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Sulfoxide-Controlled Functionalization of Arenes and Heterocycles
Transition Metal-Catalyzed Cross-Coupling Reactions of Thioethers
Chlorine-Zinc Exchange Reactions

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Erklärung

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Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig, ohne unerlaubte Hilfe bearbeitet.
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…..……

Laurin Melzig

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Parts of this Ph.D. thesis have been published

1) Christian B. Rauhut, Laurin Melzig and Paul Knochel, „*Meta*- and *para*-Difunctionalization of Arenes via a Sulfoxide-Magnesium Exchange Reaction", *Org. Lett*. **2008**, *10*, 3891.

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3) Laurin Melzig, Christian B. Rauhut, and Paul Knochel, „2,3-Functionalization of Furans, Benzofurans and Thiophenes via Magnesiation and Sulfoxide-Magnesium Exchange", *Chem. Commun*. **2009**, *24*, 3536, selected as „Hot Article".

4) Albrecht Metzger, Laurin Melzig, Christina Despotopoulou and Paul Knochel, „Pd-Catalyzed Cross-Coupling of Functionalized Organozinc Reagents with Thiomethyl-Substituted Heterocycles", *Org. Lett.* **2009**, *11*, 4228, selected for *Synfacts* **2009**, *12*, 1384, selected in „Highlights from the literature", *Org. Process Res. Dev.* **2010**, *14*, 2.

5) Laurin Melzig, Albrecht Metzger and Paul Knochel, „Ni-Catalyzed Cross-Coupling of Functionalized Organozinc Reagents with Thiomethyl-Substituted Heterocycles", *J. Org. Chem.* **2010**, *75*, 2131.

6) Laurin Melzig, Jeremy Stemper and Paul Knochel, „A novel Palladium-Catalyzed Cross-Coupling of Thiomethylated Alkynes with Functionalized Organozinc Reagents", *Synthesis* **2010**, *12*, 2085.

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8) Laurin Melzig, Albrecht Metzger and Paul Knochel, „Pd- and Ni-catalyzed Cross-Coupling Reactions of Functionalized Zinc Reagents with Thioethers", *Chem Eur. J.* **2011**, *17*, 2948.

9) Laurin Melzig, Christian B. Rauhut, Niko Naredi-Rainer and Paul Knochel, „Difunctionalization of Arenes and Heteroarenes via a Sulfoxide-Magnesium Exchange Reaction", *Chem Eur. J., ASAP*.

10) Laurin Melzig, Coura R. Diène, C. J. Rohbogner and Paul Knochel, „Preparation of Polyfunctional Zinc Organometallics using a Fe- or Co-Catalyzed Cl/Zn-Exchange", *Angew. Chem. Int. Ed., submitted.*

To Marilena

Don't walk behind me; I may not lead. Don't walk in front of me; I may not follow.
Just walk beside me and be my friend.

Albert Camus

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Abbreviations

Ac	acetyl	IR	infra-red
acac	acetylacetonate	*J*	coupling constant (NMR)
aq.	aqueous	LDA	lithium diisopropylamide
Ar	aryl	M	metal
Bn	benzyl	M	molarity
Boc	*tert*-butoxycarbonyl	*m*	meta
Bu	butyl	m	multiplet
*n*Bu	*n*-butyl	Me	methyl
*s*Bu	*s*-butyl	min	minute
*t*Bu	*t*-butyl	mmol	millimole
calc.	calculated	m.p.	melting point
conc.	concentrated	MS	mass spectroscopy
δ	chemical shifts in parts per million	MTBE	*tert*-butylmethylether
CPME	cyclopentylmethylether	NMP	1-methyl-2-pyrrolidinone
d	doublet	NMR	nuclear magnetic resonance
dba	*trans,trans*-dibenzylideneacetone	*o*	ortho
DME	1,2-dimethoxyethane	*p*	para
DMF	*N*,*N*-dimethylformamide	Ph	phenyl
DMPU	*N*,*N*'-dimethylpropyleneurea	*i*Pr	*iso*-propyl
DMSO	dimethyl sulfoxide	q	quartet
D*o*M	directed *ortho*-metalation	QUINAP	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
DPE-Phos	bis(2-diphenylphosphinophenyl)ether	R	organic substituent
dppe	diphenylphosphinoethane	s	singulet
dppf	1,1'-bis(diphenylphosphino)ferrocene	sat.	saturated
dppp	diphenylphosphinopropane	S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
dr	diastereomeric ratio	TFA	trifluoroacetic acid
E^+	electrophile	tfp	tris-2-furylphosphine
EI	electron-impact ionization	THF	tetrahydrofuran
eq.	equation	TIPS	triisopropylsilyl
equiv.	equivalent	TLC	thin layer chromatography
ESI	electrospray ionization	tmp	2,2,6,6-tetramethylpiperidyl
Et	ethy	TMS	trimethylsilyl
FG	functional group	Tol	tolyl
GC	gas chromatography	Tos	tosyl
h	hour	TP	typical procedure
HRMS	high resolution mass spectroscopy		

A. Introduction

1. General Introduction

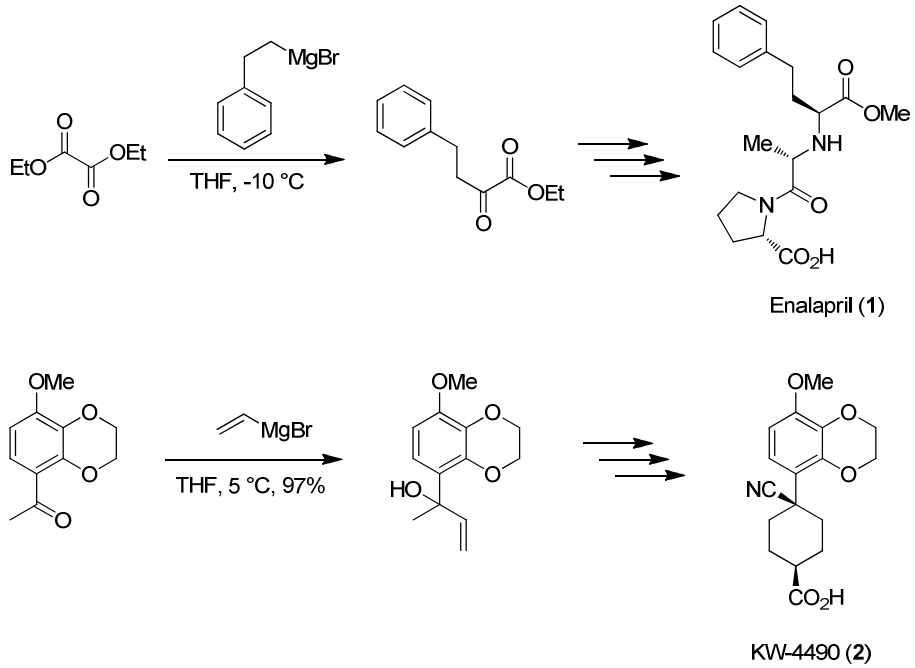
The birth of organic chemistry is considered to have been in 1828, when Friedrich Wöhler achieved the groundbreaking synthesis of urea and with the development of the elementary analysis by Justus von Liebig in the 19th century. Since then, organic chemistry has undergone fundamental progress. Along this long way are some milestones worth mentioning, like the development of nuclear magnetic resonance spectroscopy which proved to be a very powerful analytical method for all organic chemists, greatly increasing the possibilities in determining organic structures and to understand the way organic reactions proceed in the first place.[1] Another important step was the first formation of a C-C bond with the synthesis of acetic acid by *Kolbe* in 1845.[2] Only three years later, *Frankland* managed to produce the first organometallic reagent, diethyl zinc by the reaction of zinc dust with ethyl iodide.[3] This breakthrough discovery would soon emerge to a most powerful tool to form C-C and C-heteroatom bonds in the next 150 years. Today one can hardly speak about modern organic chemistry without mentioning the methods and reactions discovered by *Grignard*, *Wittig* or *Grubbs*, for instance.[4] The reason for the immense impact of organometallics in today's chemistry lies within the intensive need of new agrochemicals and materials as well as novel pharmaceuticals for mankind. Due to the permanent changes in environment and healthcare a consistent development of new synthetic methods is needed which fulfill requirements for fast adoption into the chemical community. This led, in return, to a big influence on the evolution of new techniques often implementing organometallic reagents or catalysts. These new reagents should meet standards which are at first glance quite contrary: they are asked to be highly reactive, highly selective and highly tolerant towards sensitive functionalities and also be as environmentally friendly as possible and - this goes without saying - economical at the same time.[5] Organometallic chemistry has the potential to meet these needs. For the last decades, a large range of metals were applied in synthetic organic chemistry to solve problems, the progress achieved is documented by the several Nobel prizes which have been

[1] P. J. Hore, *Nuclear Magnetic Resonance*, Oxford University Press: Oxford, **1995**.
[2] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
[3] a) E. Frankland, *Liebigs Ann. Chem.* **1848-9**, *71*, 171; b) E. Frankland, *J. Chem. Soc.* **1848-9**, *2*, 263.
[4] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4490.
[5] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259; c) C.-J. Li, B. M. Trost, *Proc. Nat. Acad. Sci.* **2008**, *105*, 13197.

awarded in this field. The still ongoing development ensures that nearly every metal in the periodic table can be used for either the preparation of (new) organometallics reagents or in catalytic processes.[6]

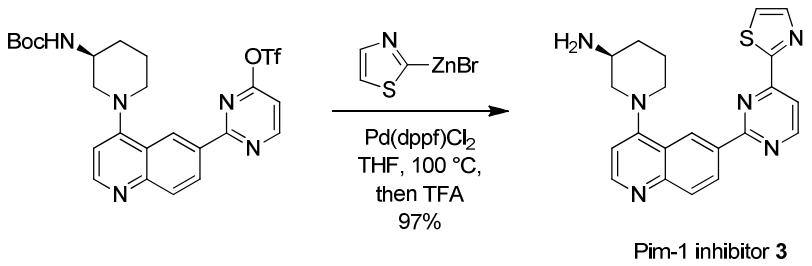
Since the reactivity of organometallics strongly depends on the character of the metal-carbon bond, this provides many possibilities for tuning the desired organometallic reagents and adjusting their chemical behaviour. Organolithium compounds for instance show excellent reactivity towards numerous electrophiles,[7] but they exhibit a low selectivity and functional group tolerance due to the ionic character of the lithium carbon bond. Reagents with a more covalent character of the carbon-metal bond can be found in organozinc or organotin reagents. These compounds offer a wider range of tolerance towards susceptible groups, but, they are often characterized by a lack of reactivity towards electrophiles. Organomagnesium and organozinc reagents play a special role in this context, as they show a good reactivity when intercepted with electrophiles, yet they possess at the same time a remarkable tolerance towards a broad range of functional groups. They can also be easily transmetalated to access other organometallic reagents. Therefore, these reagents represent formidable and flexible tools for organic synthesis, and have been applied in numerous industrial processes.[6] Examples are the commercial production of Tamoxifen,[8] where a key step is the addition of phenylmagnesium bromide to an intermediate ketone. Also the industrial synthesis of Enalapril (**1**), an ACE-inhibitor from Merck[9] and the multikilogram synthesis of PDE4 Inhibitor KW-4490 (**2**) use organomagnesium chemistry to generate the dienophile for a subsequent Diels-Alder reaction (Scheme 1).[10]

[6] (a) *Handbook of Functionalized Organometallics*; P. Knochel, Ed., Wiley-VCH: Weinheim, **2005**; (b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., A. de Meijere, F. Diederich, Wiley-VCH: Weinheim, **2004**.
[7] G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596.
[8] a) M. J. K. Harper, A. L. Walpole, *Nature* **1966**, *212*, 87; b) G. R. Bedford, D. N. Richardson, *Nature* **1966**, *212*, 733; c) D. W. Robertson, J. A. Katzenellenbogen, *J. Org. Chem.* **1982**, *47*, 2387; d) R. McCague, *J. Chem. Soc., Perkin Trans. 1* **1987**, 1011.
[9] A. A. Patchett, in *Chronicles of Drug Discovery*, Vol. 3; D. Lednicer, Ed., ACS Books, Washington, DC, **1993**, 125.
[10] A. Yanagisawa, K. Nishimura, K. Ando, T. Nezu, A. Maki, S. Kato, W. Tamaki, E. Imai, S.-I. Mohri, *Org. Process Res. Dev* **2010,** *14*, 1182.



Scheme 1: Industrial synthesis of Enalapril (**1**) and the PDE4 Inhibitor KW-4490 (**2**).

In addition, organomagnesium reagents as well as their zinc counterparts find extensive use in various kinds of cross-coupling reactions,[11] as for example in the synthesis of a proto-oncogene serine/threonine-protein kinase (Pim-1) inhibitor **3** which has been patented by Novartis in 2010 (Scheme 2).[12] The final step of the sequence is a Negishi cross-coupling reaction, named after one of the three Nobel Prize-winning chemists of the same year,[13] and both of these facts are clear tributes to the attainments of modern organometallics chemistry.



Scheme 2: Synthesis of the Pim-1 inhibitor **3**

[11] For a review about cross-coupling reactions in total synthesis, see: K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
[12] M. Burger, M. Lindvall, *PCT Int. Appl. WO* 2010026121, **2010**.
[13] Nobel Prize press release **2010**

2. Halogen-Metal Exchange Reactions

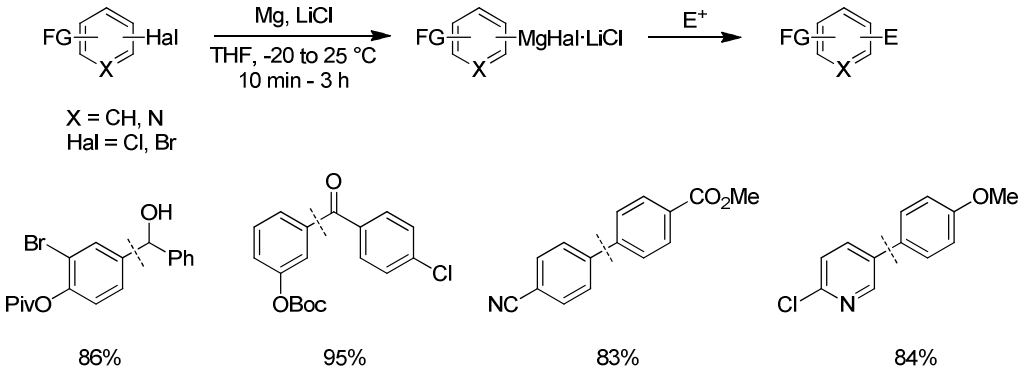
Since the initial preparation of an organomagnesium compound by Victor Grignard in 1901,[14] which was so trailblazing that he was awarded the Nobel Prize already in 1912, a wide range of synthetic improvements have been accomplished. Yet, the most convenient and also economically most advantageous method for the preparation of these reagents is still the oxidative insertion of elemental magnesium into a carbon-halogen bond. Although the detailed mechanism of the insertion is not clear, and according to *Garst* and *Ungváry* "remains rich in speculation and short on discriminating fact, a disturbing status for what may be the most-often-used nontrivial reaction", a single electron transfer is generally accepted.[15]

A better understanding of the behaviour of organomagnesium reagents in etheral solutions was achieved with the discovery of the Schlenk equilibrium.[16] Depending on the temperature, the solvent used, the counterions and also additives like 1,4-dioxane or crown ethers,[17] the equilibrium can be shifted from the monoalkyl magnesium to the dialkyl magnesium species. A problem of the direct magnesium insertion is the induction period, which greatly depends on the amount of moisture present in the reaction, and the surface of the magnesium which is generally passivated by a magnesium oxide or magnesium hydroxide layer. This requires the removal of these coatings by addition of Grignard reagent, 1,2-dibromoethane or diisobutylaluminium hydride, the latter being used in process chemistry. That and the exothermic conditions of the insertion process, severely limiting the functional group tolerance, are the major drawbacks of this method.[18]

The work of *Rieke* on highly reactive magnesium, prepared by the reaction of lithium naphthalenide with magnesium chloride, opened up new perspectives in organometallic chemistry.[19] Now it was possible to perform magnesium insertions into carbon-halogen bonds of compounds also bearing other sensitive functionalities. The latest progress was reported by *Knochel* with the utilization of LiCl in combination with magnesium, which allowed for low

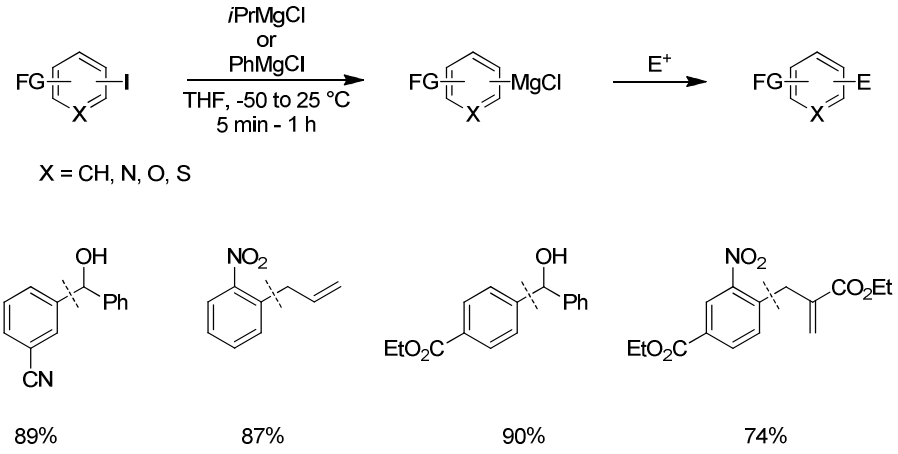
[14] V. Grignard, *Ann. Chim.* **1901**, *24*, 433.
[15] a) H. M. Walborsky, *Acc. Chem. Res.* **1990**, *23*, 286; b) J. F. Garst, *Acc. Chem. Res.* **1991**, *24*, 95; c) H. R. Rogers, C. L. Hill, Y. Fujiwara, R. J. Rogers, H. L. Mitchell, G. M. Whitesides, *J. Am. Chem. Soc.* **1980**, *102*, 217; d) J. F. Garst, in *Grignard Reagents*, H. G. Richey Jr., Ed, Wiley, Chicester, **2000**, 185; e) M. S. Kharash, O. Reinmuth, in *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, **1954**; f) C. Hamdouchi, H. M. Walborsky, in *Handbook of Grignard-Reagents*, G. S. Silverman, P. E. Rakita, Eds, Marcel Dekker, New York, **1995**, 145; g) K. Oshima, in *Main Group Metals in Organic Synthesis*, H. Yamamoto, K. Oshima, Eds, Wiley-VCH, Weinheim, **2004**.
[16] W. Schlenk, W. Schlenk Jr., *Chem. Ber.* **1929**, *62*, 920.
[17] A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159.
[18] U. Tilstam, H. Weinmann, *Org. Process Res. Dev.* **2002**, *6*, 906.
[19] a) R. D. Rieke, *Science* **1989**, *246*, 1260; b) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925; c) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428.

reaction temperatures during the preparation of various aryl and hetaryl magnesium derivatives, therefore tolerating a broad variety of functional groups (Scheme 3).[20]



Scheme 3: LiCl-facilitated Mg insertion and subsequent electrophilic reactions.

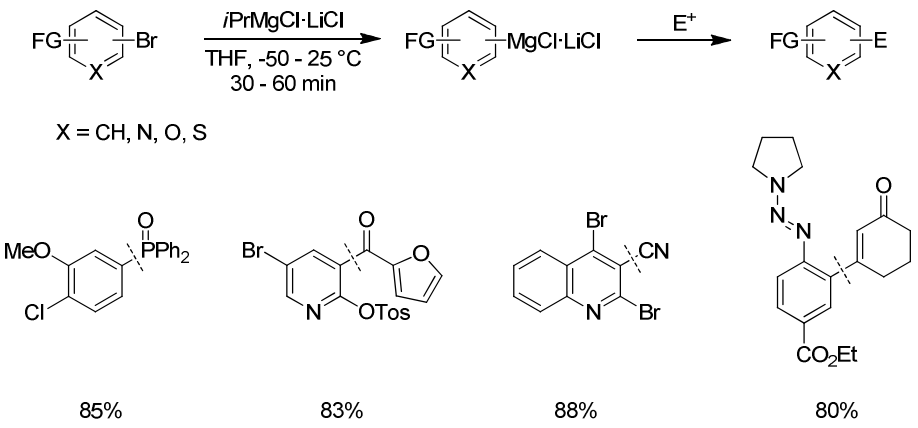
A more convenient way for the preparation of organomagnesium compounds with high functional group tolerance, avoiding many of the flaws of the direct insertion, are halogen-metal exchange reactions. The driving force of this reaction class is the formation of an organometallic reagent of higher stability ($sp > sp^2_{vinyl} > sp^2_{aryl} > sp^3_{prim} > sp^3_{sec}$).[21] Based on the preliminary work of *Prévost*[22] and *Villieras*,[23] *Knochel* demonstrated the potential of the iodine-magnesium exchange on substrates bearing sensitive functionalities in 1998 (Scheme 4).[24]



Scheme 4: I-Mg exchange and subsequent electrophilic reactions.

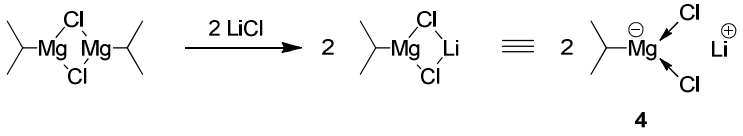
[20] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.
[21] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev*. **2006**, *10*, 733.
[22] C. Prévost, *Bull. Soc. Chim. Fr*. **1931**, *49*, 1372.
[23] a) J. Villiéras, *Bull. Chem. Soc. Fr*. **1967**, *5*, 1520; b) J. Villiéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Chem. Soc. Fr*. **1986**, *24*, 470.
[24] 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.

By applying this protocol, a wide range of polyfunctionalized organomagnesium reagents were prepared. The method was further improved by the addition of one equivalent of LiCl to the exchange reagent *i*PrMgCl, since this resulted in the formation of an organomagnesium species with the formal composition *i*PrMgCl·LiCl. Interestingly, this reagent shows a remarkably higher reactivity, also making the Br-Mg exchange now generally possible, whereas bromides were an unreactive substrate class until then (Scheme 5).[25]



Scheme 5: Br-Mg exchange and subsequent electrophilic reactions.

The assumed "ate" like intermediate **4** of this "Turbo-Grignard", which leads to deaggregation of the organometal species, is proposed to be responsible for the higher solubility and at the same time enhanced reactivity of the Grignard reagent (Scheme 6). Using this new exchange reagent, a broad range of aromatic and heteroaromatic bromides were converted into the corresponding magnesium reagents.[26]



Scheme 6: Effect of LiCl on Grignard reagents.

The increased reactivity does not limit the functional group tolerance though, but some electron-rich aromatics still resisted to undergo the Br-Mg exchange. This problem was solved with the development of exchange reagents of the type RMg_2·LiCl.[17] Quantum chemical model calculations on the halogen-magnesium exchange showed that the reaction becomes more likely when the exchange reagent's "ate" character is increased. Thus, *bis*-Mg

[25] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[26] For selected examples of Br-Mg exchange, see: H. Ren, P. Knochel, *Chem. Comm.* **2006**, 726; b) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543; c) N. Boudet, P. Knochel, *Org. Lett.* **2006**, *8*, 3737; d) F. Kopp, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2004**, 2288.

reagents of type RMg_2·LiCl could complete the exchange on substrates where *i*PrMgCl·LiCl had previously failed.[17]

Analogously to the magnesium reagents, organozinc compounds can be prepared via Zn insertion into halide bonds, either in the form of zinc dust[27] (previously typically activated with 1,2-dibromoethane and TMSCl)[28], Rieke zinc[29] or with the addition of LiCl.[30] With these methods it is possible to prepare a wide variety of sensitively functionalized aryl-, benzyl- and alkyl zinc reagents. Also iodine-zinc exchange reactions are known, leading directly to these very stable, mild and nevertheless reactive organometallic reagents.[31]

For a long time it was thought that this exchange reaction requires high reactivity of the metalating reagent, so predominantly organolithiums and Grignard reagents have been used for this transformation. However, in 1989 *Harada* and *Oku* resolved the mild reactivity of zincates by using gem-dihaloalkane derivatives as highly activated halogen substrates, and the first halogen-zinc exchange reaction of R_3ZnLi was reported.[32] Since this pioneering work, the applicability of the halogen-zinc exchange reaction has been greatly extended, in regard to both substrates and reagents.[33] In 1997 *Kondo*[34] and, more recently, *Uchiyama* thoroughly investigated the ligands in zincates and their effects on the exchange reaction, and so highly chemoselective halogen–zinc exchange reactions on aromatic rings have been developed.[35] In these interconversion reactions, bulky zincate complexes are vitally important for good reactivity and chemoselectivity and a ligand like *iso*-propyl or *tert*-butyl is more favorable for

[27] (a) T. N. Majid, P. Knochel, *Tetrahedron Lett.* **1990**, *31*, 4413; (b) H. P. Knoess, M. T. Furlong, M. J. Rozema, P. Knochel, *J. Org. Chem.* **1991**, *56*, 5974; (c) P. Knochel, C. Janakiram, *Tetrahedron* **1993**, *49*, 29; (d) T. M. Stevenson, B. Prasad, J. Citineni, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 8375.

[28] (a) M. Gaudemar, *Bull. Soc. Chim. Fr*. **1962**, *5*, 974; (b) E. Erdik, *Tetrahedron* **1987**, *43*, 2203

[29] (a) R. D. Rieke, *Science* **1989**, *246*, 1260; (b) M. V. Hanson, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445; (c) R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323; (d) M. V. Hanson, R. D. Rieke, *J. Am. Chem. Soc.* **1995**, *117*, 1445; (e) R. D: Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925.

[30] a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107; c) A. Metzger, M. A. Schade, G. Manolikakes, P. Knochel, *Chem. Asian J.* **2008**, *3*, 1678; d) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.

[31] a) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron Lett.* **1966**, *7*, 3353; b) M. J. Rozema, A. Sidduri, P. Knochel, *J. Org. Chem.* **1992**, *57*, 1956; c) M. J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 3115; d) I. Klement, P. Knochel, K. Chau, G. Cahiez, *Tetrahedron Lett.* **1994**, *35*, 1177; e) Y. Kondo, N. Takazawa, C. Yamazaki, T. Sakamoto *J. Org. Chem.* **1994**, *59*, 4717; f) S. Vettel, A. Vaupel, P. Knochel, *J. Org. Chem.* **1996**, *61*, 7473.

[32] a) T. Harada, K. Hattori, T. Katsuhira, A. Oku, *Tetrahedron Lett.* **1989**, *30*, 6035 b) T. Harada, Y. Kotani, T. Katsuhira, A. Oku, *Tetrahedron Lett.* **1991**, *32*, 1573.

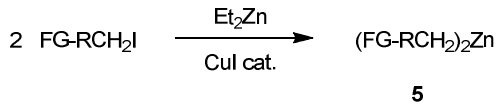
[33] M. Uchiyama, M. Koike, M. Kameda, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1996**, *118*, 8733.

[34] M. Uchiyama, S. Furumoto, M. Saito, Y. Kondo, T. Sakamoto**,** *J. Am. Chem. Soc.* **1997**, *119*, 11425.

[35] a) Y. Kondo, T. Komine, M. Fujinami, M. Uchiyama, T. Sakamoto, *J. Comb. Chem.* **1999**, *1*, 123; b) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514; c) M. Uchiyama, T. Furuyama, M. Kobayashi, Y. Matsumoto, K. Tanaka, *J. Am. Chem. Soc.* **2006**, *128*, 8204; d) M. Uchiyama, Y. Kobayashi, T. Furuyama, S. Nakamura, Y. Kajihara, T. Miyoshi, T. Sakamoto, Y. Kondo, K. Morokuma, *J. Am. Chem. Soc.* **2008**, *130*, 472.

metalation than ethyl or *n*-butyl.[36] As also the choice of substrates is relevant in this transformation, only alkenyl halides[37] and aryl halides[38] have generally been employed in this exchange reaction. When alkyl halides are used, undesired side reactions such as nucleophilic substitution, proton abstraction or reduction occasionally occur.

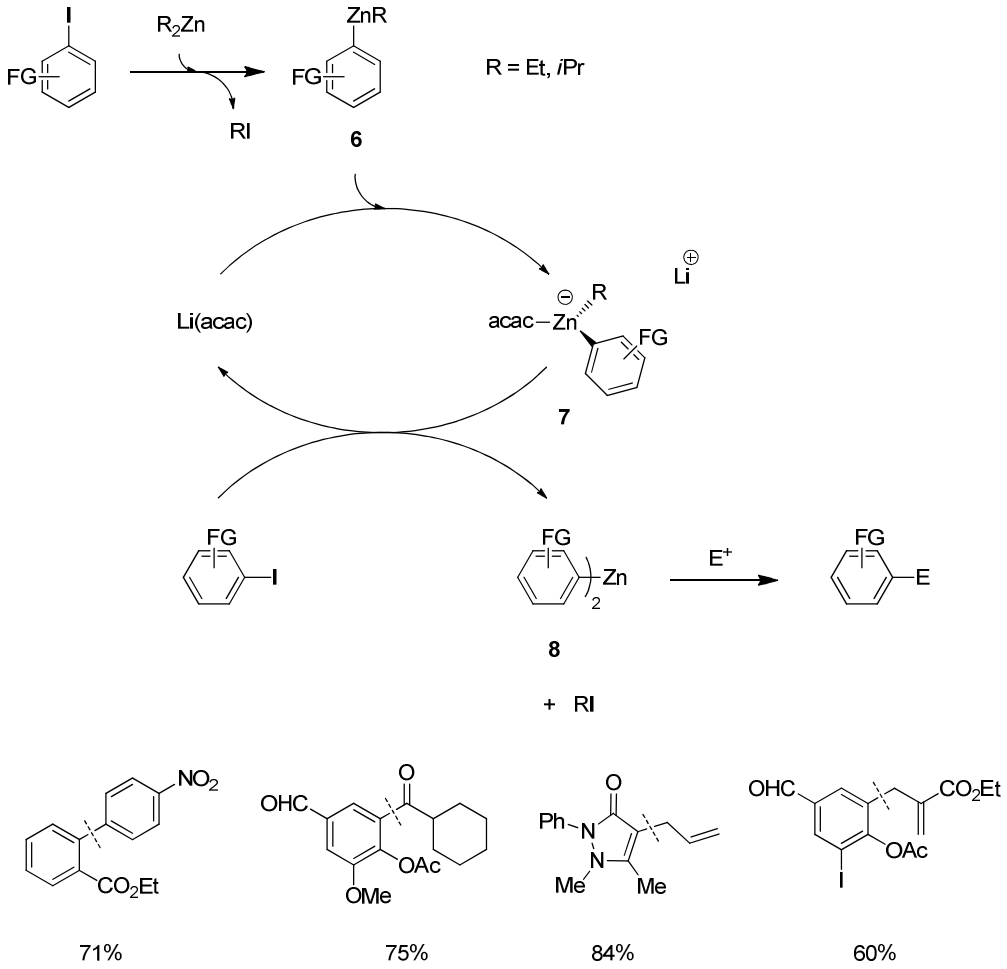
Another more practical way for the preparation of highly reactive organozincs is the iodine-zinc exchange reaction using diethylzinc, which leads to functionalized zinc reagents of the type **5** (Scheme 7).



Scheme 7: Cu^{I}-catalyzed iodine-zinc exchange reaction on alkyl iodides.

The main advantage here, compared to transmetalations from organomagnesium or especially organolithium compounds, consists of the functional group tolerance. However, the use of this method is confined to iodide compounds as source material and has to be performed with Et_2Zn[39] or $i Pr_2Zn$, since bromides and chlorides prove to be unreactive under these conditions. Furthermore, it can only be utilized for the preparation of primary and secondary dialkyl zinc compounds and fails in the case of aromatic iodides. An improved protocol was reported in 2004 consisting of a Li(acac) catalyzed iodine-zinc exchange using aryl iodides and R_2Zn (R = Et, *i*Pr, Scheme 8).[40] This new reaction provides access to functionalized diarylzinc reagents. The proposed reaction mechanism starts with the formation of a mixed aryl-alkyl zinc reagent **6**, which enters the catalytic cycle to form a zincate of type **7**. This is transmuted into the bisarylzinc **8** by reaction with another equivalent of the aryl iodide and can be trapped with various electrophilic species.

[36] L. Micouin, P. Knochel, *Synlett* **1997**, 327.
[37] a) T. Harada, D. Hara, T. Katsuhira, A. Oku, *Tetrahedron Lett.* **1988**, *29*, 3821; b) T. Harada, T. Katsuhira, D. Hara, Y. Kotani, A. Oku, *J. Org. Chem.* **1993**, *58*, 4897.
[38] a) Y. Kondo, N. Takazawa, C. Yamazaki, T. Sakamoto, *J. Org. Chem.* **1994**, *59*, 4717; b) M. Uchiyama, M. Kameda, O. Mishima, N. Yokoyama, M. Koike, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1998**, *120*, 4934.
[39] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.
[40] H. Naka, K. Ito, M. Ueno, K. Kobayashi, Y. Kondo, *New J. Chem.* **2010**, *34*, 1700.



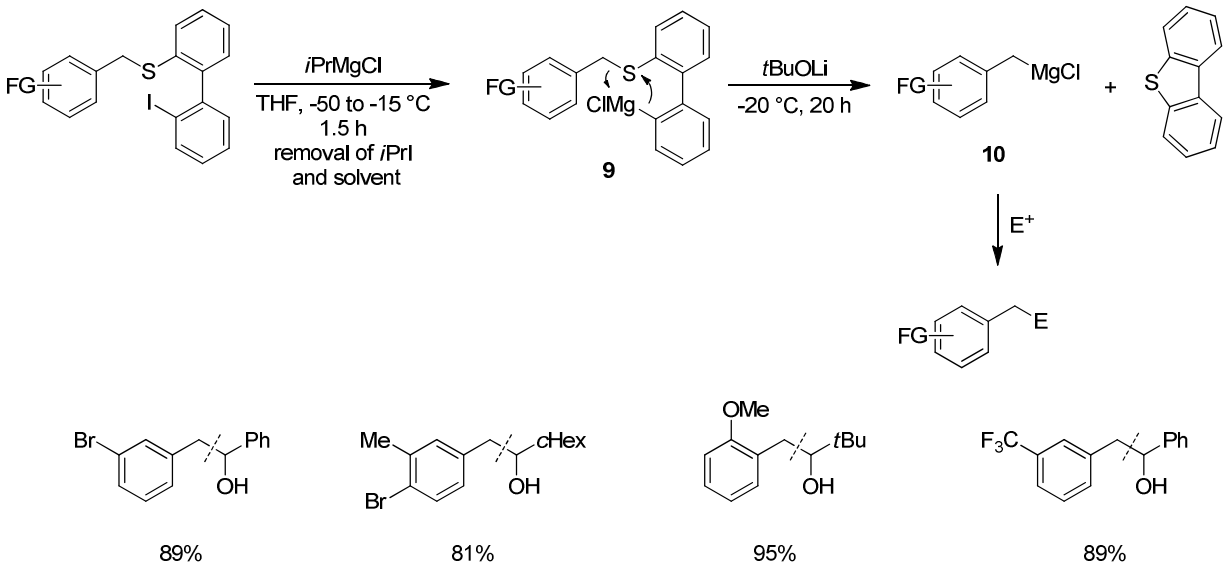
Scheme 8: Li-catalyzed iodine-zinc exchange reaction on aryl iodides.

3. Other Metal Exchange Reactions

If one is looking for drawbacks in halogen-metal exchange reactions, despite their excellent functional group tolerance, they would certainly mention the necessity of a reactive C-X bond (X = Cl, Br, I) in the molecule to be transformed. This can be problematic as many organic bromides and especially iodides suffer from dehalogenation reactions due to their thermal or photoinstability. To avoid these difficulties the use of non-halogenated source compounds for the exchange reaction has been the target of diverse investigations. The first S-Mg exchange was reported by *Knochel* and allowed the preparation of functionalized benzylic magnesium reagents.[41] These organomagnesium reagents are of special interest for their high reactivity and versatile synthetic applications. They are rather tedious to prepare by magnesium insertion into benzylic bromides, because of side products from the Wurtz homocoupling and

[41] A. H. Stoll, A. Krasovskiy, P. Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 606.

the difficult activation of the magnesium.[42] In *Knochel*'s protocol, the initial step is an I-Mg exchange reaction using *i*PrMgCl, which leads to a magnesiated species **9**. This compound underwent the S-Mg exchange together with a cyclization reaction after the addition of *t*BuOLi, furnishing the benzylic magnesium reagent **10** (Scheme 9). The formation of this cyclic dibenzothiophene is the responsible driving force in the S-Mg exchange and therefore in the generation of the new organometallic species.



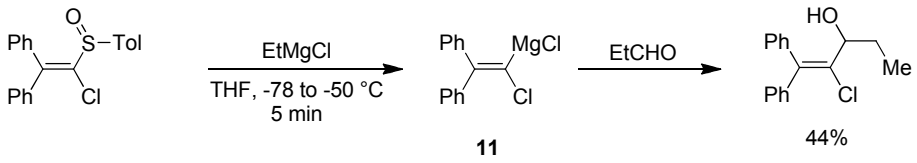
Scheme 9: S-Mg exchange and subsequent electrophilic reactions.

Another possible substitute for halogenated organics, suitable for exchange reaction for the generation of organomagnesium reagents, are sulfoxides. The fundamental work was reported by *Satoh* about ten years ago, where he demonstrated sulfoxide-magnesium exchanges on α-chloro-substituted vinylic sulfoxides, resulting in vinylic Grignard reagents of type **11** (Scheme 10).[43] Until then, such exchanges had been used for the preparation of chiral molecules and only been reported using highly reactive lithium reagents, therefore severely

[42] a) T. R. van den Ancker, C. L. Raston, *Organometallics* **1995**, *14*, 584; b) T. Alonso, S. Harvey, P. C. Junk, C. L. Raston, B. Skelton, A. H. White, *Organometallics* **1987**, *6*, 2110; c) H. Appler , L. W. Gross, B. Mayer , W. P. Neumann, *J. Organomet. Chem.* **1985**, *291*, 9; d) J. Scholz, K.-H. Thiele, *J. Organomet. Chem.* **1986**, *314*, 7; e) R. D. Rieke, *Acc. Chem. Res.* **1977**, *10*, 301; f) S. Harvey, C. L. Raston, *J. Chem. Soc. Chem. Commun.* **1988**, 652; g) L. M. Engelhardt, S. Harvey , C. L. Raston, A. H. White, *J. Organomet. Chem.* **1988**, *341*, 39; h) T. M. Nicoletti, C. L. Raston, M. V. Sargent, *J. Chem. Soc. Chem. Commun.* **1990**, 133; i) H. J. R. de Boer, O. S. Akkerman, F. Bickelhaupt, *J. Organomet. Chem.* **1987**, *321*, 291; j) T. R. van den Ancker, S. Harvey, C. L. Raston, *J. Organomet. Chem.* **1995**, *502*, 35; k) S. Harvey, P. C. Junk, C. L. Raston, G.Salem, *J. Org. Chem.* **1988**, *53*, 3134.

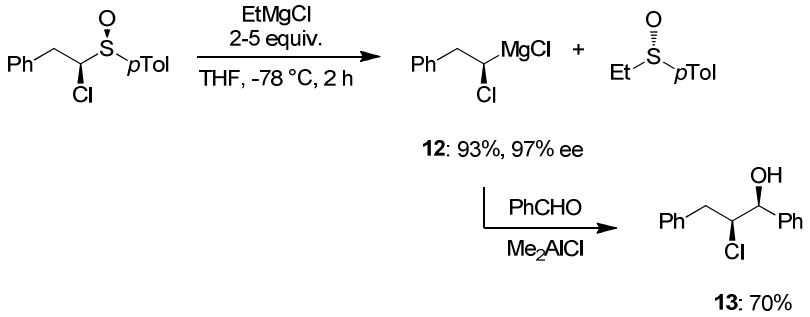
[43] T. Satoh, K. Takano, H. Someya, K. Matsuda. *Tetrahedron Lett.* **1995**, *36*, 7097; For leading references see: T. Satoh, K. Takano, H. Ota, H. Someya, K. Matsuda, K. Yamakawa, *Tetrahedron* **1998**, *54*, 5557; For a review, see: T. Satoh, *Chem. Soc. Rev.* **2007**, *36*, 1561.

limiting the functional group tolerance.[44] Also known is the related reaction of organomagnesium reagents with sulfinates by *Andersen*,[45] which gives access to diastereomerically pure sulfoxides.



Scheme 10: Sulfoxide-magnesium exchange on α-chloro vinyl sulfoxides.

The reactions utilizing magnesium exchange reagents were further explored by *Satoh*[46] and also *Hoffmann*,[47] who reported the generation of magnesium carbenoids of type **12** by a sulfoxide-magnesium exchange performed on chiral α-chloro-sulfoxides under inversion[48] of the configuration at the sulphur, while the configuration of the carbon atom remained unaffected (Scheme 11). The organomagnesium reagents from this exchange reaction could be used for the reaction with benzaldehyde to generate alcohol **13** with a second chiral center and transferring the enantiomeric purity.

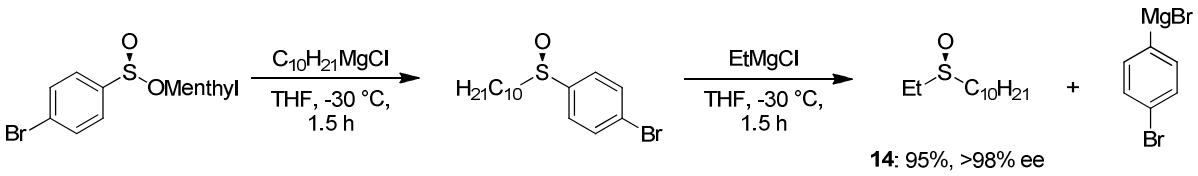


Scheme 11: Sulfoxide-magnesium exchange on chiral α-chloro alkyl sulfoxides.

The groups of *Capozzi* and *Naso* further exploited the sulfoxide-magnesium exchange for the enantioselective preparation of dialkyl sulfoxides of type **14** starting from chiral sulfoxides

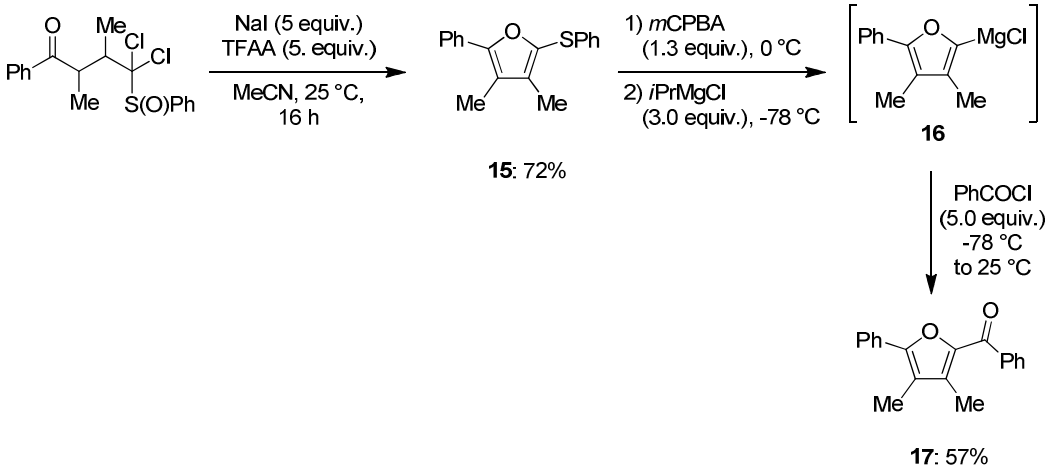
[44] a) D. Guillaneux, H. B. Kagan, *J. Org. Chem.* **1995**, *60*, 2502; b) H. B. Kagan, T. O. Luukas in *Transition Metals for Organic Synthesis* M. Beller, C. Bolm, Eds., Wiley-VCH, Weinheim, **2004**, 479; c) R. J. Kloetzing, P. Knochel, *Tetrahedron: Asymm.* **2006**, *17*, 116.
[45] a) K. K. Andersen, *Tetrahedron Lett.* **1962**, *3*, 93; b) K. K. Andersen, W. Gaffield, N. E. Papanikolau, J. W. Foley, R. I. Perkins, *J. Am. Chem. Soc.* **1964**, *86*, 5637.
[46] a) T. Satoh, D. Taguchi, C. Suzuki, S. Fujisawa, *Tetrahedron* **2001**, *57*, 493; b) T. Satoh, K. Akita, *Chem. Pharm. Bull.* **2003**, *51*, 181; c) T. Satoh, M. Miura, K. Sakai, Y. Yokoyama, *Tetrahedron* **2006**, *62*, 4253; d) S. Sugiyama, H. Shimizu, T. Satoh, *Tetrahedron Lett.* **2006**, *47*, 8771; e) T. Satoh, *Chem. Soc. Rev.* **2007**, *36*, 1561.
[47] a) R. W. Hoffmann, B. Hölzer, O. Knopff, K. Harms, *Angew. Chem. Int. Ed.* **2000**, *39*, 3072; b) B. Hölzer, R. W. Hoffmann, *Chem. Commun.* **2003**, 732; c) R. W. Hoffmann *Chem. Soc. Rev.* **2003**, *32*, 225.
[48] See *e.g.* M. Annunziata, M. Capozzi, C. Cardellicchio, F. Naso, P.Tortorella, *J. Org. Chem.* **2000**, *65*, 2843.

which had been prepared using the Andersen sulfinate (Scheme 12).[49] A similar approach had been used by *Lockard* in 1971, albeit employing lithium reagents in a large excess to accomplish the exchange.[50]



Scheme 12: Preparation of dialkyl sulfoxides.

Most of these studies focused on the preparation of chiral sulfoxides for chiral target products in general, rather disregarding the Grignard reagents generated during the sulfoxide-magnesium exchange. Recently, *Satoh* reported a preparative utilization of the sulfinyl group in the synthesis of functionalized furans.[51] After cyclization, the 2-furyl sulfide **15** is oxidized to the sulfoxide with *m*CPBA, and an exchange reaction with *i*PrMgCl furnishes the heterocyclic Grignard species **16** which can be reacted with benzoyl chloride to deliver the furan **17** (Scheme 13). The method suffers from the low compatibility of functional groups tolerated on the furan scaffold and the excess of reagents used.

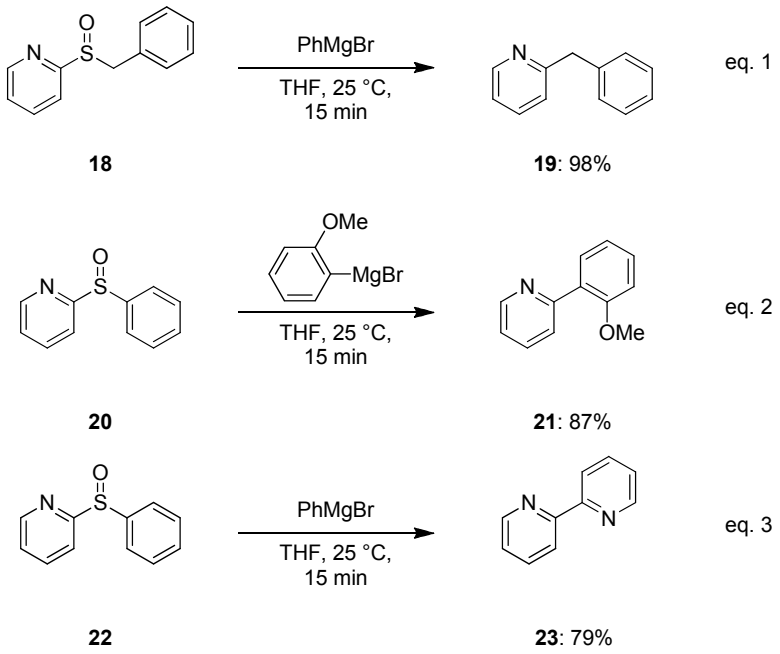


Scheme 13: Synthesis of a tetrasubstituted furan **17**.

A further interesting behaviour of sulfoxides was described by *Oae* and *Furukawa* when treating hetaryl sulfoxides with organometallic reagents.[52] Benzyl sulfoxide **18** reacts with

[49] M. A. M. Capozzi, C. Cardellicchio, F. Naso, V. Rosito, *J. Org. Chem.* **2002**, *67*, 7289; For a review, see: M. A. M. Capozzi, C. Cardellicchio, F. Naso, *Eur. J. Org. Chem.* **2004**, *9*, 1845.
[50] a) J. P. Lockard, C. W. Schroeck, C. R. Johnson, *Synthesis* **1973**, 485.
[51] T. Miyagawa, T. Satoh, *Tetrahedron Lett.* **2007**, *48*, 4849.
[52] S. Oae, T. Kawai, N. Furukawa, *Tetrahedron Lett.* **1984**, *25*, 69; b) S. Oae, *Phosphorus and Sulfur* **1986**, *27*, 13.

various magnesium or lithium compounds (PhMgBr, EtMgBr, MeMgBr, *n*BuLi) exclusively to the 2-benzyl-substituted pyridine **19**, according to the so called ligand coupling reaction (Scheme 14, eq. 1). Furthermore, when 2-(phenylsulfinyl)pyridine (**20**) reacted with an aryl Grignard, the 2-(2-methoxyphenyl)pyridine (**21**) was obtained in high yield (eq. 2). Then again, the alkyl sulfoxide **22** would undergo a reaction with PhMgBr, and furnish the 2,2'-bipyridine (**23**, eq. 3). This last reaction pathway is assumed to be an initial ligand exchange to form the 2-pyridyl Grignard reagent, which in a subsequent step attacks the original sulfoxide prior to ligand coupling.



Scheme 14: Ligand coupling and ligand exchange on 2-pyridinyl sulfoxides.

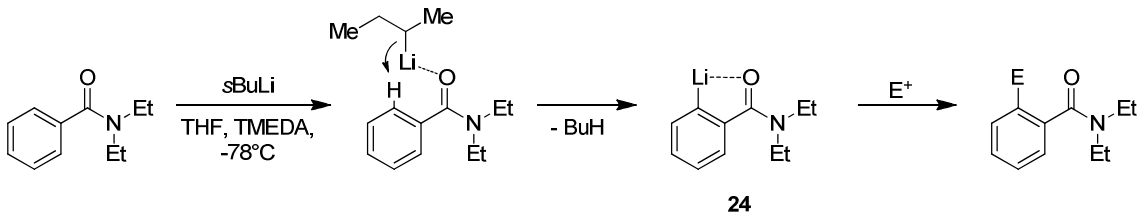
4. Metalation Reactions

Besides metal insertion and heteroatom-metal exchange, the third major pathway for the preparation of organometallics is the direct metalation of hydrocarbons using organometal (RMet) or metal amide (R_1R_2N-Met) bases.[53] The main advantage of this method, as with the sulfoxide-magnesium exchange, is in contrast to the previously presented ones (insertion and halogen-exchange reactions), the lack of a obligatory halogen-carbon bond being present. Thus, a more or less activated hydrogen-carbon bond is directly transformed into the corresponding metal species.

[53] For an early overview about metalation using organolithium compounds, see: J. M. Mallan, R. L. Bebb, *Chem. Rev.* **1969**, *69*, 693 and references therein; For reviews, see: a) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 380; b) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802.

A special case of these metalations, discovered independently by *Gilman*[54] and *Wittig*[55] in 1939/40 on anisole using *n*BuLi, is the directed *ortho*-metalation (D*o*M). Later on it was intensively investigated by *Roberts* and *Curtin*[56] as well as *Beak* and *Snieckus*[57], making use of lithium bases and what would later be known as complex-induced proximity effect (CIPE).[58] They described the D*o*M concept as the regioselective functionalization of aromatic systems, given that a directing metalation group (DMG) is present in the molecule. For a successful deprotonation to occur, the DMG must exhibit two contradicting properties, for being a good coordinating site for the organometal reagent and at the same time a poor electrophilic site for an attack by this strong base or the formed organometallic intermediates. A heteroatom is therefore almost an obligatory component of an efficient DMG. These groups can hence be amides, carbamides, sulfonamides, esters, cyanides, phosphorous-containing substituents, sulfoxides or sulfones and act as very powerful directing groups, contrary to e.g. ethers or amines.

The mode of function of these directing groups is a complexation of the metalating agent and therefore conducting the corresponding base towards the closest activated proton, which is generally in *ortho*-position to the directing group (Scheme 15). The resulting lithiated species **24** is furthermore stabilized by coordination to the DMG.[59]



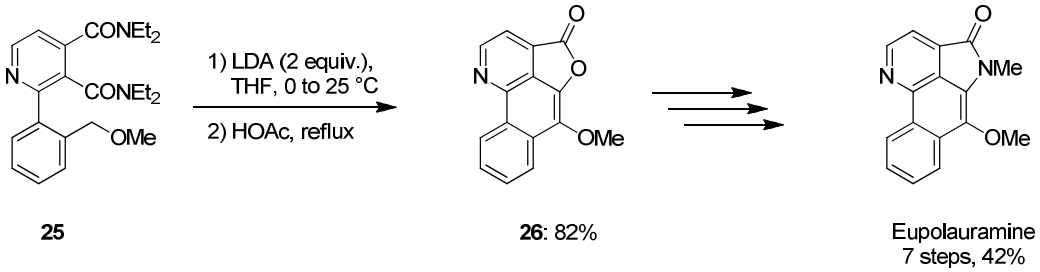
Scheme 15: *Ortho*-lithiation of aromatic system using a DMG.

Additional properties can by found in directing groups, for example steric hindrance, charge deactivation or even the combination of both effects. The rate of the deprotonation of the

[54] H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109.
[55] G. Wittig, G. Fuhrmann, *Chem. Ber.* **1940**, 73, 1197.
[56] J. D. Roberts, D. Y. Curtin, *J. Am. Chem. Soc.* **1946**, *68*, 356.
[57] For an overview, see: a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) M. C. Whisler, S. MacNeil, P. Beak, V. Snieckus, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; c) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356; d) E. Anctil, V. Snieckus, *The Directed ortho Metalation-Cross-Coupling Nexus. Synthetic Methodology for Aryl-Aryl and Aryl-Heteroatom-Aryl Bonds*, in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. F. Diederich, A. de Meijere, Eds., Wiley-VCH, Weinheim, **2004**, 761; e) C. G. Hartung, V. Snieckus, *The Directed ortho Metalation Reacton. A Point of Departure for new Synthetic Aromatic Chemistry*, in *Modern Arene Chemistry*, D. Astruc, Ed., Wiley-VCH, New York, **2002**, 330.
[58] a) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356; b) G. Klumpp, *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1.
[59] a) J. D. Roberts, D. Y. Curtin, *J. Am. Chem. Soc.* **1946**, *68*, 1658; b) A. A. Morton, *J. Am. Chem. Soc.* **1947**, *69*, 969.

substrate is also greatly influenced by substituent effects, in particular electron-withdrawing groups (EWG) are able to control the behaviour of the compounds to be metalated during the actual reaction.

There can be cases of substrates with a conflicting substitution pattern, when the directing effect of a DMG overrules that of weaker second one, or if two groups with comparable directing abilities are present leading to a decreased regioselectivity in the metalation process. The D*o*M concept has also found numerous applications in the preparation of natural products, for example in the total synthesis of Eupolauramine. Biaryl **25**, which is accessible by sequential cross-coupling and *ortho*-metalation chemistry, gives lactone **26** after acid-catalyzed cyclization (Scheme 16).

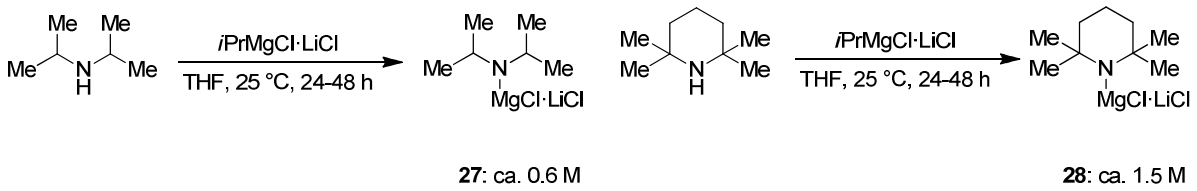


Scheme 16: D*o*M chemistry in the total synthesis of Eupolauramine.

Obviously, the use of lithium reagents very much limits the presence of functional groups and sensitive structures in the molecules to be metalated. During the last century, based on the original discoveries by *Meunier*,[60] various other groups demonstrated the feasibility of these metalations when mediated by much milder Mg-amide bases (the later on called "Hauser-Bases"). While *Hauser*[61] himself was relying on diethyl- and diisopropylaminomagnesium bromide, *Eaton*[62] and later on *Mulzer*[63] employed the sterically hindered 2,2,6,6-tetramethylpiperidine (tmp) as amine in their reagents tmpMgCl, tmpMgBr and also tmp_2Mg. Yet, these reagents tended to form aggregates similar to classic Grignard reagents, which greatly lowered their reactivity and therefore their practical use. As a consequence, large excesses of metalating agent as well as electrophile had to be used in order to cope with these problems. A big step forward was hence the development of the highly reactive Mg-amide bases of type $R_1R_2NMgX{\cdot}LiCl$ (**27** and **28**, Scheme 17). The foundation of this improvement was the observation that the addition of just one equivalent of LiCl resulted in the formation

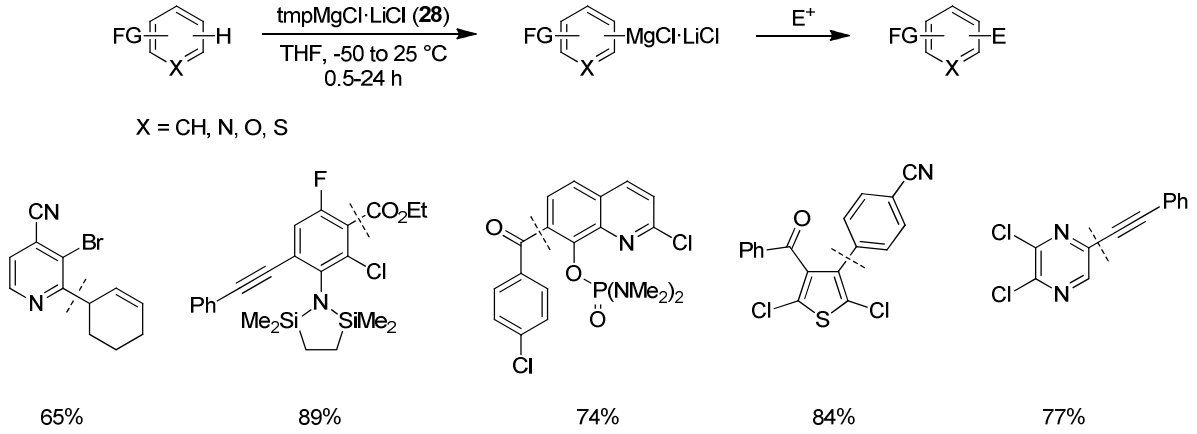
[60] L. Meunier, *C. R. Hebd. Seances Acad. Sci.* **1903**, *136*, 758.
[61] a) C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295; b) C. R. Hauser, F. C. Frostig, *J. Am. Chem. Soc.* **1949**, *71*, 1350.
[62] P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016.
[63] W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414.

of much more active, deaggregated exchange reagents ("Turbo-Grignard" e.g. *i*PrMgCl·LiCl, see above) and that the same concept could be transferred onto the amide bases (therefore called "Turbo-Hauser-Bases").[64]



Scheme 17: Preparation of Mg-amide bases (Turbo-Hauser-Bases).

The recent determination of the metalated amide's crystal structure proved that LiCl achieves complete deaggregation and is therefore able to form a monomeric species of the amide base.[65] These bases can easily be prepared from the corresponding amines by treatment with *i*PrMgCl·LiCl and are able to deprotonate many aromatics and heteroaromatics using only around 1.1 equivalents. The hereby generated organomagnesium reagents can be reacted with a broad range of electrophiles (Scheme 18).[66]

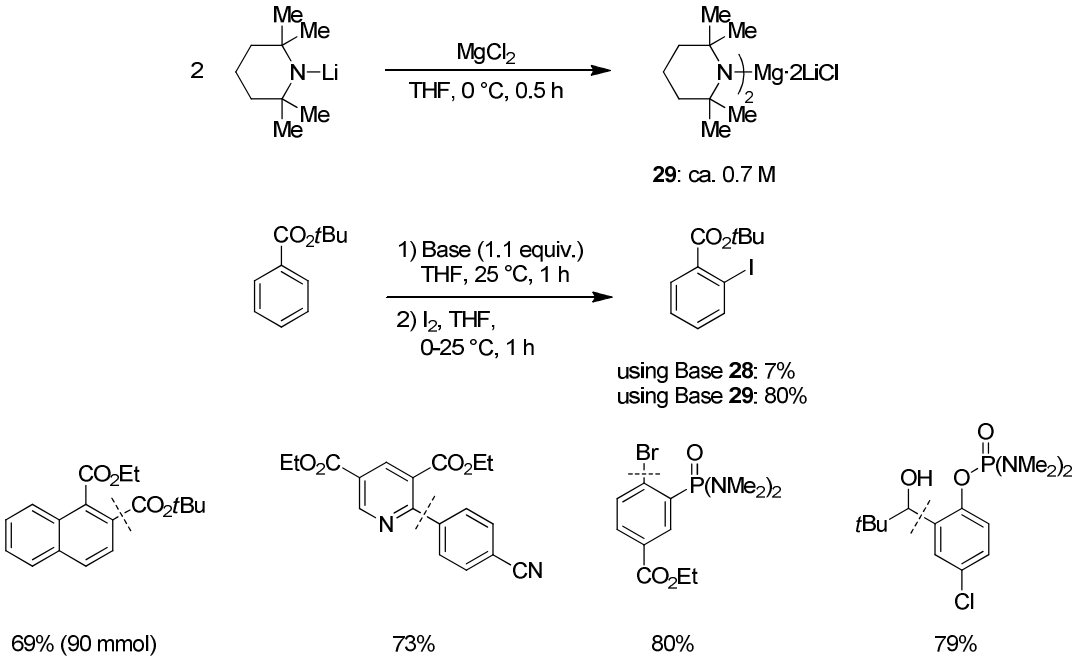


Scheme 18: Magnesiation reactions using tmpMgCl·LiCl (**28**).

The concept of these Turbo-Bases was significantly improved with the development of bis-amide bases, such as $tmp_2Mg \cdot 2LiCl$ (**29**), prepared from tmpLi and $MgCl_2$ (Scheme 19).[67] With this new mixed Li/Mg base, also less electron-poor and therefore less activated aromatics can be metalated, due to its enhanced reactivity while still maintaining an excellent

[64] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
[65] P. García-Alvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.
[66] Selected examples, see: a) A. H. Stoll, P. Knochel, *Org. Lett.* **2008**, *10*, 113; b) F. M. Piller, P. Knochel, *Org. Lett.* **2009**, 11, 445; c) M. Mosrin, T. Bresser *Org. Lett.* **2009,** *11*, 3406, d) C. J. Rohbogner, S. Wirth, P. Knochel, *Org. Lett.* **2010**, *12*, 1984; e) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.
[67] G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681.

functional group tolerance, also on larger scales.[68] By combining this magnesium base with the strong tetramethylphosphorodiamidate directing group, a range of phenol derivatives could be metalated, which facilitated access to *para*,*meta*-difunctionalized aromatics.[69]



Scheme 19: Preparation, reactivity and use of $tmp_2Mg{\cdot}2LiCl$ (**29**).

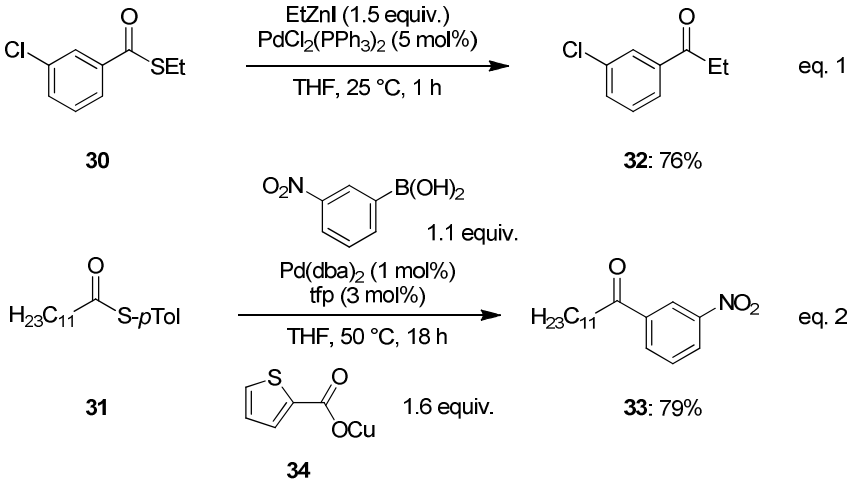
Still some substrates bearing extremely sensitive groups (e. g. nitro, aldehyde) and also some heterocycles are excluded from a magnesiation with the bases **28** and **29**. For metalating those compounds, more sensitive bases, namely tmpZnCl[70] and related to the bis-amide magnesium, $tmp_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$,[71] have been developed. These highly reactive and chemoselective bases are able to achieve zincation of various arenes and heteroarenes. Finally, also other metal amide bases have been synthesized addressing the different demands for metalating and quenching reactions with a wide palette of suitable compounds and electrophiles.[72]

[68] S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel *Org. Process Res. Dev*. **2010,** *14*, 339.
[69] C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503.
[70] M. Mosrin, P. Knochel, *Org. Lett.* 11, **2009,** 1837.
[71] S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed*. **2007**, *46*, 7685.
[72] For the preparation of Al-, Mn-, Fe-, La- and Zr-amide bases see: a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed*. **2009**, *48*, 1501; b) S. H. Wunderlich, M. Kienle, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 7256; c) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed*. **2009**, *48*, 9717; d) S. H. Wunderlich, P. Knochel, *Chem. Eur. J*. **2010**, *16*, 3304; e) M. Jeganmohan, P. Knochel, *Angew. Chem.* **2010**, *122*, 8699.

5. Cross-Coupling Reactions of Organometallics with Unsaturated Thioethers

The cross-coupling reaction of unsaturated thioethers and also thiols is known since the work of *Wenkert*[73] and *Takei*[74] in 1979. They used Grignard reagents with transition-metal catalysis for turning a carbon-sulfur bond into a carbon-carbon bond, representing an attractive variant of this type of very important bond formation.[75]

Based on these pioneering results, *Fukuyama*[76] and especially *Liebeskind*[77] were able to extremely extend the application scope of this cross-coupling reaction, turning it into a general ketone synthesis in 2000. With this methodology, functionalized thioesters like **30** and **31** could be converted into the corresponding ketones **32** and **33**. Where *Fukuyama* relied on zinc reagents with palladium catalysis (Scheme 20, eq. 1), *Liebeskind* employed boronic acids and combined a Pd catalyst with stoichiometric amounts of copper 2-thiophene carboxylate (CuTC, **34**).



Scheme 20: Synthesis of ketones from thioesters by *Fukuyama* (eq. 1) and *Liebeskind* (eq. 2).

[73] a) E. Wenkert, T. W. Ferreira, E. L. Michelotti, *J. Chem. Soc.,Chem. Commun.* **1979**, 637; b) E. Wenkert, T. W. Ferreira, *J. Chem. Soc., Chem. Commun.* **1982**, 840; c) E. Wenkert, M. E. Shepard, A. T. McPhail, *J. Chem. Soc., Chem. Commun.* **1986**, 1390; d) E. Wenkert, D. Chianelli, *J. Chem. Soc., Chem. Commun.* **1991**, 627.

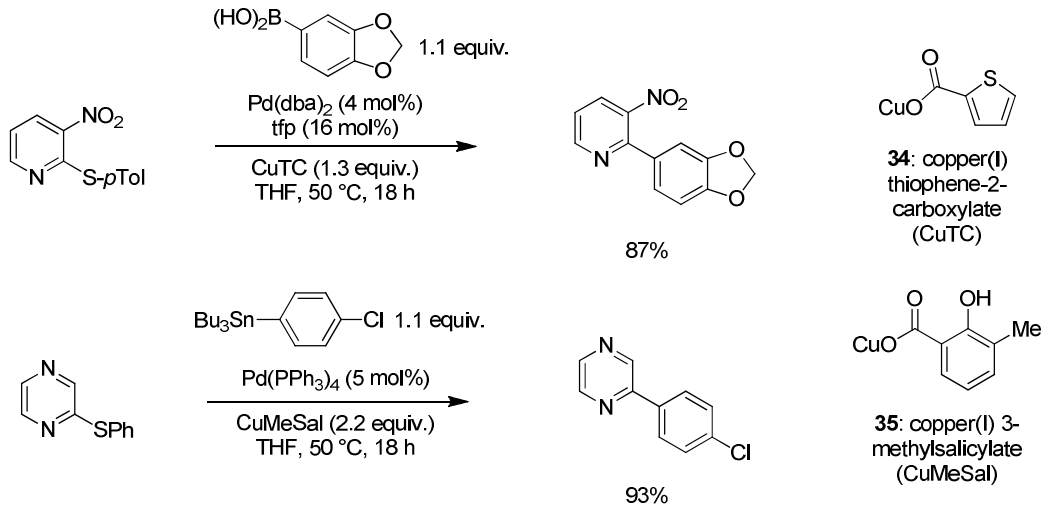
[74] a) H. Okamura, M. Miura, H. Takei, *Tetrahedron Lett.* **1979**, *20*, 43; b) H. Takei, M. Miura, H. Sugimura, H. Okamura, *Chem. Lett.* **1979**, *8*, 1447.

[75] For reviews, see: a) S. R. Dubbaka, P. Vogel, *Angew. Chem. Int. Ed.* **2005**, *44*, 7674; b) H. Prokopcova, C. O. Kappe, *Angew. Chem. Int. Ed.* **2009**, *48*, 2276; also see: H. Prokopcova, C. O. Kappe, *Angew. Chem. Int. Ed.*. **2008**, *47*, 3674.

[76] H. Tokuyama, S. Yokoshima, T. Yamashita, T. Fukuyama, *Tetrahedron Lett.* **1998**, *39*, 3189;

[77] a) J. Srogl, G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1997,** *119*, 12376; b) L. S. Liebeskind, J. Srogl, *J. Am. Chem. Soc.* **2000,** *122*, 11260; c) C. Savarin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2000**, *2*, 3229; d) C. L. Kusturin, L. S. Liebeskind, W. L. Neumann, *Org. Lett.* **2002**, *4*, 983; e) J. M. Villalobos, J. Srogl, L. S. Liebeskind, *J. Am. Chem. Soc.* **2007,** *129*, 15734; f) L. S. Liebeskind, H. Yang, H. Li, *Angew. Chem. Int. Ed.* **2009**, *48*, 1417; g) Y. Yu, L. S. Liebeskind, *J. Org. Chem.* **2004**, *69*, 3554.

In further studies, *Liebeskind* also used organostannanes[78] and later, in 2005, organoindium[79] compounds as nucleophiles for the coupling with thioesters to directly synthesize ketones. A major modification of this reaction was achieved recently when for the first time heteroaromatic thioethers could be employed in this Pd-catalyzed cross-coupling with organostannanes[80] and above all organoboronic acids,[81] furnishing various heterocycles in good yields (Scheme 21). A key feature of this method is the requirement of stoichiometric amounts of a Cu^{I}-carboxylate species as a metal cofactor, while simple Cu^{I} sources such as halides have no effect. Two copper reagents proved most suitable for this purpose, namely copper(I) thiophene-2-carboxylate (CuTC, **34**) and copper(I) 3-methylsalicylate (CuMeSal, **35**), both are commercially available, cheap and relatively air stable.[81a]

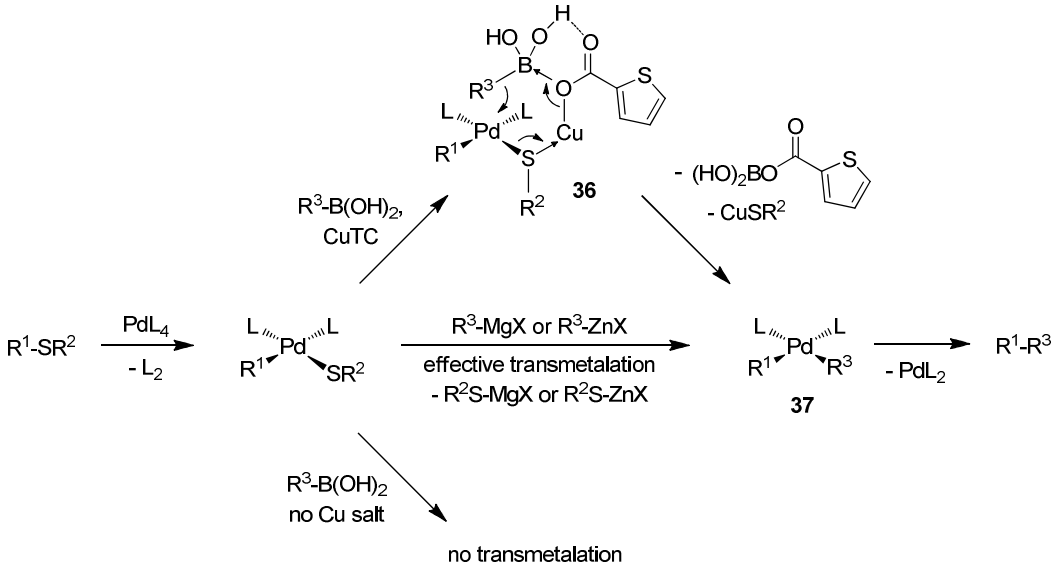


Scheme 21: Desulfitative C-C coupling with boronic acids or organostannanes (Liebeskind-Srogl reaction).

A mechanistic explanation for this unprecedented, Pd^{0}-catalyzed and Cu^{I}-mediated desulfitative cross-coupling is shown in Scheme 22.[81a] When the Cu^{I}-bound thiol ester undergoes oxidative addition to the Pd^{0} catalyst, the Cu^{I}-carboxylate serves a dual role in transition. It polarizes the Pd-S bond by coordination of Cu^{I} to the sulfur center, and on the other hand activates the trivalent boron center through coordination of the carboxylate group to the boron atom at the same time. Whereas in the traditional Suzuki-Miyaura cross-coupling

[78] R. Wittenberg, J. Srogl, M. Egi, L. S. Liebeskind, *Org. Lett.* **2003**, *5*, 3033.
[79] B. W. Fausett, L. S. Liebeskind, *J. Org. Chem.* **2005**, *70*, 4851.
[80] M. Egi, L. S. Liebeskind, *Org. Lett.* **2003**, *5*, 801.
[81] a) L. S. Liebeskind, J. Srogl, *Org. Lett.* **2002**, *4*, 979; b) S. Oumouch, M. Bourotte, M. Schmitt, J.-J. Bourguignon, *Synthesis* **2005**, 25; c) A. Aguilar-Aguilar, E. Pena-Cabrera, *Org. Lett.* **2007**, *9*, 4163; d) A. Lengar, C. O. Kappe, *Org. Lett.* **2004**, *6*, 771; e) H. Prokopcova, C. O. Kappe, *J. Org. Chem.* **2007**, *72*, 4440; f) W. van Rossom, W. Maes, L. Kishore, M. Ovaere, L. van Meervelt, W. Dehaen, *Org. Lett.* **2008**, *10*, 585; g) K. Itami, D. Yamazaki, J. Yoshida, *J. Am. Chem. Soc.* **2004**, *126*, 15396; h) C. Kusturin, L. S. Liebeskind, H. Rahman, K. Sample, B. Schweitzer, J. Srogl, W. L. Neumann, *Org. Lett.* **2003**, *5*, 4349.

reaction a base is essential for the reaction to occur,[82] here the nonbasic conditions of the unique Pd^0/Cu^I-mediated coupling protocol tolerate base-sensitive starting materials and also products. This fact combined with the observed higher reactivity of boronic acids compared to boronates[77g] led to the proposal of the hydrogen-bridged ternary complex **36**.



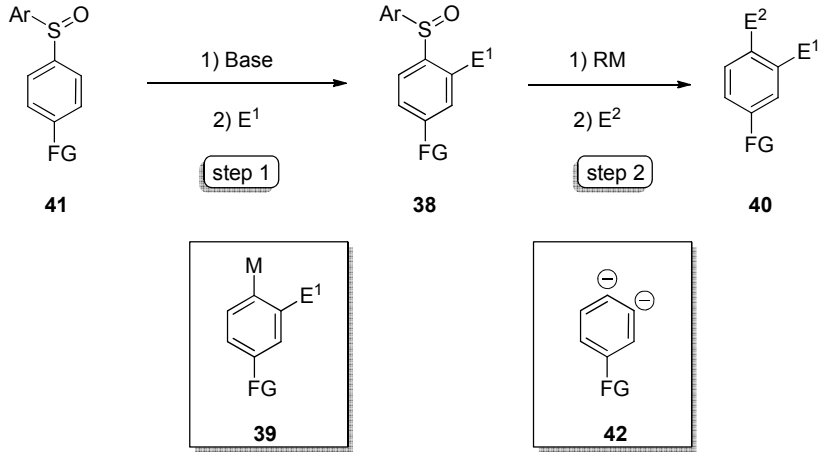
Scheme 22: Mechanism of the Cu^I-mediated Pd^0-catalyzed cross-coupling of boronic acids and transmetalation of organomagnesium or organozinc compounds.

Even in the presence of bromides, which are active electrophiles for the Suzuki cross-coupling, selective desulfitative C-C couplings can be performed in the absence of an additional base. This method is now generally referred to as Liebeskind-Srogl reaction. The reason for the success of this protocol with organomagnesium or organozinc reagents as nucleophiles is an efficient transmetalation step to intermediate **37**, promoted by the possible formation of an "ate" intermediate due to the high reactivity of Grignard reagents. In the case of organozinc compounds the explanation can by found in the polarization of the palladium-sulfur bond due to the known thiophilicity of the Zn^{2+} cation. Also other transition metals are known to be active catalysts for cross-coupling involving sulfides, like the Ni-catalyzed cross-couplings of organomagnesium reagents with vinyl sulfides,[73b,74a] and the cross-coupling of alkenyl sulfides with Grignard reagents using Fe catalysis, representing a pathway to functionalized styrenes.[83]

[82] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
[83] K. Itami, S. Higashi, M. Mineno, J. Yoshida, *Org. Lett.* **2005**, *7*, 1219.

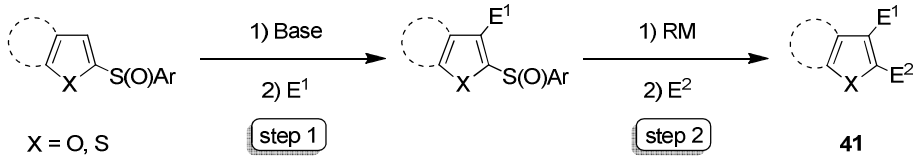
6. Objectives

Multifunctional aromatics with unusual substitution pattern are compounds still difficult to come by with standard methods. Therefore the first project of this work consisted of the idea to establish a new route to 1,2,4-trisubstituted aromatic compounds. The synthetic sequence should be general and the reagents used compatible with a broad range of functionalities. A sulfoxide moiety was the ideal centerpiece of this strategy, acting as a metalating directing group, leading to *ortho*-metalated sulfoxides, which can be reacted with electrophiles in step 1 to furnish products of type **38**. Secondly, the sulfoxide group should also be the source of a new organometallic reagent generated through a sulfoxide-metal exchange reaction in step 2 (Scheme 23). This metal species **39** can then be reacted with a second electrophile leading to the desired trisubstituted arenes of type **40**. The starting sulfoxide **41** could therefore be considered as a synthon for the bisanionic species **42**.



Scheme 23: General approach to 1,2,4-trisubstituted arenes **40**.

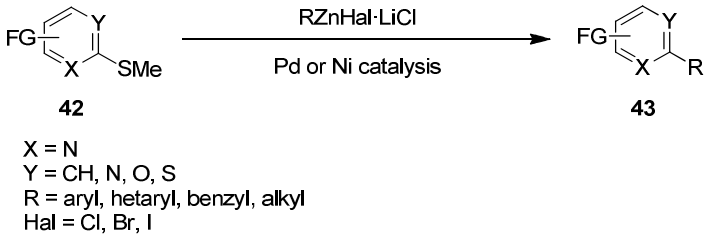
Heterocycles are aromatic structures of central importance in many biologically and pharmaceutically active molecules. So the further development of this chemistry opened up the second project, in which the two-step synthesis using the diverse properties of the sulfoxide group was to be exploited towards the synthesis of 1,2-difunctionalized 5-membered heterocycles **41** (Scheme 24).



Scheme 24: General approach to 1,2-disubstituted heterocycles **41**.

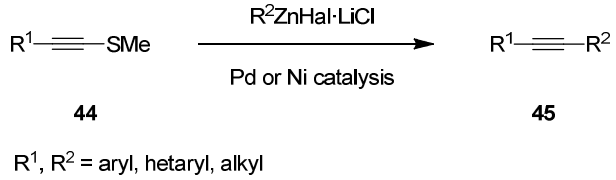
We also aimed for disubstituted pyridines, including an application of the previously mentioned ligand exchange reaction of 2-pyridinyl sulfoxides.

Due to the results of the heterocyclic sulfoxide chemistry, and the facile introduction of thioether-groups to heterocycles, advantageous compared to halogen substituents, a third project was derived. This evolved into the transition metal-catalyzed cross-coupling of methylthio-substituted N-heterocycles (**42**) with functionalized organozinc reagents, leading to various heterocyclic compounds of type **43** (Scheme 25).



Scheme 25: Pd- or Ni-catalyzed cross-coupling reactions of heterocyclic thioethers with functionalized organozinc compounds.

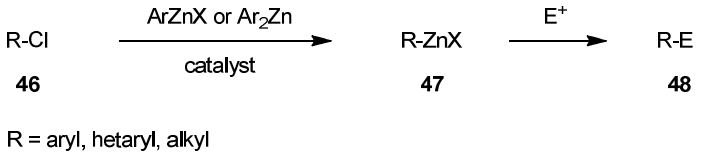
Based on this chemistry, a further extension of the method towards methylthio-substituted alkyenes **44** as electrophiles was envisioned, to furnish *bis*-substituted acetylenes of type **45** (Scheme 26).



Scheme 26: Pd- or Ni-catalyzed cross-coupling reactions of methylthio-substituted alkynes with functionalized organozinc compounds.

The possibility of employing other classes of organic thioethers for these cross-coupling reactions was also investigated.

Since zinc reagents are among the organometallics reagents with the best stability and the highest functional group tolerance, the fourth topic comprised the development of a new protocol for a direct chlorine-zinc exchange reaction. This transformation would lead from cheap and broadly available organic chlorides **46** directly to the corresponding organozinc reagents of type **47**, which can be further reacted with various electrophilic reactions to gain functionalized products **48** (Scheme 27).



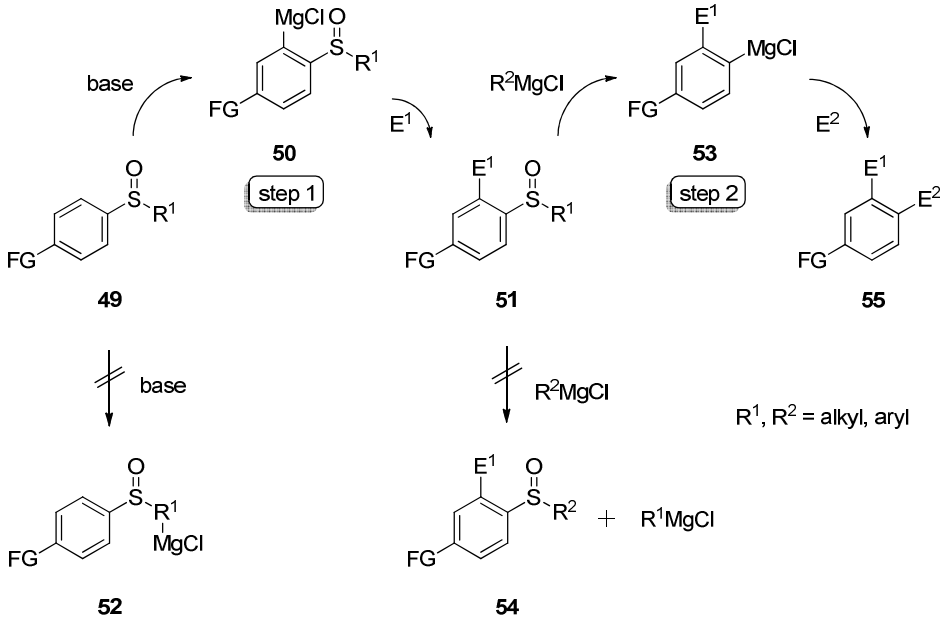
Scheme 27: Chlorine-zinc exchange reaction on organic chlorides.

B. Results and Discussion

1. Preparation of 1,2,4-Trisubstituted Arenes via D*o*M and Sulfoxide-Magnesium Exchange

1.1 Synthetic Strategy

As described in part A of this work, a multitude of reagents for executing a directed *ortho*-metalation (D*o*M) on aromatic systems are known, as well as organometallics capable of performing the sulfoxide-metal exchange. Though, as our plan for synthesizing trisubstituted arenes involved the best possible tolerance of functional groups and a minimal excess of organometallic reagents used, an optimization study had to be undertaken. In this we also investigated the best substrates for achieving high regioselectivity in both steps of the reaction sequence and focused on a very economical and convenient access to the starting materials. Therefore, we had to find an organic substituent R^1 on aryl sulfoxide **49** which would not be deprotonated in the first step of the synthesis, i.e. the directed metalation, leading via the magnesium reagent **50**, to the desired sulfoxide **51** and not the alternative compound **52** (Scheme 28). Furthermore, this substituent R^1 also had to lead to a selective cleavage of the two carbon-sulfur bonds in the second step of our sequence, so that the sulfoxide-metal exchange (triggered by R^2MgCl) would only result in the functionalized arylmetallic reagent **53**, avoiding wrong exchange leading to the side product **54**. The Grignard reagent would then be quenched in a second electrophilic reaction, furnishing the 1,2,4-trisubstituted arenes of type **55**.



Scheme 28: Tentative synthesis of 1,2,4-trisubstituted arenes **55** and possible side reactions.

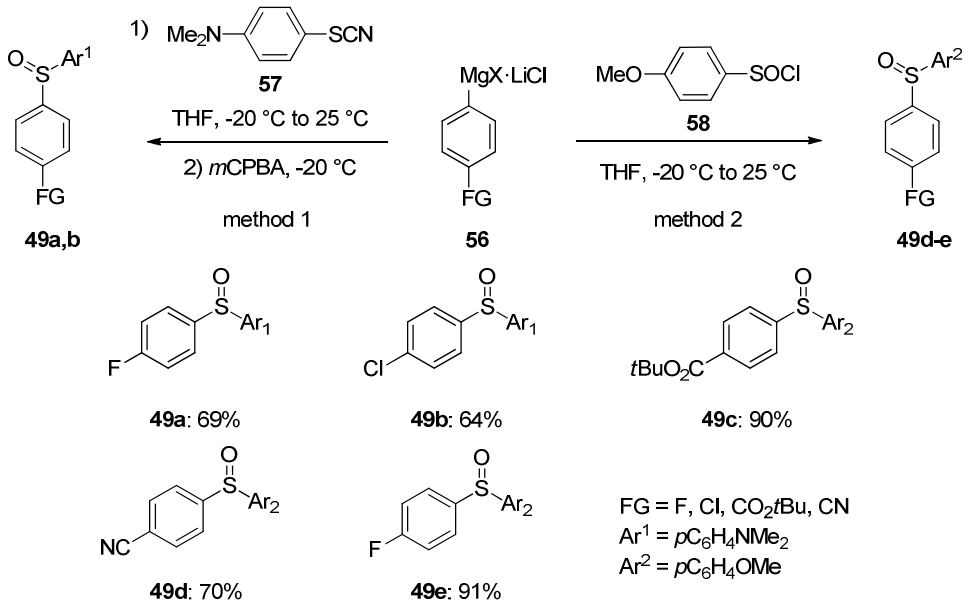
After extensive experimentation,[84] we managed to solve both of these problems by introducing donor substituents at the *para*-position of the R^1 group of **49**. Two different moieties, dimethylamino and methoxy, proved to be the most suitable in terms of efficiently controlling the selectivity of both reaction steps, as well as being easily accessible from commercially available materials.

1.2 Preparation of Diaryl Sulfoxides

We planned for a straightforward classic route to the diaryl sulfoxides via oxidation of an intermediate sulfide, prepared from *para*-substituted arylmagnesium reagents. Both of these steps should be convenient to run at multigram scales. Initially we focused on the preparation of the *N*,*N*-dimethylamino-substituted sulfoxides **49a,b**, which could be accessed by the reaction of functionalized organomagnesium reagents of type **56**[25,85] with 4-(dimethylamino)phenyl thiocyanate (**57**, $Me_2NC_6H_4SCN$; THF, -20 °C to 25 °C, 1 h) [86] followed by *m*CPBA oxidation (CH_2Cl_2, -20 °C, 2 h, 1.1 equiv)[87] in 64-69% yield (method 1, Scheme 29). The thiocyanate **57** can easily be prepared in large quantities (500 mmol) from

[84] For experimental details, see: Ph.D. thesis Christian B. Rauhut, LMU Munich, 2008.
[85] P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V.-V. Vu, *Angew., Chem. Int. Ed.* **2003**, *42*, 4302.
[86] H. Jendralla, L. Chen, *Synthesis* **1990**, 827.
[87] S. A. Lang, T. L. Fields, R. G. Wilkinson, S. M. Kang, Y. J. Lin, *Eur. Pat. Appl.* **1984**, 38.

