Dissertation zur Erlangung des Doktorgrades

der Fakultät für Chemie und Pharmazie

der Ludwig-Maximilians-Universität München

Regioselective Organometallic Functionalization of 1,5- and 2,7-Naphthyridines & Preparation of New Fluorescent Aryl Naphthalene Dicarboximides with Large Stokes Shifts and Strong Solvatochromism

von

Robert Maximilian Greiner

aus Starnberg, Deutschland

2017

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, 14. August 2017

.....
(Robert Greiner)

Dissertation eingereicht am: 14. August 2017

1. Gutachter	Prof. Dr. Paul Knochel
2. Gutachter	Prof. Dr. Konstantin Karaghiosoff
Mündliche Prüfung am:	28. September 2017

This work was carried out from August 2013 to March 2017 under the guidance of Prof. Dr. Paul Knochel at the Faculty of Chemistry and Pharmacy of the Ludwig-Maximilians Universität, Munich.

First of all, I would like to express my appreciation to Prof. Dr. Paul Knochel for giving me the opportunity to do my Ph.D. in his group and for his invaluable guidance and support in the course of my scientific research.

I am also very grateful to Prof. Dr. Konstantin Karaghiosoff for agreeing to be my "Zweitgutachter" and for his advices regarding chemical and social issues. Furthermore, I would like to thank Prof. Dr. Trapp, Prof. Dr. Bracher, Dr. Dube and Dr. Didier for their interest shown in this manuscript by accepting to be referees.

I really would like to thank Dorothée Ziegler for the careful correction of this manuscript.

I would like to thank my "naphthyridine mates" Dr. Romain Blanc, Christian Petermayer, Henning Lumpe, Dorothée Ziegler and Denise Cibu as well as my students Ivan Gospodinov, Nastassia Knödlseder, Aušra Morkūnaitė, Christoph Jessen and Felix Rainers for the successful collaboration and their important contribution to my thesis.

I would further like to thank Dr. Thorben Schlücker and Dr. Dominik Zgela for the interesting cooperation on the "4-Aryl Naphthalimides-project".

I would also like to thank Dr. Zhi-Liang Shen for the nice cooperation on the "Shen-project" and the interesting discussions.

I thank all past and present co-workers i have met in the Knochel group for creating a wonderful ambience inside and outside of the lab. Special thanks go out to my actual and former lab mates from F2.062 Tim Van Lingen, Andreas Benischke, Marcel Leroux, Andreas Bellan, Dr. Romain Blanc and Dr. Cyril François.

Furthermore, I thank Dr. Oliver Baron for the best Espresso in the world and his "Vietnam Survival Guide".

Finally, I would like to thank my mother for keeping me alive during my period of insane illness. Mother, you're the best!

Parts of this PhD thesis have been published

Communications

1) **Robert Greiner**, Romain Blanc, Christian Petermayer, Konstantin Karaghiosoff, Paul Knochel: Preparation of Functionalized 2,7-Naphthyridines by Directed Lithiation with (2,2,6,6-Tetramethylpiperidyl)lithium and Their Regioselective Iron-Catalyzed Cross-Couplings, *Synlett* **2016**, *27*, 231.

2) Zhi-Liang Shen, Vasudevan Dhayalan, Andreas Benischke, **Robert Greiner**, Konstantin Karaghiosoff, Peter Mayer, Paul Knochel: Polyfunctional Lithium, Magnesium, and Zinc Alkenyl Reagents as Building Blocks for the Synthesis of Complex Heterocycles, *Angew. Chem. Int. Ed.* **2016**, *17*, 5332.

3) **Robert Greiner**, Thorben Schlücker, Dominik Zgela, Heinz Langhals: Fluorescent Aryl Naphthalene Dicarboximides with Large Stokes' Shifts and Strong Solvatochromism Controlled by Dynamics and Molecular Geometry, *J. Mat. Chem. C* **2016**, *4*, 11244.

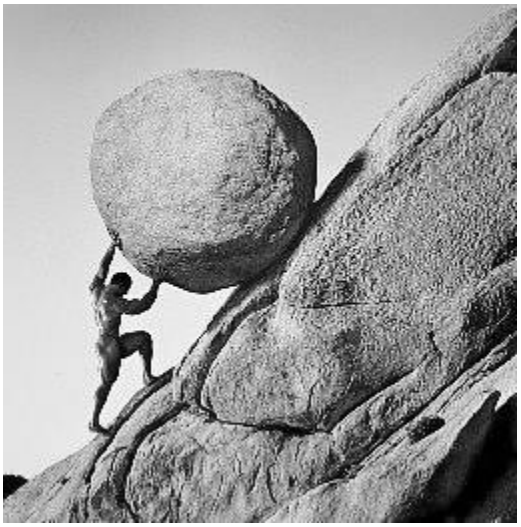
4) Moritz Balkenhohl, **Robert Greiner**, Ilya S. Makarov, Benjamin Heinz, Konstantin Karaghiosoff, Hendrik Zipse, Paul Knochel: Zn-, Mg-, and Li-TMP Bases for the Successive Regioselective Metalation of the 1,5-Naphthyridine Scaffold, *Chem. Eur. J.* **2017**, DOI: 10.1002/chem.201703638

5) Dorothée S. Ziegler, **Robert Greiner**, Henning Lumpe, Laura Kqiku, Konstantin Karaghiosoff, Paul Knochel: Directed Zincation or Magnesiation of the 2-Pyridone and 2,7-Naphthyridone Scaffold using TMP-Bases, *manuscript in preparation*.

6) **Robert Greiner**, Dorothée S. Ziegler, Denise Cibu, Andreas Jackowetz, Florian Auras, Thomas Bein, Paul Knochel: Polyfunctional Naphthyridines Prepared by Cobalt-Catalyzed Cross-Couplings of Halogenated Naphthyridines with Magnesium and Zinc Organo-metallics, *manuscript in preparation.*

Reviews

Diana Haas, Jeffrey Hammann, **Robert Greiner**, Paul Knochel: Recent Developments in Negishi Cross-Coupling Reactions, *ACS Catal*. **2016**, *6*, 1540-1552.



“Zwei Dinge sind zu unserer Arbeit nötig: Unermüdliche Ausdauer und die Bereitschaft, etwas, in das man viel Zeit und Arbeit gesteckt hat, wieder wegzuwerfen.“

Albert Einstein

Meiner Mutter

TABLE OF CONTENTS

A. INTRODUCTION

1. OVERVIEW……...2
2. ORGANOMETALLIC CHEMISTRY……...3
    2.1 Historical Background……...3
    2.2 Oxidative Insertion……....4
    2.3 Halogen-Metal Exchange……..6
    2.4 Metalation……..9
    2.5 Transition Metal Catalyzed Cross-Couplings with Iron and Cobalt…….13
3. NAPHTHYRIDINES……...20
4. 1,8-NAPHTHALIMIDES……23
5. OBJECTIVES……24

B. RESULTS & DISCUSSION

1. REGIOSELECTIVE METALATION OF THE 2,7-NAPHTHYRIDINE SCAFFOLD……..26
    1.1 Introduction……26
    1.2 Metalation of 2,7-Naphthyridines in Position 4..……28
    1.3 Metalation of 2,7-Naphthyridone in Position 3……31
2. FURTHER FUNCTIONALIZATION OF 2,7-NAPHTHYRIDINES AND SYNTHESIS OF NATURAL PRODUCTS LOPHOCLADINE A & B……35
3. REGIOSELECTIVE METALATION OF THE 1,5-NAPHTHYRIDINE SCAFFOLD……..39
    3.1 Introduction……39
    3.2 Metalation of the 1,5-Naphthyridine Scaffold in Position 4……40
    3.3 Metalation of 1,5-Naphthyridines in Position 8……...45
    3.4 Metalation of 1,5-Napthyridines in Position 2……48
4. ALTERNATIVE METAL-CATALYZED CROSS-COUPLINGS OF NAPHTHYRIDINES……..50
    4.1 Introduction……50
    4.2 Iron- and Cobalt-Catalyzed $C(sp^2)$-$C(sp^3)$ Cross-Couplings……50
    4.3 Cobalt-Catalyzed $C(sp^2)$-$C(sp^2)$ Cross-Couplings……...52
    4.4 Fluorescent Naphthyridines……58
5. FLUORESCENT ARYL NAPHTHALENE DICARBOXIMIDES WITH LARGE STOKES SHIFTS AND STRONG SOLVATOCHROMISM CONTROLLED BY DYNAMICS AND MOLECULAR GEOMETRY……...60
    5.1 Introduction……60
    5.2 Preparation of Aryl Naphthalene Dicarboximides and Discussion of Optical Measurements……63

6. SUMMARY……...71
6.1 Regioselective Organometallic Functionalization of 1,5- and 2,7-Naphthyridines……71
6.1.1 Regioselective Metalation of Naphthyridines……..71
6.1.2 Iron- and Cobalt-Catalyzed Cross-Coupling of Naphthyridines……..74
6.2 Preparation of Novel 4-Aryl Substituted Naphthalene Dicarboximides……..75

C. EXPERIMENTAL SECTION

1. GENERAL CONSIDERATIONS……...77
1.1 Solvents……...77
1.2 Reagents……..77
1.3 Content Determination of Organometallic Reagents……...79
1.4 Chromatography……..79
1.5 Analytical Data……80
2. ORGANOMETALLIC FUNCTIONALIZATION OF THE 2,7-NAPHTHYRIDINE SCAFFOLD……...81
2.1 Typical Procedures……...81
2.2 Preparation of Starting Materials……81
2.2.1 Preparation of 2,7-Naphthyridines **9a-d**……...81
2.2.2 Preparation of MEM-protected 2,7-Naphthyridone (**13**)……..85
2.3 Metalation of 2,7-Naphthyridines **9a-c** Using TMPLi (**2**)……88
2.4 Metalation of 2,7-Naphthyridone **13** using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**)……...97
2.5 Further Functionalization of 2,7-Naphthyridines and Synthesis of Natural Products Lophocladine A & B……..105
3. ORGANOMETALLIC FUNCTIONALIZATION OF THE 1,5-NAPHTHYRIDINE SCAFFOLD…….115
3.1 Typical Procedures…….115
3.2 Preparation of Starting Material 1,5-Naphthyridine (**39**)……...116
3.3 Metalation of 1,5-Naphthyridine (**39**) in Position 4 Using $TMP_2Mg{\cdot}2LiCl$ (**4**)……117
3.4 Metalation of Chloro-1,5-naphthyridines (**45a-b**) in Position 4 Using TMPMgCl·LiCl (**3**)……...123
3.5 Metalation of 1,5-Naphthyridines (**42a-c**) in Position 8 Using TMPMgCl·LiCl (**3**) and TMPZnCl·LiCl (**5**)……..……...127
3.6 Metalation of 1,5-Naphthyridines (**42a** and **42g**) in Position 2 Using TMPMgCl·LiCl (**3**) in Presence of $BF_3{\cdot}OEt_2$.....132
4. IRON- AND COBALT-CATALYZED CROSS-COUPLING OF NAPHTHYRIDINES…….136
4.1 Typical Procedures……136
4.2 Iron- and Cobalt-Catalyzed $C(sp^2)$-$C(sp^3)$ Cross-Couplings with Alkylmagnesium Reagents……137
4.3 Cobalt-Catalyzed $C(sp^2)$-$C(sp^2)$ Cross-Couplings of Naphthyridines with Arylmagnesium and Arylzinc Reagents……..……..144

5. FLUORESCENT ARYL NAPHTHALENE DICARBOXIMIDES……..159
5.1 Preparation of Starting Materials……...159
5.2 Preparation of Aryl Naphthalene Dicarboximides **73**, **77**, **78**….……160

D. APPENDIX

1. X-RAY DATA…….…175
2. PHOTOLUMINESCENCE QUANTUM EFFICIENCY MEASUREMENTS (PLQE)……..201
3. TIME-CORRELATED SINGLE PHOTON COUNTING (TCSPC)…….202
4. ADDITIONAL OPTICAL SPECTROSCOPIC DATA FOR DYES **73**……..203

Abbreviations

Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
ATR	attenuated total reflexion
br	broad
Bn	benzyl
Bu	butyl
°C	degree Celsius
calcd.	calculated
CAN	ceric ammonium nitrate
CC	cross-coupling
*c*Hex	cyclohexyl
cm^{-1}	wavenumber in reciprocal centimeters
conc.	concentrated
CyJohnPhos	2-dicyclohexylphosphino-biphenyl
δ	chemical shift in parts per million
d	doublet
dba	*trans*,*trans*-dibenzylidene acetone
DCM	dichloromethane
DEI	desorption electrospray ionization
DFT	density functional theory
DIPEA	diisopropylethylamine
DMA	dimethylacetal
DMF	*N*,*N*-dimethylformamide
DMG	directed metalation group
DMSO	dimethylsulfoxide
D*o*M	directed *ortho*-metalation
dppf	1,1'-bis(diphenylphosphino)-ferrocene
DSC	dye-sensitized solar cell
E	electrophile
EI	electron impact
equiv	equivalent
Et	ethyl
eV	electronvolt
FG	functional group
GC	gas chromatography
h	hour
Hal	halogenide
HOMO	highest occupied molecule orbital
HRMS	high resolution mass spectroscopy
ICT	intramolecular charge transfer
*i*Pr	isopropyl
IR	infrared
J	coupling constant
λ	wavelength
LiHMDS	lithiumhexamethyldisilazid
LUMO	lowest unoccupied molecule orbital
m	multiplet
m	meta
M	molarity
Me	methyl
MeCN	acetonitrile
MEM	2-methoxyethoxymethyl
Met	metal

min	minute
m. p.	melting point
mmol	millimole
MS	mass spectroscopy
nm	nanometers
NMR	nuclear magnetic resonance
NMP	*N*-methyl-2-pyrrolidone
NBS	*N*-bromosuccinimid
o	ortho
OLED	organic light emitting diode
p	para
PEPPSI-*i*Pr	[1,3-Bis(2,6-Diisopropylphenyl)-imidazol-2-ylidene] (3-chloro-pyridyl)-palladium(II) dichloride
Ph	phenyl
PICT	planarized intramolecular charge transfer
Piv	pivalate
PL	photoluminescence
PLQE	photoluminescence quantum yield
PMMA	poly(methyl methacrylate)
PPTS	pyridinium *p*-toluenesulfonate
q	quartet
quint	quintet
R	organic substituent
rt	room temperature
s	singlet
sat.	saturated
sept	septet
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
sxt	sextet
TBAF	tetrabutylammoniumfluoride
TBS	*tert*-butyldimethylsilyl
TCSPC	time-correlated single photon counting
tfp	tri-2-furylphosphine
THF	tetrahydrofuran
TICT	twisted intramolecular charge transfer
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylendiamine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
TP	typical procedure
t	triplet
UV	ultraviolet
WLED	white light emitting diode

A. INTRODUCTION

1. OVERVIEW

In a modern, fast-developing world, where epidemics, incurable diseases and narrow resources still remain as unsolved problems, mankind relies on the synthetic skills of eager chemists, who develop new pharmaceutical agents and technical materials to face the needs of our population and their future generation. Most notably, scientific discoveries in organic chemistry are of crucial importance, since carbon-atom derived molecules are the basis of all life and are responsible for a huge variety of phenomena like natural colors (pigments), poisonous animals (venoms) or antibacterial mould (penicillins). The class of heterocyclic compounds constitute one of the largest and most varied family of organic molecules. They are widely distributed in nature and their structures can be found in herbicides, pesticides, insecticides, dyes and copolymers.[1] By understanding their role in biological processes,[2] heterocycles from natural products can be targeted for pharmacologically purposes with many of them already being used in clinical routine. In particularly, the determination of the biological active site in a natural product is essential for the development of new drugs. In order to optimize the biological activity, it is indispensable to create libraries of molecules of the same scaffolds, but with different functional groups.[3] To prepare such functionalized heterocycles, chemists have developed a broad variety of synthetic methods. A very common method is to create the backbone of a heterocycle and to introduce the desired functional groups before the cyclization process is initiated. Alternatively, a more modern approach is to introduce or replace substituents in an existing heterocycle.[1a] This offers a higher flexibility, since there is a greater choice of substituents that can be easily introduced and there is less necessity of tedious protection/deprotection cycles. In this context, organometallic chemistry is a versatile tool for the functionalization of heterocycles. There are a plenty of useful metalorganic compounds with various metals, providing different reactivities for distinct purposes.[4] Their application in organic synthesis include traditional aromatic substitutions,[5] oxidative metal-insertions,[6] halogen-metal exchange reactions,[7] directed metalations[8] and cross-coupling reactions.[9] Especially cross-coupling reactions became very popular for their facile carbon-carbon bond formation, rewarding *Heck*,[10] *Suzuki*[11] and *Negishi*[12] with the Nobel prize in chemistry in 2010.

---

[1] (a) *Comprehensive Heterocyclic Chemistry III*, Vol. 1 (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Oxford, United Kingdom, **2008** (b) *Heterocycles in Live and Society* (Eds.: A. F. Pozharskii, A. T. Soldatenkov, A. R. Katrinzky), John Wiley & Sons, Chichester, United Kingdom, **2011**.

[2] *Medicinal Natural Products*, 3. Edition (Ed.: P. M. Dewick), John Wiley & Sons, United Kingdom, **2009**, 1.

[3] N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529.

[4] *(a)* A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414. (b) *Handbook of Functionalized Oganometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**. (c) *The Organometallic Chemistry of the Transition Metals (Ed.: R. H. Crabtree), Wiley & Sons, **2014**.*

[5] *Organometallic Chemisty*, Vol. 38 (Eds.: I. J. S. Fairlamb, J. N. Lynam), RSC, **2012**.

[6] (a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040. (b) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.

[7] P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A., *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.

[8] (a) V. Snieckus, *Chem. Rev*. **1990**, *90*, 879. (b) E. Bergin, *Nat. Chem.* **2015**, *7*, 8. (c) H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109.

[9] *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.

[10] *Palladium Reagents in Organic Synthesis (Best Synthetic Methods)*, Ed. Richard F. Heck, Academic Press Inc, **1985**.

[11] A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *(50)*, 6722.

[12] E.-i. Negishi, *Organometallics in Organic Synthesis*, Wiley-VCH, Weinheim, **1980**.

2. ORGANOMETALLIC CHEMISTRY

2.1 Historical background

The first organometallic compound can be traced back to 1760, where *Cadet de Gassicourt* produced As_2Me_4 from potassium acetate with arsenic trioxide, trying to prepare invisible ink.[13] The next reported organometallic compounds have been "*Zeise's salt*" and "*Frankland's diethyl zinc*".[14] Almost 150 years above from "*Cadet's fuming liquid*", at the beginning of the 20th century, *Grignard*, set a milestone in the history of organometallic chemistry by the preparation of the first organomagnesium compound.[15] Therefore, in 1912 he was rewarded with the Nobel prize and many laureates followed for their expertise in metalorganic research: *Ziegler* and *Natta* (1963), *Wilkinson* and *Fischer* (1973), *Brown* and *Wittig* (1989), *Knowles*, *Noyori* and *Sharpless* (2001), *Chauvin*, *Grubbs* and *Schrock* (2005), and as already mentioned *Heck, Negishi* and *Suzuki* (2010). Nowadays, there exists a vast number of organometallic species, which find broad application in both industry and academia.[16]
The reactivity of an organometallic compound is characterized by the polarization of its carbon-metal bond. In general, the reactivity increases with the ionic character of the respective bond (Figure 1).[17,4b]

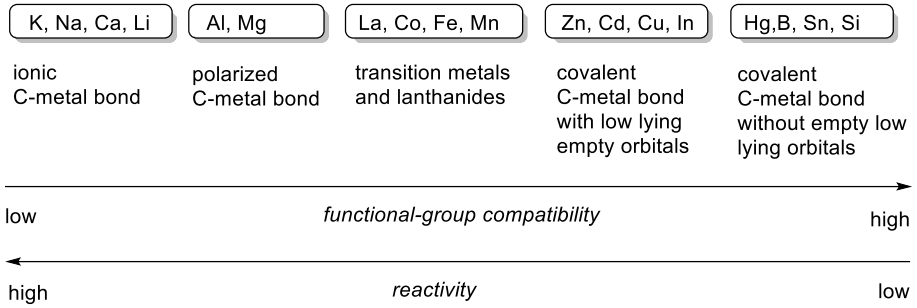


Figure 1: Polarity of organometallic reagents *versus* functional group tolerance and reactivity.[18]

Organometallics, such as organolithium, -sodium or -potassium reagents are highly reactive towards many electrophiles, but are incompatible with sensitive functional groups.[19] However, using reagents with a very covalent carbon-metal bond like organoboron, -silicon, -indium or -tin species, functional group tolerance is maintained.[20,4b] But their mild reactivity often requires harsh conditions or special catalysts in order to react with electrophiles. Organoaluminium, -magnesium and -zinc reagents are a

[13] D. Seyferth, *Organometallics* **2001**, *20*, 1488.
[14] (a) E. Frankland, *Liebigs Ann. Chem*. **1848**, *71*, 171. (b) E. Frankland, *J. Chem. Soc.* **1848**, *2*, 263.
[15] V. Grignard, *Compt. Rend. Acad. Sc. Paris* **1900**, *130*, 1322.
[16] (a) *Organomagnesium Compounds* (Eds.: Z. Rappoport, I. Marek), John Wiley & Sons, Chichester, United Kingdom, **2006**. (b) *Main Group Metals in Organic Synthesis* (Eds. H. Yamamoto, K. Oshima), VCH, Wiley, Weinheim, Germany, **2004**. (c) *Organometallics*, 3rd edition, Ed.: C. Elschenbroich, Wiley-VCH, **2003**. (d) *Organometallic Reagents in Synthesis,* 3rd issue of *Oxford Chemistry Primers, Ed. P. R. Jenkins,* Oxford University Press, **1992**.
[17] (a) *Organometallics in Organic Synthesis* (Ed.: N. Negishi), VCH, Wiley, Weinheim, Germany, **1996**. (b) *Applications of Organometallic Compounds* (Ed.: I. Omae), VCH, Wiley, Chichester, United Kingdom, **1998**. (c) *The Chemistry of Organometallic Compounds* (Eds.: E. G. Rochow, D. T. Hurd, R. N. Lewis), VCH, Wiley, New York, United States **1957**. (d) *Principle of Organometallic Chemistry* (Ed.: Powell), Chapman and Hall, London, United Kingdom, **1988**.
[18] B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed*. **2011**, *50*, 9794.
[19] J. Clayden, *Organolithiums: Selectivity for Synthesis* (Ed. J. E. Baldwin), Pergamon Press, Oxford, **2002**.
[20] *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials* (Ed. D.G. Hall), Wiley-VCH, Weinheim, **2011**.

good compromise between the two extremes, since they provide enough reactivity and show a very suitable group tolerance.

2.2 Oxidative Insertion

One of the oldest and today still very convenient method to prepare organometallic reagents, is the direct oxidative insertion of elemental metal into a carbon-halogen bond. In 1849, *Frankland* was the first chemist who discovered this method by preparing dialkylzinc reagents by treating alkyliodides with zinc.[14] Further experiments were done by *Hallwachs* and *Schaferik*, who investigated the reaction between ethyl-/methyl iodide with aluminium.[21] The final breakthrough however was made by *Grignard* in 1900, who generated the first organomagnesium reagents *via* insertion of elemental magnesium into a carbon halide bond.[15] Originally, *Barbier* developed a one pot synthesis for the preparation of functional alcohols starting from alkyl halides, magnesium metal and carbonyl compounds,[22] but it was *Grignard*, who separately prepared organomagnesium reagents in ethereal solvents before the addition of carbonyl compounds. Nowadays, so-called "*Grignard-reagents*" play a very important role in organic synthesis.

However, the first magnesium insertions had some major drawbacks. First of all, refluxing conditions were required, which limited functional group tolerance. Furthermore, those insertions have a certain induction period, making sudden exothermic reactions unpredictable for large scale productions. In addition only very less alkyl or aryl halides react with magnesium metal because of its passivized layer of magnesium oxide/magnesium hydroxide. To overcome these problems, *Rieke* developed highly reactive metal powders by reduction of an anhydrous metal chloride with an alkali metal such as lithium, sodium or potassium. This method allowed the preparation of *Grignard* reagents at very low temperatures, increasing functional group tolerance, for instance tolerating groups such as *tert*-butyl-ester or nitriles. Furthermore, "*Rieke metals*" proved to be so powerful that even relatively unreactive organohalides, such as fluorides can be transformed into the corresponding magnesium species (Scheme 1).[23]

A major drawback of "*Rieke metals*" is the circumstance that they always have to be freshly prepared and that the functional group tolerance is still limited. In recent times, *Knochel* and co-workers developed a mild and efficient method for the preparation of highly functionalized *Grignard* reagents. Starting from aromatic or heteroaromatic halides, they inserted commercially available zinc and magnesium turnings in the presence of lithium chloride (Scheme 2).[24]

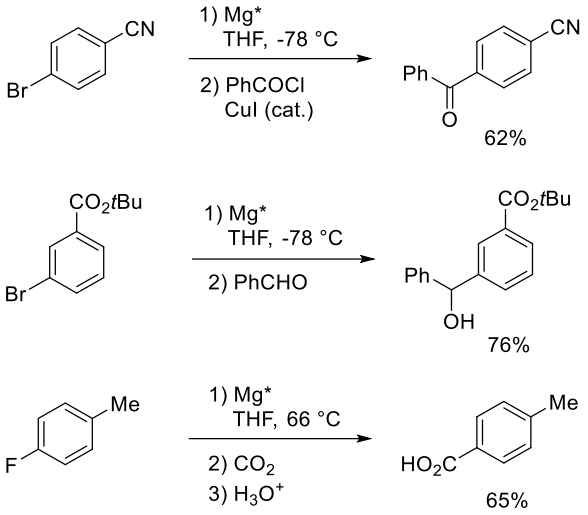
---

[21] W. Hallwachs, A. Schaferik, *Ann. Chem.***1859**, *109*, 206.

[22] P. Barbier, *C. R. Hebd. Séances Acad. Sci.***1899**, *128*, 110.

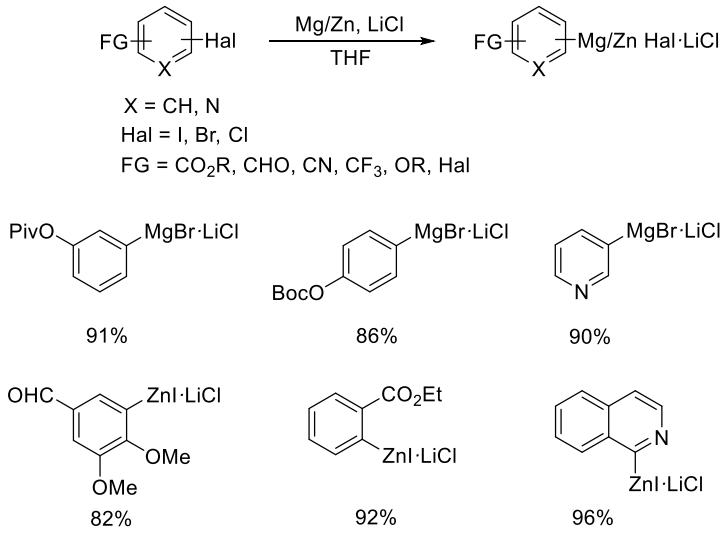
[23] (a) R. D. Rieke, L.-C. Chao, *Syn. React. Inorg. Metal-Org. Chem.* **1974**, *4*, 101. (b) R. D. Rieke, *Acc. Chem. Res.* **1977**, *10*, 301. (c) R. D. Rieke, *Science* **1989**, *246*, 1260. (d) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445. (e) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925. (f) R. D. Rieke, *Aldrichim. Acta* **2000**, 33, 52. (g) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428.

[24] (a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802. (b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192. (c) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040. (d) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358.



Scheme 1: Preparation and reaction of functionalized *Grignard* reagents using "*Rieke magnesium*".

Several studies showed that lithium chloride enhances the reaction rate of the metal insertion by lowering the energy of the transition state.[25] Furthermore, lithium chloride improves the solubility of the organometallic reagent by forming an "ate"-species of the general formula $RMetXCl^-Li^+$ (R = alkyl, aryl; Met = Mg, Zn, X = Cl, Br, I).[26]

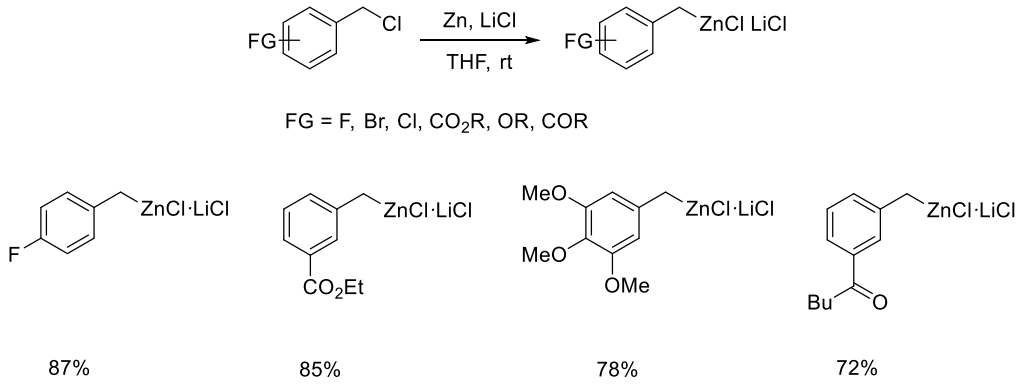


Scheme 2: Preparation of organomagnesium and organozinc reagents in the presence of LiCl.

However, in some cases the zinc insertion is still very slow and the generated zinc reagents are inert towards many electrophiles. This problem can be solved by performing a lithium chloride promoted magnesium insertion in the presence of zinc chloride. Thus, the *Grignard* reagent is still formed fast and

[25] C.-Y. Liu, X. Wang, T. Furuyama, S. Yasuike, A. Muranaka, K. Morokuma, M. Uchiyama, *Chem. Eur. J.* **2010**, *16*, 1780.
[26] (a) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159. (b) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771. (c) J. E. Fleckenstein, K. Koszinowski, *Organometallics* **2011**, *30*, 5018.

then transmetalated to zinc, creating an organozinc species of the formula RZnCl·MgXCl·LiCl (X = Cl, Br, I). These zinc species react easily with aldehydes, ketones and carbon dioxide, whereas normal zinc species without MgXCl salt often do not undergo these reactions.[27] When using $Zn(OPiv)_2 \cdot 2LiCl$ instead of $ZnCl_2 \cdot 2LiCl$, the magnesium insertion rate is even much faster. Furthermore, this method provides solid and thus easy to handle organozinc compounds, which show air stability for a period of time.[28] *Knochel* and co-workers also demonstrated many examples of lithium chloride promoted zinc insertions into benzylic chlorides (Scheme 3).[29]

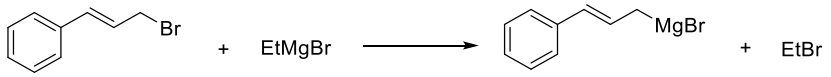


Scheme 3: LiCl-mediated preparation of functionalized benzylic organozinc reagents.

For more versatility, *Knochel* and co-workers extended the insertion into benzylic halides with indium,[30] manganese,[31] and aluminum[32] metal, tolerating a large variety of functional groups.

2.3 Halogen-Metal Exchange

Another, even more practical method to prepare an organomagnesium species is the halogen-magnesium exchange. *Prévost* was the first scientist who discovered this methodology in 1931 by reaction of cinnamyl bromide with ethylmagnesium bromide (Scheme 4).[33]



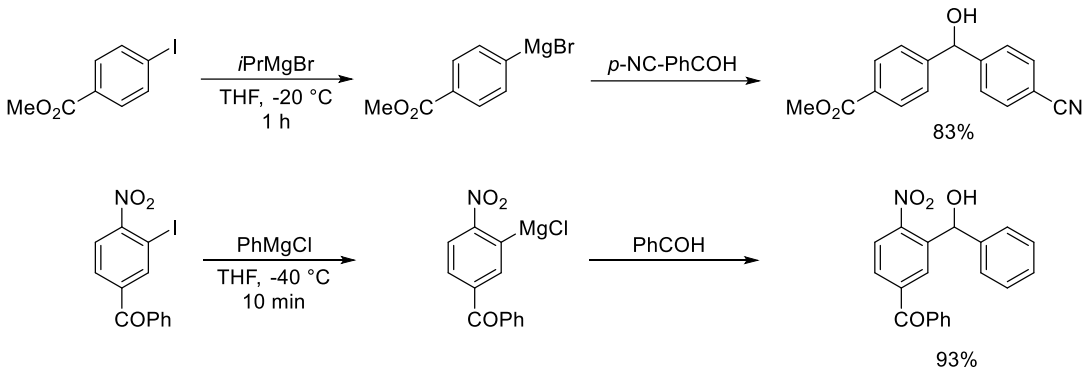
Scheme 4: First example of a halogen-magnesium exchange.

[27] A. Metzger, S. Bernhardt, G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 4665.
[28] (a) S. Bernhardt, G. Manolikakes, T. Kunz, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9205. (b) C. I. Stathakis, S. Bernhardt, V. Quint, P. Knochel, *Angew. Chem. Int. Ed.* **2012**, *51*, 9428. (c) M. Ellwart, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 10662. (d) M. S. Hofmayer, J. M. Hammann, F. H. Lutter, P. Knochel, *Synthesis* **2017**, in print. (e) J. M. Hammann, F. H. Lutter, D. Haas, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 1082.
[29] (a) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107. (b) M. A. Schade, A. Metzger, S. Hug, P. Knochel, *Chem. Comm.* **2008**, 3046. (c) A. Metzger, M. A. Schade, G. Manolikakes, P. Knochel, *Chem. Asian J.* **2008**, *3*, 1678. (d) A. Metzger, F. Piller, P. Knochel, *Chem. Comm.* **2008**, 5824. (e) A. Metzger, C. Argyo, P. Knochel, *Synthesis* **2010**, 882.
[30] (a) Y.-H. Chen, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 7648. (b) Y.-H. Chen, M. Sun, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 2236. (s) S. Bernhardt, Z. -L. Shen, P. Knochel, *Chem. Eur. J.* **2013**, *19*, 828.
[31] (a) Z. Peng, P. Knochel, *Org. Lett.* **2011**, *13*, 3198. (b) P. Quinio, A. D. Benischke, A. Moyeux, G. Cahiez, P. Knochel, *Synlett* **2015**, *26*, 514-518.
[32] T. D. Blümke, K. Groll, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2011**, 6440.
[33] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, 1372.

Further discoveries in this field followed by *Urion*[34] in 1934 and *Wittig* and *Gilman*[35] in 1938. In contrast to insertion reactions, halogen-metal exchange can be mostly performed under very mild conditions, improving the functional group tolerance. Also, this method gives access to organometallic reagents, like carbenoids, which are difficult to prepare by direct metal insertion.[36]

The halogen/metal exchange is considered to be an equilibrium in which the formation of the most stable organometallic species is formed according to its hybridization ($sp > sp^2_{vinyl} > sp^2_{aryl} > sp^3_{prim} > sp^3_{sec}$). Thus, the formed organometallic compound has a higher thermodynamic stability than the exchange reagent itself.[37] Even though, the exact mechanism of such an exchange reaction is still not known, a halogen ate complex is assumed to be an intermediate in this process.[38] The reaction rate is enhanced in the presence of electronegative substituents on the aryl halide, thus generating a more stable organometallic compound. Not to neglect are the electronic properties of the halogen and the organic substrate itself.

Until today, the halogen/magnesium exchange has become the most versatile method among all exchange reactions. In 1998, *Knochel* and co-workers further extended this method by describing iodine/magnesium exchange reactions using PhMgCl and *i*PrMgBr at low temperatures.[39] This protocol enables the use of substrates bearing sensitive functionalities like ester- or nitrogroups (Scheme 5).



Scheme 5: Preparation of polyfunctional *Grignard* reagents starting from aryl iodides using *i*PrMgBr/PhMgCl.

Knochel could further improve the halogen/magnesium exchange by development of the reagent *i*PrMgCl·LiCl (**1**).[40] This so called "Turbo-*Grignard*" is obtained by the stoichiometric addition of lithium chloride to *i*PrMgCl.

---

[34] E. Urion, *C. R. Hebd. Séances Acad. Sci.***1934**, *198*, 1244.

[35] (a) G. Wittig, U. Pockels, H. Dröge, *Chem. Ber.* **1938**, *71*, 1903. (b) R. G. Jones, H. Gilman, *Org. React.* **1951**, *6*, 339 (c) H. Gilman, W. Langham, A. L. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106.

[36] (a) J. Villiéras, *Bull. Soc. Chim. Fr.* **1967**, 1520. (b) J. Villiéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Soc. Chim. Fr*. **1986**, 470. (c) C. Tamborski, G. J. Moore, *J. Organomet. Chem.* **1971**, *26*, 153. (d) N. Furukawa, T. Shibutani, H. Fujihara, *Tetrahedron Lett.* **1987**, *28*, 5845. (e) D. J. Burton, Z.-Y. Yang, *Tetrahedron* **1992**, *48*, 189. (f) G. Cahiez, D. Bernard, J. F. Normant, *J. Organomet. Chem.* **1976**, *113*, 107. (g) C. Bolm, D. Pupowicz, *Tetrahedron Lett.* **1997**, *38*, 7349.

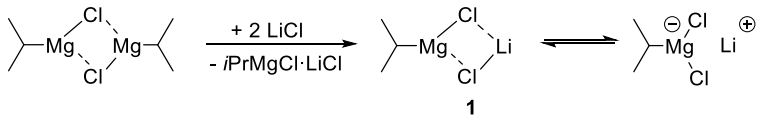
[37] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.

[38] (a) R. W. Hoffmann, M. Bönstrup, M. Müller, *Org. Lett.* **2003**, *5*, 313. (b) V. P. W. Böhm, V. Schulze, M. Bönstrup, M. Müller, R. W. Hoffmann, *Organometallics* **2003**, *22*, 2925.

[39] (a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701. (b) I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed*. **2002**, *41*, 1610. (c) A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu, P. Knochel, *Synthesis* **2002**, 565.

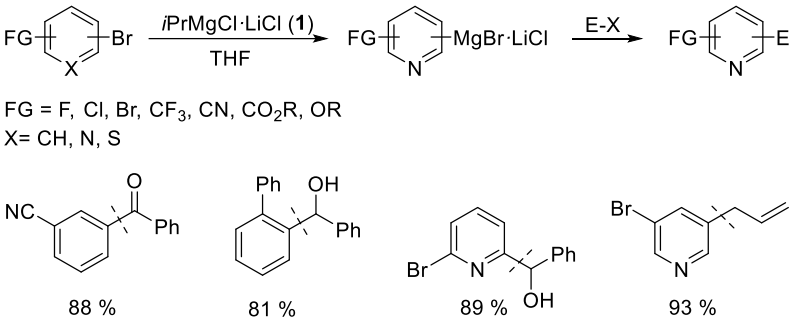
[40] (a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. (b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159. (c) H. Ren, P. Knochel, *Chem. Commun.* **2006**, 726. (d) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543. (e) F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, 2288.

It shows a remarkably high reactivity which is caused by the breakup of *i*PrMgCl aggregates and the formation of magnesium-lithium ate complexes (Scheme 6).



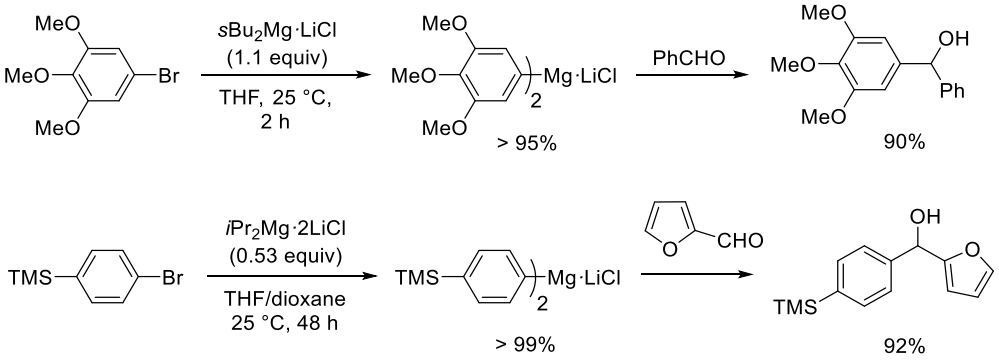
Scheme 6: Formation of lithium-ate complex through addition of LiCl to *i*PrMgCl.

Where *i*PrMgBr/PhMgCl lacked in reactivity, *i*PrMgCl·LiCl (**1**) enables facile bromine/magnesium exchange reactions. Thus, a broad range of aromatic and heteroaromatic bromides were converted into their corresponding organomagnesium reagents (Scheme 7).



Scheme 7: *i*PrMgCl·LiCl (**1**) as reagent for bromine/magnesium exchange reactions.

However, in case of electron-rich arenes, *i*PrMgCl·LiCl (**1**) fails to react with these compounds. Therefore, *bis*-magnesium reagents of type $R_2Mg·LiCl$ with an increased ate-character have been established. Thus, the *Grignard* reagents $sBu_2Mg·LiCl$ and $iPr_2Mg·LiCl$ could be successfully employed in exchange reactions with unreactive aryl bromides and iodides (Scheme 8).[41]



Scheme 8: *Grignard* reagents $sBu_2Mg·LiCl$ and $iPr_2Mg·LiCl$ as exchange reagents for electron-rich aromatics.

Iodine-zinc exchange reactions have also been reported. For instance, various iodinated aromatic and heteroaromatic substrates can be zincated using iPr_2Zn in the presence of Li(acac).[42]

[41] A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159.
[42] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.***2004**, *43*, 1017.

2.4 Metalation

Besides the halogen-metal exchange and the oxidative insertion, the metalation offers a third possibility to generate an organometallic species. The huge advantage is, that there is no need for a halogen precursor. For metalation, the respective (hetero-)arene has to have a carbon-hydrogen-bond with a relative acidic proton, which can be deprotonated using alkyl metals or metal amide bases.

Through the pioneering work of *Gilman*,[43] *Wittig* [44] and *Snieckus* [45], it became possible to regio-selectively functionalize aromatic and heteroaromatic systems in *ortho*-position to a directing group (directed *ortho*-metallation, D*o*M). Such a directing group or DMG (directing metalation group) usually contains a heteroatom with a free electron pair that can coordinate to the lithium reagent and thus leads the deprotonation in *ortho*-position. Very common DMGs are carbamates, amides, methoxy or cyano groups.

For the first directed *ortho*-metalations, organolithium compounds like *n*BuLi or PhLi were used. Due to nucleophilic side reactions, more sterically hindered lithium bases such as LDA[46] (lithium di*iso*-propylamide) or TMPLi (**2**)[47] (2,2,6,6-tetramethylpiperidyl lithium) have been developed. Many further developments in the field of D*o*M and organolithium chemistry have been made. For example, variation of the used lithium bases allows D*o*M on different *ortho*-metalation sites (Figure 2).

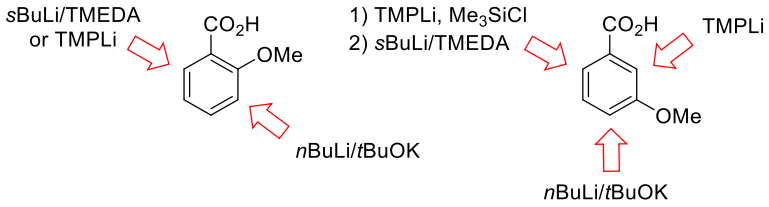
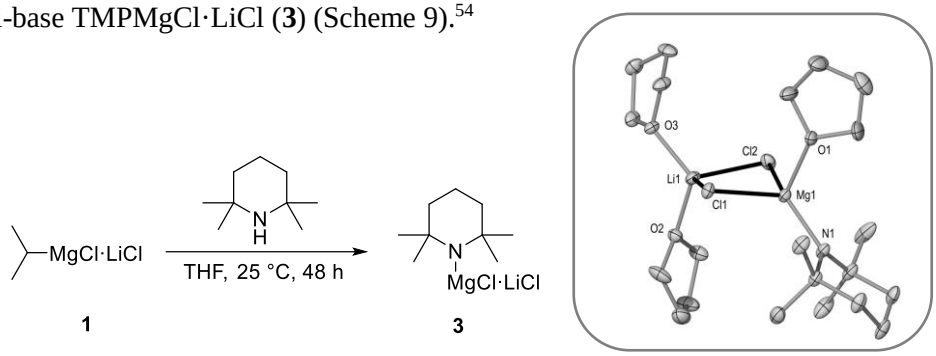


Figure 2: Regioselective *ortho*-metalation of *ortho*- and *meta*-anisic acid depending on used lithium base.[48]

However, alkyllithium reagents as well as lithium amides show such a high reactivity, that undesired side reactions, e. g. *Chichibabin* addition[49] or an attack on the functional group can occur. Furthermore, they have to be prepared in *situ* since their stability in THF is limited and most lithiations require very low temperatures (-78 to -100 °C). As an alternative, especially when dealing with sensitive functional groups, magnesium amide bases have been developed. In 1947, based on *Meunier's* original dis-coveries[50] *Hauser* and coworkers established the magnesium amide bases of type R_2NMgX and

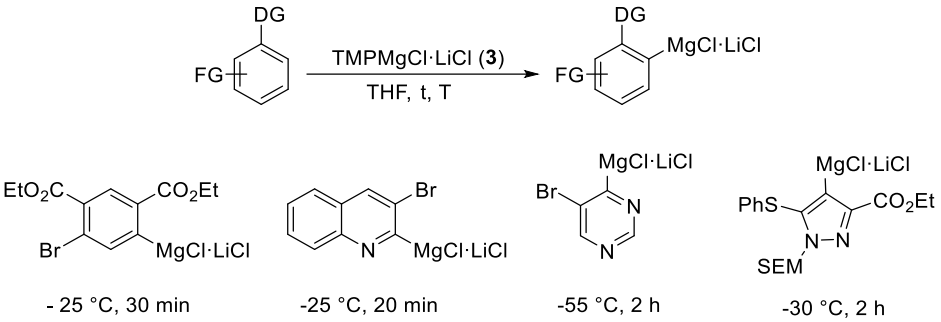
[43] H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.***1939**, *61*, 109.
[44] G. Wittig, G. Fuhrmann, *Ber. Dtsch. Chem. Ges.***1940**, *73*, 1197.
[45] (a) V. Snieckus, *Pure & Appl. Chem.* **1990**, *62*, 2047 (b) T. K. Macklin, J. Panteleev, V. Snieckus, *Angew. Chem. Int. Ed.* **2008**, *47*, 2097. (c) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.
[46] M. Hamell, R. Levine, *J. Org. Chem.* **1950**, *15*, 162.
[47] (a) C. L. Kissel, B. Rickborn, *J. Org. Chem.* **1972**, *37*, 2060. (b) M. W. Rathke, R. Kow, *J. Am. Chem. Soc.* **1972**, *94*, 6854.
[48] T.-H.Nguyen , N. T. T. Chau , A.-S.Castanet, K. P. P. Nguyen , J. Mortier, *J. Org. Chem.* **2007**, *72*, 3419.
[49] A. E. Chichibabin, O. A. Zeide, *J. Russ. Phys. Chem. Soc.* **1914**, *46*, 1216.
[50] L. Meunier, *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758.

$(R_2N)_2Mg$.[51] Several decades later, *Eaton*[52] and then *Mulzer*[53] applied sterically more demanding amide bases of the kind TMPMgX and TMP_2Mg (TMP = 2,2,6,6-Tetramethylpiperidyl) for the directed *ortho*-magnesiation of aromatic compounds. However, these magnesium amides are in an aggregated state, leading to low kinetic basicity and low solubility. As a consequence, a large excess of the used magnesium amide (up to 10 equiv) and the electrophile were necessary to overcome these drawbacks.
A huge improvement was achieved in 2006, when *Knochel* and coworkers developed the highly active mixed Mg/Li-base TMPMgCl·LiCl (**3**) (Scheme 9).[54]



Scheme 9: Preparation and crystal structure of TMPMgCl·LiCl (**3**)

The outstanding advantages of this new base are not only its excellent kinetic basicity and the very good solubility, but also the high thermal stability in THF-solutions, giving the ability to long term storage. TMPMgCl·LiCl (**3**) has proven to be a suitable reagent for the deprotonation of a wide range of activated aromatics and heterocycles with excellent regio- and chemoselectivity at moderate temperatures (Scheme 10).[55]



Scheme 10: TMPMgCl·LiCl (**3**) as suitable reagent for the magnesiation of (hetero-)aromatics.

Ever since, several lithium chloride solubilized TMP-bases have been developed by the *Knochel* group, all of them showing different reactivity, thus making them suitable for different substrates. Among

[51] (a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295. (b) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350.
[52] (a) P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016. (b) M.-X. Zhang, P. E. Eaton, *Angew. Chem. Int. Ed.* **2002**, *41*, 2169. (c) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc.* **1993**, *115*, 11375. (d) Y. Kondo, A. Yoshida, T. Sakamoto, *J. Chem. Soc., Perkin Trans 1*, **1996**, 2331.
[53] (a) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414. (b) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Liebigs Ann.* **1995**, 1441. (c) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Synthesis*, **1995**, 1225.
[54] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
[55] For a review see: B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.

them, the most practical and most used are TMPMgCl·LiCl (**3**), $TMP_2Mg·2LiCl$ (**4**)[56], TMPZnCl·LiCl (**5**)[57]and $TMP_2Zn·2MgCl_2·2LiCl$ (**6**)[58] (Figure 3).

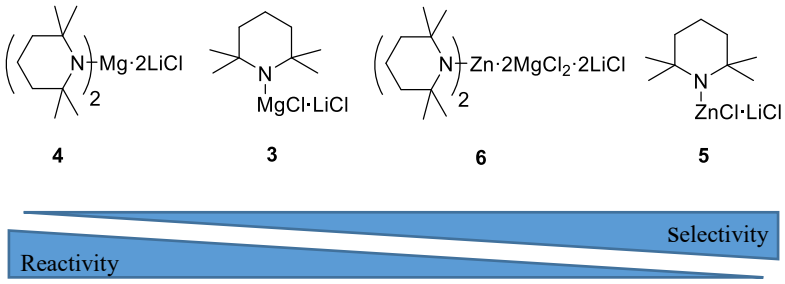


Figure 3: TMP-magnesium and zinc bases **3**-**5**; reactivity vs. selectivity.

Where TMPMgCl·LiCl (**3**) lacks in reactivity, $TMP_2Mg·2LiCl$ (**4**) is strong enough to easily magnesiate substrates bearing electron-donating substituents or weakly electron-accepting substituents. However, for the metalation of substrates with very sensitive groups (e.g. $-NO_2$, -CHO), TMPZnCl·LiCl (**5**) is a suitable reagent. Until today, the chemistry of TMP amide bases has been widely extended by *Knochel et al.* using different metals for finetuning of reactivity. Thus, $TMP_3Al·3LiCl$, (*t*Bu)NCH(*i*Pr)-(*t*Bu)]$_3$Al·3LiCl,[59] $TMP_2Mn·2LiCl$,[60] $TMP_2Fe·4LiCl$,[61] $TMP_4Zr·6LiCl$[62] and $TMP_3La·5LiCl$[63] have found broad application for the metalation of rigid substrates.

Besides D*o*M, the regioselective metalation of heterocycles has become pronounced interest in recent years. Especially, the functionalization of pyridines and quinolines is a major synthetic goal, since these heterocycles show vast biological properties[64] and are of interest for new functional materials.[65] Due to *Chichibabin*-type dimerizations[66], the stoichiometric lithiation of unactivated pyridines is complicated. However, *Kessar et al.* showed that the complexation of pyridine with BF_3 enables a low-temperature lithiation in α-position.[67]

---

[56] (a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681. (b) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503. (c) C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel, *Org. Synth.* **2009**, *86*, 374.

[57] (a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837. (b) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406. (c) M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615.

[58] (a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685. (b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705.

[59] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 1501.

[60] S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem Int. Ed.* **2010**, *49*, 4157.

[61] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.

[62] M. Jeganmohan, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, 49, 8520.

[63] S. H. Wunderlich, P. Knochel, *Chem Eur. J.* **2010**, *16*, 3304.

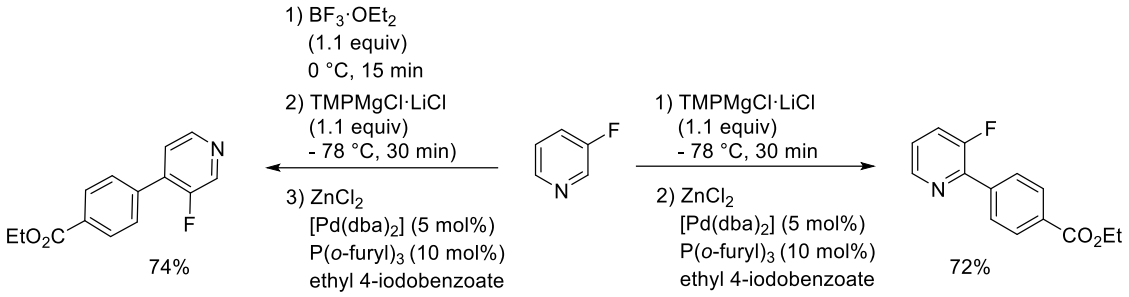
[64] (a) K. C. Nicolaou, R. Scarpelli, B. Bollbuck, B. Werschkun, M. M. A. Pereira, M. Wartmann, K.-H. Altmann, D. Zaharevitz, R. Gussio, P. Giannakakou, *Chem. Biol.* **2000**, *7*, 593. (b) B. Oliva, K. Miller, N. Caggiano, A. J. O`Neill, G. D. Cuny, M. Z. Hoemann, J. R. Hauske, I. Chopra, *Antimicrob. Agents Chemother.* **2003**, *47*, 458. (c) A. Bouillon, A. S. Voisin, A. Robic, J.-C. Lancelot, V. Collot, S. Rault, *J. Org. Chem.* **2003**, *68*, 10178. (d) E. M. Nolan, J. Jaworski, K.-I. Okamoto, Y. Hayashi, M. Sheng, S. J. Lippard, *J. Am. Chem. Soc.* **2005**, *127*, 16812. (e) A. Hayashi, M. Arai, M. Fujita, M. Kobayashi, *Biol. Pharm. Bull.* **2009**, *32*, 1261. (f) J. Quiroga, J. Trilleras, B. Insuasty, R. Abonia M. Nogueras, A. Marchal, J. Cobo, *Tetrahedron Lett.* **2010**, *51*, 1107.

[65] (a) A. Yokoyama, I. Nishiyama, A. Yoshizawa, *Ferroelectrics* **1993**, *148*, 139. (b) Y. G. Skrypnik, T. F. Doroshenko, *Mater. Sci.* **1996**, *32*, 537. (c) H. Tsutsumi, K. Okada, T. Oishi, *Electrochim. Acta* **1996**, *41*, 2657. (d) C. G. Bangcuyo, M. E. Rampey-Vaughn, L. T. Quan, S. M. Angel, M. D. Smith, U. H. F. Bunz, *Macromolecules* **2002**, *35*, 1563. (e) M. Vetrichelvan, S. Valiyaveetti, *Chem. Eur. J.* **2005**, *11*, 5889.

[66] (a) A. J. Clarke, S. McNamara, O. Meth-Cohn, *Tetrahedron Lett.* **1974**, *15*, 2373. (b) P. Gros, Y. Fort, P. Caubère, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3597.

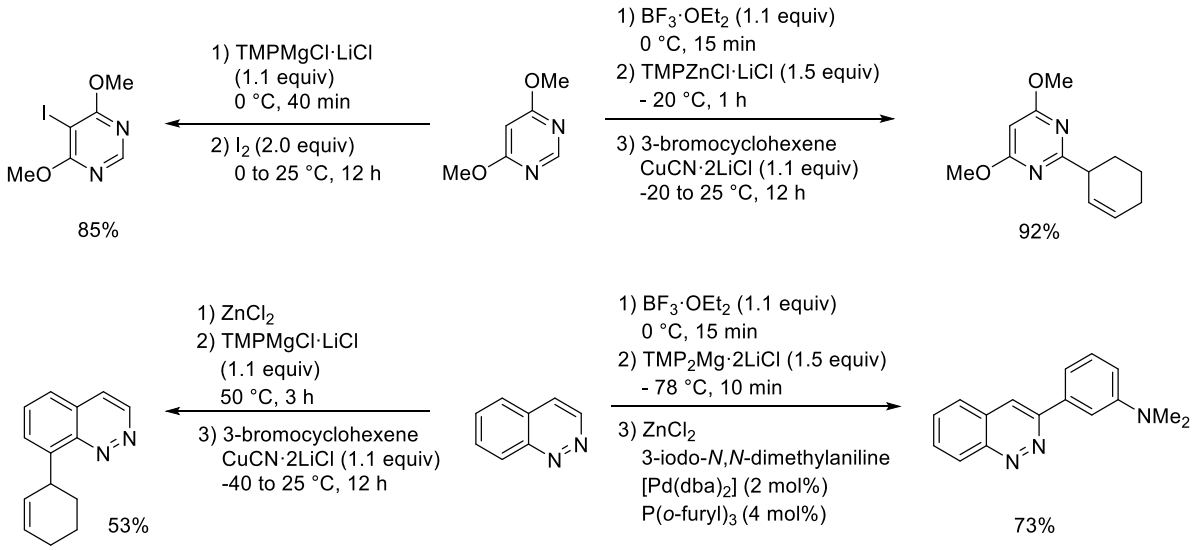
[67] S. V. Kessar, P. Singh, K. N. Singh, M. Dutt, *J. Chem. Soc. Chem. Commun.* **1991**, 570.

Furthermore, *Michl* and co-workers demonstrated the metalation of 3-alkylpyridines with $BF_3 \cdot OEt_2$ and lithium tmp zincates.[68] For a convenient and smooth metalation of pyridines *Knochel* and co-workers demonstrated that a two-step metalation by prior complexation with $BF_3 \cdot OEt_2$ and subsequent addition of TMPMgCl·LiCl (**3**), $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**6**) or (*t*Bu)NCH(*i*Pr)-(*t*Bu)]$_3$Al·3LiCl results in magnesiated, zincated or aluminated pyridines with high yield.[69] They also realized that the presence or absence of $BF_3 \cdot OEt_2$ during metalation leads to a complete switch in regioselectivity for some cases (Scheme 11).



Scheme 11: Switchable, regioselective metalation of 3-fluoropyridine in the presence or absence of $BF_3 \cdot OEt_2$.

The *Knochel* group futher extended the concept of switchable, regioselective *Lewis* acid controlled metalation to more complex heterocycles like pyrimidines or cinnolines (Scheme 12).[70,71]



Scheme 12: Switchable, regioselective metalation of 4,6-dimethoxypyrimidine and cinnoline in the presence or absence of $BF_3 \cdot OEt_2$.

[68] (a) P. Schwab, F. Fleischer, J. Michl, *J. Org. Chem.* **2002**, *67*, 443. (b) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539.
[69] (a) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451. (b) M. Jaric, B. A. Haag, S. M. Manolikakes, P. Knochel, *Org. Lett.* **2011**, 2306.
[70] (a) K. Groll, S. M. Manolikakes, X. M. du Jourdin, M. Jaric, A. Bredihhin, K. Karaghiosoff, T. Carell, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 6776. (b) K. Groll, S. M. Manolikakes, X. Mollat du Jourdin, M. Jaric, A. Bredihhin, K. Karaghiosoff, T. Carell, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 6776.
[71] T. Klatt, D. S. Roman, T. León, P. Knochel, *Org. Lett.* **2014**, *16*, 1232.

2.5 Transition Metal Catalyzed Cross-Couplings with Iron and Cobalt

Transition-metal catalyzed cross-coupling reactions are the most common methods in metalorganic chemistry to form carbon-carbon bonds. Industries from all over the world use this powerful method for the synthesis of pharmaceutical, agrochemical and technical products. The utilization of cross-couplings has increased exponentially within the last ten years and there exists a vast number of variations for each type of cross-coupling. The most famous cross-couplings in organic synthesis are the *Suzuki*-, *Negishi*-, *Kumada*-, *Heck*-, *Stille*- and *Sonogashira*-coupling. However, these types of cross-couplings require expensive and toxic palladium- and nickel-salts.[72] In addition, catalytic systems with both palladium and nickel usually require the addition of structurally complex and costly ligands. Due to these ecological and economical disadvantages, organic research is focused on the applicability of low-cost and low-toxic transition metals for cross-coupling.

Recently, iron salts have received increased interest, since they represent ideal alternative precatalysts. There is an enormous availability of iron, being the most abundant metal in the universe and the second-most abundant metal in the earth's crust. Moreover, iron is an essential metal in the human body (4g/ person). Its low toxicity makes iron-catalysts suitable for health-care related chemistry. The environmental properties and the moderate price reveal iron as the promising catalyst of the future. In the field of iron-catalyzed cross-coupling, alkyl-aryl,[73] alkyl-alkenyl,[74] aryl-alkenyl,[73b,73c,73k,75] as well as alkenyl-

[72] (a) *Handbook of the Toxikology of Metals*; L. Friberg, G. F. Nordberg, V. B. Vouk, Eds.; Elsevier, Amsterdam, **1986**. (b) M. N. Hughes, Compr. Coord. Chem. **1987**, *67*, 643. (c) *Nickel and the Skin: Absorption, Immunology, Epidermology, and Metallurgy*; J. J. Hostynek, H. I. Maibach, Eds. CRC Press, Boca Raton, **2002**.

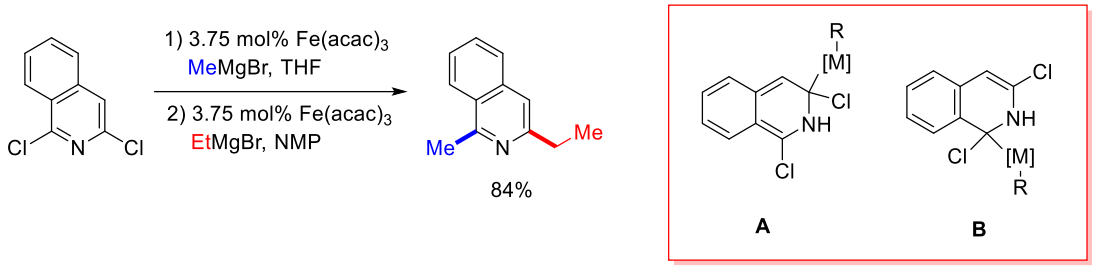
[73] (a) A. Fürstner, A. Leitner, *Angew. Chem. Int. Ed.* **2002**, *41*, 609. (b) A. Fürstner, A. Leitner, M. Méndez, H. Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (c) R. Martin, A. Fürstner, *Angew. Chem. Int. Ed.* **2004**, *43*, 3955. (d) T. Nagano, T. Hayashi, *Org. Lett.* **2004**, *6*, 1297. (e) M. Nakamura, S. Ito, K. Matsuo, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686. (f) R. B. Bedford, D. W. Bruce, R. M. Frost, J. W. Goodby, M. Hird, *Chem. Commun.* **2004**, *40*, 2822. (g) M. Nakamura, S. Ito, K. Matsuo, E. Nakamura, *Synlett* **2005**, *11*, 1794. (h) R. B. Bedford, M. Betham, D. W. Bruce, A. A. Danopoulos, R. M. Frost, M. Hird, *J. Org. Chem.* **2006**, *71*, 1104. (i) G. Cahiez, V. Habiak, C. Duplais, A. Moyeux, *Angew. Chem. Int. Ed.* **2007**, *46*, 4364. (j) A. Fürstner, R. Martin, H. Krause, G. Seidel, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 8773. (k) W. M. Czaplik, M. Mayer, A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.* **2009**, *48*, 607. (l) R. B. Bedford, M. Huwe, M. C. Wilkinson, *Chem. Commun.* **2009**, *45*, 600. (m) G. Cahiez, L. Foulgoc, A. Moyeux, *Angew. Chem. Int. Ed.* **2009**, *48*, 2969. (n) D. Noda, Y. Sunada, T. Hatakeyama, M. Nakamura, H. J. Nagashima, *J. Am. Chem. Soc.* **2009**, *131*, 6078. (o) S. Ito, Y.-i. Fujiwara, E. Nakamura, M. Nakamura, *Org. Lett.* **2009**, *11*, 4306. (p)T. M. Gøgsig, A. T. Lindhardt, T. Skrydstrup, *Org. Lett.* **2009**, *11*, 4886. (q) S. Kawamura, K. Ishizuka, H. Takaya, M. Nakamura, *Chem. Commun.* **2010**, *46*, 6054. (r) T. Hatakeyama, T. Hashimoto, Y. Kondo, Y. Fujiwara, H. Seike, H. Takaya, Y. Tamada, T. Ono, M. Nakamura, *J. Am. Chem. Soc.* **2010**, *132*, 10674. (s) A. K. Steib, T. Thaler, K. Komeyama, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 3303. (t) Y. Yamaguchi, H. Ando, M. Nagaya, H. Hinago, T. Ito, M. Asami, *Chem. Lett.* **2011**, *40*, 983. (u) M. Jin, M. Nakamura, *Chem. Lett.* **2011**, *40*, 1012. (v) T. Hatakeyama, Y.-i. Fujiwara, Y. Okada, T. Itoh, T. Hashimoto, S. Kawamura, K. Ogata, H. Takaya, M. Nakamura, *Chem. Lett.* **2011**, *40*, 1030. (w) S. Kawamura, T. Kawabata, K. Ishizuka, M. Nakamura, *Chem. Commun.* **2012**, *48*, 9376. (x) A. L. Silberstein, S. D. Ramgren, N. K. Garg, *Org. Lett.* **2012**, *14*, 3796. (y) T. Agrawal, S. P. Cook, *Org. Lett.* **2013**, *15*, 96.

[74] (a) M. Tamura, J. K. Kochi, *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) J.-L. Fabre, M. Julia, J.-N. Verpeaux, *Tetrahedron. Lett.* **1982**, *23*, 2469. (c) B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943. (d) G. Cahiez, C. Duplais, A. Moyeux, *Org. Lett.* **2007**, *9*, 3253. (e) A. Guérinot, S. Reymond, J. Cossy, *Angew. Chem. Int. Ed.* **2007**, *46*, 6521. (f) G. Cahiez, V. Habiak, O. Gager, *Org. Lett.* **2008**, *10*, 2389. (g) T. Hatakeyama, N. Nakagawa, M. Nakamura, *Org. Lett.* **2009**, *11*, 4496. (h) B.-J. Li, L. Xu, Z.-H. Wu, B.-T. Guan, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *J. Am. Chem. Soc.* **2009**, *131*, 14656. (i) H. Nishikado, H. Nakatsuji, K. Ueno, R. Nagase, Y. Tanabe, *Synlett* **2010**, *14*, 2087. (j) T. Hashimoto, T. Hatakeyama, M. Nakamura *J. Org. Chem.* **2012**, *77*, 1168. (k) G. Cahiez, O. Gager, J. Buendia, C. Patinote, *Chem. Eur. J.***2012**, *18*, 5860.

[75] (a) Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E. *Tetrahedron Lett.* **1983**, *24*, 5449. (b) K. Itami, S. Higashi, M. Mineno, J.-i. Yoshida, *Org. Lett.* **2005**, *7*, 1219.

alkynyl[76] coupling reactions are well investigated and their utilization to different substrates is still improved.

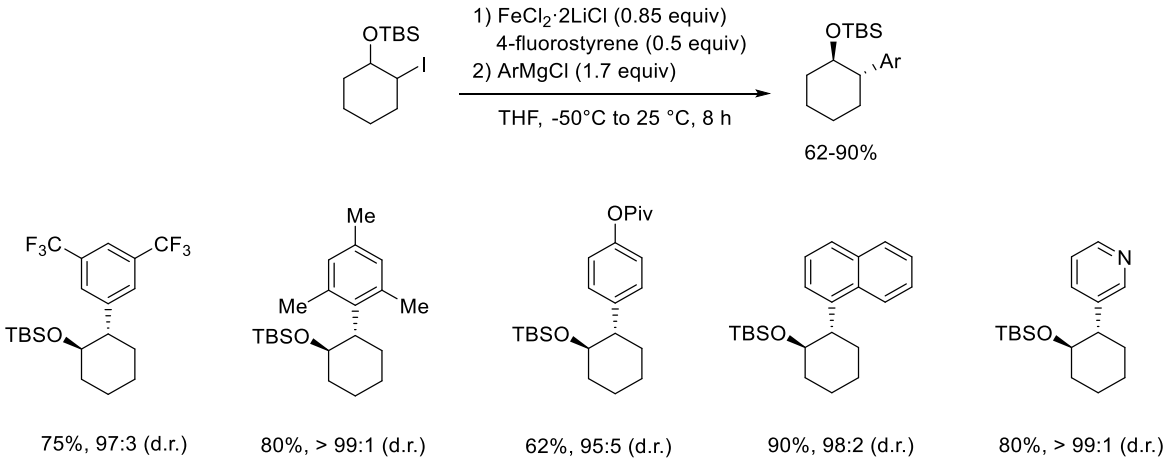
In 2013 *Malhotra* impressively showed that chemoselective iron-catalyzed sp^2-sp^3 cross-couplings in a one-pot system are feasible.[77] By the initial treatment of 1,3-dichloroisoquinoline with MeMgBr in the presence of $Fe(acac)_3$ followed by additional iron-catalyst and EtMgBr selectively furnished a differentially substituted 1,3-isoquinoline in high yield. (Scheme 13).



Scheme 13: One-pot selective iron-catalyzed dialkyl cross-coupling and mechanistic aspects.

This result indicates that the chemoselective incorporation of the alkyl groups strongly depends upon the different ability of the C-X bonds in dihaloaromatic compounds to undergo an insertion. While the aromaticity in intermediate B is retained, the aromaticity in intermediate A is lost when the first metal insertion takes place in position 3 of 1,3-dichloroquinoline (Scheme 13).[78]

Stereoselectivity also often plays an important role, when it comes to the production of bioactive substances with certain stereoinformation. In 2011, *Knochel* and co-workers developed a highly diastereoselective iron-mediated sp^2-sp^3 cross coupling between aryl *Grignard* reagents and cyclic iodohydrine derivatives (Scheme 14).[79]



Scheme 14: Iron-mediated cross-coupling of TBS-protected iodohydrine with aryl magnesium reagents.

[76] (a) T. Hatakeyama, Y. Yoshimoto, T. Gabriel, M. Nakamura, *Org. Lett.* **2008**, *10*, 5341. (b) W. M. Czaplik, M. Mayer, A. Jacobi von Wangelin, *ChemCatChem* **2011**, *3*, 135. (c) T. Hatakeyama, Y. Okada, Y. Yoshimoto, M. Nakamura, *Angew. Chem. Int. Ed.* **2011**, *50*, 10973.

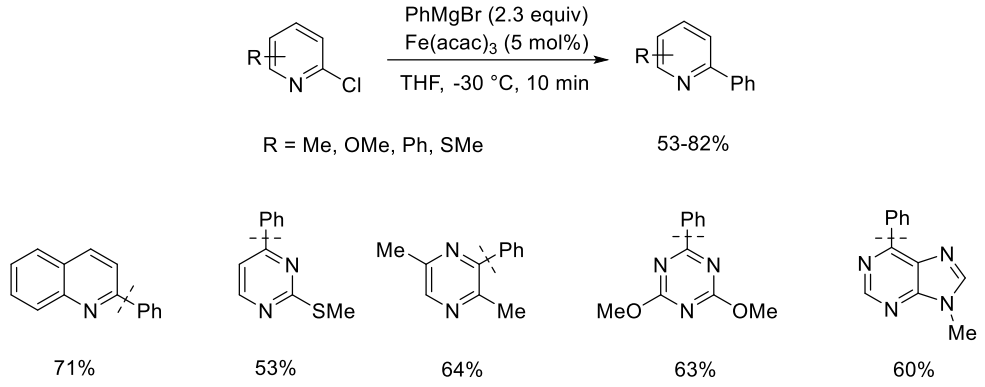
[77] S. Malhotra, P. S. Seng, S. G. König, A. J. Deese, K. A. Ford, *Org. Lett.* **2013**, *15*, 3698.

[78] A. K. Steib, O. M. Kuzmina, S. Fernandez, S. Malhotra, P. Knochel, *Chem. Eur. J.* **2015**, *21*, 1961.

[79] A. K. Steib, T. Thaler, K. Komeyama, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 3303.

In all cases the aryl magnesium reagents were coupled efficiently with high diastereoselectivity, giving the thermodynamically favored *trans*-1,2-disubstituted cyclohexanols.

In organic synthesis aryl-aryl cross-couplings belong to the utmost important ones. However, iron-catalyzed aryl-aryl couplings remained as a challenging task for a long time due to insufficient catalytic activity of the iron-catalyst and due to undesired homo-coupling side-reaction of the organometallic species.[80] In 2002, *Fürstner* reported unsymmetrical biaryl-formation mediated by an iron catalyst (Scheme 15).[73b]



Scheme 15: Iron-catalyzed aryl-aryl bond-formation reported by *Fürstner et al.*

Heteroaromatic chlorides were treated with non-functionalized (hetero)aryl *Grignard* reagents (2.3 equiv) at low temperatures (-30 °C) in the presence of 5 mol% of $Fe(acac)_3$ in THF. Within only 10 min reaction time, the reaction reached full conversion, showing the activity of the iron-catalyst. However, the large formation of homo-coupling byproduct made the use of excess *Grignard* reagent indespensible. Further investigations by *Figadère*[81] and *Plé*[82] unveiled *Fürstner's* conditions for iron catalyzed cross-couplings to still be the best.

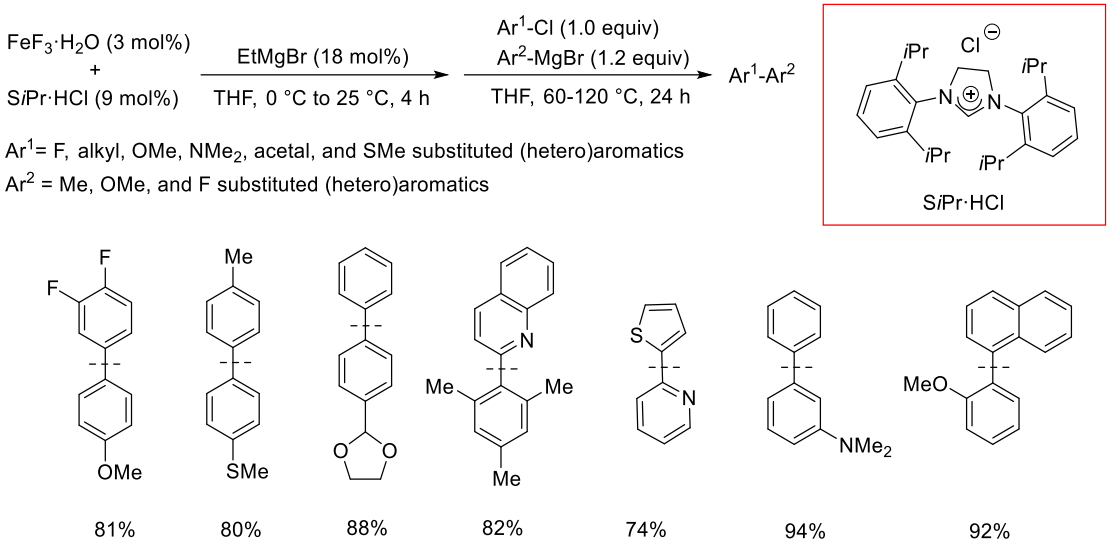
In 2007, *Nakamura et al.* made a huge improvement by suppressing the undesired homo-coupling reaction significantly. They introduced a novel catalytic system based on $FeF_3{\cdot}3H_2O$ and *N*-heterocyclic carbene ligands.[83] The active iron-species is produceed by treatment of $FeF_3{\cdot}3H_2O$ and the carbene ligand precursor S*i*Pr·HCl (1,3-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride) with EtMgBr. Subsequently, the electrophile and the desired *Grignard* reagent have to be added and the reaction mixture has to be stirred at 60-120 °C for 24 h to produce the biaryl coupling product (Scheme 16).

[80] For Fe-catalyzed homo-coupling reactions, see: (a) M. S. Kharasch, E. K. Fields, *J. Am. Chem. Soc.* **1941**, *63*, 2316. (b) H. Felkin, B. Meunier, *J. Organomet. Chem.* **1978**, *146*, 169. (c) T. Nagano, T. Hayashi, *Org. Lett.* **2005**, *7*, 491. (d) G. Cahiez, C. Chaboche, F. Mahuteau-Betzer, M. Ahr, *Org. Lett.* **2005**, *7*, 1943. (e) X. Xu, D. Cheng, W. Pei, *J. Org. Chem.* **2006**, *71*, 6637. (f) W. Liu, A. Lei, *Tetrahedron Lett.* **2007**, *49*, 610. (g) G. Cahiez, A. Moyeux, J. Buendia, C. Duplais, *J. Am. Chem. Soc.* **2007**, *129*, 13788. (h) G. Kiefer, L. Jeanbourquin, K. Severin, *Angew. Chem. Int. Ed.* **2013**, *52*, 6302. (i) D. Toummini, F. Ouzzani, M. Taillefer, *Org. Lett.* **2013**, *15*, 4690.

[81] J. Quintin, X. Franck, R. Hocquemiller, B. Fidagère, *Tetrahedron Lett.* **2002**, *43*, 3547.

[82] L. Boully, M. Darabantu, A. Turck, N. Plé, *J. Heterocycl. Chem.* **2005**, *42*, 1423.

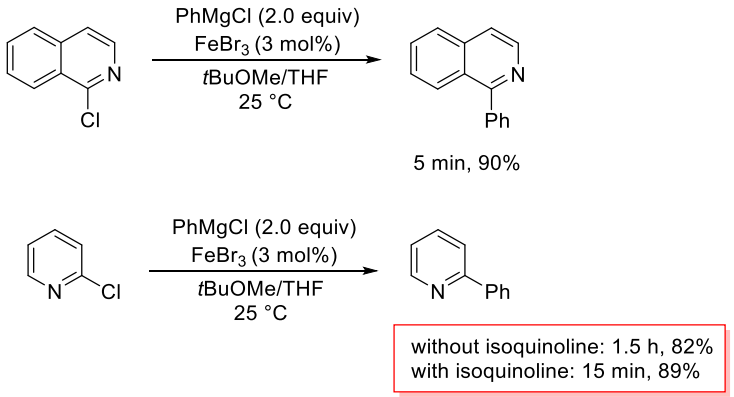
[83] (a) T. Hatakeyama, M. Nakamura, *J. Am. Chem. Soc.* **2007**, *129*, 9844. (b) T. Hatakeyama, S. Hashimoto, K. Ishizuka, M. Nakamura, *J. Am. Chem. Soc*. **2009**, *131*, 11949.



Scheme 16: Unsymmetrical biaryl cross-coupling with iron-carbene catalyst.

However, carbene ligands are quite expensive and iron fluoride salts are very toxic. Furthermore, the reaction requires high temperatures up to 120 °C and long reaction times to complete the coupling reaction. Above all, the scope of this method is quite limited. So, there was still a need for more convenient reaction conditions with easy accessible ligands for iron-catalysis.

In 2012, *Knochel et al.* found that *t*BuOMe as a cosolvent hampers homocoupling side-reactions in iron-catalyzed cross-couplings between *N*-heterocyclic chlorides/bromides with various electron-rich or poor arylmagnesium reagents.[84] The authors used $FeBr_3$ (3 mol%) as catalyst at ambient temperature and achieved high yields with this smooth method. But in their scope, they still encountered slow reaction rates in some cases. During further investigations,[85] they noted that the reaction of 1-chloroisoquinoline and PhMgCl in the presence of 3% $FeBr_3$ in the solvent mixture *t*BuOMe/THF takes only 5 min and provides the cross-coupled product, 1-phenylisoquinoline in 90% yield, whereas the cross-coupling of 2-chloropyridine under the same conditions requires 1.5 h for completion and gives 2-phenylpyridine in 82% yield (Scheme 17).

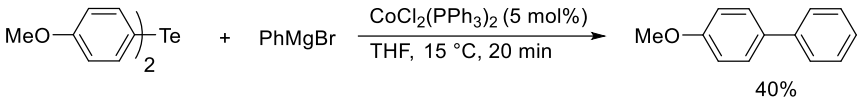


Scheme 17: Ligand accelerated iron-catalyzed cross-couplings of 1-chloroisoquinoline and 2-chloropyridine with PhMgCl.

