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Preparation of Polyfunctionalized Grignard Reagents and their Application in Aryne Chemistry

von

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aus

Taipei, Taiwan

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Erklärung

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Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig, und ohne unerlaubte Hilfe erarbeitet.

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Wenwei Lin

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2. Gutachter: Prof. Dr. Thomas Lindel

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Parts of this Ph. D. thesis have been published:

1. W. Lin, O. Baron, P. Knochel, "Highly Functionalized Benzene Syntheses by Directed Mono or Multiple Magnesiations Using TMPMgCl·LiCl", *Org. Lett.* **2006**, *accepted.*
2. W. Lin, F. Ilgen, P. Knochel, "Preparation of Highly Functionalized Arylmagnesium Reagents by the Magnesium Phenylselenide to Arynes", *Tetrahedron Lett.* **2006**, *47*, 1941-1944.
3. W. Lin, I. Sapountzis, P. Knochel, "Preparation of Functionalized Aryl Magnesium Reagents by the Magnesium Aryl Thiolates and Amides to Arynes", *Angew. Chem. Int. Ed.* **2005**, *44*, 4258-4261; *Angew. Chem.* **2005**, *117*, 4330-4333.
4. I. Sapountzis, W. Lin, C. C. Kofink, C. Despotopoulou, P. Knochel, "Iron-Catalyzed Aryl-Aryl Cross-Couplings with Magnesium-Derived Copper Reagents", *Angew. Chem. Int. Ed.* **2005**, *44*, 1654-1657; *Angew. Chem.* **2005**, *117*, 1682-1685.
5. I. Sapountzis, W. Lin, M. Fischer, P. Knochel, "Preparation of Polyfunctional Arynes *via* 2-Magnesiated Diaryl sulfonates", *Angew. Chem. Int. Ed.* **2004**, *43*, 4364-4366; *Angew. Chem.* **2004**, *116*, 4464-4466.
6. W. Lin, F. Ilgen, P. Knochel, "Preparation of Functionalized 3,4-Pyridynes *via* 2-Magnesiated Diaryl sulfonates", *manuscript in preparation.*

To my parents, my sister, and my brother, with love.

ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br.	broad
calcd.	calculated
CH_2Cl_2	dichloromethane
Cy	cyclohexyl
d	double
dba	*trans*,*trans*-dibenzylideneacetone
dec.	decomposition
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
equiv.	equivalent
EI	electron-impact
Et	ethyl
FAB	fast-atom bombardment
FG	functional group
GC	gas chromatography
h	hour
HMPT	hexamethylphosphorous triamide
HRMS	high resolution mass spectroscopy
n-Bu	*n*-butyl
i-Pr	isopropyl
IR	infra-red
J	coupling constant (NMR)
LG	leaving group
M	molarity
m	meta
m	multiplet

Me	methyl
Met	metal
min	minute
mol.	mole
mp.	melting point
MS	mass spectroscopy
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
p	para
Pent	pentyl
PG	protecting group
Ph	phenyl
Piv	pivaloyl
q	quartet
rt	room temperature
s	singlet
t	triplet
t-Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
tfp	*tri*-(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
TMP	2,2,6,6-tetramethylpiperidyl
TP	typical procedure
Ts	4-toluenesulfonyl

THEORETICAL PART

1. Overview

The continuous search for biologically active molecules for the pharmaceutical and agrochemical industries is one of the largest areas of research in which synthetic organic chemistry plays a fundamental role. Since most molecules with biological activity, even natural products of commercial use, are synthesized in chemical laboratories, there is a constant demand for the development of new methods for selective carbon-carbon and carbon-heteroatom bond formation. Such procedures should ideally be mild and highly tolerant towards a wide range of functional groups.

In 1849, Frankland already set the stage for modern organometallic chemistry with the synthesis of diethylzinc.[1] However, organomagnesium[2] and organolithium[3] reagents were the first to dominate this branch of organic chemistry, rather than zinc organometallics. The nature of the metal or of the metallic moiety ($MetL_n$) is exceedingly important for tuning the reactivity. As illustrated in Figure 1, the reactivity of organometallic species towards electrophilic species increases with the ionic character of the carbon-metal bond.

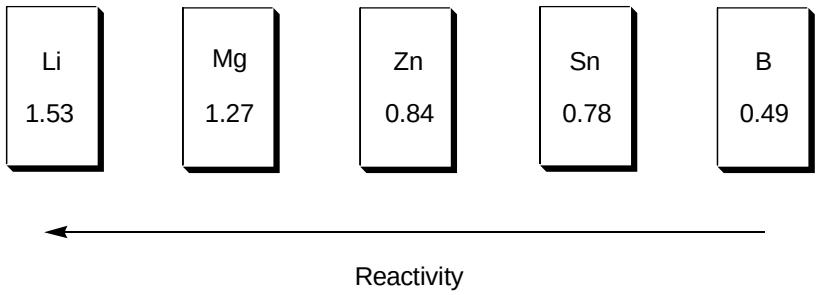


Figure 1. Electronegativity difference of some metals relative to carbon.[4]

The use of highly reactive species, like organolithium reagents, often compromises selectivity and tolerance towards sensitive functional groups. On the other hand, the reaction of the less reactive organometallic species, such as organozinc, organotin, or organoboron compounds, was necessarily promoted by using transition metal catalysts to give access to the broad field

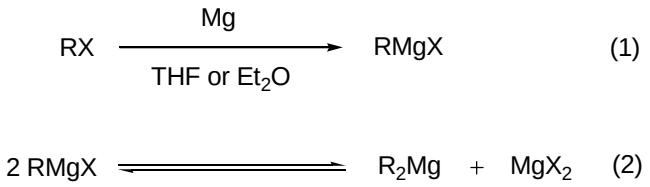
[1] a) E. Frankland, *Liebigs Ann. Chem.* **1848-49**, *71*, 171; b) E. Frankland, *J. Chem. Soc.* **1848-49**, *2*, 263.
[2] V. Grignard, *Compt. Rend.* **1900**, *130*, 1322.
[3] a) W. Schlenk, J. Holtz, *Chem. Ber.* **1917**, *50*, 262; b) K. Ziegler, H. Colonius, *Liebigs Ann. Chem.* **1930**, *479*, 135.
[4] a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem.* **2000**, *112*, 4585; *Angew. Chem. Int. Ed.* **2000**, *39*, 4415; b) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem.* **2003**, *115*, 4438; *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.