N,*N*-dimethylaniline, bromine and ammonium thiocyanate.[88] The following oxidation of the crude sulfide and the purification of the sulfoxide, being contaminated with starting material and also the diaryl sulfone turned out to be troublesome, especially on multigram batches. Hence, we investigated an alternative method, avoiding an oxidative step, and eventually a more direct approach was found in the reaction of functionalized Grignard reagents of type **56** with 4-methoxybenzenesulfinyl chloride (**58**, $MeOC_6H_4S(O)Cl$; THF, -20 °C to 25 °C, 1 h, method 2) affording the desired 4-methoxy-substituted sulfoxides **49c-e** in 70-91% yield.[89] Here, the sulfoxide-donating reagent **58** can easily be prepared in equally large scales (500 mmol and more) from anisole and Bi_2O_3 in thionyl chloride as solvent and used without purification.[90]



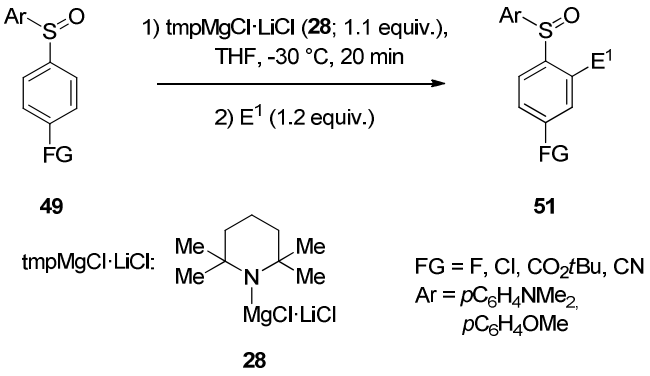
Scheme 29: Preparation of starting sulfoxides **49** from functionalized arylmagnesium reagents **56**.

1.3 *Ortho*-Metalation of Diaryl Sulfoxides

With these sulfoxides as starting compounds at hand, a practical base for the directed metalation had to be found. For reasons of compatibility with the functional groups (FG = F, Cl, CO_2tBu, CN) a hard lithium base was out of question. It turned out that tmpMgCl·LiCl[64] (**28**; tmp = 2,2,6,6-tetramethylpiperidinyl, 1.1 equiv.) was able to achieve a full magnesiation in the *ortho*-position of the electron-deficient arene in only 20 min at -30 °C. This reagent can easily be prepared by mixing tmpH and *i*PrMgCl·LiCl[25] at room temperature in THF and is

[88] R. Q. Brewster, W. Schroeder, *Org. Synth.* **1943**, *19*, 79.
[89] P. C. Unangst, D. T. Connor, S. R. Stabler, *J. Heterocycl. Chem.* **1987**, *24*, 817.
[90] M. Peyronneau, N. Roques, S. Mazieres, C. Le Roux, *Synlett* **2003**, 631.

stable at room temperature (slight loss of activity over 6 months). The reaction was monitored using GC by quenching aliquots with iodine or allyl bromide with tridecane as internal standard. Using this convenient and efficient protocol we were able to perform the directed metalation on the starting sulfoxides **49** and functionalize the resulting arylmagnesium reagents with a variety of different electrophiles (Scheme 30).



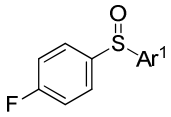
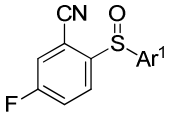
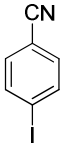
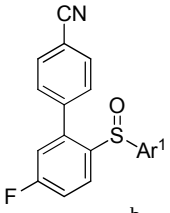
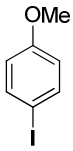
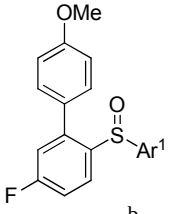
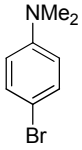
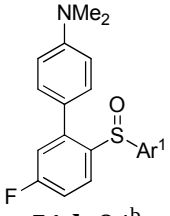
Scheme 30: Directed *ortho*-magnesiation leading to disubstituted sulfoxides **51**.

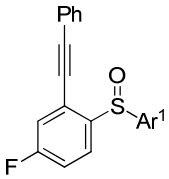
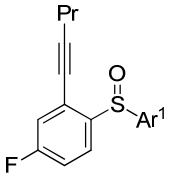
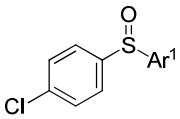
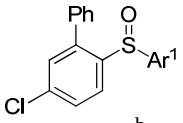
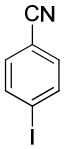
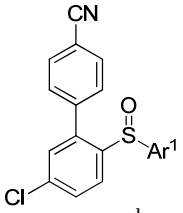
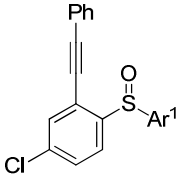
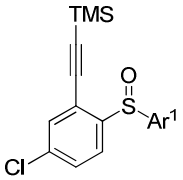
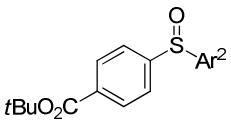
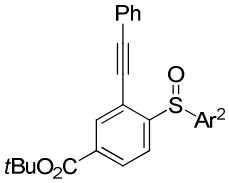
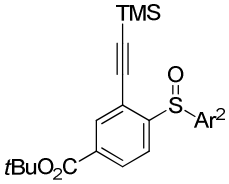
Thus, the sulfoxide **49a** (FG = F) was deprotonated with tmpMgCl·LiCl at -30 °C within 20 min and the organomagnesium species reacted with tosyl cyanide, which furnished sulfoxide **51a** bearing a cyano group in *ortho*-position in 79% yield (Table 1, entry 1). Alternatively, the organomagnesium reagent was transmetalated to the corresponding zinc reagent (using 1.0 equiv. of a 1.0 M solution of $ZnCl_2$ in THF) and subjected to a Pd-catalyzed ($Pd(PPh_3)_4$, 2 mol%) cross-coupling[91] with 4-iodobenzonitrile, giving the expected sulfoxide **51b** in 94% yield (entry 2). Similarly, the arylzinc reagent derived from **49a** underwent Negishi-type cross-coupling reactions with 4-iodoanisole or 4-bromo-*N*,*N*-dimethylaniline in the presence of 2 mol% $Pd(PPh_3)_4$, furnishing the *ortho*-substituted sulfoxides **51c** and **51d** in 84-93% yield (entries 3 and 4). By quenching the magnesiated derivative of **49a** with iodine, followed by a cross-coupling with 2-phenylethynylzinc chloride or 1-pentynylzinc chloride, we obtained the products **51e,f** in 74-94% yield (entries 5 and 6). The sulfoxide **49b** (FG = Cl) was metalated with tmpMgCl·LiCl at -30 °C within 20 min applying the same procedure as above. After transmetalating to the organozinc species, a Palladium-catalyzed cross-coupling with iodobenzene or 4-iodobenzonitrile led to the corresponding sulfoxides **51g,h** in 92-97% yield (entries 7 and 8). The organomagnesium species resulting from the reaction of **49b** with tmpMgCl·LiCl could also be quenched with iodine and cross-coupled with 2-phenylethynylzinc chloride or 2-trimethylsilylzinc chloride,

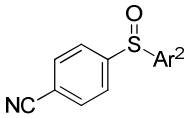
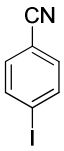
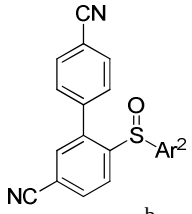
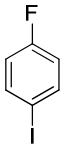
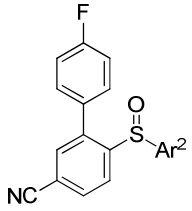
[91] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; c) E. Negishi, M. Quian, F. Zeng, L. Anastasia, D. Babinski, *Org. Lett.* **2003**, *5*, 1597; d) X. Zeng, M. Quian, Q. Hu, E. Negishi, *Angew. Chem., Int. Ed.* **2004**, *43*, 2259.

giving sulfoxides **51i,j** in 88-91% yield (entries 9 and 10). Due to the nature of the magnesium base and the low temperatures used, the tolerance towards sensitive functional group is very high, and the metalation of sulfoxide **49c** bearing an ester function occurred smoothly at -30 °C within 20 min. By adding iodine (1.2 equiv.) we could obtain the *ortho*-iodo-sulfoxide and submit it to Negishi-type cross-coupling reactions as crude material after an aqueous workup. Hence, after the reaction with 2-phenylethynylzinc chloride or 2-trimethylsilylzinc chloride we were able to isolate the diaryl sulfoxides **51k** and **51l** in 61-68% yield (entries 11 and 12). Also the presence of a nitrile function on the primary ring (**49d**, FG = CN) did not interfere with the reaction conditions for the deprotonation step. After a transmetalation ($ZnCl_2$ in THF) the organozinc species was used in a Pd-catalyzed cross-coupling reaction with 4-iodobenzonitrile or 4-iodoflourobenzene and allowed the isolation of the disubstituted benzonitriles **51m,n** in 71-88% yield (entries 13 and 14).

Table 1: Directed metalation of starting sulfoxides **49a-d** with tmpMgCl·LiCl (**28**) and electrophilic reaction leading to sulfoxides **51a-n**.

Entry	Sulfoxide	Electrophile	Product, yield [%][a]
1	 **49a**	TosCN	 **51a**: 79
2	**49a**		 **51b**: 94[b]
3	**49a**		 **51c**: 93[b]
4	**49a**		 **51d**: 84[b]

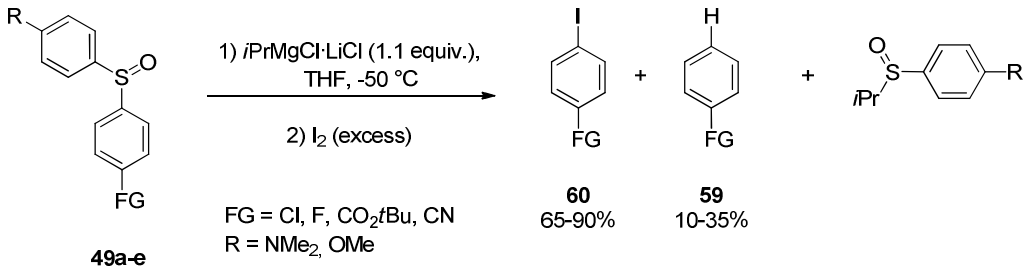
5	**49a**	1) I_2 2) Ph—≡—ZnCl	 **51e**: 94
6	**49a**	1) I_2 2) *n*Pr—≡—ZnCl	 **51f**: 74
7	 **49b**	PhI	 **51g**: 97[b]
8	**49b**		 **51h**: 92[b]
9	**49b**	1) I_2 2) Ph—≡—ZnCl	 **51i**: 91
10	**49b**	1) I_2 2) TMS—≡—ZnCl	 **51j**: 88
11	 **49c**	1) I_2 2) Ph—≡—ZnCl	 **51k**: 61
12	**49c**	1) I_2 2) TMS—≡—ZnCl	 **51l**: 68

13	 **49d**		 **51m**: 88[b]
14	**49d**		 **51n**: 71

[a] Yield of isolated analytically pure product. [b] After transmetalation ($ZnCl_2$ 1.0 M in THF). [c] $Ar^1 = pC_6H_4NMe_2$; $Ar^2 = pC_6H_4OMe$

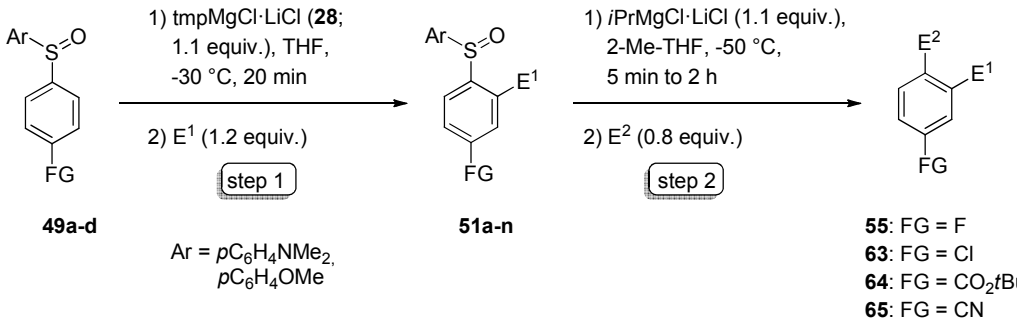
1.4 Sulfoxide-Magnesium Exchange on Diaryl Sulfoxides

Having prepared a broad variety of difunctionalized sulfoxides, we focused on step 2 of the synthesis, i.e. the sulfoxide-magnesium exchange. Since the sulfoxide group is stable in the presence of arylmagnesium reagents at low temperatures, which made the deprotonation reaction with tmpMgCl·LiCl (**28**) possible in the first place, we looked at more reactive Grignard reagents to perform the exchange. Again, lithium reagents were out of question because of their low tolerance towards the range of functional groups already established in the starting sulfoxides and further expanded with the functionalization of step 1. Experiments with different alkylmagnesium reagents, monitored by quenching reaction aliquots with iodine and determining the reaction progress by GC, revealed *i*PrMgCl·LiCl[25] to be the most efficient exchange reagent. Using the so called "Turbo-Grignard" we were able to achieve full conversion of the bisaryl sulfoxides **49a-e** at -50 °C within 15-60 min in THF, leaving the other functionalities unharmed. 1.10 Equivalents of *i*PrMgCl·LiCl were sufficient to complete the sulfoxide-magnesium exchange, but the iodolysis showed a considerable amount (up to 35%) of protonated species **59** alongside with the desired aryliodide **60** (Scheme 31).



Scheme 31: Sulfoxide-magnesium exchange reaction on bisaryl sulfoxides **49**.

Despite numerous experiments undertaken to find the source of the proton, including the use of various deuterated solvents, deuterated exchange reagents and working under extremely anaerobic conditions, we could not identify its origin.[84] To find a workaround, we tried a multitude of different solvents and solvent mixtures. While all replacements for THF and all mixtures with cosolvents (Et_2O, CH_2Cl_2, MTBE, NMP, DMPU, CPME) either led to an increase in side products formed, or to stalled exchange reactions, we discovered that changing the solvent to 2-methyl-THF reduced the percentage of protonated and therefore lost aryl species to about 10-20%. This observation led us to assume that the side reaction occurs during the exchange reaction and is most likely a radical process. By performing this reaction in 2-Me-THF and using only 0.8 equivalents of electrophile for the quenching reaction, we were able to develop a convenient and efficient synthetic protocol for preparing the trisubstituted aromatics of type **55, 63-65** (Scheme 32).



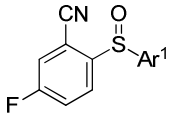
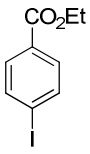
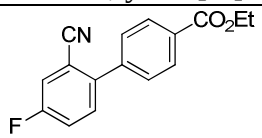
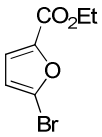
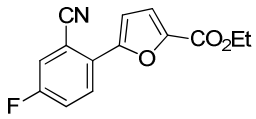
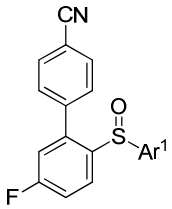
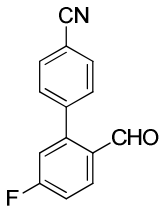
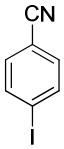
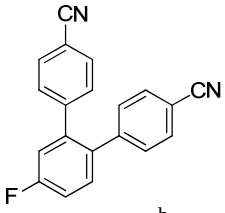
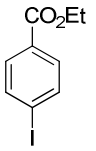
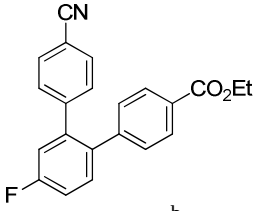
Scheme 32: Final conditions for the two-step protocol for directed metalation and sulfoxide-magnesium exchange reaction leading to 1,2,4-trisubstituted arenes **55, 63-65**.

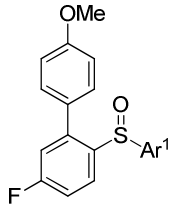
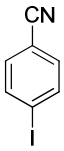
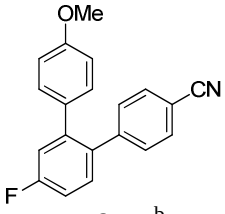
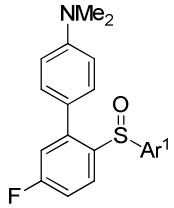
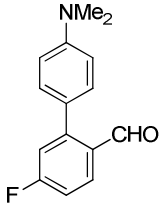
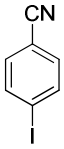
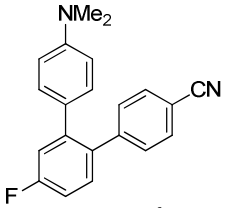
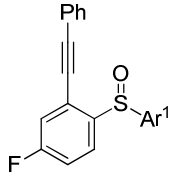
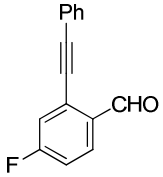
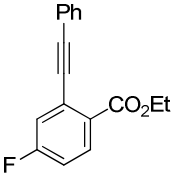
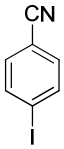
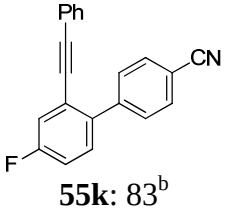
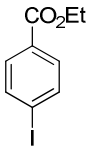
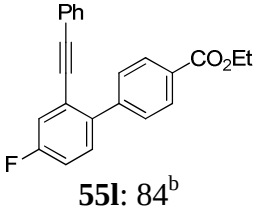
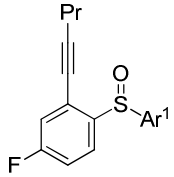
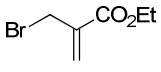
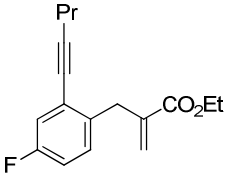
1.4.1 Sulfoxide-Magnesium Exchange on *para*-Fluoro-Diaryl Sulfoxides

Applying this procedure, sulfoxide **51a** could be exchanged with *i*PrMgCl·LiCl at -50 °C within 5 min. The functionalized Grignard reagent was transmetalated to the organozinc species ($ZnCl_2$ 1.0 M in THF) and subjected to Pd-catalyzed cross-coupling reactions with ethyl 4-iodobenzoate or ethyl 5-bromofuran-2-carboxylate, leading to the disubstituted benzonitrile derivatives **55a** and **55b** in 72-78% yield (Table 2, entries 1 and 2,). With the cyano group attached to the secondary aromatic ring, the sulfoxide-magnesium exchange was completed at -50 °C within 1 h and quenching the intermediate Grignard reagent with DMF furnished, after aqueous workup, the functionalized benzaldehyde **55c** in 76% yield (Table 2, entry 3). Alternatively, the magnesium species resulting from the exchange reaction could be transmetalated into an organozinc reagent (using $ZnCl_2$ 1.0 M in THF) and used in a Negishi-

type cross-coupling reaction with 4-iodobenzonitrile or 4-iodo ethyl benzoate, leading to terphenyls **55d,e** in 75-76% yield (entries 4 and 5). The sulfoxide-magnesium exchange could also be performed on electron-rich-substituted sulfoxides **51c,d** (0 °C, 1 h) and by performing cross-coupling reactions or directly reacting the magnesium organyl with DMF, we obtained the trisubstituted arenes **55f-h** in 72-86% yield (entries 6-8). With the 2-alkynyl-substituted *bis*aryl sulfoxides **51e** the *i*PrMgCl·LiCl-triggered exchange step took place at -50 °C within 5 min. Trapping with DMF or ethyl chloroformiate, performing a cross-coupling reaction (after transmetalation with $ZnCl_2$ in THF) with aryl iodides or an allylation reaction led to the polyfunctionalized arylacetylenes **55i-m** in 67-94% yield (entries 9-13).

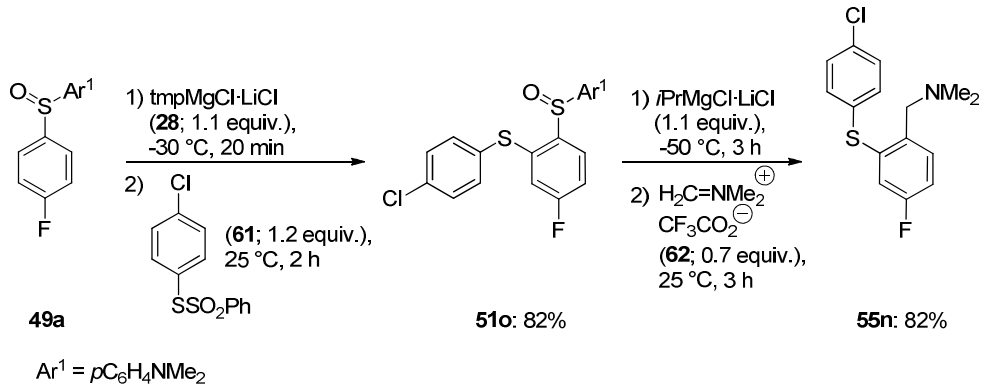
Table 2: Sulfoxide-magnesium exchange on sulfoxides **51a-e** and electrophilic reaction leading to 1,2,4-trisubstituted arenes **55a-m**.

Entry	Sulfoxide	Electrophile	Product, yield [%][a]
1	 **51a**		 **55a**: 78
2	**51a**		 **55b**: 72
3	 **51b**	DMF	 **55c**: 76
4	**51b**		 **55d**: 75[b]
5	**51b**		 **55e**: 76[b]

6	 **51c**		 **55f**: 86[b]
7	 **51d**	DMF	 **55g**: 79
8	**51d**		 **55h**: 72[b]
9	 **51e**	DMF	 **55i**: 94
10	**51e**	$ClCO_2Et$	 **55j**: 67
11	**51e**		 **55k**: 83[b]
12	**51e**		 **55l**: 84[b]
13	 **51f**		 **55m**: 71

[a] Yield of isolated analytically pure product. [b] After transmetalation ($ZnCl_2$ 1.0 M in THF). [c] $Ar^1 = pC_6H_4NMe_2$.

We have applied this sequence to the preparation of the biological active sulfide **55n**, which is a serotonin reuptake inhibitor.[92] Thus, the sulfoxide **49a** (FG = F) was metalated with tmpMgCl·LiCl (**28**, 1.1 equiv.) at -30 °C within 20 min. Quenching of the resulting magnesium species with thiosulfonate **61** led to the expected sulfide **51o** in 82% yield. This sulfoxide was treated with *i*PrMgCl·LiCl at -50 °C, furnishing the corresponding magnesium intermediate within 3 h, which reacted cleanly with the iminium salt **62** to give the serotonin reuptake inhibitor **55n** in 82% yield (Scheme 33).



Scheme 33: Two-step preparation of the serotonin reuptake inhibitor **55n**.

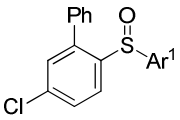
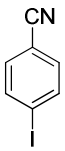
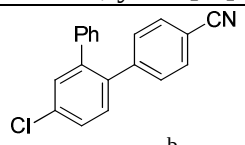
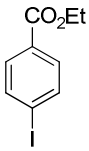
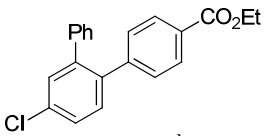
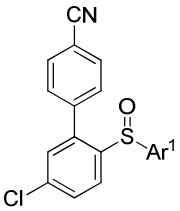
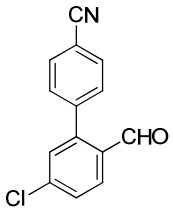
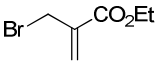
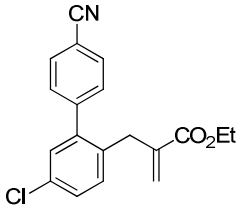
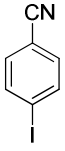
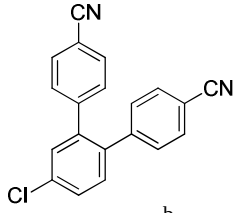
1.4.2 Sulfoxide-Magnesium Exchange on *para*-Chloro-Diaryl Sulfoxides

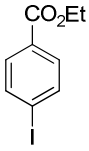
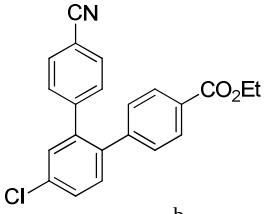
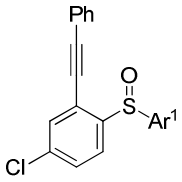
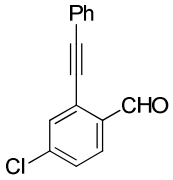
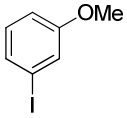
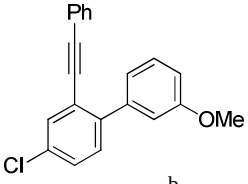
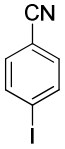
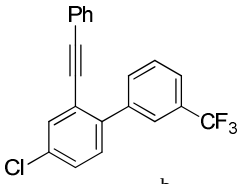
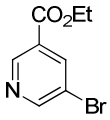
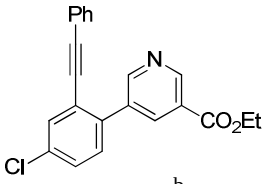
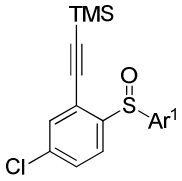
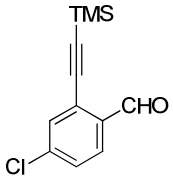
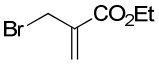
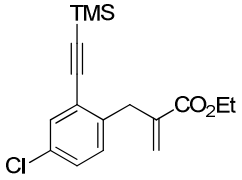
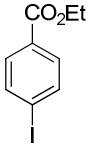
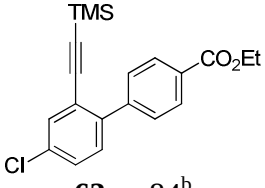
When used on sulfoxides bearing a chlorine on the primary ring (**51g-j**, FG = Cl), the exchange protocol worked equally well as previously described. Thus, the reaction of **51g** with *i*PrMgCl·LiCl at -50 °C was completed within 1 h, and followed after transmetalation with $ZnCl_2$ by a cross-coupling with 4-iodobenzonitrile, furnished the terphenyl **63a** in 93% yield (Table 3, entry 1). Alternativly, we chose ethyl 4-iodobenzoate for the Pd-catalyzed cross-coupling and isolated the terphenyl **63b** in 89% yield (entry 2). The sulfoxide-magnesium exchange could also be performed on sulfoxide **51h** bearing a cyano group on the secondary aromatic ring at -50 °C within 1 h and quenching the arylmagnesium derivative with DMF led to benzaldehyde **63c** in 74% yield (entry 3). A copper-catalyzed allylation reaction with ethyl 2-(bromomethyl)acrylate gave biphenyl **63d** in 48% yield, while a Pd-catalyzed cross-coupling with 4-iodobenzonitrile or ethyl 4-iodobenzoate furnished the disubstituted chlorobenzenes **63e,f** in 81-90% yield (entries 4-6). In the case of alkynyl-substituted sulfoxide **51i**, the sulfoxide-magnesium exchange took place at -50 °C in only 5 min and the functionalized benzaldehyde **63g** could be obtained in 93% yield after trapping

[92] Z. Polivka, K. Dobrovsk, A. Silhankova, K. Sindelar, R. Mickova, V. Valenta, I. Krejci, *PCT Int. Appl. WO 9717325*, **1997**.

with DMF (entry 7). Instead of directly functionalizing the arylmagnesium reagent, we transmetalated with $ZnCl_2$ and utilized a Pd-catalyzed cross-coupling with 3-iodoanisole, 1-iodo-3-(trifluoromethyl)benzene or ethyl 5-bromonicotinate to produce the terphenylic products **63h-j** in 59-73% yield (entries 8-10). The exchange reaction with *i*PrMgCl·LiCl at -50 °C performed equally fast and selective on sulfoxide **51j** bearing the TMS-protected acetylene, and after 5 min of stirring, we smoothly obtained the corresponding magnesium reagent. This reacted with DMF, ethyl 2-(bromomethyl)acrylate (20 mol% CuCN·2LiCl present) or ethyl 4-iodobenzoate (after transmetalation with $ZnCl_2$ and in the presence of 2% $Pd(PPh_3)_4$) to furnish a range of polyfunctional compounds **63k-m** in 84-89% yield (entries 11-13).

Table 3: Sulfoxide-magnesium exchange on sulfoxides **51g-j** and electrophilic reaction leading to 1,2,4-trisubstituted arenes **63a-m**.

Entry	Sulfoxide	Electrophile	Product, yield [%][a]
1	 **51g**		 **63a**: 93[b]
2	**51g**		 **63b**: 89[b]
3	 **51h**	DMF	 **63c**: 74
4	**51h**		 **63d**: 48
5	**51h**		 **63e**: 81[b]

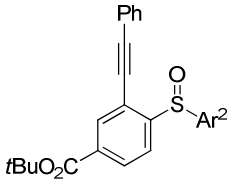
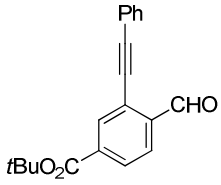
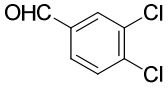
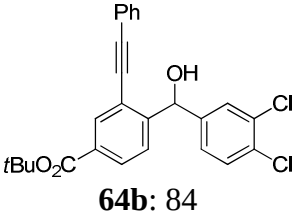
6	**51h**		 **63f**: 90[b]
7	 **51i**	DMF	 **63g**: 93
8	**51i**		 **63h**: 73[b]
9	**51i**		 **63i**: 72[b]
10	**51i**		 **63j**: 59[b]
11	 **51j**	DMF	 **63k**: 89
12	**51j**		 **63l**: 87
13	**51j**		 **63m**: 84[b]

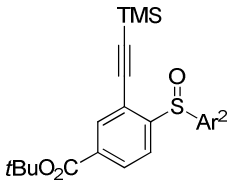
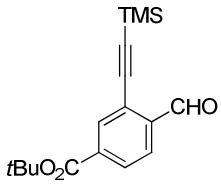
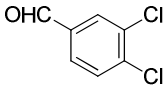
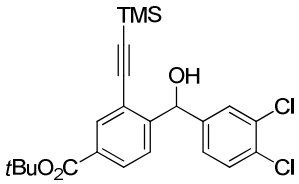
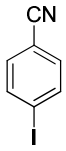
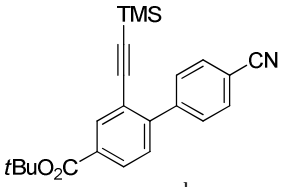
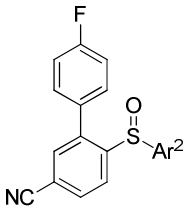
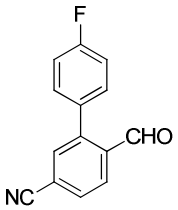
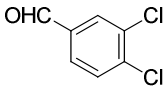
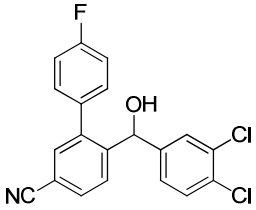
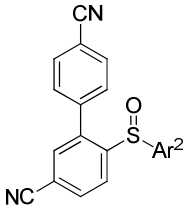
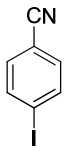
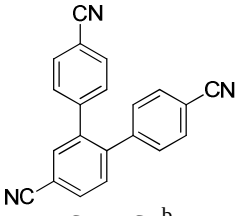
[a] Yield of isolated analytically pure product. [b] After transmetalation ($ZnCl_2$ 1.0 M in THF). [c] $Ar^1 = pC_6H_4NMe_2$.

1.4.2 Sulfoxide-Magnesium Exchange on *para*-Ester and *para*-Cyano Diaryl Sulfoxides

As mentioned before, the sulfoxide-magnesium exchange protocol is compatible with a variety of other sensitive functional groups, such as an ester or a nitrile. Thus, bisaryl sulfoxide **51k** (FG = CO_2tBu) underwent a smooth exchange reaction with *i*PrMgCl·LiCl (-50 °C, 5 min, 2-Me-THF) and quenching with DMF furnished the aldehyde **64a** in 71% yield (Table 4, entry 1). The intermediate arylmagnesium compound derived from **51k** can also be trapped with 3,4-dichlorobenzaldehyde, leading to the secondary alcohol **64b** in 84% yield (entry 2). Similarly, the TMS-acetylene-substituted sulfoxide **51l** underwent the exchange reaction (-50 °C, 5 min, 2-Me-THF) and reacted equally well with DMF or 3,4-dichlorobenzaldehyde, or in a Pd-catalyzed cross-coupling with 4-iodobenzonitrile after transmetalation to zinc. So we were able to furnish the 3,4-disubstituted benzoates **64c-e** in 77-82% yield (entries 3-5). The 4-sulfinyl-benzontrile derivate **51m** underwent the exchange reaction very rapidly, and after 5 min at -50 °C, the arylmagnesium species formed reacted with DMF or 3,4-dichlorobenzaldehyde. This lead to the 4-cyanobenzaldehyde **65a** and the secondary alcohol **65b** in 72% and 88% yield, respectively (entries 6 and 7). Sulfoxide **51n**, bearing a nitrile group on the primary (sulfoxide bearing) as well as on the secondary aromatic ring, could readily be exchanged with *i*PrMgCl·LiCl (–50 °C, 5 min, 2-Me-THF), transmetalated with $ZnCl_2$ and cross-coupled with 4-iodobenzonitrile, yielding the *tris*-cyano-terphenyl **65c** in 64% yield (entry 8).

Table 4: Sulfoxide-magnesium exchange on sulfoxides **51k-n** and electrophilic reaction leading to 1,2,4-trisubstituted arenes **64a-e, 65a-c**.

Entry	Sulfoxide	Electrophile	Product, yield [%][a]
1	 **51k**	DMF	 **64a**: 71
2	**51k**		 **64b**: 84

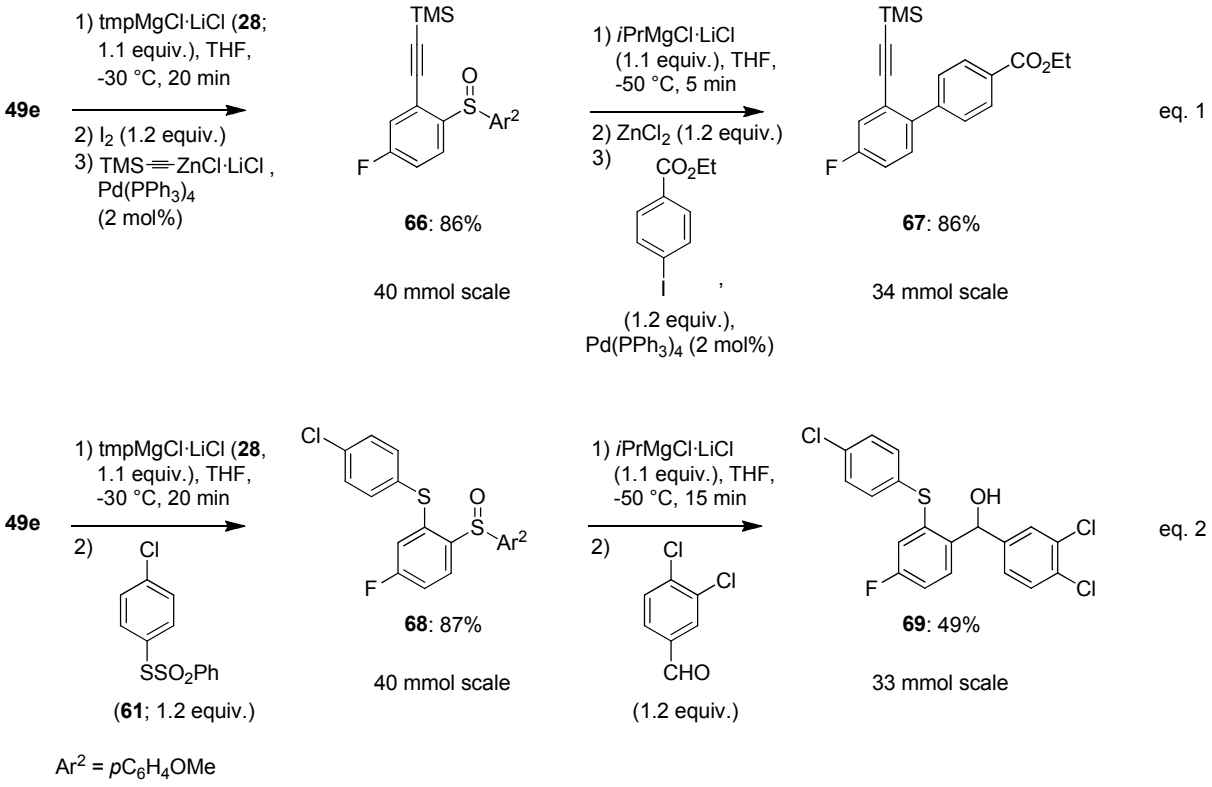
3	 **51l**	DMF	 **64c**: 78
4	**51l**		 **64d**: 82
5	**51l**		 **64e**: 77[b]
6	 **51m**	DMF	 **65a**: 72
7	**51m**		 **65b**: 88
8	 **51n**		 **65c**: 64[b]

[a] Yield of isolated analytically pure product. [b] After transmetalation ($ZnCl_2$ 1.0 M in THF). [c] $Ar^2 = pC_6H_4OMe$.

1.5 Large Scale Preparation of 1,2,4-Trisubstituted Arenes using the Two-Step Protocol

To demonstrate the synthetic advantage of the developed two-step protocol (step 1 being the metalation using tmpMgCl·LiCl (**28**) directed by the sulfoxide group, and step 2 being the sulfoxide-magnesium exchange using *i*PrMgCl·LiCl) we aimed for a large scale synthesis using our method. Thus, sulfoxide **49e** (FG = F) was magnesiated with tmpMgCl·LiCl (**28**; -30 °C, 20 min, THF) on a 40 mmol scale and trapped with iodine. The resulting aryl iodide

then underwent a smooth Negishi cross-coupling reaction with TMS-acetylenezinc chloride ($Pd(PPh_3)_4$ 2 mol%) and furnished sulfoxide **66** in 86% yield (eq. 1, Scheme 34). Treating **66** with *i*PrMgCl·LiCl (-50 °C, 5 min, 2-Me-THF) on a 34 mmol scale and subsequent transmetalation ($ZnCl_2$ in THF) and cross-coupling with ethyl 4-iodobenzoate obtained trisubstituted benzene **67** in 86% yield. Alternatively, **49e** could be deprotonated using the same conditions as above and the magnesiated species trapped with (*S*)-(4-chlorophenyl)benzene thiosulfonate (**61**) to give diaryl thioether **68** in 87% yield (eq. 2). By reacting **68** with the exchange reagent *i*PrMgCl·LiCl (-50 °C, 15 min, 33 mmol scale, 2-Me-THF) and quenching with 3,4-dichlorobenzaldehyde the benzylic alcohol **69** was isolated in 49% yield.

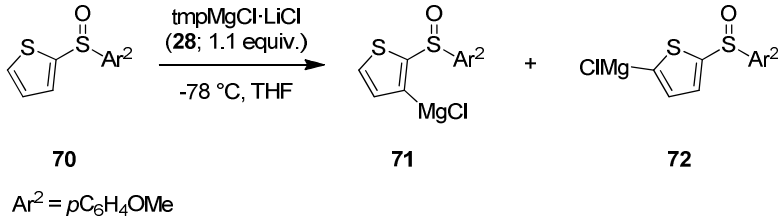


Scheme 34: Large-scale preparation of 1,2,4-trisubstituted arenes **67** and **69**.

2. Preparation of Functionalized 5-Membered Heterocycles via D*o*M and Sulfoxide-Magnesium Exchange

2.1 Synthetic Strategy and Preparation of Hetaryl Sulfoxides

The achieved promising results and the broad scope, including the possibility to perform multigram reactions, got us interested in looking for further synthetic applications of this very versatile two-step protocol. Substituted furans, benzofurans and thiophenes are important heterocycles that are found in a wide variety of natural compounds and pharmaceutical molecules.[93] They are also building blocks for the elaboration of organic materials.[94] Derivatization of such heterocycles in position 2 by metalation is well established.[95] However, the functionalization of position 3 by directed metalation is much less explored and therefore we picked this substrate family as a host for the sulfoxide moiety. Ideally, after a 2,3-disubstitution, a full functionalization of thiophene would offer the perfect possibility to demonstrate the scope of our procedure. Preliminary experiments with 2-((4-methoxyphenyl)sulfinyl)thiophene (**70**) showed that while the scaffold principally suits our requirements, the 5-position of the thiophene is too acidic. Even lowering the temperature to -78 °C resulted in a mixture of the 3- and 5-magnesiated compounds **71** and **72** after addition of tmpMgCl·LiCl (**28**; Scheme 35).



70 **71** **72**

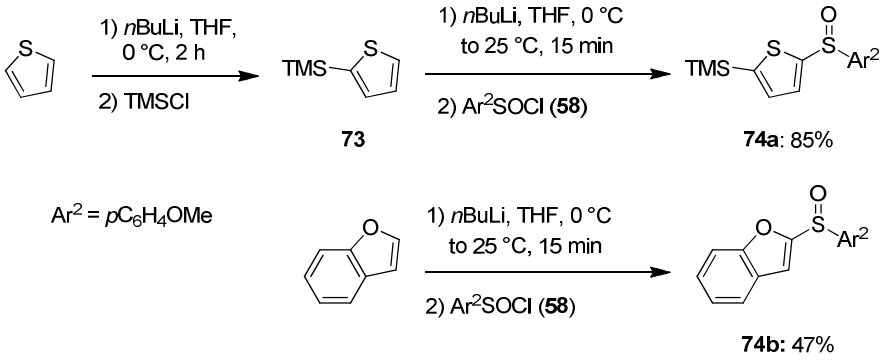
$Ar^2 = pC_6H_4OMe$

Scheme 35: Mixture of hetarylmagnesium regioisomers obtained from treating **70** with tmpMgCl·LiCl (**28**).

The simplest and most versatile way for protecting position 5 from deprotonation was by installing a TMS group at this point, which could later be removed for further synthetic

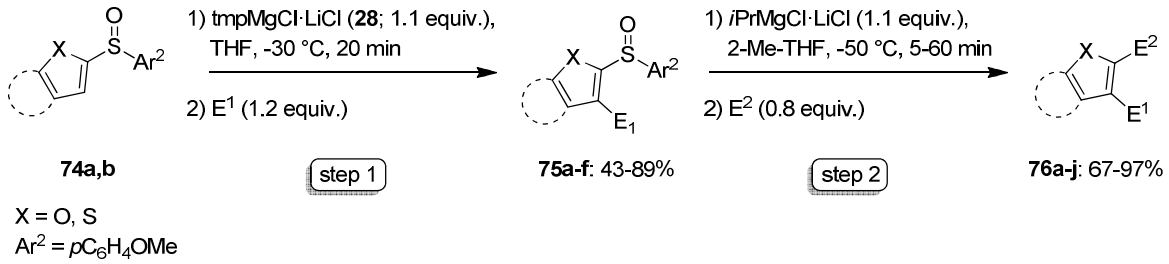
[93] X. L. Hou, Z. Yang, H. N. C. Wong, in *Progress in Heterocyclic Chemistry*, ed. G. W. Gribble and T. L. Gilchrist, Pergamon, Oxford, **2003**, *15*, 167; B. A. Keay, P.W. Dibble, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C.W. Rees, E. F. V. Scriven, Elsevier, Oxford, **1997**, *2*, 395.
[94] a) H. N. C. Wong, P. Yu and C.-Y. Yick, *Pure Appl. Chem.* **1999**, *71*, 1041; b) H.-K. Lee, K.-F. Chan, C.-W. Hui, H.-K.Yim, X.-W. Wu, H. N. C. Wong, *Pure Appl. Chem.*, **2005**, *77*, 139.
[95] a) O. Mendoza, M. Tacke, *J. Organomet. Chem.* **2006**, *691*, 1110; b) M. S. Shanmugham, J. D. White, *Chem. Commun.* **2004**, 44; c) D. J. Chadwick, C. Willbe, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 887; d) J. T. Pinhey, E. G. Roche, *J. Chem. Soc., Perkin Trans. 1*, **1988**, 2415.

purposes. By treating thiophene with *n*BuLi (0 °C, 2 h, THF), followed by reaction with TMSCl, we prepared 2-trimethylsilylthiophene (**73**) (Scheme 36). Further deprotonation with *n*BuLi (0 °C to 25 °C, 15 min, THF) led to the 2-thienyllithium which was quenched with 4-methoxybenzenesulfinyl chloride (**58**), resulting in the desired TMS-protected thienyl sulfoxide **74** in 85% yield. Another heterocyclic sulfoxide (2-((4-methoxyphenyl)sulfinyl)benzofuran, **75**) could be obtained with the same procedure from benzofuran in 47% yield.



Scheme 36: Synthesis of 5-membered heterocyclic sulfoxides **74a,b**.

Initial experiments with these two sulfoxides showed very promising results and proved that we could apply the previously developed two-step protocol without any significant change. The deprotonation using tmpMgCl·LiCl (**28**; 1.1 equiv.) at -30 °C led to a single product which could be functionalized with different electrophiles, to obtain products of type **75** (Scheme 37). Also the sulfoxide-magnesium exchange performed equally well as on the previous aromatic systems, selectively furnishing the 2-magnesiated heterocycle which was suitable for various functionalization reactions with electrophiles E^2, which yielded 2,3-disubstituted thiophenes and benzofurans of type **76**.



Scheme 37: Two-step functionalization protocol on 5-membered heterocyclic sulfoxides **74a,b**.

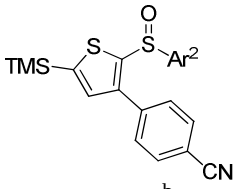
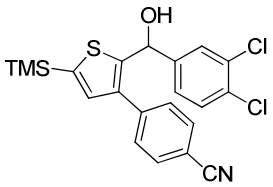
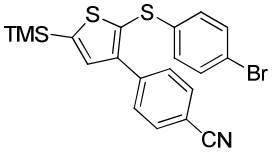
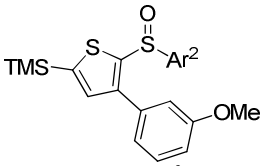
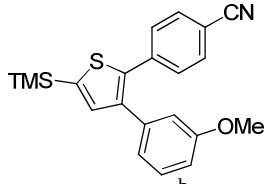
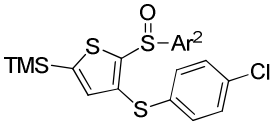
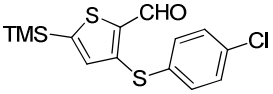
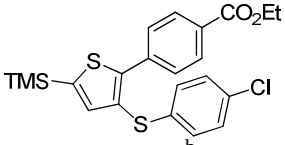
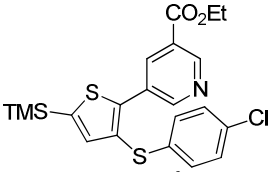
2.2 *Ortho*-Metalation and Sulfoxide-Magnesium Exchange on 5-Membered Hetaryl Sulfoxides

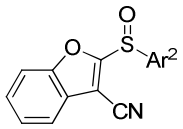
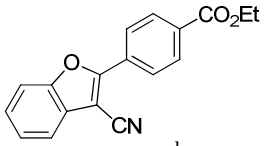
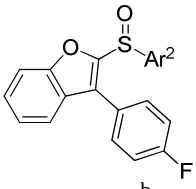
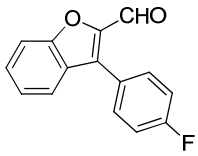
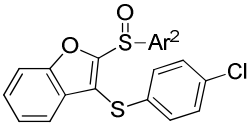
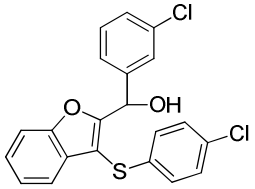
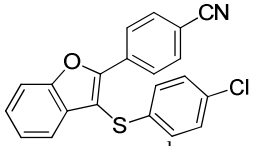
Hence, 2-thienyl sulfoxide **74a** could be selectively metalated with tmpMgCl·LiCl (**28**; -30 °C, 20 min, THF) in position 3. The resulting heterocyclic magnesium reagent was transmetalated (using $ZnCl_2$ in THF) and cross-coupled with 4-iodobenzonitrile using Pd catalysis, leading to the thiophene derivative **75a** in 89% yield (Table 5, entry 1). With *i*PrMgCl·LiCl, the sulfoxide moiety was exchanged (-50 °C, 1 h, 2-Me-THF) and the organometallic species quenched with 3,4-dichlorobenzaldehyde, giving the 2,3-disubstituted thiophene derivate **76a** in 83% yield. Alternatively, after exchanging the sulfoxide group of **75a**, *S*-(4-bromophenyl)benzene thiosulfonate was added to the mixture to form heterocycle **76b** which could be isolated in 94% yield (entry 2). After deprotonating **74a** with tmpMgCl·LiCl and transmetalating with $ZnCl_2$, a cross-coupling with 3-iodoanisole ($Pd(PPh_3)_4$, 2 mol %, 25 °C, 1 h) was performed, yielding thienyl sulfoxide **75b** in 87% yield (entry 3). After exchanging the sulfoxide group of **75b** (*i*PrMgCl·LiCl, -50 °C, 5 min, 2-Me-THF) a second cross-coupling with 4-iodobenzonitrile was performed to afford disubstituted thienyl derivate **76c** in 85% yield. In another reaction sequence, thiophene **74a** was *ortho*-metalated with tmpMgCl·LiCl and quenched by the addition of *S*-(4-chlorophenyl)benzene thiosulfonate, leading to the heterocyclic thioether **75c** in 78% yield (entry 4). This sulfoxide was submitted to a sulfoxide-magnesium exchange at -50 °C within 1 h, and could be reacted with DMF to afford the thiophene-2-carbaldehyde **76d** in 97%. Instead of direct reaction with an electrophile, a Pd-catalyzed reaction of the zinc species with ethyl 4-iodobenzoate or 5-bromonicotinic acid ethyl ester was also possible which gave the desired cross-coupling products **76e** and **76f** in 67-88% yield (entries 5 and 6).

Also, the benzofuranyl sulfoxide **74b** underwent *ortho*-magnesiation with tmpMgCl·LiCl (**28**, 1.1 equiv., -50 °C, 45 min) and led after quenching with tosyl cyanide, *S*-(4-chlorophenyl)benzene thiosulfonate or after a Negishi cross-coupling with 1-fluoro-4-iodobenzene ($Pd(PPh_3)_4$, 2 mol %, 25 °C, 1 h) to the benzofurans **75d-f** in 43-88% yield (entries 7-10). A subsequent sulfoxide-magnesium exchange of **75d** with *i*PrMgCl·LiCl (1.1 equiv., -50 °C, 5 min) and coupling with ethyl 4-iodobenzoate ($Pd(PPh_3)_4$, 2 mol %, 25 °C, 1 h) afforded the 2,3-disubstituted benzofuran **76g** in 87% yield (entry 7). The 4-fluorophenyl-substituted benzofuran **75e** can be exchanged at -50 °C in 5 min and reacted with DMF to furnish benzofuran-2-carbaldehyde **76h** in 91% yield (entry 8). Finally, the 3-thioether-substituted benzofuran **75f** underwent a smooth sulfoxide-magnesium exchange

(*i*PrMgCl·LiCl, -50 °C, 5 min, 2-Me-THF) and trapping with 3-chlorobenzaldehyde or a cross-coupling with 4-iodobenzontrile enabled the isolation of the 2,3-disubstituted benzofuran derivates **76i** and **76j** in 77-84% yield (entries 9 and 10).

Table 5: Application of the two-step protocol on heterocyclic sulfoxides **74a,b** and electrophilic reactions leading to 2,3-disubstituted heterocycles **76**.

Entry	Electrophile E^1, Sulfoxide **75,** yield [%][a]	Electrophile E^2, Product **76**, yield [%][a]
1	4-IC_6H_4CN,  **75a**: 89[b]	3,4-di-ClC_6H_4CHO,  **76a**: 83
2	**75a**: 89[b]	$PhSO_2SC_6H_4Br$,  **76b**: 94
3	3-IC_6H_4OMe,  **75b**: 87[b]	4-IC_6H_4CN,  **76c**: 85[b]
4	$PhSO_2SC_6H_4Cl$,  **75c**: 78	DMF,  **76d**: 97
5	**75c**: 78	4-$IC_6H_4CO_2Et$,  **76e**: 88[b]
6	**75c**: 78	3-Br-5-CO_2Et-C_5H_3N,  **76f**: 67[b]

7	TosCN,  **75d**: 43	4-$IC_6H_4CO_2Et$,  **76g**: 87[b]
8	4-IC_6H_4F,  **75e**: 80[b]	DMF,  **76h**: 91
9	$PhSO_2SC_6H_4Cl$,  **75f**: 88	3-ClC_6H_4CHO,  **76i**: 77
10	**75f**: 88	4-IC_6H_4CN,  **76j**: 84[b]

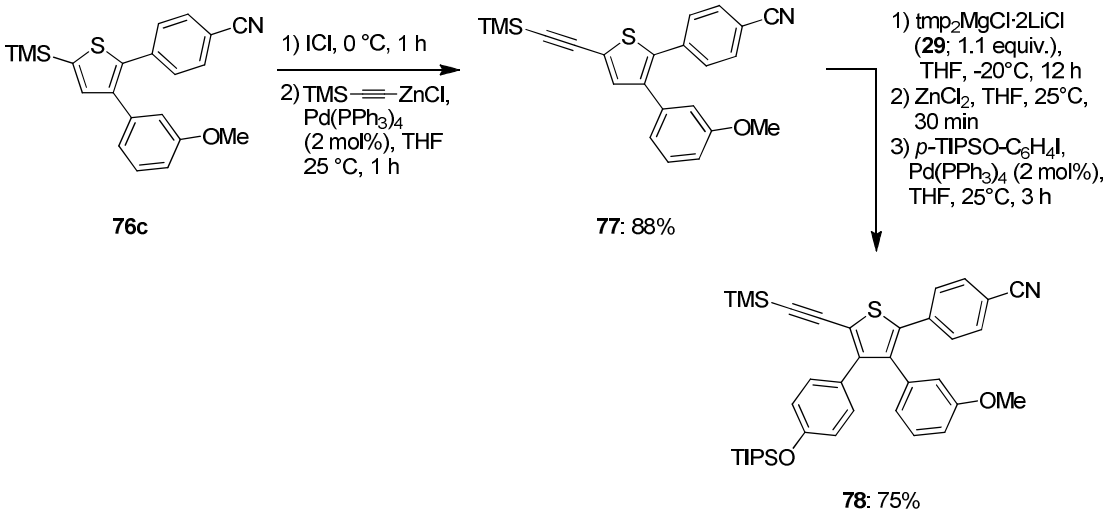
[a] Yield of isolated analytically pure product. [b] After transmetalation ($ZnCl_2$ 1.0 M in THF). [c] Ar^2 = pC_6H_4OMe.

2.3 Full Functionalization of Thiophene by Metalation Reaction

From these various 2,3-disubstituted and TMS-protected thiophenes, we chose **76c** to pursue our goal of achieving a full functionalization of this 5-membered heterocycle.[96] First, the trimethylsilyl group was converted with ICl (1.5 equiv., 0 °C, 1 h) to the corresponding 2-iodothiophene,[97] which was used in the next step without further purification (Scheme 38). It was subjected to a cross-coupling with trimethylsilylethynylzinc chloride ($Pd(PPh_3)_4$, 2 mol%, THF, 25 °C, 1 h) which resulted in the tri-substituted thiophene **77** in 88% yield. Finally, the remaining position 3 of **77** could be metalated with $tmp_2Mg\cdot LiCl$ (**29**)[67,69] (1.5 equiv., THF, -20 °C, 12 h), transmetalated to zinc ($ZnCl_2$ 1.0 M in THF) and submitted to a Negishi cross-coupling ($Pd(PPh_3)_4$, 2 mol %, THF, 25 °C, 3 h) with (4-iodophenoxy)-triisopropylsilane.[98] With this method we furnished the fully functionalized thiophene **78** in 75% yield. The tetra-

[96] For a full functionalization of the furan, see: L. Melzig, C. B. Rauhut, P. Knochel, *Chem. Commun*. **2009**, 3536; b) Ph.D. thesis Christian B. Rauhut, LMU Munich, 2008.
[97] G. Felix, J. Dunogues, R. Calas, *Angew. Chem., Int. Ed.* **1979**, *18*, 402.
[98] M. Rottlander, N. Palmer, P. Knochel, *Synlett* **1996**, 573.

substitution of the thiophene scaffold was therefore carried out in 4 steps and 49% overall yield.

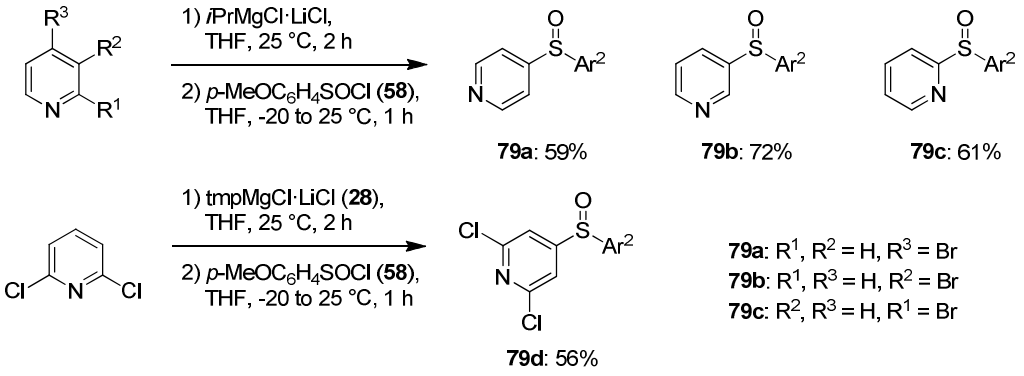


Scheme 38: Synthesis of the fully functionalized thiophene **78**.

3. Preparation of Disubstituted Pyridines via D*o*M, Sulfoxide-Magnesium Exchange and Ligand Coupling

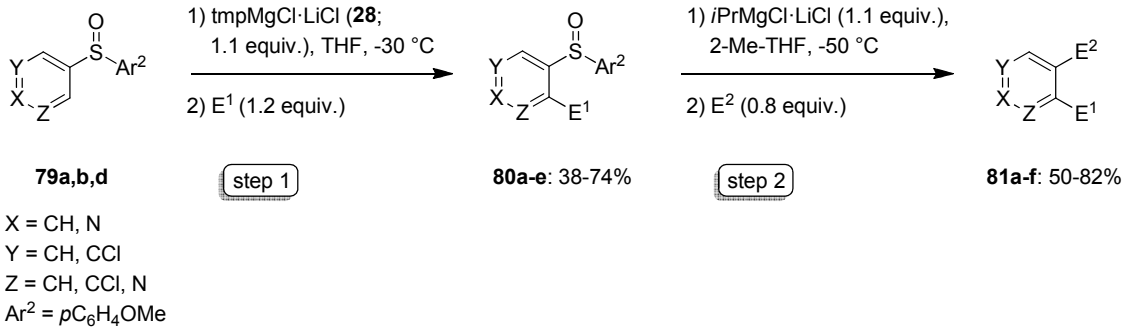
3.1 Synthetic Strategy and Preparation of Pyridinyl Sulfoxides

As pyridines are a heterocyclic class of central importance in biochemical pathways and pharmacologically active compounds, resulting in a bulk of pyridine derivatives as interesting targets for organic synthesis, we decided on this compound family to demonstrate further the potential and the versatility of our 2 step methodology. Therefore, we started by preparing different 2-, 3-, and 4-pyridinyl sulfoxides by reacting the magnesiated pyridines with 4-methoxybenzenesulfinyl chloride (**58**) at -20 °C in THF (Scheme 39). The corresponding pyridinyl Grignard reagents could either be generated by Br-Mg exchange (*i*PrMgCl·LiCl, 25 °C, 2 h, THF, pyridines **79a-c**)[85b] or by selective metalation using tmpMgCl·LiCl (**28**; 25 °C, 4 h, THF, pyridine **79d**).[64] This furnished the required starting sulfoxides **79a-d** in 56-72% yield.



Scheme 39: Synthesis of 6-membered heterocyclic sulfoxides **79a-d**.

We assumed that the metalation in step 1 of our synthesis would proceed without complications, and that the sulfoxide-magnesium exchange on sulfoxides **79a-d** would work similar to the arylic or electron-rich hetarylic sulfoxides as demonstrated above. We expected problems with the exchange reaction on 2-pyridinyl sulfoxide **79c** due to the ligand coupling reaction reported by *Oae*.[52] Therefore, our initial strategy focused on trying to apply the two-step protocol onto the sulfoxides **79a,b,d** as shown in Scheme 40.

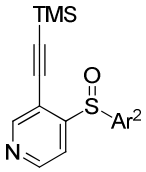
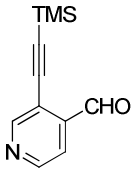
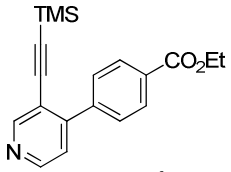
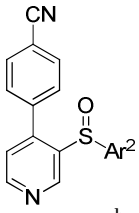
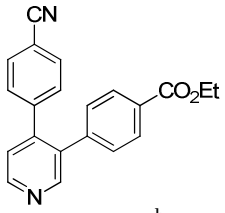
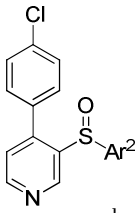
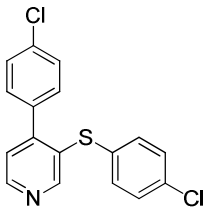
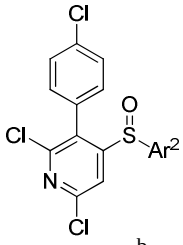
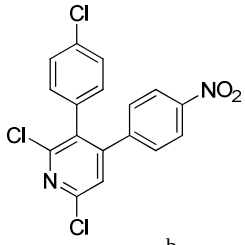
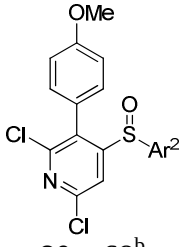
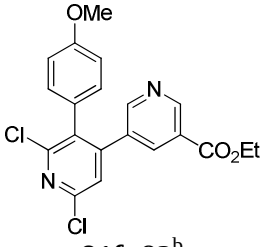


Scheme 40: Two-step functionalization protocol on 6-membered heterocyclic sulfoxides **79**.

3.2 Preparation of 3,4-Disubstituted and Tetrasubstituted Pyridines

Initial test reactions run with the pyridinyl sulfoxides showed that both of our key reagents (tmpMgCl·LiCl and *i*PrMgCl·LiCl) worked well on these substrates. Therefore, 4-((4-methoxyphenyl)sulfinyl)pyridine (**79a**) underwent smooth magnesiation with tmpMgCl·LiCl (**28**, -30 °C, 30 min, THF) in the first step of the reaction sequence and was trapped with iodine. This pyridinyl iodide was used in a Negishi-type cross-coupling reaction with trimethylsilylethynylzinc chloride and sulfoxide **80a** was obtained in 69% yield. Compound **80a** reacted with *i*PrMgCl·LiCl (-50 °C, 5 min, 2-Me-THF) in the sulfoxide-magnesium exchange (displaying the second step of the synthesis) and after trapping with DMF the 3,4-disubstituted pyridine **81a** was isolated in 58% yield (Table 6, entry 1). In another reaction sequence the exchange of the sulfoxide moiety was performed on sulfoxide **80a**, the organomagnesium reagent was transmetalated to zinc prior to a cross-coupling with ethyl 4-iodobenzoate and furnished ethyl 4-(3-((trimethylsilyl)ethynyl)pyridin-4-yl)benzoate (**81b**) in 63% yield (entry 2). Similarly, 3-pyridinyl sulfoxide **79b** was used for the reaction protocol leading to the difunctionalized pyridines **81c,d** in 50-67% yield (entries 3 and 4). Finally, 2,6-dichloropyridinyl sulfoxide **79d** was also a suitable starting material for the difunctionalization method. Hence the tetra-substituted pyridines **81e,f** were furnished after directed metalation and sulfoxide-magnesium exchange in 61-82% yield (entries 5 and 6).

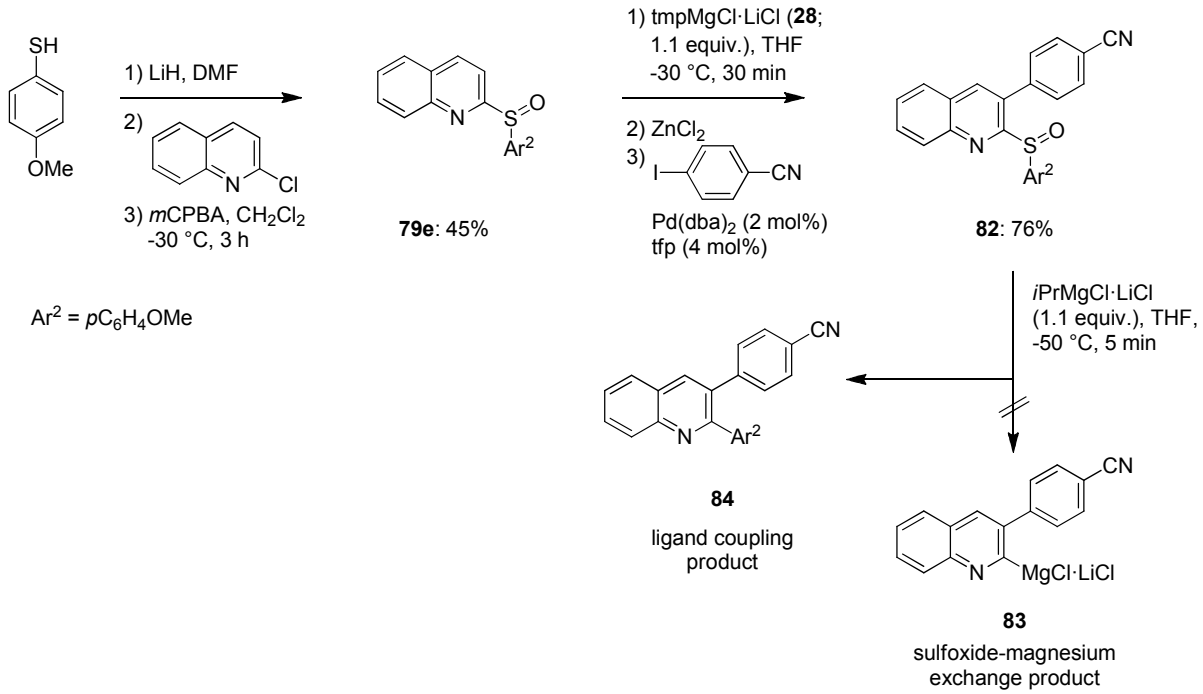
Table 6: Application of the two-step protocol on heterocyclic sulfoxides **49a,b,d** and electrophilic reactions leading to di- and tetrasubstituted pyridines **81**.

Entry	Electrophile E^1, Sulfoxide **80**, yield [%][a]	Electrophile E^2, Product **81**, yield [%][a]
1	1) I_2 2) TMS—≡—ZnCl,  **80a**: 69	DMF,  **81a**: 58
2	**80a**: 69	4-$IC_6H_4CO_2Et$,  **81b**: 63[b]
3	4-IC_6H_4CN,  **80b**: 38[b]	4-$IC_6H_4CO_2Et$,  **81c**: 50[b]
4	4-IC_6H_4Cl,  **80c**: 53[b]	$PhSO_2SC_6H_4Cl$,  **81d**: 67
5	4-IC_6H_4Cl,  **80d**: 74[b]	4-$IC_6H_4NO_2$,  **81e**: 61[b]
6	4-IC_6H_4OMe,  **80e**: 68[b]	3-Br-5-CO_2Et-C_5H_3N,  **81f**: 82[b]

[a] Yield of isolated analytically pure product. [b] After transmetalation ($ZnCl_2$ 1.0 M in THF). [c] Ar^2 = *p*C_6H_4OMe.

3.3 Ligand Coupling reactions of 2-Pyridinyl Sulfoxides

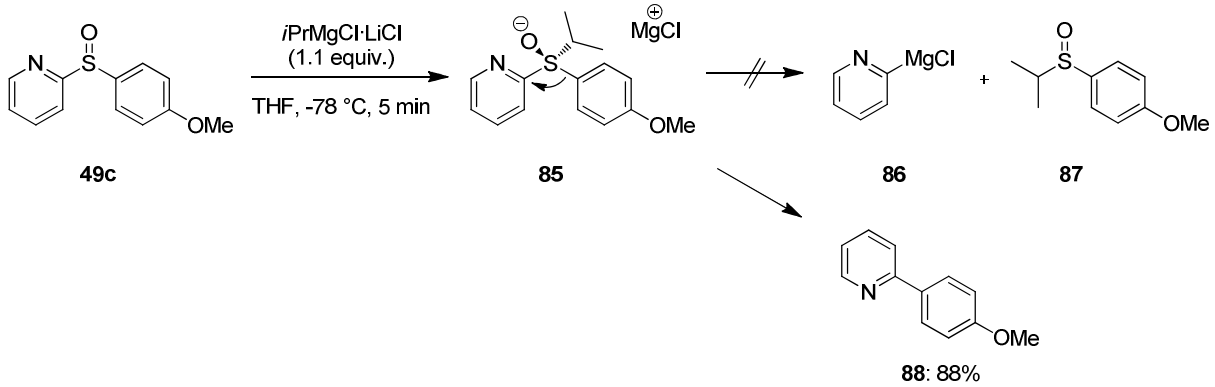
As described in the literature, hetaryl sulfoxides, especially 2-pyridinyl sulfoxides, tend to undergo a so-called ligand exchange or ligand coupling reaction when treated with an organomagnesium reagent. To circumvent this, for our methology, undesired reaction behavior, another strategy was adapted. Hence, the N-heterocyclic sulfoxide **79e** was prepared in 45% yield from 4-methoxybenzenethiol by deprotonation with LiH in DMF, nucleophilic attack on 2-chloroquinoline and subsequent oxidation with *m*CPBA (CH_2Cl_2, -30 °C, 3 h, Scheme 41). Metalation with tmpMgCl·LiCl (**28**, THF, -30 °C, 30 min) and cross-coupling with 4-iodobenzonitrile furnished the 2,3-disubstituted quinolyl sulfoxide **82** in 76% yield. This compound was treated with *i*PrMgCl·LiCl using our well established reaction conditions (-50 °C, 2-Me-THF). Full conversion of the sulfoxide was achieved after only 5 min, but no 2-hetaryl organomagnesium reagent of type **83** could be observed when quenching reaction aliquots with I_2 in THF. Instead, the ligand coupling product **84** was exclusively formed. Numerous attempts to modify the reaction conditions of the sulfoxide-magnesium exchange (exchange reagent, temperature, solvent, additives) and also varying the substituent on the 3-position of the hetaryl ring did not change the outcome of the reaction.



Scheme 41: Two-step functionalization protocol on 2-quinolyl sulfoxide **82** and ligand coupling reaction.

The proposed reaction pathway is illustrated in Scheme 42. The 2-pyridinyl sulfoxide **49c** can be treated with *i*PrMgCl·LiCl in THF at -78 °C to rapidly form the 4-membered intermediate

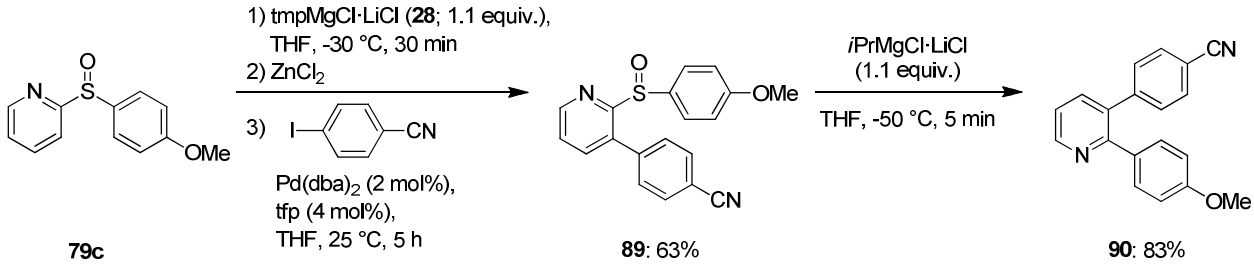
85. The breakdown of this does not result in expelling the most stable Grignard reagent, i.e. 2-pyridinylmagnesium chloride (**86**) and the isopropyl-4-anisyl sulfoxide (**87**), instead the anisyl moiety is transferred onto the 2-position of the heterocycle. Since this reaction is very fast and selective, the resulting 2-(4-methoxyphenyl)pyridine (**88**) was isolated in 88% yield.



Scheme 42: Ligand coupling reaction of 2-((4-methoxyphenyl)sulfinyl)pyridine (**85**) leading to 2-(4-methoxyphenyl)pyridine (**88**).

3.4 Preparation of a Cyclooxygenase-2 Inhibitor using the Ligand Coupling Reaction

We wanted to take advantage of this interesting and unusual behaviour by exploiting it in the form of a short total synthesis. Hence, we reacted the 2-pyridinyl sulfoxide **79c** with tmpMgCl·LiCl (**28**; -30 °C, 30 min, THF) according to the methodology described above and transmetalated it using $ZnCl_2$ (1.0 M in THF) for a subsequent Negishi cross-coupling with 4-iodobenzonitrile to furnish pyridine **89** in 63% yield (Scheme 43). To accomplish the final step of the synthesis, the ligand coupling reaction, we simply treated **89** with *i*PrMgCl·LiCl (-50 °C, 5 min, THF) and could obtain the cyclooxygenase-2 inhibitor[99] **90** in 83% yield.



Scheme 43: Synthesis of the cyclooxygenase-2 inhibitor **90**.

[99] M. Hirai, M. Kusama, T. Hosaka, S. Kohnomi, *PCT Int. Appl. WO 2005115984*, **2005**.

4. Transition Metal-Catalyzed Cross-Coupling Reactions of Functionalized Organozinc Reagents with Unsaturated Thioethers

4.1 Synthetic Goals and Synthesis of Unsaturated N-Heterocyclic and Alkynyl Thioethers

The availability and the preparation of halogenated compounds, especially heterocycles, can often be problematic. Therefore an alternative for hetaryl halides as electrophiles for transition-metal catalyzed cross-coupling reactions would be highly advantageous. A very versatile and conveniently prepared class of heterocycles lies in thioether-derivatives. These stable compounds have been used for various carbon-sulfur coupling reactions in the literature, although there are very few examples of their use as electrophiles in combination with organozinc, especially functionalized organozinc reagents.[100] We wanted to develop an efficient and versatile protocol for cross-coupling these heterocycles with highly functionalized organozinc reagents.[101]

The requisite heterocyclic thioether can be obtained in a number of ways. One of the simplest is the reaction of a halogenated heterocycle with NaSMe in DMF (eq. 1, Scheme 44).[102] Also metalation reactions, like the lithiation of position 2 of the pyrrole scaffold (eq. 2)[103] or a magnesiation using tmpMgCl·LiCl (**28**)[64] or $tmp_2MgCl\cdot 2LiCl$ (**29**),[67,69] offer ways to obtain organometallics reagents which can be transformed into thioethers by their reaction with disulfides or thio sulfonates. A very direct approach exists in the deprotonation and alkylation of thiols (eq. 3),[104] this can also be combined with classical condensation reactions, for example the preparation of 2-thiomethyl pyrimidines from 1,3-diones and thiourea (eq. 4).[105]

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[100] For reactions of organomagnesium as well as organozinc reagents with tetramethylthiuram disulfide, see: a) A. Krasovskiy, A. Gavryushin, P. Knochel, *Synlett* **2005**, 2691; b) A. Krasovskiy, A. Gavryushin, P. Knochel, *Synlett* **2006**, 792.

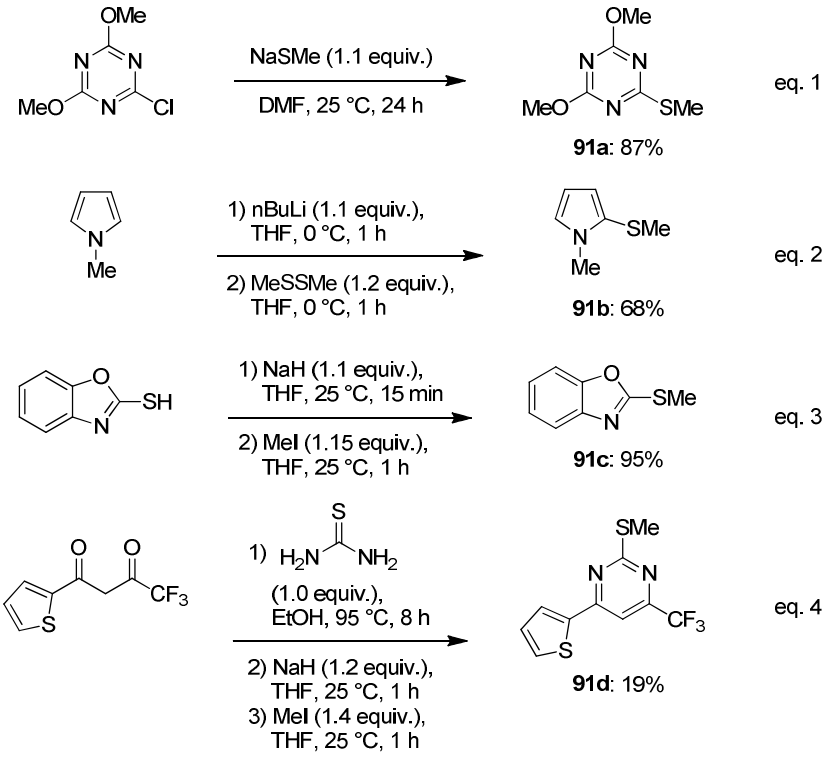
[101] For the preparation of highly functionalized organozinc reagents, see: a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; b) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107; c) S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, *J. Org. Chem.* **2008**, *73*, 7380.

[102] a) L. Testaferri, M. Tiecco, M. Tingoli, D. Bartoli, A. Massoli, *Tetrahedron* **1985**, *41*, 1373; b) B. A. Johns, K.S. Gudmundsson, E. M. Turner, S. H. Allen, V. A. Samano, J. A. Ray, G. A. Freeman, F. L. Boyd, Jr., C. J. Sexton, D. W. Selleseth, K. L. Creech, K. R. Moniri, *Bioorg. Med. Chem.* **2005**, *13*, 2397.

[103] J. M. Brittain, R. A. Jones, J. S. Arques, T. A. Saliente, *Synth. Commun.* **1982**, *12*, 231.

[104] A. K. Amegadzie, J. P. Beck, K. M. Gardinier, E. J. Hembre, J. C. Ruble, K. A. Savin, B. D. Wakefield, *PCT Int. Appl. WO 2006066174*, **2006**.

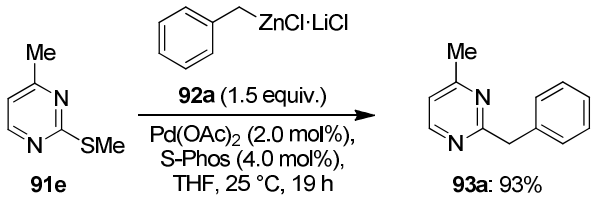
[105] a) D. G. Crosby, R. V. Berthold, H. E. Johnson, *Org. Synth.* **1963**, *43*, 68; b) L. Bethge, D. V. Jarikote, O. Seitz, *Bioorg. Med. Chem.* **2008**, *16*, 114; c) J. E. Arguello, L. C. Schmidt, A. B. Penenory, *Org. Lett.* **2003**, *5*, 4133.



Scheme 44: Various pathways for the synthesis of unsaturated thioethers **91**.

4.2 Optimization of the Pd-Catalyzed Cross-Coupling Reaction of N-Heterocyclic Thioethers

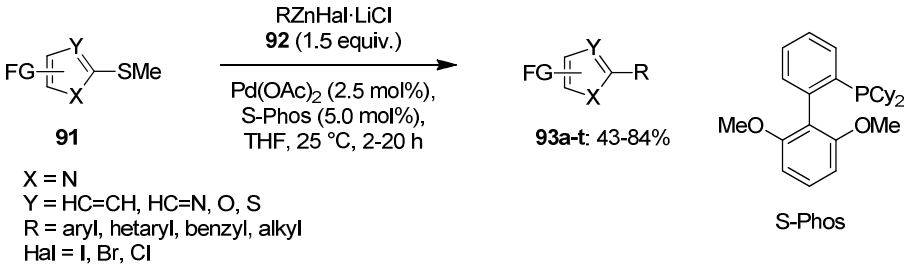
To find the optimal conditions for the cross-coupling of these N-heterocycles with organozinc reagents, various different metal salts and ligands were screened in a model reaction of 4-methyl-2-(methylthio)pyrimidine (**91e**) with benzylzinc chloride **92a** in THF at 25 °C (Scheme 45). Without any metal catalyst, no formation of the product **93a** could be observed, ruling out the mechanistic pathway of a nucleophilic attack. After 19 h reaction time, $Pd(OAc)_2$ (2 mol%) and S-Phos (4 mol%) gave the best results with 93% yield as determined by GC analysis.[106]



Scheme 45: Model reaction and best catalytic system for the reaction of 4-methyl-2-(methylthio)pyrimidine (**91e**) with benzylzinc chloride **92a**.

[106] The screening of the palladium/ligand catalytic systems was performed by Albrecht Metzger. For further information, see also: Ph.D. thesis Albrecht Metzger, LMU Munich, **2010**.

A series of experiments investigating the scope of this cross-coupling reaction showed that the catalytic system was capable of transmuting aryl, hetaryl, benzyl and also alkyl zinc reagents. Most of these reactions could be completed in THF at room temperature in a matter of several hours, without the need for any additional copper salts (Scheme 46).

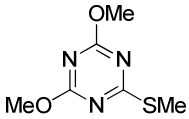
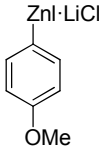
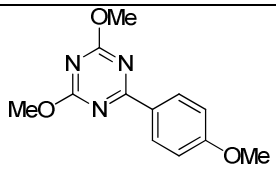
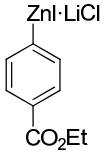
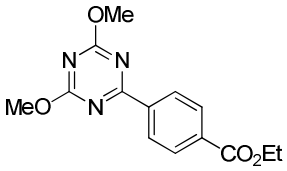
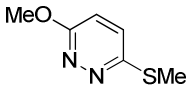
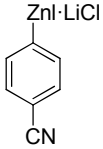
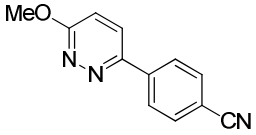
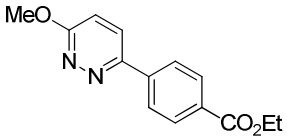
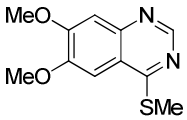
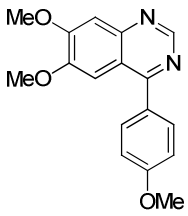
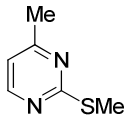
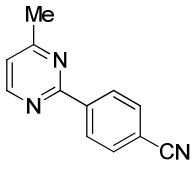
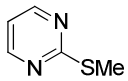
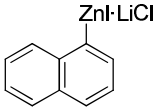
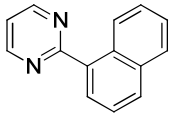
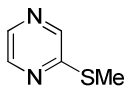
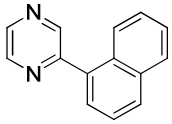
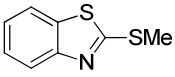
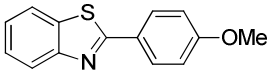


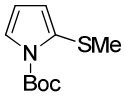
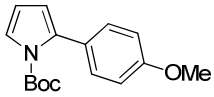
Scheme 46: Pd-catalyzed cross-coupling reaction of thiomethyl-substituted N-heterocycles **91** with functionalized organozinc reagents **92**.

4.3 Synthesis of Functionalized N-Heterocycles via Pd-Catalyzed Cross-Coupling Reactions

Thus, 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**91a**; 1.0 equiv.) reacted with 4-methoxyphenylzinc iodide (**92b**; 1.5 equiv., THF, 25 °C, 5 h) providing the triazine **93b** in 83% yield (Table 7, entry 1). Also, the triazine **91a** was used for a cross-coupling reaction with the electron-deficient arylzinc **92c** (25 °C, 5 h), which led to ethyl 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)benzoate (**93c**) in 84% yield (entry 2). Moreover, 4-cyanophenylzinc iodide (**92d**) or 4-(ethoxycarbonyl) phenylzinc iodide (**92c**) reacted smoothly with methylthio-substituted pyridazine **91f** furnishing the functionalized pyridazines **93d,e** in 76-77% yield (25 °C, 4 h, entries 3 and 4). The quinazoline **91g** was a further suitable substrate for this cross-coupling and the reaction with **92b** (25 °C, 10 h) brought the trimethoxyquinazoline **93f** in 71% yield (entry 5). Similarly, the 2-thiomethyl pyrimidines **91e** and **91h** and the pyrazine **91i** were submitted to cross-coupling reactions with 4-cyanophenylzinc iodide (**92d**) or 1-naphthylzinc iodide (**92e**; 25 °C, 16-20 h), resulting in the functionalized N-heterocycles **93g-i** in 74-83% yield (entries 6-8). The protocol was also used on benzothiazole **91j** and the electron-rich 2-thiomethylpyrrole derivative **91k**, and cross-coupled with 4-methoxyphenylzinc iodide (**92b**; 1.5 equiv., THF, 25 °C, 2 h) this furnished the functionalized benzothiazole **93j** and the Boc-protected pyrrole **93k** in 67-73% yield (entries 9 and 10).

Table 7: Pd-catalyzed cross-coupling reactions of thiomethylated N-heterocycles **91** with functionalized arylzinc reagents **92**.

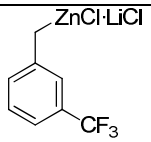
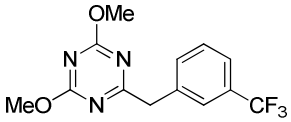
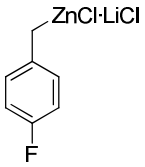
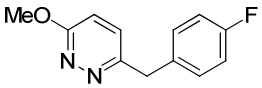
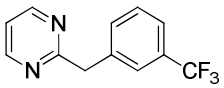
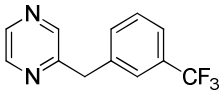
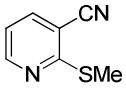
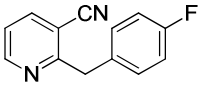
Entry	Electrophile	Zinc reagent	Reaction time [h]	Product	Yield [%][a]
1	 **91a**	 **92b**	5	 **93b**	83
2	**91a**	 **92c**	5	 **93c**	84
3	 **91f**	 **92d**	4	 **93d**	76
4	**91f**	**92c**	4	 **93e**	77
5	 **91g**	**92b**	10	 **93f**	71
6	 **91e**	**92d**	16	 **93g**	74
7	 **91h**	 **92e**	20	 **93h**	75
8	 **91i**	**92e**	18	 **93i**	83
9	 **91j**	**92b**	2	 **93j**	73

10	 **91k**	**92b**	2	 **93k**	67

[a] Yield of isolated analytically pure product.

Functionalized benzylzinc reagents underwent a straightforward reaction and the coupling of 3-(trifluoromethyl)benzylzinc chloride (**92f**) and triazine **91a** afforded the substituted diarylmethane **93l** in 70% yield (25 °C, 5 h, Table 8, entry 1). Also diazaheterocycles like pyridazine **91h**, pyrimidine **91h** or pyrazine **91i** undergo smooth cross-couplings reaction, and their functionalization with trifluoromethylated benzylzinc chloride **92f** or 4-fluorobenzylzinc chloride (**92g**) led to the desired compounds **93m-o** in 59-73% yield within 5-18 h at 25 °C (entries 2-4). The benzyl zinc **92g** reacted also well with 2-(methylthio)nicotinonitrile (**91l**) to furnish the 2,3-disubstituted pyridine **93p** in 83% after 2 h reaction time (entry 5).

Table 8: Pd-catalyzed cross-coupling reactions of thiomethylated N-heterocycles **91** with functionalized benzylzinc reagents **92**.

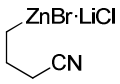
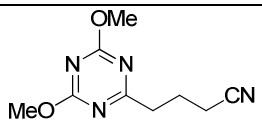
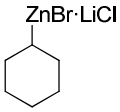
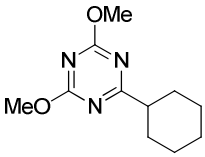
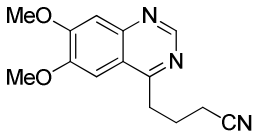
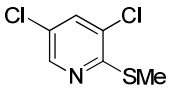
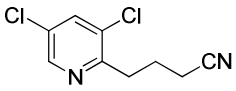
Entry	Electrophile	Zinc reagent	Reaction time [h]	Product	Yield [%][a]
1	**91a**	 **92f**	5	 **93l**	70
2	**91f**	 **92g**	5	 **93m**	73
3	**91h**	**92f**	16	 **93n**	59
4	**91i**	**92f**	18	 **93o**	68
5	 **91l**	**92g**	2	 **93p**	83

[a] Yield of isolated analytically pure product.

