with ethyl acetate (3 x 50 mL/mmol pyrazolo[1,5-*a*]pyridine). The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. If the crude product needed purification, it was purified *via* flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 15: Metalation and functionalization of pyrazolo[1,5-*a*]pyridines in the C7 position using TMPMgCl·LiCl (normal addition).

To a solution of the pyrazolo[1,5-*a*]pyridine in THF (5 mL/mmol pyrazolo[1,5-*a*]pyridine) was added dropwise a solution of TMPMgCl·LiCl (1.2 equiv) at –78 °C. After full metalation (15 min, checked *via* GC / GC-MS analysis of iodolyzed reaction aliquots), a solution of the corresponding electrophile in THF (2 mL/mmol pyrazolo[1,5-*a*]pyridine) was added dropwise and the reaction slowly warmed to 25 °C and stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL/mmol pyrazolo[1,5-*a*]pyridine) and extracted with ethyl acetate (3 x 50 mL/mmol pyrazolo[1,5-*a*]pyridine). The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. If the crude product needed purification, it was purified *via* flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 16: Metalation and functionalization of pyrazolo[1,5-*a*]pyridine **128** in the C7 position using TMPZnCl·LiCl.

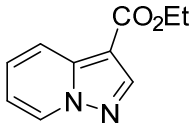
To a solution of pyrazolo[1,5-*a*]pyridine **128** in THF (5 mL/mmol pyrazolo[1,5-*a*]pyridine) was added dropwise a solution of TMPZnCl·LiCl (1.2 equiv) at 0 °C. After full metalation (15 min, checked *via* GC / GC-MS analysis of iodolyzed reaction aliquots), a solution of the corresponding electrophile in THF (2 mL/mmol pyrazolo[1,5-*a*]pyridine) was added dropwise and the reaction slowly warmed to 25 °C and stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL/mmol pyrazolo[1,5-*a*]pyridine) and extracted with ethyl acetate (3 x 50 mL/mmol pyrazolo[1,5-*a*]pyridine). The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. If the crude product needed purification, it was purified *via* flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 17: Metalation and functionalization of pyrazolo[1,5-*a*]pyridine (**128**) in the C2 position using $BF_3 \cdot OEt_2$ and TMPMgCl·LiCl.

Pyrazolo[1,5-*a*]pyridine **128** was dissolved in THF (5 mL/mmol pyrazolo[1,5-*a*]pyridine) and cooled to 0 °C. Then, $BF_3 \cdot OEt_2$ (1.1 equiv) was added dropwise and the reaction mixture stirred for 10 min. After cooling to –78 °C, TMPMgCl·LiCl (1.2 equiv) was added and the reaction stirred until full metalation was observed (10 min, checked *via* GC / GC-MS). Then, a solution of the electrophile in THF (2 mL/mmol pyrazolo[1,5-*a*]pyridine) was added dropwise and the reaction slowly warmed to 25 °C and stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL/mmol pyrazolo[1,5-*a*]pyridine) and extracted with ethyl acetate (3 x 50 mL/mmol pyrazolo[1,5-*a*]pyridine). The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. If the crude product needed purification, it was purified *via* flash chromatography on silica gel using the appropriate eluent.

6.2 Preparation of Compounds 128 to 149

Synthesis of pyrazolo[1,5-*a*]pyridine-3-carboxylate (139)



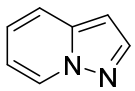
Adapted from a literature procedure,[141] 1-aminopyridinium iodide (21.4 g, 96.6 mmol) and K_2CO_3 (19.5 g, 141 mmol) were dissolved in DMF (100 mL). Then, ethyl propiolate (10.4 mL, 106 mmol) was added dropwise at room temperature. Air was introduced to the reaction mixture *via* a gas inlet and the reaction mixture was stirred for 2 h. DMF was removed *in vacuo*, and the reaction mixture was extracted with diethylether (3 x 100 mL). The organic phase was washed with an aq. 5% LiOH solution (3x100 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate = 7:3) to give **139** (12.3 g, 64.8 mmol, 67%) as an orange oil.

The spectra matched those of the literature.[142]

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.49 (dt, *J* = 6.9, 1.1 Hz, 1H), 8.38 (s, 1H), 8.13 (dt, *J* = 8.9, 1.2 Hz, 1H), 7.37 (ddd, *J* = 8.9, 6.8, 1.1 Hz, 1H), 6.91 (td, *J* = 6.9, 1.4 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

[141] (a) P. Gmeiner, J. Sommer, *Arch. Pharm.* **1988**, *321*, 505–507. (b) Löber, S.; Hübner, H.; Utz, W.; Gmeiner, P., *J. Med. Chem.* **2001,** *44*, 2691–2694.
[142] R. Chitrakar, S. Supravat, C. M. Darapaneni, K. R. N. Naresh, A. Subbarayappa, *Synthesis* **2017**, *49*, 2513–2522.

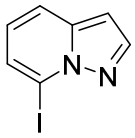
Synthesis of pyrazolo[1,5-*a*]pyridine (128)



Adapted from a literature procedure,[141] pyrazolo[1,5-*a*]pyridine-3-carboxylate **139** (9.01 g, 47.4 mmol) was dissolved in H_2SO_4 (50% v/v, 30.0 mL). Then, the reaction mixture was heated at 110 °C for 2 h. After cooling to 0 °C, an aq. 50% NaOH solution was added until basification. Then, the reaction mixture was extracted with diethylether (3 x 100 mL) and dried over Na_2SO_4. After filtration, the solvents were removed *in vacuo* and the crude product purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **128** (4.16 g, 35.2 mmol, 74%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.46 (d, *J* = 7.0 Hz, 1H), 7.94 (d, *J* = 2.1 Hz, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.10 - 7.04 (m, 1H), 6.72 (t, *J* = 6.8 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 141.9, 140.2, 128.7, 123.2, 118.2, 111.7, 96.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3432, 3108, 1633, 1515, 1460, 1434, 1370, 1338, 1252, 1225, 1176, 1140, 1008, 920, 890, 759.
MS (EI, 70 eV): m/z = 119 (8), 118 (100), 91 (19), 78 (10).
HRMS (EI) for $C_7H_6N_2$ (118.0531): 118.0525 (M^+).

Synthesis of 7-iodopyrazolo[1,5-*a*]pyridine (134a)



Pyrazolo[1,5-*a*]pyridine **134a** was prepared *via* **TP1** using **128** (59 mg, 0.50 mmol), TMPMgCl·LiCl (0.48 mL, 0.60 mmol) and iodine (190 mg, 0.75 mmol). The reaction was complete after 1 h. After quenching with a sat. aq. $Na_2S_2O_3$ solution (10 mL) followed by standard work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 95:5:1) to give **134a** (84 mg, 344 µmol, 69%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.04 (d, *J* = 2.3 Hz, 1H), 7.54 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.32 (dd, *J* = 7.1, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.8, 7.1 Hz, 1H), 6.75 (d, *J* = 2.3 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 141.2, 140.5, 123.9 (2C), 118.2, 99.5, 91.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3074, 1617, 1528, 1490, 1440, 1359, 1294, 1200, 900, 778, 714.

MS (EI, 70 eV): 244 (100), 127 (36), 117 (31), 90 (27), 63 (10).
HRMS (EI) for $C_7H_5N_2I$ (243.9497): 243.9493 (M^+).
M.p. (°C): 53–55.

Synthesis of 7-bromopyrazolo[1,5-*a*]pyridine (134b)

Pyrazolo[1,5-*a*]pyridine **134b** was prepared *via* **TP14** using **128** (591 mg, 5.00 mmol), TMPMgCl·LiCl (5.04 mL, 6.00 mmol) and 1,2-dibromotetrachloroethane (2.44 g, 7.50 mmol). The reaction was complete after 5 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **134b** (917 mg, 4.65 mmol, 93%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05 (d, *J* = 2.3 Hz, 1H), 7.55 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.07 (dd, *J* = 7.2, 1.3 Hz, 1H), 6.98 (dd, *J* = 8.7, 7.0 Hz, 1H), 6.68 (d, *J* = 2.3 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.0, 141.7, 123.7, 118.7, 117.3, 116.1, 99.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3079, 1624, 1498, 1444, 1360, 1297, 1200, 950, 901, 779, 713.
MS (EI, 70 eV): 198 (98), 196 (100), 134 (10), 116 (80), 90 (38), 63 (20).
HRMS (EI) for $C_7H_5N_2Br$ (195.9636): 195.9629 (M^+).

Synthesis of 7-(methylthio)pyrazolo[1,5-*a*]pyridine (134c)

Pyrazolo[1,5-*a*]pyridine **134c** was prepared *via* **TP14** using **128** (62 mg, 0.52 mmol), TMPMgCl·LiCl (0.50 mL, 0.62 mmol) and *S*-methyl methanethiosulfonate (60 µL, 0.64 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **134c** (39 mg, 237 µmol, 46%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 (d, *J* = 2.3 Hz, 1H), 7.39 (dd, *J* = 8.8, 1.1 Hz, 1H), 7.11 (dd, *J* = 8.8, 7.2 Hz, 1H), 6.58 - 6.53 (m, 2H), 2.61 (s, 3H).

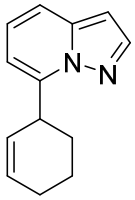
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 140.5, 140.1, 123.4, 113.7, 107.1, 97.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3082, 2922, 1616, 1500, 1436, 1356, 1307, 1208, 1147, 908, 774, 718.

MS (EI, 70 eV): 164 (97), 163 (14), 131 (100), 104 (10), 91 (12).

HRMS (EI) for $C_8H_8N_2S$ (164.0408): 164.0402 (M^+).

Synthesis of 7-(cyclohex-2-en-1-yl)pyrazolo[1,5-*a*]pyridine (134d)



Pyrazolo[1,5-*a*]pyridine **134d** was prepared *via* **TP15** using **128** (118 mg, 1.00 mmol) and TMPMgCl·LiCl (1.01 mL, 1.20 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (1.20 mL, 1.20 mmol) was added and the reaction warmed to –40 °C and stirred for 10 min. Then, 3-bromocyclohexene (0.15 mL, 1.30 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 2 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 95:5:1) to give **134d** (171 mg, 862 µmol, 86%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.99 (d, *J* = 2.3 Hz, 1H), 7.45 (dd, *J* = 8.9, 1.4 Hz, 1H), 7.09 (dd, *J* = 8.8, 6.9 Hz, 1H), 6.63 (dd, *J* = 6.9, 1.4 Hz, 1H), 6.54 (d, *J* = 2.3 Hz, 1H), 6.09 - 6.02 (m, 1H), 5.83 - 5.75 (m, 1H), 4.52 - 4.45 (m, 1H), 2.31 - 2.20 (m, 1H), 2.18 - 2.10 (m, 2H), 1.88 - 1.78 (m, 1H), 1.74 - 1.61 (m, 2H).

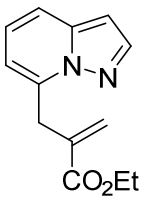
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 144.8, 141.1, 140.8, 130.5, 126.8, 123.3, 115.9, 110.1, 97.0, 35.8, 26.7, 25.4, 20.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3022, 2927, 1632, 1546, 1524, 1449, 1314, 1215, 1178, 1148, 914, 787, 724.

MS (EI, 70 eV): 198 (53), 197 (56), 183 (12), 170 (11), 169 (100), 168 (17), 157 (24), 156 (16), 155 (30), 143 (43), 132 (23), 131 (12).

HRMS (EI) for $C_{13}H_{14}N_2$ (198.1157): 198.1149 (M^+).

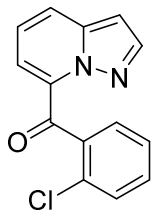
Synthesis of ethyl 2-(pyrazolo[1,5-*a*]pyridin-7-ylmethyl)acrylate (134e)



Pyrazolo[1,5-*a*]pyridine **134e** was prepared *via* **TP15** using **128** (59 mg, 0.50 mmol) and TMPMgCl·LiCl (0.48 mL, 0.60 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.60 mL, 0.60 mmol) was added and the reaction warmed to –40 °C and stirred for 10 min. Then, ethyl 2-(bromomethyl)acrylate (0.09 mL, 0.65 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 2 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **134e** (84 mg, 364 µmol, 73%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.98 (d, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 8.8, 1.3 Hz, 1H), 7.06 (dd, *J* = 8.9, 6.9 Hz, 1H), 6.60 (dd, *J* = 6.8, 1.1 Hz, 1H), 6.55 (d, *J* = 2.3 Hz, 1H), 6.37 - 6.35 (m, 1H), 5.65 (q, *J* = 1.3 Hz, 1H), 4.26 - 4.16 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.7, 141.3, 140.7, 138.9, 136.0, 127.9, 123.2, 116.4, 111.0, 97.3, 61.1, 33.3, 14.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 1710, 1635, 1548, 1526, 1454, 1369, 1299, 1204, 1141, 1026, 955, 785, 725.
MS (EI, 70 eV): 230 (11), 201 (40), 185 (11), 158 (11), 157 (100), 156 (34), 155 (35), 130 (13).
HRMS (EI) for $C_{13}H_{14}N_2O_2$ (230.1055): 230.1048 (M^+).

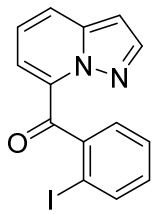
Synthesis of (2-chlorophenyl)(pyrazolo[1,5-*a*]pyridin-7-yl)methanone (134f)



Pyrazolo[1,5-*a*]pyridine **134f** was prepared *via* **TP15** using **128** (59 mg, 0.50 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.60 mL, 0.60 mmol) was added and the reaction warmed to –40 °C and stirred for 10 min. Then, 2-chlorobenzoyl chloride (85 µL, 0.65 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8.1:1.9:0.1) to give **134f** (68 mg, 265 µmol, 53%) as a red solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = δ 7.98 (d, *J* = 2.3 Hz, 1H), 7.80 - 7.73 (m, 1H), 7.68 - 7.64 (m, 1H), 7.50 - 7.43 (m, 1H), 7.43 - 7.36 (m, 2H), 7.19 - 7.14 (m, 2H), 6.65 (d, *J* = 2.3 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = δ 188.3, 142.4, 141.1, 137.8, 136.7, 132.6, 132.5, 130.7, 130.4, 127.2, 122.7, 122.2, 117.9, 98.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 1674, 1622, 1589, 1434, 1306, 1202, 1074, 1035, 892, 798, 746.
MS (EI, 70 eV): 229 (10), 227 (31), 225 (9), 222 (15), 221 (100), 204 (10), 139 (11), 75 (9).
HRMS (EI) for $C_{14}H_9N_2OCl$ (256.0403): 256.0403 (M^+).
M.p. (°C): 120–123.

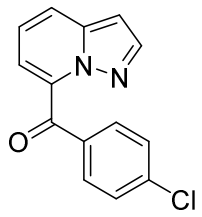
Synthesis of (2-iodophenyl)(pyrazolo[1,5-*a*]pyridin-7-yl)methanone (134g)



Pyrazolo[1,5-*a*]pyridine **134g** was prepared *via* **TP15** using **128** (59 mg, 0.50 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.60 mL, 0.60 mmol) was added and the reaction warmed to –40 °C and stirred for 10 min. Then, 2-iodobenzoyl chloride (175 mg, 0.65 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **134g** (117 mg, 336 µmol, 67%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 (d, *J* = 2.4 Hz, 1H), 7.92 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.79 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.54 - 7.41 (m, 2H), 7.25 - 7.16 (m, 1H), 7.18 - 7.07 (m, 2H), 6.68 (d, *J* = 2.3 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.1, 143.1, 142.7, 141.3, 140.3, 135.0, 132.3, 130.2, 128.3, 123.0, 122.0, 119.4, 98.3, 93.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3079, 2924, 1673, 1622, 1580, 1454, 1305, 1202, 1066, 1014, 885, 797, 740.
MS (EI, 70 eV): 348 (2), 322 (13), 222 (16), 221 (100), 220 (6), 203 (9), 192 (9), 166 (4), 90 (3), 76 (5).
HRMS (EI) for $C_{14}H_9N_2OI$ (347.9760): 347.9745 (M^+).
M.p. (°C): 150–154.

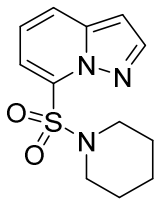
Synthesis of (4-chloroophenyl)(pyrazolo[1,5-*a*]pyridin-7-yl)methanone (134h)



Pyrazolo[1,5-*a*]pyridine **134h** was prepared *via* **TP15** using **128** (59 mg, 0.50 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.60 mL, 0.60 mmol) was added and the reaction warmed to –40 °C and stirred for 10 min. Then, 4-chlorobenzoyl chloride (85 µL, 0.65 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **134h** (90 mg, 351 µmol, 70%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.95 (d, *J* = 2.3 Hz, 1H), 7.83 (t, *J* = 1.9 Hz, 1H), 7.73 (dd, *J* = 8.9, 1.3 Hz, 1H), 7.66 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1H), 7.57 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.20 (dd, *J* = 8.9, 6.9 Hz, 1H), 6.98 (dd, *J* = 6.8, 1.3 Hz, 1H), 6.65 (d, *J* = 2.3 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 188.4, 142.5, 140.9, 137.8, 136.3, 135.2, 134.0, 130.1, 129.8, 128.2, 122.4, 121.1, 114.3, 97.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 1672, 1626, 1570, 1520, 1454, 1423, 1303, 1264, 1203, 1176, 1149, 1058, 904, 791, 738, 675.
MS (EI, 70 eV): 256 (8), 255 (13), 229 (33), 228 (13), 227 (100), 192 (8).
HRMS (EI) for $C_{14}H_8N_2OCl$ (255.0325): 255.0318 (M^+-H).
M.p. (°C): 80–83.

Synthesis of 7-(piperidin-1-ylsulfonyl)pyrazolo[1,5-*a*]pyridine (134i)



Adapted from a literature procedure,[100] DABSO (608 mg, 2.52 mmol) was dried *in vacuo* for 15 min, suspended in THF (10 mL) and then cooled to –40 °C. In a separate flask, pyrazolo[1,5-*a*]pyridine **1** (119 mg, 1.00 mmol) was dissolved in THF (4 mL) and cooled to –78 °C. Then TMPMgCl·LiCl (0.96 mL, 1.2 mmol) was added dropwise and the reaction stirred for 15 min. The formed magnesium species was then added dropwise to the DABSO suspension, and the reaction mixture stirred for 1 h at –40 °C. Then, sulfuryl chloride (0.105 mL, 1.30 mmol) was added dropwise to the reaction mixture and stirred for 20 min. Then, piperidine (1.00 mL, 10 mmol) was added to the reaction mixture, which was then slowly warmed to 25 °C and stirred for 12 h. After quenching with water (40 mL) and extraction with ethyl acetate (3 x 25 mL), the organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 7.5:2.5:0.1) to give **134i** (146 mg, 0.55 mmol, 55%) as a brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 (d, *J* = 2.3 Hz, 1H), 7.72 (dd, *J* = 8.9, 1.3 Hz, 1H), 7.57 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.16 (dd, *J* = 8.8, 7.1 Hz, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 3.50 - 3.45 (m, 4H), 1.63 - 1.55 (m, 4H), 1.54 - 1.47 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.3, 141.5, 136.5, 122.2, 121.9, 116.8, 98.4, 47.4, 26.0, 23.8.

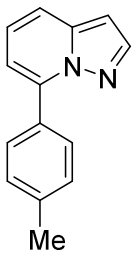
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2939, 2856, 1626, 1508, 1444, 1340, 12961164, 1139, 1052, 946, 795, 712.

MS (EI, 70 eV): 265 (1), 118 (100), 91 (11), 88 (10), 84 (42), 70 (15), 61 (22), 45 (16), 43 (76).

HRMS (EI) for $C_{12}H_{15}N_3O_2S$ (265.0885): 265.0863 (M^+).

M.p. (°C): 147–148.

Synthesis of 7-(p-tolyl)pyrazolo[1,5-*a*]pyridine (134j)



Pyrazolo[1,5-*a*]pyridine **134j** was prepared *via* **TP15** using **128** (59 mg, 0.50 mmol) and TMPMgCl·LiCl (0.48 mL, 0.60 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (0.60 mL, 0.60 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (9 mg, 15 µmol), tfp (7 mg, 30 µmol) and 4-iodotoluene (98 mg, 0.45 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **134j** (65 mg, 312 µmol, 69%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.98 (d, *J* = 2.3 Hz, 1H), 7.82 - 7.76 (m, 2H), 7.54 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.36 - 7.31 (m, 2H), 7.17 (dd, *J* = 8.8, 6.9 Hz, 1H), 6.80 (dd, *J* = 6.9, 1.4 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 1H), 2.44 (s, 3H).

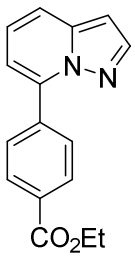
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 141.5, 141.3, 140.8, 139.5, 131.1, 129.2, 129.2, 123.5, 116.9, 112.2, 97.2, 21.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3031, 2920, 1629, 1544, 1504, 1449, 1302, 1196, 1154, 908, 818, 778, 728.

MS (EI, 70 eV): 208 (41), 208 (10), 207 (100), 192 (6), 103 (7).

HRMS (EI) for $C_{14}H_{11}N_2$ (207.0922): 207.0916 (M^+-H).

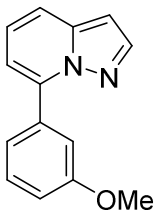
Synthesis of ethyl 4-(pyrazolo[1,5-*a*]pyridin-7-yl)benzoate (134k)



Pyrazolo[1,5-*a*]pyridine **134k** was prepared *via* **TP16** using **128** (59 mg, 0.50 mmol) and TMPZnCl·LiCl (0.79 mL, 0.60 mmol). After the metalation was complete, $Pd(dba)_2$ (9 mg, 15 µmol), tfp (7 mg, 30 µmol) and ethyl 4-iodobenzoate (70 µL, 0.40 mmol) were added and the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **134k** (103 mg, 387 µmol, 97%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.24 - 8.14 (m, 2H), 8.03 - 7.96 (m, 3H), 7.59 (dd, *J* = 8.9, 1.3 Hz, 1H), 7.19 (dd, *J* = 8.9, 6.9 Hz, 1H), 6.86 (dd, *J* = 6.9, 1.3 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.3, 141.6, 141.3, 139.6, 138.1, 131.2, 129.8, 129.2, 123.4, 118.0, 113.0, 97.6, 61.2, 14.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 1711, 1268, 1182, 1103, 1021, 791, 769, 698.
MS (EI, 70 eV): 267 (13), 266 (81), 265 (70), 238 (14), 237 (100), 221 (19), 193 (45), 192 (35), 191 (15), 164 (10), 139 (9).
HRMS (EI) for $C_{16}H_{14}N_2O_2$ (266.1055): 266.1047 (M^+).

Synthesis of 7-(3-methoxyphenyl)pyrazolo[1,5-*a*]pyridine (134l)



Pyrazolo[1,5-*a*]pyridine **134l** was prepared *via* **TP16** using **128** (59 mg, 0.50 mmol) and TMPZnCl·LiCl (0.79 mL, 0.60 mmol). After the metalation was complete, $Pd(dba)_2$ (9 mg, 15 µmol), tfp (7 mg, 30 µmol) and 3-iodoanisole (50 µL, 0.42 mmol) were added and the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **134l** (70 mg, 312 µmol, 74%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.98 (d, *J* = 2.3 Hz, 1H), 7.55 (dd, *J* = 8.8, 1.3 Hz, 1H), 7.49 - 7.41 (m, 3H), 7.17 (ddd, *J* = 8.8, 6.8, 0.5 Hz, 1H), 7.03 (ddd, *J* = 7.8, 2.6, 1.5 Hz, 1H), 6.82 (dd, *J* = 6.9, 1.4 Hz, 1H), 6.61 (d, *J* = 2.3 Hz, 1H), 3.87 (s, 3H).

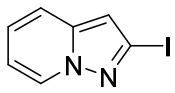
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.6, 141.6, 141.3, 140.5, 135.2, 129.6, 123.4, 121.7, 117.3, 115.2, 114.9, 112.6, 97.3, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2937, 1579, 1522, 1485, 1447, 1305, 1230, 1179, 1045, 852, 778, 728, 694.

MS (EI, 70 eV): 225 (13), 224 (87), 223 (100), 209 (23), 208 (16), 194 (13), 192 (10), 180 (17), 43 (35).

HRMS (EI) for $C_{14}H_{12}N_2O$ (224.0950): 224.0918 (M^+).

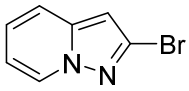
Synthesis of 2-iodopyrazolo[1,5-*a*]pyridine (136a)



Pyrazolo[1,5-*a*]pyridine **136a** was prepared *via* **TP17** using **128** (59 mg, 0.50 mmol), $BF_3 \cdot OEt_2$ (70 µL, 0.55 mmol), TMPMgCl·LiCl (0.48 mL, 0.60 mmol) and iodine (195 mg, 0.75 mmol). The reaction was complete after 12 h. After quenching with a sat. aq. $Na_2S_2O_3$ solution (10 mL) followed by standard work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **136a** (67 mg, 274 µmol, 55%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.44 - 8.38 (m, 1H), 7.48 - 7.42 (m, 1H), 7.14 - 7.07 (m, 1H), 6.72 - 6.64 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 128.2, 124.4, 116.8, 112.0, 105.9, 100.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3107, 2922, 1632, 1508, 1452, 1365, 1328, 1285, 1245, 1142, 937, 762, 735.
MS (EI, 70 eV): 244 (81), 135 (8), 127 (100), 117 (40), 90 (23), 63 (6).
HRMS (EI) for $C_7H_5N_2I$ (243.9497): 243.9490 (M^+).

Synthesis of 2-bromopyrazolo[1,5-*a*]pyridine (136b)

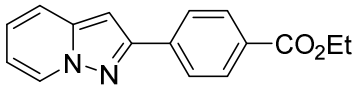


Pyrazolo[1,5-*a*]pyridine **136b** was prepared *via* **TP17** using **128** (590 mg, 5.00 mmol), $BF_3 \cdot OEt_2$ (0.70 mL, 5.50 mmol), TMPMgCl·LiCl (4.80 mL, 6.00 mmol) and dibromotetrachloroethane (3.26 g, 10 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **136b** (908 mg, 4.61 mmol, 92%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.37 (dq, *J* = 7.1, 1.0 Hz, 1H), 7.44 (dt, *J* = 9.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 9.0, 6.8, 1.1 Hz, 1H), 6.74 (td, *J* = 6.9, 1.4 Hz, 1H), 6.52 (d, *J* = 0.9 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 141.8, 130.9, 128.4, 124.6, 117.1, 112.1, 99.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3111, 1633, 1512, 1456, 1371, 1330, 1309, 1249, 1144, 946, 760, 735.

MS (EI, 70 eV): 198 (98), 196 (100), 135 (18), 117 (86), 90 (54), 81 (18), 79 (17), 63 (12).
HRMS (EI) for $C_7H_5N_2Br$ (195.9636): 195.9628 (M^+).
M.p. (°C): 44–46.

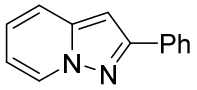
Synthesis of ethyl 4-(pyrazolo[1,5-*a*]pyridin-2-yl)benzoate (136c)



Pyrazolo[1,5-*a*]pyridine **136c** was prepared *via* **TP17** using **128** (59 mg, 0.50 mmol), $BF_3 \cdot OEt_2$ (70 µL, 0.55 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (0.60 mL, 0.60 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (9 mg, 15 µmol), tfp (7 mg, 30 µmol) and ethyl 4-iodobenzoate (70 µL, 0.42 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8.5:1.5:0.1) to give **136c** (75 mg, 282 µmol, 67%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.47 (dq, *J* = 7.0, 1.1 Hz, 1H), 8.16 - 8.08 (m, 2H), 8.06 - 8.00 (m, 2H), 7.52 (dt, *J* = 8.9, 1.3 Hz, 1H), 7.10 (ddd, *J* = 8.9, 6.7, 1.1 Hz, 1H), 6.85 (d, *J* = 0.9 Hz, 1H), 6.76 (td, *J* = 6.9, 1.4 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.6, 152.5, 141.8, 137.6, 130.3, 130.2, 128.7, 126.3, 123.8, 118.3, 112.4, 94.6, 61.1, 14.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3082, 2982, 1708, 1611, 1518, 1431, 1366, 1270, 1180, 1105, 1022, 862, 766, 734, 702.
MS (EI, 70 eV): 281 (11), 267 (16), 266 (100), 238 (48), 237 (17), 225 (19), 222 (11), 221 (80), 207 (35), 193 (37), 192 (35), 166 (23).
HRMS (EI) for $C_{16}H_{14}N_2O_2$ (266.1055): 266.1046 (M^+).
M.p. (°C): 144–146.

Synthesis of 2-phenylpyrazolo[1,5-*a*]pyridine (136d)

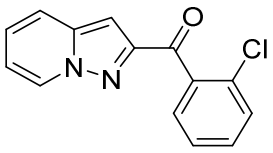


Pyrazolo[1,5-*a*]pyridine **136d** was prepared *via* **TP17** using **128** (59 mg, 0.50 mmol), $BF_3 \cdot OEt_2$ (70 µL, 0.55 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M

$ZnCl_2$ solution in THF (0.60 mL, 0.60 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (9 mg, 15 µmol), tfp (7 mg, 30 µmol) and iodobenzene (45 µL, 0.40 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **136d** (53 mg, 273 µmol, 68%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.48 (dq, *J* = 7.0, 1.0 Hz, 1H), 8.01 - 7.93 (m, 2H), 7.54 - 7.42 (m, 3H), 7.41 - 7.33 (m, 1H), 7.08 (ddd, *J* = 8.9, 6.7, 1.1 Hz, 1H), 6.80 (d, *J* = 0.9 Hz, 1H), 6.73 (td, *J* = 6.9, 1.4 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 153.7, 141.8, 133.4, 128.9, 128.7, 128.5, 126.6, 123.5, 118.1, 111.8, 93.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3086, 2927, 1631, 1509, 1468, 1328, 1252, 1143, 1125, 764, 695.
MS (EI, 70 eV): 195 (13), 194 (100), 193 (52), 192 (12), 166 (12), 103 (18).
HRMS (EI) for $C_{13}H_{10}N_2$ (194.0844): 194.0835 (M^+).
M.p. (°C): 104–107.

Synthesis of (2-chlorophenyl)(pyrazolo[1,5-*a*]pyridin-2-yl)methanone (136e)

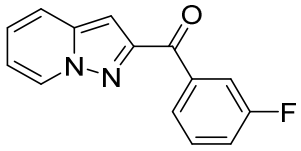


Pyrazolo[1,5-*a*]pyridine **136e** was prepared *via* **TP17** using **128** (59 mg, 0.50 mmol), $BF_3 \cdot OEt_2$ (70 µL, 0.55 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.60 mL, 0.60 mmol) was added and the reaction warmed to –40 °C and stirred for 10 min. Then, 2-chlorobenzoyl chloride (85 µL, 0.65 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **136e** (77 mg, 300 µmol, 60%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.46 (dq, *J* = 7.1, 1.0 Hz, 1H), 7.65 - 7.57 (m, 2H), 7.50 - 7.42 (m, 2H), 7.41 - 7.35 (m, 1H), 7.17 (ddd, *J* = 9.0, 6.7, 1.1 Hz, 1H), 7.09 (d, *J* = 1.0 Hz, 1H), 6.89 (ddd, *J* = 6.7, 1.4 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.0, 151.2, 141.1, 138.6, 132.0, 131.6, 130.4, 130.0, 129.2, 126.5, 124.2, 119.8, 114.6, 100.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3089, 1669, 1590, 1492, 1433, 1388, 1329, 1271, 1223, 1121, 1060, 1023, 899, 752.
MS (EI, 70 eV): 256 (7), 225 (8), 222 (14), 221 (100), 141 (11), 139 (11), 139 (33).
HRMS (EI) for $C_{14}H_9N_2O$ (221.0715): 221.0708 (M^+-Cl).

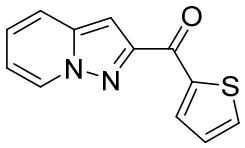
Synthesis of (3-fluorophenyl)(pyrazolo[1,5-*a*]pyridin-2-yl)methanone (136f)



Pyrazolo[1,5-*a*]pyridine **136f** was prepared *via* **TP17** using **128** (59 mg, 0.50 mmol), $BF_3 \cdot OEt_2$ (70 µL, 0.55 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.60 mL, 0.60 mmol) was added and the reaction warmed to –40 °C and stirred for 10 min. Then, 3-fluorobenzoyl chloride (80 µL, 0.65 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **136f** (52 mg, 216 µmol, 43%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.52 (dq, *J* = 7.1, 1.1 Hz, 1H), 8.13 (dt, *J* = 7.7, 1.3 Hz, 1H), 8.07 (ddd, *J* = 9.7, 2.7, 1.5 Hz, 1H), 7.64 (dt, *J* = 9.0, 1.3 Hz, 1H), 7.53 - 7.45 (m, 1H), 7.34 - 7.27 (m, 1H), 7.22 - 7.15 (m, 2H), 6.92 (td, *J* = 6.9, 1.4 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 187.6, 187.5, 163.8, 161.4, 151.2, 140.7, 139.4, 139.3, 130.0, 129.9, 129.1, 126.6, 126.6, 124.2, 120.1, 119.9, 119.6, 117.8, 117.6, 114.4, 100.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3074, 2926, 1645, 1585, 1515, 1480, 1442, 1347, 1331, 1258, 1180, 899, 852, 832, 781, 755.
MS (EI, 70 eV): 240 (46), 123 (26), 123 (100), 113 (12), 95 (10), 75 (11).
HRMS (EI) for $C_{14}H_9N_2OF$ (240.0699): 240.0692 (M^+).
M.p. (°C): 92–96.

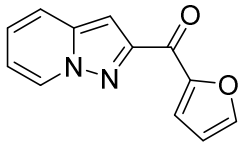
Synthesis of pyrazolo[1,5-*a*]pyridin-2-yl(thiophen-2-yl)methanone (136g)



Pyrazolo[1,5-*a*]pyridine **136g** was prepared *via* **TP17** using **128** (59 mg, 0.50 mmol), $BF_3 \cdot OEt_2$ (70 µL, 0.55 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.60 mL, 0.60 mmol) was added and the reaction warmed to –40 °C and stirred for 10 min. Then, 2-thiophenecarbonyl chloride (70 µL, 0.65 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **136g** (69 mg, 302 µmol, 60%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.58 (dd, *J* = 3.8, 1.2 Hz, 1H), 8.52 (dq, *J* = 6.8, 0.9 Hz, 1H), 7.74 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.63 (dt, *J* = 9.0, 1.2 Hz, 1H), 7.25 - 7.13 (m, 3H), 6.91 (td, *J* = 6.9, 1.4 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 180.1, 151.5, 143.0, 140.8, 136.1, 134.9, 129.1, 128.3, 124.1, 119.6, 114.2, 100.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3108, 2925, 1626, 1514, 1411, 1347, 1250, 1107, 1052, 834, 778, 755, 726.
MS (EI, 70 eV): 228 (43), 225 (19), 209 (7), 207 (8), 111 (100).
HRMS (EI) for $C_{12}H_8N_2OS$ (228.0357): 228.0351 (M^+).
M.p. (°C): 111–114.

Synthesis of furan-2-yl(pyrazolo[1,5-*a*]pyridin-2-yl)methanone (136h)

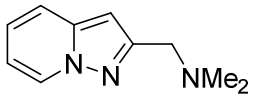


Pyrazolo[1,5-*a*]pyridine **136h** was prepared *via* **TP17** using **128** (59 mg, 0.50 mmol), $BF_3 \cdot OEt_2$ (70 µL, 0.55 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.60 mL, 0.60 mmol) was added and the reaction warmed to –40 °C and stirred for 10 min. Then, 2-furoyl chloride (65 µL, 0.65 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column

chromatography (*iso*hexane:ethyl acetate:triethylamine = 7:3:0.1) to give **136h** (50 mg, 236 µmol, 47%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.51 (dq, *J* = 7.1, 1.1 Hz, 1H), 8.03 (dd, *J* = 3.6, 0.8 Hz, 1H), 7.75 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.62 (dt, *J* = 8.9, 1.3 Hz, 1H), 7.28 - 7.22 (m, 1H), 7.17 (ddd, *J* = 9.0, 6.7, 1.1 Hz, 1H), 6.90 (td, *J* = 6.9, 1.4 Hz, 1H), 6.63 (dd, *J* = 3.6, 1.7 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 175.2, 151.9, 150.7, 147.6, 140.8, 129.0, 124.1, 122.5, 119.6, 114.3, 112.5, 100.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3138, 2925, 1637, 1564, 1494, 1463, 1390, 1330, 1271, 1166, 1118, 1018, 936, 862, 764.
MS (EI, 70 eV): 225 (23), 212 (50), 209 (9), 207 (10), 95 (100), 61 (9), 43 (9).
HRMS (EI) for $C_{12}H_8N_2O_2$ (212.0586): 212.0578 (M^+).
M.p. (°C): 109–112.

Synthesis of N,N-dimethyl-1-(pyrazolo[1,5-*a*]pyridin-2-yl)methanamine (136i)

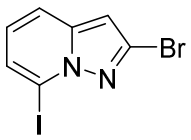


Adapted from a literature procedure,[101b] pyrazolo[1,5-*a*]pyridine **128** (117 mg, 1.00 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. Then, $BF_3 \cdot O_2Et$ (0.16 mL, 1.2 mmol) was added to the mixture and the reaction stirred for 10 min. After cooling to –78 °C, TMPMgCl·LiCl (0.97 mL, 1.30 mmol) was added dropwise and the mixture stirred for 15 min. In a separate flask, *N*,*N*,*N*',*N*'-tetramethylmethanediamine (0.19 mL, 1.50 mmol) was dissolved in DCM (2 mL) and cooled to 0 °C. Then, trifluoroacetic anhydride (0.21 mL, 1.50 mmol) was added dropwise to the diamine and the reaction mixture stirred for 15 min. The formed species was then added dropwise to the organomagnesium solution prepared in the first step, and the resulting reaction mixture stirred for 1.5 h at –78 °C. The reaction was quenched with water (40 mL) and extracted with ethyl acetate (3 x 25 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated *in vacuo* and the crude product purified *via* column chromatography (dichloromethane:methanol:triethylamine = 9:1:0.1) to give **136i** (89 mg, 0.508 µmol, 51%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.42 - 8.35 (m, 1H), 7.51 - 7.44 (m, 1H), 7.09 (ddd, *J* = 9.0, 6.7, 1.1 Hz, 1H), 6.74 (td, *J* = 6.9, 1.4 Hz, 1H), 6.60 (s, 1H), 3.98 (s, 2H), 2.55 (s, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 148.9, 141.3, 128.5, 123.8, 118.2, 112.2, 97.8, 56.3, 44.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3398, 2958, 2781, 1636, 1519, 1466, 1330, 1254, 1054, 1030, 836, 778, 745.
MS (EI, 70 eV): 175 (2), 146 (3), 133 (9), 132 (100), 131 (41), 105 (7), 104 (6), 79 (4), 78 (7), 58 (1).
HRMS (EI) for $C_{10}H_{13}N_3$ (175.1109): 175.1101 (M^+).

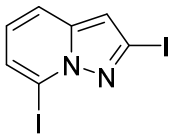
Synthesis of 2-bromo-7-iodopyrazolo[1,5-*a*]pyridine (138a)



Pyrazolo[1,5-*a*]pyridine **138a** was prepared *via* **TP15** using **136b** (99 mg, 0.50 mmol), TMPMgCl·LiCl (0.50 mL, 0.60 mmol) and iodine (200 mg, 0.79 mmol). The reaction was complete after 2 h. After quenching with a sat. aq. $Na_2S_2O_3$ solution (10 mL) followed by standard work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 92:8:1) to give **138a** (105 mg, 325 µmol, 65%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.46 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.31 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.88 (dd, *J* = 8.8, 7.2 Hz, 1H), 6.76 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 141.9, 130.5, 125.0, 124.2, 116.9, 102.0, 91.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3132, 2902, 1618, 1522, 1485, 1425, 1350, 13001180, 1140, 950, 926, 778, 708.
MS (EI, 70 eV): 324 (99), 322 (100), 261 (14), 243 (59), 134 (17), 127 (32), 116 (62).
HRMS (EI) for $C_7H_4N_2IBr$ (321.8603): 321.8598 (M^+).
M.p. (°C): 65–68.

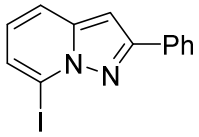
Synthesis of 2-iodo-7-iodopyrazolo[1,5-*a*]pyridine (138b)



Pyrazolo[1,5-*a*]pyridine **138b** was prepared *via* **TP15** using **136a** (122 mg, 0.50 mmol), TMPMgCl·LiCl (0.50 mL, 0.60 mmol) and iodine (190 mg, 0.75 mmol). The reaction was complete after 12 h. After quenching with a sat. aq. $Na_2S_2O_3$ solution (10 mL) followed by standard work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 96:4:1) to give **138b** (90 mg, 243 µmol, 49%) as an orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.46 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.26 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.90 (s, 1H), 6.85 (dd, *J* = 8.8, 7.2 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.1, 124.8, 124.1, 116.5, 108.7, 100.5, 90.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3128, 1613, 1482, 1419, 1343, 1295, 1180, 941, 922, 780, 709.
MS (EI, 70 eV): 370 (46), 261 (17), 243 (17), 127 (100), 116 (16), 42 (31).
HRMS (EI) for $C_7H_4N_2I_2$ (369.8464): 369.8457 (M^+).

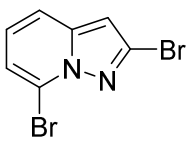
Synthesis of 7-iodo-2-phenylpyrazolo[1,5-*a*]pyridine (138c)



Pyrazolo[1,5-*a*]pyridine **138c** was prepared similar to **TP15** using **136d** (78 mg, 0.40 mmol), TMPMgCl·LiCl (0.78 mL, 1.00 mmol) and iodine (254 mg, 1.00 mmol). The reaction was complete after 12 h. After quenching with a sat. aq. $Na_2S_2O_3$ solution (10 mL) followed by standard work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 94:6:1) to give **138c** (99 mg, 309 µmol, 77%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 - 8.01 (m, 2H), 7.53 - 7.43 (m, 3H), 7.42 - 7.34 (m, 1H), 7.29 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.02 (s, 1H), 6.81 (dd, *J* = 8.7, 7.1 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 152.8, 141.8, 133.0, 128.8, 128.7, 126.8, 124.0, 123.8, 117.8, 96.2, 91.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3067, 1617, 1536, 1486, 1462, 1290, 1194, 928, 767, 691.
MS (EI, 70 eV): 321 (14), 320 (100), 192 (10), 90 (15), 61 (12), 43 (61).
HRMS (EI) for $C_{13}H_9N_2I$ (319.9810): 319.9806 (M^+).