of the transition metal-catalyzed transformations.[5] Organomagnesium reagents, which have less reactivity towards electrophiles than the corresponding organolithium reagents, have still a high-enough reactivity toward many electrophiles with a remarkable functional-group tolerance at low temperature.[6]

1.1 Preparation of Organomagnesium Compounds

1.1.1 Direct oxidative addition of magnesium to organic halides

Organomagnesium reagents are sensitive to air and moisture, and therefore an inert atmosphere is essential for their preparation and further reactions. The most common method to prepare organomagnesium reagents is the reaction of organic halides with magnesium metal in a polar, aprotic solvent like THF or diethyl ether (Scheme 1). For large-scale industrial processes,[7] these volatile and highly flammable ethers represent safety hazards and can be replaced by "butyl diglyme" ($C_4H_9OC_2H_4OC_2H_4OC_4H_9$) that possesses a high flashpoint (118 °C) and low water solubility.



Scheme 1. Synthesis of Grignard reagents by oxidative addition (Eq. 1) and Schlenk equilibrium (Eq. 2).

The mechanism of this reaction is not yet fully clarified, but a radical mechanism is generally accepted.[8] In solution, a Grignard reagent (RMgX) is in equilibrium (Schlenk equilibrium, Scheme 1, Eq. 2) with R_2Mg and MgX_2, depending on temperature, solvent and the anion X^-.

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[5] For general reviews, please see: a) F. Diederich, P. J. Stang, *Metal-catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **1998**; b) N. Miyaura, *Cross-Coupling Reactions. A Practical Guide*, Springer-Verlag, Berlin, **2002**; c) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; d) E. Negishi, *Organometallics in Organic Synthesis*, Wiley, New York, **1980**.

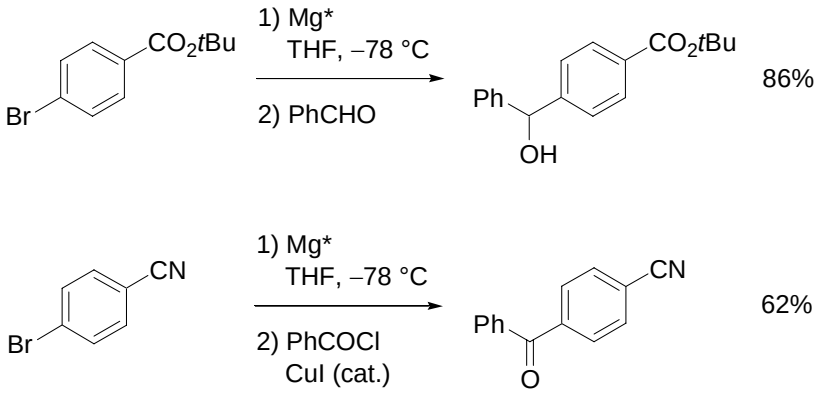
[6] P. Knochel, A. Krasovskiy, I. Sapountzis, *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**, *1*, 109.

[7] P. E. Rakita, J. F. Aultman, L. Stapleton, *Chem. Eng.* **1990**, *97*, 110.

[8] 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. Fujuwara, R. J. Rogers, H. L. Mitchell, G. M. Whitesides, *J. Am. Chem. Soc.*, **1980**, *102*, 217; d) J. F. Garst, F. Ungvary, *Grignard Reagents* (Ed.: H. G. Richey, Jr.), Wiley, Chichester, **2000**, 185; e) M. S. Kharasch, O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, **1954**; f) C. Hamdouchi, H. M. Walborsky, *Handbook of Grignard-Reagents* (Eds: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1995**, 145; g) K. Oshima, *Main Group Metals in Organic Synthesis* (Eds.: H. Yamamoto, K. Oshima), Wiley-VCH, Weinheim, **2004**.

Most Grignard reagents (RMgX) or diorganomagnesium compounds crystallize with *tetra*-coordinated Mg in a distorted tetrahedron, but *penta*- (CH_3MgBr in THF) and *hexa*- ($MgBr_2$ in THF) coordinated structures can be also observed.[9] All experimental evidences indicate similar coordination numbers in solution, emphasizing the role of coordinating ethereal solvents in Grignard reagents.

The presence of sensitive functional groups makes this insertion method complicated and difficult to approach. The direct oxidative addition reactions for the preparation of functionalized Grignard reagents are possible when they are conducted with Rieke-magnesium (Mg*) at low temperature, but generally this method still shows limitations concerning the functional-group tolerance (Scheme 2).[10]



Scheme 2. Preparation of functionalized Grignard reagents using Rieke-magnesium (Mg*).

1.1.2 Metalation reaction with magnesium amides

The direct deprotonation of organic molecules with kinetically poor bases, such as organolithium or magnesium compounds, is limited. However, the addition of amines or the presence of directing groups, which break the aggregation of these reagents, can lower this barrier. Indeed, the preparation of aryl organometallics by a directed *ortho*-lithiation using a lithium base (such as *sec*-BuLi or lithium 2,2,6,6-tetramethylpiperidide (LiTMP)) has found broad applications in recent years.[11] The major drawback of these resulting aryllithiums is the

[9] M. Vallino, *J. Organomet. Chem.* **1969**, *20*, 1.
[10] a) R. D. Rieke, *Science* **1989**, *246*, 1260; b) T. P. Burns, R. D. Rieke, *J. Org. Chem.* **1987**, *52*, 3674; c) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65*, 5428; d) R. D. Rieke, T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323; e) R. D. Rieke, M. S. Sell, W. R. Klein, T. Chen, J. D. Brown, M. V. Hansan, *Active Metals* (Ed.: A. Fuerstner), Wiley-VCH, Weinheim, **1995**.
[11] a) M. Schlosser, *Angew. Chem.* **2005**, *117*, 380; *Angew. Chem. Int. Ed.* **2005**, *44*, 376; b) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489; c) F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4059; d) M. Schlosser, *Eur. J. Org. Chem.* **2001**, *21*, 3975; e) D. M. Hodgson, C. D. Bray, N. D. Kindon, *Org. Lett.* **2005**, *7*, 2305; f) J.-C. Plaquevent, T. Perrard, D. Cahard, *Chem. Eur. J.* **2002**, *8*, 3300; g) C.-C. Chang, M. S.