Finally, this Pd-catalyzed cross-coupling reaction could also be performed with functionalized alkyl zinc reagents such as the nitrile-bearing propylzinc bromide **92h**. The reaction with dimethoxytriazine **91a** led smoothly to 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)butanenitrile (**93q**) in 66% yield (25 °C, 5 h, Table 9, entry 1). In another reaction, this heterocycle **91a**

reacted with the secondary zinc bromide **92i** (25 °C, 20 h) and 2-cyclohexyl-4,6-dimethoxy-1,3,5-triazine (**93r**) was isolated in 43% yield (entry 2). Additionally, 4-cyanopropylzinc bromide (**92h**) was used in a cross-coupling with quinazoline **91g** or the dichloro-substituted pyridine **91m** (25 °C, 5 h). The expected alkylated heterocycles **93s** and **93t** were obtained in 54 and 74% yield, respectively (entries 3 and 4).

Table 9: Pd-catalyzed cross-coupling reactions of thiomethylated N-heterocycles **91** with functionalized alkylzinc reagents **92**.

Entry	Electrophile	Zinc reagent	Reaction time [h]	Product	Yield[%][a]
1	**91a**	 **92h**	5	 **93q**	66
2	**91a**	 **92i**	20	 **93r**	43
3	**91g**	**92h**	5	 **93s**	74
4	 **91m**	**92h**	5	 **93t**	54

[a] Yield of isolated analytically pure product.

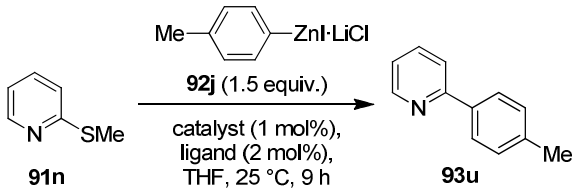
4.4 Optimization of the Ni-Catalyzed Cross-Coupling Reaction of N-Heterocyclic Thioethers

As initial test experiments had indicated that the cross-coupling of these heterocyclic thioethers with zinc reagents was also possible with a Ni catalyst, we dedicated ourselves to finding the optimal conditions for a cheap and robust catalytic system.[107] Therefore, a series of screening reactions were undertaken, 2-thiomethylpyridine (**91n**) and 4-methylphenylzinc iodide (**92j**) with 1 mol% of metal salt and 2 mol% of ligand being the standard conditions.

[107] For a review on Ni-catalyzed Negishi cross-coupling reactions, see: V. B. Phapale, D. J. Cárdenas, *Chem. Soc. Rev.* **2009**, *38*, 1598.

In the absence of a Pd or Ni catalyst system, no cross-coupling was observed (Table 10, entry 1).[108] Initial attempts with $Ni(dppe)Cl_2$ without any added ligand gave only 4% yield of the cross-coupling product **93u** at 25 °C after 9 h reaction time (Table 10, entry 2). $Ni(PPh_3)_2Br_2$[109] furnished the 2-arylated pyridine **93u** in 14% yield under these conditions (entry 4), whereas $Ni(PMe_3)_2Cl_2$ furnished 17% yield in the same time (entry 7). Using $NiCl_2 \cdot DME$[110] delivered 62% of the coupling product (entry 16), but its yield dropped dramatically when 2 mol% of 1,1,1-tris(diphenylphosphino)ethane were added (entry 5), but successfully increased back to 92% in the presence of 2 mol% of bis[2-(diphenylphosphino)phenyl]ether (DPE-Phos)[111] (entry 19). The use of inexpensive $Ni(acac)_2$ alone yielded **93u** in 62% (entry 15), and adding a variety of different ligands (2 mol%) led to further improvements. The screening was extended to simple phosphine ligands (entries 17, 18), QUINAP[112] (entry 12), 1,1'-bis(di-*tert*-butylphosphino)ferrocene[113] (entry 9) and also carbene ligands like IMes·HCl[114] (entry 6). We have found that the most efficient and robust system is $Ni(acac)_2$ (1 mol%) associated with DPE-Phos (2 mol%), giving quantitative GC yield of the cross coupling product after 9 h at 25 °C (entry 20).[115] The (*p*-tolyl)pyridine **93u** could be isolated in analytically pure form in 86% yield.

Table 10: Catalyst and ligand screening in the cross-coupling reaction of 2-thiomethylpyridine (**91n**) with 4-methylphenylzinc iodide (**92j**).



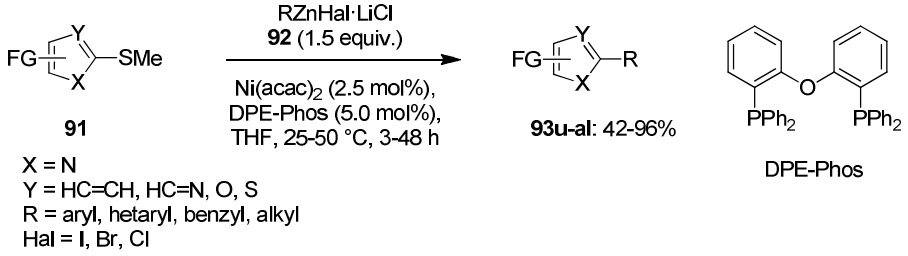
Entry	Metal	Ligand	Yield [%][a]
1	$Ni(dppe)Cl_2$	-	4
2	$Ni(dppe)Cl_2$	-	5
3	$Ni(acac)_2$	tris(3,4,5-trimethoxyphenyl)-phosphine	12
4	$Ni(PPh_3)_2Br_2$	-	14
5	$NiCl_2 \cdot DME$	$H_3CC(CH_2PPh_2)_3$	16
6	$Ni(acac)_2$	IMes·HCl	16
7	$Ni(PMe_3)_2Cl_2$	-	17

[108] We have also verified that the pyridine moiety does not act as a ligand.
[109] N. Miyaura, Y. Tanabe, H. Suginome, A. Suzuki, *J. Organomet. Chem.* **1982**, *233*, C13.
[110] F. Gonzalez-Bobes, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 5360.
[111] M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, K. Goubitz, J. Fraanje, P. W. N. M. van Leeuwen, *Organometallics* **1995**, *14*, 3081.
[112] N. W. Alcock, J. M. Brown, D. I. Hulmes, *Tetrahedron: Asymmetry* **1993**, *4*, 743.
[113] B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1998**, *120*, 7369.
[114] A. J. Arduengo III, H. V. Rasika Dias, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1992**, *114*, 5530.
[115] L. Melzig, A. Gavryushin, P. Knochel, *Org. Lett.* **2007**, *9*, 5529.

8	$Ni(acac)_2$	P(*o*Tol)$_3$	18
9	$Ni(acac)_2$	1,1'-P(*t*Bu)$_2$-ferrocene	20
10	$Ni(acac)_2$	$H_3CC(CH_2PPh_2)_3$	21
11	$Ni(acac)_2$	4,4′-di-*tert*-butyl-2,2′-dipyridyl	21
12	$Ni(acac)_2$	(R)-QUINAP	23
13	$Pd(OAc)_2$	S-Phos	33
14	$Ni(acac)_2$	$P(C_2H_4PPh_2)_3$	53
15	$Ni(acac)_2$	-	62
16	$NiCl_2 \cdot DME$	-	71
17	$Ni(acac)_2$	PPh_3	83
18	$Ni(acac)_2$	$PPhMe_2$	88
19	$NiCl_2 \cdot DME$	DPE-Phos	92
20	$Ni(acac)_2$	DPE-Phos	100

[a] GC yield using tridecane as internal standard.

Using the cheap and commercially available $Ni(acac)_2$ (2.5 mol%) and DPE-Phos (5.0 mol%),[116] a broad reaction scope was achieved and most cross-couplings could be completed in 3-48 h at 25 °C (Scheme 47).



Scheme 47: Ni-catalyzed cross-coupling reaction of thiomethyl-substituted N-heterocycles **91** with functionalized organozinc reagents **92**.

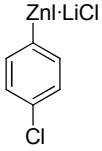
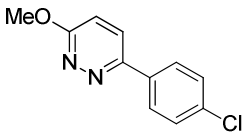
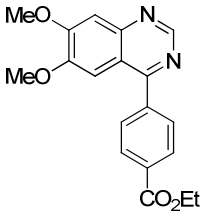
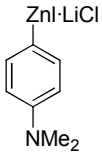
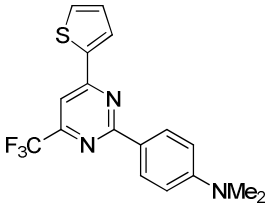
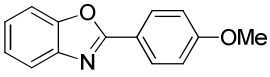
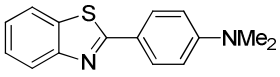
4.5 Synthesis of Functionalized N-heterocycles via Ni-catalyzed Cross-Coupling Reactions

Utilizing this protocol, the triazine **91a** (1.0 equiv.) underwent a cross-coupling with functionalized arylzinc reagent **92c** (1.5 equiv.) in 7 h at 25 °C, giving ethyl 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)benzoate (**93c**) in 81% yield (Table 11, entry 1). Thiomethyl-substituted pyridazine **91f** underwent a straightforward cross-coupling with 4-chlorophenylzinc iodide (**92k**; 6 h) leading to the 3,6-difunctionalized pyridazine **93v** in 72% yield (entry 2). 6,7-Dimethoxy-4-(methylthio)quinazoline (**91g**) was used for the cross-coupling reaction with the electron-poor ester-substituted arylzinc reagent **92c** in 24 h at room temperature, providing the 4-arylquinazoline **93w** in 82% yield (entry 3).The reaction of trifluoromethylated pyrimidine **91d**, prepared from a condensation reaction, with 4-(*N*,*N*-

[116] 1 mmol $Ni(acac)_2$: 0.81 €; 1 mmol DPE-Phos: 3.39 €; Sigma-Aldrich Catalogue, **2010**.

dimethylamino)phenylzinc iodide (**92l**) gave the trisubstituted pyrimidine **93x** in 96% yield (25 °C, 6 h, entry 4). Thiomethylated benzoxazole **91c** and benzothiazole **91j** reacted swiftly with the electron-rich arylzinc reagents **92b** and **92l** (25 °C, 3-5 h), resulting in the heterocyclic products **93j** and **93y,z** in 81-89% yield (entries 5-7).

Table 11: Ni-catalyzed cross-coupling reactions of hiomethylated N-heterocycles **91** with functionalized aryl and hetarylzinc reagents **92**.

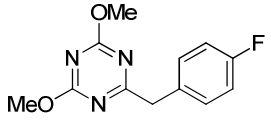
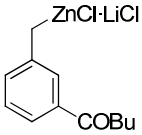
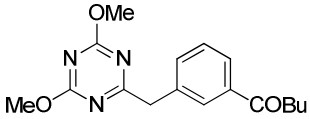
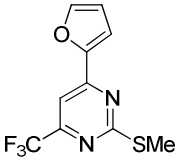
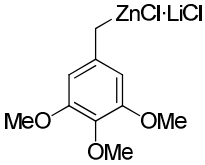
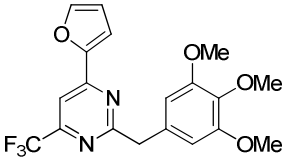
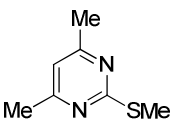
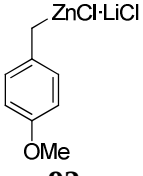
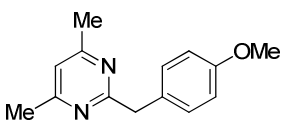
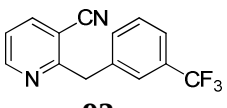
Entry	Electrophile	Zinc reagent	Reaction time [h]	Product	Yield [%][a]
1	**91a**	**92c**	7	**93c**	81
2	**91f**	 **92k**	6	 **93v**	72
3	**91g**	**92c**	24	 **93w**	82
4	**91d**	 **92l**	6	 **93x**	96
5	**91c**	**92b**	3	 **93y**	81
6	**91j**	**92b**	3	**93j**	85
7	**91j**	**92l**	5	 **93z**	89

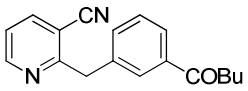
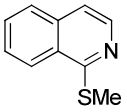
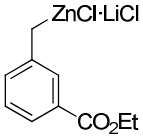
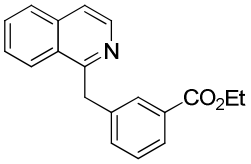
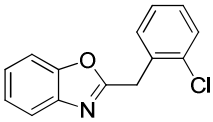
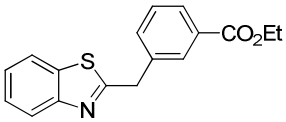
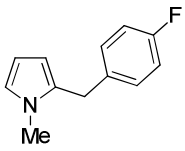
[a] Yield of isolated analytically pure product.

The reaction protocol, based on $Ni(acac)_2$ (2.5 mol%) and DPE-Phos (5.0 mol%), could also be applied to benzylic zinc reagents. The thiomethylated triazine **91a** reacted with 3-(trifluoromethyl)benzylzinc chloride (**92f**) or 4-fluorobenzylzinc chloride (**92g**) furnishing the diaryl methanes **93l** and **93aa** in 72-89% yield after 4 h at 25 °C (Table 12, entries 1 and 2). A ketone is also compatible with the reaction conditions, therefore 3-pentanoylbenzylzinc chloride (**92m**), cross-coupled with **91a**, resulted in triazine **93ab** in 82% yield (25°C, 5 h, entry 3). In the same fashion, 3-methoxy-6-(methylthio)pyridazine (**91f**) was functionalized

with benzyl zinc reagent **92g** at 25 °C in 5 h, delivering pyridazine **93m** in 74% yield (entry 4). The 4,6-disubstituted pyrimidines **91o** and **91p** were submitted to cross-coupling reactions with the methoxy-substituted benzylzinc reagents **92n** and **92o**. The corresponding heterocycles **93ac,ad** were obtained in 85-89% yield (25 °C, 3-24 h, entries 5 and 6). In another reaction, 2-(methylthio)nicotinonitrile (**91l**) coupled with the *meta*-substituted electron-poor benzylzinc reagents **92f** and **92m** (25 °C, 5-8 h) leading to the 2,3-difunctionalized pyridines **93ae** and **93af** in 73-79% yield (entries 7 and 8). Similarly, the isoquinoline **91q**, benzoxazole **91c** and benzothiazole **91j** could be cross-coupled with benzylic zinc reagents bearing sensitive functional groups like an ester or a *ortho*-chloride (25 °C, 18-48 h), leading to the heterocyclic diarylmethanes **93ag-ai** in 70-91% yield (entries 9-11). Also the electron-rich 5-membered heterocycle **91b** proved to be a suitable electrophile for our cross-coupling method, and the reaction with benzylzinc **92g** (50 °C, 18 h) provided 2-(4-fluorobenzyl)-1-methyl-1*H*-pyrrole (**93aj**) in 42% yield (entry 12).

Table 12: Ni-catalyzed cross-coupling reactions of thiomethylated N-heterocycles **91** with functionalized benzylzinc reagents **92**.

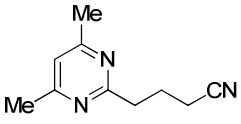
Entry	Electrophile	Zinc reagent	Reaction time [h]	Product	Yield [%][a]
1	**91a**	**92f**	4	**93l**	72
2	**91a**	**92g**	4	 **93aa**	89
3	**91a**	 **92m**	5	 **93ab**	82
4	**91f**	**92g**	5	**93m**	74
5	 **91o**	 **92n**	24	 **93ac**	89
6	 **91p**	 **92o**	3	 **93ad**	85
7	**91l**	**92f**	8	 **93ae**	73

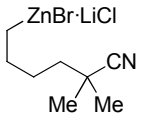
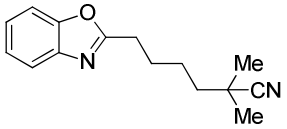
8	**91l**	**92m**	5	 **93af**	79
9	 **91q**	 **92p**	48	 **93ag**	91
10	**91c**	 **92q**	18	 **93ah**	76
11	**91j**	**92p**	48	 **93ai**	70
12	**91b**	**92g**	18	 **93aj**	42[b]

[a] Yield of isolated analytically pure product. [b] Reaction was performed at 50 °C.

Alkylzinc reagents participate also well in these Ni-catalyzed reactions. Thus, 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**91a**) underwent a cross-coupling with 4-cyanopropylzinc bromide (**92h**; 25 °C, 48 h) which furnished the alkylated triazine **93ak** in 68% yield (Table 13, entry 1). The dimethylated pyrimidine derivative **91p** reacted equally fast with this functionalized alkylzinc reagent, and the resulting 4-(4,6-dimethylpyrimidin-2-yl)butanenitrile (**93al**) was isolated in 84% yield (entry 2). Finally, 2-methylthiobenzoxazole (**91c**) was transformed in a cross-coupling reaction using 5-cyano-5-methylhexylzinc bromide (**92r**) at 25 °C within 12 h, providing the benzoxazole derivative **93am** in 82% yield (entry 3).

Table 13: Ni-catalyzed cross-coupling reactions of hiomethylated N-heterocycles **91** with functionalized alkyl zinc reagents **92**.

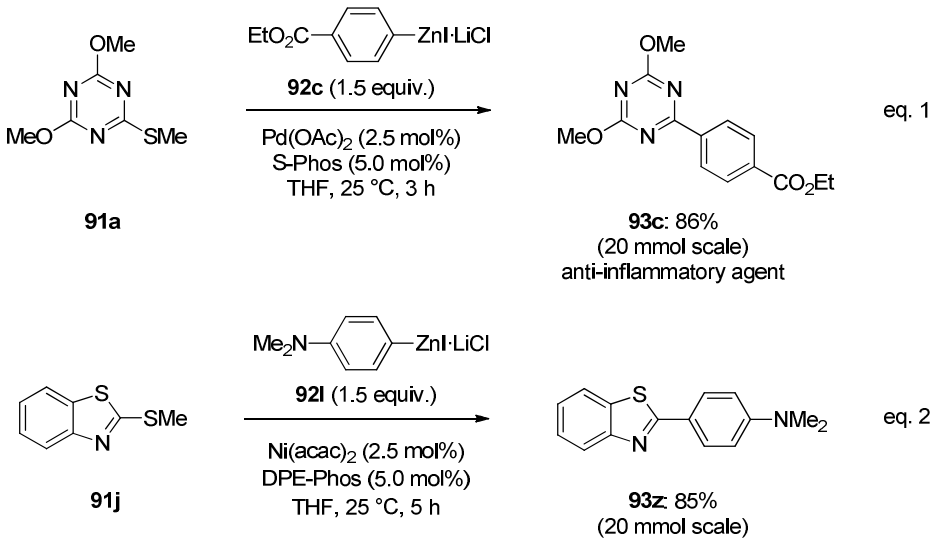
Entry	Electrophile	Zinc reagent	Reaction time [h]	Product	Yield [%][a]
1	**91a**	**92h**	48	**93q**	68
2	**91p**	**92h**	48	 **93ak**	84

3	**91c**	 **92r**	12	 **93al**	82

[a] Yield of isolated analytically pure product.

4.6 Large Scale Preparation of Functionalized N-Heterocycles via Cross-Coupling Reactions

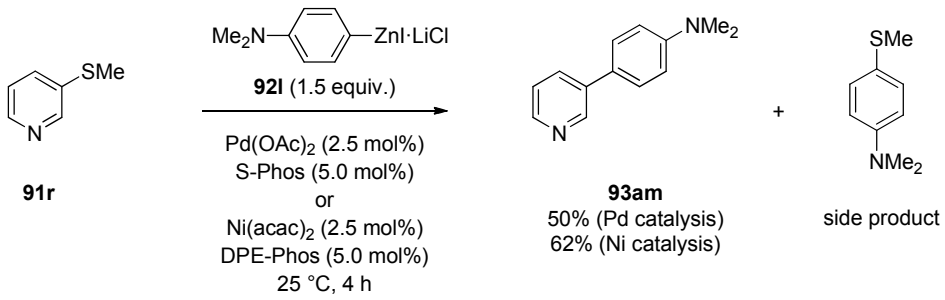
To demonstrate that these cross-coupling protocols can be scaled-up to multigram scale reactions, and therefore add synthetic value to the two methods developed, additional Pd- and Ni-catalyzed reactions were carried out on larger scale. Thus, 4-(ethoxycarbonyl)phenylzinc iodide (**92c**; 1.5 equiv.) underwent a straightforward cross-coupling with 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**91a**) on a 20 mmol scale using Pd catalysis (25 °C, 3 h). The triazine **93c**, which is an anti-inflammatory agent,[117] was obtained in 86% yield (25 °C, 18 h, Scheme 48, eq. 1). Also the electron-rich arylzinc reagent **92l** reacted smoothly with the thiomethyl-substituted benzothiazole **91j** and furnished 4-(benzo[*d*]thiazol-2-yl)-*N*,*N*-dimethylaniline (**93z**) in 85% yield (25 °C, 5 h, 20 mmol scale, eq. 2).



Scheme 48: Large-scale cross-couplings of thiomethyl-substituted N-heterocycles **91a,j** with organozinc reagents **92c,l** using Pd or Ni catalysis.

[117] a) R. Menicagli, S. Samaritani, G. Signore, F. Vaglini, L. Dalla Via, *J. Med. Chem.* **2004**, *47*, 4649; b) C. Dianzani, M. Collino, M. Gallicchio, S. Samaritani, G. Signore, R. Menicagli, R. Fantozzi, *J. Pharm. Pharmacol.* **2006**, *58*, 219; c) S. Samaritani, G. Signore, C. Malanga, R. Menicagli, *Tetrahedron* **2005**, *61*, 4475.

So far only N-heterocycles bearing the thiomethyl adjacent to the nitrogen, which is naturally the most active position for the attack from a nucleophile, had been used in the two cross-coupling protocols. The possibility to also react heterocyclic thioethers which a different substitution pattern would be a desirable addition to our procedures. Therefore we investigated the reaction of 3-(methylthio)pyridine (**91r**) with 4-(*N*,*N*-dimethylamino)phenylzinc iodide (**92l**) using our described conditions ($Pd(OAc)_2$ / S-Phos or $Ni(acac)_2$ / DPE-Phos) at 25 °C (Scheme 49). While both catalyst achieved full conversion of the pyridine within 4 h, the Ni-catalyzed reaction delivered a higher yield (62% compared to 50% with Pd-catalysis) of the desired cross-coupling product **93an**. The side reaction leading to *N*,*N*-dimethyl-4-(methylthio)aniline, probably originating from the transmetalation step of the catalytic cycle, is the reason for the low yields using this electrophile compared to the 2-thiomethylpyridines used so far. Further studies on this class of N-heterocyclic thioethers were not undertaken.

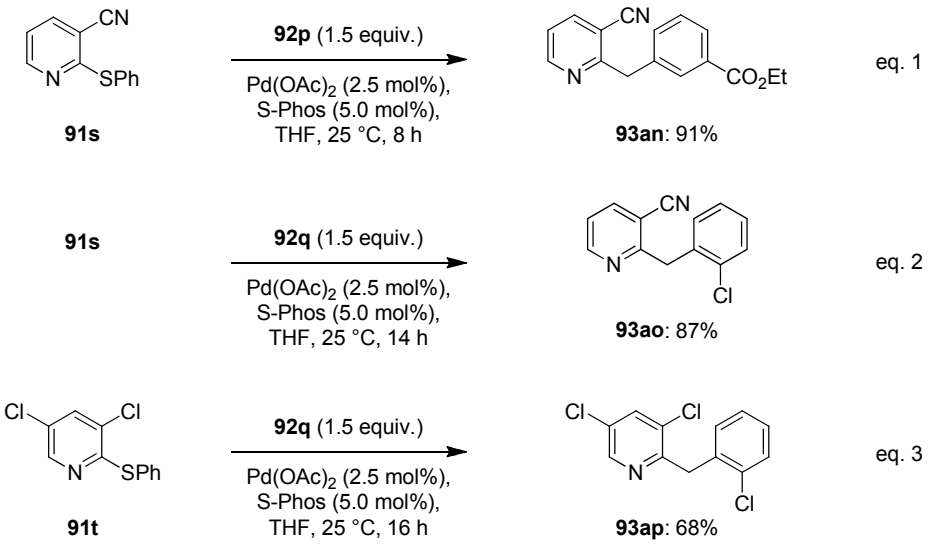


Scheme 49: Pd- and Ni-catalyzed cross-couplings of 3-(methylthio)pyridine (**91r**) with 4-(*N*,*N*-dimethylamino)phenylzinc iodide (**92l**).

4.7 Pd-Catalyzed Cross-Coupling Reactions of Thiophenylated Heterocycles

The advantages and also the generality of these cross-coupling protocols were the subject of further eperiments. Therefore we aimed at the use of other classes of thioethers as the leaving group, despite the thiomethyl moiety being the most economic. This possibility was demonstrated by employing thiophenylated N-heterocycles in the Pd-catalyted cross-coupling reaction with organozinc reagents. These electrophiles can easily be prepared by a nucleophilic attack reaction of thiophenolate on heterocyclic chlorides similar to equation 1 of Scheme 44. So the reaction of 2-(phenylthio)nicotinonitrile (**91s**) with 3-(ethoxycarbonyl)benzylzinc chloride (**92p**, 1.5 equiv.) using $Pd(OAc)_2$ and S-Phos (2.5 mol% / 5.0 mol%) provided the substituted pyridine **93an** at 25 °C within 8 h in 91% yield (Scheme 50, eq.1). Using the same pyridine **91s**, smooth cross-coupling reaction with *ortho*-

functionalized benzylzinc reagent **92q** occurred and the functionalized nicotinonitrile **93ao** was isolated in 87% yield (25 °C, 14 h, eq. 2). Organozinc **92q** could also be cross-coupled with phenylthioether **91t** leading to the trichloro-substituted *bis*-arylmethane **93ap** in 68% yield (25 °C, 16 h, eq. 3). These examples demonstrate the versatility and the scope of thioethers compatible with these reaction protocols.



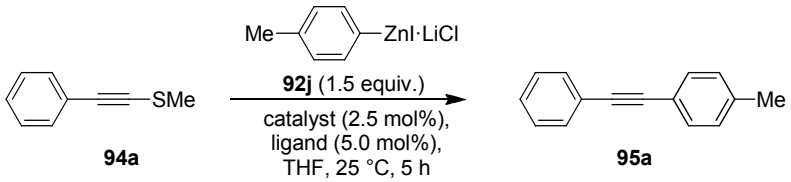
Scheme 50: Pd-catalyzed cross-coupling reaction of thiophenylated N-heterocycles **91s,t**.

4.8 Optimization of Conditions for the Synthesis of Functionalized Alkynes via Cross-Coupling Reactions

We wanted to extend these two efficient synthetic procedures on another substrate classes. As previously mentioned, also other thio-compounds are capable of undergoing such cross-coupling reaction to form new carbon-sulfur bonds. We decided on alkyne-thioethers as a promising family of electrophiles, since *Liebeskind* had shown that those compounds can be cross-coupled with boronic acids using a Pd-catalyst and stoichiometric amounts of copper(I)-thiophene-2-carboxylate. We set out for the goal of finding a catalytic system which would transmute these electrophiles with organozinc reagents, tolerating a broad range of functionalities. Methyl(phenylethynyl)sulfide (**94a**) was chosen as the electrophile in the model reaction with 4-methylphenylzinc iodide (**92j**) in the presence of 2.5 mol% of metal source and 5.0 mol% ligand (THF, 25 °C, 5 h). The first tests utilizing the two catalytic systems which had been optimized for the cross-coupling reaction with N-heterocycles ($Pd(OAc)_2$ / S-Phos and $Ni(acac)_2$ / DPE-Phos) showed a low activity of these catalysts in our desired ethynyl cross-coupling (28% and 15%, Table 14, entries 8 and 1). Especially the Ni

salt displayed a very poor performance, so we focused on Pd catalysts for the further optimization process. Catalysts without any additional ligands like PEPPSI[118] only gave 12% yield of alkyne **95a** with our model reaction (entry 4), $Pd(PPh_3)_4$ showed 40% yield by GC control (entry 15). Additional experiments with $Pd(dba)_2$ (2 mol%) and various ligands like BINAP (12%, entry 3), dppf (35%, entry 11), tfp (36%, entry 12), PCy_3 (42%, entry 16) or dppe (54%, entry 19) resulted in DPE-Phos as the best ligand for this Pd source, furnishing 79% yield of the cross-coupling product **95a**. By changing to $Pd(OAc)_2$, this yield could be further improved to quantitative yield of the bisarylacetylene **95a** after 5 h at 25 °C (entry 22).

Table 14: Catalyst and ligand screening in the cross-coupling reaction of methyl(phenylethynyl)sulfide (**94a**) with 4-methylphenylzinc iodide (**92j**).

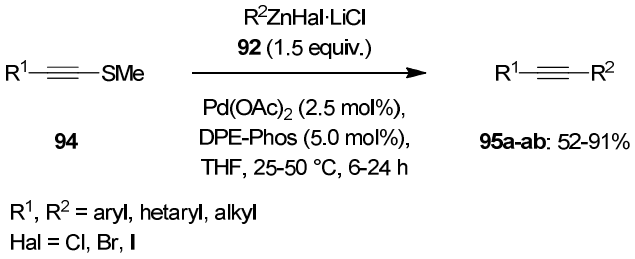


Entry	Metal	Ligand	Yield [%][a]
1	$Ni(acac)_2$	DPE-Phos	5
2	$Pd(dba)_2$	$Cy_2PC_2H_4PCy_2$	12
3	$Pd(dba)_2$	BINAP	12
4	PEPPSI	-	13
5	$Pd(dba)_2$	dppp	13
6	$Pd(dba)_2$	$H_3CC(CH_2PPh_2)_3$	18
7	$Pd(dba)_2$	PPh_2Me	23
8	$Pd(OAc)_2$	S-Phos	28
9	$Pd(dba)_2$	dpppent	30
10	$Pd(dba)_2$	$P(C_2H_4PPh_2)_3$	31
11	$Pd(dba)_2$	dppf	35
12	$Pd(dba)_2$	tfp	36
13	$Pd(dba)_2$	2,2'-bipyridine	36
14	$Pd(dba)_2$	tris(2,4,6-trimethoxyphenyl)-phosphine	37
15	$Pd(PPh_3)_4$	-	40
16	$Pd(dba)_2$	PCy_3	42
17	$Pd(dba)_2$	S-Phos	45
18	$Pd(dba)_2$	P(*o*Tol)$_3$	46
19	$Pd(dba)_2$	dppe	54
20	$Pd(OAc)_2$	dppe	66
21	$Pd(dba)_2$	DPE-Phos	79
22	$Pd(OAc)_2$	DPE-Phos	100

[a] GC yield using tridecane as internal standard.

[118] PEPPSI = pyridine-enhanced precatalyst preparation, stabilization and initiation; IPr = diisopropylphenylimidazolium derivative; a) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743; b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Eur. J. Chem.* **2006**, *12*, 4749.

This catalyst combination ($Pd(OAc)_2$ 2.5 mol%, DPE-Phos 5.0 mol%) was able to perform the desired cross-couplings smoothly, tolerating various sensitive functionalities like a nitrile or an ester in the electrophiles or the aryl, hetaryl or alkyl zinc reagent. Most of these reactions took place at room temperature in a matter of several hours in THF (Scheme 51).

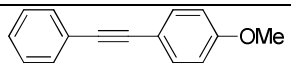
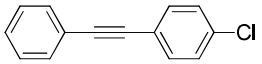
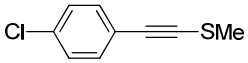
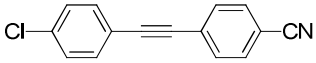
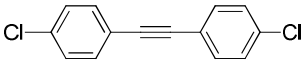
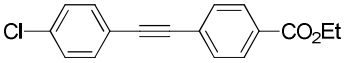
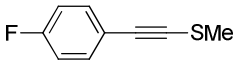
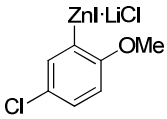
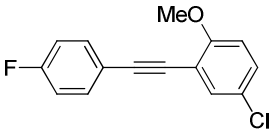
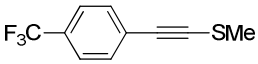
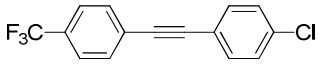
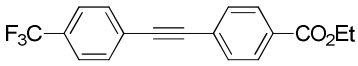
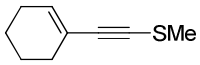
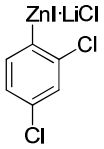
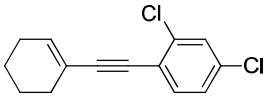
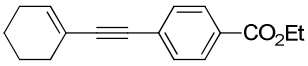
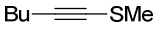
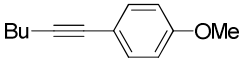


Scheme 51: Pd-catalyzed cross-coupling reaction of thiomethyl-substituted alkynes **94** with functionalized organozinc reagents **92**.

4.9 Synthesis of Functionalized Alkynes via Pd-catalyzed Cross-Coupling Reactions

Thus, methyl(phenylethynyl)sulfide (**94a**) reacted with 4-methoxyphenylzinc iodide (**92b**) at 25 °C within 2 h giving the *bis*-aryl acetylene **95b** in 91% yield (Table 15, entry 1). Also electron-deficient zinc reagents like chlorine-substituted **92k** reacted smoothly with thioalkyne **94a** leading to 1-chloro-4-(phenylethynyl)benzene (**95c**), in 24 h at 25 °C and 68% yield (entry 2). The 4-chlorophenylacetylene derivative **94b** reacted with arylzinc **92d** bearing a nitrile group, and this cross-coupling (50 °C, 4 h) furnished the substituted benzonitrile **95d** in 84% yield (entry 3). Similarly, the thiomethylated alkyne **94b** reacted well with aryl zinc reagent **92k** or the ester-substituted aryl zinc reagent **92c** and we could obtain the cross-coupling products **95e** and **95f** in 53-73% yield (50 °C, 6-12 h, entries 4 and 5). The 2,5-disubstituted arylzinc iodide **92s** was used for a cross-coupling with ((4-fluorophenyl)ethynyl)(methyl)sulphide **94c** and led to compound **95g** in 74% yield (50 °C, 4 h, entry 6). Trifluoromethyl-functionalized alkyne **94d** was submitted to a coupling reaction (25 °C, 12-20 h) with the functionalized arylzinc reagents **92k** and **92c**, delivering the corresponding *bis*-aryl acetylenes **95h** and **95i** in 76-77% yield (entries 7 and 8). Finally, also the non-aromatic electrophiles **94e** and **94f** can be reacted steadily with various substituted arylzinc iodides **92t,b,c** and the disubstituted alkynes **95j-l** are obtained in 64-76% yield (25-50 °C, 3-10 h, entries 9-11).

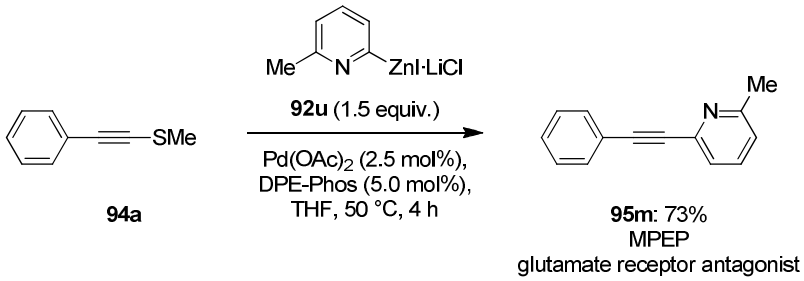
Table 15: Pd-catalyzed cross-coupling reactions of thiomethylated acetylenes **94** with functionalized aryl zinc reagents **92**.

Entry	Electrophile	Zinc reagent	Reaction time [h]	Product	Yield [%][a]
1	**94a**	**92b**	2	 **95b**	91
2	**94a**	**92k**	24	 **95c**	68
3	 **94b**	**92d**	4	 **95d**	84[b]
4	**94b**	**92k**	12	 **95e**	73[b]
5	**94b**	**92c**	6	 **95f**	53[b]
6	 **94c**	 **92s**	4	 **95g**	74[b]
7	 **94d**	**92k**	12	 **95h**	76
8	**94d**	**92c**	20	 **95i**	77
9	 **94e**	 **92t**	10	 **95j**	69
10	**94e**	**92c**	6	 **95k**	76[b]
11	 **94f**	**92b**	3	 **95l**	64

[a] Yield of isolated analytically pure product. [b] Reaction was performed at 50 °C.

The glutamate receptor antagonist[119] **95m** was chosen as a suitable heterocyclic target molecule to demonstrate the synthetic use of the cross-coupling protocol. By reacting hetarylzinc reagent 6-methylpyridin-2-ylzinc iodide (**92u**) with thioalkyne **94a** (50 °C, 4 h), we obtained 2-methyl-6-(phenylethynyl)pyridine (MPEP, **95m**), in 73% yield (Scheme 52).

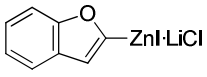
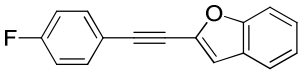
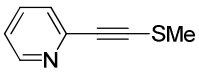
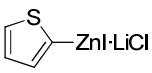
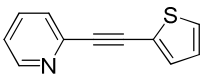
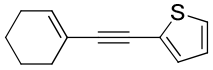
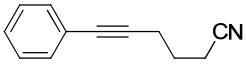
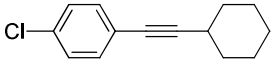
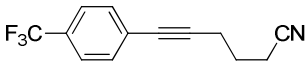
[119] P. M. IV Lea, A. I. Faden, *CNS Drug Rev.* **2006**, *12*, 149.

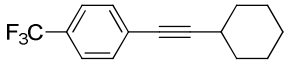


Scheme 52: Synthesis of MPEP (**95m**) using the cross-coupling protocol.

In the same fashion the 5-membered heterocyclic zinc reagents **92v** and **92w** were reacted with arylic, hetarylic and aliphatic electrophiles **94c,g,e** at 25-50 °C within 6-16 h in THF. The cross-coupling products **95n-p** were isolated in 65-82% yield (entries 1-3). This method could also be applied to alkylzinc derivatives. Therefore, the alkyne **94a** underwent a cross-coupling with 4-cyanopropylzinc bromide (**92h**) giving the hexyne **95q** after 16 h at 50 °C in 52% yield (entry 4). 1-Chloro-4-((methylthio)ethynyl)benzene (**94b**), reacted with the secondary alkyl zinc **92i**, provided the alkyne **95r** in 70% yield (50 °C, 10 h, entry 5). In two more experiments, the trifluoromethyl-substituted alkyne **94d** underwent a cross-coupling with 4-cyanopropylzinc bromide (**92h**) or cyclohexylzinc bromide (**92i**), giving the aliphatic compounds **95s,t** in 66% yield (25-50 °C, 4-18 h, entries 6-7).

Table 16: Pd-catalyzed cross-coupling reactions of thiomethylated acetylenes **94** with functionalized hetaryl and alkyl zinc reagents **92**.

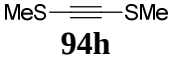
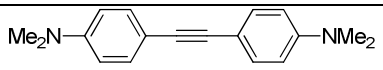
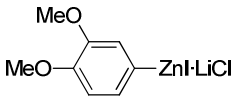
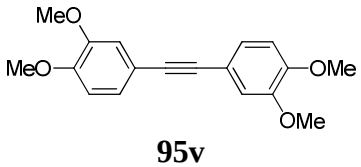
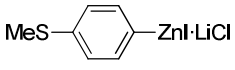
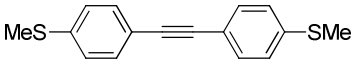
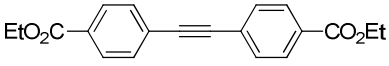
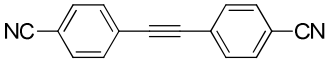
Entry	Electrophile	Zinc reagent	Reaction time [h]	Product	Yield [%][a]
1	**94c**	 **92v**	6	 **95n**	82[b]
2	 **94g**	 **92w**	8	 **95o**	72[b]
3	**94e**	**92w**	16	 **95p**	65
4	**94a**	**92h**	16	 **95q**	52[b]
5	**94b**	**92i**	10	 **95r**	70[b]
6	**94d**	**92h**	4	 **95s**	66[b]

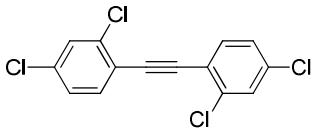
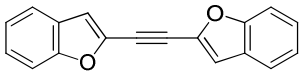
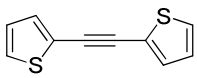
7	**94d**	**92i**	18	 **95t**	66

[a] Yield of isolated analytically pure product. [b] Reaction was performed at 50 °C.

Remarkably, *bis*(methylthio)acetylene (**94h**, 1.0 equiv.) could be easily cross-coupled using the catalytic system and 3.0 equivalents of the organozinc compound. This is especially useful since the corresponding dihaloacetylenes are known to be toxic, carcinogenic and explosive and, consequently, not practical substrates. Thus, the thioether-substituted alkyne **94h** was functionalized with 4-(dimethylamino)phenylzinc iodide (**92l**) and led to the symmetrically substituted acetylene **95u** in 81% yield (25 °C, 8 h, Table 17, entry 1). Other electron-rich arylzinc reagents **92x,y** also react smoothly with *bis*(methylthio)acetylene (**94h**) and deliver the *bis*-arylacetylenes **95v,w** in 73-79% yield (25 °C, 10-14 h, entries 2 and 3). Additionally, also the electron-deficient and susceptibly functionalized arylzinc compounds **92c,d** underwent the cross-coupling reaction and we obtained the 4,4'-difunctionalized diphenylacetylenes **95x** and **95y** in 64-67% yield (50 °C, 12-16 h, entries 4 and 5). The organozinc reagent **92t**, bearing two chlorines, reacted equally well with **94h** and furnished the tetrachloro-substituted product **95z** in 78% yield after 4 h at 50 °C (entry 6). Ultimately, also hetaryl zinc reagents were suitable nucleophiles, therefore the reaction of 2-benzofuranylzinc iodide (**92v**) and 2-thiophenyl zinc iodide (**92w**) with *bis*(methylthio)acetylene (**94h**) produced the symmetrically substituted acetylene derivatives **95aa** and **95ab** in 67-74% yield (50 °C, 3-20 h, entries 7 and 8).

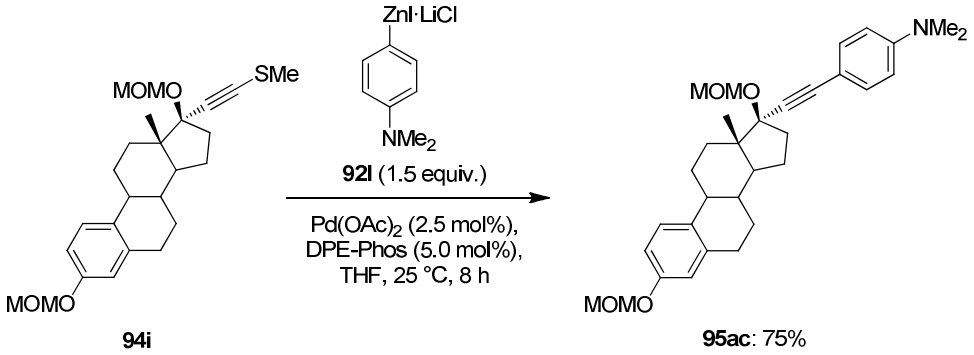
Table 17: Pd-catalyzed cross-coupling reactions of *bis*(methylthio)acetylene (**94h**) with functionalized aryl and hetaryl zinc reagents **95**.

Entry	Electrophile	Zinc reagent[c]	Reaction time [h]	Product	Yield [%][a]
1	 **94h**	**92l**	8	 **95u**	81
2	**94h**	 **92x**	10	 **95v**	79
3	**94h**	 **92y**	14	 **95w**	73
4	**94h**	**92c**	12	 **95x**	67[b]
5	**94h**	**92d**	16	 **95y**	64[b]

6	**94h**	**92t**	4	 **95z**	78[b]
7	**94h**	**92v**	3	 **95aa**	74[b]
8	**94h**	**92w**	20	 **95ab**	67[b]

[a] Yield of isolated analytically pure product. [b] Reaction was performed at 50 °C. [c] 3.0 Equivalents of zinc reagent used.

Finally, the (methylthio)ethynyl-substituted steroid **94i** was prepared starting from commercially available ethynylestradiol by deprotonation with *i*PrMgCl·LiCl (1.1 equiv., 0 °C, 10 min) and trapping with *S*-methyl methanethiosulfonate (1.2 equiv., 25 °C, 15 min). This substituted hormone was easily functionalized using 4-(dimethylamino)phenylzinc iodide (**92l**, 1.5 equiv., 25 °C, 8 h) and the protected ethynyl estradiol derivative **95ab** was obtained in 75% yield (Scheme 53).



Scheme 53: Pd-catalyzed cross-coupling reaction of the MOM-protected ethynyl estradiol derivative **94i** with 4-(*N*,*N*-dimethylamino)phenylzinc iodide (**92l**).

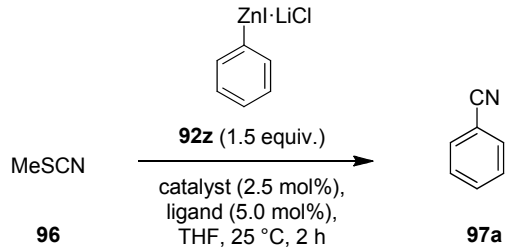
4.10 Optimization of the Catalytic System for the Preparation of Functionalized Benzonitriles

We reckoned that, based on the results of the various thiomethyl-cross-coupling reactions, we would be able to find a way for introduction a cyano group in organozinc compounds. The nitrile is a functionality of central importance for chemical synthesis as well as biological and pharmaceutical activity. The possibility of having sensitive functional groups present in the zinc reagent represents a clear advantage over older procedures using organolithium or organomagnesium compounds. Nevertheless are the ways for directly installing these onto an

organozinc species limited and usually involve toxic or expensive reagents or suffer from low yields. We put up a model reaction between phenylzinc iodide (**92z**) and methyl thiocyanate (**96**) as the cheapest, commercially available and atom economic electrophiles, following the results of the previous cross-coupling reactions experiments with thioethers. The reaction was carried out using various combinations of metal salts (2.5 mol%) and ligands (5.0 mol%) in THF at room temperature and monitored by GC with hydrolysed reaction aliquots after 2 h. Without any metal catalyst, no formation of the cyanated product **97a** could be observed, ruling out the mechanistic pathway of a simple nucleophilic attack on the thiocyanate.

First palladium catalysts like PEPPSI (Table 18, entry 1) or $Pd(OAc)_2$ / S-Phos (entry 4), which were used for the N-heterocyclic electrophiles, were examined, but they generally did not generated detectable amounts of benzonitrile **97a**. We figured the Pd-species might be deactivated by the methyl thiocyanate acting as a catalyst poison, and therefore switched to Ni-salts for further experiments. Also $Ni(PPh_3)_2Cl_2$ (entry 5) and $Ni(acac)_2$ combined with several phosphine and heterocyclic ligands like diadamantylbutylphosphine (entry 8), BINAP (entry 11), 1,1'-P(*t*Bu)$_2$-ferrocene (entry 14) or 4,4′-di-*tert*-butyl-2,2′-dipyridyl (entry 16) showed only 1% yield or less of the desired product **97a**. We focused on bridged diphenylphosphine ligands and dppe and dppp, which raised the GC yields to 11 and 17%, respectively (entries 21 and 22). Finally, $Ni(acac)_2$ / DPE-Phos (2.5 mol% / 5.0 mol%) proved to be by far the most active catalytic system, delivering full conversion and quantitative yield of the cross-coupled benzonitrile **97a** at 25 °C in 2 h (entry 24). A further reaction with the closely related Xant-Phos showed a significantly lower conversion rate (17% yield, entry 23), which is due to the more rigid diphenylether scaffold compared to DPE-Phos.

Table 18: Catalyst and ligand screening in the cross-coupling reaction of methyl thiocyanate (**96**) with phenylzinc iodide (**92z**).

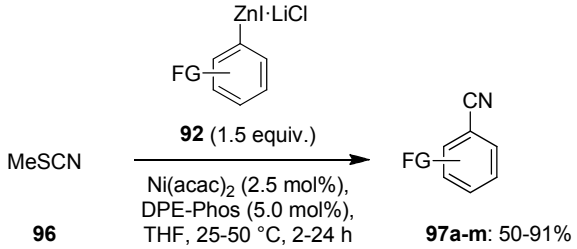


Entry	Metal	Ligand	Yield [%][a]
1	PEPPSI	-	0
2	$Pd(PPh_3)_4$	-	0
3	$Pd(dba)_2$	tfp	0
4	$Pd(OAc)_2$	S-Phos	0
5	$Ni(PPh_3)_2Cl_2$	-	0
6	$Ni(acac)_2$	dpppentane	0

7	$Ni(acac)_2$	2,2'-bipyridine	0
8	$Ni(acac)_2$	PAd_2Bu	0
9	$Ni(acac)_2$	$P(o\text{Tol})_3$	traces
10	$Ni(acac)_2$	tris(2,4,6-trimethoxyphenyl)-phosphine	traces
11	$Ni(acac)_2$	BINAP	traces
12	$Ni(acac)_2$	PPh_3	traces
13	$Ni(acac)_2$	$P(C_2H_4PPh_2)_3$	traces
14	$Ni(acac)_2$	1,1′-$P(t\text{Bu})_2$-ferrocene	traces
15	$Ni(acac)_2$	$H_3CC(CH_2PPh_2)_3$	1
16	$Ni(acac)_2$	4,4′-di-*tert*-butyl-2,2′-dipyridyl	1
17	$Ni(acac)_2$	$PPhMe_2$	2
18	$Ni(acac)_2$	PCy_3	3
19	$NiCl_2 \cdot DME$	-	5
20	$Ni(acac)_2$	dppf	7
21	$Ni(acac)_2$	dppe	11
22	$Ni(acac)_2$	dppp	17
23	$Ni(acac)_2$	Xanth-Phos	17
24	$Ni(acac)_2$	DPE-Phos	100

[a] GC yield using tridecane as internal standard.

This simple and robust catalyst is capable of converting various kinds of functionalized arylzinc reagents into their nitrile counterparts. The best results are achieved with electron-rich or non-conjugated electron-poor organozincs and the reaction delivers good to excellent yields of the substituted benzonitriles at 25-50 °C in a matter of a few hours (Scheme 54).



FG = *t*Bu, Cl, OMe, SMe, NMe_2, CN, CO_2Et

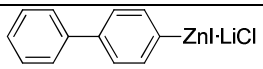
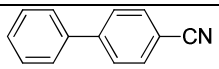
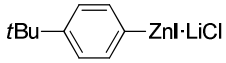
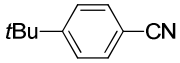
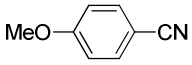
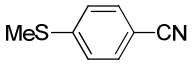
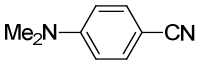
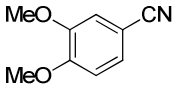
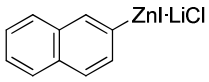
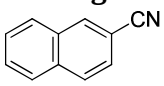
Scheme 54: Ni-catalyzed cross-coupling reaction of methyl thiocyanate (**96**) with functionalized organozinc reagents **92**.

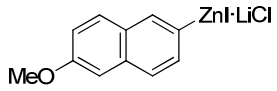
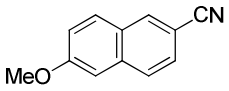
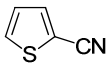
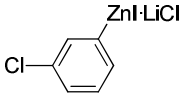
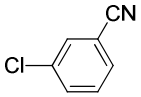
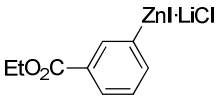
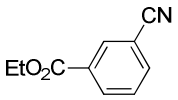
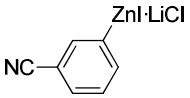
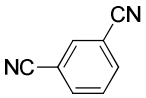
4.11 Synthesis of Functionalized Benzonitriles via Ni-catalyzed Cross-Coupling Reactions

Applying this protocol, we reacted methyl thiocyanate (**96**) with 4-biphenylzinc iodide (**92aa**, 50 °C, 10 h) and obtained the 4-phenylbenzonitrile **97b** in 73% yield (Table 19, entry 1). Also the reaction of the alkylated arylzinc reagent **92ab** or 4-methoxyphenylzinc iodide (**92b**)

furnished the expected products **97c,d** in 82-86% yield (25 °C, 2-10 h, entries 2 and 3). 4-thiomethylphenylzinc iodide (**92y**, 50 °C, 8 h) and 4-(dimethylamino)phenylzinc iodide (**92l**, 25 °C, 2 h) both reacted smoothly with the thiocyanate **96**, leading to the *para*-substituted benzonitriles **97e** and **97f** in 77-91% yield (entries 4 and 5). 3,4-Dimethoxyphenylzinc iodide (**92x**) underwent a smooth cross-coupling and furnished the trifunctionalized benzene derivative **97g** in 84% yield (50 °C, 5 h, entry 6). Also the naphthylzinc reagents **92ac** and **92ad** reacted readily and we could isolate the corresponding 2-cyanonaphthyl derivatives **97h** and **97i** in 84-89% yield (25 °C, 6 h, entries 7 and 8). 2-Thienylzinc iodide (**92w**) reacted with methyl thiocyanate (**96**) using Ni catalysis (25 °C, 24 h) and the experiment afforded thiophene-2-carbonitrile (**97j**) in 50% yield, demonstrating that also heterocyclic arylzinc reagents can be used with these conditions (entry 9). The electron-deficient *meta*-substituted arylzinc reagent **92ae** was cross-coupled with **96** and produced 3-chlorobenzonitrile (**97k**) in 78% yield (25 °C, 24 h, entry 10). Lastly, also sensitive functionalities like an ester or a second nitrile were compatible with the reaction conditions, and the 1,3-difunctionalized benzenes **97l** and **97m** were isolated in 76-79% yield at 50 °C after 8 h reaction time (entries 11 and 12).

Table 19: Ni-catalyzed cross-coupling reaction of methyl thiocyanate (**96**) with functionalized organozinc reagents **92**.

Entry	Zinc reagent	Reaction time [h]	Product	Yield [%][a]
1	 **92aa**	10	 **97b**	73[b]
2	 **92ab**	10	 **97c**	82
3	**92b**	2	 **97d**	86
4	**92y**	8	 **97e**	77[b]
5	**92l**	2	 **97f**	91
6	**92x**	5	 **97g**	84[b]
7	 **92ac**	6	 **97h**	89

8	 **92ad**	6	 **97i**	84
9	**92w**	24	 **97j**	50
10	 **92ae**	24	 **97k**	78
11	 **92af**	8	 **97l**	76[b]
12	 **92ag**	8	 **97m**	79[b]

[a] Yield of isolated analytically pure product. [b] Reaction was performed at 50 °C.

Electron-withdrawing substituents on the arylzinc iodides usually resulted in a slow conversion rate, or no reaction at all. Alkylzinc reagents suffered from the same problems, rendering them useless as organometallics species for this cross-coupling protocol. When benzylzinc chlorides were used, the main compound formed in the reaction was the benzylmethylsulfide derivative, further limiting the scope of utilizable zinc reagents. We tried to solve both of these problems, the undesirable reaction pathway of benzylzinc chlorides and the low reactivity of many organozincs by optimizing the reaction conditions. A number of different CN-donors as electrophiles (phenyl thiocyanate, benzyl thiocyanate, 4-dimethylaminophenylthiocyanate, 2-pyridinylthiocyanate, nickel(II)cyanide, cyanogen bromide) as well as organometallics species (arylmagnesium, diarylzinc, dibenzylzinc, dialkylzinc) and reaction parameters (reaction time, temperature, cosolvents: NMP, DMPU, CH_2Cl_2) were investigated, but to no avail.

5. Chlorine-Zinc Exchange with Biaryl Zincates using Iron-Catalysis

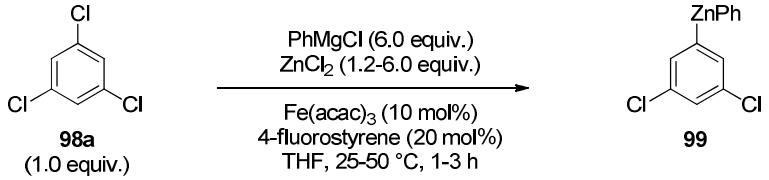
5.1 Optimization of Catalyst and Reaction Parameters

The preparation of organozinc reagents is of central importance in organometallic and general preparative chemistry due to their high stability and great tolerance towards sensitive functional groups, as described in chapter A.2. Halogen-metal exchange reactions are among the most powerful methods for preparing organometallics reagents. However the exchange rate for a halogen-zinc exchange is considerably lower than for a halogen-magnesium or even a halogen-lithium exchange, and only alkyl iodides can be used. By far the most valuable halogen for a practicable synthesis would be chlorine since organochlorides are widely available, stable, cheap and easy to prepare. Therefore we wanted to find a chlorine-zinc exchange reaction directly transforming the organohalides into versatile zinc reagents, tolerating all the possible functionalities of an organozinc compound.

Based on the investigation of side products which occurred during a cobalt-catalyzed sulfonate-copper exchange,[120] we aimed for elements from the iron group of the periodic table of elements as suitable catalysts for our reaction. First the nature of the organozinc species used as the exchange reagent was investigated. For this, different ratios of phenylmagnesium chloride and $ZnCl_2$ were premixed in THF at 25 °C and added to a model system of 1,3,5-trichlorobenzene (**98a**) in the presence of $Fe(acac)_3$ (10 mol%) and 4-fluorostyrene (20 mol%). The reaction was run at 50 °C for 3 h and the exchange process was monitored by quenching reaction aliquots with iodine in THF. The results, as shown in table 20, indicate that the active zinc species promoting the chlorine-zinc exchange is the zincate $Ph_3Zn^-\ MgCl^+$ (Table 20, entry 4). Other ratios of Grignard reagent to zinc chloride, resulting in diaryl zincs or arylzinc chlorides, showed either low conversion of 1,3,5-trichlorobenzene (**98a**) or no formation of arylzinc species (**99**) at all (entries 1-3). Further optimization was performed at lower temperatures and highest reaction speed was achieved with a ratio of $PhMgCl/ZnCl_2$ 3.3:1, obtaining full conversion of **98a** within 1 h at room temperature (entry 7).

[120] C. J. Rohbogner, C. R. Diene, T. J. Korn, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 1874; Ph.D. thesis Christoph J. Rohbogner, LMU Munich, **2010**.

Table 20: Screening of various zinc species in the model exchange reaction of 1,3,5-trichlorobenzene (**98a**) with PhMgCl and $ZnCl_2$.

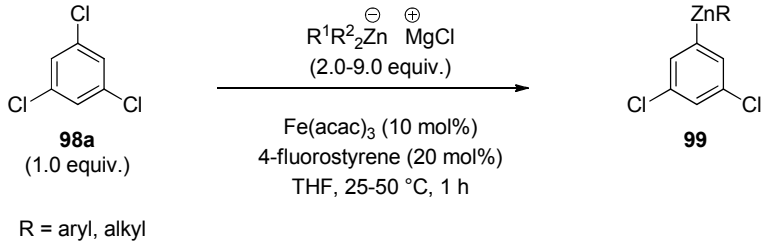


Entry	Equivalents PhMgCl	Equivalents $ZnCl_2$	Ratio PhMgCl/$ZnCl_2$	Temperature [°C], time [h]	Conversion [%][a]
1	6.0	6.0	1:1	50, 3	4[b]
2	6.0	4.5	1.5:1	50, 3	6[b]
3	6.0	3.0	2:1	50, 3	8[b]
4	6.0	2.0	3:1	50, 3	100
5	6.0	1.5	4:1	50, 3	100
6	6.0	2.4	2.5:1	25, 1	55
7	6.0	1.8	3.3:1	25, 1	100
8	6.0	1.2	5:1	25, 1	70

[a] GC conversion of **98a** using tridecane as internal standard. [b] No iodinated product was observed.

The reaction conditions needed further improvement, since we wanted to work with the minimum amount of exchange reagent necessary and the mildest conditions possible. Therefore four different zincates (Ph_3Zn^-, Ph_2iPrZn^-, $PhiPr_2Zn^-$, iPr_3Zn^-) were used in the model reaction in various stoichiometric amounts. These experiments showed that the mixed diphenylisopropyl zincate showed the highest reactivity with our reaction conditions ($Fe(acac)_3$ 10 mol%, 4-fluorostyrene 20 mol%, THF, 25 °C, 1 h) and 3.0 equiv. are sufficient for achieving a reasonable exchange rate while maintaining a good atom economy (Table 21, entries 5 and 6). The other zincates give smaller amounts of the arylzinc reagent **99** due to an increase in side product formation, namely the alkylated or phenylated 3,5-dichlorobenzene (entries 1-4, 7 and 8). Employing Co or Ni catalysts like $Co(acac)_2$ or $Ni(acac)_2$ led to a drastically reduced exchange rate in the model reaction, while omitting the 4-fluorostyrene as ligand favoured the formation of the previously named side products. Since the nature of the alkyl substituent on the zincate obviously played a major role for a straightforward exchange, we tested different alkyl groups with our reaction conditions. The results confirmed isopropyl as the most efficient substituent, achieving 63% conversion of the arylchloride **98a** after 1 h at 25 °C when only 2.0 equiv. of the zincate were used (entry 9). All others showed lower conversion rates or larger amounts of side products (entries 10-12). The phenyl moiety was later replaced by *N*,*N*'-dimethylaniline for improved purification purposes, while the observed reaction rates and GC yield only decreased slightly (entry 13), so that we achieved >95% conversion of **98a** after 6 h at room temperature.

Table 21: Further optimization of the exchange reaction of 1,3,5-trichlorobenzene (**98a**) with $R_3Zn^-MgCl^+$.



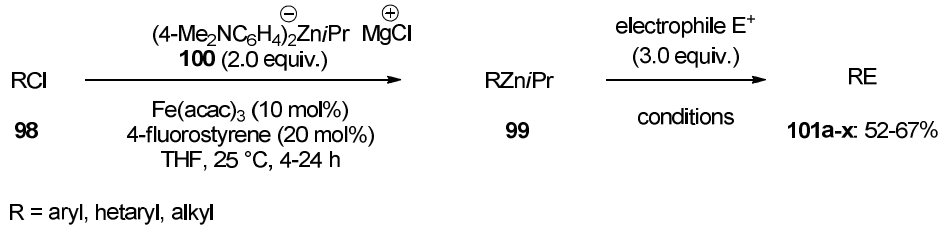
Entry	Zincate	Equivalents zincate	Temperature [°C]	Conversion [%][a]	Yield [%][b]
1	Ph_3Zn^-	3.0	25	71	31
2	Ph_3Zn^-	6.0	25	100	75
3	Ph_3Zn^-	9.0	25	100	86
4	Ph_3Zn^-	6.0	50	100	75
5	Ph_2*i*$PrZn^-$	3.0	25	80	73
6	Ph_2*i*$PrZn^-$	6.0	25	100	100
7	Ph*i*Pr_2Zn^-	6.0	25	100	89
8	*i*Pr_3Zn^-	6.0	25	100	35
9	Ph_2*i*$PrZn^-$	2.0	25	63	59
10	Ph_2*s*$BuZn^-$	2.0	25	70	38
11	Ph_2EtZn^-	2.0	25	48	34
12	Ph_2MeZn^-	2.0	25	71	49
13	$(4\text{-}Me_2NC_6H_4)_2$*i*$PrZn^-$	2.0	25	60	54

[a] GC conversion of **98a** using tridecane as internal standard. [b] GC yield of **99** using tridecane as internal standard.

To maximize the efficiency of the exchange protocol, a series of experiments with the purpose of determining the optimal solvent was undertaken, screening different mixtures of THF, 2-methyl-THF, MTBE, CPME, dimethoxyethane, NMP and DMPU. All of these cosolvents led to a significant slowdown of the reaction, some to a complete halt, while increasing the formation of protonated, alkylated or arylated side products.

5.2 Preparation of Functionalized Aromatics and Heterocycles via Chlorine-Zinc Exchange

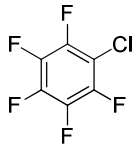
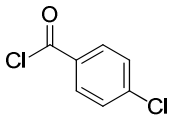
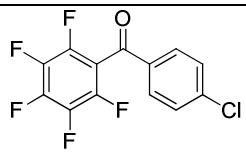
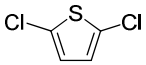
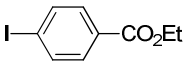
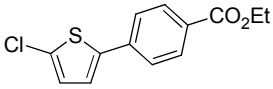
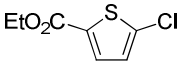
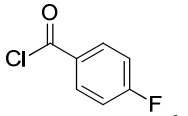
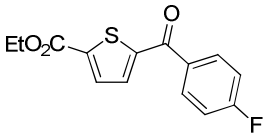
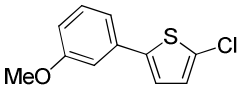
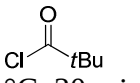
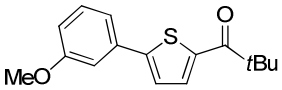
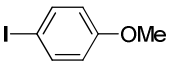
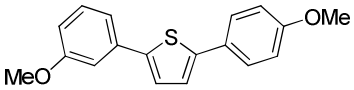
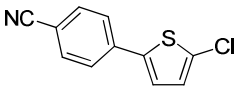
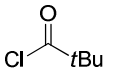
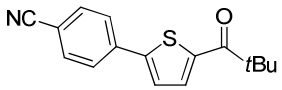
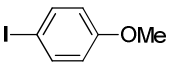
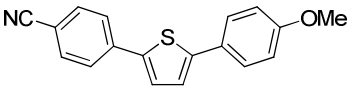
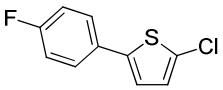
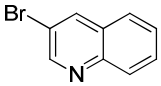
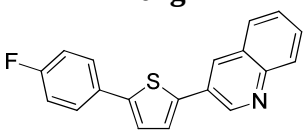
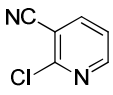
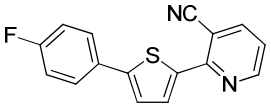
Ultimately, *bis*(4-dimethylaminophenyl)isopropyl zincate (**100**; 2.0 equiv.) in the presence of $Fe(acac)_3$ (10 mol%) and 4-fluorostyrene (20 mol%) in THF proved to be the most efficient protocol for the chlorine-zinc exchange. With this system, we were able to substitute aryl-, hetaryl- and even alkylchlorides of type **98** bearing sensitive functionalities at 25 °C. Subsequent reactions of the generated organozinc reagents **99** with various electrophiles E^+ furnished the polyfunctionalized compounds of type **101** (Scheme 55).



Scheme 55: Fe-catalyzed chlorine-zinc exchange reaction of organochlorides **98** with diarylalkyl zincate **100**.

The perfluorated chlorobenzene **98b** underwent a very rapid exchange reaction with zincate **100** (2.0 equiv., 25 °C, 4 h) and the acylation with 4-chlorobenzoyl chloride (3.0 equiv., CuCN·2LiCl 20 mol%, -20 °C, 30 min) furnished the halogenated benzophenone **101a** in 65% yield (Table **22**, entry 1). Also heterocyclic chlorides like 2,5-dichlorothiophene (**98c**) could be exchanged in 12 h, and a subsequent cross-coupling with ethyl 4-iodobenzoate (3.0 equiv., $Pd(PPh_3)_4$ 2 mol%, 25 °C, 2 h) led to the arylated thiophene **101b** in 60% yield (entry 2). Thiophene **98d**, bearing an ester function, underwent a smooth exchange with zincate **100** (12 h) and the reaction with 4-fluorobenzoyl chloride yielded ethyl 5-(4-fluorobenzoyl)thiophene-2-carboxylate (**101c**) in 52% yield (entry 3). Furthermore, the 3-anisyl-substituted thiophene **98e** was transmuted into the corresponding zinc reagent (24 h) and a Cu-catalyzed reaction with pivaloyl chloride or a Pd-catalyzed cross-coupling with 4-iodoanisole delivered the difunctionalized thiophenes **101d** and **101e** in 64-67% yield (entries 4 and 5). The developed exchange protocol is capable of tolerating nitrile groups in the reaction, so the cyano-functionalized hetaryl chloride **98f** reacted smoothly to the organozinc species in 16 h. After electrophilic reactions with pivaloyl chloride or 4-iodoanisole, the 2,5-disubstituted thiophenes **101f** and **101g** could be obtained in 57-62% yield (entries 6 and 7). 2-Chloro-5-(4-fluorophenyl)thiophene (**98g**) underwent the exchange in 16 h at room temperature when treated with *bis*(4-dimethylaminophenyl)isopropyl zincate (**100**). Two Pd-catalyzed cross-coupling reactions with 3-bromoquinoline or 2-chloronicotinonitrile (50 °C, 5 h) afforded the *bis*-heterocyclic products **101h** and **101i** in 62-65% yield (entries 8 and 9).

Table 22: Fe-catalyzed chlorine-zinc exchange reactions on aryl- and hetarylchlorides **98** and subsequent electrophilic reaction leading to functionalized compounds **101**.

Entry	Aryl or hetaryl chloride	Exchange time	Electrophile, conditions	Product	Yield [%][a]
1	 **98b**	4 h	 -20 °C, 30 min[b]	 **101a**	65
2	 **98c**	12 h	 25 °C, 2 h[c]	 **101b**	60
3	 **98d**	12 h	 -20 °C, 30 min[b]	 **101c**	52
4	 **98e**	24 h	 -20 °C, 30 min[b]	 **101d**	67
5	**98e**	24 h	 25 °C, 2 h[c]	 **101e**	64
6	 **98f**	16 h	 -20 °C, 30 min[b]	 **101f**	62
7	**98f**	16 h	 25 °C, 2 h[c]	 **101g**	57
8	 **98g**	16 h	 50 °C, 5 h[c]	 **101h**	65
9	**98g**	16 h	 50 °C, 5 h[c]	 **101i**	62

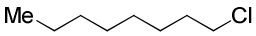
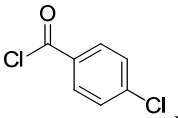
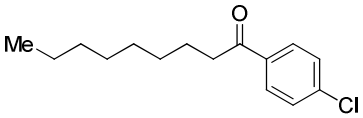
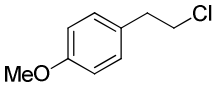
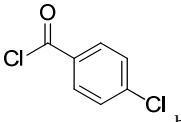
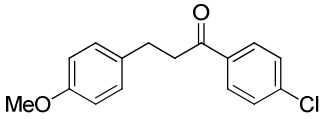
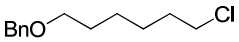
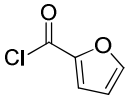
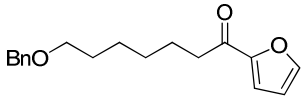
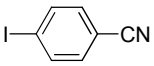
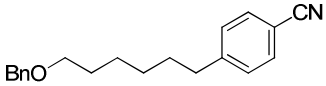
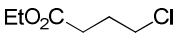
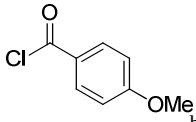
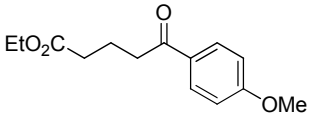
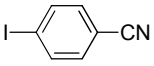
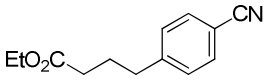
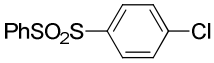
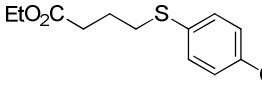
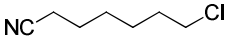
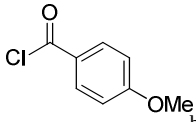
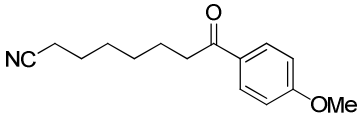
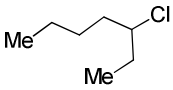
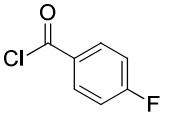
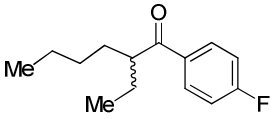
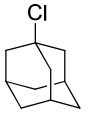
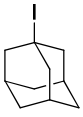
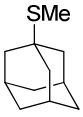
[a] Yield of isolated analytically pure product. [b] CuCN·2LiCl (20 mol%) present. [c] $Pd(PPh_3)_4$ (2 mol%) present.

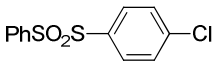
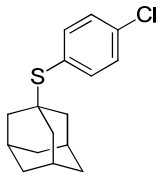
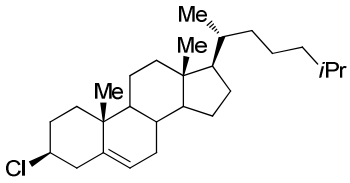
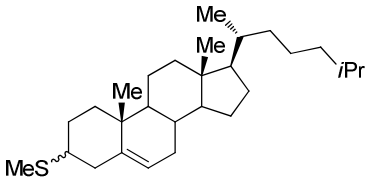
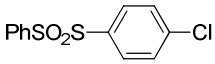
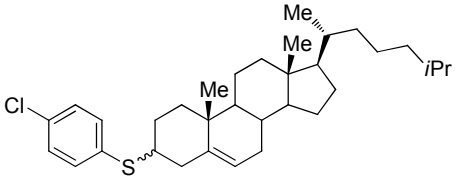
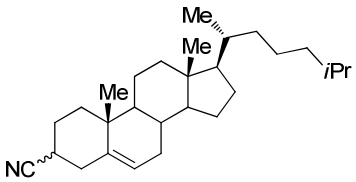
5.3 Preparation of Functionalized Aliphatics via Chlorine-Zinc Exchange

Remarkably, also functionalized alkyl chlorides underwent the chlorine-zinc exchange using the conditions optimized above. Hence, simple octyl chloride (**98h**) could be exchanged using zincate **100** in the presence of our catalytic system ($Fe(acac)_3$ 10 mol%, 4-fluoro-styrene 20 mol%, THF, 25 °C, 16 h), and a copper-catalyzed acylation with 4-chlorobenzoyl chloride

(3.0 equiv., CuCN·2LiCl 20 mol%, -20 °C, 30 min) led to the ketone **101j** in 60% yield (Table 23, entry 1). Similarly, the anisyl-substituted ethyl chloride **98i** was exchanged (14 h) and an acylation using the same conditions furnished the diaryl propanone **101k** in 56% yield (entry 2). Also the benzylated 6-chlorohexanol **98j** underwent the exchange reaction in 18 h and the functionalization with the heterocyclic acyl chloride yielded 7-(benzyloxy)-1-(furan-2-yl)heptan-1-one (**101l**) in 63% yield (entry 3). Furthermore, the resulting zincate from the exchange carried out on **98j** was used for a Pd-catalyzed cross-coupling with 4-iodobenzonitrile (3.0 equiv., $Pd(PPh_3)_4$ 2 mol%, 25 °C, 2 h) and the protected primary alcohol **101m** was obtained in 61% yield (entry 4). Sensitive groups like an ethyl ester are tolerated in our protocol, and the exchange performed with ethyl 4-chlorobutanoate (**98k**) in 16 h and subsequent quenching reaction an acyl chloride (CuCN·2LiCl 20 mol%, -20 °C, 30 min), *S*(4-chlorophenyl)benzene thiosulfonate (25 °C, 30 min) or a Pd-mediated cross-coupling (25 °C, 2 h) resulted in butane ester derivatives **101n-p** in 57-63% yield (entries 5-7). Likewise, a nitrile was compatible with the reaction conditions, therefore 7-chloroheptanenitrile (**98l**) was exchanged using zincate **100** (16 h) and followed by an acylation with 4-methoxybenzoyl chloride (CuCN·2LiCl 20 mol%, -20 °C, 30 min) we obtained the anisole derivate **101q** in 66% yield (entry 8). Secondary alkyl chlorides also reacted well in the zinc exchange reaction, so we used the zinc reagent gained from 3-chloroheptane (**98m**) for a copper-mediated acylation with 4-fluorobenzoyl chloride (CuCN·2LiCl 20 mol%, -20 °C, 30 min) and ketone **101r** was isolated in 36% yield (entry 9). Most amazingly, this protocol also allows smooth exchange of tertiary chlorides at room temperature. 1-Chloroadamantane (**98n**) was therefore turned into the corresponding zinc reagent (24 h), which was quenched with iodine or thiosulfonates (25 °C, 30 min) and we furnished the different functionalized adamantanes **101s-u** in 61-66% yield (entries 10-12). Finally, we chose cholesteryl chloride (**98o**) as an example for a more complex secondary halogenide to perform our exchange reaction on. After 24 h reaction time with exchange reagent **100** at room temperature, we were able to functionalize the generated zinc reagents with thiosulfonates or tosyl cyanate and isolated the resulting substituted hormone derivates **101v-x** in 58-66% yield (entries 13-15).

Table 23: Fe-catalyzed chlorine-zinc exchange reactions on alkylchlorides **98** and subsequent electrophilic reaction leading to functionalized compounds **101**.

Entry	Alkyl chloride, Exchange time	Electrophile, conditions	Product, Yield [%]
1	 **98h**: 16 h	 -20 °C, 30 min[b]	 **101j**: 60
2	 **98i**: 14 h	 -20 °C, 30 min[b]	 **101k**: 56
3	 **98j**: 18 h	 -20 °C, 30 min[b]	 **101l**: 63
4	**98j**: 18 h	 25 °C, 2 h[c]	 **101m**: 61
5	 **98k**: 16 h	 -20 °C, 30 min[b]	 **101n**: 60
6	**98k**: 16 h	 25 °C, 2 h[c]	 **101o**: 57
7	**98k**: 16 h	 25 °C, 30 min	 **101p**: 63
8	 **98l**: 16 h	 -20 °C, 30 min[b]	 **101q**: 66
9	 **98m**: 16 h	 -20 °C, 30 min[b]	 **101r**: 36
10	 **98n**: 24 h	I_2 25 °C, 30 min	 **101s**: 61
11	**98n**: 24 h	$MeSSO_2Me$ 25 °C, 30 min	 **101t**: 66

12	**98n**: 24 h	 25 °C, 30 min	 **101u**: 63
13	 **98o**: 24 h	$MeSSO_2Me$ 25 °C, 30 min	 **101v**: 58 (dr = 2:1)
14	**98o**: 24 h	 25 °C, 30 min	 **101w**: 60 (dr = 1.4:1)
15	**98o**: 24 h	TosCN 25 °C, 30 min	 **101x**: 66 (dr = 1.4:1)

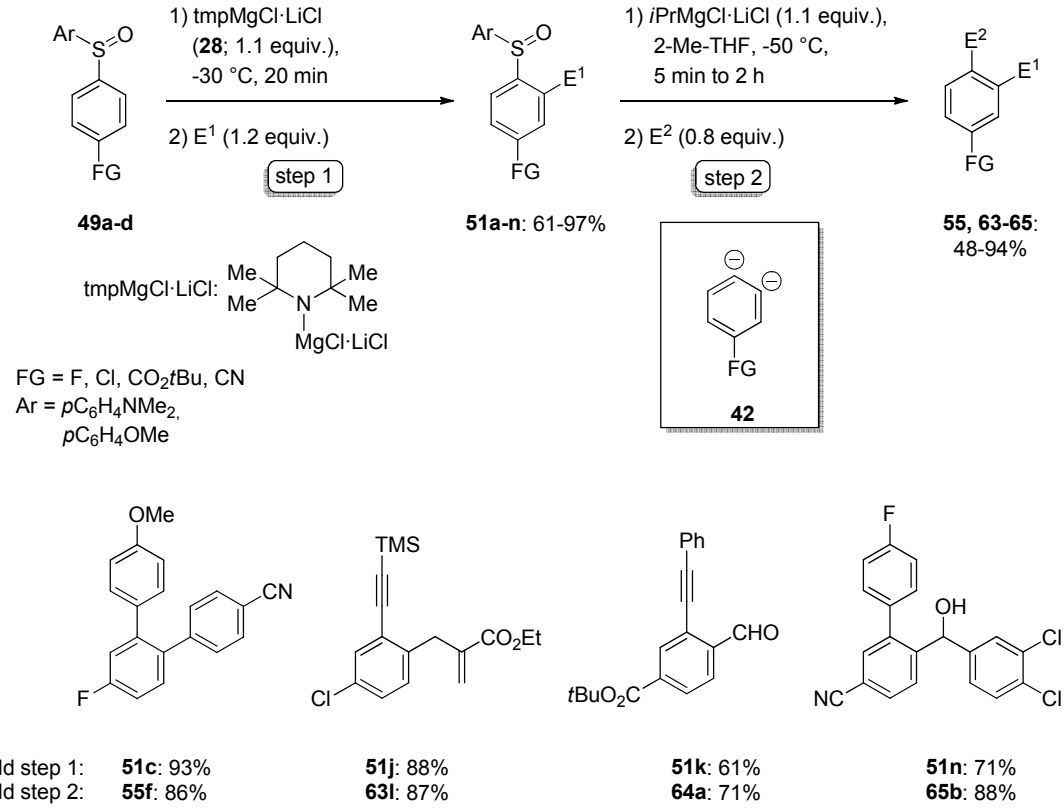
[a] Yield of isolated analytically pure product. [b] CuCN·2LiCl (20 mol%) present. [c] $Pd(PPh_3)_4$ (2 mol%) present.

6. Summary and Outlook

The goal of this work was to find access to *meta*-, *para*-trisubstituted aromatic systems using sulfoxides as key functionalities in a two-step synthesis. This concept was extended to heteroaromatic systems like thiophenes or benzofurans, and also on pyridine scaffolds. In the course of these studies, a full functionalization of thiophene was achieved. Additionally, a method for using N-heterocyclic thioethers as electrophiles in a Pd-catalyzed cross-coupling reaction with functionalized zinc reagents was developed. The protocol was cost-optimized by utilizing a cheap Ni catalyst and was furthermore applied on thiomethylated alkynes and thiomethyl cyanate. Finally we accomplished the preparation of functionalized organozinc reagents by a novel chlorine-zinc exchange reaction.

6.1 Preparation of 1,2,4-Trisubstituted Arenes via Directed Metalation and Sulfoxide-Magnesium Exchange

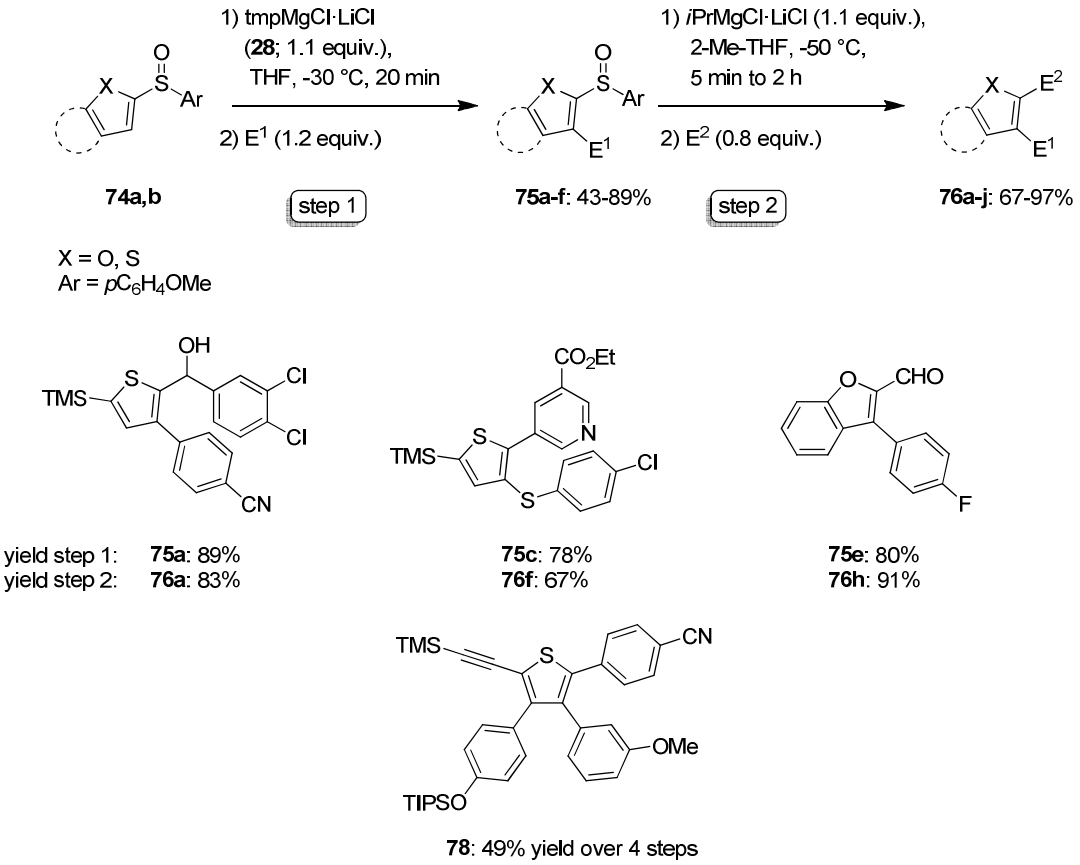
The aryl sulfoxide moiety permits an expedient two-step *meta*-, *para*-difunctionalization of readily available diaryl sulfoxides of type **49**. This substitution pattern is hard to come by using standard methods. In the first step, the sulfoxide plays the role of a directing metalation group with tmpMgCl·LiCl (**28**, tmp = 2,2,6,6-tetramethylpiperidinyl). In the second step, triggered by *i*PrMgCl·LiCl, it becomes a leaving group and undergoes a regioselective sulfoxide-magnesium exchange. These sulfoxides can therefore be considered as synthons of the bisanionic species **42**. Applying this methodology, a broad variety of trisubstituted aromatic systems **55, 63-65** bearing sensitive functional groups was prepared in good to excellent yields (Scheme 56). This two-step reaction was scaled up and works equally well with multigram assays.



Scheme 56: Two-step synthesis of 1,2,4-trisubstituted arenes **55, 63-65**.

6.2 Preparation of Disubstituted and Fully Substituted 5-Membered Heterocycles via Directed Metalation and Sulfoxide-Magnesium Exchange

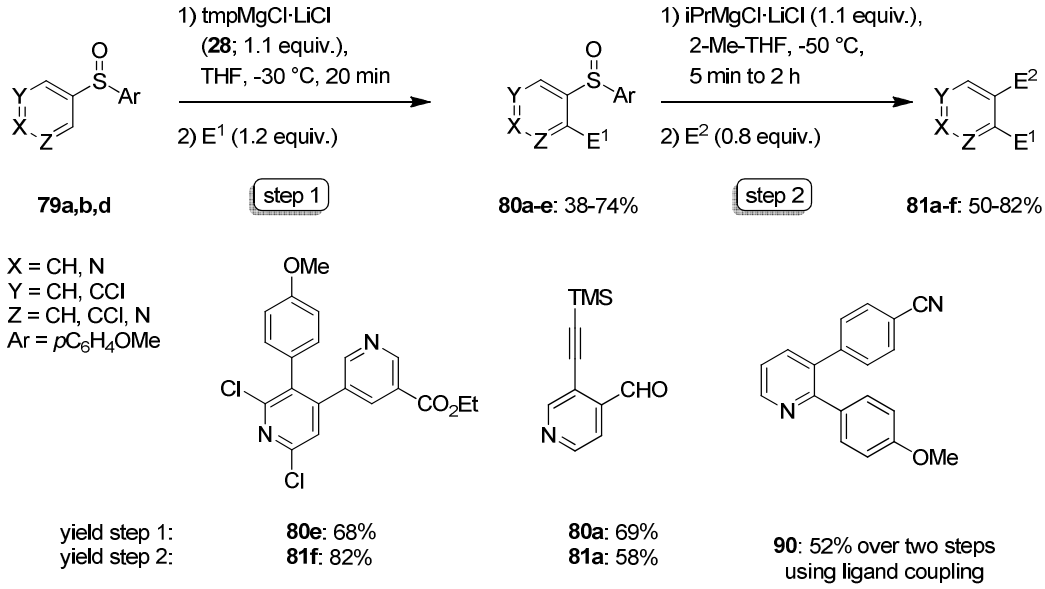
The functionalization protocol based on the sulfoxide group was extended to 5-membered heterocyclic systems and allowed the preparation of 1,2-disubstituted thiophenes and benzofurans **76** in good yields. By further deprotonation a full functionalization of the thiophene scaffold was achieved (Scheme 57).



Scheme 57: Two-step functionalization of 5-membered heterocyclic sulfoxides **74**.

6.3. Preparation of Disubstituted Pyridines via Directed Metalation, Sulfoxide-Magnesium Exchange and Ligand Coupling

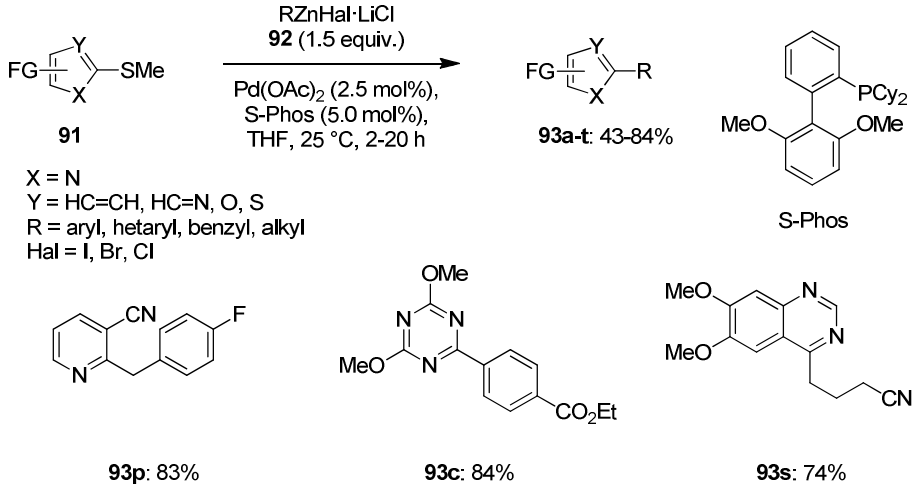
The methodology could be applied to pyridinyl sulfoxides **79**, furnishing the 3,4-disubstituted and 2,3,4,6-tetrasubstituted pyridines of type **81** after deprotonation with tmpMgCl·LiCl (**28**) and sulfoxide-magnesium exchange using *i*PrMgCl·LiCl. By exploiting the ligand coupling reaction of 2-pyridinyl sulfoxides, the cyclooxygenase-2 inhibitor **90** was prepared (Scheme 58).