Synthesis of 2,7-dibromopyrazolo[1,5-*a*]pyridine (138d)

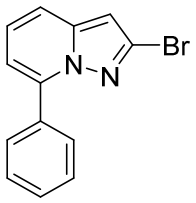


Pyrazolo[1,5-*a*]pyridine **138d** was prepared *via* **TP15** using **136b** (100 mg, 0.50 mmol), TMPMgCl·LiCl (0.50 mL, 0.60 mmol) and 1,2-dibromotetrachloroethane (250 mg, 0.75 mmol). The reaction was complete after 2 h. After work-up, the crude product was purified *via* column

chromatography (*iso*hexane:ethyl acetate:triethylamine = 92:8:1) to give **138d** (94 mg, 341 mmol, 68%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.47 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.10 - 7.01 (m, 2H), 6.70 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 143.1, 131.3, 124.9, 118.4, 116.4, 116.0, 101.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3136, 1624, 1494, 1433, 1355, 1302, 1187, 940, 780, 708.
MS (EI, 70 eV): 278 (49), 276 (100), 274 (51), 215 (17), 213 (18), 197 (76), 195 (79), 116 (67), 115 (10).
HRMS (EI) for $C_7H_4N_2Br_2$ (273.8741): 273.8738 (M^+).
M.p. (°C): 97–101.

Synthesis of 2-bromo-7-phenylpyrazolo[1,5-*a*]pyridine (138e)

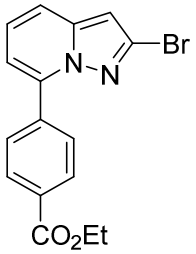


Pyrazolo[1,5-*a*]pyridine **138e** was prepared *via* **TP15** using **136b** (100 mg, 0.50 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (0.60 mL, 0.60 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (9 mg, 15 µmol), tfp (7 mg, 30 µmol) and iodobenzene (50 µL, 0.45 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 95:5:1) to give **138e** (78 mg, 286 µmol, 64%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.94 - 7.86 (m, 2H), 7.54 - 7.47 (m, 3H), 7.45 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.22 (dd, *J* = 8.9, 7.0 Hz, 1H), 6.82 (dd, *J* = 7.0, 1.4 Hz, 1H), 6.62 (s, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.9, 140.5, 133.1, 130.7, 129.8, 129.3, 128.6, 124.8, 115.9, 112.8, 99.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 1630, 1544, 1520, 1489, 1450, 1424, 1352, 1310, 1169, 952, 790, 760, 691.
MS (EI, 70 eV): 274 (55), 273 (97), 272 (58), 271 (100), 193 (12), 192 (54), 166 (47), 164 (16), 140 (22), 139 (24), 97 (26).
HRMS (EI) for $C_{13}H_8N_2Br$ (270.9871): 270.9866 (M^+-H).

M.p. (°C): 112–113.

Synthesis of ethyl 4-(2-bromopyrazolo[1,5-*a*]pyridin-7-yl)benzoate (138f)



Pyrazolo[1,5-*a*]pyridine **138f** was prepared *via* **TP15** using **136b** (100 mg, 0.50 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (0.60 mL, 0.60 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (9 mg, 15 µmol), tfp (7 mg, 30 µmol) and ethyl 4-iodobenzoate (76 µL, 0.45 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **138f** (102 mg, 295 µmol, 66%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.21 - 8.15 (m, 2H), 8.01 - 7.96 (m, 2H), 7.48 (dd, *J* = 8.9, 1.4 Hz, 1H), 7.23 (dd, *J* = 8.9, 7.1 Hz, 1H), 6.86 (dd, *J* = 7.1, 1.4 Hz, 1H), 6.64 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.2, 142.8, 139.4, 137.2, 131.5, 130.8, 129.8, 129.3, 124.7, 116.7, 113.3, 100.2, 61.3, 14.5.

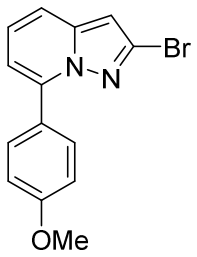
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 1713, 1630, 1435, 1350, 1271, 1170, 1105, 1021, 952, 858, 791, 769, 699.

MS (EI, 70 eV): 346 (13), 344 (14), 343 (10), 317 (10), 315 (11), 299 (17), 281 (23), 227 (10), 227 (16), 226 (13), 225 (100), 209 (38), 207 (65), 192 (14), 191 (11), 191 (14), 164 (14), 151 (12), 73 (14), 43 (17).

HRMS (EI) for $C_{16}H_{13}N_2O_2Br$ (344.0160): 344.0154 (M^+).

M.p. (°C): 121–124.

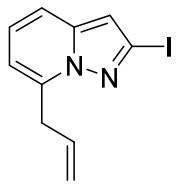
Synthesis of 2-bromo-7-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyridine (138g)



Pyrazolo[1,5-*a*]pyridine **138g** was prepared *via* **TP15** using **136b** (99 mg, 0.50 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (0.60 mL, 0.60 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (9 mg, 15 µmol), tfp (7 mg, 30 µmol) and ethyl 4-iodoanisole (96 mg, 0.40 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **138g** (120 mg, 396 µmol, 99%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.87 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.78 (dd, *J* = 7.0, 1.5 Hz, 1H), 6.60 (s, 1H), 3.88 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.8, 142.9, 140.3, 130.7, 130.6, 125.4, 124.8, 115.3, 114.0, 112.2, 99.7, 55.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932, 1607, 1501, 1435, 1349, 1297, 1251, 1180, 1031, 939, 830, 785, 729.
MS (EI, 70 eV): 305 (16), 304 (99), 303 (13), 303 (82), 302 (100), 301 (86), 223 (21), 208 (37), 207 (21), 196 (21), 192 (19), 180 (26), 179 (57), 153 (20), 152 (12), 81 (23), 79 (22).
HRMS (EI) for $C_{14}H_{11}N_2OBr$ (302.0055): 302.0051 (M^+).
M.p. (°C): 82–86.

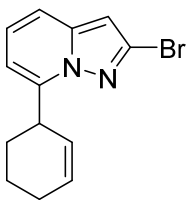
Synthesis of 7-allyl-2-iodopyrazolo[1,5-*a*]pyridine (138h)



Pyrazolo[1,5-*a*]pyridine **138h** was prepared *via* **TP15** using **136a** (61 mg, 0.25 mmol) and TMPMgCl·LiCl (0.25 mL, 0.30 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.30 mL, 0.30 mmol) was added and the reaction stirred for 10 min. Then, allyl bromide (40 mg, 0.33 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 95:5:1) to give **138h** (46 mg, 162 µmol, 65%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.41 - 7.34 (m, 1H), 7.09 (dd, *J* = 8.8, 7.0 Hz, 1H), 6.72 (s, 1H), 6.60 - 6.52 (m, 1H), 6.20 - 6.07 (m, 1H), 5.34 - 5.23 (m, 2H), 3.93 - 3.87 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.2, 140.0, 132.2, 124.3, 119.1, 114.5, 110.1, 106.4, 100.5, 35.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3078, 2922, 1633, 1546, 1516, 1436, 1408, 1355, 1313, 1283, 1247, 1203, 1158, 1100, 1029.
MS (EI, 70 eV): 284 (57), 283 (41), 269 (39), 157 (100), 156 (42), 155 (29), 130 (45), 104 (17), 78 (14), 77 (21), 63 (18), 51 (13).
HRMS (EI) for $C_{10}H_9IN_2$ (283.9810): 283.9805 (M^+).

Synthesis of 2-bromo-7-(cyclohex-2-en-1-yl)pyrazolo[1,5-*a*]pyridine (138i)

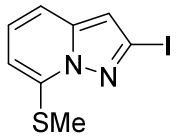


Pyrazolo[1,5-*a*]pyridine **138i** was prepared *via* **TP15** using **136b** (40 mg, 0.20 mmol) and TMPMgCl·LiCl (0.20 mL, 0.24 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.24 mL, 0.24 mmol) was added and the reaction stirred for 10 min. Then, 3-bromocyclohexene (30 µL, 0.27 mmol) was added dropwise, and the reaction slowly warmed to 25 °C

and stirred for 4 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 98:2:1) to give **138i** (31 mg, 112 µmol, 56%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.34 (dd, *J* = 8.9, 1.4 Hz, 1H), 7.12 (dd, *J* = 8.8, 7.0 Hz, 1H), 6.62 (dd, *J* = 7.0, 1.4 Hz, 1H), 6.55 (s, 1H), 6.09 - 6.00 (m, 1H), 5.78 - 5.68 (m, 1H), 4.47 - 4.39 (m, 1H), 2.30 - 2.19 (m, 1H), 2.16 - 2.09 (m, 2H), 1.83 - 1.56 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 144.9, 142.3, 130.8, 130.3, 126.4, 124.6, 114.6, 110.3, 99.5, 35.5, 26.7, 25.3, 20.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 1632, 1546, 1518, 1433, 1361, 1314, 946, 788, 722.
MS (EI, 70 eV): 278 (42), 277 (31), 276 (41), 275 (34), 249 (33), 247 (38), 223 (35), 221 (35), 212 (23), 210 (25), 197 (100), 169 (22), 155 (21), 81 (40), 79 (23), 79 (42).
HRMS (EI) for $C_{13}H_{13}N_2Br$ (276.0262): 276.0252 (M^+).

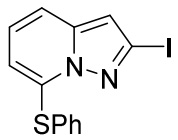
Synthesis of 2-iodo-7-(methylthio)pyrazolo[1,5-*a*]pyridine (138j)



Pyrazolo[1,5-*a*]pyridine **138j** was prepared *via* **TP15** using **136a** (61 mg, 0.25 mmol), TMPMgCl·LiCl (0.25 mL, 0.30 mmol) and *S*-methyl methanethiosulfonate (42 mg, 0.33 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 15:1:0.1) to give **138j** (38 mg, 131 mmol, 52%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.31 - 7.29 (m, 1H), 7.15 - 7.11 (m, 1H), 6.72 (s, 1H), 6.50 (d, *J* = 7.3, 1H), 2.60 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.1, 139.9, 124.3, 112.1, 107.2, 106.4, 100.9, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2987, 2915, 1905, 1688, 1609, 1532, 1489, 1437, 1416, 1341, 1308, 1280, 1221, 1198, 1152, 1096, 1059.
MS (EI, 70 eV): 291 (11), 290 (100), 257 (46), 163 (31), 136 (29), 117 (16), 90 (33), 63 (13), 62 (11), 45 (14), 43 (40).
HRMS (EI) for $C_8H_7IN_2S$ (289.9375): 289.9369 (M^+).
M.p. (°C): 131–133.

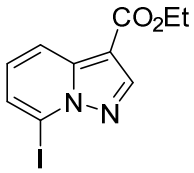
Synthesis of 2-iodo-7-(phenylthio)pyrazolo[1,5-*a*]pyridine (138k)



Pyrazolo[1,5-*a*]pyridine **138k** was prepared *via* **TP15** using **136a** (61 mg, 0.25 mmol), TMPMgCl·LiCl (0.25 mL, 0.30 mmol) and *S*-phenyl benzenethiosulfonate (83 mg, 0.33 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 15:1:0.1 to 15:10:0.1) to give **138k** (56 mg, 159 mmol, 64%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.71 - 7.66 (m, 2H), 7.56 - 7.46 (m, 3H), 7.27 (dd, *J* = 8.8, 1.2 Hz, 1H), 6.95 (dd, *J* = 8.8, 7.4 Hz, 1H), 6.74 (s, 1H), 6.00 (dd, *J* = 7.4, 1.2 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.2, 140.5, 136.2, 130.4, 130.2, 128.4, 124.5, 112.2, 108.6, 106.4, 100.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3134, 3058, 2916, 1614, 1529, 1489, 1440, 1420, 1340, 1308, 1281, 1194, 1148, 1102, 1068, 1024.
MS (EI, 70 eV): 353 (15), 352 (100), 225 (41), 224 (14), 43 (11).
HRMS (EI) for $C_{13}H_9IN_2S$ (351.9531): 351.9526 (M^+).
M.p. (°C): 119–120.

Synthesis of ethyl 7-iodopyrazolo[1,5-*a*]pyridine-3-carboxylate (141a)



Pyrazolo[1,5-*a*]pyridine **141a** was prepared *via* **TP15** using **139** (190 mg, 1.00 mmol), TMPMgCl·LiCl (0.96 mL, 1.20 mmol) and iodine (381 mg, 1.50 mmol). The reaction was complete after 12 h. After quenching with a sat. aq. $Na_2S_2O_3$ solution (10 mL) followed by standard work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **141a** (189 mg, 0.60 mmol, 60%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.48 (s, 1H), 8.20 (dd, *J* = 8.8, 1.3 Hz, 1H), 7.51 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.13 (dd, *J* = 8.8, 7.2 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.6, 144.1, 141.6, 127.7, 125.9, 119.2, 106.4, 92.7, 60.4, 14.6.

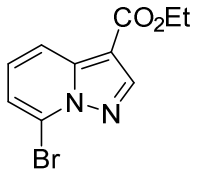
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3098, 2980, 1701, 1622, 1507, 1239, 1198, 1136, 1063, 787.

MS (EI, 70 eV): m/z = 316 (47), 288 (51), 271 (100), 244 (25), 207 (13), 144 (13).

HRMS (EI) for $C_{10}H_9N_2O_2I$ (315.9709): 315.9702 (M^+).

M.p. (°C): 105–108.

Synthesis of ethyl 7-bromopyrazolo[1,5-*a*]pyridine-3-carboxylate (141b)



Pyrazolo[1,5-*a*]pyridine **141b** was prepared *via* **TP15** using **139** (196 mg, 1.03 mmol), TMPMgCl·LiCl (0.96 mL, 1.20 mmol) and 1,2-dibromotetrachloroethane (520 mg, 1.60 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **141b** (189 mg, 0.70 mmol, 68%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm 8.51 (s, 1H), 8.21 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.34 - 7.26 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.3, 144.7, 142.6, 127.6, 119.8, 118.3, 118.2, 106.0, 60.4, 14.6.

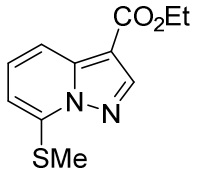
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3102, 2980, 1700, 1626, 1510, 1376, 1304, 1239, 1199, 1146, 1067, 910, 787, 722.

MS (EI, 70 eV): 270 (32), 268 (32), 242 (44), 240 (46), 225 (95), 223 (100), 198 (19), 196 (20), 116 (16).

HRMS (EI) for $C_{10}H_9N_2O_2Br$ (267.9847): 267.9841 (M^+).

M.p. (°C): 70–72.

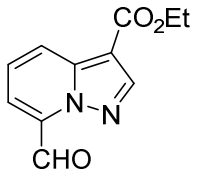
Synthesis of ethyl 7-(methylthio)pyrazolo[1,5-*a*]pyridine-3-carboxylate (141c)



Pyrazolo[1,5-*a*]pyridine **141c** was prepared *via* **TP15** using **139** (95 mg, 0.50 mmol), TMPMgCl·LiCl (0.50 mL, 0.60 mmol) and *S*-methyl methanethiosulfonate (70 µL, 0.75 mmol). The reaction was complete after 6 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 7:3) and HPLC to give **141c** (63 mg, 267 µmol, 53%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.48 - 8.40 (m, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.41 - 7.32 (m, 1H), 6.69 (d, *J* = 7.4 Hz, 1H), 4.36 (q, *J* = 7.0 Hz, 2H), 2.61 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.6, 144.5, 141.7, 141.3, 127.3, 114.3, 108.8, 104.2, 60.1, 14.6, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3115, 3086, 3000, 2981, 2930, 2904, 2861, 1692, 1617, 1507, 1395, 1385, 1345, 1196, 1077, 1024, 924, 810, 779, 726.
MS (EI, 70 eV): 236 (100), 203 (41), 191 (72), 176 (19), 175 (58), 163 (21), 159 (43), 132 (14), 131 (14), 47 (13), 45 (31), 44 (21).
HRMS (EI) for C11H12N2O2S (236.0619): 236.0613 (M^+).
M.p. (°C): 112–123.

Synthesis of ethyl 7-formylpyrazolo[1,5-*a*]pyridine-3-carboxylate (141d)



Pyrazolo[1,5-*a*]pyridine **141d** was prepared *via* **TP15** using **139** (95 mg, 0.50 mmol), TMPMgCl·LiCl (0.50 mL, 0.60 mmol) and 4-formylmorpholine (65 µL, 0.65 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8:2) to give **141d** (50 mg, 0.229 mmol, 46%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 10.91 (d, *J* = 0.6 Hz, 1H), 8.48 (s, 1H), 8.43 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.62 (dd, *J* = 7.1, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.9, 7.1, 0.7 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 184.6, 163.3, 144.9, 141.4, 134.1, 126.3, 124.7, 116.1, 105.7, 60.5, 14.6.

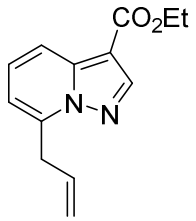
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3110, 2979, 2884, 1692, 1628, 1532, 1422, 1374, 1352, 1242, 1169, 1084, 849, 799, 782, 727.

MS (EI, 70 eV): 218 (24), 207 (15), 205 (15), 191 (10), 190 (100), 173 (81), 162 (23), 145 (47), 144 (12), 118 (18), 117 (13), 117 (47), 91 (11), 90 (28).

HRMS (EI) for $C_{11}H_{10}N_2O_3$ (218.0691): 218.0684 (M^+).

M.p. (°C): 104–106.

Synthesis of ethyl 7-allylpyrazolo[1,5-*a*]pyridine-3-carboxylate (141e)



Pyrazolo[1,5-*a*]pyridine **141e** was prepared *via* **TP15** using **139** (95 mg, 0.50 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.60 mL, 0.60 mmol) was added and the reaction warmed to –40 °C and stirred for 10 min. Then, allyl bromide (55 µL, 0.65 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 2 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **141e** (85 mg, 369 µmol, 74%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.42 (s, 1H), 8.12 - 8.04 (m, 1H), 7.36 (dd, *J* = 8.9, 7.0 Hz, 1H), 6.85 - 6.76 (m, 1H), 6.20 - 6.06 (m, 1H), 5.31 - 5.20 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.94 (d, *J* = 6.7 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

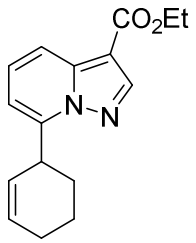
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.8, 144.3, 141.4, 141.2, 132.1, 127.4, 119.0, 117.1, 112.4, 104.2, 60.0, 35.1, 14.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3103, 2983, 2926, 2899, 1690, 1636, 1532, 1477, 1376, 1292, 1231, 1204, 1141, 1087, 999, 976, 918, 846, 794.

MS (EI, 70 eV): 230 (39), 229 (100), 215 (13), 202 (10), 201 (97), 187 (40), 185 (56), 183 (12), 157 (25), 156 (12), 155 (16), 130 (21).

HRMS (EI) for $C_{13}H_{13}N_2O_2$ (229.0977): 229.0971 (M^+-H).
M.p. (°C): 64–65.

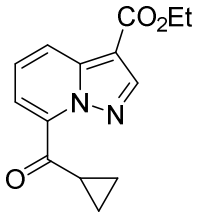
Synthesis of ethyl 7-(cyclohex-2-en-1-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (141f)



Pyrazolo[1,5-*a*]pyridine **141f** was prepared *via* **TP15** using **139** (95 mg, 0.50 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.60 mL, 0.60 mmol) was added and the reaction warmed to –40 °C and stirred for 10 min. Then, 3-bromocyclohexene (75 µL, 0.65 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 2.5 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 10:0.6) to give **141f** (112 mg, 414 µmol, 83%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.43 (s, 1H), 8.07 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.38 (dd, *J* = 8.8, 7.1 Hz, 1H), 6.83 (dd, *J* = 7.1, 1.4 Hz, 1H), 6.12 - 6.03 (m, 1H), 5.82 - 5.72 (m, 1H), 4.54 - 4.45 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.31 - 2.19 (m, 1H), 2.18 - 2.10 (m, 2H), 1.84 - 1.56 (m, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.9, 146.0, 144.2, 141.6, 131.1, 127.5, 126.2, 116.8, 112.2, 104.0, 60.0, 35.8, 27.0, 25.3, 20.2, 14.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2930, 1702, 1635, 1531, 1378, 1234, 1094, 795.
MS (EI, 70 eV): 271 (13), 270 (81), 269 (38), 241 (100), 229 (24), 227 (14), 225 (22), 215 (20), 213 (45), 204 (32), 201 (14), 199 (12), 195 (11), 187 (18), 169 (11).
HRMS (EI) for $C_{16}H_{18}N_2O_2$ (270.1368): 270.1366 (M^+).
M.p. (°C): 53–57.

Synthesis of ethyl 7-(cyclopropanecarbonyl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (141g)



Pyrazolo[1,5-*a*]pyridine **141g** was prepared *via* **TP15** using **139** (95 mg, 0.50 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.60 mL, 0.60 mmol) was added and the reaction warmed to –40 °C and stirred for 10 min. Then, cyclopropanecarbonyl chloride (70 µL, 0.75 mmol) was added dropwise, and the reaction slowly warmed to 25 °C and stirred for 1.5 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8.5:1.5) to give **141g** (70 mg, 271 µmol, 54%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.47 (s, 1H), 8.35 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.47 (dd, *J* = 8.8, 7.1 Hz, 1H), 7.38 (dd, *J* = 7.1, 1.5 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.23 - 3.13 (m, 1H), 1.46 - 1.40 (m, 5H), 1.25 - 1.18 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 196.8, 163.5, 144.7, 141.8, 138.5, 126.7, 122.3, 115.9, 104.8, 60.4, 21.5, 14.6, 14.1.

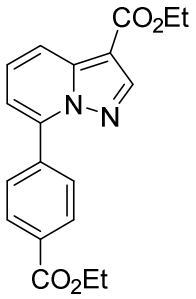
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3103, 2981, 2165, 1701, 1624, 1529, 1481, 1414, 1377, 1306, 1238, 1197, 1172, 1083, 1008, 930, 797, 741, 710.

MS (EI, 70 eV): 259 (12), (258 (57), 257 (12), 230 (16), 229 (100), 228 (31), 228 (27), 214 (12), 213 (38), 202 (37), 201 (15), 185 (11), 145 (17).

HRMS (EI) for $C_{14}H_{14}N_2O_3$ (258.1004): 258.1038 (M^+).

M.p. (°C): 52–54.

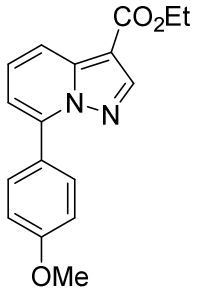
Synthesis of ethyl 7-(4-(ethoxycarbonyl)phenyl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (141h)



Pyrazolo[1,5-*a*]pyridine **141h** was prepared *via* **TP15** using **139** (95 mg, 0.50 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (0.60 mL, 0.60 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (9 mg, 15 µmol), tfp (7 mg, 30 µmol) and ethyl 4-iodobenzoate (76 µL, 0.45 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8.5:1.5) to give **141h** (60 mg, 177 µmol, 39%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.42 (s, 1H), 8.27 - 8.18 (m, 3H), 7.98 - 7.91 (m, 2H), 7.50 (dd, *J* = 8.9, 7.1 Hz, 1H), 7.05 (dd, *J* = 7.1, 1.4 Hz, 1H), 4.49 - 4.34 (m, 4H), 1.48 - 1.37 (m, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.1, 163.7, 144.6, 142.0, 140.5, 137.2, 131.7, 129.8, 129.5, 127.5, 118.8, 115.0, 104.5, 61.4, 60.2, 14.7, 14.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 1701, 1632, 1532, 1507, 1376, 1271, 1242, 1182, 1118, 1049, 917, 859, 798, 772, 736, 700.
MS (EI, 70 eV): 339 (21), 338 (100), 337 (11), 310 (10), 293 (43), 266 (10), 265 (19).
HRMS (EI) for $C_{19}H_{18}N_2O_4$ (338.1267): 338.1263 (M^+).
M.p. (°C): 94–97.

Synthesis of ethyl 7-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (141i)



Pyrazolo[1,5-*a*]pyridine **141i** was prepared *via* **TP15** using **139** (95 mg, 0.50 mmol) and TMPMgCl·LiCl (0.50 mL, 0.60 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (0.60 mL, 0.60 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (9 mg, 15 µmol), tfp (7 mg, 30 µmol) and 4-iodoanisole (105 mg, 0.45 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 8.5:1.5) to give **141i** (100 mg, 337 µmol, 75%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.40 (s, 1H), 8.13 (dd, *J* = 8.8, 1.4 Hz, 1H), 7.84 - 7.75 (m, 2H), 7.41 (dd, *J* = 8.8, 7.1 Hz, 1H), 7.06 - 6.98 (m, 2H), 6.92 (dd, *J* = 7.1, 1.4 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.6, 160.7, 144.3, 141.9, 141.3, 130.8, 127.5, 125.1, 117.2, 113.9, 113.9, 103.9, 59.9, 55.4, 14.6.

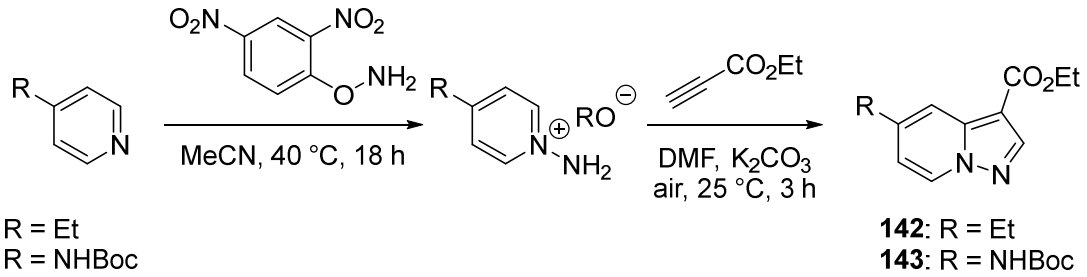
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2988, 2926, 1692, 1611, 1552, 1509, 1439, 1408, 1379, 1346, 1297, 1254, 1231, 1182, 1126, 1112, 1054, 1016, 914, 828, 789, 741.

MS (EI, 70 eV): 297 (18), 296 (100), 295 (14), 268 (17), 267 (41), 251 (56), 224 (18), 223 (26), 179 (14).

HRMS (EI) for $C_{17}H_{16}N_2O_3$ (296.1161): 296.1156 (M^+).

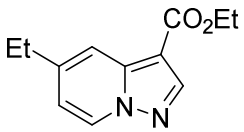
M.p. (°C): 125–126.

Synthesis of ethyl 5-ethylpyrazolo[1,5-*a*]pyridine-3-carboxylate (142) and ethyl 5-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyridine-3-carboxylate (143)



O-(2,4-dinitrophenyl)hydroxylamine was synthesized according to a literature procedure.[143]

Synthesis of ethyl 5-ethylpyrazolo[1,5-*a*]pyridine-3-carboxylate (**142**)



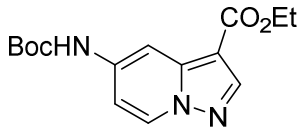
Adapted from a literature procedure,[95i] 4-ethylpyridine (0.57 mL, 5.00 mmol) was dissolved in acetonitrile (30 mL) and then *O*-(2,4-dinitrophenyl)hydroxylamine (996 mg, 5.00 mmol) added. The resulting solution was then stirred at 40 °C for 22 h. Then, the solvent was removed *in vacuo* and the crude redissolved in DMF (15 mL). Then, K_2CO_3 (1.38 g, 10 mmol) and ethyl propiolate (0.51 mL, 5.00 mmol) were added and an air inlet introduced to the solution. After stirring for 3 h at room temperature, an aq. 5% LiCl solution (100 mL) was added and the reaction mixture transferred to a separating funnel. After extraction with ethyl acetate (4 x 100 mL), the organic phase was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The crude product was then purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **142** (620 mg, 2.84 mmol, 57%) as a light yellow solid.

The spectra matched those of the literature.[95i]

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.40 (dd, *J* = 7.1, 0.9 Hz, 1H), 8.34 (s, 1H), 7.94 (m, *J* = 2.3, 1.1 Hz, 1H), 6.80 (dd, *J* = 7.1, 1.9 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.75 (q, *J* = 7.6, 2H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.6 Hz, 3H).

[143] Legault, C.; Charette, A. B., *J. Org. Chem.* **2003,** *68*, 7119–7122.

Synthesis of ethyl 5-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**143**)

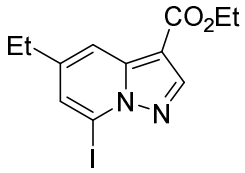


Adapted from a literature procedure,[95i] *tert*-butyl pyridin-4-ylcarbamate (0.971 mg, 5.00 mmol) was dissolved in acetonitrile (30 mL) and then *O*-(2,4-dinitrophenyl)hydroxylamine (996 mg, 5.00 mmol) added. The resulting solution was then stirred at 40 °C for 22 h. Then, the solvent was removed *in vacuo* and the crude redissolved in DMF (15 mL). Then, K_2CO_3 (1.38 g, 10 mmol) and ethyl propiolate (0.51 mL, 5.00 mmol) were added and an air inlet introduced to the solution. After stirring for 3 h at room temperature, an aq. 5%LiCl solution (100 mL) was added and the reaction mixture transferred to a separating funnel. After extraction with ethyl acetate (4 x 100 mL), the organic phase was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The crude product was then purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 7:3:0.1) to give **143** (564 mg, 1.85 mmol, 37%) as yellow solid.

The spectra matched those of the literature.[95i]

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.39 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.32 (s, 1H), 7.98 (dd, *J* = 2.5, 0.8 Hz, 1H), 7.34 - 7.28 (m, 1H), 6.91 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.54 (s, 9H), 1.40 (t, *J* = 7.1 Hz, 3H).

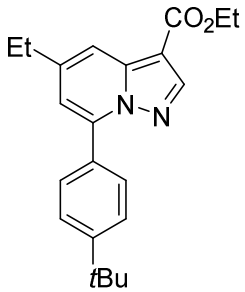
Synthesis of ethyl 5-ethyl-7-iodopyrazolo[1,5-*a*]pyridine-3-carboxylate (144a)



Pyrazolo[1,5-*a*]pyridine **144a** was prepared *via* **TP15** using **142** (22 mg, 0.10 mmol), TMPMgCl·LiCl (0.09 mL, 0,12 mmol) and iodine (40 mg, 0.15 mmol). The reaction was stirred at -78 °C and complete after 40 min. After quenching with a sat. aq. $Na_2S_2O_3$ solution (10 mL) followed by standard work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **144a** (30 mg, 87 µmol, 86%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.41 (s, 1H), 7.99 - 7.95 (m, 1H), 7.37 (d, *J* = 1.8 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.72 (q, *J* = 7.5, 2H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.6 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.8, 145.4, 144.3, 141.8, 127.2, 116.5, 105.3, 92.2, 60.2, 28.3, 14.6, 14.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3098, 2971, 2935, 1697, 1629, 1531, 1507, 1375, 1318, 1234, 1121, 1052, 930, 853, 834, 776.
MS (EI, 70 eV): m/z = 345 (12), 344 (100), 316 (18), 299 (77), 272 (18).
HRMS (EI) for $C_{12}H_{13}IN_2O_2$ (344.0022): 344.0011 (M^+).
M.p. (°C): 77–79.

Synthesis of ethyl 7-(4-(*tert*-butyl)phenyl)-5-ethylpyrazolo[1,5-*a*]pyridine-3-carboxylate (144b)

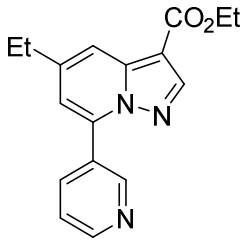


Pyrazolo[1,5-*a*]pyridine **144b** was prepared *via* **TP15** using **142** (85 mg, 0.39 mmol) and TMPMgCl·LiCl (0.35 mL, 0.47 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (0.47 mL, 0.47 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (7 mg, 12 µmol), tfp (5 mg, 24 µmol) and 4-*tert*-butyliodobenzene (81 mg, 0.31 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified

via column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9.5:0.5:0.1) to give **144b** (87 mg, 248 µmol, 80%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.37 (s, 1H), 8.00 - 7.95 (m, 1H), 7.82 - 7.76 (m, 2H), 7.59 - 7.52 (m, 2H), 6.86 (d, *J* = 2.0 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.80 (q, *J* = 7.6, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.38 (s, 9H), 1.34 (t, *J* = 7.6 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.0, 153.0, 145.0, 144.7, 142.3, 141.0, 130.2, 129.1, 125.7, 116.0, 115.1, 103.1, 60.0, 35.0, 31.4, 28.8, 14.7, 14.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2965, 2905, 2871, 1699, 1640, 1534, 1512, 1377, 1235, 1187, 1121, 1056, 834, 779.
MS (EI, 70 eV): m/z = 351 (24), 350 (100), 336 (12), 335 (43), 305 (19).
HRMS (EI) for $C_{22}H_{26}N_2O_2$ (350.1994): 350.1991 (M^+).

Synthesis of ethyl 5-ethyl-7-(pyridin-3-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (144c)



Pyrazolo[1,5-*a*]pyridine **144c** was prepared *via* **TP15** using **142** (92 mg, 0.42 mmol) and TMPMgCl·LiCl (0.40 mL, 0.50 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (0.50 mL, 0.50 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (7 mg, 13 µmol), tfp (6 mg, 26 µmol) and 3-iodopyridine (70 mg, 0.34 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 5:5:0.1) to give **144c** (50 mg, 169 µmol, 50%) as a colorless solid.

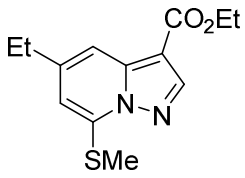
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.99 (d, *J* = 2.3 Hz, 1H), 8.71 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.33 (s, 1H), 8.29 (dt, *J* = 8.0, 2.0 Hz, 1H), 8.02 (d, *J* = 1.0 Hz, 1H), 7.47 - 7.41 (m, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.79 (q, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.6 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.7, 150.7, 149.8, 144.8, 144.6, 142.2, 137.6, 137.0, 129.2, 123.1, 116.3, 116.2, 103.6, 60.0, 28.7, 14.6, 14.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3110, 3030, 2971, 1935, 2883, 1693, 1642, 1533, 1487, 1378, 1237, 1185, 1118, 1059, 1026, 907, 868, 730, 705.

MS (EI, 70 eV): 295 (58), 281 (21), 266 (29), 250 (49), 225 (83), 222 (30), 209 (38), 207 (100), 191 (33), 78 (28), 44 (28).

HRMS (EI) for $C_{17}H_{17}N_3O_2$ (295.1321): 295.1315 (M^+).

M.p. (°C): 108–110.

Synthesis of ethyl 5-ethyl-7-(methylthio)pyrazolo[1,5-*a*]pyridine-3-carboxylate (144d)



Pyrazolo[1,5-*a*]pyridine **144d** was prepared *via* **TP15** using **142** (70 mg, 0.32 mmol), TMPMgCl·LiCl (0.29 mL, 0.39 mmol) and *S*-methyl methanethiosulfonate (61 mg, 0.48 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) and HPLC to give **144d** (53 mg, 0.20 mmol, 62%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.41 (s, 1H), 7.80 - 7.76 (m, 1H), 6.56 (d, *J* = 1.6 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.77 (q, *J* = 7.6, 2H), 2.63 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.6 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.9, 144.9, 144.7, 141.8, 140.8, 112.2, 110.5, 103.3, 60.0, 29.1, 14.8, 14.7, 14.4.

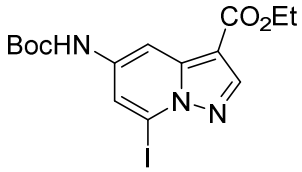
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3077, 2985, 2962, 2934, 1961, 1626, 1516, 1380, 1217, 1177, 1128, 1081, 943, 858, 774.

MS (EI, 70 eV): 264 (100), 231 (58), 219 (44), 203 (50), 187 (31), 118 (10), 49 (12).

HRMS (EI) for $C_{13}H_{16}N_2O_2S$ (264.0932): 264.0924 (M^+).

M.p. (°C): 114–116.

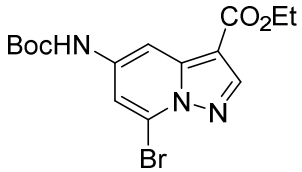
Synthesis of ethyl 5-((*tert*-butoxycarbonyl)amino)-7-iodopyrazolo[1,5-*a*]pyridine-3-carboxylate (145a)



Pyrazolo[1,5-*a*]pyridine **145a** was prepared *via* **TP15** using **143** (20 mg, 66 µmol), TMPMgCl·LiCl (0.11 mL, 144 µmol) and iodine (50 mg, 197 µmol). The reaction was stirred at –78 °C and complete after 50 min. After quenching with a sat. aq. $Na_2S_2O_3$ solution (10 mL) followed by standard work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **145a** (13 mg, 30 µmol, 46%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.37 (s, 1H), 7.98 (s, 2H), 6.86 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.54 (s, 9H), 1.40 (t, *J* = 7.1 Hz, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.8, 152.0, 144.9, 141.7, 138.6, 118.6, 105.2, 104.1, 93.2, 82.3, 60.2, 28.4, 14.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3312, 3124, 2979, 2931, 1732, 1703, 1676, 1629, 1561, 1520, 1239, 1223, 1198, 1153, 1132, 1055, 849, 774.
MS (ESI, 70 eV): m/z = 432 (55), 376 (100), 279 (10).
HRMS (ESI) for $C_{15}H_{19}IN_3O_4$ (432.0420): 432.0412 (M^++H).
M.p. (°C): 172–174.

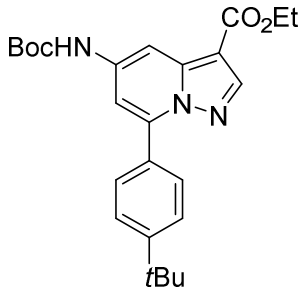
Synthesis of ethyl 7-bromo-5-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyridine-3-carboxylate (145b)



Pyrazolo[1,5-*a*]pyridine **145b** was prepared *via* **TP15** using **143** (62 mg, 0.20 mmol), TMPMgCl·LiCl (0.32 mL, 0.40 mmol) and 1,2-dibromotetrachloroethane (98 mg, 0.30 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **145b** (65 mg, 169 µmol, 83%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.39 (s, 1H), 7.95 (d, *J* = 2.3 Hz, 1H), 7.81 (s, 1H), 6.95 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.54 (s, 9H), 1.40 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.6, 152.0, 145.4, 142.7, 138.9, 120.3, 111.2, 104.7, 103.1, 82.3, 60.2, 28.3, 14.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3310, 2981, 2365, 1734, 1702, 1674, 1636, 1567, 1529, 1242, 1224, 1156, 1134, 1067, 858, 730.
MS (ESI, 70 eV): 386 (55), 330 (100), 328 (98), 302 (15), 282 (5).
HRMS (ESI) for $C_{15}H_{19}BrN_3O_4$ (384.0559): 384.0560 (M^++H).
M.p. (°C): 159–161.

Synthesis of ethyl 5-((*tert*-butoxycarbonyl)amino)-7-(4-(*tert*-butyl)phenyl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (145c)

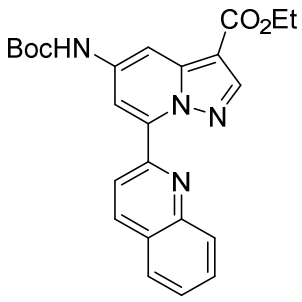


Pyrazolo[1,5-*a*]pyridine **145c** was prepared *via* **TP15** using **143** (81 mg, 0.26 mmol) and TMPMgCl·LiCl (0.42 mL, 0.57 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (0.57 mL, 0.57 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (5 mg, 8 µmol), tfp (4 mg, 16 µmol) and 4-*tert*-butyliodobenzene (55 mg, 0.21 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8.5:1.5:0.1) to give **145c** (90 mg, 206 µmol, 98%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.34 (s, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 7.80 - 7.75 (m, 2H), 7.54 - 7.49 (m, 2H), 7.42 (s, 1H), 7.26 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.53 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.34 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.0, 153.2, 152.3, 145.1, 142.7, 142.0, 139.1, 129.8, 129.1, 125.6, 107.6, 102.8, 81.7, 59.9, 34.9, 31.3, 28.4, 14.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3316, 2967, 1733, 1674, 1639, 1544, 1514, 1235, 1215, 1189, 1153, 1127, 1053, 907, 834, 727.

MS (ESI, 70 eV): 439 (25), 438 (100), 382 (25)
HRMS (ESI) for $C_{25}H_{32}N_3O_4$ (438.2393): 438.2387 (M^++H).
M.p. (°C): 167–168.

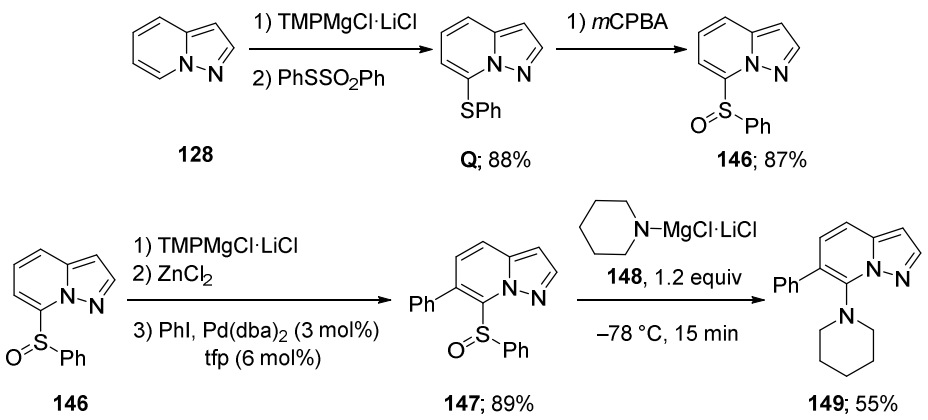
Synthesis of ethyl 5-((*tert*-butoxycarbonyl)amino)-7-(quinolin-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (145d)



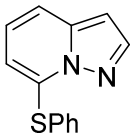
Pyrazolo[1,5-*a*]pyridine **145d** was prepared *via* **TP15** using **143** (81 mg, 0.26 mmol) and TMPMgCl·LiCl (0.42 mL, 0.57 mmol). After the metalation was complete, a 1.0 M $ZnCl_2$ solution in THF (0.57 mL, 0.57 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (5 mg, 8 µmol), tfp (4 mg, 16 µmol) and 2-bromoquinoline (43 mg, 0.21 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **145d** (50 mg, 116 µmol, 55%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.45 (d, *J* = 8.6 Hz, 1H), 8.37 (s, 1H), 8.33 (d, *J* = 2.5 Hz, 1H), 8.31 (d, *J* = 8.6 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 2.5 Hz, 1H), 7.79 - 7.71 (m, 1H), 7.64 - 7.57 (m, 1H), 7.44 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.48 (s, 9H), 1.41 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.8, 152.2, 150.8, 148.2, 145.2, 142.9, 140.2, 139.0, 136.3, 130.1, 129.9, 128.3, 127.7, 127.7, 122.5, 109.6, 104.5, 103.3, 81.7, 60.1, 28.3, 14.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3314, 2979, 2932, 1733, 1701, 1679, 1642, 1561, 1542, 1524, 1505, 1243, 1190, 1156, 1115, 1064, 775, 760, 731.
MS (ESI, 70 eV): 434 (25), 433 (100), 377 (10).
HRMS (ESI) for $C_{24}H_{25}N_4O_4$ (433.1876): 433.1870 (M^++H).