high reactivity towards electrophilic groups, which precludes the presence of sensitive functional groups like an ester or a ketone.[12] Also, the nature of the directing group is limited to functional groups which do not react with strong lithium bases.[13] In comparison to their lithium counterparts, magnesium bases have found less general applications due to their moderate solubility and low kinetic basicity.[14]

The direct metalation of organic substrates with alkylmagnesium halides requires a greater kinetic acidity for the C-H bond than for the conjugated acid of the Grignard reagent. Strongly coordinating solvents like HMPT help promote these reactions. One of the major applications is the metalation of acetylene derivatives, such as the *mono*-metalation of acetylene by *n*-BuMgCl to form ethynylmagnesium chloride.[15]

Unlike their lithium analogues, Hauser bases (R_2NMgBr) are much more stable in THF (up to reflux conditions). In 1989, Eaton reported the use of bis(2,2,6,6-tetramethylpiperidyl)magnesium, $(TMP)_2Mg$, as a selective metalating reagent (Scheme 3). Although a 6-fold excess $(TMP)_2Mg$ is necessary for reaction completion, ArMgTMP **1**, which can coexist with an ester group for some time at room temperature, is successfully prepared. [16]

Ameerunisha, *Coord. Chem. Rev.* **1999**, *189*, 199; h) F. Leroux, M. Schlosser, E. Zohar, I. Marek, *Chemistry of Organolithium Compounds* (Eds.: Z. Rappoport, I. Marek), Wiley: New York, **2004**, chap. 1, p. 435; i) K. W. Henderson, W. J. Kerr, *Chem. Eur. J.* **2001**, *7*, 3430; j) K. W. Henderson, W. J. Kerr, J. H. Moir, *Tetrahedron* **2002**, *58*, 4573; k) M. C. Whisler, S. MacNeil, V., P. Beak, *Angew. Chem.* **2004**, *116*, 2256; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; l) G. Quéguiner, F. Marsais, V. Snieckus, J. Epsztajn, *Adv. Heterocycl. Chem.* **1991**, *52*, 187; m) M. Veith, S. Wieczorek, K. Fries, V. Huch, *Z. Anorg. Allg. Chem.* **2000**, *626*, 1237. n) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827; o) M. Kauch, D. Hoppe, *Synthesis* **2006**, 1575; p) M. Kauch, D. Hoppe, *Synthesis* **2006**, 1578; q) N. Plé, A. Turck, K. Couture, G. Quéguiner, *J. Org. Chem.* **1995**, *60*, 3781; r) C. Metallinos, V. Snieckus, *Org. Lett.* **2002**, *4*, 1935; s) W. Clegg, S. H. Dale, R. W. Harrington, E. Hevia, G. W. Honeyman, R. E. Mulvey, *Angew. Chem.* **2006**, *118*, 2434; *Angew. Chem. Int. Ed.* **2006**, *45*, 2374; t) W. Clegg, S. H. Dale, E. Hevia, G. W. Honeyman, R. E. Mulvey, *Angew. Chem.* **2006**, *118*, 2430; *Angew. Chem. Int. Ed.* **2006**, *45*, 2371; (u) D. M. Hodgson, S. M. Miles, *Angew. Chem.* **2006**, *118*, 949; *Angew. Chem. Int. Ed.* **2006**, *45*, 935; (v) D. M. Hodgson, P. G. Humphreys, J. G. Ward, *Org. Lett.* **2006**, *8*, 995.

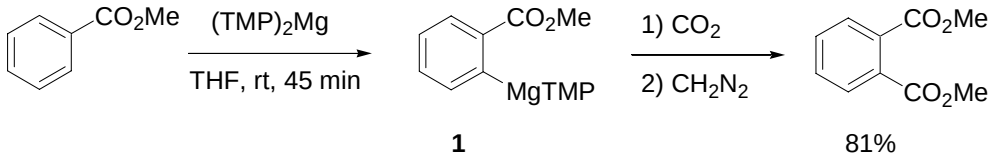
[12] M. Yus, F. Foubelo, *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH: Weinheim, **2005**, *1*, 7.

[13] a) J. Clayden, *Organolithiums: Selectivity for Synthesis* (Eds.: J. E. Baldwin, R. M. Williams), Elsevier, **2002**; b) C. G. Hartung, V. Snieckus, *Modern Arene Chemistry* (Ed.: Didier Astruc), Wiley-VCH, Weinheim, **2002**, 330; c) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; d) J. Clayden, C. C. Stimson, M. Keenan, *Chem. Commun.* **2006**, 1393.

[14] a) O. Bayh, H. Awad, F. Mongin, C. Hoarau, L. Bischoff, F. Trécourt, G. Quéguiner, F. Marsais, F. Blanco, B. Abarca, R. Ballesteros, *J. Org. Chem.* **2005**, *70*, 5190; b) O. Bayh, H. Awad, F. Mongin, C. Hoarau, F. Trécourt, G. Quéguiner, F. Marsais, F. Blanco, B. Abarca, R. Ballesteros, *Tetrahedron* **2005**, *61*, 4779; c) H. Awad, F. Mongin, F. Trécourt, G. Quéguiner, F. Marsais, F. Blanco, B. Abarca, R. Ballesteros, *Tetrahedron Lett.* **2004**, *45*, 6697.