[84] O. M. Kuzmina, A. K. Steib, D. Flubacher, P. Knochel, *Org. Lett.* **2012**, *14*, 4818.
[85] O. M. Kuzmina, A. K. Steib, S. Fernandez, W. Boudot, J. T. Markiewicz, P. Knochel, *Chem. Eur. J.* **2015**, *21*, 8242.

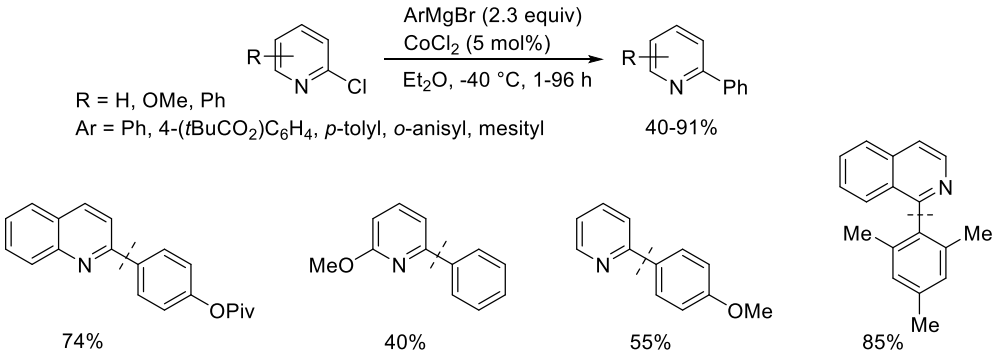
The reactivity difference of these substrates led to the assumption that the catalytically active iron species, generated in situ, may contain an isoquinoline fragment as a ligand. This hypothesis was checked by the reaction of 2-chloropyridine and PhMgCl in the presence of 7% isoquinoline. Interestingly, the arylated pyridine formed much faster (within 15 min) with an increased isolated yield of 89%. Above all these improvements, it has to be mentioned that iron salts are restricted to a very small number of certain ligands and the reaction scope is still limited.[86] An alternative display cobalt-salts, which have a similar reactivity to iron, but show a higher catalytic activity in many cases as well as a lower tendency to form homocoupling byproducts.

The first cobalt-catalyzed synthesis of unsymmetrical byaryls was described by *Uemura via* reaction of diaryltellurides with aromatic organomagnesium reagents (Scheme 18).[87]



Scheme 18: Cobalt-catalyzed cross-coupling reaction between diarylteluride and aromatic *Grignard* reagents.

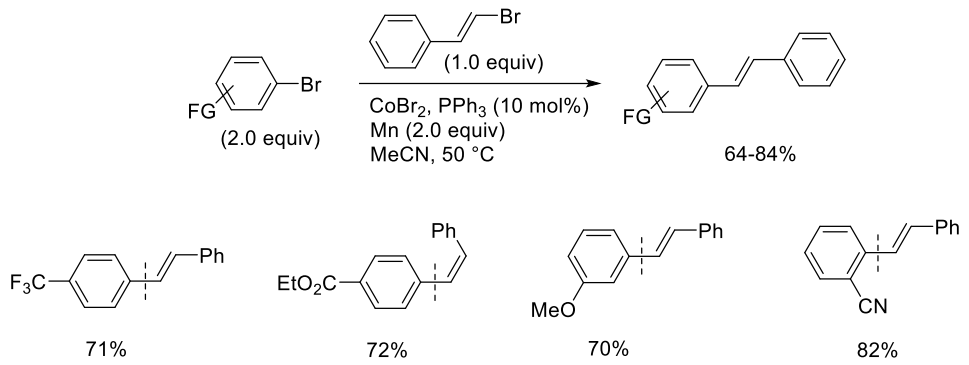
Knochel and *Cahiez* found that heteroaromatic halides can be coupled with *Grignard* reagents in the presence of catalytic amounts of $CoCl_2$. Under the described conditions, it is even possible to react sterically hindered *Grignard* reagents like mesitylmagnesium bromide (Scheme 19).[88]



Scheme 19: $CoCl_2$-catalyzed cross-coupling reactions between heteroaryl chlorides and aromatic *Grignard* reagents.

Nakamura showed that his method using *N*-heterocyclic carbene ligands for aryl-aryl cross-coupling can also be applied using cobalt fluoride salt.[83b] This method provides even better results when aromatic iodides or bromides are used, whereas iron fluoride provides better yields in case of aryl chlorides.[89]
A further interesting cobalt-catalyzed cross-coupling method was invented by *Gosmini*, who showed that the use of manganese metal as reducing agent allows an efficient cross-coupling between chloro- or bromo-styrenes and various aryl bromides (Scheme 20).[90]

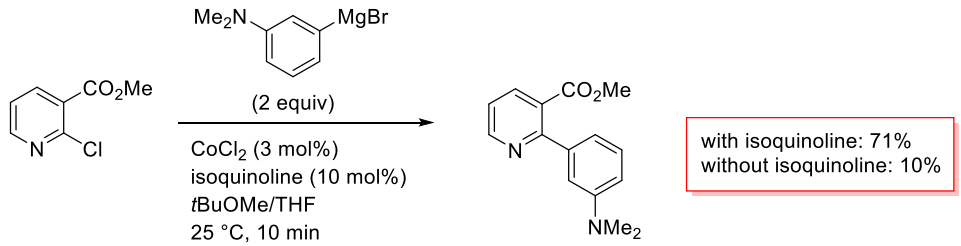
[86] (a) I. Bauer, H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170. (b) T. L. Mako, J. A. Byers, *Inorg. Chem. Front.* **2016**, *3*, 766.
[87] (a) S. Uemura, S.-I. Fukuzawa, *Tetrahedron Lett.* **1982**, *23*, 1181. (b) S. Uemura, S.-I. Fukuzawa, S. R. Path, *J. Organomet. Chem.* **1983**, *243*, 9.
[88] T. Korn, G. Cahiez, P. Knochel, *Synlett* **2003**, 1892.
[89] G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435.
[90] A. Moncomble, P. Le Floch, A. Lledos, C. Gosmini, *J. Org. Chem.* **2012**, *77*, 5056.



Scheme 20: Stereoselective cobalt-catalyzed alkenylation.

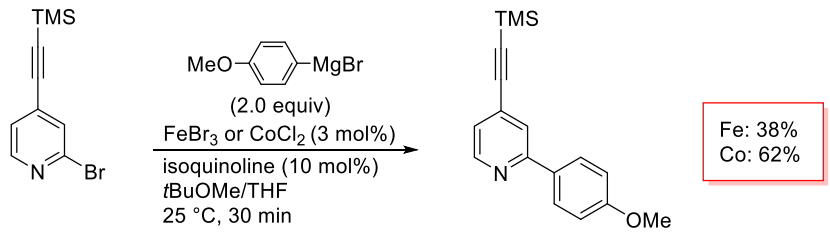
This protocol allows the smooth formation of functionalized stilbenes with the total retention of the double bond using triphenylphosphine as ligand.

Similar to iron-catalysis our group showed that using isoquinoline as ligand can accelerate the reaction-rate of cobalt-catalyzed cross-couplings between *N*-heteroaryl halides and aryl magnesium reagents.[85, 91] Thus, the cross-coupling of 3-*N*,*N*-dimethylaminophenylmagnesium bromide with methyl 2-chloro-nicotinate in the presence of $CoCl_2$ (3 mol%) and isoquinoline (10 mol%) furnishes the desired product in 71% yield within just 10 min at 25 °C, whereas the absence of isoquinoline leads to only 10% yield within the same reaction time (Scheme 21).



Scheme 21: Isoquinoline accelerated cobalt-catalyzed cross-coupling.

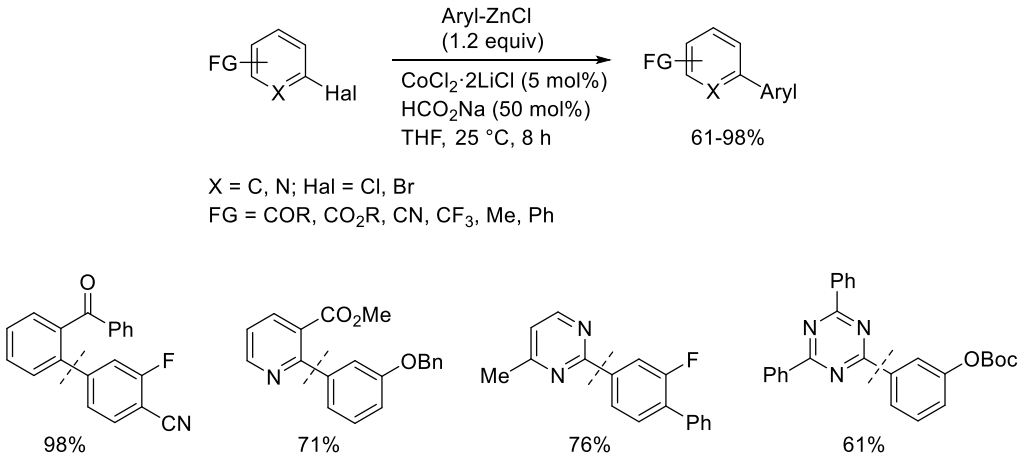
Above the superior scope and reactivity, cobalt-catalysis can also enhance the chemoselectivity. Alkynes prone to undergo carbometallation with Fe-catalysis, e. g. the coupling of 2-bromo-4-((trimethylsilyl)-ethynyl)pyridine with (4-methoxyphenyl)magnesium bromide gives only 38% yield of the desired bisaryl species. However, using $CoCl_2$ instead of $FeBr_3$ improves the yield drastically, furnishing 62% of isolated product (Scheme 22).[91]



Scheme 22: Chemoselective cross-coupling of acetylene containing bromo-pyridine.

[91] O. M. Kuzmina, A. K. Steib, J. T. Markiewicz, D. Flubacher, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 4945.

As shown on previous pages, cobalt-catalyzed cross-coupling with magnesium reagents are well investigated and optimized. However, when using (hetero)aryl substrates with sensitive functionalities like esters, mild reaction conditions with less reactive organozinc are inevitable. For that reason, *Knochel* and coworkers developed a new methodology for a mild cobalt-catalyzed *Negishi* cross-coupling of (hetero)arylzinc reagents with (hetero)aryl halides.[92] The authors used $CoCl_2 \cdot 2LiCl$ as catalyst system, which is conveniently soluble in THF. Sodium formate was found to be a suitable and cheap ligand, considerably suppressing side reactions and thus improving the yield. This protocol easily allows to react the corresponding zinc reagents with (hetero)aryls bearing sensitive groups like ketones, esters or nitriles under convenient conditions (Scheme 23).



Scheme 23: Mild cobalt-catalyzed *Negishi* cross-coupling of (hetero)arylzinc reagents with aryl halides.

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

3. NAPHTHYRIDINES

Naphthyridines[93] are a class of bicyclic heterocycles consisting of two fused pyridine rings in which the two nitrogen atoms do not occupy a bridgehead position. Through alternating of the two nitrogen atoms, six constitutional isomers can be drawn (Figure 4). All naphthyridine isomers are crystalline. The planarity of naphthyridines is based on their aromatic delocalization. Only 1,8-naphthyridine is non-planar due to the repulsion of nitrogen lonepair electrons.[94]

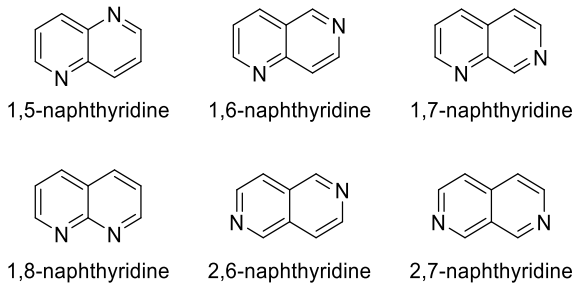


Figure 4: The six isomers of the naphthyridine class.

In 1893, *Reissert* synthesized the first naphthyridine derivative (octahydro-1,8-naphthyridine), whereupon he suggested the name naphthyridine for this kind of heterocycle. However, it lasted more than three decades until the first unsubstituted and unsaturated naphthyridines were prepared in 1927 by *Bobranski*[95] (1,5-naphthyridine) and *Koller*[96] (1,8-naphthyridine). The next isomers were synthesized by *Ikekawa*[97] (1,6-, 1,7-, and 2,6- naphthyridine) in 1958 and independently by *Albert*[98] (1,6- and 1,7-naphthyridine) in 1960. The last isomer (2,6-naphthyridine) was prepared by *Giacomello*[99] and *Tan* and *Taurnis*[100] in 1965. Ever since, the research in the chemistry of naphthyridines has sharply increased and 6080 publications and 2006 patents have appeared in the literature.[101] The strong interest in naphthyridines is due to their exceptionally broad spectrum of biological activities[102] and their physicochemical properties[103] (Figure 5).

---

[93] (a) V. P. Litinov, S. V. Roman, V. D. Dyachenko, *Russ. Chem. Rev.* **2000**, *69*, 201. (b) W. W. Paudler, T. J. Kress, *Adv. Heterocycl. Chem.* **2001**, *80*, 123. (c) P.-W. Puan, M. C. Kozlowski, *Science of Synthesis* **2005**, *15*, 947. (d) V. P. Litinov, *Adv. Heterocycl. Chem.* **2006**, *91*, 189.

[94] (a) W. Czuba, *Wiad. Chem.* **1981**, *35*, 441; *Chem Abstr. 1982*, *96*, 52192. (b) A. Clearfield, M. J. Sims, P. Singh, *Acta Crytallogr.*, *Sect. B* **1972**, 350.

[95] B. Bobranski, E. Sucharda, *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1081.

[96] G. Koller, *Ber. Dtsch Chem Gesl.* **1927**, *60*, 1918.

[97] N. Ikekawa, *Chem. Pharm. Bull.* **1958**, *6*, 263.

[98] A. Albert, *J. Chem. Soc.* **1960**, 1790.

[99] G. Giacomello, F. Gualtieri, F. M. Riccieri, M. L. Stein, *Tetraedron Lett.* **1965**, 1117.

[100] R. Tan, A. Taurins, *Tetrahedron Lett.* **1965**, 2737.

[101] SciFinder search results 26.06.17.

[102] (a) X. Z. Zhao, et al., *ACS Chemical Biology* **2016**, *11*, 1074. (b) B. A. Johns, J. G. Weatherhead, S. H. Allen, J. B. Thompson, E. P. Garvey, S. A. Foster, J. L. Jeffrey, W. H. Miller, *Bioorg. Med. Chem.* **2009**, *19*, 1807. (c) K. Schiemann, et al., *Novel naphthryidines and isoquinolines and their use as CDK8/19 inhibitors.* WO2016009076, Jan 21, **2016**. (d) A. Madaan, R. Verma, V. Kumar, A. T. Singh, S. K. Jain, M. Jaggi, *Arch. Pharm. Chem. Life Sci.* **2015**, *348*, 837.

[103] (a) Y.-Y. Wu, Y. Chen, G.-Z. Gou, W.-H. Mu, X.-J. Lv, M.-L. Du, W. F. Fu, *Org. Lett.* **2012**, *14*, 5226. (b) J. S. Vincent, *Chem. Phys. Lett.* **1971**, *8*, 37. (c) J. Zhang, F. Chen, Y.-M. He, Q.-H. Fan, *Angew. Chem. Int. Ed.* **2015**, *54*, 4622. (d) P. Pyykkö, P. Zaleski-Ejgierd, *Phys. Chem. Chem. Phys.*, **2008**, *10*, 114.

Nowadays naphthyridines already find application in diagnostics and therapy of human diseases including AIDS,[102a] antibacterial and antiparasitic agents,[104] OLEDs and semiconductor materials[105] and as ligands in analytical chemistry.[106]

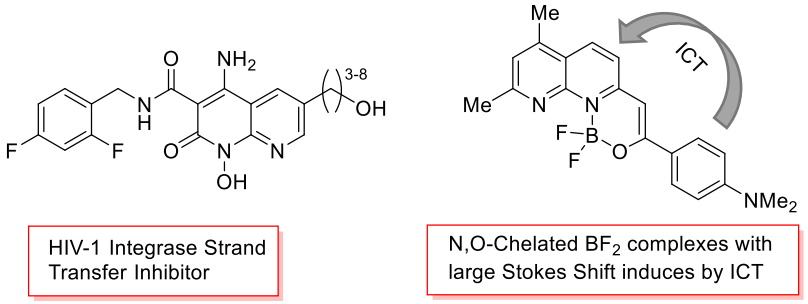
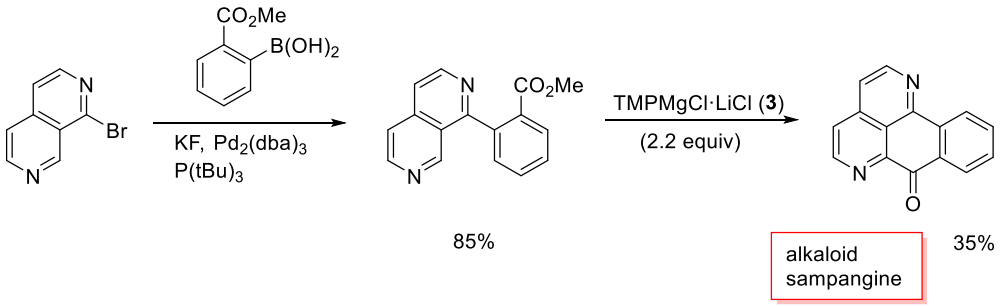


Figure 5: Anti-HIV agent[102a] and fluorescent push-pull BF_2 complexes[103a] based on the 1,8 naphthyridine scaffold.

Noteworthy, many publications on naphthyridines describe complicated functionalization procedures and there is only little known about the straightforward functionalization of naphthyridines using organometallic chemistry, especially metalation. In the following, two important discoveries will be described: In 2015, *Bracher* and co-workers used *Knochel's* TMPMgCl·LiCl (**3**) for their final cyclization step to gain access to the alkaloid sampangine and other analogues. Ring-closure was achieved through a directed remote ring metalation, followed by intramolecular trapping of the ester group (Scheme 24).[107]



Scheme 24: *Suzuki* cross-coupling of 1-bromo-2,7-naphthyridine, followed by TMPMgCl·LiCl (**3**) mediated ring closure.

In 2010, *Voight et al.* from **G**laxo**S**mith**K**line described an efficient enantioselective total synthesis of the potent antibiotic **GSK**966587. Besides two innovative Heck reactions, also a directed *ortho*-metalation using a highly selective zincate base was involved (Scheme 25).[108]

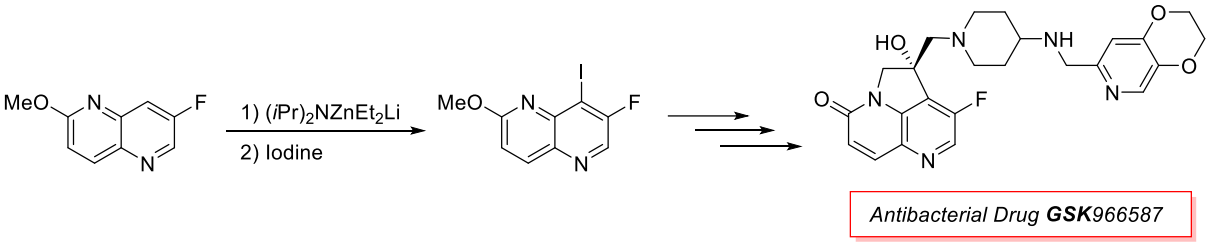
[104] (a) A. Tejería , Y. Pérez-Pertejo, R. M. Reguera, R. Balaña-Fouce, C. Alonso, M. Fuertes, M. González , G. Rubiales, F. Palacios, *Eur. J. Med. Chem.* **2016**, *124*, 740. (b) J. M. Quintela, C. Peinador, L. González, R. Iglesias, A. Paramá, F. Álvarez, M. L. Sanmartín, R. Riguera, *Eur. J. Med. Chem.* **2003**, *38*, 265. (c) J. P. Sanchez, J. M. Domagala, S. E. Hagen, C. L. Heifetz, M. P. Hutt, J. B. Nichols, A. K. Trehan, *J. Med. Chem.* 1988, *31*, 983. (d) 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.

[105] (a) C. H. Chen, J. Shi, *Coord. Chem. Rev.* **1998**, *171*, 161. (b) S.-W. Liu, C.-C. Lee, C.-F. Lin, J.-C. Huang, C.-T. Chen , J.-H. Lee, *J. Mater. Chem.* **2010**, *20*, 7800. (c) K.-Y. Wang, C. Chen., J.-F. Liu, Q. Wang, J. Chang, H.-J. Zhu, C. Li, *Org. Biomol. Chem.* **2012**, *10*, 6693.

[106] X. Li, J. Yang, M. C. Kozlowski, *Org. Lett.* **2011**, *3*, 1137.

[107] A. Plodek, M. König, F. Bracher, *Eur. J. Org. Chem.* **2015**, 1302.

[108] E. A. Voight, H. Yin, S. V. Downing, S. A. Calad, H. Matsuhashi, I. Giodano, A. J. Hennessy, R. M. Goodman, J. L. Wood, *Org. Lett.* **2010,** *12*, 3422



Scheme 25: Directed *ortho*-metalation and iodination as important step in the synthesis of antibacterial drug **GSK**966587.

These two examples show how important organometallic chemistry is for the functionalization of complex heterocycles like naphthyridines. However, very less is known about the direct metalation of naphthyridines. Thus, a detailed research in this area is desirable.

4. 1,8-NAPHTHALIMIDES

Like Naphthyridines, 1,8-Naphthalimides are heterocyclic compounds. Their systematic name is derived from the benzoisoquinoline backbone they have. Hundreds of published articles describe their use in various biological and photophysical settings. For instance, the development of new drugs includes Hepatitis C and Influenza A inhibitors. 1,8-Naphthalimides are also well acknowledged for their high stability in combination with high fluorescence quantum yields and solvatochromic effects (Figure 6).[109]

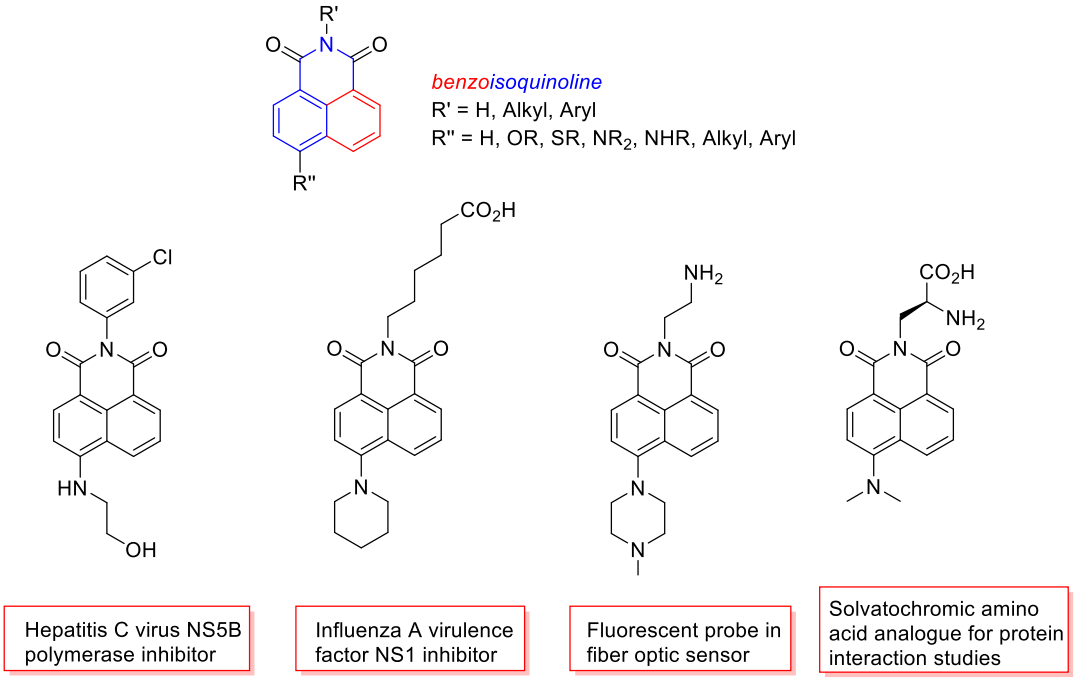


Figure 6: Examples of 4-amino-substituted 1,8-naphthalimides and their wide areas of application.

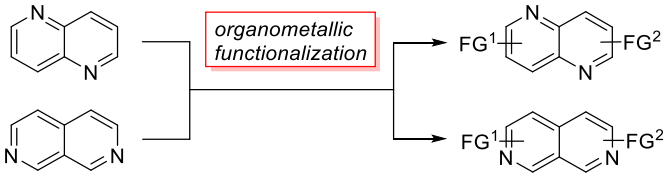
Especially 1,8-naphtalimides bearing electron-rich substituents in the *peri*-position[110] display very strong fluorescence. Among countless inventions, derivatives with acylamino or alkoxy substituents found application as optical brighteners[111] in textile industries, whereas 1,8-naphthalimides with a di- or tri-phenylamine substituent in the 4-position are investigated as OLED hole transporting materials[112] or as sensitizers in DSCs.[113] Furthermore, by the introduction of various functional groups, 1,8-naphtalimides have been extensively utilized as chemosensors for the detection of toxic metal ions.[114]

---

[109] T. Kindahl, E. and E. Chorell, *Eur. J. Org. Chem.* **2014**, 6175.
[110] (a) H. Ulla, B. Garudachari, M. N. Satyanarayan, G. Umesh, A. M. Isloor, *Opt. Mater.* **2014**, *36*, 704. (b) H. Cao, V. Chang, R. Hernandez, M. D. Heagy, *J. Org. Chem.* **2005**, *70*, 4929. (c) S. Dhar, S. S. Roy, D. K. Rana, S. Bhattacharya, S. Bhattacharya, S. C. Bhattacharya, *J. Phys. Chem. A* **2011**, *115*, 2216. (d) J.-X. Yang, X.-L. Wang, X.-M. Wang, L.-H. Xu, *Dyes Pigment.* **2005**, *66*, 83. (e) X. Liu, Q. Qiao, W. Tian, W. Liu, J. Chen, M. J. Lang, Z. Xu, *J. Am. Chem. Soc.* **2016**, *138*, 6960.
[111] A. Dorlars, C.-W. Schellhammer, J. Schröder, *Angew. Chem.* **1975**, *87*, 693.
[112] (a) L.-B. Li, S.-J. Ji, Y. Liu, *Chin. J. Chem.* **2008**, *26*, 595. (b) J. Liu, Z. Xie, Y. Cheng, Y. Geng, L. Wang, X. Jing, F. Wang, *Adv. Mater.* **2007**, *19*, 531. (c) J. Liu, G. Tu, Q. Zhou, Y. Cheng, Y. Geng, L. Wang, D. Ma, X. Jing, F. Wang, *J. Mater. Chem.*, **2006**, *16*, 1431.
[113] X. Huang, Y. Fang, X. Li, Y. Xie, W. Zhu, *Dyes Pigment.* **2011**, *90*, 297.
[114] (a) Y. Yu, X. Cheng, H. Zhang, S. Hu, X. Li, A. Zhang, *J. Polym. Sci. Pol. Chem.* **2013**, *51*, 4592. (b) M. Shahid, P. Srivastava, A. Misra, *New. J. Chem.* **2011**, *25*, 690. (c) P. Alaei, S. Pouhani, K. Ghranjig, J. Ghasemi, *Spectrochim. Acta A* **2012**, *90*, 85. (d) M. Kumar, N. Kumar, V. Bhalla, *Chem. Comm.* **2013**, *49*, 877.

5. OBJECTIVES

As previously described, there is only little reported about the organometallic functionalization of naphythyridines. Due to the potential applications of such *N*-heterocycles in medical chemistry and material science, it is utmost important to find convenient methods for the modification of such molecules. Therefore, we planned to functionalize the 1,5- and 2,7-naphthyridine scaffold by metalation and cross-coupling reactions using methods developed in our group. In spite of the probability that modifications will occur simultaneously on both rings, we envisioned to regioselectively functionalize both naphthyridines gaining access to unsymmetrically substituted rings systems (Scheme 26).[115]



Scheme 26: Regioselective organometallic functionalization off the 1,5- and 2,7 -naphthyridines.

1,8-Naphtalimides with substituents in *peri*-position are well known fluorescent dyes which find broad applications like in OLEDs or WLEDs. Naphthalimides with donor groups in position 4 such as 4-aminonaphthalene-1,8-dicarboximides and 4-alkoxynaphthalene-1,8-carboximides are of special interest since comparably large Stokes shifts and positive solvatochromism of the fluorescence are observed. In another project, we aimed for the preparation of new, highly soluble donor-substituted 1,8-naphthalimides with aryl groups as conjugating spacers between the donor group and the naphtalimide acceptor group. Thus, the fluorescent solvatochromism is expected to increase with the photo-induced dipole moment depending on the distance of the separated charges (Figure 7).[116]

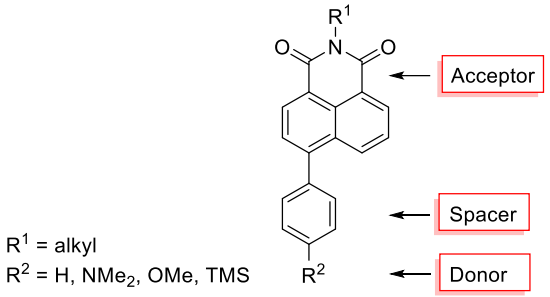


Figure 7: New push-pull 1,8-naphthalimides with aryl spacer for pronounced solvatochromism.

[115] This project was carried out in cooperation with Dr. Romain Blanc, Dorothée Ziegler, Denise Cibu and Moritz Balkenhohl.
[116] This project was carried out in cooperation with Dr. Dominik Zgela, Dr. Thorben Schlücker and Prof. Langhals.

B. RESULTS & DISCUSSION

1. Regioselective Metalation of the 2,7-Naphthyridine Scaffold

1.1 Introduction

Nitrogen-containing heterocycles are present in numerous natural products, pharmaceuticals and agrochemicals.[117] Among them, the naphthyridines have been extensively studied in the last decade. Of particular interest for this thesis is the 2,7-naphthyridine scaffold, which was originally synthesized by *Ikekawa*.[97] In terms of pharmaceutical drug development, this kind of naphthyridine is still underrepresented. However, countless alkaloids with a 2,7-naphthyridine structure have been found in natural products (Figure 8).[93d]

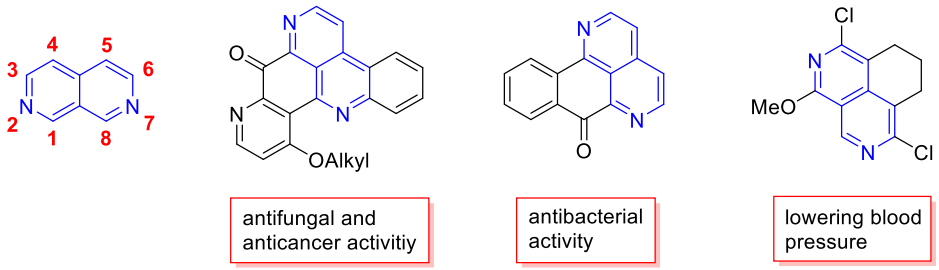
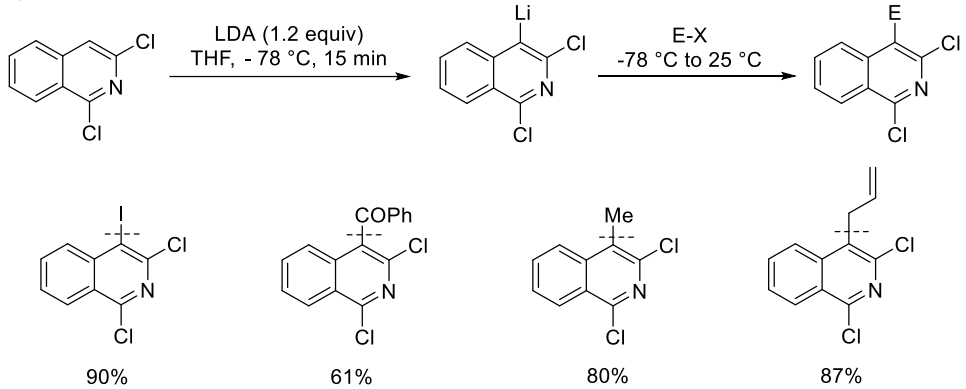


Figure 8: Bioactive 2,7-naphthyridine derivatives.

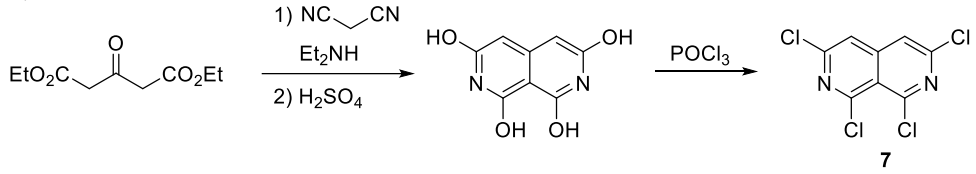
By synthetic efforts some of the known 2,7-naphthyridine alkaloids have already become accessible *via* total synthesis.[118] Despite the fact that many methods for the general construction of this scaffold exist,[93] almost nothing is reported about the direct metalation of naphthyridines. In 2009, *Yang* reported a facile synthesis of 1,3,4-trisubstituted isoquinolines by lithiation and subsequent trapping with electrophiles (Scheme 27).[119]



Scheme 27: Synthesis of 4-substituted-1,3-dichloroisoquinolines *via* lithiation and electrophilic trapping.

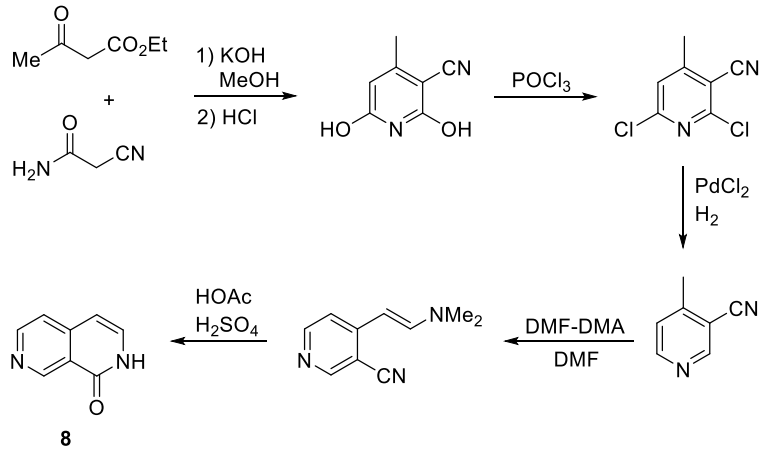
[117] T. Eicher, S. Hauptmann, A. Speicher, in *The Chemistry of Heterocycles 2nd Ed.*, Wiley-VCH, Weinheim, **2003**.
[118] (a) A. Zhang, C. Ding, C. Cheng, Q. Yao, *J. Comb. Chem.* **2007**, *9*, 916. (b) M. Lotter, J. Schilling, E. Reimann, F. Bracher, *Arch. Pham. Chem. Life. Sci.* **2006**, *339*, 677. (c) F. Bracher, K. Mink, *Liebigs Ann.* **1995**, 645. (d) A. Plodek, S. Raeder, F. Bracher; *Tetrahedron* **2012**, *68*, 4693; *Tetrahedron* **2013**, *69*, 9857. (e) W. Disadee, P. Polypradith, T. Aree, N. Chaichit, S. Ruchirawat, *Tetrahedron Lett.* **2011**, *52*, 6142. (f) E. Barbu, J. J. Wolff, I. Bolocan, F. Cuiban, *Het. Comm.* **2000**, *6*, 25. (g) S. Vijayalakshmi, S. P. Raijendran, *Oppi Briefs*, **1998**, *30*, 356.
[119] H. Yang, *Tetrahedron Lett.* **2009**, *50*, 3081.

Regarding *Yang's* discoveries, we have chosen the similar 1,3,6,8-tetrachloro-2,7-naphthyridine (**7**) as convenient starting material for our metalation experiments. Compound **7** can be easily obtained by *Knoevenagel* condensation of diethylacetonedicarboxylate with malonitrile, followed by chlorination (Scheme 28).[120]



Scheme 28: Synthetic route to 1,3,6,8-tetrachloro-2,7-naphthyridine (**7**).

Furthermore, we also decided to examine 2,7-naphthyridin-1(2*H*)-one (**8**) upon metalation since this structure is widely represented in natural products[118,121] and its analogues are investigated as enzyme inhibitors.[122] Compound **8** can be produced in a multiple step procedure starting by the condensation of ethyl acetoacetate and cyanoacetamide. Chlorination and reduction gives rise of 4-methyl-3-cyano-pyridine. Further treatment with DMF-DMA leads to the corresponding enamine, which can be cyclized to the desired naphtyridone **8** under acidic conditions (Scheme 29).[118a]



Scheme 29: Synthetic route to 2,7-naphthyridin-1(2*H*)-one (**8**).

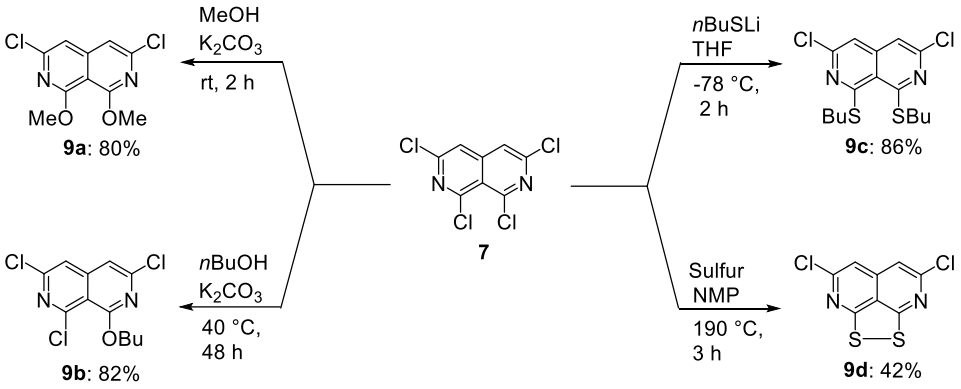
[120] (a) J. P. Plante, P. D. Jones, D. R. Powell, T. E. Glass, *Chem. Comm.* **2003**, 336. (b) B. M. Ferrier, N. J. Campbell, *Chem. Soc.* **1960**, 3513. (c) W. W. Paudler, S. J. Cornrich, *J. Heterocyclic Chem.* **1970**, *7*, 419.

[121] (a) G. Duvey, F. Nivoliers, P. Rocca, A. Godard, F. Marsais, G. Quéguiner, *J. Heterocyclic Chem.* **2001**, *38*, 1039. (b) H. Gross, D. E. Goeger, P. Hills, S. L. Mooberry, D. L. Ballantine, T. F. Murray, F. A. Valeriote, W. H. Gerwick, *J. Nat. Prod.* **2006**, *69*, 640.

[122] (a) Y. Zhang, B. Illarionov, A. Bacher, M. Fischer, G. I. Georg, Q.-Z. Ye, D. V. Velde, P. E. Fanwick, Y. Song, M. Cushman, *J. Org. Chem.* **2007**, *72*, 2769. (b) K. Kumpan, A. Nathubhai, C. Zhang, P. J. Wood, M. D. Lloyd, A. S. Thompson, T. Haikarainen, L. Lehtiö, M. D. Threadgill, *Bioorg. Med. Chem.* **2015**, *23*, 3013. (c) J. Y. L. Chung, R. J. Cvetovich, M. McLaughlin, J. Amato , F.-R. Tsay, M. Jensen, S. Weissman, D. Zewge, *J. Org. Chem.*, 2006, *71*, 8602.

1.2 Metalation of 2,7-Naphthyridines in Position 4

In several preliminary experiments, we noticed that the tetrachloro-2,7-naphthyridine **7** cannot be cleanly lithiated with various lithium bases or magnesiated using TMPMgCl·LiCl (**3**). Therefore, we converted **7** by nucleophilic substitution, using alkoxides[120a] and alkylthiolates, into the corresponding derivatives **9a-d** (42-82% yield, Scheme 30).



Scheme 30: Preparation of alkoxy- and thioalkyl- naphthyridines **9a-d**.

The reason for this substitution pattern can be explained by the formation of the most stable intermediate. While the aromaticity in intermediate A is retained according to *Hückel's* rule, aromaticity is lost in intermediate B.[78] To give evidence of this hypothesis we recorded a crystal structure of **9c** (Figure 9).

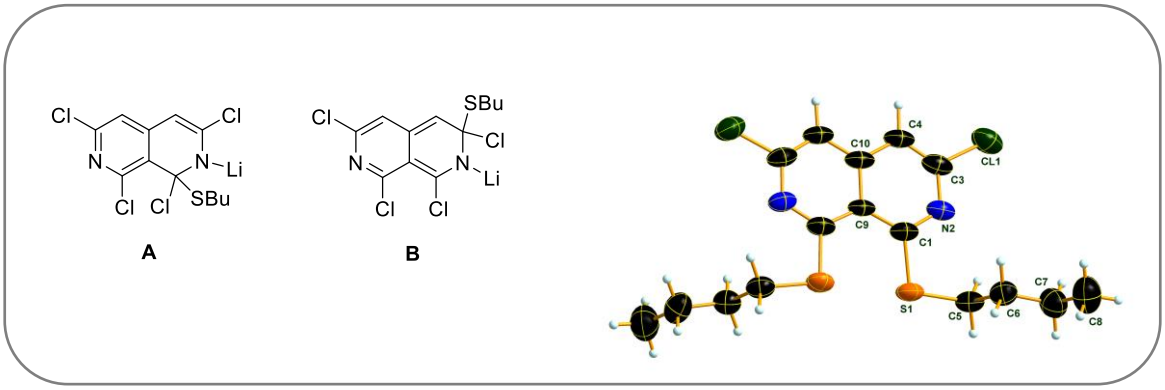
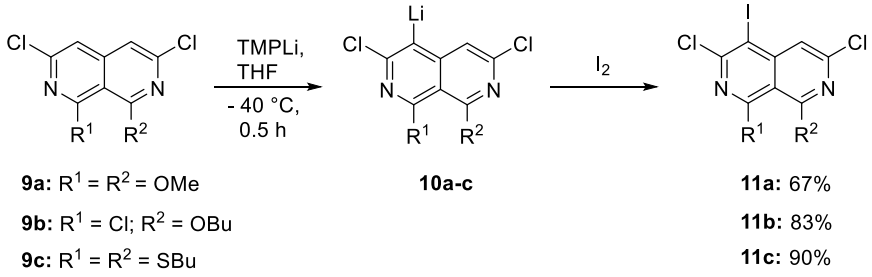


Figure 9: Mechanistic aspects of thioalkylation (left) and crystal structure of **9c (**right); thermal ellipsoids are drawn at 50% probability level.

Except derivative **9d**, which bears no alkyl residues, all other naphthyridines **9a-c** are greatly soluble in all common organic solvents, making them accessible to metalation. Since our naphthyridines have a C-Cl bond next to a nitrogen atom, strong bases like *n*BuLi, which prone to undergo nucleophilic substitution as side reaction, were not desirable. However, the sterically hindered bases TMPZnCl·LiCl (**5**) and TMPMgCl·LiCl (**3**) were not satisfactory for the metalation of **9a-c**, whereby a stronger, sterically hindered base was required. Thus, we found that TMPLi (**2**, 1.2 equiv, THF, -40 °C, 0.5 h) allows a smooth lithiation of the naphthyridines **9a-c** in position 4, leading to the lithiated 2,7-naphthy-

ridines **10a-c**. After iodolysis, the corresponding 4-iodo-2,7-naphthyridines **11a-c** were obtained in 67-90% yield (Scheme 31).



Scheme 31: Lithiation of naphthyridines **9a-c** followed by iodolysis.

Furthermore, quenching of lithiated **10b** with TMSCl provided the desired trimethylsilyl derivative **11d** in 69% yield. A crystal structure of **11d** clearly gives evidence about the regioselectivity upon the metalation of unsymmetrically **9b**. It can be clearly recognized that metalation takes place at C4 (Figure 10). This seems to be logical, since the ring moiety with two chlorine atoms is more electron deficient.

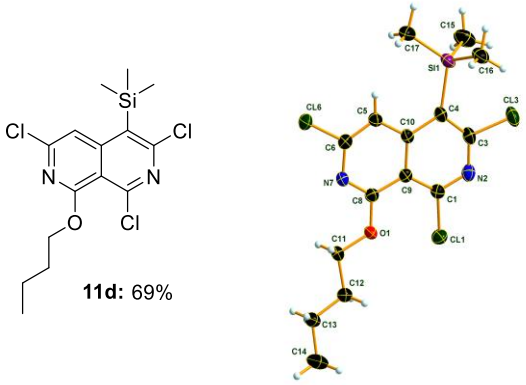


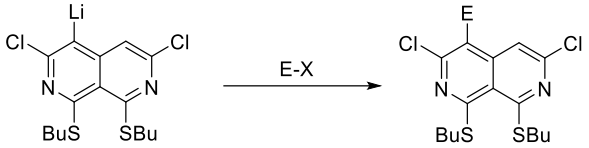
Figure 10: DIAMOND view of the molecular structure of compound **11d** in the crystal; thermal ellipsoids are drawn at 50% probability level.

Since the thiobutyl-substituted naphthyridine **9c** has an excellent solubility in organic solvents such as THF and gives the best yield upon iodolysis (**11c**: 90%), we have examined its lithiation and quenching with a range of other electrophiles (Table 1). Thus, the bromination of **10c** with bromine (1.2 equiv, -40 °C, 2 h) and the cyanation using tosyl cyanide (1.2 equiv, - 40 °C, 2 h) provides the 4-bromo-naphthyridine **12a** and the nitrile **12b**, respectively in both in 63% yield (Table 1, entries 1-2). Quenching of **10c** with Me_3SiCl (1.5 equiv, -78 °C, 1 h) gives the expected trimethylsilyl derivative **12c** in 73% yield (entry 3). The addidion of *S*-phenyl benzenethiosulfonate to **10c** (1.2 equiv, -40 °C, 2 h) gave the thioether **12d** in 80% yield (entry 4). Aminomethylation was achieved using *Eschenmoser's* salt[123] (1.2 equiv, -40 °C, 2 h) leading to the dimethylaminomethyl derivative **12e** in 81% yield (entry 5). Also, the introduction of a carbethoxy substituent was achieved by the transmetalation of lithiated naphthyridine

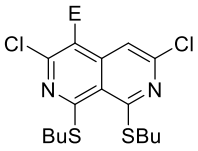
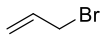
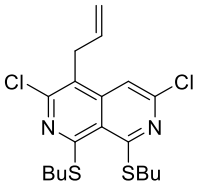
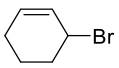
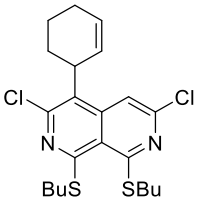
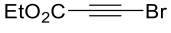
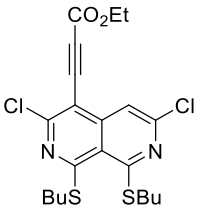
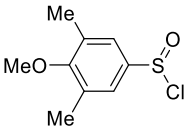
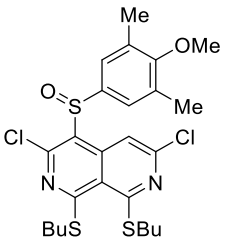
[123] (a) N. Gommermann, C. Koradin, P. Knochel, *Synthesis* **2002**, 2143. (b) J. Saczewski, M. Gdaniec, *Tetrahedron Lett.* **2007**, *48*, 7624. (c) F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry: Part B Reaction and Synthesis* **2007**, *140*, Springer. (d) N. M. Barl, E. Sansiaume-Dagousset, G. Monzón, A. J. Wagner, P. Knochel, *Org. Lett.* **2014**, *16*, 2422. (e) V. Werner, M. Ellwart, A. J. Wagner, P. Knochel, *Org. Lett.* **2015**, *17*, 2016.

10c with $MgCl_2$ and subsequent quenching with ethyl chloroformate (1.1 equiv, -30 °C, 6 h) affording the 2,7-naphthyridine ethylester **12f** in 84% yield (entry 6). Copper(I)-mediated allylation[124] with allyl

Table 1: Preparation of C(4)-substituted naphthyridines **12a-j** by quenching of **10c** with various electrophiles.



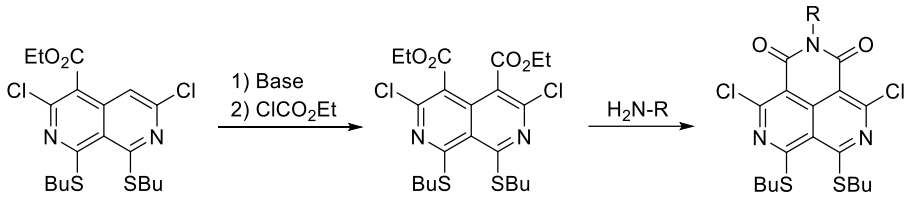
10c **12a-j**

Entry	Electrophile	Product	Yield[a] [%]
1	Br_2		**12a**: E = Br; 63%
2	*p*-TolCN		**12b**: E = CN; 63%
3	TMSCl		**12c**: E = TMS; 73%
4	$PhSSO_2Ph$		**12d**: E = SPh; 80%
5	$H_2CN(CH_3)_2^+ I^-$		**12e**: E = CH_2NMe_2; 81%
6	$ClCO_2Et$		**12f**: E = CO_2Et; 84%[c]
7			**12g**: 93%[b]
8			**12h**: 95%[b]
9			**12i**: 84%[d]
10			**12j**: 72%[c]

[a] Isolated yields of analytically pure product. [b] Allylation was performed using 1 M CuCN·2LiCl (20 mol%). [c] A transmetalation with $MgCl_2$ (1.2 equiv) was performed. [d] A transmetalation with 1 M $ZnCl_2$ (1.1 equiv) was performed followed by the addition of 1 M CuCN·2LiCl (20 mol%).

[124] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

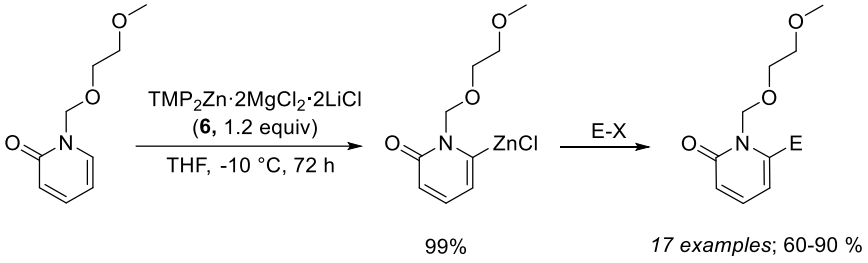
bromide or 3-bromocyclohexene gave the allylated 2,7-naphthyridines **12g-h** in 93-95% (entries 7-8). Moreover, a copper(I)-catalyzed alkynylation of the corresponding zinc derivative of **10c** with ethyl 3-bromo-propiolate (1.2 equiv, -40 °C, 12 h) provided the functionalized acetylene **12g** in 84 % yield (entry 9). Finally, sulfinylation of the magnesium derivative of **10c** using 4-methoxy-3,5-dimethyl-benzene-sulfinyl chloride gave the sulfoxide **12j** in 72% yield (entry 10). Thus, we have demonstrated lithiation of the naphthyridine **9c** in 4-position and subsequent trapping with a variety of electrophiles, furnishing new naphthyridines **12a-j** in good yields. However, further experiments to carry out classic *Negishi*-type cross-couplings with the zinc species of **10c** or with the naphthyridines **11c** and **12a** completely failed. Also, we could not achieve metalation of the naphthyridines **12** in position 5 with Mg- and Li-bases under various conditions. Solving this problem might give rise of new electron-rich and highly soluble 2,7-naphtyridineimides (Scheme 32).[125]



Scheme 32: Hypothetic pathway to new 2,7-naphthyridineimides.

1.3 Metalation of 2,7-Naphthyridone in Position 3

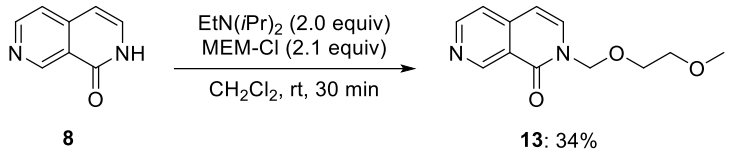
In order to functionalize the 2,7-naphthyridone **8** it is crucial to protect the free amine. Furthermore, the introduction of a DMG would give the opportunity of a regioselective metalation. *Ziegler et al.* found that a MEM-protecting group in 2-pyridones can serve as a DMG. Thus, the treatment of 1-((2-methoxy-ethoxy)methyl)pyridin-2(1*H*)-one with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**) at -10 °C proved to give the best results upon metalation. Subsequent trapping with electrophiles led to functionalized 2-pyridones in 60-90% yield (Scheme 33).



Scheme 33: Metalation of MEM-protected 2-pyridones and subsequent trapping with electrophiles.

Following this reaction protocol, we first protected naphthyridone **8** with 2-methoxyethoxymethyl ether (MEM) by a standard method [126] (Scheme 34).

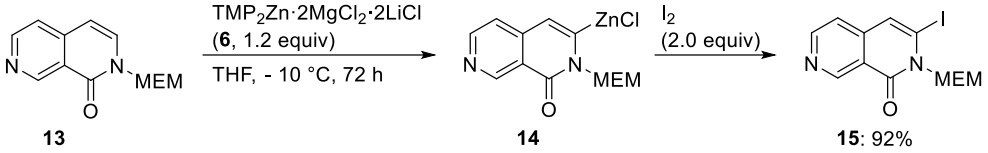
[125] T. L. Andrew, B. V. Veller, T. M. Swager, *Synlett* **2010**, *22*, 3045.
[126] A. B. Smith, *Org. Lett.* **2005**, *7*, 315-318.



Scheme 34: MEM-protection of naphthyridone **8**.

For metalation, $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**) at -10 °C also proved to give the best results, since we encountered solubility problems with TMPMgCl·LiCl (**3**) at temperatures below -20 °C, what makes the application of stronger bases at low temperatures impossible.

Interestingly, 0.6 equiv of the zinc-base (**6**) are not enough to completely metalate **13** and upon quenching with iodine only 36% of analytically pure product could be obtained.[127] This could indicate a complexation of **6** by the MEM-protected naphthyridone **13** leading to partial zincation only. To overcome this problem, we raised the amount of base to 1.2 equiv, leading to full conversion upon iodolysis after 72 h reaction time (Scheme 35).



Scheme 35: Zincation of naphthyridone **13**, followed by iodolysis.

The X-ray structure of compound **15** reveals iodination exclusively in position 3 (Figure 11). Thus, we give evidence for the *ortho*-directing effect of the MEM-protecting group in naphthyridone **13**.

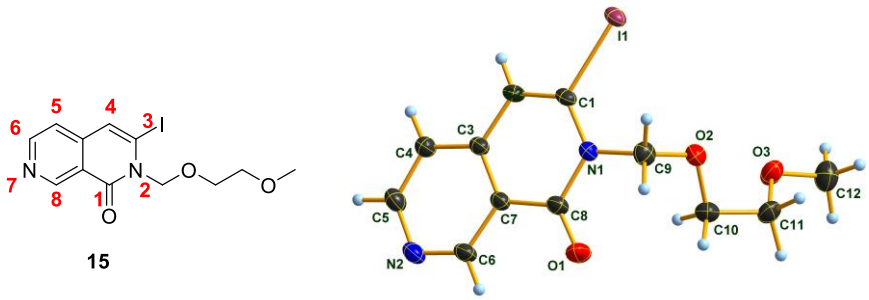


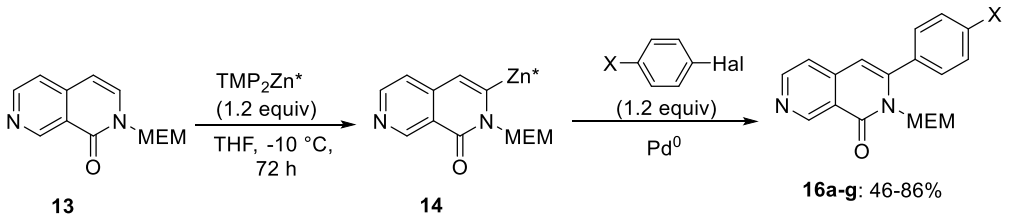
Figure 11: Molecular structure of naphthyridone **15** in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50 % probability level.

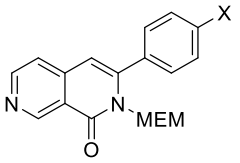
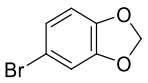
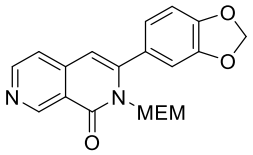
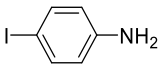
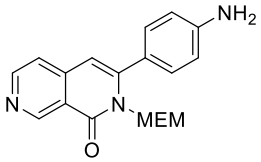
Using this method for the regioselective functionalization of naphthyridone **13**, we could successfully prepare a range of new interesting compounds by palladium-catalyzed arylations. For the most cross-coupling reactions of **14** with para-substituted iodo-benzenes, $Pd(dba)_2$ and P(*o*-furyl)$_3$ was used as catalyst system. Thus, 4-iodoanisole and 4-iodotoluene reacted smoothly with zincated naphthyridone **14** giving the desired products **16a-b** in both 83% yield (Table 2, entry 1 and 2). Also, 1-chloro-4-iodobenzene reacted easily with **14**, furnishing the corresponding chloro-naphthyridone **16c** in 86% yield (entry 3). The cross-coupling of **14** with electron-poor 4-iodobenzonitrile provided **16d** in 74% yield (entry 4). However, using 1-iodo-4-(trifluoromethyl)benzene as electrophile led to a decreased

[127] S. H. Wunderlich, P. Knochel, *Chem. Commun.* **2008**, 6387.

yield of only 46% of compound **16e** (entry 5). For the coupling of 5-bromobenzo[*d*]-[1,3]dioxole PEPPSI-*i*Pr was used as a standard catalyst, giving **16f** in 79 % yield (entry 6). In case of the coupling of 4-iodoaniline, a special method from Manolikakes[128] was used, since the electrophile bears acidic protons, which can easily react with the zinc species. Therefore, zincated naphthyridone **14** was added very slowly over 1 h *via* syringe pump to the electrophile, enabling a smooth cross-coupling and furnishing the desired amino-naphthyridone **16g** in 76% yield (entry 7).

Table 2: Zincation of naphthyridone **13** and subsequent Pd-catalyzed arylations (*$MgCl_2$ and LiCl are omitted for sake of claritiy).

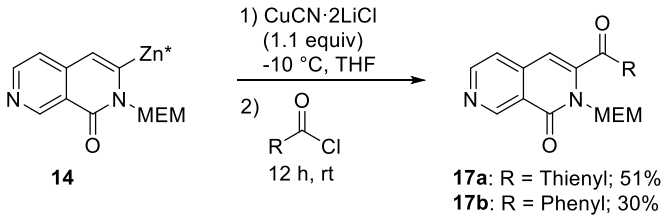


Entry	Electrophile	Product	Yield[a]
1	4-OMe-iodobenzene		**16a**: X = OMe; 83%[b]
2	4-Me-iodobenzene		**16b**: X = Me; 83%[b]
3	4-Cl-iodobenzene		**16c**: X = Cl; 86%[b]
4	4-CN-iodobenzene		**16d**: X = CN; 74%[b]
5	4-CF_3-iodobenzene		**16e**: X = CF_3; 46%[b]
6			**16f**: 79%[c]
7			**16g**: 76%[d]

[a] Isolated yield of analytically pure product. [b] $Pd(dba)_2$ (4 mol%) and P(*o*-furyl)$_3$ (8 mol%) was used; 12 h reaction time at 25 °C. [c] PEPPSI-*i*Pr (4 mol%) was used; 12 h reaction time at 60 °C. [d] reversed addition of zinc species to electrophile *via* syringe pump within 1 h; $Pd(OAc)_2$ (4 mol%) and S-Phos (8 mol%) was used; 12 h reaction time at 25°C.

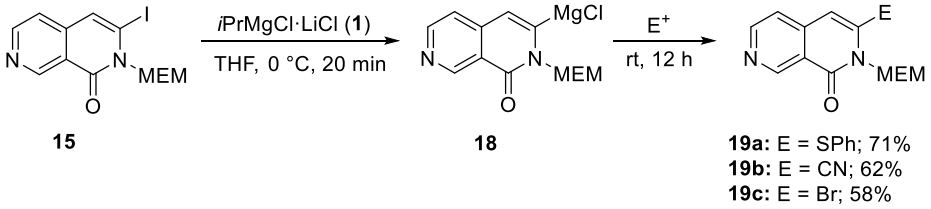
Unfortunately, several experiments to react **14** with nitrogen containing heterocycles failed. We then further tried to do copper(I)-mediated acylation reactions with **14** using stoichiometric amounts of CuCN·2LiCl (Scheme 36). Thus, the reaction of the copper derivative of **14** with thiophene-2-carbonyl chloride and benzoyl chloride only gave **17a** in 51% and **17b** in 30% yield respectively. This circumstance is due to many by-products, that form during the reaction decreasing the yield.

[128] (a) G. Manolikakes, M. A. Schade, C. Munoz Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765. (b) G. Manolikakes, C. Munoz Hernandez, M. A. Schade, A. Metzger, P. Knochel, *J. Org. Chem.* **2008**, *73*, 8422.



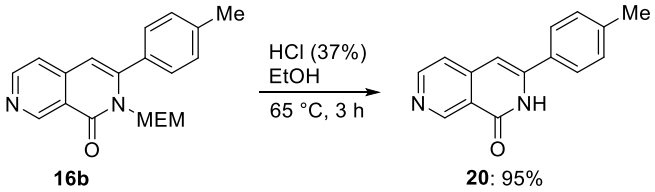
Scheme 36: Copper(I)-mediated acylation reactions of naphthyridone **14**.

The allylation of **14** with allyl bromide nether worked with catalytic amounts nor with stoichiometric amounts of CuCN·2LiCl. Also, we could not convert **14** with simple electrophiles like $PhSSO_2Ph$, indicating that the zinc species is too unreactive. Therefore, we accessed the more reactive Mg-species **18** by reacting iodinated naphthyridone **15** with *i*PrMgCl·LiCl (**1**). Subsequent trapping with electrophiles gave the desired products **19a-c**. (Scheme 37).



Scheme 37: Zinc-magnesium exchange of **15**, followed by quenching with electrophiles.

Thus, quenching **18** with $PhSSO_2Ph$ (3.0 equiv) furnished the corresponding naphthyridone-thiophenyl-ether **19a** in 71% yield. Cyanation with 4-methylbenzenesulfonyl cyanide (1.5 equiv) gave **19b** in 62% yield. Nucleophilic substitution using 1,2-dibromo-1,1,2,2-tetrachloroethane (2.0 equiv) generated the bromo-naphthyridone **19c** in 58% yield. Finally, we demonstrated that we can remove the MEM-group after functionalization. The treatment of protected naphthyridone **16b** with 37% HCl in EtOH generated the free amine **20** in 95% yield (Scheme 38).



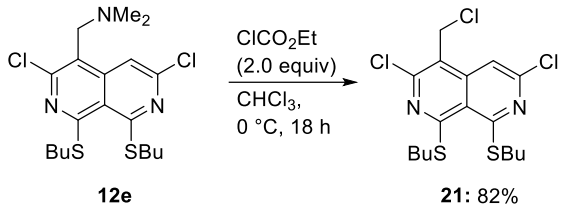
Scheme 38: Deprotection of MEM-protected naphthyridone **16b**.

In summary, we could generate a range of new functionalized naphthyridones by regioselective, MEM-directed metalation and subsequent conversion with aryl and acyl electrophiles. Also, we showed how to access the more reactive Mg-species of naphthyridone by I/Mg-exchange, which can be quenched with simple electrophiles. Finally, we demonstrated a simple method to remove the protecting group after functionalization.

2. Further Functionalization of 2,7-Naphthyridines and Synthesis of Natural Products Lophocladine A & B

We further envisioned the manifold functionalization of our new established 2,7-naphthyridines. In a vast number of experiments, we encountered many side reactions preventing us from the isolation of clean products. However, we could achieve some further modifications, which are presented in the following.

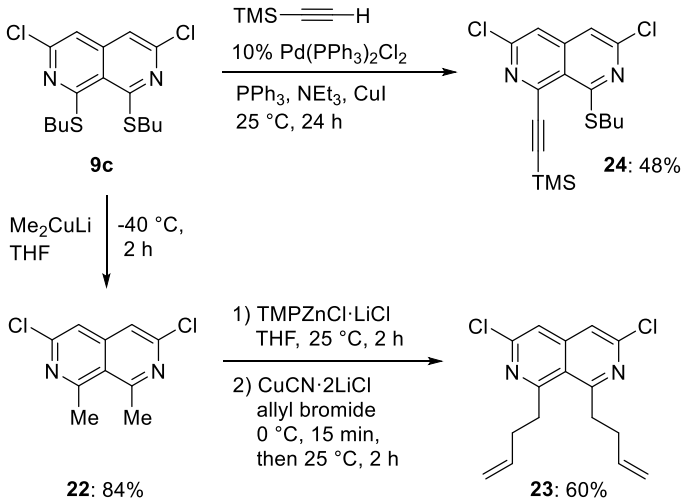
Benzylic groups are widespread scaffolds in biological active compounds and pharmaceuticals. Often benzylic chlorides are used as precursors. Therefore, we converted the naphthyridine-amine **12d** with $ClCO_2Et$ producing the corresponding chloromethyl derivative **21** in 82% yield (Scheme 39).[129]



12e **21:** 82%

Scheme 39: Conversion of naphthyridine **12e** into the chloromethyl-derivative **21**.

In order to do cross-couplings selectively in position 3 and 6 (Chapter B.4), we targeted to convert the two thiobutyl groups of **9c** into unreactive alkyl substituents, since thioethers can also undergo cross-couplings reactions.[130] Thus, we found that the thiobutyl groups of **9c** can be easily converted into methyl groups by using Me_2CuLi[131] (3.0 equiv, THF, -40 °C, 2 h), furnishing **22** in very good yield (Scheme 40).



Scheme 40: Functionalization of naphthyridine **9c** by *Sonogashira* coupling and methylation with subsequent allylation.

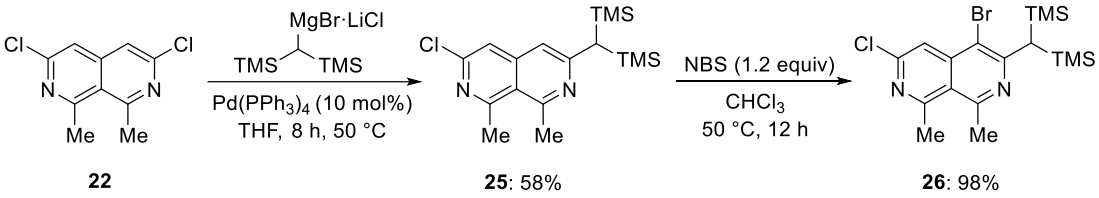
[129] (a) F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry: Part B Reaction and Synthesis* **2007**, 140, Springer. (b) C. R. Nevill, P. L. Fuchs, *Synth Commun.* **1990**, *20*,761. (c) F. Stiemke, M. Gjikaj, D. E. Kaufmann, *J. Organomet. Chem.* **2009**, *694*, 5.

[130] A. Metzger, L. Melzig, C. Despotopoulou and P. Knochel, Org. Lett. **2009**, *11*, 4228.

[131] J. F. Normant, *Synthesis* **1972**, 63. (b) N. Krause, *Modern Organocopper Chemistry*, Wiley-VCH, Weinheim, **2002**. (c) C. Piazza, P. Knochel, *Angew. Chem, Int. Ed.* **2002**, *41*, 3263.

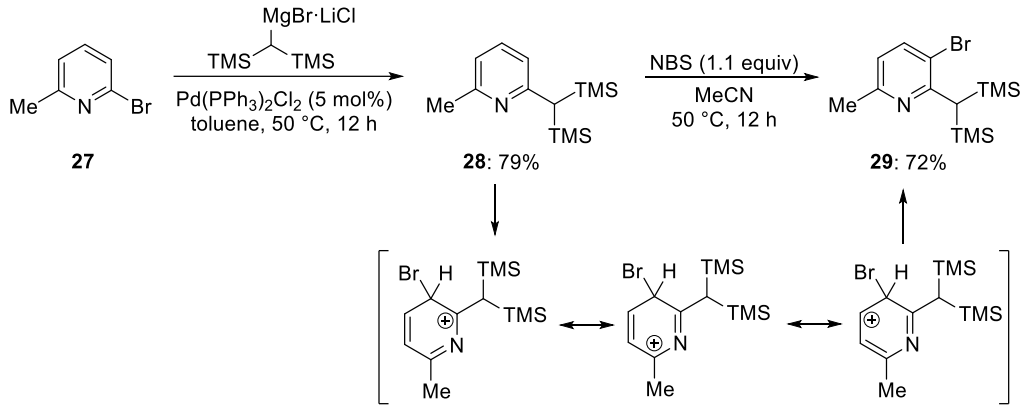
Furthermore, the methyl groups in **22** could then be allylated with allyl bromide using TMPZnCl·LiCl (**5**, 3.0 equiv, 25 °C, 2 h), producing the new 2,7-naphthyridine **23** in 60% yield (Scheme 40).[132] Interestingly, the dithiobutylnaphthyridine **9c** undergoes a selective thioalkyl-substitution with trimethylsilylacetylene (3.0 equiv) under typical *Sonogashira* reaction conditions[133] leading to the 1-butyl-thio-8-alkynylnaphthyridine **24** in 48% yield (Scheme 40).

Besides the metalation of the dimethyl-dichloro-naphthyridine **22**, a Pd-catalyzed cross-coupling with bis-trimethylsilylmethylmagnesium bromide was achieved, leading to the mono-coupled product **25** in 58% yield. We found that the bis-trimethylsilylmethyl group can facilitate regioselective bromination with NBS, furnishing the bromo-naphthyridine **26** in 98% yield (Scheme 41).



Scheme 41: Pd-catalyzed cross-coupling of **22** follwed by regioselective bromination.

To proof the generality of this discovery, we converted 2-bromo-6-methylpyridine (**27**) with bis-trimethylsilylmethylmagnesium bromide to the pyridine derivative **28**. Similar to the bromination of **25**, the reaction of **28** with NBS proceeded smoothly, furnishing 2-(bis(trimethylsilyl)methyl)-6-methyl-pyridine (**29**) in 72% yield. (Scheme 42).



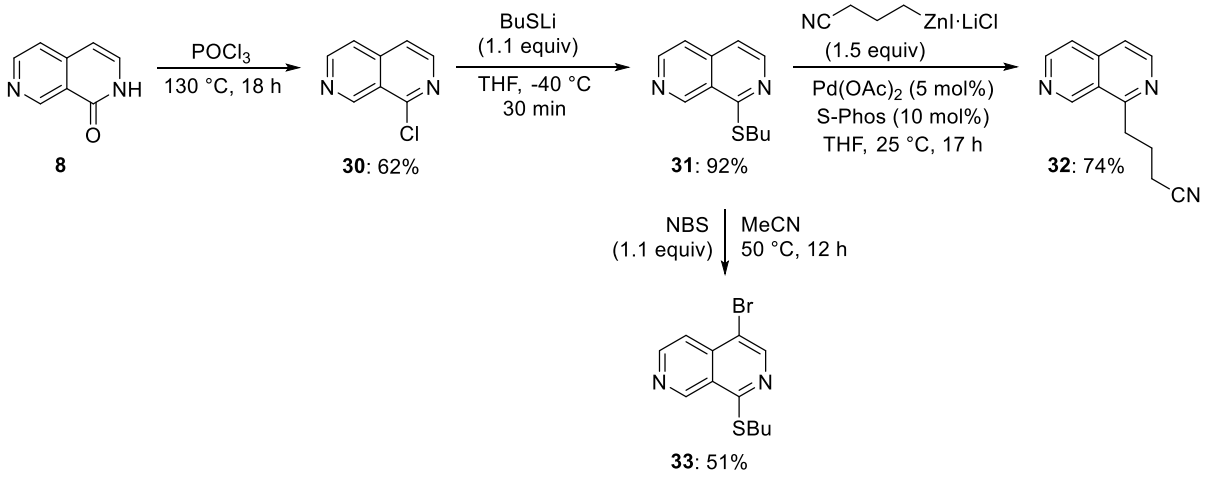
Scheme 42: Pd-catalyzed cross-coupling of **27** followed by regioselective bromination.

In the transition state, the inductive effect of the methyl group as well as of the bistrimethylsilylmethyl group stabilizes the positive charge. However, the presence of both groups seems to be essential for the bromination. Thus, further bromination experiments with 2-methylpyridine or 2-(bis(trimethylsilyl)-methyl)pyridine completely failed.

[132] (a) S. Duez, A. K. Steib, S. M. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 7686. (b) S. Duez, A. K. Steib, P. Knochel, *Org. Lett.* **2012**, *14*, 1951.

[133] (a) K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46. (b) R. Chinchilla, C. Najera, *Chem. Soc. Rev.* **2011**, *40*, 5084. (c) M. Schilz, H. Plenio, *J. Org. Chem.* **2012**, *77*, 2798.

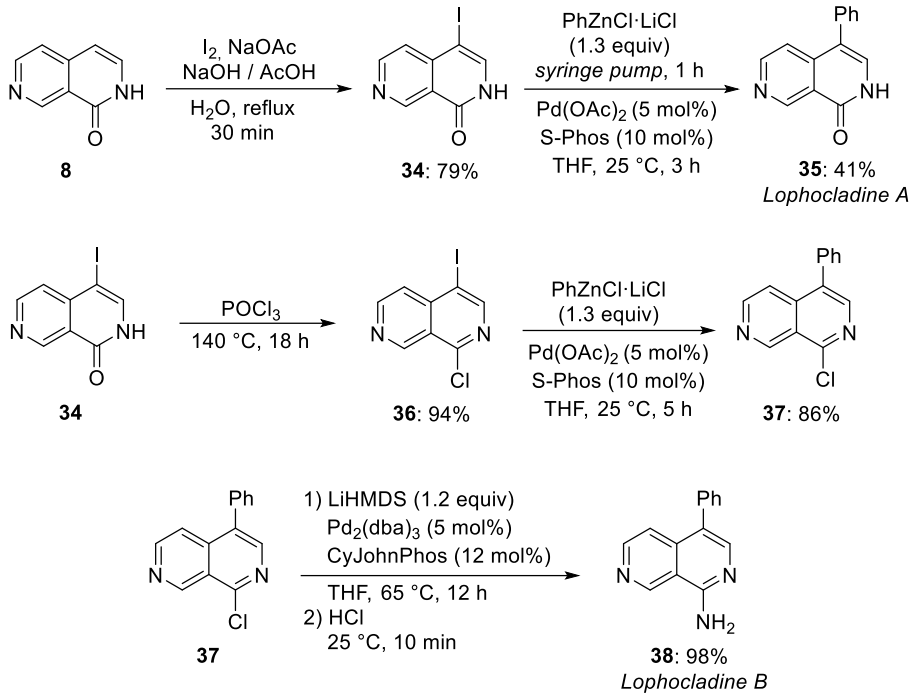
We also targeted further functionalization of the naphthyridone **8** (Scheme 43). Therefore, we chlorinated **8** according to the literature.[125] By using lithium butane-1-thiolate we further converted 1-chloro-2,7-naphthyridine (**30**) into 1-(butylthio)-2,7-naphthyridine (**31**).



Scheme 43: Further functionalization of 2,7-naphthyridin-1(2*H*)-one (**8**).

A Pd-catalyzed cross-coupling of the thioether **31** with 4-cyanopropylzinc iodide provided the alkylated naphthyridine **32** in 74% yield. The treatment of compound **31** with NBS directs the bromine in *para*-position to the butyl-thio group, furnishing the halogenated naphthyridine **33** in 51% yield.
In Chapter B 1.2, we demonstrated a new method to introduce an iodide in position 3 of naphthyridone **8**. We then realized that an iodide in position 4 would give us access to the natural products *Lophocladine A* & *B*. By using a method from the literature for the iodination of pyridin-2(1*H*)-one,[134] we efficiently produced 4-iodo-2,7-naphthyridin-1(2*H*)-one (**34**) in 79% yield (Scheme 44). A careful *Negishi* cross-coupling by the slow addition of phenylzinc chloride *via* syringe pump to acidic naphthyridone **34** furnished natural product *Lophocladine A* (**35**) in 41% yield. Furthermore, the reaction of **34** with $POCl_3$ afforded the 1-chloro-4-iodo-2,7-naphthyridine (**36**) in very good yield. Subsequent *Negishi* cross-coupling with PhZnCl gave the phenylated chloro-naphthyridine **37** in 86% yield (Scheme 44).

[134] Y. Koseki, T. Sugimura, K. Ogawa, R. Suzuki, H. Yamada, N. Suzuki, Y. Masuyama, Y. Y. Lin, T. Usuki, *Eur. J. Org. Chem.* **2015**, 4024.



Scheme 44: Synthesis of natural products *Lophocladine A* (**35**) & *B* (**38**).

Previous work by *Disadee et al.* revealed that a direct amination of **37** does not work. Instead they used phenylmethaneamine for amination and subsequently cleaved of the benzyl group with concentrated sulfuric acid, furnishing *Lophpcladine B* in 48% yield. We could improve the amination by a method from *Buchwald*,[135] employing a Pd-catalyzed reaction of **37** with LiHMDS as ammonia surrogate. Acid promoted deprotection witch HCl provided the desired *Lophocladine B* (**38**) in quantitative yield.

[135] X. Huang, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3417.

3. Regioselective Metalation of the 1,5-Naphthyridine Scaffold

3.1 Introduction

Heterocyclic ring structures are ubiquitous in pharmaceutical and agrochemical research, and the discovery of new medicinal targets requires the functionalization of always less common heterocycles.[136] Naphthyridines certainly belong to the heterocycles of the future[137] and their functionalization *via* metalation is still in its infancy.[107,108] Especially 1,5-naphthyridines have been identified as suitable candidates for antimalarial,[138] antibacterial,[93c,139] anticancer[140] and anti-HIV[141] drugs (Figure 12).

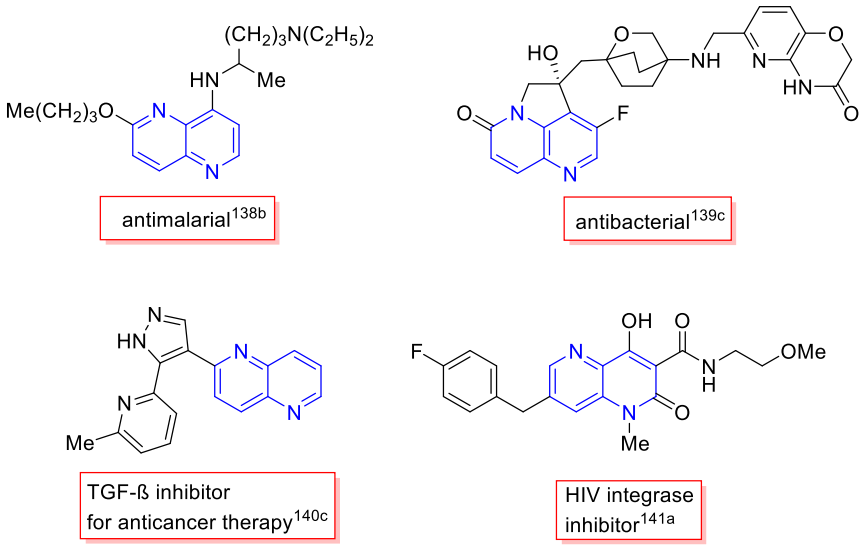


Figure 12: 1,5-Naphthyridines as medical drugs.