Synthesis of 6-phenyl-7-(piperidin-1-yl)pyrazolo[1,5-*a*]pyridine (149)



Synthesis of 7-(phenylthio)pyrazolo[1,5-*a*]pyridine (Q)



Pyrazolo[1,5-*a*]pyridine **Q** was prepared *via* **TP15** using **128** (1.18 g, 10.0 mmol), TMPMgCl·LiCl (9.60 mL, 12.0 mmol) and *S*-phenyl benzenethiosulfonate (3.76 µL, 15.0 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 10:0.8:0.1) to give **Q** (1.98 g, 8.75 mmol, 88%) as a light yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 (d, *J* = 2.3 Hz, 1H), 7.71 - 7.64 (m, 2H), 7.58 - 7.42 (m, 3H), 7.37 (dd, *J* = 8.8, 1.2 Hz, 1H), 6.95 (dd, *J* = 8.8, 7.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 1H), 6.10 (dd, *J* = 7.3, 1.1 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 141.7, 140.6, 140.3, 135.8, 130.1, 130.1, 129.0, 123.5, 114.1, 109.1, 97.2.

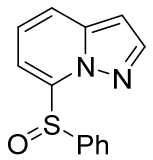
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3076, 1615, 1583, 1531, 1495, 1475, 1440, 1411, 1356, 1306, 1290, 1234, 1206, 1146, 1068, 1055, 1024, 1000.

MS (EI, 70 eV): 226 (100), 225 (90), 198 (15), 193 (50), 192 (12).

HRMS (EI) for $C_{13}H_{10}N_2S$ (226.0565): 226.0559 (M^+).

M.p. (°C): 80–81.

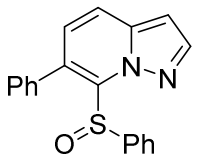
Synthesis of 7-(phenylsulfinyl)pyrazolo[1,5-*a*]pyridine (146)



Pyrazolo[1,5-*a*]pyridine **Q** (1.93 g, 8.52 mmol) was dissolved in DCM (20 mL) and cooled to -30 °C. Then, *m*CPBA (70% in H_2O, 2.31 g, 9.372 mmol) was dissolved in DCM (30 mL) and dried over Na_2SO_4. After drying, the *m*CPBA solution was added dropwise and the reaction mixture stirred for 5 h at –30 °C. The reaction was then quenched with water (50 mL) and extracted with DCM (3 x 50 mL), dried over Na_2SO_4, filtered, and the solvents removed *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 7:3:0.1) to give **146** (1.80 g, 7.43 mmol, 87%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05 - 7.98 (m, 2H), 7.94 (d, *J* = 2.3 Hz, 1H), 7.63 (dd, *J* = 8.8, 1.3 Hz, 1H), 7.55 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.46 - 7.40 (m, 3H), 7.32 (dd, *J* = 8.8, 7.0 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 143.1, 142.4, 142.1, 140.8, 132.0, 129.2, 126.4, 123.4, 119.9, 109.0, 97.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 1624, 1506, 1476, 1444, 1368, 1296, 1225, 119, 1169, 1140, 1082, 1054, 1033.
MS (EI, 70 eV): 242 (100), 225 (17), 194 (50), 193 (90), 167 (10), 149 (11), 133 (56), 105 (11), 77 (21), 42 (42).
HRMS (EI) for $C_{13}H_{10}N_2SO$ (242.0514): 242.0507 (M^+).
M.p. (°C): 110–111.

Synthesis of 6-phenyl-7-(phenylsulfinyl)pyrazolo[1,5-*a*]pyridine (147)

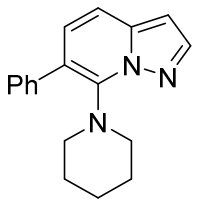


Pyrazolo[1,5-*a*]pyridine **146** (484 mg, 2.00 mmol) was dissolved in THF (10 mL) and cooled to –30 °C. Then, TMPMgCl·LiCl (1.76 mL, 2.20 mmol) was added dropwise and the reaction stirred for 15 min at the same temperature. Then, a 1.0 M $ZnCl_2$ solution in THF (2.20 mL, 2.20 mmol) was added dropwise and the reaction mixture stirred for 20 min. Then, $Pd(dba)_2$ (35 mg, 60 µmol), tfp (28 mg,

120 µmol) and iodobenzene (224 µL, 2.20 mmol) were added, the reaction warmed to 25 °C and stirred for 12 h. After quenching with water, the mixture was extracted with ethyl acetate (3 x 50 mL), dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 7:3:0.1) to give **147** (568 mg, 1.77 mmol, 89%) as a yellow-orange solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.95 (d, *J* = 2.3 Hz, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.69 - 7.64 (m, 2H), 7.56 - 7.45 (m, 5H), 7.41 - 7.35 (m, 3H), 7.16 (d, *J* = 9.0 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.3, 141.1, 140.0, 136.2, 135.9, 132.3, 130.3, 130.0, 128.5, 128.4, 125.9, 125.1, 121.3, 98.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 1731, 1615, 1475, 1443, 1408, 1281, 1199, 1086, 1050, 814, 746, 727, 696, 693.
MS (EI, 70 eV): 319 (18), 318 (82), 302 (15), 301 (46), 270 (38), 269 (100), 225 (54), 224 (52), 209 (20), 198 (17), 192 (19), 182 (29), 166 (18), 140 (25), 139 (24), 77 (18).
HRMS (EI) for $C_{19}H_{14}N_2SO$ (318.0827): 318.0831 (M^+).
M.p. (°C): 66–70.

Synthesis of 6-phenyl-7-(piperidin-1-yl)pyrazolo[1,5-*a*]pyridine (149)



Pyrazolo[1,5-*a*]pyridine **147** (64 mg, 0.20 mmol) was dissolved in THF (1 mL) and cooled to -78 °C. In a separate flask, piperidine (24 µL, 0.24 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. Then, *i*PrMgCl·LiCl (0.15 mL, 0.24 mmol) was added and the reaction stirred for 15 min at 0 °C and then 15 min at 25 °C The formed magnesium amide was then transferred dropwise to the solution of **147** and stirred at the same temperature for 40 min. The reaction was quenched with water and extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 10:0.2:0.1) to give **149** (30.4 mg, 110 µmol, 55%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.92 (d, *J* = 2.2 Hz, 1H), 7.44 - 7.32 (m, 2H), 7.31 - 7.24 (m, 3H), 7.21 (d, *J* = 8.9 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 2.98 (s, 4H), 1.52 (m, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 143.8, 141.4, 141.2, 139.6, 129.9, 128.4, 128.3, 126.9, 118.4, 112.1, 96.8, 51.2, 26.2, 24.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3053, 3026, 2930, 2848, 1622, 1599, 1520, 1491, 1443, 1292, 1276, 1100, 1029, 919, 798, 768, 700.

MS (EI, 70 eV): 277 (48), 276 (100), 248 (15), 220 (16), 209 (14), 208 (13), 194 (70), 193 (17), 166 (19), 139 (11).

HRMS (EI) for $C_{18}H_{19}N_3$ (277.1579): 277.1580 (M^+).

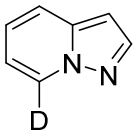
6.3 Regioselectivity Investigations

To determine the regioselectivity of the metalation, both X-Ray crystallography (see chapter 9) and deuteration experiments were carried out.

Regioselectivity Investigations

Starting from pyrazolo[1,5-*a*]pyridines **128**, **139**, and **143**, the corresponding metal species, which were prepared according to **TP15**, were quenched with a D_2O / THF solution and the obtained deuterium-incorporated product analyzed *via* ^1H NMR spectroscopy. The measured spectra were also compared with the respective starting material spectra.

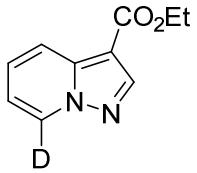
Synthesis of pyrazolo[1,5-*a*]pyridine-7-*d*



Pyrazolo[1,5-*a*]pyridine-7-*d* was prepared *via* **TP15** using **128** (59 mg, 0.50 mmol) and TMPMgCl·LiCl (0.51 mL, 0.60 mmol). Then, a solution of D_2O (0.05 mL, 2.78 mmol) in THF (2 mL) was added dropwise and the reaction mixture warmed to room temperature and stirred for 1 h. After work-up and purification *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) pyrazolo[1,5-*a*]pyridine-7-*d* was obtained (39 mg, 330 µmol, 66%) as a light yellow oil. NMR-spectroscopy revealed an incorporation of deuterium at position C7 with a ^2H:^1H ratio of 75:25.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.48 (d, *J* = 7.0 Hz, 1D), 7.95 (d, *J* = 2.2 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 1H), 7.09 (dd, *J* = 8.9, 6.7 Hz, 1H), 6.74 (d, *J* = 6.2 Hz, 1H), 6.51 (d, *J* = 2.2 Hz, 1H).

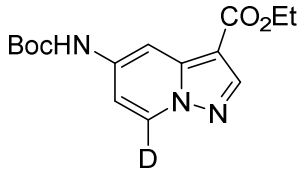
Synthesis of ethyl pyrazolo[1,5-*a*]pyridine-3-carboxylate-7-*d*



Ethyl pyrazolo[1,5-*a*]pyridine-3-carboxylate-7-*d* was prepared *via* **TP15** using **139** (95 mg, 0.50 mmol) and TMPMgCl·LiCl (0.51 mL, 0.60 mmol). Then, a solution of D_2O (0.05 mL, 2.78 mmol) in THF (2 mL) was added dropwise and the reaction mixture warmed to room temperature and stirred for 1 h. After work-up, ethyl pyrazolo[1,5-*a*]pyridine-3-carboxylate-7-*d* was obtained (85 mg, 445 µmol, 89%) as a light yellow oil. NMR-spectroscopy revealed an incorporation of deuterium at position C7 with a ^2H:^1H ratio of 80:20.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.53 (d, *J* = 6.9 Hz, 1D), 8.41 (s, 1H), 8.17 (d, *J* = 8.9 Hz, 1H), 7.41 (dd, *J* = 8.9, 6.8 Hz, 1H), 6.95 (d, *J* = 6.8 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

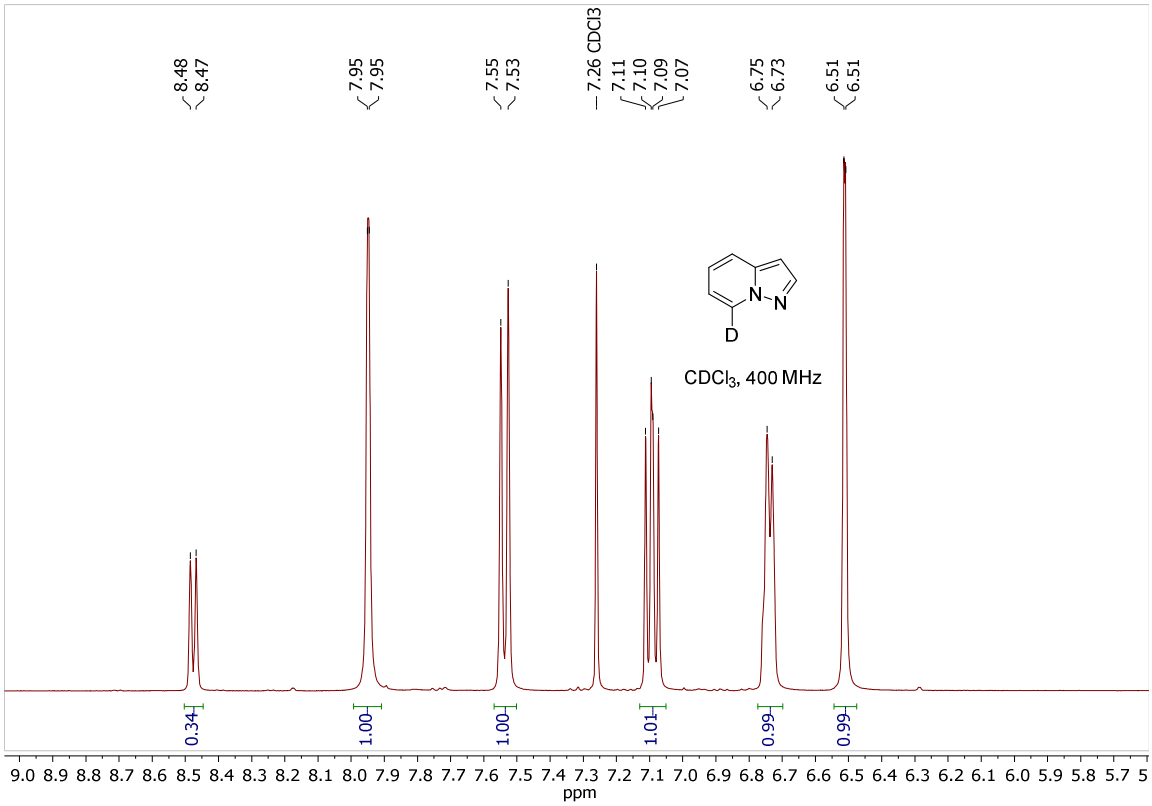
Synthesis of ethyl 5-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyridine-3-carboxylate-7-*d*



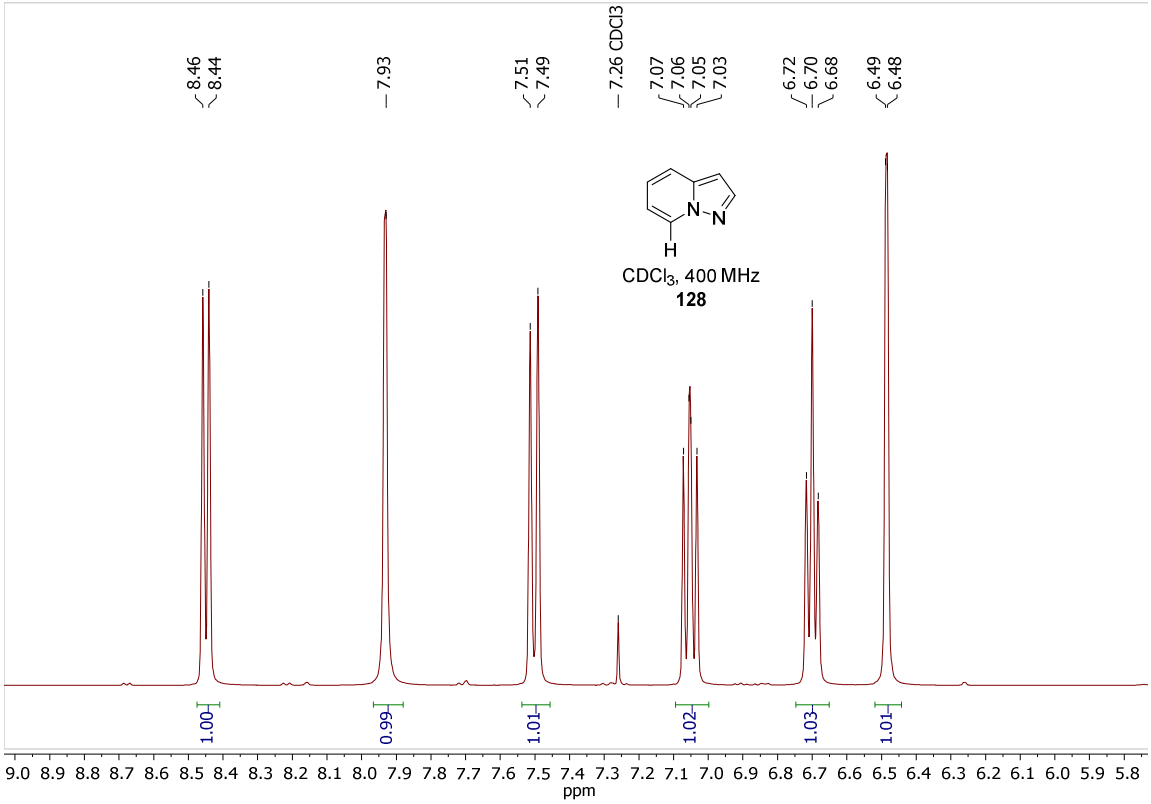
Ethyl 5-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyridine-3-carboxylate-7-*d* was prepared *via* **TP15** using **143** (19 mg, 33 µmol) and TMPMgCl·LiCl (0.06 mL, 75 µmol). Then, a solution of D_2O (0.05 mL, 2.78 mmol) in THF (2 mL) was added dropwise and the reaction mixture warmed to room temperature and stirred for 1 h. After work-up, Ethyl 5-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyridine-3-carboxylate-7-*d* was obtained (10 mg, 33 µmol, 52%) as a light yellow solid. NMR-spectroscopy revealed an incorporation of deuterium at position C7 with a ^2H:^1H ratio of 81:19.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.39 (d, *J* = 7.6 Hz, 1D), 8.32 (s, 1H), 7.98 (d, *J* = 2.5 Hz, 1H), 7.32 (s, 1H), 7.03 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.53 (s, 9H), 1.40 (t, *J* = 7.1 Hz, 3H).

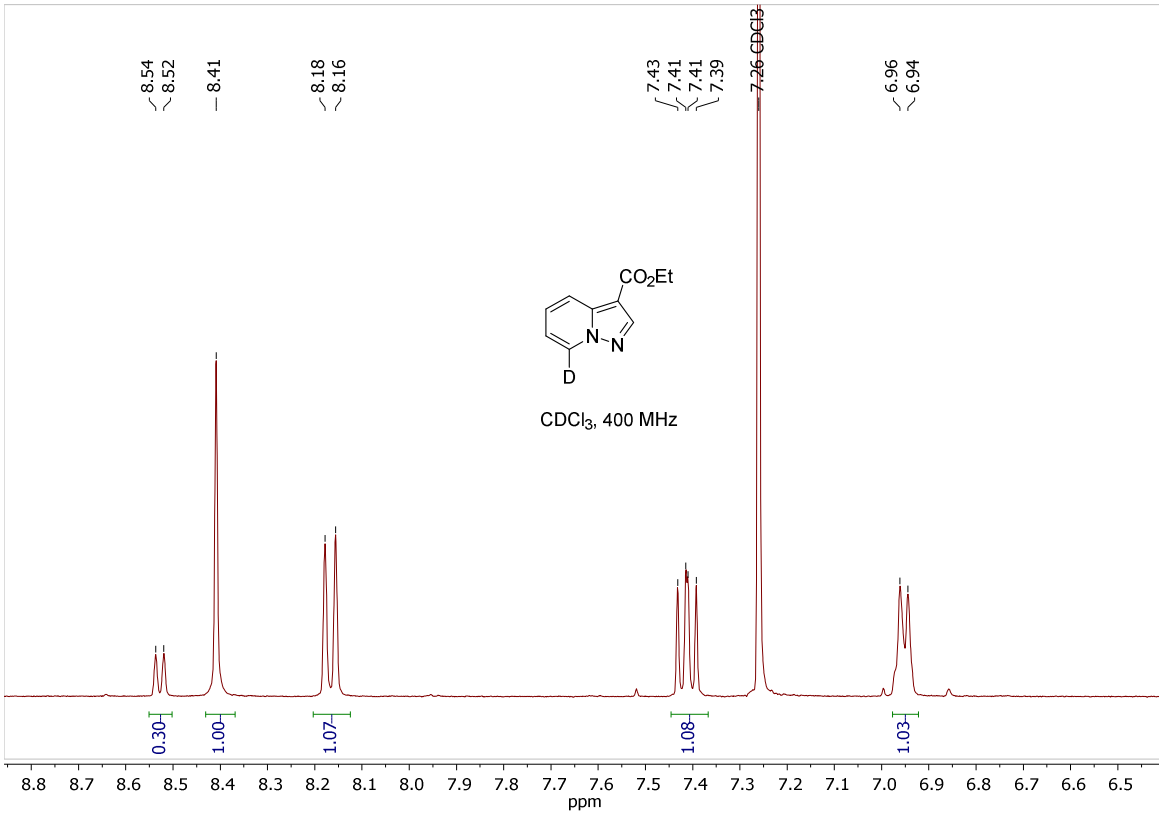
^{1}H NMR spectrum of pyrazolo[1,5-*a*]pyridine-7-*d*



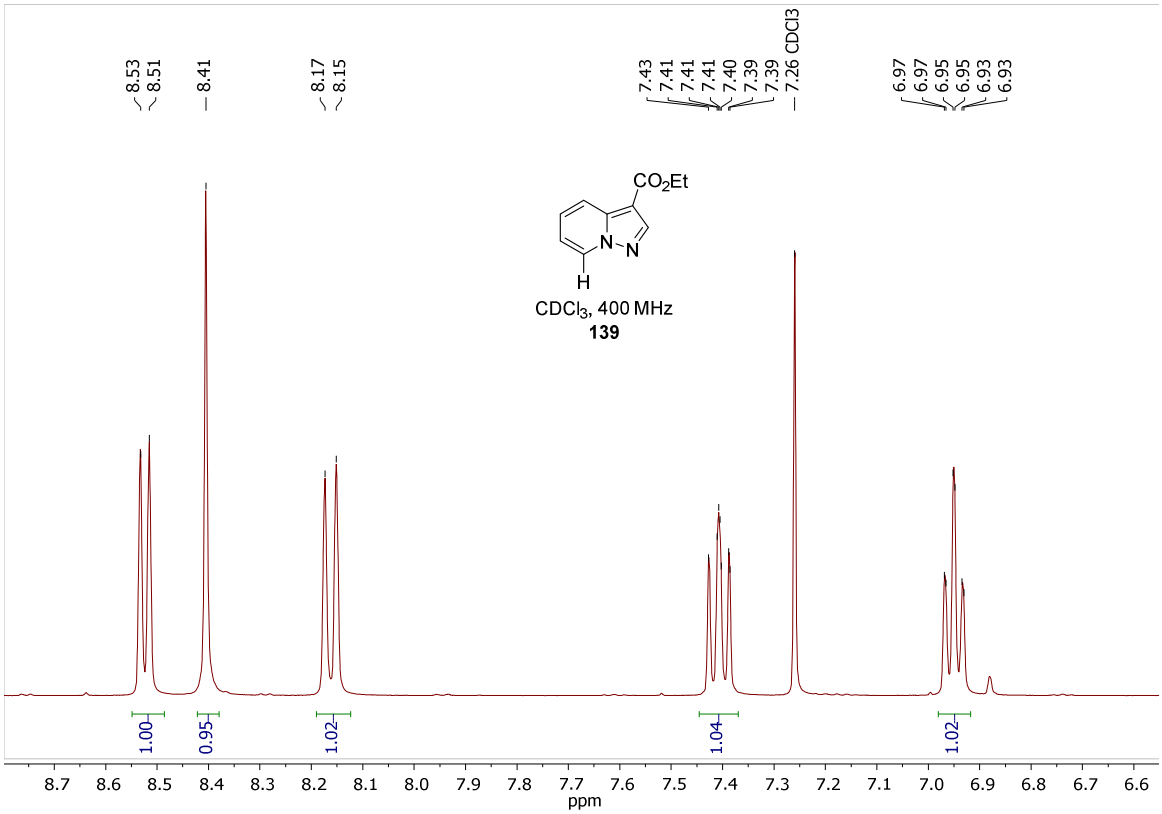
^{1}H NMR spectrum of pyrazolo[1,5-*a*]pyridine



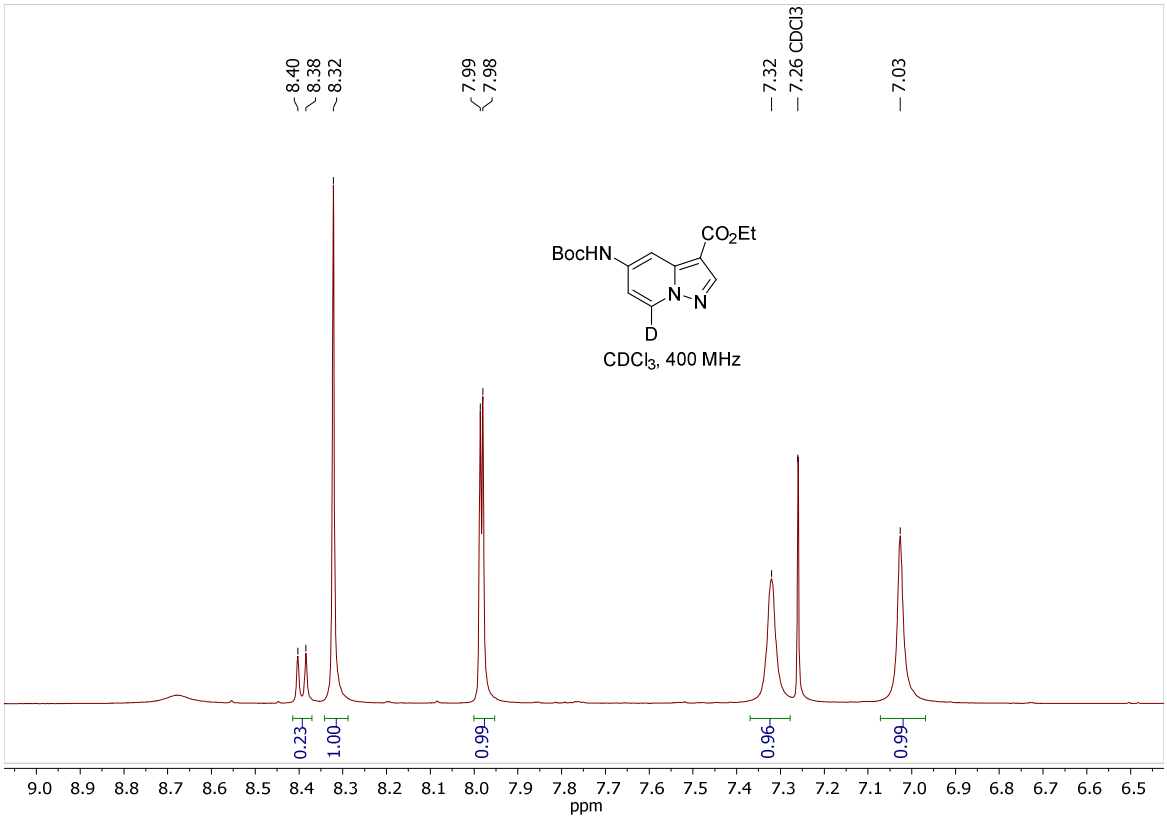
^{1}H NMR spectrum of ethyl pyrazolo[1,5-*a*]pyridine-3-carboxylate-7-*d*



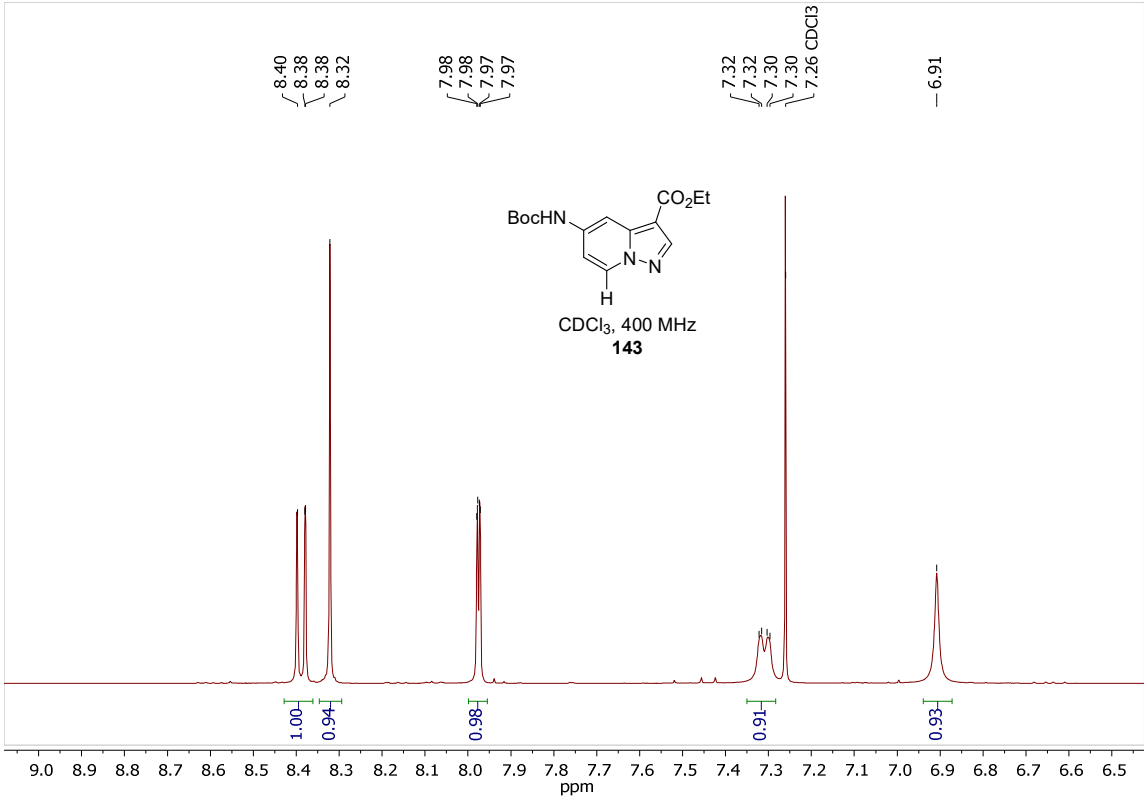
^{1}H NMR spectrum of ethyl 5-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyridine-3-carboxylate **12** (for comparison)



^{1}H NMR spectrum of ethyl 5-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyridine-3-carboxylate-7-*d*



^{1}H NMR spectrum of ethyl 5-((*tert*-butoxycarbonyl)amino)pyrazolo[1,5-*a*]pyridine-3-carboxylate **16** (for comparison)



7 Lewis Acid Directed Regioselective Metalations of Pyridazine

7.1 Typical Procedures

Typical Procedure 18: Metalation and functionalization of pyridazine in the C3 position using $BF_3 \cdot OEt_2$ and TMPZnCl·LiCl.

Pyridazine (**150**) was dissolved in THF (5 mL/mmol pyridazine) and cooled to 0 °C. $BF_3 \cdot OEt_2$ (1.1 equiv) was added dropwise and the reaction mixture stirred for 10 min. TMPZnCl·LiCl (1.5 equiv) was added and the reaction warmed to 25 °C and stirred for 6 h. Then, a solution of the electrophile in THF (5 mL/mmol pyridazine) was added dropwise and the reaction stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 x 30 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. If the crude product needed purification, it was purified via flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 19: Metalation and functionalization of pyridazine (**150**) *via* cross-coupling reactions in the C3 position using $BF_3 \cdot OEt_2$ and TMPZnCl·LiCl

Pyridazine (**150**) was dissolved in THF (5 mL/mmol pyridazine) and cooled to 0 °C. $BF_3 \cdot OEt_2$ (1.1 equiv) was added dropwise and the reaction mixture stirred for 10 min. TMPZnCl·LiCl (1.5 equiv), $Pd(dba)_2$ (4 mol%), tfp (8 mol%) and the aryl iodide (0.8 equiv) were added and the reaction warmed to 25 °C and stirred for 12 h. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 x 30 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. If the crude product needed purification, it was purified via flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 20: Metalation and functionalization of 3-phenylpyridazine (**153**) in the C6 position using TMPLi

Pyridazine **153** was dissolved in THF (5 mL/mmol pyridazine) and cooled to -78 °C. TMPLi (0.95 equiv) was added dropwise and the reaction mixture stirred until full metalation was observed (5 min, checked via TLC). A solution of the electrophile in THF (5 mL/mmol pyridazine) was added dropwise and the reaction slowly warmed to room temperature and stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL) and extracted with ethyl acetate

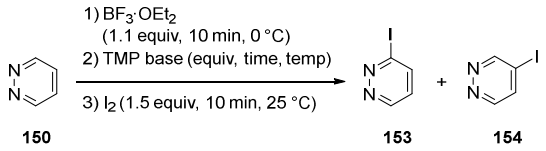
(3 x 30 mL). The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. If the crude product needed purification, it was purified by flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 21: *meta*-Metalation and functionalization of pyridazines in the C5 position using $BF_3 \cdot OEt_2$ and TMPMgCl·LiCl.

The pyridazine was dissolved in THF (5 mL/mmol pyridazine) and cooled to 0 °C. $BF_3 \cdot OEt_2$ (1.1 equiv) was added dropwise and the reaction mixture stirred for 10 min. The reaction was cooled to –78 °C and TMPMgCl·LiCl (2.0 equiv) was added and the reaction stirred for 20 min at the same temperature. A solution of the electrophile in THF (5 mL/mmol pyridazine) was added dropwise and the reaction stirred until completion. The reaction mixture was quenched with an aq. sat. NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 x 30 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. If the crude product needed purification, it was purified via flash chromatography on silica gel using the appropriate eluent.

7.2 Optimization of Reaction Conditions for the Directed *ortho*- and *meta*-Metalation of the Pyridazine Scaffold

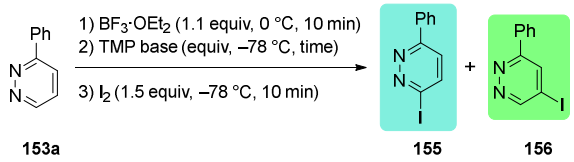
Table 17: Optimization of the reaction conditions for the directed *ortho*-metalation of pyridazine.



entry	TMP base	equiv	time	Temp [°C]	yield[a]	ratio (**153**: **154**)[b]
1	TMPMgCl·LiCl[c]	1.05	15 min	–78	12%	32:68
2	TMPMgCl·LiCl	1.05	15 min	–78	1%	96:4
3	TMPZnCl·LiCl[c]	1.1	2 h	25	45%	60:40
4	TMPZnCl·LiCl	1.3	2 h	25	45%	96:4
5	TMPZnCl·LiCl	1.5	6 h	25	72% (57%)[d]	97:3
6	TMPZnCl·LiCl	1.1	6 h	25	48%	n.d.
7	TMPZnCl·LiCl	1.3	6 h	25	64%	n.d.
8	TMPZnCl·LiCl	1.4	6 h	25	69%	n.d.

[a] NMR yield using trimethoxybenzene as standard. [b] Determined by NMR analysis. [c] $BF_3{\cdot}OEt_2$ was omitted. [d] Isolated yield of **153**.

Table 18: Optimization of the reaction conditions for the directed *ortho*-and *meta*-metalation of 3-phenylpyridazine.

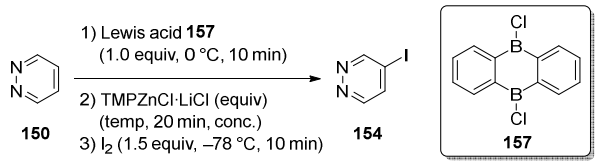


153a **155** **156**

entry	TMP base	$BF_3 \cdot OEt_2$	time	equiv	yield	ratio (**155**:**156**)[a]
1	TMPLi	-	5 min	1.1	43%[b]	95:5
2	TMPLi	-	5 min	0.95	72%[b]	96:4
3	TMPMgCl·LiCl	-	20 min	1.1	0%[c]	-
4	TMPMgCl·LiCl	1.1 equiv	20 min	1.1	65%[c]	44:56
5	TMPMgCl·LiCl	1.1 equiv	20 min	2.0	82%[c] (58%)[b]	27:73
6	TMPMgCl·LiCl	1.1 equiv	20 min	3.0	45%[c]	26:74

[a] Determined by NMR analysis. [b] Isolated yield of the main regioisomer. [c] NMR yield using trimethoxybenzene as standard.

Table 19: Optimization of the reaction conditions for the directed *meta*-metalation of pyridazine.

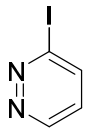


entry	equiv	temp.	conc.	yield[a]	ratio (meta:ortho)[b]
1	1.3	0 °C	0.1 M	40%[c]	99:1
2	1.3	–78 °C	0.1 M	52%	99:1
3	1.3	–78 °C	0.05 M	62%	99:1
4	2.0	–78 °C	0.07 M	69%	99:1
5	1.7	–78 °C	0.07 M	86% (63%)[c]	99:1
6	1.3	–78 °C	0.1 M	0%[d]	-

[a] NMR yield using trimethoxybenzene as standard. [b] Determined by NMR analysis. [c] Isolated yield. [d] The Lewis acid **157** was omitted.

7.3 Preparation of Compounds 150 to 160

Synthesis of 3-iodopyridazine (153)

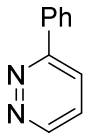


Pyridazine **153** was prepared *via* **TP18** using pyridazine (92 mg, 1.15 mmol), $BF_3 \cdot OEt_2$ (0.16 mL, 1.26 mmol), TMPZnCl·LiCl (2.08 mL, 1.73 mmol), and iodine (438 mg, 1.72 mmol). The reaction was complete after 1 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 6:4:0.1) to give **153** (134 mg, 0.65 mmol, 57%) as a light yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.15 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.88 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.16 (dd, *J* = 8.6, 4.8 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 150.6, 137.3, 127.2, 125.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3020, 1554, 1409, 1362, 1108, 1068, 980, 806, 710.
MS (EI, 70 eV): m/z (%) = 206 (100), 128 (10), 125 (5).
HRMS (EI) for $C_4H_4IN_2$ (206.9419): 206.9414 (M^++H^+).
M.p. (°C): 122–124.

The spectra matched those of the literature.[104b]

Synthesis of 3-phenylpyridazine (153a)



Pyridazine **153a** was prepared *via* **TP19** using pyridazine (45 mg, 0.56 mmol), $BF_3 \cdot OEt_2$ (0.08 mL, 0.62 mmol), and TMPZnCl·LiCl (1.01 mL, 0.84 mmol). After the metalation was complete, iodobenzene (93 mg, 0.457 µmol), $Pd(dba)_2$ (13 mg, 22 µmol), and tfp (11 mg, 45 µmol) was added and the reaction stirred at 25 °C for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 6:4:0.1) to give **153a** (48 mg, 0.31 mmol, 68%) as a light yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.15 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.10 - 8.05 (m, 2H), 7.85 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.56 - 7.48 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.6, 150.1, 136.5, 130.2, 129.2, 127.3, 126.9, 124.0.

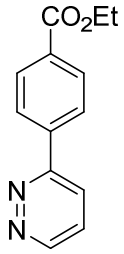
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3080, 3053, 3034, 1575, 1452, 1433, 1374, 1316, 1156, 1100, 981, 824, 760, 746, 698.

MS (EI, 70 eV): m/z (%) = 157 (10), 156 (100), 128 (17), 102 (79), 76 (7).

HRMS (EI) for $C_{10}H_8N_2$ (156.0687): 156.0681 (M^+).

M.p. (°C): 106–107.

Synthesis of ethyl 4-(pyridazin-3-yl)benzoate (153b)



Pyridazine **153b** was prepared *via* **TP19** using pyridazine (83 mg, 1.04 mmol), $BF_3{\cdot}OEt_2$ (0.15 mL, 1.14 mmol), TMPZnCl·LiCl (1.88 mL, 1.56 mmol), ethyl 4-iodobenzoate (230 mg, 0.83 mmol), $Pd(dba)_2$ (23 mg, 40 µmol), and tfp (19 mg, 80 µmol). After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 7:3:0.1) to give **153b** (110 mg, 0.48 mmol, 58%) as a light brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.21 (dt, *J* = 5.0, 1.6 Hz, 1H), 8.18 (qd, *J* = 8.7, 1.7 Hz, 4H), 7.92 (dt, *J* = 8.6, 1.4 Hz, 1H), 7.59 (ddd, *J* = 8.6, 4.9, 1.2 Hz, 1H), 4.41 (qd, *J* = 7.1, 1.2 Hz, 2H), 1.42 (td, *J* = 7.1, 1.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.3, 158.7, 150.5, 140.4, 132.0, 130.3, 127.2, 127.0, 124.4, 61.4, 14.5.

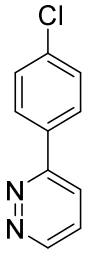
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056, 2984, 2963, 2904, 1707, 1610, 1575, 1416, 1273, 1178, 1112, 1022, 824, 767, 752, 697.

MS (EI, 70 eV): m/z (%) = 228 (72), 227 (15), 200 (70), 184 (11), 183 (100), 155 (35), 146 (45), 129 (14), 129 (51).

HRMS (EI) for $C_{13}H_{12}N_2O_2$ (228.0899): 228.0894 (M^+).

M.p. (°C): 89–91.

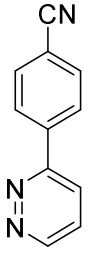
Synthesis of 3-(4-chlorophenyl)pyridazine (153c)



Pyridazine **153c** was prepared *via* **TP19** using pyridazine (85 mg, 1.06 mmol), $BF_3 \cdot OEt_2$ (0.15 mL, 1.17 mmol), and TMPZnCl·LiCl (1.92 mL, 1.59 mmol). After the metalation was complete, 1-chloro-4-iodobenzene (202 mg, 0.85 mmol), $Pd(dba)_2$ (24 mg, 42 µmol), and tfp (20 mg, 85 µmol) was added and the reaction stirred at 25 °C for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 5:5:0.1) to give **153c** (111 mg, 0.58 mmol, 69%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.17 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.07 - 8.01 (m, 2H), 7.84 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.57 - 7.48 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.6, 150.3, 136.7, 134.9, 129.5, 128.5, 127.0, 123.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3080, 3047, 2926, 2854, 1593, 1577, 1488, 1433, 1105, 1092, 1015, 851, 806, 689.
MS (EI, 70 eV): m/z (%) = 192 (18), 190 (55), 162 (10), 138 (32), 136 (100), 75 (6).
HRMS (EI) for $C_{10}H_7ClN_2$ (190.0298): 190.0291 (M^+).
M.p. (°C): 127–129.

Synthesis of 3-(4-chlorophenyl)pyridazine (153d)

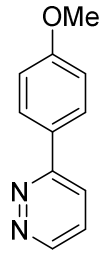


Pyridazine **153d** was prepared *via* **TP19** using pyridazine (95 mg, 1.18 mmol), $BF_3 \cdot OEt_2$ (0.17 mL, 1.38 mmol), and TMPZnCl·LiCl (2.30 mL, 1.77 mmol). After the metalation was complete, 4-iodobenzonitrile (216 mg, 0.94 mmol), $Pd(dba)_2$ (27 mg, 47 µmol), and tfp (22 mg, 94 µmol) was added and the reaction stirred at 25 °C for 12 h. After work-up, the crude product was purified *via* column

chromatography (*iso*hexane:ethyl acetate:triethylamine = 7:3:0.1) to give **153d** (91 mg, 0.50 mmol, 53%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.22 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.23 - 8.17 (m, 2H), 7.91 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.84 - 7.78 (m, 2H), 7.62 (dd, *J* = 8.6, 4.9 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.7, 150.8, 140.5, 132.9, 127.8, 127.2, 124.2, 118.5, 113.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2918, 2888, 2229, 1579, 1505, 1434, 1179, 987, 854, 806, 751.
MS (EI, 70 eV): m/z (%) = 182 (12), 181 (91), 128 (13), 127 (100), 126 (6), 76 (5), 63 (10), 50 (8).
HRMS (EI) for $C_{11}H_7N_3$ (181.0640): 181.0639 (M^+).
M.p. (°C): 152–154.