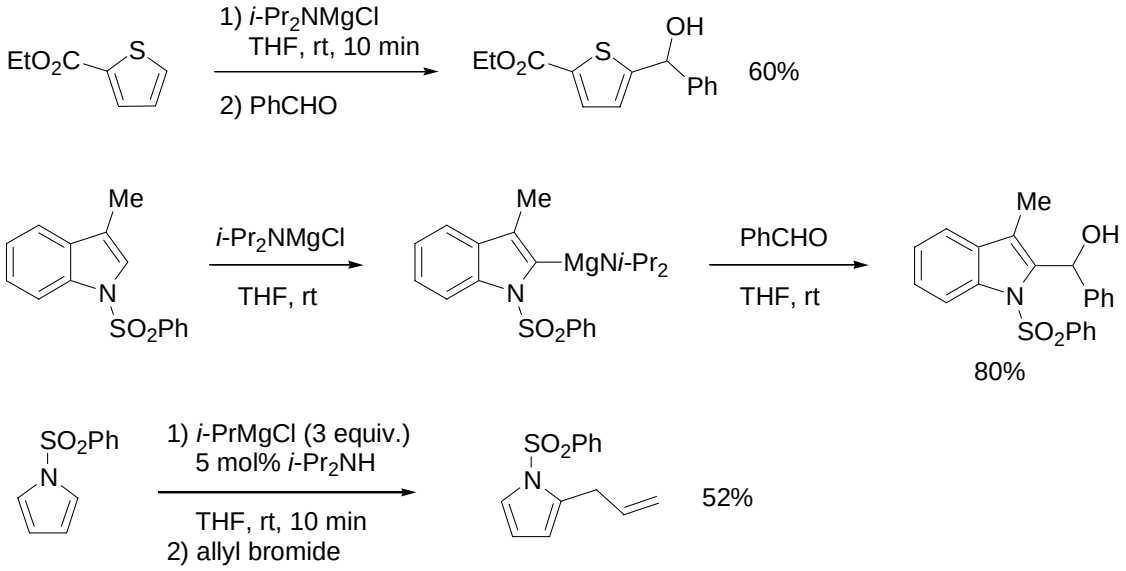
[15] a) A. B. Holmes, C. N. Sporikou, *Org. Synth.* **1987**, *65*, 61; b) H. J. Bestman, T. Brosche, K. H. Koschatzky, K. Michaelis, H. Platz, K. Roth, J. Suess, O. Vostrowsky, W. Knauf, *Tetrahedron Lett.* **1982**, *23*, 4007; c) L. Poncini, *Bulletin des Societes Chimiques Belges* **1983**, *92*, 215.

[16] P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016.



Scheme 3. Selective *ortho*-magnesiation of methyl benzoate.

Of special interest is the ease in which *ortho*-magnesiation reactions can be accomplished in the presence of an ester function, which is normally susceptible to nucleophilic attack using conventional lithium reagents.[17] This methodology was applied to the deprotonation of cyclopropylamides[18] as well as to numerous heterocycles (Scheme 4)[19].



Scheme 4. Selective *ortho*-magnesiation of heterocycles.

Recently, our group found that the mixed Mg/Li-bases ($R_2NMgCl \cdot LiCl$) (**2a** or **2b**) have an excellent kinetic basicity, very good solubility and thermal stability (Scheme 5). They can be often used just in stoichiometric amounts and perform the magnesiation of aromatics and heteroaromatics with excellent regioselectivity at practical temperatures (often −25 °C to 25 °C).[20]

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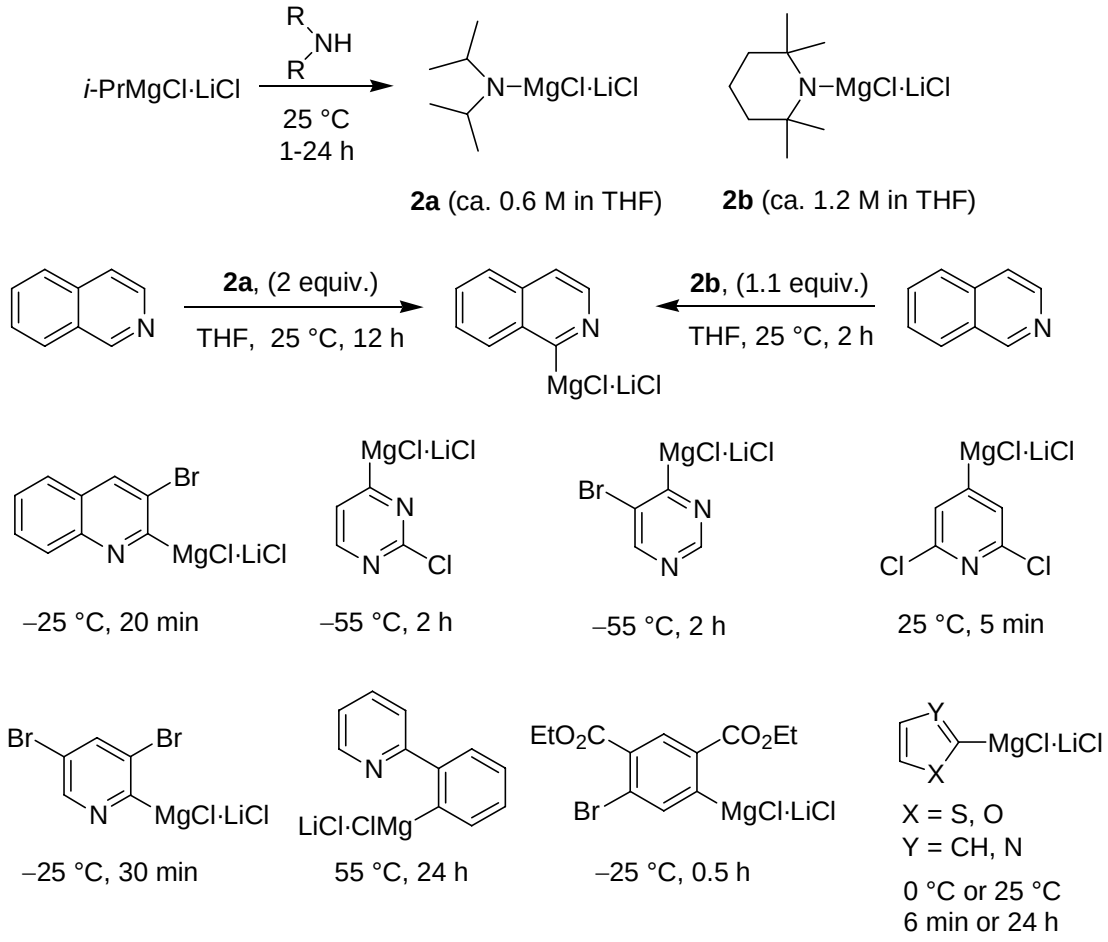
[17] P. Beak, C. J. Upton, *J. Org. Chem.* **1975**, *40*, 1094.
[18] a) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc.* **1993**, *115*, 11370; b) M. -X. Zhang, P. E. Eaton, *Angew. Chem.* **2002**, *114*, 2273; *Angew. Chem. Int. Ed.* **2002**, *41*, 2169.
[19] a) M. Shilai, Y. Kondo, T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1* **2001**, 442; b) W. Schlecker, A. Huth, E. Ottow, *J. Org. Chem.* **1995**, *60*, 8414; c) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Liebigs Ann.* **1995**, 1441; d) Y. Kondo, A. Yoshida, T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2331; e) A. Dinsmore, D. G. Billing, K. Mandy, J. P. Michael, D. Mogano, S. Patil, *Org. Lett.* **2004**, *6*, 293.
[20] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem.* **2006**, *118*, 3024; *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.