[136] (a) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257. (b) P. Martins, J. Jesus, S. Santos, L. Raposo, C. Roma- Rodrigues, P. Baptista, A. Fernandes, *Molecules* **2015**, *20*, 16852. (c) A. Gomtsyan, *Chem. Heterocycl. Comp.* **2012**, *48*, 7. (d) S. Sharma, P. K. Sharma, N. Kumar, R. Dudhe, *Biomed. Pharmacother.* **2011**, *65*, 244- 251.
[137] R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845.
[138] (a) B. R. Lahue, S.-M. Lo, Z.-K. Wan, G. H. C. Woo, J. K. Snyder, *J. Org. Chem.* **2004**, *69*, 7171. (b) E. F. Elslager, S. C. Perricone, D. F. Worth, *J. Heterocycl. Chem.* **1970**, *7*, 543. (c) J. T. Adams, C. K. Bradsher, D. S. Breslow, S. T. Amore, C. R. Hauser, *J. Am. Chem. Soc.* **1946**, *68*, 1317. (d) D. J. McCaustland, C. C. Cheng, *J. Heterocycl. Chem.* **1970**, *7*, 467-473.
[139] (a) 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. (b) H. A. Ioannidou, A. Martin, A. Gollner, P. A. Koutentis, *J. Org. Chem.* **2011**, *76*, 5113. (c) S. B. Singh, D. E. Kaelin, J. Wu, L. Miesel, C. M. Tan, P. T. Meinke, D. B. Olsen, A. Lagrutta, C. Wei, Y. Liao, X. Peng, X. Wang, H. Fukuda, R. Kishii, M. Takei, T. Shibata, T. Takeuchi, K. Ohata, A. Nishimura, Y. Fukuda, *Med. Chem. Commun.* **2015**, *6*, 1773.
[140] (a) J. M. Yingling, K. L. Blanchard, J. S. Sawyer, *Nat. Rev. Drug Discov.* **2004**, *3*, 1011. (b) Q. Chen, L. W. Deady, B. C. Baguley, W. A. Denny, *J. Med. Chem.* **1994**, *37*, 593. (c) 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. (d) A. Magnano, S. Sparapani, R. Lucciarini, M. Michela, C. Amantini, G. Santoni, I. Antonini, *Bioorg. Med. Chem.* **2004**, *12*, 5941. e) H. Cheng, C. Li, S. Bailey, S. M. Baxi, L. Goulet, L. Guo, J. Hoffman, Y. Jiang, T. O. Johnson, T. W. Johnson, D. R. Knighton, J. Li, K. K. C. Liu, Z. Liu, M. A. Marx, M. Walls, P. A. Wells, M.-J. Yin, J. Zhu, M. Zientek, *ACS Med. Chem. Lett.* **2013**, *4*, 91.
[141] (a) E. E. Boros, C. E. Edwards, S. A. Foster, M. Fuji, T. Fujiwara, E. P. Garvey, P. L. Golden, R. J. Hazen, J. L. Jeffrey, B. A. Johns, T. Kawasuji, R. Kiyama, C. S. Koble, N. Kurose, W. H. Miller, A. L. Mote, H. Murai, A. Sato, J. B. Thompson, M. C. Woodward, T. Yoshinaga, *J. Med. Chem.* 2009, *52*, 2754.

Also, their applicability as photosensitizers[142] and OLED materials[105c] has been proven (Figure 13). In order to give access to a convenient functionalization of the 1,5-naphthyridine scaffold, our target was

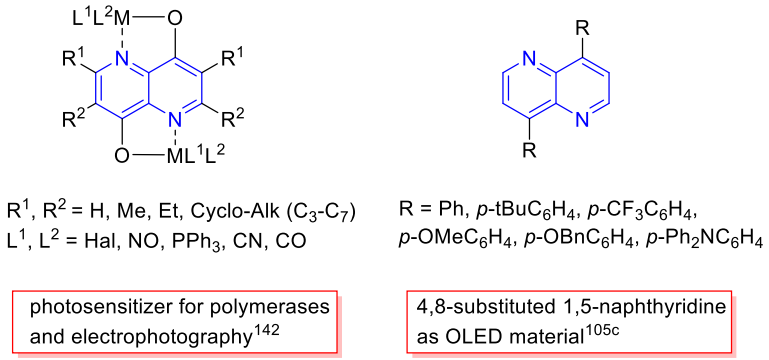
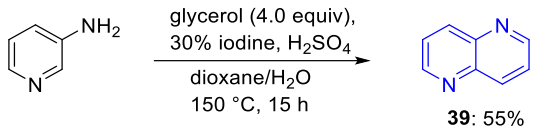


Figure 13: 1,5-Naphthyridines as photosensitizer and OLED materials.

to find was find a method for the regioselective metalation of this *N*-heterocycle. We also wanted to prove if we can enhance the metalation rate or change the regioselectivity by using *Lewis* acids such as $BF_3{\cdot}OEt_2$. 1,5-Naphthyridine (**39**) could be easily synthesized from 3-aminopyridine *via Skraup*-reaction (Scheme 45).[143]



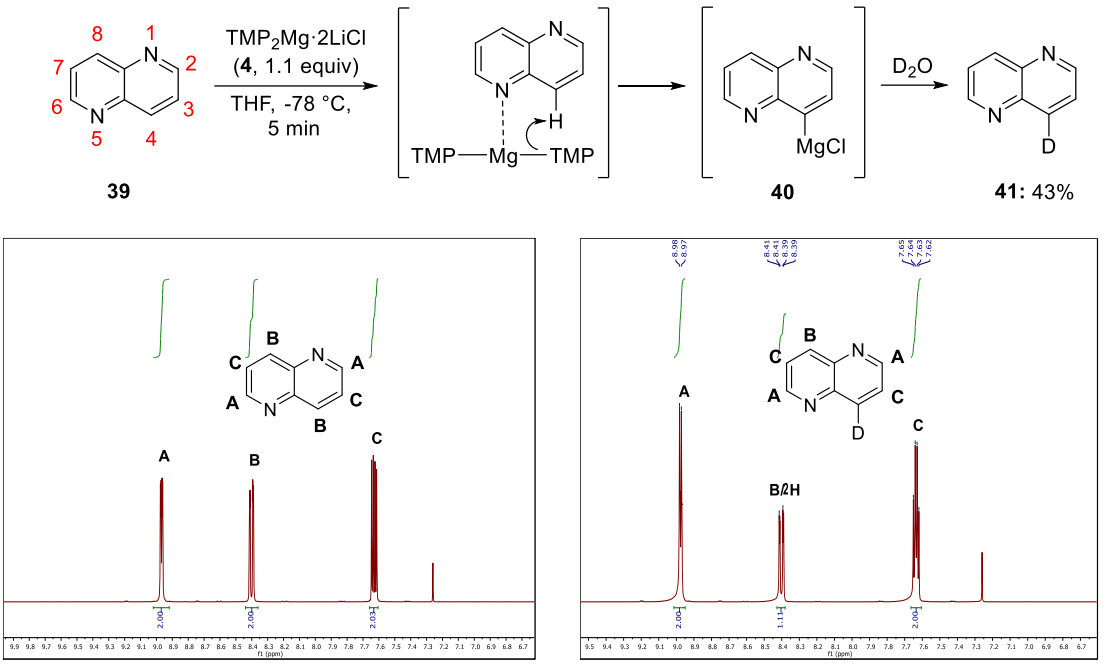
Scheme 45: Preparation of 1,5-naphthyridine *via Skraup*-reaction.

3.2 Metalation of the 1,5-Naphthyridine Scaffold in Position 4

In several screening experiments, it was found that the magnesium amide base $TMP_2Mg{\cdot}2LiCl$ (**4**) is most suitable for the metalation of 1,5-naphthyridine (**39**). Thus, it was found that the precomplexation[144] of **39** with $TMP_2Mg{\cdot}2LiCl$ (**4**; 1.1 equiv) at - 78 °C in THF induces a magnesiation within 5 min, leading to the magnesiated heterocycle **40**, which, after quenching with D_2O reveals metalation at position C(4) in ^{1}H-NMR spectra (Scheme 46). We then examined the quenching of **40** with several electrophiles, leading to novel 4-substituted 1,5-naphthyridines **42a-i** (Table 3). When the magnesium species **40** was treated with iodine and 1,2-dibromotetrachloroethane the 4-halo-1,5-naphthyridines **42a-b** were isolated in 49-62% yield (Table 3, entries 1-2). Transmetalation of **40** with $ZnCl_2$ and subsequent acylation with pivaloyl chloride in the presence of 5 mol % $Pd(PPh_3)_4$ gave the 4-acyl-1,5-naphthyridine **42c** in 63% yield (entry 3). The reaction of **40** with $PhSSO_2Ph$ provided the 4-thiophenyl-1,5-naphthyridine in 38 % yield (entry 4). Transmetalation of **40** to the corresponding copper derivative

[142] Ger. Pat. 4105386; *Chem. Abstr.* **1993**, *118*, 82835.
[143] K. C. Chunavala, S. Adimurthy, *Synth. Commun.* **2011**, *41*, 1843.
[144] M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.

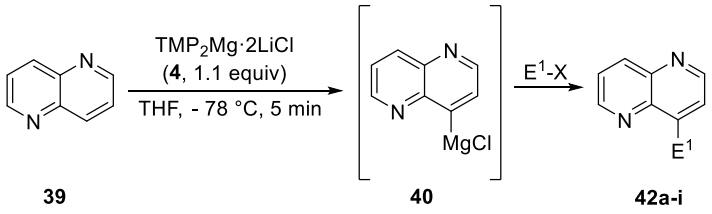
using CuCN·2LiCl[124] and reaction with 3-bromocyclohexene or *Villieras*' allylic bromide[145] provided the allylated 1,5- naphthyridines **42e-f** in 53-60% yield (entries 5-6).

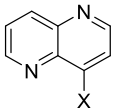
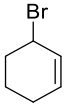
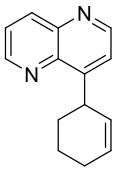


Scheme 46: Metalation of 1,5-naphthyridine (**39**) (top) and NMR-studies of 1,5-naphthyridine-4-*d* (**41**) (bottom).

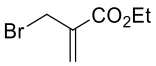
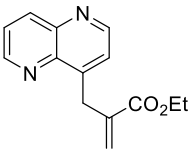
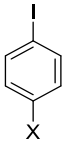
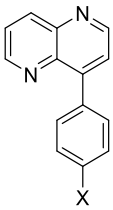
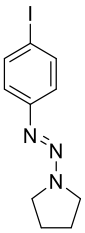
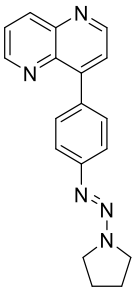
Arylation of the magnesium species **40** was performed by transmetalation with $ZnCl_2$ and *Negishi* cross-coupling with electron-rich and poor aryl iodides in the presence of 3 mol% $Pd(dba)_2$ and 6 mol% tfp leading to the novel 1,5-naphthyridines **42g-j** in 40-75% yield (entries 7-10, Figure 14).

Table 3: Metalation and functionalization of 1,5-naphthyridine (**39**) in the C(4) position using $TMP_2Mg·2LiCl$ (**4**).



Entry	Electrophile	Product	Yield[a]
1	I_2		**42a**: X = I; 62%
2	$(BrCCl_2)_2$		**42b**: X = Br; 49%
3	*t*BuCOCl		**42c**: X = CO*t*Bu; 63%[b]
4	$PhSSO_2Ph$		**42d**: X = SPh; 38%
5			**42e**: 60%[c]

[145] J. Villieras, M. Rambaud, *Org. Synth.* **1988**, *66*, 220.

6			**42f**: 53%[c]
7 8 9			**42g**: X = OMe; 75%[d] **42h**: X = CN; 48%[d] **42i**: X = CO_2Et; 40%[d]
10			**42j**: 41%[d]

[a] Isolated yields of analytically pure product. [b] Acylation was performed with 5 mol% $Pd(PPh_3)_4$ after transmetalation with 1 M $ZnCl_2$ (1.2 equiv). [c] Allylation was performed after transmetalation with 1 M CuCN·2LiCl (1.2 equiv). [d] The cross-coupling was performed with 3 mol% $Pd(dba)_2$ and 6 mol% tfp after transmetalation with 1 M $ZnCl_2$ (1.2 equiv).

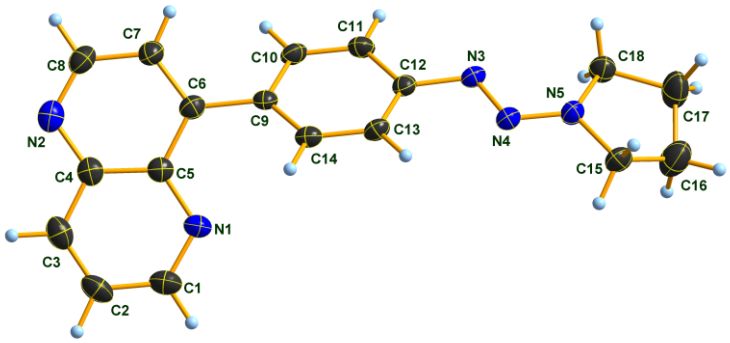
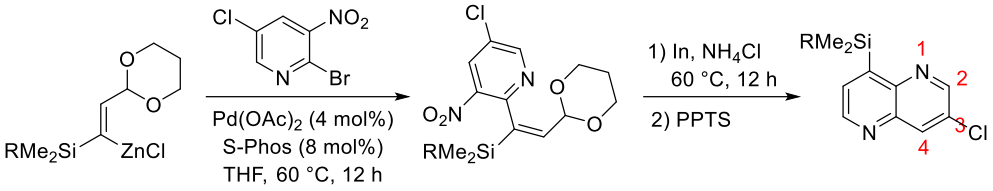


Figure 14: Molecular structure of 1,5-naphthyridine **42j** in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50 % probability level.

Thus, we could easily prepare a range of new 4-functionalized 1,5-naphthyridines. However, the pre-addition of $BF_3 \cdot OEt_2$ before the addition of $TMP_2Mg \cdot 2LiCl$ (**4**) did not influence the metalation rate or lead to a change in regioselectivity, since decomposition of **39** occurs. Simultaneously, a new method for the preparation of 1,5-naphthyridines has been developed in our group (Scheme 47 and Figure 15).



43a: R = Me
43b: R = *t*Bu

44a: R = Me: 63%
44b: R = *t*Bu: 69%

45a: R = Me: 60%
45b: R = *t*Bu: 62%

Scheme 47: Preparation of novel 3-chloro-1,5-naphthyridines **45a-b** by intramolecular imine formation.

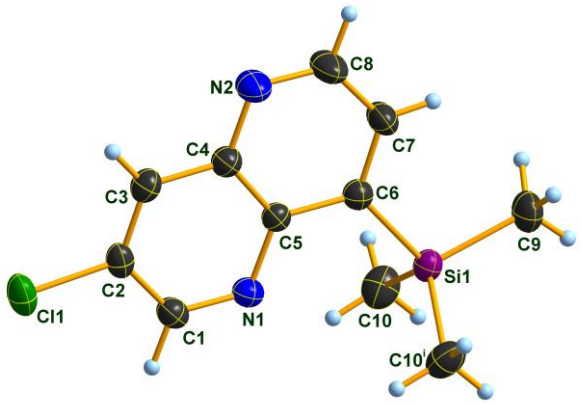
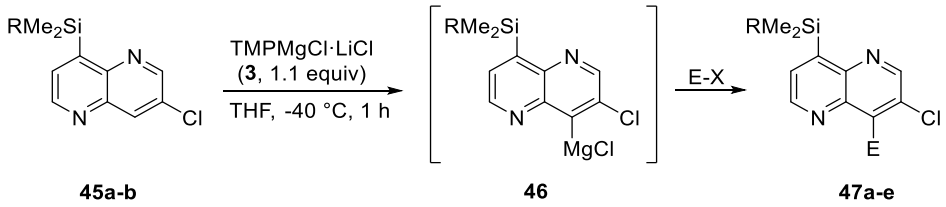


Figure 15: Crystal structure of **45a** in DIAMOND representation; thermal ellipsoids are drawn at 50 % probability level.

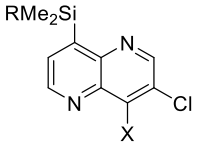
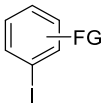
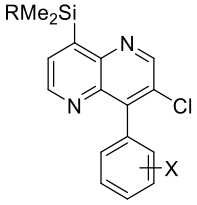
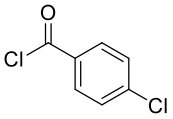
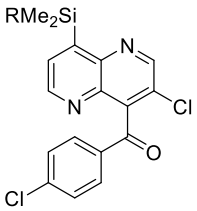
Therefore, the TBS/TMS-protected alkenyl zinc reagents **43a-b** have been cross-coupled with 2-bromo-5-chloro-3-nitropyridine, providing the alkenylated nitroarenes **44a-b** in 63-69% yield. After indium-mediated reduction and acidic acetal cleavage, the novel 3-chloro-1,5-naphthyridines **45a-b** could be obtained in 60-62% yield.

With these new derivatives in our hand, we have been also highly encouraged to metalate **45a-b** in 4-position. It was found that **45a-b** can be easily magnesiated at -40 °C within 1 h using TMPMgCl·LiCl (**3**). Subsequent quenching with electrophiles (E-X) led to the new 4-substituted-3-chloro-naphthyridines **47a-e** (Table 4). Thus, the treatment of magnesiated **46** with iodine or $PhSSO_2Ph$ gave the corresponding 4-iodo- and 4-phenylthio-1,5-naphthyridine (**47a-b**) in 82-92% yield (Table 4, entries 1-2). *Negishi* cross-coupling of **46** with ethyl 3-iodobenzoate or 4-iodo-1,2-dimethylbenzene furnished the desired arylated 1,5-naphthyridines **47c-d** in 72-78% yield (entries 3-4). A Cu(I)-mediated acylation of **46** with 4-chlorobenzoyl chloride led to the 1,5-naphthyridine-ketone **47e** in 86% yield (entry 5).

Table 4: Metalation and functionalization of 3-chloro-1,5-naphthyridines (**45a-b**) in the C(4) position using TMPMgCl·LiCl (**3**).

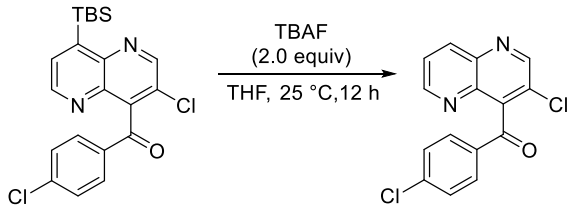


45a-b **46** **47a-e**

Entry	Electrophile	Product	Yield[a]
1 2	I_2 $PhSSO_2Ph$		**47a**: R = *t*Bu; X = I; 82% **47b**: R = Me; X = SPh; 92%
3 4			**47c**: R = Me; X = *m*-CO_2Et; 72%[b] **47d**: R = *t*Bu; X = *p*-, *m*-CH_3; 78%[b]
5			**47e**: R = *t*Bu; 86%[c]

[a] Isolated yields of analytically pure product. [b] The cross-coupling was performed with 3 mol% $Pd(dba)_2$ and 6 mol% tfp after transmetalation with 1 M $ZnCl_2$ (1.2 equiv). [c] Acylation was performed using 1 M CuCN·2LiCl (1.1 equiv).

By using a standard procedure, we further demonstrated the removal of the TBS-protecting group in **47e**, affording (3-chloro-1,5-naphthyridin-4-yl)-(4-chlorophenyl)methanone (**48**) in 82% yield (Scheme 48).

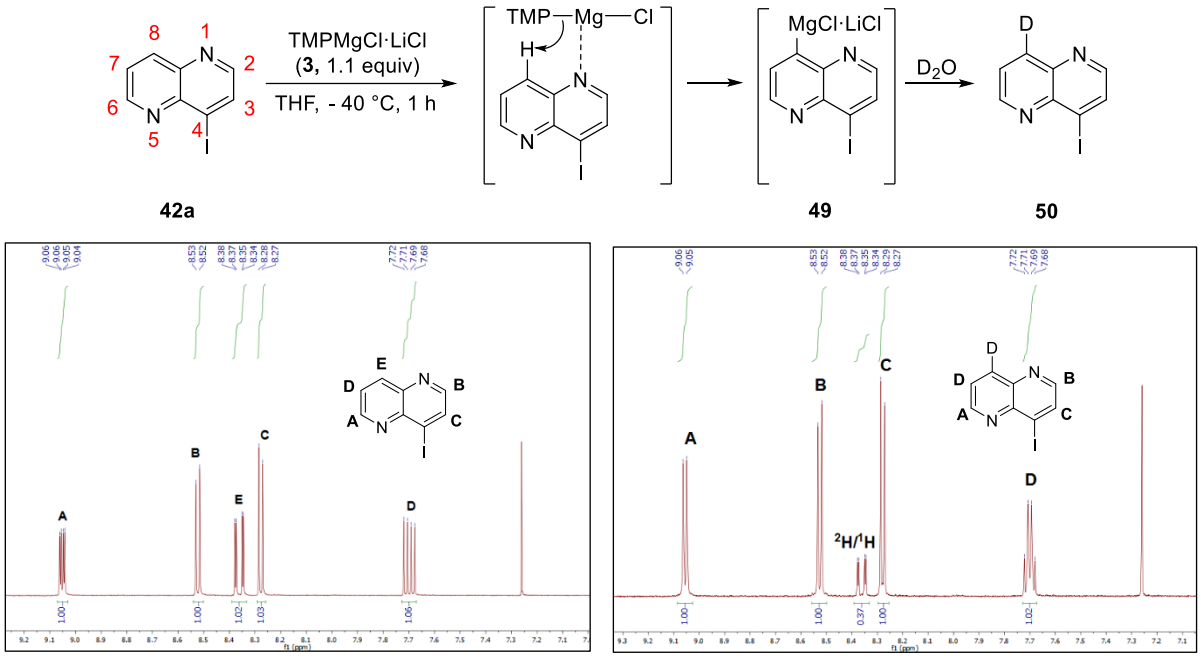


47e **48**: 82%

Scheme 48: Removal of TBS-protecting group in **47e**.

3.3 Metalation of 1,5-Naphthyridines in Position 8

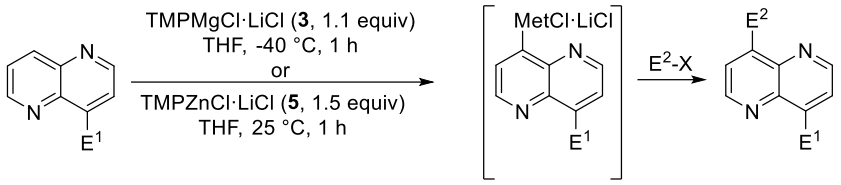
The presence of a substituent in naphthyridines **42** at position C(4) prevents further complexation of a metallic amide at N(5) and thus leads to precomplexation of the base at N(1). This favors a directed metalation at C(8). We proved this issue by the reaction of **42a** with TMPMgCl·LiCl (**3**) leading to magnesiated **49**, which, upon quenching with D_2O gave 4-iodo-1,5-naphthyridine-8-*d* (**50**). The incooperation of deuterium at C(8) can be clearly noticed in ^{1}H-NMR-spectra (Scheme 49).



Scheme 49: Metalation of 4-iodo-1,5-naphthyridine (**42a**) (top) and NMR-studies of 4-iodo-1,5-naphthyridine-8-*d* (**50**) (bottom).

We then investigated the 1,5-naphthyridines **42b-c** for the metalation with amide bases. By quenching of the corresponding metal species with several electrophiles, we could obtain some novel regioselectively defined 4,8-functionalized 1,5-naphthyridines **52a-g** (Table 5). Thus, the naphthyridine **42b** reacted with TMPMgCl·LiCl (**3**, 1.1 equiv, -40 °C, 1 h) to give the magnesiated species **51a**. Quenching of **51a** with *S*-phenyl benzenethiosulfonate gave the naphthyridine thioether **52a** in 54% yield (Table 5, entry 1). Chlorination of **51a** with 1,1,2-trichlorotrifluoroethane gave the 4,8-dihalogenated 1,5-naphthyridine **52b** in 53% yield (entry 2). Reaction of the magnesium species **51a** after transmetalation to zinc with 1-chloro-4-iodobenzene under standard *Negishi* cross-coupling conditions resulted in the arylated bromo-1,5-naphthyridine **52c** in 60% yield (entry 3). Zincation of the naphthyridine **42c** with TMPZnCl·LiCl (**5**, 1.5 equiv, 25 °C, 1 h) led to the formation of the heteroaryl zinc species **51b** which reacted with iodine to give compound **52d** in 71% yield (entry 4). Cross-coupling of **51b** with 1-iodo-4-trifluoromethylbenzene and 1-(3-iodophenyl)-2-methylpropan-1-one furnished the 4,8-functionalized 1,5-naphthyridines **52e-f** in 97-98% yield (entries 5-6). After transmetalation of the zinc species **51b** with CuCN·2LiCl, the reaction with allyl bromide provided the allylated naphthyridine **52g** in 80% yield (entry 7).

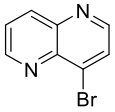
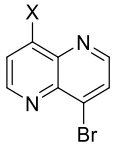
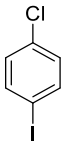
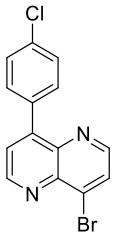
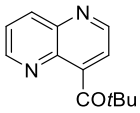
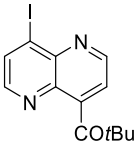
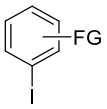
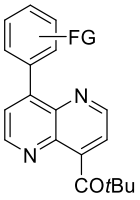
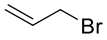
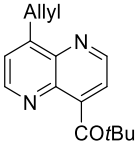
Table 5: Metalation of 4-substituted 1,5-naphthyridines in C(8)-position and quenching with electrophiles.



42b: E^1 = Br
42c: E^1 = CO*t*Bu

51a: Met = Mg
51b: Met = Zn

52

Entry	Substrate	Electrophile	Product, Yield[a]
			
1	**42b**	$PhSSO_2Ph$	**52a**: X = SPh; 54%[b]
2	**42b**	$ClCF_2CCl_2F$	**52b**: X = Cl; 53%[b]
3	**42b**		 **52c**: 60%[b][c]
4	 **42c**	I_2	 **52d**: 71%[d]
			
5	**42c**	X = *p*-CF_3	**52e**: 98%[c][d]
6	**42c**	X = CO*i*Pr	**52f**: 97%[c][d]
7	**42c**		 **52g**: 80%[d][e]

[a] Isolated yields of analytically pure product. [b] TMPMgCl·LiCl (**3**, 1.1 equiv, -40 °C, 1 h) was used. [c] The cross-coupling was performed using 3 mol% $Pd(dba)_2$ and 6 mol% tfp after transmetalation with 1 M $ZnCl_2$ (1.2 equiv). [d] TMPZnCl·LiCl (**5**, 1.5 equiv, 25 °C, 1 h) was used. [e] Allylation was performed after transmetalation with 1 M CuCN·2LiCl (1.2 equiv).

Crystal structures of compounds **52a**, **52c**, **52e** and **52g** reveal a functionalization of naphthyridines **42b** and **42c** exclusively at C(8) (Figure 16).

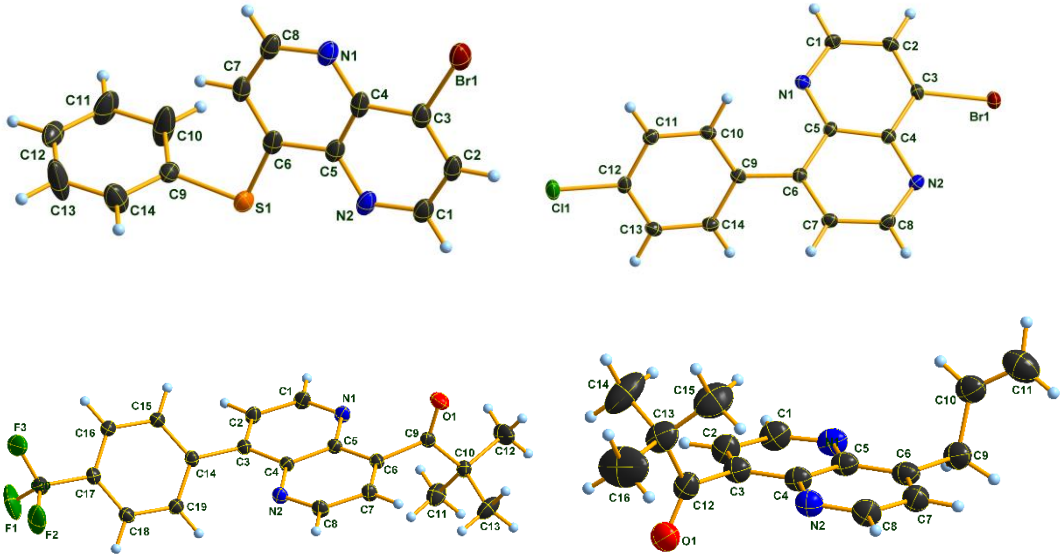
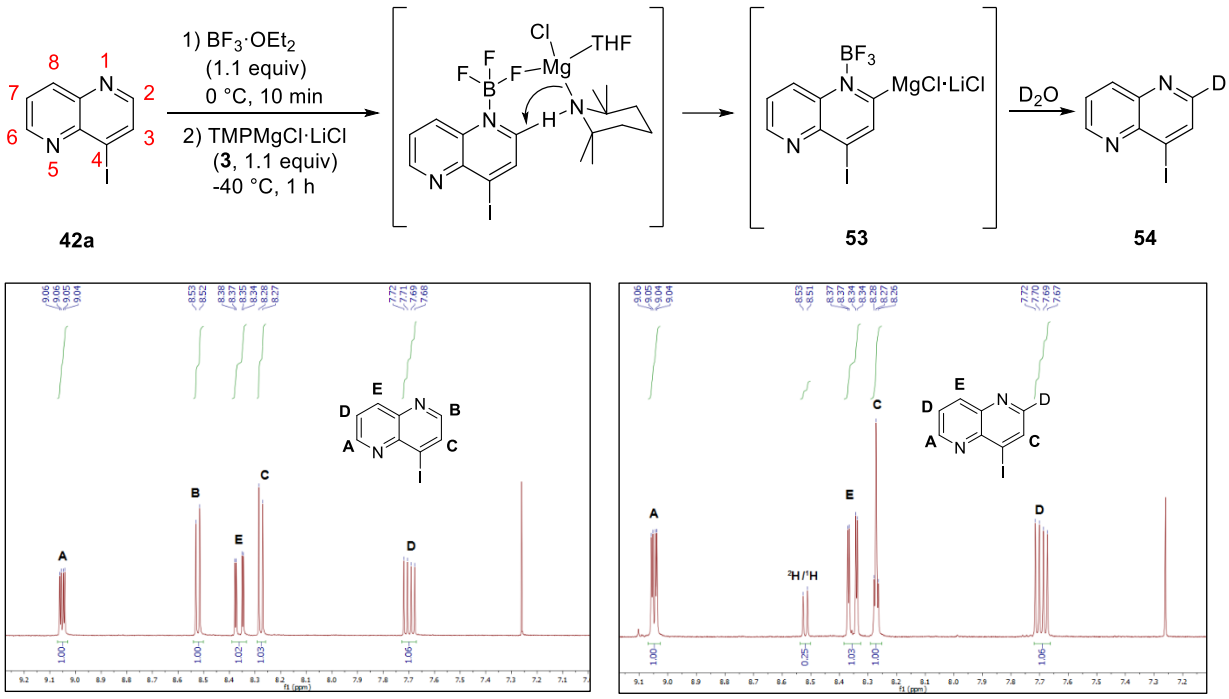


Figure 16: Molecular structure of naphthyridines **52a** (top left), **52c** (top right), **52e** (bottom left), **52g** (bottom right), in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50 % probability level.

3.4 Metalation of 1,5-Napthyridines in Position 2

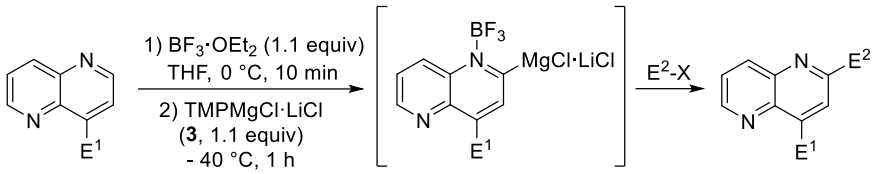
Alternatively, the naphthyridines **42** can be treated with the *Lewis* acid $BF_3 \cdot OEt_2$ which has two consequences: (1) BF_3 hampers the metalation at position C(8), since no efficient complexation of the magnesium base (**3**) at N(1) is possible; (2) the BF_3-complexation dramatically enhances the acidity at C(2). This results in a regioselective magnesiation at C(2) using TMPMgCl·LiCl (**3**). Once more, we proved this by the reaction of **42a** with $BF_3 \cdot OEt_3$ and TMPMgCl·LiCl (**3**) leading to magnesiated **53**, which, upon quenching with D_2O gave 4-iodo-1,5-naphthyridine-2-*d* (**54**). The incooperation of deuterium at C(2) can be clearly noticed in ^{1}H-NMR-spectra (Scheme 50).



Scheme 50: Metalation of 4-iodo-1,5-naphthyridine (**42a**) (top) and NMR-studies of 4-iodo-1,5-naphthyridine-2-*d* (**54**) (bottom).

We then investigated the 1,5-naphthyridines **42a** and **42g** for the *Lewis*-acid directed metalation with TMPMgCl·LiCl (**3**). By quenching of the corresponding metal species **53** and **55** with electrophiles we could obtain some novel regioselectively defined 2,4-functionalized 1,5-naphthyridines **56a-e** (Table 6). Thus, quenching of **53** with iodine or 1,2-dibromotetrachloroethane furnished the 2,4-bishalogenated 1,5-naphthyridines **56a-b** in 72-74% yield (Table 6, entries 1-2). A copper(I)-mediated acylation of **53** with benzoyl chloride provided the 4-iodo-2-benzoyl-1,5-naphthyridine **56c** in 53% yield (entry 3). Using this reaction protocol, we also achieved a copper(I)-mediated acylation of **55** with thiophene-2-carbonyl chloride affording the desired heteroaryl compound **56d** in 70% yield (entry 4). Finally, a standard *Negishi* cross-coupling of **55** with 4-iodotoluene gave the 2,4-bisarylated 1,5-naphthyridine **56e** in 56% yield (entry 5, Figure 17).

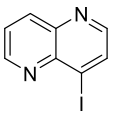
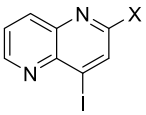
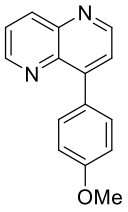
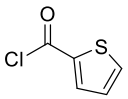
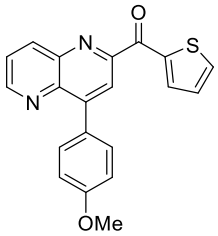
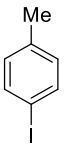
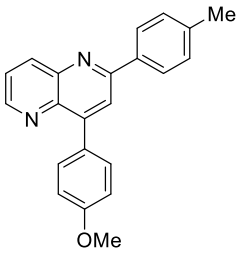
Table 6: Metalation of 4-substituted 1,5-naphthyridines in C(2)-position and quenching with electrophiles.



42a: E^1 = I
42g: E^1 = *p*-$OMeC_6H_4$

53: E^1 = I
55: E^1 = *p*-$OMeC_6H_4$

56

Entry	Substrate	Electrophile	Product, Yield[a]
			
1	**42a**	I_2	**56a**: X = I; 74%
2	**42a**	$(BrCCl_2)_2$	**56b**: X = Br; 72%
3	**42a**	PhCOCl	**56c**: X = PhCO; 53%[b]
4			
	42g		**56d**: 70%[b]
5	**42g**		
			56e: 56%[c]

[a] Isolated yields of analytically pure product. [b] Acylation was performed with 1 M CuCN·2LiCl (1.2 equiv). [c] The cross-coupling was performed with 3 mol% $Pd(dba)_2$ and 6 mol% tfp after transmetalation with 1 M $ZnCl_2$ (1.2 equiv).

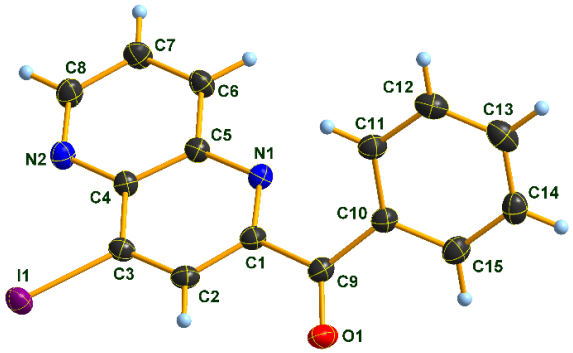


Figure 17. Molecular structure of compound **56c** in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50 % probability level.

4. Alternative Metal-Catalyzed Cross-Couplings of Naphthyridines

4.1 Introduction

N-heterocyclic scaffolds are ubiquitous building blocks for pharmaceuticals, agrochemicals and material science. There is a need for new *N*-heterocyclic structures since such ring systems may display novel useful biological or physical properties. The functionalization of naphthyridines was found to be especially difficult and no general methods are available.

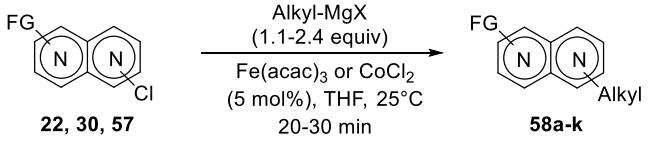
In the last chapters, we could already demonstrate the regioselective metalation of 2,7- and 1,5-naphthyridines by using the sterically hindered TMP-amide bases **2**, **3**, **5**, **6**. However, standard Pd-catalyzed *Kumada* or *Negishi* cross-couplings with halogenated nahthyridines turned out to be quite challenging.

In chapter A 2.5 we shortly described methods from us and other groups for the functionalization of *N*-heterocycles like pyridines or quinolines using the alternative metals iron and cobalt. In the following, we will describe the functionalization of several halogenated naphthyridines using such methods.

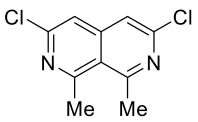
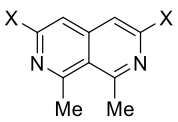
4.2 Iron- and Cobalt-Catalyzed C(sp^2)-C(sp^3) Cross-Couplings

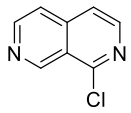
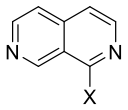
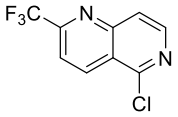
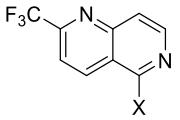
We screened several of our naphthyridines and found that the chloro-naphthyridines **22**, **30** and **57** are suitable substrates for iron- and cobalt-catalyzed C(sp^2)-C(sp^3) cross-couplings (Table 7). In preliminary experiments, we treated the 3,6-dichloro-1,8-dimethyl-2,7 naphthyridine (**22**) with various alkyl-magnesium reagents using 5 mol% $Fe(acac)_3$ according to a procedure from *Malhotra*.[77]

Table 7: Iron- and cobalt-catalyzed cross-couplings of chloro-naphthyridines.



FG = H, Me, CF_3; X = Cl, Br

Entry	Naphthyridine	Magnesium Reagent	Product, Yield[a]
			
1	**22**	EtMgCl	**58a**: X = Et; 69%[b]
2	**22**	*i*PrMgCl·LiCl (**2**)	**58b**: X = *i*Pr; 41%[c]
3	**22**	*c*HexMgBr·LiCl	**58c**: X = *c*Hex; 78%[c]
4	**22**	*c*PropMgBr·LiCl	**58d**: X = H, *c*Prop; 62%[c]
5	**22**	$Ph(CH_2)_2MgBr·LiCl$	**58e**: X = $(CH_2)_2Ph$; 83%[c]
6	**22**	$Ph(CH_2)_2MgBr·LiCl$	**58f**: X = H, $(CH_2)_2Ph$; 80%[d]

			
7	**30**	$Ph(CH_2)_2MgBr \cdot LiCl$	**58g**: X = $(CH_2)_2Ph$; 82%[d]
8	**30**	MeMgCl	**58h**: X = Me; 98%[d]
9	**30**	*s*BuMgCl	**58i**: X = *s*Bu; 54%[d]
			
10	**57**	BuMgCl	**58j**: X = Bu; 69%[d]
11	**57**	*c*PropMgBr·LiCl	**58k**: X = *c*Prop; 52%[d]

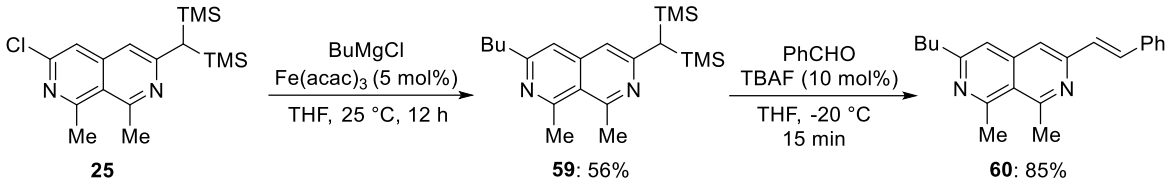
[a] Isolated yield of analytically pure product. [b] 5 mol% $Fe(acac)_3$ was used; 2 h reaction time. [c] 5 mol% $Fe(acac)_3$ was used; 30 min reaction time. [d] 5 mol% $CoCl_2$ was used; 20 min reaction time.

Thus, the reaction of **22** with EtMgCl (2.4 equiv) in the presence of 5 mol% $Fe(acac)_3$ in THF furnished the 3,6-diethyl-2,7-naphthyridine (**58a**) in 69% yield (Table 7, entry 1). *i*PrMgCl·LiCl (2.4 equiv) reacted smoothly with **22** providing the bis-alklylated naphythyridine **58b** in 41% yield (entry 2). Treating the dimethylnaphthyridine (**22**) with *c*HexMgBr·LiCl (2.4 equiv) gave the corresponding naphthyridine **58c** in 78% yield (entry 3). The use of cyclopropylmagnesium bromide (2.4 equiv) allows to perform a mono-alkylation whereupon the 3-chloro-6-cyclopropyl-2,7-naphthyridine (**58d**) was isolated in 62% yield (entry 4). The reaction of 2-phenylethylmagnesium bromide (2.4 equiv) with **22** gave the expected bis-alkylated naphthyridine (**58e**) in 83% yield (entry 5).

Similarly, reacting 2-phenylethylmagnesium bromide (1.1 equiv) with **22** using 5 mol% $CoCl_2$ provided the mono-alkylated naphthyridine (**58f**) in 80% yield (entry 6). Also, the chloro-naphthyridines **30** and **57** can be easily alkylated using 5 mol% $CoCl_2$. Thus, also 2-phenylethyl-magnesium bromide (1.1 equiv) reacted smoothly with **30**, providing the 1-alkylated-2,7-naphthyridine (**58g**) in 82% yield (entry 7). The treatment of **30** with MeMgCl gave the corresponding 1-methyl-2,7-naphthyridine (**58h**) in 98% yield (entry 8). Furthermore, sterically hindered *s*BuMgCl reacted with **30** to afford 1-(*s*butyl)-2,7-naphthyridine (**58i**) in 54% yield (entry 9). The cobalt-catalyzed alkylation of 5-chloro-2-(trifluoro-methyl)-1,6-naphthyridine (**57**) with BuMgCl provided the desired 5-butyl-2-(trifluoromethyl)-1,6-naphthyridine (**58j**) in 69% yield (entry 10). Additionally, the reaction of the chloro-1,6-naphthyridine (**57**) with cyclopropylmagnesium bromide afforded 5-cyclopropyl-2-(tri-fluoromethyl)-1,6-naph-thyridine (**58k**) in 52% yield (entry 6).

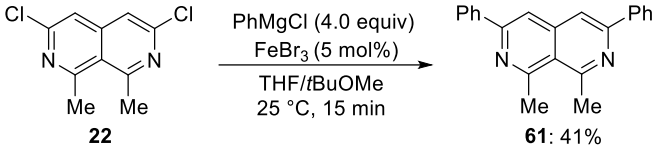
Also, we further functionalized the bis-trimethylsilylmethyl-2,7-naphthyridine (**25**) *via* iron-catalyzed cross-coupling with *n*BuMgCl (1.1 equiv) providing the unsymmetrically, *bis*-alkylated naphthyridine **59** in 56% yield. Subsequent *Peterson*-olefination[146] of **59** with benzaldehyde (1.2 equiv) in the presence of 10 mol% TBAF gave the expected styryl-derivative **60** in 85% yield (Scheme 51).

[146] L. F. Van Staden, D. Gravestock, D. J. Ager, *Chem. Soc. Rev.* **2002**, *31*, 195.



Scheme 51: Iron-catalyzed alkylation of **25**, followed by *Peterson*-olefination.

Next, we targeted C(sp^2)-C(sp^2) couplings of the 3,6-dichloro-1,8-dimethyl-2,7 naphthyridine (**22**). By using a method from our group,[84] we treated **22** with PhMgCl (4.0 equiv, THF/*t*-BuOMe, 25 °C, 15 min) in the presence of 5 mol% $FeBr_3$ (Scheme 52).

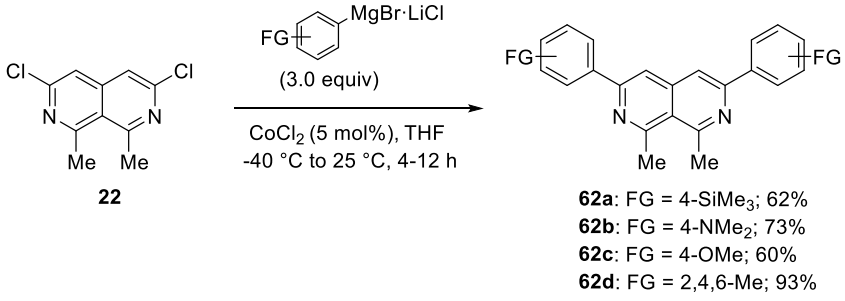


Scheme 52: Iron-catalyzed cross-coupling of **22** with PhMgCl.

However, the 3,6-phenylated-2,7-naphthyridine (**61**) could be obtained in only 41% yield. Interestingly, the addition of isoquinoline as ligand led to strong precipitation, preventing a clean reaction. Also, it remains unclear if the 2,7-naphthyridines act as ligands themselves in such reactions.

4.3 Cobalt-Catalyzed C(sp^2)-C(sp^2) Cross-Couplings

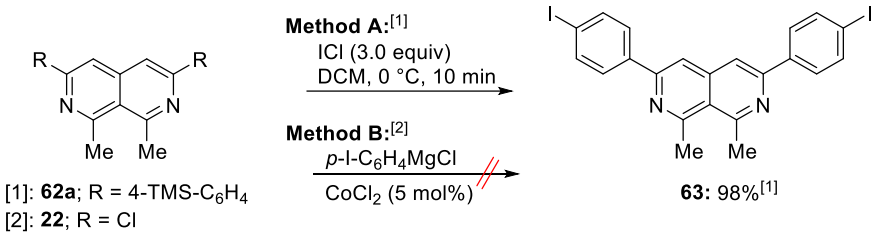
For the reaction of the 3,6-dichloro-1,8-dimethyl-2,7 naphthyridine (**22**) with aryl *Grignard* reagents, we found a difference in reactivity by using $CoCl_2$ instead of $FeBr_3$. Thus, compound **22** can be easily bis-arylated using 5 mol% $CoCl_2$, providing the novel naphthyridines **62a-d** in good yield (Scheme 53).



Scheme 53: Cobalt-catalyzed bis-arylation of naphthyridine **22** with various arylmagnesium reagents.

The reaction of **22** with 4-(trimethylsilyl)phenylmagnesium bromide provided at -40 °C within 4 h the bis(trimethylsilyl)phenylnaphthyridine (**62a**) in 62% yield. Similarly, 4-*N,N*-dimethylamino-phenylmagnesium bromide and 4-methoxyphenylmagnesium bromide underwent such smooth cobalt-catalyzed cross-couplings (-40 °C, 4-12 h) with the dichloronaphthyridine **22** leading to the desired 3,6-substituted naphthyridines (**62b-c**) in 60-73% yield. However, the sterically hindered mesitylmagnesium bromide reacted with the 3,6-dichloro-naphthyridine **22** only at 25 °C within 4 h, furnishing the desired

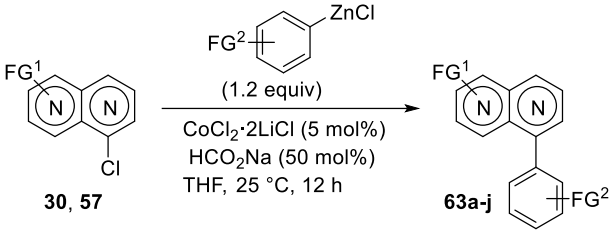
2,6-mesityl-1,8-naphthyridine (**62d**) in 93% yield. By the treatment of compound **62a** with iodine monochloride, we could obtain the corresponding bis-iodophenyl-2,7-naphthyridine **63** in quantitative yield, which is not accessible by cobalt-catalyzed cross-coupling of **22** with 4-iodophenylmagnesium chloride[147] (Scheme 54).

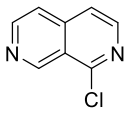
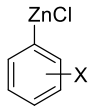
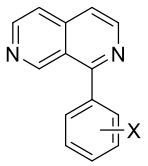


Scheme 54: Conversion of **62a** into bis-iodophenyl-2,7-naphthyridine **63**.

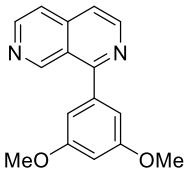
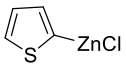
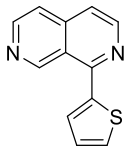
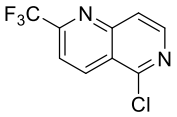
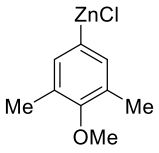
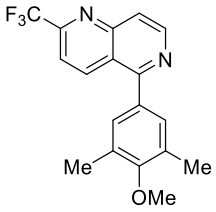
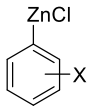
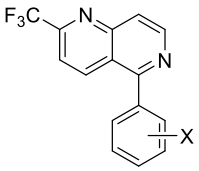
During the course of our investigations, we noticed that $C(sp^2)$-$C(sp^2)$ cross-couplings of naphthyridines **30** and **57** with PhMgCl using 5 mol% $CoCl_2$ led to diminished yields (< 30%). This problem could be solved by replacing the arylmagnesium reagents with the corresponding zinc reagents and using HCO_2Na as ligand.[92] Thus, 1-chloro-2,7-naphthyridine (**30**) reacted smoothly with PhMgCl or [1,1'-biphenyl]-4-ylzinc chloride within 12 h at 25 °C, furnishing the corresponding arylated naphthyridines **63a-b** in 80-82% yield (Table 8, entry 1-2).

Table 8: Cobalt-catalyzed arylations of arylzinc reagents with chloro-naphthyridines **30** and **57**.



Entry	Naphthyridine	Zinc Reagent	Product, Yield[a]
			
1	**30**	X = H	**63a**: 80%
2	**30**	X = *p*-Ph	**63b**: 82%[b]
3	**30**	X = *p*-CF_3	**63c**: 69%
4	**30**	X = *p*-OTBS	**63d**: 72%[b]
5	**30**	X = *p*-CN, *m*-F	**63e**: 74%

[147] F. Kopp, I. Sapountzis, P. Knochel, *Synlett* **2003**, *6*, 885.

6	**30**		 **63f**: 79%
7	**30**		 **63g**: 60%
8	 **57**		 **63h**: 74%
			
9	**57**	X = *p*-OBn	**63i**: 83%
10	**57**	X = *p*-OTIPS	**63j**: 61%

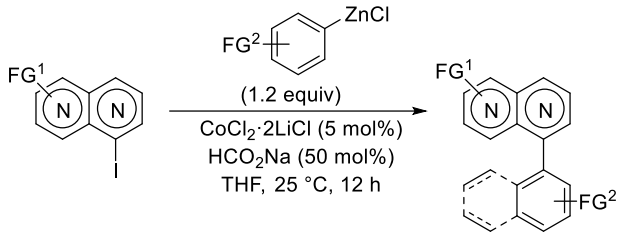
[a] Isolated yield of analytically pure product. [b] Reaction was performed by D. Ziegler

Furthermore, a range of arylzinc reagents bearing various functional groups underwent such cobalt-catalyzed *Negishi* cross-couplings with chloro-naphthyridine **30**, providing the expected products **63c-f** in 69-79% yield (entries 3-6). Heteroaryl-heteroaryl cross-couplings are utmost challenging due to catalyst deactivation when Pd or Ni is used.[148] However, in the presence of THF-soluble $CoCl_2 \cdot 2LiCl$ (5 mol%) and sodium formate (50 mol%), the cross-coupling of 1-chloronaphthyridine (**30**) with thiophen-2-ylzinc chloride afforded the thiophenyl-naphthyridine **63g** in 60% yield (entry 7). We further demonstrate, that 5-chloro-2-(trifluoromethyl)-1,6-naphthyridine (**57**) can also be easily arylated under these conditions. Thus, the cobalt-catalyzed reaction of **57** with 4-methoxy-3,5-dimethylphenylzinc chloride and 4-(benzyloxy)phenylzinc chloride provided the new 1,6-naph-thyridines **63h-i** in 74-83% yield (entries 8-9). Interestingly, the cobalt-catalyzed arylation of **57** with 2-((triisopropylsilyl)oxy)-phenylzinc chloride only succeeded at elevated temperature (60 °C, 12 h) to give the desired protected naphthyridine alcohol **63j** in 61% yield (entry 10).

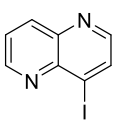
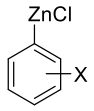
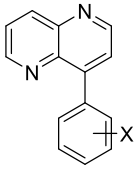
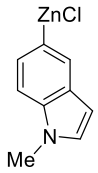
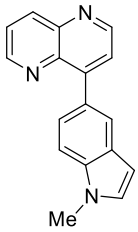
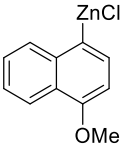
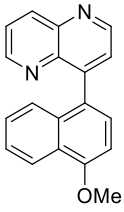
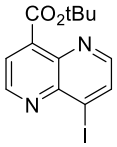
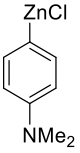
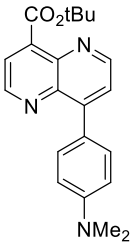
[148] (a) C. Kaes, A. Katz, M. W. Hosseini, *Chem. Rev.* **2000**, *100*, 3533. (b) S. Bedel, G. Ulrich, C. Picard, P. Tisnès, *Synthesis* **2002**, 1564. (c) *Comprehensive Coordination Chemistry II*, Vol 1; J. A. McCleverty, T. J. Meyer, Eds.; Elsevier, Oxford, **2004**, 1. (d) M. A. Düfert, K. L. Billingsley, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 12877.

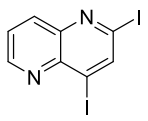
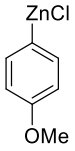
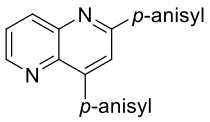
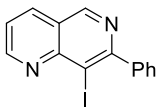
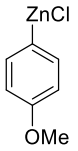
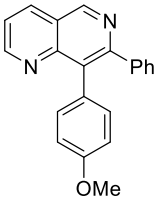
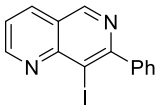
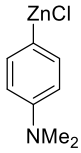
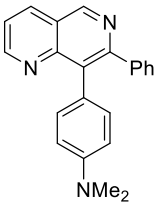
Since we observed that iodo-substituted naphthyridines prone to undergo I/Mg-exchange with aryl *Grignards*, we also employed our mild cobalt-catalyzed *Negishi* cross-coupling method for the reaction of iodonaphthyridines with arylzinc reagents (Table 9).

Table 9: Cobalt-catalyzed arylations of arylzinc reagents with iodo-naphthyridines **42a**, **52d**, **56a** and **65**.



42a, 52d, **56a**, **65** — FG_1 = H, CO*t*Bu, I, Ph; FG_2 = OMe, SMe, NMe_2, CN — **64a-i**

Entry	Naphthyridine	Zinc Reagent	Product, Yield[a]
			
1	**42a**	X = *m*-SMe	**64a**: 80%
2	**42a**	X = *p*-OMe	**64b**: 78%
3	**42a**	X = *p*-CN	**64c**: 83%
4	**42a**		 **64d**: 73%
5	**42a**		 **64e**: 47%
6	 **52d**		 **64f**: 86%

7	 **56a**		 **64g**: 75%
8	 **65**		 **64h:** 48%[b]
9	 **65**		 **64i**: 65%[b]

[a] Isolated yield of analytically pure product. [b] 3.0 equiv of the zinc reagent was necessary for a complete conversion.

Thus, the coupling of 3-(methylthio)phenylzinc chloride and 4-methoxyphenyl)zinc chloride with 4-iodo-1,5-naphthyridine (**42a**) afforded the naphthyridines **64a-b** in 78-80% yield (Table 9, entries 1-2). Similarly, the reaction of the electron-deficient arylzinc reagent *p*-NCC_6H_4ZnCl with iodo-naphthyridine **42a** led to the desired product **64c** in 83% yield (entry 3). Furthermore, (1-methyl-1*H*-indol-5-yl)zinc chloride reacted smoothly with **42a** to afford the naphthyridine-indol derivative **64d** in 73% yield (entry 4).

Remarkably, also the sterically demanding (4-methoxynaphthalen-1-yl)zinc chloride could be converted with 4-iodo-1,5-naphthyridine (**42a**) to give the new 1,5-naphthyridine **64e** in 47% yield (entry 5). This mild method also allows the coupling of sensitive iodo-naphthyridines. Thus, the coupling of the aryl zinc reagent *p*-$Me_2NC_6H_4ZnCl$ with 4-iodo-8-keto-naphthyridine (**52d**) provided the corresponding 4,8-functionalized 1,5-naphthyridine **64f** in 86% yield (entry 6). Similar to the bis-arylation of dichloro-naphthyridine **22** (Scheme 53), we also examined the cobalt-catalyzed reaction of 2,4-diiodo-1,5-naphthyridine (**56a**) with *p*-$MeOC_6H_4ZnCl$ and could afford the corresponding bis-anisyl-naphthyridine (**64g**) in 75% yield (entry 7). Finally, we could do a cobalt-catalyzed cross-coupling of the sterically hindered 8-iodo-7-phenyl-1,6-naphthyridine (**65**)[149] with *p*-$MeOC_6H_4ZnCl$ and *p*-Me_2N-C_6H_4ZnCl to give the 7,8-bisarylated-1,6-naphthyridines **64h-i** in 48-65% yield (entry 8-9, Figure 18).

[149] Q. Huang , J. A. Hunter, R. C. Larock, *Org. Lett.* 2001, *3*, 2973.

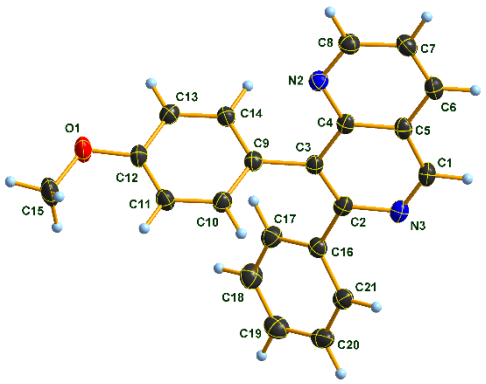
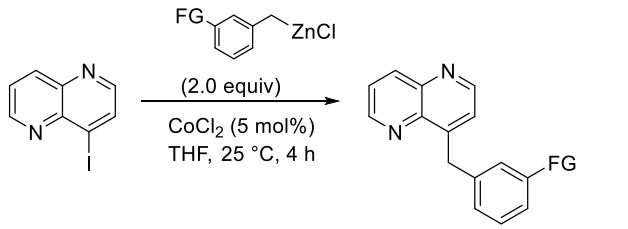


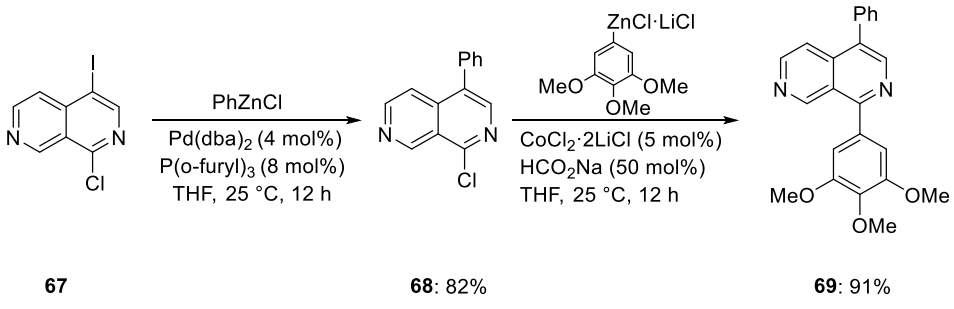
Figure 17: Molecular structure of naphthyridine **64h** in the crystal, DIAMOND representation; thermal ellipsoids are drawn at 50 % probability level.

Additionally, we have examined benzylic cross-couplings of our naphthyridine substrates using $CoCl_2$ and found that 4-iodo-1,5-naphthyridine (**42a**) reacts smoothly with benzylic zinc reagents. Thus, the coupling of **42a** with 3-(ethoxycarbonyl)benzylzinc chloride or 3-fluorobenzylzinc chloride provided the benzylic naphthyridines **66a** in 62% yield and **66b** in 75% yield, respectively (Scheme 54).



Scheme 54: Cobalt-catalyzed cross-coupling of 4-iodo-1,5-naphthyridine (**42a**) with benzylic zinc reagents.

In terms of differentially halogenated naphthyridines, we found that 1-chloro-4-iodo-2,7-naphthyridine (**67**) can be regioselectively functionalized by successive cross-coupling using Pd- and Co-catalysis (Scheme 55).



Scheme 55: Regioselective Pd- and Co-catalyzed cross-coupling of 1-chloro-4-iodo-2,7-naphthyridine **67**.

Thus, a standard Pd-catalyzed *Negishi* cross-coupling of **67** with PhZnCl selectively furnished the 1-chloro-4-phenyl-2,7-naphthyridine (**68**) in 82% yield. Subsequent Co-catalyzed *Negishi* cross-coupling with (3,4,5-trimethoxyphenyl)zinc chloride gave the desired bis-arylated naphthyridine **69** in 91% yield.

4.4 Fluorescent Naphthyridines

Naphthyridine derivatives have previously been applied as fluorescent probes[105c,125,150] or as ligands for fluorescent complexes.[103a,105a,151] The newly prepared naphthyridines **62b** and **64i** are highly fluorescent in various organic solvents and display strong solvatochromism (Figure 19).

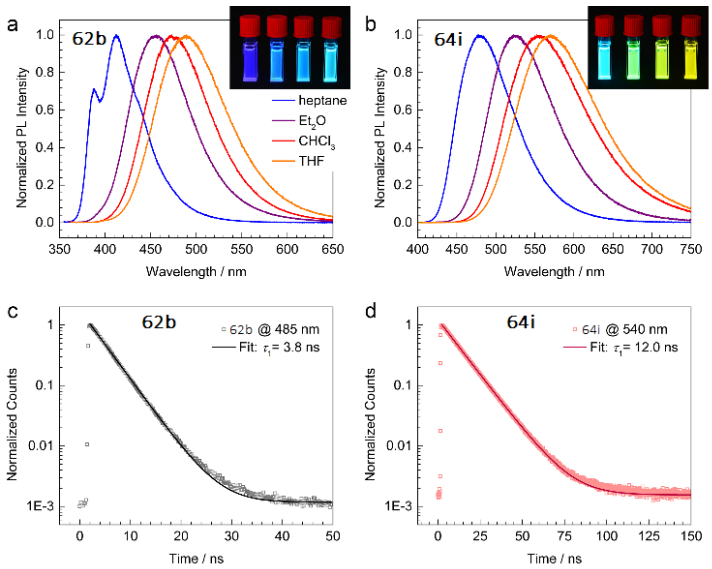


Figure 19: (a,b) PL spectra of compounds **62b** and **64i**, respectively, dissolved in heptane (blue), Et_2O (purple), $CHCl_3$ (red), and THF (orange). The excitation wavelengths are 360 and 390 nm, respectively. Insets, photographs of the solutions under UV illumination. (c,d) Time-correlated single-photon counting (TCSPC) traces of **62b** and **64i** in $CHCl_3$, measured at the peaks of the PL spectra (hollow symbols). Solid lines represent a mono-exponential fit.

While the absolute photoluminescence quantum efficiencies (PLQEs) of **62b** in various solvents are about 20%, the PLQE of **64i** is almost quantitative in non-polar solvents (toluene: 95±5%, cyclohexane: 93±5%) and drops only slightly in more polar solvents ($CHCl_3$: 81±5%, 1,4-dioxane: 80±5%, THF: 71±5%). These high emission efficiencies are accompanied by very long excited lifetimes of 3.8 ns and 12.0 ns for **62b** and **64i**, respectively (Figure 19). Compounds **62b** and **64i** also reveal considerable Stokes shifts, particularly in polar solvents like THF (Figure 20).

[150] (a) Y.-Y. Sun, J.-H. Liao, J.-M. Fang, P.-T. Chou, C.-H. Shen, C.-W. Hsu, L.-C. Chen, *Org. Lett.* **2006**, *8*, 3713. (b) L. Xiao, X. Xing, Z. Chen, B. Qu, H. Lan, Q. Gong, J. Kido, *Adv. Funct. Mater.* **2013**, *23*, 1323.
[151] (a) J.-H. Liao, C.-T. Chen, H.-C. Chou, C.-C. Cheng, P.-T. Chou, J.-M. Fang, Z. Slanina, T. J. Chow, *Org. Lett.* **2002**, *4*, 3107. (b) H.-J. Li, W.-F. Fu, L. Li, X. Gan, W.-H. Mu, W.-Q. Chen, X.-M. Duan, H.-B. Song, *Org. Lett.* **2010**, *12*, 2924. (c) Krämer, C.; Leingang, S.; Hübner, O.; Kaifer, E.; Wadepohl, H.; Himmel, H.-J. *Dalton Trans.* **2016**, *45*, 16966.

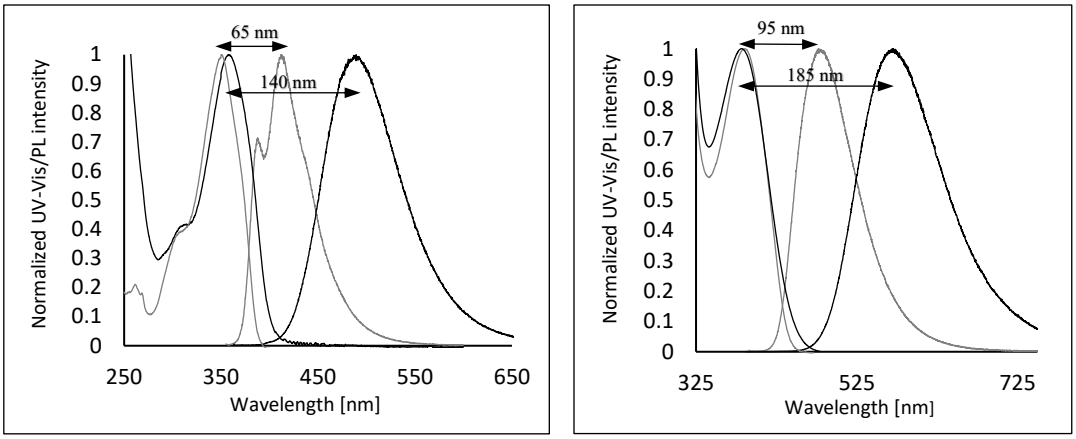


Figure 20: Normalized UV-Vis and PL spectra of **62b** and **64i** in heptane (grey) and THF (black) with corresponding Stokes shifts.

5. Fluorescent Aryl Naphthalene Dicarboximides with Large Stokes Shifts and Strong Solvatochromism Controlled by Dynamics and Molecular Geometry

5.1 Introduction

Rigid aromatic systems are preferred as basic structures for the development of highly fluorescent materials.[152] Small Stokes shifts are generally observed for such fluorophores because the electronic excitation does not induce significant geometric alterations and the conditions are similar in the electronic transitions both for absorption and fluorescence, respectively. Fluorophores with rotational freedom mostly reveal large Stokes shifts, but intramolecular dynamic processes usually prevent high fluorescence quantum yields. However, by specifically designing new fluorescent structures with limited freedom of intramolecular motions, highly fluorescent molecules with large Stokes shifts can be created.

In this context *Langhals* and co-workers investigated *C-C* coupled perylene dichromophores and oligothiophenes regarding conformational changes upon excitation with light[153] (Figure 21). For the S_0 ground state, they estimated that steric effects will force the perylene dichromophores to be nearly orthogonal, whereas the oligothiophenes are slightly twisted with dihedral angels between 3°-9°. Light absorption leads to a fast, vertical electronic transition to the S_1 state, preserving the initial geometry.

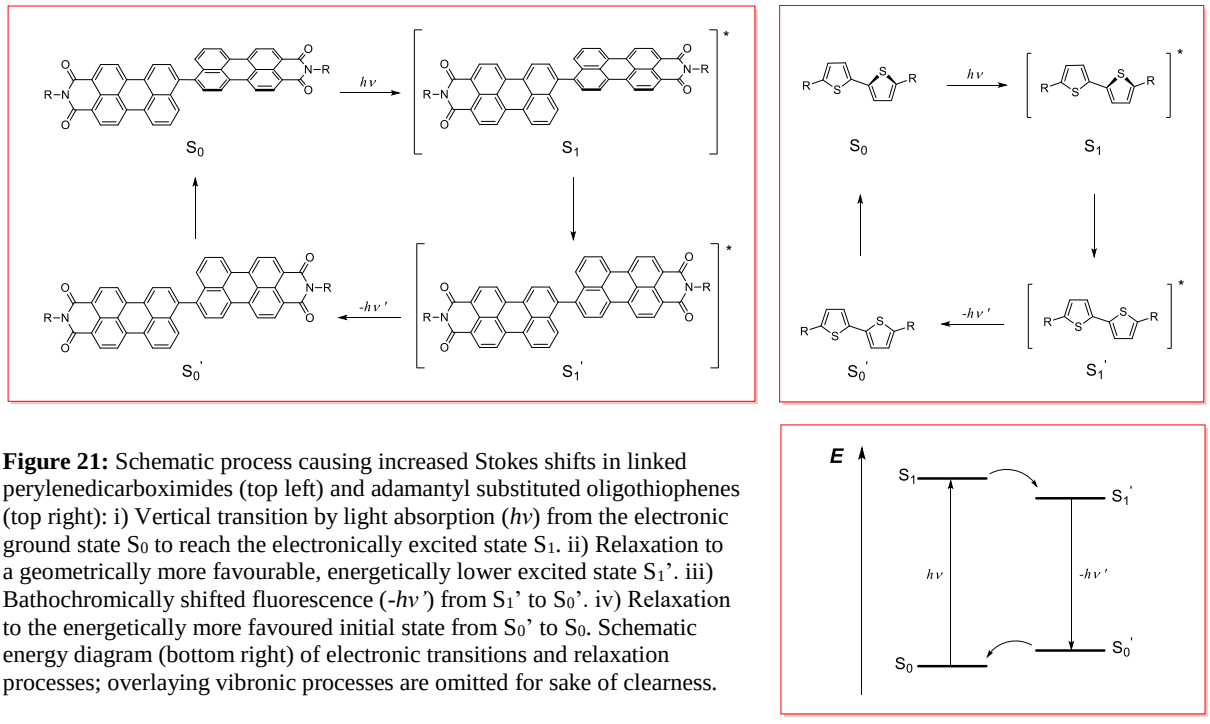


Figure 21: Schematic process causing increased Stokes shifts in linked perylenedicarboximides (top left) and adamantyl substituted oligothiophenes (top right): i) Vertical transition by light absorption (*hν*) from the electronic ground state S_0 to reach the electronically excited state S_1. ii) Relaxation to a geometrically more favourable, energetically lower excited state S_1'. iii) Bathochromically shifted fluorescence (*-hν'*) from S_1' to S_0'. iv) Relaxation to the energetically more favoured initial state from S_0' to S_0. Schematic energy diagram (bottom right) of electronic transitions and relaxation processes; overlaying vibronic processes are omitted for sake of clearness.

[152] (a) H. Zollinger, *Color Chemistry. Syntheses, Properties and Applications of Organic Dyes and Pigments*, 2nd ed.; Weinheim, **1991**; ISBN 3-527-28352-8. (b) O. S. Wolfbeis, *Fluorescence Spectroscopy, Methods and Applications;* Springer Verlag: Berlin, **1993**; ISBN 978-3-642-77372-3.

[153] (a) H. Langhals, A. Hofer, *J. Org. Chem.* **2012**, *77*, 9585. (b) T. Schlücker, V. Dhayalan, H. Langhals, C. Sämann, P. Knochel, *Asian J. Org. Chem.* **2015,** *4*, 763.

The subsequent relaxation to the S_1' state is fast enough to not affect the electronic excitation, but leads to a more planar conformation as a result of stronger conjugation between the single units (assigned by DFT calculations). Bathochromically shifted fluorescence proceeds as a vertical electronic transition to the electronic ground state S_0' where a further relaxation closes the circle to the initial state S_0.

A relatively new fluorescence phenomenon, namely Twisted Intramolecluar Charge Transfer (TICT),[154] is observed in molecules that consist of a donor D and an acceptor A linked by a single bond. In polar environments, such fluorophores undergo fast intramolecular electron transfer from the donor to the acceptor part of the molecule. This electron transfer is accompanied by intramolecular D–A twisting around the single bond and produces a relaxed perpendicular structure (Figure 22). This is a result of a one electron-excitation from the HOMO to the LUMO. The resulting singlet diradical having one unpaired electron in the HOMO and one electron in the LUMO stabilizes itself by rotation around the single bond (minimization of *Coulomb* interaction). The geometric relaxation results in large Stokes shifts of the TICT fluorescence. Since TICT represents a state with strong polarization, the most characteristic feature of TICT fluorescence is the solvatochromism, i. e., the fluorescence wavelength is sensitive to the polarity of the environment.

The equilibration between a relaxed perpendicular conformer and a coplanar conformer often results in dual fluorescence, i.e., from a high energy band through relaxation of the locally excited (LE) state and from a lower energy band due to emission from the TICT state (Figure 22). For the design of novel functional materials, the relaxation pathways can be modulated by substituents, local polarity and steric restrictions.

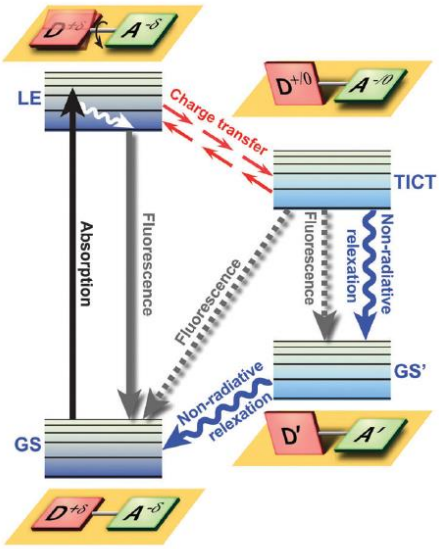


Figure 22: Twisted Intramolecular Charge Transfer (TICT): Upon excitation from the ground state (GS), the locally excited state (LE) equilibrates rapidly with the TICT state after fast charge transfer. Fluorescence from LE is strong with small Stokes shift whereas fluorescence from TICT is weak due to non-radiative relaxations, but accompanied with enhanced Stokes shift.

[154] S. Sasaki, G. P. C. Drummen, G.-i. Konishi, *J. Mater. Chem. C* **2016**, *4*, 2731.

Relatively unexplored molecules with D-A moieties are naphthalimides with donor groups in position 4 such as 4-aminonaphthalene-1,8-dicarboximides[155] and 4-alkoxynaphthalenecarboximides.[156] Here, a photo-induced shift of electron density from the donor to the carboximide is responsible for inducing a large dipole moment. Lowering of the energy of the excited state by solvation with polar solvents causes a bathochromic shift of the fluorescence. This process corresponds to the positive solvatochromism of 4-amino-*N*-methylphthalimide applied for Zelinski's solvent polarity *S* scale.[157] An even more pronounced solvatochromism of naphthalimides should be obtained through the introduction of extended electrone rich aryl moieties.

Based on the aforementioned mechanistic aspects, we targeted the synthesis and investigation of new extended naphthalimides with aryldonor groups in position 4.

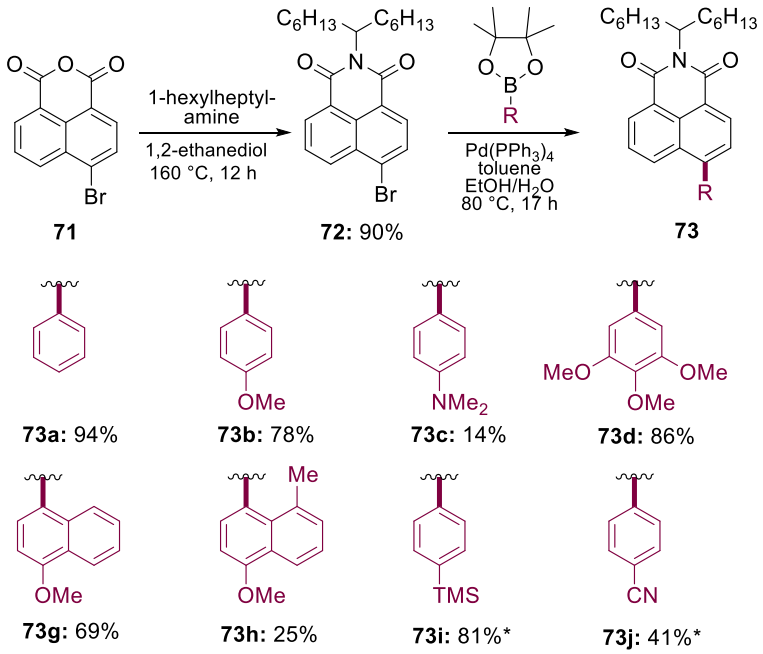
[155] (a) I. G. Farbenindustrie AG, *Brit. Patent* GB 402309 (Mar 24, 1933); *Chem. Abstr.* **1934**, *28*, 27267. (b) Gevaert Photo-Producten N. V. (inv. W. K. Koerber, F. L. Schouteden) *Ger. Patent* DE 1108560 (June 6, 1957); *Chem. Abstr.* **1962**, *56*, 32447. (c) B. M. Krasovitskii, D. G. Pereyaslova, E. G. Yushko, G. V. Tatsii, *Monokrist., Stsintill. Org. Lyuminafory* 1967, 1, 92; *Chem. Abstr.* **1968**, *69*, 60030.

[156] (a) W. Bradley, F. W. Pexton, *J. Chem. Soc.* **1954**, 4432. (b) I. Grabtchev, Tz. Philipova, *Dyes Pigments*, **1995**, *27*, 321. (c) A. Pardo, J. M. L. Poyato, E. Martin, J. J. Camacho, D. Reyman, M. F. Brana, J. M. Castellano, *Photochem. Photobiol. A: Chemistry* **1989**, *46*, 323. (d) V. Wintgens, P. Valat, J. Kossanyi, A. Demeter, L. Biczok, T. Berces, *New J. Chem.* **1996**, *20*, 1149. (e) X. Qian, Y. Zhang, K. Chen, Z. Tao, Y. Shen, *Dyes Pigments* **1996**, *32*, 229. (f) G. J.-F. Demets, E. R. Triboni, E. B. Alvarez, G. M. Arantes, P. B. Filho, M. J. Politi, *Spectrochim. Acta Mol. Biomol. Spectrosc.* **2006**, *63*, 220.

[157] (a) I. A. Zhmyreva, V. V. Zelinskii, V. P. Kolobkov, N. D. Krasnitskaya, *Dokl. Akad. Nauk SSSR* 1959, 129, 1089; *Chem. Abstr.* **1961**, *55*, 141336. (b) K. Schwetlick, *Kinetic methods for studying reaction mechanisms*, p. 165, VEB Deut. Verlag Wiss., Berlin 1971; *Chem. Abstr.* **1972**, *77*, 79990. (c) C. Reichardt, T. Welton, *Solvents and Solvent Effects in Organic Chemistry*; 4th ed.; Wiley-VCH: Weinheim **2011**; ISBN 3-527-26805-7.