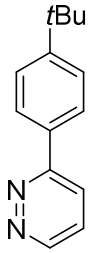
Synthesis of 3-(4-methoxyphenyl)pyridazine (153e)



Pyridazine **153e** was prepared *via* **TP19** using pyridazine (45 mg, 0.56 mmol), $BF_3 \cdot OEt_2$ (0.08 mL, 0.62 mmol), and TMPZnCl·LiCl (1.01 mL, 0.84 mmol). After the metalation was complete, 4-iodoanisole (107 mg, 0.457 µmol), $Pd(dba)_2$ (13 mg, 22 µmol), and tfp (11 mg, 45 µmol) was added and the reaction stirred at 25 °C for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 7:3:0.1) to give **153e** (62 mg, 0.33 mmol, 72%) as a light brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.08 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.07 - 8.01 (m, 2H), 7.78 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.47 (dd, *J* = 8.6, 4.9 Hz, 1H), 7.06 - 6.99 (m, 2H), 3.86 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.4, 159.0, 149.5, 128.8, 128.5, 126.7, 123.1, 114.5, 55.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3051, 3014, 2964, 2936, 2845, 1606, 1578, 1512, 1435, 1251, 1173, 1028, 844, 807, 754, 728.
MS (EI, 70 eV): m/z (%) = 186 (62), 158 (11), 133 (10), 132 (100), 117 (18), 89 (25), 63 (12).
HRMS (EI) for $C_{11}H_{10}N_2O$ (186.0793): 186.0783 (M^+).
M.p. (°C): 111–112.

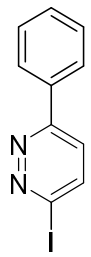
Synthesis of 3-(4-(*tert*-butyl)phenyl)pyridazine (153f)



Pyridazine **153f** was prepared *via* **TP19** using pyridazine (84 mg, 1.05 mmol), $BF_3 \cdot OEt_2$ (0.15 mL, 1.21 mmol), and TMPZnCl·LiCl (1.95 mL, 1.58 mmol). After the metalation was complete, 1-(*tert*-butyl)-4-iodobenzene (0.15 mL, 0.85 mmol), $Pd(dba)_2$ (24 mg, 42 µmol), and tfp (20 mg, 85 µmol) was added and the reaction stirred at 25 °C for 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **153f** (117 mg, 0.55 mmol, 65%) as a brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = (dd, *J* = 5.0, 1.6 Hz, 1H), 8.06 - 8.01 (m, 2H), 7.87 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.59 - 7.51 (m, 3H), 1.38 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.5, 153.6, 149.9, 133.6, 127.0, 126.9, 126.2, 123.8, 34.9, 31.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1565, 1548, 1481, 1459, 1393, 1376, 1279, 1181, 1028, 961, 841, 782.
MS (EI, 70 eV): m/z (%) = 212 (22), 198 (12), 197 (100), 169 (7), 143 (5), 115 (8).
HRMS (EI) for $C_{14}H_{16}N_2$ (212.1313): 212.1310 (M^+).
M.p. (°C): 118–122.

Synthesis of 3-iodo-6-phenylpyridazine (155)

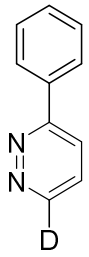


Pyridazine **155** was prepared *via* **TP20** using **153a** (17 mg, 109 µmol), TMPLi (0.17 mL, 104 µmol), and I_2 (41 mg, 0.16 mmol). The reaction was complete after 2 h. After work-up, the crude product was

purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **155** (22 mg, 73 µmol, 70%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 - 8.01 (m, 2H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.56 - 7.49 (m, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.7, 137.6, 135.4, 130.7, 129.3, 127.1, 125.1, 123.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3036, 2920, 1559, 1444, 1392, 1328, 1310, 1255, 1117, 1075, 1026, 856, 777, 741, 694.
MS (EI, 70 eV): m/z (%) = 281 (100), 254 (26), 127 (16), 102 (37), 77 (9).
HRMS (EI) for $C_{10}H_7IN_2$ (281.9654): 281.9649 (M^+).
M.p. (°C): 170–172.

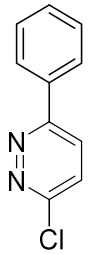
Synthesis of 3-phenylpyridazine-6-*d* (155a)



Pyridazine **155a** was prepared *via* **TP20** using **153a** (15 mg, 96 µmol), TMPLi (0.15 mL, 91 µmol), and D_2O (0.05 mL, 2.78 mmol). The reaction was complete after 1 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 6:4:0.1) to give **155a** (14 mg, 89 µmol, 93%) as a colorless solid. The NMR-spectrum reveals an incorporation of deuterium at position C6 with a ^{2}H:^{1}H ratio of 85:15. Hence, the yield of fully deuterated 3-phenylpyridazine-6-d can be estimated to be 79%.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.17 (dd, *J* = 4.9, 1.6 Hz, 1D), 8.12 - 8.05 (m, 2H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.59 - 7.47 (m, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.7, 150.2, 136.5, 130.3, 129.2, 127.3, 126.8, 124.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3046, 2935, 1569, 1448, 1406, 1312, 1120, 1068, 1024, 974, 908, 878, 749, 698.
MS (EI, 70 eV): m/z (%) = 157 (92), 129 (15), 103 (15), 102 (100), 76 (12).
HRMS (EI) for $C_{10}H_7DN_2$ (157.0750): 157.0745 (M^+).
M.p. (°C): 103–105.

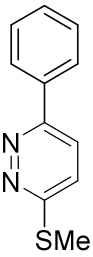
Synthesis of 3-chloro-6-phenylpyridazine (155b)



Pyridazine **155b** was prepared *via* **TP20** using **153a** (39 mg, 0.25 mmol), TMPLi (0.37 mL, 238 µmol), and a precooled solution (-40 °C) of hexachloroethane (93 mg, 0.38 mmol) in THF (1 mL). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **155b** (20 mg, 105 µmol, 44%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.07 - 8.01 (m, 2H), 7.83 (d, *J* = 8.9 Hz, 1H), 7.56 (d, *J* = 9.0 Hz, 1H), 7.55 - 7.50 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.7, 155.7, 135.2, 130.6, 129.3, 128.6, 127.2, 126.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 2924, 2853, 1562, 1446, 1386, 1100, 766, 697.
MS (EI, 70 eV): m/z (%) = 190 (27), 103 (22), 102 (75), 77 (18), 57 (23), 55 (29), 50 (15), 44 (67), 43 (27), 43 (100), 41 (34).
HRMS (EI) for $C_{10}H_7ClN_2$ (190.0298): 190.0297 (M^+).
M.p. (°C): 159–161.

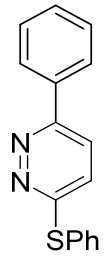
Synthesis of 3-(methylthio)-6-phenylpyridazine (155c)



Pyridazine **155c** was prepared *via* **TP20** using **153a** (39 mg, 0.25 mmol), TMPLi (0.36 mL, 238 µmol), and *S*-methyl methanethiosulfonate (35 µL, 0.38 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **155c** (31 mg, 153 µmol, 64%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 - 8.02 (m, 2H), 7.63 (d, *J* = 9.1 Hz, 1H), 7.53 - 7.44 (m, 3H), 7.38 (d, *J* = 9.1 Hz, 1H), 2.76 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.3, 156.0, 136.2, 129.9, 129.1, 126.7, 126.2, 123.1, 13.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 3038, 2923, 2853, 1581, 1569, 1446, 1402, 1162, 1094, 846, 776, 740.
MS (EI, 70 eV): m/z (%) = 203 (11), 202 (100), 201 (29), 159 (8), 157 (22), 115 (43), 102 (27).
HRMS (EI) for $C_{11}H_{10}N_2S$ (202.0565): 202.0558 (M^+).
M.p. (°C): 136–138.

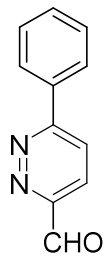
Synthesis of 3-phenyl-6-(phenylthio)pyridazine (155d)



Pyridazine **155d** was prepared *via* **TP20** using **153a** (39 mg, 0.25 mmol), TMPLi (0.36 mL, 238 µmol), and *S*-phenyl benzenethiosulfonate (94 mg, 0.38 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **155d** (44 mg, 166 µmol, 70%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.05 - 8.00 (m, 2H), 7.68 - 7.64 (m, 2H), 7.62 (d, *J* = 9.1 Hz, 1H), 7.53 - 7.44 (m, 6H), 7.13 (d, *J* = 9.0 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 164.1, 156.5, 136.0, 135.4, 130.1, 130.1, 129.8, 129.5, 129.1, 126.9, 125.5, 124.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3049, 2924, 2852, 1474, 1447, 1389, 1138, 1000, 846, 754, 745, 689.
MS (EI, 70 eV): m/z (%) = 264 (15), 263 (100), 135 (15), 115(7).
HRMS (EI) for $C_{16}H_{11}N_2S$ (263.0643): 263.0639 (M^+-H^+).
M.p. (°C): 156–158.

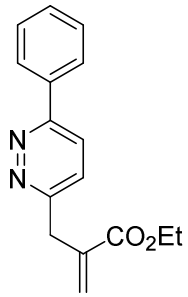
Synthesis of 6-phenylpyridazine-3-carbaldehyde (155e)



Pyridazine **155e** was prepared *via* **TP20** using **153a** (39 mg, 0.25 mmol), TMPLi (0.36 mL, 238 µmol), and 4-formylmorpholine (0.04 mL, 0.38 mmol). The reaction was complete after 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **155e** (20 mg, 109 µmol, 46%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 10.44 (d, *J* = 0.9 Hz, 1H), 8.21 - 8.16 (m, 2H), 8.10 (d, *J* = 8.8 Hz, 1H), 8.04 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.63 - 7.53 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 192.3, 161.4, 154.2, 135.3, 131.4, 129.4, 127.9, 124.9, 124.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3065, 2926, 2836, 1715, 1571, 1452, 1419, 1348, 1116, 779, 743, 689.
MS (EI, 70 eV): m/z (%) = 184 (100), 156 (13), 128 (26), 104 (22), 102 (74), 77 (13), 76 (12), 51 (14).
HRMS (EI) for $C_{11}H_8N_2O$ (184.0637): 184.0628 (M^+).
M.p. (°C): 160–162.

Synthesis of ethyl 2-((6-phenylpyridazin-3-yl)methyl)acrylate (155f)

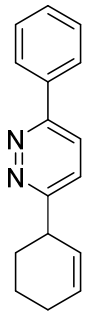


Pyridazine **155f** was prepared *via* **TP20** using **153a** (39 mg, 0.25 mmol), and TMPLi (0.36 mL, 238 µmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.03 mL, 0.25 mmol) was added and the reaction stirred at the same temperature for 20 min. Then, ethyl 2-(bromomethyl)acrylate (72 mg, 0.38 mmol) was added and the reaction slowly warmed to 25 °C over

12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **155f** (28 mg, 104 µmol, 44%) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.10 - 8.05 (m, 2H), 7.81 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.55 - 7.46 (m, 4H), 6.39 (d, *J* = 1.1 Hz, 1H), 5.83 (p, *J* = 1.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.07 (d, *J* = 1.4 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.7, 159.8, 157.7, 137.7, 136.4, 130.0, 129.1, 128.4, 127.4, 127.1, 124.1, 61.1, 38.6, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3031, 2898, 1638, 1458, 1421, 1298, 1200, 1142, 1027, 860, 757, 739, 690.
MS (EI, 70 eV): m/z (%) = 268 (13), 239 (19), 223 (9), 196 (32), 195 (100),194 (9), 102 (13).
HRMS (EI) for $C_{16}H_{16}N_2O_2$ (268.1212): 268.1204 (M^+).

Synthesis of 3-(cyclohex-2-en-1-yl)-6-phenylpyridazine (155g)

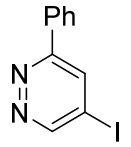


Pyridazine **155g** was prepared *via* **TP20** using **153a** (39 mg, 0.25 mmol), and TMPLi (0.36 mL, 238 µmol). After the metalation was complete, a 1.0 M CuCN·2LiCl solution in THF (0.03 mL, 0.25 mmol) was added and the reaction stirred at the same temperature for 20 min. Then, 3-bromocyclohexene (61 mg, 0.38 mmol) was added and the reaction slowly warmed to 25 °C over 12 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **155g** (26 mg, 110 µmol, 46%) as a light brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 - 8.08 (m, 2H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.57 - 7.48 (m, 3H), 7.46 (d, *J* = 8.8 Hz, 1H), 6.07 - 6.00 (m, 1H), 5.87 - 5.80 (m, 1H), 4.02 - 3.93 (m, 1H), 2.27 - 2.13 (m, 3H), 1.88 - 1.71 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.6, 157.6, 136.6, 130.2, 129.9, 129.1, 127.6, 127.0, 125.9, 124.2, 42.0, 30.7, 25.0, 21.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 3020, 2922, 2856, 2833, 1545, 1449, 1420, 1014, 861, 750, 693.
MS (EI, 70 eV): m/z (%) = 236 (12), 235 (11), 221 (13), 208 (14), 207 (100), 170 (28), 102 (10).

HRMS (EI) for $C_{16}H_{16}N_2$ (236.1313): 236.1308 (M^+).
M.p. (°C): 86–88.

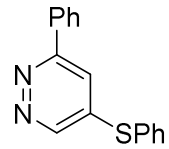
Synthesis of 5-iodo-3-phenylpyridazine (156)



Pyridazine **156** was prepared *via* **TP21** using **153a** (17 mg, 109 µmol), $BF_3 \cdot OEt_2$ (0.015 mL, 0.12 mmol), TMPMgCl·LiCl (0.18 mL, 0.22 mmol) and iodine (83 mg, 0.33 mmol). The reaction was complete after 1 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **156** (17.7 mg, 63 µmol, 58%) as a light brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.39 (d, *J* = 2.0 Hz, 1H), 8.27 (d, *J* = 2.0 Hz, 1H), 8.07 - 8.01 (m, 2H), 7.56 - 7.50 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.7, 156.4, 135.2, 133.0, 130.8, 129.3, 127.4, 101.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3054, 3019, 1546, 1493, 1386, 1364, 1038, 921, 89, 786, 772, 690.
MS (EI, 70 eV): m/z (%) = 283 (10), 282 (100), 155 (25), 127 (60), 126 (21), 77 (9).
HRMS (EI) for $C_{10}H_7IN_2$ (281.9654): 281.9649 (M^+).
M.p. (°C): 129–131.

Synthesis of 3-phenyl-5-(phenylthio)pyridazine (156a)



Pyridazine **156a** was prepared *via* **TP21** using **153a** (40 mg, 256 µmol), $BF_3 \cdot OEt_2$ (0.035 mL, 0.28 mmol), TMPMgCl·LiCl (0.42 mL, 0.51 mmol) and a precooled solution (-40 °C) of *S*-phenyl benzenethiosulfonate (193 mg, 0.77 mmol) in THF (1 mL). The reaction was complete after 10 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **156a** (26 mg, 98 µmol, 38%) as a brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.82 (d, *J* = 2.2 Hz, 1H), 7.97 - 7.90 (m, 2H), 7.66 - 7.60 (m, 2H), 7.56 - 7.51 (m, 3H), 7.51 - 7.46 (m, 3H), 7.39 (d, *J* = 2.2 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.3, 147.3, 144.0, 136.2, 135.4, 130.5, 130.5, 130.2, 129.0, 127.4, 127.3, 119.7.

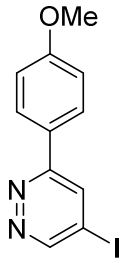
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2999, 2902, 2840, 1552, 1499, 1439, 1375, 1003, 898, 780, 760, 746.

MS (EI, 70 eV): m/z (%) = 265 (12), 264 (70), 263 (100), 235 (13), 234 (27), 202 (17), 134 (41), 127 (12), 126 (13), 121 (17), 77 (10).

HRMS (EI) for $C_{16}H_{12}N_2S$ (264.0721): 264.0722 (M^+).

M.p. (°C): 104–106.

Synthesis of 5-iodo-3-(4-methoxyphenyl)pyridazine (156b)



Pyridazine **156b** was prepared *via* **TP21** using **153e** (18 mg, 97 µmol), $BF_3 \cdot OEt_2$ (0.015 mL, 0.11 mmol), TMPMgCl·LiCl (0.16 mL, 0.195 mmol) and iodine (74 mg, 0.29 mmol). The reaction was complete after 1 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 8:2:0.1) to give **156b** (15 mg, 48 µmol, 50%) as a light brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.31 (d, *J* = 2.0 Hz, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 8.05 - 7.98 (m, 2H), 7.07 - 7.01 (m, 2H), 3.89 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.9, 159.3, 155.7, 132.2, 128.8, 127.5, 114.7, 101.5, 55.6.

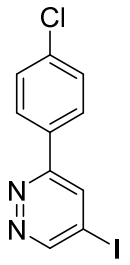
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3021, 3004, 2925, 2854, 1607, 1550, 1515, 1503, 1384, 1245, 1181, 1036, 1025, 989, 835, 826, 813, 673.

MS (EI, 70 eV): m/z (%) = 313 (11), 312 (100), 207 (17), 158 (10), 157 (89), 142 (30), 128 (27), 127 (38), 114 (21), 113 (14).

HRMS (EI) for $C_{11}H_9IN_2O$ (311.9760): 311.9753 (M^+).

M.p. (°C): 152–156 (decomposition).

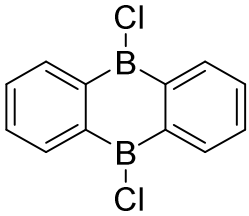
Synthesis of 3-(4-chlorophenyl)-5-iodopyridazine (156c)



Pyridazine **156c** was prepared *via* **TP21** using **153c** (18 mg, 94 µmol), $BF_3 \cdot OEt_2$ (0.015 mL, 103 µmol), TMPMgCl·LiCl (0.155 mL, 0.19 mmol) and iodine (72 mg, 0.28 mmol). The reaction was complete after 1 h. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 9:1:0.1) to give **156c** (15 mg, 47 µmol, 50%) as a light brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.39 (d, *J* = 2.0 Hz, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 8.03 - 7.97 (m, 2H), 7.53 - 7.47 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.6, 156.5, 137.2, 133.5, 132.7, 129.6, 128.6, 101.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3016, 2923, 2854, 1594, 1548, 1489, 1092, 1032, 1012, 898, 831, 796, 704, 671.
MS (EI, 70 eV): m/z (%) = 316 (24), 299 (15), 281 (37), 225 (66), 209 (23), 208 (13), 207 (100), 193 (10), 191 (15), 161 (19), 127 (17), 126 (21), 73 (14).
HRMS (EI) for $C_{10}H_6ClIN_2$ (315.9264): 315.9256 (M^+).
M.p. (°C): 160–164 (decomposition).

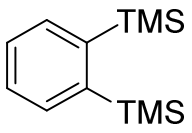
Synthesis of the bidentate Lewis acid 157



The highly moisture and air sensitive Lewis acid **157** was prepared according to literature procedures and stored in a glove box under argon.[144]

[144] S. N. Kessler, M. Neuburger, H. A. Wegner, *Eur. J. Org. Chem.* **2011**, 3238–3245.

The starting material 1,2-bis(trimethylsilyl)benzene can also be synthesized *via* an alternative pathway which does not require the use of DMI as solvent:[145]

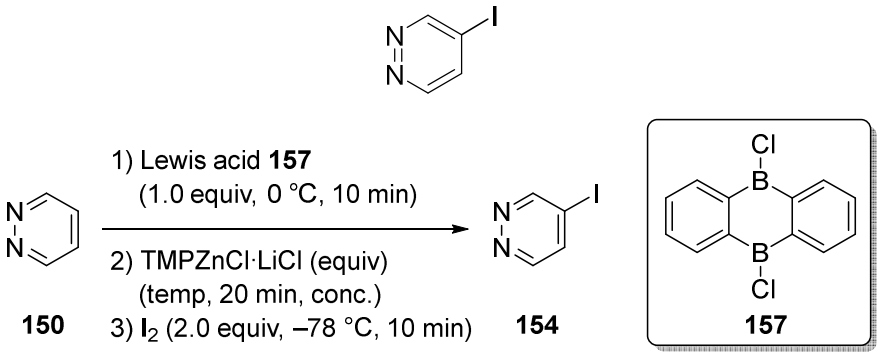


LiCl (17.07 g, 400 mmol) was added to a dry Schlenk flask and flame dried in vacuo using a heat gun at 400 °C for 10 min. After cooling to room temperature, the flask was flushed with argon and magnesium turnings (9.70 g, 400 mmol) were added and the mixture once more flame dried under vacuo for 5 min. After cooling to room temperature, the flask was again flushed with argon and THF (200 mL) was added. TMSCl (76.2 mL, 600 mmol) was added and the mixture stirred for 5 min. Then, 1,2-dibromobenzene (12.0 mL, 100 mmol) was added dropwise and the temperature of the reaction held at 25 °C using an ice bath for 20 min. After stirring at 25 °C for 12 h the reaction was quenched with water (300 mL) and extracted with hexane (3 x 200 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvents removed in vacuo. The crude product was purified first *via* column chromatography (*iso*hexane) and then *via* distillation (7 mbar, 130 °C) to give 1,2-bis(trimethylsilyl)benzene (4.68 g, 21.1 mmol, 21%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 - 7.63 (m, 2H), 7.34 (dt, *J* = 5.5, 3.3 Hz, 2H), 0.38 (d, *J* = 3.3 Hz, 18H).

The spectrum matched the one of the literature.[145]

Synthesis of 4-iodopyridazine (154)



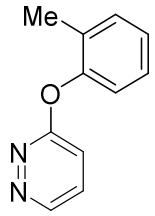
[145] T. Kitamura, R. Yamada, K. Gondo, N. Eguchi, J. Oyamada, *Synthesis* **2017**, *49*, 2495–2500.

The bidentate Lewis acid **157** (93 mg, 0.38 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. Then, a solution of pyridazine in THF (0.82 mL, 0.38 mmol, 0.462 mM) was added dropwise and the reaction stirred at the same temperature for 10 min. After cooling to –78 °C, TMPZnCl·LiCl (0.68 mL, 0.65 mmol) was added dropwise and the reaction stirred at the same temperature for 20 min. Then, a solution of iodine (193 mg, 0.76 mmol) in THF (2 mL) was added and the reaction stirred for 10 min at –78 °C and then warmed to 25 °C and stirred for additional 20 min. After quenching with a sat. aq. $Na_2S_2O_3$ solution (10 mL), the reaction was extracted with ethyl acetate (3 x 30 mL), dried over Na_2SO_4, filtered, and the solvents removed in vacuo. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 6.5:3.5:0.1) to give **154** (49 mg, 238 µmol, 63%) as a light brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.45 (dd, *J* = 2.3, 1.2 Hz, 1H), 8.84 (dd, *J* = 5.4, 1.2 Hz, 1H), 7.89 (dd, *J* = 5.4, 2.3 Hz, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.4, 151.2, 135.5, 101.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3084, 3009, 1534, 1346, 1280, 1104, 1042, 982, 913, 855, 741, 698, 668, 660.
MS (EI, 70 eV): m/z (%) = 206 (100), 152 (14), 127 (45), 79 (7).
HRMS (EI) for $C_4H_3IN_2$ (205.9341): 205.9336 (M^+).
M.p. (°C): 116–118.

The spectra matched those of the literature.[104c]

Synthesis of 3-(*o*-tolyloxy)pyridazine (credazine) (160)



3-Iodopyridazine (**153**, 63 mg, 0.306 mmol) was dissolved in toluene (2 mL) and *o*-cresol (40 mg, 0.37 mmol), $Pd(OAc)_2$ (1.4 mg, 6 µmol), *t*BuXPhos (3.9 mg, 9 µmol), and K_3PO_4 (129 mg, 0.61 mmol) were added. The reaction was stirred at 100 °C for 14 h. After addition of water (10 mL), the reaction was extracted with ethyl acetate (3 x 30 mL), dried over Na_2SO_4, filtered, and the solvents removed in vacuo. The crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate:triethylamine = 6:4:0.1) to give **160** (53 mg, 285 µmol, 93%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.92 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.47 (dd, *J* = 8.9, 4.5 Hz, 1H), 7.30 - 7.27 (m, 1H), 7.24 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.20 - 7.12 (m, 2H), 7.10 (dd, *J* = 7.9, 1.4 Hz, 1H), 2.19 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.8, 151.8, 148.1, 131.7, 130.6, 129.7, 127.4, 125.9, 121.7, 116.6, 16.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2993, 1579, 1463, 1425, 1394, 1280, 1177, 1111, 1042, 1005, 878, 815, 776, 743.

MS (EI, 70 eV): m/z (%) = 186 (20), 185 (21), 171 (19), 169 (46), 127 (19), 113 (19), 111 (23), 99 (30), 97 (36), 85 (74), 83 (40), 71 (97), 57 (100), 55 (20), 43 (38).

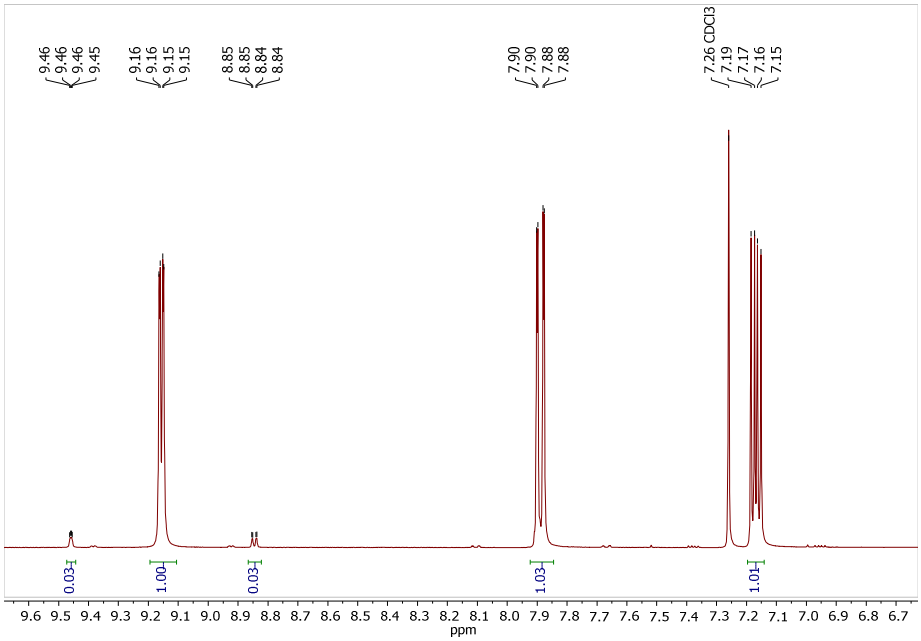
HRMS (EI) for $C_{11}H_{10}N_2O$ (186.0793): 186.0796 (M^+).

M.p. (°C): 79–80.

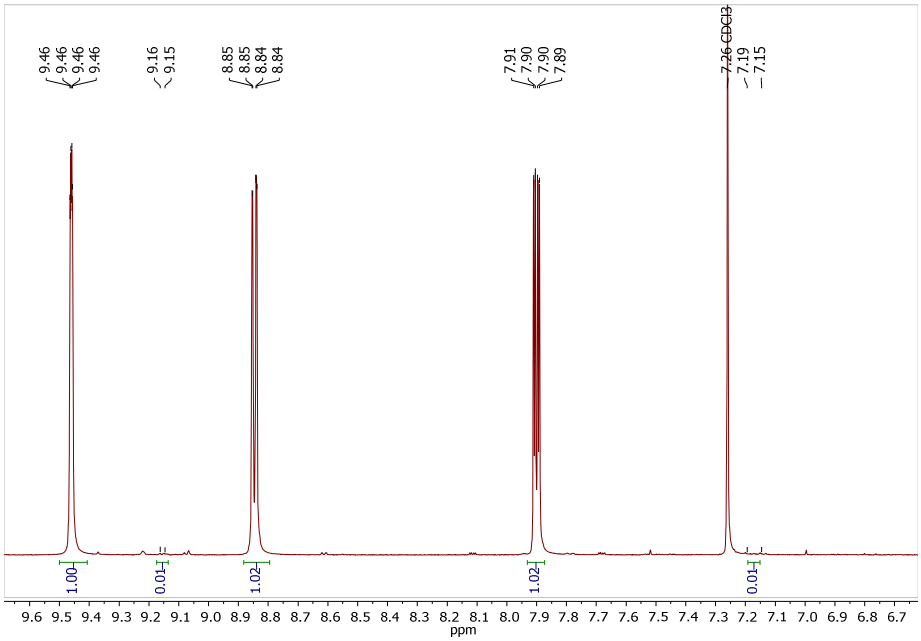
7.4 Regioselectivity Investigations

Given is A) the 1H-NMR of the mixture of regioisomers from Table 1, entry 6 (optimized reaction conditions), indicating a ratio of 3-iodopyridazine (6) to 4-iodopyridazine (7) of 97:3 and B) the 1H-NMR of the mixture of regioisomers from Table 3, entry 3 (optimized reaction conditions), indicating a ratio of 3-iodopyridazine (6) to 4-iodopyridazine (7) of 1:99.

A) ^{1}H-NMR of the mixture of regioisomers from Table 5, entry 6.

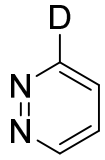


B) ^{1}H-NMR of the mixture of regioisomers from Table 7, entry 3.



To confirm the regioselectivity of the metalation on pyridazine, the resulting metal species of the *ortho*- and *meta*-metalation using either **A**) $BF_3 \cdot OEt_2$ and TMPZnCl·LiCl (**TP18**) or **B**) the bidentate Lewis acid **157** and TMPZnCl·LiCl were quenched with D_2O and the obtained deuterium-incorporated products analyzed *via* ^1H NMR spectroscopy. The measured spectra were also compared with the respective starting material spectra.

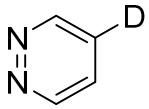
Synthesis of pyridazine-3-*d*



Pyridazine (80 mg, 1.00 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. Then, $BF_3 \cdot OEt_2$ (0.14 mL, 1.10 mmol) was added dropwise and the reaction stirred for 10 min. TMPZnCl·LiCl (1.74 mL, 1.5 mmol) was added dropwise and the reaction stirred for 6 h at 25 °C. The reaction was quenched with D_2O (5 mL) and the phases were separated. The aqueous phase was filtered and submitted to NMR spectroscopy, indicating an incorporation of deuterium at position C4 with a ^2H:^1H ratio of 33:67.

^{1}H-NMR (400 MHz, D_2O): δ / ppm = 9.16 (t, *J* = 3.5 Hz, 1H), 7.81 (d, *J* = 3.5 Hz, 1H).

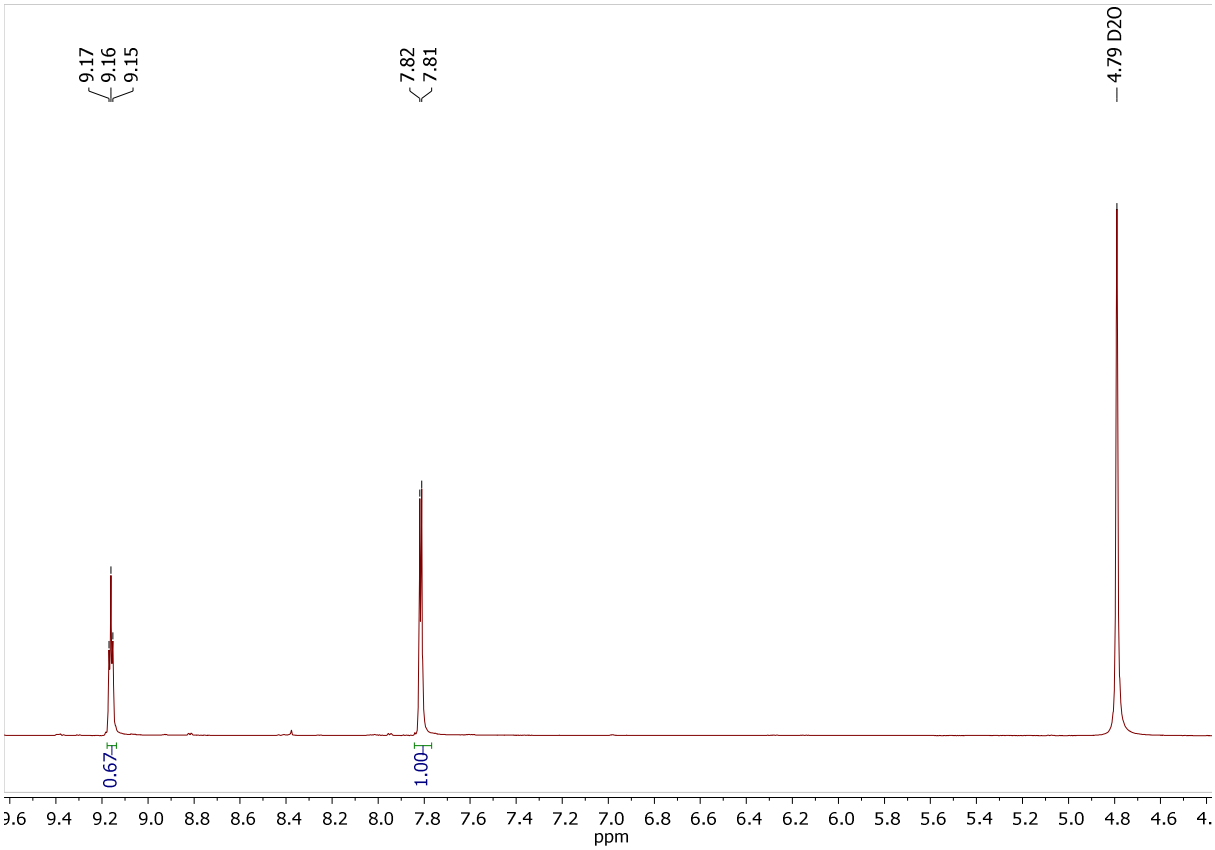
Synthesis of pyridazine-4-*d*



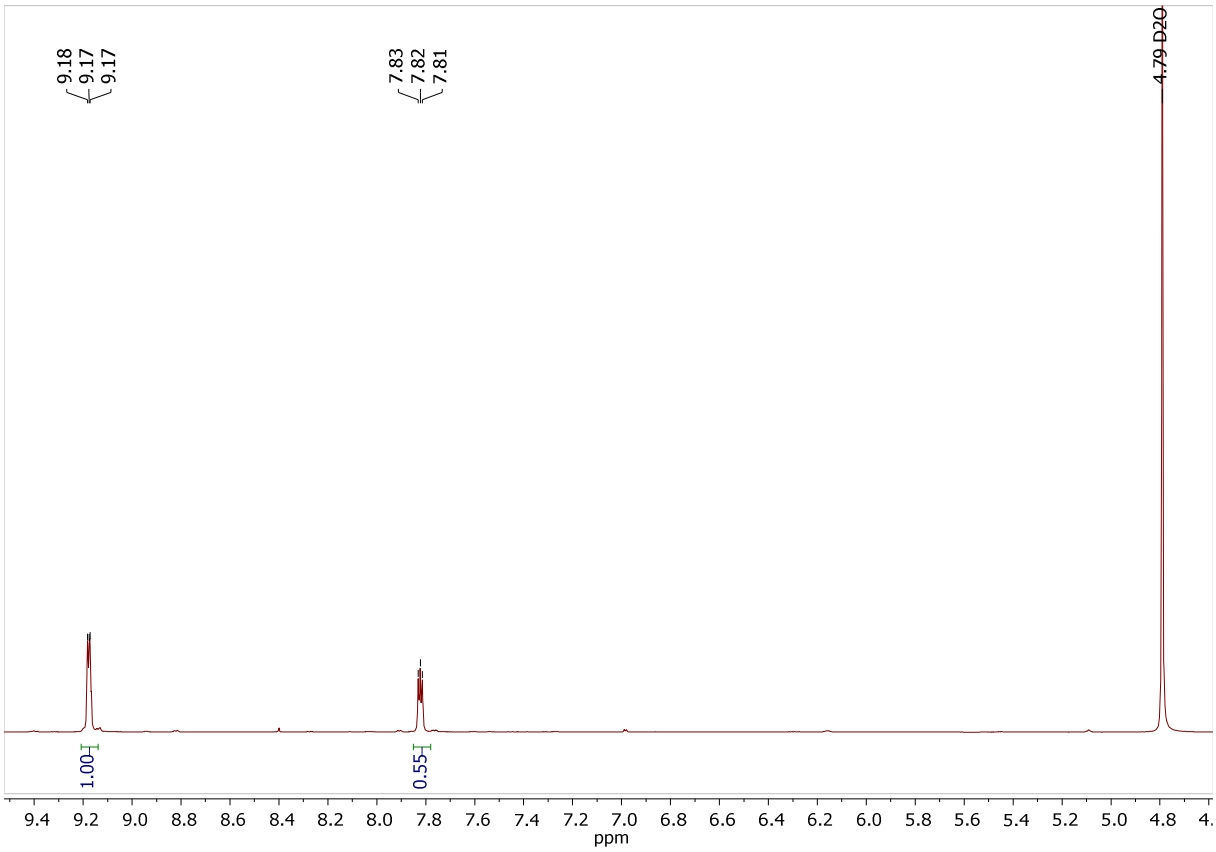
The bidentate Lewis acid **157** (99 mg, 0.41 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. Then, a solution of pyridazine in THF (0.90 mL, 0.41 mmol, 0.454 mM) was added dropwise and the reaction stirred at the same temperature for 10 min. After cooling to –78 °C, TMPZnCl·LiCl (0.81 mL, 0.70 mmol) was added dropwise and the reaction stirred at the same temperature for 20 min. The reaction was quenched with D_2O (5 mL), stirred at room temperature for 10 min and the phases were separated. The aqueous phase was filtered and submitted to NMR spectroscopy, indicating an incorporation of deuterium at position C3 with a ^2H:^1H ratio of 45:55.

^{1}H-NMR (400 MHz, D_2O): δ / ppm = 9.20 - 9.15 (m, 1H), 7.82 (t, *J* = 3.4 Hz, 1H).

^{1}H NMR spectrum of pyridazine-3-*d*



^{1}H NMR spectrum of pyridazine-4-*d*



7.5 NMR Investigations Towards the Lewis Acid-Pyridazine Complex 158

To investigate the Lewis acid - pyridazine complex **158**, several NMR experiments were performed. ^{1}H and ^{13}C spectra of pyridazine (**150**), ^{1}H, ^{13}C, ^{11}B spectra of the Lewis acid **157**, and ^{1}H, ^{13}C, ^{11}B spectra of the Lewis acid - pyridazine complex **158** were measured and are displayed below. Pyridazine was dissolved in THF (0.07 M) and measured as is. The Lewis acid **157** and the complex **158** were dissolved in THF (0.07 M) and a C_6D_6 capillary was added to the NMR tube. All NMRs were referenced to the THF peak at 1.73 ppm (^{1}H NMR) and 25.37 ppm (^{13}C NMR).

Pyridazine (**150**) in THF.

^{1}H-NMR (400 MHz, THF): δ / ppm = 9.1 (q, *J* = 3.5 Hz, 1H), 7.5 (q, *J* = 3.6 Hz, 1H).
^{13}C-NMR (101 MHz, THF): δ / ppm = 151.4, 125.7.

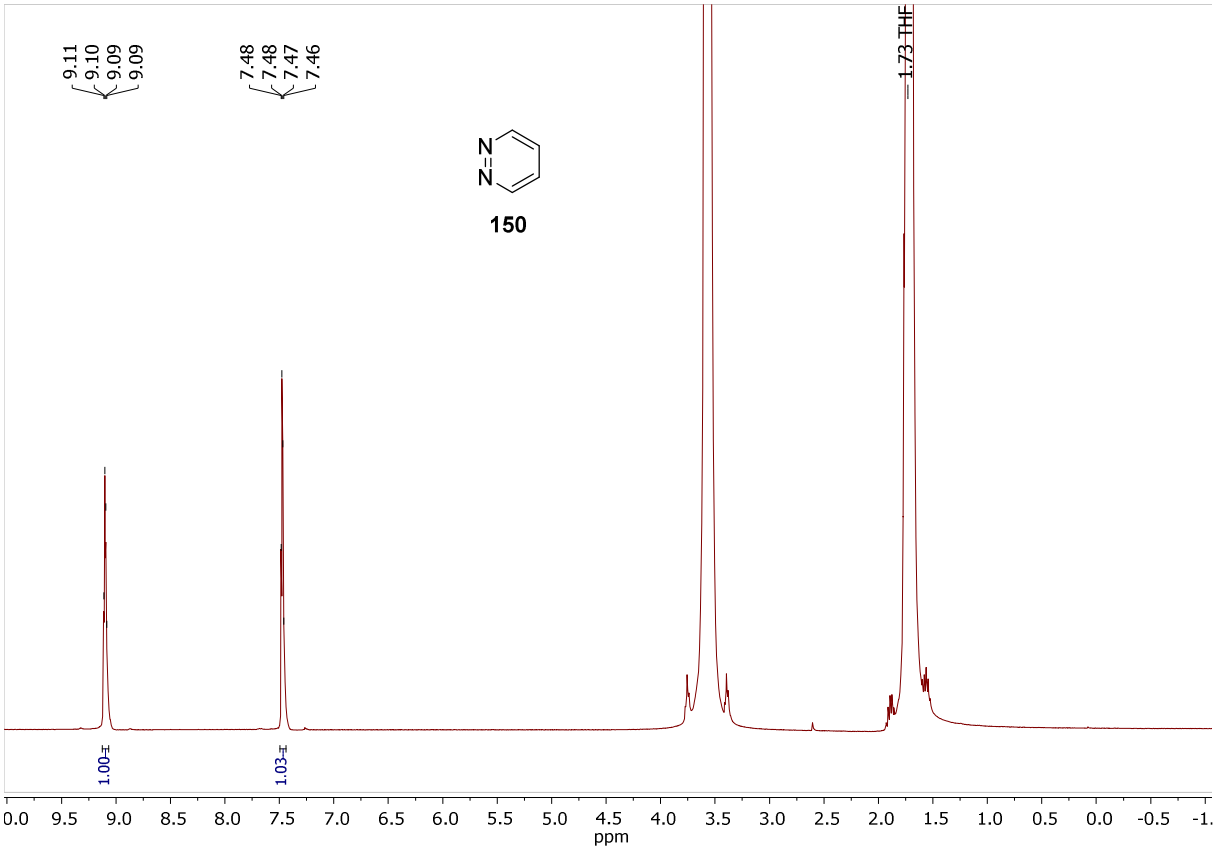
Bidentate Lewis acid **157**:

^{1}H-NMR (400 MHz, THF): δ / ppm = 7.9 (dd, *J* = 5.5, 3.3 Hz, 1H), 7.2 (dd, *J* = 5.6, 3.2 Hz, 1H).
^{13}C-NMR (101 MHz, THF): δ / ppm = 132.3, 126.5.
^{11}B-NMR (128 MHz, THF): δ / ppm = 16.6.