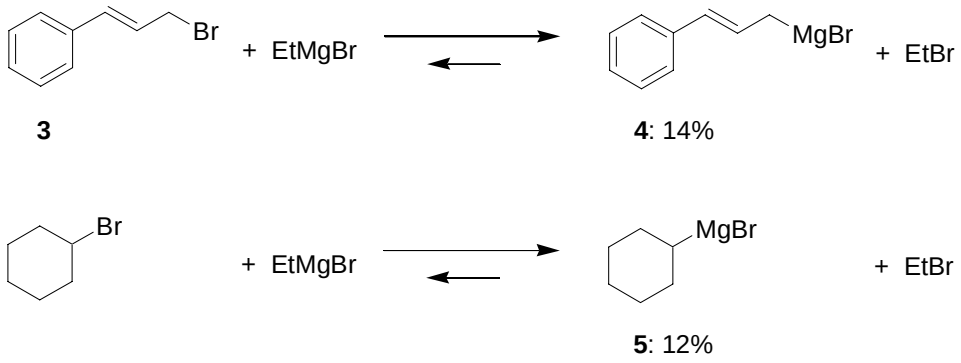


Scheme 5. Selective magnesiation of heterocycles and aromatics.

1.1.3 Halogen-magnesium-exchange reaction

Compared to the two methods previously mentioned, the halogen-magnesium-exchange has been found to be an excellent method for the preparation of functionalized organomagnesium reagents. The first example of a bromine-magnesium-exchange reaction was reported by Prévost in 1931. [21] The reaction of cinnamyl bromide (**3**) with EtMgBr furnished cinnamylmagnesium bromide **4** in low yield (Scheme 6). Urion reported the preparation of cyclohexylmagnesium bromide **5** in a similar way.[22]

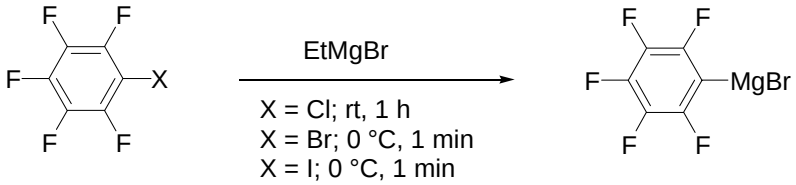
[21] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[22] E. Urion, *Comp. Rend. Acad. Sci. Paris* **1934**, *198*, 1244.



Scheme 6. First examples of a bromine-magnesium-exchange.

The halogen-magnesium-exchange is an equilibrium process favoring the formation of the more stable organomagnesium compound. Therefore, in order to shift this equilibrium to the desired side, the resulting organomagnesium species should be more stable than the Grignard reagent used for the exchange reaction ($sp > sp^2$ (vinyl) > sp^2 (aryl) > sp^3 (prim.) > sp^3 (sec.)). A halogen-ate complex is believed to be an intermediate in the exchange reaction, as proposed for the halogen-lithium-exchange.[23]

In 1971, Tamborski showed that the electronic properties of both the halogen atom and the organic molecule play an important role in the formation-rate of the new Grignard reagent.[24] Only for very electron-poor systems, such as the *tetra*- or *penta*-fluorobenzene derivatives, was the exchange of a chlorine possible. In addition, the reactivity order (I > Br > Cl >> F) is influenced by the bond-strength, the electronegativity, and the ease of polarizability of the halide (Scheme 7).