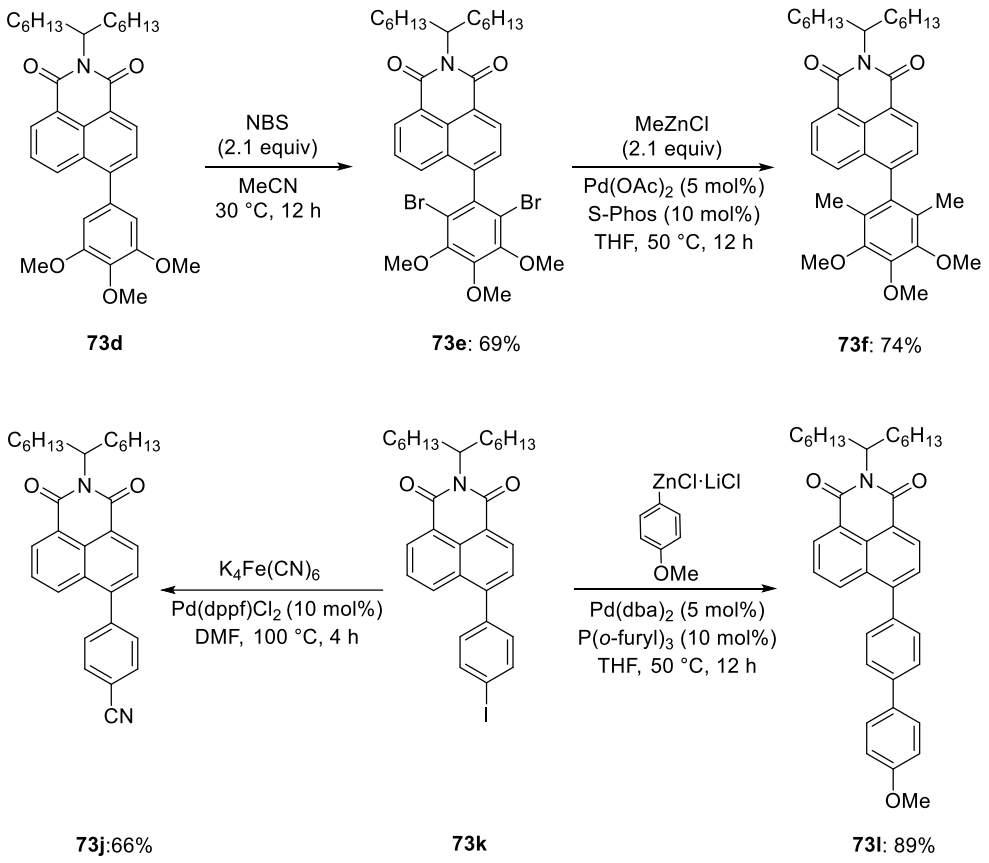
5.2 Preparation of Aryl Naphthalene Dicarboximides and Discussion of Optical Measurements

The fluorescent solvatochromism is expected to increase with the photo-induced dipole moment depending on the distance of the separated charges. Therefore, we inserted aryl groups as conjugating spacers between the donor groups and the naphthalimide acceptor moiety to achieve such a prolongation. To obtain highly soluble dyes, we started with a condensation of readily available 4-bromonaphthalic anhydride **71** with tridecan-7-amine giving the highly soluble key intermediate **72** in 90% yield. (Scheme 56). The *Suzuki* cross-coupling reaction of **72** with various aryl dioxaborolanes gave the corresponding arylated derivatives **73a-d** and **73g-j**, in 25-94% yield, respectively.



Scheme 56: Synthesis of highly soluble arylated naphthalene carboximides. (*4-(Trimethylsilyl)phenylboronic acid and 4-cyanophenylboronic acid were used for the preparation).

Substitution with the sterically hindered 2,6-dimethyl phenyl boronate failed where synthesis could be alternatively realized by stepwise peripheral introduction of the sterically demanding methyl groups. Thus, the easily accessible trimethoxy derivative **73d** was brominated with *N*-bromosuccinimide to give **73e** in 69% yield and then further treated with methylzinc chloride under typical *Negishi* cross-coupling conditions to provide **73f** in 74 % yield (Scheme 57). Since also the borylation of more complex aryl halides proved to be difficult, we converted the trimethylsilyl derivative **73i**, using iodine monochloride, into the corresponding aryl iodide **73k** in order to extend the conjugated system. A typical *Negishi* cross-coupling of **73k** with *p*-anisylzinc chloride (prepared from the reaction of 4-iodoanisole with *i*PrMgCl·LiCl, followed by $ZnCl_2$) gave the methoxy biphenyl derivative **73l** in 89% yield. Further, the cyanation of **73k** with $K_4Fe(CN)_6$ led to the corresponding arylnaphthyl cyanide **73j** in an improved yield (Scheme 57).



Scheme 57: Bromination of **73d** and subsequent cross-coupling with MeZnCl giving **73f** (top); cyanation and *Negishi* cross-coupling of **73k** leading to **73j** and **73l** respectively (bottom).

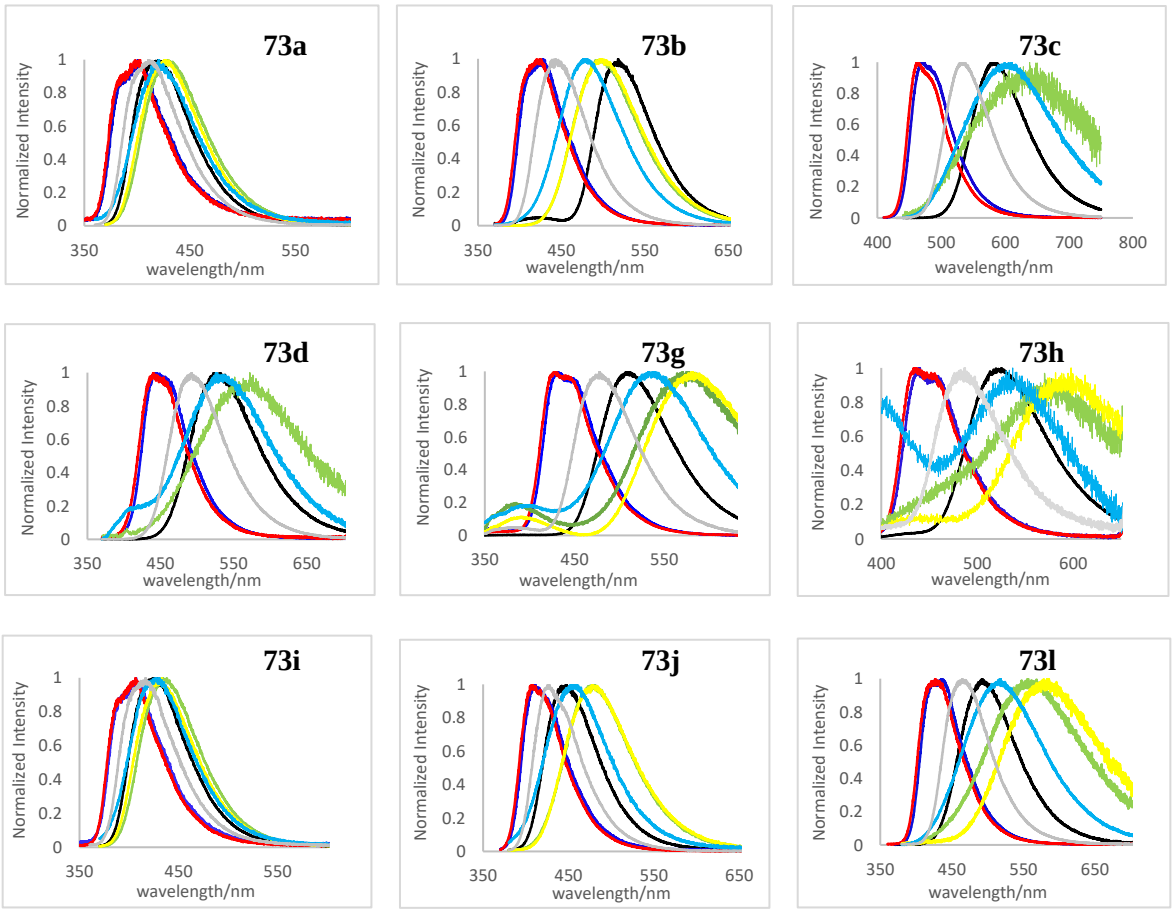
Fluorescence measurements reveal that the new dyes **73** are strongly solvatochromic in fluorescence (Figure 23), whereas compounds **73** are only moderately solvatochromic in absorbance. This indicates an optical excitation-induced increase of the dipole moment and was subject of further investigations. The molar energies of fluorescence light of various carboximides were calculated by means of equation (1) where λ_{max} is the fluorescence maximum of the individual dye in the tested solvent (E_T values are in kcal·mol^{-1} for comparison with previously reported values in the literature to avoid confusion; these may be multiplied by 4.2 to obtain SI units). The solvatochromism of the carboximides was analysed according to various theoretical approaches. Those of *Kawski*,[158] *Abboud*[159] or *Catalán*[160] fitted our experimental results well (see supporting information[161]).

$$E_T = 28591/\lambda_{max} \quad (1)$$

$$E_T = a \cdot E_T(30) + b \quad (2)$$

[158] A. Kawski, P. Bojarski and B. Kukliński, *Chem. Phys. Lett.* **2008**, *463*, 410.
[159] J.-L. M. Abboud, R. W. Taft, J. Kamlet, *J. Chem. Soc., Perkin Trans. 2* **1985**, 815.
[160] J. Catalán, *J. Phys. Chem. B*, **2009**, *113*, 5951.
[161] R. Greiner, T. Schlücker, D. Zgela, H. Langhals, *J. Mater. Chem. C* **2016**, *4*, 11244.

A



B

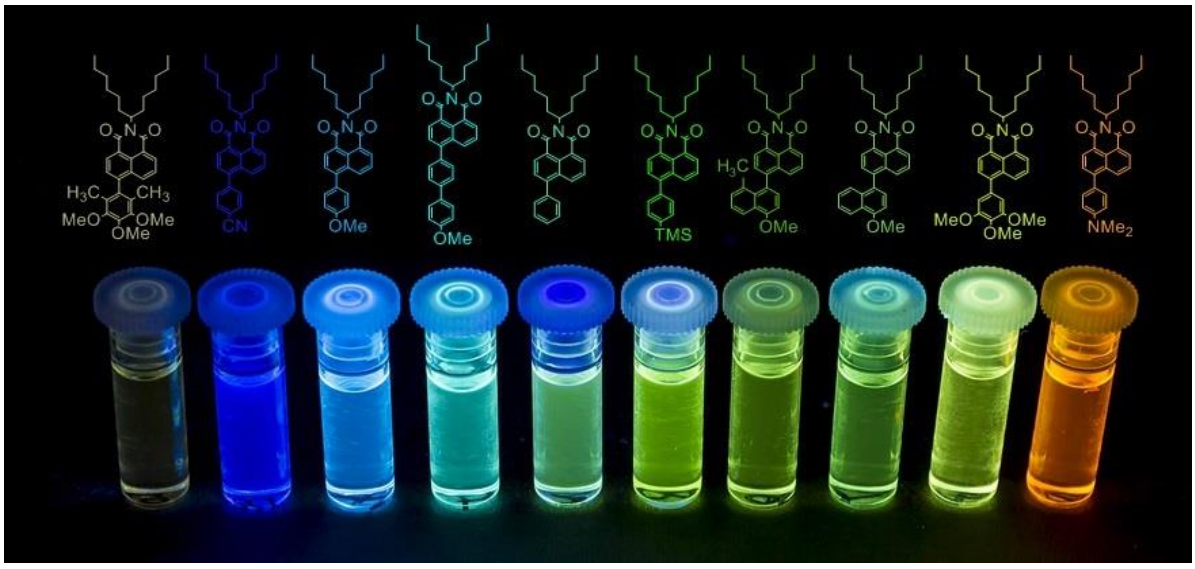


Figure 23: **(A)** Fluorescence spectra in various solvents: *n*-hexane (red), *n*-tetradecane (blue), toluene (grey), chloroform (black), 1-undecanol (turquoise), 1-butanol (green), DMF (yellow). **(B)** Aryl naphthalene carboximides in $CHCl_3$ solutions under UV-light (366 nm).

Furthermore, we investigated the fluorescent solvatochromism in more detail using the concepts of *Brooker's* χR scale[162] and *Dimroth* & *Reichardt's* $E_T(30)$ polarity scale[163] which delivered the best results. The first represents mainly the polarisability of the solvent whereas the second indicates mostly for the effect of dynamic solvation. The spectroscopic data of dyes **73** were compared to reported data to evaluate the solvent sensitivity of the fluorescence. The highly solvatochromic 4-amino-*N*-methylphthalimide (**74**) as the basis of *Zelinski's* universal solvent polarity *S* scale served as reference as well as the simple donor substituted 4-amino-*N*-methylnaphthalimide (**75**) (Figure 24). The E_T values of **74** were calculated from literature data for various solvents. A linear free energy relation (LFER)[164] of these E_T values with the $E_T(30)$ polarity scale according to equation (2) gave appreciably better results (correlation number r = 0.95 for n = 14 solvents) than with *Brooker's* χR scale (r = 0.90 for n = 14 solvents).

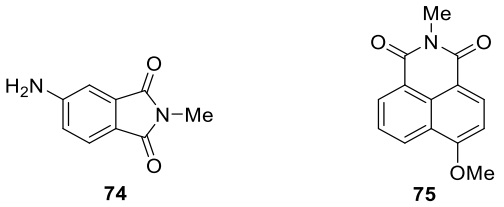


Figure 24: 4-Amino-*N*-methylphthalimide (**74**) and 4-methoxy-*N*-methylnaphthalimide (**75**) as reference for fluorescence data comparison.

Similar results were obtained for the solvatochromism of the fluorescence of **73a-j** (Table 10). As a consequence, we conclude that the solvent effects by polar dynamic orientation of the solvent molecules dominate for the reported carboximides and agreed with the $E_T(30)$ scale as most appropriate comparison. We investigated the solvents tetradecane, hexane, toluene, chloroform, *N*,*N*-dimethyl formamide (DMF), 1-undecanol and 1-butanol for an overview of solvent effects where the two protic solvents were applied for studying the influence of hydrogen bonds. Linear correlations of the E_T values with the $E_T(30)$ values were obtained. Larger deviations to higher E_T were observed for hydrogen bond-donating solvents such as 1-butanol and 1-undecanol indicating the specific influence of such interactions; the solvent viscosity seems to have a minor influence (compare hexane with tetradecane and 1-butanol with 1-decanol) and large Stokes shifts are even observed in a solid glassy matrix of PMMA. As a consequence, the further discussion was concentrated on the non-hydrogen bond-donating solvents for better comparability between the dyes **73**-**75**. A slope α of -0.60 is found for 4-amino-*N*-methylphthalimide (dye **74**, Table 10) and characterizes the sensitivity of this highly solvatochromic fluorescent dye to polar solvent effects. In comparison, this interaction is appreciably lower for the methoxynaphthalimide **75** (α = -0.27) and indicates a smaller alteration of the molecular dipole moment with optical excitation.

[162] L. G. S. Brooker, A. C. Craig, D. W. Heseltine, P. W. Jenkins, L. L. Lincoln, *J. Am. Chem. Soc.* **1965**, *87*, 2443.
[163] (a) K. Dimroth, C. Reichardt, T. Siepmann, F. Bohlmann, *Liebigs Ann. Chem.* **1963**, *661*, 1. (b) C. Reichardt, *Angew. Chem., Int. Ed.* **1965**, *4*, 29. (c) C. Reichardt, R. Müller, *Liebigs Ann. Chem.* **1976**, 1937. (d) C. Reichardt, *Pure Appl. Chem.* **2008**, *80*, 1415. (e) V. G. Machado, R. I. Stock, C. Reichardt, *Chem. Rev.* **2014**, *114*, 10429. (f) J. P. Cerón-Carrasco, D. Jacquemin, C. Laurence, A. Planchat, C. Reichardt, K. Sraïdi, *J. Phys. Org. Chem.* **2014**, *27*, 512.
[164] N. B. Chapman, J. Shorter (Eds.), *Correlation Analysis in Chemistry - Recent Advances*, Plenum Press: New York, London, **1978**; ISBN 0-306-31068-6.

Table 10: Solvatochromism of the fluorescence of the carboximides **73**, **74** and **75.**

Dye	Φ[a]	τ[b]	α[c]	r[d]
74			-0.60	-0.95
75			-0.27	-0.89
73a	0.78	3.21	-0.34	-0.99
73b	0.83	4.11	-0.74	-0.99
73c	0.64	6.99	-1.49	-0.96
73d	0.65	6.62	-1.43	-0.98
73f	< 0.05			
73g	0.39	4.07	-1.36	-0.98
73h	0.40	4.14	-1.37	-0.99
73i	0.79	3.08	-0.34	-0.99
73j	0.54	1.34	-0.80	-0.99
73l	0.67	2.93	-1.33	-0.98

Applied solvents: tetradecane, hexane, toluene, chloroform, dimethylformamide (DMF);
[a] fluorescence quantum yield Φ in chloroform. [b] fluorescence lifetime τ in ns in chloroform;
[c] slope α of the linear regression. [d] coefficient r of correlation for applications of equation (2)

An extension of the conjugated system of the naphthalimide with a phenyl group in **73a** increases the slope slightly to α = - 0.34. Further introduction of a donor group into the *p*-position of the phenyl substituent to obtain **73b** establishes a D-A system between the methoxy- and the carbonyl groups and enhances the sensitivity (α = -0.74) to exceed the solvatochromism of **74** by far. The dimethylamino group of derivative **73c** causes an even higher sensitivity towards solvents, however, the fluorescence quantum yield strongly decreases in polar solvents. Multiple donor groups as in **73d** also display a remarkably high solvatochromism with comparably high fluorescence quantum yields; even though weak fluorescence was still observed in polar DMF. A substitution with larger aryl groups like the 4-methoxynaphthyl moiety leads to **73g** which displays a very distinct solvatochromism (α = -1.36) while still exhibiting high fluorescence quantum yields in polar solvents. Further extension of the conjugated framework to the methoxybiphenyl derivative **73l** also induces such a pronounced fluorescent solvatochromism (α = -1.33) exceeding that of the anisyl-substituted species **73b**. Finally, the effect of the donor acceptor motif in **73b**, was further tested with **73j** where the electron donating methoxy group was exchanged by an electron withdrawing cyano moiety. There is still a comparably high sensitivity to solvent polarity, but as expected, the effect of the donor-substituted derivatives was not reached (Table 10). The electronic properties of the 4-methoxynaphthyl derivative **73g** are comparable to those of compound **73b**. However, the slope parameter α is found to be nearly twice as much. This observation made us focusing more intensely on the geometrical arrangement of the chromophores and prompted us to investigate the influence of steric hindrance on mesomerism. In comparison, the optical properties of **73g** and its methylated analogue **73h** are only slightly different from each other (Figure 25). This indicates a similar intramolecular geometry.

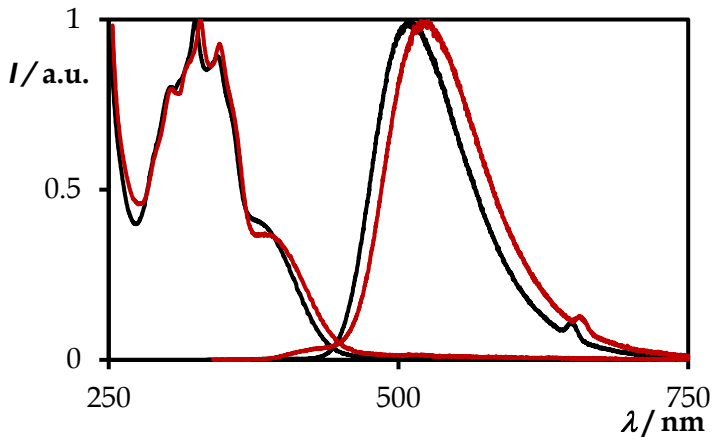


Figure 25: Comparison of absorption- (left) and fluorescence-spectra (right) **73g** (black) and **73h** (red).

A skew arrangement of the aromatic systems seems to be mainly influenced by *peri*-hydrogen atoms of the naphthalene subunits. These findings were further confirmed by quantumchemical DFT-calculations (B3LYP 6-311**G) as shown in Table 11 and Figure 26. Hence, the steric influence of the methyl group in **73h** is only subordinated (dihedral angle 75.38°) and does not affect the geometry significantly (71.60° for **73g**). Comparison of the 3,4,5-trimethoxyphenyl naphthalimides **73d** (57.34°) and **73f** (87.42°) exhibits much more pronounced effects. The steric repulsion of the methyl groups in **73f** arranges the two aromatic systems statically fixed. The nearly orthogonal geometry results in low fluorescence quantum yield of less than 0.05.

Table 11: Optimized structures and calculated dipole moments of **73** (DFT B3LYP 6-311**G).

Dye	ϑ[a]	ϑ_{ex}[b]	*dipole*[c]	$dipole_{E1}$[d]
73a	57.80	39.64	5.52	7.75
73b	55.61	35.86	6.40	9.82
73c	51.35	31.43	9.20	14.86
73d	57.34	35.67	6.77	9.22
73f	87.42	89.36	6.08	7.22
73g	71.60	43.34	6.47	12.21
73h	75.38	44.94	6.03	12.20
73i	57.31	36.39	6.01	8.53
73j	57.95	36.57	0.47	1.66
73l	56.66	32.24	6.94	11.26
	39.56[e]	31.92[e]		
74			5.20	8.92
75			6.29	7.96

Applied solvents: tetradecane, hexane, toluene, chloroform, dimethylformamide (DMF). [a] Calculated dihedral angle ϑ in ground state. [b] Calculated dihedral angle ϑ in the first electronically excited. [c] Dipole moment in electronic ground state in Debye. [d] Dipole moment in the first electronically excited state in Debye. [e] dihedral angle between phenyl moieties.

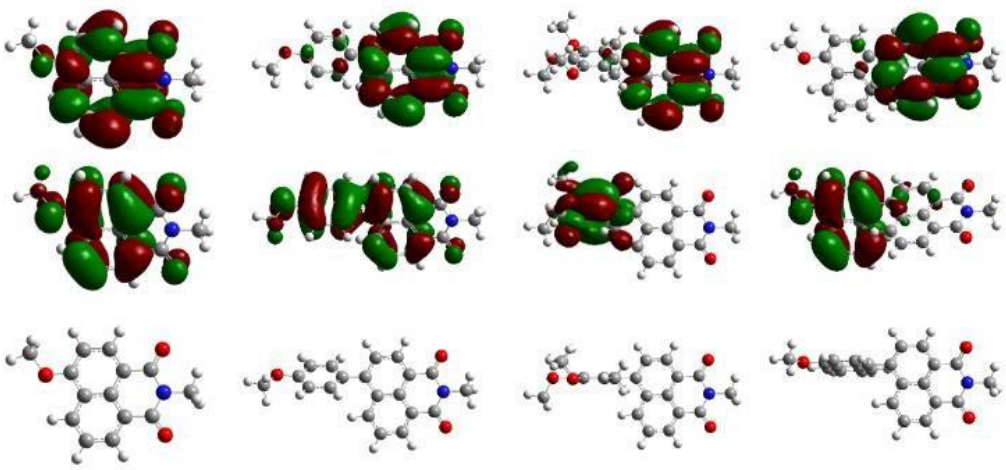


Figure 26: Quantumchemical calculations. From bottom to top: lowest energy structures (ground state, B3LYP 6-311**G), HOMO (middle) and LUMO (top) orbitals. Left to right: **75, 73b, 73f, 73g**.

A twisted geometry between the donor and the acceptor promotes charge transfer causing strong solvatochromism in fluorescence and large Stokes shifts. Moderate angles below 80° preserve high fluorescence quantum yields. A complete orthogonalisation (**73f**) quenches fluorescence where an obviously essential residual orbital overlap is lacking. We further confirmed this concept by heating a solution of **73f** in diethylene glycol diethyl ether to 200 °C where the very weak fluorescence reversibly becomes intensified by a factor of 2 (Figure 27).[165]

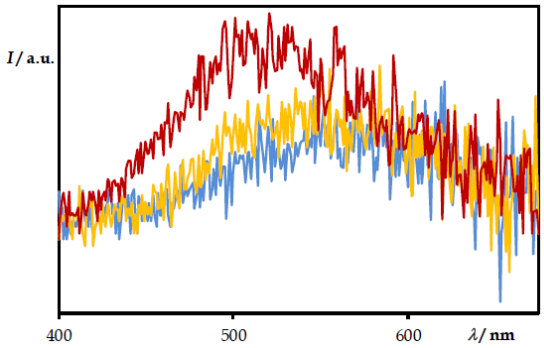
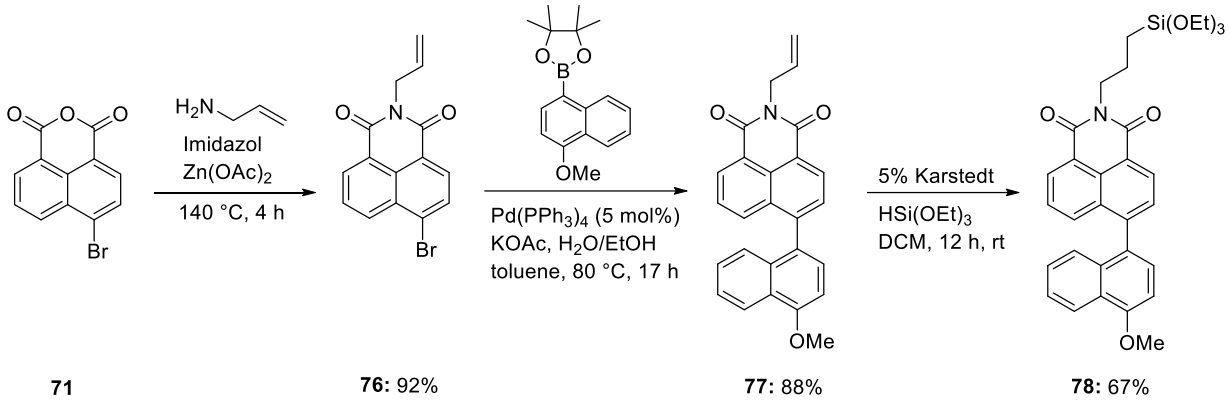


Figure 27: Temperature dependent fluorescent spectra of **73f** in diethylene glycol diethyl ether. Room temperature (blue), approx. 100 °C (yellow), approx. 200 °C (red).

This is attributed to thermally induced vibronic perturbation of the nearly orthogonal arrangement enabling fluorescence. The proposed geometrical requirements for a distinct charge transfer are related to the TICT theory. However, our results imply that orthogonal arrangements between donor and acceptor completely quench the fluorescence. Significant fluorescence is attributed to skew conformations which tend to more planar arrangements in the excited state allowing significant orbital overlap. Thus, the optical properties, particularly the fluorescent solvatochromism is not the result of a twist-induced charge transfer. It is rather the result of an interplay of conformational change and

[165] C. Cao, X. Liu, Q. Qiao, M. Zhao, W. Yin, D. Mao, H. Zhang, Z. Xu, *Chem. Commun.* **2014**, *50*, 15811.

electronic charge transfer depending on the dipole moment. By tuning the molecular geometry, we could obtain a series of chromophores with adjustable fluorescence and quantum yields up to more than 80%. Since fluorescent nanoparticles[166] are obtaining increased interest for basic research and applications, we also targeted the grafting of **73g** on silica HDK T40. Therfore, 4-bromonaphthalic anhydride **71** was condensed with allyl amine to obtain **76** in 92% yield,[167] which was subsequently reacted in a *Suzuki* cross-coupling with 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetra-methyl-1,3,2-dioxaborolane to give **77** (Scheme 58). By using the *Karstedt* catalyst, **77** was hydrosilylated with triethoxysilane, providing the triethoxysilyl derivative **78** in 67% yield.



71 **76:** 92% **77:** 88% **78:** 67%

Scheme 58: Preparation of triethoxysilyl derivative **78** for grafting on HDK T40.

Finally, by reacting **78** with HDK T40 (anhydrous) for 16 h in $CHCl_3$, highly fluorescent covalently grafted silica was obtained, from which the coloration could not be removed by washing with any common solvent (Figure 28).

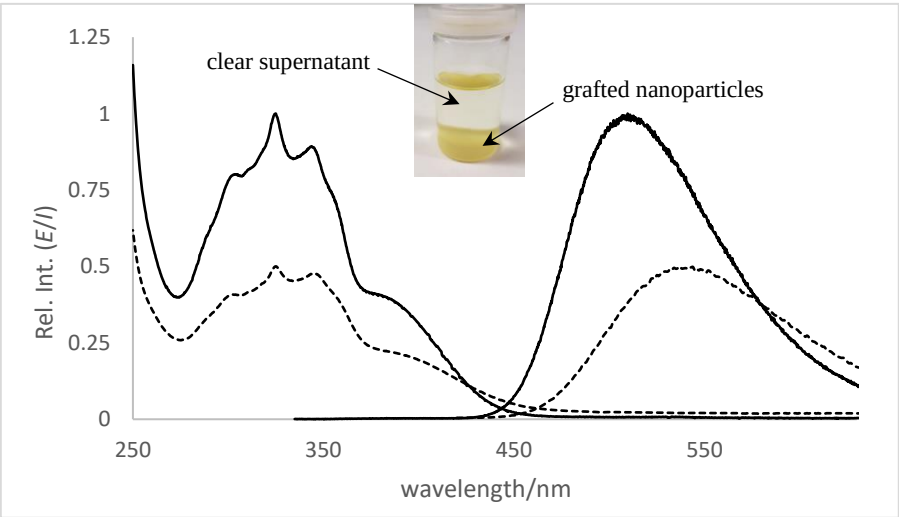


Figure 28: UV/Vis absorption (left) and fluorescence (right) spectra of dye **73g** in $CHCl_3$ solution (solid black lines) and of **78** grafted on silica as a suspension in $CHCl_3$ (dashed black lines). Inset fotograph: Grafted nanoparticles in EtOH.

[166] (a) H. Langhals, A. J. Esterbauer, *Chem. Eur. J.* **2009**, *15*, 4793. (b) H. Langhals, A. J. Esterbauer, S. Kinzel, *New J. Chem.* **2009**, *33*, 1829.
[167] A. Schulz, J. Wotschadlo, T. Heinze, G. J. Mohr, *J. Mater. Chem.* **2010**, *20*, 1475.

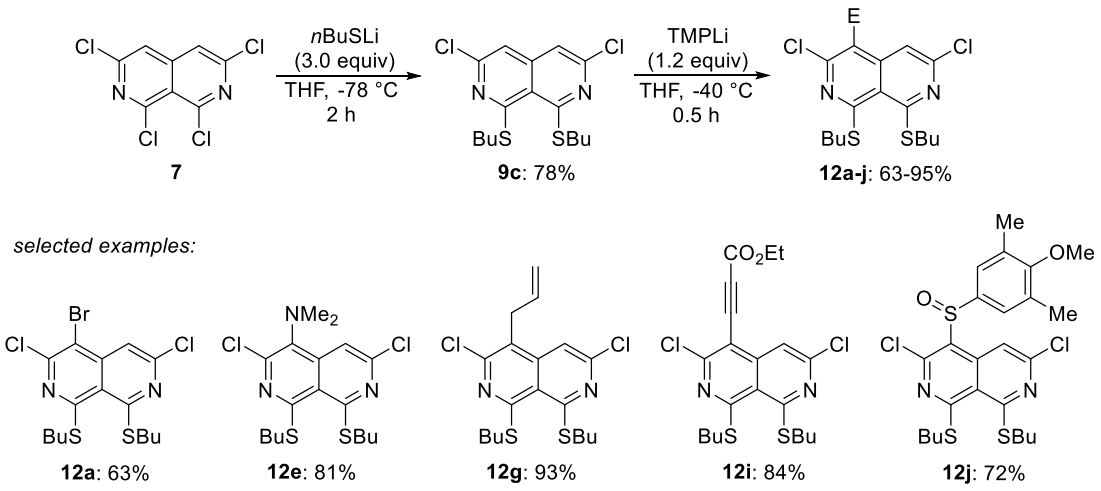
6. SUMMARY

6.1 Regioselective Organometallic Functionalization of 1,5- and 2,7-Naphthyridines

6.1.1 Regioselective Metalation of Naphthyridines

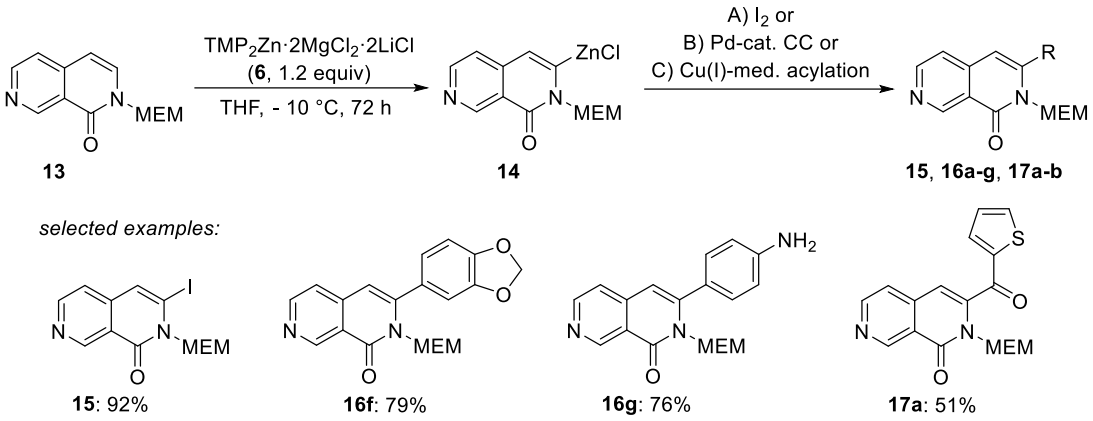
Whereas many publications report about the regioselective metalation of pyridines, only less is known about the metalation of naphthyridines. In this work, 2,7- and 1,5-naphthyridines have been regio-selectively metalated using various TMP-bases.

Due to diminished solubility of readily available 1,3,6,8-tetrachloro-2,7-naphthyridine (**7**) in organic solvents, we converted **7** into the highly soluble thioalkyl-naphtyridine derivative **9c**. The use of TMPLi, followed by trapping with electrophiles allowed the functionalization of **9c** in position 4. Thus, a range of polyfunctional 1,3,4,6,8-substituted-2,7-naphthyridines **12** could be prepared (Scheme 59).

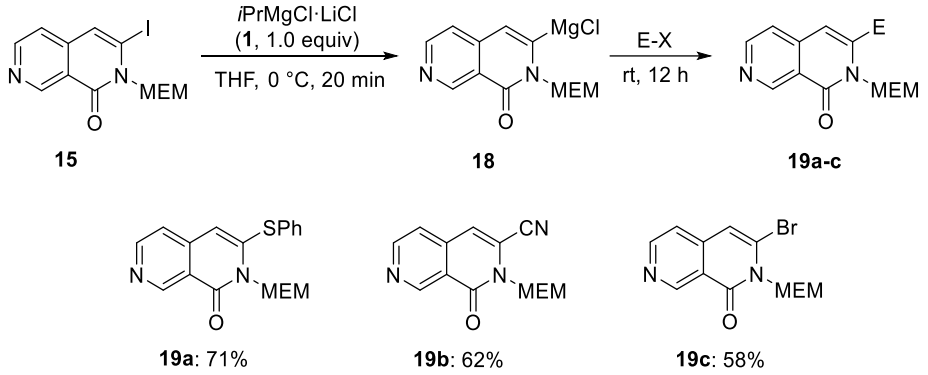


Scheme 59: Preparation of 1,3,4,6,8-functionalized 2,7-naphthyridines **12**.

Many alkaloids have a naphthyridone scaffold and thus it is desirable to develop a method for the functionalization of such structures. It was found that a MEM-protecting group in pyridones can act as a DMG. Therefore, MEM-protected 2,7-naphthyridin-1(2*H*)-one (**13**) was metalated using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**). Subsequent iodination, Pd-catalyzed cross-coupling or copper-mediated acylation gave rise of several in 3-position functionalized 2,7-naphthyridones **15**, **16a-g** and **17a-b** (Scheme 60). Where the zinc species **14** lacks in reactivity for the reaction with certain electrophiles, the corresponding magnesium species **18** (which is not accessible by direct magnesiation of **8**) could be generated by a facile I/Mg-exchange with *i*PrMgCl·LiCl (**1**). Quenching of **18** with the desired electrophiles gave the corresponding 2,7-naphthyridones **19a-c** (Scheme 61).

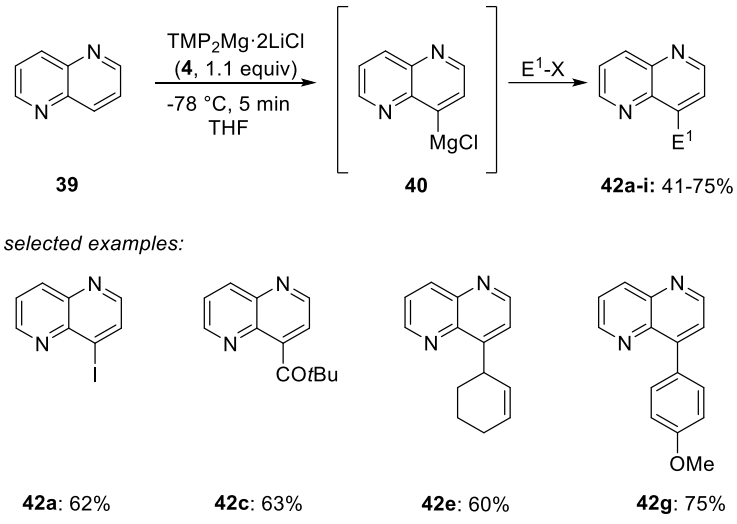


Scheme 60: D*o*M of MEM-protected 2,7-naphthyridone (**13**) and subsequent functionalization.



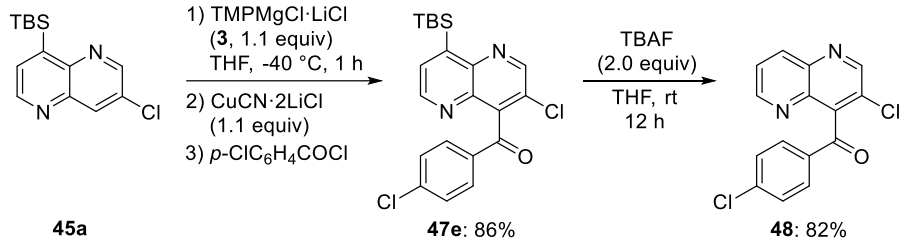
Scheme 61: Preparation of magnesiated 2,7-naphthyridone (**18**) and subsequent quenching with electrophiles.

A new general method was developed for the regioselective metalation of 1,5-naphthyridine (**39**). By using $TMP_2Mg·2LiCl$ (**4**) the 1,5-naphthyridine scaffold can be selectively metalated within 5 min at -78 °C. Subsequent treatment with electrophiles provided a range of novel 4-substituted 1,5-naphthyridines **42a-i** (Scheme 62).



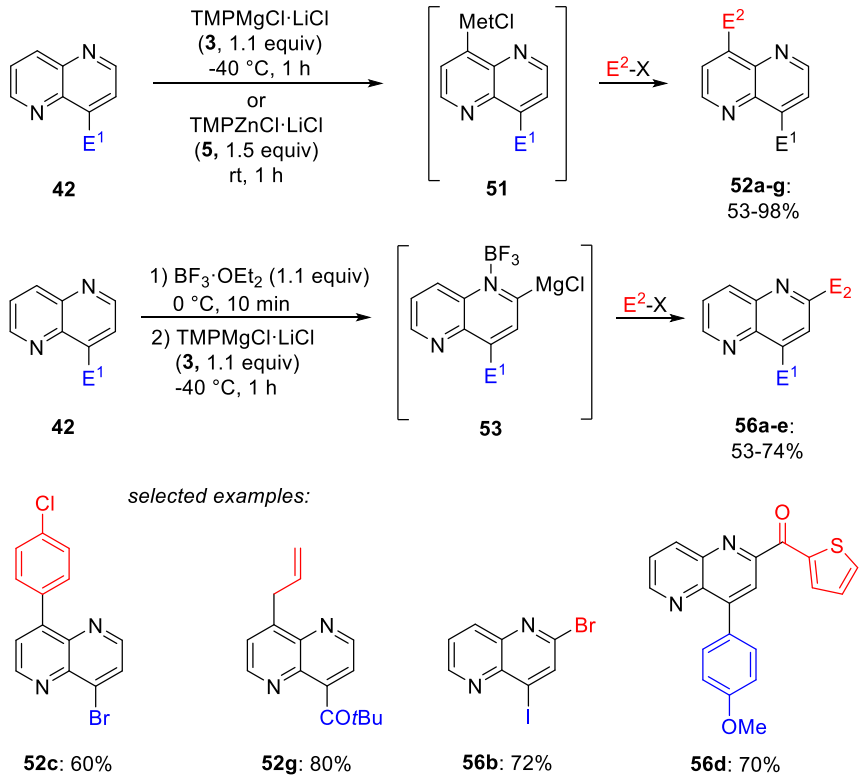
Scheme 62: Preparation of 4-substituted 1,5-naphthyridines **42a-i** by metalation with $TMP_2Mg·2LiCl$ (**4**).

Also the new 3-chloro-8-TBS/TMS-1,5-naphtyhridines **45a-b** can be selectively metalated in position 4 using TMPMgCl·LiCl (**3**) and be further treated with electrophiles. For instance, a copper(I)-mediated acylation of magnesiated **45a** furnished the expected product **47e** in 86% yield. After cleavage of the TBS-group by treatment of **47e** with TBAF, the desired 3-chloro-4-keto-1,5-naphthyridine **48** was obtained in 82% yield.



Scheme 63: Preparation of 3,4-substituted 1,5-naphthyridine **48**.

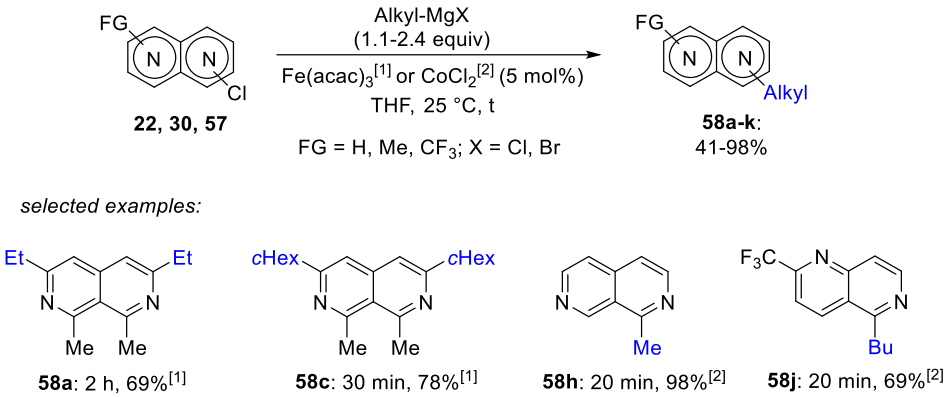
Regarding further metalation on 4-susbtituted 1,5-naphthyridines **42**, we found that regioselectivity can be switched by the prescence or absence of the *Lewis* acid $BF_3{\cdot}OEt_2$. The substituent E^1 in **42** at position C(4) prevents further complexation of a metallic amide at N(5) and thus favors precomplexation of the TMP base at N(1), providing metalation at C(8). The pre-addition of $BF_3{\cdot}OEt_2$ also leads to a complexation at N(1), which in turn increases the acidity of the proton at C(2), resulting in a magnesiation in this position. The quenching of **51** or **53** with electrophiles furnished a range of new 4,8- and 2,4-functionalized 1,5-naphthyridines **52a-g** and **56a-e** respectively (Scheme 64).



Scheme 64: Regioselective metalation of **42** in the prescence/absence of $BF_3{\cdot}OEt_2$.

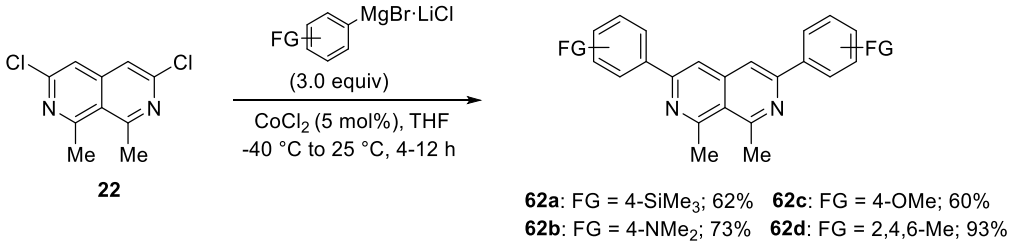
6.1.2 Iron- and Cobalt-Catalyzed Cross-Coupling of Naphthyridines

In preliminary experiments, we found that chloro-naphthyridines easily undergo $C(sp^3)$-$C(sp^2)$ cross-couplings using 5 mol% $Fe(acac)_3$ or $CoCl_2$ (Scheme 65).



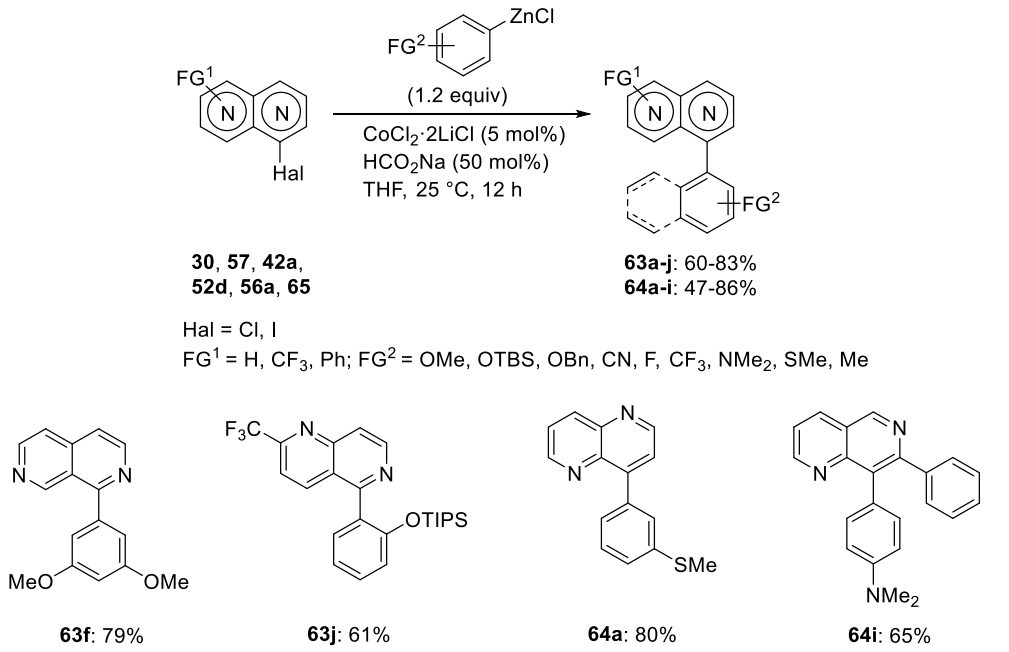
Scheme 65: Iron- and cobalt-catalyzed $C(sp^3)$-$C(sp^2)$ cross-couplings.

As we encountered low yields carrying out iron-catalyzed $C(sp^2)$-$C(sp^2)$ cross-couplings with halogenated naphthyridines, we found that the 3,6-dichloro-2,7-naphthyridine (**22**) smoothly reacts with arylmagnesium reagents using 5 mol% $CoCl_2$ (Scheme 66).



Scheme 66: Cobalt-catalyzed bis-arylation of dichloronaphthyridine **22**.

However, the cross-coupling of other chloronaphthyridines (**30** and **57**) with arylmagnesium reagents using $CoCl_2$ also led to diminished yields. This problem was solved by replacing the arylmagnesium reagents with the corresponding zinc reagents and using HCO_2Na as ligand. This method even enabled us to do cobalt-catalyzed $C(sp^2)$-$C(sp^2)$ cross-couplings with iodo-naphthyridines (Scheme 67). We further found that 4-iodo-1,5-naphthyridine **42a** smoothly reacts with benzylic zinc reagents in prescence of 5 mol% $CoCl_2$ without using any additives. Finally, we envisioned regiosoelctive cross-coupling depending on the nature of the halogen and found that 1-chloro-4-iodo-2,7-naphthyridine (**67**) can be differntially bisarylated by utilizing successive Pd- and Co-catalysis leading to the 1,4-substituted 2,7-naphthyridine **69**. Beyond synthetic efforts, we noticed that the functionalized naphthyridines **62b** and **64i** are highly fluorescent in various organic solvents and display strong solvatochromism. Compound **64i** reaches quantum efficiencies up to 95% and a long excited state lifetime of up to 12 ns. These interesting molecules should be investigated in the future to find out wether the TICT or PICT mechanism dominates intramolecular dynamics under excitation with light.



Scheme 67: Mild cobalt-catalyzed *Negishi*-type cross-couplings of halogenated naphthyridines with arylzinc reagents.

6.2 Preparation of New Fluorescent Aryl Naphthalene Dicarboximides with Large Stokes Shifts and Strong Solvatochromism

In summary, we have reported new, readily soluble and highly fluorescent derivatives of naphthalene-1,8-dicarboximides that have been obtained by Pd-catalyzed arylation in position 4. These compounds display a pronounced solvatochromic fluorescence. The sensitivity of the substituted naphthalimides towards solvent polarity was evaluated according to several theoretical approaches. A photo-induced charge transfer from the electron rich aryl moiety to the naphthalimide is enhanced in polar solvents and causes a bathochromic shift of the fluorescence. Furthermore, the electronic effects are accompanied by molecular dynamics. The intramolecular arrangement influences the intensity of the charge transfer. A skew geometry between donor and acceptor allows planarization in the first electronically excited state. This allows high fluorescent quantum yields and still favors a pronounced charge transfer resulting in both, distinct solvatochromism and large Stokes shifts. In contrast to basic TICT-theory, no orthogonalization occurs and rectangular orientation leads to strongly quenched fluorescence. The presented synergy of electronic and geometric effects results in highly fluorescent compounds such as **73b** and **73g** with easily adjustable emission spectra controlled by medium effects. This provides very large Stokes shifts exceeding 200 nm (approx. 1.6 eV) being of interest for various applications such as for frequency converters, fluorescence optical fibers and highly tunable light sources. For purposes like bioimaging we further demonstrated the synthesis of triethoxysilyl derivative **78**, an analogue to **73g**, which can be easily grafted on silica nanoparticles like HDK T40.

C. EXPERIMENTAL SECTION

1. General Considerations

If not otherwise stated, all reactions have been carried out using standard *Schlenk*-techniques in flame-dried glassware under nitrogen or argon. Prior to use, syringes and needles have been purged with the respective inert gas.

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.

$CHCl_3$ was predried over CaCl2 and distilled from CaH_2.

***t*BuOMe** was predried over $CaCl_2$ and distilled from CaH_2.

CH_3CN was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

DMF was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

NMP was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and stored over 4 Å molecular sieve under an argon atmosphere.

Toluene was predried over $CaCl_2$, distilled from CaH_2 and stored over 4 Å molecular sieve under an argon atmosphere.

NEt_3 was dried over KOH and distilled.

MeOH, **EtOH** and **BuOH** were purchased in p. A. quality and used without further purification.

Solvents for reaction workup and for column chromatography were distilled on a rotary evaporator prior to use.

1.2 Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid reagents were distilled prior to use.

TMPH was distilled under argon prior to use.

***i*PrMgCl·LiCl** solution in THF was purchased from Rockwood Lithium.

***n*BuLi** solution in hexane was purchased from Rockwood Lithium.

Preparation of CuCN·2LiCl solution:[124]

CuCN·2LiCl solution (1.0 M in THF) was prepared by drying CuCN (7.17 g, 80 mmol) and LiCl (6.77 g, 160 mmol) in a *Schlenk*-tube under high vacuum at 140 °C for 5 h. After cooling to rt, dry THF (80 mL) was added and stirring was continued until all salts were dissolved.

Preparation of $ZnCl_2$ solution:

$ZnCl_2$ solution (1.0 M in THF) was prepared by drying $ZnCl_2$ (13.63 g, 100 mmol) in a *Schlenk*-flask under high vacuum at 140 °C for 5 h. After cooling ro rt, dry THF (100 mL) was added and stirring was continued until all salts were dissolved.

Preparation of $MgCl_2$ solution:

A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum was charged with Mg turnings (2.55 g, 105 mmol) and THF (200 mL). 1,2-Dichloroethane (9.90 g, 100 mmol, 7.92 mL) was added dropwise over 1 h. The reaction mixture was stirred at rt until the gas evolution vanished.

Preparation of TMPLi (2):[47]

TMPLi solution was prepared by slow addition of *n*BuLi (2.17 mL, 5.0 mmol, 2.3 M in hexane) to a solution of TMPH (706 mg, 0.85 mL, 5.0 mmol) in THF (5 mL) at -40 °C. The mixture was stirred for 30 min at -40 °C before being titrated.

Preparation of TMPMgCl·LiCl (3):[54]

In a dry and argon-flushed *Schlenk*-flask TMPH (2,2,6,6-tetramethylpiperidine, 14.8 g, 105 mmol) was added to *i*PrMgCl·LiCl (**1**; 71.4 mL, 1.40 M in THF, 100 mmol) at rt and the mixture was stirred for 3 days at this temperature before being titrated.

Preparation of $TMP_2MgCl·LiCl$ (4):[56]

In a dry, argon-flushed *Schlenk*-flask, 2,2,6,6-tetramethylpiperidine (TMPH, 5.07 mL, 30 mmol) was dissolved in dry 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 (1.45 M in THF, 20.7 mL, 30 mmol) was then added dropwise to the TMPLi solution. 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 *in vacuo* without heating, affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring, until a complete dissolution of the salts was observed.

Preparation of TMPZnCl·LiCl (5):[57]

A dry and argon flushed 250 mL *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with freshly distilled TMPH (10.22 mL, 60 mmol) dissolved in dry 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 up 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 was stirred for 30 min at –10 °C and then for 30 min at rt. 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.

Preparation of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (6):[58]
A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of TMPMgCl·LiCl (**3**; 1.16 M in THF, 30 mL, 34.8 mmol). Then, a solution of dry $ZnCl_2$ (1.0 M in THF, 18.44 mL, 18.4 mmol, 0.53 equiv) was added dropwise and the mixture was stirred for 12 h at rt before being titrated.

1.3 Content Determination of Organometallic Reagents

Organozinc and organomagnesium reagents were titrated with I_2 in THF.[168]

***n*BuLi** was titrated with dry 2-propanol and 1,10-phenanthroline as indicator in THF.[169]

TMPLi was titrated using *N*-benzylbenzamide as titrating agent and indicator in THF.[170]

TMPMgCl·LiCl (3), **$TMP_2Mg{\cdot}2LiCl$ (4)**, **TMPZnCl·LiCl (5)** and **$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (6)** were titrated with benzoic acid and 4-(phenylazo)diphenylamine as indicator in THF.

1.4 Chromatography

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from MERCK.
Thin layer chromatography was performed using aluminium plates coated with SiO_2 (Merck 60, F-254). The spots were visualized by UV-light or staining of the TLC plate with the solution below followed by heating if necessary:

- Iodine absorbed on silica gel.
- $KMnO_4$ (3.0 g), 5 drops of conc. H_2SO_4 in water (300 mL).
- Phosphomolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12 mL) in water (230 mL).
- Ninhydrin (0.3 g) and AcOH (3.0 mL) in butanol (100 mL).

[168] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, 890.
[169] H.-S. Lin, A Paquette, *Synth. Commun.* **1994**, *24*, 2503.
[170] A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.***1997**, *542*, 281.

1.5 Analytical Data

NMR spectra were recorded on *Varian* Mercury 200, *Bruker* AC 300, WH 400 or AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the solvent peak, i.e. chloroform-d (δ = 7.26 ppm for ^{1}H-NMR and δ = 77.0 ppm for ^{13}C-NMR), DMSO-d_6 (δ = 2.50 ppm for ^{1}H-NMR and δ = 39.5 ppm for ^{13}C-NMR). For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), m (multiplet), q (quartet), quint (quintet), sxt (sextet), sept (septet) as well as br (broad).

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 (GC/MS), a HEWLETT-PACKARD HP 6890/MSD 5973 GC/MS system was used.

Infrared spectra were recorded from 4000-400 cm^{-1} on a Perkin 281 IR spectrometer. Samples were measured neat (ATR, Smiths Detection Dura Sample IR II Diamond ATR). The 10-20 most dominant absorption bands are reported (in wave numbers cm^{-1}).

Melting points were measured on a *Büchi* B540 apparatus and are uncorrected.

UV/VIS-spectra were recorded on a *Varian Cary 5000*.

Photoluminescence spectra were recorded on a *Varian Cary Eclipse*.

Time-correlated single photon counting (TCSPC): The samples are excited by a 375 nm picosecond pulsed laser (PicoQuant, LDH-375), and emitted photoluminescence is collected and detected by a highly sensitive photo-multiplier tube (PMT, PicoQuant PMA 192), which allows detection of single photons through internal amplification. The time difference between triggering the laser and registering the photon on the PMT is measured by an internal clock (PicoQuant TimeHarp 260 P) and then collected in a histogram (bin width 25 ps) which yields the TCSPC data points shown in the main text.

Photo Luminescence Quantum Efficiency (PLQE) measurements were performed with an Edinburgh Instruments FLS980 fluorescence spectrometer equipped with a 120 mm BenFlect-coated integrating sphere. Measurements were performed with 10 µM solutions of compound **62b** (5 µM in the case of cyclohexane due to low solubility) and 40 µM solutions of **64i** in dry and Ar-saturated solvents (OD ~ 0.15).
Absolute quantum efficiencies were determined from two measurements per sample. These are (1) the sphere loaded with a cuvette containing only the respective solvent and (2) the sphere loaded with the cuvette containing the solution of the sample. Assuming isotropic emission, the PLQE is calculated from the attenuation of the excitation light and the corresponding PL emission.

2. Organometallic Functionalization of the 2,7-Naphthyridine Scaffold

2.1 Typical Procedures

Typical Procedure for the Metalation of 2,7-Naphthyridines 9 with TMPLi (TP 1):
A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum, was charged with the corresponding 2,7-naphthyridine (1.0 equiv) in dry THF. After cooling to the indicated temperature, a solution of TMPLi (**2**, 1 M in THF, 1.2 equiv) was slowly added. The reaction mixture was stirred for 30 min at the same temperature. Then, the corresponding electrophile (1.2 equiv) was added and the solution was stirred at -40 °C until complete conversion of the starting material (detected by GC-analysis of reaction aliquots).

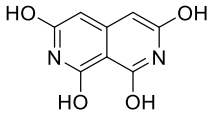
Typical Procedure for the Zincation of 2,7-Naphthyridone 13 using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (TP2):
In a dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, naphthyridone **13** (1.0 equiv) was dissolved in dry THF (3 mL). After the solution was cooled down to −10 °C, $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**, 1.2 equiv) was added and the mixture was stirred at the same temperature. The completion of the metalation was achieved after 72 h, stated by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

Typical Procedure for the Magnesiation of 2,7-Naphthyridone 15 *via* Iodine-Magnesium Exchange (TP3):
In a dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 3-iodo-2,7-naphthyridone **15** (1.0 equiv) was dissolved in dry THF. At 0 °C a solution of *i*PrMgCl·LiCl (**1**) in dry THF (1.0 equiv) was added dropwise and the mixture was stirred at the same temperature. The completion of the exchange reaction was checked by TLC-analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution.

2.2 Preparation of Starting Materials

2.2.1 Preparation of 2,7-Naphthyridines 9a-d

1,3,6,8-Tetrahydroxy-2,7-naphthyridine[120]



A round bottom flask, equipped with a magnetic stirring bar, was charged with diethyl-1,3-acetonedicarboxylate (36 mL, 200 mmol, 1.0 equiv) and diethylamine (10 mol%, 20 mmol, 2.0 mL) in ethanol (350 mL). Malonitrile (10 g, 153 mmol, 1.2 equiv) was added in portions and the resulting dark yellow solution was stirred at rt overnight. Then, the solvent was removed under reduced pressure. The remaining oil was treated with sulfuric acid (70%, 300 mL) whereupon complete dissolution occurred. Then, the solution was heated until light ebullition occurred. After cooling to rt, the reaction mixture

was poured into water (350 mL) giving a yellow precipitate, which was filtered, washed with water and finally dried to afford the pure product (32.9 g, 85 %) as a yellow powder.

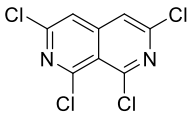
m.p.: 248–250 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3162, 2827, 2679, 1631, 1589, 1557, 1486, 1408, 1370, 1152.

MS (DEI+, 70 eV): *m/z* (%) = 194 (100), 177 (15), 149 (10), 123 (7), 95 (6), 44 (5), 18 (13).

HRMS (DEI+) calcd. for [$C_8H_6N_2O_4$]: 194.0328; found: 194.0334.

1,3,6,8-Tetrachloro-2,7-naphthyridine[120a]



A pressure tube, equipped with a magnetic stirring bar, was charged with 1,3,6,8-tetrahydroxy-2,7-naphthyridine (1.0 g, 5.2 mmol), followed by $POCl_3$ (10 mL). The reaction was heated at 180 °C for 24 h. Then, the reaction was poured on ice (150 g) and was made alkaline with potassium carbonate. The mixture was extracted extensively several times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford the desired product (730 mg, 53%) as a yellow solid.

m.p.: 157 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1583, 1505, 1343, 1258, 1122, 1102, 977, 965, 889, 816.

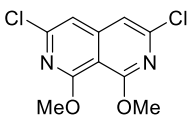
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.57 (s, 2 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 150.7, 148.4, 147.1, 118.8, 118.0.

MS (EI, 70 eV): *m/z* (%) = 272 (26), 270 (37), 268 (100), 266 (81), 233 (26), 231 (46), 219 (34), 197 (22), 111 (31), 97 (43), 95 (34), 83 (42), 81 (30), 71 (28), 69 (30), 61 (21), 57 (46), 56 (20), 55 (31), 42 (47), 40 (20).

HRMS (EI) calcd. for [$C_8H_2Cl_4N_2$]: 265.8972; found: 265.8960.

3,6-Dichloro-1,8-dimethoxy-2,7-naphthyridine (9a)[120a]



A round flask, equipped with a magnetic stirring bar, was charged with 1,3,6,8-tetrachloro-2,7-naphthyridine (267 mg, 1 mmol, 1.0 equiv) in methanol (13 mL). Then, potassium carbonate (267 mg, 2 mmol, 2 equiv) was added at rt. The solution was stirred for 2 h at the same temperature. The solvent was evaporated under reduced pressure and the crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford the pure product (206 mg, 80%) as a white solid.

m.p.: 155-157 °C.

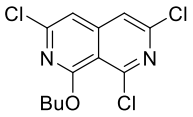
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.03 (s, 2H), 4.13 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 161.8, 148.9, 148.3, 111.1, 102.7, 55.3.

MS (EI, 70 eV): *m*/*z* (%) = 271 (41), 560 (40), 258 (54), 229 (57), 163 (44), 57 (100), 44 (27), 41 (29).

HRMS (EI) calcd. for [$C_{10}H_8Cl_2N_2O_2$]: 257.9953; found 257.9972.

1-Butoxy-3,6,8-trichloro-2,7-naphthyridine (9c)



A round flask, equipped with a magnetic stirring bar, was charged with 1,3,6,8-tetrachloro-2,7-naphthyridine (364 mg, 1.36 mmol, 1.0 equiv) in butanol (15 mL). Then, potassium carbonate (377 mg, 2.72 mmol, 2.0 equiv) was added at 25 °C. The solution was warmed to 40 °C and stirred for 24 h at the same temperature. The solvent was evaporated under reduced pressure and the crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford pure product (339 mg, 82 %) as a white solid.

m.p.: 88-90 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1588, 1579, 1531, 1339, 1332, 1297, 1193, 1128, 983, 931, 867.

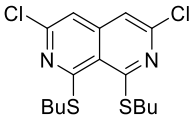
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.39 (s, 1H), 7.10 (s, 1H), 4.54 (t, *J* = 6.4 Hz, 2H), 1.95-1.83 (m, 2H), 1.66-1.51 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 160.6, 150.7, 149.0, 148.4, 117.3, 111.6, 111.1, 68.9, 30.7, 19.6, 13.9.

MS (EI, 70 eV): *m*/*z* (%) = 269 (10), 252 (32), 251 (15), 250 (100), 249 (18), 248 (97), 215 (31), 214 (15), 212 (50), 211 (17), 158 (12), 149 (12).

HRMS (EI) cacld. for [$C_{12}H_{11}Cl_3N_2O$]: 303.9937; found 303.9941.

1,8-Bis(butylthio)-3,6-dichloro-2,7-naphthyridine (9c)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar, was charged with 1-butanethiol (1.24 mL, 11.6 mmol, 3.0 equiv) in THF (10 mL). The solution was cooled to 0 °C, whereupon a solution of *n*BuLi (4.70 mL, 11.7 mmol, 2.48 M in hexane, 3.05 equiv) was slowly added. The solution was stirred at 0 °C for 30 min. Another dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar, was charged with 1,3,6,8-tetrachloro-2,7-naphthyridine (1.03 g, 3.8 mmol, 1.0 equiv) in THF (10 mL). The solution was cooled to -78 °C and the freshly prepared thiobutyllithium (13.3 mL, 9.6 mmol, 0.72 M in THF, 2.5 equiv) was slowly added. The reaction mixture was stirred at the same temperature for 2 h. After the total disappearance of the starting material, the mixture was quenched with sat. aq. NH_4Cl solution (50 mL). The layers were separated and the aqueous phase

extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (isohexane/ EtOAc = 100:1) to afford the pure product (1.24 g, 86%) as an off-white solid.

m.p.: 67-69 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2955, 2931, 2871, 1569, 1492, 1323, 1260, 1118, 1098, 986, 873, 857.

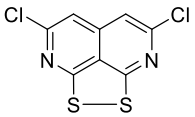
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.05 (s, 2H), 3.32 (t, *J* = 7.3 Hz, 4H), 1.78 (quint, *J* = 7.3 Hz, 4H), 1.53 (sxt, *J* = 7.4 Hz, 4H), 0.99 (t, *J* = 7.3 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 163.8, 148.2, 145.9, 120.4, 113.3, 33.3, 30.4, 22.5, 13.9.

MS (EI, 70 eV): *m*/*z* (%) = 321 (20), 319 (70), 317 (100), 265 (17), 263 (73), 262 (20), 261 (98), 225 (29), 41 (24).

HRMS (EI) calcd. for $[C_{16}H_{20}Cl_2N_2S_2]$: 374.0445; found: 374.0438.

4,7-Dichloro-[1,2]dithiolo[3,4,5-*ij*][2,7]naphthyridine (9d)[171]



A suspension of 1,3,6,8-tetrachloro-2,7-naphthyridine (0.10 g, 0.37 mmol) and sulfur (0.05 g, 1.48 mmol, 4.0 equiv) in dry NMP (14 mL) was stirred at 190 °C for 3 h. After cooling to rt, the reaction mixture was poured into water. The precipitate was filtered, washed with water and dried. The crude product was purified by flash column chromatography (isohexane/DCM = 1:1) to furnish pure product (40 mg, 42%) as a yellow solid.

m.p.: 208-210 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1584, 1571, 1490, 1343, 1327, 1282, 1092, 999, 870, 808, 681.

^{1}H-NMR (400 MHz, DMSO-d_6): δ/ ppm = 7.46 (s, 2H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ/ ppm = 169.7, 151.7, 143.9, 121.5, 111.2.

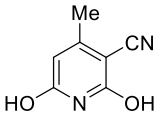
MS (EI, 70 eV): *m*/*z* (%) = 262 (72), 261 (12), 260 (100), 227 (11), 225 (29), 180 (15).

HRMS (EI) calcd. for $[C_8H_2Cl_2N_2S_2]$: 259.9036; found: 259.9032.

[171] (a) Y. Zagranyarski, L. Chen, D. Jänsch, T. Gessner, C. Li, K. Müllen, *Org. Lett.* **2014**, *16*, 2814. (b) R. Sato, *Science of Synthesis* **2004**, *16*, 57. (c) S. A. Gamage, R. A. J. Smith, *Tetrahedron* **1990**, *46*, 2111.

2.2.2 Preparation of MEM-protected 2,7-Naphthyridone (13)

2,6-Dihydroxy-4-methylnicotinonitrile[118a]



Ethyl acetoacetate (26.0 g, 200 mmol) and cyanoacetamide (16.8 g, 200 mmol, 1.0 equiv) were dissolved in methanol (150 mL). A solution of potassium hydroxide (12.4 g, 200 mmol, 1.0 equiv) in methanol (100 mL) was added and the resulting mixture was heated to 65 °C and was stirred under reflux for 4 h. The white precipitate was filtered off, washed with methanol and dissolved in hot water (100 mL). After cooling to rt, the solution was carefully acidified with hydrochloric acid (2 M), until the white solid precipitated again. The product was filtered off, washed with water and methanol and then dried to furnish the pure compound (23.9 g, 80%) as a colorless powder.

m.p.: 298-300 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2883, 2219, 1595, 1502, 1359, 1291, 1219, 1180, 833, 742.

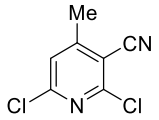
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 12.11 (br, 2H), 5.59 (s, 1H), 2.23 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 162.3, 161.5, 160.7, 117.7, 93.2, 89.4, 21.1.

MS (EI, 70 eV): *m/z* (%) = 151 (16), 150 (100), 122 (57), 121 (19), 107 (48), 94 (12), 79 (12).

HRMS (EI): calcd. for [$C_7H_6N_2O_2$]: 150.0429; found: 150.0417.

2,6-Dichloro-4-methylnicotinonitrile[118a]



A pressure tube, equipped with a magnetic stirring bar, was charged with 2,6-dihydroxy-4-methyl-nicotinonitrile (10 g, 67 mmol) and $POCl_3$ (24 mL, 268 mmol, 4.0 equiv). The mixture was heated to 160 °C and was stirred at that temperature for 14 h. After cooling to rt, the mixture was carefully poured onto ice (500 g). The brown precipitate was filtered off and washed with water. Recrystallization from EtOAc and washing with isohexane gave the pure compound (12 g, 95%) as light yellow crystals.

m.p.: 110-113 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3367, 3056, 2231, 1776, 1568, 1337, 1261, 1190, 1115, 1101, 922, 889, 850.

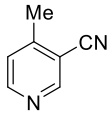
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.27 (q, *J* = 0.8 Hz, 1H), 2.57 (d, *J* = 0.8 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 156.5, 153.7, 152.6, 124.0, 113.3, 110.3, 20.6.

MS (EI, 70 eV): *m/z* (%) = 186 (100), 168 (15), 153 (13), 151 (42), 150 (38), 133 (13), 124 (16), 115 (21).

HRMS (EI): calcd. for [$C_7H_4Cl_2N_2$]: 185.9752; found: 185.9752.

4-Methylnicotinonitrile[118a]



In a dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, 2,6-dichloro-4-methylnicotinonitrile (32.5 g, 174 mmol), sodium acetate trihydrate (29.2 g, 348 mmol, 2.0 equiv) and palladium(II) chloride (0.5 g, 3 mmol, 2 mol%) were suspended in methanol (400 mL). The argon was removed *in vacuo* and the reaction vessel was backflushed with hydrogen. This step was repeated three times, until the reaction mixture clearly turned black. After stirring at rt for 18 h under hydrogen atmosphere, the reaction mixture was filtered and washed with methanol. The solvent was removed under reduced pressure and the residue was diluted in sat. aq. NH_4Cl solution (200 mL). The mixture was extracted with EtOAc (3 × 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (iso-hexane/EtOAc = 1:1) to give the pure compound (12.9 g, 63%) as colorless crystals.

m.p.: 46-48 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3020, 2223, 1884, 1592, 1388, 1195, 845, 837, 745, 723.

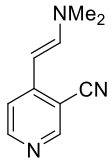
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 8.77 (s, 1H), 8.62 (d, *J* = 5.3 Hz, 1H), 7.27 - 7.25 (m, 1H), 2.54 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 152.7, 152.6, 150.8, 124.8, 115.8, 110.9, 20.1.

MS (EI, 70 eV): *m/z* (%) = 118 (100), 91 (22).

HRMS (EI): calcd. for [$C_7H_6N_2$]: 118.0531; found: 118.0511.

(*E*)-4-(2-(dimethylamino)vinyl)nicotinonitrile[118a]



In an oven-dried flask, equipped with a magnetic stirring bar and a reflux condenser, 4-methyl-nicotinonitrile (13.8 g, 117 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (13.9 g, 15.5 mL, 117 mmol, 1.0 equiv) were dissolved in dry DMF (100 mL). The mixture was heated to reflux at 160 °C and was stirred for 5 h at that temperature. After cooling to rt, the solvent was removed *in vacuo* and the residue was diluted in water (100 mL). The suspension was extracted with EtOAc (6 × 50 mL) and the combined organic phases were washed with water (6 × 100 mL) and brine (4 × 100 mL). After drying over $MgSO_4$ and filtration, the solvent was evaporated *in vacuo* to give the desired compound (18.5 g, 91%) as dark red crystals.

m.p.: 88-90 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2905, 2213, 1635, 1582, 1383, 1286, 1199, 1102, 843, 781.

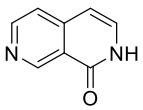
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 8.47 (s, 1H), 8.22 (d, *J* = 5.9 Hz, 1H), 7.28 (d, *J* = 13.2 Hz, 1H), 7.08 (d, *J* = 5.9 Hz, 1H), 5.22 (d, *J* = 13.2 Hz, 1H), 2.97 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 153.7, 150.7, 146.4, 124.8, 117.7, 114.4, 103.3, 90.4, 40.7.

MS (EI, 70 eV): *m/z* (%) = 173 (100), 158 (22), 145 (18), 131 (43), 117 (10), 104 (13), 78 (11), 70 (15), 56 (10).

HRMS (EI): calcd. for [$C_{10}H_{11}N_3$]: 173.0953; found: 173.0949.

2,7-Naphthyridin-1(2*H*)-one (8)[118a]



(*E*)-4-(2-(dimethylamino)vinyl)nicotinonitrile (18.5 g, 107 mmol) was dissolved in a mixture of concentrated acetic acid (135 mL) and concentrated sulfuric acid (135 mL). The mixture was heated to reflux at 165 °C and was stirred for 60 h at that temperature. After cooling to rt, the resulting solution was diluted with water (CAUTION!) and neutralized with aq. NH_3 solution. The brown precipitate was filtered off. The remaining solution was extracted with chloroform (5 × 200 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH = 9:1) to give the desired compound (6.82 g, 44%) as a light brown powder.

m.p.: 260-263 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3152, 3000, 2919, 2856, 1659, 1627, 1593, 858, 813, 795.

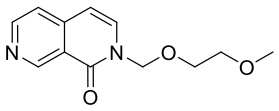
^{1}H-NMR (400 MHz, DMSO-d_6): δ/ ppm = 11.55 (br, 1H), 9.26 (s, 1H), 8.65 (d, *J* = 5.5 Hz, 1H), 7.54 (dd, *J* = 5.5 Hz, 1H), 7.39 (dd, *J* = 7.1 Hz, 1H), 6.51 (d, *J* = 7.1 Hz, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ/ ppm = 161.8, 151.1, 150.3, 143.6, 134.8, 121.4, 119.8, 103.2.

MS (EI, 70 eV): *m/z* (%) = 146 (100), 119 (39), 91 (68), 77 (10), 65 (14), 63 (87), 53 (13), 50 (27), 43 (14), 41 (20), 39 (23), 38 (22), 28 (54).

HRMS (EI): calcd. for [$C_8H_6N_2O$]: 146.0480; found: 146.0488.

2-((2-Methoxyethoxy)methyl)-2,7-naphthyridin-1(2*H*)-one (13)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with 2,7-naphthyridone (**8**, 260 mg, 1.78 mmol) in dry DCM (50 mL). DIPEA (483 mg, 3.74 mmol) and 2-methoxyethoxymethylchloride (443 mg, 3.56 mmol) were added at rt and the mixture was stirred for 12 h. Then, the reaction mixture was poured into sat. aq. $NaHCO_3$ solution (100 mL) and the aq. phase was extracted with DCM (3 × 50 mL). The combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was

purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give **13** (142 mg, 34%) as a light-brown powder.

m.p.: 85.2 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3070, 3045, 2926, 2885, 1667, 1625, 1082, 1050, 844, 757.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.55 (s, 1H), 8.69 (d, *J* = 5.4 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 5.4 Hz, 1H), 6.45 (d, *J* = 7.4 Hz, 1H), 5.45 (s, 2H), 3.84 – 3.69 (m, 2H), 3.56 – 3.45 (m, 2H), 3.32 (s, 3H).

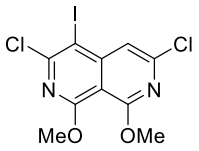
^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 162.0, 151.4, 151.2, 142.8, 135.6, 121.1, 119.2, 104.7, 77.0, 71.6, 69.0, 59.1.

MS (EI, 70 eV): *m/z* (%) = 234 (7), 176 (61), 175 (28), 160 (22), 159 (84), 147 (36), 146 (100), 129 (11), 128 (53), 84 (20), 77 (12), 59 (77), 57 (12), 46 (12), 45 (19).

HRMS (EI): *m/z* calcd. for [$C_{12}H_{14}N_2O_3$]: 234.1004; found: 234.1011.

2.3 Metalation of 2,7-Naphthyridines 9a-c Using TMPLi (2)

3,6-Dichloro-4-iodo-1,8-dimethoxy-2,7-naphthyridine (11a)



According to **TP1**, 3,6-dichloro-1,8-dimethoxy-2,7-naphthyridine (**9a**, 108 mg, 0.41 mmol in 2 mL dry THF) was metalated within 30 min at -78 °C. Then, iodine (155 mg, 0.62 mmol, 1.5 equiv) was added and the mixture was continuously stirred at -78 °C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 × 5 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford **11a** (106 mg, 67%) as a brown solid.

m.p.: 196-198 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1587, 1560, 1526, 1377, 1338, 1283, 1136, 901, 780.

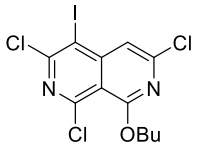
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.48 (s, 1H), 4.15 (s, 3H), 4.11 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 162.2, 161.7, 153.0, 150.8, 150.1, 117.4, 103.4, 83.3, 55.7, 55.5.

MS (EI, 70 eV): *m/z* (%) = 388 (12), 386 (63), 385 (24), 384 (100), 383 (18), 357 (35), 355 (56), 241 (15), 197 (18).

HRMS (EI) calcd. for [$C_{10}H_7Cl_2IN_2O_2$]: 383.8929; found: 383.8930.

8-Butoxy-1,3,6-trichloro-4-iodo-2,7-naphthyridine (11b)



According to **TP1**, 1-butoxy-3,6,8-trichloro-2,7-naphthyridine (**9b**, 100 mg, 0.33 mmol in 2 mL dry THF) was metalated within 30 min at -78 °C. The mixture was stirred for 30 min at the same temperature. Then, iodine (125 mg, 0.50 mmol, 1.5 equiv) was added and the solution was continuously stirred at - 78 °C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 × 5 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc =100:1) to afford **11b** (118 mg, 83%) as a white solid.

m.p.: 88-90 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2952, 2870, 1577, 1545, 1506, 1352, 1297, 1252, 1186, 1084, 977.

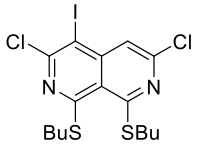
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.54 (s, 1H), 4.57 (t, *J* = 6.4 Hz, 2H), 1.97-1.82 (m, 2H), 1.67-1.50 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 161.5, 153.8, 151.4, 151.1, 150.8, 118.0, 112.0, 93.7, 69.8, 31.1, 20.0, 14.3.