Scheme 58: Two-step functionalization of pyridinyl sulfoxides **79**.

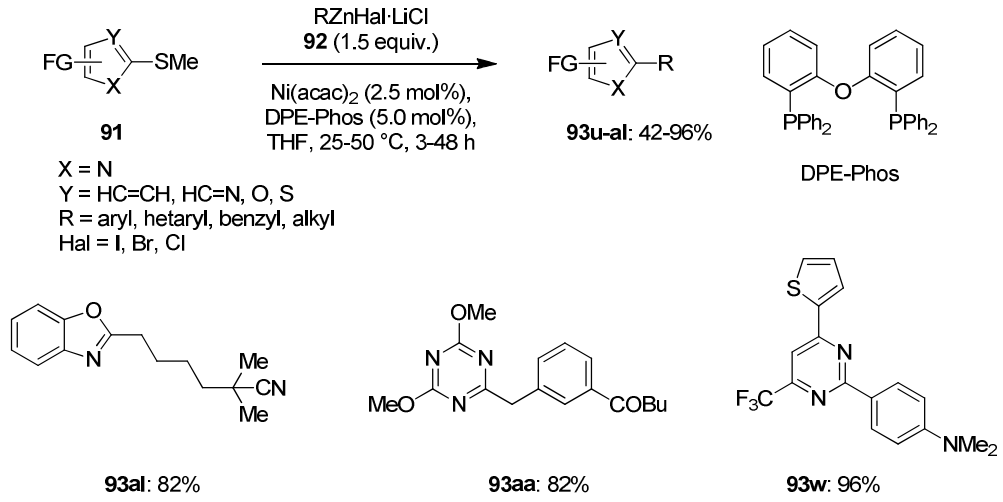
6.4. Transition Metal-Catalyzed Cross-Coupling Reactions of Functionalized Organozinc Reagents with Unsaturated Thioethers

A mild Pd-catalyzed cross-coupling of various substituted thiomethylated N-heterocycles **91** with functionalized aryl, hetaryl, benzyl and alkylzinc reagents of type **92** was developed. The reaction takes place at room temperature without the need for additional copper salts and delivers the functionalized heterocyclic products **93a-k** in good to excellent yields (Scheme 59). Also heterocycles bearing thiophenyl as a leaving group are readily converted using this protocol.



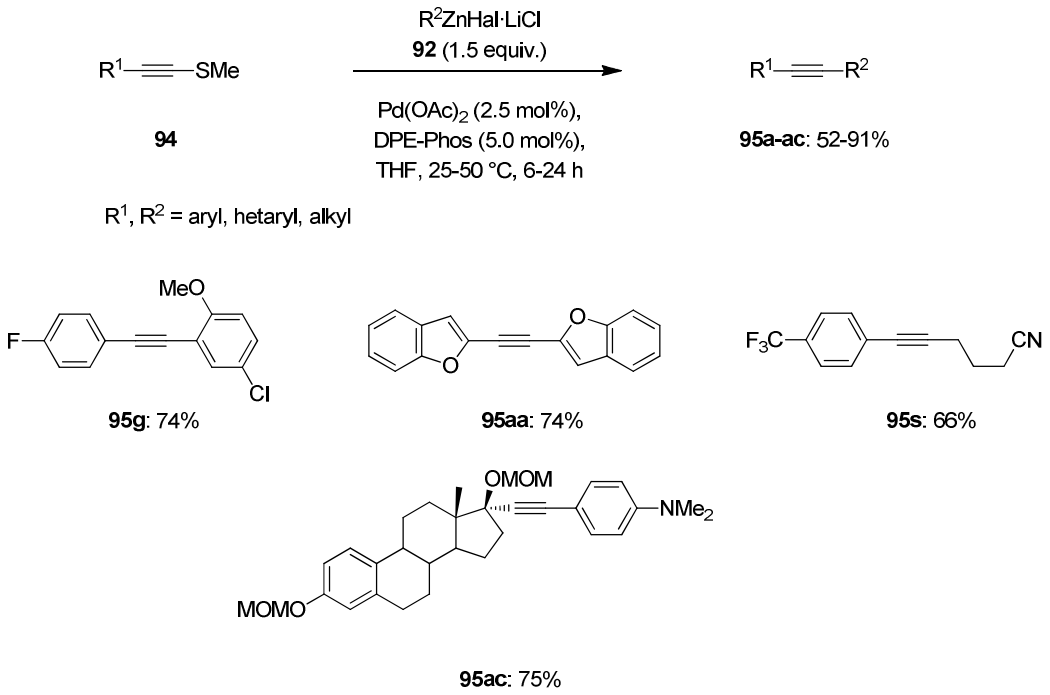
Scheme 59: Pd-catalyzed cross-coupling reaction of thiomethyl-substituted N-heterocycles **91** with functionalized organozinc reagents **92**.

The method was extended to the more cost-efficient Ni-catalysis after optimization studies. The explored reaction scope and the obtained yields for the obtained products **93t-y** are comparable to the Pd-catalyzed cross-coupling reaction (Scheme 60). Both developed methods were tested on multigram reactions and proved to be suitable for scale-up without loss of yield.



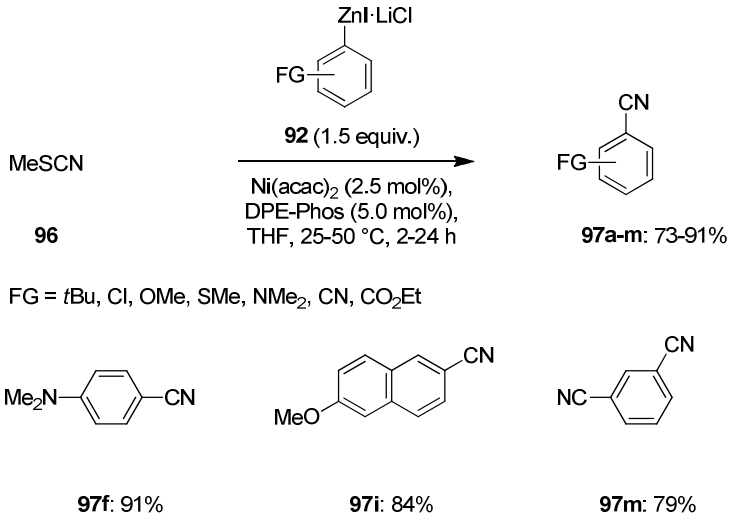
Scheme 60: Ni-catalyzed cross-coupling reaction of thiomethyl-substituted N-heterocycles **91** with functionalized organozinc reagents **92**.

After further optimizing the reaction conditions, the cross-coupling was employed for the use of aryl, hetaryl and alkylzinc reagents **92** with thiomethylated alkyenes of type **94** as electrophiles. Various functionalized ethyne derivatives **95a-ac** were prepared, also *bis*(thiomethyl)acetylene underwent the coupling reaction to furnish symmetrically substituted *bis*arylacetylenes in good yields (Scheme 61).



Scheme 61: Pd-catalyzed cross-coupling reaction of thiomethyl-substituted alkynes **94** with functionalized organozinc reagents **92**.

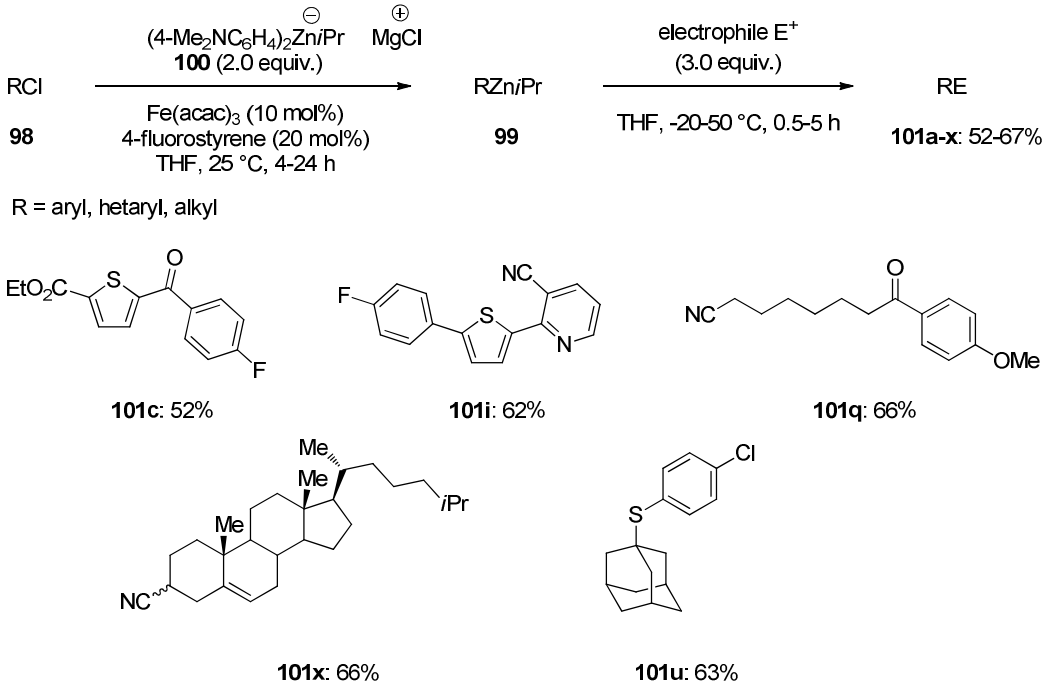
Additionally, methylthiocyanate (**96**) can be used as electrophile for the cross-coupling, optimization experiments revealed a Ni catalyst as the most active system. With this mild procedure, various functionalized benzonitriles **97a-m** were obtained in good to excellent yield (Scheme 62).



Scheme 62: Ni-catalyzed cross-coupling reaction of methylthiocyanate (**96**) with functionalized organozinc reagents **92**.

6.5. Chlorine-Zinc Exchange with Bisaryl Zincates using Iron Catalysis

Finally, a novel exchange protocol for generating functionalized organozinc reagents directly from aryl and hetaryl chlorides of type **98** was developed, using a diarylalkyl zincate **100** in the presence of an iron catalyst at room temperature. The obtained zinc species were reacted in a variety of electrophilic quenching reactions such as acylations or cross-couplings to furnish the higly functionalized products **101a-x**. Remarkably, the system is also able to exchange primary, secondary and even tertiary alkyl chlorides (Scheme 63).



Scheme 63: Fe-catalyzed chlorine-zinc exchange reaction of organochlorides **98** with diarylalkyl zincate **100**

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C. Experimental Section

1. General Considerations

All reactions were carried out with magnetic stirring and, if the reagents were air or moisture sensitive, in flame-dried glassware under argon. Syringes which were used to transfer reagents and solvents were purged with argon prior to use.

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.
DMF was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.
EtOH was treated with phthalic anhydride (25 g/L) and sodium, heated to reflux for 6 h and distilled.
Et_2O was predried over CaH_2 and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.
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.
Triethylamine was dried over KOH and distilled.
Solvents for column chromatography were distilled prior to use.

1.2. Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Liquid aldehydes and acid chlorides were distilled prior to use. Following compounds were prepared according to literature procedures:
4-(Dimethylamino)phenyl thiocyanate (**57**): R. Q. Brewster, W. Schroeder, *Org. Synth.* **1943**, *19*, 79.

4-Methoxybenzenesulfinyl chloride (**58**): M. Peyronneau, N. Roques, S. Mazieres, C. Le Roux, *Synlett* **2003**, 631.

N-Methyl-N-methylenemethanaminium 2,2,2-trifluoroacetate (**62**): a) N. Millot, C. Piazza, S. Avolio, P. Knochel, P. *Synthesis* **2000**, 941; b) N. Gommermann, C. Koradin, P. Knochel, *Synthesis* **2002**, 2143.

2-Thiophenyl(trimethyl)silane (**73**): T. J. Barton, G. P. Hussmann, *J. Org. Chem.* **1985**, *50*, 5881.

Bis(methylthio)acetylene (**94h**): H. D. Verkruijsse, L. Brandsma, L. *Synthesis* **1991**, 818.

MOM-protected ethynylestradiol **94i**: F. Wüst, K. E. Carlson, J. A. Katzenellenbogen, H. Spies, B. Johannsen, *Steroids* **1998**, *63*, 665.

Sulfonothioate derivatives: K. Fujiki, N. Tanifuji, Y. Sasaki, T. Yokoyama, *Synthesis* **2002**, 343.

Ethyl (2-bromomethyl)-acrylate: a) J. Villieras, M. Rambaud, *Synthesis* **1982**, *11*, 924; b) J. Villieras, M. Rambaud, *Org. Synth*. **1988**, *66*, 220.

Preparation of Organometallic Reagents:

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

***i*PrMgCl** solution in THF was purchased from Chemetall

PhMgCl solution in THF was purchased from Chemetall

***n*BuLi** solution in hexane was purchased from Chemetall.

TMPMgCl·LiCl (28) was prepared according to: A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.

TMP_2Mg·2LiCl (29) was prepared according to: G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681.

Zinc reagents were prepared according to: (a) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; (b) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107; (c) S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, P. *J. Org. Chem.* **2008**, *73*, 7380.

CuCN·2LiCl solution (1.00 M) was prepared by drying CuCN (7.17 g, 80.0 mmol) and LiCl (6.77 g, 160 mmol) in a Schlenk-flask under vacuum at 140 °C for 5 h. After cooling, THF (80 mL) was added and stirring was continued until the salts were dissolved.

$ZnCl_2$ solution (1.00 M) was prepared by drying $ZnCl_2$ (136 g, 100 mmol) in a Schlenk-flask under vacuum at 140 °C for 5 h. After cooling, THF (100 mL) was added and stirring was continued until the salt was dissolved.

1.3. Content Determination of Organometallic Reagents

Organzinc and organomagnesium reagents were titrated against I_2 in a 0.5 M LiCl solution in THF according to: A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.
Organolithium reagents were titrated against menthol using 1,10-phenanthroline as indicator in THF according to: H.-S. Lin, L. A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.
TMPMgCl·LiCl and **TMP_2Mg·2LiCl** were titrated against benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.

1.4. Chromatography

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from Merck.
Thin layer chromatography was performed using SiO_2 pre-coated aluminium plates (Merck 60, F-254). The chromatograms were examined under UV light at 254 nm and/or by staining of the TLC plate with one of the solutions given below followed by heating with a heat gun:
- $KMnO_4$ (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).

1.5. Analytical Data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the residual solvent peak of $CHCl_3$ (dH: 7.25, dC: 77.0). For the characterization of the observed signal multiplicities the following appreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet).
Mass spectroscopy: High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an electron energy of 70 eV.
For the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890/MSD 5973 was used.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSampl*IR* II Diamond ATR sensor was used. The absorption bands are reported in wavenumbers (cm^{-1})
Melting points (m.p.) were determined on a BÜCHI B-540 apparatus and are uncorrected.

2. Typical Procedures (TP)

Typical Procedure for Preparation of Sulfoxides 49a,b (TP1):
In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, 4-(dimethylamino)phenyl thiocyanate (**57**, 1.78 g, 10.0 mmol) was dissolved in THF (10 mL) and cooled to -20 °C. A solution of the functionalized magnesium reagent (**56**, 11.0 mmol, approx 1.0 M) was added and the reaction mixture was allowed to warm to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl-solution (50 mL) and extracted with EtOAc (3 x 50 mL). The organic layers were combined and the solvent was removed under reduced pressure. The crude sulfide was dissolved in CH_2Cl_2 (40 mL) and cooled to -20 °C. *m*CPBA (2.70 g, 11.0 mmol, 70% in water) dissolved in CH_2Cl_2 (10 mL) was added slowly. After stirring at -20 °C for 1 h the reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$-solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification yielded the products **49a,b**.

Typical Procedure for Preparation of Sulfoxides 49c-e, 79 (TP2):
A dry and argon-flushed Schlenk-*flask*, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-methoxybenzenesulfinyl chloride (**58**, 13.0 mmol) in THF (10 mL) and cooled to -20 °C. The appropriate magnesium reagent (**56**, 10.0 mmol, approx. 1.0 M) was added slowly and the reaction mixture was allowed to warm to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl-solution (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification yielded the products **49c-e, 79**.

Typical Procedure for Preparation of Sulfoxides 74a,b (TP3):

A dry and argon-flushed Schlenk-flask, equipped with a stirring bar and a septum, was charged with 2-thiophene(trimethyl)silane (**73**, 2.34 g, 15.0 mmol) or benzofuran (1.77 g, 15.0 mmol) in Et_2O (45 mL). The reaction mixture was cooled to 0 °C and *n*BuLi (7.40 mL, 17.5 mmol, 2.36 M in hexane) was added dropwise. The reaction mixture was allowed to warm to 25 °C and stirred for additional 10 min. In a second dry and argon-flushed Schlenk-flask, equipped with a stirring bar and a septum, 4-methoxybenzenesulfinyl chloride (**58**, 4.19 g, 22.0 mmol) was dissolved in THF (20 mL) and cooled to -50 °C. The lithiated heterocycle was added dropwise and the reaction mixture was allowed to warm to 25 °C and was then stirred for additional 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl-solution (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographical purification yielded the products **74a,b**.

Typical Procedure for Preparation of Sulfoxides 51, 75, 80 by Metalation of Sulfoxides 49, 74, 79 and Reaction with an Electrophile (TP4):

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with a sulfoxide (**49, 74, 79**, 10.0 mmol) dissolved in THF (20 mL). The reaction mixture was cooled to -30 °C and tmpMgCl·LiCl (11.0 mmol, 1.20 M in THF) was added dropwise. After 20 min of stirring at -30 °C an electrophile (12.0 mmol) was added and the reaction mixture was stirred at the given temperature for the given time. The reaction mixture was quenched with sat. aq. NH_4Cl-solution (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification yielded the products **51, 75, 80**.

Typical Procedure for Preparation of Sulfoxides 51, 75, 80 by Metalation of Sulfoxides 49, 74, 79 and Negishi Cross-Coupling Reaction (TP5):

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with a sulfoxide (**49, 74, 79**, 10.0 mmol) dissolved in THF (20 mL). The reaction mixture was cooled to -30 °C and tmpMgCl·LiCl (10.0 mL, 11.0 mmol, 1.10 M in THF) was added dropwise. After stirring at -30 °C for 20 min $ZnCl_2$ (11.0 mL, 11.0 mmol, 1.00 M in THF) was added, and the reaction mixture was allowed to warm to 25 °C. A palladium catalyst and an electrophile (12.0 mmol) were added and the reaction mixture was stirred at the given temperature for the given time. The reaction mixture was quenched with sat. aq.

NH_4Cl-solution (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification yielded the products **51, 75, 80**.

Typical Procedure for Preparation of Sulfoxides 51, 75, 80 by Metalation of Sulfoxides 49, 74, 79 and Functionalization with Alkynyl Substrates (TP6):

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with a sulfoxide (**49, 74, 79**, 10.0 mmol) dissolved in THF (20 mL). The reaction mixture was cooled to -30 °C and tmpMgCl·LiCl (10.0 mL, 11.0 mmol, 1.10 M in THF) was added dropwise. After stirring at -30 °C for 20 min, I_2 (3.05 g, 12.0 mmol) was added and the reaction mixture was allowed to warm to 25 °C. Then the reaction mixture was diluted with EtOAc (200 mL) and extracted with a sat. aq. $Na_2S_2O_3$ solution (100 mL). The organic layer was dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. The crude product was dried in high vacuum for 3 h and then dissolved in THF (20 mL). In a second dry and argon flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, the desired alkyne (11.0 mmol) was mixed slowly with *i*PrMgCl·LiCl (8.80 mL, 10.5 mmol, 1.20 M in THF). After cessation of gas evolution the reaction mixture was heated to 60 °C for 5 min. After cooling to 25 °C, a $ZnCl_2$ solution (11.0 mmol, 11.0 mL, 1.0 M in THF) was added slowly. The resulting zinc reagent was transferred to the previously prepared crude sulfoxide and a palladium catalyst (2 mol%) was added. The reaction mixture was stirred at the given temperature until GC analysis showed full conversion of the iodide. The reaction mixture was quenched with sat. aq. NH_4Cl-solution (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification yielded the products **51, 75, 80**.

Typical Procedure for Preparation of Products 55, 63-65, 76, 81 by Sulfoxide-Magnesium Exchange on Sulfoxides 51, 75, 80 (TP7):

A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with a solution of the sulfoxide (**51, 75, 80**, 1.00 mmol) in 2-Methyl-THF (2 mL). The reaction mixture was cooled to -50 °C and *i*PrMgCl·LiCl (0.92 mL, 1.1 mmol, 1.20 M in THF) was added dropwise. After stirring at -50 °C until GC analysis showed full conversion of the sulfoxide, the desired electrophile (0.80 mmol) was added at -50°C. In case of a cross-coupling or an allylation reaction, $ZnCl_2$ (1.10 mL, 1.10 mmol, 1.00 M in THF) was added

and the solution stirred at -50 °C for 30 min, then the desired electrophile (0.80 mmol) and a transition metal catalyst (2-5%) were added. The reaction mixture was warmed up to the given temperature and stirred until GC analysis showed full conversion of the electrophile. The reaction mixture was quenched with sat. aq. NH_4Cl-solution (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification yielded the products **55, 63-65, 76, 81**.

Typical Procedure for Preparation of Heterocycles 93 by Pd-catalyzed Cross-Coupling Reaction of N-Heterocyclic Thioethers 91 with Zinc Reagents 92 (TP8):

In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, the aromatic thioether (**91**, 1.00 mmol), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) were dissolved in THF (1 mL). After 10 min of stirring, the zinc reagent (**92**, 1.50 mmol) was added dropwise and the reaction mixture was stirred for the given time at the given temperature until GC-analysis of a hydrolyzed aliquot showed full conversion of the electrophile. The reaction mixture was quenched with sat. aq. K_2CO_3-solution (15 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification yielded the products **93**.

Typical Procedure for Preparation of Heterocycles 93 by Ni-catalyzed Cross-Coupling Reaction of N-Heterocyclic Thioethers 91 with Zinc Reagents 92 (TP9):

In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, the aromatic thioether (**91**, 1.00 mmol), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) were dissolved in THF (1 mL). After 10 min of stirring, the zinc reagent (**92**, 1.50 mmol) was added dropwise and the reaction mixture was stirred for the given time at the given temperature until GC-analysis of a hydrolyzed aliquot showed full conversion of the electrophile. The reaction mixture was quenched with sat. aq. K_2CO_3-solution (15 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification yielded the products **93**.

Typical Procedure for Preparation of Alkynes 95 by Pd-catalyzed Cross-Coupling Reaction of Thiomethylated Alkynes 94 with Zinc Reagents 92 (TP10):

In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, the aromatic thioether (**94**, 1.00 mmol), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (27.0 mg, 5.0 mol%) were dissolved in THF (1 mL). After 10 min of stirring, the zinc reagent (**92**, 1.50 mmol) was added dropwise and the reaction mixture was stirred for the given time at the given temperature until GC-analysis of a hydrolyzed aliquot showed full conversion of the electrophile. The reaction mixture was quenched with sat. aq. K_2CO_3-solution (15 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification yielded the products **95**.

Typical Procedure for Preparation of Nitriles 97 by Ni-catalyzed Cross-Coupling Reaction of Methyl Thiocyanate (96) with Zinc Reagents 92 (TP11):

In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, methyl thiocyanate (**96**, 73 mg, 1.00 mmol), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (27.0 mg, 5.0 mol%) were dissolved in THF (1 mL). After 10 min of stirring, the zinc reagent (1.50 mmol) was added dropwise and the reaction mixture was stirred for the given time at the given temperature until GC-analysis of a hydrolyzed aliquot showed full conversion of the electrophile. The reaction mixture was quenched with sat. aq. K_2CO_3-solution (15 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification yielded the products **97**.

Typical Procedure for Preparation of Products 101 by Fe-catalyzed Chlorine-Zinc Exchange Reaction of Organic Chlorides 98 (TP12):

In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, 4-*N*,*N*-dimethylanilinemagnesium bromide (4.21 mL, 4.00 mmol, 0.95 M in THF) was treated with $ZnCl_2$ (2.00 mL, 2.00 mmol, 1.00 M in THF) and stirred for 15 min at 25 C. Then *i*PrMgCl·LiCl (1.67 mL, 2.00 mmol, 1.20 M in THF) was added and the solution stirred for 15 min at 25 C to form zincate **100**. In another dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, the organochloride (**98**, 1.00 mmol), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) were dissolved in THF (1 mL). The zincate **100** was added and the reaction mixture stirred at 25 °C until GC analysis of an hydrolyzed reaction aliquot showed full conversion of the chloride. Then the desired electrophile (3.00 mmol) and, where stated, a transition metal catalyst (2-20%) were added

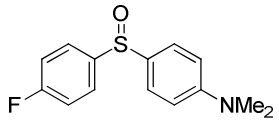
and the reaction mixture was stirred at the given temperature for the given time. The reaction mixture was quenched with 2N HCl-solution (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification yielded the products **101**.

3. Synthetic Procedures

3.1 Preparation 1,2,4-Trisubstituted Arenes 55, 63-65

3.1.1 Preparation of Sulfoxides 49

4-((4-Fluorophenyl)sulfinyl)-*N*,*N*-dimethylaniline (**49a**)



Prepared according to **TP1** sulfoxide from 4-fluorophenylmagnesium bromide (116.0 mL, 110 mmol, 0.95 M in THF) and dimethyl-(4-thiocyanatophenyl)amine (**57**, 17.8 g, 100 mmol,) and purified by flash chromatography (pentane/EtOAc 1:1, silica gel), furnishing **49a** as a colourless solid (18.2 g, 69% yield).

m.p. (°C): 118-121.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.60-7.55 (m, 2H), 7.44 (d, *J* = 9.04 Hz, 2H), 7.15-7.09 (m, 2H), 6.69 (d, *J* = 9.04 Hz, 2H), 2.99 (s, 6 H).

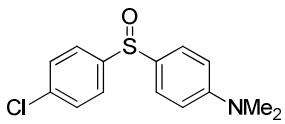
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.8 (d, *J* = 250.3 Hz, CF), 152.4, 141.7 (d, *J* = 3.18 Hz), 130.1, 127.2 (CH), 126.8 (d, *J* = 8.74 Hz, CH), 116.2 (d, *J* = 22.52 Hz, CH), 112.0 (CH), 40.1 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2896 (w), 1598 (s), 1587 (s), 1555 (w), 1513 (m), 1489 (vs), 1444 (m), 1368 (m), 1294 (w), 1217 (s), 1196 (s), 1152 (m), 1090 (s), 1074 (m), 1055 (m), 1039 (vs), 1015 (m), 835 (s), 807 (s), 605 (w).

MS (EI, 70 eV): *m/z* (%) = 263 (33, M^+), 247 (6), 216 (12), 215 (100), 214 (22), 169 (10), 168 (24), 136 (33), 119 (8), 107 (9).

HRMS (EI): calcd. for $C_{14}H_{14}FNO^{32}S$: 263.0780, found: 263.0779.

4-((4-Chlorophenyl)sulfinyl)-*N*,*N*-dimethylaniline (**49b**)



Prepared according to **TP1** from 4-chlorophenylmagnesium bromide (125 mL, 110 mmol, 0.88 M in THF) and dimethyl-(4-thiocyanatophenyl)amine (**57**, 17.8 g, 100 mmol) and

purified by flash chromatography (pentane/EtOAc 1:1, silica gel), furnishing **49b** as a colourless solid (17.9 g, 64% yield).

m.p. (°C): 128-129.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.54-7.49 (m, 2H), 7.46-7.38 (m, 4H), 6.70-6.65 (m, 2H), 2.99 (s, 6H).

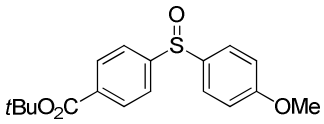
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 152.5, 144.8, 136.3, 130.3, 129.2 (CH), 127.7 (CH), 126.0 (CH), 112.0 (CH), 40.1 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2892 (w), 1596 (s), 1570 (w), 1554 (w), 1509 (m), 1471 (m), 1446 (m), 1388 (w), 1363 (m), 1233 (m), 1192 (m), 1091 (s), 1083 (s), 1060 (m), 1045 (vs), 1010 (s), 826 (s), 815 (m), 807 (s), 799 (m), 738 (s), 711 (w), 607 (w).

MS (EI, 70 eV): *m/z* (%) = 279 (19, M^+), 263 (34), 233 (25), 232 (23), 231 (80), 230 (30), 168 (100), 152 (25), 136 (30), 44 (19).

HRMS (EI): calcd. for $C_{14}H_{14}{}^{35}ClNO^{32}S$: 279.0485, found: 279.0479.

Tert-butyl 4-((4-methoxyphenyl)sulfinyl)benzoate (**49c**)



Prepared according to **TP2** from 4-(*tert*-butoxycarbonyl)phenylmagnesium chloride (33.7 mL, 30.0 mmol, 0.89 M in THF) and 4-methoxybenzenesulfinyl chloride (**58**, 6.27 g, 33.0 mmol) and purified by flash chromatography (pentane/Et_2O 1:1, silica gel) furnishing **49c** as a colourless solid (9.01 g, 90% yield).

m.p. (°C): 73-75.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.86 (d, J = 8.75 Hz, 2H), 7.48 (d, J = 8.75 Hz, 2H), 7.38 (d, J = 8.99 Hz, 2H), 6.73 (d, J = 8.99 Hz, 2H), 3.55 (s, 3H), 1.36 (s, 9H).

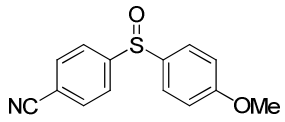
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.9, 161.7, 150.0, 135.8, 133.4, 129.6 (CH), 126 (CH), 123.5 (CH), 114.4 (CH), 80.9, 54.9 (CH_3), 27.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2978 (m), 2931 (w), 1705 (vs), 1594 (s), 1576 (m), 1493 (m), 1458 (m), 1394 (m), 1366 (s), 1301 (s), 1290 (s), 1246 (vs), 1183 (m), 1167 (s), 1121 (s), 1108 (m), 1087 (s), 1040 (s), 1023 (s), 1011 (s), 844 (m), 827 (m), 819 (m), 794 (m), 763 (s), 716 (m), 690 (m), 557 (m).

MS (EI, 70 eV): *m/z* (%) = 332 (11, M^+), 284 (30), 260 (7), 259 (6), 229 (13), 228 (100), 155 (34), 139 (45), 123 (59), 57 (7).

HRMS (EI): calcd. for $C_{18}H_{20}O_4{}^{32}S$: 332.1082, found: 322.1066.

4-(4-Methoxybenzenesulfinyl)benzonitrile (**49d**)



Prepared according to **TP2** from 4-cyanophenylmagnesium bromide (51.0 mL, 50.0 mmol, 0.98 M in THF) and 4-methoxybenzenesulfinyl chloride (**58**, 10.5 g, 55.0 mmol) and purified by flash chromatography (Et_2O, silica gel), furnishing **49d** as a colourless solid (9.01 g, 70% yield).

m.p. (°C): 121-123.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.76-7.67 (m, 4H), 6.57-6.52 (m, 2H), 6.98-6.93 (m, 2H), 3.80 (s, 3H).

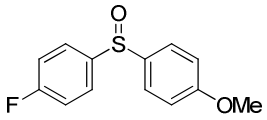
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.6, 151.5, 135.5, 132.8 (CH), 127.4 (CH), 124.9 (CH), 117.7, 115.2 (CH), 114.3, 55.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3086 (w), 3066 (w), 2228 (s), 1590 (s), 1575 (s), 1495 (s), 1482 (m), 1445 (m), 1409 (m), 1385 (w), 1311 (m), 1258 (s), 1184 (w), 1174 (m), 1086 (s), 1070 (m), 1039 (vs), 1024 (s), 1013 (s), 828 (s), 796 (m), 575 (m).

MS (EI, 70 eV): *m/z* (%) = 257 (15, M^+), 210 (14), 209 (56), 194 (10), 166 (7), 154 (100), 139 (21), 123 (40), 92 (7), 64 (7).

HRMS (EI): calcd. for $C_{14}H_{11}NO_2{}^{32}S$: 257.0510, found: 257.0500.

1-Fluoro-4-((4-methoxyphenyl)sulfinyl)benzene (**49e**)



Prepared according to **TP2** from 4-fluorophenylmagnesium bromide (95.2 mL, 100.0 mmol, 1.05 M in THF) and 4-methoxybenzenesulfinyl chloride (**58**, 21.0 g, 110.0 mmol) and purified by recrystallization from heptane, furnishing **49e** as a colourless solid (22.9 g, 91% yield).

m.p. (°C): 83-85.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.60-7.51 (m, 4H), 7.15-7.09 (m, 2H), 6.92-6.95 (m, 2H), 3.79 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 164.0 (d, *J* = 251.2 Hz, CF), 162.1, 141.4 (d, *J* = 3.04 Hz), 136.5, 127.0 (CH), 126.9 (d, *J* = 8.85 Hz, CH), 116.4 (d, *J* = 22.67 Hz, CH), 114.8 (CH), 55.4 (CH_3).

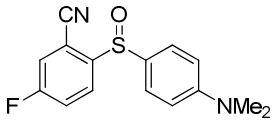
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3052 (w), 2836 (w), 1592 (s), 1577 (s), 1496 (s), 1436 (m), 1410 (m), 1311 (m), 1303 (m), 1254 (s), 1215 (s), 1154 (m), 1089 (s), 1076 (s), 1035 (s), 855 (s), 828 (vs), 810 (s), 798 (s).

MS (EI, 70 eV): *m/z* (%) = 251 (8), 250 (49, M^+), 233 (8), 203 (13), 202 (100), 187 (17), 154 (43), 139 (23), 123 (60), 101 (8).

HRMS (EI): calcd. for $C_{13}H_{11}FO_2{}^{32}S$: 250.0464, found: 250.0470.

3.1.2 Preparation of sulfoxides 51 by deprotonation of sulfoxides 49

2-((4-(Dimethylamino)phenyl)sulfinyl)-5-fluorobenzonitrile (**51a**)



Prepared according to **TP4** by treating sulfoxide **49a** (1.32 g, 5.00 mmol) with tmpMgCl·LiCl (5.00 mL, 5.50 mmol, 1.10 M in THF) at -30 °C for 20 min and tosyl cyanide (1.09 g, 6.00 mmol) at 25 °C for 1 h. Flash chromatographic purification (Et_2O, silica gel) furnished **51a** as a clear oil (1.14 g, 79% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.24 (dd, *J* = 8.60, 5.07 Hz, 1H), 7.56-7.48 (m, 3H), 7.34 (dd, *J* = 7.72, 2.65 Hz, 1H), 6.70-6.65 (m, 2H), 2.99 (s, 6H).

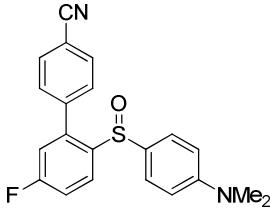
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.8 (d, *J* = 254.1 Hz, CF), 152.8, 145.4 (d, *J* = 3.65 Hz), 128.5 (CH), 127.4, 126.8 (d, *J* = 8.98 Hz, CH), 121.2 (d, *J* = 21.60 Hz, CH), 120.8 (d, *J* = 25.53 Hz, CH), 114.9, 113.9 (d, *J* = 2.81 Hz), 111.7 (CH), 39.9 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3078 (w), 3023 (w), 2864 (w), 2645 (w), 2216 (w), 1592 (s), 1512 (m), 1492 (m), 1404 (m), 1368 (m), 1284 (w), 1196 (s), 1128 (w), 1084 (s), 1052 (m), 944 (s), 916 (m), 872 (s), 848 (m), 812 (s), 752 (vs), 720 (m), 690 (s), 608 (s), 591 (m).

MS (EI, 70 eV): *m/z* (%) = 288 (100, M^+), 2772 (44), 271 (19), 240 (78), 239 (34), 170 (21), 169 (41), 168 (75), 136 (53), 119 (19).

HRMS (EI): calcd. for $C_{15}H_{13}FN_2O^{32}S$: 288.0733, found: 288.0725.

2'-((4-(Dimethylamino)phenyl)sulfinyl)-5'-fluoro-[1,1'-biphenyl]-4-carbonitrile (**51b**)



Prepared according to **TP5** from sulfoxide **49a** (2.63 g, 10.0 mmol), with $Pd(PPh_3)_4$ (0.22 g, 0.20 mmol) and 4-iodobenzonitrile (2.75 g, 12.0 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 1:1, silica gel) furnished **51b** as an off-white solid (3.41 g, 94% yield).

m.p. (°C): 184-186.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.23 (dd, *J* = 8.82, 5.48 Hz, 1H), 7.62-7.59 (m, 2H), 7.32 (dd, *J* = 5.48, 2.62 Hz, 1H), 7.23-7.20 (m, 2H), 6.90 (dd, *J* = 8.82, 2.62 Hz, 1H), 6.87-6.84 (m, 2H), 6.44-6.41 (m, 2H), 2.93 (s, 6H).

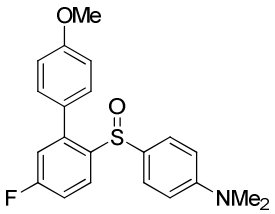
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 163.6 (d, *J* = 251.9 Hz, CF), 152.2, 141.8, 140.5 (d, *J* = 8.48 Hz), 139.5 (d, *J* = 2.91 Hz), 132.0 (CH), 130.0 (CH), 128.9, 128.0 (CH), 127.0 (d, *J* = 9.01 Hz, CH), 118.4, 117.2 (d, *J* = 23.05 Hz, CH), 116.0 (d, *J* = 21.72 Hz, CH), 112.2 (CH), 111.5, 40.0 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2922 (w), 2228 (w), 1592 (vs), 1580 (s), 1510 (s), 1460 (m), 1446 (m), 1398 (w), 1364 (s), 1296 (w), 1282 (m), 1232 (w), 1184 (m), 1086 (s), 1068 (s), 1038 (vs), 1028 (s), 1018 (s), 944 (w), 874 (m), 846 (s), 832 (s), 804 (s), 610 (m).

MS (EI, 70 eV): *m/z* (%) = 365 (7), 364 (23, M^+), 348 (14), 334 (7), 316 (8), 258 (9), 169 (12), 168 (100), 152 (8), 136 (19).

HRMS (EI): calcd. for $C_{21}H_{17}FN_2O^{32}S$: 364.1046, found: 364.1047.

4-((5-Fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)sulfinyl)-*N*,*N*-dimethylaniline (**51c**)



Prepared according to **TP5** from sulfoxide **49a** (1.05 g, 4.00 mmol), with $Pd(PPh_3)_4$ (0.08 g, 0.08 mmol) and 4-iodoanisole (1.12 g, 4.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 1:1, silica gel) furnished a colourless solid (1.37 g, 93% yield).

m.p. (°C): 99-102.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.15 (dd, *J* = 8.58, 5.72 Hz, 1H), 7.21 (dd, *J* = 8.58, 2.62 Hz, 1H), 7.08-7.06 (m, 2H), 6.93-6.90 (m, 2H), 6.89 (dd, *J* = 5.72, 2.62 Hz, 1H), 6.87-6.85 (m, 2H), 6.46-6.43 (m, 2H), 3.84 (s, 3H), 2.91 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.6 (d, *J* = 250.6 Hz, CF), 159.6, 151.9, 142.5 (d, *J* = 8.74 Hz), 139.8 (d, *J* = 2.91 Hz), 130.5 (CH), 129.5, 129.4, 127.4 (CH), 126.3 (d, *J* = 9.27

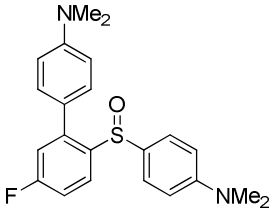
Hz, CH), 117.3 (d, *J* = 22.25 Hz, CH), 114.8 (d, *J* = 21.72 Hz, CH), 113.7 (CH), 111.5 (CH), 55.3 (CH_3), 40.0 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2894 (m), 1590 (vs), 1511 (vs), 1453 (s), 1443 (s), 1420 (m), 1357 (s), 1298 (m), 1275 (m), 1245 (s), 1196 (m), 1174 (s), 1085 (s), 1066 (m), 1039 (vs), 1019 (s), 875 (m), 836 (s), 816 (s), 805 (s).

MS (EI, 70 eV): *m/z* (%) = 370 (8), 369 (40, M^+), 353 (7), 321 (14), 320 (5), 170 (5), 169 (7), 168 (100), 152 (5), 136 (30).

HRMS (EI): calcd. for $C_{21}H_{20}FNO_2{}^{32}S$: 369.1199, found: 369.1185.

4-((5-Fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)sulfinyl)-*N*,*N*-dimethylaniline (**51d**)



Prepared according to **TP5** from sulfoxide **49a** (1.32 g, 5.00 mmol), with $Pd(PPh_3)_4$ (0.11 g, 0.10 mmol) and 4-bromo-*N*,*N*-dimethylaniline (1.20 g, 6.00 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 1:1, silica gel) furnished **51d** as a yellow solid (1.61 g, 84% yield).

m.p. (°C): 159-161.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.12 (dd, *J* = 9.00, 5.84 Hz, 1H), 7.18-7.14 (m, 1H), 7.07-7.05 (m, 2H), 6.97-6.96 (m, 2H), 6.90 (dd, *J* = 9.00, 2.62 Hz, 1H), 6.69-6.67 (m, 2H), 6.48-6.46 (m, 2H), 2.99 (s, 6H), 2.91 (s, 6H).

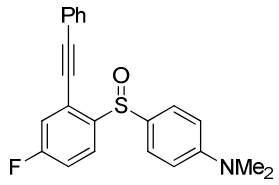
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.7 (d, *J* = 251.4 Hz, CF), 151.8, 150.3, 143.3 (d, *J* = 8.48 Hz), 139.8 (d, *J* = 2.65 Hz), 130.28, 130.13 (CH), 127.18 (CH), 126.3 (d, *J* = 9.27 Hz), 117.1 (CH), 117.0 (CH), 114.2 (d, *J* = 21.99 Hz, CH), 111.9 (CH), 111.5 (CH), 40.4 (CH_3), 40.0 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} =2921 (w), 2857 (w), 2807 (w), 2356 (w), 1739 (m), 1591 (s), 1525 (s), 1511 (s), 1455 (s), 1443 (s), 1358 (vs), 1275 (m), 1084 (s), 1065 (s), 1035 (vs), 1026 (vs), 884 (s), 867 (s), 815 (vs), 806 (vs).

MS (EI, 70 eV): *m/z* (%) = 383 (27), 382 (100, M^+), 367 (17), 366 (65), 334 (32), 333 (18), 170 (18), 168 (90), 136 (38), 43 (55).

HRMS (EI): calcd. for $C_{22}H_{23}FN_2O^{32}S$: 382.1515, found: 382.1518.

4-((4-Fluoro-2-(phenylethynyl)phenyl)sulfinyl)-*N*,*N*-dimethylaniline (**51e**)



Prepared according to **TP6** from sulfoxide **49a** (2.63 g, 10.0 mmol), with $Pd(PPh_3)_4$ (0.22 g, 0.20 mmol) and phenylacetylene (1.12 g, 11.0 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 1:1, silica gel) furnished **51e** as an off-white solid (3.43 g, 94% yield).

m.p. (°C): 126-127.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.12 (dd, *J* = 8.82, 5.48 Hz, 1H), 7.50-7.49 (m, 4H), 7.38-7.39 (m, 3 H), 7.27-7.23 (m, 1H), 7.18 (dd, *J* = 8.82, 2.62 Hz, 1H), 6.60 (d, *J* = 8.58 Hz, 2H), 2.94 (s, 6H).

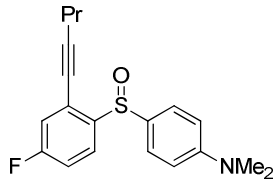
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.3 (d, *J* = 250.30 Hz, CF), 152.3, 143.2 (d, *J* = 2.91 Hz), 131.6 (CH), 129.2 (CH), 128.5 (CH), 128.0 (CH), 125.9 (d, *J* = 9.27 Hz), 122.2 (d, *J* = 10.33 Hz, CH), 122.0, 119.4 (d, *J* = 24.11 Hz, CH), 116.5 (d, *J* = 22.25 Hz, CH), 111.7 (CH), 98.3, 84.1, 84.0, 40.1 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3067 (w), 2896 (m), 2820 (w), 1593 (vs), 1568 (s), 1512 (s), 1490 (m), 1452 (s), 1443 (s), 1404 (m), 1367 (s), 1303 (m), 1232 (m), 1196 (s), 1085 (m), 1051 (m), 1028 (vs), 945 (m), 871 (m), 846 (m), 811 (s), 753 (s), 688 (m), 609 (m).

MS (EI, 70 eV): *m/z* (%) = 347 (15), 335 (9), 334 (36), 291 (8), 259 (17), 258 (100), 215 (10), 168 (11), 147 (11), 136 (8).

HRMS (EI): calcd. for $C_{22}H_{18}FNO^{32}S$: 363.1093, found: 363.1079.

4-((4-Fluoro-2-(pent-1-yn-1-yl)phenyl)sulfinyl)-*N*,*N*-dimethylaniline (**51f**)



Prepared according to **TP6** from sulfoxide **49a** (2.63 g, 10.0 mmol), with $Pd(PPh_3)_4$ (0.22 g, 0.20 mmol) and 1-pentyne (0.75 g, 11.0 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 1:1, silica gel) furnished **51f** as an off-white solid (2.43 g, 74% yield).

m.p. (°C): 78-80.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.02 (dd, *J* = 8.67, 5.70 Hz, 1H), 7.46-7.42 (m, 2H), 7.19-7.13 (m, 1H), 7.03 (dd, *J* = 9.04, 2.60 Hz, 1H), 6.64-6.59 (m, 2H), 2.94 (s, 6H), 2.37 (t, *J* = 7.06 Hz, 2H), 1.65-1.53 (m, 2H), 1.00 (t, *J* =7.31 Hz, 3H),

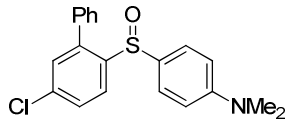
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.2 (d, *J* = 249.9 Hz, CF), 152.2, 142.7 (d, *J* = 3.09 Hz), 130.2 (d, *J* = 1.40 Hz), 127.8 (CH), 125.8 (d, *J* = 9.54 Hz, CH), 123.1 (d, *J* = 10.38 Hz), 119.4 (d, *J* = 23.84 Hz, CH), 115.7 (d, *J* = 22.16 Hz, CH), 111.5 (CH), 100.2, 75.8 (d, *J* = 3.09 Hz), 40.0 (CH_3), 21.6 (CH_2), 21.5 (CH_2), 13.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2894 (w), 2228 (vw), 1594 (s), 1568 (m), 1512 (m), 1454 (m), 1406 (w), 1364 (m), 1272 (m), 1230 (w), 1194 (m), 1166 (m), 1086 (s), 1062 (m), 1030 (vs), 988 (m), 942 (w), 890 (w), 862 (m), 842 (m), 812 (s), 610 (w).

MS (EI, 70 eV): *m/z* (%) = 287 (11), 286 (53), 259 (19), 258 (100), 215 (13), 168 (50), 136 (30), 121 (12), 119 (11), 43 (29).

HRMS (EI): calcd. for $C_{19}H_{20}FNO^{32}S$: 329.1250, found: 329.1247.

4-((5-Chloro-[1,1'-biphenyl]-2-yl)sulfinyl)-*N*,*N*-dimethylaniline (**51g**)



Prepared according to **TP5** from sulfoxide **49b** (2.80 g, 10.0 mmol), with $Pd(PPh_3)_4$ (0.22 g, 0.20 mmol) and iodobenzene (2.45 g, 12.0 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 1:1, silica gel) furnished **51g** as a colourless solid (3.45 g, 97% yield).

m.p. (°C): 146-148.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.16 (d, *J* = 8.46 Hz, 1H), 7.55 (dd, *J* = 8.46, 2.15 Hz, 1H), 7.38-7.31 (m, 3H), 7.20 (d, *J* = 2.15 Hz 1H), 7.12-7.11 (m, 2H), 6.87-6.85 (m, 2H), 6.47 (m, 2H), 2.92 (s, 6H).

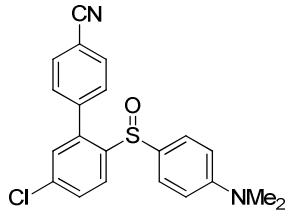
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 150.1, 142.8, 141.9, 137.0, 136.3, 130.2, 129.3 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 127.7 (CH), 125.4 (CH), 119.2 (CH), 111.9 (CH), 40.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} 3069 (w), 3050 (w), 1589 (vs), 1554 (m), 1509 (m), 1458 (m), 1441 (m), 1361 (s), 1224 (w), 1196 (m), 1085 (s), 1063 (m), 1039 (s), 1031 (s), 1014 (m), 996 (m), 831 (m), 809 (s), 767 (m), 698 (m).

MS (EI, 70 eV): *m/z* (%) = 357 (27), 356 (17), 355 (100, M^+), 309 (12), 307 (48), 170 (14), 169 (25), 168 (26), 152 (28), 136 (92).

HRMS (EI): calcd. for $C_{20}H_{18}{}^{35}ClNO^{32}S$: 355.0798, found: 355.0797.

5'-Chloro-2'-((4-(dimethylamino)phenyl)sulfinyl)-[1,1'-biphenyl]-4-carbonitrile (**51h**)



Prepared according to **TP5** from sulfoxide **49b** (2.80 g, 10.0 mmol), with $Pd(PPh_3)_4$ (0.22 g, 0.20 mmol) and 4-iodobenzonitrile (2.75 g, 12.0 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 1:1, silica gel) furnished **51h** as a colourless solid (3.50 g, 92% yield).

m.p. (°C): 161-163.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.21 (d, *J* = 8.38 Hz, 1H), 7.62- 7.57 (m, 2 H), 7.49-7.44 (m, 1H), 7.38-7.35 (m, 1H), 7.17-7.16 (m, 1H), 7.08-7.07 (m, 1H), 6.78 (d, *J* = 8.82 Hz, 2H), 6.37 (d, *J* = 8.82 Hz, 2H), 2.90 (s, 6H).

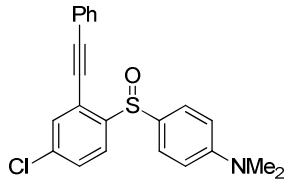
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 152.5, 143.2, 140.3, 138.1, 136.6, 132.7 (CH), 130.3 (CH), 129.1 (CH), 129.0, 128.7, 128.4 (CH), 126.1, 126.0 (CH), 125.2 (CH), 111.7 (CH), 40.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2228 (w) ,1588 (vs), 1508 (s), 1444 (m), 1364 (s), 1304 (w), 1228 (m), 1192 (m), 1084 (s), 1036 (vs), 944 (m), 844 (s), 828 (s), 800 (s), 756 (m), 608 (m), 588 (m), 568 (m).

MS (EI, 70 eV): *m/z* (%) = 382 (29), 380 (77, M^+), 332 (28), 177 (27), 170 (23), 169 (51), 168 (56), 152 (26), 136 (100), 119 (20).

HRMS (EI): calcd. for $C_{21}H_{17}{}^{35}ClN_2O^{32}S$: 380.0750, found: 380.0753.

4-((4-Chloro-2-(phenylethynyl)phenyl)sulfinyl)-*N*,*N*-dimethylaniline (**51i**)



Prepared according to **TP6** from sulfoxide **49b** (2.80 g, 10.0 mmol), with $Pd(PPh_3)_4$ (0.22 g, 0.20 mmol) and phenylacetylene (1.12 g, 11.0 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 7:3, silica gel) furnished **51i** as a colourless solid (3.45 g, 91% yield).

m.p. (°C): 121-123.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.23 (d, *J* = 8.31 Hz, 1H), 7.52 (dd, *J* = 8.31, 1.87 Hz, 1H), 7.50-7.48 (m, 4H), 7.46 (d, *J* = 1.87, 1H), 7.40-7.37 (m, 3H), 6.61-6.59 (m, 2H), 2.95 (s, 6H).

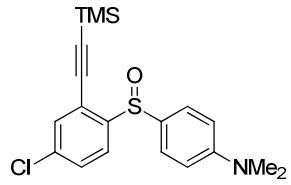
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 152.4, 146.1, 136.0, 132.3 (CH), 131.6 (CH), 129.8, 129.3 (CH), 129.2 (CH), 128.5 (CH), 128.2 (CH), 125.1 (CH), 122.1, 121.8, 111.7 (CH), 98.5, 84.0, 40.1 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2890 (w), 2810 (w), 2216 (w), 1594 (s), 1572 (m), 1548 (m), 1510 (m), 1490 (m), 1444 (m), 1360 (m), 1300 (w), 1226 (w), 1194 (m), 1144 (w), 1126 (w), 1084 (s), 1052 (s), 1032 (vs), 998 (m), 944 (w), 888 (m), 826 (m), 810 (s), 754 (vs), 692 (m), 608 (w).

MS (EI, 70 eV): *m/z* (%) = 363 (29), 352 (19), 350 (49), 276 (43), 275 (20), 274 (100), 260 (16), 168 (19), 148 (24), 136 (19).

HRMS (EI): calcd. for $C_{22}H_{18}ClNO^{32}S$: 379.0798, found: 379.0782.

4-((4-Chloro-2-((trimethylsilyl)ethynyl)phenyl)sulfinyl)-*N*,*N*-dimethylaniline (**51j**)



Prepared according to **TP6** from sulfoxide **49b** (2.80 g, 10.0 mmol), with $Pd(PPh_3)_4$ (0.22 g, 0.20 mmol) and trimethylsilylacetylene (1.08 g, 11.0 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 1:1, silica gel) furnished **51j** as an off-white solid (3.31 g, 88% yield).

m.p. (°C): 129-130.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.03 (d, *J* = 8.47 Hz, 1H), 7.49 (dd, *J* = 8.47, 2.15 Hz, 1H), 7.48-7.45 (m, 2H), 7.39 (d, *J* = 2.15, 1H), 6.63-6.60 (m, 2H), 2.96 (s, 6H), 0.24 (s, 9H).

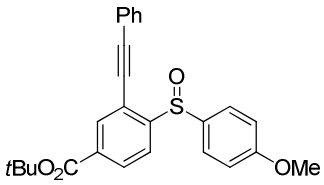
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 152.3, 146.3, 135.8, 132.8 (CH), 129.8, 129.5 (CH), 128.3 (CH), 124.8 (CH), 121.6, 111.6 (CH), 104.8, 98.7, 40.1 (CH_3), -0.40 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2894 (vw), 2158 (vw), 1594 (s), 1548 (w), 1512 (m), 1446 (m), 1364 (m), 1248 (w), 1194 (m), 1090 (m), 1050 (m), 1032 (s), 890 (s), 876 (m), 842 (vs), 810 (s), 760 (m), 724 (w), 646 (w), 610 (w).

MS (EI, 70 eV): *m/z* (%) = 377 (25), 376 (19), 375 (56, M^+), 359 (17), 274 (29), 168 (54), 152 (19), 148 (19), 136 (31), 73 (100).

HRMS (EI): calcd. for $C_{19}H_{22}{}^{35}ClNO^{32}S^{28}Si$: 375.0880, found: 375.0867.

Tert-butyl 4-((4-methoxyphenyl)sulfinyl)-3-(phenylethynyl)benzoate (**51k**)



Prepared according to **TP6** from sulfoxide **49c** (2.32 g, 7.00 mmol), with $Pd(PPh_3)_4$ (0.15 g, 0.14 mmol) and phenylacetylene (0.81 g, 8.00 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 1:1, silica gel) furnished **51k** as an off-white solid (1.86 g, 61% yield).

m.p. (°C): 142-143.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.18 (dd, J = 8.24, 0.55 Hz, 1H), 8.14 (dd, J = 8.24, 1.65 Hz, 1H), 8.07 (d, J = 1.65, 0.55 Hz, 1H), 7.64-7.60 (m, 2H), 7.51-7.48 (m, 2H), 7.40-7.36 (m, 3H), 6.87-6.83 (m, 2H), 3.74 (s, 3H), 1.57 (s, 9H).

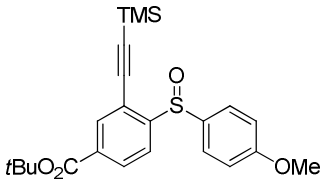
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 164.0, 162.1, 151.1, 135.7, 133.9, 133.6 (CH), 131.5 (CH), 129.8 (CH), 129.2 (CH), 128.5 (CH), 128.0, (CH) 123.4 (CH), 121.9, 120.2, 114.5 (CH), 98.1, 84.4, 81.9, 55.3 (CH_3), 28.0 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 2210 (vw), 1712 (s), 1592 (m), 1578 (m), 1492 (m), 1456 (m), 1442 (w), 1368 (w), 1308 (m), 1250 (vs), 1168 (s), 1146 (s), 1124 (s), 1082 (s), 1058 (s), 1036 (s), 1026 (s), 936 (w), 832 (m), 796 (w), 754 (s), 720 (m), 686 (m).

MS (EI, 70 eV): *m/z* (%) = 376 (15), 359 (9), 348 (12), 347 (40), 327 (8), 317 (17), 272 (14), 271 (100), 241 (8), 135 (16).

HRMS (EI): calcd. for $C_{26}H_{24}O_4{}^{32}S$: 432.1395, found: 432.1385.

Tert-butyl 4-((4-methoxyphenyl)sulfinyl)-3-((trimethylsilyl)ethynyl)benzoate (**51l**)



Prepared according to **TP6** from sulfoxide **49c** (2.32 g, 7.00 mmol), with $Pd(PPh_3)_4$ (0.15 g, 0.14 mmol) and trimethylsilylacetylene (0.79 g, 8.00 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 1:1, silica gel) furnished **51l** as a colourless solid (2.03 g, 68% yield).

m.p. (°C): 134-135.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.12-8.08 (m, 2H), 7.99-7.96 (m, 1H), 7.59 (d, *J* = 8.58 Hz, 2H), 6.86 (d, *J* = 8.79 Hz, 2H), 3.74 (s, 3H), 1.53 (s, 9H), 0.23 (s, 9H).

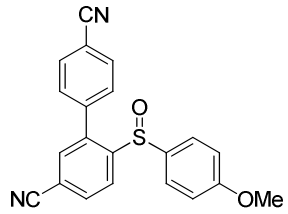
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.9, 162.0, 151.4, 135.7, 134.1 (CH), 133.8, 129.9 (CH), 128.1 (CH), 123.1 (CH), 120.0, 114.4 (CH), 104.4, 99.4, 81.8, 55.3 (CH_3), 27.9 (CH_3), -0.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2970 (m), 1713 (vs), 1590 (m), 1495 (m), 1457 (m), 1368 (m), 1300 (s), 1250 (vs), 1160 (s), 1108 (m), 1084 (m), 1058 (m), 1036 (s), 939 (m), 841 (vs), 833 (vs), 796 (m), 762 (s).

MS (EI, 70 eV): *m/z* (%) = 412 (16), 373 (20), 372 (60), 358 (27), 357 (98), 356 (35), 254 (50), 139 (21), 73 (100), 43 (24).

HRMS (EI): calcd. for $C_{23}H_{28}O_4{}^{32}S^{28}Si$: 428.1478, found: 428.1468.

6-((4-Methoxyphenyl)sulfinyl)-[1,1'-biphenyl]-3,4'-dicarbonitrile (**51m**)



Prepared according to **TP5** from sulfoxide **49d** (1.80 g, 7.00 mmol), with $Pd(PPh_3)_4$ (0.15 g, 0.14 mmol) and 4-iodobenzonitrile (1.93 g, 8.40 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (Et_2O, silica gel) furnished **51m** as a yellow solid (2.21 g, 88% yield).

m.p. (°C): 221-223.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.39 (d, *J* = 8.17 Hz, 1H), 7.94 (dd, *J* = 8.17, 1.61 Hz, 1H), 7.67-7.63 (m, 2H), 7.44 (d, *J* = 1.61 Hz, 1H), 7.23-7.18 (m, 2H), 6.90-6.85 (m, 2H), 6.70-6.66 (m, 2H), 3.73 (s, 3H).

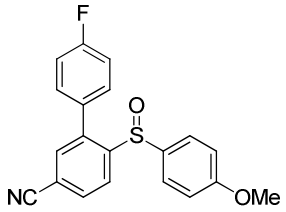
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.4, 149.4, 140.4, 139.2, 133.8, 133.1 (CH), 132.7 (CH), 132.3 (CH), 129.9 (CH), 128.2 (CH), 125.0 (CH), 117.9, 117.3, 114.7, 114.6 (CH), 112.8, 55.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2960 (w), 2836 (w), 2224 (m), 1594 (m), 1580 (m), 1496 (m), 1464 (m), 1444 (w), 1412 (w), 1308 (m), 1246 (s), 1178 (m), 1084 (s), 1068 (m), 1042 (vs), 1030 (vs), 956 (w), 854 (w), 834 (s), 824 (s), 794 (s), 722 (m), 696 (w).

MS (EI, 70 eV): *m/z* (%) = 358 (15, M^+), 277 (26), 155 (96), 139 (14), 124 (14), 123 (37), 77 (13), 61 (19), 45 (13), 43 (100).

HRMS (EI): calcd. for $C_{21}H_{14}N_2O_2{}^{32}S$: 358.0776, found: 358.0774.

4'-Fluoro-6-(4-methoxy-benzenesulfinyl)-biphenyl-3-carbonitrile (**51n**)



Prepared according to **TP5** from sulfoxide **49d** (1.29 g, 5.00 mmol), with $Pd(PPh_3)_4$ (0.11 g, 0.10 mmol) and 1-fluoro-4-iodobenzene (1.33 g, 6.00 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 3:7, silica gel) furnished **51n** as a colourless solid (1.25 g, 71% yield).

m.p. (°C): 121-122.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 3.75 (s, 3 H), 6.68-6.72 (m, 2 H), 6.88-6.93 (m, 2 H), 7.05-7.08 (m, 4 H), 7.44 (dd, *J* = 1.67, 0.48 Hz, 1 H), 7.89 (d, *J* = 8.11, 1.67 Hz, 1 H), 8.38 (dd, *J* = 8.11, 0.48 Hz, 1 H).

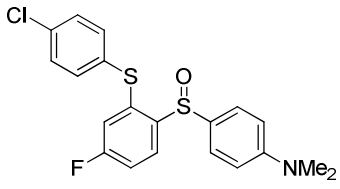
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 55.3 (CH_3), 114.3, 114.4 (CH), 115.7 (d, *J* = 21.72 Hz, CH), 117.5, 124.5 (CH), 127.9 (CH), 130.8 (d, *J* = 8.48 Hz, CH), 131.8 (CH), 131.9 (d, *J* = 2.39 Hz), 133.3 (CH), 134.1, 140.1, 149.6, 162.0, 162.8 (d, *J* = 249.8 Hz, CF).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3071 (w), 2836 (w), 2230 (m), 1591 (vs), 1577 (m), 1509 (vs), 1494 (vs), 1460 (s), 1441 (m), 1409 (m), 1303 (m), 1249 (vs), 1220 (s), 1173 (m), 1159 (m), 1083 (s), 1065 (m), 1042 (vs), 1026 (vs), 825 (vs), 796 (m), 612 (m), 593 (w).

MS (EI, 70 eV): *m/z* (%) = 352 (25), 351 (9), 303 (14), 156 (10), 155 (100), 139 (20), 124 (26), 123 (36), 114 (12), 44 (7).

HRMS (EI): calcd. for $C_{20}H_{14}FNO_2{}^{32}S$: 351.0729, found: 351.0717.

4-((2-((4-Chlorophenyl)thio)-4-fluorophenyl)sulfinyl)-*N*,*N*-dimethylaniline (**51o**)



Prepared according to **TP4** from sulfoxide **49a** (1.32 g, 5.00 mmol), and (*S*)-(4-chlorophenyl)benzene thiosulfonate (1.71 g, 6.00 mmol, 25 °C, 1 h). Flash chromatographic purification (Et_2O, silica gel) furnished **51o** as an off-white solid (1.67 g, 82% yield).

m.p. (°C): 121-122.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.17 (dd, *J* = 8.72, 5.96, 1H), 7.44-7.42 (m, 2H), 7.21 (dd, *J* = 5.96, 2.38 Hz, 1H), 7.18-7.17 (m, 2H), 7.00-6.99 (m, 2H), 6.82 (dd, *J* = 8.72, 2.38 Hz, 1H), 6.57-6.56 (m, 2H), 2.96 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.9 (d, *J* = 252.9 Hz, CF), 152.2, 142.3 (d, *J* = 2.31 Hz), 135.0 (d, *J* = 8.21 Hz), 134.0, 132.3 (CH), 132.1, 129.5 (CH), 128.7 (CH), 127.5, 127.0 (d, *J* = 9.01 Hz, CH), 119.5 (d, *J* = 24.11 Hz, CH), 115.8 (d, *J* = 22.25 Hz, CH), 111.7 (CH), 50.1 (CH_3).

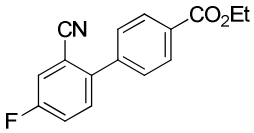
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2895 (w), 1588 (vs), 1568 (s), 1553 (m), 1513 (s), 1472 (m), 1452 (s), 1443 (m), 1437 (s), 1369 (s), 1231 (m), 1203 (m), 1196 (s), 1081 (s), 1040 (s), 1026 (s), 1011 (s), 890 (m), 817 (s), 811 (s).

MS (EI, 70 eV): *m/z* (%) = 407 (11), 405 (27, M^+), 389 (9), 357 (15), 278 (13), 202 (11), 169 (9), 168 (100), 152 (8), 136 (53).

HRMS (EI): calcd. for $C_{20}H_{17}{}^{35}ClFNO^{32}S_2$: 405.0424, found: 405.0414.

3.1.3 Preparation of Trisubstituted Arenes 55 by Sulfoxide-Magnesium Exchange on Sulfoxides 51

Ethyl 2'-cyano-4'-fluoro-[1,1'-biphenyl]-4-carboxylate (**55a**)



Prepared according to **TP7** by treating sulfoxide **51a** (288 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and ethyl 4-iodobenzoate (221 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 7:3, silica gel) furnished **55a** as a colourless solid (168 mg, 78% yield).

m.p. (°C): 124-127.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.16 (d, *J* = 8.60 Hz, 2H), 7.58 (d, *J* = 8.60 Hz, 2H), 7.53-7.46 (m, 2H), 7.42-7.35 (m, 1H), 4.41 (q, *J* = 7.13 Hz, 2H), 1.41 (t, *J* = 7.13 Hz, 3H).

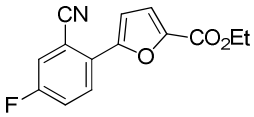
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 166.0, 161.6 (d, *J* = 251.2 Hz, CF), 141.3, 140.8 (d, *J* = 3.59 Hz), 133.8 (d, *J* = 19.35 Hz, CH), 132.0 (d, *J* = 8.29 Hz), 130.9, 130.0 (CH), 128.8 (CH), 120.7 (d, *J* = 13.55 Hz, CH), 120.4 (d, *J* = 17.14 Hz, CH), 112.7, 61.2 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3068 (vw), 3052 (w), 2984 (w), 2916 (w), 2232 (w), 1932 (vw), 1708 (vs), 1608 (m), 1572 (w), 1524 (w), 1480 (s), 1420 (m), 1368 (m), 1292 (vs), 1272 (s), 1220 (s), 1188 (s), 1156 (s), 1128 (s), 1108 (s), 1024 (s), 944 (s), 880 (vs), 832 (vs), 772 (vs), 728 (s), 704 (vs), 584 (s).

MS (EI, 70 eV): *m/z* (%) = 269 (14, M^+), 242 (6), 241 (36), 225 (15), 224 (100), 197 (22), 196 (28), 195 (20), 176 (6), 169 (17).

HRMS (EI): calcd. for $C_{21}H_{14}ClNO_2$: 269.0852, found: 269.0860.

Ethyl 5-(2-cyano-4-fluorophenyl)furan-2-carboxylate (**55b**)



Prepared according to **TP7** by treating sulfoxide **51a** (288 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and ethyl 5-bromofuran-2-carboxylate (175 mg, 0.80 mmol) for the cross-coupling (50 °C, 5 h).Flash chromatographic purification (pentane/EtOAc 1:1, silica gel) furnished **55b** as a colourless solid (150 mg, 72% yield).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.07 (dd, *J* = 8.94, 5.36 Hz, 1H), 7.43 (dd, *J* = 7.87, 2.86 Hz, 1H), 7.41-7.38 (m, 1H), 7.35 (d, *J* = 3.58 Hz, 1H), 7.27 (d, *J* = 3.58 Hz, 1H), 4.39 (q, *J* = 7.15 Hz, 2H), 1.39 (t, *J* = 7.15 Hz, 3H).

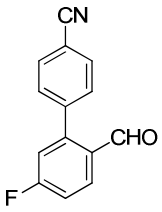
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 161.5 (d, *J* = 253.2, CF), 158.4, 151.7 (d, *J* = 1.12 Hz), 144.9, 132.1 (d, *J* = 9.82 Hz), 129.4 (d, *J* = 8.41 Hz, CH), 128.5, 121.0 (d, *J* = 21.32 Hz, CH), 120.9 (d, *J* = 25.24 Hz, CH), 119.6 (CH), 117.2, 111.5 (CH), 61.3 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3163 (vw), 3134 (w), 3078 (m), 3054 (m), 3004 (m), 2964 (m), 2924 (m), 2232 (m), 1725 (vs), 1581 (w), 1480 (s), 1407 (s), 1371 (m), 1294 (s), 1256 (s), 1211 (s), 1138 (vs), 1042 (s), 951 (m), 902 (m), 805 (s), 763 (m), 590 (m).

MS (EI, 70 eV): *m/z* (%) = 260 (14), 259 (100, M^+), 231 (64), 215 (14), 214 (90), 187 (59), 159 (21), 158 (85), 132 (9), 131 (16).

HRMS (EI): calcd. for $C_{14}H_{10}FNO_3$: 259.0645, found: 259.0646.

5'-Fluoro-2'-formyl-[1,1'-biphenyl]-4-carbonitrile (**55c**)



Prepared according to **TP7** by treating sulfoxide **51b** (363 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 1 h and DMF (58 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/EtOAc 10:1, silica gel) furnished **55c** as a pale flesh-coloured solid (136 mg, 76% yield).

m.p. (°C): 127-128.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 9.84 (d, *J* = 0.49 Hz, 1H), 8.08 (dd, *J* = 8.87, 5.83 Hz, 1H), 7.80-7.76 (m, 2H), 7.51-7.48 (m, 2H), 7.29-7.22 (m, 1H), 7.09 (dd, *J* = 8.87, 2.43 Hz, 1H).

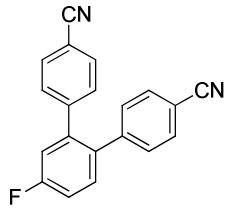
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 189.4 (CH), 165.5 (d, *J* = 258.2 Hz, CF), 146.2 (d, *J* = 9.28 Hz), 141.4, 132.3 (CH), 131.7 (d, *J* =9.80 Hz, CH), 130.4 (CH), 130.2 (d, *J* =3.09 Hz), 118.2, 117.5 (d, *J* = 22.68 Hz, CH), 116.4 (d, *J* = 21.65 Hz, CH), 112.8.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2228 (m), 1694 (s), 1606 (m), 1574 (s), 1506 (w), 1488 (w), 1436 (w), 1408 (w), 1394 (m), 1316 (w), 1308 (w), 1286 (w), 1186 (vs), 1120 (m), 1018 (w), 904 (m), 892 (m), 844 (s), 820 (s), 802 (m), 610 (s).

MS (EI, 70 eV): *m/z* (%) = 226 (7), 225 (69, M^+), 224 (100), 197 (10), 196 (14), 195 (17), 176 (4), 170 (5), 169 (11), 122 (5).

HRMS (EI): calcd. for $C_{14}H_8FNO$: 225.0590, found: 225.0576.

4'-Fluoro-[1,1':2',1"-terphenyl]-4,4"-dicarbonitrile (**55d**)



Prepared according to **TP7** by treating sulfoxide **51b** (363 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 1 h, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and 4-iodobenzonitrile (183 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 10:1, silica gel) furnished **55d** as a colourless solid (179 mg, 75% yield).

m.p. (°C): 181-183.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.56-7.51 (m, 4H), 7.40 (dd, *J* = 8.50, 5.59 Hz, 1H), 7.24-7.17 (m, 4H), 7.16-7.12 (m, 2H).

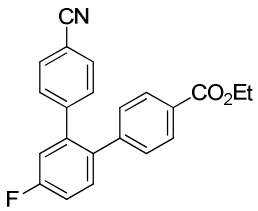
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.6 (d, *J* = 250.1 Hz, CF), 144.5, 144.3 (d, *J* = 1.75 Hz), 140.6 (d, *J* = 7.98 Hz), 134.8, 134.7, 132.4 (d, *J* = 8.37 Hz, CH), 132.2 (CH), 132.1 (CH), 130.5 (CH), 130.3 (CH), 118.4 (d, *J* = 11.09 Hz), 117.4 (d, J = 22.38 Hz, CH), 115.8 (d, *J* = 21.21 Hz, CH), 111.5, 111.1.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2958 (m), 2926 (m), 2856 (m), 2226 (m), 1728 (s), 1606 (m), 1584 (m), 1476 (m), 1392 (m), 1276 (s), 1258 (s), 1178 (m), 1120 (s), 1074 (m), 884 (m), 836 (vs), 822 (vs), 772 (m), 738 (m), 632 (w).

MS (EI, 70 eV): *m/z* (%) = 299 (21), 298 (100, M^+), 297 (45), 296 (8), 283 (12), 271 (9), 270 (8), 269 (13), 258 (30), 245 (6).

HRMS (EI): calcd. for $C_{20}H_{11}FN_2$: 298.0906, found: 298.0920.

Ethyl 4''-cyano-4'-fluoro-[1,1':2',1''-terphenyl]-4-carboxylate (**55e**)



Prepared according to **TP7** by treating sulfoxide **51b** (363 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 1 h, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and ethyl 4-iodobenzoate (221 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 20:1, silica gel) furnished **55e** as colourless crystals (191 mg, 76% yield).

m.p. (°C): 123-125.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.92-7.88 (m, 2H), 7.53-7.49 (m, 2H), 7.42 (dd, *J* = 8.50, 5.83 Hz, 1H), 7.22-7.18 (m, 2H), 7.17-7.10 (m, 4H), 4.36 (q, *J* = 7.19 Hz, 2H), 1.38 (t, *J* = 7.19 Hz, 3H).

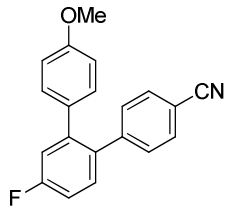
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.2, 162.4 (d, *J* = 248.9 Hz, CF), 144.8 (d, *J* = 2.06 Hz), 144.3, 140.5 (d, *J* = 7.73 Hz), 135.8, 132.4 (d, *J* = 8.25 Hz, CH), 132.0 (CH), 130.3 (CH), 129.8 (CH), 129.5 (CH), 129.2, 118.5, 117.2 (d, *J* = 22.68 Hz, CH), 115.6 (d, *J* = 21.14 Hz, CH), 111.2, 61.1 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2926 (w), 2230 (w), 1714 (vs), 1606 (m), 1584 (m), 1480 (m), 1394 (m), 1312 (w), 1284 (vs), 1188 (m), 1180 (m), 1118 (s), 1102 (s), 1024 (m), 1006 (m), 886 (m), 866 (m), 846 (s), 834 (s), 774 (m), 704 (m).

MS (EI, 70 eV): *m/z* (%) = 346 (21), 345 (88, M^+), 317 (18), 301 (23), 300 (100), 273 (23), 272 (59), 271 (29), 269 (13), 251 (15).

HRMS (EI): calcd. for $C_{22}H_{16}FNO_2$: 345.1165, found: 345.1158.

4'-Fluoro-4''-methoxy-[1,1':2',1''-terphenyl]-4-carbonitrile (**55f**)



Prepared according to **TP7** by treating sulfoxide **51c** (369 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at 0 °C for 1 h, with $Pd(PPh_3)_4$ (0.02 mmol, 22 mg) and 4-iodobenzonitrile (183 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 10:1, silica gel) furnished **55f** as a colourless solid (208 mg, 86% yield).

m.p. (°C): 106-107.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 7.51-7.49 (m, 2H), 7.32 (dd, *J* = 8.42, 5.94 Hz, 1H), 7.21-7.19 (m, 2H), 7.13 (dd, *J* = 9.66, 2.72 Hz, 1H), 7.12-7.08 (m, 1H), 6.99-6.96 (m, 2H), 6.78-6.75 (m, 2H), 3.78 (s, 3H).

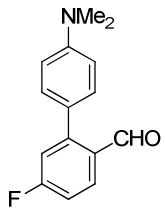
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 162.6 (d, *J* = 248.9 Hz, CF), 159.0, 145.8, 142.4 (d, *J* = 7.73 Hz), 134.6 (d, *J* = 3.10 Hz), 131.9 (d, *J* = 8.76 Hz, CH), 131.8 (d, *J* = 2.06 Hz), 131.8 (CH), 130.7 (CH), 130.5 (CH), 118.9, 117.4 (d, *J* = 21.13 Hz, CH), 114.2 (d, *J* = 21.14 Hz, CH), 113.8 (CH), 110.3, 55.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2934 (w), 2840 (vw), 2224 (w), 1608 (m), 1588 (m), 1516 (m), 1510 (m), 1476 (m), 1446 (w), 1302 (m), 1292 (m), 1250 (s), 1192 (w), 1178 (s), 1122 (w), 1108 (w), 1046 (w), 1026 (m), 1006 (w), 884 (m), 850 (m), 828 (vs), 810 (m), 794 (m), 690 (w).

MS (EI, 70 eV): *m/z* (%) = 304 (20), 303 (100, M^+), 302 (15), 272 (20), 260 (12), 259 (12), 258 (24), 245 (15), 129 (10), 45 (12).

HRMS (EI): calcd. for $C_{20}H_{14}FNO$: 303.1059, found: 303.1049.

4'-(Dimethylamino)-5-fluoro-[1,1'-biphenyl]-2-carbaldehyde (**55g**)



Prepared according to **TP7** by treating sulfoxide **51d** (383 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at 0 °C for 1 h and DMF (58 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 5:1, silica gel) furnished **55g** as a yellow oil (154 mg, 79% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 9.93 (d, *J* = 0.73 Hz, 1H), 8.00 (ddd, *J* = 6.07, 2.43, 0.49 Hz, 1H), 7.26-7.21 (m, 2H), 7.13-7.04 (m, 2H), 6.81-6.76 (m, 2H), 3.02 (s, 6H).

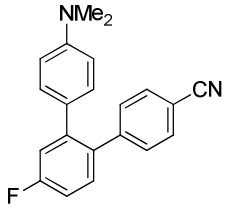
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 191.5 (CH), 165.5 (d, *J* = 250.3 Hz, CF), 150.6, 149.2 (d, *J* = 9.28 Hz), 130.9 (CH), 130.6 (d, *J* = 10.31 Hz, CH), 130.2 (d, *J* = 2.58 Hz), 123.9 (d, *J* = 2.06 Hz), 116.9 (d, *J* = 21.65 Hz, CH), 114.2 (d, *J* = 22.17 Hz, CH), 112.0 (CH), 50.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2850 (w), 1682 (s), 1602 (vs), 1580 (s), 1524 (s), 1476 (s), 1446 (m), 1392 (m), 1356 (s), 1270 (s), 1248 (m), 1226 (m), 1190 (s), 1166 (s), 1128 (m), 1102 (m), 1062 (m), 946 (m), 896 (m), 874 (m), 816 (vs), 756 (w), 652 (w), 628 (m), 612 (w).

MS (EI, 70 eV): *m/z* (%) = 244 (13), 243 (100, M^+), 242 (17), 215 (12), 214 (28), 200 (19), 199 (12), 171 (18), 170 (18), 120 (10).

HRMS (EI): calcd. for $C_{15}H_{14}FNO$: 243.1059, found: 243.1055.

4''-(Dimethylamino)-4'-fluoro-[1,1':2',1''-terphenyl]-4-carbonitrile (**55h**)



Prepared according to **TP7** by treating sulfoxide **51d** (383 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at 0 °C for 1 h, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and 4-iodobenzonitrile (183 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 5:1, silica gel) furnished **55h** as a colourless solid (182 mg, 72% yield).

m.p. (°C): 120-122.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 7.52-7.50 (m, 2H), 7.30 (dd, *J* = 8.55, 5.82 Hz, 1H), 7.23 (d, *J* = 8.42 H, 2H), 7.13 (dd, *J* = 9.78, 2.60 Hz, 1H), 7.07-7.04 (m, 1H), 6.92 (d, *J* = 8.42 Hz, 2H), 6.58-6.56 (m, 2H), 2.94 (s, 6H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 162.7 (d, *J* = 248.5 Hz, CF), 153.5, 146.2, 144.6, 134.3 (d, *J* = 3.09 Hz), 131.9 (d, *J* = 8.25 Hz, CH), 131.8 (CH), 131.7 (CH), 130.5 (CH),

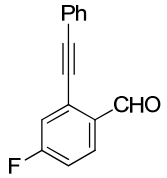
130.4 (CH), 119.0, 117.2 (d, *J* = 21.65 Hz, CH), 113.6 (d, *J* = 22.17 Hz, CH), 111.9, 110.0, 40.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2970 (vw), 2801 (vw), 2223 (w), 1738 (m), 1601 (s), 1526 (s), 1477 (s), 1354 (s), 1225 (m), 1183 (s), 1167 (m), 1105 (m), 1005 (m), 947 (m), 888 (m), 817 (s), 807 (vs), 630 (w), 603 (m).

MS (EI, 70 eV): *m/z* (%) = 317 (16), 316 (100, M^+), 315 (53), 272 (7), 271 (6), 269 (3), 256 (3), 245 (3), 158 (3), 122 (3).

HRMS (EI): calcd. for $C_{21}H_{17}FN_2$: 316.1376, found: 316.1376.

4-Fluoro-2-(phenylethynyl)benzaldehyde (**55i**)



Prepared according to **TP7** by treating sulfoxide **51e** (363 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and DMF (58 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 20:1, silica gel) furnished **55i** as a yellow solid (168 mg, 94% yield).

m.p. (°C): 39-41.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 10.56 (s, 1H), 7.97 (dd, *J* = 8.80, 5.95 Hz, 1H), 7.57-7.55 (m, 2H), 7.42-7.37 (m, 3H), 7.31 (dd, *J* = 8.80, 2.48 Hz, 1H), 7.16-7.12 (m, 1H).

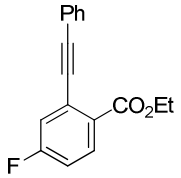
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 190.0 (CH), 165.7 (d, *J* = 256.7 Hz, CF), 132.6 (d, *J* = 3.09 Hz), 131.8 (CH), 130.1 (d, *J* = 10.31 Hz, CH), 129.4 (CH), 129.3, 128.6 (CH), 121.8, 119.7 (d, *J* = 23.71 Hz, CH), 116.5 (d, *J* = 22.17 Hz, CH), 97.4, 83.7.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3062 (w), 2924 (w), 2838 (w), 2754 (w), 2206 (m), 1692 (vs), 1600 (s), 1592 (s), 1570 (s), 1492 (m), 1470 (m), 1440 (m), 1394 (m), 1320 (m), 1284 (s), 1212 (vs), 1086 (m), 1068 (m), 954 (m), 862 (m), 822 (s), 756 (vs), 688 (s), 646 (m).

MS (EI, 70 eV): *m/z* (%) = 224 (100, M^+), 223 (27), 196 (50), 195 (26), 194 (28), 170 (20), 97 (37), 85 (37), 75 (20), 74 (20).

HMS (EI): calcd. for $C_{15}H_9FO$: 224.0637, found: 224.0621.

Ethyl 4-fluoro-2-(phenylethynyl)benzoate (**55j**)



Prepared according to **TP7** by treating sulfoxide **51e** (363 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and ethyl chloroformate (89 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 20:1, silica gel) furnished **55j** as a clear oil (144 mg, 67% yield).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.00 (dd, *J* = 8.82, 5.96 Hz, 1H), 7.58-7.55 (m, 2H), 7.37-7.35 (m, 3H), 7.32 (dd, *J* = 9.06, 2.62 Hz, 1H), 7.08-7.05 (m, 1H), 4.40 (q, *J* = 7.15 Hz, 2H), 1.39 (t, *J* = 7.15 Hz, 3H).

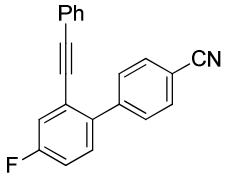
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 165.3, 164.2 (d, *J* = 253.8 Hz, CF), 133.0 (d, *J* = 9.82 Hz, CH), 131.7 (CH), 128.8 (CH), 128.4 (CH), 128.3, 126.3 (d, *J* = 10.38 Hz), 122.9, 120.6 (d, *J* = 23.28 Hz, CH), 115.3 (d, *J* = 21.60 Hz, CH), 95.4, 87.2, 61.3 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3052 (w), 2892 (w), 2808 (w), 2216 (w), 1592 (s), 1548 (m), 1508 (s), 1492 (m), 1444 (m), 1364 (s), 1196 (m), 1084 (s), 1052 (s), 1032 (vs), 944 (m), 888 (s), 808 (s), 752 (vs), 688 (s), 572 (s).

MS (EI, 70 eV): *m/z* (%) = 268 (46, M^+), 240 (70), 239 (21), 223 (33), 194 (23), 183 (30), 149 (26), 45 (24), 44 (72), 43 (100).

HRMS (EI): calcd. for $C_{17}H_{13}FO_2$: 268.0900, found: 268.0886.

4'-Fluoro-2'-(phenylethynyl)-[1,1'-biphenyl]-4-carbonitrile (**55k**)



Prepared according to **TP7** by treating sulfoxide **51e** (363 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and 4-iodobenzonitrile (183 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et2O 20:1, silica gel) furnished **55k** as a colourless solid (230 mg, 83% yield).

m.p. (°C): 132-133.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 7.75-7.71 (m, 4H), 7.37-7.28 (m, 7H), 7.15-7.12 (m, 1H).

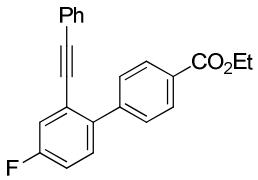
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 162.1 (d, J = 248.9 Hz, CF), 144.3, 138.0 (d, J = 3.09 Hz), 131.8 (CH), 131.4 (CH), 130.9 (d, J = 8.76 Hz, CH), 130.1 (CH), 128.9 (CH), 128.5 (CH), 123.5 (d, J = 9.79 Hz), 122.4, 119.5 (d, J = 23.20 Hz, CH), 118.9, 116.1 (d, J = 21.65 Hz, CH), 111.3, 93.9, 87.3 (d, J = 3.09 Hz).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3059 (m), 2226 (s), 2209 (s), 1607 (s), 1602 (s), 1573 (s), 1492 (s), 1481 (s), 1468 (s), 1442 (m), 1313 (m), 1195 (s), 1182 (m), 1090 (m), 952 (s), 866 (s), 847 (s), 809 (vs), 750 (vs), 683 (s).

MS (EI, 70 eV): *m/z* (%) = 298 (16), 297 (90, M^+), 296 (100), 295 (49), 293 (12), 270 (12), 268 (14), 148 (12), 135 (11), 134 (19).

HRMS (EI): calcd. For $C_{21}H_{12}FN$: 297.0954, found: 297.0956.

Ethyl 4'-fluoro-2'-(phenylethynyl)-[1,1'-biphenyl]-4-carboxylate (**55l**)



Prepared according to **TP7** by treating sulfoxide **51e** (363 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and ethyl 4-iodobenzoate (221 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et2O 20:1, silica gel) furnished **55l** as a yellow solid (230 mg, 84% yield).

m.p. (°C): 107-109.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.13-8.11 (m, 2H), 7.70-7.68 (m, 2H), 7.38 (dd, J = 8.42, 5.70 Hz, 1H), 7.35 (dd, J = 9.17, 2.73 Hz, 1H), 7.32-7.29 (m, 5H), 7.13-7.10 (m, 1H), 4.41 (q, J = 7.14 Hz, 2H), 1.42 (t, J = 7.14, 3H).

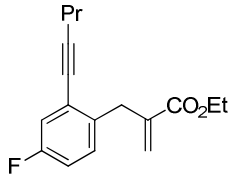
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 168.5, 161.9 (d, J = 248.4 Hz, CF), 144.1, 138.9 (d, J = 3.61 Hz), 131.4 (CH), 131.1 (d, J = 8.76 Hz, CH), 129.5, 129.3 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 123.6 (d, J = 9.79 Hz), 122.6, 119.4 (d, J = 22.68 Hz, CH), 115.9 (d, J = 21.65 Hz, CH), 93.4, 87.7 (d, J = 3.09 Hz), 61.0 (CH_2), 14.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2982 (w), 2212 (vw), 1708 (vs), 1610 (w), 1602 (w), 1576 (w), 1492 (w), 1474 (m), 1398 (w), 1364 (w), 1312 (w), 1272 (vs), 1198 (m), 1174 (m), 1124 (m), 1104 (s), 1028 (m), 822 (m), 774 (m), 756 (s), 734 (m), 704 (m), 688 (s).