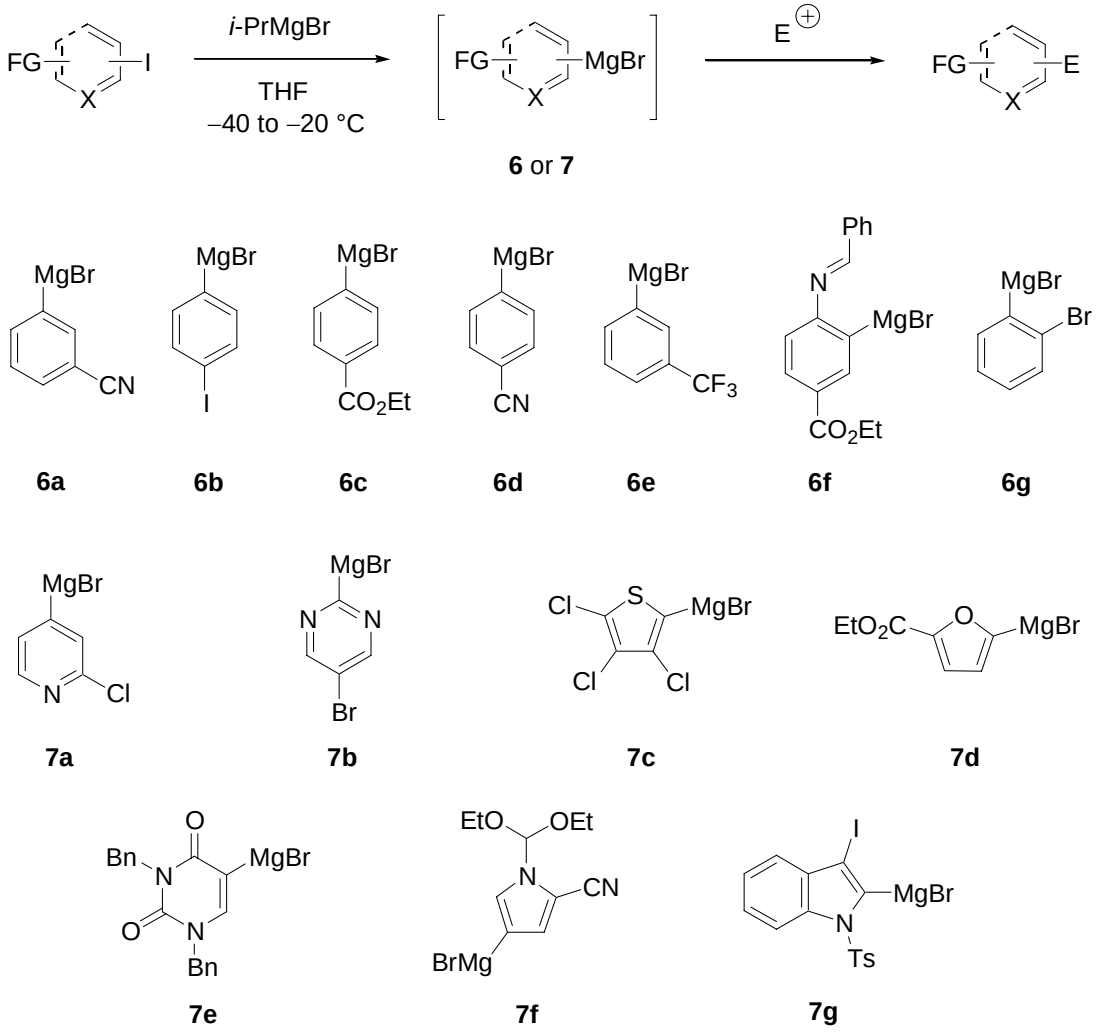


Scheme 7. Preparation of polyhalogenated Grignard reagents.

In 1998, our research group showed for the first time the excellent functional group tolerance of this method using a low-temperature I/Mg-exchange for the preparation of various

[23] a) W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1; b) H. J. Reich, N. H. Phillips, I. L. Reich, *J. Am. Chem. Soc.* **1985**, *107*, 4101; c) W. B. Farnham, J. C. Calabrese, *J. Am. Chem. Soc.* **1986**, *108*, 2449.
[24] C. Tamborski, G. J. Moore, *J. Organomet. Chem.* **1971**, *26*, 153.

functionalized aromatic Grignard reagents of type **6** (Scheme 8).[25] Besides, many functionalized magnesiated heterocycles of type **7**, such as pyridines (**7a**), pyrimidines (**7b**), thiophenes (**7c**), furans (**7d**), uracils (**7e**), pyrroles (**7f**), indoles (**7g**) were prepared in a similar way.[26]



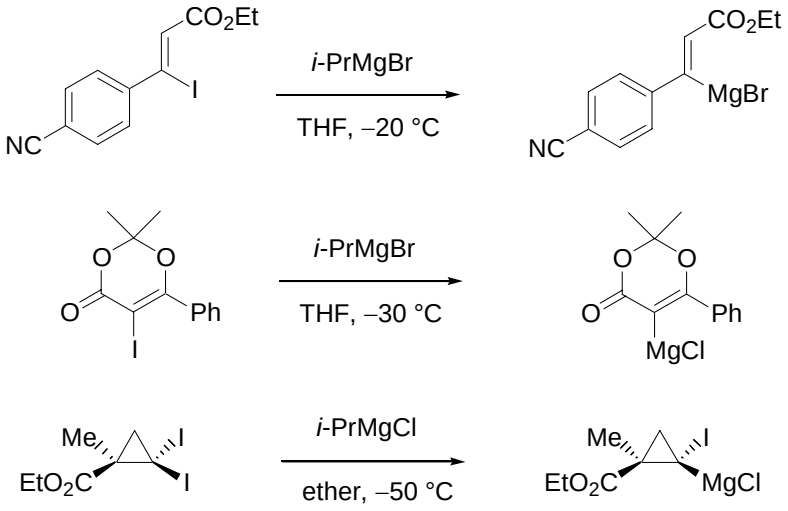
Scheme 8. Functionalized arylmagnesium reagents of type **6** and heterocycles of type **7** prepared *via* an iodine-magnesium-exchange.

In addition, the I/Mg-exchange can also be applied to the synthesis of alkenyl- and cyclopropylmagnesium reagents (Scheme 9).[27]

[25] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem.* **1998**, *110*, 1801; *Angew. Chem. Int. Ed.* **1998**, *37*, 1701; b) G. Varchi, A. E. Jensen, W. Dohle, A. Ricci, P. Knochel, *Synlett* **2001**, 477.

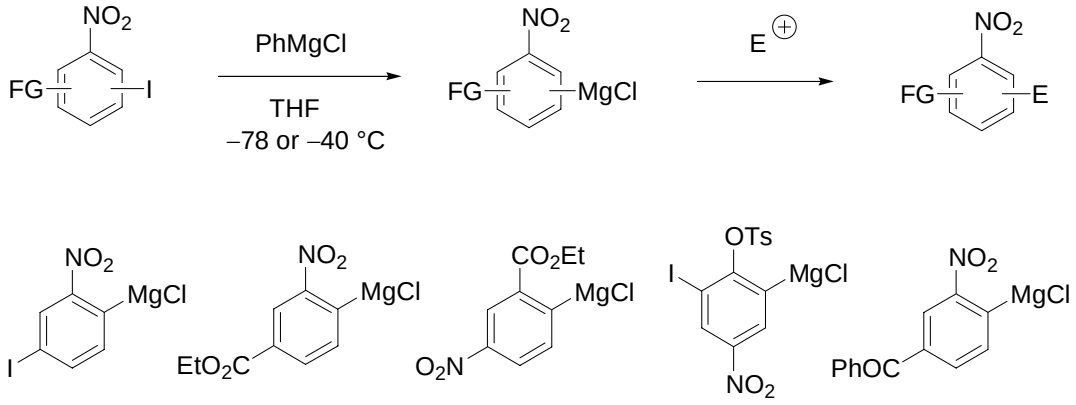
[26] a) L. Bérillon, A. Leprêtre, A. Turck, N. Plé, G. Quéguiner, G. Cahiez, P. Knochel, *Synlett* **1998**, 1359 ; b) M. Abarbri, J. Thibonnet, L. Bérillon, F. Dehmel, M. Rottländer, P. Knochel, *J. Org. Chem.* **2000**, *65*, 4618; c) M. Abarbri, F. Dehmel, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 7449; d) M. Abarbri, P. Knochel, *Synlett* **1999**, 1577; e) F. Dehmel, M. Abarbri, P. Knochel, *Synlett* **2000**, 345.