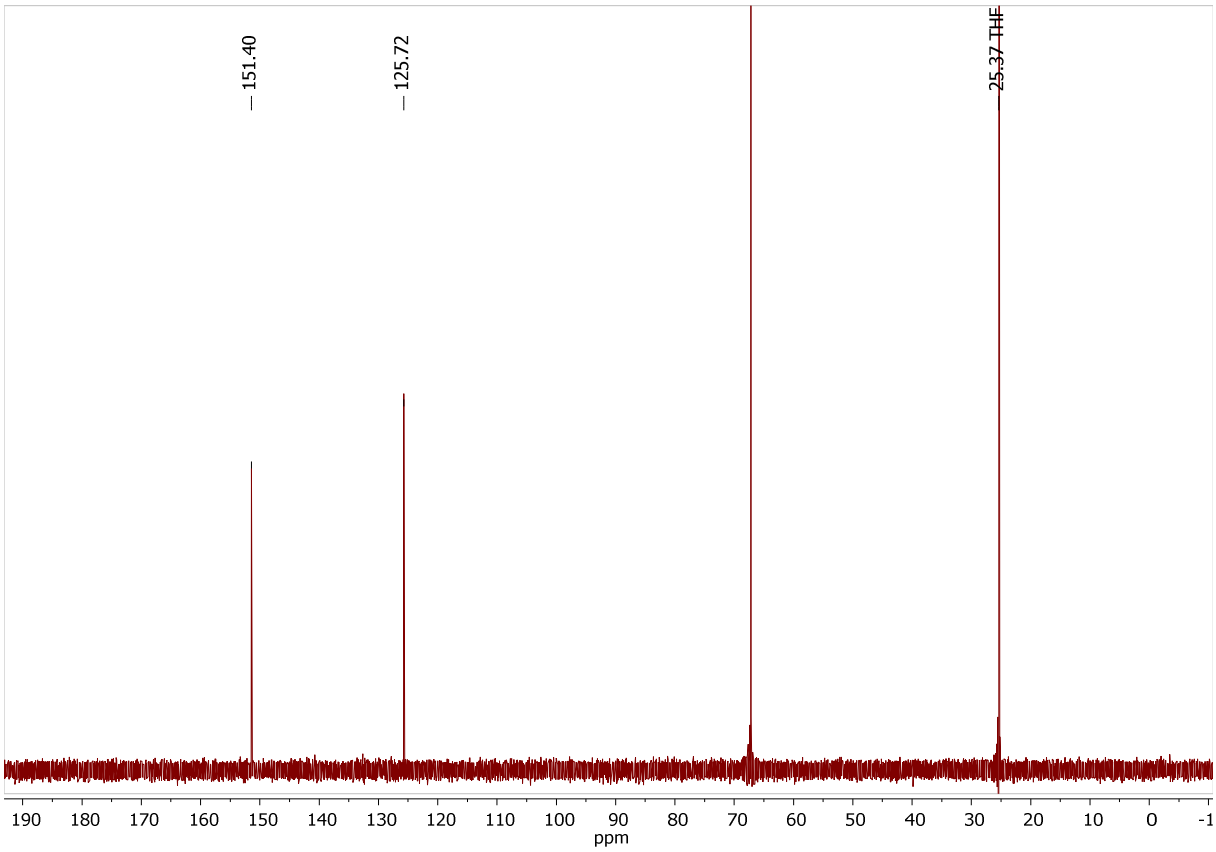
Lewis acid - pyridazine complex **158**:

^{1}H-NMR (400 MHz, THF): δ / ppm = 10.1 - 10.1 (m, 1H), 8.2 - 8.1 (m, 1H), 7.6 - 7.5 (m, 2H), 6.9 - 6.8 (m, 2H).
^{13}C-NMR (101 MHz, THF): δ / ppm = 147.3, 135.0, 127.2, 124.6.
^{11}B-NMR (128 MHz, THF): δ / ppm = 10.7.

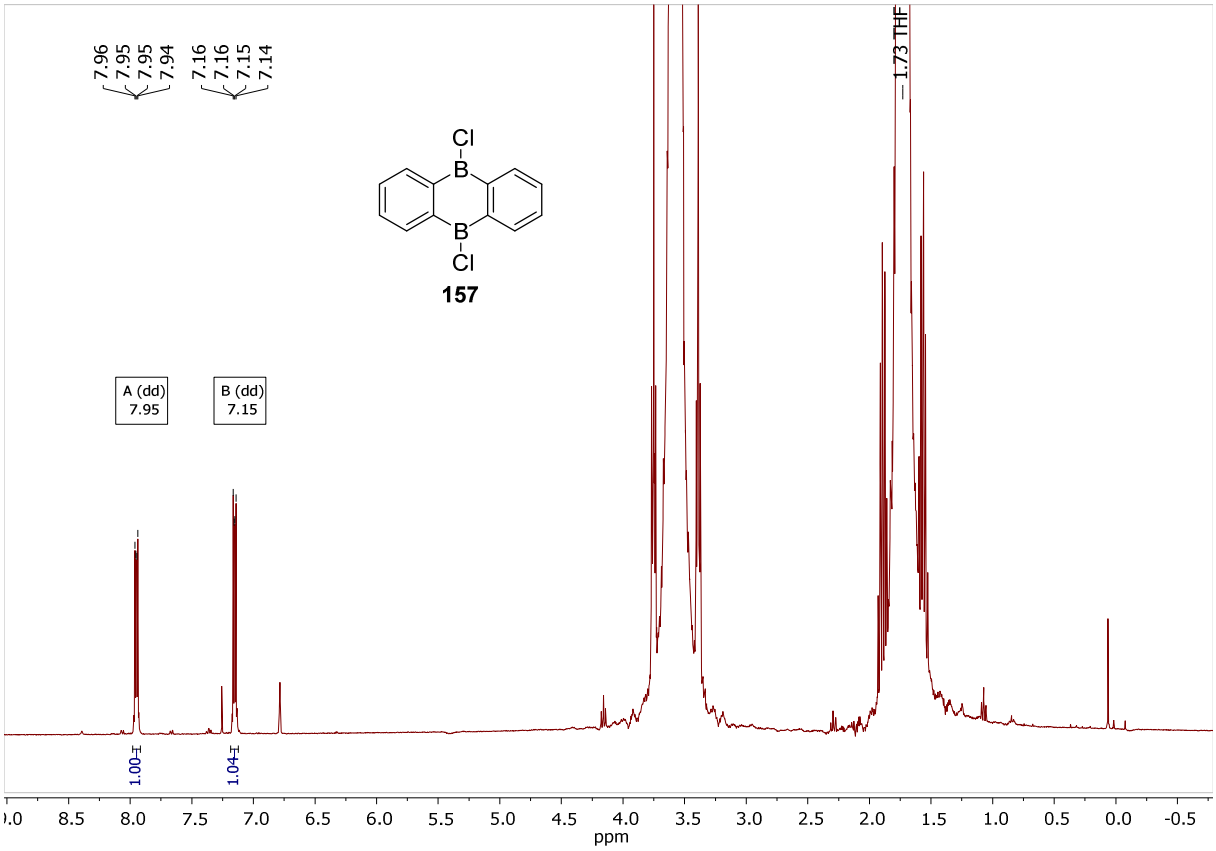
^{1}H NMR spectrum of pyridazine (**150**) in THF



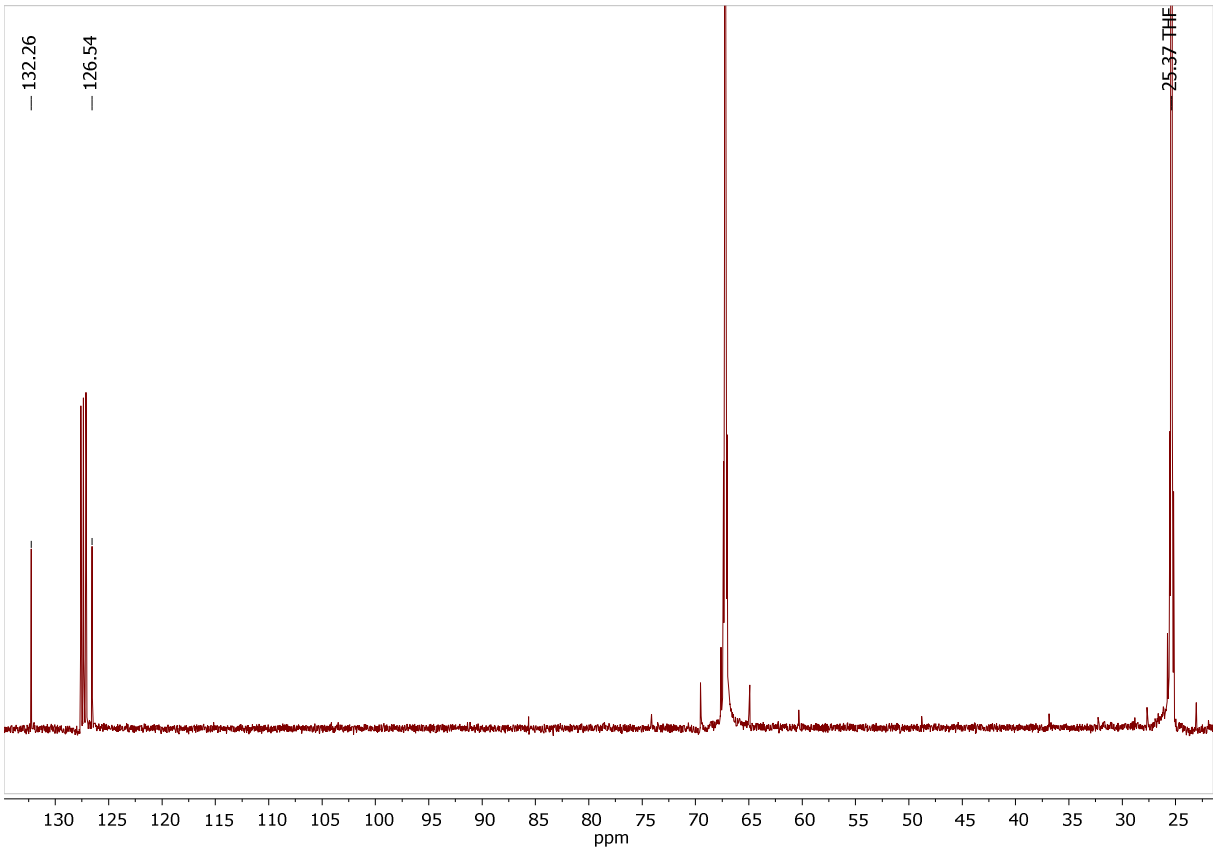
^{13}C NMR spectrum of pyridazine (**150**) in THF



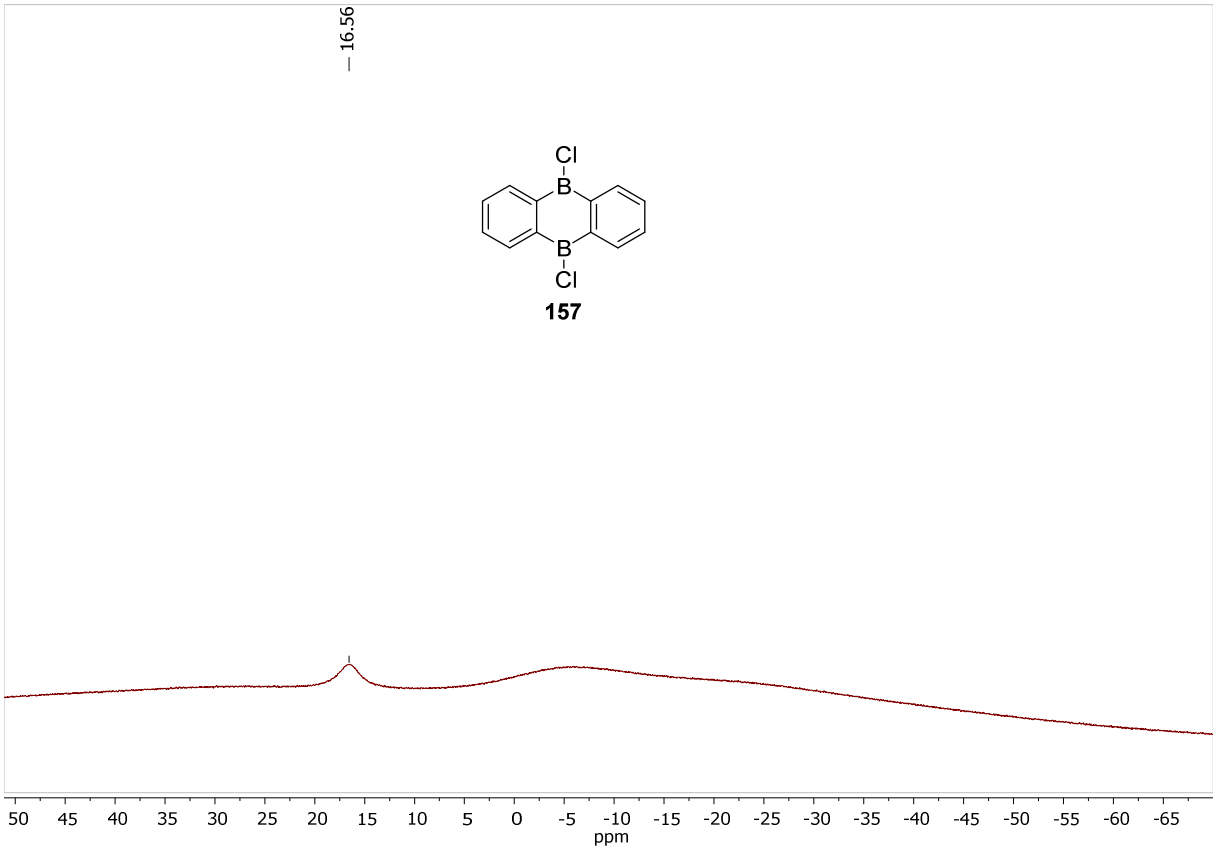
^{1}H NMR spectrum of the bidentate Lewis acid **157** in THF



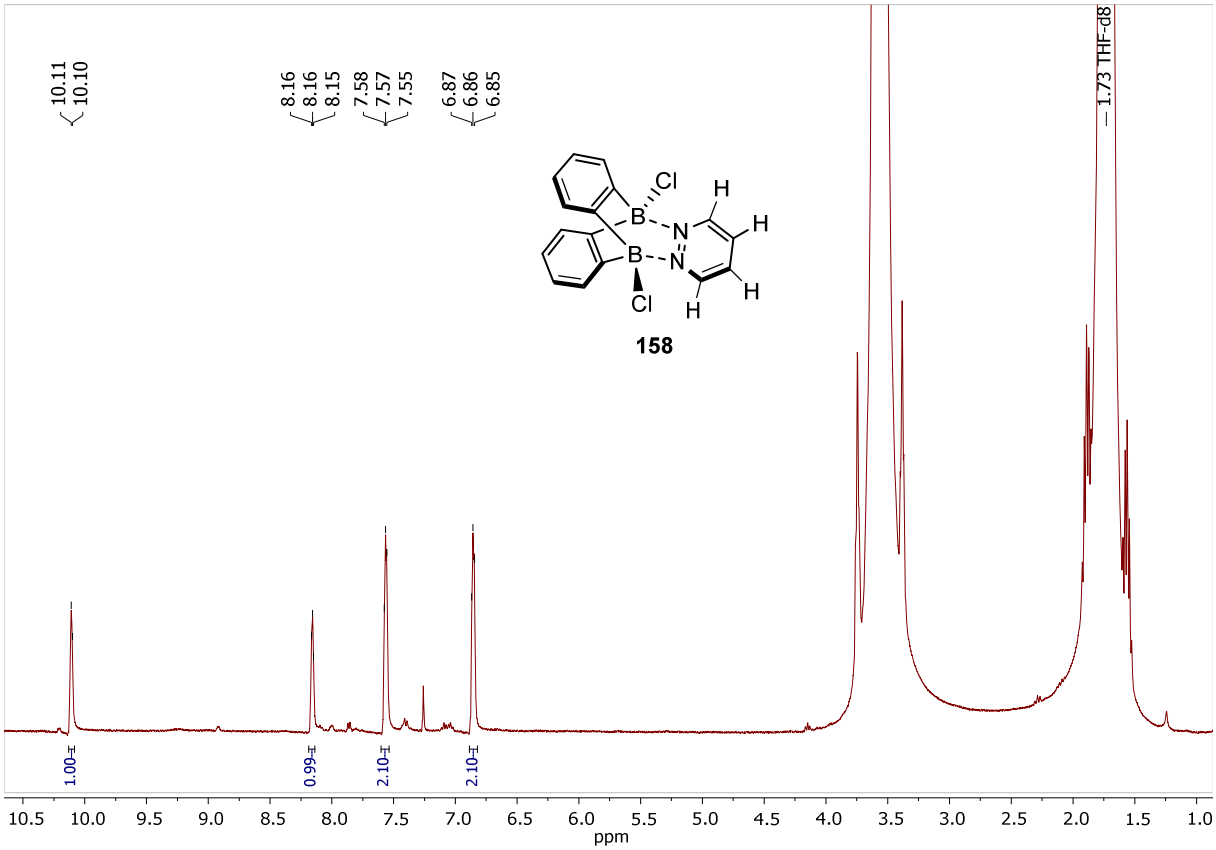
^{13}C NMR spectrum of the bidentate Lewis acid **157** in THF



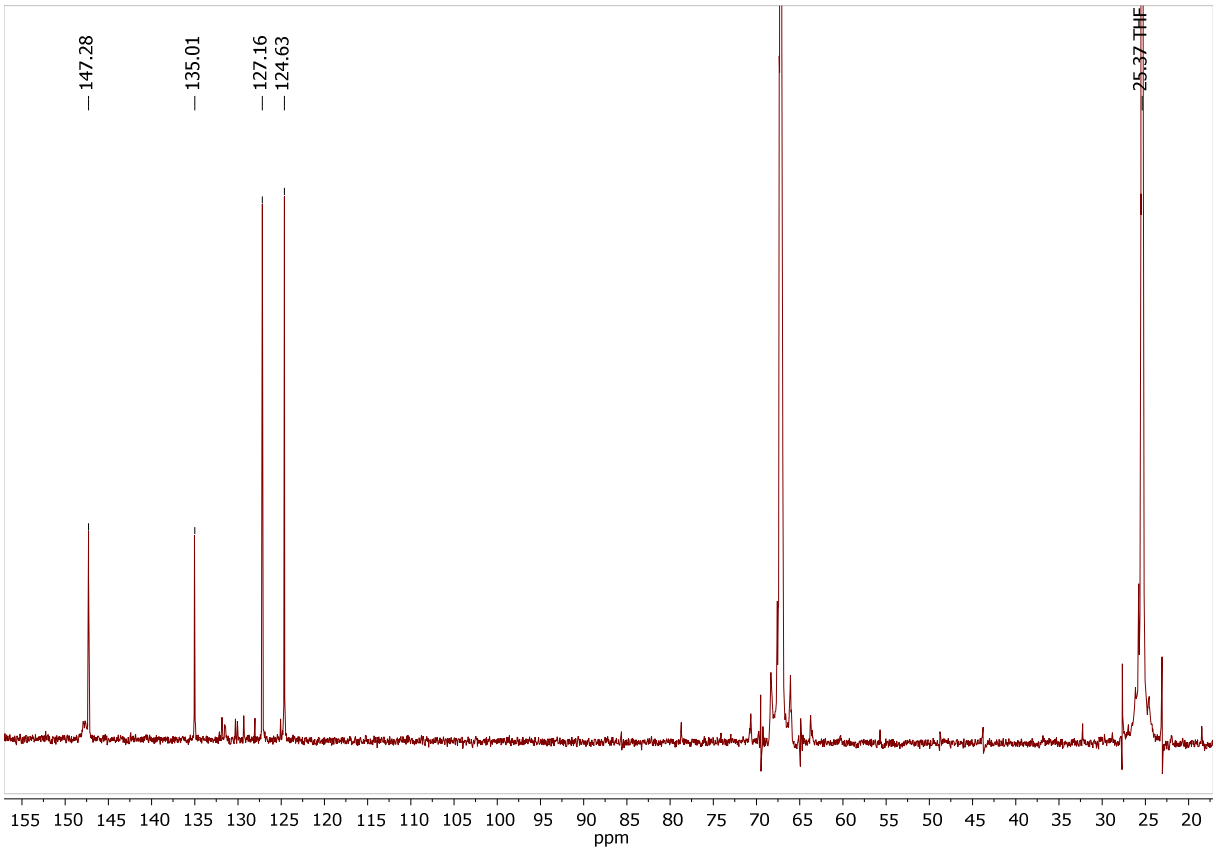
^{11}B NMR spectrum of the bidentate Lewis acid **157** in THF



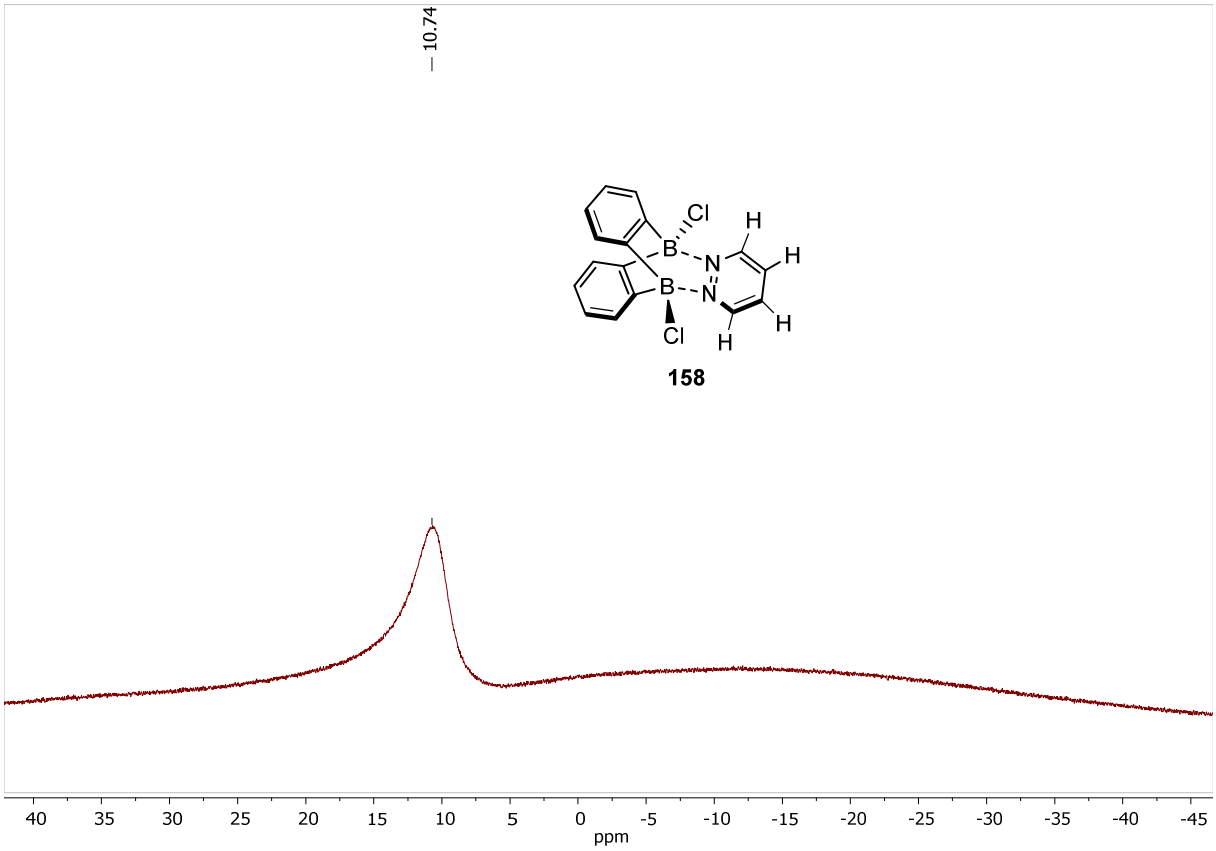
^{1}H NMR spectrum of the Lewis acid - pyridazine complex **158** in THF



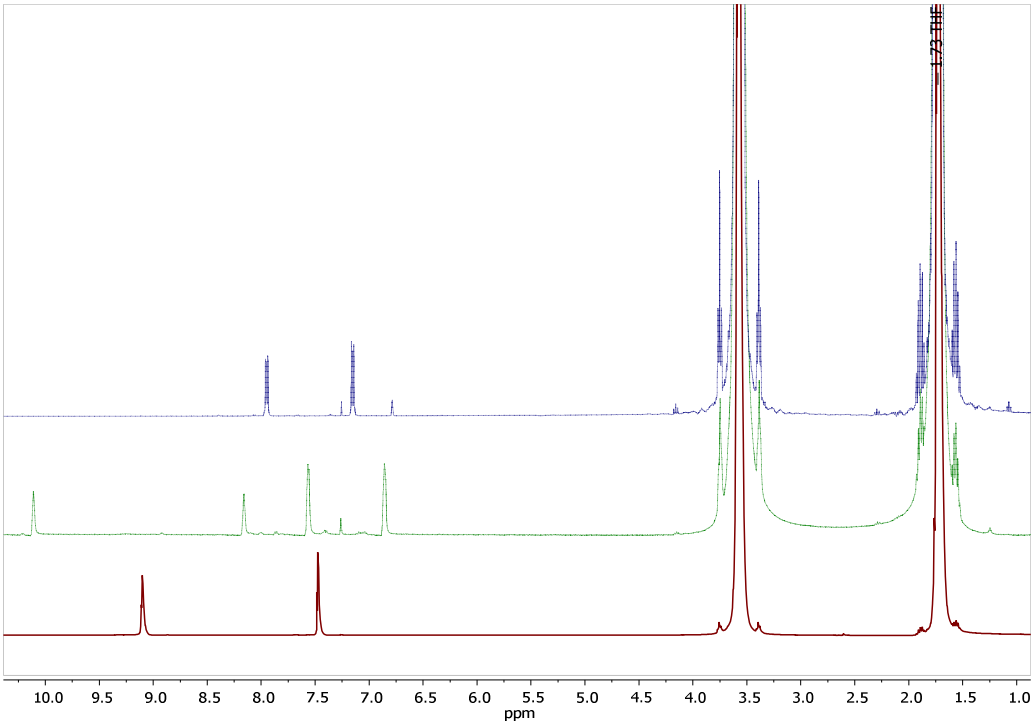
^{13}C NMR spectrum of the Lewis acid - pyridazine complex **158** in THF



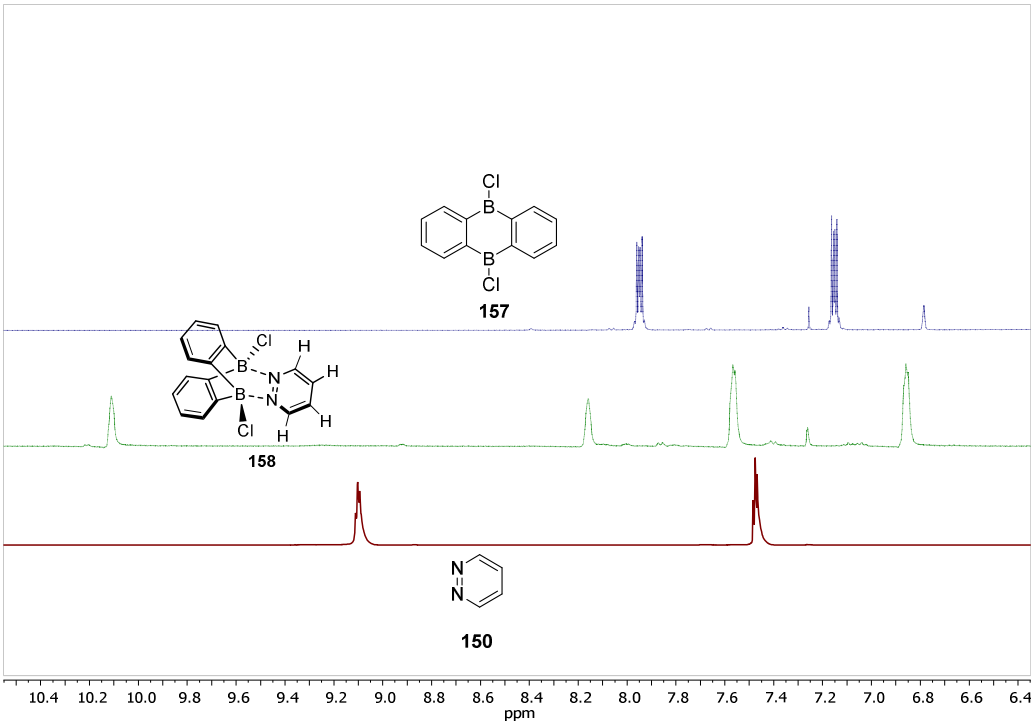
^{11}B NMR spectrum of the Lewis acid - pyridazine complex **158** in THF



Stacked ^{1}H spectra of pyridazine (**150**; red), the bidentate Lewis acid **157** (blue), and the Lewis acid - pyridazine complex **158** (green) with THF set as a reference to 1.73 ppm.[a]

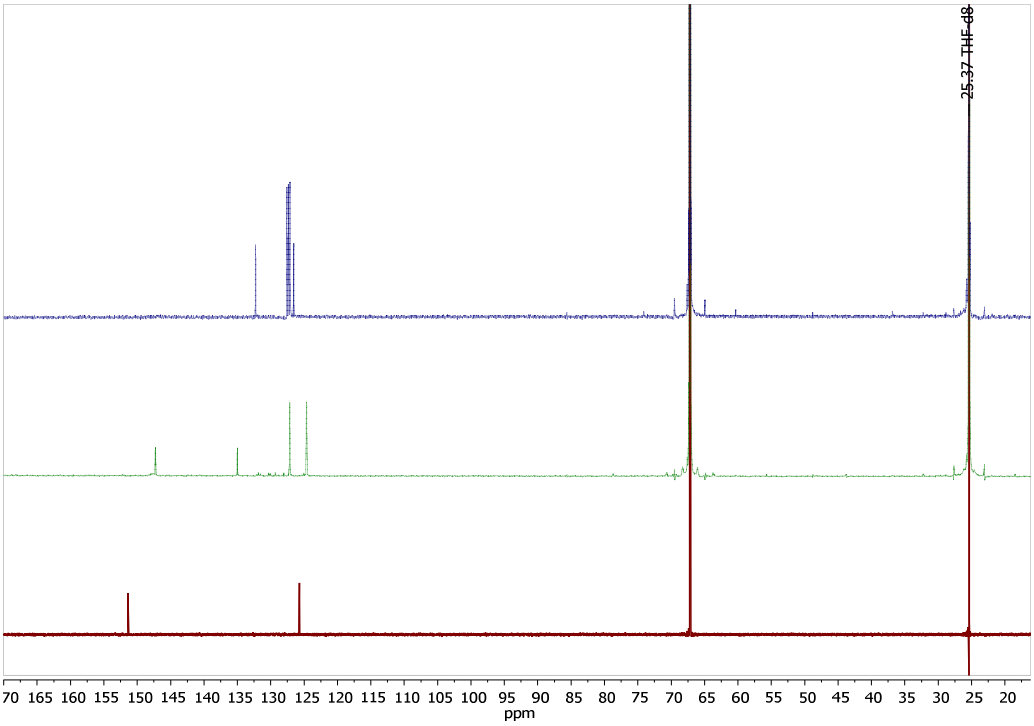


Stacked ^{1}H NMR spectra of **150** (red), **157** (blue), and **158** (green) from 10.4–6.40 ppm.[a]

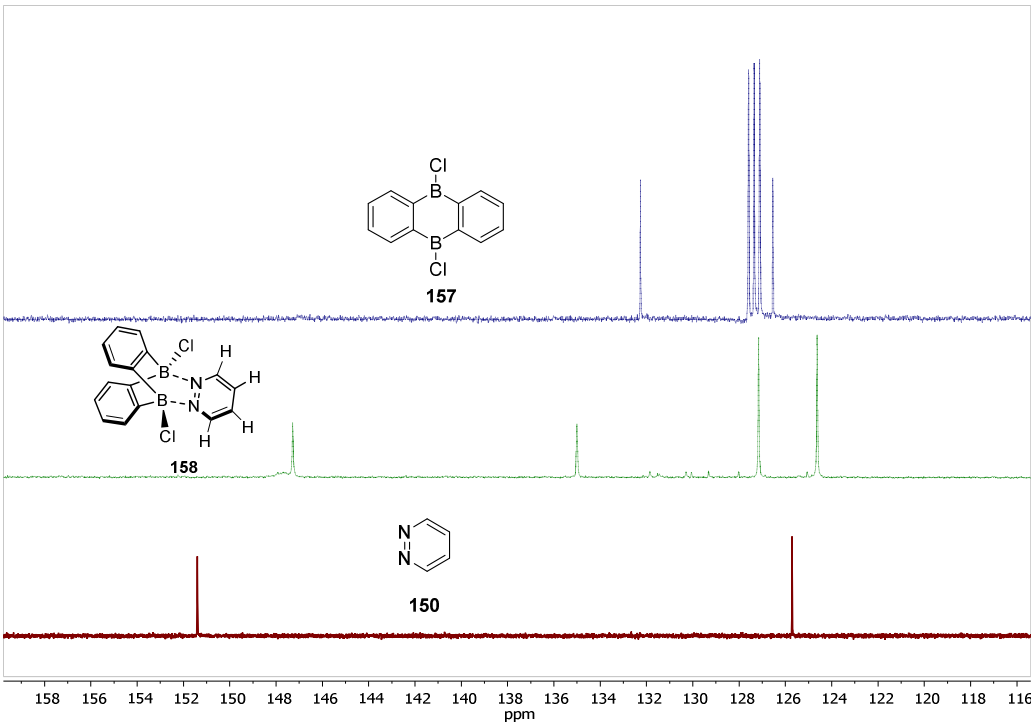


[a]The peak at 7.26 ppm in the spectrum of **157** (blue) and **158** (green) corresponds to the C_6D_6 solvent residual peak.

Stacked ^{13}C spectra of pyridazine (**150**; red), the bidentate Lewis acid **157** (blue), and the Lewis acid - pyridazine complex **158** (green) with THF set as a reference to 1.73 ppm.[b]



Stacked ^{1}H NMR spectra of **150** (red), **157** (blue), and **158** (green) from 10.4–6.40 ppm.[b]

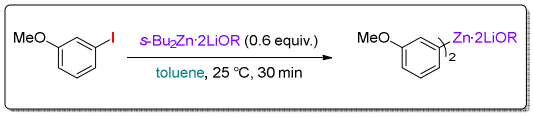


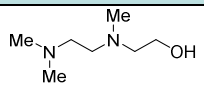
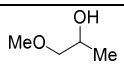
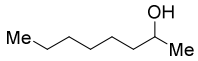
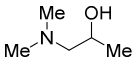
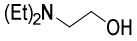
[b] The peak at 128 ppm in the spectrum of **157** (blue) corresponds to the C_6D_6 solvent residual peak.

8 Preparation of Polyfunctional Arylzinc Organometallics in Toluene via Halogen/Zinc Exchange Reactions

8.1 Screening Tables

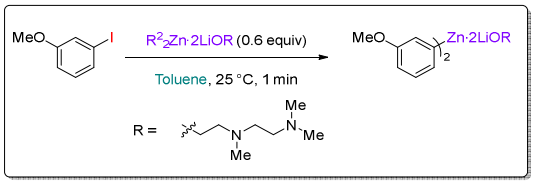
Variation of the alkoxide residue



Nr.	R^1	Exchange reagent	GC-yield (%)[a]
1		1a	99
2		1b	97
3		1c	23
3		1d	91
4		1e	95

[a] Yield determined by GC-analysis of water quenched reaction aliquots

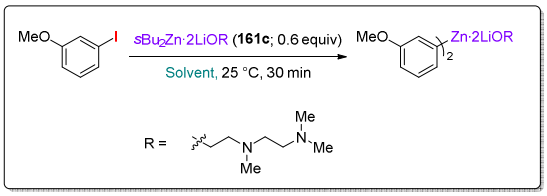
Variation of the alkyl residue



Nr.	R^2	GC-yield (%)[a]
1	*n*Bu	80
2	*s*Bu	99
3	*t*Bu	89

[a] Yield determined by GC-analysis of water quenched reaction aliquots

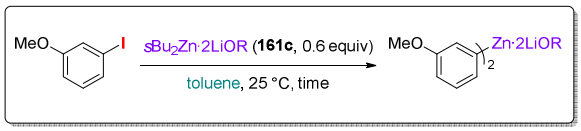
Solvent screening



Nr.	Solvent	GC Yield (%)[a]	
		Hydrolysis	Iodolysis
1	Et_2O	99	91
2	THF	99	87
3	2-MeTHF	99	85
4	Dioxane	99	86
5	MTBE	99	89
6	Acetone	9	0
7	MeCN	99	36
8	DMF	99	31
9	Ethylacetate	99	19
10	1,2-Dichlorethane	99	80
11	Chlorbenzene	99	60
12	Toluene	99	86
13	Hexane	99	90

[a] Yield determined by GC-analysis of water quenched reaction aliquots (hydrolysis), or iodine quenched reaction aliquots (iodolysis)

Reaction time screening

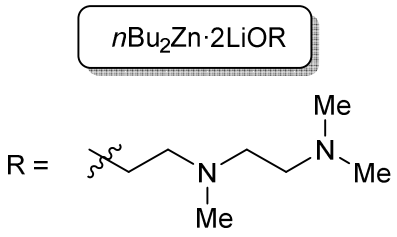


Nr.	time (min)	GC-yield (%)
1	0.5	93
2	1	99
3	60	99

[a] Yield determined by GC-analysis of water quenched reaction aliquots

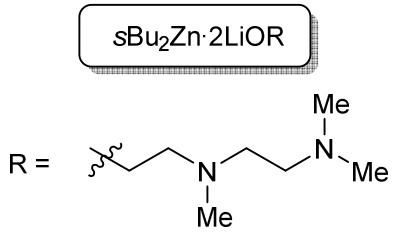
8.2 Preparation of Reagents of Type $R_2Zn \cdot 2LiOR$

Preparation of *n*$Bu_2Zn \cdot 2LiOR$:



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with Et_2Zn (1.11 M in toluene, 9.01 mL, 10.0 mmol) and the reaction mixture was cooled to –40 °C. Then, 2-((2-(dimethylamino)ethyl)(methyl)amino)ethane-1-ol (2.925 g, 20.0 mmol) was added dropwise and the reaction stirred for 2 h. Then, the reaction mixture was cooled to –40 °C and *n*BuLi (2.4 M in hexane, 8.33 mL, 20.0 mmol)) added dropwise. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stir for 2 h. The solvents were removed *in vacuo* affording a light yellow oil. Freshly distilled toluene (8 mL) was added under vigorous stirring. The prepared *n*$Bu_2Zn \cdot 2LiO(CH_2)_2N(Me)(CH_2)_2N(Me)_2$ was titrated prior to use at 0 °C by iodometric titration. The *n*$Bu_2Zn \cdot 2LiO(CH_2)_2N(Me)(CH_2)_2N(Me)_2$ concentration of the resulting clear solution was 0.68 M

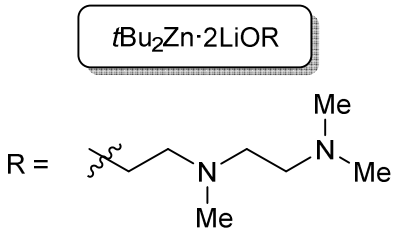
Preparation of *s*$Bu_2Zn \cdot 2LiOR$ (161c):



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with Et_2Zn (1.11 M in toluene, 9.01 mL, 10.0 mmol) and the reaction mixture was cooled to –40 °C. Then, 2-((2-(dimethylamino)ethyl)(methyl)amino)ethane-1-ol (2.925 g, 20.0 mmol) was added dropwise and the reaction stirred for 2 h. Then, the reaction mixture was cooled to –40 °C and *s*BuLi (1.32 M in hexane, 15.15 mL, 20.0 mmol)) added dropwise. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stir for 2 h. The solvents were removed *in vacuo* affording a light yellow oil. Freshly distilled toluene (8 mL) was added under vigorous stirring.

The prepared *s*$Bu_2Zn\cdot 2LiO(CH_2)_2N(Me)(CH_2)_2N(Me)_2$ was titrated prior to use at 0 °C by iodometric titration. The *s*$Bu_2Zn\cdot 2LiO(CH_2)_2N(Me)(CH_2)_2N(Me)_2$ concentration of the resulting clear solution was 0.60–1.00 M.

Preparation of *t*$Bu_2Zn\cdot 2LiOR$ (168):



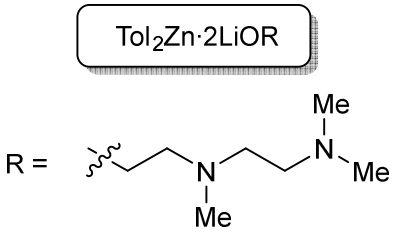
A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with Et_2Zn (1.11 M in toluene, 9.01 mL, 10.0 mmol) and the reaction mixture was cooled to –40 °C. Then, 2-((2-(dimethylamino)ethyl)(methyl)amino)ethane-1-ol (2.925 g, 20.0 mmol) was added dropwise and the reaction stirred for 2 h. Then, the reaction mixture was cooled to –40 °C and *t*BuLi (1.93 M in pentane, 10.36 mL, 20.0 mmol)) added dropwise. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stir for 2 h. The solvents were removed *in vacuo* affording a light yellow oil. Freshly distilled toluene (8 mL) was added under vigorous stirring. The prepared *t*$Bu_2Zn\cdot 2LiO(CH_2)_2N(Me)(CH_2)_2N(Me)_2$ was titrated prior to use at 0 °C by iodometric titration. The *t*$Bu_2Zn\cdot 2LiO(CH_2)_2N(Me)(CH_2)_2N(Me)_2$ concentration of the resulting clear solution was 0.68 M

Titration Using Iodine[146]

A dry flask was charged with accurately weighed I_2 (128 mg, 0.504 mmol), fitted with a rubber septum, and flushed with argon. THF (2 mL) was added and stirring was started. After the iodine was completely dissolved, the resulting brown solution was cooled to 0 °C in an ice bath and the organozinc reagent was added dropwise via a 1.00-mL syringe (0.01-mL graduations) until the brown color disappeared. The obtained concentration needs to be divided by 2 to obtain the concentration of the dialkyl zinc species.

[146] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890.