MS (EI, 70 eV): *m/z* (%) = 344 (36, M^+), 343 (13), 315 (14), 299 (21), 285 (13), 272 (25), 271 (100), 270 (91), 268 (25), 135 (20).

HRMS (EI): calcd. for $C_{23}H_{17}FO_2$: 344.1213, found: 344.1209.

Ethyl 2-(4-fluoro-2-(pent-1-yn-1-yl)benzyl)acrylate (**55m**)



Prepared according to **TP7** by treating sulfoxide **51f** (329 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with CuCN·2LiCl (0.05 mL, 0.05 mmol, 1.00 M in THF) and ethyl 2-(bromomethyl)acrylate (154 mg, 0.80 mmol) for the allylation (-20 °C, 30 min). Flash chromatographic purification (pentane/Et_2O, 20:1, silica gel) furnished **55m** as a yellow oil (156 mg, 71% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.12 (dd, *J* = 8.43, 5.70 Hz, 1H), 7.07 (dd, *J* = 9.41, 2.97 Hz, 1H), 6.93-6.86 (m, 1H), 6.23-6.22 (m, 1H), 5.33-5.32 (m, 1H), 4.19 (q, *J* = 7.18 Hz, 2H), 3.74 (s, 2H), 2.37 (t, *J* = 6.94 Hz, 2H), 1.65-1.53 (m, 2H), 1.27 (t, *J* =7.18 Hz, 3H), 1.01 (t, *J* = 7.31 Hz, 3H).

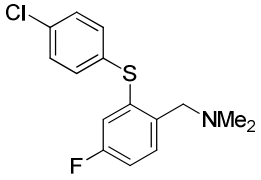
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.9, 160.9 (d, *J* = 244.6 Hz, CF), 139.3 (d, *J* = 1.03 Hz), 136.3 (d, *J* = 3.09 Hz), 130.7 (d, *J* = 8.50 Hz, CH), 126.0 (CH_2), 125.7 (d, *J* = 9.54 Hz), 118.6 (d, *J* = 22.42 Hz, CH), 114.8 (d, *J* = 21.39 Hz, CH), 95.3, 78.4 (d, *J* = 3.09 Hz), 60.7 (CH_2), 35.5 (CH_2), 22.1 (CH_2), 21.5 (CH_2), 14.1 (CH_3), 13.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2964 (w), 2936 (w), 2230 (vw), 1714 (vs), 1632 (w), 1610 (m), 1580 (w), 1492 (m), 1430 (w), 1368 (w), 1276 (s), 1252 (m), 1196 (m), 1166 (s), 1134 (vs), 1028 (m), 994 (w), 948 (m), 896 (w), 868 (s), 830 (m), 816 (m), 798 (m), 774 (w).

MS (EI, 70 eV): *m/z* (%) = 245 (69), 217 (27), 203 (38), 201 (25), 173 (29), 171 (39), 170 (27), 160 (15), 159 (100), 146 (16).

HRMS (EI): calcd. for $C_{17}H_{19}FO_2$: 274.1369, found: 274.1362.

1-(2-((4-Chlorophenyl)thio)-4-fluorophenyl)-*N*,*N*-dimethylmethanamine (**55n**)



Prepared according to **TP7** by treating sulfoxide **51o** (406 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 3 h. $(TFA)_2O$ (80 mg, 0.70 mmol) and *N*,*N*,*N*',*N*'-tetramethyldiaminomethane (72 mg, 0.70 mmol) were dissolved in CH_2Cl_2 (1 mL), stirred at 25 °C for 1 h and then added to the solution at -50 °C and the mixture was allowed

to warm to 25 °C and stirred for additional 2 h. Flash chromatographic purification (Et_2O, silica gel) furnished **55n** as a colourless solid (169 mg, 82% yield).

m.p. (°C): 55-57.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.42-7.28 (m, 5H), 6.90-6.86 (m, 1H), 6.75 (dd, *J* = 9.30, 2.62 Hz, 1H), 3.57 (s, 2H), 2.29 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.1 (d, *J* = 148.2 Hz, CF), 138.9 (d, *J* = 7.95 Hz, CH), 134.1, 133.7 (CH), 132.8, 129.7 (CH), 129.6, 128.1, 117.0 (d, *J* = 23.84 Hz, CH), 113.6 (d, *J* = 21.46 Hz, CH), 61.0 (CH_2), 44.8 (CH_3).

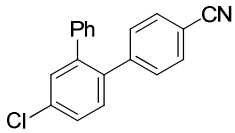
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2972 (m), 2942 (m), 2812 (s), 2763 (s), 1602 (m), 1576 (m), 1475 (vs), 1451 (s), 1440 (m), 1362 (m), 1246 (m), 1219 (s), 1090 (s), 1023 (m), 1012 (s), 903 (m), 866 (m), 851 (m), 830 (m), 824 (vs), 792 (m), 587 (w).

MS (EI, 70 eV): *m/z* (%) = 280 (15), 215 (17), 211 (18), 183 (18), 170 (16), 169 (100), 168 (48), 152 (65), 136 (29), 58 (13).

HRMS (EI): calcd. for $C_{15}H_{15}{}^{35}ClFN^{32}S$: 295.0598, found: 295.0597.

3.1.4 Preparation of Trisubstituted Arenes 63 by Sulfoxide-Magnesium Exchange on Sulfoxides 51

4'-Chloro-[1,1':2',1''-terphenyl]-4-carbonitrile (**63a**)



Prepared according to **TP7** by treating sulfoxide **51g** (356 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 1 h, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and 4-iodobenzonitrile (183 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc, 20:1, silica gel) furnished **63a** as a colourless solid (215 mg, 93% yield).

m.p. (°C): 112-114.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.49 (d, *J* = 8.42 Hz, 2H), 7.44 (d, *J* = 2.16 Hz, 1H), 7.42 (dd, *J* = 8.23, 2.16 Hz, 1H), 7.32 (d, *J* = 8.23 Hz, 1H), 7.25-7.22 (m, 3H), 7.19 (d, *J* = 8.42 Hz, 2H), 7.07-7.05 (m, 2H).

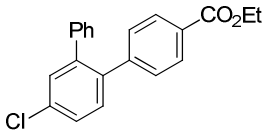
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 110.6, 118.8, 127.5 (CH), 127.8 (CH), 128.3 (CH), 129.6 (CH), 130.4 (CH), 130.7 (CH), 131.5 (CH), 131.8 (CH), 134.5, 137.0, 139.3, 142.2, 145.3.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2222 (vs), 1605 (m), 1587 (m), 1476 (m), 1462 (m), 1444 (m), 1385 (m), 1097(m), 1004 (m), 882 (m), 848 (m), 818 (vs), 767 (s), 747 (m), 699 (s), 596 (w), 586 (w), 570 (s).

MS (EI, 70 eV): *m/z* (%) = 291 (30), 290 (37), 289 (100, M^+), 281 (14), 255 (22), 254 (99), 253 (53), 252 (21), 251 (26), 207 (38).

HRMS (EI): calcd. for $C_{19}H_{12}{}^{35}ClN$: 289.0658, found: 289.0663.

Ethyl 4'-chloro-[1,1':2',1''-terphenyl]-4-carboxylate (**63b**)



Prepared according to **TP7** by treating sulfoxide **51g** (356 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 1 h, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and ethyl 4-iodobenzoate (221 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 20:1, silica gel) furnished **63b** as a colourless oil (240 mg, 89% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.89-7.87 (m, 2H), 7.44-7.33 (m, 3H), 7.23-7.14 (m, 5H), 7.10-7.07 (m, 2H), 4.34 (q, *J* = 7.05 Hz, 2H), 1.37 (t, *J* = 7.17 Hz, 3H).

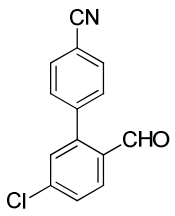
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.4, 145.1, 142.2, 139.8, 138.0, 133.9, 131.6 (CH), 130.6 (CH), 129.7 (CH), 129.6 (CH), 129.2 (CH), 128.8, 128.2 (CH), 127.6 (CH), 127.2 (CH), 60.9 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2979 (w), 1712 (vs), 1608 (m), 1589 (w), 1475 (w), 1464 (m), 1444 (m), 1366 (m), 1269 (vs), 1177 (m), 1098 (s), 1044 (w), 1025 (m), 1003 (m), 820 (m), 776 (w), 768 (m), 699 (m), 680 (w).

MS (EI, 70 eV): *m/z* (%) = 338 (28), 337 (19), 336 (79, M^+), 291 (51), 263 (30), 229 (22), 228 (100), 227 (23), 226 (35), 113 (20).

HRMS (EI): calcd. for $C_{21}H_{17}{}^{35}ClO_2$: 336.0917, found: 336.0913.

5'-Chloro-2'-formyl-[1,1'-biphenyl]-4-carbonitrile (**63c**)



Prepared according to **TP7** by treating sulfoxide **51h** (381 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 1 h and DMF (58 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/EtOAc 10:1, silica gel) furnished **63c** as a yellow solid (144 mg, 74% yield).

m.p. (°C): 117-119.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 9.85 (d, *J* = 0.74 Hz, 1H), 7.97 (d, *J* = 8.42 Hz, 1H), 7.79-7.75 (m, 2H), 7.53 (ddd, *J* = 8.42, 2.27, 0.74 Hz, 1H), 7.50-7.47 (m, 2H), 7.40 (d, *J* = 2.27 Hz, 1H).

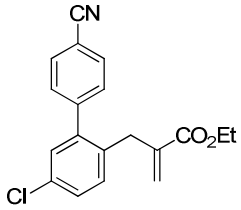
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 189.7 (CH), 144.7, 141.2, 140.2, 132.3 (CH), 131.8 (CH), 130.5, 130.4 (CH), 130.0 (CH), 129.2 (CH), 118.1, 112.7.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2860 (w), 2766 (w), 2228 (w), 1686 (s), 1608 (w), 1586 (s), 1548 (m), 1508 (w), 1470 (w), 1396 (w), 1278 (m), 1254 (s), 1192 (m), 1090 (m), 1018 (m), 910 (w), 860 (m), 842 (vs), 824 (vs), 794 (m), 764 (w), 602 (w).

MS (EI, 70 eV): *m/z* (%) = 243 (26), 242 (46), 241 (79, M^+), 240 (100), 206 (50), 178 (25), 177 (85), 150 (22), 138 (33), 43 (43).

HRMS (EI): calcd. for $C_{14}H_8{}^{35}ClNO$: 241.0294, found: 241.0286.

Ethyl 2-((5-chloro-4'-cyano-[1,1'-biphenyl]-2-yl)methyl)acrylate (**63d**)



Prepared according to **TP7** by treating sulfoxide **51h** (381 mg, 1.00 mmol) with *i*PrMgCl·LiCl (1.10 mmol, 0.92 mL, 1.20 M in THF) at -50 °C for 1 h, with CuCN·2LiCl (0.05 mL, 0.05 mmol, 1.00 M in THF) and ethyl 2-(bromomethyl)acrylate (154 mg, 0.80 mmol) for the allylation (-20 °C, 30 min). Flash chromatographic purification (pentane/EtOAc, 20:1, silica gel) furnished **63d** as a yellow oil (126 mg, 48% yield).

m.p. (°C): 72-73.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.76-7.70 (m, 2H), 7.42-7.38 (m, 2H), 7.31 (dd, *J* = 8.26, 2.19 Hz, 1H), 7.21-7.18 (m, 2H), 6.20 (d, *J* = 1.22 Hz, 1H), 5.21 (d, *J* = 1.22 Hz, 1H), 4.12 (q, *J* = 7.05 Hz, 2H), 3.49 (s, 2H), 1.22 (t, *J* = 7.05 Hz, 3H).

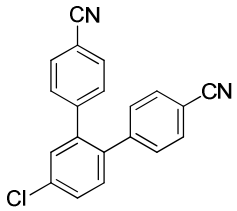
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.3, 144.8, 141.9, 139.7, 134.3, 132.4, 132.1 (CH), 131.5 (CH), 129.7 (CH), 129.6 (CH), 128.4 (CH), 126.6 (CH_2), 118.6, 111.5, 60.9 (CH_2), 34.6 (CH_2), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2226 (w), 1710 (s), 1632 (w), 1606 (w), 1594 (w), 1478 (m), 1464 (w), 1388 (m), 1300 (w), 1256 (vs), 1176 (m), 1150 (s), 1096 (m), 1032 (w), 1018 (m), 952 (m), 898 (w), 858 (m), 848 (s), 834 (s), 820 (m), 788 (w), 672 (w), 646 (m).

MS (EI, 70 eV): *m/z* (%) = 325 (26, M^+), 254 (21), 253 (24), 252 (83), 251 (48), 250 (47), 224 (22), 217 (50), 216 (100), 190 (37).

HRMS (EI): calcd. for $C_{19}H_{16}{}^{35}ClNO_2$: 325.0870, found: 325.0856.

4'-Chloro-[1,1';2',1"]terphenyl-4,4"-dicarbonitrile (**63e**)



Prepared according to **TP7** by treating sulfoxide **51h** (381 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 1 h, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and 4-iodobenzonitrile (183 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O, 10:1, silica gel) furnished **63e** as a colourless solid (205 mg, 81% yield).

m.p. (°C): 190-194.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.55-7.52 (m, 4 H), 7.49-7.47 (m, 1 H), 7.42 (d, *J* = 1.91 Hz, 1 H), 7.38 (d, *J* = 8.11 Hz, 1 H), 7.20-7.16 (m, 4 H).

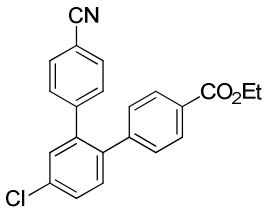
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 144.3, 144.1, 140.1, 137.1, 134.9, 132.2 (CH), 132.1 (CH), 131.8 (CH), 130.5 (CH), 130.4 (CH), 130.3 (CH), 128.9 (CH), 118.4, 118.3, 111.5, 111.3.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2917 (w), 2225 (m), 1605 (m), 1588 (w), 1468 (m), 1435 (w), 1409 (w), 1383 (m), 1285 (w), 1275 (w), 1178 (m), 1097 (m), 1003 (m), 903 (w), 844 (s), 822 (vs), 749 (m), 691 (m), 597 (m), 587 (m), 578 (s), 554 (w).

MS (EI, 70 eV): *m/z* (%) = 316 (31), 315 (24), 314 (95, M^+), 280 (20), 279 (100), 278 (30), 276 (17), 251 (22), 125 (19), 112 (19).

HRMS (EI): calcd. for $C_{20}H_{11}{}^{35}ClN_2$: 314.0611, found: 314.0603.

Ethyl 4'-chloro-4"-cyano-[1,1':2',1"-terphenyl]-4-carboxylate (**63f**)



Prepared according to **TP7** by treating sulfoxide **51h** (381 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 1 h, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and ethyl 4-iodobenzoate (221 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc, 10:1, silica gel) furnished **63f** as a colourless solid (261 mg, 90% yield).

m.p. (°C): 156-158.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.90 (d, *J* = 8.42 Hz, 2H), 7.52 (d, *J* =8.42 Hz, 2H), 7.46 (dd, *J* = 8.18, 1.98 Hz, 1H), 7.41-7.37 (m, 2H), 7.20 (d, *J* = 8.55 Hz, 2H), 7.12 (d, *J* = 8.55 Hz, 2H), 4.36 (q, *J* = 7.12 Hz, 2H), 1.38 (t, *J* = 7.12, 3H).

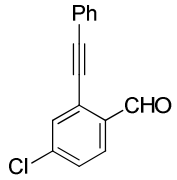
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.1, 144.6, 144.1, 140.2, 138.1, 134.3, 132.0 (CH), 131.9 (CH), 130.3 (CH), 130.2 (CH), 129.6 (CH), 129.5 (CH), 129.4 (CH), 127.2, 118.5, 111.2, 61.1 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2226 (w), 1712 (vs), 1608 (m), 1590 (w), 1472 (m), 1390 (w), 1380 (w), 1362 (m), 1284 (vs), 1266 (s), 1236 (m), 1180 (m), 1118 (s), 1100 (vs), 1036 (m), 1022 (m), 1004 (m), 846 (s), 834 (vs), 774 (m), 752 (m), 734 (m), 704 (vs).

MS (EI, 70 eV): *m/z* (%) = 363 (29), 361 (100, M+), 318 (28), 317 (20), 316 (92), 288 (21), 254 (29), 253 (99), 252 (24), 251 (31).

HRMS (EI): calcd. for $C_{22}H_{16}{}^{35}ClNO_2$: 361.0870, found: 361.0863.

4-Chloro-2-(phenylethynyl)benzaldehyde (**63g**)



Prepared according to **TP7** by treating sulfoxide **51i** (380 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and DMF (58 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/EtOAc, 50:1, silica gel) furnished **63g** as a neon yellow solid (179 mg, 93% yield).

m.p. (°C): 111-112.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 10.57 (s, 1H), 7.88 (d, *J* = 8.50 Hz, 1H), 7.63 (d, *J* = 2.19 Hz, 1H), 7.57-7.54 (m, 2H), 7.44-7.37 (m, 4H).

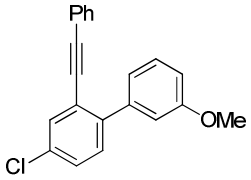
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 190.4 (CH), 140.3, 134.1, 132.9 (CH), 131.8 (CH), 129.4 (CH), 129.1 (CH), 128.7 (CH), 128.6 (CH), 128.3, 121.8, 97.5, 83.6.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2836 (w), 2216 (w), 1694 (vs), 1584 (m), 1550 (m), 1490 (m), 1458 (w), 1440 (w), 1396 (w), 1390 (w), 1276 (w), 1256 (w), 1194 (m), 1150 (w), 1108 (w), 1074 (m), 1026 (w), 896 (m), 874 (m), 822 (s), 750 (s), 686 (s), 616 (w).

MS (EI, 70 eV): *m/z* (%) = 242 (35), 240 (95, M^+), 212 (24), 206 (22), 205 (94), 177 (70), 176 (100), 151 (23), 150 (20), 88 (25).

HRMS (EI): calcd. for $C_{15}H_9{}^{35}ClO$: 240.0342, found: 240.0330.

4-Chloro-3'-methoxy-2-(phenylethynyl)-1,1'-biphenyl (**63h**)



Prepared according to **TP7** by treating sulfoxide **51i** (380 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and 3-bromoanisole (150 mg, 0.80 mmol) for the cross-coupling (50 °C, 4 h). Flash chromatographic purification (pentane, silica gel) furnished **63h** as a yellow oil (186 mg, 73% yield).

m.p. (°C): 153-155.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.63-7.62 (m, 1H), 7.39-7.34 (m, 4H), 7.33-7.28 (m, 4H), 7.21-7.20 (m, 1H), 7.20-7.19 (m, 1H), 6.95 (ddd, *J* = 8.19, 2.53, 0.97 Hz, 1H), 3.82 (s, 3H).

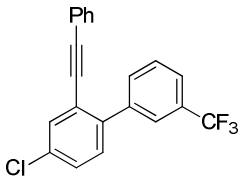
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 159.2, 142.1, 140.8, 132.9, 132.4 (CH), 131.4 (CH), 130.6 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 123.2, 122.9, 121.7 (CH), 114.7 (CH), 113.6 (CH), 93.4, 88.0, 55.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2934 (w), 2834 (w), 2218 (vw), 1598 (m), 1580 (m), 1550 (w), 1490 (m), 1464 (s), 1442 (m), 1428 (m), 1386 (m), 1292 (m), 1248 (m), 1208 (s), 1178 (m), 1092 (m), 1048 (m), 1020 (s), 898 (m), 878 (m), 822 (s), 780 (s), 754 (vs), 738 (m), 688 (vs), 664 (m).

MS (EI, 70 eV): *m/z* (%) = 320 (33), 318 (96, M^+), 283 (43), 268 (30), 265 (35), 252 (55), 240 (44), 239 (100), 214 (35), 119 (42).

HRMS (EI): calcd. for $C_{21}H_{15}{}^{35}ClO$: 318.0811, found: 318.0803.

4-Chloro-2-(phenylethynyl)-3'-(trifluoromethyl)-1,1'-biphenyl (**63i**)



Prepared according to **TP7** by treating sulfoxide **51i** (380 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and 3-bromo trifluoromethylbenzene (180 mg, 0.80 mmol) for the cross-coupling (50 °C, 5 h). Flash chromatographic purification (pentane, silica gel) furnished **63i** as a colourless solid (206 mg, 72% yield).

m.p. (°C): 65-66.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.94 (s, 1H), 7.78 (d, *J* = 7.50 Hz, 1H), 7.67-7.65 (m, 2H), 7.57 (dd, *J* = 7.94, 7.50 Hz, 1H), 7.39 (dd, *J* = 8.38, 1.99 Hz, 1H), 7.34 (d, *J* = 8.38 Hz, 1H), 7.32-7.28 (m, 5H).

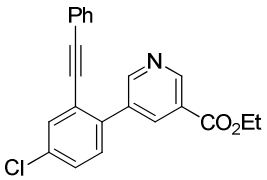
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 140.5, 140.2, 133.7, 132.6 (CH), 132.5 (q, *J* = 1.38 Hz, CH), 131.4 (CH), 130.6 (CH), 130.5 (q, *J* = 32.07 Hz), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 126.1 (q, *J* = 3.87 Hz, CH), 124.5 (q, *J* = 3.68 Hz, CH), 124.1 (q, *J* = 272.2 Hz, CF_3), 123.3, 122.5, 93.9, 87.3.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3080 (vw), 3024 (vw), 1596 (w), 1552 (w), 1432 (m), 1332 (vs), 1268 (m), 1236 (m), 1180 (m), 1160 (s), 1116 (vs), 1088 (s), 1076 (s), 1028 (m), 892 (s), 876 (m), 800 (s), 752 (s), 700 (s), 688 (s), 672 (m), 648 (m), 576 (m).

MS (EI, 70 eV): *m/z* (%) = 358 (30), 357 (18), 356 (100, M^+), 321 (41), 320 (40), 301 (25), 253 (17), 252 (94), 250 (20), 125 (15).

HRMS (EI): calcd. for $C_{21}H_{12}{}^{35}ClF_3$: 356.0580, found: 356.0578.

Methyl 5-(4-chloro-2-(phenylethynyl)phenyl)nicotinate (**63j**)



Prepared according to **TP7** by treating sulfoxide **51i** (380 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and methyl 5-bromonicotinate (173 mg, 0.80 mmol) for the cross-coupling (50 °C, 5 h). Flash chromatographic purification (pentane/EtOAc 7:3, silica gel) furnished **63j** as an off-white solid (170 mg, 59% yield).

m.p. (°C): 114-115.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 9.24 (s, 1H), 9.04 (s, 1H), 8.62 (s, 1H), 7.68 (d, *J* = 2.15 Hz, 1H), 7.42 (dd, J = 8.11, 2.27 Hz, 1H), 7.38 (d, *J* = 8.11 Hz, 1H), 7.35-7.34 (m, 2H), 7.31-7.27 (m, 3H), 3.95 (s, 3H).

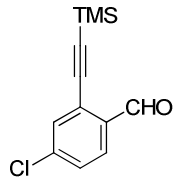
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 165.7, 153.3 (CH), 149.7 (CH), 137.4 (CH), 137.2, 135.0, 134.5, 132.8 (CH), 131.5 (CH), 130.4 (CH), 129.1 (CH), 128.9 (CH), 128.4 (CH), 125.4, 123.7, 122.2, 94.4, 86.8, 52.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3108 (vw), 3080 (vw), 3052 (vw), 2952 (w), 2216 (w), 1912 (vw), 1880 (vw), 1724 (vs), 1588 (w), 1496 (m), 1444 (m), 1392 (w), 1324 (s), 1268 (s), 1240 (m), 1156 (m), 1120 (m), 1092 (m), 1028 (m), 964 (m), 896 (m), 884 (m), 824 (s), 764 (s), 748 (s), 736 (m), 708 (s), 680 (vs), 648 (m), 584 (m).

MS (EI, 70 eV): *m/z* (%) = 348 (44), 347 (91, M^+), 346 (100), 332 (19), 288 (24), 254 (20), 252 (16), 251 (17), 226 (18), 224 (13).

HRMS (EI): calcd. for $C_{21}H_{14}ClNO_2$: 347.0713, found: 347.0706.

4-Chloro-2-((trimethylsilyl)ethynyl)benzaldehyde (**63k**)



Prepared according to **TP7** by treating sulfoxide **51j** (376 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and DMF (58 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane, silica gel) furnished **63k** as a yellow oil (169 mg, 89% yield).

m.p. (°C): 66-68.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 10.46 (s, 1H), 7.83 (d, *J* = 8.38 Hz, 1H), 7.55 (d, *J* = 1.98 Hz, 1H), 7.39 (dd, *J* = 8.38, 1.98 Hz, 1H), 0.27 (s 9H).

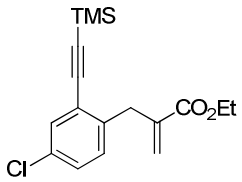
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 190.5 (CH), 140.1, 134.5, 133.2 (CH), 129.3 (CH), 128.3 (CH), 128.2, 104.0, 98.6, -0.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2958 (vw), 2160 (vw), 1690 (m), 1584 (m), 1552 (w), 1460 (w), 1388 (w), 1248 (m), 1212 (m), 1080 (w), 898 (m), 876 (m), 844 (vs), 832 (vs), 814 (s), 760 (s), 702 (w), 688 (w), 646 (w), 622 (w).

MS (EI, 70 eV): *m/z* (%) = 221 (80), 162 (38), 115 (32), 78 (57), 73 (100), 65 (35), 63 (93), 53 (37), 45 (30), 43 (73).

HRMS (EI): calcd. for $C_{12}H_{13}{}^{35}ClO^{28}Si$: 236.0424, found: 236.0413.

Ethyl 2-(4-chloro-2-((trimethylsilyl)ethynyl)benzyl)acrylate (**63l**)



Prepared according to **TP7** by treating sulfoxide **51j** (376 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with CuCN·2LiCl (0.05 mL, 0.05 mmol, 1.00 M in THF) and ethyl 2-(bromomethyl)acrylate (154 mg, 0.80 mmol) for the allylation (-20 °C, 30 min). Flash chromatographic purification (pentane/Et_2O, 20:1, silica gel) furnished **63l** as a yellow oil (224 mg, 87% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.43 (d, *J* = 2.23 Hz, 1H), 7.21 (dd, *J* = 8.17, 2.23 Hz, 1H), 7.14 (d, *J* =8.17 Hz, 1H), 6.24 (d, *J* = 1.24 Hz, 1H), 5.40 (d, *J* = 1.24 Hz, 1H), 4.19 (q, *J* = 7.18 Hz, 2H), 3.76 (s, 2H), 1.27 (t, *J* = 7.18 Hz, 3H), 0.22 (s, 9H).

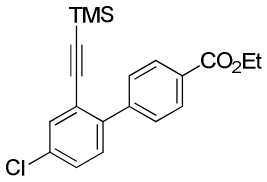
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.7, 139.6, 138.7, 132.1 (CH), 131.9, 130.7 (CH), 128.7 (CH), 126.4 (CH_2), 124.8, 102.2, 99.9, 60.8 (CH_2), 35.7 (CH_2), 14.2 (CH_3), -0.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2960 (w), 2160 (w), 1716 (m), 1632 (w), 1592 (w), 1482 (w), 1392 (w), 1368 (w), 1300 (w), 1278 (w), 1250 (m), 1196 (w), 1178 (w), 1138 (m), 1114 (w), 1088 (w), 1028 (w), 948 (w), 932 (w), 898 (s), 840 (vs), 758 (m), 700 (w), 644 (m).

MS (EI, 70 eV): *m/z* (%) = 291 (56), 277 (42), 231 (32), 174 (34), 153 (40), 152 (30), 139 (27), 75 (68), 73 (100), 59 (24).

HRMS (EI): calcd. for $C_{17}H_{21}{}^{35}ClO_2{}^{28}Si$: 320.0999, found: 320.1015.

Ethyl 4'-chloro-2'-((trimethylsilyl)ethynyl)-[1,1'-biphenyl]-4-carboxylate (**63m**)



Prepared according to **TP7** by treating sulfoxide **51j** (376 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and ethyl 4-iodobenzoate (221 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/EtOAc 50:1, silica gel) furnished **63m** as a yellow oil (240 mg, 84% yield).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.08-8.06 (m, 2H), 7.64-7.62 (m, 2H), 7.57 (d, *J* = 2.23 Hz, 1H), 7.35 (dd, *J* = 8.42, 2.23 Hz, 1H), 7.29 (d, *J* = 8.42 Hz, 1H), 4.40 (q, *J* = 7.18 Hz, 2H), 1.41 (t, *J* = 7.18 Hz, 3H), 0.12 (s, 9H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 166.4, 143.6, 141.4, 133.4, 133.0 (CH), 130.5 (CH), 129.7, 129.2 (CH), 129.1 (CH), 129.0 (CH), 123.0, 102.7, 99.7, 61.0 (CH_2), 14.3 (CH_3), -0.5 (CH_3).

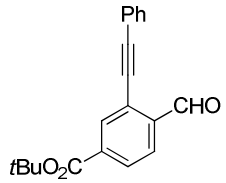
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2960 (w), 2156 (vw), 1716 (s), 1610 (w), 1476 (w), 1464 (w), 1410 (w), 1384 (w), 1368 (w), 1272 (s), 1250 (s), 1182 (m), 1100 (s), 1026 (m), 1004 (m), 896 (s), 840 (vs), 822 (s), 774 (s), 758 (m), 734 (m), 704 (m), 646 (m).

MS (EI, 70 eV): *m/z* (%) = 356 (55, M^+), 341 (32), 313 (37), 299 (42), 298 (27), 297 (100), 189 (33), 75 (36), 44 (57), 43 (38).

HRMS (EI): calcd. for $C_{20}H_{21}{}^{35}ClO_2{}^{28}Si$: 356.0999, found: 356.1002.

3.1.5 Preparation of Trisubstituted Arenes 64 by Sulfoxide-Magnesium Exchange on Sulfoxides 51

Tert-butyl 4-formyl-3-(phenylethynyl)benzoate (**64a**)



Prepared according to **TP7** by treating sulfoxide **51k** (432 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and DMF (58 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 20:1, silica gel) furnished **64a** as a yellow oil (173 mg, 71% yield).

m.p. (°C): 98-100.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 10.67 (s, 1H), 8.22 (s, 1H), 8.01 (d, *J* = 8.15 Hz, 1H), 7.96 (d, *J* = 8.01 Hz, 1H), 7.58-7.56 (m, 2H), 7.41-7.38 (m, 3H), 1.61 (s, 9H).

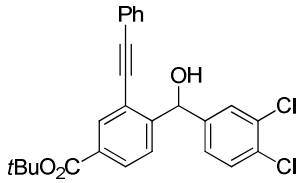
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) =191.2 (CH), 164.0, 137.9, 136.6, 134.3 (CH), 131.7 (CH), 129.3 (CH), 129.1 (CH), 128.5 (CH), 127.2 (CH), 126.8, 122.0, 96.9, 84.3, 82.3, 28.1 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 2846 (w), 2214 (vw), 1694 (vs), 1602 (w), 1564 (w), 1492 (w), 1390 (w), 1368 (w), 1316 (m), 1282 (m), 1268 (m), 1256 (m), 1194 (w), 1170 (m), 1148 (m), 1120 (w), 1110 (m), 1080 (w), 910 (w), 850 (w), 756 (vs), 688 (m).

MS (EI, 70 eV): *m/z* (%) = 251 (14), 250 (100), 233 (17), 205 (23), 177 (9), 176 (12), 85 (9), 71 (13), 57 (27), 43 (11).

HRMS (EI): calcd. for $C_{20}H_{18}O_3$: 306.1256, found: 306.1243.

Tert-butyl 4-((3,4-dichlorophenyl)(hydroxy)methyl)-3-(phenylethynyl)benzoate (**64b**)



Prepared according to **TP7** by treating sulfoxide **51k** (432 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and 3,4-dichlorobenzaldehyde (140 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 10:1, silica gel) furnished **64b** as a colourless solid (305 mg, 84% yield).

m.p. (°C): 117-119.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.10 (d, *J* = 1.83 Hz, 1H), 7.95 (dd, *J* = 8.15, 1.83 Hz, 1H), 7.63 (d, *J* = 8.15 Hz, 1H), 7.57 (d, *J* = 2.01 Hz, 1H), 7.49-7.46 (m, 2H), 7.39-7.34 (m, 4H), 7.23 (dd, *J* = 8.42, 2.01 Hz, 1H), 6.31 (s, 1H), 2.83 (s, 1H), 1.58 (s, 9H).

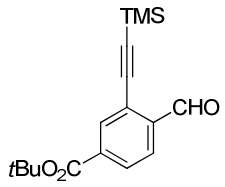
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 164.8, 148.4, 142.7, 133.6, 132.5 (CH), 131.7 (CH), 131.6 (CH), 131.5 (CH), 130.4 (CH), 129.8 (CH), 128.9 (CH), 128.7 (CH), 128.5 (CH), 126.1, 126.0, 122.3, 121.2, 95.6, 86.3, 81.7, 72.7 (CH), 28.1 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3522 (w), 3486 (w), 2976 (vw), 1692 (m), 1468 (w), 1410 (m), 1384 (m), 1366 (m), 1316 (m), 1288 (s), 1254 (m), 1164 (m), 1148 (s), 1130 (s), 1090 (m), 1054 (m), 1028 (m), 942 (w), 912 (w), 892 (w), 846 (m), 800 (m), 774 (m), 748 (vs), 688 (m).

MS (EI, 70 eV): *m/z* (%) = 398 (62), 397 (27), 396 (100), 379 (23), 353 (31), 351 (40), 318 (21), 252 (23), 250 (28), 57 (18).

HRMS (EI): calcd. for $C_{26}H_{22}{}^{35}Cl_2O_3$: 452.0946, found: 452.0943.

4-Formyl-3-trimethylsilanylethynyl-benzoic acid *tert*-butyl ester (**64c**)



Prepared according to **TP7** by treating sulfoxide **51l** (429 mg, 1.00 mmol) with *i*PrMgCl·LiCl (1.10 mmol, 0.92 mL, 1.20 M in THF) at -50 °C for 5 min and DMF (58 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 20:1, silica gel) furnished **64c** as a colourless solid (189 mg, 78% yield).

m.p. (°C): 116-118.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 10.56 (d, J = 0.77 Hz, 1 H), 8.13 (dd, J = 1.65, 0.69 Hz, 1 H), 7.98 (ddd, J = 8.15, 1.65, 0.77 Hz, 1 H), 7.91 (dd, J = 8.15, 0.69 Hz, 1 H), 1.59 (s, 9 H), 0.27 (s, 9 H).

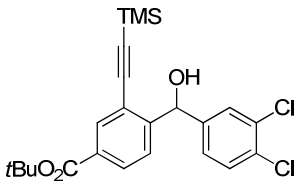
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 191.3 (CH), 164.0, 138.3, 136.4, 134.5 (CH), 129.3 (CH), 126.8 (CH), 126.6, 103.3, 99.3, 82.3, 28.1 (CH_3), –0.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2977 (w), 1716 (s), 1693 (s), 1600 (w), 1390 (m), 1371 (m), 1365 (w), 1300 (m), 1247 (m), 1213 (m), 1186 (w), 1161 (m), 1113 (m), 1106 (m), 1087 (w), 941 (w), 842 (vs), 825 (m), 810 (m), 758 (s), 667 (w).

MS (EI, 70 eV): *m/z* (%) = 246 (57), 233 (21). 232 (100), 231 (24), 229 (83), 201 (93), 186 (19), 107 (26), 73 (23), 57 (49).

HRMS (EI): calcd. for $C_{17}H_{22}O_3{}^{28}Si$: 302.1338, found: 302.1344.

Tert-butyl 4-((3,4-dichlorophenyl)(hydroxy)methyl)-3-((trimethylsilyl)ethynyl)benzoate (**64d**)



Prepared according to **TP7** by treating sulfoxide **51l** (429 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and 3,4-dichlorobenzaldehyde (140 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 4:1, silica gel) furnished **64d** as a colourless solid (294 mg, 82% yield).

m.p. (°C): 114-116.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.01 (d, J = 1.83 Hz, 1H), 7.92 (dd, J = 8.15, 1.83 Hz, 1H), 7.58 (d, J = 8.15 Hz, 1H), 7.53 (d, J = 1.99 Hz, 1H), 7.35 (d, J = 8.24 Hz, 1H), 7.21 (dd, J = 8.24, 1.99 Hz, 1H), 6.22 (s, 1H), 2.90 (s, 1H), 1.57 (s, 9H), 0.24 (s, 9H).

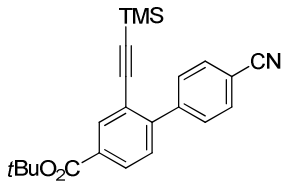
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 164.7, 148.9, 142.7, 133.9, 132.4 (CH), 131.6 (CH), 131.4 (CH), 130.3 (CH), 130.0 (CH), 128.7 (CH), 125.9, 120.9, 102.0, 101.6, 81.6, 72.6 (CH), 44.7, 28.1 (CH_3), -0.20 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3478 (w), 2968 (vw), 2156 (vw), 1694 (m), 1568 (vw), 1466 (w), 1392 (w), 1370 (w), 1314 (s), 1252 (m), 1160 (m), 1122 (m), 1100 (w), 1052 (m), 1032 (w), 948 (w), 890 (w), 842 (vs), 806 (m), 772 (m), 760 (m), 752 (m), 664 (w).

MS (EI, 70 eV): *m/z* (%) = 393 (73), 392 (38), 391 (100), 377 (46), 320 (36), 319 (57), 302 (37), 274 (34), 57 (36), 43 (67).

HRMS (EI): calcd. for $C_{23}H_{26}{}^{35}Cl_2O_3{}^{28}Si$: 448.1028, found: 448.1031.

Tert-butyl 4'-cyano-2-((trimethylsilyl)ethynyl)-[1,1'-biphenyl]-4-carboxylate (**64e**)



Prepared according to **TP7** by treating sulfoxide **51l** (429 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and 4-iodobenzonitrile (183 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 20:1, silica gel) furnished **64e** as a colourless crystals (232 mg, 77% yield).

m.p. (°C): 98-100.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.12 (d, *J* = 1.79 Hz, 1H), 7.98 (dd, *J* = 8.11, 1.79 Hz, 1H), 7.73-7.68 (m, 4H), 7.39 (d, *J* = 8.11 Hz, 1H), 1.60 (s, 9H), 0.13 (s, 9H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 164.5, 145.4, 144.0, 134.5, 131.8 (CH), 131.6 (CH), 130.0 (CH), 129.6 (CH), 129.1 (CH), 121.6, 118.8, 111.6, 102.9, 99.5, 81.7, 28.1 (CH_3), -0.50 (CH_3).

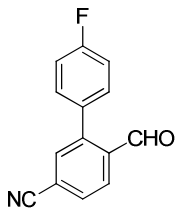
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2960 (vw), 2228 (w), 2164 (vw), 1710 (m), 1602 (w), 1480 (w), 1368 (w), 1310 (m), 1284 (w), 1250 (m), 1206 (w), 1162 (m), 1126 (m), 946 (vw), 920 (vw), 834 (vs), 770 (m), 760 (m), 748 (m), 698 (w), 646 (w).

MS (EI, 70 eV): *m/z* (%) = 375 (100, M^+), 361 (25), 360 (90), 319 (41), 305 (97), 304 (88), 304 (77), 302 (49), 258 (40), 57 (25).

HRMS (EI): calcd. for $C_{23}H_{25}NO_2{}^{28}Si$: 375.1655, found: 375.1648.

3.1.6 Preparation of Trisubstituted Arenes 65 by Sulfoxide-Magnesium Exchange on Sulfoxides 51

4'-Fluoro-6-formyl-[1,1'-biphenyl]-3-carbonitrile (**65a**)



Prepared according to **TP7** by treating sulfoxide **51m** (351 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and DMF (58 mg,

0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 10:1, silica gel) furnished **65a** as a colourless solid (129 mg, 72% yield).

m.p. (°C): 116-118.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 10.01 (d, J = 0.73 Hz, 1H), 8.12 (dd, J = 8.02, 0.49 Hz, 1H), 7.82-7.79 (m, 1H), 7.78-7.77 (m, 1H), 7.42-7.36 (m, 2H), 7.29-7.21 (m, 2H).

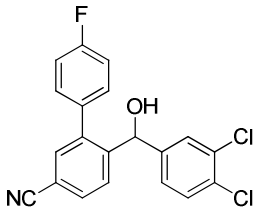
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 190.4 (CH), 163.3 (d, J = 250.0 Hz, CF), 145.0, 136.2, 134.5 (d, J = 1.03 Hz), 131.6 (d, J = 8.51 Hz, CH), 131.5 (d, J = 3.35 Hz, CH), 131.1 (CH), 128.6 (CH), 117.6, 116.9, 116.1 (d, J = 22.01 Hz, CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3040 (w), 2857 (m), 2230 (m), 1691 (vs), 1659 (m), 1602 (s), 1507 (s), 1478 (m), 1415 (m), 1390 (m), 1259 (m), 1226 (s), 1197 (s), 1160 (m), 1118 (m), 1101 (m), 1007 (m), 920 (m), 832 (vs), 819 (m), 777 (m).

MS (EI, 70 eV): *m/z* (%) = 226 (10), 225 (93, M^+), 224 (100), 197 (20), 196 (26), 195 (19), 170 (7), 169 (15), 168 (6), 129 (8).

HRMS (EI): calcd. for $C_{14}H_8FNO$: 225.0590, found: 225.0585.

6-((3,4-Dichlorophenyl)hydroxymethyl)-4'-fluorobiphenyl-3-carbonitrile (**65b**)



Prepared according to **TP7** by treating sulfoxide **51m** (351 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and 3,4-dichlorobenzaldehyde (140 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 7:3, silica gel) furnished **65b** as a clear oil (262 mg, 88% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.89 (d, J = 8.26 Hz, 1H), 7.82 (dd, J = 8.26, 1.70 Hz, 1H), 7.62 (d, J = 1.46 Hz, 1H), 7.44-7.38 (m, 2H), 7.23-7.21 (m, 4H), 6.95 (dd, J = 8.26, 2.19 Hz, 1H), 5.97 (s, 1H).

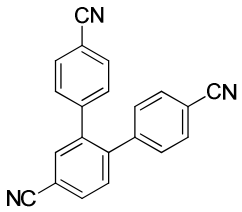
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.7 (d, J = 248.7 Hz, CF), 145.3, 142.5, 141.1, 134.1 (J = 3.61 Hz, CH), 133.7 (d, J = 1.03 Hz), 132.7, 132.1, 131.7 (CH), 130.7 (CH), 130.5 (CH), 128.7 (CH), 127.7 (CH), 125.9 (CH), 118.2, 115.7 (d, J = 21.65 Hz, CH), 111.9, 71.3 (CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3420 (m), 2230 (s), 1604 (m), 1510 (vs), 1483 (m), 1467 (s), 1394 (m), 1222 (s), 1186 (m), 1158 (m), 1130 (m), 1044 (m), 1029 (s), 1015 (m), 900 (w), 836 (s), 811 (m), 736 (m), 615 (w), 596 (w).

MS (EI, 70 eV): *m/z* (%) = 373 (28), 371 (45, M^+), 355 (29), 353 (36), 320 (37), 318 (100), 282 (18), 224 (76), 208 (43), 172 (18).

HRMS (EI): calcd. for $C_{20}H_{12}{}^{35}Cl_2FNO$: 371.0280, found: 371.0274.

[1,1':2',1"-Terphenyl]-4,4',4"-tricarbonitrile (**65c**)



Prepared according to **TP7** by treating sulfoxide **51n** (357 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and 4-iodobenzonitrile (183 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 1:1, silica gel) furnished **65c** as a colourless solid (155 mg, 64% yield).

m.p. (°C): 202-203.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.79 (dd, *J* = 8.06, 1.47 Hz, 1H), 7.72 (d, *J* = 1.47 Hz, 1H), 7.58-7.56 (m, 4H), 7.55 (d, *J* = 8.06 Hz, 1H), 7.21-7.19 (m, 4H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 143.4, 143.1, 143.0, 139.8, 133.9 (CH), 132.4 (CH), 132.3, (CH) 132.3 (CH), 132.1, 131.4 (CH), 130.2 (CH), 130.1 (CH), 118.1, 117.8, 112.9, 112.1, 112.0.

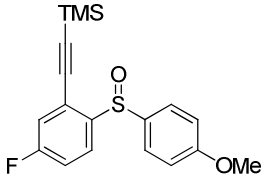
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2918 (vw), 2228 (m), 1936 (vw), 1818 (vw), 1706 (vw), 1602 (w), 1504 (vw), 1480 (w), 1390 (w), 1178 (vw), 1006 (vw), 902 (w), 860 (m), 838 (vs), 644 (vw), 614 (m).

MS (EI, 70 eV): *m/z* (%) = 306 (29), 305 (100, M^+), 304 (53), 290 (11), 278 (17), 277 (13), 276 (18), 265 (55), 250 (13), 44 (12).

HRMS (EI): calcd. for $C_{21}H_{11}N_3$: 305.0953, found: 305.0940.

3.1.7 Large Scale Preparation of Trisubstituted Arenes 67, 69 using the Two-Step Protocol

((5-Fluoro-2-((4-methoxyphenyl)sulfinyl)phenyl)ethynyl)trimethylsilane (**66**)



Prepared according to **TP6** from sulfoxide **49e** (10.2 g, 40.0 mmol), with $Pd(PPh_3)_4$ (0.88 g, 0.80 mmol) and trimethylsilylacetylene (4.32 g, 44.0 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 1:1, silica gel) furnished **66** as a colourless solid (11.9 g, 86% yield).

m.p. (°C): 83-85.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.02 (dd, *J* = 8.80, 5.67 Hz, 1H), 7.63-7.59 (m, 2H), 7.24-7.20 (m, 1H), 7.13 (dd, *J* = 8.80, 2.35 Hz, 1H), 6.92-6.89 (m, 2H), 3.80 (s, 3H), 0.26 (s, 9H).

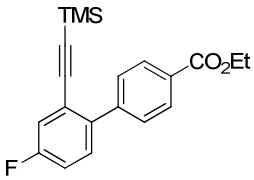
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.3 (d, *J* = 251.4 Hz, CF), 162.0, 143.1 (d, *J* = 3.11 Hz), 136.3 (d, *J* = 1.17 Hz), 127.8 (CH), 125.8 (d, *J* = 9.34 Hz), 122.2 (d, *J* = 10.32 Hz, CH), 120.0 (d, *J* = 24.13 Hz, CH), 117.0 (d, *J* = 22.19 Hz, CH), 114.5 (CH), 104.9, 99.9 (d, *J* = 2.72 Hz), 55.4 (CH_3), -0.42 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 2161 (w), 1738 (m), 1591 (m), 1576 (m), 1495 (m), 1457 (s), 1365 (m), 1305 (m), 1249 (vs), 1217 (m), 1148 (m), 1083 (s), 1058 (s), 1037 (s), 952 (s), 846 (vs), 833 (vs), 821 (vs), 760 (s), 647 (m), 607 (m).

MS (EI, 70 eV): *m/z* (%) = 346 (40, M^+), 332 (24), 331 (100), 330 (14), 316 (14), 245 (13), 155 (14), 139 (14), 123 (15), 73 (88).

HRMS (EI): calcd. for $C_{18}H_{19}FO_2{}^{32}S^{28}Si$: 346.0859, found: 346.0863

Ethyl 4'-fluoro-2'-((trimethylsilyl)ethynyl)-[1,1'-biphenyl]-4-carboxylate (**67**)



Prepared according to **TP7** by treating sulfoxide **66** (11.7 g, 34.0 mmol) with *i*PrMgCl·LiCl (31.2 mL, 37.4 mmol, 1.20 M in THF) at -50 °C for 5 min, with $Pd(PPh_3)_4$ (748 mg, 0.68 mmol) and ethyl 4-iodobenzoate (7.51 g, 27.2 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 50:1, silica gel) furnished **67** as a colourless oil (5.29 g, 86% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.07-8.03 (m, 2H), 7.61-7.57 (m, 2H), 7.30-7.22 (m, 2H), 7.07-7.00 (m, 1H), 4.38 (q, *J* = 7.11 Hz, 2H), 1.38 (t, *J* = 7.11 Hz, 3H), 0.11 (s, 9H).

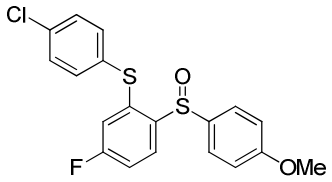
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.3, 161.6 (d, *J* = 248.2 Hz, CF), 143.8, 139.2 (d, *J* = 3.35 Hz), 130.9 (d, *J* = 8.76 Hz), 129.4, 129.2 (CH), 129.0 (CH), 123.1 (d, *J* = 9.54 Hz, CH), 119.7 (d, *J* = 22.68 Hz, CH), 116.1 (d, *J* = 21.39 Hz, CH), 102.8, 99.3, 60.9 (CH_2), 14.3 (CH_3), -0.56 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2961 (w), 2898 (w), 2156 (w), 1716 (w), 1610 (w), 1475 (m), 1395 (w), 1367 (w), 1269 (vs), 1250 (s), 1180 (m), 1156 (m), 1099 (s), 1026 (m), 959 (s), 840 (vs), 775 (s), 758 (s), 704 (s), 649 (m).

MS (EI, 70 eV): *m/z* (%) = 341 (16), 340 (61, M^+), 325 (37), 297 (28), 295 (19), 282 (24), 280 (100), 189 (16), 140 (28), 75 (17).

HRMS (EI): calcd. for $C_{20}H_{21}FO_2{}^{28}Si$: 340.1295, found: 340.1295.

(4-Chlorophenyl)(5-fluoro-2-((4-methoxyphenyl)sulfinyl)phenyl)sulfane (**68**)



Prepared according to **TP4** from sulfoxide **49e** (10.2 g, 40.0 mmol), and (*S*)-(4-chlorophenyl)benzene thiosulfonate (13.7 g, 48.0 mmol, 25 °C, 1 h). Flash chromatographic purification (pentane/Et_2O 3:7, silica gel) furnished **51o** as a colourless solid (13.7 g, 87% yield).

m.p. (°C): 119-120.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.11 (dd, *J* = 8.70, 5.72 Hz, 1H), 7.57 (d, *J* = 8.11 Hz, 2H), 7.21 (d, *J* = 8.58 Hz, 2H), 7.17 (dd, *J* = 5.72, 2.15 Hz, 1H), 7.03 (d, *J* = 8.11 Hz, 2H), 6.86 (d, *J* = 8.58 Hz, 2H), 6.81 (dd, *J* = 8.70, 2.15 Hz, 1H), 3.77 (s, 3H).

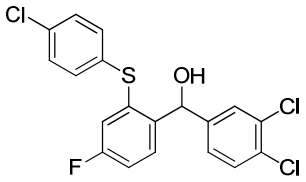
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 164.1 (d, *J* = 253.7 Hz, CF), 162.1, 141.8 (d, *J* = 2.92 Hz), 135.6 (d, *J* = 1.33 Hz), 135.4 (d, *J* = 8.21 Hz), 134.3, 132.5 (CH), 131.5, 129.7 (CH), 128.4 (CH), 127.0 (d, *J* = 9.27 Hz, CH), 119.3 (d, *J* = 24.11 Hz, CH), 116.0 (d, *J* = 22.25 Hz, CH), 114.6 (CH), 55.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2980 (vw), 1588 (m), 1572 (m), 1496 (m), 1474 (m), 1452 (m), 1414 (w), 1384 (w), 1308 (m), 1262 (s), 1202 (m), 1178 (m), 1088 (s), 1082 (s), 1044 (s), 1024 (s), 1012 (s), 888 (m), 862 (w), 842 (s), 818 (vs), 798 (s), 746 (w).

MS (EI, 70 eV): *m/z* (%) = 392 (45), 376 (45), 265 (100), 236 (22), 234 (90), 232 (27), 218 (26), 202 (44), 155 (58), 123 (78).

HRMS (EI): calcd. for $C_{19}H_{14}{}^{35}ClFO_2{}^{32}S_2$: 392.0108, found: 392.0100..

(2-((4-Chlorophenyl)thio)-4-fluorophenyl)(3,4-dichlorophenyl)methanol (**69**)



Prepared according to **TP7** by treating sulfoxide **68** (13.1 g, 33.3 mmol) with *i*PrMgCl·LiCl (30.5 mL, 36.6 mmol, 1.20 M in THF) at -50 °C for 15 min and 3,4-dichlorobenzaldehyde (46.6 g, 26.6 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 10:1, silica gel) furnished **69** as a yellow oil (5.40 g, 49% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.47 (dd, *J* = 8.80, 5.95 Hz, 1H), 7.39 (d, *J* = 1.98 Hz, 1H), 7.34 (d, *J* = 8.42 Hz, 1H), 7.29-7.24 (m, 2H), 7.16-7.11 (m, 3H), 7.02-6.96 (m, 1H), 6.88 (dd, *J* = 8.80, 2.48 Hz, 1H), 6.19 (s, 1H), 2.79 (s, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.2 (d, *J* = 250.2 Hz, CF), 142.6, 138.7 (d, *J* = 3.09 Hz), 135.4 (d, *J* = 7.73 Hz), 134.0, 132.5, 132.4 (CH), 132.3, 131.7, 130.3 (CH), 129.7 (CH), 129.2 (d, *J* = 8.50 Hz, CH), 128.8 (CH), 126.1 (CH), 118.9 (d, *J* = 23.46 Hz, CH), 115.2 (d, *J* = 21.39 Hz, CH), 71.5 (CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3310 (w), 2962 (w), 1898 (vw), 1596 (m), 1576 (m), 1474 (vs), 1388 (m), 1260 (m), 1220 (s), 1192 (m), 1172 (m), 1130 (m), 1092 (s), 1050 (m), 1028 (s), 1012 (vs), 908 (m), 878 (m), 814 (vs), 790 (s), 746 (m), 714 (w), 674 (m).

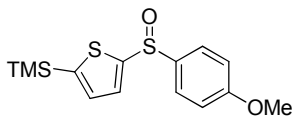
MS (EI, 70 eV): *m/z* (%) = 414 (55), 412 (58, M^+), 361 (40), 359 (57), 299 (27), 267 (44), 265 (100), 249 (42), 235 (32), 233 (99).

HRMS (EI): calcd. for $C_{19}H_{12}{}^{35}Cl_3FO^{32}S$: 411.9658, found: 411.9645.

3.2 Preparation of Disubstituted 5-Membered Heterocycles 76 via Directed Metalation and Sulfoxide-Magnesium Exchange

3.2.1 Preparation of Hetaryl Sulfoxides 74

(5-((4-Methoxyphenyl)sulfinyl)thiophen-2-yl)trimethylsilane (**74a**)



Prepared according to **TP3** from 2-thiophenyl(trimethyl)silane (**73**; 7.10 g, 50.0 mmol), *n*BuLi (23.3 mL, 55.0 mmol, 2.36 M in hexane) and 4-methoxybenzenesulfinyl chloride (**58**; 14.3 g, 75.0 mmol). Flash chromatographical purification (pentane/Et_2O 6:4, silica gel) furnished **74a** as an orange oil (13.2 g, 85% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.62-7.57 (m, 2H), 7.48 (d, *J* = 3.37 Hz, 1H), 7.11 (d, *J* = 3.37 Hz, 1H), 6.98-6.93 (m, 2H), 3.78 (s, 3H), 0.24 (s, 9H).

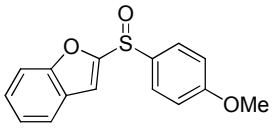
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 161.8, 152.5, 148.3, 136.0, 133.6 (CH), 131.4 (CH), 126.2 (CH), 114.5 (CH), 55.3 (CH), -0.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 1592 (m), 1578 (m), 1494 (s), 1462 (w), 1442 (w), 1408 (w), 1302 (m), 1248 (s), 1206 (m), 1180 (w), 1170 (m), 1086 (s), 1046 (s), 1026 (m), 1000 (s), 978 (m), 828 (vs), 796 (s), 756 (s), 740 (m), 698 (w), 624 (m).

MS (EI, 70 eV): *m/z* (%) = 295 (11), 264 (17), 263 (40), 262 (100), 249 (17), 248 (38), 247 (96), 139 (24), 123 (13), 73 (24).

HRMS (EI): calcd. for $C_{14}H_{18}O_2{}^{32}S_2{}^{28}Si$: 310.0517, found: 310.0528.

2-((4-Methoxyphenyl)sulfinyl)-1-benzofuran (**74b**)



Prepared according to **TP3** from benzofuran (11.8 g, 100 mmol), *n*BuLi (46.6 mL, 110 mmol, 2.36 M in hexane) and 4-methoxybenzenesulfinyl chloride (**58**, 24.8 g, 130 mmol). Flash chromatographical purification (pentane/Et_2O 1:1, silica gel) furnished **74b** as a brown solid (12.7 g, 47%).

m.p. (°C): 52-54.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.75-7.70 (m, 2H), 7.61-7.58 (m, 1H), 7.46-7.43 (m, 1H), 7.37-7.31 (m, 1H), 7.28-7.22 (m, 1H), 7.16 (s, 1H), 7.04-7.00 (m, 2H), 3.83 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.5, 156.6, 156.3, 132.3, 127.3 (CH), 126.6 (CH), 126.5, 123.7 (CH), 122.2 (CH), 114.9 (CH), 112.0 (CH), 110.5 (CH), 55.5 (CH_3).

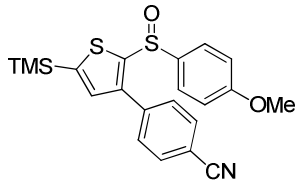
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3092 (w), 1594 (m), 1578 (m), 1532 (w), 1494 (s), 1462 (m), 1442 (m), 1408 (w), 1306 (m), 1254 (s), 1232 (s), 1170 (s), 1086 (s), 1072 (s), 1048 (vs), 1022 (s), 920 (m), 878 (m), 812 (m), 790 (s), 752 (vs), 634 (m).

MS (EI, 70 eV): *m/z* (%) = 256 (13), 225 (49), 224 (96), 210 (17), 209 (83), 181 (33), 152 (11), 139 (100), 112 (12), 77 (11).

HRMS (EI): calcd. for $C_{15}H_{12}O_3{}^{32}S$: 272.0507, found: 272.0510.

3.2.2 Preparation of sulfoxides 75 by deprotonation of sulfoxides 74

4-(2-((4-Methoxyphenyl)sulfinyl)-5-(trimethylsilyl)thiophen-3-yl)benzonitrile (**75a**)



Prepared according to **TP5** by treating sulfoxide **74a** (2.17 g, 7.00 mmol), with tmpMgCl·LiCl (19.8 mL, 22.0 mmol, 1.11 M in THF) at -30 °C for 20 min, with $ZnCl_2$ (22.0 mL, 22.0 mmol, 1.0 M in THF), $Pd(PPh_3)_4$ (0.15 g, 0.14 mmol) and 4-iodobenzonitrile (1.93 g, 8.40 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 1:1, silica gel) furnished **75a** as an off-white solid (2.57 g, 89% yield).

m.p. (°C): 152-154.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.74-7.67 (m, 3H), 7.37-7.31 (m, 1H), 7.57-7.52 (m, 2H), 7.18 (s, 1H), 6.99-6.94 (m, 2H), 3.82 (s, 3H), 0.28 (s, 9H).

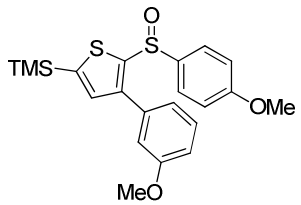
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.0, 149.3, 148.3, 145.2, 138.7, 135.5, 134.9 (CH), 132.3 (CH), 129.9 (CH), 126.5 (CH), 118.5, 114.5 (CH), 111.8, 55.4 (CH_3), -0.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 2224 (w), 1592 (m), 1578 (m), 1492 (m), 1462 (w), 1440 (w), 1406 (w), 1332 (vw), 1300 (w), 1248 (s), 1180 (w), 1170 (m), 1084 (m), 1048 (s), 992 (s), 830 (vs), 796 (s), 756 (s), 702 (w), 664 (w), 628 (m).

MS (EI, 70 eV): *m/z* (%) = 395 (10), 365 (9), 364 (24), 363 (100), 349 (14), 348 (53), 154 (8), 138 (14), 123 (8), 73 (18).

HRMS (EI): calcd. for $C_{21}H_{21}NO_2{}^{32}S_2{}^{28}Si$: 411.0783, found: 411.0769.

(4-(3-Methoxyphenyl)-5-((4-methoxyphenyl)sulfinyl)furan-2-yl)trimethylsilane (**75b**)



Prepared according to **TP5** by treating sulfoxide **74a** (6.20 g, 20.0 mmol) with tmpMgCl·LiCl (19.8 mL, 22.0 mmol, 1.11 M in THF) at -30 °C for 20 min, with $ZnCl_2$ (22.0 mL, 22.0 mmol, 1.00 M in THF), $Pd(PPh_3)_4$ (0.46 g, 0.40 mmol) and 3-iodoanisole (5.61 g, 24.0 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O, 7:3, silica gel) furnished **75b** as an orange solid (7.28 g, 87% yield).

m.p. (°C): 107-108.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.63-7.59 (m, 1H), 7.45-7.44 (m, 1H), 7.35-7.32 (m, 1H), 7.21 (s, 1H), 6.86 (ddd, *J* = 8.22, 2.55, 0.98 Hz, 1H), 6.58-6.54 (m, 2H), 3.43 (s, 3H), 3.08 (s, 3H), -0.08 (s, 9H).

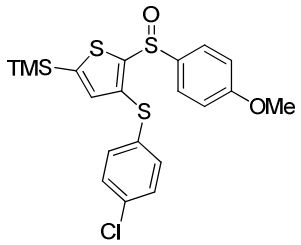
^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 162.0, 160.4, 150.6, 147.8, 146.5, 137.4, 136.5 (CH), 136.4, 130.1 (CH), 126.7 (CH), 122.1 (CH), 115.2 (CH), 114.8 (CH), 114.7 (CH), 55.0 (CH_3), 54.8 (CH_3), -0.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2952 (w), 1594 (m), 1490 (m), 1466 (m), 1344 (w), 1308 (w), 1244 (vs), 1202 (w), 1186 (w), 1086 (m), 1036 (s), 1018 (m), 1000 (s), 926 (m), 836 (vs), 818 (s), 798 (s), 782 (s), 752 (m), 700 (m), 680 (w), 630 (w).

MS (EI, 70 eV): *m/z* (%) = 416 (10, M^+), 401 (8), 400 (19), 370 (9), 369 (23), 368 (100), 354 (12), 353 (50), 249 (7), 73 (34).

HRMS (EI): calcd. for $C_{21}H_{24}O_3{}^{32}S_2{}^{28}Si$: 416.0936, found: 416.0941.

(4-((4-Chlorophenyl)thio)-5-((4-methoxyphenyl)sulfinyl)thiophen-2-yl)trimethylsilane (**75c**)



Prepared according to **TP4** by treating sulfoxide **74a** (2.17 g, 7.00 mmol) with tmpMgCl·LiCl (7.57 mL, 8.40 mmol, 1.11 M in THF) at -30 °C for 20 min and *S*(4-chlorophenyl)benzene thiosulfonate (2.39 g, 8.40 mmol) at 25 °C for 1 h. Flash chromatographical purification (pentane/Et_2O 7:3, silica gel) furnished **75c** as an orange oil (2.46 g, 78% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.64-7.59 (m, 2H), 7.17-7.12 (m, 2H), 7.01-6.97 (m, 3H), 6.91-6.87 (m, 2H), 3.77 (s, 3H), 0.24 (s, 9H).

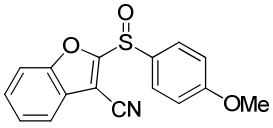
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.0, 155.4, 147.5, 138.6, 135.4, 134.2, 132.4, 131.5 (CH), 129.7 (CH), 129.1 (CH), 126.7 (CH), 114.5 (CH), 55.3 (CH_3), -0.6 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2954 (w), 2360 (w), 1738 (w), 1592 (m), 1578 (m), 1494 (m), 1474 (m), 1440 (w), 1408 (w), 1390 (w), 1304 (w), 1248 (s), 1170 (m), 1084 (s), 1048 (s), 1024 (m), 1010 (m), 990 (s), 826 (vs), 796 (s), 756 (m), 732 (m), 700 (m), 624 (m).

MS (EI, 70 eV): *m/z* (%) = 452 (10), 436 (11), 407 (10), 406 (43), 405 (25), 404 (100), 391 (14), 390 (8), 389 (33), 73 (41).

HRMS (EI): calcd. for $C_{20}H_{21}{}^{35}ClO_2{}^{32}S_3{}^{28}Si$: 452.0161, found: 452.0156.

2-((4-Methoxyphenyl)sulfinyl)benzofuran-3-carbonitrile (**75d**)



Prepared according to **TP4** by treating sulfoxide **74b** (1.63 g, 6.00 mmol) with tmpMgCl·LiCl (6.00 mL, 6.60 mmol, 1.10 M in THF) at -30 °C for 20 min and tosyl cyanide (1.30 g, 7.20 mmol,) at 25 °C for 1 h. Flash chromatographical purification (pentane/Et_2O 1:1, silica gel) furnished **75d** as a yellow solid (768 mg, 43% yield).

m.p. (°C): 139-140.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.85-7.80 (m, 2H), 7.74-7.71 (m, 1H), 7.57-7.53 (m, 1H), 7.51-7.45 (m, 1H), 7.44-7.39 (m, 1H), 7.09-7.04 (m, 2H), 3.85 (s, 3H).

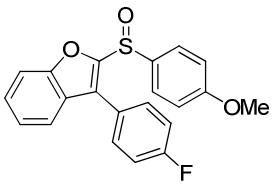
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 163.4, 163.3, 155.3, 131.2, 128.4 (CH), 127.4 (CH), 125.5 (CH), 125.2, 120.9 (CH), 115.4 (CH), 112.7 (CH), 110.3, 96.0, 55.6 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3014 (w), 2236 (w), 1742 (w), 1588 (m), 1574 (m), 1492 (s), 1448 (m), 1410 (m), 1304 (m), 1252 (vs), 1170 (s), 1154 (m), 1128 (m), 1082 (s), 1064 (s), 1016 (s), 832 (s), 814 (s), 794 (m), 750 (vs), 714 (w), 662 (w), 642 (w).

MS (EI, 70 eV): *m/z* (%) = 282 (9), 281 (43), 363 (100), 266 (12), 250 (19), 249 (100), 238 (8), 234 (26), 206 (14), 139 (16).

HRMS (EI): calcd. for $C_{16}H_{11}NO_3{}^{32}S$: 297.0460, found: 297.0455.

3-(4-Fluorophenyl)-2-[(4-methoxyphenyl)sulfinyl]-1-benzofuran (**75e**)



Prepared according to **TP5** by treating sulfoxide **74b** (1.90 g, 7.00 mmol) with tmpMgCl·LiCl (7.00 mL, 7.70 mmol, 1.10 M in THF) at -30 °C for 20 min, with $ZnCl_2$ (8.40 mL, 8.40 mmol, 1.00 M in THF), $Pd(PPh_3)_4$ (162 mg, 0.14 mmol) and 1-fluoro-4-iodobenzene (1.86 g, 8.40 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et2O, 1:1, silica gel) furnished **75e** as a colourless solid (2.04 g, 80% yield).

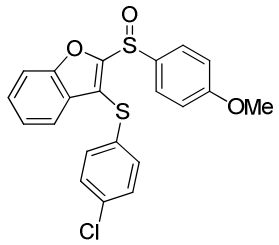
m.p. (°C): 100-102.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.72-7.68 (m, 2H), 7.67-7.61 (m, 3H), 7.51-7.47 (m 1H), 7.45-7.39 (m, 1H), 7.33-7.29 (m, 1H), 7.28-7.21 (m, 2H), 7.04-6.99 (m, 2H), 3.83 (s, 3H),

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 163.1 (d, J = 249.3 Hz, CF), 162.1, 155.6, 150.4, 131.9, 131.5 (d, J = 8.25 Hz, CH), 127.7 (CH), 127.0 (CH), 126.7, 126.6, 125.4 (d, J = 3.35 Hz), 123.9 (CH), 121.4 (CH), 116.2 (d, J = 21.91 Hz, CH), 114.8 (CH), 112.5 (CH), 55.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3062 (w), 2952 (w), 1592 (s), 1576 (m), 1496 (vs), 1456 (m), 1442 (m), 1302 (m), 1250 (s), 1232 (s), 1216 (s), 1134 (s), 1102 (s), 1084 (s), 1044 (vs), 1018 (s), 966 (m), 828 (vs), 814 (s), 794 (s), 748 (vs), 718 (m), 660 (m), 642 (w), 632 (w).
MS (EI, 70 eV): *m/z* (%) = 350 (6), 334 (100), 319 (17), 317 (3), 316 (26), 231 (15), 184 (4), 172 (4), 171 (4), 139 (7).
HRMS (EI): calcd. for $C_{21}H_{15}{}^{19}FO_3{}^{32}S$: 366.4064, found: 366.4075.

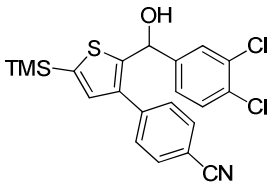
3-((4-Chlorophenyl)thio)-2-((4-methoxyphenyl)sulfinyl)benzofuran (**75f**)



Prepared according to **TP4** by treating sulfoxide **74b** (1.90 g, 7.00 mmol) with tmpMgCl·LiCl (7.00 mL, 7.70 mmol, 1.10 M in THF), at -30 °C for 20 min and *S*(4-chlorophenyl)benzene thiosulfonate (2.39 g, 8.40 mmol) at 25 °C for 1 h. Flash chromatographical purification (pentane/Et_2O 1:1, silica gel) furnished **75f** as an orange oil (2.56 g, 88% yield).
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.71-7.67 (m, 2H), 7.52-7.50 (m, 1H), 7.42-7.35 (m, 2H), 7.25-7.22 (m, 1H), 7.21-7.17 (m, 2H), 7.16-7.11 (m, 2H), 7.00-6.95 (m, 2H), 3.82 (s, 3H).
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 162.4, 157.6, 155.9, 132.8, 132.7, 132.1, 129.6, 129.4 (CH), 127.7 (CH), 127.6 (CH), 126.9, 124.3 (CH), 121.2 (CH), 115.2 (CH), 114.9 (CH), 112.7 (CH), 55.5 (CH_3).
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3064 (w), 2836 (w), 1590 (s), 1576 (m), 1492 (s), 1474 (s), 1440 (m), 1390 (w), 1304 (m), 1250 (vs), 1218 (m), 1170 (m), 1138 (m), 1084 (vs), 1052 (s), 1026 (s), 1010 (s), 882 (w), 826 (s), 806 (vs), 746 (vs), 712 (m), 660 (w), 648 (w).
MS (EI, 70 eV): *m/z* (%) = 398 (16), 369 (20), 368 (100), 367 (57), 366 (87), 275 (26), 255 (41), 227 (23), 224 (28), 139 (17).
HRMS (EI): calcd. for $C_{21}H_{15}{}^{35}ClO_3{}^{32}S_2$: 414.0151, found: 414.0152.

3.2.3 Preparation of sulfoxides 76 by sulfoxide-magnesium exchange on sulfoxides 75

4-(2-((3,4-Dichlorophenyl)(hydroxy)methyl)-5-(trimethylsilyl)thiophen-3-yl)benzonitrile (**76a**)



Prepared according to **TP7** by treating sulfoxide **75a** (411 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and 3,4-dichlorbenzaldehyde (140 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 4:1, silica gel) furnished **76a** as a white solid (287 mg, 83% yield).

m.p. (°C): 145-146.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.32 (dd, *J* = 2.15, 0.39 Hz, 1H), 7.08-7.06 (m, 2H), 7.03-7.01 (m, 2H), 6.97 (s, 1H), 6.93 (dd, *J* = 8.20, 0.39 Hz, 1H), 6.74 (dd, *J* = 8.20, 2.15 Hz, 1H), 5.48 (d, *J* = 4.20 Hz, 1H), 1.61 (d, *J* = 4.20 Hz, 1H), 0.18 (s, 9H).

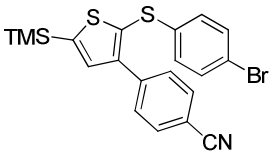
^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 148.4, 143.9, 141.0, 140.4, 140.3, 135.7 (CH), 132.9, 132.3 (CH), 132.1, 130.6 (CH), 129.5 (CH), 128.4 (CH), 125.8 (CH), 118.7, 111.8, 69.0 (CH), -0.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3468 (w), 2954 (w), 2234 (w), 1740 (w), 1604 (w), 1538 (w), 1498 (w), 1468 (w), 1384 (m), 1248 (m), 1144 (w), 1124 (w), 1028 (m), 1004 (m), 910 (w), 868 (m), 834 (vs), 820 (s), 758 (m), 738 (m), 712 (m), 676 (m), 626 (w).

MS (EI, 70 eV): *m/z* (%) = 431 (36, M^+), 418 (54), 417 (51), 416 (100), 415 (28), 402 (53), 400 (75), 73 (69), 44 (99), 43 (30).

HRMS (EI): calcd. for $C_{21}H_{19}{}^{35}Cl_2NO^{32}S^{28}Si$: 431.0334, found: 431.0323.

4-(2-((4-Bromophenyl)thio)-5-(trimethylsilyl)thiophen-3-yl)benzonitrile (**76b**)



Prepared according to **TP7** by treating sulfoxide **75a** (411 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and (*S*)-(4-bromophenyl)benzene thiosulfonate (263 mg, 0.8 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 50:1, silica gel) furnished **76b** as a yellow solid (334 mg, 94% yield).

m.p. (°C): 126-127.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.15 (s, 1H), 7.14-7.12 (m, 2H), 7.01-6.98 (m, 2H), 6.96-6.92 (m, 2H), 6.73-6.69 (m, 2H), 0.20 (s, 9H).

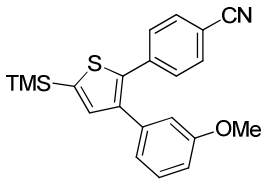
^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 147.3, 139.4, 137.3, 136.2 (CH), 132.9, 132.5 (CH), 132.1 (CH), 129.4 (CH), 129.2 (CH), 126.9, 120.6, 118.7, 111.9, -0.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2946 (w), 2360 (w), 2226 (w), 1740 (w), 1602 (m), 1524 (w), 1474 (w), 1392 (m), 1248 (m), 1216 (w), 1180 (w), 1070 (w), 1010 (m), 992 (m), 830 (vs), 816 (vs), 752 (m), 732 (m), 694 (w), 658 (w), 626 (w).

MS (EI, 70 eV): *m/z* (%) = 446 (27), 445 (100), 444 (25), 443 (87, M^+), 431 (28), 430 (98), 429 (25), 428 (93), 166 (19), 73 (43).

HRMS (EI): calcd. for $C_{20}H_{18}{}^{81}BrN^{32}S_2{}^{28}Si$: 442.9833, found: 442.9823.

4-(3-(3-Methoxyphenyl)-5-(trimethylsilyl)thiophen-2-yl)benzonitrile (**76c**)



Prepared according to **TP7** by treating sulfoxide **75b** (6.67 g, 16.0 mmol) with *i*PrMgCl·LiCl (14.7 mL, 17.6 mmol, 1.20 M in THF) at -50 °C for 5 min, with $ZnCl_2$ (17.6 mL, 17.6 mmol, 1.00 M in THF), $Pd(PPh_3)_4$ (370 mg, 0.32 mmol) and 4-iodobenzonitrile (2.93 g, 12.8 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 20:1, silica gel) furnished **76c** as a colourless solid (3.97 g, 85% yield).

m.p. (°C): 141-143.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.28 (s, 1H), 7.07-7.04 (m, 3H), 6.88-6.87 (m, 1H), 6.82-6.79 (m, 3H), 6.72 (ddd, *J* = 8.22, 2.54, 0.98 Hz, 1H), 3.23 (s, 3H), -0.28 (s, 9H).

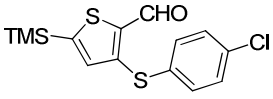
^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 160.4, 142.2, 141.6, 141.1, 138.8, 138.1, 137.9 (CH), 132.3 (CH), 130.0 (CH), 129.8 (CH), 121.8 (CH), 118.6, 115.1 (CH), 113.2 (CH), 111.4, 54.7 (CH_3), -0.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2954 (w), 2226 (w), 1744 (w), 1602 (m), 1574 (m), 1448 (w), 1424 (w), 1334 (w), 1288 (w), 1242 (m), 1222 (m), 1208 (m), 1178 (m), 1052 (m), 1000 (s), 962 (m), 884 (w), 836 (vs), 778 (s), 754 (m), 702 (m), 684 (m), 628 (w).

MS (EI, 70 eV): *m/z* (%) = 365 (14), 364 (40), 363 (100, M^+), 350 (26), 349 (74), 348 (99), 332 (5), 215 (5), 174 (6), 115 (12).

HRMS (EI): calcd. for $C_{21}H_{21}NO^{32}S^{28}Si$: 363.1113, found: 363.1099.

3-((4-Chlorophenyl)thio)-5-(trimethylsilyl)thiophene-2-carbaldehyde (**76d**)



Prepared according to **TP7** by treating sulfoxide **75c** (453 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.1 mmol, 1.20 M in THF) at -50 °C for 1 h and DMF (58 mg, 0.80 mmol) at 25 °C

for 1 h. Flash chromatographic purification (pentane/Et_2O 50:1, silica gel) furnished **76d** as a yellow solid (253 mg, 97% yield).

m.p. (°C): 71-73.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 10.14 (s, 1H), 6.90 (s, 1H), 6.87-6.78 (m, 4H), 0.01 (s, 9H).

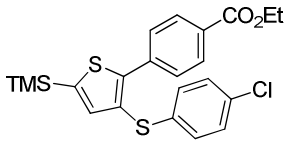
^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 181.4 (CH), 151.3, 145.5, 140.1, 138.1 (CH), 134.0, 133.7, 131.6 (CH), 129.7 (CH), -0.9 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 2360 (vw), 1744 (vw), 1656 (s), 1476 (m), 1424 (m), 1390 (w), 1356 (w), 1288 (m), 1248 (m), 1206 (s), 1164 (w), 1090 (m), 1004 (s), 876 (m), 844 (vs), 818 (vs), 760 (s), 742 (m), 700 (m), 670 (m), 628 (m).

MS (EI, 70 eV): *m/z* (%) = 329 (14), 328 (49), 327 (43), 326 (100, M^+), 325 (36), 313 (46), 312 (21), 311 (86), 214 (25), 207 (15).

HRMS (EI): calcd. for $C_{14}H_{15}{}^{35}ClO^{32}S_2{}^{28}Si$: 326.0022, found: 326.0011.

Ethyl 4-(3-((4-chlorophenyl)thio)-5-(trimethylsilyl)thiophen-2-yl)benzoate (**76e**)



Prepared according to **TP7** by treating sulfoxide **75c** (453 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.1 mmol, 1.20 M in THF) at -50 °C for 1 h, with $ZnCl_2$ (1.10 mL, 1.10 mmol, 1.00 M in THF), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) and ethyl 4-iodobenzoate (221 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 50:1, silica gel) furnished **76e** as a clear oil (315 mg, 88% yield).

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 8.12-8.09 (m, 2H), 7.67-7.64 (m, 2H), 7.23 (s, 1H), 6.86-6.81 (m, 4H), 4.11 (q, *J* = 7.13 Hz, 2H), 1.01 (t, *J* = 7.13 Hz, 3H), 0.19 (s, 9H).

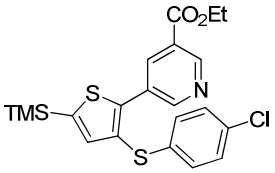
^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = -0.4 (CH_3), 14.2 (CH_3), 60.9 (CH_2), 126.3, 129.0 (CH), 129.2 (CH), 129.4 (CH), 130.1 (CH), 130.7, 132.0, 136.8, 137.7, 141.0 (CH), 141.4, 150.2, 165.7.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 2360 (vw), 1714 (s), 1606 (m), 1474 (m), 1404 (w), 1366 (w), 1270 (vs), 1250 (s), 1180 (m), 1090 (s), 998 (s), 962 (m), 872 (m), 834 (vs), 812 (s), 768 (s), 756 (m), 740 (m), 698 (m), 654 (w), 626 (m).

MS (EI, 70 eV): *m/z* (%) = 449 (10), 448 (40), 447 (24), 446 (100, M^+), 434 (7), 433 (29), 432 (16), 431 (60), 193 (12), 73 (11).

HRMS (EI): calcd. for $C_{22}H_{23}{}^{35}ClO_2{}^{32}S_2{}^{28}Si$: 446.0597, found: 446.0583.

Ethyl 5-(3-((4-chlorophenyl)thio)-5-(trimethylsilyl)-2-thienyl)nicotinate (**76f**)



Prepared according to **TP7** by treating sulfoxide **75c** (453 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 1 h, with $ZnCl_2$ (1.10 mL, 1.10 mmol, 1.00 M in THF), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) and 5-bromonicotinic acid ethyl ester (184 mg, 0.80 mmol) for the cross-coupling (50 °C, 5 h). Flash chromatographic purification (pentane/Et_2O 10:1, silica gel) furnished **76f** as a colourless solid (239 mg, 67% yield).

m.p. (°C): 90-91.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 9.37 (d, *J* = 2.16 Hz, 1H), 9.15 (d, *J* = 2.14 Hz, 1H), 8.60 (dd, *J* = 2.16 2.14 Hz, 1H) 7.21 (s, 1H), 6.81-6.72 (m, 4H), 4.00 (q, *J* = 7.23 Hz, 2H), 0.92 (t, *J* = 7.23 Hz, 3H), 0.17 (s, 9H).

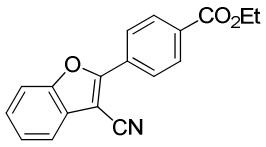
^{13}C-NMR (C_6D_6, 100 MHz, Me_4Si): δ (ppm) = 164.6, 153.1 (CH), 150.6 (CH), 146.6, 142.1, 140.9 (CH), 136.8 (CH), 136.4, 132.1, 129.5, 129.4 (CH), 129.0 (CH), 127.5, 126.4, 61.2 (CH_2), 14.0 (CH_3), -0.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 2360 (w), 1716 (s), 1574 (w), 1474 (m), 1392 (w), 1366 (w), 1292 (s), 1248 (s), 1222 (s), 1120 (m), 1108 (m), 1092 (m), 1022 (m), 1012 (m), 984 (s), 836 (vs), 816 (s), 764 (s), 704 (m), 652 (w), 624 (w).

MS (EI, 70 eV): *m/z* (%) = 450 (11), 449 (45), 448 (27), 447 (100, M^+), 435 (8), 434 (44), 433 (19), 432 (70), 165 (6), 73 (9).

HRMS (EI): calcd. for $C_{21}H_{22}{}^{35}ClNO_2{}^{32}S_2{}^{28}Si$: 447.0550, found: 447.0535.

Ethyl 4-(3-cyanobenzofuran-2-yl)benzoate (**76g**)



Prepared according to **TP7** by treating sulfoxide **75d** (297 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with $ZnCl_2$ (1.10 mL, 1.10 mmol, 1.00 M in THF), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) and ethyl 4-iodobenzoate (221 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 10:1, silica gel) furnished **76g** as a colourless solid (202 mg, 87% yield).

m.p. (°C): 128-130.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 8.05-7.98 (m, 4H), 7.35-7.33 (m, 1H), 7.11-7.09 (m, 1H), 6.97-6.89 (m, 2H), 4.12 (t, *J* = 7.19 Hz, 2H), 1.04 (q, *J* = 7.19 Hz, 3H).

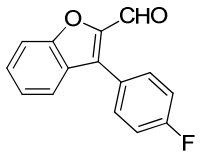
^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 165.2, 160.0, 153.7, 132.8, 131.5, 130.4 (CH), 127.6, 126.8 (CH), 126.4 (CH), 124.9 (CH), 120.3 (CH), 113.8, 111.7 (CH), 90.5, 61.1 (CH_2), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 2224 (w), 1714 (vs), 1610 (m), 1592 (m), 1476 (w), 1448 (m), 1410 (m), 1368 (m), 1274 (vs), 1198 (m), 1178 (m), 1144 (m), 1104 (s), 1016 (s), 978 (m), 898 (w), 860 (m), 826 (m), 774 (m), 758 (s), 700 (s), 644 (m).

MS (EI, 70 eV): *m/z* (%) = 292 (16), 291 (83, M^+), 263 (36), 247 (21), 246 (100), 219 (12), 218 (23), 190 (39), 123 (13), 43 (17).

HRMS (EI): calcd. for $C_{18}H_{13}NO_3$: 291.0895, found: 291.0890.

3-(4-Fluorophenyl)-1-benzofuran-2-carbaldehyde (**76h**)



Prepared according to **TP7** by treating sulfoxide **75e** (366 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and DMF (58 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 20:1, silica gel) furnished **76h** as a yellow solid (174 mg, 91% yield).

m.p. (°C): 145-146.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 9.58 (s, 1H), 7.29-7.24 (m, 2H), 7.10-7.05 (m, 1H), 6.96-6.90 (m, 3H), 6.80-6.74 (m, 2H).

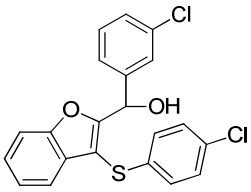
^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 112.8 (CH), 116.1 (d, *J* = 21.8 Hz, CH), 122.3 (CH), 124.1 (CH), 125.6 (d, *J* = 3.50 Hz), 127.4 (d, *J* = 0.78 Hz), 129.3 (CH), 131.4, 131.9 (d, *J* = 8.17 Hz, CH) 148.1, 155.5, 163.5 (d, *J* = 248.9 Hz, CF), 178.7 (CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2876 (w), 1668 (s), 1608 (m), 1562 (m), 1506 (s), 1450 (m), 1394 (w), 1358 (m), 1332 (m), 1288 (m), 1274 (m), 1230 (m), 1210 (s), 1160 (s), 1100 (m), 1012 (m), 980 (m), 866 (s), 840 (s), 814 (m), 750 (vs), 648 (m), 638 (m).

MS (EI, 70 eV): *m/z* (%) = 241 (12), 240 (83, M^+), 239 (100), 184 (9), 183 (52), 182 (7), 181 (9), 120 (9), 92 (8), 57 (8).

HRMS (EI): calcd. for $C_{15}H_9{}^{19}FO_2$: 240.0587, found: 240.0582.

(3-Chlorophenyl)(3-((4-chlorophenyl)thio)benzofuran-2-yl)methanol (**76i**)



Prepared according to **TP7** by treating sulfoxide **75f** (414 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and 3-chlorobenzaldehyde (112 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 10:1, silica gel) furnished **76i** as a yellow oil (248 mg, 77% yield).

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.55-7.54 (m, 1H), 7.36-7.34 (m, 1H), 7.14-7.12 (m, 2H), 6.99-6.97 (m, 1H), 6.95-6.92 (m, 2H), 6.83-6.73 (m, 5H), 6.02 (d, *J* = 5.38 Hz, 1H), 2.06 (d, *J* = 5.38 Hz, 1H).

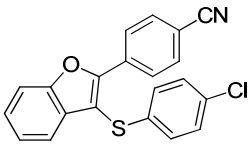
^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 161.1, 155.1, 142.7, 134.9, 134.7, 132.1, 130.0 (CH), 129.5 (CH), 128.9 (CH), 127.0, 126.9 (CH), 126.0 (CH), 124.8 (CH), 124.6 (CH), 124.0 (CH), 120.5 (CH), 112.2 (CH), 106.7, 67.7 (CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3342 (m), 3062 (w), 2962 (w), 2872 (w), 1706 (w), 1596 (w), 1574 (w), 1474 (vs), 1450 (m), 1426 (m), 1388 (m), 1246 (m), 1176 (m), 1090 (s), 1034 (m), 1010 (s), 868 (w), 812 (m), 790 (m), 744 (s), 722 (m), 644 (w).

MS (EI, 70 eV): *m/z* (%) = 402 (66), 401 (25), 400 (95, M^+), 383 (33), 292 (57), 290 (28), 222 (37), 177 (29), 141 (35), 139 (100).

HRMS (EI): calcd. for $C_{21}H_{14}{}^{35}Cl_2O_2{}^{32}S$: 400.0092, found: 400.0090.

4-(3-((4-Chlorophenyl)thio)benzofuran-2-yl)benzonitrile **(76j)**



Prepared according to **TP7** by treating sulfoxide **75f** (414 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.1 mmol, 1.20 M in THF) at -50 °C for 5 min, with $ZnCl_2$ (1.10 mL, 1.10 mmol, 1.00 M in THF), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) and 4-iodobenzonitrile (183 mg, 0.80 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 20:1, silica gel) furnished **76j** as a colourless solid (244 mg, 84% yield).

m.p. (°C): 190-192.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.92-7.89 (m, 2H), 7.40-7.37 (m, 1H), 7.32-7.30 (m, 1H), 7.08-7.03 (m, 1H), 6.99-6.95 (m, 3H), 6.82-6.79 (m, 2H), 6.76-6.72 (m, 2 H),

^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 155.2, 154.5, 134.0, 133.1, 132.3, 132.2 (CH), 130.5, 129.6 (CH), 128.2 (CH), 127.4 (CH), 126.7 (CH), 124.3 (CH), 120.9 (CH), 118.4, 113.2, 111.7 (CH), 107.8.