[27] a) I. Sapountzis, W. Dohle, P. Knochel, *Chem. Commun.* **2001**, 2068; b) V. A. Vu, L. Bérillon, P. Knochel, *Tetrahedron Lett.* **2001**, *42*, 6847 ; c) V. A. Vu, I. Marek, K. Polborn, P. Knochel, *Angew. Chem.* **2002**, *114*, 361; *Angew. Chem. Int. Ed.* **2002**, *41*, 351.



Scheme 9. Preparation of alkenyl- and alkylmagnesium reagents.

Although *i*-PrMgCl is the magnesium reagent of choice for performing an iodine-magnesium-exchange, in the case of nitroarenes, the use of a less reactive organomagnesium compound is essential. A broad range of functionalized arylmagnesium compounds bearing a nitro function can be prepared by an I/Mg-exchange using phenylmagnesium chloride as an exchange reagent (Scheme 10).[28]



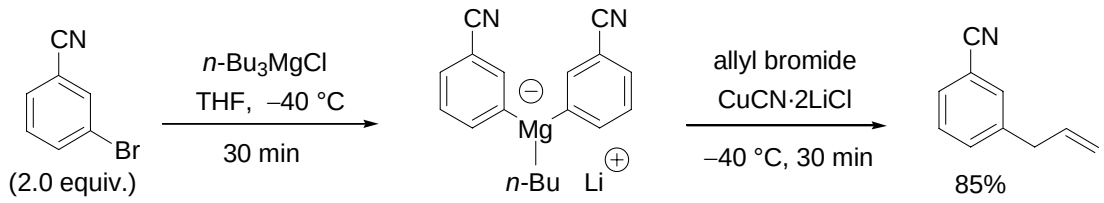
Scheme 10. Preparation of arylmagnesium reagents bearing a nitro function.

Oshima has showed that besides alkylmagnesium halides, lithium trialkylmagnesiates are prepared by the reaction of an organolithium reagent (RLi; 2 equiv.) with an alkylmagnesium halide (RMgX; 1 equiv.) in THF at 0 °C (30 min).[29] 1 or 0.5 equiv. of lithium

[28] a) I. Sapountzis, P. Knochel, *Angew. Chem.* **2002**, *114*, 1680; *Angew. Chem. Int. Ed.* **2002**, *41*, 1610; b) I. Sapountzis, H. Dube, R. Lewis, N. Gommermann, P. Knochel, *J. Org. Chem.* **2005**, *70*, 2445.

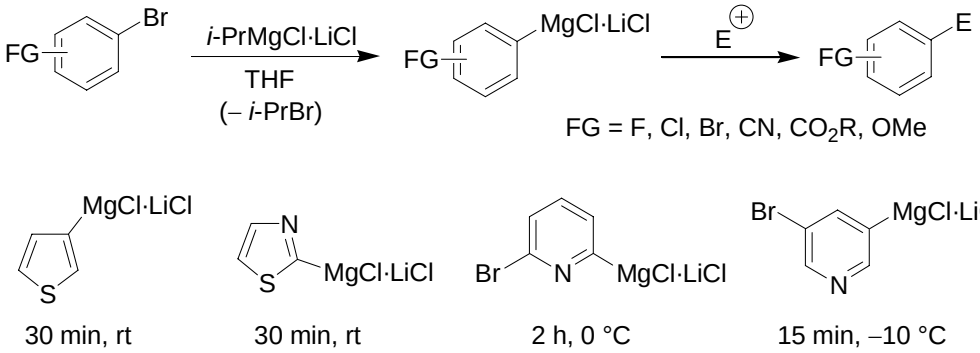
[29] a) K. Oshima, *J. Organomet. Chem.* **1999**, *575*, 1; b) K. Kitagawa, A. Inoue, H. Shinokubo, K. Oshima, *Angew. Chem.* **2000**, *112*, 2594; *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 2481; c) A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2001**, *66*, 4333; d) A. Inoue, K. Kitagawa, H. Shinokubo, K. Oshima,

tributylmagnesiate (*n*-Bu_3MgLi), relative to the aromatic halide, can be used, showing that two of the three butyl groups undergo the exchange reaction. Compared to *i*-PrMgCl, *n*-Bu_3MgLi undergoes the exchange reaction more readily and is less sensitive to the electronic density of the aromatic ring. For example, *n*-Bu_3MgLi reacted more readily with 3-bromobenzonitrile than did *i*-PrMgCl, which was followed by quenching with allyl bromide in the presence of CuCN·2LiCl giving rise to 3-allylbenzonitrile in 85 % yield. For this reagent, however, the excess of an electrophile was required (Scheme 11).



Scheme 11. Preparation of aryl- and heteroarylmagnesium reagents *via* a Br/Mg-exchange.

By using the mixed organometallic *i*-PrMgCl·LiCl which has a higher reactivity than *i*-PrMgCl, a fast Br/Mg-exchange can be achieved leading to the desired Grignard reagents in high yields under mild conditions (Scheme 12). Further applications of *i*-PrMgCl·LiCl in Br/Mg-exchange of functionalized pyrimidines and I/Mg-exchange of aromatic systems bearing a boronic ester and a triazene functionality or alkenyl iodides were also successfully achieved.[30]



Scheme 12. Preparation of aryl- and heteroarylmagnesium reagents *via* a Br/Mg-exchange using *i*-PrMgCl·LiCl.

Tetrahedron **2000**, *56*, 9601; e) R. I. Yousef, T. Rüffer, H. Schmidt, D. Steinborn, *J. Organomet. Chem.* **2002**, *655*, 111.

[30] A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3369; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. For Br/Mg-exchange of functionalized pyrimidines, please see: N. Boudet, P. Knochel, *Organic Lett.* **2006**, *8*, 3737; for I/Mg-exchange, please see: a) O. Baron, P. Knochel, *Angew. Chem.* **2005**, *117*, 3193; *Angew. Chem. Int. Ed.* **2005**, *44*, 3133; b) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543; c) H. Ren, A. Krasovskiy, P. Knochel, *Chem. Commun.* **2005**, 543; d) H. Ren, A. Krasovskiy, P. Knochel, *Org. Lett.* **2004**, *6*, 4215.