Preparation of $Tol_2Zn{\cdot}2LiOR$ (Tol = *p*-tolyl-, 167)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with Et_2Zn (1.11 M in toluene, 9.01 mL, 10.0 mmol) and the reaction mixture was cooled to –40 °C. Then, 2-((2-(dimethylamino)ethyl)(methyl)amino)ethane-1-ol (2.925 g, 20.0 mmol) was added dropwise and the reaction stirred for 2 h. Then, the reaction mixture was cooled to –40 °C and TolLi (0.98 M in Et_2O, 20.4 mL, 20.0 mmol)) added dropwise. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stir for 2 h. The solvents were removed *in vacuo* affording a light yellow oil. Freshly distilled toluene (8 mL) was added under vigorous stirring. The prepared $Tol_2Zn{\cdot}2LiO(CH_2)_2N(Me)(CH_2)_2N(Me)_2$ was titrated prior to use at 0 °C by iodometric titration. The $Tol_2Zn{\cdot}2LiO(CH_2)_2N(Me)(CH_2)_2N(Me)_2$ concentration of the resulting clear solution was 0.69 M.

8.3 Typical Procedures

Typical Procedure 22: Preparation of diarylzinc alkoxides via an iodine/zinc Exchange followed by electrophilic functionalization

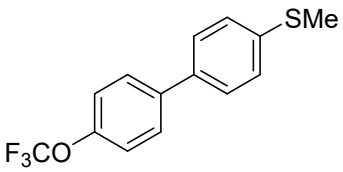
A dry and argon-flushed *Schlenk* flask, equipped with a magnetic stirring bar and a septum, was charged with the corresponding aryl halide (1.0 equiv) and dissolved in dry toluene (0.5 M): Then, the exchange reagent $R_2Zn \cdot 2LiO(CH_2)_2N(Me)(CH_2)_2N(Me)_2$ (**161c**, **167** or **168**) (0.6–0.8 equiv) was added dropwise and the reaction stirred for 10 minutes at 25 °C unless otherwise stated. The completion of the halogen/zinc exchange was checked by GC-analysis of reaction aliquots quenched with water, using undecane as internal standard. Subsequent reactions with electrophiles were carried out under the indicated conditions. After complete conversion, the mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), diluted with water (10 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. If the crude product needed purification, it was purified by flash chromatography on silica gel using the appropriate eluent.

Typical Procedure 23: Preparation of diarylzinc alkoxides via a bromine/zinc exchange followed by electrophilic functionalization

A dry and argon-flushed *Schlenk* flask, equipped with a magnetic stirring bar and a septum, was charged with the corresponding aryl halide (1.0 equiv) and dissolved in dry toluene (1.0 M): Then, $s Bu_2Zn \cdot 2LiO(CH_2)_2N(Me)(CH_2)_2N(Me)_2$ (**161c**, 0.8 equiv) was added dropwise and the reaction stirred for 5 h at 25 °C unless otherwise stated. The completion of the halogen/zinc exchange was checked by GC-analysis of reaction aliquots quenched with water, using undecane as internal standard. Subsequent reactions with electrophiles were carried out under the indicated conditions. After complete conversion, the mixture was quenched with a sat. aq. NH_4Cl solution (10 mL), diluted with water (10 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. If the crude product needed purification, it was purified by flash chromatography on silica gel using the appropriate eluent.

8.4 Preparation of Compounds 166 to 170

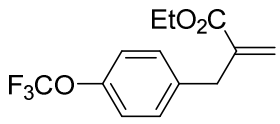
Synthesis of methyl(4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)sulfane (166d)



Biaryl **166d** was prepared *via* **TP22** using 1-iodo-4-(trifluoromethoxy)benzene (139 mg, 0.48 mmol) and *s*$Bu_2Zn \cdot 2LiOR$ (**161c**, 0.30 mL, 0.29 mmol). After the exchange was complete, $Pd(OAc)_2$ (3 mg, 14 µmol), SPhos (12 mg, 29 µmol) and 4-iodothioanisole (100 mg, 0.40 mmol) were added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 10:0.04) to give **166d** (55 mg, 193 µmol, 48%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.60 – 7.55 (m, 2H), 7.51 – 7.47 (m, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.26 (m, 2H), 2.53 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 148.7 (q, *J* = 2 Hz), 139.4, 138.4, 136.6, 128.2, 127.5, 127.0, 121.4, 120.6 (q, *J* = 257 Hz), 15.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2623, 1594, 1523, 1484, 1205, 1155, 1100, 805.
MS (EI, 70 eV): m/z (%) = 284 (100), 269 (42), 236 (10), 184 (9), 139 (14).
HRMS (EI) for $C_{14}H_{11}F_3OS$ (284.0483): 284.0475 (M^+).
M.p. (°C): 103–105.

Synthesis of 2',4'-dichloro-1,2,3,4-tetrahydro-1,1'-biphenyl (166e)

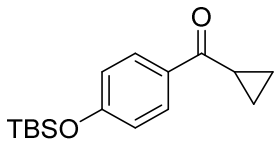


Arene **166e** was prepared *via* **TP22** using 1-iodo-4-(trifluoromethoxy)benzene (139 mg, 0.48 mmol) and *s*$Bu_2Zn \cdot 2LiOR$ (**161c**, 0.30 mL, 0.29 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (19 mg, 0.1 mmol) was added. After stirring at 0 °C for 30 min, ethyl 2-(bromomethyl)acrylate (139 mg, 0.72 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl

acetate = 1000:1 to 9:1) to give **166e** (88 mg, 321 µmol, 67%) as a colorless oil. The product was detected by GC-analysis.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.25 – 7.19 (m, 2H), 7.16 – 7.11 (m, 2H), 6.25 (q, *J* = 0.9 Hz, 1H), 5.49 (q, *J* = 1.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.63 (d, *J* = 1.2 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.8, 147.9, 140.0, 137.7, 130.4, 126.5, 121.1, 61.0, 37.6, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2984, 2932, 1716, 1634, 1508, 1257, 1222, 1196, 1161, 1021, 950, 813.
MS (EI, 70 eV): m/z (%) = 274 (25), 229 (12), 201 (24), 200 (100), 199 (17), 161 (11), 131 (15), 115 (47), 103 (15).
HRMS (EI) for $C_{13}H_{13}F_3O_3$ (274.0817): 274.0811 (M^+).

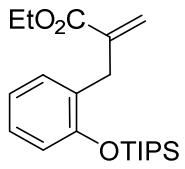
Synthesis of (4-((*tert*-butyldimethylsilyl)oxy)phenyl)(cyclopropyl)methanone (166f)



Arene **166f** was prepared *via* **TP22** using *tert*-butyl(4-iodophenoxy)dimethylsilane (154 mg, 0.46 mmol) and *s*Bu_2Zn·2LiOR (**161c**, 0.29 mL, 0.28 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (53 mg, 0.28 mmol) was added. After stirring at 0 °C for 30 min, cyclopropanecarbonyl chloride (0.13 mL, 1.38 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 10:0.5) to give **166f** (77 mg, 279 µmol, 61%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.98 – 7.92 (m, 2H), 6.92 – 6.86 (m, 2H), 2.63 (tt, *J* = 7.8, 4.5 Hz, 1H), 1.20 (dt, *J* = 4.5, 3.4 Hz, 2H), 0.99 (s, 11H), 0.23 (s, 6H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 199.4, 160.2, 131.7, 130.3, 120.0, 25.7, 18.4, 16.8, 11.4, -4.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3008, 2955, 2930, 2858, 1664, 1599, 1508, 1415, 1272, 1257, 1225, 1164, 994, 910, 840, 782.
MS (ESI): m/z (%) = 277 (100).
HRMS (ESI) for $C_{16}H_{25}O_2Si$ (277.1624): 277,1620 (M^++H^+).

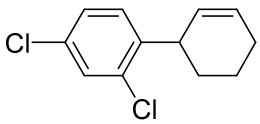
Synthesis of ethyl 2-(2-((triisopropylsilyl)oxy)benzyl)acrylate (166g)



Arene **166g** was prepared *via* **TP22** using (2-iodophenoxy)triisopropylsilane (376 mg, 1.00 mmol) and *s*Bu$_2$Zn·2LiOR (**161c**, 0.62 mL, 0.60 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (38 mg, 0.2 mmol) was added. After stirring at 0 °C for 30 min, ethyl 2-(bromomethyl)acrylate (289 mg, 1.50 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 10:0.5) to give **166g** (300 mg, 827 µmol, 83%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.09 (dd, *J* = 8.2, 6.5 Hz, 2H), 6.87 (td, *J* = 7.4, 1.2 Hz, 1H), 6.80 (dt, *J* = 7.3, 1.1 Hz, 1H), 6.20 (q, *J* = 1.4 Hz, 1H), 5.22 (q, *J* = 1.7 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.64 (t, *J* = 1.6 Hz, 2H), 1.34 – 1.23 (m, 6H), 1.08 (d, *J* = 7.3 Hz, 18H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.4, 154.2, 139.7, 131.0, 128.9, 127.6, 125.5, 120.8, 118.1, 60.7, 32.6, 18.2, 14.4, 13.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2945, 2867, 1718, 1491, 1453, 1265, 1132, 1108, 910, 755, 683.
MS (EI, 70 eV): m/z (%) = 319 (100), 291 (33), 175 (23), 161 (24), 159 (17), 149 (18), 131 (35), 115 (18), 103 (46), 89 (14), 75 (55), 61 (11).
HRMS (EI) for $C_{18}H_{27}O_3Si$ (319.1729): 319.1725 (M^+-*i*Pr).

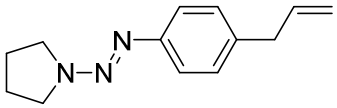
Synthesis of 2',4'-dichloro-1,2,3,4-tetrahydro-1,1'-biphenyl (166j)



Arene **166j** was prepared *via* **TP22** using 2,4-dichloro-1-iodobenzene (273 mg, 1.00 mmol) and *s*Bu$_2$Zn·2LiOR (**161c**, 0.85 mL, 0.60 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (38 mg, 0.20 mmol) was added. After stirring at 0 °C for 30 min, 3-bromo cyclohexene (0.17 mL, 1.50 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 1000:1) to give **166j** (202 mg, 889 µmol, 89%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.36 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.22 – 7.17 (m, 2H), 5.98 (m, 1H), 5.66 – 5.56 (m, 1H), 3.84 (m, 1H), 2.15 – 2.01 (m, 3H), 1.65 (m, 2H), 1.52 – 1.41 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.1, 134.4, 132.3, 130.2, 129.8, 129.2, 128.8, 127.0, 37.7, 30.0, 25.1, 20.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3020, 2928, 2858, 2834, 2360, 1587, 1557, 1468, 1378, 1101, 1052, 881, 865, 819, 804, 728, 681, 670.
MS (EI, 70 eV): m/z (%) = 226 (57), 211 (23), 192 (41), 165 (32), 163 (100), 155 (20), 128 (55), 127 (20).
HRMS (EI) for $C_{12}H_{12}Cl_2$ (226.0316): 226.0311 (M^+).

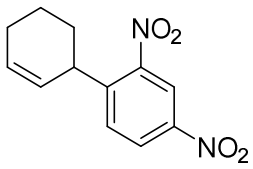
Synthesis of 1-((4-allylphenyl)diazenyl)pyrrolidine (166q)



Arene **166q** was prepared *via* **TP22** using 1-((4-iodophenyl)diazenyl)pyrrolidine (301 mg, 1.00 mmol) and *s*Bu_2Zn·2LiOR (**161c**, 0.58 mL, 0.60 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (38 mg, 0.20 mmol) was added. After stirring at 0 °C for 30 min, allyl bromide (0.13 mL, 1.50 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 10:0.2) to give **166q** (166 mg, 771 µmol, 77%) as a light yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.38 – 7.33 (m, 2H), 7.18 – 7.13 (m, 2H), 5.99 (m, 1H), 5.13 – 5.02 (m, 2H), 3.79 (s, 4H), 3.38 (dt, *J* = 6.6, 1.6 Hz, 2H), 2.06 – 1.96 (m, 4H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.9, 137.9, 136.9, 129.1, 120.4, 115.6, 48.8, 39.9, 23.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3025, 2986, 2972, 2921, 2874, 1500, 1427, 1404, 1347, 1319, 1261, 1154, 886, 923, 849, 810, 689.
MS (EI, 70 eV): m/z (%) = 215 (9), 145 (92), 117 (7), 115 (100), 91 (29).
HRMS (EI) for $C_{13}H_{17}N_3$ (215.1422): 215.1416 (M^+).
M.p. (°C): 50–52.

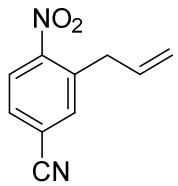
Synthesis of 2',4'-dinitro-1,2,3,4-tetrahydro-1,1'-biphenyl (166s)



Arene **166s** was prepared *via* **TP22** using 1-iodo-2,4-dinitrobenzene (294 mg, 1.00 mmol) and $Tol_2Zn \cdot 2LiOR$ (**167**, 0.76 mL, 0.60 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (38 mg, 0.20 mmol) was added. After stirring at 0 °C for 30 min, 3-bromocyclohexene (0.17 mL, 1.50 mmol) was added and the reaction stirred for 2 h at the same temperature. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.8:0.2) to give **166s** (196 mg, 0.79 mmol, 79%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.62 (d, J = 2.4 Hz, 1H), 8.38 – 8.31 (m, 1H), 7.69 (d, J = 8.7 Hz, 1H), 6.10 – 6.01 (m, 1H), 5.57 (m, 1H), 4.02 (m, 1H), 2.27 – 2.18 (m, 1H), 2.17 – 2.10 (m, 2H), 1.80 – 1.61 (m, 2H), 1.51 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.6, 147.9, 146.2, 131.9, 131.2, 127.3, 126.7, 119.8, 37.3, 31.6, 24.8, 20.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3105, 3025, 2930, 1603, 1526, 1447, 1341, 1065, 901, 834, 788, 743, 724, 661.
MS (EI, 70 eV): m/z (%) = 231 (56), 214 (32), 203 (32), 191 (94), 185 (61), 184 (51), 175 (35), 168 (43), 167 (100), 166 (28), 157 (64), 156 (61), 155 (21), 154 (26), 153 (41), 152 (58), 145 (39), 139 (34), 130 (31), 129 (24), 129 (38), 128 (77), 127 (30), 126 (23), 117 (27), 115 (96), 102 (28), 89 (36), 77 (39).
HRMS (EI) for $C_{12}H_{12}N_2O_4$ (248.0797): 248.0746 (M^+).

Synthesis of 3-allyl-4-nitrobenzonitrile (166t)

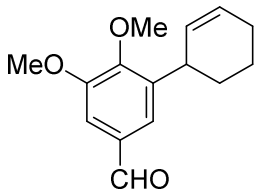


Arene **166t** was prepared *via* **TP22** using 3-iodo-4-nitrobenzonitrile (132 mg, 0.48 mmol) and $Tol_2Zn \cdot 2LiOR$ (**167**, 0.42 mL, 0.29 mmol) at -15 °C for 15 min. After the exchange was complete, the reaction was cooled to -40 °C and CuI (19 mg, 0.10 mmol) and allyl bromide (0.06 mL, 0.72 mmol)

were added and the reaction stirred for 30 min at the same temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **166t** (64 mg, 340 µmol, 71%) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.21 (d, *J* = 1.8 Hz, 1H), 7.82 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.62 – 7.53 (m, 1H), 5.93 (m, 1H), 5.29 – 5.08 (m, 2H), 3.75 (dt, *J* = 6.5, 1.5 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.5, 140.4, 135.9, 133.5, 133.3, 128.5, 118.9, 116.7, 111.9, 37.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2983, 2236, 1616, 1531, 1412, 1352, 1195, 1074, 995, 922, 902, 845, 812, 678.
MS (EI, 70 eV): m/z (%) = 187 (24), 171 (98), 154 (40), 143 (49), 142 (57), 141 (40), 140 (100), 129 (55), 116 (82), 114 (32), 113 (36), 89 (40).
HRMS (EI) for $C_{10}H_7N_2O_2$ (187.0508): 187.0498 (M^+-H^+).

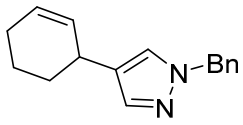
Synthesis of 5,6-dimethoxy-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carbaldehyde (166u)



Arene **166u** was prepared *via* **TP22** using 3-iodo-4,5-dimethoxybenzaldehyde (115 mg, 0.394 mmol) and *t*Bu_2Zn·2LiOR (**168**, 0.35 mL, 0.24 mmol) at 0 °C for 10 min. After the exchange was complete, CuI (15 mg, 0.08 mmol) and 3-bromo cyclohexene (0.07 mL, 0.59 mmol) were added and the reaction stirred for 30 min at the same temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **166u** (47 mg, 191 µmol, 48%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.87 (s, 1H), 7.34 (dd, *J* = 13.0, 1.9 Hz, 2H), 5.96 (dtd, *J* = 9.9, 3.7, 2.4 Hz, 1H), 5.65 – 5.57 (m, 1H), 3.97 – 3.78 (m, 7H), 2.18 – 1.95 (m, 3H), 1.78 – 1.59 (m, 2H), 1.50 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.8, 153.3, 152.4, 140.7, 132.3, 129.6, 129.4, 125.7, 108.6, 61.2, 56.0, 34.9, 31.2, 25.1, 21.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3018, 2932, 2858, 2835, 2736, 1689, 1583, 1482, 1455, 1426, 1386, 1296, 1134, 1086, 1002, 977, 859, 723, 670.
MS (EI, 70 eV): m/z (%) = 246 (100), 231 (42), 217 (31), 192 (28), 165 (22), 137 (17), 115 (15).
HRMS (EI) for $C_{15}H_{18}O_3$ (246.1256): 246.1249 (M^+).

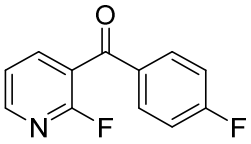
Synthesis of 1-benzyl-4-(cyclohex-2-en-1-yl)-1H-pyrazole (169c)



Pyrazole **169c** was prepared *via* **TP22** using 1-benzyl-4-iodopyrazole (142 mg, 0.50 mmol) and *s*Bu$_2$Zn·2LiOR (**161c**, 0.38 mL, 0.30 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (19 mg, 0.10 mmol) was added. After stirring at 0 °C for 30 min, 3-bromo cyclohexene (0.09 mL, 0.75 mmol) was added and the reaction stirred for 2 h at room temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate:triethylamine = 9:1:0.1) to give **169c** (95 mg, 0.40 mmol, 80%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.32 (s, 1H), 7.28 – 7.17 (m, 3H), 7.14 – 7.10 (m, 2H), 7.09 (s, 1H), 5.71 – 5.59 (m, 2H), 5.17 (s, 2H), 3.27 – 3.23 (m, 1H), 1.97 – 1.84 (m, 3H), 1.67 – 1.41 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 138.3, 137.0, 130.3, 128.8, 128.0, 127.7, 127.6, 127.1, 127.1, 56.1, 31.7, 31.6, 25.0, 20.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933, 1709, 1649, 1455, 1431, 1358, 1221, 1177, 1072, 996, 848, 714.
MS (EI, 70 eV): m/z (%) = 238 (48), 147 (17), 119 (29), 91 (100), 65 (16).
HRMS (EI) for $C_{16}H_{18}N_2$ (238.1470): 238.1465 (M^+).

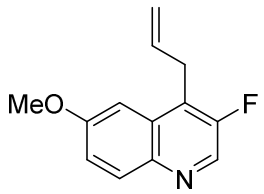
Synthesis of (4-fluorophenyl)(2-fluoropyridin-3-yl)methanone (169d)



Pyridine **169d** was prepared *via* **TP22** using 2-fluoro-3-iodopyridine (118 mg, 0.53 mmol) and *s*Bu$_2$Zn·2LiOR (**161c**, 0.38 mL, 0.32 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (61 mg, 0.32 mmol) was added. After stirring at 0 °C for 30 min, 4-fluorobenzoyl chloride (0.19 mL, 1.59 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 8:2) to give **169d** (111 mg, 506 µmol, 96%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.41 (ddd, *J* = 4.9, 2.1, 1.1 Hz, 1H), 8.03 (ddd, *J* = 9.2, 7.4, 2.0 Hz, 1H), 7.88 – 7.81 (m, 2H), 7.37 (ddd, *J* = 7.3, 4.9, 1.9 Hz, 1H), 7.20 – 7.12 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.2 (d, *J* = 5 Hz), 166.2 (d, *J* = 257 Hz), 156.0 (d, *J* = 243 Hz), 150.6 (d, p*J* = 15 Hz), 141.8 (d, *J* = 3 Hz), 132.9 (t, *J* = 3, 1 Hz), 132.4 (dd, *J* = 10, 1 Hz), 121.8 (d, *J* = 5 Hz), 121.3 (d, *J* = 30 Hz), 116.0 (d, *J* = 22 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3071, 2360, 2343, 1664, 1596, 1573, 1412, 1430, 1229, 1150, 930, 855, 772.
MS (EI, 70 eV): m/z (%) = 219 (28), 123 (12), 123 (100), 96 (5), 75 (6).
HRMS (EI) for $C_{12}H_7F_2NO$ (219.0496): 219.0490 (M^+).
M.p. (°C): 77–78.

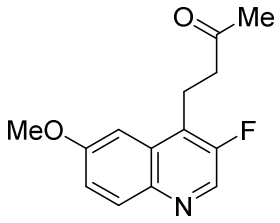
Synthesis of 4-allyl-3-fluoro-6-methoxyquinoline (169l)



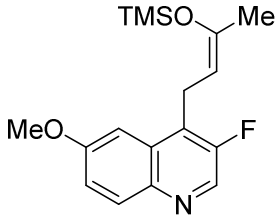
Quinoline **169l** was prepared *via* **TP22** using 3-fluoro-4-iodo-6-methoxyquinoline (155 mg, 0.51 mmol) and *s*Bu_2Zn·2LiOR (**161c**, 0.37 mL, 0.31 mmol) at 0 °C for 10 min. After the exchange was complete, CuI (19 mg, 0.09 mmol) was added. After stirring at 0 °C for 30 min, allyl bromide (0.07 mL, 0.77 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 9:1) to give **169l** (102 mg, 0.47 mmol, 92%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.61 (d, *J* = 1.2 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.14 (d, *J* = 2.8 Hz, 1H), 5.97 (ddt, *J* = 17.2, 10.1, 6.0 Hz, 1H), 5.11 (dq, *J* = 10.1, 1.6 Hz, 1H), 5.05 (dq, *J* = 17.0, 1.7 Hz, 1H), 3.90 (s, 3H), 3.77 (dq, *J* = 6.1, 1.7 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.62, 154.91 (d, *J* = 252.6 Hz), 141.60 (d, *J* = 2.5 Hz), 138.35 (d, *J* = 29.3 Hz), 133.72, 131.68, 129.33 (d, *J* = 3.6 Hz), 127.10 (d, *J* = 12.8 Hz), 120.52 (d, *J* = 2.7 Hz), 117.09, 102.09 (d, *J* = 5.5 Hz), 55.58, 28.39 (d, *J* = 4.0 Hz).
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3081, 3007, 2938, 2831, 2360, 1620, 1506, 1468, 1360, 1320, 1263, 1216, 1136, 1029, 908, 827, 784, 699, 674.
MS (ESI): m/z (%) = 218 (100).
HRMS (ESI) for $C_{13}H_{13}FNO$ (218.0981): 218.0974 (M^++H^+).

Synthesis of 4-(3-fluoro-6-methoxyquinolin-4-yl)butan-2-one (169m)



Step 1: Synthesis of **R**



Quinoline **R** was prepared *via* **TP22** using 3-fluoro-4-iodo-6-methoxyquinoline (155 mg, 0.51 mmol) and *s*$Bu_2Zn \cdot 2LiOR$ (**161c**, 0.44 mL, 0.31 mmol) at 0 °C for 10 min. After the exchange was complete, CuI (19 mg, 0.09 mmol) was added. After stirring at 0 °C for 30 min, a solution of methyl vinyl ketone (MVK, 0.13 mL, 0.53 mL) and TMSCl (0.28 mL, 2.15 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was obtained as a yellow oil and used as is in the next step.

Step 2: Synthesis of **169m**

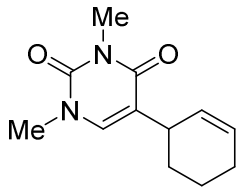
The crude product **R** was dissolved in THF (2.5 mL) and TBAF (1 M in THF, 0.6 mL, 0.6 mmol) added dropwise. The reaction was stirred at room temperature for 1 h. Then, a sat. aq. NH_4Cl solution (10 mL) was added and the reaction mixture extracted with ethyl acetate (3 x 30 mL). After purification *via* column chromatography (pentane:ethyl acetate = 7:3) **169m** (71 mg, 287 µmol, 56%) was obtained as a colorless solid over two steps.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.56 (d, *J* = 1.3 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.29 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.16 (d, *J* = 2.7 Hz, 1H), 3.92 (s, 3H), 3.28 (td, *J* = 8.3, 7.9, 1.8 Hz, 2H), 2.83 – 2.77 (m, 2H), 2.17 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 206.93, 158.87, 155.05 (d, *J* = 252.2 Hz), 141.63 (d, *J* = 2.4 Hz), 138.15 (d, *J* = 29.0 Hz), 131.85, 128.96 (d, *J* = 3.7 Hz), 128.81 (d, *J* = 12.7 Hz), 120.59 (d, *J* = 2.8 Hz), 101.57 (d, *J* = 5.4 Hz), 55.73, 42.45 (d, *J* = 1.3 Hz), 30.01, 18.20 (d, *J* = 3.5 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3003, 2958, 2835, 1712, 1620, 1508, 1469, 1359, 1229, 1207, 1027, 907, 829, 788, 731.
MS (EI): m/z (%) = 247 (100), 205 (11), 204 (91), 190 (60), 173 (19), 172 (20), 161 (11), 160 (11).
HRMS (EI) for $C_{14}H_{14}FNO_2$ (247.1009): 247.1003 (M^+).

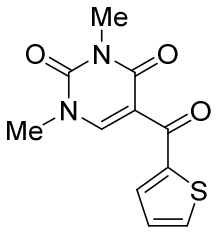
Synthesis of 5-(cyclohex-2-en-1-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (169n)



Uracil **169n** was prepared *via* **TP22** using 5-iodo-1,3-dimethyluracil (137 mg, 0.515 mmol) and *s*$Bu_2Zn \cdot 2LiOR$ (**161c**, 0.37 mL, 0.31 mmol) in THF (1 mL) at 0 °C for 10 min. After the exchange was complete, CuI (19 mg, 0.10 mmol) was added. After stirring at 0 °C for 30 min, 3-bromo cyclohexene (0.09 mL, 0.77 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate:triethylamine = 6:4:0.1) to give **169n** (91 mg, 413 µmol, 80%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.87 (d, *J* = 0.8 Hz, 1H), 5.93 (dtd, *J* = 9.8, 3.7, 2.1 Hz, 1H), 5.49 (ddt, *J* = 10.1, 4.0, 2.2 Hz, 1H), 3.54 – 3.47 (m, 1H), 3.38 (s, 3H), 3.35 (s, 3H), 2.06 – 1.99 (m, 2H), 1.97 – 1.87 (m, 1H), 1.59 (m, 1H), 1.55 – 1.42 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.4, 151.8, 139.9, 130.6, 127.6, 117.2, 37.1, 32.4, 28.3, 28.1, 25.2, 19.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062, 3019, 2927, 2860, 2836, 1696, 1656, 1632, 1449, 1338, 1238, 1089, 784, 756.
MS (EI, 70 eV): m/z (%) = 220 (90), 205 (43), 192 (13), 191 (41), 179 (19), 166 (100), 165 (23), 153 (20), 148 (12), 134 (14), 107 (10).
HRMS (EI) for $C_{12}H_{16}N_2O_2$ (220.1212): 220.1205 (M^+).
M.p. (°C): 79–82.

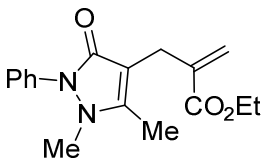
Synthesis of 1,3-dimethyl-5-(thiophene-2-carbonyl)pyrimidine-2,4(1H,3H)-dione (169o)



Uracil **169o** was prepared *via* **TP22** using 5-iodo-1,3-dimethyluracil (136 mg, 0.51 mmol) and *s*$Bu_2Zn\cdot 2LiOR$ (**161c**, 0.44 mL, 0.31 mmol) in THF (1 mL) at 0 °C for 10 min. After the exchange was complete, CuI (58 mg, 0.31 mmol) was added. After stirring at 0 °C for 30 min, 2-thiophenecarbonyl chloride (0.17 mL, 1.53 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 4:6) to give **169o** (99 mg, 396 µmol, 77%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.88 (s, 1H), 7.78 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.68 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.13 (dd, *J* = 4.9, 3.9 Hz, 1H), 3.51 (s, 3H), 3.41 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 181.8, 160.4, 151.2, 148.2, 143.5, 135.0, 134.8, 128.1, 113.5, 37.9, 28.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3105, 301, 2953, 1706, 1648, 1635, 1599, 1410, 1335, 1220, 1056, 794, 748, 670.
MS (EI, 70 eV): m/z (%) = 250 (61), 222 (21), 221 (100), 207 (15), 167 (27), 124 (11), 111 (58).
HRMS (EI) for $C_{11}H_{10}N_2O_3S$ (250.0412): 250.0409 (M^+).
M.p. (°C): 193–196.

Synthesis of ethyl 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)methyl)acrylate (169p)

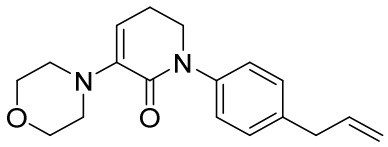


Antipyrine **169p** was prepared *via* **TP22** using iodoantipyrine (145 mg, 0.46 mmol) and *s*$Bu_2Zn\cdot 2LiOR$ (**161c**, 0.33 mL, 0.28 mmol) in THF (1 mL) at 0 °C for 10 min. After the exchange was complete, CuI (19 mg, 0.09 mmol) was added. After stirring at 0 °C for 30 min, ethyl 2-(bromomethyl)acrylate (134 mg, 0.69 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up,

the crude product was purified *via* column chromatography (pentane:ethyl acetate = 4:6) to give **169p** (103 mg, 343 µmol, 74%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.44 – 7.37 (m, 4H), 7.22 (ddt, *J* = 6.6, 5.7, 2.6 Hz, 1H), 6.22 (q, *J* = 1.0 Hz, 1H), 5.71 (q, *J* = 1.5 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.30 (t, *J* = 1.2 Hz, 2H), 3.01 (s, 3H), 2.21 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.1, 166.0, 154.4, 137.3, 135.5, 129.1, 126.3, 126.1, 123.4, 107.6, 60.8, 36.4, 24.8, 14.3, 11.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2906, 1713, 1667, 1595, 1496, 1292, 1254, 1025, 946, 757, 696.
MS (EI, 70 eV): m/z (%) = 300 (31), 299 (31), 271 (89), 255 (19), 254 (20), 227 (100), 226 (19), 208 (18), 207 (29), 201 (19), 196 (18), 152 (22), 124 (18).
HRMS (EI) for $C_{17}H_{20}N_2O_3$ (300.1474): 300.1471 (M^+).

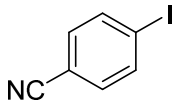
Synthesis of 1-(4-allylphenyl)-3-(piperidin-1-yl)-5,6-dihydropyridin-2(1H)-one (169q)



Quinoline **169q** was prepared *via* **TP22** using 1-(4-iodophenyl)-3-(piperidin-1-yl)-5,6-dihydropyridin-2(1H)-one (76 mg, 0.20 mmol) and *s*Bu_2Zn·2LiOR (**161c**, 0.17 mL, 0.12 mmol) at 0 °C for 10 min. After the exchange was complete, CuI (8 mg, 0.04 mmol) was added. After stirring at 0 °C for 30 min, allyl bromide (0.03 mL, 0.30 mmol) was added and the reaction stirred for 2 h at room temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 6:4) to give **169q** (50 mg, 168 µmol, 85%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.37 – 7.26 (m, 4H), 6.09 – 5.97 (m, 1H), 5.71 (t, *J* = 4.7 Hz, 1H), 5.21 – 5.11 (m, 2H), 3.93 – 3.88 (m, 4H), 3.85 (t, *J* = 6.7 Hz, 2H), 3.48 – 3.43 (m, 2H), 3.01 – 2.96 (m, 4H), 2.60 – 2.52 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.5, 143.9, 141.0, 138.0, 137.3, 129.0, 125.1, 116.0, 114.2, 66.9, 50.6, 48.7, 39.9, 23.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2924, 2892, 2854, 2818, 1659, 1620, 1511, 1219, 1118, 924, 811, 782.
MS (EI): m/z (%) = 298 (5), 280 (100), 279 (29), 239 (34), 212 (55), 146 (39), 117 (18), 115 (27).
HRMS (EI) for $C_{19}H_{24}N_2O$ (298.1681): 298.1681 (M^+).

Synthesis of 4-iodobenzonitrile (170a)

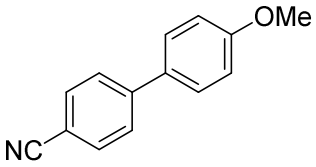


Benzonitrile **170a** was prepared *via* **TP23** using 4-bromobenzonitrile (94 mg, 516 µmol) and *s*Bu_2Zn·2LiOR (**161c**, 0.55 mL, 413 µmol). After the exchange was complete, a solution of I_2 (262 mg, 1.03 mmol) in THF (2 mL) was added and the reaction stirred for 30 min. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **170a** (91 mg, 397 µmol, 77%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.88 – 7.81 (m, 2H), 7.40 – 7.32 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 138.6, 133.3, 118.3, 111.8, 100.5.

The spectra matched those of the literature.[147]

Synthesis of 4'-methoxy-[1,1'-biphenyl]-4-carbonitrile (170b)



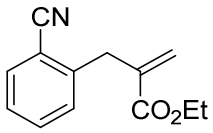
Biaryl **170b** was prepared *via* **TP23** using 4-bromobenzonitrile (52 mg, 286 µmol) and *s*Bu_2Zn·2LiOR (**161c**, 0.305 mL, 229 µmol). After the exchange was complete, $Pd(OAc)_2$ (2 mg, 9 µmol), SPhos (7 mg, 17 µmol) and 4-iodoanisole (53 mg, 0.23 mmol) were added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **170b** (31 mg, 148 µmol, 64%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.72 – 7.61 (m, 4H), 7.57 – 7.50 (m, 2H), 7.04 – 6.97 (m, 2H), 3.87 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.3, 145.3, 132.7, 131.6, 128.5, 127.2, 119.3, 114.7, 110.2, 55.5.

[147] Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236–2239.

The spectra matched those of the literature.[148]

Synthesis of ethyl 2-(2-cyanobenzyl)acrylate (170c)

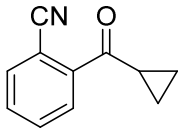


Benzonitrile **170c** was prepared *via* **TP23** using 2-bromobenzonitrile (89 mg, 0.49 mmol) and *s*Bu$_2$Zn·2LiOR (**161c**, 0.47 mL, 0.39 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (19 mg, 0.10 mmol) was added. After stirring at 0 °C for 30 min, ethyl 2-(bromomethyl)acrylate (171 mg, 0.74 mmol) was added and the reaction stirred for 2 h at the same temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 7:3) to give **170c** (66 mg, 0.31 mmol, 63%) as a colorless oil.

^{1}H-NMR (400 MHz, CDCl$_3$): δ / ppm = 7.63 (ddd, *J* = 7.8, 1.5, 0.6 Hz, 1H), 7.51 (td, *J* = 7.7, 1.4 Hz, 1H), 7.37 (ddd, *J* = 7.9, 1.2, 0.6 Hz, 1H), 7.32 (td, *J* = 7.6, 1.2 Hz, 1H), 6.33 (q, *J* = 0.9 Hz, 1H), 5.57 (q, *J* = 1.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, CDCl$_3$): δ / ppm = 166.3, 142.8, 138.3, 133.0, 132.9, 130.3, 127.6, 127.2, 118.0, 113.1, 61.1, 36.7, 14.2.

The spectra matched those of the literature.[149]

Synthesis of 2-(cyclopropanecarbonyl)benzonitrile (170d)



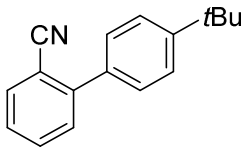
Benzonitrile **170d** was prepared *via* **TP23** using 2-bromobenzonitrile (85 mg, 0.47 mmol) and *s*Bu$_2$Zn·2LiOR (**161c**, 0.48 mL, 0.38 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (71 mg, 0.38 mmol) was added. After stirring at 0 °C for 30 min, cyclopropanecarbonyl chloride (147 mg, 1.41 mmol) was added and the reaction stirred for 12 h at room temperature. After

[148] S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205–9209.
[149] M. Ketels, M. A. Ganiek, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12770–12773.

work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 7:3) to give **170d** (54 mg, 315 µmol, 67%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.99 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.79 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.71 (td, *J* = 7.7, 1.4 Hz, 1H), 7.62 (td, *J* = 7.6, 1.3 Hz, 1H), 2.59 (tt, *J* = 7.7, 4.5 Hz, 1H), 1.35 (p, *J* = 3.8 Hz, 2H), 1.16 (dq, *J* = 7.4, 3.7 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 199.6, 141.5, 134.8, 132.7, 132.0, 129.3, 118.1, 110.8, 19.4, 13.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3076, 3006, 2220, 1673, 1590, 1571, 1486, 1383, 1223, 989, 871, 756.
MS (EI, 70 eV): m/z (%) = 170 (10), 143 (13), 130 (100), 115 (8), 75 (6).
HRMS (EI) for $C_{11}H_9NO$ (171.0684): 171.0678 (M^+).
M.p. (°C): 66-67.

Synthesis of 4'-(tert-butyl)-[1,1'-biphenyl]-2-carbonitrile (170e)



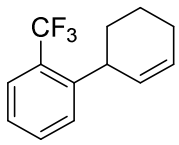
Biaryl **170e** was prepared *via* **TP23** using 2-bromobenzonitrile (93 mg, 0.51 mmol) and *s*$Bu_2Zn\cdot 2LiOR$ (**161c**, 0.49 mL, 0.41 mmol). After the exchange was complete, the reaction was cooled to 0 °C and TMSCl (0.05 mL, 0.41 mmol) added at 0 °C and stirred for 10 min. Then, $Pd(OAc)_2$ (4 mg, 15 µmol), SPhos (13 mg, 31 µmol) and 4-*tert*butyliodobenzene (107 mg, 0.41 mmol) were added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 10:0.2) to give **170e** (62 mg, 263 µmol, 64%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.76 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H), 7.63 (ddd, *J* = 7.5, 1.4 Hz, 1H), 7.54 – 7.50 (m, 5H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H), 1.38 (s, 9H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 151.9, 145.6, 135.3, 133.9, 132.9, 130.2, 128.6, 127.4, 125.8, 119.1, 111.2, 34.8, 31.4.

The spectra matched those of the literature.[150]

[150] S. Sarkar, M. Jana, T. Narender, *Eur. J. Org. Chem.* **2013**, *2013*, 6491–6495.

Synthesis of 2'-(trifluoromethyl)-1,2,3,4-tetrahydro-1,1'-biphenyl (170f)

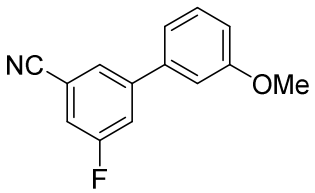


Arene **170f** was prepared *via* **TP23** using 1-bromo-2-(trifluoromethyl)benzene (238 mg, 1.06 mmol) and *s*Bu_2Zn·2LiOR (**161c**, 1.15 mL, 0.85 mmol). After the exchange was complete, the reaction was cooled to 0 °C and a 1 M CuCN·2LiCl solution in THF (0.21 mL, 0.21 mmol) was added. After stirring at 0 °C for 10 min, 3-bromocyclohexene (0.18 mL, 1.59 mmol) was added and the reaction stirred for 2 h at the same temperature. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:diethyl ether = 1000:1) to give **170f** (185 mg, 818 µmol, 77%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.61 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.52 – 7.40 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 5.97 – 5.87 (m, 1H), 5.64 – 5.55 (m, 1H), 3.86 – 3.77 (m, 1H), 2.17 – 2.03 (m, 3H), 1.86 – 1.76 (m, 1H), 1.74 – 1.61 (m, 1H), 1.53 – 1.41 (m, 1H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 145.84 (d, *J* = 1.5 Hz), 131.90, 130.02 (d, *J* = 29.3 Hz), 128.71, 128.03 (q, *J* = 29.2 Hz), 126.18, 126.04, 125.70 (q, *J* = 5.9 Hz), 123.45, 37.93 (d, *J* = 2.0 Hz), 32.84, 24.96, 21.79.

The spectra matched those of the literature.[151]

Synthesis of 5-fluoro-3'-methoxy-[1,1'-biphenyl]-3-carbonitrile (170g)



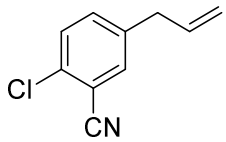
Biaryl **170g** was prepared *via* **TP23** using 3-bromo-5-fluorobenzonitrile (193 mg, 0.96 mmol) and *s*Bu_2Zn·2LiOR (**161c**, 1.04 mL, 0.77 mmol). After stirring at 25 °C for 30 min the exchange was complete, the reaction cooled to 0 °C and TMSCl (0.08 mL, 0.77 mmol) added at 0 °C and stirred for 10 min. Then, $Pd(OAc)_2$ (7 mg, 29 µmol), SPhos (25 mg, 58 µmol) and 3-iodoanisole (157 mg, 0.67 mmol) were added and the reaction stirred for 12 h at room temperature. After work-up, the crude

[151] L. Baker, T. Minehan, *J. Org. Chem.* **2004**, *69*, 3957–3960.

product was purified *via* column chromatography (pentane:ethyl acetate = 10:0.5) to give **170g** (93 mg, 409 µmol, 60%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.66 (t, *J* = 1.5 Hz, 1H), 7.51 (ddd, *J* = 9.6, 2.5, 1.6 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.32 (ddd, *J* = 7.7, 2.5, 1.4 Hz, 1H), 7.12 (ddd, *J* = 7.6, 1.8, 0.9 Hz, 1H), 7.05 (t, *J* = 2.1 Hz, 1H), 6.98 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 3.88 (s, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.6 (d, *J* = 250.1 Hz), 160.3, 145.0 (d, *J* = 8.1 Hz), 139.2 (d, *J* = 2.1 Hz), 130.5, 126.9 (d, *J* = 3.2 Hz), 119.5, 119.1 (d, *J* = 21.8 Hz), 117.8 (d, *J* = 3.5 Hz), 117.7 (d, *J* = 24.7 Hz), 114.4, 114.2 (d, *J* = 10.0 Hz), 112.9, 55.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3081, 2928, 2234, 1580, 1460, 1440, 1403, 1332, 1287, 1240, 1193, 1134, 1046, 966, 865, 776, 685.
MS (EI, 70 eV): m/z (%) = 228 (15), 227 (100), 197 (49), 196 (15), 184 (26), 158 (29).
HRMS (EI) for $C_{14}H_{10}FNO$ (227.0746): 227.0740 (M^+).
M.p. (°C): 109-110.