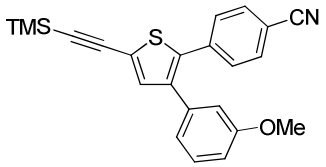
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2924 (w), 2224 (m), 1734 (w), 1610 (w), 1574 (w), 1492 (w), 1474 (s), 1450 (m), 1410 (m), 1390 (w), 1340 (w), 1250 (w), 1196 (m), 1084 (vs), 1008 (m), 890 (w), 836 (m), 818 (m), 802 (m), 750 (vs), 680 (w).

MS (EI, 70 eV): *m/z* (%) = 364 (9), 363 (38), 362 (24), 361 (100, M^+), 293 (13), 259 (17), 230 (13), 222 (10), 190 (19), 139 (8).

HRMS (EI): calcd. for $C_{21}H_{12}{}^{35}ClNO^{32}S$: 361.0328, found: 361.0323.

3.2.4 Preparation of Fully Functionalized 5-Membered Thiophene 78

4-(3-(3-Methoxyphenyl)-5-((trimethylsilyl)ethynyl)thiophen-2-yl)benzonitrile (**77**)



A dry and argon-flushed Schlenk-flask, equipped with a stirring bar and a septum, was charged with a solution of 4-(3-(3-methoxyphenyl)-5-(trimethylsilyl)-2-thienyl)benzonitrile (**76c**; 3.27 g, 9.00 mmol) in CH_3CN (60 mL). The reaction mixture was cooled to 0 °C and ICl (2.19 g, 13.5 mmol) was added dropwise. The reaction mixture was allowed to warm to 25 °C and stirred for additional 1 h. Then the reaction mixture was quenched with a sat. aq. NH_4Cl-solution (20 mL) and a sat. aq $Na_2S_2O_3$ (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and after filtration, the solvent was removed under reduced pressure. The product was used for the next step without further purification.

A dry and argon-flushed Schlenk-flask, equipped with a stirring bar and a septum, was charged with a solution of 4-(5-iodo-3-(3-methoxyphenyl)-2-thienyl)benzonitrile (1.98 g, 4.50 mmol) in THF (6 mL). In a second dry and argon-flushed Schlenk-flask, equipped with a stirring bar and a septum, trimethylsilylacetylene (884 mg, 9.00 mmol) was added slowly to *i*PrMgCl·LiCl (5.66 mL, 9.00 mmol, 1.59 M in THF). After cessation of gas evolution the reaction mixture was heated to 60 °C for 5 min. After cooling to 25 °C a $ZnCl_2$ solution (9.00 mL, 9.00 mmol, 1.00 M in THF) was added slowly. The resulting zinc reagent was transferred to the crude iodide, $Pd(PPh_3)_4$ (208 mg, 0.18 mmol) was added and the reaction mixture was stirred at 50 °C for 2 h. Then the reaction mixture was quenched with a sat. aq.

NH_4Cl-solution (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and after filtration, the solvent was removed under reduced pressure. Flash chromatographical purification (pentane/Et_2O 9:1, silica gel) furnished **77** as a colourless solid (1.53 g, 88% yield).

m.p. (°C): 138-139.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.19 (s, 1H), 6.96-6.92 (m, 1H), 6.85-6.82 (m, 2H), 6.72-6.69 (m, 2H), 6.66-6.64 (m, 2H), 6.62-6.60 (m, 1H), 3.19 (s, 3H), 0.23 (s, 9H).

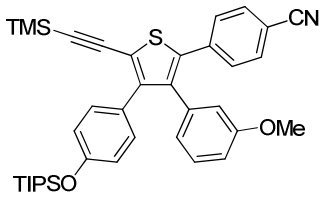
^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 160.3, 139.9, 138.1, 137.6, 136.7 (CH), 136.5, 132.1 (CH), 129.9 (CH), 129.5 (CH), 123.8, 121.5 (CH), 118.4, 114.8 (CH), 113.7 (CH), 111.8, 101.2, 97.6, 54.7 (CH_3), -0.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 2226 (w), 2142 (m), 1742 (m), 1602 (m), 1576 (m), 1482 (m), 1418 (m), 1374 (w), 1284 (w), 1236 (m), 1178 (w), 1148 (w), 1054 (w), 856 (s), 838 (vs), 792 (m), 774 (m), 696 (w), 630 (w).

MS (EI, 70 eV): *m/z* (%) = 389 (7), 388 (17), 387 (63, M^+), 374 (9), 373 (26), 372 (100), 356 (5), 328 (4), 186 (6), 185 (4).

HRMS (EI): calcd. for $C_{23}H_{21}NO^{32}S^{28}Si$: 387.1113, found: 387.1115.

4-(3-(3-Methoxyphenyl)-4-(4-((triisopropylsilyl)oxy)phenyl)-5-((trimethylsilyl)ethynyl)thiophen-2-yl)benzonitrile (**78**)



A dry and argon-flushed Schlenk-flask, equipped with a stirring bar and a septum, was charged with a solution of the thiophene **77** (387 mg, 1.00 mmol) in THF (2 mL). The reaction mixture was cooled to -20 °C and $tmp_2Mg\cdot 2LiCl$ (2.50 mL, 1.50 mmol, 0.60 M in THF) was added dropwise. The reaction mixture was stirred at this temperature for 12 h then $ZnCl_2$ (1.50 mL, 1.50 mmol, 1.00 M in THF) was added and the reaction mixture stirred at -20 °C for 30 min. (4-Iodo-phenoxy)-triisopropylsilane (541 mg, 1.50 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were added and the reaction stirred at 25 °C for 3 h. Then the reaction mixture was quenched with a sat. aq. NH_4Cl-solution (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographical purification (pentane/Et_2O 20:1, silica gel) furnished **78** as a yellow solid (476 mg, 75% yield).

m.p. (°C): 67-69.

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.26-7.22 (m, 4H), 6.98-6.94 (m, 2H), 6.90-6.86 (m, 3H), 6.76-6.74 (m, 1H), 6.70-6.66 (m, 2H), 3.20 (s, 3H), 1.18-1.11 (m, 3H), 1.08-1.06 (m, 18H), 0.24 (s, 9H).

^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 160.4, 157.2, 145.2, 140.1, 138.3, 137.7, 136.9, 136.4 (CH), 134.1 (CH), 130.9 (CH), 130.3 (CH), 130.0, 123.8, 121.7 (CH), 120.4 (CH), 118.6, 114.9 (CH), 113.7 (CH), 110.6, 101.2, 97.8, 54.7 (CH_3), 18.0 (CH_3), 12.9 (CH), -0.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2944 (s), 2892 (m), 2866 (s), 2222 (m), 2146 (m), 1600 (s), 1512 (s), 1486 (s), 1462 (m), 1368 (w), 1266 (s), 1248 (s), 1174 (m), 1042 (w), 996 (w), 908 (m), 882 (m), 838 (vs), 786 (m), 740 (m), 674 (m).

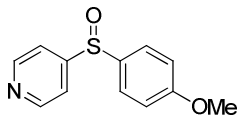
MS (EI, 70 eV): *m/z* (%) = 635 (37, M^+), 594 (27), 593 (48), 592 (100), 564 (45), 536 (43), 262 (23), 261 (38), 260 (82), 253 (42).

HRMS (EI): calcd. for $C_{38}H_{45}NO_2{}^{32}S^{28}Si_2$: 635.2710, found: 635.2711.

3.3 Preparation of Disubstituted Pyridines 81 via Directed Metalation and Sulfoxide-Magnesium Exchange

3.3.1 Preparation of Sulfoxides 79

4-((4-Methoxyphenyl)sulfinyl)pyridine **(79a)**



Prepared according to **TP2** from 4-pyridinylmagnesium chloride (74.1 mL, 60.8 mmol, 0.82 M in THF) and 4-methoxybenzene sulfinyl chloride (**58**, 15.1 g, 79.0 mmol) and purified by flash chromatography (Et_2O/EtOH 10:1, silica gel) furnishing **79a** as a colourless solid (8.36 g, 59% yield).

m.p. (°C): 87-89.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.65-8.63 (m, 2H), 7.56-7.51 (m, 2H), 7.45-7.43 (m, 2H), 6.95-6.90 (m, 2H).

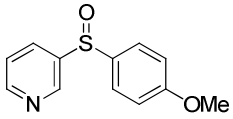
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.6, 155.9, 150.2 (CH), 135.2, 127.5 (CH), 118.3 (CH), 115.1 (CH), 55.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3034 (w), 2956 (w), 2836 (w), 1592 (s), 1570 (s), 1496 (m), 1458 (m), 1440 (w), 1404 (s), 1302 (m), 1266 (s), 1218 (m), 1172 (m), 1086 (m), 1040 (vs), 1026 (vs), 844 (m), 820 (s), 808 (s), 796 (m), 640 (w), 622 (w).

MS (EI, 70 eV): *m/z* (%) = 233 (19, M^+), 186 (6), 185 (48), 156 (8), 155 (100), 139 (8), 123 (28), 92 (5), 77 (5), 51 (11).

HRMS (EI): calcd. for $C_{12}H_{11}NO_2{}^{32}S$: 233.0510, found: 233.0503.

3-((4-Methoxyphenyl)sulfinyl)pyridine (**79b**)



Prepared according to **TP2** from 3-pyridinylmagnesium chloride (58.1 mL, 50.0 mmol, 0.86 M in THF) and 4-methoxybenzene sulfinyl chloride (**58**, 12.4 g, 65.0 mmol) and purified by flash chromatography (Et_2O/EtOH 20:1, silica gel), furnishing **79b** as a yellow oil (8.44 g, 72% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.68 (dd, *J* = 2.27, 0.75 Hz, 1H), 8.60 (dd, *J* = 4.80, 1.55 Hz, 1H), 7.91 (ddd, *J* = 8.11, 2.27, 1.55 Hz, 1H), 7.56-7.51 (m, 2H), 7.35 (ddd, *J* = 8.11, 4.80, 0.75 Hz, 1H), 6.95-6.91 (m, 2H), 3.76 (s, 3H).

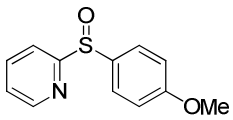
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.3, 151.4 (CH), 146.2 (CH), 142.5, 135.4, 132.1 (CH), 127.0 (CH), 124.0 (CH), 115.0 (CH), 55.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3048 (w), 2966 (w), 2942 (w), 2838 (w), 1592 (s), 1576 (m), 1494 (s), 1462 (m), 1410 (m), 1304 (m), 1250 (vs), 1172 (m), 1082 (s), 1044 (vs), 1026 (s), 1014 (vs), 830 (s), 796 (s), 732 (m), 722 (m), 702 (s), 616 (w).

MS (EI, 70 eV): *m/z* (%) = 233 (21, M^+), 216 (100), 186 (9), 185 (81), 170 (9), 156 (6), 155 (100), 139 (16), 123 (36), 51 (7).

HRMS (EI): calcd. for $C_{12}H_{11}NO_2{}^{32}S$: 233.0510, found: 233.0496.

2-((4-Methoxyphenyl)sulfinyl)pyridine (**79c**)



Prepared according to **TP2** from 2-pyridinylmagnesium chloride (61.7 mL, 50.0 mmol, 0.81 M in THF) and 4-methoxybenzene sulfinyl chloride (**58**, 12.4 g, 65.0 mmol) and purified by flash chromatography (Et_2O, silica gel), furnishing **79c** as a colourless solid (7.11 g, 61% yield).

m.p. (°C): 98-99.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.54 (d, *J* = 4.05 Hz, 1H), 8.07 (d, *J* = 7.87 Hz, 1H), 7.91-7.85 (m, 1H), 7.69 (d, *J* = 8.82 Hz, 2H), 7.31-7.27 (m, 1H), 6.95 (d, *J* = 8.82 Hz, 2H).

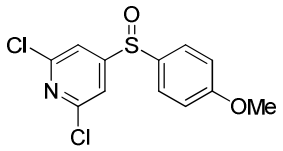
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.0, 162.0, 149.7 (CH), 138.0 (CH), 135.2, 127.2 (CH), 124.4 (CH), 118.4 (CH), 114.7 (CH), 55.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3080 (w), 2966 (w), 2838 (w), 1592 (m), 1574 (m), 1558 (m), 1494 (m), 1466 (m), 1442 (m), 1416 (s), 1300 (m), 1282 (m), 1256 (s), 1170 (m), 1122 (m), 1086 (s), 1048 (vs), 1032 (vs), 1018 (vs), 990 (s), 828 (m), 812 (m), 776 (s), 740 (m), 640 (w), 620 (w).

MS (EI, 70 eV): *m/z* (%) = 233 (69, M^+), 218 (25), 217 (10), 216 (61), 185 (25), 155 (75), 139 (100), 123 (53), 78 (36), 51 (18).

HRMS (EI): calcd. for $C_{12}H_{11}NO_2{}^{32}S$: 233.0510, found: 233.0510.

2,6-Dichloro-4-((4-methoxyphenyl)sulfinyl)pyridine (**79d**)



Prepared according to **TP2** from (2,6-dichloropyridin-4-yl)magnesium chloride (65.8 mL, 50.0 mmol, 0.76 M in THF) and 4-methoxybenzene sulfinyl chloride (**58**, 12.4 g, 65.0 mmol) and purified by flash chromatography (pentane/Et_2O 4:6, silica gel) furnishing **79d** as a colourless solid (8.45 g, 56% yield).

m.p. (°C): 121-123.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.60-7.55 (m, 2H), 7.41 (s, 2H), 7.03-6.98 (m, 2H), 3.83 (s, 3H).

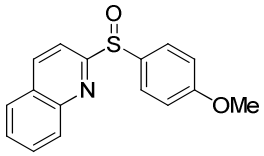
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.2, 162.0, 151.3, 134.0, 127.6 (CH), 117.7 (CH), 115.5 (CH), 55.6 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3072 (vw), 2932 (vw), 2846 (vw), 1592 (m), 1572 (m), 1556 (s), 1542 (s), 1494 (m), 1346 (s), 1314 (m), 1256 (s), 1178 (m), 1154 (s), 1086 (s), 1048 (vs), 1020 (s), 884 (w), 858 (m), 838 (vs), 818 (s), 810 (s), 796 (s), 712 (w), 626 (w).

MS (EI, 70 eV): *m/z* (%) = 303 (7), 255 (9), 253 (18), 156 (11), 155 (100), 139 (5), 123 (22), 92 (6), 77 (5), 44 (15).

HRMS (EI): calcd. for $C_{12}H_9Cl_2NO_2S$: 300.9731, found: 300.9720.

2-((4-Methoxyphenyl)sulfinyl)quinoline (**79e**)



In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, lithium hydride (160 mg, 20.0 mmol) was dissolved in DMF (15 mL). 4-Methoxybenzenethiol (2.10 g, 15.0 mmol) was added slowly at 25 °C and the solution stirred at that temperature for 30 min. 2-Chloroquinoline (2.45 g, 15.0mmol) was added at 25 °C and the solution stirred at that temperature for 16 h. The reaction mixture was quenched with sat. aq. K_2CO_3-solution (50 mL) and extracted with EtOAc (3 x 50 mL). The organic layers were combined and the solvent was removed under reduced pressure. The crude sulfide was dissolved in CH_2Cl_2 (20 mL) and cooled to -30 °C. *m*CPBA (4.40 g, 18.0 mmol, 70% in water) dissolved in CH_2Cl_2 (10 mL) was added slowly. After stirring at -30 °C for 3 h the reaction mixture was quenched with a sat. aq. $Na_2S_2O_3$-solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification (pentane/Et_2O 3:7, silica gel) furnished **79e** as a colourless solid (1.92 g, 45% yield).

m.p. (°C): 120-122.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.31 (d, *J* = 8.58 Hz, 1H), 8.09 (d, *J* = 8.58 Hz, 1H), 8.08 (d, *J* = 8.57 Hz, 1H), 7.82 (d, *J* = 7.63, 1H), 7.77-7.74 (m, 2H), 7.73-7.71 (m, 1H), 7.58-7.55 (m, 1H), 6.93-6.91 (m, 2H), 3.75 (s, 3H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 165.9, 161.9, 147.4, 138.6 (CH), 135.2, 130.6 (CH), 129.3 (CH), 128.2, 127.9 (CH), 127.8 (CH), 126.7 (CH), 114.7 (CH), 114.5 (CH), 55.4 (CH_3).

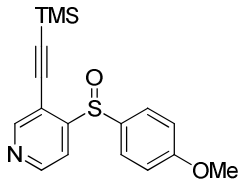
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3060 (w), 2838 (w), 1590 (m), 1582 (m), 1512 (vw), 1494 (m), 1462 (w), 1302 (m), 1246 (s), 1192 (m), 1172 (w), 1142 (m), 1092 (m), 1078 (m), 1046 (vs), 1020 (s), 872 (vw), 828 (s), 822 (vs), 794 (m), 784 (m), 748 (s), 712 (w), 660 (vw), 626 (vw).

MS (EI, 70 eV): *m/z* (%) = 284 (12), 283 (68, M^+), 268 (14), 266 (26), 235 (18), 155 (12), 139 (100), 128 (48), 123 (17), 101 (16).

HRMS (EI): calcd. for $C_{16}H_{13}NO_2{}^{32}S$: 283.0667, found: 283.0659.

3.3.2 Preparation of Sulfoxides 80 by Metalation of Sulfoxides 79

4-((4-Methoxyphenyl)sulfinyl)-3-((trimethylsilyl)ethynyl)pyridine (**80a**)



Prepared according to **TP6** by treating sulfoxide **79a** (1.17 g, 5.00 mmol) with tmpMgCl·LiCl (5.00 mL, 5.50 mmol, 1.10 M in THF) at -30 °C for 20 min, with trimethylsilylethynylzinc chloride (prepared from trimethylsilylacetylene (0.59 g, 6.00 mmol), *i*PrMg·LiCl (4.58 mL, 5.50 mmol, 1.20 M in THF) and $ZnCl_2$ (6.00 mL, 6.00 mmol, 1.00 M in THF) and $Pd(PPh_3)_4$ (110 mg, 0.01 mmol,) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (Et_2O, silica gel) furnished **80a** as a brown oil (1.13 g, 69% yield).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.69 (d, J = 5.25 Hz, 1H), 8.55 (s, 1H), 7.96 (d, J = 5.25 Hz, 1H), 7.58 (d, J = 8.58 Hz, 2H), 6.87 (d, J = 8.58 Hz, 2H), 3.74 (s, 3H), 0.22 (s, 9H).

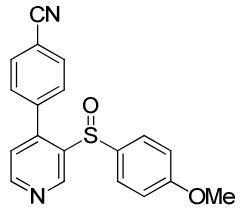
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 162.3, 156.8, 153.0 (CH), 149.6 (CH), 134.4, 128.3 (CH), 116.5 (CH), 116.2, 114.5 (CH), 107.0, 97.1, 55.3 (CH_3), -0.60 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2958 (vw), 2840 (vw), 2160 (vw), 1590 (m), 1498 (w), 1462 (w), 1446 (w), 1394 (w), 1302 (w), 1288 (w), 1254 (s), 1186 (w), 1092 (m), 1054 (m), 1030 (m), 946 (vw), 860 (s), 842 (vs), 830 (vs), 798 (m), 760 (m), 744 (w), 694 (w), 656 (w).

MS (EI, 70 eV): *m/z* (%) = 329 (20, M^+), 316 (8), 315 (19), 314 (100), 298 (10), 286 (10), 228 (11), 155 (32), 139 (12), 73 (65).

HRMS (EI): calcd. for $C_{17}H_{19}NO_2{}^{32}S^{28}Si$: 329.0906, found: 329.0898.

4-(3-((4-Methoxyphenyl)sulfinyl)pyridin-4-yl)benzonitrile (**80b**)



Prepared according to **TP5** by treating sulfoxide **79b** (1.63 g, 7.00 mmol) with tmpMgCl·LiCl (7.00 mL, 7.70 mmol, 1.10 M in THF) at -30 °C for 20 min, with 4-iodobenzonitrile (1.92 g, 8.40 mmol), $ZnCl_2$ (8.40 mL, 8.40 mmol, 1.00 M in THF) and $Pd(PPh_3)_4$ (154 mg, 0.014 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (Et_2O/EtOH 20:1, silica gel) furnished **80b** as a colourless solid (883 mg, 38% yield).

m.p. (°C): 212-215.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 9.30 (s, 1H), 8.78 (d, J = 4.53 Hz, 1H), 7.68 (d, J = 8.11 Hz, 2H), 7.30 (d, J = 8.11 Hz, 2H), 7.12 (d, J = 4.35 Hz, 1H), 7.04 (d, J = 8.11 Hz, 2H), 6.76 (d, J = 8.11 Hz, 2H), 3.77 (s, 3H).

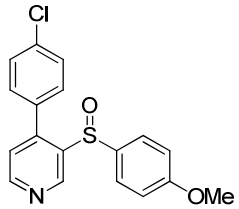
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 162.3, 152.1 (CH), 146.8 (CH), 146.3, 140.3, 139.2, 134.2, 132.4 (CH), 129.6 (CH), 127.9 (CH), 123.8 (CH), 118.0, 114.7 (CH), 113.1, 55.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3042 (w), 2998 (w), 2836 (w), 2222 (m), 1592 (m), 1578 (s), 1494 (m), 1466 (m), 1444 (w), 1410 (w), 1396 (m), 1304 (m), 1246 (vs), 1178 (m), 1080 (s), 1046 (vs), 1028 (s), 862 (w), 842 (m), 832 (vs), 806 (m), 796 (m), 758 (w), 724 (w).

MS (EI, 70 eV): *m/z* (%) = 334 (18, M^+), 318 (18), 317 (23), 286 (8), 157 (5), 156 (8), 155 (100), 139 (13), 124 (5), 123 (33).

HRMS (EI): calcd. for $C_{19}H_{14}N_2O_2{}^{32}S$: 334.0776, found: 334.0772.

4-(4-Chlorophenyl)-3-((4-methoxyphenyl)sulfinyl)pyridine (**80c**)



Prepared according to **TP5** by treating sulfoxide **79b** (1.16 g, 5.00 mmol) with tmpMgCl·LiCl (5.00 mL, 5.50 mmol, 1.10 M in THF) at -30 °C for 20 min, with 1-chloro-4-iodobenzene (1.43 g, 6.00 mmol), $ZnCl_2$ (6.00 mL, 6.00 mmol, 1.00 M in THF) and $Pd(PPh_3)_4$ (110 mg, 0.01 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (Et_2O, silica gel) furnished **80c** as an off-white solid (911 mg, 53% yield).

m.p. (°C): 139-140.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 9.26 (s, 1H), 8.72 (d, J = 4.95 Hz, 1H), 7.38-7.35 (m, 2H), 7.14-7.03 (m, 5H), 6.76-6.73 (m, 2H), 3.75 (s, 3H).

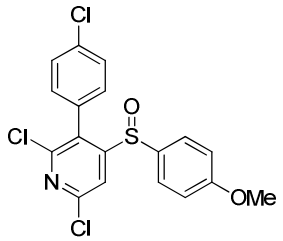
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.1, 151.8 (CH), 147.1, 146.4 (CH), 139.4, 135.5, 134.5, 134.1, 130.1 (CH), 129.0 (CH), 127.8 (CH), 124.0 (CH), 114.5 (CH), 55.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2832 (w), 1740 (w), 1592 (m), 1578 (m), 1494 (s), 1466 (m), 1440 (w), 1408 (w), 1394 (w), 1304 (m), 1244 (vs), 1190 (w), 1176 (m), 1080 (s), 1048 (vs), 1034 (s), 1012 (m), 860 (w), 832 (s), 826 (s), 800 (m), 776 (m), 754 (m).

MS (EI, 70 eV): *m/z* (%) = 345 (10), 343 (25, M^+), 328 (12), 327 (14), 326 (28), 295 (10), 155 (100), 139 (20), 124 (10), 123 (37).

HRMS (EI): calcd. for $C_{18}H_{14}{}^{35}ClNO_2{}^{32}S$: 343.0434, found: 343.0439.

2,6-Dichloro-3-(4-chlorophenyl)-4-((4-methoxyphenyl)sulfinyl)pyridine (**80d**)



Prepared according to **TP5** by treating sulfoxide **79d** (1.51 g, 5.00 mmol) with tmpMgCl·LiCl (5.00 mL, 5.50 mmol, 1.10 M in THF) at -30 °C for 20 min, with 1-chloro-4-iodobenzene (1.43 g, 6.00 mmol), $ZnCl_2$ (6.00 mL, 6.00 mmol, 1.00 M in THF) and $Pd(PPh_3)_4$ (110 mg, 0.01 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 7:3, silica gel) furnished **80d** as a colourless solid (1.53 g, 74% yield).

m.p. (°C): 134-136.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.16 (s, 1H), 7.50-7.49 (m, 1H), 7.25-7.24 (m, 1H), 7.18-7.16 (m, 1H), 6.92 (d, J = 9.06 Hz, 2H), 6.75 (d, J = 9.06 Hz, 2H), 6.42-6.41 (m, 1H), 3.79 (s, 3H).

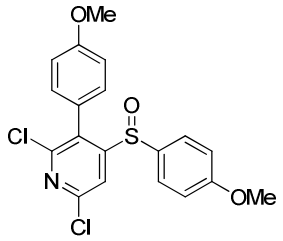
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 162.8, 160.5, 151.0, 149.8, 135.7, 132.5 (CH), 131.5, 130.9 (CH), 130.6, 130.3 (CH), 129.0 (CH), 128.7 (CH), 127.4, 118.0 (CH), 114.8 (CH), 55.6 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2966 (vw), 1592 (m), 1576 (w), 1562 (w), 1550 (w), 1524 (w), 1496 (m), 1408 (m), 1396 (m), 1308 (m), 1298 (m), 1256 (s), 1244 (m), 1178 (w), 1154 (m), 1096 (s), 1082 (s), 1050 (s), 1028 (m), 994 (m), 880 (w), 824 (vs), 796 (m), 778 (m), 734 (m).

MS (EI, 70 eV): *m/z* (%) = 415 (30), 413 (92), 411 (92, M^+), 397 (42), 395 (42), 157 (33), 156 (56), 139 (29), 124 (100), 123 (27).

HRMS (EI): calcd. for $C_{18}H_{12}{}^{35}Cl_3NO_2{}^{32}S$: 410.9654, found: 410.9653.

2,6-Dichloro-3-(4-methoxyphenyl)-4-((4-methoxyphenyl)sulfinyl)pyridine (**80e**)



Prepared according to **TP5** by treating sulfoxide **79d** (1.51 g, 5.00 mmol) with tmpMgCl·LiCl (5.00 mL, 5.50 mmol, 1.10 M in THF) at -30 °C for 20 min, with 4-iodoanisole (1.40 g, 6.00 mmol), $ZnCl_2$ (6.00 mL, 6.00 mmol, 1.00 M in THF) and $Pd(PPh_3)_4$ (110 mg, 0.01 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 1:1, silica gel) furnished **80e** as a colourless solid (1.38 g, 68% yield).

m.p. (°C): 113-114.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.12 (s, 1H), 7.22 (dd, *J* = 8.58, 1.91 Hz, 1H), 7.01 (dd, *J* = 8.58, 2.86 Hz, 1H), 6.89-6.87 (m, 2H), 6.74-6.71 (m, 3H), 6.43 (dd, *J* = 8.58, 1.91 Hz, 1H).

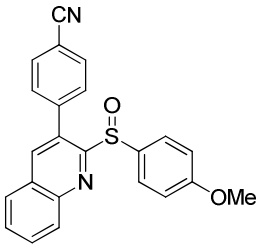
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 162.6, 160.8, 160.3, 150.2, 132.8, 131.9 (CH), 131.5, 131.4, 130.6 (CH), 128.4 (CH), 123.9, 117.6 (CH), 114.7 (CH), 114.6 (CH), 113.5 (CH), 55.5 (CH_3), 55.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3000 (vw), 2838 (w), 1610 (w), 1592 (m), 1576 (m), 1558 (m), 1510 (m), 1496 (m), 1404 (m), 1306 (m), 1258 (s), 1246 (vs), 1178 (s), 1152 (m), 1096 (m), 1084 (m), 1050 (s), 1034 (s), 1028 (s), 994 (m), 880 (w), 828 (s), 812 (m), 792 (s).

MS (EI, 70 eV): *m/z* (%) = 409 (28), 408 (9), 407 (41, M^+), 391 (9), 261 (20), 156 (13), 155 (100), 139 (9), 124 (15), 43 (10).

HRMS (EI): calcd. for $C_{19}H_{15}{}^{35}Cl_2NO_3{}^{32}S$: 407.0150, found: 407.0142.

4-(2-((4-Methoxyphenyl)sulfinyl)quinolin-3-yl)benzonitrile (**82**)



Prepared according to **TP5** by treating sulfoxide **79e** (1.42 g, 5.00 mmol) with tmpMgCl·LiCl (5.00 mL, 5.50 mmol, 1.10 M in THF) at -30 °C for 20 min, with 4-iodobenzonitrile (1.37 g, 6.00 mmol), $ZnCl_2$ (6.00 mL, 6.00 mmol, 1.00 M in THF) and $Pd(PPh_3)_4$ (110 mg, 0.01 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (EtOAc, silica gel) furnished **82** as a colourless solid (1.46 mg, 76% yield).

m.p. (°C): 190-196.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.84-8.42 (m, 1H), 7.95 (s, 1H), 7.86-7.82 (m, 2H), 7.69-7.66 (m, 3H), 7.35-7.32 (m, 2H), 7.15-7.11 (m, 2H), 6.73-6.69 (m, 2H), 3.73 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 162.2, 160.4, 147.4, 140.6, 138.2 (CH), 133.7, 132.1 (CH), 131.7, 131.1 (CH), 130.7 (CH), 130.1 (CH), 128.7 (CH), 128.6 (CH), 128.0, 127.6 (CH), 118.3, 114.5 (CH), 112.4, 55.4 (CH_3).

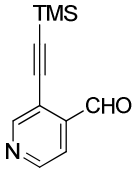
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3040 (w), 2932 (w), 2840 (w), 2226 (w), 1664 (m), 1588 (m), 1572 (w), 1490 (m), 1462 (w), 1440 (w), 1370 (w), 1300 (w), 1252 (s), 1170 (w), 1092 (m), 1080 (m), 1064 (vs), 1030 (m), 838 (m), 828 (s), 794 (m), 788 (m), 768 (m), 722 (w).

MS (EI, 70 eV): *m/z* (%) = 384 (22, M^+), 368 (16), 367 (27), 278 (44), 277 (100), 229 (21), 201 (22), 199 (17), 139 (44), 43 (16).

HRMS (EI): calcd. for $C_{23}H_{16}N_2O_2{}^{32}S$: 384.0932, found: 384.0923.

3.3.3 Preparation of Sulfoxides 81 by Sulfoxide-Magnesium Exchange on Sulfoxides 80

3-((Trimethylsilyl)ethynyl)isonicotinaldehyde (**81a**)



Prepared according to **TP7** by treating sulfoxide **80a** (329 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min and DMF (58 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 8:2, silica gel) furnished **81a** as a yellow oil (94 mg, 58% yield).

m.p. (°C): 178-182.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 10.52 (d, J = 0.78 Hz, 1H), 8.89 (d, J = 0.97 Hz, 1H), 8.71 (dd, J = 5.07, 0.78 Hz, 1H), 7.69 (dd, J = 5.07, 0.97 Hz, 1H), 0.29 (s, 9H).

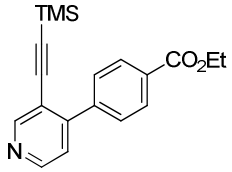
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 190.7 (CH), 154.6 (CH), 149.1 (CH), 141.0, 123.6, 119.0 (CH), 106.3, 96.7, -0.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2958 (w), 2924 (w), 2854 (vw), 2158 (vw), 1698 (w), 1598 (w), 1396 (m), 1304 (m), 1246 (m), 1202 (m), 1092 (w), 1060 (m), 882 (m), 870 (m), 834 (vs), 798 (s), 788 (s), 756 (s), 698 (m), 670 (s).

MS (EI, 70 eV): *m/z* (%) = 205 (16), 204 (92), 188 (34), 158 (19), 75 (12), 73 (14), 70 (14), 61 (20), 45 (15), 43 (100).

HRMS (EI): calcd. for $C_{11}H_{13}NO^{28}Si$: 203.0766, found: 203.0769.

Ethyl 4-(3-((trimethylsilyl)ethynyl)pyridin-4-yl)benzoate (**81b**)



Prepared according to **TP7** by treating sulfoxide **80a** (329 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with ethyl 4-iodobenzoate (221 mg, 0.80 mmol), $ZnCl_2$ (1.10 mL, 1.10 mmol, 1.00 M in THF) and $Pd(PPh_3)_4$ (23 mg,

0.02 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 7:3, silica gel) furnished **81b** as a yellow oil (164 mg, 63% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.76 (d, J = 0.78 Hz, 1H), 8.55 (d, J = 5.17 Hz, 1H), 8.12-8.09 (m, 2H), 7.73-7.70 (m, 2H), 8.55 (s, 1H), 7.29 (dd, J = 5.17, 0.78 Hz, 1H), 4.40 (q, J = 7.21 Hz, 2H), 1.40 (t, J = 7.21 Hz, 3H), 0.15 (s, 9H).

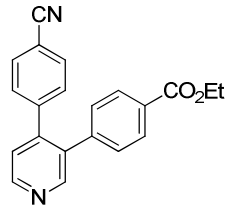
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 166.1, 154.0 (CH), 149.5 (CH), 148.9, 141.8, 130.7, 129.3 (CH), 128.9 (CH), 123.0 (CH), 118.2, 101.9, 100.8, 61.1 (CH_2), 14.3 (CH_3), -0.48 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2960 (w), 2160 (w), 1716 (s), 1610 (w), 1580 (w), 1476 (w), 1394 (m), 1368 (w), 1310 (w), 1270 (s), 1250 (s), 1182 (m), 1102 (s), 1032 (m), 1016 (w), 860 (s), 838 (vs), 780 (m), 750 (s), 702 (m), 662 (m), 650 (m).

MS (EI, 70 eV): *m/z* (%) = 323 (33, M^+), 308 (36), 280 (22), 278 (12), 266 (12), 265 (20), 264 (100), 234 (11), 220 (10), 132 (11).

HRMS (EI): calcd. for $C_{19}H_{21}NO_2{}^{28}Si$: 323.1342, found: 323.1332.

Ethyl 4-(4-(4-cyanophenyl)pyridin-3-yl)benzoate (**81c**)



Prepared according to **TP7** by treating sulfoxide **80b** (334 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 1 h, with ethyl 4-iodobenzoate (221 mg, 0.80 mmol), $ZnCl_2$ (1.10 mL, 1.10 mmol, 1.00 M in THF) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 2:8, silica gel) furnished **81c** as a colourless solid (132 mg, 50% yield).

m.p. (°C): 140-141.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.72-8.68 (m, 2H), 7.96 (d, J = 8.58 Hz, 2H), 7.56 (d, J = 8.11 Hz, 2H), 7.34 (d, J = 4.77 Hz, 1H), 7.24 (d, J = 8.11 Hz, 2H), 7.18 (d, J = 8.58 Hz, 2H), 4.37 (q, J = 7.15 Hz, 2H), 1.38 (q, J = 7.15 Hz, 3H).

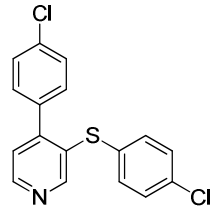
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 166.0, 151.0 (CH), 149.6 (CH), 145.8, 142.9, 141.3, 134.8, 132.2 (CH), 130.0 (CH), 129.9 (CH), 129.8 (CH), 129.7 (CH), 124.1, 118.3, 112.1, 61.2 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2924 (w), 2228 (w), 1704 (s), 1608 (w), 1586 (w), 1478 (w), 1414 (w), 1394 (m), 1364 (w), 1280 (vs), 1248 (m), 1178 (m), 1128 (m), 1104 (m), 1020 (m), 1002 (w), 860 (m), 848 (m), 836 (m), 782 (m), 768 (m), 708 (m), 690 (w).

MS (EI, 70 eV): *m/z* (%) = 329 (14), 328 (70, M^+), 300 (19), 284 (19), 283 (100), 255 (22), 254 (56), 253 (8), 252 (10), 227 (21).

HRMS (EI): calcd. for $C_{21}H_{16}N_2O_2$: 328.1212, found: 328.1209.

4-(4-Chlorophenyl)-3-((4-chlorophenyl)thio)pyridine (**81d**)



Prepared according to **TP7** by treating sulfoxide **80c** (344 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 15 min and (*S*)-(4-chlorophenyl)benzene thiosulfonate (228 mg, 0.80 mmol) at 25 °C for 1 h. Flash chromatographic purification (pentane/Et_2O 7:3, silica gel) furnished **81d** as an off-white solid (179 mg, 67% yield).

m.p. (°C): 80-82.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.52-8.48 (m, 2H), 7.40-7.36 (m, 2H), 7.31-7.27 (m, 2H), 7.23-7.19 (m, 3H), 7.12-7.08 (m, 2H).

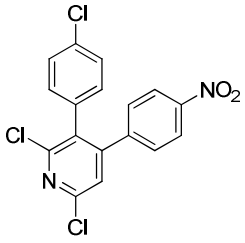
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 152.6 (CH), 149.6, 148.5 (CH), 136.1, 134.9, 133.8, 132.7, 132.6 (CH), 131.0, 130.1 (CH), 129.5 (CH), 128.6 (CH), 124.5 (CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2926 (vw), 1724 (vw), 1592 (w), 1574 (w), 1492 (w), 1474 (m), 1462 (m), 1388 (m), 1292 (w), 1250 (w), 1174 (w), 1108 (w), 1090 (s), 1042 (w), 1024 (w), 1010 (m), 824 (vs), 814 (vs), 776 (m), 758 (m), 722 (w).

MS (EI, 70 eV): *m/z* (%) = 334 (17), 333 (76), 332 (37), 331 (100, M^+), 330 (21), 298 (14), 296 (15), 207 (20), 126 (30), 75 (21).

HRMS (EI): calcd. for $C_{17}H_{11}{}^{35}Cl_2N^{32}S$: 330.9989, found: 330.9973.

2,6-Dichloro-3-(4-chlorophenyl)-4-(4-nitrophenyl)pyridine (**81e**)



Prepared according to **TP7** by treating sulfoxide **80d** (412 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with 1-iodo-4-nitrobenzene (199 mg, 0.80 mmol), $ZnCl_2$ (1.10 mL, 1.10 mmol, 1.00 M in THF) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (pentane/Et_2O 9:1, silica gel) furnished **81e** as a colourless solid (186 mg, 61% yield).

m.p. (°C): 140-142.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.14-8.10 (m, 2H), 7.39-7.37 (m, 1H), 7.32-7.24 (m, 4H), 7.07-7.03 (m, 2H).

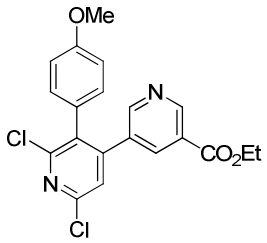
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 151.7, 150.7, 149.6, 147.6, 143.2, 134.8, 132.9, 132.6, 131.5 (CH), 129.9 (CH), 128.9 (CH), 123.6 (CH), 123.5 (CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3114 (vw), 3080 (vw), 1604 (w), 1572 (m), 1562 (m), 1528 (s), 1510 (s), 1494 (m), 1422 (m), 1398 (w), 1348 (vs), 1336 (vs), 1228 (m), 1140 (m), 1108 (w), 1090 (m), 1078 (m), 998 (w), 854 (m), 836 (m), 826 (s), 806 (vs), 774 (m), 736 (m), 722 (w), 698 (m).

MS (EI, 70 eV): *m/z* (%) = 392 (29), 380 (96), 379 (18), 378 (100, M^+), 299 (18), 297 (30), 261 (48), 227 (27), 226 (18), 225 (20).

HRMS (EI): calcd. for $C_{17}H_9{}^{35}Cl_3N_2O_2$: 377.9730, found: 377.9726.

Ethyl 2',6'-dichloro-3'-(4-methoxyphenyl)-[3,4'-bipyridine]-5-carboxylate (**81f**)



Prepared according to **TP7** by treating sulfoxide **80e** (402 mg, 1.00 mmol) with *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) at -50 °C for 5 min, with ethyl 5-bromonicotinate (184 mg, 0.80 mmol), $ZnCl_2$ (1.10 mL, 1.10 mmol, 1.00 M in THF) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) for the cross-coupling (50 °C, 5 h). Flash chromatographic purification (pentane/Et_2O 7:3, silica gel) furnished **81f** as a colourless solid (265 mg, 82% yield).

m.p. (°C): 120-121.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 9.07 (d, *J* = 1.73 Hz, 1H), 8.41 (d, *J* = 2.23 Hz, 1H), 8.02 (dd, *J* = 2.23, 1.73 Hz, 1H), 7.36 (s, 1H), 7.02-6.97 (m, 2H), 6.83-6.78 (m, 2H), 4.37 (q, *J* =7.18 Hz, 2H), 3.76 (s, 3H), 1.37 (t, *J* = 7.18 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 164.4, 159.6, 152.7 (CH), 151.2, 150.3 (CH), 149.6, 149.1, 137.1 (CH), 134.2, 133.1, 131.5 (CH), 126.0, 125.8, 123.6 (CH), 114.1 (CH), 61.7 (CH_2), 55.2 (CH_3), 14.2 (CH_3).

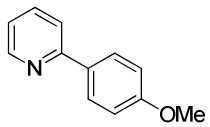
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2936 (vw), 1716 (s), 1608 (w), 1564 (m), 1528 (m), 1430 (m), 1370 (w), 1336 (m), 1306 (m), 1292 (s), 1272 (s), 1254 (vs), 1226 (m), 1178 (m), 1162 (m), 1136 (m), 1114 (m), 1088 (m), 1028 (m), 1016 (m), 882 (w), 858 (w), 840 (s), 820 (m), 794 (m), 764 (m), 706 (m), 698 (m).

MS (EI, 70 eV): *m/z* (%) = 406 (14), 405 (18), 404 (73), 403 (48), 402 (100, M^+), 401 (34), 375 (21), 373 (30), 357 (11), 44 (55).

HRMS (EI): calcd. for $C_{20}H_{16}Cl_2N_2O_3$: 402.0538, found: 402.0533.

3.3.4 Preparation of Cyclooxygenase-2 Inhibitor 90 using Ligand Coupling

2-(4-Methoxyphenyl)pyridine (**88**):



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with a solution of sulfoxide **79c** (233 mg, 1.00 mmol) in THF (2 mL). The reaction mixture was cooled to -50 °C and *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) was added dropwise. After stirring at -50 °C for 5 min, the reaction mixture was quenched with sat. aq. NH_4Cl-solution (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification (pentane/Et_2O 1:1, silica gel) furnished **88** as a colourless solid (163 mg, 88% yield).

m.p. (°C): 53-54.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.65-8.63 (m, 1H), 7.97-7.92 (m, 2H), 7.72-7.63 (m, 2H), 7.17-7.13 (m, 1H), 7.01-6.96 (m, 2H), 3.85 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 160.4, 157.1, 149.5 (CH), 136.6 (CH), 132.0, 128.1 (CH), 121.3 (CH), 119.7 (CH), 114.1 (CH), 55.3 (CH_3).

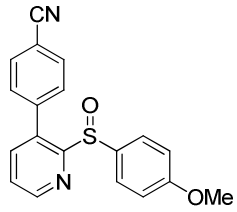
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3052 (vw), 2998 (w), 2836 (vw), 1602 (m), 1580 (m), 1564 (w), 1514 (m), 1460 (m), 1432 (m), 1306 (w), 1272 (w), 1244 (s), 1176 (m), 1152 (w), 1112 (w), 1058 (w), 1036 (m), 1022 (m), 1006 (w), 988 (w), 838 (m), 806 (w), 778 (vs), 738 (m), 718 (w).

MS (EI, 70 eV): *m/z* (%) = 186 (13), 185 (100, M^+), 170 (34), 142 (42), 141 (23), 115 (7), 70 (6), 63 (6), 51 (6), 43 (25).

HRMS (EI): calcd. for $C_{12}H_{11}NO$: 185.0841, found: 185.0834.

These data match the literature: L. Ackermann, A. Althammer, *Org. Lett.* **2006**, *8*, 3457.

4-(2-((4-Methoxyphenyl)sulfinyl)pyridin-3-yl)benzonitrile (**89**)



Prepared according to **TP5** by treating sulfoxide **79c** (1.17 g, 5.00 mmol) with tmpMgCl·LiCl (5.00 mL, 5.50 mmol, 1.10 M in THF) at -30 °C for 20 min, with 4-iodobenzonitrile (1.38 g, 6.00 mmol), $ZnCl_2$ (6.00 mL, 6.00 mmol, 1.00 M in THF) and $Pd(PPh_3)_4$ (110 mg, 0.01 mmol) for the cross-coupling (50 °C, 2 h). Flash chromatographic purification (EtOAc, silica gel) furnished **89** as a colourless solid (1.26 g, 63% yield).

m.p. (°C): 165-167.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.83 (dd, *J* = 4.65, 1.79 Hz, 1H), 7.72 (d, *J* = 8.11 Hz, 2H), 7.56 (dd, *J* = 7.63, 1.79 Hz, 1H), 7.45 (dd, *J* = 7.63, 4.65 Hz, 1H), 7.36 (d, *J* = 8.11 Hz, 2H), 7.25 (d, *J* = 9.06 Hz, 2H), 6.80 (d, *J* = 9.06 Hz, 2H), 3.77 (s, 3H).

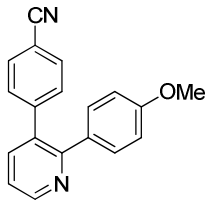
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 162.2, 160.7, 150.5 (CH), 140.3, 138.5 (CH), 135.3, 134.0, 132.2 (CH), 130.4 (CH), 128.0 (CH), 125.1 (CH), 118.2, 114.6 (CH), 112.7, 55.5 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3070 (w), 3032 (w), 2228 (w), 1590 (m), 1574 (m), 1488 (m), 1442 (m), 1408 (m), 1392 (m), 1304 (m), 1248 (vs), 1184 (w), 1166 (m), 1130 (w), 1100 (m), 1080 (vs), 1064 (vs), 1054 (s), 1024 (s), 1000 (m), 832 (s), 814 (s), 796 (s), 758 (m), 710 (w), 640 (w).

MS (EI, 70 eV): *m/z* (%) = 334 (33, M^+), 318 (34), 317 (100), 211 (22), 155 (80), 152 (25), 139 (87), 124 (33), 123 (33), 44 (38).

HRMS (EI): calcd. for $C_{19}H_{14}N_2O_2{}^{32}S$: 334.0776, found: 334.0781.

4-(2-(4-methoxyphenyl)pyridin-3-yl)benzonitrile (**90**):



A dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with a solution of sulfoxide **89** (334 mg, 1.00 mmol) in THF (2 mL). The reaction mixture was cooled to -50 °C and *i*PrMgCl·LiCl (0.92 mL, 1.10 mmol, 1.20 M in THF) was added dropwise. After stirring at -50 °C for 5 min, the reaction mixture was quenched with sat. aq. NH_4Cl-solution (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Flash chromatographic purification (pentane/Et_2O 1:1, silica gel) furnished **90** as a colourless solid (238 mg, 83% yield).

m.p. (°C): 123-124.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.74 (dd, *J* = 4.77, 1.67 Hz, 1H), 7.72 (dd, *J* = 7.87, 1.67 Hz, 1H), 7.59 (d, *J* = 8.35, 2H), 7.36 (dd, *J* = 7.87, 4.77 Hz, 1H), 7.32 (d, *J* = 8.35 Hz, 2H), 7.26 (d, *J* = 8.82 Hz, 2H), 6.80 (d, *J* = 8.82 Hz, 2H), 3.80 (s, 3H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 159.9, 156.5, 148.8 (CH), 144.8, 138.6 (CH), 134.0, 132.2 (CH), 131.3 (CH), 130.2 (CH), 121.8 (CH), 118.6, 113.7 (CH), 111.1, 108.7, 55.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2836 (vw), 2228 (w), 1604 (m), 1580 (w), 1574 (w), 1510 (m), 1460 (w), 1444 (w), 1424 (s), 1396 (m), 1306 (w), 1298 (w), 1248 (s), 1186 (m), 1174 (m), 1106 (w), 1042 (m), 1024 (m), 1000 (w), 842 (vs), 814 (s), 804 (s), 782 (vs), 740 (w), 722 (w).

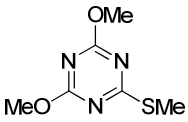
MS (EI, 70 eV): *m/z* (%) = 287 (10), 286 (63, M^+), 285 (100), 271 (2), 270 (3), 243 (5), 242 (22), 241 (4), 214 (2), 121 (1).

HRMS (EI): calcd. for $C_{19}H_{14}N_2O$: 286.1106, found: 286.1096.

3.4 Preparation of Functionalized Heterocycles 93 by Transition Metal-Catalyzed Cross-Coupling Reaction of Unsaturated Thioethers 91 with Functionalized Organozinc Reagents 92

3.4.1 Preparation of Heterocyclic Thioethers 91

2,4-Dimethoxy-6-(methylthio)-1,3,5-triazine (**91a**)



2-Chloro-4,6-dimethoxy-1,3,5-triazine (1.76 g, 10.0 mmol) and sodium thiomethanolate (780 mg, 11.0 mmol) were dissolved in DMF (10 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (30 mL) followed by extraction using EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Recrystallisation from Et_2O furnished **91a** as a colourless solid (1.63 g, 87% yield).

m.p. (°C): 117-120.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 3.99 (s, 6H), 2.52 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 185.4, 170.9, 55.2 (CH_3), 13.4 (CH_3).

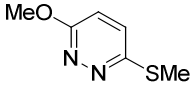
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3000 (vw), 1549 (vs), 1531 (s), 1499 (s), 1453 (m), 1395 (m), 1345 (vs), 1327 (s), 1296 (s), 1286 (s), 1194 (m), 1105 (s), 1045 (s), 980 (m), 940 (m), 901 (m), 806 (s).

MS (EI, 70 eV): *m/z* (%) = 189 (4), 188 (7), 187 (100, M^+), 186 (5), 172 (16), 142 (7), 141 (11), 126 (17), 101 (5), 70 (4).

HRMS (EI): calcd. for $C_6H_9N_3O_2S$: 187.0415, found: 187.0407.

These data match the literature: Tosato, M. L.; Soccorsi, L. *J. Chem. Soc., Perkin Trans. 2,* **1982**, *11*, 1321-1326.

3-Methoxy-6-(methylthio)pyridazine (**91f**)



3-Chloro-6-methoxypyridazine (1.45 g, 10.0 mmol) and sodium thiomethanolate (780 mg, 11.0 mmol) were dissolved in DMF (10 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (20 mL) followed by extraction using EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and after

filtration the solvent was removed under reduced pressure. Recrystallisation from Et_2O furnished **91f** as a colourless solid (1.49 g, 95% yield).

m.p. (°C): 93-94.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.20 (d, *J* = 9.30 Hz, 1H), 6.80 (d, *J* = 9.30 Hz, 1H), 4.06 (s, 3H), 2.66 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.2, 156.5, 129.0, 117.5, 54.6, 13.4.

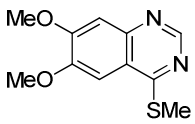
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2958 (vw), 1564 (s), 1542 (vs), 1454 (m), 1409 (m), 1363 (vs), 1299 (m), 1258 (s), 1143 (m), 1104 (s), 1021 (s), 1013 (m), 941 (m), 815 (s), 808 (s), 605 (w).

MS (EI, 70 eV): *m/z* (%) = 157 (7), 156 (100, M^+), 155 (26), 123 (6), 111 (5), 99 (5), 98 (10), 85 (13), 80 (6), 79 (6).

HRMS (EI): calcd. for $C_6H_8N_2O^{32}S$: 156.0357, found: 156.0363.

These data match the literature: Metzger, A.; Melzig, L.; Despotopoulou, C.; Knochel, P. *Org. Lett*. **2009**, *11*, 4228-4231.

6,7-Dimethoxy-4-(methylthio)quinazoline (**91g**)



4-Chloro-6,7-dimethoxyquinazoline (997 mg, 4.44 mmol) and sodium thiomethanolate (346 mg, 4.88 mmol) were dissolved in DMF (5 mL). After stirring at 25 °C for 24 h, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (10 mL) followed by extraction using EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Recrystallisation from Et_2O furnished **91g** as a colourless solid (1.00 g, 95% yield).

m.p. (°C): 165-166.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.85 (s, 1H), 7.24 (s, 1H), 7.18 (s, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 2.70 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 168.0, 155.5, 152.4 (CH), 149.9, 145.1, 119.1, 107.0 (CH), 101.4 (CH), 56.4 (CH_3), 56.2 (CH_3), 12.6 (CH_3).

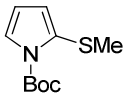
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2918 (w), 1614 (w), 1571 (w), 1542 (m), 1506 (s), 1450 (m), 1411 (s), 1358 (s), 1342 (s), 1230 (vs), 1204 (s), 1158 (vs), 1124 (s), 1019 (m), 970 (m), 871 (m), 845 (s), 827 (m), 799 (s), 700 (m), 658 (m).

MS (EI, 70 eV): *m/z* (%) = 237 (14), 236 (100, M^+), 235 (21), 222 (7), 221 (48), 204 (7), 190 (10), 189 (11), 175 (9), 163 (14).

HRMS (EI): calcd. for $C_{11}H_{12}N_2O_2{}^{32}S$: 236.0619, found: 236.0616.

These data match the literature: Alexandre, F.-R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron*, **2003**, *59*, 1413-1419.

Tert-butyl 2-(methylthio)-1*H*-pyrrole-1-carboxylate (**91k**)



In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, *n*BuLi (8.13 mL, 10.0 mmol, 1.23 M in hexane) was slowly added to a solution of 2,2,6,6-tetramethylpiperidine (1.41 g, 10.0 mmol) in THF (10 mL) at -78 °C. The mixture was allowed to stir at -78 °C for 10 min and then at -10 °C for 10 min, whereupon it was cooled to -78 °C. To the resulting yellow solution *N*-Boc-pyrrole (1.67 g, 10 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h followed by rapid addition of dimethyl disulfide (2.07 g, 22.0 mmol) at -78 °C. The mixture was warmed to 25 °C slowly. After stirring at 25 °C for 1 h, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (20 mL) followed by extraction using EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **91k** as a pale yellow liquid (0.77 g, 36% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.23 (dd, *J* = 3.34, 1.80 Hz, 1H), 6.18 (dd, *J* = 3.47, 3.34 Hz, 1H), 5.94 (dd, *J* = 3.47, 1.80 Hz, 1H), 2.39 (s, 3H), 1.59 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 149.0, 129.3, 121.5 (CH), 111.4 (CH), 110.2 (CH), 84.3, 28.0 (CH_3), 17.0 (CH_3).

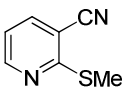
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2979 (w), 1763 (m), 1726 (s), 1476 (w), 1455 (w), 1393 (w), 1368 (m), 1327 (s), 1302 (s), 1252 (s), 1147 (vs), 1099 (s), 1058 (m), 1023 (m), 1001 (m), 969 (w), 843 (m), 775 (m), 712 (w).

MS (EI, 70 eV): *m/z* (%) = 213 (10, M^+), 159 (13), 157 (79), 113 (54), 98 (45), 82 (11), 57 (100), 56 (15), 44 (19), 41(45).

HRMS (EI): calcd. for $C_{10}H_{15}NO_2{}^{32}S$: 213.0823, found: 213.0825.

These data match the literature: Semmelhack, M. F.; Chlenov, A. M.; Ho, D. M. *J. Am. Chem. Soc.* **2005**, *127*, 7759-7773.

2-(Methylthio)nicotinonitrile (**91l**)



2-Chloronicotinonitrile (2.77 g, 20.0 mmol) and sodium thiomethanolate (2.31 g, 33.0 mmol) were dissolved in DMF (10 mL). After stirring at 25 °C for 24 h, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (50 mL) followed by extraction using EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane/Et_2O 3:1, silica gel) furnished **91l** as a yellow solid (665 mg, 22% yield).

m.p. (°C): 90-91.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.57 (dd, J = 5.01, 1.85 Hz, 1H), 7.77 (dd, J = 7.69, 1.85 Hz, 1H), 7.05 (dd, J = 7.69, 5.01 Hz, 1H), 2.60 (s, 3H).

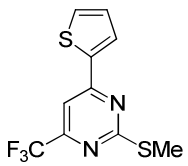
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.4, 152.0 (CH), 140.3 (CH), 118.2 (CH), 115.5, 107.2, 13.1 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3046 (w), 2929 (w), 2224 (m), 1574 (m), 1546 (m), 1391 (vs), 1316 (m), 1232 (m), 1184 (m), 1143 (m), 1078 (m), 959 (w), 801 (vs), 736 (m), 721 (m), 667 (m).

MS (EI, 70 eV): *m/z* (%) = 150 (100, M^+), 123 (27), 104 (40), 79 (30), 75 (11), 45 (10), 43 (16).

HRMS (EI): calcd. for $C_7H_6N_3{}^{32}S$: 150.0252, found: 150.0245.

2-(Methylthio)-4-(2-thienyl)-6-(trifluoromethyl)pyrimidine (**91d**)



4,4,4-Trifluoro-1-(2-thienyl)butane-1,3-dione (7.11 g, 32.0 mmol) and thiourea (2.43 g, 32.0 mmol) were dissolved in EtOH (20 mL). HCl conc. (1.0 mL) was added and the reaction mixture was heated at 95 °C for 8 h. After cooling to 25 °C a precipitate formed which was filtered off, washed with pentane and dried in vacuo, giving 6-(2-thienyl)-4-(trifluoromethyl)pyrimidine-2-(1*H*)-thione (2.63 g, 31%) as an orange solid.

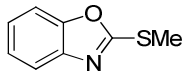
6-(2-Thienyl)-4-(trifluoromethyl)pyrimidine-2-(1*H*)-thione (2.63 g, 10.0 mmol) was dissolved in THF (25 mL), and sodium hydride (288 mg, 12.0 mmol) was added in small portions at -20 °C. The yellow mixture was warmed to 25 °C and stirred for 1 h. Then, iodomethane (1.99 g, 14.0 mmol) was added. After stirring for 1 h at 25 °C, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (40 mL) followed by extraction using EtOAc (3 x 40 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane/Et_2O 20:1, silica gel) furnished **91d** as a yellow crystalline solid (1.68 mg, 61% yield).

m.p. (°C): 69-71.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.83 (dd, J = 3.83, 1.12 Hz, 1H), 7.59 (dd, J = 5.05, 1.12 Hz, 1H), 7.45 (s, 1H), 7.17 (dd, J = 5.05, 3.83 Hz, 1H), 2.63 (s, 3H).

These data match the literature: Flores, A. F. C.; Pizzuti, L.; Brondani, S.; Rossato, M.; Zanatta, N.; Martins, M. A. P. *J. Braz. Chem. Soc.* **2007**, *18*, 1316-1321.

2-(Methylthio)-1,3-benzoxazole (**91c**)

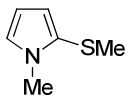


1,3-Benzoxazole-2-thiol (3.02 g, 20.0 mmol) was dissolved in THF (10 mL) and sodium hydride (880 mg, 22.0 mmol) was added in small portions. After stirring at 25 °C for 15 min, iodomethane (3.12 g, 23.0 mmol) was added. After stirring at 25 °C for 1 h, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (40 mL) followed by extraction using Et_2O (3 x 40 mL). Evaporation of the solvent furnished **91c** as a brown oil (3.14 g, 95% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.60-7.57 (m, 1H), 7.42-7.39 (m, 1H), 7.28-7.18 (m, 2H), 2.73 (s, 3H).

These data match the literature: Kamat, M. N.; Rath, N. P.; Demchenko, A. V. *J. Org. Chem.* **2007**, *72*, 6938-6946.

1-Methyl-2-(methylthio)-*1H*-pyrrole (**91b**)



In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, *n*BuLi (22.5 mL, 55.0 mmol, 2.44 M in hexane) was slowly added to a solution of *N*-methyl-pyrrole (4.06 g, 50.0 mmol) in THF (30 mL) at 0 °C. The mixture was allowed to warm to 25 °C and, after stirring for 1 h at 25 °C, dimethyl disulfide (5.65 g, 60.0 mmol) was added at 0 °C. The reaction mixture was warmed to 25 °C and after stirring for 1 h, quenched with sat. aqueous K_2CO_3 solution (30 mL) followed by extraction using EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane, silica gel) furnished **91b** as a clear liquid (4.32 g, 68% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.78-6.77 (m, 1H), 6.37-6.35 (m, 1H), 6.14-6.12 (m, 1H), 3.71 (s, 3H), 2.28 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 124.4 (CH), 123.1, 115.7 (CH), 107.8 (CH), 33.8 (CH_3), 21.1 (CH_3).

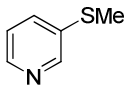
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2918 (w), 1516 (W), 1460 (m), 1432 (w), 1422 (w), 1409 (m), 1391 (w), 1311 (w), 1291 (s), 1216 (w), 1086 (m), 1044 (w), 998 (w), 966 (m), 882 (w), 858 (vw), 789 (w), 712 (vs), 684 (m).

MS (EI, 70 eV): *m/z* (%) = 129 (5), 128 (9), 127 (100, M^+), 114 (4), 113 (5), 112 (71), 85 (8), 78 (11), 71 (5), 68 (8).

HRMS (EI): calcd. for $C_6H_9N^{32}S$: 127.0456, found: 127.0452.

These data match the literature: Nedolyaa, N. A.; Brandsmab, L.; Verkruijsseb, H. D.; Trofimova, B. A. *Tetrahedron Let.* **1997**, *38*, 7247-7248.

3-(Methylthio)pyridine (**91r**)



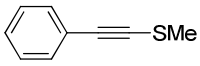
In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, 3-bromopyridine (3.16 g, 20.0 mmol) was dissolved in THF (20 mL). The solution was cooled to 0 °C and *i*PrMgCl·LiCl (18.5 mL, 22.0 mmol, 1.19 M in THF) was added dropwise. After stirring at 25 °C for 1 h, *S*-methyl methanethiosulfonate (3.03 g, 24.0 mmol) was added and the solution was allowed to warm to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous K_2CO_3 solution and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane/Et_2O 4:1, silica gel) furnished **91r** as a yellow liquid (1.74 g, 69% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.47 (dd, *J* = 2.43, 0.80 Hz, 1H), 8.34 (dd, *J* = 4.79, 1.52 Hz, 1H), 7.52 (ddd, *J* = 8.06, 2.43, 1.52, 1H), 7.16 (ddd, *J* = 8.06, 4.79, 0.80 Hz, 1H), 2.46 (s, 3H).

These data match the literature: A. Doudouh, C. Woltermann, P. C. Gros, *J. Org. Chem.* **2007**, *72*, 4978.

3.4.2 Preparation of Alkynyl Thioethers 94

((Methylthio)ethynyl)benzene (**94a**)

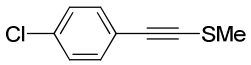


In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, phenylacetylene (5.11 g, 50.0 mmol) was dissolved in THF (50 mL). The solution was cooled to -78 °C and *n*BuLi (55.0 mmol, 22.7 mL, 2.42 M in hexane) was added dropwise. After stirring at -78 °C for 10 min, dimethyl disulfide (5.65 g, 60.0 mmol) was added and the solution was allowed to warm to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl-solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane, silica gel) furnished **94a** as a clear liquid (5.89 g, 79% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.40-7.37 (m, 2H), 7.28-7.25 (m, 3H), 2.45 (s, 3H).

These data match the literature: Stefani, H. A.; Cella, R.; Doerr, F. A.; de Pereira, C. M. P.; Gomes, F. P.; Zeni, G. *Tetrahedron Lett.* **2005**, *46*, 2001.

1-Chloro-4-((methylthio)ethynyl)benzene (**94b**)



In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, 1-ethynyl-4-chlorobenzene (4.10 g, 30.0 mmol) was dissolved in THF (30 mL). The solution was cooled to -78 °C and *n*BuLi (33.0 mmol, 13.6 mL, 2.42 M in hexane) was added dropwise. After stirring at -78 °C for 10 min, dimethyl disulfide (3.39 g, 36.0 mmol) was added and the solution was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl-solution and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane, silica gel) furnished **94b** as a clear liquid (4.83 g, 88% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.34-7.31 (d, J = 8.84 Hz, 2H). 7.27-7.24 (d, J = 8.84 Hz, 2H), 2.46 (s, 3H).

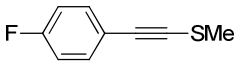
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 134.0, 132.6 (CH), 128.6 (CH), 121.9, 90.7, 82.2, 19.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2927 (w), 2166 (w), 1899 (vw), 1739 (vw), 1590 (vw), 1485 (s), 1432 (w), 1420 (w), 1398 (w), 1312 (w), 1243 (w), 1088 (s), 1013 (m), 976 (m), 957 (w), 867 (w), 823 (vs), 709 (w), 688 (w)

MS (EI, 70 eV): *m/z* (%) = 185 (3), 184 (33), 183 (9), 182 (100, M^+), 169 (25), 168 (6), 167 (72), 132 (12), 125 (7), 123 (20).

HRMS (EI): calcd. for $C_9H_7{}^{35}Cl^{32}S$: 181.9957, found: 181.9949.

1-Fluoro-4-((methylthio)ethynyl)benzene (**94c**)



In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, 1-ethynyl-4-fluorobenzene (2.40 g, 20.0 mmol) was dissolved in THF (20 mL). The solution was cooled to 0 °C and *i*PrMgCl·LiCl (18.5 mL, 22.0 mmol, 1.19 M in THF) was added dropwise. After stirring at 0 °C for 10 min, *S*-methyl methanethiosulfonate (3.03 g, 24.0 mmol) was added and the solution was allowed to warm to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl-solution and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane, silica gel) furnished **94c** as a yellow liquid (2.77 g, 83% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.41-7.36 (m, 2H), 7.01-6.95 (m, 2H), 2.46 (s, 3H).

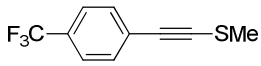
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.4 (d, J = 249.5 Hz, CF), 133.5 (d, J = 8.53 Hz, CH), 119.5 (d, J = 3.35), 115.5 (d, J = 22.2 Hz, CH), 90.7, 80.6, 19.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2928 (w), 2170 (w), 1739 (w), 1600 (m), 1501 (vs), 1434 (w), 1423 (w), 1313 (w), 1230 (s), 1217 (s), 1155 (m), 1092 (w), 1013 (w), 977 (w), 957 (w), 873 (w), 831 (vs), 794 (s), 692 (vw).

MS (EI, 70 eV): *m/z* (%) = 166 (100, M^+), 152 (11), 151 (74), 107 (84), 69 (10), 57 (14), 55 (12), 44 (17), 43 (20), 41 (12).

HRMS (EI): calcd. for $C_9H_7F^{32}S$: 166.0252; found: 166.0246.

1-((Methylthio)ethynyl)-4-(trifluoromethyl)benzene (**94d**)



In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, 1-ethynyl-4-trifluoromethylbenzene (5.10 g, 30.0 mmol) was dissolved in THF (30 mL). The solution was cooled to -78 °C and *n*BuLi (33.0 mmol, 13.6 mL, 2.42 M in hexane) was added dropwise. After stirring at -78 °C for 10 min, dimethyl disulfide (3.39 g, 36.0 mmol) was added and the solution was allowed to warm to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl-solution and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO4) and after filtration the solvent was

removed under reduced pressure. Purification by flash chromatography (pentane, silica gel) furnished **94d** as a clear liquid (3.24 g, 51% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.55-7.52 (d, J = 8.33 Hz, 2H), 7.48-7.45 (d, J = 8.33 Hz, 2H), 2.49 (s, 3H).

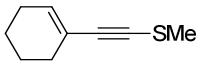
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 131.2 (CH), 129.5 (q, J = 32.7 Hz), 127.2 (q, J = 1.37 Hz), 125.2 (q, J = 3.87 Hz, CH), 123.9 (q, J = 272.0 Hz, CF_3), 90.8, 84.4, 19.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2932 (vw), 2167 (m), 1613 (m), 1405 (w), 1318 (vs), 1242 (w), 1163 (s), 1120 (s), 1104 (s), 1064 (vs), 1016 (m), 978 (w), 957 (w), 837 (s), 766 (w), 666 (w).

MS (EI, 70 eV): *m/z* (%) = 216 (100, M^+), 202 (9), 201 (71), 181 (12), 157 (50), 137 (9), 132 (8), 45 (8) 44 (17), 43 (11).

HRMS (EI): calcd. for $C_{10}H_7F_3{}^{32}S$: 216.0221, found: 216.0217.

1-((Methylthio)ethynyl)cyclohexene (**94e**)



In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, 1-ethynyl-cyclohexene (3.18 g, 30.0 mmol,) was dissolved in THF (30 mL). The solution was cooled to -78 °C and *n*BuLi (13.6 mL, 33.0 mmol, 2.42 M in THF) was added dropwise. After stirring at -78 °C for 10 min, dimethyl disulfide (3.39 g, 36.0 mmol) was added and the solution was allowed to warm to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous K_2CO_3-solution and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane, silica gel) furnished **94e** as a clear liquid (3.90 g, 85% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.09-6.05 (m, 1H), 2.37 (s, 3H), 2.13-2.04 (m, 4H), 1.65-1.51 (m, 4H).

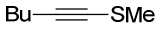
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 134.9 (CH), 120.9, 93.7, 77.5, 29.2 (CH_2), 25.7 (CH_2), 22.3 (CH_2), 21.5 (CH_2), 19.6 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = (vs), 2857 (m), 2830 (m), 1739 (w), 1626 (vw), 1446 (m), 1434 (s), 1348 (m), 1311 (m), 1136 (w), 1077 (w), 1045 (w), 975 (m), 956 (m), 918 (s), 840 (s), 802 (m), 797 (m), 706 (w).

MS (EI, 70 eV): *m/z* (%) = 152 (51, M^+), 137 (61), 109 (100), 105 (43), 104 (39), 103 (56), 97 (50), 93 (54), 91 (59), 77 (39).

HRMS (EI): calcd. for $C_9H_{12}{}^{32}S$: 152.0660, found: 152.0653.

1-(Methylthio)hex-1-yne (**94f**)

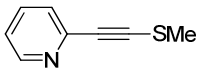


In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, 1-hexyne (1.64 g, 20.0 mmol) was dissolved in THF (20 mL). The solution was cooled to 0 °C and *i*PrMgCl·LiCl (18.5 mL, 22.0 mmol, 1.19 M in THF) was added dropwise. After stirring at 0 °C for 10 min, *S*-methyl methanethiosulfonate (3.03 g, 24.0 mmol) was added and the solution was allowed to warm to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl-solution and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane, silica gel) furnished **94f** as a clear liquid (2.33 g, 91% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 2.35 (s, 3H), 2.26 (t, J = 6.81 Hz, 2H), 1.32-1.50 (m, 4H), 0.88 (t, J = 6.78 Hz, 2H).

These data match the literature: Zhao, S. H.; Samuel, O.; Kagan, H. B. Tetrahedron **1987**, *43*, 5135.

2-((Methylthio)ethynyl)pyridine (**94g**)



In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, 2-ethynylpyridine (3.09 g, 30.0 mmol) was dissolved in THF (30 mL). The solution was cooled to 0 °C and *i*PrMgCl·LiCl (33.0 mmol, 27.7 mL, 1.19 M in THF) was added dropwise. After stirring at 0 °C for 10 min, *S*-methyl methanethiosulfonate (4.55 g, 36.0 mmol) was added and the solution was allowed to warm to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl-solution and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane/Et_2O 2:1, silica gel) furnished **94g** as a clear liquid (2.12 g, 47% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.52-8.50 (m, 1H), 7.62-7.56 (m, 1H), 7.34-7.31 (m, 1H), 7.18-7.13 (m, 1H), 2.48 (s, 3H).

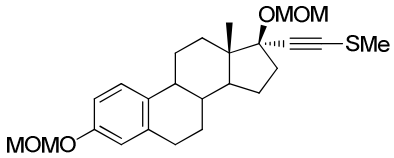
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 149.7 (CH), 143.2, 136.1 (CH), 126.2 (CH), 122.3 (CH), 91.6, 83.0, 19.0 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3040 (w), 3002 (w), 2926 (w), 2170 (m), 2131 (w), 1739 (w), 1638 (w), 1579 (s), 1560 (m), 1508 (m), 1459 (s), 1424 (s), 1312 (m), 1258 (m), 1148 (m), 1080 (m), 988 (m), 823 (w), 773 (vs), 738 (m), 664 (w).

MS (EI, 70 eV): *m/z* (%) =149 (92, M^+), 148 (100), 134 (55), 83 (33), 69 (42), 57 (41), 55 (44), 44 (56), 43 (36), 40 (35).

HRMS (EI): calcd. for $C_8H_7N^{32}S$: 149.0299, found: 149.0283.

(17b)-3,17-*Bis*(methoxymethoxy)-17-((methylthio)ethynyl)estra-1(10),2,4-triene (**94i**)



In a dry argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, MOM-protected ethinylestradiol (2.11 g, 5.48 mmol) was dissolved in THF (10 mL). The solution was cooled to 0 °C and *i*PrMgCl·LiCl (6.03 mmol, 5.07 mL, 1.19 M in THF) was added dropwise. After 10 min of stirring at 0 °C, *S*-methyl methanethiosulfonate (830 mg, 6.58 mmol) was added and the solution was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated aqueous K_2CO_3-solution and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **94i** as a clear oil (1.96 g, 83% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.20 (d, *J* = 8.37 Hz, 1H), 6.83 (dd, *J* = 8.37, 2.61 Hz, 1H), 6.77 (d, *J* = 2.61 Hz, 1H), 5.14 (s, 2H), 5.02 (d, *J* = 6.45 Hz, 1H), 4.79 (d, *J* = 6.45 Hz, 1H), 3.47 (s, 3H), 3.40 (s, 3H), 2.86-2.84 (m, 2H), 2.40 (s, 3H), 2.35-2.30 (m, 1H), 2.25-2.20 (m, 2H), 2.17-2.11 (m, 1H), 1.89-1.85 (m, 1H), 1.83-1.71 (m, 4H), 1.51-1.35 (m, 4H), 0.90 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 155.0, 138.0, 133.8, 126.3 (CH), 116.1 (CH), 113.7 (CH), 94.4 (CH_2), 93.5, 93.4 (CH_2), 86.1, 79.7, 55.8 (CH_3), 55.7 (CH_3), 48.9 (CH), 48.2, 43.6 (CH), 39.1 (CH), 37.5 (CH_2), 33.3 (CH_2), 29.7 (CH_2), 27.2 (CH_2), 26.3 (CH_2), 23.0 (CH_2), 19.4 (CH_3), 13.1 (CH_3).

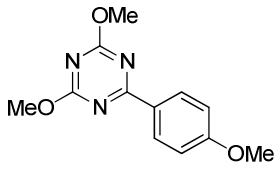
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2928 (m), 2162 (vw), 1739 (vw), 1497 (m), 1440 (w), 1241 (m), 1231 (m), 1150 (s), 1094 (m), 1076 (m), 1033 (s), 1015 (vs), 920 (m), 871 (w), 819 (w), 735 (m).

MS (EI, 70 eV): *m/z* (%) = 430 (2, M^+), 416 (13), 415 (45), 385 (12), 383 (38), 339 (15), 272 (12), 147 (11), 85 (13), 45 (100).

HRMS (EI): calcd. for $C_{25}H_{34}O_4{}^{32}S$: 430.2178, found: 430.2178.

3.4.3 Preparation of Heterocycles 93 via Pd-Catalyzed Cross-Coupling Reaction

2,4-Dimethoxy-6-(4-methoxyphenyl)-1,3,5-triazine (**93b**)



Prepared according to **TP8** from dimethoxy-6-(methylthio)-1,3,5-triazine (**91a**; 187 mg, 1.00 mmol), (4-methoxyphenyl)zinc iodide (**92b**, 1.38 mL, 1.50 mmol, 1.09 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 5 h. Purification by flash chromatography (pentane/Et_2O 3:2, silica gel) furnished **93b** as a colourless solid (205 mg, 83% yield).

m.p. (°C): 99-100.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.47-8.42 (m, 2H), 6.98-6.93 (m, 2H), 4.09 (s, 6H), 3.86 (s, 3H).

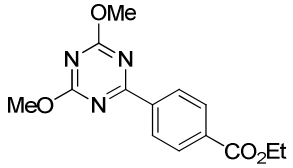
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 174.3, 172.7, 163.5, 130.9 (CH), 127.5, 113.7 (CH), 55.4 (CH_3), 55.0 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2959 (vw), 1592 (m), 1562 (s), 1540 (vs), 1523 (s), 1490 (m), 1454 (m), 1421 (m), 1409 (m), 1372 (s), 1362 (vs), 1299 (m), 1258 (s), 1190 (m), 1183 (m), 1171 (m), 1142 (s), 1103 (s), 1020 (s), 1011 (m), 941 (s), 814 (vs), 807 (s).

MS (EI, 70 eV): *m/z* (%) = 248 (14), 247 (100, M^+), 246 (25), 217 (20), 216 (8), 202 (26), 176 (16), 134 (43), 133 (8), 69 (7).

HRMS (EI): calcd. for $C_{12}H_{13}N_3O_3$: 247.0957, found: 247.0943.

Ethyl 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)benzoate (**93c**)



Prepared according **TP8** from 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**91a**; 181 mg, 1.00 mmol) and 4-(ethoxycarbonyl)phenylzinc iodide (**92c**, 2.03 mL, 1.50 mmol, 0.74 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 5 h. Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **93c** as a yellow

solid (243 mg, 84% yield). Alternatively, by applying **TP9** (25 °C, 7 h), **93c** was obtained in 81% yield.

Large scale preparation:

Prepared according to **TP8** from 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**91a**; 3.74 g, 20.0 mmol in 10 mL THF), 4-(ethoxycarbonyl)phenylzinc iodide (**92c**, 40.5 mL, 30.0 mmol, 0.74 M in THF), $Pd(OAc)_2$ (112 mg, 2.5 mol%) and S-Phos (411 mg, 5.0 mol%). After 3 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (30 mL) followed by extraction using EtOAc (3 x 50 mL). Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **93c** as a yellow solid (4.95 g, 86% yield).

m.p. (°C): 97-98.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.53 (d, J = 8.58 Hz, 2H), 8.13 (d, J = 8.58 Hz, 2H), 4.40 (q, J = 7.15 Hz, 2H), 4.12 (s, 6H), 1.41 (t, J = 7.15 Hz, 3H).

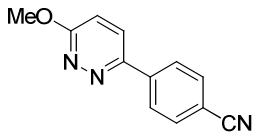
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 174.0, 173.0, 166.0, 138.9, 134.0, 129.6 (CH), 128.8 (CH), 61.3 (CH_3), 55.3 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2990 (w), 1714 (m), 1590 (m), 1541 (vs), 1496 (s), 1457 (s), 1354 (vs), 1274 (s), 1198 (m), 1128 (m), 1102 (s), 1034 (m), 1018 (s), 940 (m), 852 (w), 820 (m), 782 (m), 718 (m), 676 (w).

MS (EI, 70 eV): *m/z* (%) = 290 (17), 289 (97, M^+), 288 (21), 261 (13), 259 (27), 245 (13), 244 (100), 216 (14), 186 (18), 159 (12).

HRMS (EI): calcd. for $C_{14}H_{15}N_3O_4$: 289.1063, found: 289.1057.

4-(6-Methoxypyridazin-3-yl)benzonitrile (**93d**)



Prepared according to **TP8** from 3-methoxy-6-(methylthio)pyridazine (**91f**; 156 mg, 1.00 mmol), (4-cyanophenyl)zinc iodide (**92d**, 2.11 mL, 1.50 mmol, 0.71 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 4 h. Purification by flash chromatography (pentane/Et_2O 2:3, silica gel) furnished **93d** as a colourless solid (161 mg, 76% yield).

m.p. (°C): 161-162.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.11-8.15 (m, 2H), 7.76-7.82 (m, 3H), 7.10 (d, J = 9.17 Hz, 1H), 4.20 (s, 3H).

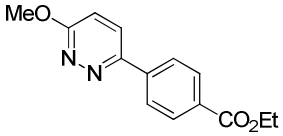
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 164.7, 140.2, 153.3, 132.7 (CH), 127.1 (CH), 127.0 (CH), 118.5, 118.0 (CH), 113.1, 55.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3059 (w), 2952 (w), 2224 (m), 1593 (m), 1548 (w), 1460 (s), 1408 (s), 1341 (m), 1299 (s), 1177 (m), 1116 (m), 1020 (m), 1001 (s), 860 (w), 834 (vs), 768 (w), 670 (w), 627 (w).

MS (EI, 70 eV): *m/z* (%) = 212 (15), 211 (100, M^+), 210 (72), 204 (12), 182 (39), 140 (60), 129 (31), 127 (17), 113 (13), 53 (14).

HRMS (EI): calcd. for $C_{12}H_9N_3O$: 211.0746, found: 211.0738.

Ethyl 4-(6-methoxypyridazin-3-yl)benzoate (**93e**)



Prepared according to **TP8** from 3-methoxy-6-(methylthio)pyridazine (**91f**; 156 mg, 1.00 mmol), (4-(ethoxycarbonyl)phenyl)zinc iodide (**92c**, 2.03 mL, 1.50 mmol, 0.74 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 4 h. Purification by flash chromatography (pentane/Et_2O 1:1, silica gel) furnished **93e** as a colourless solid (199 mg, 77% yield).

m.p. (°C): 140-142.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.13-8.16 (m, 2H), 8.05–8.09 (m, 2H), 7.81 (d, *J* = 9.3 Hz, 1H), 7.06 (d, *J* = 9.3 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 4.18 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H).

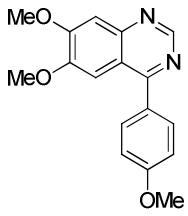
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.2, 164.5, 154.2, 140.1, 131.1, 130.1 (CH), 127.2 (CH), 126.3 (CH), 117.8 (CH), 61.1 (CH_2), 55.0 (CH_3), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2951 (w), 1712 (vs), 1596 (m), 1463 (s), 1411 (s), 1304 (s), 1262 (vs), 1180 (m), 1100 (s), 1020 (s), 1014 (s), 1002 (s), 874 (m), 829 (s), 782 (m), 756 (s), 702 (m).

MS (EI, 70 eV): *m/z* (%) = 259 (14), 258 (100, M^+), 257 (72), 229 (15), 213 (31), 199 (7), 187 (7), 176 (8), 159 (10), 129 (7).

HRMS (EI): calcd. for $C_{14}H_{14}N_2O_3$: 258.1004, found: 258.1000.

6,7-Dimethoxy-4-(4-methoxyphenyl)quinazoline (**93f**)



Prepared according to **TP8** from 6,7-dimethoxy-4-(methylthio)quinazoline (**91g**; 236 mg, 1.00 mmol), 4-methoxyphenylzinc iodide (**92b**, 1.38 mL, 1.50 mmol, 1.09 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 10 h. Purification by flash chromatography (Et_2O/EtOH 10:1, silica gel) furnished **93f** as a colourless solid (211 mg, 71% yield).

m.p. (°C): 149-150.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 9.14 (s, 1H), 7.77-7.72 (m, 2H), 7.37 (s, 1H), 7.36 (s, 1H), 7.10-7.05 (m, 2H), 4.06 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H).

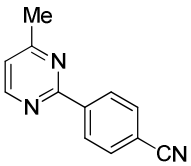
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 164.7, 161.0, 155.7, 153.3 (CH), 150.2, 148.9, 131.1 (CH), 129.9, 118.6, 114.1 (CH), 106.8 (CH), 104.1 (CH), 56.4 (CH_3), 56.1 (CH_3), 55.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 1608 (m), 1571 (w), 1516 (m), 1502 (vs), 1476 (m), 1458 (m), 1445 (m), 1412 (m), 1370 (m), 1300 (w), 1257 (s), 1236 (vs), 1218 (s), 1175 (s), 1137 (s), 1025 (s), 1004 (m), 860 (m), 831 (m), 816 (m), 792 (m).

MS (EI, 70 eV): *m/z* (%) = 297 (21), 296 (100, M^+), 295 (43), 282 (17), 281 (86), 265 (37), 264 (54), 251 (10), 250 (11), 238 (11).

HRMS (EI): calcd. for $C_{17}H_{16}N_2O_3$: 296.1161, found: 296.1152.

4-(4-Methylpyrimidin-2-yl)benzonitrile (**93g**)



Prepared according to **TP8** from 4-methyl-2-(methylthio)pyrimidine (**91e**; 140 mg, 1.00 mmol), 4-cyanophenylzinc iodide (**92d**, 2.31 mL, 1.50 mmol, 0.65 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 16 h. Purification by flash chromatography (pentane/Et_2O/EtOAc 2:6:1, silica gel) furnished **93g** as a colourless solid (144 mg, 74% yield). Alternatively, applying **TP9** (25 °C, 18 h), **93g** was obtained in 73% yield.

m.p. (°C): 191-193.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.66 (d, J = 5.47 Hz, 1H), 8.60-8.52 (m, 2H), 7.78-7.71 (m, 2H), 7.11 (d, J = 5.47 Hz, 1H), 2.59 (s, 3H).

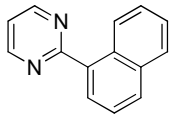
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 167.7, 162.4, 156.9 (CH), 141.8, 132.3 (CH), 128.6 (CH), 119.5 (CH), 118.8, 113.8, 24.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3047 (w), 2224 (w), 1678 (w), 1606 (w), 1583 (s), 1550 (s), 1378 (s), 1288 (m), 1254 (w), 1197 (w), 1108 (w), 1018 (w), 994 (w), 949 (w), 868 (m), 860 (m), 836 (vs), 789 (vs), 706 (w).

MS (EI, 70 eV): *m/z* (%) = 196 (1), 195 (100, M^+), 194 (1), 180 (1), 129 (2), 128 (4), 102 (1), 101 (1), 67 (1), 50 (1).

HRMS (EI): calcd. for $C_{12}H_9N_3$: 195.0796, found: 195.0796.

2-(1-Naphthyl)pyrimidine (**93h**)



Prepared according **TP8** from 2-thiomethyl-pyrimidine (**91h**; 126 mg, 1.00 mmol), 1-naphtylzinc iodide (**92e**, 1.50 mL, 1.50 mmol, 1.00 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 20 h. Purification by flash chromatography (pentane/Et_2O 1:1, silica gel) furnished **93h** as a yellow oil (154 mg, 75% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.96 (d, J = 4.95 Hz, 2H), 8.64-8.61 (m, 1H), 8.06 (dd, J = 7.18, 1.24 Hz, 1H), 7.97 (d, J = 8.42 Hz, 1H), 7.93-7.90 (m, 1H), 7.62-7.49 (m, 3H), 7.28 (t, J = 4.83 Hz, 1H).

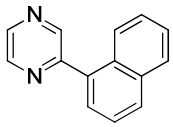
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 167.2, 157.1 (CH), 135.7, 134.0, 130.8, 130.5 (CH), 129.3 (CH), 128.4 (CH), 126.9 (CH), 125.9 (CH), 125.6 (CH), 125.1 (CH), 118.8 (CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3043 (w), 1519 (w), 1474 (m), 1386 (m), 1340 (w), 1288 (w), 1251 (w), 1194 (w), 1188 (w), 1146 (m), 1070 (w), 1051 (m), 1014 (s), 969 (w), 850 (w), 793 (s), 776 (s), 764 (vs), 733 (m), 644 (w).

MS (EI, 70 eV): *m/z* (%) = 207 (6), 206 (50, M^+), 205 (100), 153 (8), 152 (3), 151 (5), 127 (4), 126 (4), 103 (4), 76 (3).

HRMS (EI): calcd. for $C_{14}H_{10}N_2$: 206.0844, found: 206.0831.

2-(1-Naphthyl)pyrazine (**93i**)



Prepared according **TP8** from 2-thiomethyl-pyrazine (**91i**; 126 mg, 1.00 mmol), 1-naphtylzinc iodide (**92e**, 1.50 mL, 1.50 mmol, 1.00 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos

(20.5 mg, 5.0 mol%) at 25 °C for 18 h. Purification by flash chromatography (pentane/Et_2O 1:1, silica gel) furnished **93i** as a yellow oil (170 mg, 83% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.90 (d, *J* = 1.49 Hz, 1H), 8.76 (dd, *J* = 2.60, 1.49 Hz, 1H), 8.62 (d, *J* = 2.60 Hz, 1H), 8.12-8.06 (m, 1H), 7.99-7.91 (m, 2H), 7.65-7.48 (m, 4H).

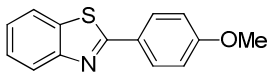
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 155.0, 145.8 (CH), 144.0 (CH), 142.8 (CH), 134.6, 133.9, 130.9, 129.9 (CH), 128.5 (CH), 128.1 (CH), 127.0 (CH), 126.2 (CH), 125.3 (CH), 124.9 (CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3050 (w), 2921 (w), 1567 (m), 1551 (s), 1509 (w), 1463 (w), 1432 (m), 1417 (s), 1388 (s), 1340 (w), 1252 (w), 808 (m), 799 (vs), 789 (vs), 773 (vs), 742 (m), 721 (m), 631 (m).