MS (EI, 70 eV): *m*/*z* (%) = 378 (30), 376 (98), 375 (14), 374 (100), 339 (19), 338 (15).

HRMS (EI) calcd. for [$C_{12}H_{10}Cl_3IN_2O$]: 429.8903; found: 429.8902.

1,8-Bis(butylthio)-3,6-dichloro-4-iodo-2,7-naphthyridine (11c)



According to **TP1**, 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 616 mg, 1.64 mmol in 2 mL dry THF) was metalated within 30 min at -40 °C. Subsequently, iodine (830 mg, 3.28 mmol, 2.0 equiv) in dry THF (2.0 mL) was added at -40 °C and the mixture was continuously stirred for 2 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 × 10 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc = 100:1) to give **11c** (744 mg, 90%) as slightly yellow solid.

m.p.: 107-109 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2954, 2927, 1561, 1528, 1477, 1460, 1231, 1115, 1001, 835, 821.

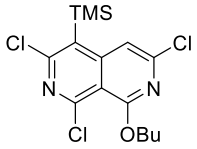
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.55 (s, 1H), 3.39-3.24 (m, 4H), 1.84-1.71 (m, 4H), 1.60-1.45 (m, 4H), 0.99 (t, *J* = 7.3 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 164.5, 163.5, 153.2, 150.1, 147.8, 120.9, 119.8, 88.2, 33.7, 33.5, 30.4, 30.3, 22.5, 13.9.

MS (EI, 70 eV): *m/z* (%) = 446 (76), 444 (100), 389 (64), 387 (88), 57 (23), 41 (33).

HRMS (EI) calcd. for [$C_{16}H_{19}Cl_2IN_2S_2$]: 499.9411; found: 499.9406.

8-Butoxy-1,3,6-trichloro-4-(trimethylsilyl)-2,7-naphthyridine (11d)



According to **TP1**, 1-butoxy-3,6,8-trichloro-2,7-naphthyridine (**9b**, 100 mg, 0.33 mmol in 2 mL dry THF) was metalated within 30 min at -78 °C. Then, TMSCl (0.062 mL, 0.49 mmol, 1.5 equiv) was added and the solution was continuously stirred at -78 °C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 × 5 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc = 99:1) to afford **11d** (85 mg, 69%) as a white solid.

m.p.: 114-116 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2962, 2931, 2868, 1578, 1535, 1497, 1298, 1222, 1189, 1084, 883, 838, 737.

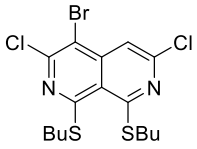
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.50 (s, 1H), 4.53 (t, *J* = 6.4 Hz, 2H), 1.95-1.81 (m, 2H), 1.67-1.48 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H), 0.57 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 161.4, 154.4, 153.0, 151.4, 148.6, 125.8, 112.3, 111.1, 68.7, 30.8, 19.6, 13.9, 2.6 (3 x C).

MS (EI, 70 eV): *m/z (%)* = 378 (14), 376 (14), 343 (14), 341 (22), 322 (59), 320 (59), 309 (36), 307 (89), 273 (21), 271 (100).

HRMS (EI): calcd. for [$C_{15}H_{19}Cl_3N_2OSi$]: 376.0332; found: 376.0328.

4-Bromo-1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (12a)



According to **TP1**, 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 188 mg, 0.5 mmol in 2 mL dry THF) was metalated within 30 min at -40 °C. Bromine (0.03 ml, 0.6 mmol, 1.2 equiv) was added at -40 °C and the reaction mixture was stirred further 2 h at this temperature. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 × 10 mL) and dried over $MgSO_4$. After filtration, the solvents were removed *in vacuo*. Purification by flash column chromatography (isohexane/EtOAc = 80:1) gave the desired product **12a** (144 mg, 63%) as beige crystals.

m.p.: 80-82 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2957, 2928, 1562, 1537, 1482, 1235, 1115, 1010, 836, 825, 662.

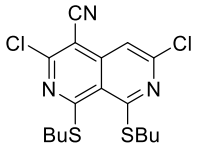
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.59 (s, 1H), 3.34 (t, *J* = 7.2 Hz, 2H), 3.30 (t, *J* = 7.2 Hz, 2H), 1.84-1.71 (m, 4H), 1.61-1.45 (m, 4H), 0.99 (t, *J* = 7.3 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 164.5, 162.2, 149.8, 148.4, 144.9, 121.1, 114.3, 110.3, 33.6, 33.5, 30.3, 30.3, 22.5, 13.9.

MS (EI, 70 eV): *m*/*z* (%) = 399 (53), 395 (56), 343 (50), 342 (21), 341 (100), 340 (21), 339 (60), 305 (19), 41 (19).

HRMS (EI) calcd. for [$C_{16}H_{19}BrCl_2N_2S_2$]: 451.9550; found 451.9531.

1,8-Bis(butylthio)-3,6-dichloro-2,7-naphthyridine-4-carbonitrile (12b)



According to **TP1**, 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 375 mg, 1 mmol in 4 mL dry THF) was metalated within 30 min at - 40 °C. Subsequently, tosyl cyanide (218 mg, 1.2 mmol, 1.2 equiv) was added at -40 °C and the reaction mixture was continuously stirred for 2 h. Then, the mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over $MgSO_4$. After filtration, the solvents were removed *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc = 80:2) to give **12b** (251 mg, 63%) as a white solid.

m.p.: 73-75 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2957, 2927, 1566, 1546, 1478, 1329, 1276, 1133, 1082, 923, 838, 717.

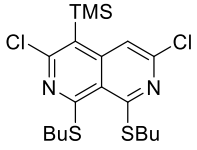
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.35 (s, 1H), 3.40-3.29 (m, 4H), 1.84-1.70 (m, 4H), 1.59-1.45 (m, 4H), 0.99 (t, *J* = 7.5 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 167.1, 164.7, 162.4, 150.3, 144.3, 118.0, 115.1, 110.7, 94.4, 33.5, 33.3, 30.4, 30.2, 22.4, 22.2, 13.9, 13.8.

MS (EI, 70 eV): *m*/*z* (%) = 399 (6), 346 (19), 344 (73), 342 (100), 310 (14), 290 (15), 288 (71), 286 (92), 252 (12), 250 (22), 57 (25), 55 (10), 41 (42).

HRMS (EI) calcd. for [$C_{17}H_{19}Cl_2N_3S_2$]: 399.0397; found: 399.0396.

1,8-Bis(butylthio)-3,6-dichloro-4-(trimethylsilyl)-2,7-naphthyridine (12c)



According to **TP1**, 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 250 mg, 0.66 mmol in 2.5 mL dry THF) was metalated within 30 min at -40 °C. Subsequently, TMSCl (0.10 mL, 0.79 mmol, 1.2 equiv) was added at -40 °C and the reaction mixture was continuously stirred for 2 h. Then, the mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 × 10 mL) and dried over $MgSO_4$.

After filtration, the solvents were removed *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc = 100:0.5) to give **12c** (207 mg, 73%) as a brown solid.

m.p.: 42-44 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2955, 2928, 1563, 1514, 1470, 1263, 1216, 1119, 1023, 892, 845, 822.

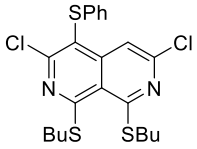
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.49 (s, 1H), 3.36-3.26 (m, 4H), 1.85-1.71 (m, 4H), 1.60-1.45 (m, 4H), 0.99 (t, *J* = 7.3 Hz, 6H), 0.54 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 164.2, 164.1, 154.6, 150.6, 147.8, 120.2, 120.1, 114.5, 33.3, 33.2, 30.5, 22.4, 13.9, 2.8.

MS (EI, 70 eV): *m/z* (%) = 393 (22), 392 (21), 391 (82), 390 (28), 389 (100), 357 (20), 335 (62), 333 (80), 41 (23).

HRMS (EI) calcd. for [$C_{19}H_{28}C_{l2}N_2S_2Si$]: 446.0840; found: 446.0844.

1,8-Bis(butylthio)-3,6-dichloro-4-(phenylthio)-2,7-naphthyridine (12d)



According to **TP1**, 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 187 mg, 0.5 mmol in 2 mL dry THF) was metalated within 30 min at -40 °C. Subsequently, *S*-phenyl benzenethiosulfonate (150 mg, 0.6 mmol, 1.2 equiv) was added at -40 °C and the reaction mixture was continuously stirred for 2 h. Then, the mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 10 mL) and dried over $MgSO_4$. After filtration, the solvents were removed *in vacuo*. Purification by flash column chromatography (isohexane/EtOAc = 200:1) gave the desired product **12d** (192 mg, 80%) as a slightly yellow solid.

m.p.: 115-117 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2958, 2926, 1588, 1525, 1473, 1261, 1233, 1113, 1029, 898, 739, 687.

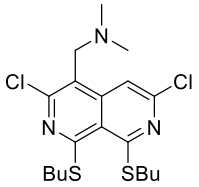
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.90 (s, 1H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 2H), 3.36-3.33 (m, 4H), 1.83-1.76 (m, 4H), 1.57-1.50 (m, 4H), 0.99 (t, *J* = 7.2 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 165.2, 164.4, 154.8, 149.8, 149.8, 135.4, 129.4, 127.3, 126.4, 121.0, 115.9, 113.5, 33.6, 33.5, 30.4, 30.3, 22.4, 22.4, 13.6.

MS (EI, 70 eV): *m/z* (%) = 484 (15), 482 (19), 428 (18), 427 (14), 426 (76), 425 (23), 424 (100), 395 (11), 373 (20), 371 (68), 333 (11), 298 (17), 109 (11), 77 (15), 57 (38), 55 (11), 41 (48).

HRMS (EI) calcd. for [$C_{22}H_{24}Cl_2N_2S_3$]: 482.0479; found: 482.0467.

1-(1,8-Bis(butylthio)-3,6-dichloro-2,7-naphthyridin-4-yl)-*N*,*N*-dimethylmethanamine (12e)



According to **TP1**, 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 250 mg, 0.66 mmol in 2 mL dry THF) was metalated within 30 min at -40 °C. Subsequently, *N,N*-dimethylmethyleneiminium iodide (147 mg, 0.79 mmol, 1.2 equiv) was added at -40 °C and the reaction mixture was continuously stirred for 2 h. Then, the mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 × 10 mL) and dried over $MgSO_4$. After filtration, the solvents were removed *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc = 95:5) to give **12e** (230 mg, 81%) as a yellow solid.

m.p.: 68-70 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2959, 2926, 1573, 1552, 1486, 1458, 1272, 1241, 1128, 1094, 1019, 996, 840, 829.

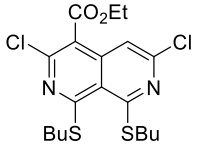
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.59 (s, 1H), 3.72 (s, 2H), 3.37-3.28 (m, 4H), 2.30 (s, 6H), 1.84-1.72 (m, 4H), 1.61-1.45 (m, 4H), 0.98 (t, *J* = 7.2 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 163.8, 162.2, 148.8, 148.6, 146.0, 120.8, 119.0, 112.2, 58.0, 45.3, 33.3, 33.2, 30.5, 22.5, 22.4, 13.9.

MS (EI, 70 eV): *m*/*z* (%) = 389 (70), 388 (43), 274 (42), 72 (40), 69 (43), 58 (83), 57 (100), 55 (57), 43 (60), 41 (81).

HRMS (EI) calcd. for [$C_{19}H_{27}Cl_2N_3S_2$]: 431.1023; found: 431.1014.

Ethyl 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine-4-carboxylate (12f)



According to **TP1**, 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 207 mg, 0.55 mmol in 2.5 mL dry THF) was metalated within 30 min at -40 °C. Then, a 0.4 M solution of $MgCl_2$ (1.5 mL, 0.61 mmol, 1.1 equiv) was added to the mixture at -40 °C. After further 30 min, ethyl chloroformate (0.06 mL, 0.61 mmol, 1.1 equiv) was added. The reaction mixture was warmed up to -30 °C and stirred for 5 h at this temperature until complete conversion of the starting material. Then, the mixture was quenched with sat. aq. NH_4Cl (20 mL) solution and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc = 80:1) to afford **12f** (206 mg, 84%) as a yellow solid.

m.p.: 72-74°C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2956, 2928, 1729, 1552, 1487, 1218, 1208, 1153, 1122, 1061, 867.

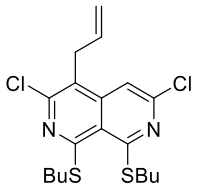
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.18 (s, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 3.33 (t, *J* = 7.2 Hz, 4H), 1.85-1.72 (m, 4H), 1.59-1.48 (m, 4H), 1.45 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.3 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 165.2, 165.1, 164.2, 149.1, 145.1, 142.8, 119.5, 117.6, 110.9, 62.4, 33.3, 33.2, 30.2, 30.1, 22.2, 14.0, 13.7.

MS (EI, 70 eV): *m/z* (%) = 446 (5), 401 (7), 391 (74), 389 (100), 359 (9), 357 (13), 337 (11); 335 (46), 334 (11), 333 (65), 307 (18), 305 (24), 287 (15), 57 (10), 41 (14).

HRMS (EI) calcd. for [$C_{19}H_{24}Cl_2N_2O_2S_2$]: 446.0656; found: 446.0645.

4-Allyl-1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (12g)



According to **TP1**, 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 187 mg, 0.5 mmol in 2 mL dry THF) was metalated within 30 min at -40 °C. Then, a solution of CuCN·2LiCl (0.1 mL, 0.1 mmol, 1.0 M in THF, 0.2 equiv) was added dropwise at -40 °C, followed by the addition of allyl bromide (72 mg, 0.6 mmol, 1.2 equiv). The reaction mixture was slowly warmed up to rt within 1 h. Then, the mixture was quenched with sat. aq. NH_4Cl/NH_3 (10:1 v/v, 10 mL) solution and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc = 100:0.5) to afford **12g** (192 mg, 93%) as a white solid.

m.p.: 61-63 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2957, 2930, 1573, 1551, 1484, 1454, 1255, 1125, 1081, 908, 889, 830.

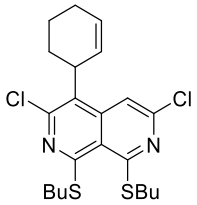
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.24 (s, 1H), 5.99-5.85 (m, 1H), 5.10 (d, *J* = 10.0 Hz, 1H), 4.98 (d, *J* = 17.1 Hz, 1H), 3.69 (d, *J* = 5.3 Hz, 2H), 3.38-3.26 (m, 4H), 1.78 (quint, *J* = 7.3 Hz, 4H), 1.52 (sxt, *J* = 7.3 Hz, 4H), 0.99 (t, *J* = 7.3 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 164.4, 161.2, 148.6, 148.4, 145.0, 133.5, 120.6, 119.9, 117.1, 111.2, 33.4, 33.2, 33.0, 30.5, 30.4, 22.5, 13.9.

MS (EI, 70 eV): *m/z* (%) = 359 (70), 303 (62), 301 (85), 97 (34), 71 (30), 57 (57).

HRMS (EI) calcd. for [$C_{19}H_{24}Cl_2N_2S_2$]: 414.0758; found 414.0742.

1,8-Bis(butylthio)-3,6-dichloro-4-(cyclohex-2-en-1-yl)-2,7-naphthyridine (12h)



According to **TP1**, 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 187 mg, 0.5 mmol in 2 mL dry THF) was metalated within 30 min at -40 °C. Then, a solution of CuCN·2LiCl (0.1 mL, 0.1 mmol, 1.0 M in THF, 0.2 equiv) was added dropwise at -40 °C, followed by the addition of 3-bromocyclohexene (96 mg, 0.6 mmol, 1.2 equiv). The reaction mixture was slowly warmed up to rt within 1 h. Then, the mixture was quenched with sat. aq. NH_4Cl/NH_3 (10:1 v/v, 10 mL) solution and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc = 100:0.5) to afford **12h** (216 mg, 95%) as brown oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2955, 2927, 2859, 1568, 1541, 1484, 1279, 1229, 1126, 1101, 983, 658.

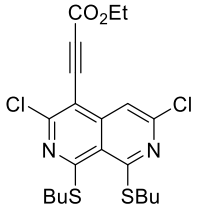
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 7.79 (s, 1H), 5.99-5.89 (m, 1H), 5.75-5.66 (m, 1H), 4.30 (s, 1H), 3.36-3.25 (m, 4H), 2.24 (s, 2H), 2.04-1.93 (m, 2H), 1.85-1.70 (m, 4H), 1.59-1.46 (m, 6H), 0.98 (t, *J* = 7.2 Hz, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 164.1, 160.7, 148.2, 147.4, 144.7, 130.5, 128.0, 124.8, 121.2, 112.1, 39.2, 33.3, 33.2, 30.6, 30.5, 28.1, 24.8, 23.1, 22.5, 22.5, 22.4, 13.9.

MS (EI, 70 eV): *m*/*z* (%) = 401 (17), 400 (18), 399 (74), 398 (22), 397 (100), 365 (18), 57 (18).

HRMS (EI) calcd. for [$C_{22}H_{28}Cl_2N_2S_2$]: 454.1071; found 454.1068.

Ethyl 3-(1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridin-4-yl)propiolate (12i)



According to **TP1**, 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 187 mg, 0.5 mmol in 2 mL dry THF) was metalated within 30 min at -40 °C. Then, a solution of $ZnCl_2$ (0.55 mL, 0.55 mmol, 1.0 M in THF, 1.1 equiv) was added to the mixture at -40 °C. After 30 min, a solution of CuCN·2LiCl (0.1 mL, 0.1 mmol, 1.0 M in THF, 0.2 equiv) was added, followed by the addition of ethyl 3-bromopropiolate (106 mg, 0.6 mmol, 1.2 equiv). The reaction mixture was continuously stirred overnight, letting it slowly warm up to rt. Then, the mixture was quenched with sat. aq. NH_4Cl/NH_3 (10:1 v/v, 10 mL) solution and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (isohexane/ EtOAc = 140:1) to afford **12i** (198 mg, 84%) as an orange solid.

m.p: 61-63 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2961, 2924, 2213, 1713, 1538, 1476, 1288, 1229, 1136, 1090, 799 741.

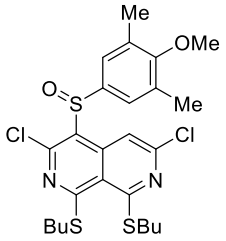
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.55 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.34 (t, *J* = 7.1 Hz, 4H), 1.78 (quint, *J* = 7.3 Hz, 4H), 1.53 (sxt, *J* = 7.4 Hz, 4H), 1.40 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.3 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 166.0, 164.6, 153.7, 151.9, 150.0, 146.1, 119.5, 112.3, 105.0, 91.4, 78.9, 62.6, 33.7, 33.6, 30.3, 30.2, 22.5, 22.4, 14.3, 13.8, 13.8.

MS (EI, 70 eV): *m/z* (%) = 470 (7), 417.0 (18), 416 (15), 415 (66), 413 (100), 381 (16), 360 (10), 358 (52), 357 (11), 356 (68), 331 (14), 286 (11), 249 (12), 57 (16), 41.2 (12).

HRMS (EI) calcd. for [$C_{21}H_{24}Cl_2N_2O_2S_2$]: 470.0656; found: 470.0655.

1,8-Bis(butylthio)-3,6-dichloro-4-((4-methoxy-3,5-dimethylphenyl)sulfinyl)-2,7-naphthyridine (12j)



According to **TP1**, 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 260 mg, 0.69 mmol in 3 mL dry THF) was metalated within 30 min at -40 °C. Subsequently, a solution of $MgCl_2$ (2.08 mL, 0.83 mmol, 0.40 M in THF, 1.2 equiv) was added to the reaction mixture at -40 °C. After further 30 min, 4-methoxy-3,5-dimethylbenzene-1-sulfinic chloride (225 mg, 1.03 mmol, 1.5 equiv) was added and the solution was stirred at -40 °C for 2 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 10 mL) and dried over $MgSO_4$. After filtration, the solvents were removed *in vacuo*. The crude product was purified by flash column chromatography (isohexane/ EtOAc = 19:1) to afford **12j** (276 mg, 72%) as a yellow solid.

m.p.: 140-142 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2958, 2931, 1559, 1535, 1478, 1271, 1220, 1123, 1056, 1017, 970, 893.

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 8.25 (s, 1H), 7.30 (s, 2H), 3.71 (s, 3H), 3.41-3.21 (m, 4H), 2.30 (s, 6H), 1.88-1.65 (m, 4H), 1.63-1.39 (m, 4H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).

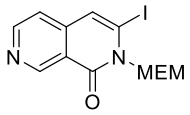
^{13}C NMR (75 MHz, $CDCl_3$): δ/ ppm = 168.3, 164.5, 159.2, 149.6, 147.9, 143.4, 137.0, 132.8, 124.7, 123.4, 121.1, 110.2, 59.9, 33.8, 33.4, 30.3, 30.2, 22.5, 22.4, 16.5, 13.9, 13.8.

MS (EI, 70 eV): *m/z* (%) = 501 (33), 453 (33), 451 (46), 183 (49), 91 (42), 57 (56), 55 (30), 41 (100).

HRMS (EI) calcd. for [$C_{25}H_{30}Cl_2N_2O_2S_3$]: 556.0846; found: 556.0848.

2.4 Metalation of 2,7-Naphthyridone 13 using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (6)

3-Iodo-2-((2-methoxyethoxy)methyl)-2,7-naphthyridin-1(2*H*)-one (15)



According to **TP2**, 2,7-naphthyridone (**13**, 60 mg, 0.26 mmol) was metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**, 1.1 mL, 0.31 mmol, 0.28 M in THF, 1.2 equiv). Iodine (132 mg, 0.52 mmol) dissolved in dry THF (2 mL) was then added dropwise at −10 °C. The resulting mixture was allowed to warm up to rt and was further stirred for 30 min. Then, the reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with EtOAc (3 × 20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give **15** (86 mg, 92%) as a brown crystalline solid.

dec.: 120 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3080, 2953, 2921, 1662, 1597, 1197, 1088, 1036, 871, 789.

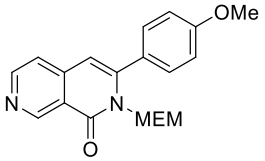
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.52 (s, 1H), 8.73 (d, *J* = 5.4 Hz, 1H), 7.18 (dd, *J* = 5.4 Hz, 1H), 7.15 (s, 1H), 5.79 (s, 2H), 3.81–3.78 (m, 2H), 3.57 –3.53 (m, 2H), 3.35 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 161.7, 152.1, 152.0, 142.8, 120.2, 118.5, 117.5, 99.7, 80.7, 71.7, 69.1, 59.2.

MS (EI, 70 eV): *m/z* (%) = 360 (3), 302 (14), 285 (16), 272 (39), 232 (13), 159 (11), 158 (17), 24 (145), 89 (88), 59 (100).

HRMS (EI) calcd. for [$C_{12}H_{13}IN_2O_3$]: 359.9971; found: 359.9983.

2-((2-Methoxyethoxy)methyl)-3-(4-methoxyphenyl)-2,7-naphthyridin-1(2*H*)-one (16a)



According to **TP2**, 2,7-naphthyridone (**13**, 60 mg, 0.26 mmol) was metalated within 72 h using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**, 1.1 mL, 0.31 mmol, 0.28 M in THF, 1.2 equiv). A solution of $Pd(dba)_2$ (6 mg, 4 mol %), tfp (5 mg, 8 mol %) and 1-iodo-4-methoxybenzene (72 mg, 0.31 mmol) in dry THF (1 mL) was added at −10 °C. The resulting mixture was allowed to warm up to rt and was further stirred for 12 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/isohexane = 8:2) to give **16a** (72 mg, 81%) as a yellow solid.

m.p.: 84 -86 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3077, 2913, 2854, 1660, 1606, 1510, 1299, 1091, 947, 786.

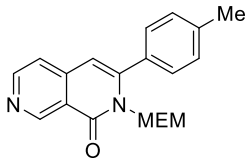
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.56 (s, 1H), 8.68 (d, *J* = 5.1 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 5.1 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.33 (s, 1H), 5.32 (s, 2H), 3.85 (s, 3H), 3.80 –3.76 (m, 2H), 3.53 –3.49 (m, 2H), 3.32 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 163.2, 160.7, 151.3, 150.7, 150.0, 142.5, 130.7, 127.1, 120.1, 119.1, 113.9, 106.1, 74.3, 71.9, 69.1, 59.1, 55.5.

MS (EI, 70 eV): *m/z* (%) = 340 (10), 265 (55), 253 (38), 252 (100), 89 (12), 59 (43).

HRMS (EI) calcd. for [$C_{19}H_{20}N_2O_4$]: 340.1423; found: 340.1416.

2-((2-Methoxyethoxy)methyl)-3-(*p*-tolyl)-2,7-naphthyridin-1(2*H*)-one (16b)



According to **TP2**, 2,7-naphthyridone (**13**, 117 mg, 0.50 mmol) was metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**, 2.86 mL, 0.60 mmol, 0.21 M in THF, 1.2 equiv). A solution of $Pd(dba)_2$ (12 mg, 4 mol%), tfp (9 mg, 8 mol%) and 1-iodo-4-methylbenzene (131 mg, 0.60 mmol) in dry THF (1 mL) was added at −10 °C. The resulting mixture was allowed to warm up to rt and was further stirred for 12 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH= 9.5:0.5) to give **16b** (135 mg, 84%) as a yellow solid.

m.p.: 56-58 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3077, 2912, 2867, 1662, 1618, 1544, 1093, 1008, 882, 813.

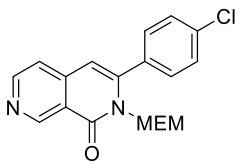
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.55 (s, 1H), 8.66 (d, *J* = 5.4 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.28 –7.20 (m, 3H), 6.30 (s, 1H), 5.29 (s, 2H), 3.87–3.62 (m, 2H), 3.60–3.39 (m, 2H), 3.29 (s, 3H), 2.38 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 163.1, 151.5, 151.1, 149.7, 142.1, 139.7, 131.8, 129.1, 129.1, 120.0, 118.9, 106.0, 74.1, 71.8, 68.9, 58.9, 21.4.

MS (EI, 70 eV): *m/z (%)* = 324 (4), 266 (13), 249 (59), 236(100), 89 (10), 59 (39).

HRMS (EI): calcd. for [$C_{19}H_{20}N_2O_3$]: 324.1474; found: 324.1473.

3-(4-Chlorophenyl)-2-((2-methoxyethoxy)methyl)-2,7-naphthyridin-1(2*H*)-one (16c)



According to **TP2**, 2,7-naphthyridone (**13**, 117 mg, 0.5 mmol) was metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**, 2.86 mL, 0.6 mmol, 0.21 M in THF, 1.2 equiv). A solution of $Pd(dba)_2$ (12 mg, 4 mol %), tfp (9 mg, 8 mol %) and 1-chloro-4-iodobenzene (143 mg, 0.60 mmol) in dry THF

(1 mL) was added at −10 °C. The resulting mixture was allowed to warm up to rt and was further stirred for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH= 9.5:0.5) to give **16c** (148 mg, 86%) as a yellow crystalline solid.

m.p.: 102 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3078, 2917, 2871, 1657, 1618, 1092, 1008, 946, 881, 820.

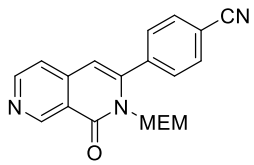
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.58 (s, 1H), 8.71 (d, *J* = 5.5 Hz, 1H), 7.56–7.47 (m, 2H), 7.47 –7.39 (m, 2H), 7.31 (d, *J* = 5.5 Hz, 1H), 6.33 (s, 1H), 5.29 (s, 2H), 3.79–3.75 (m, 2H), 3.52–3.47 (m, 2H), 3.32 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 163.0, 151.4, 151.1, 148.6, 142.2, 136.1, 133.1, 130.7, 128.8, 120.2, 119.1, 106.4, 74.2, 71.9, 69.1, 59.0.

MS (EI, 70 eV): *m/z (%)* = 344 (4), 286 (22), 269 (35), 256 (87), 234 (35), 89 (39), 59 (100).

HRMS (EI) calcd. for [$C_{18}H_{17}ClN_2O_3$]: 344.0928; found: 344.0924.

4-(2-((2-Methoxyethoxy)methyl)-1-oxo-1,2-dihydro-2,7-naphthyridin-3-yl)benzonitrile (16d)



According to **TP2**, 2,7-naphthyridone (**13**, 117 mg, 0.5 mmol) was metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**, 2.86 mL, 0.6 mmol, 0.21 M in THF, 1.2 equiv). A solution of $Pd(dba)_2$ (12 mg, 4 mol%), tfp (9 mg, 8 mol%) and 4-iodobenzonitrile (137 mg, 0.60 mmol) in dry THF (1 mL) was added at −10 °C. The resulting mixture was allowed to warm up to rt and was further stirred for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH= 9.5:0.5) to give **16d** (124 mg, 74%) as a yellow crystalline solid.

m.p.: 106-108 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3080, 3046, 2926, 2361, 2231, 1650, 1622, 1103, 1082, 850, 792.

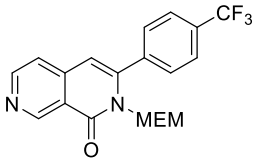
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.59 (s, 1H), 8.74 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 5.2 Hz, 1H), 6.34 (s, 1H), 5.26 (s, 2H), 3.78-3.74 (m, 2H), 3.50–3.46 (m, 2H), 3.30 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 162.7, 151.3, 151.2, 147.8, 142.0, 138.9, 132.3, 130.2, 120.3, 119.3, 118.2, 113.8, 106.7, 74.2, 71.8, 69.1, 59.1.

MS (EI, 70 eV): *m/z (%)* = 335 (2), 277 (20), 260 (39), 247 (61), 230 (13), 89 (55), 59 (100).

HRMS (EI) calcd. for [$C_{19}H_{17}N_3O_3$]: 335.1270; found: 335.1261.

2-((2-Methoxyethoxy)methyl)-3-(4-(trifluoromethyl)phenyl)-2,7-naphthyridin-1(2*H*)-one (16e)



According to **TP2**, 2,7-naphthyridone (**13**, 117 mg, 0.5 mmol) was metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**, 2.86 mL, 0.6 mmol, 0.21 M in THF, 1.2 equiv). A solution of $Pd(dba)_2$ (12 mg, 4 mol%), tfp (9 mg, 8 mol%) and 4-iodobenzotrifluoride (163 mg, 0.6 mmol) in dry THF (1 mL) was added at −10 °C. The resulting mixture was allowed to warm up to rt and was further stirred for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH= 9.5:0.5) to give **16e** (88 mg, 46%) as a yellow solid.

m.p.: 97-99 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3080, 2926, 2891, 2824, 2361, 2340, 1660, 1611, 1126, 1107, 1065, 1007, 848.

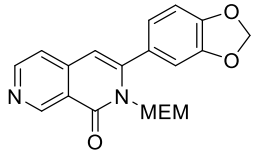
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.60 (s, 1H), 8.74 (d, *J* = 5.5 Hz, 1H), 7.80–7.67 (m, 4H), 7.34 (d, *J* = 5.5 Hz, 1H), 6.36 (s, 1H), 5.30 (s, 2H), 3.83–3.75 (m, 2H), 3.55–3.47 (m, 2H), 3.31 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 162.8, 151.3, 151.0, 148.4, 142.2, 138.1 (q, J_{CF} = 1.1 Hz), 131.9 (q, J_{CF} = 32.9 Hz), 129.9, 125.6 (q, J_{CF} = 3.7 Hz), 123.9 (q, J_{CF} = 272.8 Hz), 120.3, 119.3, 106.6, 74.2, 71.9, 69.1, 59.0.

MS (EI, 70 eV): *m/z (%)* = 378 (2), 320 (21), 303 (50), 290 (81), 89 (43), 59 (100).

HRMS (EI) calcd. for [$C_{19}H_{17}F_3N_2O_3$]: 378.1191; found: 378.1187.

3-(Benzo[*d*][1,3]dioxol-5-yl)-2-((2-methoxyethoxy)methyl)-2,7-naphthyridin-1(2*H*)-one (16f)



According to **TP2**, 2,7-naphthyridone (**13**, 117mg, 0.5 mmol) was metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**, 1.71 mL, 0.6 mmol, 0.35 M in THF, 1.2 equiv). A solution of PEPPSI-*i*Pr (14 mg, 4 mol%) and 5-bromobenzo[*d*][1,3]dioxole (121 mg, 0.60 mmol) in dry THF (1 mL) was added at −10 °C. The resulting mixture was allowed to warm up to rt and was further stirred for 12 h at 60 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH= 9.5:0.5) to give **16f** (141 mg, 80%) as a colorless solid.

m.p.: 107 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3071, 2932, 2820, 1657, 1615, 1482, 1234, 1086, 1036, 821.

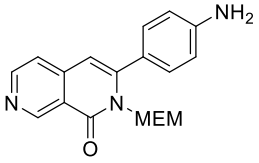
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.57 (s, 1H), 8.69 (d, *J* = 5.6 Hz, 1H), 7.39 (d, *J* = 5.6 Hz, 1H), 7.09 (d, *J* = 1.6 Hz, 1H), 7.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.38 (s, 1H), 6.06 (s, 2H), 5.36 (s, 2H), 3.85 –3.76 (m, 2H), 3.56 –3.50 (m, 2H), 3.34 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 162.8, 151.0, 150.0, 149.2, 148.7, 147.8, 143.5, 128.1, 123.5, 120.4, 119.7, 109.9, 108.5, 106.0, 101.8, 74.5, 71.9, 69.3, 59.1.

MS (EI, 70 eV): *m/z (%)* = 354 (14), 279 (20), 278 (12), 267 (34), 266 (100), 249 (23), 89 (10), 59 (41).

HRMS (EI) calcd. for [$C_{19}H_{18}N_2O_5$]: 354.1216; found: 354.1215.

3-(4-Aminophenyl)-2-((2-methoxyethoxy)methyl)-2,7-naphthyridin-1(2*H*)-one (16g)



According to **TP2**, 2,7-naphthyridone (**13**, 117 mg, 0.50 mmol) was metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**, 2.86 mL, 0.6 mmol, 0.21 M in THF, 1.2 equiv). Using a syringe-pump, the zinc-species was then added dropwise to a solution of $Pd(OAc)_2$ (5 mg, 4 mol%), tfp (16 mg, 8 mol%) and 4-iodoaniline (131 mg, 0.60 mmol) in dry THF (1 mL) over 1 h at rt. The resulting mixture was further stirred for 12 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give **16g** (124 mg, 76%) as a yellow solid.

m.p.: 109 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3326, 3193, 2926, 1665, 1602, 1511, 1294, 1088, 1044, 832.

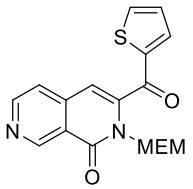
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.51 (s, 1H), 8.71–8.55 (m, 1H), 7.32–7.27 (m, 1H), 7.24–7.20 (m, 1H), 6.72–6.64 (m, 2H), 6.27 (s, 1H), 5.30 (s, 2H), 4.04 (br, 2H, NH_2), 3.78–3.71 (m, 2H), 3.55–3.45 (m, 2H), 3.29 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 163.3, 151.4, 150.9, 150.2, 148.0, 142.3, 130.4, 124.2, 119.7, 118.8, 114.3, 105.7, 74.4, 71.8, 68.9, 58.9.

MS (EI, 70 eV): *m/z (%)* = 325 (31), 250 (52), 237 (100), 59 (39).

HRMS (EI) calcd. for [$C_{18}H_{19}N_3O_3$]: 325.1426; found: 325.1422.

2-((2-Methoxyethoxy)methyl)-3-(thiophene-2-carbonyl)-2,7-naphthyridin-1(2*H*)-one (17a)



According to **TP2**, 2-7-naphthyridone (**13**, 117 mg, 0.5 mmol) was metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**, 2.86 mL, 0.6 mmol, 0.21 M in THF, 1.2 equiv). A solution of CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF, 1.1 equiv) was added and the reaction mixture was stirred for

10 min at −10 °C before thiophene-2-carbonyl chloride (95 mg, 0.07 mL 0.65 mmol) was added. The resulting mixture was allowed to warm up to rt and was further stirred for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 (10:1 v/v, 10 mL) solution, extracted with EtOAc (3 × 20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/isohexane = gradient 2:8–10:0, then EtOAc/MeOH = 9.5:0.5) to give **17a** (88 mg, 52%) as an orange crystalline solid.

m.p.: 79-81°C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3077, 2922, 2855, 1643, 1616, 1407, 1100, 855, 755, 724.

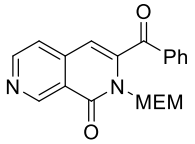
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.66 (s, 1H), 8.83 (s, 1H), 7.85 (d, *J* = 4.7 Hz, 1H), 7.77 (d, *J* = 3.3 Hz, 1H), 7.46 (s, 1H), 7.23–7.19 (m, 1H), 6.73 (s, 1H), 5.92–5.66 (m, 2H), 3.62–3.46 (m, 2H), 3.30–3.15 (m, 2H), 3.12 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 181.4, 161.5, 150.9, 143.0, 142.4, 141.4, 136.8, 136.4, 135.4, 134.3, 132.6, 128.6, 107.8, 72.5, 71.2, 68.6, 58.9.

MS (EI, 70 eV): *m/z (%)* = 344 (2), 268 (100), 256 (36), 228 (17),111 (35), 97 (18), 89 (25), 59 (84), 43 (16).

HRMS (EI) calcd. for [$C_{17}H_{16}N_2O_4S$]: 344.0831; found: 344.0830.

3-Benzoyl-2-((2-methoxyethoxy)methyl)-2,7-naphthyridin-1(2*H*)-one (17b)



According to **TP2**, 2,7-naphthyridone (**13**, 117 mg, 0.5 mmol) was metalated within 72 h, using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**6**, 1.67 mL, 0.6 mmol, 0.36 M in THF, 1.2 equiv). A solution of CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF, 1.1 equiv) was added and the reaction mixture was stirred for 10 min at −10 °C before benzoyl chloride (91 mg, 0.08 mL, 0.65 mmol, 1.3 equiv) was added. The resulting mixture was allowed to warm up to rt and was further stirred for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 (10:1 v/v, 10 mL) solution, extracted with EtOAc (3 × 20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/isohexane = gradient 2:8–10:0, then EtOAc/MeOH = 9.5:0.5) to give **17b** (51 mg, 30%) as a yellow solid.

m.p.: 108 –109 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3063, 2926, 2875, 2361, 2340, 1666, 1618, 1254, 1099, 721.

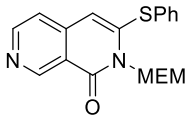
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.64 (s, 1H), 8.79 (d, *J* = 4.7 Hz, 1H), 7.97 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.68 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.40 (d, *J* = 5.3 Hz, 1H), 6.53 (s, 1H), 5.77 (s, 2H), 3.56–3.51 (m, 2H), 3.25–3.20 (m, 2H), 3.11 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 189.6, 161.5, 150.8, 150.6, 143.7, 141.5, 135.4, 134.6, 130.6, 128.8, 120.2, 107.8, 77.4, 72.5, 71.1, 68.7, 58.9.

MS (EI, 70 eV): *m/z (%)* = 338 (2), 264 (10), 263 (54), 262 (100), 251 (13), 250 (29), 221 (11), 105 (32), 91 (14), 89 (18), 77 (28), 59 (70), 45 (15), 43 (20).

HRMS (EI) calcd. for [$C_{19}H_{18}N_2O_4$]: 338.1267; found: 338.1257.

2-((2-Methoxyethoxy)methyl)-3-(phenylthio)-2,7-naphthyridin-1(2*H*)-one (19a)



According to **TP3**, the I/Mg-exchange of 3-iodo-2,7-naphthyridone (**15**, 144 mg, 0.4 mmol) was finished within 20 min, using a solution of *i*PrMgCl·LiCl (**1**) in dry THF (0.32 mL, 0.4 mmol, 1.26 M, 1.0 equiv). The corresponding magnesium derivative was then added dropwise to a solution of *S*-phenyl benzene-thiosulfonate (300 mg, 1.2 mmol) in dry THF (5 mL) at 0 °C *via* syringe. The resulting mixture was allowed to warm up to rt and was further stirred for 12 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **23a** (98 mg, 0.29 mmol, 72%) as a brown solid.

m.p.: 69-70 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3070, 2924, 2883, 2815, 1660, 1596, 1523, 1102, 1080, 740.

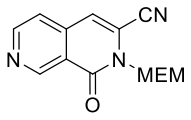
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.44 (s, 1H), 8.55 (d, *J* = 5.4 Hz, 1H), 7.55–7.48 (m, 2H), 7.47–7.39 (m, 3H), 6.99 (d, *J* = 5.4 Hz, 1H), 5.96 (s, 1H), 5.82 (s, 2H), 3.87–3.73 (m, 2H), 3.56–3.45 (m, 2H), 3.33 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 162.9, 151.5, 151.1, 148.4, 141.6, 134.2, 130.2, 130.1, 129.9, 118.5, 118.1, 105.5, 74.0, 71.6, 69.1, 59.1.

MS (EI, 70 eV): *m/z* (%) = 342 (31), 267 (29), 254 (81), 195 (11), 165 (11), 145 (10), 89 (31), 59 (100).

HRMS (EI) calcd. for [$C_{18}H_{18}N_2O_3S$]: 342.1038; found: 342.1034.

2-((2-Methoxyethoxy)methyl)-1-oxo-1,2-dihydro-2,7-naphthyridine-3-carbonitrile (19b)



According to **TP3**, the I/Mg-exchange of 3-iodo-2,7-naphthyridone (**15**, 72 mg, 0.2 mmol) was finished within 20 min using a solution of *i*PrMgCl·LiCl (**1**) in dry THF (0.16 mL, 0.2 mmol, 1.26 M, 1.0 equiv). The corresponding magnesium derivative was then added dropwise to a solution of *p*-toluenesulfonyl cyanide (54 mg, 0.3 mmol) in dry THF (3 mL) at 0 °C *via* syringe. The resulting mixture was allowed to warm up to rt and was further stirred for 12 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromato-

graphy (EtOAc/MeOH = 9:1) to give the title compound **19b** (32 mg, 0.12 mmol, 60%) as a light brown solid.

m.p.: 75 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3064, 2925, 2854, 2236, 1665, 1616, 1126, 1071, 978, 791.

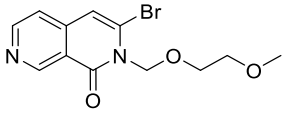
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.64 (s, 1H), 8.89 (s, 1H), 7.44 (d, *J* = 5.2 Hz, 1H), 7.08 (s, 1H), 5.68 (s, 2H), 3.97–3.72 (m, 2H), 3.63–3.45 (m, 2H), 3.30 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 160.8, 152.5, 151.8, 140.1, 122.0, 120.4, 119.7, 115.7, 112.6, 75.5, 71.7, 69.8, 59.2.

MS (EI, 70 eV): *m/z* (%) = 259 (1), 200 (14), 184 (33), 172 (14), 171 (159), 154 (25), 89 (55), 59 (100), 58 (21), 45 (21).

HRMS (EI) calcd. for [$C_{13}H_{13}N_3O_3$]: 259.0957; found: 259.0961.

3-Bromo-2-((2-methoxyethoxy)methyl)-2,7-naphthyridin-1(2*H*)-one (19c)



According to **TP3**, the I/Mg-exchange of 3-iodo-2,7-naphthyridone (**15**, 144 mg, 0.4 mmol) was finished within 20 min using a solution of *i*PrMgCl·LiCl (**1**) in dry THF (0.32 mL, 0.4 mmol, 1.26 M, 1.0 equiv). The corresponding magnesium derivative was then added dropwise to a solution of 1,2-dibromo-tetrachloroethane (260 mg, 0.80 mmol) in dry THF (5 mL) at 0 °C *via* syringe. The resulting mixture was allowed to warm up to rt and was further stirred for 12 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (10 mL), extracted with EtOAc (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/MeOH = 9.5:0.5) to give the title compound **19c** (74 mg, 0.24 mmol, 60%) as a black crystalline solid.

dec.: 345 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3044, 2924, 2854, 1738, 1689, 1634, 1574, 1531, 1175, 1076.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.48 (s, 1H), 8.71 (d, *J* = 5.5 Hz, 1H), 7.24 (d, *J* = 5.5 Hz, 1H), 6.79 (s, 1H), 5.77 (s, 2H), 3.97–3.72 (m, 2H), 3.64–3.46 (m, 2H), 3.31 (s, 3H).

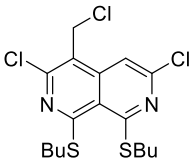
^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 162.3, 151.7, 151.6, 142.3, 127.1, 119.6, 118.2, 109.7, 76.9, 71.7, 69.4, 59.1.

MS (EI, 70 eV): *m/z* (%) = 312 (1), 226 (16), 224 (17), 145 (17), 89 (72), 59 (100), 45 (19).

HRMS (EI) calcd. for [$C_{12}H_{13}BrN_2O_3$]: 312.0110; found: 312.0104.

2.5 Further Functionalization of 2,7-Naphthyridines and Synthesis of Natural Products Lophocladine A & B

1,8-Bis(butylthio)-3,6-dichloro-4-(chloromethyl)-2,7-naphthyridine (21)[129]



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with (1,8-bis-(butylthio)-3,6-dichloro-2,7-naphthyridin-4-yl)methyl)-*N*,*N*-dimethyl-methane-amine (**12e**, 593 mg, 1.29 mmol, 1.0 equiv) in dry $CHCl_3$ (2 mL). The solution was cooled to 0 °C and ethyl chloroformate (278 mg, 2.58 mmol, 2.0 equiv) was added dropwise. After stirring the reaction for 18 h at 0 °C, the mixture was then quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with a sat. aq. NaCl solution (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc = 100:1) to afford **21** (452 mg, 82%) as a slightly yellow solid.

m.p.: 80-82 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2955, 2929, 1588, 1554, 1535, 1480, 1455, 1422, 1131, 1089, 892, 832.

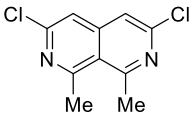
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.36 (s, 1H), 4.92 (s, 2H), 3.37-3.29 (m, 4H), 1.82-1.73 (m, 4H), 1.58-1.47 (m, 4H), 0.99 (t, *J* = 7.4 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 164.8, 164.5, 149.4, 140.5, 144.3, 120.6, 114.6, 110.5, 40.0, 33.5, 30.4, 22.5, 13.9.

MS (EI, 70 eV): *m*/*z* (%) = 369 (39), 367 (100), 365 (94), 330 (30), 311 (92), 309 (80), 277 (33), 273 (51), 57 (65), 41 (94).

HRMS (EI) calcd. for [$C_{17}H_{21}Cl_3N_2S_2$]: 422.0212; found: 422.0207.

3,6-Dichloro-1,8-dimethyl-2,7-naphthyridine (22)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with copper iodide (16.56 g, 87 mmol, 3.0 equiv) and dried for 10 min at 450 °C under high vacuum. The flask was refilled with argon, followed by dry THF (500 mL). Then, the flask was cooled to -40 °C and a solution of MeLi (115 mL, 174 mmol, 1.51 M in THF, 6.0 equiv) was slowly added. The mixture was stirred at -40 °C for approximately 30 min until the solution was completely clear. Another dry, argon-flushed round-bottom *Schlenk*-flask, equipped with a magnetic stirring bar, was charged with 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 10.85 g, 29 mmol, 1.0 equiv) in dry THF (270 mL). The solution was cooled to -40 °C and then slowly added *via* cannula to the Me_2CuLi solution.

After the complete addition, the reaction mixture was stirred at -40 °C for 2 h. Then, the mixture was quenched with sat. aq. NH_4Cl/NH_3 solution (10:1 v/v, 10 mL, extracted with EtOAc (3 × 100 mL) and dried over $MgSO_4$. After filtration, the crude product was purified by flash column chromatography (isohexane/EtOAc = 8:2) to afford **22** (5.5 g, 84%) as an off-white solid.

m.p.: 143-145 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2960, 2932, 1588, 1534, 1454, 1421, 1388, 1323, 1184, 1131, 1048, 891.

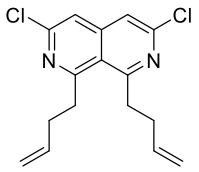
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.43 (s, 2H), 3.13 (s, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 162.0, 148.3, 145.0, 121.7, 116.9, 29.2.

MS (EI, 70 eV): *m/z* (%) = 228 (64), 227 (19), 226 (100), 191 (13), 189 (11), 164 (14), 156 (11), 155 (16), 128 (12), 123 (10), 114 (8), 63 (11).

HRMS (EI) calcd. for [$C_{10}H_8Cl_2N_2$]: 226.0065; found: 226.0071.

1,8-Di(but-3-en-1-yl)-3,6-dichloro-2,7-naphthyridine (23)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 113 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL). The solution was cooled to 0 °C and TMPZnCl·LiCl (**5**, 1.83 mL, 1.5 mmol, 0.82 M in THF 3.0 equiv) was slowly added. Then, the reaction mixture was allowed to warm to 25 °C and stirred for 2 h. After cooling back to 0 °C, a 1.0 M solution of CuCN·2LiCl (0.1 mL, 0.1 mmol, 0.2 equiv) and allyl bromide (0.26 mL, 3.0 mmol, 6.0 equiv) was added. The reaction mixture was allowed to slowly warm up to rt and was further stirred for 2 h. Then, the mixture was quenched with sat. aq. NH_4Cl/NH_3 solution (10:1 v/v, 10 mL), extracted with EtOAc (3 × 10 mL) and dried over $MgSO_4$. After filtration, the crude product was purified by flash column chromatography (isohexane/EtOAc = 100:0.4) to afford **23** (92 mg, 60%) as a brown oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3076, 2977, 2908, 1580, 1526, 1332, 1129, 901, 894, 875.

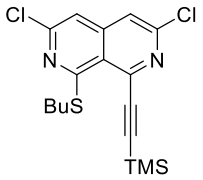
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.43 (s, 2H), 5.97-5.90 (m, 2H), 5.12 (d, *J* = 17.1 Hz, 2H), 5.04 (d, *J* = 10.1 Hz, 2H), 3.47 (t, *J* = 8.2 Hz, 4H), 2.62 (m, 4H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 164.2, 148.2, 145.4, 137.0, 120.6, 117.0, 115.9, 39.0, 33.8.

MS (EI, 70 eV): *m/z* (%) = 306 (15), 293 (39), 291 (64), 279 (50), 277 (68), 267 (26), 265 (54), 263 (31), 253 (56), 251 (100), 239 (42), 237 (58), 229 (20), 201 (25).

HRMS (EI) calcd. for [$C_{16}H_{16}Cl_2N_2$]: 306.0691; found: 306.0672.

1-(Butylthio)-3,6-dichloro-8-((trimethylsilyl)ethynyl)-2,7-naphthyridine (24)[131]



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with 1,8-bis(butylthio)-3,6-dichloro-2,7-naphthyridine (**9c**, 100 mg, 0.27 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (19 mg, 0.027 mmol, 0.1 equiv), triphenylphosphine (3.5 mg, 0.013 mmol, 0.05 equiv), (trimethylsilyl)acetylene (0.11 mL, 0.80 mmol, 3.0 equiv) and triethylamine (0.11 mL, 0.80 mmol, 3.0 equiv) in dry THF (1 mL). The mixture was stirred at 25 °C for 20 min, followed by the addition of copper iodide (1 mg, 0.005 mmol, 0.02 equiv). After stirring the reaction at 25 °C for 24 h, the solvent was removed on a rotary evaporator. The residue was redissolved in DCM (5 mL) and filtered through Celite. The filtrate was concentrated *in vacuo* and finally purified by flash column chromato-graphy (isohexane/EtOAc = 100:2) to afford **24** (49 mg, 48%) as yellow crystals.

m.p.: 160-162 °C.

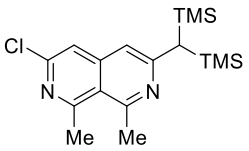
IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2954, 2899, 1590, 1501, 1321, 1244, 1121, 892, 839, 756, 700.

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.42 (s, 1H), 7.14 (s, 1H), 3.27 (t, *J* = 7.4 Hz, 2H), 1.76 (quint, *J* = 7.4 Hz, 2H), 1.55 (sxt, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.1 Hz, 3H), 0.35 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 165.3, 149.3, 148.7, 144.6, 142.5, 121.7, 118.6, 112.8, 109.1, 103.6, 32.3, 30.1, 22.5, 13.9, -0.8.

HRMS (EI) calcd. for [$C_{17}H_{20}Cl_2N_2SSi$]: 382.0494; found: 382.0488.

3-(Bis(trimethylsilyl)methyl)-6-chloro-1,8-dimethyl-2,7-naphthyridine (25)[172]



A dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 113 mg, 0.5 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol, 0.1 equiv) in dry toluene (2.5 mL). Then, $(TMS)_2CHMgBr{\cdot}LiCl$ (2.2 mL, 1.5 mmol, 0.68 M in THF, 3.0 equiv) was added dropwise and the reaction mixture was stirred for 8 h at 50 °C. After a full conversion was monitored by GC analysis of reaction aliquots, sat. aq. NH_4Cl solution (10 mL) was added, followed by extraction with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (isohexane/EtOAc = 19:1) to afford **25** (102 mg, 58%) as a white solid.

[172] (a) T. Klatt, V. Werner, M. G. Maximova, D. Didier, Y. Apeloig, P. Knochel, *Chem. Eur. J.* **2015**, *21*, 7830. (b) V. Werner, T. Klatt, M. Fujii, J. Markiewicz, Y. Apeloig, P. Knochel, *Chem. Eur. J.* **2014**, *20*, 8338.

m.p.: 136-137 °C.

IR (Diamond ATR): $\tilde{\nu}$/ cm^{-1} = 2952, 1591, 1535, 1245, 1199, 1135, 1038, 889, 824, 776, 683, 665.

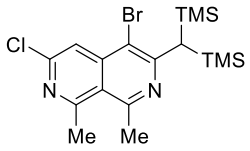
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.30 (s, 1 H), 6.86 (s, 1 H), 3.07 (s, 3 H), 3.04 (s, 3 H), 1.88 (s, 1H), 0.04 (s, 18 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 161.6, 161.1, 158.6, 146.5, 143.8, 119.7, 116.6, 113.9, 33.2, 29.1, 28.8, 0.18.

MS (EI, 70 eV): *m*/*z* (%) = 350 (10), 338 (12), 337 (45), 336 (30), 335 (100), 262 (15), 241 (12), 73 (55).

HRMS (EI) calcd. for [$C_{17}H_{27}ClN_2Si_2$]: 350.1401; found: 350.1395.

3-(Bis(trimethylsilyl)methyl)-4-bromo-6-chloro-1,8-dimethyl-2,7-naphthyridine (26)



3-(Bis(trimethylsilyl)methyl)-6-chloro-1,8-dimethyl-2,7-naphthyridine (**25**, 70 mg, 0.2 mmol) was dissolved in dry MeCN (8 mL). Then NBS (178 mg, 1.0 mmol, 5.0 equiv) was added and the reaction mixture was stirred at 30 °C overnight. Subsequently, the solvent was removed *in vacuo* and the residue dissolved in a small amount of EtOAc. Purification *via* column chromatography (100% EtOAc) afforded pure **26** (69 mg, 98%) as a brown solid.

dec.: 102 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1577, 1532, 1420, 1378, 1337, 1284, 1248, 1181, 1142, 1072, 1035, 965, 901, 840, 826, 779, 685.

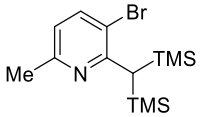
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 7.87 (s, 1H), 3.10 (s, 3H), 3.02 (s, 3H), 2.73 (s, 1H), 0.07 (s, 18H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.8, 161.7, 148.9, 143.1, 121.3, 117.8, 113.8, 33.4, 29.4, 29.1.

MS (EI, 70 eV): *m/z (%)* = 428 (5), 417 (32), 415 (100), 413 (69), 349 (15), 342 (18), 340 (12), 321 (10), 139 (15), 137 (12), 73 (47).

HRMS (EI) calcd. for [$C_{17}H_{26}BrClN_2Si_2$]: 428.0506; found: 428.0508.

2-(Bis(trimethylsilyl)methyl)-3-bromo-6-methylpyridine (29)



2-(Bis(trimethylsilyl)methyl)-6-methylpyridine (**28**, 753 mg, 3.3 mmol) was dissolved in dry MeCN (10 mL). Then, NBS (578 mg, 3.3 mmol, 1.1 equiv) was added in portions and the reaction mixture was stirred at 30 °C overnight. Subsequently, the solvent was removed *in vacuo* and the residue dissolved

in a small amount of EtOAc. Purification *via* column chromatography (100% isohexane) afforded pure **29** (706 mg, 72%) as a colorless oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2953, 2914, 2849, 1735, 1560, 1471, 1427, 1269, 1247, 1176, 1028, 861, 836, 772, 716, 686.

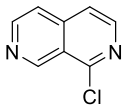
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 7.51 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 8.7 Hz, 1H), 2.55 (s, 3H), 1.77 (s, 1H), 0.02 (s, 18H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 162.5, 155.7, 139.1, 121.5, 115.5, 32.6, 24.8, 0.3.

MS (EI, 70 eV): *m/z (%)* = 329 (5), 317 (19), 316 (100), 314 (93), 241 (14), 73 (50), 43 (69).

HRMS (EI) calcd. for [$C_{13}H_{24}BrNSi_2$]: 329.0631; found: 329.0636.

1-Chloro-2,7-naphthyridine (30)



2,7-Naphthyridin-1-one (**8**, 3.02 g, 20.7 mmol) and $POCl_3$ (21 mL, 0.22 mol) were sealed in a pressure tube, equipped with a magnetic stirring bar, and heated to 130 °C for 18 h. The resulting solution was then poured on ice and neutralized with K_2CO_3. The brown suspension was extracted with DCM (5 × 200 mL), the organic phase washed with brine and dried over $MgSO_4$. After removing the solvent *in vacuo*, the crude compound was purified by flash column chromatography (DCM/Methanol = 10:0.3) to afford **30** (1.51 g, 44%) as a yellow solid.

m.p.: 117 – 119 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1615, 1536, 1329, 1263, 1229, 978, 860, 854, 796, 697.

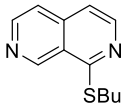
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.74 (s, 1H), 8.81 (d, *J* = 5.7 Hz, 1H), 8.46 (d, *J* = 5.8 Hz, 1H), 7.65 (dd, *J* = 5.8 Hz, 1H), 7.59 (d, *J* = 5.8 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 152.2, 151.5, 147.9, 145.7, 140.7, 122.0, 119.3, 118.9.

MS (EI, 70 eV): *m/z (%)* = 166 (32), 165 (10), 164 (100), 129 (48), 102 (11).

HRMS (EI) calcd. for [$C_8H_5ClN_2$]: 164.0141; found: 164.0151.

1-(Butylthio)-2,7-naphthyridine (31)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with 1-chloro-2,7-naphthyridine (**30**, 436 mg, 2.65 mmol, 1.0 equiv) and dry THF (6 mL). Lithium *n*buthylthiolate (4 mL, 3.97 mmol, 1.0 M in THF 1.5 equiv) was added dropwise to the solution at -40 °C. After stirring the mixture for 30 min at this temperature, the reaction was quenched with sat. aq. NH_4Cl solution and extracted with EtOAc (450 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (isohexane/EtOAc = 8:2) to afford **31** (531 mg, 92%) as a yellow oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2957, 2929, 1610, 1580, 1531, 1464, 1324, 1266, 1222, 1202, 1047, 987, 846, 700.

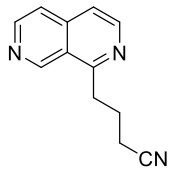
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm= 9.62 (s, 1H), 8.68 (d, *J* = 5.8 Hz, 1H), 8.43 (d, *J* = 5.8 Hz, 1H), 7.52 (d, *J* = 5.5 Hz, 1H), 7.24 (d, *J* = 5.5 Hz, 1H), 3.38 (t, *J* = 7.2 Hz, 2H), 1.77 (quint, *J* = 7.2 Hz, 2H), 1.52 (sxt, *J* = 7.2 Hz, 2H), 0.96 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.9, 149.6, 147.2, 145.8, 138.8, 122.4, 119.4, 115.1, 31.2, 29.3, 22.1, 13.7.

MS (EI, 70 eV): *m/z (%)* = 218 (15), 189 (29), 185 (11), 176 (68), 175 (43), 163 (17), 162 (100), 130 (16), 129 (31).

HRMS (EI) calcd. for [$C_{12}H_{14}N_2S$]: 218.0878; found: 218.0877.

4-(2,7-Naphthyridin-1-yl)butanenitrile (32)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with 1-(*n*butylthio)-2,7-naphthyridine (**31**, 85 mg, 0.4 mmol), $Pd(OAc)_2$ (5.0 mg, 5 mol%), S-Phos (16 mg, 10 mol%) and dry THF (1 mL). Then, (3-cyanopropyl)zinc iodide (0.64 mL, 0.6 mmol, 0.94 M in THF, 1.5 equiv) was added and the mixture was stirred at rt overnight. The reaction was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 10 mL) and dried over $MgSO_4$. After filtration, the solvents were removed *in vacuo*. Purification by flash column chromatography (isohexane/ EtOAc = 8:2, gradient to 100% EtOAc) furnished pure **32** (59 mg, 74%) as a brown solid.

m.p.: 85-86 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1616, 1552, 1456, 1430, 1398, 1384, 1275, 1216, 1111, 1076, 1046, 995, 864, 740.

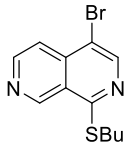
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.61 (s, 1H), 8.73 (d, *J* = 5.5 Hz ,1H), 8.60 (d, *J* = 5.8 Hz, 1H), 7.63 (d, *J* = 5.5 Hz, 1H), 7.51 (d, *J* = 5.8 Hz, 1H), 3.54 (t, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 7.1 Hz, 2H), 2.35 (quint, *J* = 7.3 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 160.6, 150.1, 147.0, 145.9, 139.1, 122.3, 119.8, 119.5, 118.3, 32.4, 23.9, 17.0.

MS (EI, 70eV): *m/z (%)* = 197 (3), 196 (3), 157 (24), 145 (10), 144 (100), 130 (6).

HRMS (EI) calcd. for [$C_{12}H_{11}N_3$]: 197.0953; found: 197.0943.

1-(4-Bromo-1-(butylthio)-2,7-naphthyridine (33)



1-(Butylthio)-2,7-naphthyridine (**31**, 110 mg, 0.50 mmol, 1.0 equiv) was dissolved in dry MeCN (3 mL). NBS (223 mg, 1.25 mmol, 2.5 equiv) was added and the reaction mixture was stirred at 35 °C for 17 h. Subsequently, the solvent was removed *in vacuo* and the residue dissolved in a small amount of EtOAc. Purification *via* column chromatography (isohexane/EtOAc = 40:1) afforded pure **33** (75 mg, 51%) as a colorless oil.

m.p.: 60 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2954, 2924, 2857, 1597, 1520, 1466, 1375, 1323, 1275, 1229, 1213, 1048, 993, 915, 828, 822, 721, 705.

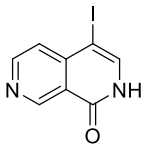
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.59 (s, 1H), 8.81 (d, *J* = 5.6 Hz, 1H), 8.61 (s, 1H), 7.84 (d, *J* = 5.8 Hz, 1H), 3.36 (t, *J* = 7.4 Hz, 2H), 1.76 (quint, *J* = 7.5 Hz, 2H), 1.52 (sept, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.7, 149.8, 148.6, 147.1, 138.1, 123.3, 118.7, 113.6, 31.2, 29.7, 22.3, 13.8.

MS (EI, 70 eV): *m/z (%)* = 298 (24), 296 (24), 269 (24), 267 (25), 256 (76), 255 (52), 254 (75), 253 (42), 242 (100), 230 (100), 161 (34), 160 (22), 129 (27), 128 (20), 41 (25).

HRMS (EI) calcd. for [$C_{12}H_{13}BrN_2S$]: 295.9983; found: 295.9975.

4-Iodo-2,7-naphthyridin-1(2*H*)-one (34)[134]



To a solution of 2,7-naphthyridin-1(2*H*)-one (**8**, 0.5 g, 3.42 mmol) in H_2O (10 mL) was added a solution of NaOH (0.86 g, 21.5 mmol, 6.3 equiv) and NaOAc (4.33 g, 31.8 mmol, 9.3 equiv) in H_2O (30 mL). The solution was stirred under reflux. Then I_2 (3.04 g, 12.0 mmol, 3.5 equiv) was added. The solution was acidified with 50% AcOH and subsequently neutralized with 32% NaOH. This acidification-neutralization procedure was performed under reflux conditions and repeated three more times within 20 min. In the third acidification step, 50% AcOH was added until free iodine was generated. After removal of excess iodine by boiling, the residue was filtered, washed with hot water, and dried to give compound **34** (0.56 g, 60%) as a light brown solid.

dec.: 280 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3033, 2605, 1880, 1681, 1599, 1472, 1194, 837, 807, 650.

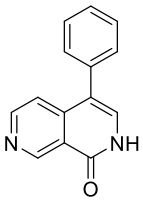
^{1}H-NMR (400 MHz, DMSO-d_6): δ/ ppm = 11.87 (s, 1H), 9.21 (s, 1H), 8.81 (s, 1H), 7.83 (s, 1H), 7.45 (s, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ/ ppm = 160.6, 152.3, 150.2, 143.6, 140.6, 122.6, 121.7, 67.9.

MS (EI, 70 eV): *m/z (%)* = 272 (100), 145 (10), 90 (13), 73 (19), 63 (12), 44 (13).

HRMS (EI): calcd. for [$C_8H_5IN_2O$]: 271.9447; found: 271.9437.

4-Phenyl-2,7-naphthyridin-1(2*H*)-one (*Lophocladine A*) (35)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with 4-iodo-2,7-naphthyridin-1(2*H*)-one (**34**, 200 mg, 0.74 mmol, 1.0 equiv), followed by $Pd(OAc)_2$ (8 mg, 0.04 mmol, 5 mol%) and S-Phos (30 mg, 0.08 mmol, 10 mol%) in dry THF (2 mL). Then, a solution of phenylzinc chloride (3.03 mL, 1.09 mmol, 0.36 M in THF, 1.5 equiv) was added *via* syringe pump within 1 h to the reaction mixture. The reaction was stirred for further 3 h at rt. Then, the reaction was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with chloroform (3 × 10 mL) and dried over $MgSO_4$. After filtration, the solvents were removed *in vacuo*. The crude product was purified *via* HPLC with a gradient of MeCN/H_2O. After removal of MeCN, the aq. layer was extracted with chloroform (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give pure *Lophocladine A* (**35**, 67 mg, 41%) as a white solid.

m.p.: 260 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1667, 1590, 1474, 1339, 1244, 1193, 1031, 883, 842, 797, 765, 705.

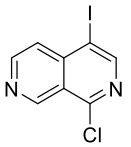
^{1}H-NMR (400 MHz, DMSO-d_6): δ/ ppm = 11.84 (br, 1H), 9.40 (d, *J* = 0.8 Hz, 1H), 8.70 (d, *J* = 5.7 Hz, 1H), 7.52-7.42 (m, 5H), 7.40-7.37 (m, 2H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ/ ppm = 160.8, 151.2, 150.3, 141.8, 134.8, 132.9, 129.5, 128.8, 127.7, 120.6, 117.2, 115.7.

MS (EI, 70 eV): *m/z (%)* = 222 (100), 221 (28), 166 (11), 139 (17), 84 (7).

HRMS (EI) calcd. for [$C_{14}H_{10}N_2O$]: 222.0793; found: 222.0788.

1-Chloro-4-iodo-2,7-naphthyridine (36)



A pressure tube, equipped with a magnetic stirring bar, was charged with 4-iodo-2,7-naphthyridin-1(2*H*)-one (**34**, 0.50 g, 1.84 mmol) and $POCl_3$ (5.0 mL, 54.8 mmol, 30 equiv). The mixture was heated up to 140 °C and was stirred at that temperature for 18 h. After cooling to rt, the mixture was carefully poured onto ice (50 g) and was made alkaline with potassium carbonate. The mixture was extracted extensively several times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered

and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (isohexane/ EtOAc = 9:1) to afford **36** (502 mg, 94%) as a light-yellow solid.

m.p.: 189 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1732, 1602, 1526, 1413, 1385, 1328, 1269, 1220, 1046, 985, 912, 836, 783, 699.

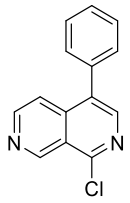
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.65 (s, 1H), 8.92 (d, *J* = 5.9 Hz, 1H), 8.87 (s, 1H), 7.83 (dd, *J* = 5.9, 0.8 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 153.1, 151.9, 149.5, 142.7, 123.1, 93.7.

MS (EI, 70 eV): *m/z (%)* = 289 (50), 232 (18), 189 (19), 163 (21), 107 (28), 61 (20), 44 (26) 43 (100).

HRMS (EI) calcd. for [$C_8H_4ClIN_2$]: 289.9108; found: 289.9091

1-Chloro-4-phenyl-2,7-naphthyridine (37)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with 1-chloro-4-iodo-2,7-naphthyridine (**36**, 250 mg, 0.86 mmol), $Pd(dba)_2$ (26 mg, 0.05 mmol, 5.0 mol%), tfp (21 mg, 0.09 mmol, 10 mol%) and dry THF (1 mL). Then, phenylzinc chloride (2 mL, 0.90 mmol, 0.45 M in THF, 1.5 equiv) was added and the reaction mixture was stirred at rt overnight. The reaction was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 10 mL) and dried over $MgSO_4$. After filtration, the solvents were removed *in vacuo*. Purification by flash column chromatography (first isohexane, then isohexane/EtOAc = 7:3) furnished pure **37** (170 mg, 82%) as a brown solid.

m.p.: 149 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1601, 1532, 1450, 1426, 1392, 1340, 1308, 1267, 1176, 1044, 985, 916, 844, 828, 755, 700.

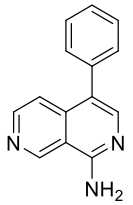
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.84 (s, 1H), 8.78 (d, *J* = 6.0 Hz, 1H), 8.50 (s, 1H), 7.81 (d, *J* = 6.7 Hz, 1H), 7.61–7.52 (m, 3H), 7.50–7.45 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 151.7, 151.0, 146.7, 145.8, 140.1, 134.3, 132.7, 130.0, 129.3, 129.1, 121.8, 118.4.

MS (EI, 70 eV): *m/z (%)* = 242 (33), 241 (27), 240 (100), 239 (38), 205 (12), 177 (10), 151 (7).

HRMS (EI) calcd. for [$C_{14}H_9ClN_2$]: 240.0454; found: 240.0444.

4-Phenyl-2,7-naphthyridin-1-amine (*Lophocladine B*) (38)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with $Pd_2(dba)_3$ (20 mg, 0.021 mmol, 5 mol%) and 2-dicyclohexylphosphinobiphenyl (18 mg, 0.050 mmol, 12 mol%). The *Schlenk*-flask was evacuated and back-filled with argon. 1-chloro-4-phenyl-2,7-naphthyridine (100 mg, 0.42 mmol) in 2 mL dry THF and LiHMDS (0.50 mL, 0.50 mmol, 1.0 M in THF, 1.2 equiv) were added *via* syringe. The reaction mixture was heated at 65 °C for 12 h. After cooling to rt, aq. HCl (5 mL, 1 M) was added and the mixture was stirred for 10 min. Then, the solution was neutralized by the addition of aq. NaOH. The crude mixture was extracted with chloroform (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by flash column chromatography (first only EtOAc, then add 1% NEt_3) to give pure *Lophocladine B* (**38**, 90 mg, 98%) as a white solid.

m.p.: 229-232 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 3114, 1678, 1615, 1585, 1545, 1463, 1447, 1353, 1316, 1277, 1202, 1030, 933, 826, 802, 752, 700.

^{1}H-NMR (400 MHz, DMSO-d_6): δ/ ppm = 9.61 (s, 1H), 8.57 (d, *J* = 5.9 Hz, 1H), 7.98 (s, 1H), 7.51-7.36 (m, 6H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ/ ppm = 157.5, 149.2, 147.5, 146.2, 138.2, 136.5, 129.6, 128.7, 127.1, 120.2, 116.4, 111.8.

MS (EI, 70 eV): *m/z (%)* = 222 (16), 221 (100), 220 (68), 192 (8), 84 (40), 46 (10), 44 (29).

HRMS (EI) calcd. for [$C_{14}H_{11}N_3$]: 221.0953; found: 221.0951.

3. Organometallic Functionalization of the 1,5-Naphthyridine Scaffold

3.1 Typical Procedures

Typical Procedure for the Metalation of 1,5-naphthyridine (39) in Position 4 (TP1):
To a solution of 1,5-naphthyridine (**39**) in THF (0.5 M related to substrate) was added dropwise a solution of $TMP_2Mg \cdot 2LiCl$ (**4**, 1.1 equiv) at -78 °C. After full metalation (5 min, checked by iodolysis *via* GC/GC-MS), the solution was cannulated dropwise to a solution of the electrophile in THF, which was precooled to -78 °C. After warming to rt, the reaction mixture was stirred until completion. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL/mmol 1,5-naphthyridine) and extracted with EtOAc (3 × 50 mL/mmol 1,5-naphthyridine). The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography on silica gel using the appropriate eluent.

Typical Procedure for the Metalation of 3-chloro-1,5-naphthyridines (45a-b) in Position 4 (TP2):
3-Chloro-1,5-naphthyridine derivative **45a** or **45b** was dissolved in THF (0.25 M related to substrate) and cooled to -40 °C. Then, TMPMgCl·LiCl (**3**, 1.1 equiv) was added dropwise and the reaction was stirred until full metalation was observed (1 h, checked by iodolysis *via* GC/GC-MS). Then, a solution of the electrophile in THF was added dropwise and the reaction was stirred until completion. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL/mmol 1,5-naphthyridine) and extracted with EtOAc (3 × 50 mL/mmol 1,5-naphthyridine). The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified *via* flash column chromatography on silica gel using the appropriate eluent.

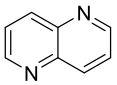
Typical Procedure for the Metalation of 4-bromo-1,5-naphthyridine (42b) in Position 8 (TP3):
4-Bromo-1,5-naphthyridine (**42b**) was dissolved in THF (0.25 M related to substrate) and cooled to -40 °C. Then, TMPMgCl·LiCl (**3**, 1.1 equiv) was added dropwise and the reaction was stirred until full metalation was observed (1 h, checked by iodolysis *via* GC/GC-MS). Then, a solution of the electrophile in THF was added dropwise and the reaction was stirred until completion. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL/mmol 1,5-naphthyridine) and extracted with EtOAc (3 × 50 mL/mmol 1,5-naphthyridine). The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified *via* flash column chromatography on silica gel using the appropriate eluent.

Typical Procedure for the Metalation of 1,5-naphthyridine derivative 42c in Position 8 (TP4):
1,5-Naphthyridine derivative **42c** was dissolved in THF (0.25 M related to substrate) and TMPZnCl·LiCl (**5**, 1.5 equiv) was added dropwise. The reaction was stirred at rt until full metalation was observed (1 h, checked by iodolysis *via* GC/GC-MS). Then, a solution of the electrophile in THF was added dropwise and the reaction was stirred until completion. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL/mmol 1,5-naphthyridine) and extracted with EtOAc (3 × 50 mL/mmol 1,5-naphthyridine). The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography on silica gel using the appropriate eluent.

Typical Procedure for the Metalation of 1,5-naphthyridine derivatives 42a and 42g in Position 2 (TP 5):

1,5-Naphthyridine derivative **42a** or **42g** was dissolved in THF (0.25 M related to substrate) and cooled to 0 °C. Then, $BF_3 \cdot OEt_2$ (1.1 equiv) was added dropwise and the reaction mixture was stirred for 10 min. After cooling to -40 °C, TMPMgCl·LiCl (**3**, 1.1 equiv) was added and the reaction was stirred until full metalation was observed (1 h, checked by iodolysis *via* GC/GC-MS). Then, a solution of the electrophile in THF was added dropwise and the reaction was stirred until completion. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (10 mL/mmol 1,5-naphthyridine) and extracted with EtOAc (3 × 50 mL/mmol 1,5-naphthyridine). The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified *via* flash column chromatography on silica gel using the appropriate eluent.

3.2 Preparation of Starting Material 1,5-Naphthyridine (39)[143]



3-Aminopyridine (5.0 g, 53.2 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 rt, the mixture was basified using aq. NaOH solution (50%, 250 mL). After addition of sat. aq. $Na_2S_2O_3$ solution (150 mL) and filtration over celite, the reaction mixture was diluted with water (500 mL), extracted with Et_2O (3 × 500 mL) and dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The crude product was purified *via* flash column chromatography (isohexane/EtOAc = 1:1, 1% NEt_3) to give pure **39** (3.8 g, 55%) as an off-white solid.

m.p.: 73 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1586, 1492, 1300, 1216, 1194, 1106, 1017, 834, 819.

^{1}H-NMR (400 MHz, $CDCl_3$):[173] δ/ ppm = 8.97 (dd, *J* = 4.1, 1.6 Hz, 2H), 8.40 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.63 (dd, *J* = 8.4, 4.1 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):[173] δ/ ppm = 151.2, 144.0, 137.6, 124.4.

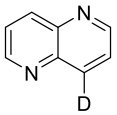
MS (EI, 70 eV): *m/z (%)* = 130 (100), 129 (29), 104 (15), 103 (18), 79 (10), 58 (10), 44 (10), 43 (38).

HRMS (EI) calcd. for [$C_8H_6N_2$]: 130.0531; found: 130.0526.

[173] B. R. Lahue, S.-M. Lo, Z.-K. Wan, G. H. C. Woo, J. K. Snyder, *J. Org. Chem.* **2004**, *69*, 7171.

3.3 Metalation of 1,5-Naphthyridine (39) in Position 4 Using $TMP_2Mg·2LiCl$ (4)

1,5-Naphthyridine-4-*d* (41)



According to **TP 1**, 1,5-Naphthyridine (**39**, 130 mg, 1 mmol) was metalated using $TMP_2Mg·2LiCl$ (**4**, 1.72 mL, 1.1 mmol, 0.64 M in THF, 1.1 equiv) followed by the reaction with D_2O (0.1 mL, 5.5 mmol, 5.5 equiv) in dry THF (2 mL). After workup, the crude product was purified by flash column chromatography (isohexane/ EtOAc = 8:2, 1 % NEt_3) to give 1,5-naphthyridine-4-*d* (**41**) as a beige solid (60 mg, 43 %). NMR-spectroscopy revealed an incorporation of deuterium at position 4 with a ^2H:^1H ratio of 89:11.

m.p.: 59-61 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1586, 1488, 1402, 1300, 1246, 1217, 1194, 1106, 1018, 905, 884, 834, 821, 797, 746, 695.

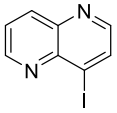
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.98 (d, *J* = 4.2 Hz, 2H), 8.40 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.67-7.61 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 151.3, 144.1/144.0 (C_H/C_D), 137.6, 124.5, 124.4.

MS (EI, 70 eV): *m/z (%)* = 132 (12), 131 (52), 130 (100), 129 (19), 104 (18), 103 (15), 76 (8).

HRMS (EI) calcd for [$C_8H_5DN_2$]: 131.0594; found: 131.0576.

4-Iodo-1,5-naphthyridine (42a)



According to **TP 1**, 1,5-Naphthyridine (**39**, 130 mg, 1 mmol) was metalated using $TMP_2Mg·2LiCl$ (**4**, 1.72 mL, 1.1 mmol, 0.64 M in THF, 1.1 equiv) followed by the reaction with I_2 (395 mg, 1.6 mmol, 1.6 equiv) in dry THF (3 mL). After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 8:2, 1 % NEt_3) to give **42a** (158 mg, 62 %) as a white solid.

m.p.: 91-93 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1565, 1548, 1481, 1459, 1393, 1376, 1279, 1181, 1028, 961, 841, 782.