Synthesis of 5-allyl-2-chlorobenzonitrile (170h)

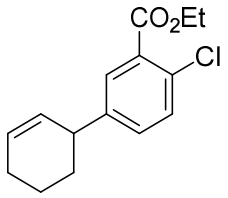


Arene **170h** was prepared *via* **TP23** using 5-bromo-2-chlorobenzonitrile (222 mg, 1.03mmol) and *s*Bu_2Zn·2LiOR (**161c**, 1.11 mL, 0.82 mmol). After stirring at 25 °C for 1 h the exchange was complete and the reaction cooled to 0 °C and a 1 M CuCN·2LiCl solution in THF (0.21 mL, 0.21 mmol) was added. After stirring at 0 °C for 10 min, allyl bromide (0.13 mL, 1.55 mmol) was added and the reaction stirred for 1 h at the same temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 10:0.2) to give **170h** (144 mg, 811 µmol, 79%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.5 (d, *J* = 2.1 Hz, 1H), 7.4 (d, *J* = 8.4 Hz, 1H), 7.4 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.9 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H), 5.2 – 5.1 (m, 2H), 3.4 – 3.3 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 139.8, 135.4, 134.6, 134.4, 134.0, 130.0, 117.8, 116.2, 113.3, 39.0.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3082, 3981, 2902, 2837, 1711, 1640, 1472, 1432, 1359, 1221, 1155, 1055, 994, 919, 829, 822.
MS (EI, 70 eV): m/z (%) = 179 (17), 177 (54), 150 (10), 143 (10), 142 (100), 141 (11), 140 (33); 115 (70).

HRMS (EI) for $C_{10}H_8NCl$ (177.0345): 177.0338 (M^+).

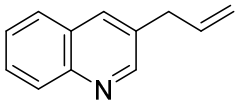
Synthesis of ethyl 4-chloro-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylate (170i)



Arene **170i** was prepared *via* **TP23** using ethyl 5-bromo-2-chlorobenzoate (130 mg, 0.49 mmol) and *s*Bu_2Zn·2LiOR (**161c**, 0.46 mL, 0.39 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (18 mg, 0.10 mmol) was added. After stirring at 0 °C for 30 min, 3-bromo cyclohexene (0.09 mL, 0.74 mmol) was added and the reaction stirred for 12 h at the same temperature. After work-up, the crude product was purified *via* column chromatography (pentane:ethyl acetate = 10:0.05) to give **170i** (95 mg, 359 µmol, 73%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.55 (d, *J* = 2.3 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.20 – 7.17 (m, 1H), 5.90 – 5.82 (m, 1H), 5.61 – 5.55 (m, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.39 – 3.30 (m, 1H), 2.06 – 1.98 (m, 2H), 1.98 – 1.90 (m, 1H), 1.69 – 1.59 (m, 1H), 1.59 – 1.49 (m, 1H), 1.49 – 1.39 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.3, 145.6, 131.9, 131.0, 130.9, 130.6, 130.5, 129.5, 129.1, 61.7, 41.2, 32.5, 25.0, 21.0, 14.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3020, 2981, 2930, 2858, 1731, 1472, 1294, 1251, 1189, 1118, 1045, 827.
MS (EI, 70 eV): m/z (%) = 264 (100), 219 (48), 191 (46), 183 (52), 163 (67), 129 (55), 128 (98), 115 (50).
HRMS (EI) for $C_{15}H_{17}ClO_2$ (264.0917): 264.0912 (M^+).

Synthesis of 3-allylquinoline (170j)



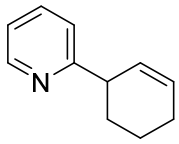
Quinoline **170j** was prepared *via* **TP23** using 3-bromoquinoline (100 mg, 0.48 mmol) and *s*Bu_2Zn·2LiOR (**161c**, 0.45 mL, 0.38 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (18 mg, 0.10 mmol) was added. After stirring at 0 °C for 30 min, allyl bromide

(0.07 mL, 0.72 mmol) was added and the reaction stirred for 2 h at the same temperature. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **170j** (57 mg, 337 µmol, 70%) as a light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.77 (d, *J* = 2.2 Hz, 1H), 8.09 (dq, *J* = 8.4, 0.9 Hz, 1H), 7.92 (dd, *J* = 2.2, 1.0 Hz, 1H), 7.76 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.66 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.11 – 5.95 (m, 1H), 5.21 – 5.09 (m, 2H), 3.62 – 3.53 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 152.1, 147.1, 136.2, 134.7, 132.7, 129.3, 128.9, 128.3, 127.5, 126.8, 117.2, 37.5.

The spectra matched those of the literature.[152]

Synthesis of 2-(cyclohex-2-en-1-yl)pyridine (170k)

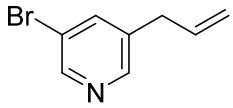


Pyridine **170k** was prepared *via* **TP23** using 2-bromopyridine (82 mg, 0.52 mmol) and *s*Bu_2Zn·2LiOR (**161c**, 0.56 mL, 0.42 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (18 mg, 0.10 mmol) was added. After stirring at 0 °C for 30 min, 3-bromo cyclohexene (0.09 mL, 0.78 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **170k** (51 mg, 0.32 mmol, 62%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.53 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.59 (td, *J* = 7.6, 1.9 Hz, 1H), 7.18 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.09 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 5.96 – 5.89 (m, 1H), 5.81 – 5.75 (m, 1H), 3.62 – 3.51 (m, 1H), 2.18 – 1.97 (m, 3H), 1.79 – 1.58 (m, 3H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.5, 149.4, 136.5, 129.1, 128.8, 121.9, 121.2, 44.1, 30.8, 25.0, 21.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3018, 2928, 2859, 2835, 2360, 1587, 1568, 1469, 1432, 1150, 880, 774, 749, 723, 686.
MS (EI, 70 eV): m/z (%) = 159 (2), 158 (20), 144 (16), 131 (10), 130 (100), 117 (14).
HRMS (EI) for $C_{11}H_{13}N$ (159.1048): 159.1041 (M^+).

[152] D. Seomoon, P. H. Lee, *J. Org. Chem.* **2008**, *73*, 1165–1168.

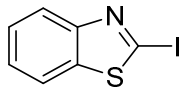
Synthesis of 3-allyl-5-bromopyridine (170l)



Pyridine **170l** was prepared *via* **TP23** using 3,5-dibromopyridine (235 mg, 1.00 mmol) and *s*$Bu_2Zn \cdot 2LiOR$ (**161c**, 0.76 mL, 0.60 mmol). After the exchange was complete, the reaction was cooled to 0 °C and CuI (38 mg, 0.20 mmol) was added. After stirring at 0 °C for 30 min, allyl bromide (0.13 mL, 1.50 mmol) was added and the reaction stirred for 12 h at room temperature. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9.7:0.3) to give **170l** (120 mg, 0.61 mmol, 61%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.56 (d, J = 2.1 Hz, 1H), 8.40 (d, J = 1.5 Hz, 1H), 7.69 (t, J = 2.0 Hz, 1H), 5.99 – 5.89 (m, 1H), 5.23 – 5.11 (m, 2H), 3.40 (d, J = 6.6 Hz, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 148.7, 148.1, 138.8, 137.2, 135.2, 120.7, 117.7, 36.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 2356, 1640, 1580, 1555, 1421, 1096, 1022, 993, 921, 884, 851.
MS (EI, 70 eV): m/z (%) = 199 (36), 198 (99), 197 (36), 196 (100), 118 (39), 117 (84), 91 (23).
HRMS (EI) for C_8H_8BrN (196.9840): 196.9833 (M^+).

Synthesis of 2-iodobenzothiazole (170m)



Benzothiazole **170m** was prepared *via* **TP23** using 2-bromobenzothiazole (110 mg, 0.51 mmol) and *s*$Bu_2Zn \cdot 2LiOR$ (**161c**, 0.55 mL, 41 mmol). After the exchange was complete, a solution of I_2 (261 mg, 1.02 mmol) in THF (2 mL) was added and the reaction stirred for 30 min. After work-up, the crude product was purified *via* column chromatography (*iso*hexane:ethyl acetate = 9:1) to give **170m** (100 mg, 383 µmol, 75%) as a colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.06 – 8.00 (m, 1H), 7.87 – 7.81 (m, 1H), 7.48 – 7.34 (m, 2H).
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.3, 139.2, 126.5, 125.7, 122.7, 120.6, 105.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3054, 3026, 2965, 2927, 2831, 1451, 1416, 1308, 1228, 951, 940, 750, 722.
MS (EI, 70 eV): m/z (%) = 260 (100), 134 (35), 90 (6).
HRMS (EI) for C_7H_4INS (260.9109): 260.9103 (M^+).
M.p. (°C): 79–80.

9 Single Crystal X-Ray Diffraction Studies

Single crystals of compound **134f, 134g, 137g, 138g, 141i**, and **155c** suitable for X-ray diffraction, were obtained by slow evaporation of dichloromethane solutions. Single crystals of compound **114b**,**153a**, and **156c** suitable for X-ray diffraction, were obtained by vapour diffusion: **114b**, **153a**, and **156c** were dissolved in dichloromethane in a small vial which was placed in a larger vial containing *iso*hexane which was then closed and left standing for several days. Single crystals of **151** was obtained by the following procedure: In a Schlenk tube under argon, pyridazine (46 mg, 0.58 mmol) was dissolved in THF (1.45 mL) to obtain a 0.4 M solution. Then, BF_3 (0.08 mL, 0.58 mmol) was added and the mixture shaken for 5 seconds. After closing the Schlenk tube with a glass stopper, crystals formed after 1 week at room temperature. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection was performed with the CrysAlis CCD software;[a)] CrysAlis RED software[b)] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method[c)] was applied. The structures were solved with SHELXS-97,[d)] refined with SHELXL-97[e)] and finally checked using PLATON.[f)] Details for data collection and structure refinement are summarized in Table 20, 24, 28, 32, 36, 40, 44, 48, 52 and 56.

CCDC 1559514 (**114b**), CCDC 1836478 (**134f**), CCDC 1836477 (**134g**), CCDC 1836476 (**136g**), CCDC 1836475 (**138g**), CCDC 1836479 (**141i**), CCDC 1906337 (**156c**), CCDC 1906338 (**155c**), CCDC 1906339 (**153a**), and CCDC 1906340 (**151**) contain the supplementary crystallographic data for this thesis. These data are provided free of charge by The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 20. Details for X-ray data collection and structure refinement for compound **114b**.

	114b
Empirical formula	$C_{15}H_{10}BrIN_2S$
Formula mass	457.12
T[K]	173(2)
Crystal size [mm]	0.47 × 0.04 × 0.03
Crystal description	colorless rod
Crystal system	orthorhombic
Space group	*Pbcn*
a [Å]	12.7276(4)
b [Å]	7.3359(3)
c [Å]	31.9815(9)
α [°]	90.0
β [°]	90.0
γ [°]	90.0
V [Å^3]	2986.06(18)
Z	8
$\rho_{calcd.}$ [g cm^{-3}]	2.034
μ [mm^{-1}]	4.951
F(000)	1744
Θ range [°]	4.29 – 25.24
Index ranges	$-16 \leq h \leq 16$
	$-9 \leq k \leq 9$
	$-42 \leq l \leq 42$
Reflns. collected	42322
Reflns. obsd.	2706
Reflns. unique	3681
	(R_{int} = 0.0717)
R_1, wR_2 (2σ data)	0.0366, 0.0670
R_1, wR_2 (all data)	0.0601, 0.0750
GOOF on F^2	1.082
Peak/hole [e Å^{-3}]	0.884 / -0.520

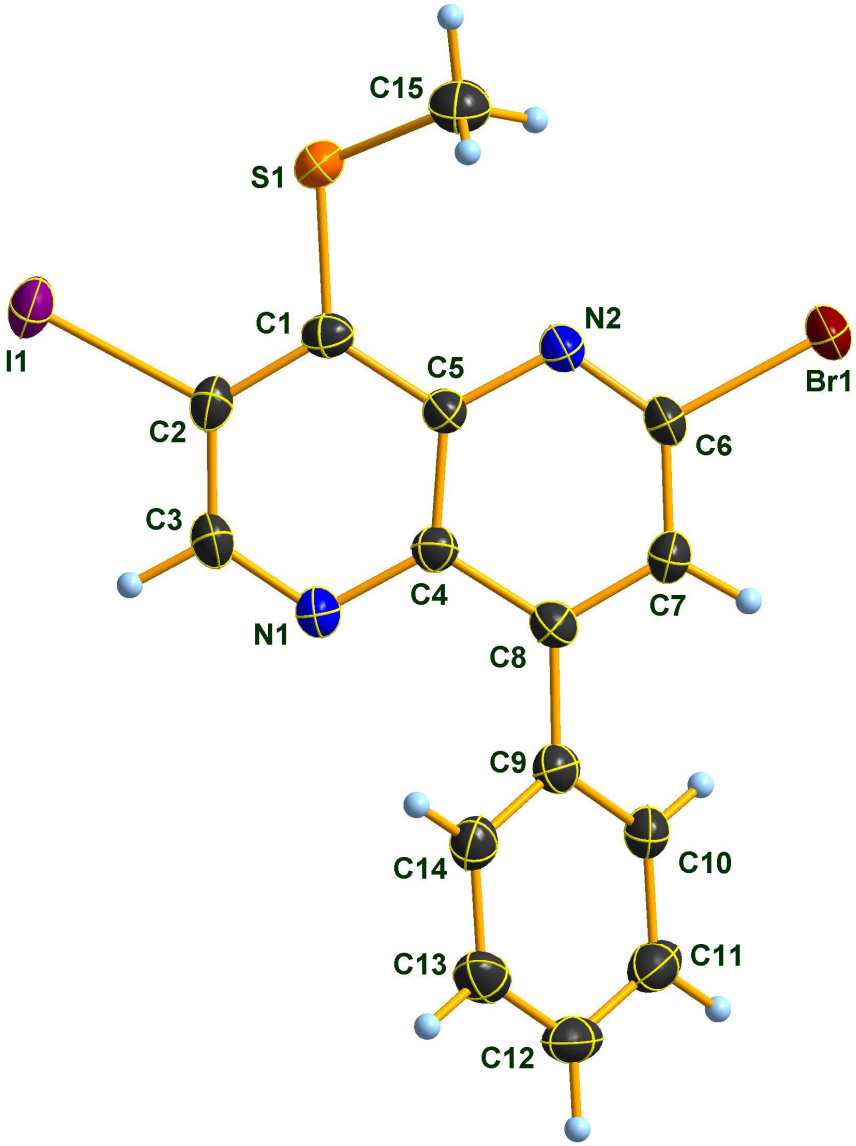


Figure 6. Molecular structure of compound **114b** in the crystal, DIAMOND[g)] representation; thermal ellipsoids are drawn at 50 % probability level.

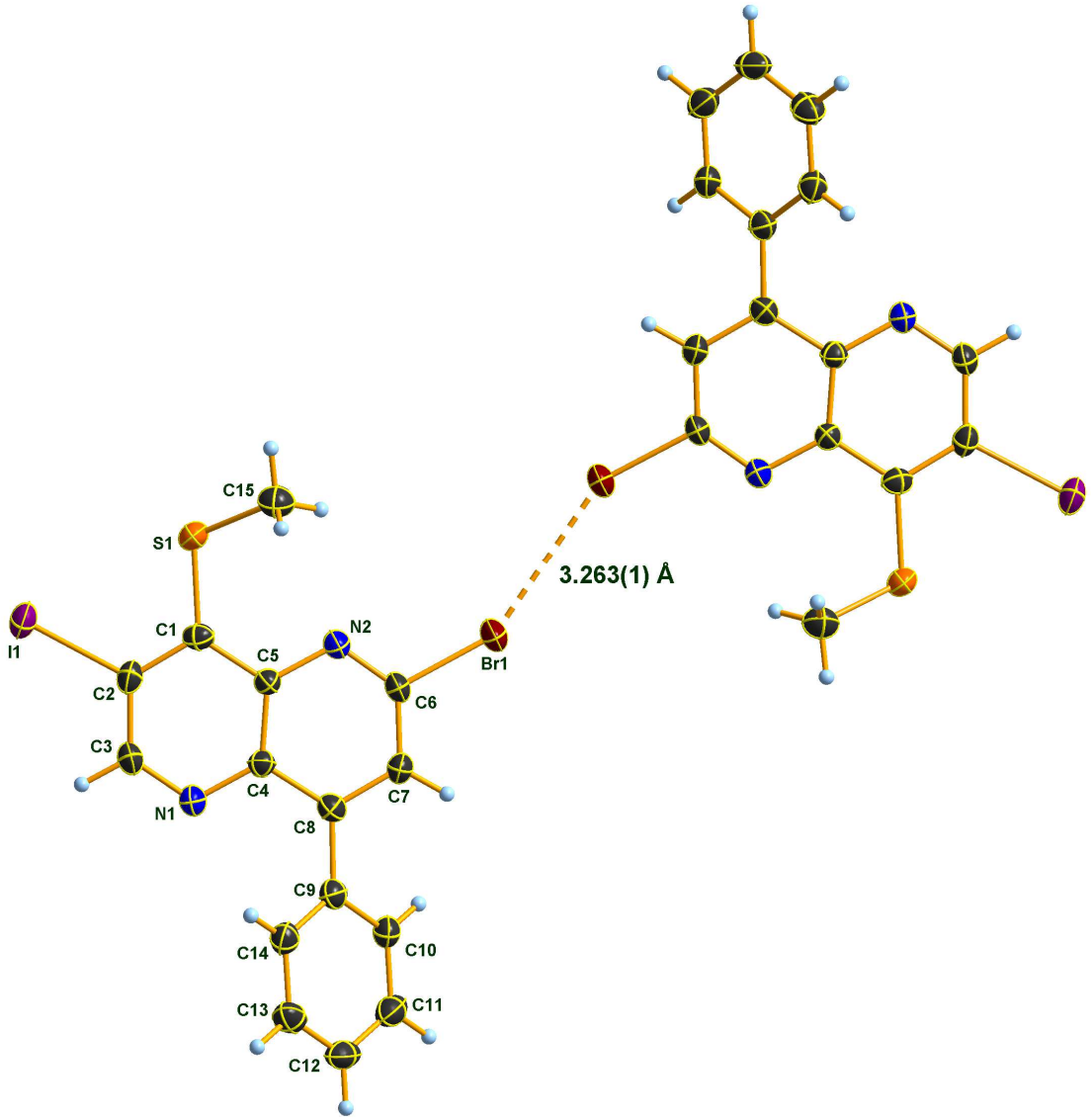


Figure 7. Crystal structure of compound **114b** showing Br···Br interactions within pairs of molecules in the crystal, DIAMOND[g)] representation; thermal ellipsoids are drawn at 50 % probability level. Symmetry code for the unlabeled molecule: 2-x, y, -0.5-z.

Table 21. Selected bond lengths (Å) of compound **114b**.

I1 – C2	2.097(3)	C9 – C14	1.389(5)
Br1 – C6	1.905(4)	C9 – C8	1.489(5)
S1 – C1	1.758(3)	C4 – C5	1.427(4)
S1 – C15	1.792(4)	C4 – C8	1.440(5)
C10 – C11	1.379(5)	C6 – N2	1.295(5)
C10 – C9	1.391(5)	C6 – C7	1.404(5)
C13 – C14	1.385(5)	C3 – C2	1.415(5)
C13 – C12	1.387(6)	C8 – C7	1.371(5)
N1 – C3	1.310(5)	N2 – C5	1.364(4)
N1 – C4	1.358(4)	C2 – C1	1.383(5)
C11 – C12	1.386(6)	C5 – C1	1.425(5)

Table 22. Selected bond angles (°) of compound **114b**.

C1 – S1 – C15	108.2(2)	N1 – C3 – C2	124.0(3)
C11 – C10 – C9	120.9(4)	C7 – C8 – C4	117.7(3)
C14 – C13 – C12	120.1(4)	C7 – C8 – C9	119.0(3)
C3 – N1 – C4	117.6(3)	C4 – C8 – C9	123.3(3)
C10 – C11 – C12	120.1(4)	C6 – N2 – C5	116.9(3)
C14 – C9 – C10	118.7(3)	C13 – C14 – C9	120.6(4)
C14 – C9 – C8	122.0(3)	C1 – C2 – C3	120.4(3)
C10 – C9 – C8	119.2(3)	C1 – C2 – I1	121.7(3)
N1 – C4 – C5	122.6(3)	C3 – C2 – I1	117.9(3)
N1 – C4 – C8	119.2(3)	N2 – C5 – C1	119.2(3)
C5 – C4 – C8	118.2(3)	N2 – C5 – C4	122.0(3)
N2 – C6 – C7	126.7(3)	C1 – C5 – C4	118.8(3)
N2 – C6 – Br1	116.8(3)	C2 – C1 – C5	116.4(3)
C7 – C6 – Br1	116.5(3)	C2 – C1 – S1	117.6(3)
C11 – C12 – C13	119.6(4)	C5 – C1 – S1	125.7(3)
		C8 – C7 – C6	118.3(3)

Table 23. Selected torsion angles (°) of compound **114b**.

C9 – C10 – C11 – C12	-0.4(6)	C6 – N2 – C5 – C4	-1.6(5)
C11 – C10 – C9 – C14	0.1(5)	N1 – C4 – C5 – N2	-172.6(3)
C11 – C10 – C9 – C8	178.2(3)	C8 – C4 – C5 – N2	4.3(5)

C3 – N1 – C4 – C5	-1.0(5)	N1 – C4 – C5 – C1	4.9(5)
C3 – N1 – C4 – C8	-177.9(3)	C8 – C4 – C5 – C1	-178.3(3)
C4 – N1 – C3 – C2	-1.8(5)	C3 – C2 – C1 – C5	3.0(5)
N1 – C4 – C8 – C7	173.8(3)	I1 – C2 – C1 – C5	-175.7(2)
C5 – C4 – C8 – C7	-3.2(5)	C3 – C2 – C1 – S1	177.8(2)
N1 – C4 – C8 – C9	-4.8(5)	I1 – C2 – C1 – S1	-0.9(4)
C5 – C4 – C8 – C9	178.2(3)	N2 – C5 – C1 – C2	172.0(3)
C14 – C9 – C8 – C7	139.5(4)	C4 – C5 – C1 – C2	-5.6(5)
C10 – C9 – C8 – C7	-38.6(5)	N2 – C5 – C1 – S1	-2.4(5)
C14 – C9 – C8 – C4	-41.9(5)	C4 – C5 – C1 – S1	-179.9(2)
C10 – C9 – C8 – C4	140.0(4)	C15 – S1 – C1 – C2	153.3(3)
C7 – C6 – N2 – C5	-2.3(6)	C15 – S1 – C1 – C5	-32.5(3)
Br1 – C6 – N2 – C5	177.7(2)	C4 – C8 – C7 – C6	-0.1(5)
C12 – C13 – C14 – C9	-0.9(6)	C9 – C8 – C7 – C6	178.6(3)
C10 – C9 – C14 – C13	0.6(5)	N2 – C6 – C7 – C8	3.1(6)
C8 – C9 – C14 – C13	-177.5(3)	Br1 – C6 – C7 – C8	-176.8(3)
N1 – C3 – C2 – C1	0.8(5)	C10 – C11 – C12 – C13	0.1(6)
N1 – C3 – C2 – I1	179.5(3)	C14 – C13 – C12 – C11	0.5(6)
C6 – N2 – C5 – C1	-179.1(3)		

Table 24. Details for X-ray data collection and structure refinement for compound **134f**.

	134f
Empirical formula	$C_{14}H_9ClN_2O$
Formula mass	256.68
T[K]	143(2)
Crystal size [mm]	0.41 × 0.36 × 0.24
Crystal description	pale yellow block
Crystal system	orthorhombic
Space group	*P*212121
a [Å]	6.6737(2)
b [Å]	7.5084(2)
c [Å]	23.4225(7)
α [°]	90.0
β [°]	90.0
γ [°]	90.0
V [Å^3]	1173.67(6)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.453
μ [mm^{-1}]	0.312
F(000)	528
Θ range [°]	4.18 – 25.24
Index ranges	$-9 \leq h \leq 7$
	$-10 \leq k \leq 9$
	$-28 \leq l \leq 33$
Reflns. collected	12137
Reflns. obsd.	3280
Reflns. unique	3567 (R_{int} = 0.0275)
R_1, wR_2 (2σ data)	0.0323, 0.0732
R_1, wR_2 (all data)	0.0368, 0.0759
GOOF on F^2	1.057
Peak/hole [e Å^{-3}]	0.215 / -0.183

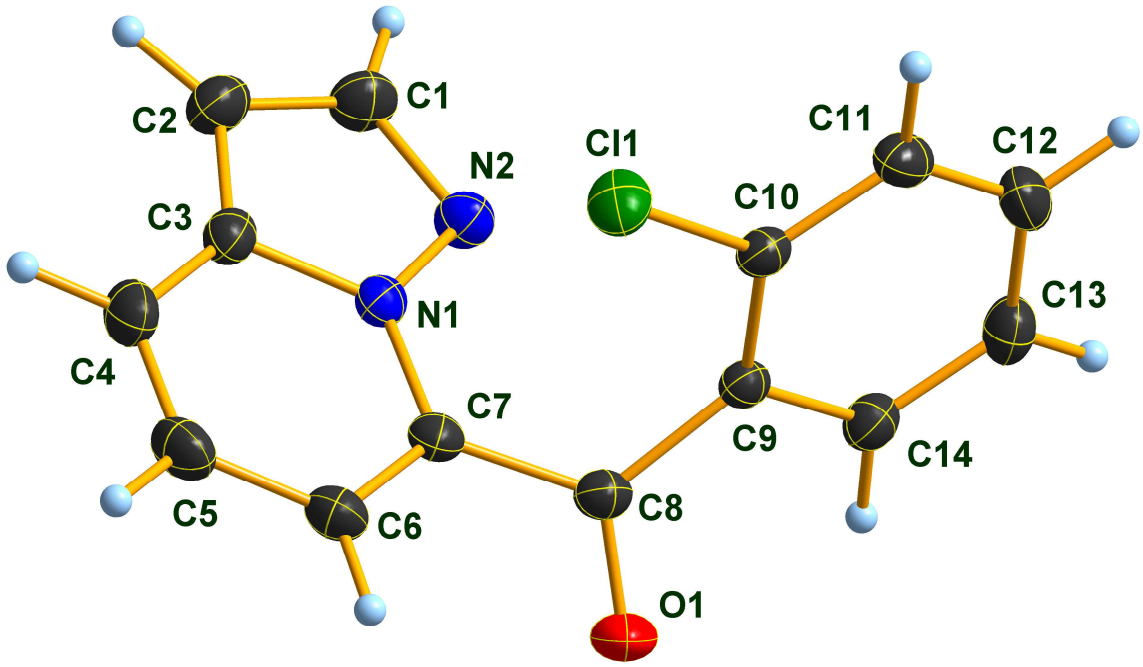


Figure 8. Molecular structure of compound **134f** in the crystal, DIAMOND[g)] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 25. Selected bond lengths (Å) of compound **134f**.

Cl1 – C10	1.741(2)	C6 – C5	1.415(3)
O1 – C8	1.220(2)	N2 – C1	1.341(2)
N1 – N2	1.357(2)	C10 – C11	1.392(2)
N1 – C7	1.377(2)	C10 – C9	1.397(2)
N1 – C3	1.386(2)	C9 – C14	1.400(2)
C8 – C7	1.489(2)	C11 – C12	1.383(3)
C8 – C9	1.494(2)	C1 – C2	1.390(3)
C13 – C14	1.379(3)	C3 – C4	1.417(3)
C13 – C12	1.391(3)	C4 – C5	1.364(3)
C3 – C2	1.384(3)	C6 – C7	1.366(2)

Table 26. Selected bond angles (°) of compound **134f**.

N2 – N1 – C7	124.1(1)	C10 – C9 – C8	126.1(2)
N2 – N1 – C3	112.8(1)	C14 – C9 – C8	115.8(2)
C7 – N1 – C3	123.0(2)	C12 – C11 – C10	119.6(2)
O1 – C8 – C7	118.5(2)	C4 – C5 – C6	120.1(2)
O1 – C8 – C9	119.5(2)	C6 – C7 – N1	118.4(2)
C7 – C8 – C9	122.0(1)	C6 – C7 – C8	121.9(2)

C14 – C13 – C12	120.0(2)	N1 – C7 – C8	119.7(2)
C2 – C3 – N1	105.5(2)	C13 – C14 – C9	121.1(2)
C2 – C3 – C4	136.9(2)	N2 – C1 – C2	113.3(2)
N1 – C3 – C4	117.7(2)	C3 – C2 – C1	105.1(2)
C5 – C4 – C3	120.1(2)	C11 – C12 – C13	120.2(2)
C7 – C6 – C5	120.7(2)	C11 – C10 – Cl1	116.9(1)
C1 – N2 – N1	103.3(2)	C9 – C10 – Cl1	121.8(1)
C11 – C10 – C9	121.1(2)	C10 – C9 – C14	118.0(2)

Table 27. Selected torsion angles (°) of compound **134f**.

N2 – N1 – C3 – C2	-1.1(2)	C5 – C6 – C7 – N1	-3.2(3)
C7 – N1 – C3 – C2	-178.0(2)	C5 – C6 – C7 – C8	174.9(2)
N2 – N1 – C3 – C4	179.1(2)	N2 – N1 – C7 – C6	-175.9(2)
C7 – N1 – C3 – C4	2.1(3)	C3 – N1 – C7 – C6	0.7(3)
C2 – C3 – C4 – C5	177.6(2)	N2 – N1 – C7 – C8	6.0(2)
N1 – C3 – C4 – C5	-2.5(3)	C3 – N1 – C7 – C8	-177.4(2)
C7 – N1 – N2 – C1	177.8(2)	O1 – C8 – C7 – C6	48.4(2)
C3 – N1 – N2 – C1	0.8(2)	C9 – C8 – C7 – C6	-130.1(2)
C11 – C10 – C9 – C14	0.6(2)	O1 – C8 – C7 – N1	-133.5(2)
Cl1 – C10 – C9 – C14	-175.7(1)	C9 – C8 – C7 – N1	47.9(2)
C11 – C10 – C9 – C8	178.0(2)	C12 – C13 – C14 – C9	0.9(3)
Cl1 – C10 – C9 – C8	1.7(2)	C10 – C9 – C14 – C13	-1.4(3)
O1 – C8 – C9 – C10	-144.1(2)	C8 – C9 – C14 – C13	-179.0(2)
C7 – C8 – C9 – C10	34.4(2)	N1 – N2 – C1 – C2	-0.3(2)
O1 – C8 – C9 – C14	33.3(2)	N1 – C3 – C2 – C1	0.8(2)
C7 – C8 – C9 – C14	-148.2(2)	C4 – C3 – C2 – C1	-179.4(2)
C9 – C10 – C11 – C12	0.6(3)	N2 – C1 – C2 – C3	-0.3(3)
Cl1 – C10 – C11 – C12	177.1(2)	C10 – C11 – C12 – C13	-1.2(3)
C3 – C4 – C5 – C6	0.2(3)	C14 – C13 – C12 – C11	0.4(3)
C7 – C6 – C5 – C4	2.8(3)		

Table 28. Details for X-ray data collection and structure refinement for compound **134g**.

	134g
Empirical formula	$C_{14}H_9IN_2O$
Formula mass	348.13
T[K]	143(2)
Crystal size [mm]	0.43 × 0.26 × 0.15
Crystal description	pale yellow block
Crystal system	triclinic
Space group	*P*-1
a [Å]	7.9150(4)
b [Å]	8.6083(4)
c [Å]	9.1999(5)
α [°]	103.172(4)
β [°]	93.199(4)
γ [°]	95.217(4)
V [Å^3]	605.92(5)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.908
μ [mm^{-1}]	2.630
F(000)	336
Θ range [°]	4.27 – 25.24
Index ranges	$-11 \leq h \leq 11$
	$-12 \leq k \leq 12$
	$-13 \leq l \leq 13$
Reflns. collected	12199
Reflns. obsd.	3227
Reflns. unique	3678 (R_{int} = 0.0405)
R_1, wR_2 (2σ data)	0.0292, 0.0575
R_1, wR_2 (all data)	0.0371, 0.0607
GOOF on F^2	1.039
Peak/hole [e Å^{-3}]	1.240 / -0.630

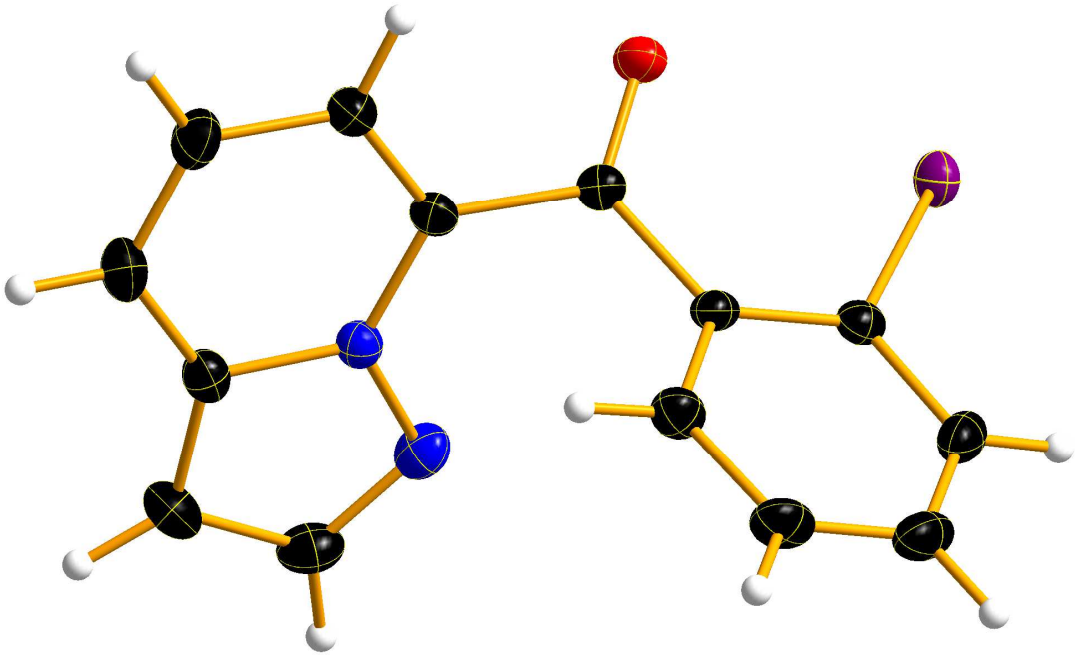


Figure 9. Molecular structure of compound **134g** in the crystal, DIAMOND[g)] representation; thermal ellipsoids are drawn at 50 % probability level.

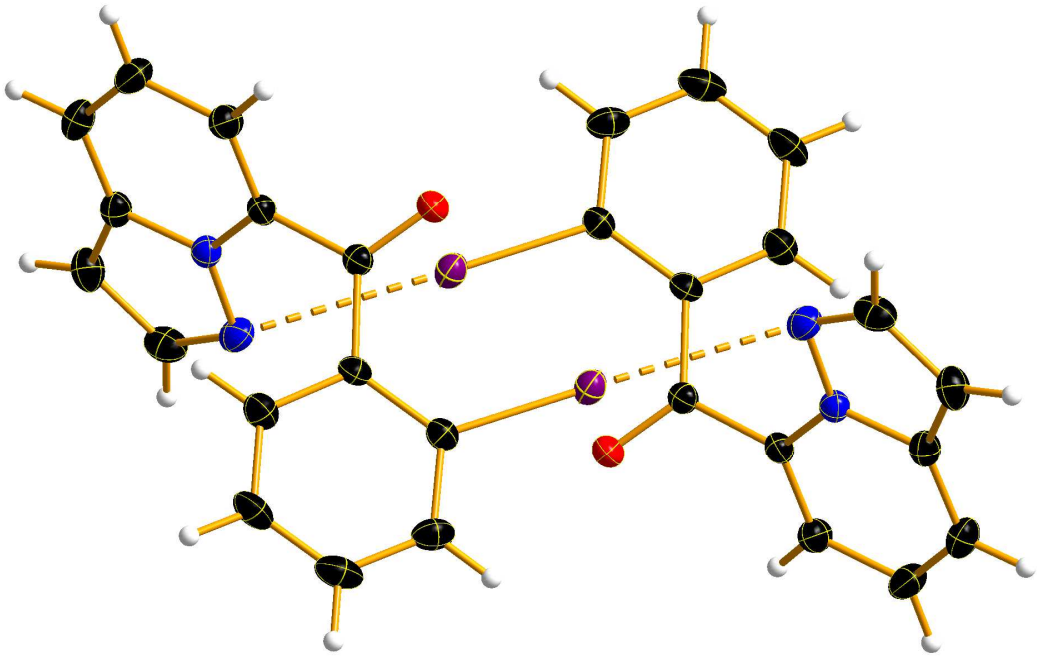


Figure 10. View of a I ⋯ N halogen bonded dimers of compound **134g** in the crystal, DIAMOND[g)] representation; thermal ellipsoids are drawn at 50 % probability level. Symmetry code for the second molecule (not labeled): -x, 1-y, -z.

Table 29. Selected bond lengths (Å) of compound **134g**.

I1 – C14	2.104(2)	C10 – C11	1.389(4)
O1 – C8	1.216(3)	C5 – C4	1.367(4)
N1 – N2	1.364(3)	C1 – C2	1.407(4)
N1 – C7	1.379(3)	C3 – C2	1.387(4)
N1 – C3	1.385(3)	C3 – C4	1.416(4)
N2 – C1	1.305(4)	C11 – C12	1.377(4)
C9 – C10	1.393(4)	C7 – C6	1.362(3)
C9 – C14	1.408(3)	C14 – C13	1.386(3)
C9 – C8	1.490(3)	C6 – C5	1.412(4)
C8 – C7	1.502(3)	C13 – C12	1.387(4)

Table 30. Selected bond angles (°) of compound **134g**.

N2 – N1 – C7	124.7(2)	C4 – C5 – C6	120.2(2)
N2 – N1 – C3	112.1(2)	N2 – C1 – C2	113.4(2)
C7 – N1 – C3	123.0(2)	N1 – C3 – C2	105.4(2)
C1 – N2 – N1	104.4(2)	N1 – C3 – C4	118.2(2)
C10 – C9 – C14	118.5(2)	C2 – C3 – C4	136.4(2)
C10 – C9 – C8	117.6(2)	C5 – C4 – C3	119.3(2)
C14 – C9 – C8	123.7(2)	C12 – C11 – C10	119.6(3)
O1 – C8 – C9	122.3(2)	C3 – C2 – C1	104.6(2)
O1 – C8 – C7	118.2(2)	C11 – C12 – C13	120.2(2)
C9 – C8 – C7	119.1(2)	C13 – C14 – I1	116.3(2)
C6 – C7 – N1	117.9(2)	C9 – C14 – I1	123.9(2)
C6 – C7 – C8	120.9(2)	C7 – C6 – C5	121.3(2)
N1 – C7 – C8	121.1(2)	C14 – C13 – C12	120.6(3)
C13 – C14 – C9	119.8(2)	C11 – C10 – C9	121.2(3)

Table 31. Selected torsion angles (°) of compound **134g**.

C7 – N1 – N2 – C1	-176.2(2)	C9 – C14 – C13 – C12	-2.5(4)
C3 – N1 – N2 – C1	-0.6(3)	I1 – C14 – C13 – C12	179.0(2)
C10 – C9 – C8 – O1	146.8(2)	C14 – C9 – C10 – C11	0.8(4)
C14 – C9 – C8 – O1	-28.8(4)	C8 – C9 – C10 – C11	-175.0(2)
C10 – C9 – C8 – C7	-26.2(3)	C7 – C6 – C5 – C4	-0.3(4)
C14 – C9 – C8 – C7	158.2(2)	N1 – N2 – C1 – C2	0.1(3)
N2 – N1 – C7 – C6	174.5(2)	N2 – N1 – C3 – C2	0.8(3)
C3 – N1 – C7 – C6	-0.7(3)	C7 – N1 – C3 – C2	176.6(2)
N2 – N1 – C7 – C8	-6.4(3)	N2 – N1 – C3 – C4	-176.9(2)

C3 – N1 – C7 – C8	178.4(2)	C7 – N1 – C3 – C4	-1.2(4)
O1 – C8 – C7 – C6	-46.8(3)	C6 – C5 – C4 – C3	-1.6(4)
C9 – C8 – C7 – C6	126.4(3)	N1 – C3 – C4 – C5	2.4(4)
O1 – C8 – C7 – N1	134.0(2)	C2 – C3 – C4 – C5	-174.5(3)
C9 – C8 – C7 – N1	-52.7(3)	C9 – C10 – C11 – C12	-2.3(4)
C10 – C9 – C14 – C13	1.6(3)	N1 – C3 – C2 – C1	-0.7(3)
C8 – C9 – C14 – C13	177.1(2)	C4 – C3 – C2 – C1	176.4(3)
C10 – C9 – C14 – I1	179.9(2)	N2 – C1 – C2 – C3	0.4(3)
C8 – C9 – C14 – I1	-4.6(3)	C10 – C11 – C12 – C13	1.3(4)
N1 – C7 – C6 – C5	1.5(4)	C14 – C13 – C12 – C11	1.1(4)
C8 – C7 – C6 – C5	-177.7(2)		

Table 32. Details for X-ray data collection and structure refinement for compound **136g**.