MS (EI, 70 eV): *m/z* (%) = 207 (8), 206 (55, M^+), 205 (100), 153 (9), 152 (8), 126 (5), 85 (8), 71 (9), 57 (13), 43 (8).

HRMS (EI): calcd. for $C_{14}H_{10}N_2$: 206.0844, found: 206.0831.

2-(4-Methoxyphenyl)-1,3-benzothiazole (**93j**)



Prepared according to **TP8** from 2-(methylthio)-1,3-benzothiazole (**91j**; 181 mg, 1.00 mmol), (4-methoxyphenyl)zinc iodide (**92b**, 1.61 mL, 1.50 mmol, 0.93 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 2 h. Purification by flash chromatography (pentane/Et_2O 9:1, silica gel) furnished **93j** as a colourless solid (176 mg, 73% yield). Alternatively, applying **TP9** (25 °C, 2 h), **93j** was obtained in 85% yield.

m.p. (°C): 127-128.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.04-8.03 (m, 3H), 7.86 (d, *J* = 7.63 Hz, 1H), 7.48-7.45 (m, 1H), 7.36-7.33 (m, 1H), 6.99 (d, *J* = 8.58 Hz, 2H), 3.87 (s, 3H).

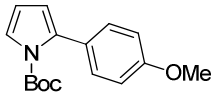
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 167.9, 161.9, 154.0, 134.7, 129.1 (CH), 126.3, 126.2 (CH), 124.8 (CH), 122.8 (CH), 121.5 (CH), 114.4 (CH), 55.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2994 (w), 2835 (w), 1604 (m), 1483 (m), 1433 (m), 1310 (m), 1255 (s), 1225 (s), 1171 (m), 1027 (m), 968 (s), 832 (vs), 791 (m), 758 (vs), 731 (s), 691 (m), 623 (m).

MS (EI, 70 eV): *m/z* (%) = 243 (5), 242 (14), 241 (100, M^+), 227 (6), 226 (33), 198 (27), 197 (8), 154 (5), 121 (5), 69 (4).

HRMS (EI): calcd. for $C_{14}H_{11}NO^{32}S$: 241.0561; found: 241.0557.

Tert-butyl 2-(4-methoxyphenyl)-*1H*-pyrrole-1-carboxylate (**93k**)



Prepared according to **TP8** from *tert*-butyl 2-(methylthio)-1*H*-pyrrole-1-carboxylate (**91k**; 213 mg, 1.00 mmol), (4-methoxyphenyl)zinc iodide (**92b**, 1.38 mL, 1.50 mmol, 1.09 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 2 h. Purification by flash chromatography (pentane/Et_2O 50:1, silica gel) furnished **93k** as a clear oil (183 mg, 67% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.31 (dd, *J* = 3.47, 1.73 Hz, 1H), 7.29-7.24 (m, 2H), 6.90-6.86 (m, 2H), 6.20 (dd, *J* = 3.47, 3.22 Hz, 1H), 6.13 (dd, *J* = 3.22, 1.73 Hz, 1H), 3.82 (s, 3H), 1.38 (s, 9H).

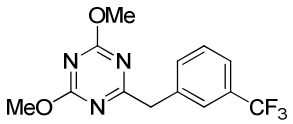
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 158.8, 149.4, 134.8, 130.4 (CH), 126.8, 122.1 (CH), 114.0 (CH), 113.0 (CH), 110.4 (CH), 83.4, 55.2 (CH_3), 27.7 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 1776 (m), 1733 (m), 1602 (m), 1513 (m), 1475 (m), 1393 (m), 1369 (m), 1334 (m), 1310 (s), 1246 (vs), 1142 (vs), 1075 (m), 1029 (s), 972 (m), 841 (m), 772 (m), 729 (m).

MS (EI, 70 eV): *m/z* (%) = 273 (20, M^+), 218 (15), 217 (100), 173 (46), 158 (41), 135 (15), 130 (13), 57 (89), 43 (39), 41 (31).

HRMS (EI): calcd. for $C_{16}H_{19}NO_3$: 273.1365, found: 273.1356.

2,4-Dimethoxy-6-(3-(trifluoromethyl)benzyl)-1,3,5-triazine (**93l**)



Prepared according to **TP8** from 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**91a**; 187 mg, 1.00 mmol), (3-trifluoromethyl)benzylzinc chloride (**92f**, 1.03 mL, 1.50 mmol, 1.45 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 5 h. Purification by flash chromatography (pentane/Et_2O 1:1, silica gel) furnished **93l** as a yellow solid (208 mg, 70% yield). Alternatively, applying **TP9** (25 °C, 4 h), **93l** was obtained in 72% yield.

m.p. (°C): 55-57.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.66 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.40-7.42 (m, 1H), 4.07 (s, 2H), 4.01 (s, 6H).

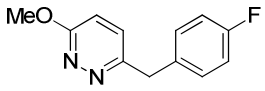
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 180.6, 176.2, 137.3 (CH), 132.8 (CH), 130.7 (q, *J* = 32.17 Hz), 128.9, 126.3 (q, *J* = 3.93 Hz, CH), 124.1 (q, *J* = 272.3 Hz, CF_3), 123.8 (q, *J* = 3.93 Hz, CH), 55.2 (CH_3), 44.8 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2944 (vw), 1548 (s), 1502 (m), 1472 (m), 1386 (m), 1358 (s), 1326 (s), 1235 (m), 1162 (m), 1107 (vs), 1090 (s), 1066 (s), 943 (m), 923 (w), 902 (m), 836 (m), 810 (m), 772 (m), 737 (m), 699 (m), 687 (m), 604 (w).

MS (EI, 70 eV): *m/z* (%) = 300 (7), 299 (43, M^+), 298 (100), 284 (26), 227 (8), 226 (7), 200 (18), 184 (9), 159 (16), 58 (9).

HRMS (EI): calcd. for $C_{13}H_{12}F_3N_3O_2$: calc.: 299.0882, found: 299.0872.

3-(4-Fluorobenzyl)-6-methoxypyridazine (**93m**)



Prepared according to **TP8** from 3-methoxy-6-(methylthio)pyridazine (**91f**; 156 mg, 1.00 mmol), 4-fluorobenzylzinc chloride (**92g**, 1.95 mL, 1.50 mmol, 0.77 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 5 h. Purification by flash chromatography (pentane/Et_2O 3:7, silica gel) furnished **93m** as a colourless solid (160 mg, 73% yield). Alternatively, applying **TP9** (25 °C, 5 h), **93m** was obtained in 74% yield.

m.p. (°C): 72-73.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.24-7.18 (m, 2H), 7.14 (d, *J* = 9.17 Hz, 1H), 7.01-6.93 (m, 2H), 6.86 (d, *J* = 9.17 Hz, 1H), 4.21 (s, 2H), 4.09 (s, 3H).

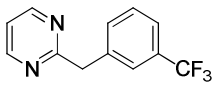
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 164.0, 161.8 (d, *J* = 245.1 Hz, CF), 157.8, 134.2 (d, *J* = 3.35 Hz), 130.5 (d, *J* = 7.99 Hz, CH), 129.5 (CH), 117.9 (CH), 115.5, (d, *J* = 21.39 Hz, CH), 54.7 (CH_3), 40.9 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 1596 (m), 1508 (m), 1472 (s), 1463 (s), 1418 (s), 1308 (vs), 1286 (m), 1232 (s), 1157 (w), 1090 (m), 1011 (vs), 872 (m), 845 (s), 827 (s), 788 (m), 775 (m), 604 (w).

MS (EI, 70 eV): *m/z* (%) = 218 (29, M^+), 217 (100), 203 (3), 161 (4), 146 (10), 133 (6), 109 (12), 83 (4), 44 (30), 43 (5).

HRMS (EI): calcd. for $C_{12}H_{11}FN_2O$: 218.0855, found: 218.0842.

2-(3-(Trifluoromethyl)benzyl)pyrimidine (**93n**)



Prepared according to **TP8** from 2-thiomethyl-pyrimidine (**91h**; 126 mg, 1.00 mmol), 3-(trifluoromethyl)benzylzinc chloride (**92f**, 1.03 mL, 1.50 mmol, 1.45 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 16 h. Purification by flash

chromatography (pentane/Et_2O 3:7, silica gel) furnished **93n** as a yellow oil (140 mg, 59% yield).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.67 (d, *J* = 4.77 Hz, 2H), 7.62 (s, 1H), 7.54 (d, *J* = 7.87, 1H), 7.47 (d, *J* = 7.63 Hz, 1H), 7.40 (dd, *J* = 7.87, 7.63 Hz, 1H), 7.14 (t, *J* = 4.77 Hz, 1H), 4.33 (s, 2H).

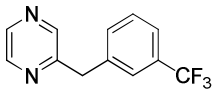
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 169.1, 157.4 (CH), 139.0, 132.6 (q, *J* = 1.33 Hz, CH), 130.7 (q, *J* = 32.2 Hz), 128.9 (CH), 125.9 (q, *J* = 3.71, CH), 124.1 (q, *J* = 272.1 Hz, CF_3), 123.5 (q, *J* = 3.97, CH), 118.9 (CH), 45.6 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3044 (vw), 1562 (s), 1494 (vw), 1451 (w), 1418 (s), 1324 (s), 1252 (w), 1193 (m), 1161 (s), 1117 (vs), 1099 (s), 1072 (vs), 994 (w), 879 (w), 794 (m), 742 (w), 701 (s), 668 (m), 658 (m), 635 (m).

MS (EI, 70 eV): *m/z* (%) = 238 (71, M^+), 237 (100), 217 (15), 169 (14), 168 (16), 85 (21), 71 (29), 69 (11), 57 (32), 43 (16).

HRMS (EI): calcd. for $C_{12}H_9F_3N_2$: 238.0718, found: 238.0711.

2-(3-(Trifluoromethyl)benzyl)pyrazine (**93o**)



Prepared according to **TP8** from 2-(methylthio)pyrazine (**91i**; 126 mg, 1.00 mmol), 3-(trifluoromethyl)benzylzinc chloride (**92f**, 1.03 mL, 1.50 mmol, 1.45 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 18 h. Purification by flash chromatography (pentane/Et_2O 3:7, silica gel) furnished **93o** as a yellow oil (163 mg, 68% yield).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.51 (dd, *J* = 2.5, 1.24 Hz, 1H), 8.48 (d, *J* = 1.2 Hz, 1H), 8.44 (d, *J* = 2.5 Hz, 1H), 7.53-7.39 (m, 4H), 4.21 (s, 2H).

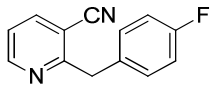
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 155.4, 144.6 (CH), 144.3 (CH), 142.7 (CH), 139.0, 132.4 (q, *J* = 1.29 Hz, CH), 131.0 (q, *J* = 32.2 Hz), 129.2 (CH), 125.7 (q, *J* = 3.87, CH), 124.0 (q, *J* = 272.4 Hz, CF_3), 123.7 (q, *J* = 3.87, CH), 41.5 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3059 (vw), 1474 (w), 1450 (w), 1404 (w), 1326 (s), 1230 (w), 1193 (m), 1160 (s), 1117 (vs), 1093 (m), 1073 (s), 1056 (m), 1018 (s), 918 (w), 878 (w), 825 (w), 797 (m), 768 (m), 744 (w), 701 (s), 658 (m).

MS (EI, 70 eV): *m/z* (%) = 239 (7), 238 (M+, 55), 237 (100), 217 (15), 168 (10), 85 (14), 71 (18), 57 (21), 55 (7), 43 (11).

HRMS (EI): calcd. for $C_{12}H_9F_3N_2$: 238.0718; found: 238.0712.

2-(4-Fluorobenzyl)nicotinonitrile (**93p**)



Prepared according to **TP8** from 2-(methylthio)nicotinonitrile (**91l**; 150 mg, 1.00 mmol), (4-fluorobenzyl)zinc chloride (**92g**, 2.21 mL, 1.50 mmol, 0.68 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 2 h. Purification by flash chromatography (pentane/Et_2O 1:1, silica gel) furnished **93p** as a yellow solid (175 mg, 83% yield).

m.p. (°C): 57-58.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.73 (dd, J = 4.95, 1.86 Hz, 1H), 7.91 (dd, J = 7.93, 1.86 Hz, 1H), 7.24-7.36 (m, 3H), 6.94-7.02 (m, 2H), 4.34 (s, 2H).

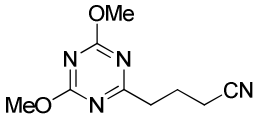
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 163.5, 161.8 (d, J = 241.2, CF), 152.7 (CH), 140.6 (CH), 133.1 (d, J = 3.35 Hz), 130.6 (d, J = 7.99 Hz, CH), 121.4 (CH), 116.8, 115.5 (d, J = 21.39 Hz, CH), 108.9, 42.3 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3043 (vw), 2925 (w), 2854 (vw), 2223 (m), 1886 (vw), 1604 (w), 1578 (m), 1561 (m), 1506 (vs), 1428 (s), 1417 (m), 1215 (vs), 1159 (m), 1099 (m), 815 (s), 794 (vs), 717 (w), 606 (m).

MS (EI, 70 eV): *m/z* (%) = 295 (7), 294 (9), 212 (45, M^+), 211 (100), 210 (14), 186 (15), 185 (10), 109 (22), 83 (8), 44 (7).

HRMS (EI): calcd. for $C_{13}H_9FN_2$: 212.0750, found: 212.0745.

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)butanenitrile (**93q**)



Prepared according to **TP8** from 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**91a**; 187 mg, 1.00 mmol), (3-cyanopropyl)zinc bromide (**92h**, 1.49 mL, 1.50 mmol, 1.01 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 5 h. Purification by flash chromatography (pentane/Et_2O 3:7, silica gel) furnished **93q** as a yellow solid (137 mg, 66% yield). Alternatively, applying **TP9** (25 °C, 48 h), **93q** was obtained in 68% yield.

m.p. (°C): 48-50.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 4.01 (s, 6H), 2.88 (t, J = 7.31 Hz, 2H), 2.47 (t, J = 7.18 Hz, 2H), 2.21-2.11 (m, 2H).

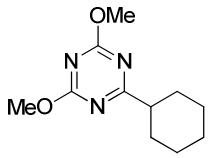
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 180.9, 172.4, 119.1, 55.2 (CH_3), 36.6 (CH_2), 22.4 (CH_2), 16.6 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2931 (w), 2244 (vw), 1554 (vs), 1498 (m), 1456 (m), 1384 (m), 1364 (s), 1323 (m), 1306 (m), 1202 (m), 1112 (s), 1084 (m), 1068 (m), 999 (m), 951 (m), 931 (m), 898 (m), 818 (s), 786 (m).

MS (EI, 70 eV): *m/z* (%) = 208 (1, M^+), 207 (2), 169 (3), 168 (39), 156 (6), 155 (100), 125 (6), 72 (2), 69 (3), 58 (3).

HRMS (EI): calcd. for $C_9H_{12}N_4O_2$: 208.0960, found: 208.0951.

2-Cyclohexyl-4,6-dimethoxy-1,3,5-triazine (**93r**)



Prepared according to **TP8** from 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**91a**; 187 mg, 1.00 mmol), cyclohexylzinc bromide (**92i**, 1.58 mL, 1.50 mmol, 0.95 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 20 h. Purification by flash chromatography (pentane/Et_2O 4:1, silica gel) furnished **93r** as a yellow oil (100 mg, 43% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 4.00 (s, 6H), 2.66-2.60 (m, 1H), 1.95-1.93 (m, 2H), 1.81-1.78 (m, 2H), 1.61-1.53 (m, 2H), 1.38-1.30 (m, 2H), 1.28-1.20 (m, 2H).

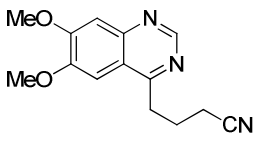
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 186.6, 172.5, 54.9 (CH_3), 46.6 (CH), 30.8 (CH_2), 25.9 (CH_2), 25.8 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2929 (m), 2853 (w), 1543 (vs), 1499 (s), 1457 (s), 1385 (s), 1361 (s), 1343 (vs), 1293 (m), 1242 (m), 1200 (m), 1105 (s), 1082 (m), 1008 (m), 960 (w), 937 (w), 828 (s).

MS (EI, 70 eV): *m/z* (%) = 223 (77, M^+), 222 (32), 208 (100), 194 (57), 182 (16), 181 (46), 180 (25), 169 (15), 168 (80), 58 (18).

HRMS (EI): calcd. for $C_{11}H_{17}N_3O_2$: 223.1321, found: 223.1320.

4-(6,7-Dimethoxyquinazolin-4-yl)butanenitrile (**93s**)



Prepared according to **TP8** from 6,7-dimethoxy-4-(methylthio)quinazoline (**91g**; 236 mg, 1.00 mmol), (3-cyanopropyl)zinc bromide (**92h**, 1.49 mL, 1.50 mmol, 1.01 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 5 h. Purification by flash chromatography (Et_2O/EtOH 10:1, silica gel) furnished **93s** as a colourless solid (190 mg, 74% yield).

m.p. (°C): 156-157.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 9.01 (s, 1H). 7.30 (s, 1H), 7.22 (s, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.34 (t, J = 7.18 Hz, 2H), 2.54 (t, J = 6.81 Hz, 2H), 2.25-2.34 (m, 2H).

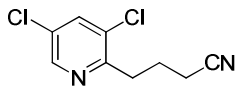
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 164.8, 155.8, 153.1 (CH), 150.5, 147.8, 119.6, 119.5, 107.2 (CH), 101.1 (CH), 56.4 (CH_3), 56.3 (CH_3), 31.7 (CH_2), 23.1 (CH_2), 16.8 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2972 (vw), 1615 (m), 1578 (w), 1553 (w), 1502 (vs), 1432 (s), 1361 (m), 1233 (vs), 1210 (s), 1175 (s), 1128 (m), 1026 (m), 1007 (m), 983 (m), 854 (vs), 830 (s), 732 (m), 606 (m).

MS (EI, 70 eV): *m/z* (%) = 257 (11, M^+), 242 (4), 218 (3), 217 (19), 205 (12), 204 (100), 203 (3), 190 (5), 189 (15), 161 (7).

HRMS (EI): calcd. for $C_{14}H_{15}N_3O_2$: 257.1164, found: 257.1156.

4-(3,5-Dichloropyridin-2-yl)butanenitrile (**93t**)



Prepared according to **TP8** from 3,5-dichloro-2-(methylthio)pyridine (**91m**; 194 mg, 1.00 mmol), (3-cyanopropyl)zinc bromide (**92h**, 1.49 mL, 1.50 mmol, 1.01 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 5 h. Purification by flash chromatography (pentane/Et_2O 8:2, silica gel) furnished **93t** as a yellow solid (116 mg, 54% yield).

m.p. (°C): 41-42.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.39 (d, J = 2.1 Hz, 1H), 7.68 (d, J = 2.1 Hz, 1H), 3.04 (t, J = 7.3 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 2.09-2.19 (m, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 154.9, 146.1 (CH), 136.4 (CH), 131.4, 130.1, 119.3, 32.9 (CH_2), 23.2 (CH_2), 16.7 (CH_2).

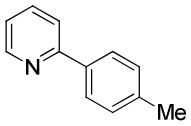
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3056 (m), 2929 (w), 2246 (w), 1723 (w), 1566 (w), 1543 (w), 1444 (vs), 1384 (s), 1324 (m), 1116 (s), 1059 (s), 1038 (s), 916 (s), 858 (vs), 745 (vs), 700 (m), 657 (m).

MS (EI, 70 eV): *m/z* (%) = 176 (25), 174 (39), 165 (10), 164 (5), 163 (63), 162 (11), 161 (100), 160 (6), 147 (5), 126 (7).

HRMS (EI): calcd. for $C_9H_8Cl_2N_2$: 214.0065; found: 214.0071.

3.4.4 Preparation of Heterocycles 93 via Ni-catalyzed Cross-Coupling Reaction

2-(*p*-Tolyl)pyridine (**93u**)



Prepared according to **TP9** from 2-(methylthio)pyridine (**91n**; 125 mg, 1.00 mmol), 4-methylphenylzinc iodide (**92j**, 2.24 mL, 1.50 mmol, 0.67 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 9 h. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **93u** as a clear oil (145 mg, 86% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.69-8.66 (m, 1H), 7.91-7.87 (m, 2H), 7.76-7.68 (m, 2H), 7.29-7.25 (m, 2H), 7.22-7.17 (m, 1H), 2.40 (s, 3H).

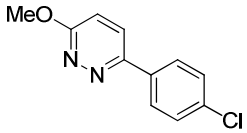
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 157.3, 149.3 (CH), 139.0, 136.8 (CH), 136.3, 129.5 (CH), 126.8 (CH), 121.8 (CH), 120.3 (CH), 21.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3049 (vw), 3006 (w), 2919 (vw), 2862 (vw), 1614 (w), 1587 (m), 1562 (m), 1514 (w), 1465 (s), 1431 (m), 1298 (w), 1266 (w), 1184 (w), 1152 (w), 1110 (w), 1094 (w), 1059 (w), 1036 (w), 1016 (w), 988 (w), 829 (m), 770 (vs), 741 (m), 721 (m), 642 (w), 621 (w).

MS (EI, 70 eV): *m/z* (%) = 170 (9), 169 (100, M^+), 168 (58), 167 (20), 166 (4), 154 (6), 141 (3), 139 (3), 91 (4), 84 (8).

HRMS (EI): calcd. for $C_{12}H_{11}N$: 169.0891, found: 169.0884.

3-(4-Chlorophenyl)-6-methoxypyridazine (**93v**)



Prepared according to **TP9** from 3-methoxy-6-(methylthio)pyridazine (**91f**; 156 mg, 1.00 mmol), 4-chlorophenylzinc iodide (**92k**, 1.92 mL, 1.50 mmol, 0.78 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 6 h. Purification by flash

chromatography (pentane/Et_2O 1:1, silica gel) furnished **93v** as a pale yellow solid (159 mg, 72% yield).

m.p. (°C): 177-178.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.97-7.92 (m, 2H), 7.74 (d, J = 9.17 Hz, 1H), 7.48-7.43 (m, 2H), 7.04 (d, J = 9.17 Hz, 1H), 4.18 (s, 3H).

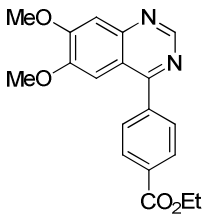
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 164.3, 154.1, 135.7, 134.6, 129.1 (CH), 127.7 (CH), 126.8 (CH), 117.8 (CH), 54.9 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2945 (vw), 1598 (m), 1492 (vw), 1463 (s), 1412 (m), 1332 (w), 1308 (m), 1176 (w), 1118 (w), 1089 (w), 1018 (m), 1010 (m), 1000 (m), 838 (m), 824 (vs), 767 (w), 748 (w).

MS (EI, 70 eV): *m/z* (%) = 222 (30), 221 (38), 220 (100, M^+), 219 (81), 191 (40), 155 (20), 151 (20), 149 (59), 138 (38), 136 (23).

HRMS (EI): calcd. for $C_{11}H_9ClN_2O$: 220.0403, found: 220.0399.

Ethyl 4-(6,7-dimethoxyquinazolin-4-yl)benzoate (**93w**)



Prepared according to **TP9** from 6,7-dimethoxy-4-(methylthio)quinazoline (**91g**; 236 mg, 1.00 mmol), 4-ethoxycarbonylphenylzinc iodide (**92c**, 2.03 mL, 1.50 mmol, 0.74 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 24 h. Purification by flash chromatography (Et_2O, silica gel) furnished **93w** as a sand-coloured solid (276 mg, 82% yield).

m.p. (°C): 190-192.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 9.30 (s, 1H), 8.24 (d, J = 8.11 Hz, 1H), 7.84 (d, J = 8.11 Hz, 1H), 7.43 (s, 1H), 7.27 (s, 1H), 4.43 (q, J = 7.15 Hz, 2H), 4.08 (s, 3H), 3.88 (s, 3H), 1.43 (t, J = 7.15 Hz, 3H).

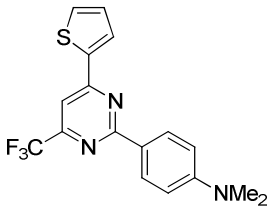
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.0, 163.9, 156.0, 152.9 (CH), 150.7, 149.3, 141.8, 131.6, 130.0, 129.8 (CH), 129.5 (CH), 107.2 (CH), 103.4 (CH), 61.3 (CH_2), 56.5 (CH_3), 56.1 (CH_3), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2978 (vw), 1709 (m), 1498 (s), 1472 (m), 1425 (m), 1313 (m), 1279 (s), 1231 (vs), 1219 (m), 1137 (m), 1113 (m), 1098 (m), 1020 (m), 878 (s), 858 (m), 805 (m), 773 (s), 723 (m), 707 (m).

MS (EI, 70 eV): *m/z* (%) = 339 (22), 338 (100, M^+), 337 (20), 323 (45), 307 (29), 295 (22), 293 (18), 279 (16), 265 (59), 221 (17).

HRMS (EI): calcd. for $C_{19}H_{18}N_2O_4$: 338.1267, found: 338.1259.

N,*N*-Dimethyl-4-(4-(2-thienyl)-6-(trifluoromethyl)pyrimidin-2-yl)aniline (**93x**)



Prepared according to **TP9** from 2-(methylthio)-4-(2-thienyl)-6-(trifluoromethyl)pyrimidine (**91d**; 276 mg, 1.00 mmol), 4-(dimethylamino)phenylzinc iodide (**92l**, 1.52 mL, 1.50 mmol, 0.99 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 6 h. Purification by flash chromatography (pentane/Et_2O 20:1, silica gel) furnished **93x** as a yellow solid (334 mg, 96% yield).

m.p. (°C): 152-153.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 3.06 (s, 3H), 6.76-6.79 (m, 2H), 7.17 (dd, *J* = 4.94, 3.84 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, *J* = 4.94, 1.10 Hz, 1H), 7.83 (dd, *J* = 3.84, 1.10 Hz, 1H), 8.43-8.46 (m, 2H).

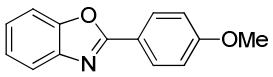
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 40.2 (CH_3), 106.4 (q, *J* = 2.81 Hz, CH), 111.6, 120.9 (q, *J* = 275.1 Hz, CF_3), 128.1 (CH), 128.4 (CH), 129.9 (CH), 130.1 (CH), 130.8 (CH), 142.4, 152.5, 156.1 (q, *J* = 35.25 Hz), 160.7, 165.5.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 1602 (m), 1584 (m), 1541 (s), 1434 (m), 1401 (m), 1377 (s), 1364 (s), 1257 (s), 1235 (m), 1188 (s), 1172 (m), 1141 (vs), 1095 (s), 1061 (m), 945 (m), 846 (m), 825 (s), 783 (m), 711 (s), 698 (s).

MS (EI, 70 eV): *m/z* (%) = 351 (6), 350 (19), 349 (100, M^+), 348 (64), 333 (7), 332 (4), 305 (6), 175 (9), 174 (13), 134 (5).

HRMS (EI): calcd. for $C_{17}H_{14}F_3N_3{}^{32}S$: 349.0861, found: 349.0850.

2-(4-Methoxyphenyl)-1,3-benzoxazole (**93y**)



Prepared according to **TP9** from 2-(methylthio)-1,3-benzoxazole (**91c**; 165 mg, 1.00 mmol), 4-methoxyphenylzinc iodide (**92b**, 1.38 mL, 1.50 mmol, 1.09 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 3 h. Purification by flash

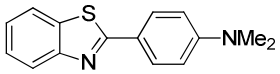
chromatography (pentane/Et_2O 9:1, silica gel) furnished **93y** as a colourless solid (182 mg, 81% yield).

m.p. (°C): 110-111.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 3.88 (s, 3H), 7.01-7.04 (m, 2H), 7.30-7.34 (m, 2H), 7.55 (dd, J = 7.15, 1.91 Hz, 3H), 7.73 (dd, J = 7.39, 1.67 Hz, 3H), 8.19-8.21 (m, 2H).

These data match the literature: Bonnamour, J.; Bolm, C. *Org. Lett.* **2008**, *10*, 2665-2667.

4-(1,3-Benzothiazol-2-yl)-*N*,*N*-dimethylaniline (**93z**)



Prepared according to **TP9** from 2-(methylthio)benzothiazole (**91j**; 181 mg, 1.00 mmol), 4-(*N*,*N*-dimethylamino)phenylzinc iodide (**92l**, 1.74 mL, 1.50 mmol, 0.86 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 5 h. Purification by flash chromatography (pentane/Et_2O 4:1, silica gel) furnished **93z** as a light brown solid (226 mg, 89% yield).

Large scale preparation:

Prepared according **TP9** from 2-(methylthio)benzothiazole (**91j**; 3.63 g, 20.0 mmol in 10 mL THF), 4-(*N*,*N*-dimethylamino)phenylzinc iodide (34.9 mL, 30.0 mmol, 0.86 M in THF), $Ni(acac)_2$ (129 mg, 2.5 mol%) and DPE-Phos (539 mg, 5.0 mol%). After 5 h at 25 °C, the reaction mixture was quenched with sat. aq. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (pentane/Et_2O 4:1, silica gel) furnished **93z** as a light brown solid (4.30 g, 85% yield).

m.p. (°C): 173-175.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.00-7.93 (m, 3H), 7.83 (d, J = 7.39 Hz, 1H) 7.46-7.40 (m, 1H), 7.32-7.27 (m, 1H), 6.75-6.70 (m, 2H), 3.02 (s, 6H).

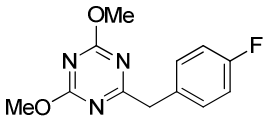
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 168.7, 154.3, 152.1, 134.5, 128.8 (CH), 125.9 (CH), 124.1 (CH), 122.2 (CH), 121.4, 121.3 (CH), 111.6 (CH), 40.1 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 1608 (vs), 1556 (m), 1514 (m), 1480 (s), 1454 (m), 1430 (s), 1368 (s), 1314 (m), 1228 (s), 1186 (s), 1126 (m), 1062 (m), 964 (m), 942 (m), 816 (vs), 800 (m), 750 (s), 718 (s), 688 (m).

MS (EI, 70 eV): *m/z* (%) = 256 (4), 255 (15), 254 (100, M^+), 253 (37), 239 (13), 238 (8), 237 (2), 210 (4), 127 (4), 126 (5).

HRMS (EI): calcd. for $C_{15}H_{14}N_2{}^{32}S$: 254.0878, found: 254.0876.

2-(4-Fluorobenzyl)-4,6-dimethoxy-1,3,5-triazine (**93aa**)



Prepared according to **TP9** from dimethoxy-6-(methylthio)-1,3,5-triazine (**91a**; 187 mg, 1.00 mmol), 4-fluorobenzylzinc chloride (**92g**, 1.24 mL, 1.50 mmol, 1.21 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 4 h. Purification by flash chromatography (pentane/Et_2O 1:1, silica gel) furnished **93aa** as a yellow oil (222 mg, 89% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.36-7.30 (m, 2H), 7.00-6.92 (m, 2H), 3.99 (s, 6H), 3.97 (s, 2H).

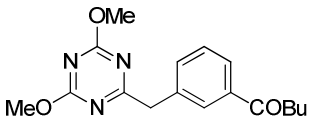
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 181.2, 172.5, 161.9 (d, J = 246.4 Hz, CF), 132.1 (d, J = 3.35 Hz), 130.8 (d, J = 7.73 Hz, CH), 115.3 (d, J = 20.88 Hz, CH), 55.1 (CH_3), 44.3 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2953 (vw), 1546 (vs), 1500 (s), 1459 (s), 1379 (m), 1349 (vs), 1219 (s), 1158 (m), 1128 (m), 1108 (s), 1091 (s), 1069 (m), 1016 (w), 937 (w), 862 (w), 820 (s), 784 (s), 724 (m), 602 (m).

MS (EI, 70 eV): *m/z* (%) = 249 (45, M^+), 248 (100), 234 (16), 150 (23), 135 (14), 134 (16), 109 (30), 107 (7), 83 (9), 44 (13).

HRMS (EI): calcd. for $C_{12}H_{12}FN_3O_2$: 249.0914, found: 249.0895.

1-(3-((4,6-Dimethoxy-1,3,5-triazin-2-yl)methyl)phenyl)pentan-1-one (**93ab**)



Prepared according to **TP9** from dimethoxy-6-(methylthio)-1,3,5-triazine (**91a**; 187 mg, 1.00 mmol), 3-pentanoylbenzylzinc chloride (**92m**, 3.41 mL, 1.50 mmol, 0.44 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 5 h. Purification by flash chromatography (pentane/Et_2O 1:1, silica gel) furnished **93ab** as a yellow oil (258 mg, 82% yield).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 7.96-7.95 (m, 1H), 7.83-7.79 (m, 1H), 7.58-7.54 (m, 1H), 7.50-7.35 (m, 1H), 4.06 (s, 2H), 3.99 (s, 6H), 2.93 (t, J = 7.43 Hz, 2H), 1.73-1.63 (m, 2H), 1.44-1.32 (m, 2H), 0.92 (t, J = 7.31 Hz, 3H).

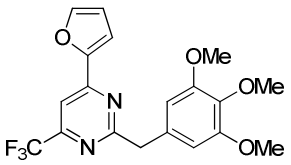
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 200.3, 180.9, 172.5, 137.3, 136.9, 133.9 (CH), 129.0 (CH), 128.7 (CH), 126.7 (CH), 55.1 (CH_3), 44.9 (CH_2), 38.4 (CH_2), 26.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2955 (w), 1682 (m), 1546 (vs), 1500 (s), 1458 (m), 1378 (m), 1350 (vs), 1264 (m), 1231 (m), 1202 (m), 1106 (m), 1091 (m), 1069 (m), 820 (m), 731 (m), 690 (m).

MS (EI, 70 eV): *m/z* (%) = 316 (4), 315 (15, M^+), 274 (7), 273 (40), 259 (15), 258 (100), 245 (6), 231 (11), 230 (4), 158 (6).

HRMS (EI): calcd. for $C_{17}H_{21}N_3O_3$: 315.1583, found: 315.1577.

4-(2-Furyl)-6-(trifluoromethyl)-2-(3,4,5-trimethoxybenzyl)pyrimidine (**93ac**)



Prepared according to **TP9** from 4-(2-furyl)-2-(methylthio)-6-(trifluoromethyl)pyrimidine (**91o**; 260 mg, 1.00 mmol), (**92n**, 3,4,5-trimethoxybenzyl)zinc chloride (3.41 mL, 1.50 mmol, 0.44 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 24 h. Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **93ac** as a white solid (394 mg, 89% yield).

m.p. (°C): 117-119.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.73 (s, 1H), 7.64 (d, *J* = 1.31 Hz, 1H), 7.38 (d, *J* = 3.70 Hz, 1H), 6.72 (s, 2H), 6.60 (dd, *J* = 3.70, 1.31 Hz, 1H), 4.26 (s, 2H), 3.84 (s, 6H), 3.80 (s, 3H).

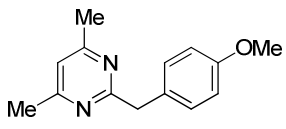
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 170.6, 157.7, 156.3 (q, *J* = 35.62 Hz), 153.1, 151.1, 146.1 (CH), 136.7, 133.0, 120.6 (q, *J* = 275.2 Hz, CF_3), 114.1 (CH), 112.9 (CH), 108.0 (q, *J* = 2.99 Hz, CH), 106.2 (CH), 60.8 (CH_3), 56.0 (CH_3), 45.8 (CH_2),

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3124 (vw), 2968 (vw), 1606 (m), 1594 (m), 1487 (w), 1458 (m), 1362 (m), 1336 (m), 1260 (m), 1238 (m), 1156 (m), 1144 (s), 1124 (vs), 1008 (m), 874 (w), 772 (s), 721 (w), 703 (m), 626 (w).

MS (EI, 70 eV): *m/z* (%) = 395 (18), 394 (100, M^+), 380 (14), 379 (74), 351 (12), 319 (4), 293 (11), 265 (6), 182 (11), 147 (6).

HRMS (EI): calcd. for $C_{19}H_{17}F_3N_2O_4$: 394.1140, found: 394.1132.

2-(4-Methoxybenzyl)-4,6-dimethylpyrimidine (**93ad**)



Prepared according to **TP9** from 4,6-dimethyl-2-methylthiopyrimidine (**91p**; 154 mg, 1.00 mmol), 4-methoxybenzylzinc chloride (**92o**, 1.92 mL, 1.50 mmol, 1.78 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 3 h. Purification by flash chromatography (pentane/Et_2O 1:1, silica gel) furnished **93ad** as a white solid (194 mg, 85% yield).

m.p. (°C): 92-94.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.32-7.27 (m, 2H), 6.83 (s, 1H), 6.82-6.77 (m, 2H), 4.14 (s, 2H), 3.75 (s, 3H), 2.43 (s, 6H).

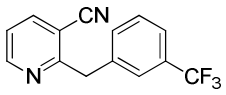
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 169.1, 166.8, 158.2, 130.7, 130.0 (CH), 117.5 (CH), 113.7 (CH), 55.2 (CH_3), 44.9 (CH_2), 24.0 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 1598 (s), 1542 (w), 1509 (s), 1462 (w), 1430 (m), 1368 (m), 1300 (m), 1240 (vs), 1176 (m), 1040 (s), 860 (m), 817 (m), 799 (m), 737 (w), 723 (w), 668 (m).

MS (EI, 70 eV): *m/z* (%) = 229 (14), 228 (M^+, 100), 227 (43), 214 (15), 213 (91), 212 (6), 196 (6), 185 (16), 121 (14), 77 (7).

HRMS (EI): calcd. for $C_{14}H_{16}N_2O$: 228.1263, found: 228.1256.

2-(3-(Trifluoromethyl)benzyl)nicotinonitrile (**93ae**)



Prepared according to **TP9** from 2-(methylthio)nicotinonitrile (**91l**; 150 mg, 1.00 mmol), (3-(trifluoromethyl)benzyl)zinc chloride (**92f**, 1.58 mL, 1.50 mmol, 0.95 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 8 h. Purification by flash chromatography (pentane/Et_2O 1:1, silica gel) furnished **93ae** as a clear oil (192 mg, 73% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.74 (dd, *J* = 5.01, 1.67 Hz, 1H), 7.92 (dd, *J* = 7.87, 1.67 Hz, 1H), 7.62 (s, 1H), 7.56 (d, *J* = 7.61 Hz, 1H), 7.49 (d, *J* = 7.65 Hz, 1H), 7.42 (dd, *J* = 7.65, 7.61 Hz, 1H), 7.29 (dd, *J* = 7.87, 5.01 Hz, 1H), 4.42 (s, 2H).

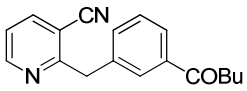
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.6, 152.8 (CH), 140.6 (CH), 138.2, 132.5 (q, *J* = 1.21 Hz, CH), 130.9 (q, *J* = 32.16 Hz), 129.1 (CH), 125.8 (q, *J* = 3.93 Hz, CH), 124.0 (q, *J* = 272.3, CF_3), 123.8 (q, *J* = 3.83 Hz, CH), 121.6 (CH), 116.7, 109.1, 42.7 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2229 (w), 1582 (w), 1565 (w), 1451 (w), 1433 (m), 1327 (s), 1161 (s), 1118 (vs), 1099 (s), 1073 (s), 917 (w), 908 (w), 879 (w), 803 (m), 782 (m), 700 (s), 660 (m), 649 (w).

MS (EI, 70 eV): *m/z* (%) = 263 (6), 262 (44, M^+), 261 (100), 260 (4), 241 (9), 236 (21), 235 (5), 216 (14), 193 (6), 192 (19).

HRMS (EI): calcd. for $C_{14}H_9F_3N_2$: 262.0718, found: 262.0699.

2-(3-Pentanoylbenzyl)nicotinonitrile (**93af**)



Prepared according to **TP9** from 2-(methylthio)nicotinonitrile (**91l**; 150 mg, 1.00 mmol), (3-pentanoylbenzyl)zinc chloride (**92m**, 3.41 mL, 1.50 mmol, 0.44 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 5 h. Purification by flash chromatography (pentane/Et_2O 4:6, silica gel) furnished **93af** as a clear oil (221 mg, 79% yield).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 8.73 (dd, *J* = 4.83, 1.36 Hz, 1H), 7.96-7.91 (m, 2H), 7.83-7.79 (m, 1H), 7.57-7.53 (m, 1H), 7.41-7.36 (m, 1H), 7.28 (dd, *J* = 7.80, 4.83 Hz, 1H), 4.43 (s, 2H), 2.93 (t, *J* = 7.43 Hz, 2H), 1.73-1.63 (m, 2H), 1.44-1.32 (m, 2H), 0.92 (t, *J* = 7.31 Hz, 3H),

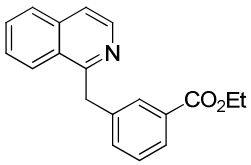
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 200.3, 162.9, 152.6 (CH), 140.7 (CH), 137.8, 137.5, 133.5 (CH), 128.9 (CH), 128.7 (CH), 126.6 (CH), 121.5 (CH), 116.7, 109.2, 42.8 (CH_2), 38.3 (CH_2), 26.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2956 (m), 2931 (m), 2870 (w), 2227 (w), 1680 (vs), 1580 (m), 1564 (m), 1429 (s), 1265 (m), 1255 (m), 1225 (m), 1174 (m), 1157 (m), 1093 (m), 804 (s), 776 (m), 712 (m), 691 (s).

MS (EI, 70 eV): *m/z* (%) = 278 (13, M^+), 237 (7), 236 (40), 235 (11), 222 (15), 221 (100), 219 (7), 194 (6), 193 (23), 192 (32).

HRMS (EI): calcd. for $C_{18}H_{18}N_2O$: 278.1419, found: 278.1417.

Ethyl 3-(isoquinolin-1-ylmethyl)benzoate (**93ag**)



Prepared according to **TP9** from 1-(methylthio)isoquinoline (**91q**; 175 mg, 1.00 mmol), (3-(ethoxycarbonyl)benzyl)zinc chloride (**92p**, 1.74 mL, 1.50 mmol, 0.86 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 48 h. Purification by

flash chromatography (pentane/Et_2O 1:1, silica gel) furnished **93ag** as a yellow oil (266 mg, 91% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.49 (d, *J* = 5.72 Hz, 1H), 8.11 (d, *J* = 8.58 Hz, 1H), 8.03 (s, 1H), 7.85 (d, *J* = 7.63 Hz, 1H), 7.79 (d, *J* = 8.11 Hz, 1H), 7.63-7.61 (m, 1H), 7.55 (d, *J* = 5.72 Hz, 1H), 7.53-7.51 (m, 1H), 7.41 (d, *J* = 7.63 Hz, 1H), 7.30-7.27 (m, 1H), 4.71 (s, 2H), 4.33 (q, *J* = 7.15 Hz, 2H), 1.34 (t, *J* = 7.15 Hz, 3H).

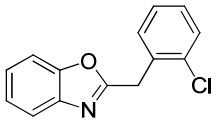
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.5, 159.4, 141.8 (CH), 139.6, 136.5, 133.0 (CH), 130.7, 129.9 (CH), 129.7 (CH), 128.5 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 127.0, 125.5 (CH), 120.0 (CH), 60.9 (CH_2), 41.6 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2979 (w), 2916 (w), 1712 (vs), 1586 (w), 1561 (w), 1443 (w), 1385 (w), 1366 (w), 1275 (vs), 1258 (vs), 1186 (s), 1103 (s), 1081 (s), 1018 (s), 866 (w), 822 (s), 798 (s), 745 (vs), 722 (s), 614 (w).

MS (EI, 70 eV): *m/z* (%) = 291 (36, M^+), 290 (100), 263 (13), 262 (78), 246 (14), 244 (22), 218 (19), 217 (49), 216 (24), 108 (19).

HRMS (EI): calcd. for $C_{19}H_{17}NO_2$: 291.1259, found: 291.1277.

2-(2-Chlorobenzyl)-1,3-benzoxazole (**93ah**)



Prepared according to **TP9** from 2-(methylthio)-1,3-benzoxazole (**91c**; 165 mg, 1.00 mmol), 2-chlorobenzylzinc chloride (**92q**, 1.70 mL, 1.50 mmol, 0.88 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 18 h. Purification by flash chromatography (pentane/Et_2O 9:1, silica gel) furnished **93ah** as a yellow oil (182 mg, 76% yield).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 7.71-7.69 (m, 1H), 7.48-7.46 (m, 1H), 7.43-7.40 (m, 1H), 7.39-7.36 (m, 1H), 7.31-7.28 (m, 2H), 7.26-7.23 (m, 2H), 4.42 (s, 2H).

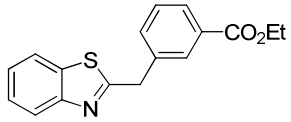
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 164.2, 150.9, 141.2, 134.3, 132.8, 131.1 (CH), 129.7 (CH), 128.9 (CH), 127.1 (CH), 124.7 (CH), 124.2 (CH), 119.9 (CH), 110.5 (CH), 32.9 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3059 (vw), 1613 (w), 1568 (m), 1475 (w), 1454 (m), 1444 (m), 1424 (w), 1240 (m), 1143 (m), 1123 (w), 1052 (m), 1040 (m), 1002 (w), 841 (m), 760 (m), 739 (vs), 686 (m).

MS (EI, 70 eV): *m/z* (%) = 243 (2, M^+), 209 (11), 208 (100), 207 (5), 180 (3), 178 (2), 127 (3), 125 (9), 89 (4), 63 (3).

HRMS (EI): calcd. for $C_{14}H_{10}{}^{35}ClNO$: 243.0451, found: 243.0443.

Ethyl 3-(1,3-benzothiazol-2-ylmethyl)benzoate (**93ai**)



Prepared according to **TP9** from 2-(methylthio)-1,3-benzothiazole (**91j**; 181 mg, 1.00 mmol), (3-(ethoxycarbonyl)benzyl)zinc chloride (**92p**, 1.74 mL, 1.50 mmol, 0.86 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 48 h. Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **93ai** as a yellow oil (207 mg, 70% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.06 (s, 1H), 7.99 (dd, *J* = 8.35, 0.95 Hz, 1H), 7.97 (dd, *J* = 8.10, 0.95 Hz, 1H), 7.78 (d, *J* = 8.11 Hz, 1H), 7.55 (d, *J* = 7.63 Hz, 1H), 7.44 (ddd, *J* = 8.35, 7.16, 0.95 Hz, 1H), 7.40 (dd, *J* = 8.11, 7.63 Hz, 1H), 7.33 (ddd, *J* = 8.10, 7.16, 0.95 Hz, 1H), 4.48 (s, 2H), 4.36 (q, *J* = 7.15 Hz, 2H), 1.38 (t, *J* = 7.15 Hz, 3H).

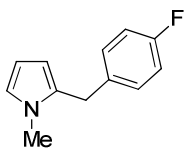
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 170.3, 166.2, 153.1, 137.4, 135.5, 133.5 (CH), 131.1, 130.2 (CH), 128.9 (CH), 128.6 (CH), 126.1 (CH), 124.9 (CH), 122.8 (CH), 121.5 (CH), 61.0 (CH_2), 40.2 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 1713 (vs), 1589 (w), 1515 (w), 1436 (m), 1366 (w), 1304 (m), 1275 (vs), 1190 (s), 1101 (s), 1080 (s), 1061 (m), 1014 (m), 860 (w), 756 (vs), 728 (s), 713 (s), 678 (m), 640 (w).

MS (EI, 70 eV): *m/z* (%) = 298 (18), 297 (100, M^+), 296 (21), 252 (46), 251 (58), 225 (67), 224 (42), 223 (98), 222 (12), 112 (20).

HRMS (EI): calcd. for $C_{17}H_{15}NO_2{}^{32}S$: 297.0823, found: 297.0825.

2-(4-Fluorobenzyl)-1-methyl-1*H*-pyrrole (**93aj**)



Prepared according to **TP9** from 1-methyl-2-(methylthio)-1*H*-pyrrole (**91b**; 127 mg, 1.00 mmol), 4-fluorobenzylzinc chloride (**92g**, 1.24 mL, 1.50 mmol, 1.21 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 18 h. Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **93aj** as a yellow oil (80 mg, 42% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.13-7.07 (m, 2H), 7.01-6.93 (m, 2H), 6.59-6.57 (m, 1H), 6.08-6.05 (m, 1H), 5.88-5.86 (m, 1H), 3.91 (s, 2H), 3.42 (s, 3H).

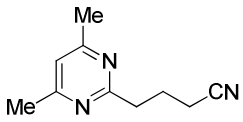
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 161.4 (d, J = 243.8 Hz, CF), 135.0 (d, J = 3.35 Hz), 131.2, 129.8 (d, J = 7.73 Hz, CH), 121.9 (CH), 115.2 (d, J = 21.14 Hz, CH), 107.9 (CH), 106.6 (CH), 33.7 (CH_2), 32.0 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2922 (w), 1706 (m), 1649 (m), 1630 (w), 1601 (m), 1506 (vs), 1471 (m), 1417 (m), 1300 (m), 1218 (vs), 1156 (m), 1129 (w), 1089 (m), 1015 (w), 824 (m), 756 (m), 705 (vs).

MS (EI, 70 eV): *m/z* (%) = 189 (33, M^+), 163 (18), 141 (36), 127 (74), 113 (46), 99 (23), 94 (27), 71 (87), 57 (24), 43 (100).

HRMS (EI): calcd. for $C_{12}H_{12}FN$: 189.0954, found: 189.0946.

4-(4,6-Dimethylpyrimidin-2-yl)butanenitrile (**93ak**)

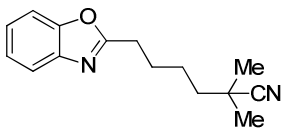


Prepared according to **TP9** from 4,6-dimethyl-2-(methylthio)pyrimidine (**91p**; 154 mg, 1.00 mmol), 4-cyanopropylzinc bromide (**92h**, 1.76 mL, 1.50 mmol, 0.85 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 48 h. Purification by flash chromatography (pentane/Et_2O 2:8, silica gel) furnished **93ak** as a yellow oil (147 mg, 84% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.84 (s, 1H), 2.95 (t, J = 7.27 Hz, 2H), 2.42 (t, J = 7.63 Hz, 2H), 2.39 (s, 6H), 2.19-2.10 (m, 2H).

These data match the literature: Yamanaka, H.; Komatsu, M.; Tanji, K.; Ogawa, S.; Konno, S.; Mizugaki, M. *Yakugaku Zasshi* **1979**, *99*, 342-8.

6-(1,3-Benzoxazol-2-yl)-2,2-dimethylhexanenitrile (**93al**)



Prepared according to **TP9** from 2-(methylthio)-1,3-benzoxazole (**91c**; 165 mg, 1.00 mmol), (5-cyano-5-methylhexyl)zinc bromide (**92r**, 1.95 mL, 1.50 mmol, 0.77 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 12 h. Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **93al** as a yellow oil (198 mg, 82% yield).

m.p. (°C): 65-66.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.67-7.64 (m, 1H), 7.49-7.46 (m, 1H), 7.32-7.27 (m, 2H), 2.96 (t, *J* = 7.53 Hz, 2H), 1.98-1.89 (m, 2H), 1.66-1.55 (m, 4H), 1.32 (s, 6H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.7, 150.7, 140.9, 124.9, 124.6 (CH), 124.2 (CH), 119.4 (CH), 110.3 (CH), 32.3, 40.6 (CH_2), 28.3 (CH_2), 26.7 (CH_3), 26.6 (CH_2), 24.8 (CH_2).

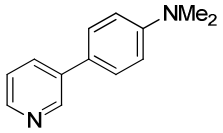
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2944 (w), 2231 (vw), 1619 (m), 1573 (m), 1461 (m), 1448 (m), 1388 (w), 1369 (w), 1241 (m), 1142 (m), 1105 (w), 1006 (w), 942 (m), 836 (m), 786 (m), 773 (vs), 761 (m), 736 (m), 715 (w).

MS (EI, 70 eV): *m/z* (%) = 242 (7, M^+), 227 (11), 175 (8), 174 (57), 147 (16), 146 (65), 134 (9), 133 (100), 132 (19), 65 (6).

HRMS (EI): calcd. for $C_{15}H_{18}N_2O$: 242.1419, found: 242.1412.

3.4.5 Preparation of Heterocycles 93 using other Electrophiles

N,*N*-Dimethyl-4-(pyridin-3-yl)aniline (**93am**)



Prepared according to **TP8** from 3-(methylthio)pyridine (**91r**; 125 mg, 1.00 mmol), 4-(*N*,*N*-dimethylamino)phenylzinc iodide (**92l**, 1.74 mL, 1.50 mmol, 0.86 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 4 h. Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **93am** as a colourless solid (100 mg, 50% yield). Alternatively, by applying **TP9** (25 °C, 4 h), **93am** was obtained in 62% yield.

m.p. (°C): 150-152.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.82 (s, 1H), 8.49-8.48 (m, 1H), 7.81 (d, *J* = 7.60 Hz, 1H), 7.50-7.47 (m, 2H), 7.29 (dd, *J* = 7.60, 4.87 Hz, 1H), 6.83-6.79 (m, 2H), 3.00 (s, 6H).

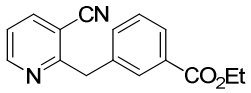
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 150.3, 147.6 (CH), 147.0 (CH), 136.6, 133.2 (CH), 127.6 (CH), 125.3, 123.4 (CH), 112.7 (CH), 40.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2988 (w), 2896 (w), 2814 (w), 1604 (m), 1526 (m), 1478 (m), 1438 (m), 1398 (w), 1352 (m), 1330 (m), 1286 (m), 1228 (m), 1218 (m), 1186 (m), 1166 (m), 1120 (m), 1058 (m), 1016 (m), 942 (m), 826 (m), 796 (vs), 706 (s).

MS (EI, 70 eV): *m/z* (%) = 198 (100, M^+), 197 (91), 182 (18), 168 (3), 154 (14), 140 (2), 127 (11), 99 (5), 77 (6), 63 (4).

HRMS (EI): calcd. for $C_{13}H_{14}N_2$: 198.1157, found: 198.1148.

Ethyl 3-((3-cyanopyridin-2-yl)methyl)benzoate (**93an**)



Prepared according to **TP8** from 2-(phenylthio)nicotinonitrile (**91s**; 212 mg, 1.00 mmol), (3-(ethoxycarbonyl)benzyl)zinc chloride (**92p**, 1.74 mL, 1.50 mmol, 0.86 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 8 h. Purification by flash chromatography (pentane/Et_2O 3:7, silica gel) furnished **93an** as a yellow oil (242 mg, 91% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.73 (dd, J = 4.98, 1.86 Hz, 1H), 8.02-8.01 (m, 1H), 7.93-7.89 (m, 2H), 7.55-7.52 (m, 1H), 7.37 (t, J = 7.71 Hz, 1H), 7.27 (dd, J = 7.91, 4.98 Hz, 1H), 4.42 (s, 2H), 4.34 (q, J = 7.18, 2H), 1.36 (t, J = 7.18 Hz, 3H).

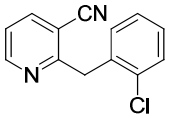
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.4, 162.9, 152.7 (CH), 140.6 (CH), 137.7, 133.5 (CH), 130.9, 130.1 (CH), 128.6 (CH), 128.2 (CH), 121.4 (CH), 116.7, 109.1, 61.0 (CH_2), 42.7 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2983 (w), 2228 (w), 1712 (vs), 1581 (m), 1564 (m), 1431 (m), 1367 (m), 1276 (vs), 1240 (w), 1188 (s), 1106 (s), 1092 (s), 1082 (m), 1022 (m), 1003 (w), 806 (m), 746 (vs), 714 (m), 691 (m), 670 (m), 621 (m).

MS (EI, 70 eV): *m/z* (%) = 266 (62, M^+), 265 (94), 240 (18), 237 (46), 222 (21), 221 (100), 194 (24), 193 (61), 192 (99), 43 (61).

HRMS (EI): calcd. for $C_{16}H_{14}N_2O_2$: 266.1055, found: 266.1052.

2-(2-Chlorobenzyl)nicotinonitrile (**93ao**)



Prepared according to **TP8** from 2-(phenylthio)nicotinonitrile (**91s**; 212 mg, 1.00 mmol), 2-chlorobenzylzinc chloride (**92q**, 1.70 mL, 1.50 mmol, 0.88 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 14 h. Purification by flash chromatography (pentane/Et_2O 1:1, silica gel) furnished **93ao** as a colourless solid (199 mg, 87% yield).

m.p. (°C): 74-76.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.71 (dd, J = 5.01, 1.77 Hz, 1H), 7.96 (dd, J = 7.92, 1.70 Hz, 1H), 7.41-7.34 (m, 1H), 7.29 (dd, J = 7.92, 4.68 Hz, 1H), 7.26-7.18 (m, 3H), 4.53 (s, 2H).

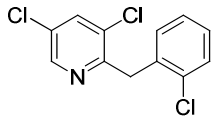
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.1, 152.3 (CH), 140.7 (CH), 135.2, 134.4 (CH), 131.4, 129.6 (CH), 128.5 (CH), 126.9 (CH), 121.4 (CH), 116.4, 109.8, 40.3 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3057 (vw), 2923 (vw), 2228 (w), 1579 (m), 1562 (m), 1474 (m), 1434 (s), 1164 (w), 1127 (w), 1090 (m), 1050 (m), 1038 (m), 987 (w), 949 (w), 910 (w), 805 (m), 752 (vs), 717 (m), 704 (m), 678 (m), 623 (m).

MS (EI, 70 eV): *m/z* (%) = 228 (1, M^+), 227 (14), 193 (100), 192 (81), 164 (4), 112 (9), 96 (4), 82 (2), 63 (2), 43 (66).

HRMS (EI): calcd. for $C_{13}H_9ClN_2$: 227.0376 ($[M-H]^+$), found: 227.0377 ($[M-H]^+$).

3,5-Dichloro-2-(2-chlorobenzyl)pyridine (**93ap**)



Prepared according to **TP8** from 3,5-dichloro-2-(phenylthio)pyridine (**91t**; 256 mg, 1.00 mmol), 2-chlorobenzylzinc chloride (**92q**, 1.70 mL, 1.50 mmol, 0.88 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and S-Phos (20.5 mg, 5.0 mol%) at 25 °C for 16 h. Purification by flash chromatography (pentane/Et_2O 40:1, silica gel) furnished **93ap** as a clear oil (184 mg, 68% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.40 (d, *J* = 2.25 Hz, 1H), 7.71 (d, *J* = 2.25 Hz, 1H), 7.39-7.37 (m, 1H), 7.22-7.16 (m, 2H), 7.06-7.03 (m, 1H), 4.37 (s, 2H)

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 154.8, 146.3 (CH), 136.4 (CH), 135.7, 134.3, 131.6, 130.6 (CH), 130.0, 129.5 (CH), 128.0 (CH), 126.7 (CH), 38.4 (CH_2).

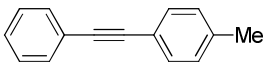
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3064 (vw), 1566 (w), 1542 (vw), 1474 (m), 1440 (s), 1419 (m), 1376 (s), 1198 (w), 1113 (m), 1049 (s), 1040 (s), 889 (m), 866 (m), 777 (m), 744 (vs), 717 (m), 699 (m), 680 (m), 655 (w).

MS (EI, 70 eV): *m/z* (%) = 271 (6, M^+), 238 (31), 237 (11), 236 (47), 235 (9), 201 (6), 70 (13), 61 (19), 45 (15), 43 (100).

HRMS (EI): calcd. for $C_{12}H_8{}^{35}Cl_3N$: 270.9722, found: 270.9716.

3.4.6 Preparation of Alkynes 95 via Pd-Catalyzed Cross-Coupling Reaction

1-Methyl-4-(phenylethynyl)benzene (**95a**)



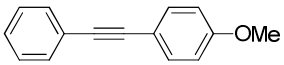
Prepared according to **TP10** from ((methylthio)ethynyl)benzene (**94a**; 148 mg, 1.00 mmol), 4-methylphenylzinc iodide (**95a**, 2.24 mL, 1.50 mmol, 0.67 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 5 h. Purification by flash chromatography (pentane, silica gel) furnished **95a** as a colourless solid (169 mg, 88% yield).

m.p. (°C): 68-70.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.52-7.50 (m, 2H), 7.43 (d, J = 7.76 Hz, 2H), 7.35-7.30 (m, 3H), 7.15 (d, J = 7.76 Hz, 2H), 2.36 (s, 3H).

These data match the literature: N. Kakusawa, K. Yamaguchi, J. Kurita, *J. Organomet. Chem.* **2005**, *690*, 2956.

1-Methoxy-4-(phenylethynyl)benzene (**95b**)



Prepared according to **TP10** from ((methylthio)ethynyl)benzene (**94a**; 148 mg, 1.00 mmol), 4-methoxyphenylzinc iodide (**92b**, 1.61 mL, 1.50 mmol, 0.93 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 2 h. Purification by flash chromatography (pentane/Et_2O 40:1, silica gel) furnished **95b** as a colourless solid (189 mg, 91% yield).

m.p. (°C): 71-73.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.52-7.50 (m, 2H), 7.48-7.46 (m, 2H), 7.35-7.29 (m, 3H), 6.89-6.86 (m, 2H), 3.82 (s, 3H).

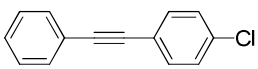
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 159.6, 133.0 (CH), 131.4 (CH), 128.3 (CH), 127.9 (CH), 123.6, 115.4, 114.0 (CH), 89.4, 88.1, 55.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3010 (w), 2838 (w), 2360 (m), 2341 (m), 2213 (w), 1604 (m), 1592 (m), 1507 (s), 1457 (m), 1439 (m), 1286 (m), 1246 (vs), 1174 (s), 1137 (m), 1107 (m), 1025 (s), 836 (vs), 779 (m), 752 (vs), 688 (s), 668 (w).

MS (EI, 70 eV): *m/z* (%) = 208 (100, M^+), 194 (10), 193 (64), 165 (46), 164 (12), 163 (11), 139 (11), 69 (9), 57 (11), 43 (22).

HRMS (EI): calcd. for $C_{15}H_{12}O$: 208.0888, found: 208.874.

1-Chloro-4-(phenylethynyl)benzene (**95c**)



Prepared according to **TP10** from ((methylthio)ethynyl)benzene (**94a**; 148 mg, 1.00 mmol), 4-chlorophenylzinc iodide (**92k**, 1.92 mL, 1.50 mmol, 0.78 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 24 h. Purification by flash chromatography (pentane, silica gel) furnished **95c** as a colourless solid (145 mg, 68% yield).

m.p. (°C): 86-88.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.54-7.49 (m, 2H), 7.48-7.43 (m, 2H), 7.37-7.30 (m, 5H).

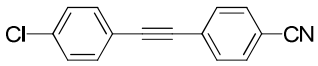
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 134.2, 132.8 (CH), 131.6 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 122.9, 121.8, 90.3, 88.2.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3048 (w), 1910 (w), 1658 (w), 1585 (w), 1531 (w), 1494 (s), 1479 (m), 1440 (m), 1399 (m), 1308 (w), 1268 (w), 1179 (w), 1161 (w), 1089 (s), 1071 (m), 1028 (w), 1010 (s), 909 (m), 830 (vs), 823 (s), 750 (vs), 730 (s), 685 (s).

MS (EI, 70 eV): *m/z* (%) = 214 (35), 213 (16), 212 (100, M^+), 177 (6), 176 (20), 151 (7), 149 (17), 88 (5), 57 (7), 43 (9).

HRMS (EI): calcd. for $C_{14}H_9{}^{35}Cl$: 212.0393, found: 212.0390.

4-((4-Chlorophenyl)ethynyl)benzonitrile (**95d**)



Prepared according to **TP10** from 1-chloro-4-((methylthio)ethynyl)benzene (**94b**; 182 mg, 1.00 mmol), 4-cyanophenylzinc iodide (**92d**, 2.11 mL, 1.50 mmol, 0.71 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 4 h. Purification by flash chromatography (pentane/Et_2O 20:1, silica gel) furnished **95d** as a colourless solid (198 mg, 84% yield).

m.p. (°C): 179-181.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.65-7.62 (m, 2H), 7.60-7.57 (m, 2H), 7.49-7.44 (m, 2H), 7.37-7.32 (m, 2H).

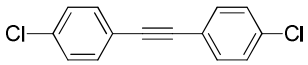
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 135.3, 133.0 (CH), 132.1 (CH), 132.0 (CH), 128.9 (CH), 127.9, 120.7, 118.4, 111.7, 92.5, 88.6.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2229 (m), 2216 (w), 1739 (m), 1604 (m), 1590 (w), 1498 (m), 1484 (m), 1406 (m), 1398 (m), 1366 (m), 1229 (m), 1217 (m), 1090 (m), 1080 (m), 1012 (m), 827 (vs), 770 (w), 679 (w).

MS (EI, 70 eV): *m/z* (%) = 239 (31), 238 (18), 237 (100, M^+), 202 (11), 201 (25), 176 (9), 175 (16), 119 (5), 87 (10), 42 (6).

HRMS (EI): calcd. for $C_{15}H_8{}^{35}ClN$: 237.345, found: 237.0333.

1,1'-Ethyne-1,2-diylbis(4-chlorobenzene) (**95e**)



Prepared according to **TP10** from 1-chloro-4-((methylthio)ethynyl)benzene (**94b**; 182 mg, 1.00 mmol), 4-chlorophenylzinc iodide (**92k**, 1.92 mL, 1.50 mmol, 0.78 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 12 h. Purification by flash chromatography (pentane, silica gel) furnished **95e** as a colourless solid (180 mg, 73% yield).

m.p. (°C): 172-174.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.46-7.42 (m, 4H), 7.34-7.30 (m, 4H).

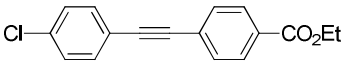
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 134.5, 132.8 (CH), 128.8 (CH), 121.4, 89.2.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2926 (w), 1912 (m), 1658 (w), 1593 (w), 1503 (m), 1490 (s), 1400 (m), 1260 (w), 1086 (vs), 1053 (m), 1010 (s), 830 (s), 824 (vs), 770 (m), 736 (w), 704 (w), 654 (m), 635 (w).

MS (EI, 70 eV): *m/z* (%) = 250 (9), 249 (8), 248 (62), 247 (12), 246 (100, M^+), 177 (5), 176 (38), 175 (7), 123 (7), 88 (5).

HRMS (EI): calcd. for $C_{14}H_8{}^{35}Cl_2$: 246.0003, found: 246.0006.

Ethyl 4-((4-chlorophenyl)ethynyl)benzoate (**95f**)



Prepared according to **TP10** from 1-chloro-4-((methylthio)ethynyl)benzene (**94b**; 182 mg, 1.00 mmol), 4-(ethoxycarbonyl)phenylzinc iodide (**92c**, 2.59 mL, 1.50 mmol, 0.58 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 6 h. Purification by flash chromatography (pentane/EtOAc 20:1, silica gel) furnished **95f** as a colourless solid (151 mg, 53% yield).

m.p. (°C): 114-115.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.04-8.00 (m, 2H), 7.58-7.54 (m, 2H), 7.49-7.44 (m, 2H), 7.35-7.31 (m, 2H), 4.38 (q, *J* = 7.15 Hz, 2H), 1.40 (t, *J* = 7.15 Hz, 3H).

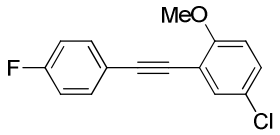
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.0, 134.8, 132.9 (CH), 131.4 (CH), 130.1, 129.5 (CH), 128.8 (CH), 127.5, 121.2, 91.0, 89.6, 61.2 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2981 (vw), 2214 (vw), 1712 (s), 1604 (m), 1482 (w), 1462 (w), 1386 (w), 1368 (w), 1306 (w), 1267 (vs), 1161 (w), 1138 (w), 1100 (s), 1088 (s), 1010 (m), 858 (w), 826 (m), 784 (w), 767 (m), 694 (w), 639 (w).

MS (EI, 70 eV): *m/z* (%) = 284 (100, M^+), 256 (29), 241 (26), 240 (15), 239 (86), 211 (13), 176 (56), 119 (12), 105 (10), 88 (12).

HRMS (EI): calcd. for $C_{17}H_{13}{}^{35}ClO_2$: 284.0604, found: 284.0603.

4-Chloro-2-((4-fluorophenyl)ethynyl)-1-methoxybenzene (**95g**)



Prepared according to **TP10** from 1-fluoro-4-((methylthio)ethynyl)benzene (**94c**; 166 mg, 1.00 mmol), 5-chloro-2-methoxyphenylzinc iodide (**92s**, 1.79 mL, 1.50 mmol, 0.84 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 4 h. Purification by flash chromatography (pentane, silica gel) furnished **95g** as a yellow oil (192 mg, 74% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.48-7.55 (m, 2H), 7.44 (d, *J* = 2.73 Hz, 1H), 7.24 (dd, *J* = 8.92, 2.73 Hz, 1H), 6.99-7.01 (m, 2H), 6.81 (d, *J* = 8.92 Hz, 1H), 3.88 (s, 3H).

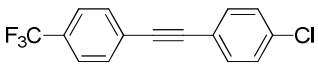
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.6 (d, *J* = 250.0 Hz, CF), 158.6, 133.6 (d, *J* = 8.51 Hz, CH), 132.8 (CH), 129.5 (CH), 125.2, 119.2 (d, *J* = 3.61 Hz), 115.6, (d, *J* = 22.17 Hz, CH), 113.9, 111.9 (CH), 93.3, 84.1, 56.1 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2939 (w), 2844 (vw), 2360 (vw), 1738 (w), 1591 (w), 1508 (vs), 1486 (s), 1462 (m), 1397 (m), 1282 (s), 1263 (m), 1242 (s), 1224 (vs), 1154 (m), 1122 (s), 1024 (s), 896 (m), 833 (vs), 804 (s), 769 (m), 676 (w).

MS (EI, 70 eV): *m/z* (%) = 261 (31), 260 (81, M^+), 259 (55), 217 (72), 197 (32), 196 (57), 182 (74), 181 (100), 167 (33), 165 (91).

HRMS (EI): calcd. for $C_{15}H_{10}{}^{35}ClFO$: 260.0404; found: 260.0384.

1-Chloro-4-((4-(trifluoromethyl)phenyl)ethynyl)benzene (**95h**)



Prepared according to **TP10** from 1-((methylthio)ethynyl)-4-(trifluoromethyl)benzene (**94d**; 216 mg, 1.00 mmol), 4-chlorophenylzinc iodide (**92k**, 1.92 mL, 1.50 mmol, 0.78 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 12 h. Purification by flash chromatography (pentane, silica gel) furnished **95h** as a colourless solid (213 mg, 76% yield).

m.p. (°C): 109-111.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.62-7.59 (m, 4H), 7.49-7.44 (m, 2H), 7.36-7.32 (m, 2H).

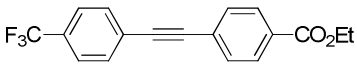
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 134.9, 132.9 (CH), 132.8, 131.8 (CH), 130.1 (q, J = 32.7 Hz), 128.8 (CH), 126.8, (q, J = 1.55 Hz), 125.3 (q, J = 3.87 Hz, CH), 123.9 (q, J = 272.1 Hz), 90.6, 88.9.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2217 (w), 1915 (w), 1612 (w), 1588 (w), 1516 (w), 1488 (w), 1478 (m), 1405 (w), 1315 (s), 1168 (s), 1128 (s), 1105 (s), 1089 (s), 1064 (s), 1013 (m), 964 (w), 844 (s), 829 (vs), 774 (m), 631 (w).

MS (EI, 70 eV): *m/z* (%) = 282 (31), 281 (18), 280 (100, M^+), 225 (15), 69 (15), 57 (22), 55 (20), 44 (40), 43 (16), 42 (26).

HRMS (EI): calcd. for $C_{15}H_8{}^{35}ClF_3$: 280.0267, found: 280.0253.

Ethyl 4-((4-(trifluoromethyl)phenyl)ethynyl)benzoate (**95i**)



Prepared according to **TP10** from 1-((methylthio)ethynyl)-4-(trifluoromethyl)benzene (**94d**; 216 mg, 1.00 mmol), 4-(ethoxycarbonyl)phenylzinc iodide (**92c**; 2.59 mL, 1.50 mmol, 0.58 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 20 h. Purification by flash chromatography (pentane/EtOAc 20:1, silica gel) furnished **95i** as a colourless solid (195 mg, 77% yield).

m.p. (°C): 71-72.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.06-8.02 (m, 2H), 7.66-7.57 (m, 6H), 4.39 (q, J = 7.15 Hz, 2H), 1.40 (t, J = 7.15 Hz, 3H).

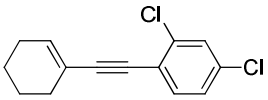
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 165.9, 131.9 (CH), 131.6 (CH), 130.1 (q, J = 32.8 Hz), 129.6 (CH), 129.5, 127.1, 126.6, (q, J = 1.80 Hz), 125.4 (q, J = 3.95 Hz, CH), 123.8 (q, J = 272.2 Hz, CF_3), 90.9, 90.6, 61.2 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2994 (vw), 1712 (s), 1605 (m), 1403 (w), 1370 (w), 1324 (m), 1307 (m), 1275 (s), 1163 (s), 1121 (s), 1101 (vs), 1065 (s), 1027 (m), 1013 (m), 860 (m), 854 (m), 842 (s), 834 (m), 766 (s), 712 (w), 690 (m).

MS (EI, 70 eV): *m/z* (%) = 318 (84, M^+), 291 (6), 290 (26), 274 (23), 273 (100), 246 (5), 245 (20), 225 (13), 176 (21), 137 (8).

HRMS (EI): calcd. for $C_{18}H_{13}F_3O_2$: 318.0868, found: 318.0857.

2,4-Dichloro-1-(cyclohex-1-en-1-ylethynyl)benzene (**95j**)



Prepared according to **TP10** from 1-(methylthio)hex-1-yne (**94e**; 152 mg, 1.00 mmol), 2,4-dichlorophenylzinc iodide (**92t**; 2.38 mL, 1.50 mmol, 0.63 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 10 h. Purification by flash chromatography (pentane, silica gel) furnished **95j** as a yellow oil (172 mg, 69% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.39 (d, *J* = 1.92 Hz, 1H), 7.25 (d, *J* = 8.36 Hz, 1H), 7.16 (dd, *J* = 8.36, 1.92 Hz, 1H), 6.29-6.25 (m, 1H), 2.26-2.20 (m, 2H), 2.18-2.11 (m, 2H), 1.72-1.57 (m, 4H).

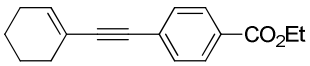
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 136.5 (CH), 136.3, 133.8, 133.5 (CH), 129.1 (CH), 126.8 (CH), 122.3, 120.4, 97.5, 82.7, 29.0 (CH_2), 25.8 (CH_2), 22.2 (CH_2), 21.4 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2929 (m), 2859 (w), 2205 (w), 1674 (w), 1582 (w), 1544 (w), 1471 (vs), 1446 (m), 1435 (m), 1379 (m), 1348 (w), 1099 (s), 1053 (m), 918 (m), 866 (m), 842 (m), 829 (s), 817 (vs), 800 (m), 767 (m), 696 (w).

MS (EI, 70 eV): *m/z* (%) = 252 (61), 250 (100, M^+), 224 (25), 222 (39), 215 (23), 180 (89), 179 (61), 178 (28), 165 (59), 152 (63).

HRMS (EI): calcd. for $C_{14}H_{12}{}^{35}Cl_2$: 250.0316, found: 250.0301.

Ethyl 4-(cyclohex-1-en-1-ylethynyl)benzoate (**95k**)



Prepared according to **TP10** from 1-(methylthio)hex-1-yne (**94e**; 152 mg, 1.00 mmol), 4-ethoxycarbonylphenylzinc iodide (**92c**; 2.59 mL, 1.50 mmol, 0.58 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 6 h. Purification by flash chromatography (pentane/Et_2O 9:1, silica gel) furnished **95k** as a colourless solid (194 mg, 76% yield).

m.p. (°C): 80-82.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.98-7.94 (m, 2H), 7.47-7.43 (m, 2H), 6.27-6.24 (m, 1H), 4.36 (q, *J* = 7.14, 2H), 2.24-2.12 (m, 4H), 1.72-1.57 (m, 4H), 1.38 (t, *J* = 7.14, 3H).

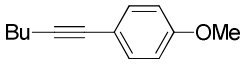
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.2, 136.4 (CH), 131.3 (CH), 129.4 (CH), 128.5, 120.5, 94.3, 86.2, 61.0 (CH_2), 29.7 (CH_2), 25.8 (CH_2), 22.3 (CH_2), 21.5 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2937 (w), 2196 (w), 1714 (vs), 1601 (m), 1403 (m), 1367 (m), 1283 (s), 1272 (vs), 1238 (m), 1176 (m), 1129 (m), 1104 (m), 1094 (m), 1028 (m), 1016 (m), 856 (m), 766 (s), 694 (m).

MS (EI, 70 eV): *m/z* (%) =254 (100, M^+), 226 (10), 209 (24), 182 (9), 181 (49), 180 (8), 166 (30), 165 (21), 153 (11), 152 (16).

HRMS (EI): calcd. for $C_{17}H_{18}O_2$: 254.1307; found: 254.1298.

1-(Hex-1-ynyl)-4-methoxybenzene (**95l**)



Prepared according to **TP10** from 1-(methylthio)hex-1-yne (**94f**; 128 mg, 1.00 mmol), 4-methoxyphenylzinc iodide (**92b**; 1.61 mL, 1.50 mmol, 0.93 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 3 h. Purification by flash chromatography (pentane/Et_2O 50:1, silica gel) furnished **95l** as a yellow oil (120 mg, 64% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.34-7.30 (m, 2H), 6.82-6.78 (m, 2H), 3.78 (s, 3H), 2.38 (t, *J* = 6.94 Hz, 2H), 1.41-1.63 (m, 4H), 0.94 (t, *J* = 7.18 Hz, 3H),

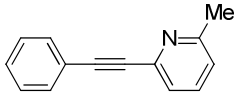
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 159.0, 132.8 (CH), 116.3, 113.8 (CH), 88.7, 80.2, 55.2 (CH_3), 31.0 (CH_2), 22.0 (CH_2), 19.1 (CH_2), 13.6 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2957 (w), 2932 (m), 1739 (w), 1607 (m), 1508 (s), 1464 (m), 1442 (w), 1378 (w), 1288 (m), 1242 (vs), 1218 (w), 1171 (m), 1106 (w), 1033 (s), 829 (s), 809 (m), 800 (w), 794 (w).

MS (EI, 70 eV): *m/z* (%) = 188 (100, M^+), 187 (19), 173 (56), 159 (44), 158 (33), 146 (15), 145 (30), 144 (15), 115 (18), 102 (16).

HRMS (EI): calcd. for $C_{13}H_{16}O$: 188.1201, found: 188.1193.

2-Methyl-6-(phenylethynyl)pyridine (**95m**)



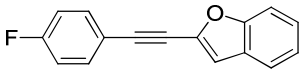
Prepared according to **TP10** from ((methylthio)ethynyl)benzene (**94a**; 148 mg, 1.00 mmol), 6-methylpyridin-2-ylzinc iodide (**92u**; 3.41 mL, 1.50 mmol, 0.44 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 4 h. Purification by flash

chromatography (pentane/Et_2O 8:2, silica gel) furnished **95m** as a clear oil (141 mg, 73% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.61-7.52 (m, 3H), 7.37-7.30 (m, 4H), 7.09-7.03 (m, 1H), 2.55 (s, 3H).

These data match the literature: Sorensen, U. S.; Pombo-Villar, E. *Tetrahedron* **2005**, *61*, 269.

2-((4-Fluorophenyl)ethynyl)benzofuran (**95n**)



Prepared according to **TP10** from 1-fluoro-4-((methylthio)ethynyl)benzene (**94c**; 166 mg, 1.00 mmol), 1-benzofuran-2-ylzinc iodide (**92v**; 2.14 mL, 1.50 mmol, 0.70 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 6 h. Purification by flash chromatography (pentane, silica gel) furnished **95n** as a colourless solid (194 mg, 82% yield).

m.p. (°C): 95-96

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.60-7.53 (m, 3H), 7.50-7.46 (m, 1H), 7.38-7.31 (m, 1H), 7.29-7.23 (m, 1H), 7.11-7.04 (m, 2H), 7.00 (d, *J* = 0.95 Hz, 1H).

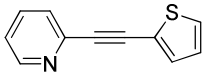
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.0 (d, *J* = 251.3 Hz, CF), 154.9, 138.6, 133.7 (d, *J* = 8.76 Hz, CH), 127.7, 125.6 (CH), 123.3 (CH), 121.2 (CH), 118.0, (d, *J* = 3.61 Hz), 115.9 (d, *J* = 22.17 Hz, CH), 111.6 (CH), 111.2 (CH), 93.9, 79.4.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2360 (w), 1896 (w), 1739 (w), 1598 (w), 1564 (m), 1498 (m), 1469 (m), 1448 (m), 1440 (m), 1346 (w), 1302 (w), 1256 (w), 1210 (m), 1168 (m), 1155 (m), 948 (m), 835 (vs), 812 (vs), 749 (vs), 736 (s).

MS (EI, 70 eV): *m/z* (%) = 238 (2), 237 (15), 236 (100, M^+), 208 (6), 207 (36), 206 (3), 187 (2), 182 (2), 104 (1), 44 (3).

HRMS (EI): calcd. for $C_{16}H_9FO$: 236.0637; found: 236.0643.

2-(2-Thienylethynyl)pyridine (**95o**)



Prepared according to **TP10** from 2-((methylthio)ethynyl)pyridine (**94g**; 149 mg, 1.00 mmol), 2-thienylzinc iodide (**92w**; 1.90 mL, 1.50 mmol, 0.79 M in THF), $Pd(OAc)_2$ (5.6 mg,

2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 8 h. Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **95o** as a yellow solid (133 mg, 72% yield).

m.p. (°C): 55-57.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.63-8.61 (m, 1H), 7.73 (ddd, *J* = 7.91, 7.72, 1.94 Hz, 1H), 7.54-7.51 (m, 1H), 7.41 (dd, *J* = 3.62, 1.10 Hz, 1H), 7.35 (dd, *J* = 5.22, 1.10 Hz, 1H), 7.30-7.27 (m, 1 H), 7.03 (dd, *J* = 5.22, 3.62 Hz, 1H).

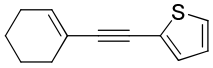
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 149.3 (CH), 142.6, 136.9 (CH), 133.7 (CH), 128.7 (CH), 127.3 (CH), 127.1 (CH), 122.9 (CH), 121.9, 91.5, 87.8.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3103 (w), 2204 (m), 1739 (w), 1578 (m), 1560 (m), 1459 (m), 1432 (m), 1416 (m), 1276 (w), 1212 (m), 1152 (m), 1125 (w), 1045 (w), 987 (w), 853 (m), 835 (m), 776 (s), 738 (w), 706 (vs), 669 (w).

MS (EI, 70 eV): *m/z* (%) = 185 (100, M^+), 184 (9), 159 (8), 158 (5), 152 (5), 141 (7), 140 (8), 114 (4), 113 (4), 79 (6).

HRMS (EI): calcd. for $C_{11}H_7N^{32}S$: 185.0299, found: 185.0284.

2-(Cyclohex-1-en-1-ylethynyl)thiophene (**95p**)



Prepared according to **TP10** from 1-(methylthio)hex-1-yne (**94e**; 152 mg, 1.00 mmol), 2-thienylzinc iodide (**92w**; 1.90 mL, 1.50 mmol, 0.79 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 16 h. Purification by flash chromatography (pentane, silica gel) furnished **95p** as a yellow oil (122 mg, 65% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.20 (dd, *J* = 5.01, 1.19 Hz, 1H), 7.14 (dd, *J* = 3.58, 1.19 Hz, 1H), 6.94 (dd, *J* = 5.01, 3.58 Hz, 1H), 6.21-6.18 (m, 1H), 2.22-2.17 (m, 2H), 2.16-2.06 (m, 2H), 1.74-1.56 (m, 4H).

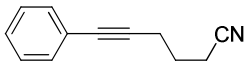
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 135.5 (CH), 131.2 (CH), 126.9 (CH), 126.5 (CH), 123.9, 120.5, 94.9, 79.9, 29.0 (CH_2), 25.8 (CH_2), 22.3 (CH_2), 21.5 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2932 (m), 2859 (w), 2182 (m), 1720 (w), 1661 (m), 1516 (w), 1446 (w), 1434 (w), 1412 (m), 1353 (w), 1205 (m), 1135 (w), 1076 (m), 1031 (m), 918 (w), 848 (m), 830 (m), 798 (w), 697 (vs).

MS (EI, 70 eV): *m/z* (%) = 188 (100, M^+), 187 (28), 173 (25), 160 (46), 153 (18), 147 (22), 135 (36), 129 (17), 128 (20), 115 (32).

HRMS (EI): calcd. for $C_{12}H_{12}{}^{32}S$: 188.0660, found: 188.0652.

6-Phenylhex-5-ynenitrile (**95q**)



Prepared according to **TP10** from ((methylthio)ethynyl)benzene (**94a**; 148 mg, 1.00 mmol), (3-cyanopropyl)zinc bromide (**92h**; 1.47 mL, 1.50 mmol, 1.02 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 16 h. Purification by flash chromatography (pentane/Et_2O 4:1, silica gel) furnished **95q** as a clear oil (88 mg, 52% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.44-7.39 (m, 2H), 7.34-7.30 (m, 3H), 2.59 (t, J = 6.94 Hz, 2H), 2.55 (t, J = 6.93 Hz, 2H), 1.99 (m, 2H).

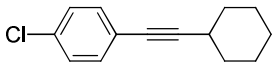
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 131.5 (CH), 128.3 (CH), 128.0 (CH), 123.2, 119.1, 86.9, 82.4, 24.6 (CH_2), 18.5 (CH_2), 16.2 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2942 (vw), 2361 (vw), 2248 (w), 1740 (vw), 1598 (w), 1490 (m), 1442 (w), 1430 (w), 1348 (w), 1070 (w), 1028 (vw), 917 (w), 756 (vs), 691 (vs), 669 (w).

MS (EI, 70 eV): *m/z* (%) = 169 (76, M^+), 168 (47), 142 (15), 129 (31), 128 (67), 127 (22), 116 (18), 115 (100), 89 (14), 63 (17).

HRMS (EI): calcd. for $C_{12}H_{11}N$: 169.0891, found: 169.0879.

1-Chloro-4-(cyclohexylethynyl)benzene (**95r**)



Prepared according to **TP10** from 1-chloro-4-((methylthio)ethynyl)benzene (**94b**; 182 mg, 1.00 mmol), cyclohexanezinc bromide (**92i**; 1.58 mL, 1.50 mmol, 0.95 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 10 h. Purification by flash chromatography (pentane, silica gel) furnished **95r** as a yellow oil (153 mg, 70% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.33-7.29 (m, 2H), 7.25-7.21 (m, 2H), 2.61-2.52 (m, 1H), 1.91-1.83 (m, 2H), 1.79-1.69 (m, 2H), 1.57-1.46 (m, 4H), 1.41-1.30 (m, 2H).

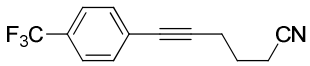
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 133.3, 132.8 (CH), 128.4 (CH), 122.7, 95.5, 79.5, 32.6 (CH_2), 29.7 (CH), 25.9 (CH_2), 24.9 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2931 (m), 2855 (m), 2230 (vw), 1899 (vw), 1738 (w), 1592 (vw), 1489 (s), 1447 (m), 1398 (w), 1304 (w), 1089 (s), 1028 (w), 1014 (m), 952 (w), 933 (w), 826 (vs), 798 (w).

MS (EI, 70 eV): *m/z* (%) = 218 (90, M^+), 189 (52), 183 (50), 175 (66), 155 (54), 141 (100), 136 (36), 129 (49), 127 (40), 125 (74).

HRMS (EI): calcd. for $C_{14}H_{15}{}^{35}Cl$: 218.0862; found: 218.0859.

6-(4-(Trifluoromethyl)phenyl)hex-5-ynenitrile (**95s**)



Prepared according to **TP10** from 1-((methylthio)ethynyl)-4-(trifluoromethyl)benzene (**94d**; 216 mg, 1.00 mmol), 4-cyanopropylzinc bromide (**92h**; 1.47 mL, 1.50 mmol, 1.02 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 4 h. Purification by flash chromatography (pentane/Et_2O 9:1, silica gel) furnished **95s** as a clear oil (156 mg, 66% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.55 (d, *J* = 8.51 Hz, 2H), 7.48 (d, *J* = 8.51 Hz, 2H), 2.62 (t, J = 6.83 Hz, 2H), 2.55 (t, *J* = 7.20 Hz, 2H), 1.97 (dt, *J* = 6.83, 7.20 Hz, 2H).

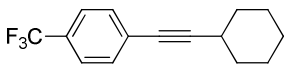
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 131.8 (CH), 129.8 (q, *J* = 32.6 Hz), 127.0 (q, *J* = 1.55 Hz), 125.2 (q, *J* = 3.87 Hz, CH), 119.0, 123.9 (q, *J* = 272.1 Hz, CF_3), 89.7, 81.2, 24.4 (CH_2), 18.5 (CH_2), 16.3 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2942 (vw), 2361 (vw), 2248 (w), 2166 (m), 1740 (vw), 1612 (m), 1598 (w), 1491 (m), 1444 (w), 1431 (w), 1346 (w), 1321 (vs), 1102 (s), 1070 (w), 1026 (vw), 917 (w), 758 (vs), 690 (vs), 669 (w).