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 9.05 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.52 (d, *J* = 4.5 Hz, 1H), 8.36 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.28 (d, *J* = 4.5 Hz, 1H), 7.70 (dd, *J* = 8.5 Hz, 4.2 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 152.2, 150.8, 143.9 (2C), 138.3, 135.4, 125.5, 116.4.

MS (EI, 70 eV): *m/z* (%) = 257 (9), 256 (100), 129 (73), 102 (57), 76 (16), 75 (21), 74 (14), 64 (10), 50 (18).

HRMS (EI) calcd. for [$C_8H_5IN_2$]: 255.9497; found: 255.9492.

4-Bromo-1,5-naphthyridine (42b)

According to **TP 1**, 1,5-Naphthyridine (**39**, 130 mg, 1 mmol) was metalated using $TMP_2Mg{\cdot}2LiCl$ (**4**, 1.72 mL, 1.1 mmol, 0.64 M in THF, 1.1 equiv) followed by the reaction with 1,2-dibromotetrachloroethane (651 mg, 2 mmol) in dry THF (2 mL). After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 7:2, 1 % NEt_3) to give **42b** (102 mg, 49 %) as an off-white solid.

m.p.: 94 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1579, 1547, 1475, 1462, 1376, 1282, 1187, 1066, 1027, 965, 855, 821, 807, 786.

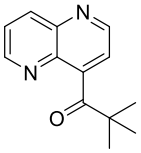
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 9.10 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.75 (d, *J* = 4.6 Hz, 1H), 8.43 (d, *J* = 8.5, 1.6 Hz, 1H), 7.99 (d, *J* = 4.6 Hz, 1H), 7.72 (dd, *J* = 8.5, 4.2 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 151.9, 150.8, 144.9, 142.1, 138.3, 136.4, 128.4, 125.5.

MS (EI, 70 eV): *m/z* (%) = 210 (98), 208 (100), 129 (75), 126 (86), 102 (50), 86 (19), 75 (20), 70 (41), 58 (21), 55 (17), 41 (24).

HRMS (EI) calcd. for [$C_8H_5BrN_2$]: 207.9636; found: 207.9616.

2,2-Dimethyl-1-(1,5-naphthyridin-4-yl)propan-1-one (42c)



According to **TP 1**, 1,5-Naphthyridine (**39**, 130 mg, 1 mmol) was metalated using $TMP_2Mg{\cdot}2LiCl$ (**4**, 1.72 mL, 1.1 mmol, 0.64 M in THF, 1.1 equiv) followed by transmetalation with $ZnCl_2$ (1.1 mL, 1.1 mmol, 1.0 M in THF, 1.1 equiv). The reaction mixture was stirred for further 10 min before warming up to rt. Subsequently, a solution of pivaloyl chloride (1.5 mmol, 180 mg) and $Pd(PPh_3)_4$ (0.02 mmol, 23 mg, 2 mol%) in dry THF (1 mL) was added dropwise. After workup, the crude product was purified by flash column chromatography (EtOAc) to give **42c** (135 mg, 63 %) as a white solid.

m.p.: 86-88 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2969, 1693, 1494, 1477, 1268, 1220, 1132, 1094, 1019, 946, 877, 803, 781.

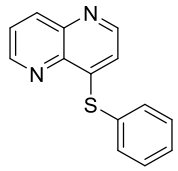
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 8.98 (d, *J* = 4.3 Hz, 1H), 8.95 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.40 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.65 (dd, *J* = 8.6, 4.2 Hz, 1H), 7.37 (d, *J* = 4.3 Hz, 1H), 1.30 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 212.5, 151.3, 150.5, 148.8, 143.9, 141.1, 137.4, 124.9, 119.8, 45.2, 26.8.

MS (EI, 70 eV): *m/z (%)* = 214 (38), 157 (36), 130 (100), 102 (13), 57 (23), 41 (11).

HRMS (EI) calcd. for [$C_{13}H_{14}N_2O$]: 214.1106: found: 214.1099.

4-(Phenylthio)-1,5-naphthyridine (42d)



According to **TP 1**, 1,5-Naphthyridine (**39**, 130 mg, 1 mmol) was metalated using $TMP_2Mg{\cdot}2LiCl$ (**4**, 1.72 mL, 1.1 mmol, 0.64 M in THF, 1.1 equiv) followed by the reaction with *S*-phenyl benzenethiosulfonate (500 mg, 2 mmol, 2.0 equiv) in dry THF (1 mL). After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 6:2, 1% NEt_3) to give **42d** (90 mg, 38 %) as a white oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1555, 1481, 1459, 1439, 1439, 1371, 1355, 1278, 988, 838, 818, 784, 750, 691.

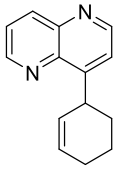
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 8.99 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.57 (d, *J* = 4.8 Hz, 1H), 8.37 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.73-7.64 (m, 3H), 7.57-7.50 (m, 3H), 6.79 (d, *J* = 4.8 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 152.7, 150.0, 149.3, 142.5, 140.7, 137.4, 135.9, 129.9, 129.8, 128.9, 124.8, 118.4.

MS (EI, 70 eV): *m/z (%)* = 238 (50), 237 (100), 205 (20), 103 (10), 51 (18).

HRMS (EI) calcd. for [$C_{14}H_{10}N_2S$]: 238.0565; found: 238.0549.

4-(Cyclohex-2-en-1-yl)-1,5-naphthyridine (42e)



According to **TP 1**, 1,5-Naphthyridine (**39**, 130 mg, 1 mmol) was metalated using $TMP_2Mg{\cdot}2LiCl$ (**4**, 1.72 mL, 1.1 mmol, 0.64 M in THF, 1.1 equiv) followed by the addition of CuCN·2LiCl (1.1 mL, 1.1 mmol, 1.0 M in THF, 1.1 equiv). The reaction mixture was stirred for further 20 min before 3-bromocyclohex-1-ene (0.17 mL, 1.5 mmol, 1.5 equiv) was added dropwise. Then, the reaction was slowly warmed to rt overnight. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 7:2, 1% NEt_3) to give **42e** (125 mg, 60 %) as a colorless oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2925, 1673, 1587, 1493, 1303, 854, 790, 723, 675, 658.

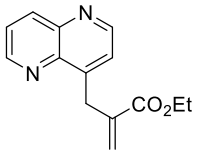
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 8.91 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.83 (d, *J* = 4.5 Hz, 1H), 8.33 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.55 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.43 (d, *J* = 4.4 Hz, 1H), 6.02-5.94 (m, 1H), 5.74-5.66 (m, 1H), 4.83-4.75 (m, 1H), 2.25-2.13 (m, 1H), 2.12-2.03 (m, 2H), 1.72-1.50 (m, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 154.3, 151.1, 149.8, 143.6, 142.6, 137.8, 129.9, 128.7, 124.0, 122.6, 34.8, 30.7, 25.2, 20.9.

MS (EI, 70 eV): *m/z (%)* = 210 (100), 209 (79), 207 (30), 195 (31), 181 (85), 169 (44), 155 (46), 130 (14), 77 (15), 57 (20), 43 (22).

HRMS (EI) calcd. for [$C_{14}H_{14}N_2$]: 210.1157; found: 210.1148.

Ethyl 2-((1,5-naphthyridin-4-yl)methyl)acrylate (42f)



According to **TP 1**, 1,5-Naphthyridine (**39**, 130 mg, 1 mmol) was metalated using $TMP_2Mg·2LiCl$ (**4**, 1.72 mL, 1.1 mmol, 0.64 M in THF, 1.1 equiv) followed by the addition of CuCN·2LiCl (1.1 mL, 1.1 mmol, 1.0 M in THF, 1.1 equiv). The reaction mixture was stirred for further 20 min before ethyl 2-(bromomethyl)acrylate (288 mg, 1.5 mmol, 1.5 equiv) was added dropwise. Then, the reaction was slowly warmed to rt overnight. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 1:1, 1% NEt_3) to give **42f** (128 mg, 53 %) as a yellow oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1711, 1496, 1368, 1292, 1231, 1191, 1126, 1070, 1024, 954, 848, 801, 764, 736, 675.

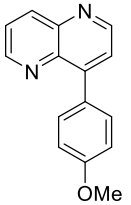
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 8.93 (dd, *J* = 4.1 Hz, 1.7 Hz, 1 H), 8.83 (d, *J* = 4.4 Hz, 1 H), 8.35 (dd, *J* = 8.5 Hz, 1.7 Hz, 1 H), 7.58 (dd, *J* = 8.5 Hz, 4.1 Hz, 1 H), 7.42 (d, *J* = 4.4 Hz, 1 H), 6.30 (s, 1 H), 5.55 (q, *J* = 1.3 Hz, 1 H), 4.32 (s, 2 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 1.17 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ppm = 166.7, 150.9, 150.1, 147.8, 143.6, 142.9, 138.5, 137.6, 127.7, 124.3, 123.9, 60.9, 32.2, 14.1.

MS (EI, 70 eV): *m/z (%)* = 242 (11), 213 (33), 207 (14), 197 (12), 167 (100), 140 (12).

HRMS (EI) calcd. for [$C_{14}H_{14}N_2O_2$]: 242.1055; found: 242.1081.

4-(4-Methoxyphenyl)-1,5-naphthyridine (42g)



According to **TP 1**, 1,5-Naphthyridine (**39**, 260 mg, 2 mmol) was metalated using $TMP_2Mg·2LiCl$ (**4**, 3.44 mL, 2.2 mmol, 0.64 M in THF, 1.1 equiv) followed by transmetalation with $ZnCl_2$ (2.2 mL, 2.2

mmol, 1.0 M in THF, 1.1 equiv). The reaction mixture was stirred for further 20 min before a solution of $Pd(dba)_2$ (34 mg, 0.06 mmol, 3 mol%), tfp (28 mg, 0.12 mmol, 6 mol%) and 4-iodoanisole (374 mg, 1.6 mmol) in dry THF (1 mL) was added dropwise. The reaction mixture was allowed to warm to rt overnight. After workup, the crude product was purified by flash column chromatography (isohexane/ EtOAc = 7:1, 1% NEt_3) to give **42g** (285 mg, 75 %) as a white solid.

m.p.: 107 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1603, 1492, 1466, 1382, 1307, 1284, 1235, 1180, 1126, 1027, 835, 818, 800, 783.

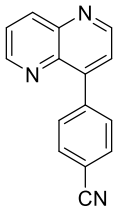
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 9.01 (dd, *J* = 4.1, 1.7 Hz, 1 H), 8.98 (d, *J* = 4.5 Hz, 1 H), 8.44 (dd, *J* = 8.5, 1.8 Hz, 1 H), 7.78 (d, *J* = 8.9 Hz, 2 H), 7.64 (dd, *J* = 8.5, 4.1 Hz, 1 H), 7.62 (d, *J* = 4.5 Hz, 1 H), 7.07 (d, *J* = 8.9 Hz, 2 H), 3.89 (s, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 160.4, 151.1, 150.7, 148.1, 144.7, 142.2, 137.8, 132.0, 129.1, 124.2, 123.8, 114.0, 55.5.

MS (EI, 70 eV): *m/z (%)* = 236 (90), 235 (100), 221 (46), 205 (35), 192 (52).

HRMS (EI) for calcd. for [$C_{15}H_{12}N_2O$]: 236.0950; found: 236.0937.

4-(1,5-Naphthyridin-4-yl)benzonitrile (42h)



According to **TP 1**, 1,5-Naphthyridine (**39**, 130 mg, 1 mmol) was metalated using $TMP_2Mg{\cdot}2LiCl$ (**4**, 1.72 mL, 1.1 mmol, 0.64 M in THF, 1.1 equiv) followed by transmetalation with $ZnCl_2$ (1.1 mL, 1.1 mmol, 1.0 M in THF, 1.1 equiv). The reaction mixture was stirred for further 20 min before a solution of $Pd(PPh_3)_4$ (58 mg, 0.05 mmol, 5 mol%) and 4-bromobenzonitrile (146 mg, 0.8 mmol) in dry THF (1 mL) was added dropwise. The reaction mixture was allowed to warm to rt and stirred at 50 °C overnight. After workup, the crude product was purified by flash column chromatography (isohexane/ EtOAc = 8:2, 1% NEt_3) to give **42h** (89 mg, 48 %) as a white solid.

m.p.: 160 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2227, 1584, 1492, 1408, 1261, 1118, 1026, 876, 841, 836, 826, 791, 655.

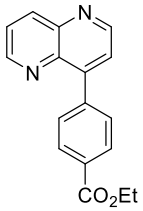
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 9.07 (d, *J* = 4.4 Hz, 1H), 9.01 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.50 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.71 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.64 (dd, *J* = 8.5, 4.4 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 151.4, 151.2, 146.5, 144.7, 141.5, 141.4, 138.1, 132.1, 131.4, 124.8, 124.1, 118.8, 112.7.

MS (EI, 70 eV): *m/z (%)* = 231 (47), 230 (100), 203 (5), 176 (5), 116 (5), 102 (4).

HRMS (EI) for calcd. for [$C_{15}H_9N_3$]: 231.0796; found: 231.0767.

Ethyl 4-(1,5-naphthyridin-4-yl)benzoate (42i)



According to **TP 1**, 1,5-Naphthyridine (**39**, 130 mg, 1 mmol) was metalated using $TMP_2Mg{\cdot}2LiCl$ (**4**, 1.72 mL, 1.1 mmol, 0.64 M in THF, 1.1 equiv) followed by transmetalation with $ZnCl_2$ (1.1 mL, 1.1 mmol, 1.0 M in THF, 1.1 equiv). The reaction mixture was stirred for further 20 min before a solution of $Pd(PPh_3)_4$ (58 mg, 0.05 mmol, 5 mol%) and ethyl 4-bromobenzoate (183 mg, 0.8 mmol) in dry THF (1.0 mL) was added dropwise. The reaction mixture was allowed to warm to rt and stirred at 50 °C overnight. After workup, the crude product was purified by flash column chromatography (isohexane/ EtOAc = 7:2, 1% NEt_3) to give **42i** (89 mg, 40 %) as a white solid.

m.p.: 114-117 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1714, 1492, 1407, 1364, 1270, 1102, 1023, 847, 824, 795, 766, 714, 699, 661.

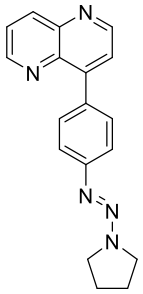
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.91 (d, *J* = 4.4 Hz, 1H), 8.88 (d, *J* = 4.0 Hz, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.55 (m, 1H), 7.52 (d, *J* = 4.2 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 166.3, 151.0, 150.9, 147.3, 144.4, 141.6, 141.1, 137.7, 130.5, 130.4, 129.4, 124.3, 124.0, 61.1, 14.4.

MS (EI, 70 eV): *m/z (%)* = 278 (52), 250 (19), 249 (74), 233 (19), 206 (20), 205 (100), 203 (16), 103 (13).

HRMS (EI) calcd. for [$C_{17}H_{14}N_2O_2$]: 278.1055; found: 278.1049.

(*E*)-4-(4-(pyrrolidin-1-yldiazenyl)phenyl)-1,5-naphthyridine (42j)



According to **TP 1**, 1,5-Naphthyridine (**39**, 130 mg, 1 mmol) was metalated using $TMP_2Mg{\cdot}2LiCl$ (**4**, 0.64 M in THF, 1.72 mL, 1.1 equiv) followed by transmetalation with $ZnCl_2$ (1.1 mL, 1.1 mmol, 1.0 M in THF, 1.1 equiv). The reaction mixture was stirred for further 20 min before a solution of $Pd(dba)_2$

(29 mg, 0.05 mmol, 5 mol%), tfp (23 mg, 0.10 mmol, 10 mol%) and (*E*)-1-((4-iodophenyl)-diazenyl)pyrrolidine (240 mg, 0.8 mmol) in dry THF (1 mL) was added dropwise. The reaction mixture was allowed to warm to rt overnight. After workup, the crude product was purified by flash column chromatography (EtOAc) to give **42j** (100 mg, 41 %) as a brown solid.

m.p.: 134 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1489, 1421, 1392, 1354, 1342, 1313, 1261, 1146, 841, 821, 801, 660.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.03 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.99 (d, *J* = 4.5 Hz, 1H), 8.49 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.81 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 4.6 Hz, 1H), 7.66 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 3.98-3.68 (m, 4H), 2.10-2.01 (m, 4H).

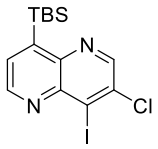
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 152.2, 150.9, 150.6, 149.2, 144.2, 142.2, 137.4, 133.1, 131.5, 124.4, 123.9, 120.5, 24.0

MS (EI, 70 eV): *m/z (%)* = 303 (10), 206 (21), 205 (100), 83 (8).

HRMS (EI) calcd. for [$C_{18}H_{17}N_5$]: 303.1484; found: 303.1478.

3.4 Metalation of Chloro-1,5-naphthyridines (45a-b) in Position 4 Using TMPMgCl·LiCl (3)

8-(*Tert*-butyldimethylsilyl)-3-chloro-4-iodo-1,5-naphthyridine (47a)



According to **TP2**, 3-chloro-1,5-naphthyridine derivative **45b** (139 mg, 0.5 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.5 mL, 0.55 mmol, 1.1 M in THF, 1.1 equiv) followed by the reaction with I_2 (256 mg, 1.0 mmol) in dry THF (2 mL). After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to give **47a** (165 mg, 82 %) as a brown crystalline solid.

m.p.: 162 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2950, 2926, 2852, 1545, 1460, 1433, 1352, 1247, 1222, 1144, 1056, 1004, 903, 827, 803, 775, 672.

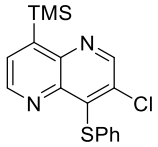
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 8.95 (d, *J* = 4.1 Hz, 1H), 8.75 (s, 1H), 7.76 (d, *J* = 4.1 Hz, 1H), 0.91 (s, 9H), 0.48 (s, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 152.1, 151.5, 147.7, 145.6, 144.1, 137.8, 132.3, 119.4, 27.5, 17.7, -3.8.

MS (EI, 70 eV): *m/z (%)* = 404 (0.23), 349 (33), 348 (19), 347 (100), 220 (9).

HRMS (EI) calcd. for [$C_{14}H_{18}ClN_2Si$]: 403.9977; found: 403.9950.

3-Chloro-4-(phenylthio)-8-(trimethylsilyl)-1,5-naphthyridine (47b)



According to **TP 2**, 3-chloro-1,5-naphthyridine derivative **45a** (84 mg, 0.35 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.35 mL, 0.39 mmol, 1.1 M in THF, 1.1 equiv) followed by the reaction with *S*-phenyl benzenethiolsulfonate (114 mg, 0.45 mmol, 1.3 equiv) in dry THF (1 mL). After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to give **47b** (111 mg, 92 %) as a yellow solid.

m.p.: 82 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1478, 1441, 1242, 1203, 1148, 1061, 1034, 1022, 936, 905, 837, 755, 734, 969, 685.

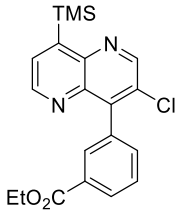
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.88 (d, *J* = 4.0 Hz, 1H), 8.81 (s, 1H), 7.68 (d, *J* = 4.1 Hz, 1H), 7.24-7.11 (m, 5H), 0.39 (s, 9H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 153.1, 150.8, 149.9, 146.5, 143.3, 142.4, 135.3, 134.7, 130.4, 130.2, 129.1, 127.0, 0.5.

MS (EI, 70 eV): *m*/*z* (%) = 344 (63), 343 (42), 331 (38), 329 (100), 309 (23), 293 (12), 165 (13), 164 (28).

HRMS (EI) calcd. for [$C_{17}H_{17}ClN_2SSi$]: 344.0570; found: 344.0560.

Ethyl 3-(3-chloro-8-(trimethylsilyl)-1,5-naphthyridin-4-yl)benzoate (47c)



According to **TP 2**, 3-chloro-1,5-naphthyridine derivative **45a** (90 mg, 0.38 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.38 mL, 0.42 mmol, 1.1 M in THF, 1.1 equiv) followed by transmetalation with $ZnCl_2$ (0.42 mL, 0.42 mmol, 1.0 M in THF, 1.1 equiv). The reaction mixture was stirred for further 20 min before a solution of $Pd(dba)_2$ (9 mg, 0.016 mmol, 4 mol%), tfp (7 mg, 0.032 mmol, 8 mol%) and ethyl 3-iodo-benzoate (110 mg, 0.40 mmol, 1.05 equiv) in THF (1.0 mL) was added dropwise. The reaction mixture was allowed to warm to rt overnight. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to give **47c** (105 mg, 72 %) as a white solid.

m.p.: 98 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1717, 1471, 1366, 1281, 1234, 1178, 1143, 1106, 1059, 905, 838, 755, 701.

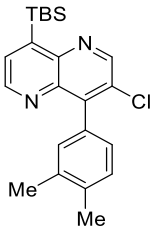
^{1}H-NMR ($CDCl_3$, 600 MHz): δ/ ppm = 9.03 (s, 1H), 8.87 (d, *J* = 4.0 Hz, 1H), 8.20 (dt, *J* = 7.2, 1.8 Hz, 1H), 8.16-8.15 (m, 1H), 7.73 (d, *J* = 4.0 Hz, 1H), 7.66-7.61 (m, 2H), 7.40 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 0.49 (s, 9H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ/ ppm = 166.4, 152.2, 150.9, 149.6, 146.6, 145.4, 141.7, 134.7, 134.7, 131.5, 130.6, 129.9 (2C), 128.3, 61.2, 14.5, 0.6.

MS (EI, 70 eV): *m/z (%)* = 384 (72), 383 (93), 371 (43), 369 (100), 355 (24), 343 (19), 341 (50), 314 (22), 311 (20), 162 (20), 148 (20).

HRMS (EI) calcd. for [$C_{20}H_{21}ClN_2O_2Si$]: 384.1061; found: 384.1050.

8-(*Tert*-butyldimethylsilyl)-3-chloro-4-(3,4-dimethylphenyl)-1,5-naphthyridine (47d)



According to **TP 2**, 3-chloro-1,5-naphthyridine derivative **45b** (139 mg, 0.50 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.5 mL, 0.55 mmol, 1.1 M in THF, 1.1 equiv) followed by transmetalation with $ZnCl_2$ (0.55 mL, 0.55 mmol, 1.0 M in THF, 1.1 equiv). The reaction mixture was stirred for further 20 min before a solution of $Pd(dba)_2$ (14 mg, 0.025 mmol, 5 mol%), tfp (11 mg, 0.05 mmol, 10 mol%) and 4-iodo-1,2-dimethylbenzene (104 mg, 0.45 mmol) in dry THF (1 mL) was added dropwise. The reaction mixture was allowed to warm to rt overnight. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to give **47d** (149 mg, 78 %) as a white solid.

m.p.: 150 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2926, 1467, 1253, 1218, 1142, 1124, 1065, 911, 830, 802, 774,676, 656.

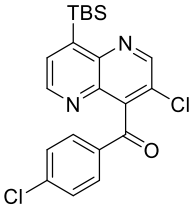
^{1}H-NMR ($CDCl_3$, 400 MHz): δ/ ppm = 8.98 (s, 1H), 8.89 (d, *J* = 4.1 Hz, 1H), 7.71 (d, *J* = 4.1 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.23-7.16 (m, 2H), 2.36 (s, 3H), 2.35 (s, 3H), 0.96 (s, 9H), 0.50 (s, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ/ ppm = 150.9, 150.5, 149.3, 146.8, 146.4, 142.4, 137.3, 136.4, 132.0, 131.3, 131.2, 129.9, 129.6, 127.7, 27.6, 20.1, 20.0, 17.8, 3.8.

MS (EI, 70 eV): *m/z (%)* = 382 (2), 328 (10), 327 (36), 326 (29), 325 (100), 311 (6), 155 (6).

HRMS (EI) calcd. for [$C_{22}H_{27}ClN_2Si$]: 382.1632; found: 382.1626.

(8-(*Tert*-butyldimethylsilyl)-3-chloro-1,5-naphthyridin-4-yl)(4-chlorophenyl)methanone (47e)



According to **TP 2**, 3-chloro-1,5-naphthyridine derivative **45b** (139 mg, 0.5 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.5 mL, 0.55 mmol, 1.1 M in THF, 1.1 equiv) followed by the addition of CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.0 M in THF, 1.1 equiv). The reaction mixture was stirred for further 20 min before 4-chlorobenzoyl chloride (0.13 mL, 1.0 mmol, 2.0 equiv) was added dropwise. Then, the reaction was slowly warmed to rt over 2 h. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to give **47e** (178 mg, 86 %) as a white solid.

m.p.: 138-140 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2925, 2853, 1676, 1589, 1467, 1402, 1314, 1263, 1227, 1177, 1153, 1088, 1056, 1015, 933, 913, 839, 826, 804, 777, 749, 679, 669.

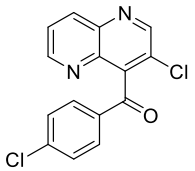
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.97 (s, 1H), 8.80 (d, *J* = 4.1 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.75 (s, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 0.95 (s, 9H), 0.50 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 192.5, 151.3, 151.1, 149.1, 146.4, 143.8, 141.0, 141.0, 134.4, 132.1, 131.2, 129.4, 126.8, 27.5, 17.7, 4.0.

MS (EI, 70 eV): *m/z (%)* = 416 (<1), 363 (31), 361 (79), 360 (63), 359 (100), 333 (17), 331 (28), 221 (12), 185 (12).

HRMS (EI) calcd. for [$C_{21}H_{22}Cl_2N_2OSi$]: 416.0878; found 416.0869.

(3-Chloro-1,5-naphthyridin-4-yl)(4-chlorophenyl)methanone (48)



TBAF (0.46 mL, 0.46 mmol, 1.0 M in THF, 2.0 equiv) was added dropwise to a solution of **47e** (90 mg, 0.22 mmol) in dry THF (1 mL). The reaction was stirred for 12 h at rt, before the solvent was removed *in vacuo* and redissolved in a small amount of EtOAc. The crude product was purified by flash column chromatography (isohexane/EtOAc = 1:1) to give **48** (52 mg, 82%) as a white solid.

m.p.: 196-198 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1681, 1587, 1572, 1482, 1401, 1259, 1209, 1159, 1115, 1091, 1032, 1012, 921, 905, 860, 815, 785, 753, 692.

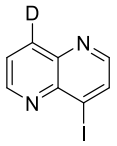
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.02 (s, 1H), 8.90 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.48 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.68 (dd, *J* = 8.6, 4.2 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 191.7, 152.5, 150.9, 143.6, 142.0, 141.6, 141.1, 137.5, 134.1, 131.0, 129.4, 127.5, 124.9.

MS (EI, 70 eV): *m/z (%)* = 302 (1), 275 (42), 273 (66), 241 (32), 239 (100), 203 (10).
HRMS (EI) calcd. for [$C_{15}H_8Cl_2N_2O$]: 302.0014; found: 302.0013.

3.5 Metalation of 1,5-Naphthyridines (42a-c) in Position 8 Using TMPMgCl·LiCl (3) and TMPZnCl·LiCl (5)

4-Iodo-1,5-naphthyridine-8-*d* (50)



According to **TP 3**, 4-iodo-1,5-naphthyridine (**42a**, 128 mg, 0.50 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.5 mL, 0. 55 mmol, 1.1 M in THF, 1.1 equiv) followed by the reaction with D_2O (0.05 mL, 3.0 mmol, 6.0 equiv) in dry THF (2 mL). The reaction mixture was allowed to warm to rt. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1, 1% NEt_3) to give **50** (100 mg, 78%) as a beige solid. NMR-spectroscopy revealed an incorporation of deuterium at position 8 with a ^{2}H:^{1}H ration of 63:37.

m.p.: 86-88 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1737, 1565, 1543, 1469, 1373, 1276, 1259, 1241, 1181, 1169, 1032, 962, 840, 782, 705.

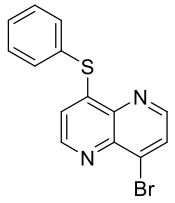
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 9.06 (d, *J* = 4.2 Hz, 1H), 8.53 (d, *J* = 4.5 Hz, 1H), 8.28 (d, *J* = 4.5 Hz, 1H), 7.70 (dd, *J* = 8.4, 4.2 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 152.2, 150.9, 144.0/143.9 (C_H/C_D), 138.4, 135.4, 125.5, 125.4, 116.4.

MS (EI, 70 eV): *m/z (%)* = 257 (100), 256 (95), 130 (59), 103 (45), 102 (46), 76 (24), 75 (26), 50 (23).

HRMS (EI) calcd. for [$C_8H_4DIN_2$]: 256.9560; found: 256.9564.

4-Bromo-8-(phenylthio)-1,5-naphthyridine (52a)



According to **TP 3**, 4-bromo-1,5-naphthyridine (**42b**, 100 mg, 0.48 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.48 mL, 0.53 mmol, 1.1 M in THF, 1.1 equiv) followed by the reaction with *S*-phenyl benzenethiolsulfonate (180 mg, 0.72 mmol, 1.5 equiv) in dry THF (2 mL). After workup, the

crude product was purified by flash column chromatography (isohexane/EtOAc = 8:2) to give **52a** (82 mg, 54%) as a yellow solid.

m.p.: 152-153 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1567, 1470, 1387, 1256, 1185, 1041, 1025, 833, 747, 728, 688.

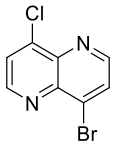
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.72 (d, *J* = 4.6 Hz, 1H), 8.65 (d, *J* = 4.8 Hz, 1H), 8.00 (d, *J* = 4.6 Hz, 1H), 7.69-7.63 (m, 2H), 7.56-7.50 (m, 3H), 6.82 (d, *J* = 4.8 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 154.2, 150.9, 149.1, 141.6, 141.0, 136.4, 136.3, 135.5, 130.4, 130.1, 129.1, 119.7.

MS (EI, 70 eV): *m/z (%)* = 318 (63), 317 (99), 316 (55), 315 (100), 283 (16), 236 (22), 235 (14), 210 (11), 51 (10).

HRMS (EI) calcd. for [$C_{14}H_9BrN_2S$]: 315.9670; found: 315.9671.

4-Bromo-8-chloro-1,5-naphthyridine (52b)



According to **TP 3**, 4-bromo-1,5-naphthyridine (**42b**, 129 mg, 0.62 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.62 mL, 0.68 mmol, 1.1 M in THF, 1.1 equiv) followed by the reaction with 1,1,2-trichloro-1,2,2-trifluoroethane (232 mg, 1.24 mmol, 2.0 equiv) in dry THF (1 mL). After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 1:1) to give **52b** (80 mg, 53%) as a white solid.

m.p.: 260-262 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2923, 1576, 1457, 1375, 1263, 1185, 1091, 1042, 863, 825, 731, 709.

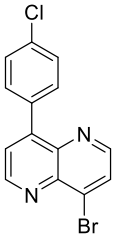
^{1}H-NMR (400 MHz, DMSO-d_6): δ/ ppm = 9.02 (d, *J* = 4.7 Hz, 1H), 8.90 (d, *J* = 4.6 Hz, 1H), 8.33 (d, *J* = 4.5 Hz, 1H), 8.14 (d, *J* = 4.7 Hz, 1H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ/ ppm = 151.9, 151.7, 143.3, 142.0, 140.8, 129.6, 129.6, 125.8.

MS (EI, 70 eV): *m/z (%)* = 246 (23), 244 (100), 242 (73), 165 (14), 163 (45), 136 (11), 100 (16).

HRMS (EI) for [$C_8H_4BrClN_2$]: 241.9246; found: 241.9230.

4-Bromo-8-(4-chlorophenyl)-1,5-naphthyridine (52c)



According to **TP 3**, 4-bromo-1,5-naphthyridine (**42b**, 100 mg, 0.48 mmol) was metalated using TMPMgCl·LiCl (**3**, 0. 48 mL, 0.53 mmol, 1.1 M in THF, 1.1 equiv) followed by transmetalation with

$ZnCl_2$ (0.53 mL, 0.53 mmol, 1.0 M in THF, 1.1 equiv). The reaction mixture was stirred for further 20 min before a solution of $Pd(dba)_2$ (14 mg, 0.024 mmol, 5 mol%), tfp (11 mg, 0.048 mmol, 10 mol%) and 1-chloro-4-iodobenzene (0.38 mmol, 91 mg, 0.8 equiv) in dry THF (1 mL) was added dropwise. The reaction mixture was allowed to warm to rt overnight. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 1:1) to give **52c** (72 mg, 59%) as a yellow solid.

m.p.: 162 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1578, 1471, 1391, 1258, 1094, 1085, 1018, 864, 806, 763, 717, 685, 665.

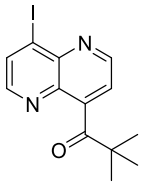
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.13 (d, *J* = 4.4 Hz, 1H), 8.76 (d, *J* = 4.5 Hz, 1H), 8.02 (d, *J* = 4.5 Hz, 1H), 7.71-7.68 (m, 3H), 7.52 (d, *J* = 8.6 Hz, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 151.6, 150.5, 148.3, 142.7, 142.4, 136.6, 135.6, 134.7, 132.0, 128.8, 128.5, 125.0.

MS (EI, 70 eV): *m/z (%)* = 320 (54), 319 (100), 318 (43), 317 (70), 285 (19), 283 (19), 203 (24).

HRMS (EI) calcd. for [$C_{14}H_8BrClN_2$]: 317.9559; found: 317.9525.

1-(8-Iodo-1,5-naphthyridin-4-yl)-2,2-dimethylpropan-1-one (52d)



According to **TP 4**, 2,2-dimethyl-1-(1,5-naphthyridin-4-yl)propan-1-one (**42c**, 107 mg, 0.5 mmol) was metalated using TMPZnCl·LiCl (**5**, 0.58 mL, 0.75 mmol, 1.3 M in THF, 1.5 equiv) followed by the reaction with I_2 (254 mg, 1.0 mmol, 2.0 equiv) in dry THF (3 mL). After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to give **52d** (121 mg, 71%) as a white solid.

m.p.: 131 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1692, 1476, 1454, 1209, 1104, 1080, 954, 875, 844, 834, 714, 660.

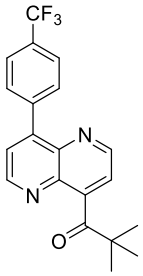
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.04 (d, *J* = 4.3 Hz, 1H), 8.48 (d, *J* = 4.5 Hz, 1H), 8.28 (d, *J* = 4.5 Hz, 1H), 7.43 (d, *J* = 4.3 Hz, 1H), 1.29 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 211.9, 151.4, 150.8, 149.6, 143.9, 141.0, 135.8, 120.9, 116.2, 45.3, 26.9.

MS (EI, 70 eV): *m/z* (%) = 340 (13), 283 (27), 256 (100), 129 (10), 101 (10), 74 (11), 57 (31).

HRMS (EI) calcd. for [$C_{13}H_{13}IN_2O$]: 340.0073; found: 340.0066.

2,2-Dimethyl-1-(8-(4-(trifluoromethyl)phenyl)-1,5-naphthyridin-4-yl)propan-1-one (52e)



According to **TP 4**, 2,2-dimethyl-1-(1,5-naphthyridin-4-yl)propan-1-one (**42c**, 107 mg, 0.5 mmol) was metalated using TMPZnCl·LiCl (**5**, 0.58 mL, 0.75 mmol, 1.3 M in THF, 1.5 equiv), followed by the dropwise addition of a solution of $Pd(dba)_2$ (12 mg, 0.02 mmol, 4 mol%), tfp (9 mg, 0.04 mmol, 8 mol%) and 1-iodo-4-(trifluoromethyl)benzene (109 mg, 0.4 mmol, 0.8 equiv) in dry THF (1 mL). After stirring the reaction overnight and subsequent workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 8:2) to give **52e** (140 mg, 98%) as an off-white solid.

m.p.: 139-141 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2973, 1704, 1478, 1324, 1314, 1194, 1159, 1111, 1083, 1064, 1067, 960, 860, 850, 829, 731.

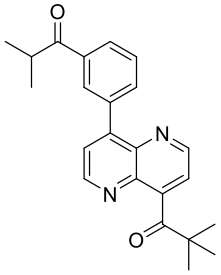
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.02 (d, *J* = 4.4 Hz, 1H), 9.00 (d, *J* = 4.2 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 4.4 Hz, 1H), 7.42 (d, *J* = 4.2 Hz, 1H), 1.34 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 212.6, 151.1, 150.5, 149.2, 147.1, 141.7, 140.2, 131.0, 125.4 (CF_3), 124.4, 124.6, 119.9, 45.4, 26.9.

MS (EI, 70 eV): *m/z (%)* = 358 (11), 302 (25), 275 (14), 274 (100), 273 (42), 57 (19).

HRMS (EI) calcd. for $[C_{20}H_{17}F_3N_2O]$: 358.1293; found: 358.1280.

1-(8-(3-Isobutyrylphenyl)-1,5-naphthyridin-4-yl)-2,2-dimethylpropan-1-one (52f)



According to **TP 4**, 2,2-dimethyl-1-(1,5-naphthyridin-4-yl)propan-1-one (**42c**, 107 mg, 0.5 mmol) was metalated using TMPZnCl·LiCl (**5**, 0.58 mL, 0.75 mmol, 1.3 M in THF, 1.5 equiv), followed by the dropwise addition of a solution of $Pd(dba)_2$ (12 mg, 0.02 mmol, 4 mol%), tfp (9 mg, 0.04 mmol, 8 mol%) and 1-(3-iodophenyl)-2-methylpropan-1-one (110 mg, 0.4 mmol, 0.8 equiv) in dry THF (1 mL) was added dropwise. After stirring the reaction overnight and subsequent workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 8:2) to give **52f** (139 mg, 97%) as a red oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2971, 1735, 1682, 1581, 1503, 1478, 1462, 1372, 1234, 1187, 1156, 1082, 1044, 993, 961, 861, 809, 746, 697.

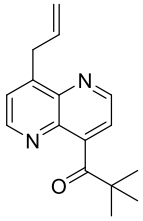
^{1}H-NMR ($CDCl_3$, 600 MHz): δ/ ppm = 9.00 (d, *J* = 4.4 Hz, 1H), 8.99 (d, *J* = 4.2 Hz, 1H), 8.35 (t, *J* = 1.6 Hz, 1H), 8.08 (ddd, *J* = 7.9, 1.7, 1.2 Hz, 1H), 7.96 (ddd, *J* = 7.6, 1.8, 1.2 Hz, 1H), 7.67 (d, *J* = 4.4 Hz, 1H), 7.65–7.61 (m, 1H), 7.40 (d, *J* = 4.2 Hz, 1H), 3.61 (sept, *J* = 6.8 Hz, 1H), 1.33 (s, 9H), 1.26 (d, *J* = 6.9 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ/ ppm = 212.7, 204.0, 151.1, 150.3, 149.1, 147.5, 141.8, 141.6, 137.0, 136.3, 134.9, 130.6, 128.8, 128.7, 124.5, 119.8, 45.3, 35.6, 26.9, 19.3.

MS (EI, 70 eV): *m*/*z* (%) = 360 (53), 317 (49), 303 (46), 277 (50), 276 (100), 43 (66).

HRMS (EI) calcd. for [$C_{23}H_{24}N_2O_2$]: 360.1838; found: 360.1826.

1-(8-Allyl-1,5-naphthyridin-4-yl)-2,2-dimethylpropan-1-one (52g)



According to **TP 4**, 2,2-dimethyl-1-(1,5-naphthyridin-4-yl)propan-1-one (**42c**, 107 mg, 0.5 mmol) was metalated using TMPZnCl·LiCl (**5**, 0.58 mL, 0.75 mmol, 1.3 M in THF, 1.5 equiv). Then, the reaction mixture was cooled to -20 °C and CuCN·2LiCl (0.1 mL, 0.1 mmol, 1.0 M in THF, 0.2 equiv) was added. After 5 min of stirring at -20 °C, the mixture was cooled down to –50 °C and allylbromide (0.07 mL, 0.75 mmol, 1.5 equiv) was added. The mixture was allowed to warm up to rt and was further stirred for 3 h. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 8:2) to give **52g** (102 mg, 80%) as a brown solid.

m.p.: 72-74 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2970, 1691, 1500, 1478, 1392, 1273, 1228, 1162, 1050, 988, 912, 873, 736.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ/ ppm = 8.97 (d, *J* = 4.2 Hz, 1H), 8.84 (d, *J* = 4.3 Hz, 1H), 7.48 (d, *J* = 4.3 Hz, 1H), 7.36 (d, *J* = 4.2 Hz, 1H), 6.19 – 6.07 (m, 1H), 5.20 (t, *J* = 1.3 Hz, 1H), 5.19–5.16 (m, 1H), 4.09–4.06 (m, 2H), 1.29 (s, 9H).

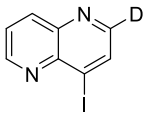
^{13}C-NMR ($CDCl_3$, 150 MHz): δ/ ppm = 213.0, 151.2, 149.4, 149.0, 148.7, 143.1, 140.8, 135.3, 124.1, 119.7, 117.7, 45.3, 34.6, 26.9.

MS (EI, 70 eV): *m*/*z* (%) = 254 (38), 197 (86), 171 (13), 170 (100), 156 (28), 57 (24), 41 (20).

HRMS (EI) calcd. for [$C_{16}H_{18}N_2O$]: 254.1419; found: 254.1412.

3.6 Metalation of 1,5-Naphthyridines (42a and 42g) in Position 2 Using TMPMgCl·LiCl (3) in Presence of $BF_3 \cdot OEt_2$

4-Iodo-1,5-naphthyridine-2-*d* (54)



According to **TP 5**, 4-iodo-1,5-naphthyridine (**42a**, 128 mg, 0.5 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.5 mL, 0.55 mmol, 1.1 M in THF, 1.1 equiv) in the presence of $BF_3 \cdot OEt_2$ (0.07 mL, 0.55 mmol, 1.1 equiv), followed by the reaction with D_2O (0.05 mL, 2.5 mmol, 5.0 equiv) in dry THF (1 mL). After workup, the crude product was purified by flash column chromatography (EtOAc) to give **54** (86 mg, 67%) as an off-white solid. NMR-spectroscopy revealed an incorporation of deuterium at position 2 with a $^2H:^1H$ ration of 76:24.

m.p.: 96-97 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1556, 1547, 1467, 1379, 1030, 964, 893, 847, 821, 786.

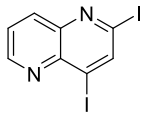
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 9.05 (dd, *J* = 4.2 Hz, 1.6 Hz, 1H), 8.35 (dd, *J* = 8.5 Hz, 1.6 Hz, 1H), 8.29-8.24 (m, 1H), 7.69 (dd, *J* = 8.5 Hz, 4.2 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 152.1, 150.8, 143.9 (C_D/C_H), 138.4, 135.4, 135.3, 125.5, 116.4.

MS (EI, 70 eV): *m/z* (%) = 257 (100), 256 (37), 130 (29), 129 (11), 102 (12).

HRMS (EI) calcd. for [$C_8H_4DIN_2$]: 256.9560; found: 256.9555.

2,4-Diiodo-1,5-naphthyridine (56a)



According to **TP 5**, 4-iodo-1,5-naphthyridine (**42a**, 100 mg, 0.39 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.39 mL, 0.43 mmol, 1.1 M in THF, 1.1 equiv) in the presence of $BF_3 \cdot OEt_2$ (0.05 mL, 0.43 mmol, 1.1 equiv), followed by the reaction with I_2 (200 mg, 0.80 mmol, 2.0 equiv) in dry THF (2 mL). After workup, the crude product was purified by flash column chromatography (isohexane/ EtOAc = 9:1) to give **56a** (110 mg, 74%) as an off-white solid.

m.p.: 166 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1536, 1465, 1449, 1364, 1348, 1248, 1230, 1184, 1084, 1035, 960, 855, 845, 819, 801, 781.

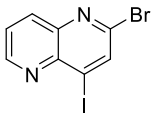
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.02 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.58 (s, 1H), 8.27 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.66 (dd, *J* = 8.5, 4.4 Hz, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 152.2, 144.9, 144.8, 143.4, 137.5, 126.0, 118.9, 117.4.

MS (EI, 70 eV): *m/z* (%) = 382 (94), 256 (10), 255 (100), 128 (34), 101 (10), 75 (9).

HRMS (EI) calcd. for [$C_8H_4I_2N_2$]: 381.8464; found: 381.8464.

2-Bromo-4-iodo-1,5-naphthyridine (56b)



According to **TP 5**, 4-iodo-1,5-naphthyridine (**42a**, 256 mg, 1.0 mmol) was metalated using TMPMgCl·LiCl (**3**, 1.0 mL, 1.1 mmol, 1.1 M in THF, 1.1 equiv) in the presence of $BF_3 \cdot OEt_2$ (0.14 mL, 1.1 mmol, 1.1 equiv), followed by the reaction with 1,2-dibromotetrachlororethane (615 mg, 2.0 mmol, 2.0 equiv) in dry THF (2 mL). After workup, the crude product was purified by flash column chromatography (isohexane/ EtOAc = 8:2, 1% NEt_3) to give **56b** (240 mg, 72%) as an off-white solid.

m.p.: 165 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1544, 1456, 1376, 1249, 1233, 1185, 1086, 1033, 854, 813, 803, 778, 665.

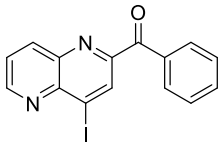
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.04 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.39 (s, 1H), 8.29 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.70 (dd, *J* = 8.5, 4.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 152.2, 143.6, 143.2, 142.0, 139.1, 137.4, 126.2, 118.1.

MS (EI, 70 eV): *m*/*z* (%) = 336 (97), 334 (100), 290 (9), 128 (35), 102 (13), 75 (16).

HRMS (EI) calcd. for [$C_8H_4BrIN_2$]: 333.8603; found: 333.8598.

(4-Iodo-1,5-naphthyridin-2-yl)(phenyl)methanone (56c)



According to **TP 5**, 4-iodo-1,5-naphthyridine (**42a**, 100 mg, 0.39 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.39 mL, 0.43 mmol, 1.1 M in THF, 1.1 equiv) in the presence of $BF_3 \cdot OEt_2$ (0.05 mL, 0.43 mmol, 1.1 equiv), followed by the addition of CuCN·2LiCl (0.43 mL 0.43 mmol, 1.0 M in THF, 1.1 equiv) and benzoyl chloride (0.09 mL, 0.78 mmol, 2.0 equiv). After workup, the crude product was purified by flash column chromatography (isohexane/ EtOAc = 9:1) to give **56c** (74 mg, 53%) as a white solid.

m.p.: 159 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 1654, 1473, 1457, 1322, 1310, 1195, 986, 885, 863, 821, 808, 786, 739, 699.

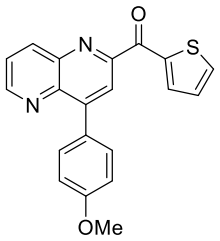
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.12 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.90 (s, 1H), 8.42 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.21-8.15 (m, 2H), 7.74 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.66-7.60 (m, 1H), 7.54-7.47 (m, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 191.7, 154.7, 153.7, 144.3, 142.0, 139.1, 135.6, 135.2, 133.6, 131.4, 128.4, 126.0, 117.3.

MS (EI, 70 eV): *m*/*z* (%) = 360 (25), 359 (15), 332 (43), 330 (20), 234 (15), 233 (88), 205 (30), 128 (13), 105 (100), 77 (85).

HRMS (EI) calcd. for [$C_{15}H_9IN_2O$]: 359.9760; found: 359.975.

(4-(4-Methoxyphenyl)-1,5-naphthyridin-2-yl)(thiophen-2-yl)methanone (56d)



According to **TP 5**, 4-(4-methoxyphenyl)-1,5-naphthyridine (**42g**, 100 mg, 0.42 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.46 mmol, 0.42 mL, 1.1 M in THF, 1.1 equiv) in the presence of $BF_3{\cdot}OEt_2$ (0.06 mL, 0.46 mmol, 1.1 equiv). Then a solution of CuCN·2LiCL (0.46 mL, 0.46 mmol, 1.0 M in THF, 1.1 equiv) and thiophene-2-carbonyl chloride (0.053 mL, 0.50 mmol, 1.2 equiv) was added. The resulting mixture was allowed to warm up to rt and stirred overnight. After workup, the crude product was purified by flash column chromatography (first EtOAc, then EtOH) to give **56d** (102 mg, 70%) as a white solid.

m.p.: 176 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1740, 1637, 1605, 1582, 1514, 1488, 1408, 1376, 1358, 1300, 1255, 1180, 1148, 1031, 940, 917, 826, 799, 715, 668.

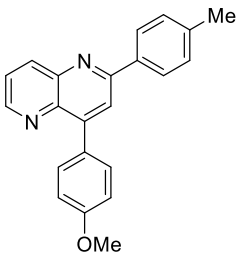
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.12 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.63 (dd, *J* = 8.5 Hz, 1.7 Hz, 1H), 8.51 (dd, *J* = 3.9 Hz, 1.2 Hz, 1H), 8.48 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.83 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.75 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.25-7.23 (m, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 3.91 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 183.4, 160.7, 154.0, 152.5, 149.3, 143.3, 142.8, 139.8, 138.8, 137.2, 137.1, 132.2, 128.7, 127.8, 124.8, 122.7, 114.1, 55.6.

MS (EI, 70 eV): *m*/*z* (%) = 346 (100), 345 (39), 317 (96), 303 (25), 287 (13), 274 (11), 234 (13), 192 (17), 111 (61).

HRMS (EI) calcd. for [$C_{20}H_{14}N_2O_2S$]: 346.0776; found: 346.0769.

4-(4-Methoxyphenyl)-2-(*p*-tolyl)-1,5-naphthyridine (56e)



According to **TP 5**, 4-(4-methoxyphenyl)-1,5-naphthyridine (**42g**, 118 mg, 0.50 mmol) was metalated using TMPMgCl·LiCl (**3**, 0.5 mL, 0.55 mmol, 1.1 M in THF, 1.1 equiv) in the presence of $BF_3{\cdot}OEt_2$ (0.07 mL, 0.55 mmol, 1.1 equiv), followed by transmetalation with $ZnCl_2$ (0.6 mL, 0.6 mmol, 1.0 M in

THF, 1.2 equiv). After stirring the reaction for further 10 min, a solution of $Pd(dba)_2$ (9 mg, 0.015 mmol, 3 mol%), tfp (7 mg, 0.030 mmol, 6 mol%) and 1-iodo-4-methylbenzene (98 mg, 0.45 mmol, 0.9 equiv) in dry THF (1 mL) was added dropwise. The reaction mixture was allowed to warm to rt overnight. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to give **56e** (82 mg, 56%) as a yellow solid.

m.p.: 133 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1606, 1588, 1543, 1514, 1486, 1462, 1363, 1290, 1247, 1181, 1153, 1112, 1020, 834, 820, 786, 718, 679.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.96 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.48 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 2H), 8.07 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.62 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 3.09 (s, 3H), 2.45 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 160.3, 157.8, 150.1, 148.4, 144.5, 141.5, 139.9, 137.7, 136.4, 131.9, 129.7, 129.5, 127.6, 124.2, 121.7, 114.0, 55.5, 21.5.

MS (EI, 70 eV): *m*/*z* (%) = 327 (16), 326 (91), 325 (100), 311 (27), 282 (15), 163 (7).

HRMS (EI) calcd. for $[C_{22}H_{18}N_2O]$: 326.1419; found: 326.1397.

4. Iron- and Cobalt-Catalyzed Cross-Coupling of Naphthyridines

4.1 Typical Procedures

Typical Procedure for Iron-Catalyzed C(sp^2)-C(sp^3) Cross-Couplings of Naphthyridines with Alkylmagnesium reagents (TP 1):

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum, was charged with 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 113 mg, 0.50 mmol) and $Fe(acac)_3$ (9 mg, 0.025 mmol, 5 mol%) followed by dry THF (2 mL). After dropwise addition of the alkylmagnesium reagent (2.4 equiv), the reaction mixture was stirred at rt for the indicated time until complete conversion of the starting material (detected by GC-analysis of reaction aliquots). Then, the mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 × 10 mL) and dried over $MgSO_4$. After filtration, the solvents were removed *in vacuo* and the residue was subjected to column chromatography on silica yielding the respective title compound.

Typical Procedure for Cobalt-Catalyzed C(sp^2)-C(sp^3) Cross-Couplings of Naphthyridines with Alkylmagnesium Reagents (TP2):

A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and septum, was charged with anhydrous $CoCl_2$ (5 mol%). The flask was evacuated under high vacuum at 400 °C for 5 min, cooled to rt and then backfilled with argon. Subsequently, the respective aryl halide (1.0 equiv) was added, followed by dry THF (0.5 M). Then, a solution of the appropriate alkylmagnesium reagent (1.1 equiv) was added dropwise *via* syringe. The reaction was stirred for 20 min at rt until complete consumption of starting material was detected by GC-analysis. Saturated aqueous NH_4Cl solution (10 mL) and EtOAc (10 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography on silica yielding the respective title compound.

Typical Procedure for Cobalt-Catalyzed C(sp^2)-C(sp^2) Cross-Couplings of Naphthyridine 22 with Arylmagnesium reagents (TP3):

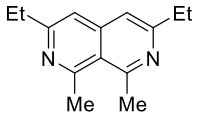
A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and septum, was charged with anhydrous $CoCl_2$ (5 mol%). The flask was evacuated under high vacuum at 400 °C for 5 min, cooled to rt and then backfilled with Argon. Subsequently, the respective aryl halide (1.0 equiv) was added, followed by dry THF (0.5 M). The solution was cooled to the indicated temperature. Then, a solution of the appropriate arylmagnesium reagent (3.0 equiv) was added dropwise *via* syringe. The reaction was stirred at the adjusted temperature until complete consumption of starting material, detected by GC-analysis. Saturated aqueous NH_4Cl solution (5 mL) and EtOAc (5 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography on silica yielding the respective title compound.

Typical Procedure for Cobalt-Catalyzed C(sp^2)-C(sp^2) Cross-Couplings of Naphthyridines with Arylzinc Reagents (TP4):

A dry and argon-flushed *Schlenk*-flask, equipped with a stirring bar and a septum, was charged with a solution of $CoCl_2 \cdot 2LiCl$ (1 M in THF, 5 mol%) and dry THF (2 mL). The respective aryl halide (1.0 equiv) and HCO_2Na (50 mol%) were added at rt. Then, a solution of the appropriate zinc reagent (1.2 equiv) was added dropwise over 15 min *via* syringe. The reaction was stirred and monitored by GC-analysis. Upon consumption of the starting material (approx. 12 h), saturated aqueous NH_4Cl solution (5 mL) and EtOAc (5 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4. The solvents were evaporated and the residue was subjected to column chromatography on silica yielding the respective title compound.

4.2 Iron- and Cobalt-Catalyzed C(sp^2)-C(sp^3) Cross-Couplings with Alkyl-magnesium Reagents

3,6-Diethyl-1,8-dimethyl-2,7-naphthyridine (58a)



According to **TP1**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 0.5 mmol, 113 mg, 1.0 equiv) reacted with EtMgCl (0.44 mL, 1.05 mmol, 2.4 M in THF, 2.1 equiv) within 2 h at rt. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford **58a** (74 mg, 69 %) as a redbrown solid.

m.p.: 56-57 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2967, 2925, 1606, 1545, 1456, 1373, 1329, 1062, 963, 915, 895.

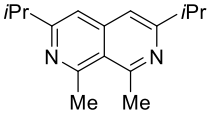
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.13 (s, 2H), 3.06 (s, 6H), 2.85 (q, *J* = 7.5 Hz, 4H), 1.32 (t, *J* = 7.5 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 158.9, 158.7, 142.7, 120.8, 114.8, 30.9, 29.1, 13.2.

MS (EI, 70 eV): *m*/*z* (%) = 214 (52), 213 (100), 186 (12), 185 (11), 115 (8), 63 (6), 42 (8).

HRMS (EI) calcd. for [$C_{14}H_{18}N_2$]: 214.1470; found: 214.1470.

3,6-Diisopropyl-1,8-dimethyl-2,7-naphthyridine (58b)



According to **TP1**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 0.5 mmol, 113 mg, 1.0 equiv) reacted with *i*PrMgCl·LiCl (0.91 mL, 1.15 mmol, 1.26 M in THF, 2.3 equiv) within 30 min at rt. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford **58b** (50 mg, 41%) as a yellow oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2961, 1608, 1549, 1457, 1426, 1379, 1332, 1091, 936, 886.

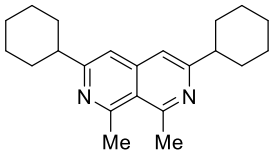
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 7.20 (s, 2H), 3.16-3.05 (m, 2H), 3.03 (s, 6H), 1.35 (s, 6H), 1.34 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 162.6, 158.7, 142.8, 121.1, 113.4, 35.8, 29.2, 22.4.

MS (EI, 70 eV): *m*/*z* (%) = 242 (46), 241 (38), 228 (18), 227 (100), 225 (14), 215 (11), 214 (66), 211 (22), 200 (9), 106 (11).

HRMS (EI) calcd. for [$C_{16}H_{22}N_2$]: 242.1783; found: 242.1776.

3,6-Dicyclohexyl-1,8-dimethyl-2,7-naphthyridine (58c)



According to **TP1**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 0.5 mmol, 113 mg, 1.0 equiv) reacted with *c*HexMgBr·LiCl (2.6 mL, 1.2 mmol, 0.46 M in THF, 2.4 equiv) within 30 min at rt. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford **58c** (126 mg, 78%) as a white solid.

m.p.: 78-79 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2922, 2850, 1604, 1540, 1447, 1423, 1328, 939, 900, 876, 849.

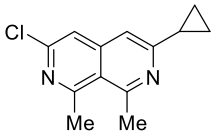
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 7.10 (s, 2H), 3.02 (s, 6H), 2.74-2.63 (m, 2H), 2.04-1.92 (m, 4H), 1.86-1.76 (m, 4H), 1.74-1.66 (m, 2H), 1.51-1.32 (m, 8H), 1.30-1.17 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.8, 158.6, 142.7, 121.2, 113.8, 45.9, 32.9, 29.3, 26.6, 26.2.

MS (EI, 70 eV): *m*/*z* (%) = 322 (38), 321 (20), 293 (15), 281 (16), 268 (25), 267 (100), 254 (29).

HRMS (EI) calcd. for [$C_{22}H_{30}N_2$]: 322.2409; found: 322.2402.

3-Chloro-6-cyclopropyl-1,8-dimethyl-2,7-naphthyridine (58d)



According to **TP1**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 0.5 mmol, 113 mg, 1.0 equiv) reacted with cyclopropylmagnesium bromide (1.2 mmol, 1.2 mL, 1.0 M in THF, 2.4 equiv) within 30 min at rt. After workup, the crude product was purified by flash column chromatography (isohexane/ EtOAc = 7:1) to afford **58d** (72 mg, 62%) as an off-white solid.

m.p.: 93-94 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1601, 1583, 1536, 1424, 1216, 1131, 892, 865.

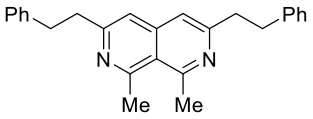
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 7.29 (s, 1H), 7.07 (s, 1H), 3.03 (s, 3H), 3.00 (s, 3H), 2.11-1.99 (m, 1H), 1.13-1.06 (m, 2H), 1.04-0.95 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 161.0, 159.6, 159.1, 146.7, 143.4, 120.9, 116.7, 113.2, 29.3, 28.8, 16.9, 9.7.

MS (EI, 70 eV): *m*/*z* (%) = 234 (18), 233 (36), 232 (51), 231 (100), 206 (9), 197 (10), 84 (9).

HRMS (EI) calcd. for [$C_{13}H_{13}ClN_2$]: 232.0767; found: 232.0750.

1,8-Dimethyl-3,6-diphenethyl-2,7-naphthyridine (58e)



According to **TP1**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 0.5 mmol, 113 mg, 1.0 equiv) reacted with Ph(CH_2)$_2$MgBr·LiCl (1.35 mL, 1.15 mmol, 0.85 M in THF, 2.4 equiv) within 30 min at rt. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford **58e** (152 mg, 83 %) as a white solid.

m.p.: 102-103 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2924, 2858, 1607, 1546, 1493, 1452, 1328, 893, 750, 713, 696.

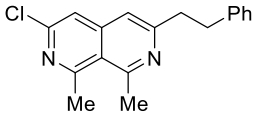
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 7.24-7.08 (m, 10H), 7.00 (s, 2H), 3.10-3.00 (m, 8H), 3.07 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 159.3, 156.5, 142.5, 141.7, 128.6, 128.5, 126.1, 121.2, 116.3, 39.7, 35.7, 29.4.

MS (EI, 70 eV): *m*/*z* (%) = 367 (27), 366 (100), 365 (49), 289 (27), 275 (15), 274 (17), 262 (12), 198 (12), 91 (48), 43 (27).

HRMS (EI) calcd. for [$C_{26}H_{26}N_2$]: 366.2096; found: 366.2098.

3-Chloro-1,8-dimethyl-6-phenethyl-2,7-naphthyridine (58f)



According to **TP2**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 0.5 mmol, 113 mg, 1.0 equiv) reacted with Ph(CH_2)$_2$MgBr·LiCl (0.65 mL, 0.55 mmol, 0.85 M in THF, 1.1 equiv) within 20 min at rt. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford **58f** (119 mg, 80%) as a white solid.

m.p.: 90 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1605, 1580, 1536, 1497, 1454, 1420, 1380, 1328, 1135, 887, 750, 729, 688.

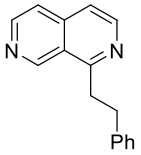
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 7.35 (s, 1H), 7.30-7.15 (m, 5H), 7.07 (s, 1H), 3.22-3.03 (m, 10H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.3, 159.9, 157.7, 147.1, 143.8, 141.4, 128.6, 128.5, 126.2, 121.3, 117.4, 115.7, 39.7, 35.5, 29.4, 29.1.

MS (EI, 70 eV): *m/z* (%) = 298 (30), 297 (41), 296 (100), 295 (83), 281 (9), 221 (17), 191 (17), 91 (31).

HRMS (EI) calcd. for [$C_{18}H_{17}N_2Cl$]: 296.1080; found: 296.1076.

1-Phenethyl-2,7-naphthyridine (58g)



According to **TP2**, 1-chloro-2,7-naphthyridine (**30**, 0.5 mmol, 82 mg, 1.0 equiv) reacted with $Ph(CH_2)_2MgBr{\cdot}LiCl$ (0.65 mL, 0.55 mmol, 0.85 M in THF, 1.1 equiv) within 20 min at rt. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 1:1) to afford **58g** (94 mg, 82%) as a yellow solid.

m.p.: 76 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1617, 1550, 1496, 1452, 1376, 1311, 1282, 1238, 1214, 1056, 1017, 973, 915, 896, 868, 795, 753, 738.

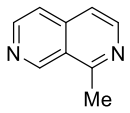
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.58 (s, 1H), 8.70 (d, *J* = 5.7 Hz, 1H), 8.66 (d, *J* = 5.8 Hz, 1H), 7.63 (dd, *J* = 5.7, 1.0 Hz, 1H), 7.51 (d, *J* = 5.8 Hz, 1H), 7.34-7.17 (m, 5H), 3.73-3.64 (m, 2H), 3.35-3.12 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 162.8, 150.6, 146.7, 146.2, 141.3, 139.2, 128.7, 128.6, 126.4, 122.4, 119.8, 117.9, 36.8, 35.9.

MS (EI, 70 eV): *m/z (%)* = 235 (16), 234 (95), 233 (100), 219 (15), 218 (19), 157 (33), 130 (22), 116 (10), 91 (34), 65 (10).

HRMS (EI) calcd. for [$C_{16}H_{14}N_2$]: 234.1157; found: 234.1148.

1-Methyl-2,7-naphthyridine (58h)



According to **TP2**, 1-chloro-2,7-naphthyridine (**30**, 329 mg, 2.0 mmol, 1.0 equiv) reacted with MeMgCl (0.81 mL, 2.2 mmol, 2.72 M in THF, 1.1 equiv) within 20 min at rt. After workup, the crude product was purified by flash column chromatography (EtOAc) to afford **58h** (286 mg, 98%) as a yellow solid.

m.p.: 45 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1615, 1549, 1435, 1393, 1374, 1356, 1276, 1248, 1215, 1081, 1019, 964, 885, 851, 800, 728, 578.

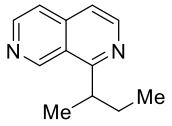
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.59 (s, 1H), 8.72 (d, *J* = 5.8 Hz, 1H), 8.57 (d, *J* = 5.8 Hz, 1H), 7.61 (dd, *J* = 5.7, 1.0 Hz, 1H), 7.48 (d, *J* = 5.8 Hz, 1H), 3.05 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 160.2, 151.1, 146.9, 146.1, 138.9, 122.8, 119.6, 117.8, 21.9.

MS (EI, 70 eV): *m/z (%)* = 145 (13), 144 (100), 118 (15), 117 (9), 116 (8), 75 (7), 63 (8), 50 (7).

HRMS (EI) calcd. for [$C_9H_8N_2$]: 144.0687; found: 144.0679.

1-(*Sec*butyl)-2,7-naphthyridine (58i)



According to **TP2**, 1-chloro-2,7-naphthyridine (**30**, 82 mg, 0.5 mmol, 1.0 equiv) reacted with *s*BuMgCl·LiCl (0.42 mL, 0.55 mmol, 1.3 M in THF, 1.1 equiv) within 20 min at rt. The crude product was purified by flash column chromatography (isohexane/EtOAc = 1:1) to afford **58i** (50 mg, 54%) as a colorless oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2963, 2929, 1615, 1548, 1461, 1380, 1332, 1265, 1215, 981, 852.

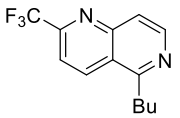
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.66 (s, 1H), 8.67 (d, *J* = 5.8 Hz, 1H), 8.65 (d, *J* = 5.8 Hz, 1H), 7.60 (dd, *J* = 5.7, 0.8 Hz, 1H), 7.44 (dd, *J* = 5.7, 0.8 Hz, 1H), 3.80 (sept, *J* = 6.8 Hz, 1H), 2.08-1.95 (m, 1H), 1.77 (dquint, *J* = 14.2, 7.3 Hz, 1H), 1.42 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 167.7, 150.3, 146.4, 146.1, 139.2, 122.2, 119.9, 117.3, 37.9, 29.9, 20.4, 12.4.

MS (EI, 70 eV): *m/z (%)* = 186 (15), 185 (25), 172 (11), 171 (82), 159 (13), 158 (100), 157 (78), 156 (16), 144 (23), 130 (25), 129 (18), 78 (11).

HRMS (EI) calcd. for [$C_{12}H_{14}N_2$]: 186.1157; found: 186.1170.

5-Butyl-2-(trifluoromethyl)-1,6-naphthyridine (58j)



According to **TP2**, 5-chloro-2-(trifluoromethyl)-1,6-naphthyridine (**57**, 0.43 mmol, 100 mg, 1.0 equiv) reacted with *n*BuMgCl (0.35 mL, 0.47 mmol, 1.37 M in THF, 1.1 equiv) within 20 min at rt. The crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford **58j** (76 mg, 69 %) as a colorless oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2959, 1607, 1584, 1571, 1471, 1337, 1189, 1139, 1114, 1097, 837, 741.

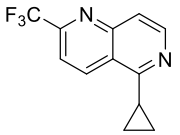
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.75 (d, *J* = 8.7 Hz, 1H), 8.68 (d, J = 8.7 Hz, 1H), 7.87 (d, *J* = 6.0 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 3.36-3.30 (m, 2H), 1.89-1.80 (m, 2H), 1.49 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 164.0, 151.7 (q, *J* = 35.1 Hz), 150.2, 147.1, 136.3, 122.6, 120.8, 119.8, 117.9 (q, *J* = 2.2 Hz), 35.0, 32.0, 23.0, 14.1.

MS (EI, 70 eV): *m/z* (%) = 254 (7), 253 (11), 239 (36), 225 (75), 212 (100), 177 (11).

HRMS (EI) calcd. for [$C_{13}H_{13}F_3N_2$]: 254.1031; found: 254.0986.

5-Cyclopropyl-2-(trifluoromethyl)-1,6-naphthyridine (58k)



According to **TP2**, 5-chloro-2-(trifluoromethyl)-1,6-naphthyridine (**57**, 0.43 mmol, 100 mg, 1.0 equiv) reacted with *c*PropylMgBr·LiCl (0.45 mL, 0.47 mmol, 1.05 M in THF, 1.1 equiv) within 20 min at rt. After workup, the crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford **58k** (53 mg, 52 %) as a colorless oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2950, 2854, 1740, 1606, 1572, 1462, 1378, 1340, 1258, 1192, 1146, 1110, 1096, 1008, 840.

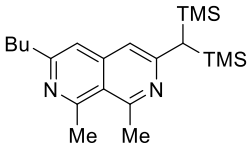
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.92 (d, *J* = 8.7 Hz, 1H), 8.67 (d, *J* = 6.0 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.80 (d, *J* = 6.0 Hz, 1H), 2.76-2.66 (m, 1H), 1.37-1.31 (m, 2H), 1.23-1.17 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 163.7, 151.3 (q, *J* = 35.1 Hz), 149.9, 147.0, 135.9, 123.0 (2C), 122.5, 119.7, 117.6 (q, *J* = 2.1 Hz), 13.4, 10.7.

MS (EI, 70 eV): *m*/*z* (%) = 238 (10), 237 (100), 223 (7), 217 (30), 168 (34), 167 (11).

HRMS (EI) calcd. for [$C_{12}H_9F_3N_2$]: 238.0718; found: 238.0712.

3-(Bis(trimethylsilyl)methyl)-6-butyl-1,8-dimethyl-2,7-naphthyridine (59)



According to **TP1**, 3-(bis(trimethylsilyl)methyl)-6-chloro-1,8-dimethyl-2,7-naphthyridine (**25**, 1.14 mmol, 113 mg, 1.0 equiv) reacted with *n*BuMgCl (0.87 mL, 1.25 mmol, 1.4 M in THF, 1.1 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/ EtOAc = 19:1) to afford **59** (240 mg, 56%) as a yellow oil.

IR (Diamond ATR): $\tilde{\nu}$/ cm^{-1} = 2954, 1605, 1586, 1543, 1458, 1423, 1379, 1331, 1246, 1207, 1194, 1302, 1001, 941, 858, 826, 775, 684.

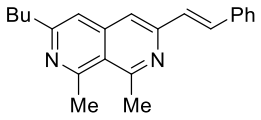
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 7.06 (s, 1H), 6.87 (s, 1H), 3.08 (s, 3H), 3.03 (s, 3H), 2.81 (t, *J* = 7.8 Hz, 2 H), 1.87 (s, 1H), 1.75 (quint, *J* = 7.6 Hz, 2H), 1.43 (sxt, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.05 (s, 18H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 159.9, 158.9, 158.0, 157.0, 142.5, 119.5, 115.2, 114.5, 37.8, 32.7, 31.7, 29.1, 22.6, 14.0, 0.2.

MS (EI, 70 eV): *m*/*z* (%) = 372 (8), 358 (28), 357 (100), 331 (9), 330 (34), 73 (14).

HRMS (EI) calcd.for [$C_{21}H_{36}N_2Si_2$]: 372.2417; found: 372.2418.

(*E*)-3-butyl-1,8-dimethyl-6-styryl-2,7-naphthyridine (60)



3-(Bis(trimethylsilyl)methyl)-6-butyl-1,8-dimethyl-2,7-naphthyridine (**59**, 308 mg, 0.83 mmol, 1.0 equiv) was dissolved in dry THF (13 mL) and reacted with benzaldehyde (106 mg, 1.0 mmol, 1.2 equiv), catalyzed by TBAF (0.08 mL, 0.08 mmol, 1.0 M in THF, 0.1 equiv) at -20 °C within 15 min. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 × 30 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc = 9:1) to give **60** (222 mg, 85%) as a white solid.

m.p.: 67-68 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2950, 1599, 1545, 1452, 1424, 1380, 1327, 974, 894, 754, 737, 703, 688, 556.

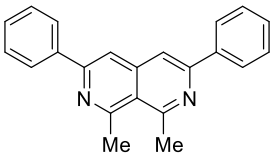
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 7.77 (d, *J* = 15.8 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.27-7.21 (m, 2H), 7.17-7.08 (m, 2H), 3.09 (s, 3H), 3.05 (s, 3H), 2.79 (t, *J* = 7.7 Hz, 2H), 1.70 (quint, *J* = 7.7 Hz, 2H), 1.36 (sxt, *J* = 7.41 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 159.6, 159.1, 158.2, 150.5, 142.7, 136.9, 133.5, 128.7, 128.3, 127.3, 127.2, 121.5, 116.3, 116.1, 37.8, 31.7, 29.6, 29.2, 22.6, 14.0.

MS (EI, 70 eV): *m/z (%)* = 316 (5), 301 (7), 287 (11), 275 (20), 274 (100), 137 (8).

HRMS (EI) calcd. for [$C_{22}H_{24}N_2$]: 316.1939; found: 316.1939.

1,8-Dimethyl-3,6-diphenyl-2,7-naphthyridine (61)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a septum, was charged with 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 0.5 mmol, 113 mg, 1.0 equiv) and anhydrous $FeBr_3$ (7.4 mg, 0.025 mmol, 5 mol%) in dry THF/*t*BuOMe (1:1, 4 mL). Upon dropwise addition of PhMgCl (1.12 mL, 1.78 M in THF, 2.0 mmol, 4.0 equiv) the reaction was stirred for 15 min at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford **61** (65 mg, 42%) as a white solid.

m.p.: 158-160 °C.

IR (Diamond ATR): $\tilde{\nu}$/ cm^{-1} = 3058, 3035, 2994, 2938, 1601, 1547, 1498, 1461, 1418, 1378, 1332, 1257, 1225, 1177, 1156, 1101, 1073, 1026, 978, 893, 794, 774, 763, 695, 682, 644, 579.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.09 (d, *J* = 7.3 Hz, 4H), 7.79 (s, 2H), 7.44 (t, *J* = 7.5 Hz, 4H), 7.40-7.32 (m, 2H), 3.16 (s, 6H).

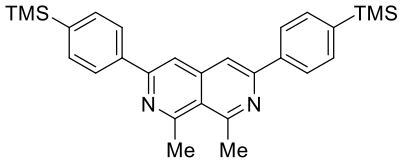
^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 159.7, 152.6, 143.2, 138.8, 129.3, 128.9, 127.3, 121.9, 114.8, 29.6.

MS (EI, 70 eV): *m*/*z* (%) = 311 (24), 310 (100), 309 (15), 268 (4), 165 (3), 155 (6), 77 (4).

HRMS (EI) calcd. for [$C_{22}H_{18}N_2$]: 310.1470; found: 310.1465.

4.3 Cobalt-Catalyzed C(sp^2)-C(sp^2) Cross-Couplings of Naphthyridines with Arylmagnesium and Arylzinc Reagents

1,8-Dimethyl-3,6-bis(4-(trimethylsilyl)phenyl)-2,7-naphthyridine (62a)



According to **TP3**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 113 mg, 0.5 mmol, 1.0 equiv) reacted with 4-(trimethylsilyl)phenylmagnesium bromide (1.78 mL, 1.5 mmol, 0.84 M in THF, 3.0 equiv) within 4 h at -40 °C. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 1:1) to afford **62a** (140 mg, 62%) as a white solid.

m.p.: 135-137 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2956, 1602, 1549, 1378, 1332, 1245, 1115, 1092, 824, 752, 722, 692.

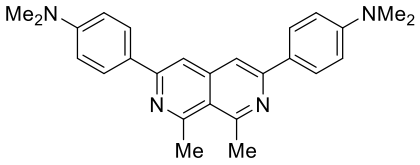
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.14 (d, *J* = 8.2 Hz, 4H), 7.87 (s, 2H), 7.68 (d, *J* = 8.2 Hz, 4H), 3.24 (s, 6H), 0.33 (s, 18H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 159.7, 152.7, 143.2, 141.9, 138.9, 133.9, 126.5, 121.9, 114.9, 29.5, 0.9.

MS (EI, 70 eV): *m*/*z* (%) = 455 (17), 454 (45), 441 (16), 440 (40), 439 (100), 213 (23), 212 (57), 73 (18).

HRMS (EI) calcd. for [$C_{28}H_{34}N_2Si_2$]: 454.2261; found: 454.2258.

4,4'-(1,8-Dimethyl-2,7-naphthyridine-3,6-diyl)bis(*N*,*N*-dimethylaniline) (62b)



According to **TP3**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 113 mg, 0.5 mmol, 1.0 equiv) reacted with 4-(dimethylamino)phenylmagnesium bromide (1.36 mL, 1.5 mmol, 1.1 M in THF, 3.0 equiv) within 4 h at -40 °C. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 1:1) to afford **62b** (145 mg, 73%) as a yellow solid.

m.p.: 240-242 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1591, 1544, 1525, 1428, 1357, 1191, 1166, 1126, 946, 879, 822.

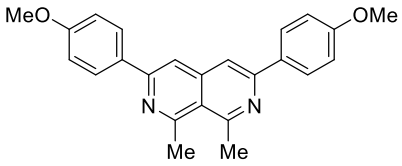
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.09 (d, *J* = 9.0 Hz, 4H), 7.69 (s, 2H), 6.83 (d, *J* = 9.0 Hz, 4H), 3.22 (s, 6H), 3.04 (s, 12H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 159.4, 152.5, 151.4, 143.7, 128.3, 120.7, 112.4, 40.5, 29.3.

MS (EI, 70 eV): *m*/*z* (%) = 397 (28), 396 (100), 395 (7), 380 (8), 198 (12), 197 (11).

HRMS (EI) calcd. for [$C_{26}H_{28}N_4$]: 396.2314; found: 396.2311.

3,6-Bis(4-methoxyphenyl)-1,8-dimethyl-2,7-naphthyridine (62c)



According to **TP3**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 113 mg, 0.5 mmol, 1.0 equiv) reacted with (4-methoxyphenyl)magnesium bromide (1.92 mL, 1.5 mmol, 0.78 M in THF, 3.0 equiv) within 12 h at -40 °C. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 1:1) to afford **62c** (110 mg, 60%) as a white solid.

m.p.: 191-193 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1605, 1543, 1514, 1423, 1399, 1378, 1293, 1248, 1173, 1024, 837, 827, 810, 791, 659.

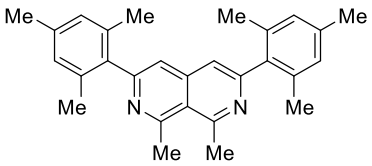
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.13 (d, *J* = 8.9 Hz, 4H), 7.77 (s, 2H), 7.04 (d, *J* = 8.9 Hz, 4H), 3.89 (s, 6H), 3.22 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 160.8, 159.6, 143.4, 128.6, 121.3, 114.4, 113.5, 55.6, 29.5.

MS (EI, 70 eV): *m*/*z* (%) = 371 (29), 370 (100), 355 (8), 185 (12).

HRMS (EI) calcd. for [$C_{24}H_{22}N_2O_2$]: 370.1681; found: 370.1670.

3,6-Dimesityl-1,8-dimethyl-2,7-naphthyridine (62d)



According to **TP3**, 3,6-dichloro-1,8-dimethyl-2,7-naphthyridine (**22**, 113 mg, 0.5 mmol, 1.0 equiv) reacted with mesitylmagnesium bromide (1.58 mL, 1.5 mmol, 0.95 M in THF, 3.0 equiv) within 4 h at rt. The crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford **62d** (183 mg, 93%) as a white crystalline solid.

m.p.: 198 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1604, 1543, 1437, 1377, 1327, 1093, 1031, 878, 848.

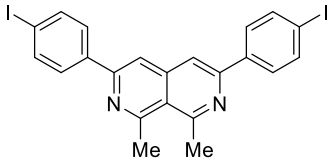
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 7.34 (s, 2H), 6.97 (s, 4H), 3.25 (s, 6H), 2.33 (s, 6H), 2.10 (s, 12H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 159.8, 142.2, 137.8, 136.0, 128.6, 121.1, 119.0, 21.3, 20.5.

MS (EI, 70 eV): *m*/*z* (%) = 394 (64), 393 (91), 392 (13), 377 (10), 189 (10), 44 (100), 42 (10).