	136g
Empirical formula	$C_{12}H_8N_2OS$
Formula mass	228.26
T[K]	143(2)
Crystal size [mm]	0.47 × 0.24 × 0.19
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	10.3883(6)
b [Å]	11.4775(5)
c [Å]	8.7580(5)
α [°]	90.0
β [°]	99.608(5)
γ [°]	90.0
V [Å^3]	1029.58(10)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.473
μ [mm^{-1}]	0.290
F(000)	472
Θ range [°]	4.26 – 25.24
Index ranges	$-14 \leq h \leq 14$
	$-14 \leq k \leq 16$
	$-10 \leq l \leq 12$
Reflns. collected	10783
Reflns. obsd.	2412
Reflns. unique	3129 (R_{int} = 0.0307)
R_1, wR_2 (2σ data)	0.0409, 0.0984
R_1, wR_2 (all data)	0.0579, 0.1097
GOOF on F^2	1.046
Peak/hole [e Å^{-3}]	0.340 / -0.309

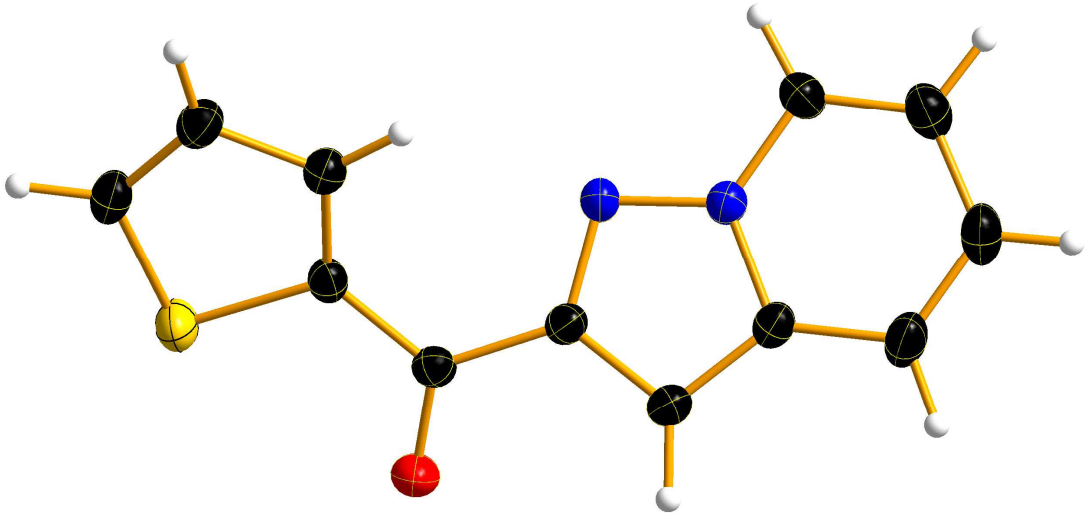


Figure 11. Molecular structure of compound **136g** in the crystal, DIAMOND[g] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 33. Selected bond lengths (Å) of compound **136g**.

S1 – C12	1.710(2)	C10 – C11	1.417(2)
S1 – C9	1.728(1)	C12 – C11	1.358(2)
C9 – C10	1.376(2)	C6 – C5	1.360(2)
C9 – C1	1.465(2)	C6 – C7	1.420(2)
N1 – C2	1.348(2)	C8 – C7	1.355(2)
N1 – N2	1.353(2)	C5 – C4	1.419(2)
O1 – C1	1.228(2)	C2 – C3	1.402(2)
N2 – C8	1.375(2)	C2 – C1	1.484(2)
N2 – C4	1.387(2)	C3 – C4	1.390(2)

Table 34. Selected bond angles (°) of compound **136g**.

C12 – S1 – C9	91.5(1)	C5 – C6 – C7	120.3(1)
C10 – C9 – C1	129.8(1)	C7 – C8 – N2	118.1(2)
C10 – C9 – S1	111.3(1)	C12 – C11 – C10	112.8(1)
C1 – C9 – S1	118.6(1)	C6 – C5 – C4	119.4(2)
C2 – N1 – N2	103.6(1)	C8 – C7 – C6	121.1(2)
N1 – N2 – C8	123.8(1)	N2 – C4 – C3	105.5(1)
N1 – N2 – C4	113.1(1)	N2 – C4 – C5	118.0(1)
C8 – N2 – C4	123.1(1)	C3 – C4 – C5	136.5(1)
N1 – C2 – C3	112.8(1)	O1 – C1 – C9	121.0(1)
N1 – C2 – C1	122.2(1)	O1 – C1 – C2	119.1(1)

C3 – C2 – C1	125.0(1)	C9 – C1 – C2	119.9(1)
C4 – C3 – C2	105.0(1)	C11 – C12 – S1	112.3(1)
C9 – C10 – C11	112.2(1)		

Table 35. Selected torsion angles (°) of compound **136g**.

C12 – S1 – C9 – C10	0.3(1)	C3 – C2 – C1 – C9	154.7(1)
C12 – S1 – C9 – C1	174.2(1)	C9 – S1 – C12 – C11	-0.3(1)
C2 – N1 – N2 – C8	177.8(1)	N1 – N2 – C8 – C7	-179.2(1)
C2 – N1 – N2 – C4	-0.3(2)	C4 – N2 – C8 – C7	-1.3(2)
N2 – N1 – C2 – C3	0.3(2)	S1 – C12 – C11 – C10	0.3(2)
N2 – N1 – C2 – C1	-177.7(1)	C9 – C10 – C11 – C12	-0.1(2)
N1 – C2 – C3 – C4	-0.1(2)	C7 – C6 – C5 – C4	0.0(3)
C1 – C2 – C3 – C4	177.7(1)	N2 – C8 – C7 – C6	0.8(2)
C1 – C9 – C10 – C11	-173.2(1)	C5 – C6 – C7 – C8	-0.2(3)
S1 – C9 – C10 – C11	-0.2(2)	N1 – N2 – C4 – C3	0.2(2)
C10 – C9 – C1 – O1	162.7(2)	C8 – N2 – C4 – C3	-177.9(1)
S1 – C9 – C1 – O1	-9.9(2)	N1 – N2 – C4 – C5	179.3(1)
C10 – C9 – C1 – C2	-15.3(2)	C8 – N2 – C4 – C5	1.1(2)
S1 – C9 – C1 – C2	172.1(1)	C2 – C3 – C4 – N2	-0.1(2)
N1 – C2 – C1 – O1	154.3(1)	C2 – C3 – C4 – C5	-178.8(2)
C3 – C2 – C1 – O1	-23.3(2)	C6 – C5 – C4 – N2	-0.5(2)
N1 – C2 – C1 – C9	-27.7(2)	C6 – C5 – C4 – C3	178.2(2)

Table 36. Details for X-ray data collection and structure refinement for compound **138g**.

	138g
Empirical formula	$C_{14}H_{11}BrN_2O$
Formula mass	303.16
T[K]	143(2)
Crystal size [mm]	0.31 × 0.22 × 0.09
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*-1
a [Å]	5.9056(4)
b [Å]	7.2277(5)
c [Å]	15.8858(11)
α [°]	96.483(6)
β [°]	96.206(6)
γ [°]	112.954(7)
V [Å^3]	611.75(8)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.646
μ [mm^{-1}]	3.348
F(000)	304
Θ range [°]	4.22 – 25.24
Index ranges	$-8 \leq h \leq 8$
	$-9 \leq k \leq 10$
	$-22 \leq l \leq 22$
Reflns. collected	6325
Reflns. obsd.	3162
Reflns. unique	3715 (R_{int} = 0.0262)
R_1, wR_2 (2σ data)	0.0381, 0.0820
R_1, wR_2 (all data)	0.0482, 0.0886
GOOF on F^2	1.037
Peak/hole [e Å^{-3}]	1.034 / -0.694

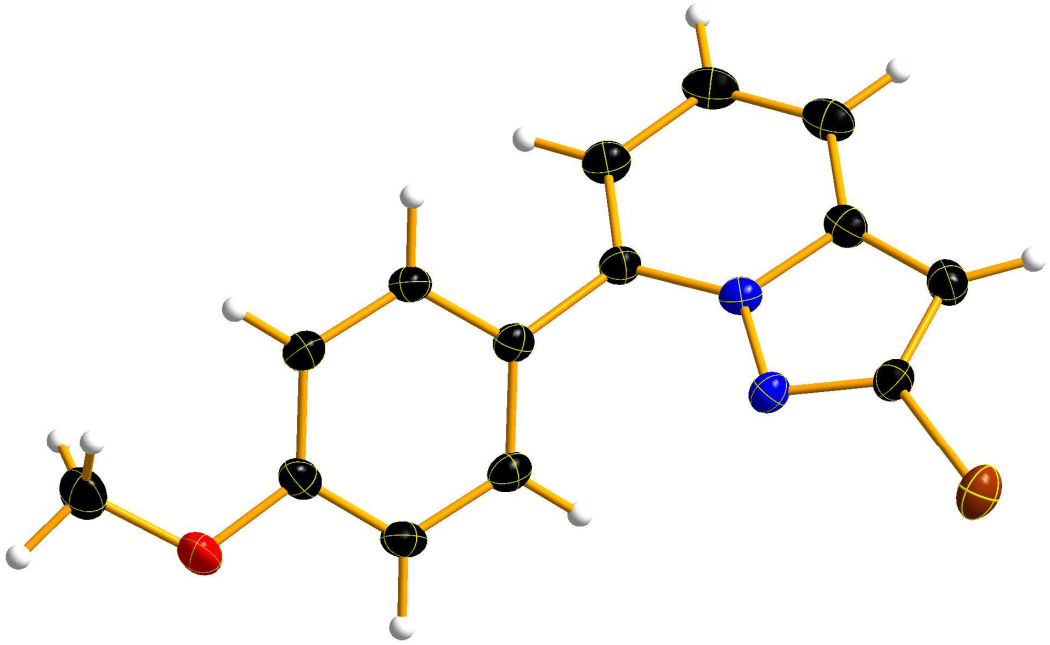


Figure 12. Molecular structure of compound **138g** in the crystal, DIAMOND[g] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 37. Selected bond lengths (Å) of compound **138g**.

Br1 – C1	1.873(2)	C7 – C8	1.476(3)
O1 – C11	1.369(3)	C8 – C9	1.391(3)
O1 – C14	1.428(3)	C8 – C13	1.399(3)
N1 – N2	1.371(2)	C9 – C10	1.385(3)
N1 – C7	1.383(3)	C10 – C11	1.393(3)
N1 – C3	1.391(3)	C11 – C12	1.391(3)
N2 – C1	1.338(3)	C12 – C13	1.383(3)
C1 – C2	1.383(3)	C4 – C5	1.361(3)
C2 – C3	1.394(3)	C5 – C6	1.415(3)
C3 – C4	1.414(3)	C6 – C7	1.368(3)

Table 38. Selected bond angles (°) of compound **138g**.

C11 – O1 – C14	117.5(2)	N1 – C7 – C8	119.6(2)
N2 – N1 – C7	124.1(2)	C9 – C8 – C13	118.3(2)
N2 – N1 – C3	112.4(2)	C9 – C8 – C7	119.2(2)
C7 – N1 – C3	123.4(2)	C13 – C8 – C7	122.4(2)
C1 – N2 – N1	102.1(2)	C10 – C9 – C8	121.8(2)

N2 – C1 – C2	115.7(2)	C9 – C10 – C11	119.0(2)
N2 – C1 – Br1	118.5(2)	O1 – C11 – C12	115.9(2)
C2 – C1 – Br1	125.7(2)	O1 – C11 – C10	124.1(2)
C1 – C2 – C3	103.6(2)	C12 – C11 – C10	120.0(2)
N1 – C3 – C2	106.2(2)	C13 – C12 – C11	120.2(2)
N1 – C3 – C4	118.3(2)	C12 – C13 – C8	120.6(2)
C2 – C3 – C4	135.4(2)	C7 – C6 – C5	121.8(2)
C5 – C4 – C3	119.3(2)	C6 – C7 – N1	116.9(2)
C4 – C5 – C6	120.4(2)	C6 – C7 – C8	123.5(2)

Table 39. Selected torsion angles (°) of compound **138g**.

C7 – N1 – N2 – C1	-176.6(2)	C3 – N1 – C7 – C6	0.4(3)
C3 – N1 – N2 – C1	-0.6(2)	N2 – N1 – C7 – C8	-2.7(3)
N1 – N2 – C1 – C2	-0.1(2)	C3 – N1 – C7 – C8	-178.3(2)
N1 – N2 – C1 – Br1	179.7(1)	C6 – C7 – C8 – C9	-49.0(3)
N2 – C1 – C2 – C3	0.7(3)	N1 – C7 – C8 – C9	129.5(2)
Br1 – C1 – C2 – C3	-179.0(2)	C6 – C7 – C8 – C13	127.2(2)
N2 – N1 – C3 – C2	1.0(2)	N1 – C7 – C8 – C13	-54.2(3)
C7 – N1 – C3 – C2	177.1(2)	C13 – C8 – C9 – C10	-1.2(3)
N2 – N1 – C3 – C4	-176.3(2)	C7 – C8 – C9 – C10	175.3(2)
C7 – N1 – C3 – C4	-0.3(3)	C8 – C9 – C10 – C11	-0.7(3)
C1 – C2 – C3 – N1	-1.0(2)	C14 – O1 – C11 – C12	-166.9(2)
C1 – C2 – C3 – C4	175.7(2)	C14 – O1 – C11 – C10	14.7(3)
N1 – C3 – C4 – C5	0.3(3)	C9 – C10 – C11 – O1	-179.4(2)
C2 – C3 – C4 – C5	-176.1(2)	C9 – C10 – C11 – C12	2.2(3)
C3 – C4 – C5 – C6	-0.4(3)	O1 – C11 – C12 – C13	179.7(2)
C4 – C5 – C6 – C7	0.6(3)	C10 – C11 – C12 – C13	-1.8(3)
C5 – C6 – C7 – N1	-0.5(3)	C11 – C12 – C13 – C8	-0.1(3)
C5 – C6 – C7 – C8	178.1(2)	C9 – C8 – C13 – C12	1.6(3)
N2 – N1 – C7 – C6	176.0(2)	C7 – C8 – C13 – C12	-174.7(2)

Table 40. Details for X-ray data collection and structure refinement for compound **141i**.

	141i
Empirical formula	$C_{17}H_{16}N_2O_3$
Formula mass	296.32
T[K]	143(2)
Crystal size [mm]	0.40 × 0.12 × 0.08
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*n*
a [Å]	3.9038(2)
b [Å]	28.3121(10)
c [Å]	12.6695(5)
α [°]	90.0
β [°]	93.301(4)
γ [°]	90.0
V [Å^3]	1397.97(10)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.408
μ [mm^{-1}]	0.098
F(000)	624
Θ range [°]	4.31 – 25.24
Index ranges	$-5 \leq h \leq 5$
	$-37 \leq k \leq 40$
	$-18 \leq l \leq 17$
Reflns. collected	14363
Reflns. obsd.	3472
Reflns. unique	4260 (R_{int} = 0.0275)
R_1, wR_2 (2σ data)	0.0407, 0.1013
R_1, wR_2 (all data)	0.0528, 0.1092
GOOF on F^2	1.036
Peak/hole [e Å^{-3}]	0.400 / -0.189

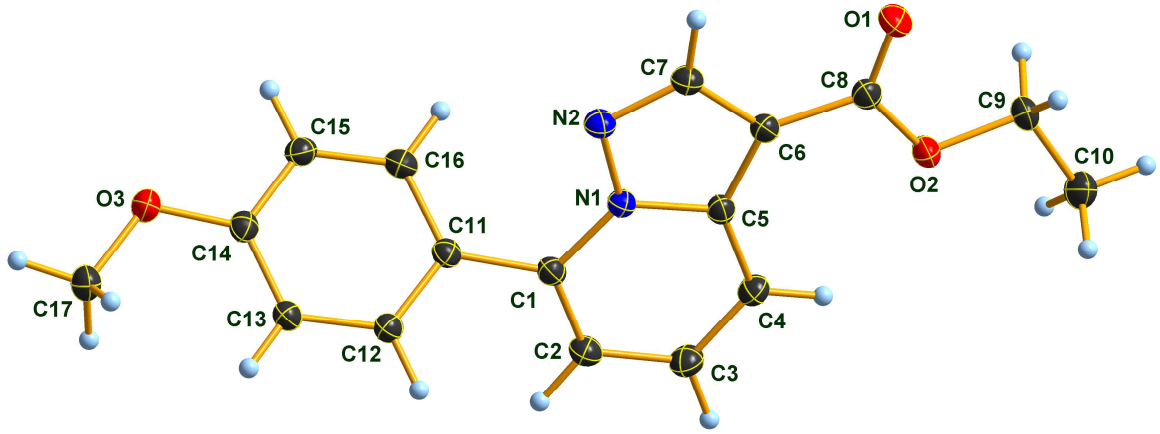


Figure 13. Molecular structure of compound **141i** in the crystal, DIAMOND[g] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 41. Selected bond lengths (Å) of compound **141i**.

O2 – C8	1.350(1)	C15 – C16	1.380(2)
O2 – C9	1.455(1)	C12 – C13	1.394(1)
O3 – C14	1.365(1)	C4 – C3	1.367(2)
O3 – C17	1.435(1)	C4 – C5	1.409(1)
C11 – C12	1.393(1)	C9 – C10	1.505(2)
C11 – C16	1.406(2)	N2 – N1	1.376(1)
C11 – C1	1.471(1)	N1 – C1	1.382(1)
O1 – C8	1.214(1)	N1 – C5	1.385(1)
C6 – C7	1.402(1)	C2 – C1	1.372(1)
C6 – C5	1.403(1)	C2 – C3	1.415(2)
C6 – C8	1.455(1)	C14 – C13	1.395(2)
N2 – C7	1.331(1)	C14 – C15	1.398(2)

Table 42. Selected bond angles (°) of compound **141i**.

C8 – O2 – C9	115.4(1)	C15 – C16 – C11	120.2(1)
C14 – O3 – C17	116.5(1)	C3 – C4 – C5	118.7(1)
C12 – C11 – C16	118.7(1)	O2 – C9 – C10	106.9(1)
C12 – C11 – C1	119.8(1)	N1 – C5 – C6	105.3(1)
C16 – C11 – C1	121.4(1)	N1 – C5 – C4	118.4(1)
C7 – C6 – C5	104.8(1)	C6 – C5 – C4	136.2(1)
C7 – C6 – C8	124.7(1)	C4 – C3 – C2	121.0(1)
C5 – C6 – C8	130.4(1)	C12 – C13 – C14	119.0(1)
C7 – N2 – N1	103.6(1)	O1 – C8 – C6	123.9(1)

N2 – N1 – C1	123.4(1)	O2 – C8 – C6	112.9(1)
N2 – N1 – C5	112.6(1)	C16 – C15 – C14	120.6(1)
C1 – N1 – C5	124.0(1)	C11 – C12 – C13	121.5(1)
C1 – C2 – C3	121.2(1)	N2 – C7 – C6	113.6(1)
O3 – C14 – C13	124.1(1)	C2 – C1 – N1	116.6(1)
O3 – C14 – C15	115.9(1)	C2 – C1 – C11	123.9(1)
C13 – C14 – C15	120.0(1)	N1 – C1 – C11	119.5(1)
O1 – C8 – O2	123.2(1)		

Table 43. Selected torsion angles (°) of compound **141i**.

C7 – N2 – N1 – C1	178.8(1)	C12 – C11 – C1 – C2	48.1(2)
C7 – N2 – N1 – C5	0.1(1)	C16 – C11 – C1 – C2	-126.6(1)
C17 – O3 – C14 – C13	-1.3(1)	C12 – C11 – C1 – N1	-133.8(1)
C17 – O3 – C14 – C15	178.3(1)	C16 – C11 – C1 – N1	51.5(1)
C9 – O2 – C8 – O1	-8.3(2)	C14 – C15 – C16 – C11	1.6(2)
C9 – O2 – C8 – C6	170.7(1)	C12 – C11 – C16 – C15	0.1(2)
C7 – C6 – C8 – O1	1.1(2)	C1 – C11 – C16 – C15	174.8(1)
C5 – C6 – C8 – O1	179.0(1)	C8 – O2 – C9 – C10	176.9(1)
C7 – C6 – C8 – O2	-177.9(1)	N2 – N1 – C5 – C6	-0.6(1)
C5 – C6 – C8 – O2	0.0(2)	C1 – N1 – C5 – C6	-179.3(1)
O3 – C14 – C15 – C16	178.2(1)	N2 – N1 – C5 – C4	177.5(1)
C13 – C14 – C15 – C16	-2.2(2)	C1 – N1 – C5 – C4	-1.2(2)
C16 – C11 – C12 – C13	-1.2(2)	C7 – C6 – C5 – N1	0.8(1)
C1 – C11 – C12 – C13	-176.0(1)	C8 – C6 – C5 – N1	-177.4(1)
N1 – N2 – C7 – C6	0.5(1)	C7 – C6 – C5 – C4	-176.7(1)
C5 – C6 – C7 – N2	-0.9(1)	C8 – C6 – C5 – C4	5.1(2)
C8 – C6 – C7 – N2	177.5(1)	C3 – C4 – C5 – N1	-2.1(2)
C3 – C2 – C1 – N1	-2.8(2)	C3 – C4 – C5 – C6	175.1(1)
C3 – C2 – C1 – C11	175.3(1)	C5 – C4 – C3 – C2	2.9(2)
N2 – N1 – C1 – C2	-174.8(1)	C1 – C2 – C3 – C4	-0.4(2)
C5 – N1 – C1 – C2	3.7(2)	C11 – C12 – C13 – C14	0.7(2)
N2 – N1 – C1 – C11	6.9(2)	O3 – C14 – C13 – C12	-179.3(1)
C5 – N1 – C1 – C11	-174.5(1)	C15 – C14 – C13 – C12	1.1(2)

Table 44. Details for X-ray data collection and structure refinement for compound **151**.

	151
Empirical formula	$C_4H_4BF_3N_2$
Formula mass	147.90
T[K]	143(2)
Crystal size [mm]	0.15 × 0.15 × 0.10
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*n*
a [Å]	4.9485(2)
b [Å]	9.1216(4)
c [Å]	12.7420(5)
α [°]	90.0
β [°]	93.815(4)
γ [°]	90.0
V [Å^3]	573.88(4)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.712
μ [mm^{-1}]	0.173
F(000)	296
Θ range [°]	4.53 – 25.24
Index ranges	-7 ≤ *h* ≤ 7
	-13 ≤ *k* ≤ 13
	-18 ≤ *l* ≤ 18
Reflns. collected	10726
Reflns. obsd.	1430
Reflns. unique	1734
	(R_{int} = 0.0342)
R_1, wR_2 (2σ data)	0.0340, 0.0769
R_1, wR_2 (all data)	0.0443, 0.0832
GOOF on F^2	1.038
Peak/hole [e Å^{-3}]	0.315 / -0.213

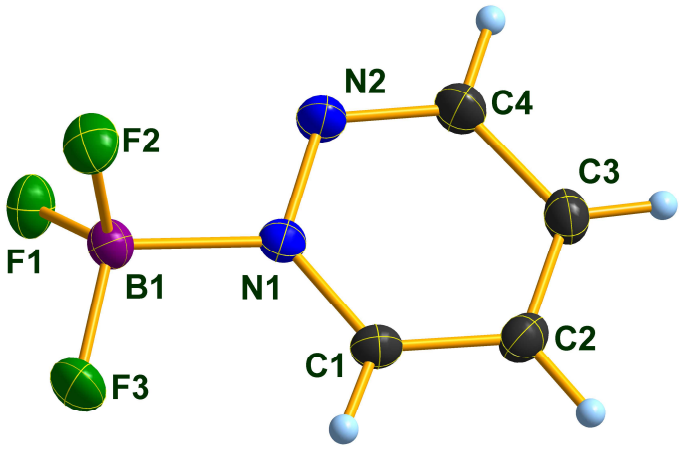


Figure 14. Molecular structure of compound **151** in the crystal, DIAMOND[e)] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 45. Selected bond lengths (Å) of compound **151**.

N1 – C1	1.320(1)	C3 – C2	1.364(2)
N1 – N2	1.345(1)	C3 – C4	1.399(2)
N1 – B1	1.610(2)	C1 – C2	1.393(2)
F3 – B1	1.378(1)	F2 – B1	1.377(1)
F1 – B1	1.378(1)	N2 – C4	1.319(2)

Table 46. Selected bond angles (°) of compound **151**.

C1 – N1 – N2	123.0(1)	F2 – B1 – F1	111.3(1)
C1 – N1 – B1	123.6(1)	F2 – B1 – F3	111.7(1)
N2 – N1 – B1	113.4(1)	F1 – B1 – F3	111.6(1)
C4 – N2 – N1	117.0(1)	F2 – B1 – N1	107.4(1)
C2 – C3 – C4	117.8(1)	F1 – B1 – N1	107.0(1)
N1 – C1 – C2	120.9(1)	F3 – B1 – N1	107.6(1)
N2 – C4 – C3	123.7(1)	C3 – C2 – C1	117.7(1)

Table 47. Selected torsion angles (°) of compound **151**.

C1 – N1 – N2 – C4	0.7(2)	N2 – N1 – B1 – F2	-72.0(1)
B1 – N1 – N2 – C4	-179.5(1)	C1 – N1 – B1 – F1	-132.5(1)
N2 – N1 – C1 – C2	-0.6(2)	N2 – N1 – B1 – F1	47.6(1)
B1 – N1 – C1 – C2	179.5(1)	C1 – N1 – B1 – F3	-12.4(1)
N1 – N2 – C4 – C3	-0.1(2)	N2 – N1 – B1 – F3	167.7(1)
C2 – C3 – C4 – N2	-0.5(2)	C4 – C3 – C2 – C1	0.6(2)
C1 – N1 – B1 – F2	107.9(1)	N1 – C1 – C2 – C3	-0.1(2)

Table 48. Details for X-ray data collection and structure refinement for compound **153a**.

	153a
Empirical formula	$C_{10}H_8N_2$
Formula mass	156.18
T[K]	143(2)
Crystal size [mm]	0.40 × 0.30 × 0.20
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	18.4159(8)
b [Å]	5.8109(2)
c [Å]	7.3249(3)
α [°]	90.0
β [°]	100.034(4)
γ [°]	90.0
V [Å^3]	771.87(5)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.344
μ [mm^{-1}]	0.082
F(000)	328
Θ range [°]	3.37 – 25.24
Index ranges	-26 ≤ *h* ≤ 26
	-8 ≤ *k* ≤ 8
	-10 ≤ *l* ≤ 10
Reflns. collected	14786
Reflns. obsd.	1886

Reflns. unique	2363
	(R_{int} = 0.0401)
R_1, wR_2 (2σ data)	0.0451, 0.1134
R_1, wR_2 (all data)	0.0598, 0.1259
GOOF on F^2	1.044
Peak/hole [e Å^{-3}]	0.355 / -0.222

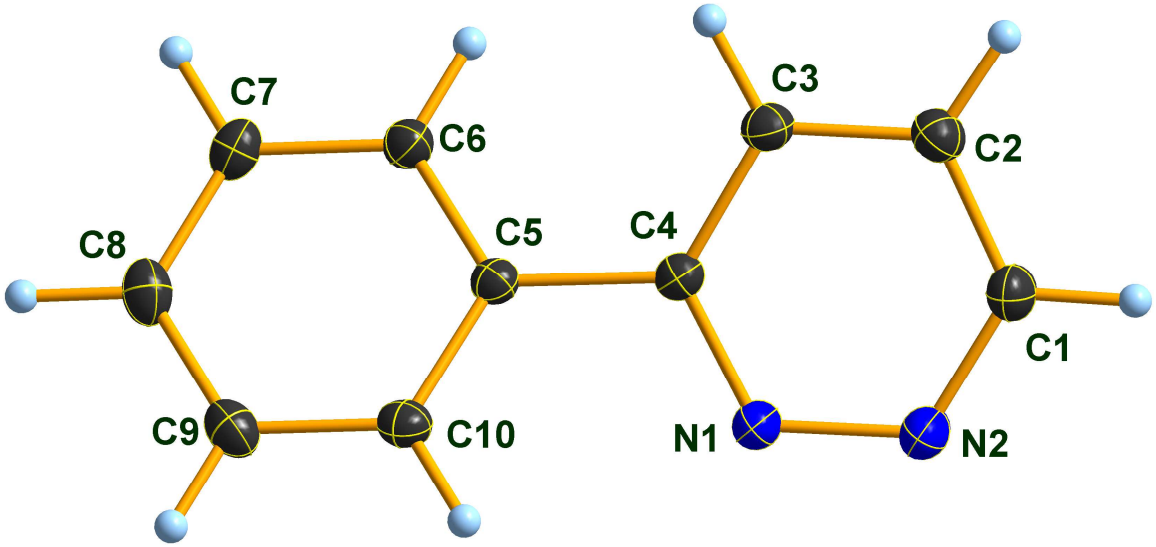


Figure 15. Molecular structure of compound **153a** in the crystal. DIAMOND[e)] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 49. Selected bond lengths (Å) of compound **153a**.

C4 – N1	1.341(1)	C8 – C7	1.391(2)
C4 – C3	1.403(1)	C6 – C7	1.389(2)
C4 – C5	1.483(1)	C9 – C10	1.388(2)
C5 – C6	1.397(2)	C2 – C3	1.369(2)
C5 – C10	1.402(1)	C2 – C1	1.390(2)
N1 – N2	1.346(1)	C8 – C9	1.390(2)
N2 – C1	1.332(2)		

Table 50. Selected bond angles (°) of compound **153a**.

N1 – C4 – C3	122.1(1)	C6 – C7 – C8	120.2(1)
N1 – C4 – C5	115.6(1)	N2 – C1 – C2	123.4(1)
C3 – C4 – C5	122.3(1)	C2 – C3 – C4	118.0(1)
C6 – C5 – C10	119.0(1)	C10 – C9 – C8	120.5(1)
C6 – C5 – C4	120.4(1)	C9 – C10 – C5	120.2(1)
C10 – C5 – C4	120.5(1)	C1 – N2 – N1	119.5(1)
C4 – N1 – N2	119.7(1)	C3 – C2 – C1	117.3(1)
C9 – C8 – C7	119.6(1)	C7 – C6 – C5	120.5(1)

Table 51. Selected torsion angles (°) of compound **153a**.

N1 – C4 – C5 – C6	-151.0(1)	C9 – C8 – C7 – C6	0.7(2)
C3 – C4 – C5 – C6	29.0(2)	N1 – N2 – C1 – C2	0.0(2)
N1 – C4 – C5 – C10	28.6(1)	C3 – C2 – C1 – N2	0.2(2)
C3 – C4 – C5 – C10	-151.4(1)	C1 – C2 – C3 – C4	-0.1(2)
C3 – C4 – N1 – N2	0.3(2)	N1 – C4 – C3 – C2	-0.2(2)
C5 – C4 – N1 – N2	-179.7(1)	C5 – C4 – C3 – C2	179.8(1)
C4 – N1 – N2 – C1	-0.2(2)	C7 – C8 – C9 – C10	-0.5(2)
C10 – C5 – C6 – C7	-0.9(2)	C8 – C9 – C10 – C5	-0.5(2)
C4 – C5 – C6 – C7	178.7(1)	C6 – C5 – C10 – C9	1.2(2)
C5 – C6 – C7 – C8	0.0(2)	C4 – C5 – C10 – C9	-178.4(1)

Table 52. Details for X-ray data collection and structure refinement for compound **155c**.

	155c
Empirical formula	$C_{11}H_{10}N_2S$
Formula mass	202.27
T[K]	143(2)
Crystal size [mm]	0.35 × 0.15 × 0.10
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	22.6579(7)
b [Å]	5.7173(2)
c [Å]	7.4545(2)
α [°]	90.0
β [°]	93.893(3)
γ [°]	90.0
V [Å^3]	963.44(5)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.394
μ [mm^{-1}]	0.292
F(000)	424
Θ range [°]	3.61 – 25.24
Index ranges	-32 ≤ *h* ≤ 32
	-8 ≤ *k* ≤ 8
	-10 ≤ *l* ≤ 10
Reflns. collected	9508
Reflns. obsd.	2442
Reflns. unique	2939
	(R_{int} = 0.0270)
R_1, wR_2 (2σ data)	0.0386, 0.0933
R_1, wR_2 (all data)	0.0494, 0.0998
GOOF on F^2	1.048
Peak/hole [e Å^{-3}]	0.408 / -0.210

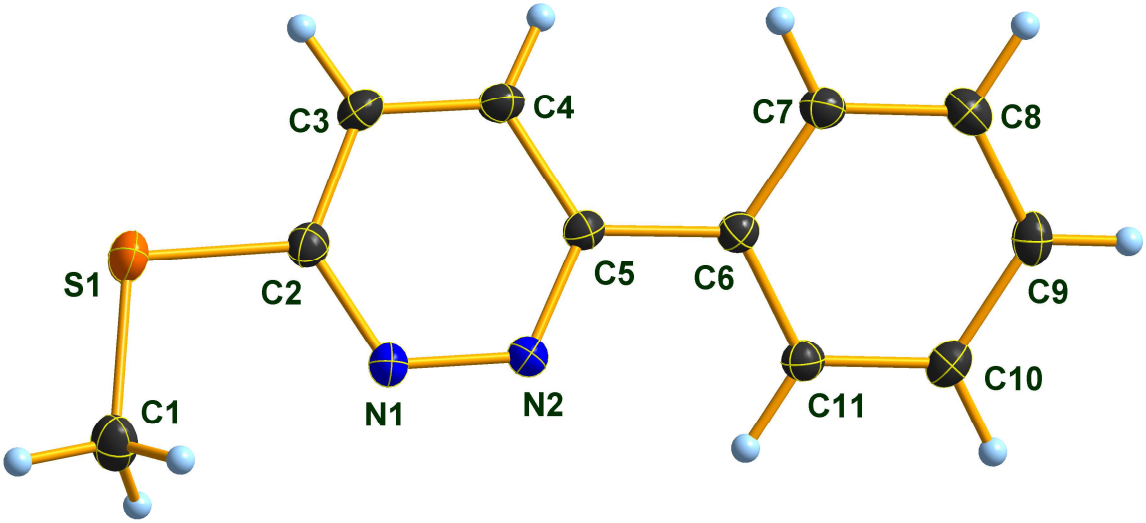


Figure 16. Molecular structure of compound **155c** in the crystal, DIAMOND[e)] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 53. Selected bond lengths (Å) of compound **155c**.

S1 – C2	1.754(1)	C8 – C9	1.390(2)
S1 – C1	1.801(1)	C3 – C4	1.365(2)
N2 – C5	1.336(2)	C6 – C5	1.482(2)
N2 – N1	1.353(1)	C4 – C5	1.407(2)
C2 – N1	1.333(2)	C11 – C6	1.402(2)
C2 – C3	1.405(2)	C7 – C8	1.389(2)
C10 – C11	1.391(2)	C7 – C6	1.400(2)
C10 – C9	1.394(2)		

Table 54. Selected bond angles (°) of compound **155c**.

C2 – S1 – C1	102.3(1)	C7 – C6 – C11	118.7(1)
C5 – N2 – N1	120.4(1)	C7 – C6 – C5	120.8(1)
N1 – C2 – C3	123.1(1)	C11 – C6 – C5	120.5(1)
N1 – C2 – S1	118.7(1)	C3 – C4 – C5	118.3(1)
C3 – C2 – S1	118.3(1)	C8 – C9 – C10	119.6(1)
C11 – C10 – C9	120.2(1)	N2 – C5 – C4	121.8(1)
C2 – N1 – N2	119.1(1)	N2 – C5 – C6	116.0(1)
C10 – C11 – C6	120.5(1)	C4 – C5 – C6	122.2(1)
C8 – C7 – C6	120.6(1)	C4 – C3 – C2	117.4(1)
C7 – C8 – C9	120.3(1)		

Table 55. Selected torsion angles (°) of compound **155c**.

C1 – S1 – C2 – N1	4.1(1)	C10 – C11 – C6 – C5	-178.2(1)
C1 – S1 – C2 – C3	-176.7(1)	C2 – C3 – C4 – C5	-0.4(2)
C3 – C2 – N1 – N2	1.4(2)	C7 – C8 – C9 – C10	0.6(2)
S1 – C2 – N1 – N2	-179.4(1)	C11 – C10 – C9 – C8	-0.8(2)
C5 – N2 – N1 – C2	-0.4(2)	N1 – N2 – C5 – C4	-1.0(2)
C9 – C10 – C11 – C6	0.3(2)	N1 – N2 – C5 – C6	178.7(1)
C6 – C7 – C8 – C9	0.1(2)	C3 – C4 – C5 – N2	1.4(2)
N1 – C2 – C3 – C4	-1.0(2)	C3 – C4 – C5 – C6	-178.2(1)
S1 – C2 – C3 – C4	179.8(1)	C7 – C6 – C5 – N2	-152.8(1)
C8 – C7 – C6 – C11	-0.6(2)	C11 – C6 – C5 – N2	25.7(2)
C8 – C7 – C6 – C5	177.9(1)	C7 – C6 – C5 – C4	26.9(2)
C10 – C11 – C6 – C7	0.4(2)	C11 – C6 – C5 – C4	-154.7(1)

Table 56. Details for X-ray data collection and structure refinement for compound **156c**.

	156c
Empirical formula	$C_{10}H_6ClIN_2$
Formula mass	316.52
T[K]	143(2)
Crystal size [mm]	0.40 × 0.15 × 0.02
Crystal description	colorless platelet
Crystal system	triclinic
Space group	*P*1
a [Å]	4.5667(3)
b [Å]	4.5669(3)
c [Å]	12.2111(6)
α [°]	95.502(5)
β [°]	95.480(4)
γ [°]	95.919(5)
V [Å^3]	250.71(3)
Z	1
$\rho_{calcd.}$ [g cm^{-3}]	2.096
μ [mm^{-1}]	3.417
F(000)	150
Θ range [°]	4.51 – 25.24
Index ranges	-6 ≤ *h* ≤ 6
	-6 ≤ *k* ≤ 6
	-17 ≤ *l* ≤ 17
Reflns. collected	4651
Reflns. obsd.	3033
Reflns. unique	3033
	(R_{int} = 0.0275)
R_1, wR_2 (2σ data)	0.0273, 0.0479
R_1, wR_2 (all data)	0.0273, 0.0479
GOOF on F^2	0.985
Peak/hole [e Å^{-3}]	0.665 / -0.692

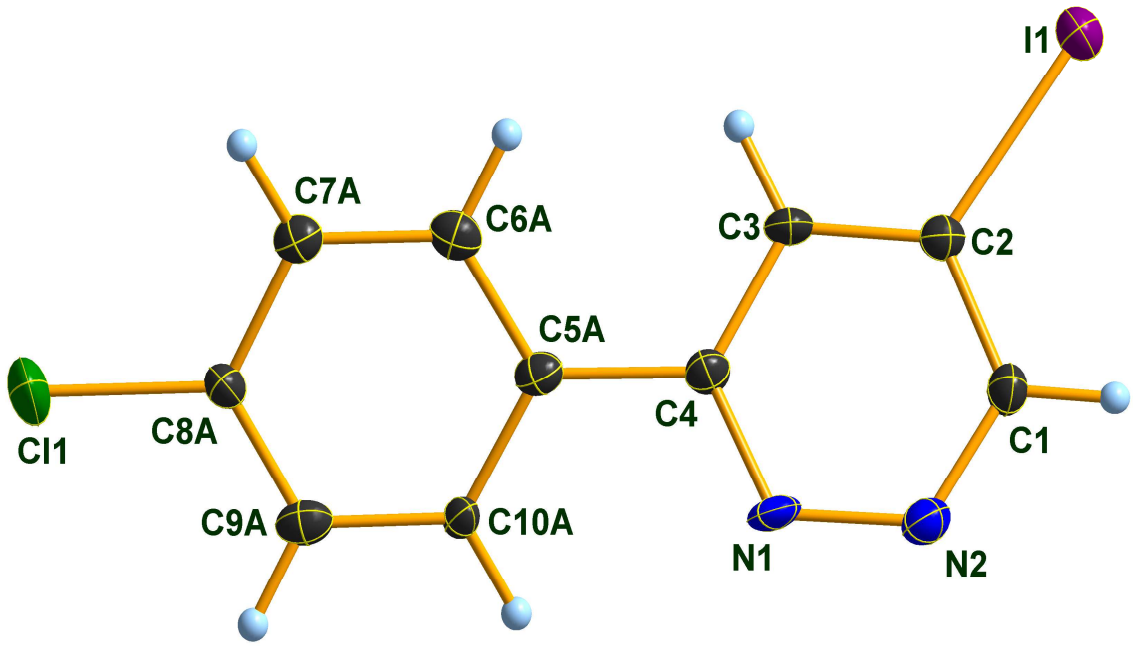


Figure 17. Molecular structure of compound **156c** in the crystal. The phenyl ring of the 4-chlorophenyl substituent is disordered over two positions with respect to a rotation around the C3-C5 bond. Only one of the two positions is represented for reasons of clarity. DIAMOND[e)] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 57. Selected bond lengths (Å) of compound **156c**.

N2 – C1	1.319(7)	C8A – C7A	1.409(11)
N2 – N1	1.343(8)	C7A – C6A	1.389(14)
C1 – C2	1.396(7)	C10A – C9A	1.384(16)
I1 – C2	2.090(5)	C4 – C5A	1.489(9)
Cl1 – C8A	1.732(7)	C5A – C6A	1.378(11)
C3 – C2	1.356(7)	C5A – C10A	1.405(13)
C3 – C4	1.408(8)	C8A – C9A	1.347(13)
N1 – C4	1.327(7)		

Table 58. Selected bond angles (°) of compound **156c**.

C1 – N2 – N1	120.0(5)	C9A – C8A – Cl1	119.7(7)
N2 – C1 – C2	122.5(5)	C7A – C8A – Cl1	118.9(6)
C2 – C3 – C4	116.5(5)	C6A – C7A – C8A	118.0(9)
C4 – N1 – N2	119.3(5)	C5A – C6A – C7A	121.3(9)
N1 – C4 – C3	123.1(6)	C9A – C10A – C5A	120.4(12)
N1 – C4 – C5A	115.9(6)	C8A – C9A – C10A	119.8(11)
C3 – C4 – C5A	121.0(6)	C6A – C5A – C10A	118.5(8)
C3 – C2 – C1	118.5(5)	C6A – C5A – C4	121.3(7)
C3 – C2 – I1	121.4(3)	C10A – C5A – C4	120.2(8)
C1 – C2 – I1	120.1(4)	C9A – C8A – C7A	121.3(8)

Table 59. Selected torsion angles (°) of compound **156c**.

N1 – N2 – C1 – C2	0.3(8)	N1 – C4 – C5A – C10A	-20.7(12)
C1 – N2 – N1 – C4	-0.6(9)	C3 – C4 – C5A – C10A	157.5(7)
N2 – N1 – C4 – C3	1.0(11)	C9A – C8A – C7A – C6A	7.4(14)
N2 – N1 – C4 – C5A	179.2(6)	Cl1 – C8A – C7A – C6A	-177.0(7)
C2 – C3 – C4 – N1	-1.0(10)	C10A – C5A – C6A – C7A	4.8(15)
C2 – C3 – C4 – C5A	-179.2(6)	C4 – C5A – C6A – C7A	-175.5(9)
C4 – C3 – C2 – C1	0.6(8)	C8A – C7A – C6A – C5A	-5.9(15)
C4 – C3 – C2 – I1	-179.6(4)	C6A – C5A – C10A – C9A	-5.1(15)
N2 – C1 – C2 – C3	-0.3(8)	C4 – C5A – C10A – C9A	175.3(11)
N2 – C1 – C2 – I1	180.0(4)	C7A – C8A – C9A – C10A	-7.8(16)
N1 – C4 – C5A – C6A	159.6(8)	Cl1 – C8A – C9A – C10A	176.6(9)
C3 – C4 – C5A – C6A	-22.1(12)	C5A – C10A – C9A – C8A	6.6(17)

References (Crystallography)

a) CrysAlis CCD, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).

b) CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).

c) SCALE3 ABSPACK – An Oxford Diffraction Program (1.0.4, gui:1.0.3) (C), Oxford Diffraction, Ltd., 2005.

d) Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.

e) Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.

f) Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

g) DIAMOND, Crystal Impact GbR., Version 3.2i.