MS (EI, 70 eV): *m/z* (%) = 237 (100, M^+), 236 (45), 218 (26), 197 (25), 196 (61), 183 (96), 177 (58), 168 (35), 133 (24), 43 (94).

HRMS (EI): calcd. for $C_{13}H_{10}F_3N$: 237.0765; found: 237.0754

1-(Cyclohexylethynyl)-4-(trifluoromethyl)benzene (**95t**)



Prepared according to **TP10** from 1-((methylthio)ethynyl)-4-(trifluoromethyl)benzene (**94d**; 216 mg, 1.00 mmol), cyclohexanezinc bromide (**92i**; 1.58 mL, 1.50 mmol, 0.95 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 18 h. Purification by flash chromatography (pentane, silica gel) furnished **95t** as a pale yellow solid (130 mg, 66% yield).

m.p. (°C): 35-37.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.53-7.46 (m, 4H), 2.64-2.55 (m, 1H), 1.90-1.85 (m, 2H), 1.77-1.72 (m, 2H), 1.57-1.52 (m, 3H), 1.40-1.32 (m, 3H).

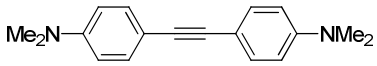
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 131.7 (CH), 129.2 (q, J = 33.0 Hz), 128.0 (q, J = 1.55 Hz), 125.0 (q, J = 3.95 Hz, CH), 124.0 (q, J = 271.9 Hz, CF_3), 97.3, 79.5, 32.5 (CH_2), 29.7 (CH), 25.9 (CH_2), 24.9 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2930 (m), 2856 (w), 2229 (w), 1614 (w), 1449 (w), 1404 (w), 1322 (vs), 1300 (m), 1264 (w), 1258 (w), 1167 (s), 1125 (s), 1103 (vs), 1066 (vs), 1046 (m), 1014 (m), 952 (w), 888 (w), 840 (vs), 720 (w).

MS (EI, 70 eV): *m/z* (%) = 252 (22, M^+), 210 (26), 209 (42), 196 (18), 184 (31), 183 (20), 141 (32), 67 (39), 54 (18), 41 (100).

HRMS (EI): calcd. for $C_{15}H_{15}F_3$: 252.1126, found: 252.1117.

4,4'-Ethyne-1,2-diylbis(*N*,*N*-dimethylaniline) (**95u**)



Prepared according to **TP10** from bis(methylthio)acetylene (**94h**; 118 mg, 1.00 mmol), 4-(*N*,*N*-dimethylamino)phenylzinc iodide (**92l**; 3.03 mL, 3.00 mmol, 0.99 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 8 h. Purification by flash chromatography (pentane/CH_2Cl_2 6:4, silica gel) furnished **95u** as a yellow solid (215 mg, 81% yield).

m.p. (°C): 232-234

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.41-7.36 (m, 4H), 6.68-6.63 (m, 4H), 2.97 (s, 12H).

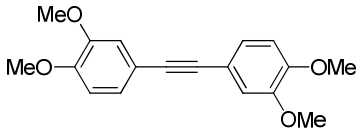
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 149.7, 132.3 (CH), 111.9 (CH), 111.2, 88.1, 40.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2890 (w), 2807 (w), 2361 (w), 1739 (w), 1608 (s), 1526 (s), 1480 (m), 1444 (m), 1352 (s), 1321 (m), 1227 (s), 1190 (s), 1164 (m), 1137 (m), 1062 (m), 941 (m), 827 (m), 816 (vs).

MS (EI, 70 eV): *m/z* (%) = 265 (19), 264 (100, M^+), 263 (6), 250 (5), 249 (20), 248 (12), 247 (4), 233 (4), 132 (5), 131 (6).

HRMS (EI): calcd. for $C_{18}H_{20}N_2$: 264.1626; found: 264.1617.

1,1'-Ethyne-1,2-diylbis(3,4-dimethoxybenzene) (**95v**)



Prepared according to **TP10** from bis(methylthio)acetylene (**94h**; 118 mg, 1.00 mmol), 3,4-dimethoxyphenylzinc iodide (**92x**; 2.78 mL, 3.00 mmol, 1.08 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 10 h. Purification by flash chromatography (pentane/Et_2O 1:1, silica gel) furnished **95v** as an orange solid (235 mg, 79% yield).

m.p. (°C): 132-134.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.14-7.09 (m, 2H), 7.02-6.99 (m, 2H), 6.83-6.78 (m, 2H), 3.89 (s, 6H), 3.87 (s, 6H).

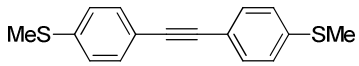
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 149.3, 148.7, 124.7 (CH), 115.7, 114.2 (CH), 111.1 (CH), 88.0, 56.0 (CH_3), 55.9 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2931 (w), 2837 (w), 1599 (w), 1575 (w), 1515 (s), 1508 (s), 1462 (m), 1414 (m), 1324 (m), 1264 (m), 1243 (s), 1228 (s), 1214 (s), 1170 (s), 1134 (s), 1019 (vs), 965 (w), 851 (m), 806 (s), 795 (m), 764 (m), 617 (w), 612 (w).

MS (EI, 70 eV): *m/z* (%) = 299 (9), 298 (49, M^+), 284 (12), 283 (15), 275 (20), 274 (100), 260 (24), 259 (44), 132 (12), 216 (16).

HRMS (EI): calcd. for $C_{18}H_{18}O_4$: 298.1205, found: 298.1201.

1,1'-Ethyne-1,2-diylbis(4-(methylthio)benzene) (**95w**)



Prepared according to **TP10** from bis(methylthio)acetylene (**94h**; 118 mg, 1.00 mmol), 4-thiomethylphenylzinc iodide (**92y**; 2.14 mL, 3.00 mmol, 1.40 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 14 h. Purification by flash chromatography (pentane, silica gel) furnished **95w**as a yellow solid (198 mg, 73% yield).

m.p. (°C): 142-144.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.44-7.40 (m, 4H), 7.21-7.17 (m, 4H), 2.49 (s, 6H).

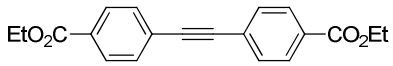
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 129.2, 131.8 (CH), 125.9 (CH), 119.6, 89.3, 15.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2915 (w), 1899 (w), 1593 (w), 1498 (m), 1478 (m), 1459 (w), 1432 (m), 1397 (m), 1319 (w), 1220 (w), 1184 (w), 1089 (s), 1011 (w), 968 (w), 954 (w), 815 (vs), 808 (s), 746 (w), 723 (s), 692 (w).

MS (EI, 70 eV): *m/z* (%) = 270 (100, M^+), 255 (58), 240 (14), 239 (4), 209 (3), 208 (10), 195 (5), 164 (3), 163 (5), 135 (6).

HRMS (EI): calcd. for $C_{16}H_{14}{}^{32}S_2$: 270.0537, found: 270.0528.

Diethyl 4,4'-ethyne-1,2-diyldibenzoate (**95x**)



Prepared according to **TP10** from bis(methylthio)acetylene (**94h**; 118 mg, 1.00 mmol), 4-ethoxycarbonylphenylzinc iodide (**92c**; 5.17 mL, 3.00 mmol, 0.58 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 12 h. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **95x** as an orange solid (216 mg, 67% yield).

m.p. (°C): 143-145.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.03-8.00 (m, 4H), 7.59-7.56 (m, 4H), 4.37 (q, J = 7.18 Hz, 4H), 1.39 (t, J = 7.18 Hz, 6H).

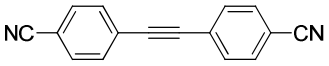
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 165.9, 131.5 (CH), 130.3, 129.5 (CH), 127.2, 91.3, 61.1 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2975 (w), 1709 (vs), 1606 (m), 1560 (w), 1477 (w), 1403 (m), 1368 (m), 1306 (m), 1271 (vs), 1175 (m), 1128 (m), 1103 (s), 1028 (m), 1014 (m), 881 (w), 855 (m), 846 (m), 830 (w), 764 (vs), 692 (s), 638 (vw).

MS (EI, 70 eV): *m/z* (%) = 323 (22), 322 (89, M^+), 294 (15), 278 (23), 277 (100), 266 (12), 249 (40), 176 (38), 116 (13), 102 (13).

HRMS (EI): calcd. for $C_{20}H_{18}O_4$: 322.1205, found: 322.1209.

4,4'-Ethyne-1,2-diyldibenzonitrile (**95y**)



Prepared according to **TP10** from bis(methylthio)acetylene (**94h**; 118 mg, 1.00 mmol), 4-cyanophenylzinc iodide (**92d**; 4.23 mL, 3.00 mmol, 0.71 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 16 h. Purification by flash chromatography (pentane/Et_2O 2:1, silica gel) furnished **95y** as a yellow solid (146 mg, 64% yield).

m.p. (°C): 205-211.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.67-7.65 (m, 4H), 7.63-7.61 (m, 4H).

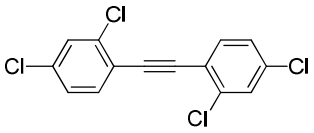
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 132.3 (CH), 132.2 (CH), 127.1, 118.2, 112.4, 91.5.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2958 (w), 2923 (m), 2853 (w), 2226 (m), 1661 (w), 1603 (m), 1502 (w), 1491 (w), 1406 (w), 1398 (w), 1276 (w), 1261 (m), 1180 (w), 1099 (m), 1017 (m), 929 (w), 857 (w), 817 (vs),768 (w).

MS (EI, 70 eV): *m/z* (%) = 229 (15), 228 (100, M^+), 227 (7), 204 (7), 202 (5), 201 (10), 200 (8), 175 (4), 114 (4), 100 (3).

HRMS (EI): calcd. for $C_{16}H_8N_2$: 228.0687, found: 228.0675.

1,1'-Ethyne-1,2-diylbis(2,4-dichlorobenzene) (**95z**)



Prepared according to **TP10** from bis(methylthio)acetylene (**94h**; 118 mg, 1.00 mmol), 2,4-dichlorophenylzinc iodide (**92t**; 4.76 mL, 3.00 mmol, 0.63 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 4 h. Purification by flash chromatography (pentane, silica gel) furnished **95z** as a colourless solid (246 mg, 78% yield).

m.p. (°C): 132-134.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.51 (d, *J* = 8.42 Hz, 2H), 7.46 (d, *J* = 2.15 Hz, 2H), 7.24 (dd, *J* = 2.15, 8.42 Hz, 2H),

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 136.8, 135.2, 134.0 (CH), 129.5 (CH), 127.1 (CH), 121.3, 91.0.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 1739 (w), 1722 (w), 1587 (w), 1544 (w), 1487 (s), 1471 (m), 1462 (m), 1426 (w), 1378 (m), 1230 (w), 1217 (w), 1141 (w), 1096 (s), 1051 (m), 873 (w), 859 (s), 816 (vs), 810 (vs), 737 (s).

MS (EI, 70 eV): *m/z* (%) = 314 (100, M^+), 246 (18), 245 (6), 244 (31), 174 (8), 158 (11), 157 (8), 123 (8), 122 (11), 104 (7).

HRMS (EI): calcd. for $C_{14}H_6{}^{35}Cl_4$: 313.9224; found: 313.9216.

2,2'-Ethyne-1,2-diylbis-1-benzofuran (**95aa**)

Prepared according to **TP10** from bis(methylthio)acetylene (**94h**; 118 mg, 1.00 mmol), benzofuran-2-ylzinc iodide (**92v**; 4.29 mL, 3.00 mmol, 0.70 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 3 h. Purification by flash

chromatography (pentane/CH_2Cl_2 40:1, silica gel) furnished **95aa** as a colourless solid (191 mg, 74% yield).

m.p. (°C): 139-140.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.60 (d, *J* = 7.15 Hz, 2H), 7.50 (d, *J* = 7.39 Hz, 2H), 7.25-7.40 (m, 4H), 7.13 (s, 2H).

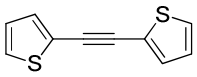
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 155.2, 137.6, 127.4, 126.2 (CH), 123.5 (CH), 121.5 (CH), 113.2 (CH), 111.4 (CH), 85.2.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 1739 (w), 1450 (m), 1442 (m), 1349 (m), 1296 (m), 1254 (m), 1200 (m), 1160 (m), 1142 (m), 1104 (w), 1012 (w), 960 (m), 931 (m), 885 (w), 833 (m), 826 (m), 799 (m), 746 (vs), 735 (s), 692 (m).

MS (EI, 70 eV): *m/z* (%) = 260 (2), 259 (17), 258 (100, M^+), 234 (4), 229 (5), 202 (5), 201 (4), 200 (5), 129 (3), 88 (2).

HRMS (EI): calcd. for $C_{18}H_{10}O_2$: 258.0681, found: 258.0675.

2,2'-Ethyne-1,2-diyldithiophene (**95ab**)



Prepared according to **TP10** from bis(methylthio)acetylene (**94h**; 118 mg, 1.00 mmol), 2-thienylzinc iodide (**92w**; 3.80 mL, 3.00 mmol, 0.79 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 20 h. Purification by flash chromatography (pentane, silica gel) furnished **95ab** as a pale yellow solid (127 mg, 67% yield).

m.p. (°C): 105-106.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.30 (dd, *J* = 5.19, 1.13 Hz, 2H), 7.27 (dd, *J* = 3.70, 1.13 Hz, 2H), 7.00 (dd, *J* = 5.19, 3.70 Hz, 2H).

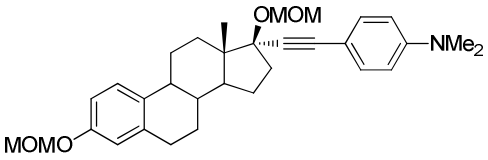
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 132.1 (CH), 127.6 (CH), 127.1 (CH), 122.9, 86.2.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3098 (vw), 3081 (vw), 2919 (vw), 1432 (w), 1406 (w), 1361 (w), 1199 (m), 1194 (m), 1097 (w), 1083 (w), 1073 (w), 1040 (w), 1028 (w), 895 (w), 849 (s), 824 (m), 748 (w), 723 (w), 693 (vs).

MS (EI, 70 eV): *m/z* (%) = 190 (100, M^+), 189 (9), 158 (11), 146 (14), 145 (16), 114 (11), 57 (9), 55 (10), 44 (10), 43 (13).

HRMS (EI): calcd. for $C_{10}H_6{}^{32}S_2$: 189.9911, found: 189.9903.

4-((3,17b-*Bis*(methoxymethoxy)estra-1(10),2,4-trien-17ayl)ethynyl)-*N*,*N*-dimethylaniline (**95ac**)



Prepared according to **TP10** from 3,17b-bis(methoxymethoxy)-17a-((methylthio)ethynyl)estra-1(10),2,4-triene (**94i**; 431 mg, 1.00 mmol), 4-(*N*,*N*-dimethylamino)phenylzinc iodide (**92l**; 1.52 mL, 1.50 mmol, 0.99 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 8 h. Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **95ac** as a yellow oil (377 mg, 75% yield).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 7.36-7.34 (m, 2H), 7.24 (d, *J* = 8.78 Hz, 1H), 6.85 (dd, *J* = 8.78, 2.74 Hz, 1H), 6.79 (d, *J* = 2.74 Hz, 1H), 6.66-6.63 (m, 2H), 5.16 (s, 2H), 5.14 (d, *J* = 6.31 Hz, 1H), 4.89 (d, *J* = 6.31 Hz, 1H), 3.49 (s, 3H), 3.45 (s, 3H), 2.97 (s, 6H), 2.89-2.84 (m, 2H), 2.39-2.34 (m, 2H), 2.28-2.20 (m, 2H), 2.08-2.03 (m, 1H), 1.92-1.83 (m, 4H), 1.56-1.36 (m, 4H), 0.97 (s, 3H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 154.9, 150.0, 138.0, 134.0, 132.8 (CH), 132.7 (CH), 126.3 (CH), 116.1 (CH), 113.6 (CH), 111.8, 94.4 (CH_2), 93.6 (CH_2), 89.0, 87.6, 85.9, 55.8 (CH_3), 55.7 (CH_3), 49.0 (CH), 48.1, 43.6 (CH), 40.2 (CH_3), 39.2 (CH), 37.7 (CH_2), 33.4 (CH_2), 29.8 (CH_2), 27.2 (CH_2), 26.4 (CH_2), 23.0 (CH_2), 13.1 (CH_3).

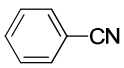
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2928 (m), 2360 (w), 2213 (vw), 1739 (w), 1607 (s), 1520 (s), 1497 (m), 1444 (m), 1357 (m), 1230 (m), 1150 (s), 1075 (s), 1061 (m), 1014 (vs), 972 (m), 945 (m), 919 (m), 871 (w), 815 (s), 784 (w), 730 (m).

MS (EI, 70 eV): *m/z* (%) = 503 (16, M^+), 460 (22), 459 (69), 458 (32), 443 (46), 442 (46), 441 (100), 200 (40), 148 (50), 45 (21).

HRMS (EI): calcd. for $C_{32}H_{41}NO_4$: 503.3036, found: 503.3035.

3.4.7 Preparation of Nitriles 97 via Ni-catalyzed Cross-Coupling Reaction

Benzonitrile (**97a**)

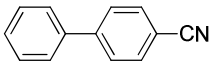


Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), phenylzinc iodide (**92z**; 1.46 mL, 1.50 mmol, 1.03 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 2 h. Purification by flash chromatography (pentane/Et_2O 50:1, silica gel) furnished **97a** as a clear oil (84 mg, 81% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.75-7.35 (m, 5H).

These data match the literature: Z. Zhang, L. S. Liebeskind, *Org. Lett.* **2006**, *8*, 4331.

[1,1'-Biphenyl]-4-carbonitrile (**97b**)



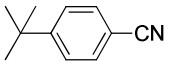
Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), 4-biphenylzinc iodide (**92aa**; 2.03 mL, 1.50 mmol, 0.74 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 10 h. Purification by flash chromatography (pentane/Et_2O 20:1, silica gel) furnished **97b** as a colourless solid (130 mg, 73% yield).

m.p. (°C): 89-90.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.74-7.66 (m, 4H), 7.60-7.56 (m, 2H), 7.51-7.40 (m, 3H).

These data match the literature: O. Grossman, D. Gelman, *Org. Lett.* **2006**, *8*, 1189.

4-(*Tert*-butyl)benzonitrile (**97c**)

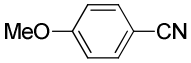


Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), 4-(*tert*-butyl)phenylzinc iodide (**92ab**; 1.46 mL, 1.50 mmol, 1.03 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 12 h. Purification by flash chromatography (pentane, silica gel) furnished **97c** as a clear oil (130 mg, 82% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.59-7.55 (m, 2H), 7.49-7.45 (m, 2H), 1.32 (s, 9H).

These data match the literature: O. Grossman, D. Gelman, *Org. Lett.* **2006**, *8*, 1189.

4-Methoxybenzonitrile (**97d**)



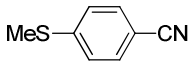
Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), 4-methoxyphenylzinc iodide (**92b**; 1.61 mL, 1.50 mmol, 0.93 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 2 h. Purification by flash chromatography (pentane/Et_2O 8:2, silica gel) furnished **97d** as a colourless solid (115 mg, 86% yield).

m.p. (°C): 63-64.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.60-7.55 (m, 2H), 6.96-6.91 (m, 2H), 3.85 (s, 3H).

These data match the literature: O. Grossman, D. Gelman, *Org. Lett.* **2006**, *8*, 1189.

4-(Methylthio)benzonitrile (**97e**)



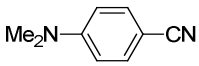
Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), 4-thiomethylphenylzinc iodide (**92y**; 2.14 mL, 3.00 mmol, 1.40 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 8 h. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **97e** as a colourless solid (115 mg, 77% yield).

m.p. (°C): 65-66.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.54-7.49 (m, 2H), 7.27-7.22 (m, 2H), 2.50 (s, 3H).

These data match the literature: V. Dichiarante, M. Fagnoni, A. Albini, *Chem. Commun.* **2006**, *28*, 3001.

4-(Dimethylamino)benzonitrile (**97f**)



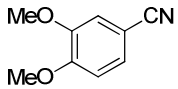
Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), 4-(*N*,*N*-dimethylamino)phenylzinc iodide (**92l**; 1.52 mL, 1.50 mmol, 0.99 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 2 h. Purification by flash chromatography (pentane/Et_2O 4:1, silica gel) furnished **97f** as a colourless solid (133 mg, 91% yield).

m.p. (°C): 78-79 (Lit).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.49-7.44 (m, 2H), 6.70-6.65 (m, 2H), 3.03 (s, 6H).

These data match the literature: Z. Zhang, L. S. Liebeskind, *Org. Lett.* **2006**, *8*, 4331.

3,4-Dimethoxybenzonitrile (**97g**)



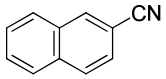
Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), 3,4-dimethoxyphenylzinc iodide (**92x**; 1.39 mL, 1.50 mmol, 1.08 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 5 h. Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **97g** as a colourless solid (137 mg, 84% yield).

m.p. (°C): 72-73.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.27 (dd, J = 8.38, 1.86 Hz, 1H), 7.06 (d, J = 1.86 Hz, 1H), 6.89 (d, J = 8.38 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H).

These data match the literature: E.-C. Wang, K.-S. Huang, H.-M. Chen, C.-C. Wu, G.-J. Lin, *J. Chin. Chem. Soc.* **2004**, *51*, 619.

2-Naphthonitrile (**97h**)



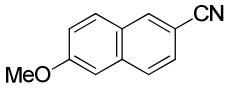
Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), 2-napthylzinc iodide (**92ac**; 2.24 mL, 1.50 mmol, 0.67 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 6 h. Purification by flash chromatography (pentane/Et_2O 40:1, silica gel) furnished **97h** as a colourless solid (136 mg, 89% yield).

m.p. (°C): 72-74 (Lit).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.22-8.21 (m, 1H), 7.92-7.86 (m, 3H), 7.67-7.57 (m, 3H).

These data match the literature: Z. Zhang, L. S. Liebeskind, *Org. Lett.* **2006**, *8*, 4331.

6-Methoxy-2-naphthonitrile (**97i**)



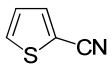
Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), (6-methoxynaphthalen-2-yl)zinc iodide (**92ad**; 2.00 mL, 1.50 mmol, 0.75 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 6 h. Purification by flash chromatography (pentane/Et_2O 20:1, silica gel) furnished **97i** as a colourless solid (154 mg, 84% yield).

m.p. (°C): 109-110.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.13-8.12 (m, 1H), 7.78-7.75 (m, 2H), 7.55 (dd, J = 8.52, 1.59 Hz, 1H), 7.23 (dd, J = 8.82, 2.48, Hz, 1H), 7.14 (d, J = 2.48 Hz, 1H).

These data match the literature: P. Anbarasan, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 4725.

Thiophene-2-carbonitrile (**97j**)



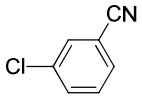
Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), 2-thienylzinc iodide (**92w**; 1.90 mL, 1.50 mmol, 0.79 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-

Phos (26.9 mg, 5.0 mol%) at 25 °C for 24 h. Purification by flash chromatography (pentane/Et_2O 20:1, silica gel) furnished **97j** as a clear oil (55 mg, 50% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.66 (dd, J = 3.78, 1.18 Hz, 1H), 7.63 (dd, J = 5.08, 1.18 Hz, 1H), 7.15 (d, J = 5.08, 3.78 Hz, 1H).

These data match the literature: E.-C. Wang, K.-S. Huang, H.-M. Chen, C.-C. Wu, G.-J. Lin, *J. Chin. Chem. Soc.* **2004**, *51*, 619.

3-Chlorobenzonitrile (**97k**)



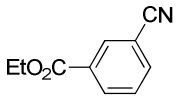
Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), 3-chlorophenylzinc iodide (**92ae**; 1.46 mL, 1.50 mmol, 1.03 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 25 °C for 24 h. Purification by flash chromatography (pentane/Et_2O 40:1, silica gel) furnished **97k** as a colourless solid (107 mg, 78% yield).

m.p. (°C): 48-50.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.63-7.53 (m, 3H), 7.44-7.39 (m, 1H).

These data match the literature: C. Yang, J. M. Williams, *Org. Lett.* **2004**, *6*, 2837.

Ethyl 3-cyanobenzoate (**97l**)



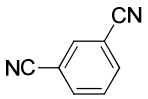
Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), 3-ethoxycarbonylphenylzinc iodide (**92af**; 3.00 mL, 1.50 mmol, 0.50 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 8 h. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **97l** as a colourless solid (133 mg, 76% yield).

m.p. (°C): 50-51.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.32-8.24 (m, 2H), 7.83-7.78 (m, 1H), 7.59-7.52 (m, 1H), 4.40 (q, J = 7.15 Hz, 2H), 1.40 (t, J = 7.15 Hz, 3H).

These data match the literature: O. Exner, M. Budesinsky, *Mag. Res. Chem.* **1989**, *27*, 27.

Isophthalonitrile (**97m**)



Prepared according to **TP11** from methyl thiocyanate (**96**; 73 mg, 1.00 mmol), 3-cyanophenylzinc iodide (**92ag**; 2.23 mL, 1.50 mmol, 0.67 M in THF), $Ni(acac)_2$ (6.4 mg, 2.5 mol%) and DPE-Phos (26.9 mg, 5.0 mol%) at 50 °C for 8 h. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **97m** as a colourless solid (101 mg, 79% yield).

m.p. (°C): 165-166.

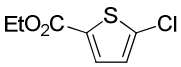
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.95-7.94 (m, 1H), 7.91-7.90 (m, 1H), 7.88-7.87 (m, 1H), 7.67-7.62 (m, 1H).

These data match the literature: R. S. Ramon, N. Marion, S. P. Nolan, *Chem. Eur. J.* **2009**, *15*, 8695.

3.5 Chlorine-Zinc Exchange with Biaryl Zincates using Iron-Catalysis

3.5.1 Preparation of Chlorides 98

Ethyl 5-chlorothiophene-2-carboxylate (**98d**)



In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, ethyl thiophene-2-carboxylate (3.12 g, 20.0 mmol) and *N*-chlorosuccinimide (2.94 g, 22.0 mmol) were dissvoled in DMF (10 mL) and stirred at 80 C for 16 h. The reaction mixture was quenched with 2N HCl-solution (20 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane/Et_2O, 50:1, silica gel) furnished **98d** as a clear liquid (2.07 g, 54% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.55 (d, J = 4.05 Hz, 1H), 6.89 (d, J = 4.05 Hz, 1H), 4.32 (q, J = 7.15 Hz, 2H), 1.33 (t, J = 7.15 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 161.1, 137.0, 132.7 (CH), 132.2, 127.1 (CH), 61.3 (CH_2), 14.2 (CH_3).

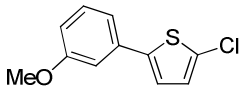
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3104 (vw), 2982 (w), 1706 (s), 1536 (w), 1464 (w), 1444 (w), 1424 (vs), 1366 (w), 1332 (m), 1278 (s), 1248 (vs), 1212 (m), 1172 (w), 1086 (vs), 1060 (s), 1018 (w), 996 (m), 892 (vw), 860 (w), 810 (m), 764 (w), 744 (s), 674 (vw), 664 (vw).

MS (EI, 70 eV): *m/z* (%) = 192 (7), 190 (33, M^+), 164 (10), 162 (32), 147 (37), 146 (14), 145 (100), 82 (7), 73 (18), 41 (6).

HRMS (EI): calcd. for $C_7H_7{}^{35}ClO_2{}^{32}S$: 189.9855, found: 189.9858.

These data match the literature: A. S.-Y. Lee, C.-C. Wu, L.-S. Lin, H.-F. Hsu, *Synthesis*, **2004**, 568.

2-Chloro-5-(3-methoxyphenyl)thiophene (**98e**)



In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, 2-chlorothiophene (2.37 g, 20.0 mmol) was dissvoled in THF (20 mL) and cooled to 0 °C. *n*BuLi (22.0 mmol, 9.36 mL, 2.35 M in hexane) was added and the reaction stirred at 0 °C for 2 h, then $ZnCl_2$ (22.0 mmol, 22.0 mL, 1.0 M in THF) was added and the solution stirred at 0 °C for 30 min. 3-Bromoanisole (4.14 g, 22.0 mmol) and $Pd(PPh_3)_4$ (231 mg, 0.20 mmol) were added and the reaction was stirred at 50 °C for 5 h. The reaction mixture was quenched with sat. aq. NH_4Cl-solution (20 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane/Et_2O, 10:1, silica gel) furnished **98e** as a clear liquid (3.27 g, 73% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.30 (dd, *J* = 7.89, 7.85 Hz, 1H), 7.13-7.10 (m, 1H), 7.08-7.05 (m, 2H), 6.90-6.85 (m, 2H), 3.85 (s, 3H).

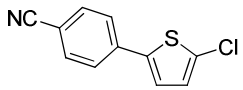
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 159.9, 142.7, 134.9, 129.9 (CH), 129.1, 127.0 (CH), 122.3 (CH), 118.0 (CH), 113.1 (CH), 111.2 (CH), 55.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3000 (vw), 2956 (w), 2936 (w), 2834 (w), 1738 (vw), 1598 (s), 1588 (m), 1578 (s), 1484 (m), 1454 (m), 1434 (m), 1334 (w), 1288 (m), 1266 (m), 1216 (s), 1200 (m), 1166 (s), 1070 (w), 1044 (m), 1010 (s), 988 (m), 864 (w), 794 (s), 770 (vs), 684 (s), 644 (w), 622 (w).

MS (EI, 70 eV): *m/z* (%) = 226 (41), 225 (13), 224 (100, M^+), 183 (10), 181 (26), 145 (9), 102 (10), 57 (9), 55 (7), 43 (10).

HRMS (EI): calcd. for $C_{11}H_9{}^{35}ClO^{32}S$: 224.0063, found: 224.0055.

Ethyl 5-chlorothiophene-2-carboxylate (**98f**)



In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, 2-chlorothiophene (2.37 g, 20.0 mmol) was dissvoled in THF (20 mL) and cooled to 0 °C. *n*BuLi (22.0 mmol, 9.36 mL, 2.35 M in hexane) was added and the reaction stirred at 0 C for 2 h, then $ZnCl_2$ (22.0 mmol, 22.0 mL, 1.00 M in THF) was added and the solution stirred at 0 °C for 30 min. 4-Bromobenzonitrile (4.00 g, 22.0 mmol) and $Pd(PPh_3)_4$ (231 mg, 0.20 mmol) were added and the reaction was stirred at 50 °C for 5 h. The reaction mixture was quenched with sat. aq. NH_4Cl-solution (20 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane/Et_2O, 4:1, silica gel) furnished **98f** as an off-white solid (3.33 g, 76% yield).

m.p. (°C): 99-100.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.65-7.61 (m, 2H), 7.58-7.54 (m, 2H), 7.17 (d, *J* = 4.05 Hz, 1H), 6.93 (d, *J* = 4.05 Hz, 1H).

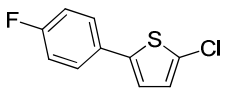
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 140.4, 137.7, 132.8 (CH), 131.7, 127.6 (CH), 125.6 (CH), 124.4 (CH), 118.6, 110.9.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3092 (vw), 2224 (w), 1738 (w), 1602 (w), 1494 (w), 1434 (m), 1410 (w), 1334 (w), 1308 (w), 1252 (w), 1230 (w), 1214 (w), 1178 (w), 1122 (w), 1108 (w), 1076 (w), 998 (w), 950 (w), 888 (vw), 836 (w), 824 (w), 802 (vs), 774 (w), 736 (w), 720 (w), 666 (vw).

MS (EI, 70 eV): *m/z* (%) = 222 (5), 221 (40), 220 (15), 219 (100, M^+), 183 (7), 140 (28), 139 (4), 109 (5), 92 (5), 91 (10).

HRMS (EI): calcd. for $C_{11}H_6{}^{35}ClN^{32}S$: 218.9909, found: 218.9901.

2-Chloro-5-(4-fluorophenyl)thiophene (**98g**)



In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, 2-chlorothiophene (2.37 g, 20.0 mmol) was dissvoled in THF (20 mL) and cooled to 0 °C. *n*BuLi (22.0 mmol, 9.36 mL, 2.35 M in hexane) was added and the reaction stirred at 0 C for 2 h, then $ZnCl_2$ (22.0 mmol, 22.0 mL, 1.00 M in THF) was added and the solution stirred at 0 °C for 30 min. 1-Bromo-4-fluorobenzene (3.85 g, 22.0 mmol) and $Pd(PPh_3)_4$ (231 mg, 0.20 mmol) were added and the reaction was stirred at 50 °C for 5 h. The reaction mixture was quenched with sat. aq. NH_4Cl-solution (20 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed

under reduced pressure. Purification by flash chromatography (pentane/Et_2O, 40:1, silica gel) furnished **98g** as an off-white solid (3.49 g, 82% yield).

m.p. (°C): 90-92.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.49-7.42 (m, 2H), 7.10-7.02 (m, 2H), 6.98 (d, *J* = 4.04 Hz, 1H), 6.87 (d, *J* = 4.04 Hz, 1H).

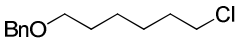
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.4 (d, *J* = 247.9 Hz, CF), 141.8, 130.0 (d, *J* = 3.37 Hz), 129.1 (d, *J* = 1.12 Hz), 127.3 (d, *J* = 8.13 Hz, CH), 127.1 (CH), 122.2 (d, *J* = 1.12 Hz, CH), 116.0 (d, *J* = 21.88 Hz, CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3100 (w), 1754 (w), 1598 (m), 1544 (w), 1536 (w), 1498 (s), 1462 (m), 1440 (m), 1412 (m), 1304 (w), 1232 (s), 1160 (m), 1100 (m), 1072 (m), 1014 (w), 1002 (m), 946 (w), 878 (w), 832 (s), 810 (m), 794 (vs), 670 (m), 630 (w).

MS (EI, 70 eV): *m/z* (%) = 213 (11), 212 (30, M^+), 133 (23), 70 (12), 69 (9), 61 (12), 57 (11), 55 (10), 46 (14), 46 (100).

HRMS (EI): calcd. for $C_{10}H_6{}^{35}ClF^{32}S$: 211.9863, found: 211.9855.

(((6-Chlorohexyl)oxy)methyl)benzene (**98j**)



In a dry and argon-flushed Schlenk-flask, equipped with a magnetic stirrer and a septum, sodium hydride (0.60 g, 25.0 mmol, 60% in mineral oil) was suspended in THF (20 mL). 6-Chlorohexan-1-ol (2.73 g, 20.0 mmol) was added slowly and the reaction stirred at 25 °C for 2 h, then benzyl bromide (4.28 g, 25.0 mmol) was added and the reaction stirred at 25 C for 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl-solution (20 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and after filtration the solvent was removed under reduced pressure. Purification by flash chromatography (pentane/Et_2O 20:1, silica gel) furnished **98j** as a clear liquid (3.76 g, 80% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.36-7.25 (m, 5H), 4.50 (s, 2H), 3.53 (t, *J* = 6.68 Hz, 2H), 3.48 (t, *J* = 6.44 Hz, 2H), 1.82-1.73 (m, 2H), 1.68-1.59 (m, 2H), 1.49-1.38 (m, 4H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 138.6, 128.3 (CH), 127.6 (CH), 127.5 (CH), 72.9 (CH_2), 70.2 (CH_2), 45.0 (CH_2), 32.5 (CH_2), 29.6 (CH_2), 26.7 (CH_2), 25.5 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3064 (vw), 3030 (vw), 2936 (m), 2858 (m), 2794 (vw), 1738 (vw), 1496 (w), 1454 (m), 1362 (m), 1310 (w), 1204 (w), 1156 (vw), 1100 (s), 1028 (w), 964 (w), 948 (w), 906 (w), 818 (vw), 732 (vs), 696 (vs), 650 (m), 612 (w).

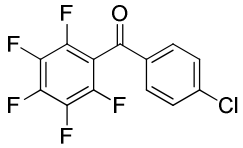
MS (EI, 70 eV): *m/z* (%) = 226 (1, M^+), 108 (5), 107 (4), 93 (3), 92 (53), 91 (100), 79 (4), 65 (5), 55 (3), 41 (3).

HRMS (EI): calcd. for $C_{13}H_{19}{}^{35}ClO$: 226.1124, found: 226.1115.

These data match the literature: K. M. Penov Gasi, K. N. Kuhajda, S. M. Cvjeticanin, E. A. Durendic, L. D. Medic-Mijacevic, V. M. Pejanovic, M .N. Sakac, *Acta Periodica Technologica* **2003**, *34*, 111.

3.5.2 Preparation of Aromatic Products 101 via Chlorine-Zinc Exchange using Zincate 100

(4-Chlorophenyl)(perfluorophenyl)methanone (**101a**)



Prepared according to **TP12** from 1-chloro-2,3,4,5,6-pentafluorobenzene (**98b**; 203 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 4 h. The reaction was cooled to -20 °C, 4-chlorobenzoyl chloride (525 mg, 3.00 mmol) and CuCN·2LiCl (0.20 mmol, 0.20 mL, 1.00 M in THF) were added and the reaction stirred at -20 °C for 30 min. Purification by flash chromatography (pentane/Et_2O 50:1, silica gel) furnished **101a** as a colourless solid (199 mg, 65% yield).

m.p. (°C): 57-59.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.80-7.76 (m, 2H), 7.52-7.47 (m, 2H).

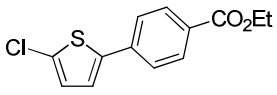
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 184.0, 141.8, 134.3, 131.0 (CH), 129.5 (CH), 4 C omitted.

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2962 (w), 1676 (m), 1650 (m), 1588 (m), 1572 (w), 1520 (m), 1484 (s), 1400 (m), 1324 (m), 1260 (w), 1242 (m), 1228 (m), 1176 (m), 1108 (m), 1088 (s), 1008 (s), 996 (s), 982 (s), 850 (w), 820 (s), 794 (vs), 748 (w), 712 (m), 674 (w), 618 (w).

MS (EI, 70 eV): *m/z* (%) = 306 (21, M^+), 141 (36), 139 (100), 111 (23), 83 (14), 69 (19), 57 (25), 55 (23), 43 (35), 41 (17).

HRMS (EI): calcd. for $C_{13}H_4{}^{35}ClF_5O$: 305.9871, found: 305.9862.

Ethyl 4-(5-chlorothiophen-2-yl)benzoate (**101b**)



Prepared according to **TP12** from 2,5-dichlorothiophene (**98c**; 153 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol)

at 25 °C for 12 h. Ethyl 4-iodobenzoate (828 mg, 3.00 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were added and the reaction stirred at 25 °C for 2 h. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **101b** as an off-white solid (161 mg, 60% yield).

m.p. (°C): 76-78.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.02 (d, *J* = 8.58 Hz, 2H), 7.54 (d, *J* = 8.58 Hz, 2H), 7.16 (d, *J* = 3.81 Hz, 1H), 6.91 (d, *J* = 3.81 Hz, 1H), 4.38 (q, *J* = 7.15 Hz, 2H), 1.39 (t, *J* = 7.15 Hz, 3H).

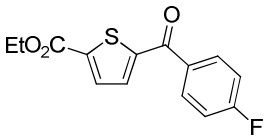
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 166.1, 141.6, 137.7, 130.7, 130.3 (CH), 129.5, 127.4 (CH), 125.0 (CH), 123.6 (CH), 61.0 (CH_2), 14.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2984 (w), 1708 (vs), 1604 (m), 1464 (w), 1434 (m), 1410 (m), 1392 (w), 1364 (m), 1314 (w), 1272 (vs), 1246 (s), 1208 (m), 1182 (m), 1106 (vs), 1072 (m), 1018 (m), 1004 (m), 948 (w), 868 (w), 848 (m), 794 (m), 764 (vs), 712 (w), 694 (m), 658 (w).

MS (EI, 70 eV): *m/z* (%) = 268 (35), 267 (14), 266 (98, M^+), 240 (11), 238 (29), 223 (34), 222 (13), 221 (100), 158 (43), 79 (14).

HRMS (EI): calcd. for $C_{13}H_{11}{}^{35}ClO_2{}^{32}S$: 266.0168, found: 266.0167.

Ethyl 5-(4-fluorobenzoyl)thiophene-2-carboxylate (**101c**)



Prepared according to **TP12** ethyl 5-chlorothiophene-2-carboxylate (**98d**; 191 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 12 h. The reaction was cooled to -20 °C, 4-fluorobenzoyl chloride (476 mg, 3.00 mmol) and CuCN·2LiCl (0.20 mmol, 0.20 mL, 1.00 M in THF) were added and the reaction stirred at -20 °C for 30 min. Purification by flash chromatography (pentane/Et_2O 40:1, silica gel) furnished **101c** as a yellow solid (145 mg, 52% yield).

m.p. (°C): 93-95.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.94-7.89 (m, 2H), 7.78 (d, *J* = 3.90 Hz, 1H), 7.57 (d, *J* = 3.90 Hz, 1H), 7.22-7.16 (m, 2H), 4.39 (q, *J* = 7.15 Hz, 2H), 1.39 (t, *J* = 7.15 Hz, 3H).

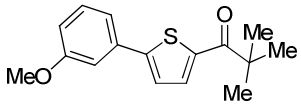
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 186.5, 165.6 (d, *J* = 255.2 Hz, CF), 161.6, 147.4, 140.4, 133.6 (CH), 133.5, (d, *J* = 3.07 Hz), 132.9 (CH), 131.9 (d, *J* = 9.32 Hz, CH), 115.8 (d, *J* = 21.88 Hz, CH), 61.9 (CH_2), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3118 (vw), 2986 (w), 1704 (s), 1626 (m), 1596 (s), 1526 (m), 1504 (m), 1452 (w), 1406 (w), 1366 (w), 1272 (s), 1222 (s), 1154 (m), 1130 (m), 1098 (s), 1050 (s), 1008 (m), 878 (m), 850 (s), 840 (s), 748 (vs), 702 (m), 688 (m), 632 (w), 614 (m).

MS (EI, 70 eV): *m/z* (%) = 279 (11), 278 (72, M^+), 250 (12), 234 (12), 233 (69), 205 (12), 183 (28), 155 (19), 123 (100), 95 (34).

HRMS (EI): calcd. for $C_{14}H_{11}FO_3{}^{32}S$: 278.0413, found: 278.0401.

1-(5-(3-Methoxyphenyl)thiophen-2-yl)-2,2-dimethylpropan-1-one (**101d**)



Prepared according to **TP12** from 2-chloro-5-(3-methoxyphenyl)thiophene (**98e**; 225 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 24 h. The reaction was cooled to -20 °C, pivaloyl chloride (362 mg, 3.00 mmol) and CuCN·2LiCl (0.20 mmol, 0.20 mL, 1.00 M in THF) were added and the reaction stirred at -20 °C for 30 min. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **101d** as a colourless solid (185 mg, 67% yield).

m.p. (°C): 100-102.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.76 (d, *J* = 4.05 Hz, 1H), 7.37-7.31 (m, 1H), 7.30 (d, *J* = 4.05 Hz, 1H), 7.28-7.25 (m, 1H), 7.20-7.19 (m, 1H), 6.92 (dd, *J* = 7.99, 2.50 Hz, 1H), 3.87 (s, 3H), 1.44 (s, 9H).

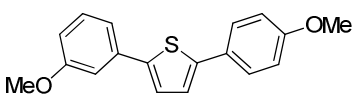
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 198.7, 160.0, 150.9, 141.2, 134.7, 132.8 (CH), 130.1 (CH), 123.7 (CH), 118.8 (CH), 114.3 (CH), 111.8 (CH), 55.3 (CH_3), 43.8, 28.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2966 (w), 1634 (s), 1608 (m), 1578 (m), 1474 (m), 1456 (s), 1436 (m), 1368 (w), 1334 (w), 1284 (s), 1274 (s), 1228 (s), 1180 (s), 1170 (vs), 1096 (w), 1070 (m), 1048 (s), 984 (m), 898 (m), 868 (m), 820 (s), 798 (m), 776 (s), 750 (m), 688 (m).

MS (EI, 70 eV): *m/z* (%) = 275 (11), 274 (64, M^+), 219 (22), 218 (63), 217 (100), 174 (8), 145 (52), 102 (14), 57 (11), 41 (11).

HRMS (EI): calcd. for $C_{16}H_{18}O_2{}^{32}S$: 274.1028, found: 274.1015.

2-(3-Methoxyphenyl)-5-(4-methoxyphenyl)thiophene (**101e**)



Prepared according to **TP12** from 2-chloro-5-(3-methoxyphenyl)thiophene (**98e**; 225 mg, 1.0 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene

(24.5 mg, 0.20 mmol) at 25 °C for 24 h. 4-Iodoanisole (702 mg, 3.00 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were added and the reaction stirred at 25 °C for 2 h. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **101e** as a colourless solid (195 mg, 64% yield).

m.p. (°C): 115-117.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.58-7.53 (m, 2H), 7.32-7.27 (m, 1H), 7.26 (d, *J* = 3.84 Hz, 1H), 7.23-7.20 (m, 1H), 7.16 (d, *J* = 3.84 Hz, 1H), 7.15-7.14 (m, 1H), 6.95-6.90 (m, 2H), 6.83 (ddd, *J* = 8.06, 2.54, 1.05 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H).

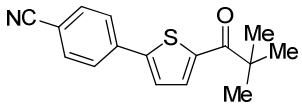
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 160.0, 159.3, 143.7, 142.4, 135.7, 129.9 (CH), 127.2, 126.9 (CH), 124.1 (CH), 122.9 (CH), 118.2 (CH), 114.3 (CH), 112.8 (CH), 111.2 (CH), 55.4 (CH_3), 55.3 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2934 (w), 2834 (w), 1602 (m), 1576 (m), 1510 (m), 1482 (M), 1464 (m), 1438 (m), 1284 (m), 1244 (s), 1212 (m), 1184 (m), 1168 (m), 1114 (w), 1048 (m), 1032 (s), 982 (w), 864 (m), 832 (m), 796 (vs), 772 (s), 682 (m), 656 (w).

MS (EI, 70 eV): *m/z* (%) = 298 (9), 297 (20), 296 (100, M^+), 282 (9), 281 (45), 253 (8), 210 (14), 148 (15), 69 (6), 57 (4).

HRMS (EI): calcd. for $C_{18}H_{16}O_2{}^{32}S$: 296.0871, found: 296.0859.

4-(5-Pivaloylthiophen-2-yl)benzonitrile (**101f**)



Prepared according to **TP12** from 4-(5-chlorothiophen-2-yl)benzonitrile (**98f**; 220 mg, 1.0 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 16 h. The reaction was cooled to -20 °C, pivaloyl chloride (362 mg, 3.00 mmol) and CuCN·2LiCl (0.20 mmol, 0.20 mL, 1.00 M in THF) were added and the reaction stirred at -20 °C for 30 min. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **101f** as a colourless solid (166 mg, 62% yield).

m.p. (°C): 153-154.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 7.75 (d, *J* = 4.00 Hz, 1H), 7.74-7.72 (m, 2H), 7.69-7.67 (m, 2H), 7.38 (d, *J* = 4.00 Hz, 1H), 1.41 (s, 9H).

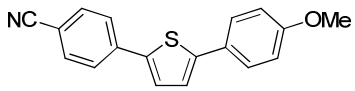
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 198.6, 148.0, 143.2, 137.6, 132.9 (CH), 132.8 (CH), 126.6 (CH), 125.3 (CH), 118.4, 112.0, 43.9, 28.1 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3100 (w), 2972 (m), 2224 (m), 1636 (vs), 1604 (m), 1536 (w), 1476 (m), 1446 (s), 1368 (w), 1284 (s), 1256 (m), 1182 (vs), 1082 (s), 1026 (m), 964 (w), 940 (w), 894 (s), 838 (s), 828 (s), 812 (vs), 800 (s), 750 (m), 696 (w).

MS (EI, 70 eV): *m/z* (%) = 270 (2), 269 (9, M^+), 214 (6), 213 (17), 212 (100), 185 (2), 141 (3), 140 (22), 57 (16), 41 (10).

HRMS (EI): calcd. for $C_{16}H_{15}NO^{32}S$: 269.0874, found: 269.0864.

4-(5-(4-Methoxyphenyl)thiophen-2-yl)benzonitrile (**101g**)



Prepared according to **TP12** from 4-(5-chlorothiophen-2-yl)benzonitrile (**98f**; 220 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 16 h. 4-Iodoanisole (702 mg, 3.00 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were added and the reaction stirred at 25 °C for 2 h. Purification by flash chromatography (pentane/Et_2O 4:1, silica gel) furnished **101g** as a yellow solid (165 mg, 57% yield).

m.p. (°C): 157-158.

^{1}H-NMR ($CDCl_3$, 600 MHz): δ (ppm) = 7.68-7.66 (m, 2H), 7.56-7.54 (m, 2H), 7.36 (d, *J* = 3.79 Hz, 1H), 7.20 (d, *J* = 3.79 Hz, 1H), 6.94-6.92 (m, 2H), 3.84 (s, 3H).

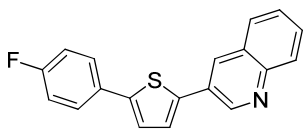
^{13}C-NMR ($CDCl_3$, 150 MHz): δ (ppm) = 159.7, 146.1, 139.9, 138.7, 132.7 (CH), 127.1 (CH), 126.5, 126.1 (CH), 125.5 (CH), 123.3 (CH), 118.9, 114.4 (CH), 110.1, 55.4 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2964 (vw), 2228 (w), 1600 (m), 1538 (w), 1514 (w), 1496 (m), 1452 (w), 1436 (w), 1348 (vw), 1294 (w), 1276 (w), 1254 (m), 1178 (m), 1112 (w), 1070 (w), 1026 (m), 940 (vw), 848 (w), 830 (m), 820 (m), 800 (vs), 720 (vw), 678 (vw).

MS (EI, 70 eV): *m/z* (%) = 293 (7), 292 (20), 291 (100, M^+), 277 (10), 276 (41), 249 (4), 248 (18), 246 (7), 146 (4), 145 (8).

HRMS (EI): calcd. for $C_{18}H_{13}NO^{32}S$: 291.0718, found: 291.0721.

3-(5-(4-Fluorophenyl)thiophen-2-yl)quinoline (**101h**)



Prepared according to **TP12** from 2-chloro-5-(4-fluorophenyl)thiophene (**98g**; 213 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 16 h. 3-Bromoquinoline (624 mg, 3.0 mmol) and

$Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were added and the reaction stirred at 50 °C for 5 h. Purification by flash chromatography (CH_2Cl_2, silica gel) furnished **101h** as a yellow solid (189 mg, 65% yield).

m.p. (°C): 155-157.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 9.20 (d, *J* = 2.23 Hz, 1H), 8.26 (d, *J* = 2.23 Hz, 1H), 8.09 (d, *J* = 8.42 Hz, 1H), 7.83 (dd, *J* = 8.30, 1.11 Hz, 1H), 7.72-7.66 (m, 1H), 7.64-7.53 (m, 3H), 7.46 (d, *J* = 3.72 Hz, 1H), 7.27 (d, *J* = 3.72 Hz, 1H), 7.14-7.06 (m, 2H).

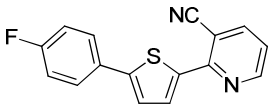
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.5 (d, *J* = 247.9 Hz, CF), 148.2 (CH), 147.3, 143.9, 139.9, (d, *J* = 1.12 Hz), 131.0 (CH), 130.2 (d, *J* = 3.37 Hz), 129.4 (CH), 129.3 (CH), 127.9, 127.8 (CH), 127.5 (d, *J* = 8.13 Hz, CH), 127.3 (CH), 125.4 (CH), 124.3, 124.2 (CH), 116.0 (d, *J* = 21.88 Hz, CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3060 (w), 2922 (w), 2852 (w), 1736 (w), 1598 (w), 1542 (w), 1508 (m), 1492 (m), 1472 (m), 1346 (w), 1288 (w), 1230 (s), 1160 (w), 1120 (w), 1100 (w), 1018 (vw), 1002 (w), 900 (w), 888 (w), 850 (w), 822 (m), 802 (vs), 792 (vs), 778 (s), 744 (vs), 704 (w), 678 (w).

MS (EI, 70 eV): *m/z* (%) = 306 (27), 305 (100, M^+), 304 (15), 86 (12), 84 (25), 70 (14), 61 (19), 49 (31), 45 (15), 43 (99).

HRMS (EI): calcd. for $C_{19}H_{12}FN^{32}S$: 305.0674, found: 305.0671.

2-(5-(4-Fluorophenyl)thiophen-2-yl)nicotinonitrile (**101i**)



Prepared according to **TP12** from 2-chloro-5-(4-fluorophenyl)thiophene (**98g**; 213 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 16 h. 2-Chloronicotinonitrile (416 mg, 3.00 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were added and the reaction stirred at 50 °C for 5 h. Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **101i** as an orange solid (175 mg, 62% yield).

m.p. (°C): 209-211.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.73 (dd, *J* = 4.83, 1.86 Hz, 1H), 8.23 (d, *J* = 3.96 Hz, 1H), 7.98 (dd, *J* = 7.80, 1.86 Hz, 1H), 7.68-7.61 (m, 2H), 7.30 (d, *J* = 3.96 Hz, 1H), 7.23 (dd, *J* = 7.80, 4.83 Hz, 1H), 7.14-7.06 (m, 2H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 162.9 (d, J = 248.8 Hz, CF), 153.3, 152.6 (CH), 148.1, 142.1 (CH), 140.7, 130.0 (CH), 127.8 (d, J = 8.13 Hz, CH), 124.6 (CH), 120.7 (CH), 117.8, 116.1 (d, J = 21.88 Hz, CH), 108.7, 103.5.

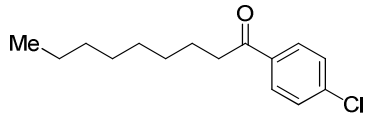
IR (ATR): $\tilde{\nu}$ / cm^{-1} = 3076 (w), 3062 (w), 2222 (w), 1878 (w), 1578 (m), 1544 (m), 1510 (m), 1456 (s), 1446 (s), 1426 (s), 1306 (w), 1224 (s), 1206 (m), 1168 (m), 1106 (w), 1086 (m), 1014 (w), 986 (w), 954 (w), 826 (s), 814 (s), 798 (s), 790 (s), 758 (vs), 646 (m).

MS (EI, 70 eV): *m/z* (%) = 281 (17), 280 (100, M^+), 279 (10), 249 (3), 247 (9), 147 (3), 139 (6), 133 (8), 118 (4), 43 (5).

HRMS (EI): calcd. for $C_{16}H_9FN_2{}^{32}S$: 280.0470, found: 280.0472.

3.5.3 Preparation of Aliphatic Products 101 via Chlorine-Zinc Exchange using Zincate 100

1-(4-Chlorophenyl)nonan-1-one (**101j**)



Prepared according to **TP12** from 1-chlorooctane (**98h**; 149 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 16 h. The reaction was cooled to -20 °C, 4-chlorobenzoyl chloride (525 mg, 3.00 mmol) and CuCN·2LiCl (0.20 mmol, 0.20 mL, 1.00 M in THF) were added and the reaction stirred at -20 °C for 30 min. Purification by flash chromatography (pentane/Et_2O 20:1, silica gel) furnished **101j** as a colourless solid (152 mg, 60% yield).

mp (°C): 65-67.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.90-7.86 (m, 2H), 7.41-7.39 (m, 2H), 2.91 (t, J = 7.39 Hz, 2H), 1.76-1.66 (m, 2H), 1.38-1.20 (m, 10H), 0.87 (t, J =6.92 Hz, 3H).

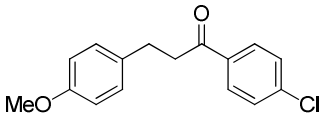
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 199.3, 139.2, 135.4, 129.5 (CH), 128.8 (CH), 38.6 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 24.3 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2958 (m), 2920 (s), 2852 (m), 1674 (vs), 1588 (s), 1570 (m), 1488 (w), 1466 (m), 1398 (m), 1374 (m), 1338 (w), 1282 (w), 1262 (m), 1224 (m), 1194 (m), 1092 (s), 1012 (m), 996 (m), 972 (s), 888 (w), 832 (s), 796 (s), 754 (m), 724 (m).

MS (EI, 70 eV): *m/z* (%) = 167 (9), 156 (29), 155 (8), 154 (100), 141 (25), 140 (6), 139 (84), 113 (6), 111 (18), 41 (7).

HRMS (EI): calcd. for $C_{15}H_{21}{}^{35}ClO$: 252.1281, found: 252.1282.

1-(4-Chlorophenyl)-3-(4-methoxyphenyl)propan-1-one (**101k**)



Prepared according to **TP12** from 1-(2-chloroethyl)-4-methoxybenzene (**98i**; 171 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 14 h. The reaction was cooled to -20 °C, 4-chlorobenzoyl chloride (525 mg, 3.00 mmol) and CuCN·2LiCl (0.20 mmol, 0.20 mL, 1.00 M in THF) were added and the reaction stirred at -20 °C for 30 min. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **101k** as a yellow solid (153 mg, 56% yield).

m.p. (°C): 59-62.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.90-7.86 (m, 2H), 7.43-7.40 (m, 2H), 7.17-7.14 (m, 2H), 6.85-6.82 (m, 2H), 3.78 (s, 3H), 3.23 (t, J = 7.56 Hz, 2H), 3.00 (t, J =7.56 Hz, 2H).

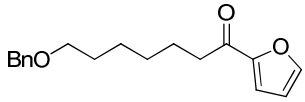
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 198.1, 158.0, 139.4, 135.1, 133.0, 129.4 (CH), 129.3 (CH), 128.9 (CH), 113.9 (CH), 55.2 (CH_3), 40.6 (CH_2), 29.2 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2924 (w), 1738 (m), 1676 (s), 1610 (m), 1588 (s), 1570 (m), 1512 (s), 1488 (m), 1400 (m), 1364 (w), 1246 (vs), 1202 (m), 1176 (m), 1152 (w), 1090 (vs), 1028 (m), 1012 (s), 978 (m), 848 (w), 816 (s), 798 (s), 774 (m), 750 (m), 680 (w).

MS (EI, 70 eV): *m/z* (%) = 276 (10), 275 (6), 274 (30, M^+), 141 (8), 139 (23), 135 (9), 122 (8), 121 (100), 111 (10), 108 (11).

HRMS (EI): calcd. for $C_{16}H_{15}{}^{35}ClO_2$: 274.0761, found: 274.0757.

7-(Benzyloxy)-1-(furan-2-yl)heptan-1-one (**101l**)



Prepared according to **TP12** from (((6-chlorohexyl)oxy)methyl)benzene (**98j**; 227 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 18 h. The reaction was cooled to -20 °C, 2-furoyl chloride (392 mg, 3.00 mmol) and CuCN·2LiCl (0.20 mmol, 0.20 mL, 1.00 M in THF) were added and the reaction stirred at -20 °C for 30 min. Purification by flash chromatography (pentane/Et_2O 10:1, silica gel) furnished **101l** as a yellow liquid (180 mg, 63% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.55 (dd, J = 1.67, 0.68 Hz, 1H), 7.33-7.22 (m, 5H), 7.15 (dd, J = 3.59, 0.68 Hz, 1H), 6.50 (dd, J = 3.59, 1.67 Hz, 1H), 4.48 (s, 2H), 3.45 (t, J = 6.56 Hz, 2H), 2.79 (t, J = 7.43 Hz, 2H), 1.76-1.66 (m, 2H), 1.64-1.57 (m, 2H), 1.43-1.35 (m, 4H).

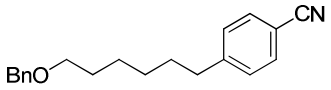
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 189.6, 152.8, 146.1 (CH), 138.6, 128.2 (CH), 127.5 (CH), 127.4 (CH), 116.7 (CH), 112.0 (CH), 72.8 (CH_2), 70.2 (CH_2), 38.3 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 25.9 (CH_2), 24.1 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2934 (m), 2858 (m), 1674 (s), 1568 (m), 1496 (w), 1468 (s), 1454 (m), 1394 (m), 1362 (m), 1268 (w), 1246 (w), 1228 (w), 1206 (w), 1158 (w), 1098 (s), 1028 (m), 1012 (m), 908 (m), 882 (m), 758 (s), 732 (vs), 698 (s), 646 (w).

MS (EI, 70 eV): *m/z* (%) = 195 (22), 180 (12), 151 (7), 124 (6), 123 (62), 110 (44), 95 (55), 92 (11), 91 (100), 65 (6).

HRMS (EI): calcd. for $C_{18}H_{22}O_3$: 286.1569, found: 286.1564.

4-(6-(Benzyloxy)hexyl)benzonitrile (**101m**)



Prepared according to **TP12** from (((6-chlorohexyl)oxy)methyl)benzene (**98j**; 227 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 18 h. 4-Iodobenzonitrile (687 mg, 3.00 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were added and the reaction stirred at 25 °C for 2 h. Purification by flash chromatography (pentane/Et_2O 4:1, silica gel) furnished **101m** as a yellow liquid (178 mg, 61% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.55-7.51 (m, 2H), 7.34-7.28 (m, 4H), 7.27-7.22 (m, 3H), 4.48 (s, 2H), 3.45 (t, *J* = 6.56 Hz, 2H), 2.64 (t, *J* = 7.63 Hz, 2H), 1.66-1.55 (m, 4H), 1.45-1.29 (m, 4H).

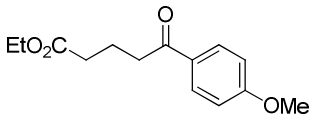
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 148.4, 138.6, 132.0 (CH), 129.1 (CH), 128.3 (CH), 127.5, (CH) 127.4 (CH), 119.1, 109.4, 72.8 (CH_2), 70.2 (CH_2), 35.9 (CH_2), 30.8 (CH_2), 29.5 (CH_2), 28.9 (CH_2), 25.9 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2932 (m), 2856 (m), 2226 (m), 1608 (w), 1504 (w), 1496 (w), 1454 (m), 1414 (w), 1362 (m), 1308 (w), 1204 (w), 1176 (w), 1098 (s), 1028 (m), 908 (w), 842 (m), 820 (m), 734 (vs), 696 (vs), 612 (vw).

MS (EI, 70 eV): *m/z* (%) = 293 (12, M^+), 142 (15), 116 (23), 107 (12), 92 (16), 91 (100), 70 (14), 91 (12), 45 (11), 43 (72).

HRMS (EI): calcd. for $C_{20}H_{23}NO$: 293.1780, found: 293.1769.

Ethyl 5-(4-methoxyphenyl)-5-oxopentanoate (**101n**)



Prepared according to **TP12** from ethyl 4-chlorobutanoate (**98k**; 151 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 16 h. The reaction was cooled to -20 °C, 4-methoxybenzoyl chloride (512 mg, 3.00 mmol) and CuCN·2LiCl (0.20 mmol, 0.20 mL, 1.00 M in THF) were added and the reaction stirred at -20 °C for 30 min. Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **101n** as a colourless solid (150 mg, 60% yield).

m.p. (°C): 56-58.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.96-7.91 (m, 2H), 6.94-6.89 (m, 2H), 4.13 (q, J = 7.04 Hz, 2H), 3.86 (s, 3H), 2.98 (t, J = 7.18 Hz, 2H), 2.41 (t, J = 7.06 Hz, 2H), 2.09-2.00 (m, 2H), 2.41 (t, J = 7.04 Hz, 3H).

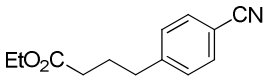
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 198.0, 173.3, 163.4, 130.3 (CH), 130.0, 113.7 (CH), 60.3(CH_2), 55.4(CH_3), 37.1(CH_2), 33.5(CH_2), 19.6 (CH_2), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2982 (w), 2960 (w), 2900 (w), 1730 (vs), 1668 (s), 1600 (s), 1576 (m), 1510 (m), 1416 (m), 1382 (m), 1278 (s), 1256 (vs), 1218 (m), 1184 (s), 1168 (vs), 1112 (s), 1080 (s), 1030 (vs), 986 (s), 864 (m), 834 (m), 816 (m), 752 (s), 632 (vw), 606 (w).

MS (EI, 70 eV): *m/z* (%) = 250 (6, M^+), 204 (13), 177 (4), 150 (14), 149 (4), 136 (9), 135 (100), 92 (7), 77 (9), 43 (6).

HRMS (EI): calcd. for $C_{14}H_{18}O_4$: 250.1205, found: 250.1197.

Ethyl 4-(4-cyanophenyl)butanoate (**101o**)



Prepared according to **TP12** from ethyl 4-chlorobutanoate (**98k**; 151 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 16 h. 4-Iodobenzonitrile (687 mg, 3.00 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were added and the reaction stirred at 25 °C for 2 h. Purification by flash chromatography (pentane/Et_2O 7:3, silica gel) furnished **101o** as a yellow liquid (123 mg, 57% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.58-7.54 (m, 2H), 7.29-7.25 (m, 2H), 4.11 (q, J = 7.15 Hz, 2H), 2.70 (t, J = 7.75 Hz, 2H), 2.30 (t, J = 7.39 Hz, 2H), 1.99-1.89 (m, 2H), 1.24 (t, J = 7.15 Hz, 3H).

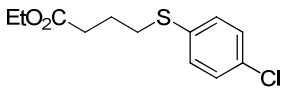
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 173.0, 147.1, 132.2 (CH), 129.2 (CH), 118.9, 109.9, 60.4 (CH_2), 35.2 (CH_2), 33.4 (CH_2), 25.9 (CH_2), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 2938 (w), 2870 (vw), 2228 (m), 1728 (vs), 1608 (w), 1504 (w), 1446 (w), 1416 (w), 1374 (m), 1350 (w), 1322 (W), 1304 (w), 1246 (m), 1178 (s), 1146 (s), 1112 (m), 1098 (w), 1040 (m), 1022 (m), 946 (vw), 844 (m), 816 (m), 740 (vw).

MS (EI, 70 eV): *m/z* (%) = 217 (26, M^+), 172 (56), 130 (77), 129 (44), 116 (95), 89 (48), 88 (100), 70 (46), 61 (40), 60 (56).

HRMS (EI): calcd. for $C_{13}H_{15}NO_2$: 217.1103, found: 217.1102.

Ethyl 4-((4-chlorophenyl)thio)butanoate (**101p**)



Prepared according to **TP12** from ethyl 4-chlorobutanoate (**98k**; 151 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 16 h. *S*-(4-chlorophenyl) benzenesulfonothioate (854 mg, 3.00 mmol) was added and the reaction stirred at 25 °C for 30 min. Purification by flash chromatography (pentane/Et_2O 4:1, silica gel) furnished **101p** as a clear liquid (162 mg, 63% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.30-7.23 (m, 4H), 4.12 (q, *J* = 7.18 Hz, 2H), 2.93 (t, *J* = 7.18 Hz, 2H), 2.44 (t, *J* = 7.18 Hz, 2H), 1.98-1.88 (m, 2H), 1.24 (t, *J* = 7.18 Hz, 3H).

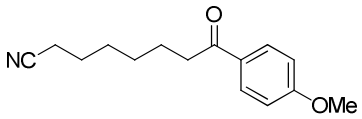
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 172.8, 134.6, 132.0, 130.7 (CH), 129.0 (CH), 60.5 (CH_2), 33.2 (CH_2), 32.8 (CH_2), 24.3 (CH_2), 14.2 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2978 (w), 2930 (w), 1728 (s), 1644 (w), 1594 (w), 1572 (w), 1476 (s), 1446 (m), 1390 (m), 1374 (m), 1312 (m), 1284 (m), 1258 (m), 1204 (s), 1178 (s), 1146 (s), 1094 (vs), 1034 (m), 1010 (s), 910 (vw), 812 (vs), 744 (m), 716 (w), 686 (w).

MS (EI, 70 eV): *m/z* (%) = 285 (13, M^+), 263 (58), 169 (46), 144 (39), 143 (49), 123 (43), 115 (66), 108 (43), 87 (100), 43 (38).

HRMS (EI): calcd. for $C_{12}H_{15}{}^{35}ClO_2{}^{32}S$: 258.0481, found: 258.0486.

8-(4-Methoxyphenyl)-8-oxooctanenitrile (**101q**)



Prepared according to **TP12** from 7-chloroheptanenitrile (**98l**; 146 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 16 h. The reaction was cooled to -20 °C, 4-methoxybenzoyl chloride (512 mg, 3.00 mmol) and CuCN·2LiCl (0.20 mmol, 0.20 mL, 1.00 M in THF) were added and the

reaction stirred at -20 °C for 30 min. Purification by flash chromatography (CH_2Cl_2, silica gel) furnished **101q** as a colourless solid (161 mg, 66% yield).

m.p. (°C): 52-54.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.95-7.90 (m, 2H), 6.95-6.90 (m, 2H), 3.86 (s, 3H), 2.91 (t, *J* = 7.31 Hz, 2H), 2.33 (t, *J* = 7.06 Hz, 2H), 1.79-1.62 (m, 4H), 1.58-1.37 (m, 4H).

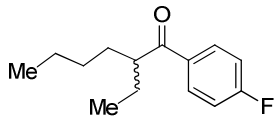
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 198.7, 163.4, 130.3 (CH), 130.1, 119.7, 113.7 (CH), 55.5 (CH_3), 37.9 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 25.2 (CH_2), 24.0 (CH_2), 17.1 (CH_2).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2940 (w), 2916 (w), 2852 (w), 2248 (w), 1672 (s), 1596 (s), 1572 (m), 1508 (m), 1466 (m), 1418 (m), 1374 (m), 1316 (m), 1262 (s), 1228 (s), 1196 (s), 1166 (vs), 1026 (s), 974 (s), 834 (s), 814 (m), 786 (m), 728 (m), 634 (w), 606 (w).

MS (EI, 70 eV): *m/z* (%) = 245 (2, M^+), 163 (3), 151 (3), 150 (32), 136 (8), 135 (100), 107 (3), 92 (7), 83 (2), 77 (8).

HRMS (EI): calcd. for $C_{15}H_{19}NO_2$: 245.1416, found: 245.1412.

2-Ethyl-1-(4-fluorophenyl)hexan-1-one (**101r**)



Prepared according to **TP12** from 3-chloroheptane (**98m**; 135 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 16 h. The reaction was cooled to -20 °C, 4-fluorobenzoyl chloride (476 mg, 3.00 mmol) and CuCN·2LiCl (0.20 mmol, 0.20 mL, 1.00 M in THF) were added and the reaction stirred at -20 °C for 30 min. Purification by flash chromatography (pentane/Et_2O 20:1, silica gel) furnished **101r** as a clear oil (80 mg, 36% yield, dr = 1.77:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.00-7.95 (m, 2H), 7.14-7.08 (m, 2H), 3.32-3-26 (m, 1H), 1.81-1.67 (m, 2H), 1.59-1.41 (m, 2H), 1.30-1.16 (m, 4H), 0.87-0.81 (m, 6H).

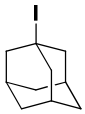
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 203.0, 165.6 (d, *J* = 253.7 Hz, CF), 134.1, (d, *J* = 3.07 Hz), 130.7 (d, *J* = 9.21 Hz, CH), 115.6 (d, *J* = 21.88 Hz, CH), 47.6 (CH), 31.7 (CH_2), 29.7 (CH_2), 25.4 (CH_2), 22.9 (CH_2), 13.9 (CH_3), 11.9 (CH_3)

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2960 (m), 2932 (m), 2874 (w), 2862 (w), 1678 (s), 1596 (s), 1506 (m), 1460 (m), 1410 (m), 1380 (w), 1298 (w), 1264 (w), 1222 (vs), 1206 (s), 1156 (s), 1106 (w), 994 (w), 934 (w), 846 (s), 814 (m), 754 (m), 686 (w).

MS (EI, 70 eV): *m/z* (%) = 222 (1, M^+), 194 (2), 167 (3), 166 (29), 165 (3), 151 (8), 124 (7), 123 (100), 95 (13), 41 (3).

HRMS (EI): calcd. for $C_{14}H_{19}FO$: 222.1420, found: 222.1419.

1-Iodoadamantane (**101s**)



Prepared according to **TP12** from 1-chloroadamantane (**98n**; 171 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 24 h. Iodine (762 mg, 3.00 mmol) was added and the reaction stirred at 25 °C for 30 min. Purification by flash chromatography (pentane, silica gel) furnished **101s** as a colourless solid (160 mg, 61% yield).

m.p. (°C): 67-70.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 2.62 (d, J = 2.72 Hz, 6H), 1.97-1.91 (m, 3H), 1.85-1.75 (m, 6H).

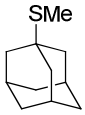
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 52.5 (CH_2), 51.1, 35.6 (CH_2), 33.1 (CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2904 (vs), 2850 (s), 1738 (vw), 1472 (vw), 1452 (m), 1340 (m), 1310 (w), 1288 (m), 1258 (w), 1100 (m), 1022 (s), 980 (w), 942 (s), 888 (w), 806 (w), 794 (s), 760 (m), 698 (w), 668 (m), 656 (m), 640 (w).

MS (EI, 70 eV): *m/z* (%) = 240 (17), 149 (9), 136 (12), 135 (100), 107 (6), 93 (13), 91 (14), 81 (6), 79 (14), 77 (6).

HRMS (EI): calcd. for $C_{10}H_{15}{}^{127}I$: 262.0218, found: 262.0213.

Adamantan-1-yl(methyl)sulfane (**101t**)



Prepared according to **TP12** from 1-chloroadamantane (**98n**; 171 mg, 1.00 mmol), zincate **100** (2.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 24 h. *S*-methyl methane thiosulfonate (379 mg, 3.00 mmol) was added and the reaction stirred at 25 °C for 30 min. Purification by flash chromatography (pentane, silica gel) furnished **101t** as a clear liquid (120 mg, 66% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 2.06-2.00 (m, 3H), 1.99 (s, 3H), 1.82 (d, J = 2.72 Hz, 6H), 1.72-1.63 (m, 6H).

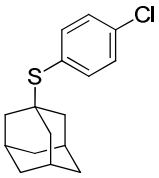
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 42.8 (CH_2), 42.7, 36.4 (CH_2), 29.6 (CH), 8.7 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2902 (vs), 2848 (s), 1738 (vw), 1596 (vw), 1504 (vw), 1450 (m), 1342 (w), 1300 (w), 1254 (w), 1100 (w), 1046 (m), 982 (w), 960 (w), 952 (w), 924 (vw), 838 (w), 810 (w), 768 (vw), 734 (w), 700 (w), 686 (w).

MS (EI, 70 eV): *m/z* (%) = 182 (14), 136 (9), 135 (100), 107 (7), 93 (19), 91 (9), 79 (19), 77 (7), 43 (15), 41 (7).

HRMS (EI): calcd. for $C_{11}H_{18}{}^{32}S$: 182.1129, found: 182.1120.

Adamantan-1-yl(4-chlorophenyl)sulfane (**101u**)



Prepared according to **TP12** from 1-chloroadamantane (**98n**; 171 mg, 1.0 mmol), zincate **100** (2.00 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 24 h. *S*-(4-chlorophenyl) benzenesulfonothioate (854 mg, 3.00 mmol) was added and the reaction stirred at 25 °C for 30 min. Purification by flash chromatography (pentane, silica gel) furnished **101u** as a colourless solid (177 mg, 63% yield).

m.p. (°C): 111-114.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.43-7.38 (m, 2H), 7.30-7.25 (m, 2H).2.04-1.97 (m, 3H), 1.78 (d, *J* = 2.73 Hz, 6H), 1.71-1.51 (m, 6H).

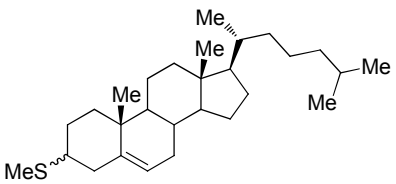
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 138.8 (CH), 135.0, 129.1, 128.5 (CH), 48.2, 43.5 (CH_2), 36.1 (CH_2), 30.0 (CH).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2920 (vs), 2900 (vs), 2848 (s), 1572 (w), 1474 (s), 1452 (m), 1382 (w), 1350 (w), 1342 (w), 1296 (m), 1258 (w), 1176 (vw), 1092 (s), 1080 (m), 1038 (m), 1012 (s), 972 (w), 960 (w), 840 (s), 814 (s), 768 (w), 746 (m), 700 (w), 684 (w), 642 (vw).

MS (EI, 70 eV): *m/z* (%) = 278 (6, M^+), 136 (10), 135 (100), 107 (8), 93 (17), 91 (7), 81 (5), 79 (17), 77 (7), 67 (8).

HRMS (EI): calcd. for $C_{16}H_{19}{}^{35}Cl^{32}S$: 278.0896, found: 278.0893.

((3S,10R,13R,17R)-10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)(methyl)sulfane (**101v**)



Prepared according to **TP12** from cholesteryl chloride (**98o**; 405 mg, 1.00 mmol), zincate **100** (2.00 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at

25 °C for 24 h. *S*-methyl methane thiosulfonate (379 mg, 3.00 mmol) was added and the reaction stirred at 25 °C for 30 min. Purification by flash chromatography (pentane, silica gel) furnished **101v** as a colourless solid (240 mg, 58% yield, dr = 2:1).

m.p. (°C): 126-128.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 5.33-5.31 (m, 1H), 2.51-2.41 (m, 1H), 2.33-2.22 (m, 2H), 2.10 (s, 3H), 2.03-1.76 (m, 6H), 1.62-0.95 (m, 23H), 0.90 (d, *J* = 6.44 Hz, 3H), 0.85 (dd, *J* = 6.69, 1.24 Hz, 6H), 0.67 (s, 3H).

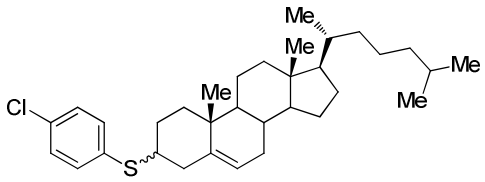
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 141.9, 120.8 (CH), 56.8 (CH), 56.2 (CH), 50.3 (CH), 45.9 (CH), 42.3, 39.8 (CH_2), 39.6 (CH_2), 39.5 (CH_2), 39.4 (CH_2), 36.9, 36.2 (CH_2), 35.8 (CH), 31.9 (CH), 31.8 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 28.0 (CH), 24.3 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 20.9 (CH_2), 19.4 (CH_3), 18.7 (CH_3), 13.2 (CH_3), 11.9 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2952 (s), 2928 (vs), 2912 (vs), 2870 (s), 2852 (s), 1462 (S), 1444 (m), 1432 (m), 1382 (m), 1374 (m), 1332 (w), 1314 (w), 1236 (w), 1196 (w), 1156 (w), 1134 (w), 1024 (w), 988 (w), 960 (m), 880 (vw), 826 (m), 800 (m), 770 (w), 732 (w), 714 (vw), 698 (vw), 622 (vw).

MS (EI, 70 eV): *m/z* (%) = 416 (17, M^+), 369 (62), 368 (100), 147 (44), 105 (51), 95 (48), 91 (45), 81 (51), 55 (45), 43 (56).

HRMS (EI): calcd. for $C_{28}H_{48}{}^{32}S$: 416.3477, found: 416.3475.

(4-Chlorophenyl)((3S,10R,13R,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)sulfane (**101w**)



Prepared according to **TP12** from cholesteryl chloride (**98o**; 405 mg, 1.00 mmol), zincate **100** (2.00 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 24 h. *S*-(4-chlorophenyl) benzenesulfonothioate (854 mg, 3.00 mmol) was added and the reaction stirred at 25 °C for 30 min. Purification by flash chromatography (pentane, silica gel) furnished **101w** as a colourless solid (310 mg, 60% yield, dr = 1.38:1).

m.p. (°C): 100-103.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.33-7.28 (m, 2H), 7.26-7.21 (m, 2H), 5.30-5.29 (m, 1H), 3.02-2.91 (m, 1H), 2.30-2.25 (m, 2H), 2.03-1.76 (m, 6H), 1.64-0.94 (m, 23H), 0.90 (d, *J* = 6.69 Hz, 3H), 0.86 (dd, *J* = 6.44, 1.24 Hz, 6H), 0.66 (s, 3H).

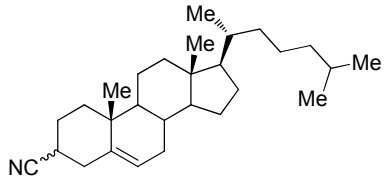
^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 141.4, 133.4, 133.1 (CH), 132.7, 128.9 (CH), 121.3 (CH), 56.8 (CH), 56.1 (CH), 50.3 (CH), 47.7 (CH), 42.3, 39.7 (CH_2), 39.6, (CH_2) 39.5 (CH_2), 39.4 (CH_2), 36.8, 36.2 (CH_2), 35.8 (CH), 31.9 (CH), 31.8 (CH_2), 29.4, (CH_2) 28.2 (CH_2), 28.0 (CH), 24.3 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 20.9 (CH_2), 19.3 (CH_3), 18.7 (CH_3), 11.9 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2926 (s), 2906 (s), 2894 (s), 2862 (s), 1740 (w), 1474 (s), 1432 (m), 1386 (m), 1374 (m), 1366 (m), 1334 (w), 1292 (w), 1192 (w), 1152 (w), 1108 (w), 1092 (s), 1024 (w), 1008 (m), 992 (w), 958 (w), 932 (w), 914 (w), 864 (w), 808 (vs), 766 (m), 742 (w), 724 (w), 702 (w).

MS (EI, 70 eV): *m/z* (%) = 512 (13, M^+), 370 (28), 269 (100), 161 (23), 147 (29), 109 (20), 105 (22), 95 (31), 93 (20), 81 (24).

HRMS (EI): calcd. for $C_{33}H_{49}Cl^{32}S$: 512.3243, found: 512.3238.

(3S,10R,13R,17R)-10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-3-carbonitrile (**101x**)



Prepared according to **TP12** from cholesteryl chloride (**98o**; 405 mg, 1.00 mmol), zincate **100** (2.00 equiv.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and 4-fluorostyrene (24.5 mg, 0.20 mmol) at 25 °C for 24 h. Tosyl cyanide (544 mg, 3.00 mmol) was added and the reaction stirred at 25 °C for 30 min. Purification by flash chromatography (pentane/Et_2O 40:1, silica gel) furnished **101x** as a colourless solid (260 mg, 66% yield, dr = 1.36:1).

m.p. (°C): 184-186.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 5.39-5.38 (m, 1H), 2.52-2.45 (m, 1H), 2.40-2.29 (m, 2H), 2.04-1.73 (m, 6H), 1.60-0.94 (m, 23H), 0.90 (d, *J* = 6.69 Hz, 3H), 0.85 (dd, *J* = 6.69, 1.24 Hz, 6H), 0.66 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 138.7, 122.9 (CH), 122.5, 56.7 (CH), 56.1 (CH), 50.1 (CH), 42.3, 39.6 (CH_2), 39.5 (CH_2), 38.1 (CH), 36.7 (CH_2), 36.2 (CH_2), 35.8 (CH), 35.5 (CH_2), 31.7 (CH), 31.6 (CH_2), 29.5 (CH_2), 28.2 (CH_2), 28.0 (CH), 26.2, 24.2 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.8 (CH_2), 19.1 (CH_3), 18.7 (CH_3), 11.8 (CH_3).

IR (ATR): $\tilde{\nu}$ / cm^{-1} = 2944 (vs), 2904 (s), 2890 (s), 2866 (s), 2238 (w), 1730 (vw), 1670 (vw), 1464 (m), 1446 (m), 1378 (m), 1368 (m), 1334 (w), 1166 (w), 1138 (w), 1030 (w), 1018 (w), 976 (w), 960 (w), 944 (w), 912 (vw), 880 (vw), 838 (w), 806 (w), 736 (w).

MS (EI, 70 eV): *m/z* (%) = 396 (32), 395 (100, M^+), 380 (39), 282 (52), 275 (30), 241 (27), 240 (64), 185 (20), 170 (17), 43 (27).

HRMS (EI): calcd. for $C_{28}H_{45}N$: 395.3552, found: 395.3551.

D. Curriculum Vitae

L A U R I N M E L Z I G

PERSONAL INFORMATION

Marital status: never married

Nationality: german

Date and place of birth: April 13th 1981, Starnberg, Germany

EDUCATION

1987 - 1991	Primary school Wessling (Oberbayern)
1991 - 2000	Carl-Spitzweg-Gymnasium Unterpfaffenhofen-Germering, degree: Abitur (university-entrance diploma)
September 2000 - August 2001	Civilian service in the BRK nursing home Gilching (janitor)
October 2001 - December 2006	Study of chemistry at the Ludwig-Maximilians-University Munich, degree: Master of Science (Note 1.24, very good)
	Bachelor thesis: „Steps in the total synthesis of the hypermodificated tRNA-nucleosides Archaeosin and Queuosin" with Prof. Dr. Thomas Carell (grade 1.7, good)
	Master thesis: „Nickel-catalyzed aryl-alkyl cross-coupling reactions for the direct introduction of aminoalkyls" with Prof. Dr. Paul Knochel (grade: 1.0, very good)
March 2007 – December 2010	PhD with Prof. Dr. Paul Knochel

LANGUAGE AND OTHER SKILLS

German: mother tongue

English: fluent in written and spoken form

Italian: advanced skills

Latin: Latinum (certificate awarded after five years)

Computer skills: Experienced in working with Windows, office applications (e.g. Word, Excel, Access, Powerpoint), general chemistry software (e.g. Chemdraw, ISIS draw, ACDlabs) as well as specialized software (e.g. HPLC, GC, GCMS, NMR, IR)

INTERESTS

Playing soccer, climbing, modelling, tabletop games

WORK EXPERIENCE

January 1999 – July 2001	Callcenteragent in national and international opinion research as well as election surveys at TNS Infratest Munich, former Infratel Burke group
April – July 2006	Student assistant in the group of Prof. Dr. H. Mayr und Dr. B. Straub, supervision of lectures and seminars
Since March 2007	Research assistant in the group of Prof. Dr. Paul Knochel - Supervision of chemistry and medical science students in the organic and inorganic chemical laboratory - Supervision of several research internships and a master thesis - Supervision and correction of exams

AWARDS

Dr. Klaus Römer Award 2009 for excellent performance in the category: PhD thesis

PUBLICATIONS

Laurin Melzig, Andrey Gavryushin and Paul Knochel, „Direct Aminoalkylation of Arenes and Hetarenes via Ni-catalyzed Negishi Cross-Coupling Reactions", *Org. Lett.* **2007**, *9*, 5529, selected for *Synfacts* **2008**, *3*, 302.

Christian B. Rauhut, Laurin Melzig, and Paul Knochel, „*Meta*- and *para*-Difunctionalization of Arenes via a Sulfoxide-Magnesium Exchange Reaction", *Org. Lett.* **2008**, *10*, 3891.

Laurin Melzig, Christian B. Rauhut, and Paul Knochel, „*Meta*- and *para*-Difunctionalization of Arenes via an *ortho*-Magnesiation and a subsequent Sulfoxide-Magnesium exchange", *Synthesis* **2009**, *6*, 1041.

Laurin Melzig, Christian B. Rauhut, and Paul Knochel, „2,3-Functionalization of Furans, Benzofurans and Thiophenes via Magnesiation and Sulfoxide-magnesium exchange", *Chem. Commun.* **2009**, *24*, 3536, selected as „Hot Article".

Albrecht Metzger, Laurin Melzig, Christina Despotopoulou and Paul Knochel, „Pd-Catalyzed Cross-Coupling of Functionalized Organozinc Reagents with Thiomethyl-Substituted Heterocycles", *Org. Lett.* **2009**, *11*, 4228, selected for *Synfacts* **2009**, *12*, 1384, selected in „Highlights from the literature", *Org. Process Res. Dev.* **2010**, *14*, 2.

Laurin Melzig, Albrecht Metzger and Paul Knochel, „Ni-Catalyzed Cross-Coupling of Functionalized Organozinc Reagents with Thiomethyl-Substituted Heterocycles", *J. Org. Chem.* **2010**, *75*, 2131.

Laurin Melzig, Jeremy Stemper and Paul Knochel, „A novel Palladium-Catalyzed Cross-Coupling of Thiomethylated Alkynes with Functionalized Organozinc Reagents", *Synthesis* **2010**, *12*, 2085.

Albrecht Metzger, Laurin Melzig and Paul Knochel, „Up-Scaled Transition Metal-Catalyzed Cross-Couplings of Thioether-Substituted *N*-Heterocycles with Organozinc Reagents", *Synthesis* **2010**, *16*, 2853.

Laurin Melzig, Albrecht Metzger and Paul Knochel, „Pd- and Ni-catalyzed Cross-Coupling Reactions of Functionalized Zinc Reagents with Thioethers", *Chem Eur. J.* **2011**, *17*, 2948.

Laurin Melzig, Christian B. Rauhut, and Paul Knochel, „Difunctionalization of Arenes and Heteroarenes via a Sulfoxide-Magnesium Exchange Reaction", *Chem Eur. J., ASAP.*

Laurin Melzig, Coura R. Diène, Christoph J. Rohbogner and Paul Knochel, „A novel Chlorine-Zinc Exchange using Iron and Cobalt Catalysis", *Angew. Chem. Int. Ed., submitted.*

Laurin Melzig, Teresa Dennenwaldt, Andrey Gavryushin and Paul Knochel, „Direct Aminoalkylation of Arenes, Heteroarenes and Alkenyls via Ni-catalyzed Negishi Cross-Coupling Reactions", *Chem Eur. J., submitted.*

ORAL PRESENTATIONS

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