HRMS (EI) calcd. for [$C_{28}H_{30}N_2$]: 394.2409; found: 394.2356.

3,6-Bis(4-iodophenyl)-1,8-dimethyl-2,7-naphthyridine (63)



1,8-Dimethyl-3,6-bis(4-(trimethylsilyl)phenyl)-2,7-naphthyridine (**62a**, 174 mg, 0.38 mmol, 1.0 equiv) was dissolved in dry DCM (2 mL). ICl (0.06 mL, 1.14 mmol, 3.0 equiv) was added dropwise at 0 °C and the reaction mixture was stirred for further 10 min. Then, the reaction was quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with DCM (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (100% isohexane) to give **63** (209 mg, 98%) as a white solid.

m.p.: 175-178 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2922, 2853, 1603, 1548, 1485, 1459, 1427, 1379, 1330, 1260, 1099, 1059, 1034, 1000, 980, 888, 822, 715.

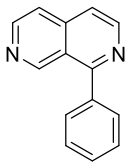
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 7.91 (d, *J* = 8.6 Hz, 4H), 7.84 (d, *J* = 8.6 Hz, 4H), 7.84 (s, 2H), 3.23 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 160.0, 151.6, 143.1, 138.1, 130.0, 122.1, 114.6, 95.9, 29.9, 29.5.

MS (EI, 70 eV): *m*/*z* (%) = 563 (24), 562 (100), 435 (14), 308 (9), 146 (10), 128 (19), 127 (11), 57 (13), 41 (9).

HRMS (EI) calcd. for [$C_{22}H_{16}I_2N_2$]: 561.9403; found: 561.9394.

1-Phenyl-2,7-naphthyridine (63a)



According to **TP4**, 1-chloro-2,7-naphthyridine (**30**, 82 mg, 0.5 mmol, 1.0 equiv) reacted with PhZnCl (0.69 mL, 0.6 mmol, 0.87 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 8:2) to afford **63a** (82 mg, 80%) as a light-yellow solid.

m.p.: 129 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1612, 1543, 1450, 1382, 1351, 1217, 1022, 974, 860, 772, 702.

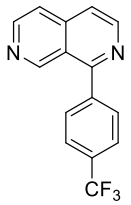
^{1}H-NMR (600 MHz, CDCl$_3$): δ/ ppm = 9.53 (s, 1H), 8.80 (d, *J* = 5.7 Hz, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 7.77-7.73 (m, 2H), 7.70 (dd, *J* = 5.7, 1.1 Hz, 1H), 7.63 (dd, *J* = 5.8, 0.9 Hz, 1H), 7.60-7.55 (m, 3H).

^{13}C-NMR (150 MHz, CDCl$_3$): δ/ ppm = 162.0, 153.0, 146.7, 146.3, 139.8, 138.1, 130.3, 129.6, 128.8, 121.9, 119.4, 118.4.

MS (EI, 70 eV): *m*/*z* (%) = 207 (6), 206 (45), 205 (100).

HRMS (EI) calcd. for [$C_{14}H_{10}N_2$]: 206.0844; found: 206.0833.

1-(4-(Trifluoromethyl)phenyl)-2,7-naphthyridine (63c)



According to **TP4**, 1-chloro-2,7-naphthyridine (**30**, 110 mg, 0.67 mmol, 1.0 equiv) reacted with 4-(trifluoromethyl)phenylzinc chloride (1.27 mL, 0.8 mmol, 0.63 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 1:1) to afford **63c** (127 mg, 69%) as a white solid.

m.p.: 126-127 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1615, 1539, 1324, 1246, 1157, 1099, 1067, 1022, 976, 850, 837, 810, 716, 693, 660.

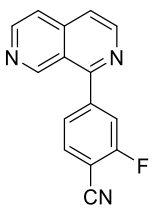
^{1}H-NMR (400 MHz, CDCl$_3$): δ/ ppm = 9.45 (s, 1H), 8.80 (d, *J* = 5.7 Hz, 1H), 8.75 (d, *J* = 5.7 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 5.7 Hz, 1H), 7.67 (d, *J* = 5.7 Hz, 1H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ/ ppm = 160.3, 152.3, 146.9, 146.3, 141.5, 139.7, 131.6 (q, *J* = 32.7 Hz), 125.7 (q, *J* = 3.8 Hz), 121.8, 119.4, 119.1.

MS (EI, 70 eV): *m*/*z* (%) = 275 (12), 274 (77), 273 (100), 253 (10), 248 (10), 206 (22), 204 (11), 58 (12), 57 (19), 50 (11), 44 (73), 43 (50).

HRMS (EI) calcd. for [$C_{15}H_9F_3N_2$]: 274.0718; found: 274.0684.

2-Fluoro-4-(2,7-naphthyridin-1-yl)benzonitrile (63e)



According to **TP4**, 1-chloro-2,7-naphthyridine (**30**, 82 mg, 0.5 mmol, 1.0 equiv) reacted with (4-cyano-3-fluorophenyl)zinc chloride (1.1 mL, 0.6 mmol, 0.54 M in THF, 1.2 equiv) within 12 h at rt. After

workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 1:1) to afford **63e** (92 mg, 74%) as a white solid.

m.p.: 186 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2234, 1616, 1562, 1538, 1430, 1406, 1372, 1250, 1221, 1133, 1109, 1068, 996, 915, 878, 855, 767, 756, 737, 694.

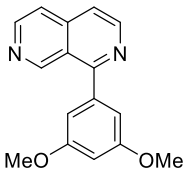
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.45 (s, 1H), 8.82 (d, *J* = 5.7 Hz, 1H), 8.79 (d, *J* = 5.7 Hz, 1H), 7.87-7.82 (m, 1H), 7.76 (dd, *J* = 5.7, 0.9 Hz, 1H), 7.73 (dd, *J* = 5.7, 0.7 Hz, 1H), 7.68-7.67 (m, 1H), 7.67-7.64 (m, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 163.2 (d, *J* = 260.6 Hz), 158.2, 151.5, 147.2, 146.3, 145.0 (d, *J* = 7.5 Hz), 139.7, 133.8, 126.7, 121.5, 119.7 (d, *J* = 34.0 Hz), 118.4 (d, *J* = 21.2 Hz), 113.7, 102.5 (d, *J* = 17.1 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 250 (9), 249 (65), 248 (100), 230 (8).

HRMS (EI) calcd. for [$C_{15}H_8FN_3$]: 249.0702; found: 249.0699.

1-(3,5-Dimethoxyphenyl)-2,7-naphthyridine (63f)



According to **TP4**, 1-chloro-2,7-naphthyridine (**30**, 82 mg, 0.5 mmol, 1.0 equiv) reacted with (3,5-dimethoxyphenyl)zinc chloride (0.7 mL, 0.6 mmol, 0.86 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1) to afford **63f** (105 mg, 79%) as a yellow solid.

m.p.: 75 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1600, 1586, 1540, 1450, 1424, 1376, 1299, 1236, 1206, 1157, 1066, 1034, 995, 929, 830, 826, 708, 687, 675.

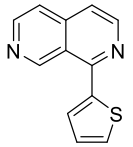
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.57 (s, 1H), 8.78 (d, *J* = 5.7 Hz, 1H), 8.73 (d, *J* = 5.7 Hz, 1H), 7.69 (dd, *J* = 5.7, 1.1 Hz, 1H), 7.63 (dd, *J* = 5.7, 0.9 Hz, 1H), 6.86 (d, *J* = 2.3 Hz, 2H), 6.65 (t, *J* = 2.3 Hz, 1H), 3.87 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.8, 161.1, 153.0, 146.8, 146.2, 139.9, 139.7, 122.0, 119.3, 118.6, 108.4, 102.0, 55.7.

MS (EI, 70 eV): *m*/*z* (%) = 267 (16), 266 (100), 265 (51), 251 (42), 236 (25), 235 (74), 221 (13), 208 (16), 192 (20) 179 (13).

HRMS (EI) calcd. for [$C_{16}H_{14}N_2O_2$]: 266.1055; found: 266.1050.

1-(Thiophen-2-yl)-2,7-naphthyridine (63g)



According to **TP4**, 1-chloro-2,7-naphthyridine (**30**, 82 mg, 0.5 mmol, 1.0 equiv) reacted with thiophen-2-ylzinc chloride (0.71 mL, 0.6 mmol, 0.84 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (EtOAc) to afford **63g** (64 mg, 60%) as a brown solid.

m.p.: 66-67 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1607, 1530, 1429, 1365, 1339, 1284, 1213, 1078, 1022, 944, 864, 850, 803, 720, 700.

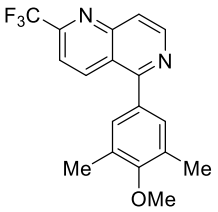
^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 9.89 (s, 1H), 8.79-8.63 (m, 2H), 7.69 (d, *J* = 3.7 Hz, 1H), 7.66 (d, *J* = 5.7 Hz, 1H), 7.60 (d, *J* = 5.1 Hz, 1H), 7.53 (d, *J* = 5.7 Hz, 1H), 7.25 (t, *J* = 4.4 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 154.7, 152.1, 146.8, 146.2, 141.5, 140.0, 130.1, 129.5, 128.1, 121.3, 119.4, 118.1.

MS (EI, 70eV): *m/z (%)* = 213 (19), 212 (100), 211 (97), 168 (9).

HRMS (EI) calcd. for [$C_{12}H_8N_2S$]: 212.0408; found: 212.0415.

5-(4-Methoxy-3,5-dimethylphenyl)-2-(trifluoromethyl)-1,6-naphthyridine (63h)



According to **TP4**, 5-chloro-2-(trifluoromethyl)-1,6-naphthyridine (**57**, 100 mg, 0.43 mmol, 1.0 equiv) reacted with (4-methoxy-3,5-dimethylphenyl)zinc chloride (0.63 mL, 0.51 mmol, 0.82 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 8:2) to afford **63h** (106 mg, 74%) as a white solid.

m.p.: 131-132 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1604, 1570, 1464, 1337, 1249, 1187, 1122, 1092, 1007, 922, 886, 852, 838, 741, 727, 707.

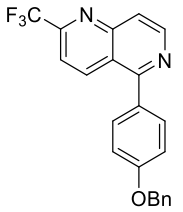
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.88 (d, *J* = 5.9 Hz, 1H), 8.69 (d, *J* = 8.8 Hz, 1H), 7.97 (dd, *J* = 5.9, 0.9 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.34 (s, 2H), 3.80 (s, 3H), 2.38 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.9, 158.4, 151.7 (q, *J* = 35.1 Hz), 150.6, 147.2, 138.9, 133.5, 131.6, 130.6, 125.3, 122.6, 122.3, 121.1, 119.8, 118.0, 118.0 (q, *J* = 2.1 Hz), 59.9, 16.4.

MS (EI, 70eV): *m/z (%)* = 332 (96), 331 (25), 318 (21), 317 (100), 302 (25), 301 (47), 287 (12), 273 (30) 263 (24).

HRMS (EI) calcd. for [$C_{18}H_{15}F_3N_2O$]: 332.1136; found: 332.1129.

5-(4-(Benzyloxy)phenyl)-2-(trifluoromethyl)-1,6-naphthyridine (63i)



According to **TP4**, 5-chloro-2-(trifluoromethyl)-1,6-naphthyridine (**57**, 100 mg, 0.43 mmol, 1.0 equiv) reacted with (4-(benzyloxy)phenyl)zinc chloride (0.57 mL, 0.51 mmol, 0.9 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/ EtOAc = 8:2) to afford **63i** (135 mg, 83%) as a yellow oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1604, 1567, 1465, 1436, 1336, 1292, 1220, 1191, 1141, 1125, 1081, 1026, 980, 916, 841, 788, 741, 696.

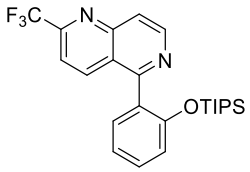
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.95 (d, *J* = 5.9 Hz, 1H), 8.60 (d, *J* = 8.8 Hz, 1H), 8.05 (dd, *J* = 5.9, 0.9 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.54-7.45 (m, 3H), 7.45-7.34 (m, 3H), 7.33-7.28 (m, 2H), 7.21 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 5.19 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.6, 159.0, 151.8 (q, *J* = 35.1 Hz), 150.6, 147.1, 139.2, 138.6, 136.8, 130.0, 128.8, 128.2, 127.6, 122.8, 122.5, 122.3, 121.6, 119.79, 118.1 (q, *J* = 2.0 Hz), 116.5, 116.4, 70.3.

MS (EI, 70eV): *m/z (%)* = 381 (12), 380 (47), 92 (7), 91 (100).

HRMS (EI) calcd. for [$C_{22}H_{15}F_3N_2O$]: 380.1136; found: 380.1124.

2-(Trifluoromethyl)-5-(2-((triisopropylsilyl)oxy)phenyl)-1,6-naphthyridine (63j)



According to **TP4**, 5-chloro-2-(trifluoromethyl)-1,6-naphthyridine (**57**, 140 mg, 0.6 mmol, 1.0 equiv) reacted with 2-((triisopropylsilyl)oxy)phenylzinc chloride (1.8 mL, 0.72 mmol, 0.4 M in THF, 1.2 equiv) within 12 h at 60 °C. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 8:2) to afford **63j** (163 mg, 61%) as a clear oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2947, 1603, 1570, 1464, 1338, 1276, 1247, 1194, 1145, 1131, 1084, 1007, 920, 885, 839, 759.

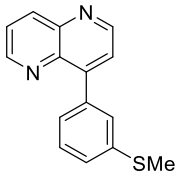
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.92 (d, *J* = 6.0 Hz, 1H), 8.36 (d, *J* = 8.7 Hz, 1H), 8.01 (d, *J* = 6.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.49 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.44-7.37 (m, 1H), 7.15 (td, *J* = 7.5, 1.0 Hz, 1H), 7.00 (dd, *J* = 8.2, 0.9 Hz, 1H), 0.97-0.83 (m, 3H), 0.73 (d, *J* = 7.4 Hz, 9H), 0.69 (d, *J* = 7.4 Hz, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 160.9, 153.5, 151.7 (q, *J* = 35.0 Hz), 149.7, 147.4, 139.9, 131.4, 130.9, 129.5, 123.5, 122.6, 121.8, 121.5, 119.9, 119.2, 117.8 (q, *J* =2.2 Hz), 17.6, 12.7.

MS (EI, 70eV): *m/z (%)* = 446 (3), 404 (26), 403 (100), 318 (7), 317 (22).

HRMS (EI) calcd. for [$C_{24}H_{29}F_3N_2OSi$]: 446.2001; found: 446.1993.

4-(3-(Methylthio)phenyl)-1,5-naphthyridine (64a)



According to **TP4**, 4-iodo-1,5-naphthyridine (**42a**, 128 mg, 0.5 mmol, 1.0 equiv) reacted with (3-(methylthio)phenyl)zinc chloride (0.68 mL, 0.6 mmol, 0.88 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 7:1, 1% NEt_3) to afford **64a** (101 mg, 80%) as a white solid.

m.p.: 89-91 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1566, 1496, 1474, 1464, 1436, 1376, 1164, 1082, 1026, 954, 904, 882, 868, 800, 784, 742, 692, 656.

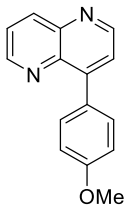
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.02 (dd, *J* = 4.2, 1.7 Hz, 2H), 8.47 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.71–7.61 (m, 3H), 7.57–7.50 (m, 1H), 7.51–7.34 (m, 2H), 2.54 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 151.0, 150.9, 148.2, 144.4, 141.8, 138.7, 137.6, 137.3, 128.7, 128.5, 127.3, 127.0, 124.3, 124.1, 16.0.

MS (EI, 70 eV): *m*/*z* (%) = 250 (15), 249 (92), 248 (100), 234 (14), 233 (13), 232 (38), 205 (60), 203 (10), 123 (11).

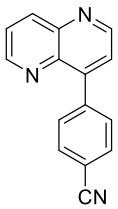
HRMS (EI) calcd. for [$C_{15}H_{12}N_{2S}$]: 252.0721; found: 252.0715.

4-(4-Methoxyphenyl)-1,5-naphthyridine (64b)



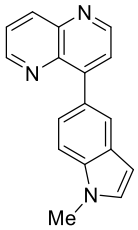
According to **TP4**, 4-iodo-1,5-naphthyridine (**42a**, 128 mg, 0.5 mmol, 1.0 equiv) reacted with (4-methoxyphenyl)zinc chloride (0.61 mL, 0.6 mmol, 0.98 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 7:1, 1% NEt_3) to afford **64b** (92 mg, 78%) as a white solid. For analytics see compound **42g** (same).

4-(1,5-Naphthyridin-4-yl)benzonitrile (64c)



According to **TP4**, 4-iodo-1,5-naphthyridine (**42a**, 128 mg, 0.5 mmol, 1.0 equiv) reacted with (4-cyanophenyl)zinc chloride (0.6 mL, 0.6 mmol, 1.0 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 8:2, 1% NEt_3) to afford **64c** (96 mg, 83%) as a white solid. For analytics see compound **42h** (same).

4-(1-Methyl-1*H*-indol-6-yl)-1,5-naphthyridine (64d)



According to **TP4**, 4-iodo-1,5-naphthyridine (**42a**, 128 mg, 0.5 mmol, 1.0 equiv) reacted with (1-methyl-1*H*-indol-5-yl)zinc chloride (0.62 mL, 0.6 mmol, 0.97 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 7:3, 1% NEt_3) to afford **64d** (94 mg, 73%) as a yellow solid.

m.p.: 178-180 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1576, 1485, 1369, 1335, 1244, 1157, 1081, 865, 809, 796, 766, 737, 668.

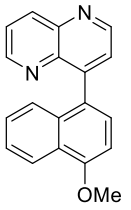
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.03 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.99 (d, *J* = 4.5 Hz, 1H), 8.48 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.06 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.72 (d, *J* = 4.5 Hz, 1H), 7.69 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.65 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.12 (d, *J* = 3.1 Hz, 1H), 6.59 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.86 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 150.8, 150.7, 150.5, 144.4, 142.6, 137.5, 137.2, 129.7, 128.7, 127.8, 124.6, 124.4, 124.2, 123.5, 109.1, 102.0, 33.1.

MS (EI, 70eV): *m/z* (%) = 259 (31), 258 (100), 243 (21), 207 (7).

HRMS (EI) calcd. for [$C_{17}H_{13}N_3$]: 259.1109; found: 259.1114.

4-(4-Methoxynaphthalen-1-yl)-1,5-naphthyridine (64e)



According to **TP4**, 4-iodo-1,5-naphthyridine (**42a**, 128 mg, 0.5 mmol, 1.0 equiv) reacted with (4-methoxynaphthalen-1-yl)zinc chloride (0.74 mL, 0.6 mmol, 0.81 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 7:2, 1% NEt_3) to afford **64e** (67 mg, 47%) as a white solid.

m.p.: 220-221 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1582, 1510, 1490, 1457, 1422, 1376, 1325, 1304, 1268, 1238, 1184, 1160, 1122, 1092, 1070, 1042, 868, 824, 812, 804, 764, 712, 666.

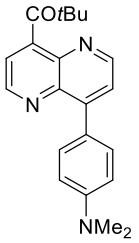
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.07 (d, *J* = 4.3 Hz, 1H), 8.89 (dd, *J* = 4.0, 1.7 Hz, 1H), 8.50 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.37 (dt, *J* = 8.6, 1.0 Hz, 1H), 7.68 (d, *J* = 4.2 Hz, 1H), 7.64 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.37 – 7.32 (m, 2H), 6.97 (d, *J* = 7.9 Hz, 1H), 4.08 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 156.0, 151.0, 150.8, 148.7, 144.2, 143.4, 137.6, 132.8, 128.0, 127.1, 126.6, 126.2, 125.7, 125.6, 125.2, 124.2, 122.3, 103.3, 55.6.

MS (EI, 70 eV): *m*/*z* (%) = 286 (36), 285 (100), 271 (15), 270 (63), 242 (35), 241 (13), 121 (15).

HRMS (EI) calcd. for [$C_{19}H_{14}N_2O$]: 286.1106; found: 286.1108.

1-(8-(4-(Dimethylamino)phenyl)-1,5-naphthyridin-4-yl)-2,2-dimethylpropan-1-one (64f)



According to **TP4**, 1-(8-iodo-1,5-naphthyridin-4-yl)-2,2-dimethylpropan-1-one (**52d**, 170 mg, 0.5 mmol, 1.0 equiv) reacted with 4-(dimethylamino)phenyl)zinc chloride (0.69 mL, 0.6 mmol, 0.87 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 8:2) to afford **64f** (143 mg, 86%) as a white solid.

m.p.: 165-167 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1188, 1166, 1130, 1100, 1084, 1060, 1038, 1006, 962, 950, 914, 880, 864, 838, 820, 812, 782, 752, 724, 682.

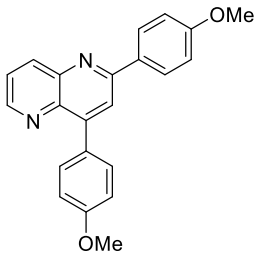
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.99 (d, *J* = 4.2 Hz, 1H), 8.89 (d, *J* = 4.5 Hz, 1H), 7.83–7.72 (m, 2H), 7.60 (d, *J* = 4.5 Hz, 1H), 7.34 (d, *J* = 4.2 Hz, 1H), 6.94–6.81 (m, 2H), 3.05 (s, 6H), 1.33 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 213.1, 150.9, 150.9, 149.4, 148.8, 148.3, 142.3, 141.6, 131.7, 123.8, 123.3, 119.2, 112.0, 45.2, 40.4, 26.8.

MS (EI, 70 eV): *m*/*z* (%) = 333 (44), 332 (12), 276 (11), 250 (15), 249 (100), 248 (42), 232 (23).

HRMS (EI) calcd. for [$C_{21}H_{23}N_3O$]: 333.1841; found: 333.1835.

2,4-Bis(4-methoxyphenyl)-1,5-naphthyridine (64g)



According to **TP4**, 2,4-diiodo-1,5-naphthyridine (**56a**, 150 mg, 0.39 mmol, 1.0 equiv) reacted with (4-methoxyphenyl)zinc chloride (0.95 mL, 0.94 mmol, 0.98 M in THF, 2.4 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (isohexane/EtOAc = 7:1, 1% NEt_3) to afford **64g** (100 mg, 75%) as a yellow solid.

m.p.: 109 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2927, 1606, 1590, 1578, 1542, 1513, 1483, 1459, 1416, 1365, 1286, 1237, 1175, 1108, 1022, 822, 800, 729, 680.

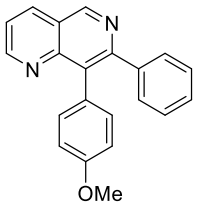
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.93 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.45 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.18 (d, *J* = 8.9 Hz, 2H), 8.04 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.60 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 161.2, 160.2, 157.3, 149.9, 148.4, 144.5, 141.4, 137.6, 131.9, 131.8, 129.6, 129.1, 124.2, 121.4, 114.4, 114.0, 55.5.

MS (EI, 70 eV): *m*/*z* (%) = 343 (17), 342 (94), 341 (100), 327 (24), 298 (10), 255 (9).

HRMS (EI) calcd. for [$C_{22}H_{18}N_2O_2$]: 342.1368; found: 342.1366.

8-(4-Methoxyphenyl)-7-phenyl-1,6-naphthyridine (64h)



According to **TP4**, 8-iodo-7-phenyl-1,6-naphthyridine (**65**, 100 mg, 0.3 mmol, 1.0 equiv) reacted with (4-methoxyphenyl)zinc chloride (0.92 mL, 0.98 M in THF, 0.9 mmol, 3.0 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (EtOAc) to afford **64h** (45 mg, 48%) as a white solid.

m.p.: 168-170 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1600, 1514, 1466, 1368, 1292, 1244, 1174, 1034, 964, 922, 834, 814, 770, 708, 694.

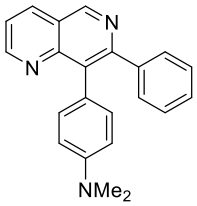
^{1}H-NMR (400 MHz, CDCl$_3$): δ/ ppm = 9.38 (s, 1H), 9.14 (dd, *J* = 4.2, 1.9 Hz, 1H), 8.37 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.54 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.45-7.41 (m, 2H), 7.28-7.23 (m, 5H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ/ ppm = 159.0, 155.0, 154.9, 151.7, 150.2, 140.8, 135.7, 133.0, 131.8, 130.5, 128.3, 128.0, 127.5, 122.5, 122.1, 113.7, 55.3.

MS (EI, 70 eV): *m*/*z* (%) = 313 (11), 312 (48), 311 (100), 296 (13), 281 (16), 268 (29), 267 (23), 266 (12), 235 (12), 140 (10), 134 (17).

HRMS (EI) calcd. for [$C_{21}H_{16}N_2O$]: 312.1263; found: 312.1252.

***N*,*N*-Dimethyl-4-(7-phenyl-1,6-naphthyridin-8-yl)aniline (64i)**



According to **TP4**, 8-iodo-7-phenyl-1,6-naphthyridine (**65**, 100 mg, 0.3 mmol, 1.0 equiv) reacted with 4-(dimethylamino)phenylzinc chloride (1.0 mL, 0.9 mmol, 0.87 M in THF, 3.0 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (EtOAc) to afford the desired product (63 mg, 65%) as a bright yellow solid.

m.p.: 184-186 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1610, 1601, 1520, 1466, 1434, 1362, 1334, 1202, 1160, 1130, 1048, 942, 830, 814, 786, 770, 708, 694.

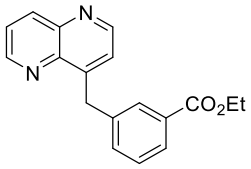
^{1}H-NMR (400 MHz, CDCl$_3$): δ/ ppm = 9.33 (s, 1H), 9.12 (dd, *J* = 4.2, 1.9 Hz, 1H), 8.32 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.49 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.47-7.42 (m, 2H), 7.29-7.26 (m, 1H), 7.25-7.22 (m, 2H), 7.21-7.16 (m, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 2.97 (s, 6H).

^{13}C-NMR (100 MHz, CDCl$_3$): δ/ ppm = 154.8, 151.1, 150.4, 141.1, 135.6, 132.8, 130.5, 127.9, 127.3, 122.6, 122.0.

MS (EI, 70 eV): *m*/*z* (%) = 326 (23), 325 (100), 324 (59), 308 (21), 281 (22), 279 (16), 161 (12).

HRMS (EI) calcd. for [$C_{22}H_{19}N_3$]: 325.1579; found: 325.1573.

Ethyl 3-((1,5-naphthyridin-4-yl)methyl)benzoate (66a)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum, was charged with $CoCl_2$ (3 mg, 0.02 mmol, 5 mol%) and heated up to 450 °C for 5 min under high vacuum. After cooling to rt, 4-iodo-1,5-naphthyridine (**42a**, 100 mg, 0.4 mmol, 1.0 equiv) and dry THF (2 mL) were added. Thereupon, 3-(ethoxycarbonyl)benzylzinc chloride (2.1 mL, 0.8 mmol, 0.38 M in THF, 2.0 equiv) was added dropwise and the reaction mixture was stirred at rt for 4 h until complete consumption of **42a** was observed by GC. A sat. aq. solution of NH_4Cl (5 mL) was added and the aq. layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (isohexane/EtOAc = 9:1 + 1% NEt_3) to afford **66a** (142 mg, 75%) as a yellow oil (73 mg, 62%) as a yellow oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2989, 1712, 1588, 1495, 1443, 1366, 1273, 1190, 1104, 1081, 1023, 754, 726, 691.

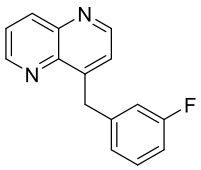
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.00 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.83 (d, *J* = 4.4 Hz, 1H), 8.39 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.04-8.02 (m, 1H), 7.92 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.64 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.52-7.48 (m, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 4.4 Hz, 1H), 4.73 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 166.6, 151.1, 150.3, 149.2, 143.7, 142.9, 139.7, 137.7, 134.0, 130.9, 130.5, 128.7, 127.8, 124.5, 124.0, 61.0, 35.9, 14.4.

MS (EI, 70 eV): *m*/*z* (%) = 292 (93), 291 (39), 263 (54), 247 (49), 219 (47), 218 (100), 205 (10), 119 (20).

HRMS (EI) calcd. for [$C_{18}H_{16}N_2O_2$]: 292.1212; found: 292.1203.

4-(3-Fluorobenzyl)-1,5-naphthyridine (66b)



A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirring bar and a rubber septum, was charged with $CoCl_2$ (3 mg, 0.02 mmol, 5 mol%) and heated up to 450 °C for 5 min under high vacuum. After cooling to rt, 4-iodo-1,5-naphthyridine (**42a**, 100 mg, 0.4 mmol, 1.0 equiv) and dry THF (2 mL) were added. Thereupon, 3-fluorobenzylzinc chloride (3.8 mL, 0.8 mmol, 0.21 M in THF, 2.0 equiv) was added dropwise and the reaction mixture was stirred at rt for 4 h until complete consumption of **42a** was observed by GC. A sat. aq. solution of NH_4Cl (5 mL) was added and the aq. layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated

under reduced pressure. The crude residue was purified by flash column chromatography (isohexane/ EtOAc = 9:1 + 1% NEt_3) to afford **66b** (72 mg, 75%) as a clear oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2981, 1713, 1587, 1495, 1443, 1414, 1246, 1177, 1136, 1114, 1073, 1021, 877, 818, 754, 726.

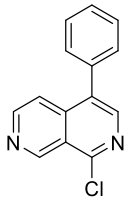
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.02 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.86 (d, *J* = 4.4 Hz, 1H), 8.41 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.66 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.32 (d, *J* = 4.4 Hz, 1H), 7.30-7.23 (m, 1H), 7.12-7.07 (m, 1H), 7.05-6.99 (m, 1H), 6.96-6.88 (m, 1H), 6.68 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 163.1 (d, ^1J(C,F) = 246 Hz), 151.2, 150.4, 149.0, 143.8, 142.9, 142.0 (d, ^3J(C,F) = 7.4 Hz), 137.8, 130.1 (d, ^3J(C,F) = 8.3 Hz), 125.1 (d, ^4J(C,F) = 2.8 Hz), 124.5, 124.1, 116.4 (d, ^2J(C,F) = 21.3 Hz), 113.5 (d, ^2J(C,F) = 21.0 Hz), 35.9.

MS (EI, 70 eV): *m*/*z* (%) = 239 (10), 238 (75), 237 (100), 236 (26).

HRMS (EI) calcd. for [$C_{15}H_{11}FN_2$]: 238.0906; found: 239.0909.

1-Chloro-4-phenyl-2,7-naphthyridine (68)



A dry and argon-flushed *Schlenk*-flask was charged with a solution of $Pd(dba)_2$ (26 mg, 0.045 mmol, 5 mol%), tfp (21 mg, 0.09 mmol, 10 mol%) and 1-chloro-4-iodo-2,7-naphthyridine (**67**, 250 mg, 0.86 mmol) in dry THF (2 mL). Phenylzinc chloride (2.73 mL, 0.9 mmol, 0.33 M in THF, 1.05 equiv) was added dropwise and the reaction was stirred at rt overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 ×15 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane/EtOAc = 7:3) to give **68** (169 mg, 82%) as a white solid.

m.p.: 149 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1601, 1532, 1451, 1392, 1340, 1308, 1267, 1176, 1044, 985, 916, 844, 828, 755, 700.

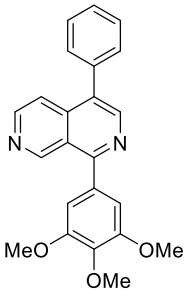
^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 9.84 (s, 1H), 8.78 (d, *J* = 6.0 Hz, 1H), 8.50 (s, 1H), 7.81 (d, *J* = 6.7 Hz, 1H), 7.61-7.51 (m, 3H), 7.49-7.44 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 151.7, 151.0, 146.7, 145.8, 140.9, 134.3, 132.7, 130.0, 129.3, 129.1, 121.8, 118.4.

MS (EI, 70 eV): *m*/*z* (%) = 242 (33), 241 (27), 240 (100), 239 (38), 205 (12), 177 (10), 151 (7), 150 (5).

HRMS (EI) calcd. for [$C_{14}H_9ClN_2$]: 240.0454; found: 240.0444.

4-Phenyl-1-(3,4,5-trimethoxyphenyl)-2,7-naphthyridine (69)



According to **TP4**, 1-chloro-4-phenyl-2,7-naphthyridine (**68**, 90 mg, 0.38 mmol, 1.0 equiv) reacted with (3,4,5-trimethoxyphenyl)zinc chloride (0.54 mL, 0.45 mmol, 0.84 M in THF, 1.2 equiv) within 12 h at rt. After workup, the crude residue was purified by flash column chromatography (EtOAc) to afford the desired product (127 mg, 91%) as a white solid.

m.p.: 178-181 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2922, 2850, 1601, 1582, 1505, 1464, 1413, 1384, 1237, 1123, 1102, 951, 932, 830, 767, 711.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 9.65 (s, 1H), 8.76 (s, 1H), 8.73-8.67 (m, 1H), 7.80 (d, *J* = 5.8 Hz, 1H), 7.60-7.56 (m, 2H), 7.56-7.51 (m, 3H), 7.01 (s, 2H), 3.97 (s, 3H), 3.95 (s, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 160.9, 153.6, 153.1, 146.9, 145.5, 139.4, 138.3, 135.7, 133.5, 131.3, 130.1, 129.1, 128.6, 121.6, 117.6, 107.7, 61.2, 56.5, 29.9.

MS (EI, 70 eV): *m*/*z* (%) = 373 (20), 372 (100), 357 (18), 342 (10), 341 (40), 299 (12), 57 (11).

HRMS (EI) calcd. for [$C_{23}H_{20}N_2O_3$]: 372.1474; found: 372.1475.

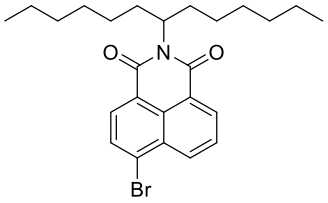
5. Fluorescent Aryl Naphthalene Dicarboximides

5.1 Preparation of Starting Materials

Aryl dioxaborolanes

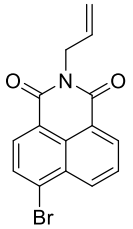
4-(Trimethylsilyl)phenylboronic acid and the pinacol esters of phenylboronic acid, 4-methoxy-phenylboronic acid, 4-(*N,N*-dimethylamino)-phenylboronic acid and 4-cyanophenylboronic acid have been purchased from commercial sources. 2-(4-Methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 4,4,5,5-tetramethyl-2-(3,4,5-trimethoxy-phenyl)-1,3,2-dioxa-borolane and 2-(4-methoxy-8-methylnaphthalen-1-yl)-4,4,5,5-tetra-methyl-1,3,2-dioxaborolane[174] have been prepared by reacting the corresponding aryl bromides with bis(pinacolato)diboron according to standard procedures.[175]

6-Bromo-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (72)[176]



A mixture of 1-hexylheptylamine (33 mmol, 6.6 g, 1.5 equiv) and 4-bromo-1,8-naphthalic anhydride (**71**, 22 mmol, 6.0 g, 1.0 equiv) in ethylene glycol (50 mL) was heated at 160 °C. After 12 h, hydrochloric acid (2 M, 50 mL) was added to the reaction mixture, which was subsequently extracted with $CHCl_3$ (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (100% $CHCl_3$) gave **72** (9.05 g, 90%) as a yellow oil. For analytics see ref. 175.

2-Allyl-6-bromo-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (76)[167]



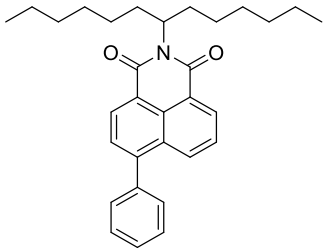
4-bromo-1,8-naphthalic anhydride (1.0 g, 3.4 mmol, 1.0 equiv) was suspended in 25 mL of absolute EtOH and heated up to 70 °C. Upon addition of allyl amine (0.33 mL, 4.4 mmol, 1.3 equiv) the reaction mixture turned brown. Afterwards the mixture was heated under reflux until the starting compound was completely dissolved. After 30 minutes of stirring the product precipitated and the reaction was refluxed for further 2 hours. The reaction was cooled to rt and the solid product was filtered, washed with ethanol and dried *in vacuo*. The product was purified by recrystallization from EtOH to yield **76** (0.98g, 92%) as pale brown needles. For analytics see ref. 167.

---

[174] A. K. Banerjee, P. S. Poon, M. S. Laya, J. A. Azocar, *Russ. J. Gen. Chem.* **2003**, *73*, 1815.
[175] (a) Y. Avlasevich, K. Müllen, *J. Org. Chem*. **2007**, *72*, 10243. (b) K. Mutoh, Y. Kobayashi, Y. Hirao, T. Kubo, J. Abe, *Chem. Commun.* **2016**, *52*, 6797. (c) P. B. Dzhevakov, M. A. Topchiy, D. A. Zharkova, O. S. Morozov, A. F. Asachenko, M. S. Nechaev, *Adv. Synth. Catal.* **2016**, *358*, 977.
[176] A. Hofer, *dissertation* **2012**, LMU Munich.

5.2 Preparation of Aryl Naphthalene Dicarboximides 73, 77, 78

6-Phenyl-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (73a)



A *Schlenk*-flask was charged with 6-bromo-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**72**, 480 mg, 1.05 mmol, 1.0 equiv) and 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (265 mg, 1.30 mmol, 1.2 equiv). Both compounds were dissolved in toluene (20 mL) under a light argon-stream. K_2CO_3 (2.76 g, 20 mmol) was dissolved in a mixture of water (10 mL) and EtOH (4 mL) and added to the *Schlenk*-flask followed by tetrakis(triphenylphosphine)palladium(0) (116 mg, 0.10 mmol, 10 mol%). The mixture was purged with argon for 30 min and then heated to 80 °C. The reaction mixture was stirred for further 17 h at this temperature. After cooling to rt, the organic phase was separated and the aqueous phase was extracted with toluene (3 × 10 mL). Purification by column chromatography (isohexane/$CHCl_3$ = 1:1) gave compound **73a** (450 mg, 94%) as a bright yellow solid.

m.p.: 97 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2919, 2852, 1696, 1653, 1587, 1396, 1348, 1237, 1176, 1100, 784, 768, 702.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 8.69-8.56 (m, 2H), 8.25 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.74-7.66 (m, 1H), 7.58-7.53 (m, 2H), 7.53-7.48 (m, 3H), 5.23-5.16 (m, 1H, NCH), 2.31-2.20 (m, 2H, *β*-CH_2), 1.89-1.80 (m, 2H, *β*-CH_2), 1.40-1.16 (m, 16H, 8 × CH_2), 0.83 (t, *J* = 7.1 Hz, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 165.7, 165.5, 164.6, 164.4, 146.6, 139.0, 132.4, 131.7, 131.3, 130.9, 130.6, 130.1, 130.0, 129.0, 128.8, 128.6, 128.0, 127.0, 123.7, 123.0, 122.6, 121.9, 54.6, 32.6, 31.9, 29.4, 27.1, 22.7, 14.2.

MS (EI, 70 eV): *m/z (%)* = 455 (14), 275 (22), 274 (100), 273 (22), 256 (12), 202 (8).

HRMS (EI) calcd. for [$C_{31}H_{37}NO_2$]: 455.2824; found: 455.2820.

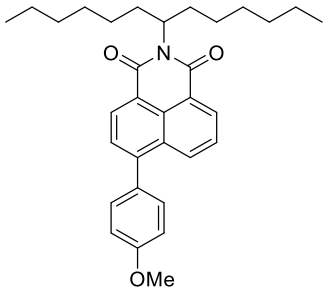
EA for [$C_{31}H_{37}NO_2$]:	calculated:	C 81.72	N 3.07	H 8.19
	found:	C 81.52	N 3.10	H 8.31

UV/Vis ($CHCl_3$): λ_{max} (ε) = 355.4 nm (17100).

Fluorescence ($CHCl_3$, λ_{exc} = 355.4 nm): λ_{max} = 420.0 nm.

Fluorescence quantum yield ($CHCl_3$, λ_{exc} = 355.4 nm, $E_{355.4\ nm}$ = 0.1341 cm^{-1}, reference: *N*,*N*'-bis(tridecan-7-yl)perylene-3,4:9,10-tetracarboxylic diimide with Φ = 1.00): Φ = 0.78.

6-(4-Methoxyphenyl)-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (73b)



A *Schlenk*-flask was charged with 6-bromo-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**72**, 215 mg, 0.47 mmol, 1.04 equiv) and 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (100 mg, 0.45 mmol, 1.0 equiv). Both compounds were dissolved in toluene (10 mL) under a light argon-stream. K_2CO_3 (1.40 g, 10 mmol) was dissolved in a mixture of water (5 mL) and EtOH (1 mL) and added to the *Schlenk*-flask followed by tetrakis(triphenylphosphine)-palladium(0) (20 mg, 0.018 mmol, 5 mol%). The mixture was purged with argon for 30 min and then heated to 80 °C. The reaction mixture was stirred for further 17 h at this temperature. After cooling to rt, the organic phase was separated and the aqueous phase was extracted with toluene (3 × 10 mL). Purification by column chromatography (isohexane/$CHCl_3$ = 1:1) gave compound **73b** (176 mg, 78%) as an off-white solid.

m.p.: 63 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2922, 2852, 1698, 1656, 1608, 1588, 1518, 1506, 1463, 1397, 1348, 1288, 1239, 1176, 1096, 1078, 1036, 963, 867, 838, 785, 760, 724.

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 8.66-8.52 (br, 2H), 8.29 (dd, *J* = 8.5 Hz, 1.1 Hz, 1H), 7.72-7.63 (m, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 5.26-5.13 (m, 1 H, NCH), 3.90 (s, 3H, OCH_3), 2.33-2.17 (m, 2H, *β*-CH_2), 1.91-1.77 (m, 2H, *β*-CH_2), 1.42-1.11 (m, 16H, 8 × CH_2), 0.82 (t, *J* = 9.0 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 165.5, 164.5, 160.0, 146.4, 132.5, 131.3, 131.2, 130.2, 129.1, 127.9, 126.8, 123.7, 123.1, 122.2, 121.6, 114.3, 55.5, 54.6, 32.6, 31.9, 29.4, 27.0, 22.7, 14.2.

MS (EI, 70 eV): *m/z (%)* = 485 (23), 316 (10), 304 (100), 303 (54), 286 (13), 198 (34), 180 (12).

HRMS (EI) calcd. for [$C_{32}H_{39}NO_3$]: 485.2930; found: 485.2924.

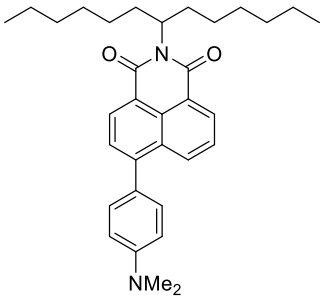
EA for [$C_{32}H_{39}NO_3$]:	calculated:	C 79.14	N 2.88	H 8.09
	found:	C 79.18	N 2.69	H 8.22

UV/Vis ($CHCl_3$): λ_{max} (ε) = 364.8 nm (16900).

Fluorescence ($CHCl_3$, λ_{exc} = 364.8 nm): λ_{max} = 459.6 nm.

Fluorescence quantum yield ($CHCl_3$, λ_{exc} = 364.8 nm, $E_{364.8nm}$ = 0.2522 cm^{-1}, reference: *N*,*N*'-bis(tridecan-7-yl)perylene-3,4:9,10-tetracarboxylic diimide with Φ = 1.00): Φ = 0.83.

6-(4-(Dimethylamino)phenyl)-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (73c)



A *Schlenk*-flask was charged with 6-bromo-2-(tridecan-7-yl)-1*H*-benzo[*de*]iso-quinoline-1,3(2H)-dione (**72**, 480 mg, 1.05 mmol, 1.05 equiv) and *N,N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (247 mg, 1.0 mmol, 1.0 equiv). Both compounds were dissolved in toluene (20 mL) under a light argon stream. K_2CO_3 (2.80 g, 20 mmol) was dissolved in a mixture of water (10 mL) and EtOH (3 mL) and added to the *Schlenk*-flask followed by tetrakis(triphenylphosphine)-palladium(0) (115 mg, 0.10 mmol, 10 mol%). The mixture was purged with argon for 30 min and then heated to 80 °C. The reaction mixture was stirred for further 17 h at this temperature. After cooling to rt, the organic phase was separated and the aqueous phase was extracted with toluene (3 × 10 mL). Purification by column chromatography (isohexane/$CHCl_3$ = 5:2) gave compound **73c** (70 mg, 14 %) as a bright yellow solid.

m.p.: 125 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2921, 2852, 1694, 1654, 1609, 1587, 1524, 1465, 1397, 1349, 1237, 1199, 1101, 943, 872, 818, 785, 761.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 8.64-8.54 (m, 2H), 8.40 (d, *J* = 8.5 Hz, 1H), 7.70-7.65 (m, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.22-5.15 (m, 1H), 3.07 (s, 6H, NMe_2), 2.29-2.20 (m, 2H, *β*-CH_2), 1.88-1.80 (m, 2H, *β*-CH_2), 1.35-1.18 (m, 16H, 8 × CH_2), 0.82 (t, *J* = 7.0 Hz, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 165.9, 165.6, 164.8, 164.6, 150.7, 147.3, 132.9, 131.6, 131.1, 130.8, 130.2, 129.3, 127.6, 126.6, 126.5, 112.2, 123.7, 123.0, 121.5, 120.8, 54.5, 40.6, 32.6, 31.9, 29.41, 27.1, 22.6, 14.2.

MS (EI, 70 eV): *m/z (%)* = 499 (22), 498 (59), 318 (10), 317 (43), 316 (100), 315 (19).

HRMS (EI) calcd. for [$C_{33}H_{42}N_2O_2$]: 498.3246; found: 498.3227.

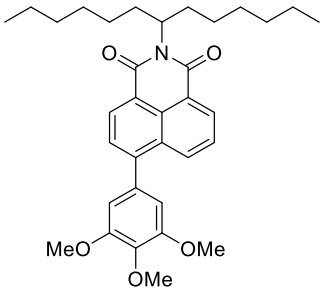
EA for [$C_{33}H_{42}N_2O_2$]:	calculated:	C 79.48	N 5.62	H 8.49
	found:	C 79.42	N 5.64	H 8.36

UV/Vis ($CHCl_3$): λ_{max} (ε) = 426.2 nm (17100).

Fluorescence ($CHCl_3$, λ_{exc} = 426.2 nm): λ_{max} = 578.4 nm.

Fluorescence quantum yield ($CHCl_3$, λ_{exc} = 426.2 nm, $E_{426.2\ nm}$ = 0.1138 cm^{-1}, reference: *N*,*N*'-bis(tridecan-7-yl)perylene-3,4:9,10-tetracarboxylic diimide with Φ = 1.00): Φ = 0.64.

6-(3,4,5-Trimethoxyphenyl)-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (73d)



A *Schlenk*-flask was charged with 6-bromo-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**72**, 361 mg, 0.79 mmol, 1.05 equiv) and 4,4,5,5-tetramethyl-2-(3,4,5-trimethoxy-phenyl)-1,3,2-dioxaborolane (220 mg, 0.75 mmol, 1.0 equiv). Both compounds were dissolved in toluene (20 mL) under a light argon-stream. K_2CO_3 (2.80 g, 20 mmol) was dissolved in a mixture of water (10 mL) and EtOH (2 mL) and added to the *Schlenk*-flask followed by tetrakis(triphenylphosphine)palladium(0) (0.038 mmol, 43 mg, 5 mol%). The mixture was purged with argon for 30 min and then heated to 80 °C. The reaction mixture was stirred for further 17 h at this temperature. After cooling to rt, the organic phase was separated and the aqueous phase was extracted with toluene (3 × 20 mL). Purification by column chromatography (100% $CHCl_3$) gave compound **73d** (350 mg, 86 %) as a yellow oil.

IR (Diamond-ATR, neat): / cm^{-1} = 2924, 2855, 1698, 1656, 1616, 1586, 1503, 1454, 1415, 1397, 1350, 1322, 1237, 1180, 1126, 1104, 1060, 1006, 928, 912, 860, 842, 831, 785, 760, 725, 702, 678.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.69 (br, 2H), 8.31 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.71 (t, *J* = 7.1 Hz, 1H), 6.70 (s, 2H), 5.24-5.13 (m, 1H, NCH), 3.95 (s, 3H, OMe), 3.89 (s, 6H, OMe), 2.31-2.18 (m, 2H, *ß*-CH_2), 1.90-1.77 (m, 2H, *ß*-CH_2), 1.35-1.16 (m, 16H, 8 × CH_2), 0.81 (t, *J* = 6.9 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 165.6, 165.4, 164.5, 164.3, 153.5, 146.6, 138.4, 134.5, 132.4, 131.7, 131.2, 130.9, 130.4, 130.1, 128.9, 127.7, 127.0, 123.7, 123.0, 122.6, 121.8, 107.3, 61.1, 56.4, 54.6, 32.5, 31.9, 29.3, 27.0, 22.7, 14.1.

MS (EI, 70 eV): *m/z (%)* = 545 (40), 365 (16), 364 (76), 363 (100), 348 (19).

HRMS (EI) calcd. for [$C_{34}H_{43}NO_5$]: 545.3141; found: 545.3135.

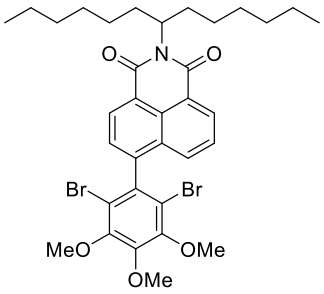
EA for [$C_{36}H_{41}NO_3$]:	calculated:	C 74.83	N 2.57	H 7.94
	found:	C 73.47	N 2.58	H 7.75

UV/Vis ($CHCl_3$): λ_{max} (ε) = 362.2 nm (15900).

Fluorescence ($CHCl_3$, λ_{exc} = 362.2 nm): λ_{max} = 525.1 nm.

Fluorescence quantum yield ($CHCl_3$, λ_{exc} = 362.2 nm, $E_{362.2\ nm}$ = 0.2207 cm^{-1}, reference: *N*,*N*'-bis(tridecan-7-yl)perylene-3,4:9,10-tetracarboxylic diimide with Φ = 1.00): Φ = 0.65.

6-(2,6-Dibromo-3,4,5-trimethoxyphenyl)-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (73e)



2-(Tridecan-7-yl)-6-(3,4,5-trimethoxyphenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**73d**, 175 mg, 0.32 mmol) was dissolved in MeCN (10 mL). NBS (120 mg, 0.67 mmol, 2.1 equiv) was added at once to the solution and the reaction mixture was stirred for 12 h at 30 °C. The crude mixture was treated with brine solution and extracted with $CHCl_3$ (3 × 10 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (100% $CHCl_3$) gave **73e** (155 mg, 69%) as a colorless oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2925, 2855, 1699, 1658, 1590, 1461, 1397, 1352, 1321, 1237, 1179, 1087, 1008, 986, 935, 909, 861, 784, 763, 729.

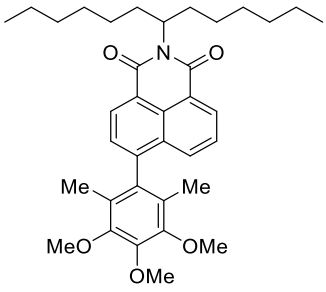
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 8.68-8.54 (m, 2H), 7.72-7.65 (m, 2H), 7.56 (d, *J* = 7.5 Hz, 1H), 5.22-5.15 (m, 1H, NCH), 4.06 (s, 3H, OMe), 3.98 (s, 6H, OMe), 2.28-2.20 (m, 2H, *β*-CH_2), 1.88-1.82 (m, 2H, *β*-CH_2), 1.36-1.20 (m, 16H, 8 × CH_2), 0.82 (t, *J* = 7.0 Hz, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 165.4, 165.2, 164.5, 164.1, 151.2, 147.9, 144.8, 135.5, 131.8, 131.3, 131.1, 130.5, 129.6, 128.6, 128.6, 127.4, 123.9, 123.9, 123.5, 123.2, 122.8, 114.6, 61.5, 61.3, 54.6, 32.6, 31.9, 29.4, 27.1, 22.7, 14.2.

MS (EI, 70 eV): *m/z (%)* = 703 (25), 701 (13), 525 (12), 524 (48), 523 (31), 522 (100), 521 (31), 520 (50), 399 (9), 397 (9), 361 (25).

HRMS (EI) calcd. for [$C_{34}H_{41}Br_2NO_5$]: 701.1351; found: 701.1357.

2-(Tridecan-7-yl)-6-(3,4,5-trimethoxy-2,6-dimethylphenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (73f)



A dry and argon-flushed *Schlenk*-flask was charged with a solution of $ZnCl_2$ (0.43 mL, 0.43 mmol, 1.0 M in THF, 2.1 equiv). MeMgCl (0.14 mL, 0.43 mmol, 3.0 M in THF, 2.1 equiv) was added dropwise at 0 °C to the solution. Another dry, argon-flushed *Schlenk*-flask was charged with 6-(2,6-dibromo-3,4,5-trimethoxyphenyl)-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**73e**, 145 mg, 0.2 mmol,

1.0 equiv), $Pd(OAc)_2$ (3 mg, 0.01 mmol, 5 mol%,) and S-Phos (9 mg, 0.02 mmol, 10 mol%) in dry THF (1 mL). After stirring for 10 min, this solution was added dropwise to the freshly prepared MeZnCl solution. The reaction mixture was stirred overnight at 60 °C and then quenched with sat. aq. NH_4Cl solution. The crude mixture was extracted with $CHCl_3$ and concentrated *in vacuo*. Column chromatography (100% $CHCl_3$) gave **73f** (85.0 mg, 74%) as a colorless oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2925, 2856, 1700, 1658, 1589, 1456, 1399, 1349, 1320, 1237, 1110, 1081, 862, 785, 764.

^{1}H-NMR (100 MHz, $CDCl_3$): δ/ ppm = 8.67-8.52 (br, 2H), 7.71 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.65-7.59 (m, 1H), 7.51 (d, *J* = 7.4 Hz, 1H), 5.25-5.13 (m, 1H, NCH), 4.02 (s, 3H, OMe), 3.89 (s, 6H, OMe), 2.30-2.20 (m, 2H, *ß*-CH_2), 1.90-1.80 (m, 2H, *ß*-CH_2), 1.75 (s, 6H, 2 × CH_3), 1.35-1.19 (m, 16H, 8 × CH_2), 0.81 (t, *J* = 6.9 Hz, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 165.6, 164.5, 150.1, 146.2, 145.4, 133.8, 131.7, 131.6, 131.0, 130.8, 130.5, 128.8, 128.2, 127.2, 125.9, 123.9, 123.1, 122.6, 121.9, 60.9, 60.9, 54.6, 32.6, 31.9, 29.4, 27.1, 22.7, 14.2, 13.5.

MS (EI, 70 eV): *m/z (%)* = 574 (18), 573 (43), 393 (24), 392 (100), 391 (92), 348 (7), 55 (8).

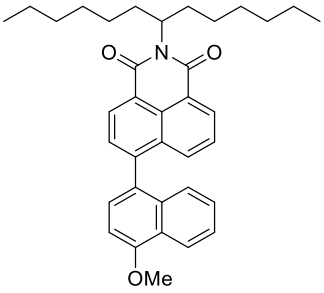
HRMS (EI) calcd. for [$C_{36}H_{47}NO_5$]: 573.3454; found: 573.3448.

UV/Vis ($CHCl_3$): λ_{max} (ε) = 358.2 (14300), 344.0 nm (16000).

Fluorescence ($CHCl_3$, λ_{exc} = 344.0 nm): λ_{max} = 541.6 nm.

Fluorescence quantum yield ($CHCl_3$, λ_{exc} = 344.0 nm, $E_{344.0\ nm}$ = 0.0938 cm^{-1}, reference: *N*,*N*'-bis(tridecan-7-yl)perylene-3,4:9,10-tetracarboxylic diimide with Φ = 1.00): Φ = 0.046.

6-(4-Methoxynaphthalen-1-yl)-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (73g)



A *Schlenk*-flask was charged with 6-bromo-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**72**, 348 mg, 0.76 mmol, 1.1 equiv) and 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (200 mg, 0.70 mmol, 1.0 equiv). Both compounds were dissolved in toluene (10 mL) under a light argon-stream. K_2CO_3 (1.4 g, 10 mmol) was dissolved in a mixture of water (5 mL) and EtOH (1 mL) and added to the *Schlenk*-flask followed by tetrakis(triphenylphosphine)-palladium(0) (20 mg, 0.018 mmol, 5 mol%). The mixture was purged with argon for 30 min and then heated to 80 °C. The reaction mixture was stirred further 17 h at this temperature. After cooling to rt, the organic phase was separated and the aqueous phase was extracted with toluene (3 × 20 mL). Purification by column chromatography (isohexane/$CHCl_3$ = 1:1) gave compound **73g** (260 mg, 69 %) as a bright yellow solid.

m.p.: 98 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2920, 2853, 1697, 1655, 1615, 1586, 1511, 1459, 1421, 1398, 1348, 1311, 1235, 1177, 1157, 1106, 1084, 1025, 881, 817, 784, 759, 735, 712, 667.

^{1}H-NMR (300 MHz, $CDCl_3$): δ/ ppm = 8.74-8.64 (br, 1H), 8.64–8.52 (br, 1H), 8.41 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.57-7.46 (m, 2H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.36-7.27 (m, 2H), 6.97 (d, *J* = 7.9 Hz, 1H) 5.32-5.17 (m, 1H, NCH), 4.11 (s, 3H, OMe), 2.39-2.22 (m, 2H, *ß*-CH_2), 1.96-1.81 (m, 2H, *ß*-CH_2), 1.47-1.15 (m, 16H, 8 × CH_2), 0.85 (t, *J* = 6.6 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ/ ppm = 165.5, 164.6, 156.1, 145.5, 133.3, 132.9, 131.6, 131.2, 130.9, 130.5, 129.4, 128.7, 128.7, 128.1, 127.1, 126.8, 125.8, 125.7, 125.6, 122.5, 103.4, 55.8, 54.6, 32.6, 31.9, 29.4, 27.1, 22.7, 14.2.

MS (EI, 70 eV): *m/z (%)* = 535 (32), 355 (16), 354 (69), 353 (100), 239 (8).

HRMS (EI) calcd. for [$C_{36}H_{41}NO_3$]: 535.3086; found: 535.3080.

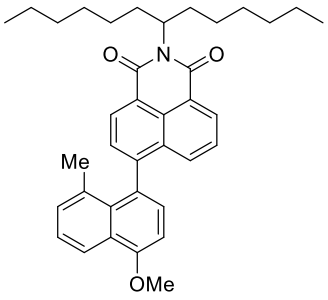
EA for [$C_{36}H_{41}NO_3$]:	calculated:	C 80.71	N 2.61	H 7.71
	found:	C 80.86	N 2.49	H 7.84

UV/Vis ($CHCl_3$): λ_{max} (ε) = 325.0 nm (15300).

Fluorescence ($CHCl_3$, λ_{exc} = 325.0 nm): λ_{max} = 509.7 nm.

Fluorescence quantum yield ($CHCl_3$, λ_{exc} = 325.0 nm, $E_{325.0\ nm}$ = 0.1386 cm^{-1}, reference: *N*,*N*'-bis(tridecan-7-yl)perylene-3,4:9,10-tetracarboxylic diimide with Φ = 1.00): Φ = 0.39.

6-(4-Methoxy-8-methylnaphthalen-1-yl)-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (73h)



A *Schlenk*-flask was charged with 6-bromo-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**72**, 124 mg, 0.27 mmol, 1.05 equiv) and 2-(4-methoxy-8-methylnaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (77 mg, 0.26 mmol, 1.0 equiv). Both compounds were dissolved in toluene (5 mL) under a light argon-stream. K_2CO_3 (0.70 g, 5 mmol) was dissolved in a mixture of water (3 mL) and EtOH (0.5 mL) and added to the *Schlenk*-flask followed by tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.013 mmol, 5 mol%). The mixture was purged with argon for 30 min and then heated to 80 °C. The reaction mixture was stirred further 17 h at this temperature. After cooling to rt, the organic phase was separated and the aqueous phase was extracted with toluene (3 × 5 mL). Purification by column chromatography (isohexane/$CHCl_3$ = 1:1) gave compound **73h** (36 mg, 25 %) as a bright yellow solid.

m.p.: 164 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2920, 2853, 1697, 1656, 1587, 1513, 1450, 1397, 1344, 1314, 1233, 1153, 1099, 1045, 815, 784, 765, 726, 677.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 8.66-8.50 (br, 2H), 8.38 (d, *J* = 7.9 Hz, 1H), 7.76 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.70 (d, *J* = 7.4 Hz, 1H), 7.57-7.53 (m, 1H), 7.45-7.41 (m, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.24-5.17 (m, 1H, NCH), 4.09 (s, 3H, OMe), 2.30-2.21 (m, 2H, *β*-CH_2), 1.92-1.82 (m, 2H, *β*-CH_2), 1.74 (s, 3H, CH_3), 1.36-1.20 (m, 16H, 8 × CH_2), 0.84 (t, *J* = 6.5 Hz, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm =165.6, 164.7, 156.4, 149.9, 134.5, 132.9, 132.5, 132.2, 131.6, 130.9, 130.1, 128.7, 128.3, 127.0, 126.8, 125.5, 123.6, 122.9, 122.4, 121.6, 121.2, 102.9, 55.9, 54.7, 32.6, 31.9, 29.4, 27.1, 24.6, 22.8, 14.2.

MS (EI, 70 eV): *m/z (%)* = 550 (22), 549 (50), 380 (6), 369 (13), 368 (62), 367 (100), 352 (8), 309 (5).

HRMS (EI) calcd. for [$C_{37}H_{43}NO_3$]: 549.3243; found: 549.3238.

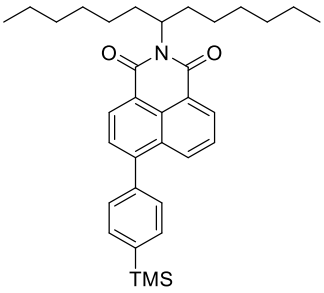
EA for [$\mathbf{C_{37}H_{43}NO_3}$]:	calculated:	C 80.84	N 2.55	H 7.88
	found:	C 80.32	N 2.54	H 8.00

UV/Vis ($CHCl_3$): λ_{max} (ε) = 329.0 nm (17100).

Fluorescence ($CHCl_3$, λ_{exc} = 329.0 nm): λ_{max} = 522.7 nm.

Fluorescence quantum yield ($CHCl_3$, λ_{exc} = 329.0 nm, $E_{329.0\ nm}$ = 0.0630 cm^{-1}, reference: *N*,*N*'-bis(tridecan-7-yl)perylene-3,4:9,10-tetracarboxylic diimide with Φ = 1.00): Φ = 0.40.

2-(Tridecan-7-yl)-6-(4-(trimethylsilyl)phenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (73i)



A *Schlenk*-flask was charged with 6-bromo-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**72**, 1.33 g, 2.92 mmol, 1.05 equiv) and (4-(trimethylsilyl)phenyl)boronic acid (540 mg, 2.78 mmol, 1.0 equiv). Both compounds were dissolved in toluene (40 mL) under a light argon-stream. K_2CO_3 (8.40 g, 60 mmol) was dissolved in a mixture of water (30 mL) and EtOH (5 mL) and added to the *Schlenk*-flask followed by tetrakis(triphenylphosphine)palladium(0) (160 mg, 0.14 mmol, 5 mol%). The mixture was purged with argon for 30 min and then heated to 80 °C. The reaction mixture was stirred further 17 h at this temperature. After cooling to rt, the organic phase was separated and the aqueous phase was extracted with toluene (3 × 30 mL). Purification by column chromatography (isohexane/$CHCl_3$ = 1:1) gave compound **73i** (1.19 g, 81 %) as a green fluorescent oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2923, 2855, 1698, 1656, 1587, 1455, 1398, 1349, 1237, 1179, 1111, 838, 820, 784, 761, 726, 695.

^{1}H-NMR (400 MHz, $CDCl_3$): δ/ ppm = 8.71-8.56 (br, 2H), 8.30 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.71 (dd, *J* = 7.9, 2.6 Hz, 3H), 7.51 (d, *J* = 8.1 Hz, 1 H), 5.28-5.16 (m, 1H, NCH), 2.35-2.22 (m, 2H, *β*-CH_2), 1.93-1.79 (m, 2H, *β*-CH_2), 1.46-1.14 (m, 16H, 8 × CH_2), 0.83 (t, *J* = 6.9 Hz, 6H), 0.36 (s, 9H, TMS).

^{13}C-NMR (100 MHz, $CDCl_3$): δ/ ppm = 165.6, 165.5, 164.6, 164.4, 146.7, 141.1, 139.3, 133.7, 132.4, 131.7, 131.3, 130.9, 130.6, 130.0, 129.3, 129.0, 127.9, 126.9, 123.7, 123.0, 122.6, 121.8, 54.6, 32.6, 31.9, 29.4, 27.0, 22.7, 14.2, -1.0.

MS (EI, 70 eV): *m/z (%)* = 527 (20), 348 (8), 347 (29), 346 (100), 345 (26), 331 (11), 330 (33).

HRMS (EI) calcd. for [$C_{34}H_{45}NO_2Si$]: 527.3220; found: 535.3216.

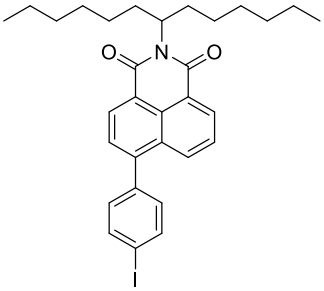
EA for [$C_{36}H_{41}NO_3$]:	calculated:	C 77.37	N 2.65	H 8.59
	found:	C 77.02	N 2.73	H 8.63

UV/Vis ($CHCl_3$): λ_{max} (ε) = 356.0 nm (18600).

Fluorescence ($CHCl_3$, λ_{exc} = 356.0 nm): λ_{max} = 425.4 nm.

Fluorescence quantum yield ($CHCl_3$, λ_{exc} = 356.0 nm, $E_{356.0\ nm}$ = 0.0676 cm^{-1}, reference: *N*,*N*'-bis(tridecan-7-yl)perylene-3,4:9,10-tetracarboxylic diimide with Φ = 1.00): Φ = 0.79.

6-(4-Iodophenyl)-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (73k)



A dry and argon-flushed *Schlenk*-flask was charged with 2-(tridecan-7-yl)-6-(4-(trimethyl-silyl)-phenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**73i**, 840 mg, 1.6 mmol, 1.0 equiv) and dry DCM (3.5 mL). The flask was cooled to 0 °C and ICl (260 mg, 1.6 mmol, 1.0 equiv) was added dropwise to the mixture. After stirring for 10 min at 0 °C, the reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with DCM (3 × 10 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (100% $CHCl_3$) to give **73k** (770 mg, 83 %) as a yellow oil.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2922, 2854, 1698, 1656, 1588, 1487, 1463, 1398, 1349, 1324, 1238, 1178, 1101, 1005, 821, 784, 758.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 8.65-8.56 (m, 2H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2 H), 7.70-7.66 (m, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 2 H), 5.22-5.15 (m, 1H, NCH), 2.27-2.20 (m, 2H, *β*-CH_2), 1.86-1.79 (m, 2H, *β*-CH_2), 1.32-1.15 (m, 16H, *β*-CH_2), 0.79 (t, *J* = 7.1 Hz, 6H).

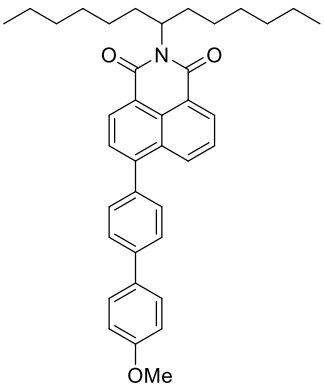
^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 165.4, 165.2, 164.4, 164.1, 145.2, 138.4, 137.9, 133.5, 131.8, 131.7, 131.2, 131.0, 130.4, 129.7, 128.9, 127.8, 127.1, 127.0, 123.7, 123.0, 122.9, 122.2, 94.6, 54.6, 32.5, 31.8, 29.3, 27.0, 22.7, 14.1.

MS (EI, 70 eV): *m/z (%)* = 581 (11), 401 (12), 400 (68), 399 (16), 199 (12), 198 (100).

HRMS (EI) calcd. for [$C_{31}H_{36}INO_2$]: 581.1791; found: 581.1781.

EA for [$C_{31}H_{36}INO_2$]:	calculated:	C 64.03	N 2.41	H 6.24
	found:	C 63.88	N 2.49	H 6.32

6-(4'-Methoxy-[1,1'-biphenyl]-4-yl)-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (73l)



A dry and argon-flushed *Schlenk*-flask was charged with 4-iodoanisole (40 mg, 0.16 mmol, 1.0 equiv) and dry THF (1 mL). An iodine/magnesium exchange was performed using *i*PrMgCl·LiCl (0.13 mL, 0.16 mmol, 1.26 M in THF, 1.0 equiv) within 20 min at 0 °C, followed by transmetalation with $ZnCl_2$ (0.18 mL, 0.18 mmol, 1.0 M in THF, 1.1 equiv). The freshly prepared zinc species was transferred *via* syringe to another argon-flushed *Schlenk*-flask which was previously charged with 6-(4-iodophenyl)-2-(tridecan-7-yl)-1*H*-benzo[*de*]isoquinoline-1,3-(2*H*)-dione (**73k**, 96 mg, 0.16 mmol, 1.0 equiv), palladium(0)bis-(dibenzylideneacetone) (5 mg, 0.008 mmol, 5 mol%), tfp (4 mg, 0.016 mmol, 10 mol%) and dry THF (3 mL). The reaction mixture was stirred for 12 h at 50 °C. Then, the reaction was quenched with sat. aq. NH_4Cl solution, extracted with DCM (3 × 5 mL) and dried over $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (isohexane/DCM= 1:1) to give **73l** (80 mg, 89 %) as a yellow solid.

m.p.: 104 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2924, 2854, 1697, 1652, 1604, 1587, 1497, 1464, 1396, 1349, 1288, 1238, 1177, 1106, 1039, 823, 784, 760.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 8.70-8.56 (m, 2H), 8.35 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.76-7.73 (m, 3H), 7.73-7.69 (m, 1H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 5.23 (m, 1H, NCH), 7.04 (s, 3H, OMe), 2.31-2.21 (m, 2H, *ß*-CH_2), 1.89-1.80 (m, 2H, *ß*-CH_2), 1.36-1.20 (m, 16H, 8 × CH_2), 0.83 (t, *J* = 7.1 Hz, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 165.7, 164.5, 159.7, 146.4, 141.1, 137.3, 132.9, 132.5, 131.7, 131.4, 131.0, 130.6, 130.5, 130.1, 129.1, 128.3, 128.0, 127.0, 127.0, 123.8, 123.0, 122.5, 121.8, 114.6, 55.6, 54.7, 32.6, 31.9, 29.4, 27.1, 22.8, 14.2.

MS (EI, 70 eV): *m/z (%)* = 562 (11), 561 (25), 392 (7), 381 (20), 380 (76), 379 (100), 364 (7), 336 (7).

HRMS (EI) calcd. for [$C_{38}H_{43}NO_3$]: 561.3243; found: 561.3229.

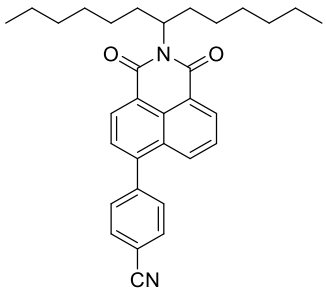
EA for [$C_{38}H_{43}NO_3$]: calculated: C 81.25 N 2.49 H 7.72
found: C 81.37 N 2.49 H 7.76.

UV/Vis ($CHCl_3$): λ_{max} (ε) = 364.4 nm (27500).

Fluorescence ($CHCl_3$, λ_{exc} = 364.4 nm): λ_{max} = 492.2 nm.

Fluorescence quantum yield ($CHCl_3$, λ_{exc} = 364.4 nm, $E_{364.4\ nm}$ = 0.0528 cm^{-1}, reference: *N*,*N*'-bis(tridecan-7-yl)perylene-3,4:9,10-tetracarboxylic diimide with Φ = 1.00): Φ = 0.67.

6-(4-Cyanophenyl)-2-(tridecan-7-yl)-1-benzo[*de*]isoquinoline-1,3(2*H*)-dione (73j)



Procedure A: Suzuki-Coupling:
A *Schlenk*-flask was charged with 6-bromo-2-(tridecan-7-yl)-1*H*-benzo[*de*]iso-quinoline-1,3(2*H*)-dione (**72**, 980 mg, 2.1 mmol, 1.0 equiv) and 4-Cyanophenylboronic acid (370 mg, 2.52 mmol, 1.2 equiv). Both compounds were dissolved in toluene (40 mL) under a light argon stream. K_2CO_3 (5.0 g, 36.2 mmol) was dissolved in a mixture of water (20 mL) and EtOH (8 mL) and added to the *Schlenk*-flask followed by tetrakis(triphenylphosphine)-palladium(0) (115 mg, 0.11 mmol, 5 mol%). The mixture was purged with argon for 30 min and then heated to 80 °C. The reaction mixture was stirred for further 17 h at this temperature. After cooling to rt, the organic phase was separated and the aqueous phase was extracted with toluene (3 × 20 mL). Purification by column chromatography (isohexane/$CHCl_3$ = 1:1) gave compound **73j** (416 mg, 41 %) as a bright yellow oil.

Procedure B: Cyanation with $K_4Fe(CN)_6$:[177]
A dry, argon-flushed *schlenk*-flask was charged with $K_4Fe(CN)_6$ (128 mg, 0.35 mmol, 2.0 equiv), K_2CO_3 (72 mg, 0.52 mmol, 3.0 equiv) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (13 mg, 0.017 mmol, 10 mol%). A solution of 6-(4-iodophenyl)-2-(tridecan-7-yl)-1*H*-benzo[*de*]iso-quinoline-1,3(2*H*)-dione (**73k**, 101 mg, 0.174 mmol) in dry DMF (2 mL) was added at rt under argon. The reaction mixture was stirred at 100 °C for 4 h, allowed to cool down and the solvent was removed under reduced pressure. The crude residue was treated with sat. aq. NH_4Cl solution (15 mL) and extracted with $CHCl_3$ (3 × 15 mL). Purification by column chromatography (isohexane/$CHCl_3$ = 1:1) gave compound **73j** (55 mg, 66 %) as a bright yellow oil.

[177] T. Schlücker, *dissertation* **2016**, LMU Munich

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2923, 2855, 1699, 1656, 1588, 1465, 1397, 1349, 1327, 1238, 1179, 1103, 844, 784, 759.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 8.71-8.60 (br, 2H), 8.36 (dd, *J* = 8.5 Hz, 1.0 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.77-7.73 (m, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 5.23-5.18 (m, 1H, NCH), 2.30-2.23 (m, 2H, *ß*-CH_2), 1.89-1.82 (m, 2H, *ß*-CH_2), 1.37-1.20 (m, 16H, 8×CH_2), 0.84 (t, *J* = 7.1 Hz, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 165.7, 165.5, 164.6, 164.4, 146.1, 140.6, 138.5, 132.3, 131.8, 131.4, 131.0, 130.7, 130.1, 129.1, 128.0, 127.6, 127.1, 123.8, 123.1, 122.8, 122.1, 54.7, 32.6, 31.9, 29.4, 27.1, 22.8, 14.2.

MS (EI, 70 eV): *m/z (%)* = 480 (11), 300 (25), 299 (100), 298 (10), 97 (9), 85 (10), 57 (14).

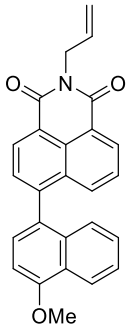
HRMS (EI) calcd. for [$C_{32}H_{39}NO_3$]: 480.2777; found: 480.2773.

UV/Vis ($CHCl_3$): λ_{max} (ε) = 366.4 nm (23700).

Fluorescence ($CHCl_3$, λ_{exc} = 366.4 nm): λ_{max} = 447.4 nm.

Fluorescence quantum yield ($CHCl_3$, λ_{exc} = 366.4 nm, $E_{366.4nm}$ = 0.0732 cm^{-1}, Reference *N,N'*-bis(tridecan-7-yl)perylene-3,4:9,10-tetracarboxylic diimide Φ = 1.00): Φ = 0.54.

2-Allyl-6-(4-methoxynaphthalen-1-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (77)



A *Schlenk*-flask was charged with 2-allyl-6-bromo-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**76**, 205 mg, 0.65 mmol, 1.0 equiv) and 2-(4-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (200 mg, 0.70 mmol, 1.1 equiv). Both compounds were dissolved in toluene (10 mL) under a light argon-stream. K_2CO_3 (1.40 g, 10 mmol) was dissolved in a mixture of water (5 mL) and EtOH (1 mL) and added to the *Schlenk*-flask followed by tetrakis(triphenylphosphine)palladium(0) (37 mg, 0.03 mmol, 5 mol%). The mixture was purged with argon for 30 min and then heated to 80 °C. The reaction mixture was stirred further 17 h at this temperature. After cooling to rt, the organic phase was separated and the aqueous phase was extracted with toluene (3 × 30 mL). Purification by column chromatography (isohexane/$CHCl_3$ = 1:1) gave compound **77** (225 mg, 88 %) as a bright yellow solid.

m.p.: 178 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 1696, 1656, 1580, 1510, 1372, 1328, 1232, 1085, 810, 780,759.

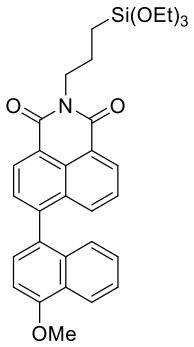
^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 8.71 (d, *J* = 7.4 Hz, 1H), 8.62 (dd, *J* = 7.2, 1.1 Hz, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 7.84 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.58-7.54 (m, 1H), 7.53-7.48 (m, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.37-7.32 (m, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.10-6.00 (m, 1H), 5.37 (dd, *J* = 17.2, 1.4 Hz), 5.24 (dd, *J* = 10.2, 1.3 Hz, 2H), 4.87 (d, *J* = 5.7 Hz, 2H), 4.11 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 164.2, 164.1, 156.2, 146.1, 133.4, 133.3, 132.4, 131.8, 131.5, 131.1, 129.4, 128.6, 128.6, 128.2, 127.2, 126.9, 125.7, 125.7, 122.9, 122.5, 122.0, 117.7, 103.4, 55.9, 42.6.

MS (EI, 70 eV): *m/z (%)* = 394 (26), 293 (100), 381 (19), 380 (69), 267 (13), 264 (13), 239 (41), 238 (10), 237 (12), 119 (12).

HRMS (EI) calcd. for [$C_{26}H_{19}NO_3$]: 393.1365; found: 393.1359.

6-(4-methoxynaphthalen-1-yl)-2-(3-(triethoxysilyl)propyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (78)



2-Allyl-6-(4-methoxynaphthalen-1-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**77**, 145 mg, 0.37 mmol) was dissolved in anhydrous DCM (10 mL) under argon. Then, a solution of triethoxysilane (0.34 mL, 1.85 mmol, 5.0 equiv) and *Karstedt's* catalyst (4 mg, 0.011 mmol, 3 mol%, ~2% Pt in xylene: 212 mg, 0.25 mL) in dry DCM (1 mL) was added slowly. The reaction mixture was stirred for 12 h, then purified by flash column chromatography (Florisil 60-100 mesh, $CHCl_3$/EtOH = 80:1) to give the title compound (138 mg, 67%) as a yellow solid.

m. p.: 129-131 °C.

IR (Diamond-ATR, neat): $\tilde{\nu}$/ cm^{-1} = 2971, 2924, 1702, 1663, 1588, 1509, 1460, 1439, 1380, 1349, 1287, 1241, 1164, 1075, 1014, 956, 820, 784, 767, 756.

^{1}H-NMR (600 MHz, $CDCl_3$): δ/ ppm = 8.69 (d, *J* = 7.4 Hz, 1H), 8.60 (dd, *J* = 7.2, 1.0 Hz, 1H), 8.40 (d, *J* = 8.4 Hz, 1H), 7.82 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.76 (d, *J* = 7.4 Hz, 1H), 7.56-7.52 (m, 1H), 7.52-7.47 (m, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.36-7.32 (m, 1H), 7.25 (d, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 4.26-4.20 (m, 2H), 4.11 (s, 3H), 3.84 (q, *J* = 7.0 Hz, 6H), 1.94-1.86 (m, 2H), 1.23 (t, *J* = 7.0 Hz, 9H), 0.82-0.77 (m, 2H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ/ ppm = 164.4, 164.3, 156.1, 145.9, 133.3, 133.2, 131.8, 131.3, 130.9, 129.4, 128.7, 128.6, 128.2, 127.2, 126.8, 125.8, 125.7, 123.1, 122.5, 122.2, 103.4, 60.5, 58.6, 55.9, 43.1, 29.9, 21.7, 18.5, 14.4, 8.2.

MS (EI, 70 eV): *m/z (%)* = 557 (50), 512 (32), 470 (26), 431 (15), 395 (30), 366 (11), 359 (45), 358 (100), 355 (11), 276 (11), 241 (21), 163 (36).

HRMS (EI) calcd. for [$C_{32}H_{35}NO_6Si$]: 557.2234; found 557.2220.

General procedure for grafting silica with 78:

HDK T40 silica nanoparticles were heated under medium vacuum at 80 °C for 1 h to remove any water attached to the surface, then the particles (100 mg) were put in dry $CHCl_3$ (8 mL) with stirring for 16 h reaching fine dipersion. The resulting suspension was treated with dissolved **78** (20 mg, 36 μmol in 1 mL dry $CHCl_3$), then typically allowed to react for 5 h at 50 °C and separated 3-4 times by centrifugation (15 min at 19000 rpm) until the supernatant is completely clear. The grafted nanoparticles can be applied in the final solvent by redispersion (5 days).

D. APPENDIX

1. X-RAY DATA

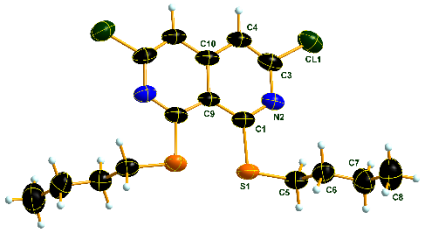
Single Crystal X-Ray Diffraction Studies

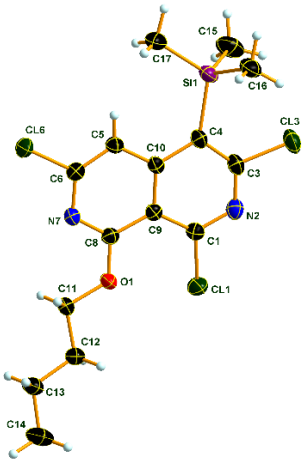
Single crystals, suitable for X-ray diffraction, were obtained by slow evaporation of DCM or $CHCl_3$ solutions. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 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;[178] CrysAlis RED software[179] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method[180] was applied. The structures were solved with SHELXS-97,[181] refined with SHELXL-97[182] and finally checked using PLATON.[183] Details for data collection and structure refinement are summarized in Tables below. Supplementary crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif.

[178] CrysAlis CCD, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).
[179] CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34)
[180] SCALE3 ABSPACK – An Oxford Diffraction Program (1.0.4, gui:1.0.3) (C), Oxford Diffraction, Ltd., 2005.
[181] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[182] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[183] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 12: Details for X-ray data collection and structure refinement for compounds **9c** and **11d**.





	9c	**11d**
Empirical formula	$C_{16}H_{20}Cl_2N_2S_2$	$C_{15}H_{19}Cl_3N_2OSi$
Formula mass	375.36	377.76
T[K]	253(2)	173(2)
Crystal size [mm]	0.45 × 0.12 × 0.03	0.41 × 0.08 × 0.03
Crystal description	colorless platelet	colorless platelet
Crystal system	monoclinic	monoclinic
Space group	*C*2/*c*	*P*21/*c*
a [Å]	24.1939(15)	9.2449(8)
b [Å]	8.5126(4)	26.6605(18)
c [Å]	9.0802(7)	7.1883(6)
α [°]	90	90
β [°]	99.150(7)	92.108(8)
γ [°]	90	90
V [Å^3]	1846.3(2)	1770.5(2)
Z	4	4
$\rho_{calcd.}$ [g cm^{-3}]	1.350	1.417
μ [mm^{-1}]	0.575	0.587
F(000)	784	784
Θ range [°]	4.39 – 26.37	4.17 – 26.37
Index ranges	$-24 \leq h \leq 30$	$-11 \leq h \leq 11$
	$-10 \leq k \leq 10$	$-28 \leq k \leq 33$
	$-11 \leq l \leq 11$	$-8 \leq l \leq 8$
Reflns. collected	5984	12200
Reflns. obsd.	1187	2358

Reflns. unique	1881 (R_{int} = 0.0461)	3596 (R_{int} = 0.0628)
R_1, wR_2 (2σ data)	0.0503, 0.0992	0.0594, 0.1307
R_1, wR_2 (all data)	0.0922, 0.1140	0.0995, 0.1467
GOOF on F^2	1.026	0.993
Peak/hole [e Å^{-3}]	0.327 / -0.259	0.672 / -0.269

Table 13: Selected bond lengths (Å) of compound **9c**.

Cl1—C3	1.729(3)	C5—C6	1.512(4)
S1—C1	1.758(2)	C6—C7	1.505(4)
S1—C5	1.807(3)	C7—C8	1.509(5)
C4—C3	1.344(4)	N2—C3	1.345(3)
C4—C10	1.400(3)	C9—C10	1.430(4)
C1—N2	1.325(3)	C9—C1^{i}	1.434(3)
C1—C9	1.434(3)	C10—C4^{i}	1.400(3)

(i) -x, y, 0.5-z.

Table 14: Selected bond angles (°) of compound **9c**.

C1—S1—C5	102.3(1)	C7—C6—C5	113.2(2)
C3—C4—C10	118.5(2)	C6—C7—C8	113.2(3)
N2—C1—C9	122.8(2)	C10—C9—C1	116.0(2)
N2—C1—S1	115.2(2)	C10—C9—C1^{i}	116.0(2)
C9—C1—S1	121.9(2)	C1—C9—C1^{i}	128.1(3)
C1—N2—C3	118.4(2)	C4^{i}—C10—C4	121.4(3)
C4—C3—N2	124.9(3)	C4^{i}—C10—C9	119.3(2)
C4—C3—Cl1	121.0(2)	C4—C10—C9	119.3(2)
N2—C3—Cl1	114.1(2)	C6—C5—S1	112.9(2)

(i) -x, y, 0.5-z.

Table 15: Selected torsion angles (°) of compound **9c**.

C5—S1—C1—N2	5.9(2)	S1—C1—C9—C1^{i}	7.9(1)
C5—S1—C1—C9	-177.6(2)	C3—C4—C10—C4^{i}	-178.1(3)
C9—C1—N2—C3	-1.9(3)	C3—C4—C10—C9	1.9(3)
S1—C1—N2—C3	174.5(2)	C1—C9—C10—C4^{i}	176.1(2)
C10—C4—C3—N2	0.5(4)	C1—C9—C10—C4^{i}	-3.9(2)
C10—C4—C3—Cl1	179.5(2)	C1—C9—C10—C4	-4.0(2)
C1—N2—C3—C4	-0.5(4)	C1—C9—C10—C4	176.1(2)
C1—N2—C3—Cl1	-179.6(2)	C1—S1—C5—C6	83.7(2)
N2—C1—C9—C10	4.1(3)	S1—C5—C6—C7	177.8(2)
S1—C1—C9—C10	-172.1(1)	C5—C6—C7—C8	-179.7(3)
N2—C1—C9—C1^{i}	-175.9(3)		

Table 16: Selected bond lengths (Å) of compound **11d**.

Cl6—C6	1.731(4)	C11—C12	1.488(5)
Cl1—C1	1.728(3)	C12—C13	1.515(5)
Cl3—C3	1.745(3)	C13—C14	1.501(5)
Si1—C17	1.848(4)	N2—C1	1.303(4)
Si1—C16	1.855(4)	N2—C3	1.353(4)
Si1—C15	1.862(4)	C8—C9	1.435(4)
Si1—C4	1.927(4)	C9—C1	1.413(5)
O1—C8	1.335(4)	C9—C10	1.428(4)
O1—C11	1.441(4)	C10—C5	1.417(5)
N7—C8	1.308(4)	C10—C4	1.437(4)
N7—C6	1.346(4)	C4—C3	1.372(5)
C6—C5	1.344(4)		

Table 17: Selected bond angles (°) of compound **11d**.

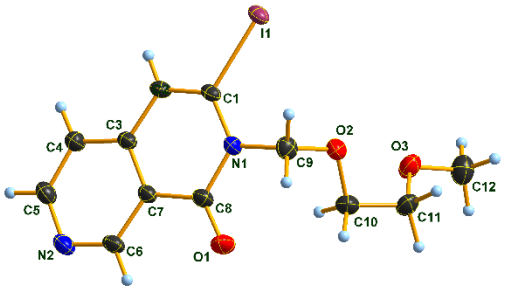
C17—Si1—C16	105.1(2)	O1—C11—C12	107.9(3)
C17—Si1—C15	106.5(2)	C11—C12—C13	112.1(3)
C16—Si1—C15	113.4(2)	C14—C13—C12	114.1(4)
C17—Si1—C4	115.9(2)	C9—C10—C4	120.7(3)
C16—Si1—C4	109.2(2)	C3—C4—C10	113.7(3)
C15—Si1—C4	106.9(2)	C3—C4—Si1	118.8(2)
C8—O1—C11	118.1(3)	C10—C4—Si1	127.5(3)
C8—N7—C6	116.5(3)	N2—C3—C4	127.5(3)
C1—N2—C3	117.3(3)	N2—C3—Cl3	110.7(3)
N7—C8—O1	118.3(3)	C4—C3—Cl3	121.8(3)
N7—C8—C9	124.2(3)	N2—C1—C9	124.2(3)
O1—C8—C9	117.5(3)	N2—C1—Cl1	112.8(3)
C1—C9—C10	116.3(3)	C9—C1—Cl1	122.9(3)
C1—C9—C8	126.5(3)	C5—C6—N7	126.3(3)
C10—C9—C8	117.2(3)	C5—C6—Cl6	119.7(3)
C5—C10—C9	116.9(3)	N7—C6—Cl6	114.1(3)
C5—C10—C4	122.3(3)	C6—C5—C10	118.9(3)

Table 18: Selected torsion angles (°) of compound **11d**.

C6—N7—C8—O1	177.8(3)	C1—N2—C3—C4	-2.9(5)
C6—N7—C8—C9	-1.1(5)	C1—N2—C3—Cl3	177.9(2)
C11—O1—C8—N7	-3.4(4)	C10—C4—C3—N2	4.9(5)
C11—O1—C8—C9	175.6(3)	Si1—C4—C3—N2	-173.5(3)
N7—C8—C9—C1	-178.6(3)	C10—C4—C3—Cl3	-176.0(2)
O1—C8—C9—C1	2.5(5)	Si1—C4—C3—Cl3	5.6(4)
N7—C8—C9—C10	2.8(5)	C3—N2—C1—C9	-1.4(5)
O1—C8—C9—C10	-176.0(3)	C3—N2—C1—Cl1	175.5(2)
C1—C9—C10—C5	178.9(3)	C10—C9—C1—N2	3.1(5)
C8—C9—C10—C5	-2.4(4)	C8—C9—C1—N2	-175.5(3)

C1—C9—C10—C4	-0.7(5)	C10—C9—C1—Cl1	-173.6(2)
C8—C9—C10—C4	178.0(3)	C8—C9—C1—Cl1	7.9(5)
C5—C10—C4—C3	177.6(3)	C8—N7—C6—C5	-1.1(5)
C9—C10—C4—C3	-2.8(4)	C8—N7—C6—Cl6	178.7(2)
C5—C10—C4—Si1	-4.1(5)	N7—C6—C5—C10	1.4(6)
C9—C10—C4—Si1	175.5(2)	Cl6—C6—C5—C10	-178.5(2)
C17—Si1—C4—C3	175.0(3)	C9—C10—C5—C6	0.5(5)
C16—Si1—C4—C3	-66.5(3)	C4—C10—C5—C6	-179.9(3)
C15—Si1—C4—C3	56.5(3)	C8—O1—C11—C12	-173.0(3)
C17—Si1—C4—C10	-3.2(4)	O1—C11—C12—C13	178.3(3)
C16—Si1—C4—C10	115.3(3)	C11—C12—C13—C14	178.4(4)
C15—Si1—C4—C10	-121.7(3)		

Table 19: Details for X-ray data collection and structure refinement for compound **15**.



	15
Empirical formula	$C_{12}H_{13}IN_2O_3$
Formula mass	360.14
T[K]	100(2)
Crystal size [mm]	0.42 × 0.17 × 0.11
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*-1
a [Å]	8.5985(2)
b [Å]	8.9813(2)
c [Å]	10.1508(2)
α [°]	113.998(2)
β [°]	91.780(2)
γ [°]	111.582(2)
V [Å^3]	650.70(3)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.838

μ [mm^{-1}]	2.463
F(000)	352
Θ range [°]	4.15 – 30.50
Index ranges	$-12 \leq h \leq 12$
	$-12 \leq k \leq 12$
	$-14 \leq l \leq 14$
Reflns. collected	12980
Reflns. obsd.	3629
Reflns. unique	3946 (R_{int} = 0.0320)
R_1, wR_2 (2σ data)	0.0214, 0.0480
R_1, wR_2 (all data)	0.0253, 0.0499
GOOF on F^2	1.041
Peak/hole [e Å^{-3}]	0.526 / -0.759

Table 20: Selected bond lengths (Å) of compound **15**.

I1 – C1	2.114(2)	N2 – C5	1.356(3)
C1 – C2	1.339(2)	C11 – C10	1.501(3)
C1 – N1	1.394(2)	C4 – C5	1.370(3)
O2 – C9	1.402(2)	C7 – C3	1.403(2)
O2 – C10	1.435(2)	C7 – C8	1.460(3)
N1 – C8	1.405(2)	C3 – C4	1.403(3)
N1 – C9	1.468(2)	C3 – C2	1.426(2)
O3 – C12	1.411(3)	O1 – C8	1.228(2)
O3 – C11	1.413(3)	N2 – C6	1.324(3)
C7 – C6	1.402(3)		

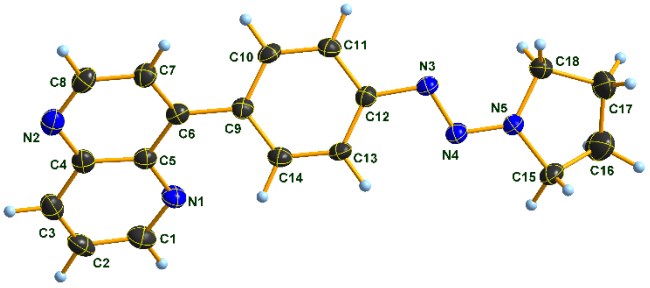
Table 21: Selected bond angles (°) of compound **15**.

C2 – C1 – N1	122.6(2)	C5 – C4 – C3	119.3(2)
C2 – C1 – I1	117.0(1)	O1 – C8 – N1	120.7(2)
N1 – C1 – I1	120.4(1)	O1 – C8 – C7	123.6(2)
C9 – O2 – C10	114.1(2)	N1 – C8 – C7	115.7(2)
C1 – N1 – C8	121.5(2)	O2 – C9 – N1	113.6(2)
C1 – N1 – C9	121.5(2)	N2 – C5 – C4	123.9(2)
C8 – N1 – C9	116.9(2)	O2 – C10 – C11	109.0(2)
C12 – O3 – C11	113.1(2)	C4 – C3 – C2	124.0(2)
C6 – C7 – C3	118.8(2)	C6 – N2 – C5	117.0(2)
C6 – C7 – C8	119.8(2)	O3 – C11 – C10	109.6(2)
C3 – C7 – C8	121.4(2)	N2 – C6 – C7	123.7(2)
C7 – C3 – C4	117.2(2)	C1 – C2 – C3	119.9(2)
C7 – C3 – C2	118.8(2)		

Table 22: Selected torsion angles (°) of compound **15**.

C2 – C1 – N1 – C8	-0.5(3)	C2 – C3 – C4 – C5	-179.5(2)
I1 – C1 – N1 – C8	-178.4(1)	C1 – N1 – C8 – O1	178.9(2)
C2 – C1 – N1 – C9	-177.3(2)	C9 – N1 – C8 – O1	-4.2(3)
I1 – C1 – N1 – C9	4.9(2)	C1 – N1 – C8 – C7	-0.7(2)
C6 – C7 – C3 – C4	-3.0(3)	C9 – N1 – C8 – C7	176.2(2)
C8 – C7 – C3 – C4	176.1(2)	C6 – C7 – C8 – O1	1.8(3)
C6 – C7 – C3 – C2	178.2(2)	C3 – C7 – C8 – O1	-177.3(2)
C8 – C7 – C3 – C2	-2.7(3)	C6 – C7 – C8 – N1	-178.6(2)
C12 – O3 – C11 – C10	-171.8(2)	C3 – C7 – C8 – N1	2.4(3)
C5 – N2 – C6 – C7	0.6(3)	C10 – O2 – C9 – N1	-76.2(2)
C3 – C7 – C6 – N2	1.8(3)	C1 – N1 – C9 – O2	-83.2(2)
C8 – C7 – C6 – N2	-177.2(2)	C8 – N1 – C9 – O2	99.9(2)
N1 – C1 – C2 – C3	0.2(3)	C6 – N2 – C5 – C4	-1.9(3)
I1 – C1 – C2 – C3	178.1(1)	C3 – C4 – C5 – N2	0.6(3)
C7 – C3 – C2 – C1	1.4(3)	C9 – O2 – C10 – C11	-167.4(2)
C4 – C3 – C2 – C1	-177.3(2)	O3 – C11 – C10 – O2	-69.2(2)
C7 – C3 – C4 – C5	1.8(3)		

Table 23: Details for X-ray data collection and structure refinement for compound **42j**.



	42j
Empirical formula	$C_{18}H_{17}N_5$
Formula mass	303.36
T[K]	123(2)
Crystal size [mm]	0.15 × 0.03 × 0.03
Crystal description	pale yellow needle
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	11.7463(8)
b [Å]	11.2886(6)
c [Å]	11.8659(7)
α [°]	90.0
β [°]	104.554(6)

γ [°]	90.0
V [Å^3]	1522.92(16)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.323
μ [mm^{-1}]	0.083
F(000)	640
Θ range [°]	4.22 – 25.24
Index ranges	$-14 \leq h \leq 14$
	$-13 \leq k \leq 13$
	$-13 \leq l \leq 14$
Reflns. collected	10831
Reflns. obsd.	1975
Reflns. unique	2986 (R_{int} = 0.0586)
R_1, wR_2 (2σ data)	0.0567, 0.1160
R_1, wR_2 (all data)	0.0947, 0.1362
GOOF on F^2	1.010
Peak/hole [e Å^{-3}]	0.585 / -0.274

Table 24: Selected bond lengths (Å) of compound **42j**.

N5 – N4	1.316(2)	C7 – C8	1.403(3)
N5 – C15	1.455(3)	C5 – N1	1.370(3)
N5 – C18	1.462(3)	C9 – C10	1.402(3)
C12 – C11	1.397(3)	C1 – N1	1.321(3)
C12 – C13	1.397(3)	C1 – C2	1.399(4)
C12 – N3	1.420(3)	C18 – C17	1.526(3)
N3 – N4	1.282(2)	C15 – C16	1.527(4)
C6 – C7	1.373(3)	C17 – C16	1.489(4)
C6 – C5	1.427(3)	C3 – C4	1.408(3)
C6 – C9	1.484(3)	N2 – C8	1.316(3)
C13 – C14	1.381(3)	N2 – C4	1.371(3)
C14 – C9	1.399(3)	C11 – C10	1.372(3)
C3 – C2	1.362(4)	C4 – C5	1.417(3)

Table 25: Selected bond angles (°) of compound **42j**.

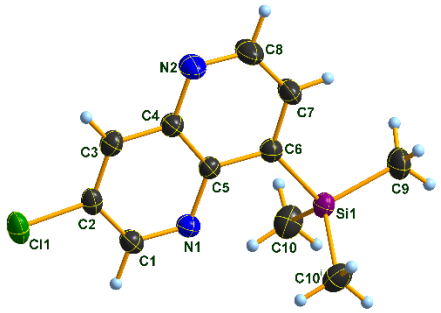
N4 – N5 – C15	119.9(2)	C14 – C9 – C6	122.0(2)
N4 – N5 – C18	125.2(2)	C10 – C9 – C6	120.7(2)
C15 – N5 – C18	114.0(2)	C11 – C10 – C9	121.5(2)
C11 – C12 – C13	118.4(2)	N1 – C1 – C2	124.9(3)
C11 – C12 – N3	116.4(2)	N5 – C18 – C17	102.0(2)
C13 – C12 – N3	125.2(2)	C1 – N1 – C5	117.4(2)

N4 – N3 – C12	111.9(2)	C3 – C2 – C1	118.2(2)
N3 – N4 – N5	113.2(2)	N5 – C15 – C16	101.5(2)
C7 – C6 – C5	116.2(2)	C16 – C17 – C18	105.6(2)
C7 – C6 – C9	120.9(2)	C17 – C16 – C15	104.1(2)
C5 – C6 – C9	122.9(2)	C3 – C4 – C5	118.2(2)
C14 – C13 – C12	120.4(2)	C6 – C7 – C8	121.2(2)
C13 – C14 – C9	121.6(2)	N2 – C8 – C7	124.3(2)
C2 – C3 – C4	119.6(2)	N1 – C5 – C4	121.5(2)
C8 – N2 – C4	116.2(2)	N1 – C5 – C6	119.7(2)
C10 – C11 – C12	120.8(2)	C4 – C5 – C6	118.7(2)
N2 – C4 – C3	118.4(2)	C14 – C9 – C10	117.3(2)
N2 – C4 – C5	123.3(2)		

Table 26: Selected torsion angles (°) of compound **42j**.

C11 – C12 – N3 – N4	-173.5(2)	C7 – C6 – C5 – C4	-2.2(3)
C13 – C12 – N3 – N4	5.4(3)	C9 – C6 – C5 – C4	178.0(2)
C12 – N3 – N4 – N5	178.4(2)	C13 – C14 – C9 – C10	-1.4(3)
C15 – N5 – N4 – N3	-175.4(2)	C13 – C14 – C9 – C6	179.6(2)
C18 – N5 – N4 – N3	-6.9(3)	C7 – C6 – C9 – C14	139.6(2)
C11 – C12 – C13 – C14	2.3(3)	C5 – C6 – C9 – C14	-40.5(3)
N3 – C12 – C13 – C14	-176.5(2)	C7 – C6 – C9 – C10	-39.3(3)
C12 – C13 – C14 – C9	-0.7(4)	C5 – C6 – C9 – C10	140.5(2)
C13 – C12 – C11 – C10	-1.8(3)	C12 – C11 – C10 – C9	-0.3(4)
N3 – C12 – C11 – C10	177.1(2)	C14 – C9 – C10 – C11	1.9(3)
C8 – N2 – C4 – C3	179.8(2)	C6 – C9 – C10 – C11	-179.0(2)
C8 – N2 – C4 – C5	0.3(3)	N4 – N5 – C18 – C17	-172.5(2)
C2 – C3 – C4 – N2	176.9(2)	C15 – N5 – C18 – C17	-3.4(3)
C2 – C3 – C4 – C5	-3.5(4)	C2 – C1 – N1 – C5	-1.4(4)
C5 – C6 – C7 – C8	0.4(3)	C4 – C5 – N1 – C1	-1.9(3)
C9 – C6 – C7 – C8	-179.7(2)	C6 – C5 – N1 – C1	-180.0(2)
C4 – N2 – C8 – C7	-2.3(4)	C4 – C3 – C2 – C1	0.6(4)
C6 – C7 – C8 – N2	2.0(4)	N1 – C1 – C2 – C3	2.0(4)
N2 – C4 – C5 – N1	-176.2(2)	N4 – N5 – C15 – C16	151.7(2)
C3 – C4 – C5 – N1	4.3(3)	C18 – N5 – C15 – C16	-18.0(3)
N2 – C4 – C5 – C6	1.9(3)	N5 – C18 – C17 – C16	24.4(3)
C3 – C4 – C5 – C6	-177.6(2)	C18 – C17 – C16 – C15	-36.0(3)
C7 – C6 – C5 – N1	176.0(2)	N5 – C15 – C16 – C17	32.4(3)
C9 – C6 – C5 – N1	-3.9(3)		

Table 27: Details for X-ray data collection and structure refinement for compound **45a**.



	45a
Empirical formula	$C_{11}H_{13}ClN_2Si$
Formula mass	236.77
T[K]	173(2)
Crystal size [mm]	0.47 × 0.19 × 0.08
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*21/*m*
a [Å]	8.7215(4)
b [Å]	7.0286(4)
c [Å]	10.0617(4)
α [°]	90.0
β [°]	101.810(4)
γ [°]	90.0
V [Å^3]	603.73(5)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.302
μ [mm^{-1}]	0.385
F(000)	248
Θ range [°]	4.14 – 25.24
Index ranges	$-12 \leq h \leq 12$
	$-10 \leq k \leq 10$
	$-14 \leq l \leq 14$
Reflns. collected	11994
Reflns. obsd.	1602
Reflns. unique	1954 (R_{int} = 0.0366)
R_1, wR_2 (2σ data)	0.0357, 0.0866

R_1, wR_2 (all data)	0.0468, 0.0939
GOOF on F^2	1.039
Peak/hole [e Å^{-3}]	0.296 / -0.265

Table 28: Selected bond lengths (Å) of compound **45a**.

Cl1 – C2	1.732(2)	C3 – C4	1.410(2)
Si1 – C10^{i}	1.854(1)	C4 – N2	1.369(2)
Si1 – C10	1.854(1)	C7 – C8	1.413(3)
Si1 – C9	1.862(2)	N2 – C8	1.310(3)
Si1 – C6	1.896(2)	C2 – C1	1.412(3)
N1 – C1	1.314(2)	C5 – C4	1.419(2)
N1 – C5	1.367(2)	C5 – C6	1.423(2)
C2 – C3	1.356(2)	C6 – C7	1.371(2)

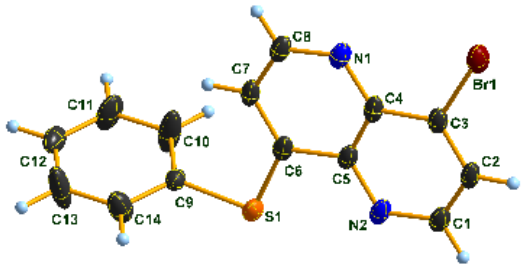
Table 29: Selected bond angles (°) of compound **45a**.

C10^{i} – Si1 – C10	112.1(1)	N2 – C4 – C3	118.7(2)
C10^{i} – Si1 – C9	109.3(1)	N2 – C4 – C5	122.8(2)
C10 – Si1 – C9	109.3(1)	C3 – C4 – C5	118.5(2)
C10^{i} – Si1 – C6	109.4(1)	C6 – C7 – C8	121.1(2)
C10 – Si1 – C6	109.4(1)	C8 – N2 – C4	116.3(2)
C9 – Si1 – C6	107.3(1)	N2 – C8 – C7	124.6(2)
C1 – N1 – C5	118.3(2)	C4 – C5 – C6	119.7(2)
C3 – C2 – C1	120.7(2)	C7 – C6 – C5	115.6(2)
C3 – C2 – Cl1	121.0(1)	C7 – C6 – Si1	122.4(1)
C1 – C2 – Cl1	118.3(1)	C5 – C6 – Si1	122.0(1)
N1 – C5 – C4	121.9(2)	N1 – C1 – C2	122.7(2)
N1 – C5 – C6	118.5(1)	C2 – C3 – C4	118.0(2)

Table 30: Selected torsion angles (°) of compound **45a**.

C1 – N1 – C5 – C4	0.0 (1)	C1 – C2 – C3 – C4	0.0 (1)
C1 – N1 – C5 – C6	180.0(1)	Cl1 – C2 – C3 – C4	180.0(1)
N1 – C5 – C6 – C7	180.0 (1)	C2 – C3 – C4 – N2	180.0(1)
C4 – C5 – C6 – C7	0.0(1)	C2 – C3 – C4 – C5	0.0(1)
N1 – C5 – C6 – Si1	0.0(1)	N1 – C5 – C4 – N2	180.0(1)
C4 – C5 – C6 – Si1	180.0(1)	C6 – C5 – C4 – N2	0.0(1)
C10 – Si1 – C6 – C7	118.4(1)	N1 – C5 – C4 – C3	0.0 (1)
C10 – Si1 – C6 – C7	-118.4(1)	C6 – C5 – C4 – C3	180.0 (1)
C9 – Si1 – C6 – C7	0.0(1)	C5 – C6 – C7 – C8	0.0 (1)
C10 – Si1 – C6 – C5	-61.6(1)	Si1 – C6 – C7 – C8	180.0 (1)
C10 – Si1 – C6 – C5	61.6(1)	C3 – C4 – N2 – C8	180.0 (1)
C9 – Si1 – C6 – C5	180.0(1)	C5 – C4 – N2 – C8	0.0(1)
C5 – N1 – C1 – C2	0.0(1)	C4 – N2 – C8 – C7	0.0(1)
C3 – C2 – C1 – N1	0.0(1)	C6 – C7 – C8 – N2	0.0(1)
Cl1 – C2 – C1 – N1	180.0(1)		

Table 31: Details for X-ray data collection and structure refinement for compound **52a**.



	52a
Empirical formula	$C_{14}H_9BrN_2S$
Formula mass	317.20
T[K]	123(2)
Crystal size [mm]	0.40 × 0.10 × 0.05
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*1
a [Å]	4.4749(2)
b [Å]	5.3850(2)
c [Å]	12.9818(5)
α [°]	100.622(4)
β [°]	93.295(4)
γ [°]	95.666(4)
V [Å^3]	305.05(2)
Z	1
$\rho_{calcd.}$ [g cm^{-3}]	1.727
μ [mm^{-1}]	3.520
F(000)	158
Θ range [°]	4.47 – 25.24
Index ranges	$-6 \leq h \leq 6$
	$-7 \leq k \leq 7$
	$-18 \leq l \leq 18$
Reflns. collected	5948
Reflns. obsd.	3506
Reflns. unique	3725 (R_{int} = 0.0307)
R_1, wR_2 (2σ data)	0.0362, 0.0784
R_1, wR_2 (all data)	0.0404, 0.0826

GOOF on F^2	1.074
Peak/hole [e Å^{-3}]	0.459 / -0.803

Table 32: Selected bond lengths (Å) of compound **52a**.

Br1 – C3	1.885(5)	C4 – C5	1.421(6)
C1 – N2	1.325(6)	C9 – C14	1.357(8)
C1 – C2	1.401(7)	C9 – C10	1.388(8)
S1 – C6	1.757(7)	C11 – C12	1.349(8)
S1 – C9	1.780(6)	C11 – C10	1.376(8)
N1 – C8	1.329(6)	C14 – C13	1.381(8)
N1 – C4	1.356(6)	C13 – C12	1.370(9)
N2 – C5	1.365(6)	C6 – C5	1.430(7)
C2 – C3	1.365(7)	C3 – C4	1.420(7)
C6 – C7	1.378(8)	C8 – C7	1.404(7)

Table 33: Selected bond angles (°) of compound **52a**.

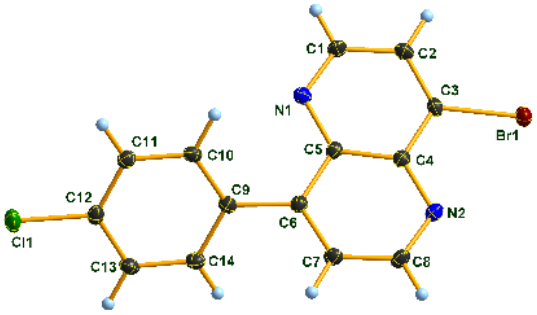
N2 – C1 – C2	123.8(5)	N2 – C5 – C4	124.4(4)
C6 – S1 – C9	102.7(3)	N2 – C5 – C6	117.7(5)
C8 – N1 – C4	116.6(4)	C4 – C5 – C6	117.9(4)
C1 – N2 – C5	116.8(4)	C14 – C9 – C10	118.4(6)
C3 – C2 – C1	119.3(4)	C14 – C9 – S1	120.2(5)
C7 – C6 – C5	117.5(6)	C10 – C9 – S1	121.2(5)
C7 – C6 – S1	126.6(5)	C12 – C11 – C10	121.2(6)
C5 – C6 – S1	115.9(5)	C11 – C10 – C9	120.3(6)
C2 – C3 – C4	120.2(5)	C9 – C14 – C13	120.4(6)
C2 – C3 – Br1	120.5(4)	C12 – C13 – C14	121.2(5)
C4 – C3 – Br1	119.3(4)	C11 – C12 – C13	118.5(5)
N1 – C8 – C7	124.5(4)	C3 – C4 – C5	115.5(4)
N1 – C4 – C3	120.9(4)	C6 – C7 – C8	119.8(4)
N1 – C4 – C5	123.7(4)		

Table 34: Selected torsion angles (°) of compound **52a**.

C2 – C1 – N2 – C5	-0.4(7)	N1 – C4 – C5 – N2	-178.9(5)
N2 – C1 – C2 – C3	-0.1(7)	C3 – C4 – C5 – N2	0.6(6)
C9 – S1 – C6 – C7	3.3(7)	N1 – C4 – C5 – C6	-0.4(6)
C9 – S1 – C6 – C5	-175.8(3)	C3 – C4 – C5 – C6	179.2(5)
C1 – C2 – C3 – C4	0.9(7)	C7 – C6 – C5 – N2	-179.3(4)
C1 – C2 – C3 – Br1	-178.4(3)	S1 – C6 – C5 – N2	-0.1(6)
C4 – N1 – C8 – C7	0.6(7)	C7 – C6 – C5 – C4	2.0(7)
C8 – N1 – C4 – C3	179.6(4)	S1 – C6 – C5 – C4	-178.8(3)
C8 – N1 – C4 – C5	-0.9(6)	C6 – S1 – C9 – C14	-108.7(5)
C2 – C3 – C4 – N1	178.4(5)	C6 – S1 – C9 – C10	76.5(7)
Br1 – C3 – C4 – N1	-2.2(6)	C12 – C11 – C10 – C9	0.0(13)
C2 – C3 – C4 – C5	-1.1(6)	C14 – C9 – C10 – C11	-0.5(12)

Br1 – C3 – C4 – C5	178.2(3)	S1 – C9 – C10 – C11	174.4(7)
C5 – C6 – C7 – C8	-2.4(8)	C10 – C9 – C14 – C13	1.1(11)
S1 – C6 – C7 – C8	178.5(4)	S1 – C9 – C14 – C13	-173.9(6)
N1 – C8 – C7 – C6	1.1(8)	C9 – C14 – C13 – C12	-1.1(12)
C1 – N2 – C5 – C4	0.2(6)	C10 – C11 – C12 – C13	0.1(12)
C1 – N2 – C5 – C6	-178.4(5)	C14 – C13 – C12 – C11	0.5(12)

Table 35: Details for X-ray data collection and structure refinement for compound **52c**.



	52c
Empirical formula	$C_{14}H_8BrClN_2$
Formula mass	319.58
T[K]	123(2)
Crystal size [mm]	0.20 × 0.10 × 0.04
Crystal description	colorless block
Crystal system	orthorhombic
Space group	*Pca*21
a [Å]	27.5991(11)
b [Å]	3.8124(2)
c [Å]	11.2078(5)
α [°]	90.0
β [°]	90.0
γ [°]	90.0
V [Å^3]	1179.27(9)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.800
μ [mm^{-1}]	3.691
F(000)	632
Θ range [°]	4.43 – 25.24
Index ranges	-38 ≤ *h* ≤ 38

	$-5 \leq k \leq 5$
	$-11 \leq l \leq 15$
Reflns. collected	10713
Reflns. obsd.	2662
Reflns. unique	2791 (R_{int} = 0.0317)
R_1, wR_2 (2σ data)	0.0233, 0.0497
R_1, wR_2 (all data)	0.0254, 0.0507
GOOF on F^2	1.054
Peak/hole [e Å^{-3}]	0.294 / -0.255

Table 36: Selected bond lengths (Å) of compound **52c**.

Br1 – C3	1.885(2)	C9 – C10	1.384(4)
Cl1 – C12	1.743(3)	C9 – C14	1.399(4)
C5 – N1	1.362(4)	C2 – C3	1.364(4)
C5 – C4	1.427(3)	C2 – C1	1.415(4)
C5 – C6	1.435(4)	C11 – C10	1.393(3)
C7 – C6	1.368(4)	C13 – C14	1.387(3)
C7 – C8	1.405(4)	C3 – C4	1.417(4)
C6 – C9	1.491(4)	N2 – C8	1.315(4)
C12 – C13	1.384(4)	N2 – C4	1.359(3)
C12 – C11	1.384(4)	N1 – C1	1.323(3)

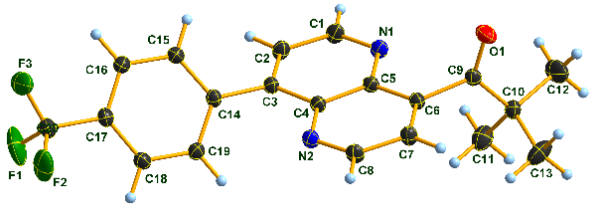
Table 37: Selected bond angles (°) of compound **52c**.

N1 – C5 – C4	123.2(2)	C12 – C11 – C10	119.3(3)
N1 – C5 – C6	119.8(2)	C9 – C10 – C11	120.4(2)
C4 – C5 – C6	116.9(3)	C12 – C13 – C14	118.1(3)
C6 – C7 – C8	120.8(3)	C2 – C3 – C4	120.9(2)
C7 – C6 – C5	117.4(2)	C2 – C3 – Br1	120.2(2)
C7 – C6 – C9	119.7(2)	C4 – C3 – Br1	118.9(2)
C5 – C6 – C9	122.9(2)	N2 – C8 – C7	124.0(3)
C13 – C12 – C11	121.8(3)	C13 – C14 – C9	121.5(3)
C13 – C12 – Cl1	119.3(2)	N2 – C4 – C3	119.7(2)
C11 – C12 – Cl1	118.9(2)	N2 – C4 – C5	124.0(2)
C8 – N2 – C4	116.7(2)	C3 – C4 – C5	116.3(2)
C1 – N1 – C5	117.2(2)	C14 – C9 – C6	117.9(2)
C10 – C9 – C14	119.0(2)	C3 – C2 – C1	117.6(3)
C10 – C9 – C6	123.0(2)	N1 – C1 – C2	124.7(3)

Table 38: Selected torsion angles (°) of compound **52c**.

C8 – C7 – C6 – C5	-2.1(4)	C11 – C12 – C13 – C14	0.3(4)
C8 – C7 – C6 – C9	176.5(2)	Cl1 – C12 – C13 – C14	-179.0(2)
N1 – C5 – C6 – C7	-177.5(2)	C1 – C2 – C3 – C4	-1.6(4)
C4 – C5 – C6 – C7	4.3(3)	C1 – C2 – C3 – Br1	177.2(2)
N1 – C5 – C6 – C9	4.0(4)	C4 – N2 – C8 – C7	2.5(4)
C4 – C5 – C6 – C9	-174.2(2)	C6 – C7 – C8 – N2	-1.5(4)
C4 – C5 – N1 – C1	-0.3(4)	C12 – C13 – C14 – C9	-1.0(4)
C6 – C5 – N1 – C1	-178.3(2)	C10 – C9 – C14 – C13	1.0(4)
C7 – C6 – C9 – C10	131.9(3)	C6 – C9 – C14 – C13	177.4(3)
C5 – C6 – C9 – C10	-49.6(4)	C8 – N2 – C4 – C3	-179.6(2)
C7 – C6 – C9 – C14	-44.4(3)	C8 – N2 – C4 – C5	0.1(4)
C5 – C6 – C9 – C14	134.1(3)	C2 – C3 – C4 – N2	-177.5(2)
C5 – N1 – C1 – C2	1.8(4)	Br1 – C3 – C4 – N2	3.8(3)
C3 – C2 – C1 – N1	-0.9(4)	C2 – C3 – C4 – C5	2.9(4)
C13 – C12 – C11 – C10	0.5(4)	Br1 – C3 – C4 – C5	-175.9(2)
Cl1 – C12 – C11 – C10	179.8(2)	N1 – C5 – C4 – N2	178.4(2)
C14 – C9 – C10 – C11	-0.2(4)	C6 – C5 – C4 – N2	-3.5(4)
C6 – C9 – C10 – C11	-176.4(2)	N1 – C5 – C4 – C3	-2.0(3)
C12 – C11 – C10 – C9	-0.6(4)	C6 – C5 – C4 – C3	176.1(2)

Table 39: Details for X-ray data collection and structure refinement for compound **52e**.



	52e
Empirical formula	$C_{20}H_{17}F_3N_2O$
Formula mass	358.35
T[K]	173(2)
Crystal size [mm]	0.20 × 0.15 × 0.05
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*-1
a [Å]	7.4440(3)
b [Å]	8.4203(4)
c [Å]	14.3590(6)
α [°]	76.844(4)
β [°]	86.589(4)

γ [°]	75.684(4)
V [Å^3]	849.19(7)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.401
μ [mm^{-1}]	0.110
F(000)	372
Θ range [°]	4.25 – 25.24
Index ranges	$-10 \leq h \leq 10$
	$-12 \leq k \leq 12$
	$-20 \leq l \leq 20$
Reflns. collected	16413
Reflns. obsd.	3772
Reflns. unique	5159 (R_{int} = 0.0337)
R_1, wR_2 (2σ data)	0.0496, 0.1185
R_1, wR_2 (all data)	0.0721, 0.1329
GOOF on F^2	1.030
Peak/hole [e Å^{-3}]	0.425 / -0.397

Table 40: Selected bond lengths (Å) of compound **52e**.

N1 – C1	1.316(2)	C6 – C7	1.369(2)
N1 – C5	1.369(2)	C18 – C19	1.387(2)
C5 – C6	1.418(2)	C18 – C17	1.391(2)
C5 – C4	1.419(2)	C17 – C20	1.497(2)
N2 – C8	1.319(2)	F3 – C20	1.331(2)
N2 – C4	1.369(2)	C10 – C11	1.518(2)
F2 – C20	1.325(2)	C10 – C12	1.523(2)
C16 – C17	1.386(2)	C10 – C13	1.535(2)
C16 – C15	1.389(2)	C2 – C3	1.375(2)
O1 – C9	1.209(2)	C2 – C1	1.410(2)
C9 – C6	1.513(2)	C14 – C15	1.396(2)
C9 – C10	1.525(2)	C14 – C19	1.399(2)
C8 – C7	1.413(2)	C14 – C3	1.484(2)
F1 – C20	1.326(2)	C3 – C4	1.429(2)

Table 41: Selected bond angles (°) of compound **52e**.

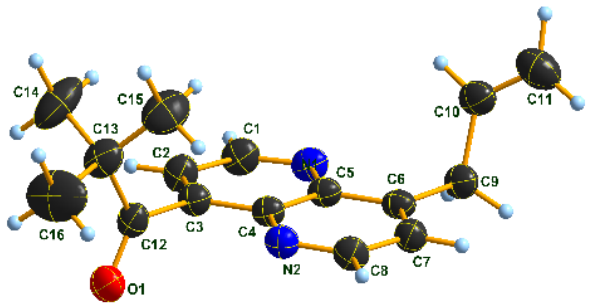
C1 – N1 – C5	116.6(1)	N1 – C1 – C2	124.1(1)
N1 – C5 – C6	118.0(1)	N2 – C4 – C5	122.4(1)
N1 – C5 – C4	123.7(1)	N2 – C4 – C3	119.6(1)
C6 – C5 – C4	118.3(1)	C5 – C4 – C3	118.0(1)
C8 – N2 – C4	117.3(1)	C11 – C10 – C12	110.4(1)
C17 – C16 – C15	119.3(1)	C11 – C10 – C9	111.3(1)
O1 – C9 – C6	118.4(1)	C12 – C10 – C9	109.5(1)
O1 – C9 – C10	122.3(1)	C11 – C10 – C13	109.3(1)
C6 – C9 – C10	119.2(1)	C12 – C10 – C13	109.7(1)
N2 – C8 – C7	124.2(1)	C9 – C10 – C13	106.5(1)
C3 – C2 – C1	120.7(1)	F2 – C20 – F1	105.9(1)
C15 – C14 – C19	118.9(1)	F2 – C20 – F3	106.5(1)
C15 – C14 – C3	118.3(1)	F1 – C20 – F3	105.5(1)
C19 – C14 – C3	122.8(1)	F2 – C20 – C17	113.2(1)
C2 – C3 – C4	117.0(1)	F1 – C20 – C17	112.2(1)
C2 – C3 – C14	120.1(1)	F3 – C20 – C17	113.0(1)
C4 – C3 – C14	122.7(1)	C16 – C17 – C18	120.5(1)
C7 – C6 – C5	118.4(1)	C16 – C17 – C20	120.0(1)
C7 – C6 – C9	121.8(1)	C18 – C17 – C20	119.4(1)
C5 – C6 – C9	119.6(1)	C6 – C7 – C8	119.3(1)
C19 – C18 – C17	119.9(1)	C16 – C15 – C14	121.0(1)
C18 – C19 – C14	120.3(1)		

Table 42: Selected torsion angles (°) of compound **52e**.

C1 – N1 – C5 – C6	-178.3(1)	C17 – C16 – C15 – C14	-0.8(2)
C1 – N1 – C5 – C4	0.1(2)	C19 – C14 – C15 – C16	2.2(2)
C4 – N2 – C8 – C7	-0.1(2)	C3 – C14 – C15 – C16	-177.8(1)
C1 – C2 – C3 – C4	-0.8(2)	C5 – N1 – C1 – C2	0.8(2)
C1 – C2 – C3 – C14	174.0(1)	C3 – C2 – C1 – N1	-0.5(2)
C15 – C14 – C3 – C2	-43.3(2)	C8 – N2 – C4 – C5	0.5(2)
C19 – C14 – C3 – C2	136.8(1)	C8 – N2 – C4 – C3	-177.4(1)
C15 – C14 – C3 – C4	131.3(1)	N1 – C5 – C4 – N2	-179.2(1)
C19 – C14 – C3 – C4	-48.7(2)	C6 – C5 – C4 – N2	-0.8(2)
N1 – C5 – C6 – C7	179.3(1)	N1 – C5 – C4 – C3	-1.4(2)
C4 – C5 – C6 – C7	0.8(2)	C6 – C5 – C4 – C3	177.1(1)
N1 – C5 – C6 – C9	3.2(2)	C2 – C3 – C4 – N2	179.6(1)
C4 – C5 – C6 – C9	-175.3(1)	C14 – C3 – C4 – N2	4.9(2)
O1 – C9 – C6 – C7	-89.1(2)	C2 – C3 – C4 – C5	1.7(2)
C10 – C9 – C6 – C7	86.8(2)	C14 – C3 – C4 – C5	-173.0(1)
O1 – C9 – C6 – C5	86.8(2)	O1 – C9 – C10 – C11	-145.3(1)
C10 – C9 – C6 – C5	-97.3(2)	C6 – C9 – C10 – C11	38.9(2)
C17 – C18 – C19 – C14	-0.8(2)	O1 – C9 – C10 – C12	-23.0(2)
C15 – C14 – C19 – C18	-1.3(2)	C6 – C9 – C10 – C12	161.3(1)
C3 – C14 – C19 – C18	178.6(1)	O1 – C9 – C10 – C13	95.6(2)
C15 – C16 – C17 – C18	-1.4(2)	C6 – C9 – C10 – C13	-80.2(2)

C15 – C16 – C17 – C20	-178.9(1)	C16 – C17 – C20 – F2	-143.3(1)
C19 – C18 – C17 – C16	2.2(2)	C18 – C17 – C20 – F2	39.1(2)
C19 – C18 – C17 – C20	179.7(1)	C16 – C17 – C20 – F1	96.9(2)
C5 – C6 – C7 – C8	-0.5(2)	C18 – C17 – C20 – F1	-80.7(2)
C9 – C6 – C7 – C8	175.5(1)	C16 – C17 – C20 – F3	-22.2(2)
N2 – C8 – C7 – C6	0.1(2)	C18 – C17 – C20 – F3	160.2(1)

Table 43: Details for X-ray data collection and structure refinement for compound **52g**.



	52g
Empirical formula	$C_{16}H_{18}N_2O$
Formula mass	254.32
T[K]	173(2)
Crystal size [mm]	0.35 × 0.35 × 0.20
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	7.3079(2)
b [Å]	17.9474(6)
c [Å]	11.0031(4)
α [°]	90
β [°]	95.142(3)
γ [°]	90
V [Å^3]	1437.33(8)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.175
μ [mm^{-1}]	0.074
F(000)	544
Θ range [°]	4.17 – 30.51
Index ranges	-10 ≤ *h* ≤ 10
	-25 ≤ *k* ≤ 25

	$-15 \leq l \leq 15$
Reflns. collected	29342
Reflns. obsd.	3192
Reflns. unique	4372 (R_{int} = 0.0326)
R_1, wR_2 (2σ data)	0.0502, 0.1310
R_1, wR_2 (all data)	0.0725, 0.1484
GOOF on F^2	1.036
Peak/hole [e Å^{-3}]	0.305 / -0.144

Table 44: Selected bond lengths (Å) of compound **52g**.

N2 – C8	1.316(2)	C10 – C11	1.304(2)
N2 – C4	1.365(1)	C13 – C15	1.524(2)
C5 – N1	1.365(1)	C13 – C16	1.524(2)
C5 – C6	1.419(2)	C13 – C14	1.528(2)
C5 – C4	1.422(2)	O1 – C12	1.208(2)
C7 – C6	1.371(2)	C3 – C12	1.513(2)
C7 – C8	1.413(2)	N1 – C1	1.312(2)
C2 – C3	1.370(2)	C12 – C13	1.523(2)
C2 – C1	1.415(2)	C6 – C9	1.511(2)
C4 – C3	1.415(2)	C9 – C10	1.491(2)

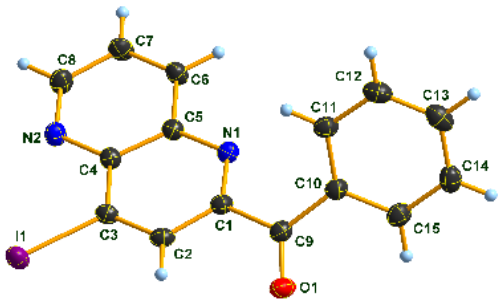
Table 45: Selected bond angles (°) of compound **52g**.

C8 – N2 – C4	116.6(1)	C11 – C10 – C9	124.9(2)
N1 – C5 – C6	119.3(1)	C12 – C13 – C15	111.5(1)
N1 – C5 – C4	122.4(1)	C12 – C13 – C16	109.2(1)
C6 – C5 – C4	118.4(1)	C15 – C13 – C16	109.8(2)
C6 – C7 – C8	120.3(1)	C12 – C13 – C14	107.0(1)
C3 – C2 – C1	119.1(1)	C15 – C13 – C14	107.7(2)
N2 – C4 – C3	118.6(1)	C16 – C13 – C14	111.6(2)
N2 – C4 – C5	123.3(1)	C3 – C12 – C13	118.7(1)
C3 – C4 – C5	118.2(1)	C7 – C6 – C5	117.2(1)
C2 – C3 – C4	118.5(1)	C7 – C6 – C9	121.9(1)
C2 – C3 – C12	121.8(1)	C5 – C6 – C9	120.9(1)
C4 – C3 – C12	119.6(1)	C10 – C9 – C6	111.0(1)
C1 – N1 – C5	117.6(1)	N1 – C1 – C2	124.3(1)
O1 – C12 – C3	118.6(1)	N2 – C8 – C7	124.2(1)
O1 – C12 – C13	122.6(1)		

Table 46: Selected torsion angles (°) of compound **52g**.

C8 – N2 – C4 – C3	178.4(1)	C8 – C7 – C6 – C9	177.9(1)
C8 – N2 – C4 – C5	-0.5(2)	N1 – C5 – C6 – C7	-177.0(1)
N1 – C5 – C4 – N2	177.5(1)	C4 – C5 – C6 – C7	1.4(2)
C6 – C5 – C4 – N2	-0.8(2)	N1 – C5 – C6 – C9	4.4(2)
N1 – C5 – C4 – C3	-1.4(2)	C4 – C5 – C6 – C9	-177.2(1)
C6 – C5 – C4 – C3	-179.7(1)	C7 – C6 – C9 – C10	-97.3(1)
C1 – C2 – C3 – C4	-1.8(2)	C5 – C6 – C9 – C10	81.3(2)
C1 – C2 – C3 – C12	-178.4(1)	C5 – N1 – C1 – C2	1.8(2)
N2 – C4 – C3 – C2	-176.3(1)	C3 – C2 – C1 – N1	-0.4(2)
C5 – C4 – C3 – C2	2.7(2)	C4 – N2 – C8 – C7	1.3(2)
N2 – C4 – C3 – C12	0.4(2)	C6 – C7 – C8 – N2	-0.7(2)
C5 – C4 – C3 – C12	179.4(1)	C6 – C9 – C10 – C11	114.9(2)
C6 – C5 – N1 – C1	177.5(1)	O1 – C12 – C13 – C15	138.7(1)
C4 – C5 – N1 – C1	-0.8(2)	C3 – C12 – C13 – C15	-44.3(2)
C2 – C3 – C12 – O1	86.0(2)	O1 – C12 – C13 – C16	17.2(2)
C4 – C3 – C12 – O1	-90.6(2)	C3 – C12 – C13 – C16	-165.8(2)
C2 – C3 – C12 – C13	-91.1(2)	O1 – C12 – C13 – C14	-103.8(2)
C4 – C3 – C12 – C13	92.3(1)	C3 – C12 – C13 – C14	73.2(2)
C8 – C7 – C6 – C5	-0.7(2)		

Table 47: Details for X-ray data collection and structure refinement for compound **56c**.



	52c
Empirical formula	$C_{15}H_9IN_2O$
Formula mass	360.14
T[K]	143(2)
Crystal size [mm]	0.25 × 0.18 × 0.15
Crystal description	colorless block
Crystal system	orthorhombic
Space group	*Pbca*
a [Å]	12.3308(2)
b [Å]	10.3497(2)
c [Å]	20.1918(3)

α [°]	90.0
β [°]	90.0
γ [°]	90.0
V [Å^3]	2576.88(8)
Z	8
$\rho_{calcd.}$ [g cm^{-3}]	1.857
μ [mm^{-1}]	2.477
F(000)	1392
Θ range [°]	4.35 – 25.24
Index ranges	-17 ≤ *h* ≤ 17
	-14 ≤ *k* ≤ 14
	-28 ≤ *l* ≤ 28
Reflns. collected	49702
Reflns. obsd.	3406
Reflns. unique	3872 (R_{int} = 0.0343)
R_1, wR_2 (2σ data)	0.0269, 0.0513
R_1, wR_2 (all data)	0.0330, 0.0534
GOOF on F^2	1.196
Peak/hole [e Å^{-3}]	0.538 / -0.555

Table 48: Selected bond lengths (Å) of compound **56c**.

I1 – C3	2.081(2)	N2 – C8	1.318(3)
C1 – N1	1.319(2)	N2 – C4	1.357(3)
C1 – C2	1.411(3)	O1 – C9	1.221(3)
C1 – C9	1.506(3)	C7 – C8	1.410(3)
C6 – C7	1.362(3)	C2 – C3	1.366(3)
C6 – C5	1.417(3)	C15 – C14	1.381(3)
C11 – C12	1.388(3)	C15 – C10	1.393(3)
C11 – C10	1.394(3)	C9 – C10	1.491(3)
N1 – C5	1.367(3)	C3 – C4	1.420(3)
C5 – C4	1.421(3)	C13 – C14	1.392(4)
C13 – C12	1.377(3)		

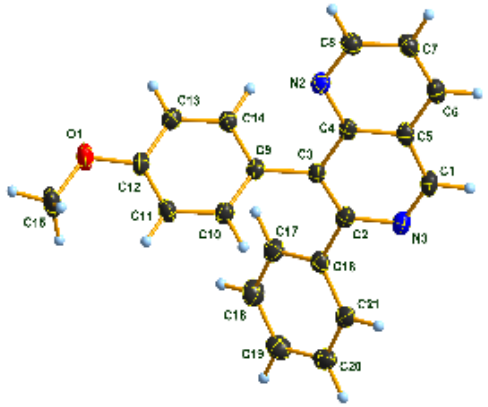
Table 49: Selected bond angles (°) of compound **56c**.

N1 – C1 – C2	124.7(2)	C13 – C12 – C11	120.6(2)
N1 – C1 – C9	118.6(2)	O1 – C9 – C10	120.5(2)
C2 – C1 – C9	116.7(2)	O1 – C9 – C1	119.0(2)
C7 – C6 – C5	118.6(2)	C10 – C9 – C1	120.4(2)
C12 – C11 – C10	119.6(2)	N2 – C8 – C7	123.8(2)
C1 – N1 – C5	116.7(2)	C15 – C14 – C13	120.2(2)
N1 – C5 – C6	119.0(2)	C2 – C3 – C4	119.6(2)
N1 – C5 – C4	123.5(2)	C2 – C3 – I1	120.3(2)
C6 – C5 – C4	117.5(2)	C4 – C3 – I1	120.1(2)
C12 – C13 – C14	119.8(2)	N2 – C4 – C3	120.0(2)
C8 – N2 – C4	117.3(2)	N2 – C4 – C5	123.2(2)
C6 – C7 – C8	119.7(2)	C3 – C4 – C5	116.8(2)
C3 – C2 – C1	118.6(2)	C15 – C10 – C11	119.7(2)
C14 – C15 – C10	120.1(2)	C15 – C10 – C9	118.6(2)
C11 – C10 – C9	121.3(2)		

Table 50: Selected torsion angles (°) of compound **56c**.

C2 – C1 – N1 – C5	0.3(3)	C1 – C2 – C3 – I1	-175.6(1)
C9 – C1 – N1 – C5	179.6(2)	C8 – N2 – C4 – C3	178.3(2)
C1 – N1 – C5 – C6	179.1(2)	C8 – N2 – C4 – C5	-0.1(3)
C1 – N1 – C5 – C4	1.3(3)	C2 – C3 – C4 – N2	-179.0(2)
C7 – C6 – C5 – N1	-176.6(2)	I1 – C3 – C4 – N2	-1.5(3)
C7 – C6 – C5 – C4	1.2(3)	C2 – C3 – C4 – C5	-0.4(3)
C5 – C6 – C7 – C8	-1.2(3)	I1 – C3 – C4 – C5	177.1(1)
N1 – C1 – C2 – C3	-1.9(3)	N1 – C5 – C4 – N2	177.2(2)
C9 – C1 – C2 – C3	178.8(2)	C6 – C5 – C4 – N2	-0.6(3)
C14 – C13 – C12 – C11	0.3(3)	N1 – C5 – C4 – C3	-1.2(3)
C10 – C11 – C12 – C13	1.5(3)	C6 – C5 – C4 – C3	-179.0(2)
N1 – C1 – C9 – O1	-154.7(2)	C14 – C15 – C10 – C11	0.1(3)
C2 – C1 – C9 – O1	24.7(3)	C14 – C15 – C10 – C9	-172.9(2)
N1 – C1 – C9 – C10	27.2(3)	C12 – C11 – C10 – C15	-1.7(3)
C2 – C1 – C9 – C10	-153.5(2)	C12 – C11 – C10 – C9	171.2(2)
C4 – N2 – C8 – C7	0.2(3)	O1 – C9 – C10 – C15	30.6(3)
C6 – C7 – C8 – N2	0.5(4)	C1 – C9 – C10 – C15	-151.3(2)
C10 – C15 – C14 – C13	1.6(3)	O1 – C9 – C10 – C11	-142.4(2)
C12 – C13 – C14 – C15	-1.8(3)	C1 – C9 – C10 – C11	35.8(3)
C1 – C2 – C3 – C4	1.9(3)		

Table 51: Details for X-ray data collection and structure refinement for compound **64h**.



	64h
Empirical formula	$C_{21}H_{16}N_2O$
Formula mass	312.36
T[K]	173(2)
Crystal size [mm]	0.39 × 0.12 × 0.09
Crystal description	colorless rod
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	11.6198(6)
b [Å]	5.8801(3)
c [Å]	22.9235(13)
α [°]	90.0
β [°]	92.639(5)
γ [°]	90.0
V [Å^3]	1564.60(14)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.326
μ [mm^{-1}]	0.083
F(000)	656
Θ range [°]	4.24 – 26.37
Index ranges	$-14 \leq h \leq 12$
	$-7 \leq k \leq 7$
	$-26 \leq l \leq 28$
Reflns. collected	10124
Reflns. obsd.	2309
Reflns. unique	3198

	(R_{int} = 0.0394)
R_1, wR_2 (2σ data)	0.0433, 0.0939
R_1, wR_2 (all data)	0.0663, 0.1067
GOOF on F^2	1.022
Peak/hole [e Å^{-3}]	0.225 / -0.209

Table 52: Selected bond lengths (Å) of compound **64h**.

N2 – C8	1.315(2)	C7 – C6	1.360(2)
N2 – C4	1.372(2)	C21 – C20	1.384(2)
O1 – C12	1.374(2)	C21 – C16	1.400(2)
O1 – C15	1.420(2)	C17 – C18	1.388(2)
N3 – C1	1.305(2)	C17 – C16	1.396(2)
N3 – C2	1.379(2)	C20 – C19	1.381(2)
C3 – C2	1.391(2)	C18 – C19	1.387(2)
C3 – C4	1.430(2)	C11 – C10	1.395(2)
C3 – C9	1.493(2)	C14 – C13	1.380(2)
C9 – C10	1.384(2)	C5 – C4	1.410(2)
C9 – C14	1.397(2)	C5 – C1	1.411(2)
C2 – C16	1.489(2)	C5 – C6	1.414(2)
C12 – C11	1.380(2)	C8 – C7	1.408(2)
C12 – C13	1.390(2)		

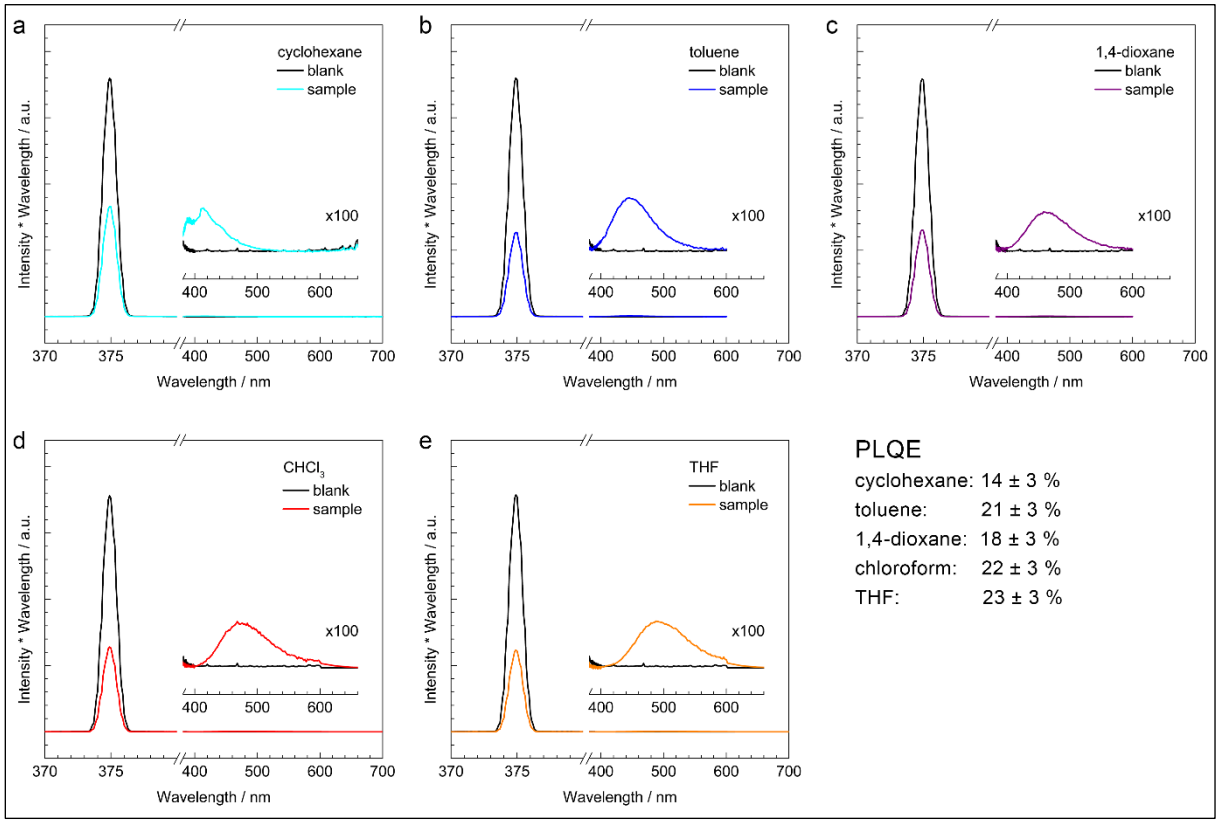
Table 53: Selected bond angles (°) of compound **64h**.

C8 – N2 – C4	116.7(1)	C5 – C4 – C3	119.0(1)
C12 – O1 – C15	117.5(1)	C9 – C10 – C11	121.5(1)
C1 – N3 – C2	119.0(1)	C20 – C21 – C16	121.2(2)
C2 – C3 – C4	117.9(1)	C7 – C6 – C5	118.5(1)
C2 – C3 – C9	123.3(1)	N3 – C1 – C5	124.1(1)
C4 – C3 – C9	118.8(1)	C18 – C17 – C16	120.9(2)
C10 – C9 – C14	118.2(1)	C19 – C20 – C21	120.2(2)
C10 – C9 – C3	120.8(1)	C19 – C18 – C17	120.2(2)
C14 – C9 – C3	121.0(1)	C20 – C19 – C18	119.6(2)
N3 – C2 – C3	122.3(1)	C17 – C16 – C21	117.8(2)
N3 – C2 – C16	112.9(1)	C17 – C16 – C2	123.3(1)
C3 – C2 – C16	124.8(1)	C21 – C16 – C2	118.8(1)
O1 – C12 – C11	124.8(1)	C1 – C5 – C6	123.5(1)
O1 – C12 – C13	115.2(1)	N2 – C8 – C7	125.3(2)
C11 – C12 – C13	120.0(1)	C6 – C7 – C8	118.6(2)
C12 – C11 – C10	119.3(1)	C14 – C13 – C12	120.1(1)
C13 – C14 – C9	120.9(1)	N2 – C4 – C5	122.0(1)
C4 – C5 – C1	117.6(1)	N2 – C4 – C3	119.1(1)
C4 – C5 – C6	119.0(1)		

Table 54: Selected torsion angles (°) of compound **64h**.

C2 – C3 – C9 – C10	63.6(2)	C6 – C5 – C4 – C3	179.6(1)
C4 – C3 – C9 – C10	-116.2(2)	C2 – C3 – C4 – N2	176.4(1)
C2 – C3 – C9 – C14	-116.4(2)	C9 – C3 – C4 – N2	-3.8(2)
C4 – C3 – C9 – C14	63.8(2)	C2 – C3 – C4 – C5	-2.8(2)
C1 – N3 – C2 – C3	-4.1(2)	C9 – C3 – C4 – C5	177.1(1)
C1 – N3 – C2 – C16	174.2(1)	C14 – C9 – C10 – C11	1.4(2)
C4 – C3 – C2 – N3	5.6(2)	C3 – C9 – C10 – C11	-178.7(2)
C9 – C3 – C2 – N3	-174.2(1)	C12 – C11 – C10 – C9	0.1(3)
C4 – C3 – C2 – C16	-172.5(1)	C8 – C7 – C6 – C5	0.0(2)
C9 – C3 – C2 – C16	7.7(2)	C4 – C5 – C6 – C7	-0.7(2)
C15 – O1 – C12 – C11	-2.3(2)	C1 – C5 – C6 – C7	-179.7(2)
C15 – O1 – C12 – C13	178.1(2)	C2 – N3 – C1 – C5	-0.4(2)
O1 – C12 – C11 – C10	179.4(2)	C4 – C5 – C1 – N3	3.1(2)
C13 – C12 – C11 – C10	-0.9(2)	C6 – C5 – C1 – N3	-177.9(2)
C10 – C9 – C14 – C13	-2.1(2)	C16 – C21 – C20 – C19	0.5(2)
C3 – C9 – C14 – C13	177.9(2)	C16 – C17 – C18 – C19	-0.4(3)
C4 – N2 – C8 – C7	-1.2(2)	C21 – C20 – C19 – C18	0.5(3)
N2 – C8 – C7 – C6	1.0(3)	C17 – C18 – C19 – C20	-0.5(3)
C9 – C14 – C13 – C12	1.4(2)	C18 – C17 – C16 – C21	1.4(2)
O1 – C12 – C13 – C14	179.9(2)	C18 – C17 – C16 – C2	176.9(2)
C11 – C12 – C13 – C14	0.2(2)	C20 – C21 – C16 – C17	-1.4(2)
C8 – N2 – C4 – C5	0.4(2)	C20 – C21 – C16 – C2	-177.1(1)
C8 – N2 – C4 – C3	-178.7(1)	N3 – C2 – C16 – C17	-146.1(2)
C1 – C5 – C4 – N2	179.6(1)	C3 – C2 – C16 – C17	32.1(2)
C6 – C5 – C4 – N2	0.5(2)	N3 – C2 – C16 – C21	29.4(2)
C1 – C5 – C4 – C3	-1.3(2)	C3 – C2 – C16 – C21	-152.4(2)

2. PHOTOLUMINESCENCE QUANTUM EFFICIENCY MEASUREMENTS (PLQE)



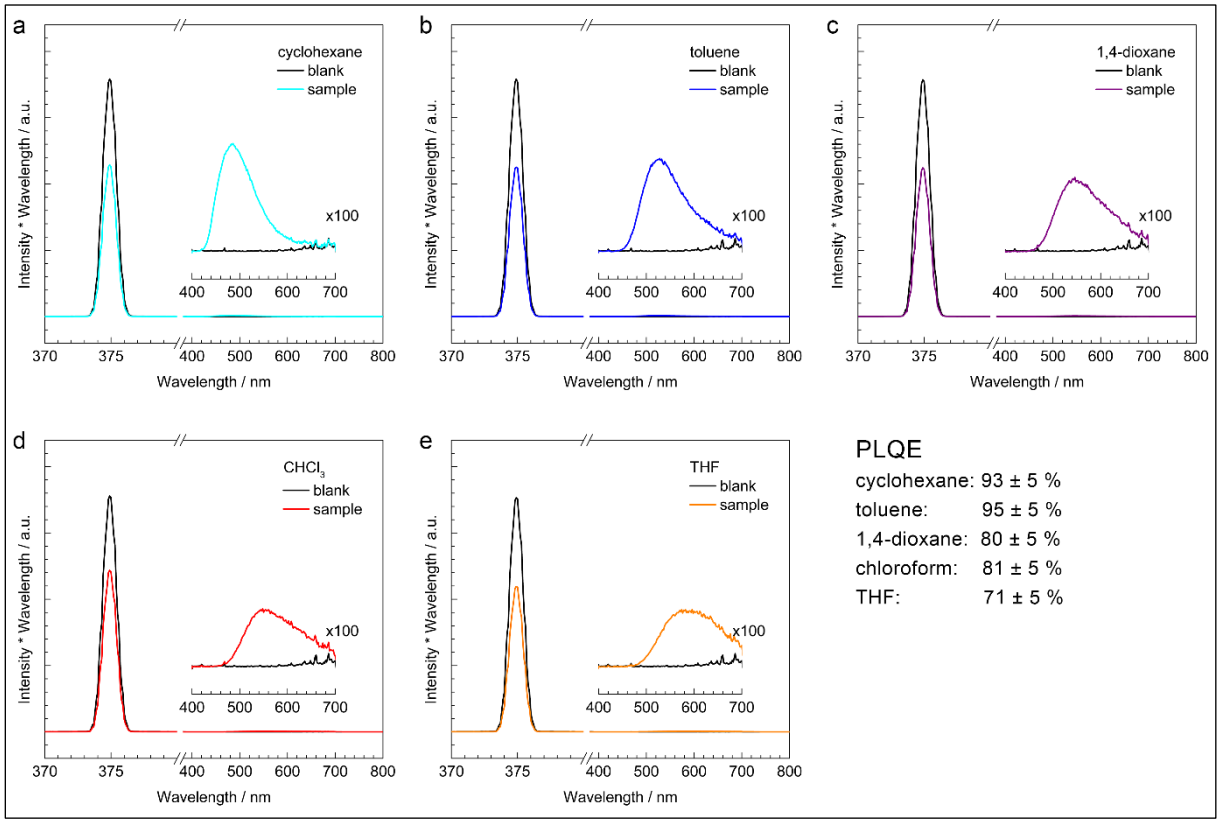


Figure 28: PLQE measurements of **62b** (top) and **64i** (bottom) in various solvents. The *y*-axis scale is proportional to the number of photons collected in each wavelength interval.

3. TIME-CORRELATED SINGLE PHOTON COUNTING (TCSPC)

The solutions are excited at 20 MHz and 5.8 MHz for **62b** and **64i**, respectively, adjusted to their respective decay times. The instrument response function (IRF) of the setup is mostly determined by the laser pulse length and is measured at around 120 ps. Mono-exponential fits to the data follow the equation

$$I(t) = I_0 \cdot exp\left(\frac{t - t_0}{\tau}\right) + I_{bg}$$

with initial intensity I_0, time offset t_0, background intensity I_{bg}, and lifetime τ. The latter are given in Table S1 including their fitting uncertainties. We note that the uncertainties are one order of magnitude smaller than the time resolution of the setup. However, measured lifetimes are considerably larger than the IRF.

Table 55: Lifetimes of mono-exponential fits to the TCSPC data including their fitting uncertainties.

62b	(3.80 ± 0.02) ns
64i	(11.95 ± 0.03) ns

4. ADDITIONAL OPTICAL SPECTROSCOPIC DATA FOR DYES 73

Table 56: Overview of spectroscopic data.

73a	**$CHCl_3$**	**Tetradecane**	***n*-Hexane**	**1-Butanol**	**1-Undecanol**	**DMF**	**Toluene**
λ_{Abs}[a]	355.4	343.4	342.2	355.2	353.4	355.2	346.8
λ_{Fluo}[b]	420.0	402.3	402.7	429.1	420.6	427.2	410.6
ε [c]	17100	17600	16800	19000	18500	17700	16900
Φ[d]	0.78	0.094	0.076	0.95	0.76	0.74	0.50
τ[e]	3.21			3.85		3.62	
73b	**$CHCl_3$**	**Tetradecane**	***n*-Hexane**	**1-Butanol**	**1-Undecanol**	**DMF**	**Toluene**
λ_{Abs}[a]	364.8	356.4	354.2	366.2	365.6	368.0	364.2
λ_{Fluo}[b]	459.6	427.8	424.0	498.1	476.4	497.2	443.2
ε [c]	16900	15800	15700	17100	16700	16400	16400
Φ[d]	0.83	0.79	0.65	0.83	0.83	0.82	0.75
τ[e]	4.11	3.12	2.65	5.18	4.78	5.24	3.50
73c	**$CHCl_3$**	**Tetradecane**	***n*-Hexane**	**1-Butanol**	**1-Undecanol**	**DMF**	**Toluene**
λ_{Abs}[a]	426.2	403.8	401.2	430.2	428.6	433.8	418.2
λ_{Fluo}[b]	578.4	469.8	462.7	638.4	610.0		532.4
ε [c]	11200	16500	12300	10300	11800	10700	10800
Φ [d]	0.64	0.73	0.70	0.013	0.14	0.0037	0.65
τ[e]	6.99	3.61	3.47	3.50	5.51		5.12
73d	**$CHCl_3$**	**Tetradecane**	***n*-Hexane**	**1-Butanol**	**1-Undecanol**	**DMF**	**Toluene**
λ_{Abs}[a]	362.2	357.0	354.8	361.4	362.6	365.6	360.8
λ_{Fluo}[b]	525.1	442.3	440.2	572.1	526.4	618.8	492.4
ε [c]	15900	17100	16500	16600	16900	16500	17000
Φ [d]	0.65	0.51	0.41	0.022	0.26	0.0065	0.71
τ[e]	6.62	2.78	2.03	0.208	1.75	0.119	5.40
73g	**$CHCl_3$**	**Tetradecane**	***n*-Hexane**	**1-Butanol**	**1-Undecanol**	**DMF**	**Toluene**
λ_{Abs}[a]	325.0	322.6	322.6	323.6	323.8	323.8	324.0
λ_{Fluo}[b]	509.7	431.7	427.1	576.8	532.4	581.8	478.0
ε [c]	15300	16200	14900	16200	18800	15200	16000
Φ [d]	0.39	0.34	0.33	0.088	0.23	0.13	0.18
τ[e]	4.07	1.83	1.70	1.80	4.85	3.85	1.53
73h	**$CHCl_3$**	**Tetradecane**	***n*-Hexane**	**1-Butanol**	**1-Undecanol**	**DMF**	**Toluene**
λ_{Abs}[a]	329.0	327.2	326.6	327.8	329.0	328.8	328.8
λ_{Fluo}[b]	522.7	440.2	434.8	570.1	537.0	597.8	487.0
ε [c]	17100	16000	16800	18100	15900	17000	16900
Φ [d]	0.40	0.34	0.34	0.047	0.28	0.055	0.19
τ[e]	4.14	1.89	1.88	1.05	3.10	3.01	1.59
73i	**$CHCl_3$**	**Tetradecane**	***n*-Hexane**	**1-Butanol**	**1-Undecanol**	**DMF**	**Toluene**
λ_{Abs}[a]	356.0	344.4	343.4	357.6	355.0	356.0	353.4
λ_{Fluo}[b]	425.4	407.0	406.7	434.2	430.6	432.7	416.7
ε [c]	18600	18800	17400	18600	19100	17900	18200
Φ[d]	0.79	0.18	0.14	0.89	0.85	0.64	0.51
τ[e]	3.08	5.08		3.63	3.81	3.38	2.03
73j	**$CHCl_3$**	**Tetradecane**	***n*-Hexane**	**1-Butanol**	**1-Undecanol**	**DMF**	**Toluene**
λ_{Abs}[a]	366.4	356.2	355.6	367.8	365.8	367.8	364.6
λ_{Fluo}[b]	447.4	410.8	407.4	480.0	457.5	478.3	427.5
ε [c]	23700	26400	22600	24100	24600	22800	22400
Φ[d]	0.54	0.54	0.53	0.70	0.71	0.55	0.51
τ[e]	1.34	0.994	1.02	2.21	2.12	2.15	1.16
73l	**$CHCl_3$**	**Tetradecane**	***n*-Hexane**	**1-Butanol**	**1-Undecanol**	**DMF**	**Toluene**
λ_{Abs}[a]	364.4	357.6	354.0	366.0	369.4	369.0	364.8
λ_{Fluo}[b]	492.2	436.7	426.8	556.6	518.2	583.4	454.6
ε [c]	27500	29300	28300	27500	26800	28300	27500
Φ [d]	0.67	0.50	0.50	0.16	0.56	0.15	0.40
τ[e]	2.93	1.43	1.35	1.05	3.21	1.91	1.40

[a] Absorption maxima in nm. [b] Fluorescence maxima in nm. [c] Molar extinction coefficients in $Lmol^{-1}cm^{-1}$. [d] Fluorescence quantum yields, exc = λ_{max}, reference: *N*,*N*'-Bis(tridecan-7-yl)perylene-3,4:9,10-tetracarboxylic diimide with Φ = 1.00; [e] Fluorescence lifetimes in ns.