1.2 Aryne Chemistry

1.2.1 Introduction

One of the most interesting topics for chemists is aryne chemistry and its application in organic syntheses. Arynes and heteroarynes are reactive intermediates, formally derived by the removal of two adjacent hydrogen atoms from an aromatic ring or a heterocyclic aromatic ring, respectively. Prototypical examples are *o*-benzyne (benzyne) and 3,4-didehydropyridine (3,4-pyridyne) depicted in Figure 2. In 1874, it was observed that the three isomeric bromobenzenesulfonates were converted mainly to resorcinol by molten alkali hydroxide.[31] Numerous rearrangements in nucleophilic aromatic substitutions that did not fit the accepted addition-elimination mechanism[32] became known and were collected by Bunnett and Zahler[33] in a masterly review. In 1953, J. D. Roberts´ experiments on the conversion of ^{14}C-labeled chlorobenzene with potassium amide to aniline gave strong support to the intermediacy of benzyne in this and related reactions.[34] Finally, benzyne was trapped as a stable guest in a hemicarcerand.[35]

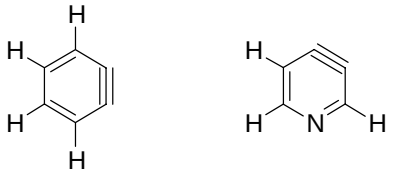


Figure 2. Structures of benzyne and 3,4-pyridyne.

Additional direct evidences for the existence of benzyne were provided by the observation of its infrared spectrum,[36] solid-state ^{13}C dipolar NMR spectrum,[37] ^{1}H and ^{13}C NMR in a molecular container[38] and by ultraviolet photoelectron spectroscopy.[39] The experimental findings and theoretical calculations agree in concluding that benzyne has the general structure depicted above, in which a degree of triple bond with some diradical character exists

[31] H. Limpricht, *Ber. Dtsch. Chem. Ges.* **1874**, *7*, 1349.
[32] J. Sauer, R. Huisgen, *Angew. Chem.* **1960**, *72*, 294.
[33] J. F. Bunnett, R. E. Zahler, *Chem. Rev.* **1951**, *49*, 273.
[34] R. W. Hoffmann, *Dehydrobenzene and cycloalkynes*, Academic Press, New York, **1967**.
[35] R. Warmuth, *Eur. J. Org. Chem.* **2001**, 423.
[36] J. G. Radziszewski, B. A. Hess Jr., R. Zahradnik, *J. Am. Chem. Soc.* **1992**, *114*, 52.
[37] A. M. Orendt, J. C. Facelli, J. G. Radziszewski, W. J. Horton, D. M. Grant, J. Michl, *J. Am. Chem. Soc.* **1996**, *118*, 846.
[38] a) R. Warmuth, *Chem. Commun.* **1998**, 59; b) R. Warmuth, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1347.
[39] a) P. G. Wenthold, R. R. Squires, W. C. Lineberger, *J. Am. Chem. Soc.* **1998**, *120*, 5279; b) A. Schweig, N. Münzel, H. Meyer, A. Heidenreich, *Struct. Chem.* **1990**, *1*, 89.

between positions 1 and 2. A similar conclusion has been proposed for the heterocyclic analogues.[40]

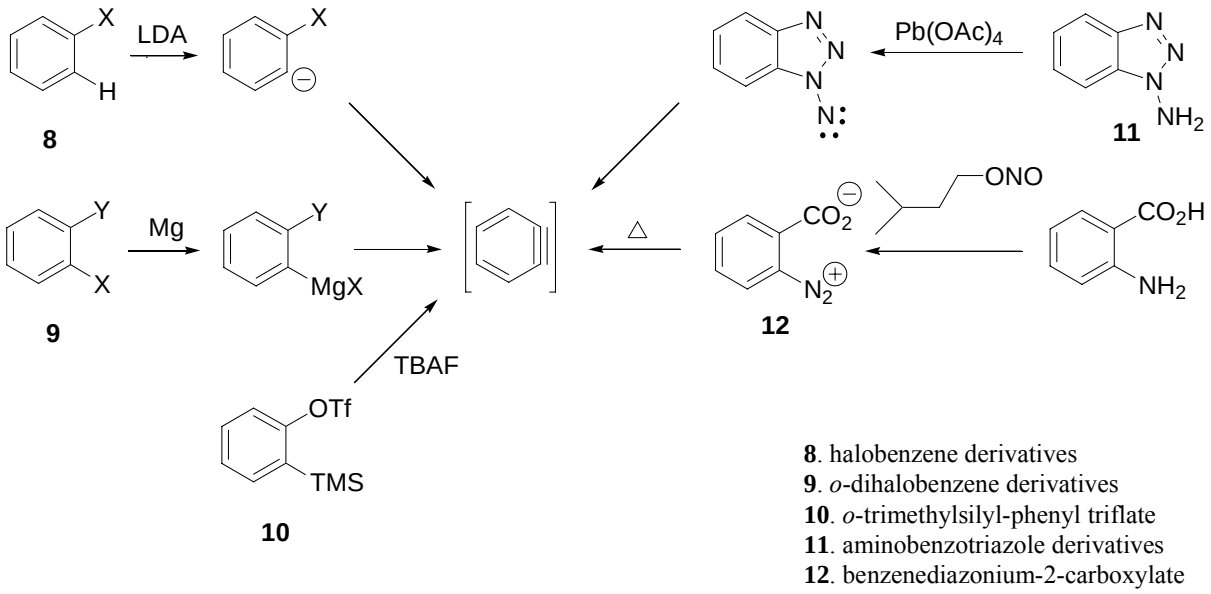
Benzyne is an important reactive intermediate and many studies on its generation and reactions have been undertaken.[32,34,41] Their reactions can be divided into three groups: the pericyclic reactions of arynes, the nucleophilic additions to arynes, and the transition metal-catalyzed reactions of arynes. The pericyclic reactions can be divided into several categories such as the Diels–Alder reactions occurring in an inter- or intramolecular mode, the [2+2] cycloadditions, the 1,3-dipolar cycloadditions, the 1,4-dipolar cycloadditions, and the ene reactions. Arynes react with practically all kinds of nucleophiles. From a synthetic point of view, the most interesting are the nitrogen-bearing nucleophiles and carbanions. Also, the developing research concerning the insertion of arynes into σ bonds (Sn-C, N-C, Si-Si, Sn-Sn, S-Sn, N-Si C-C, N-S, C-P) provides a promising future as a means of preparing complex *ortho*-disubstituted arenes.[42] More recently, the transition metal-catalyzed reactions of arynes have been studied and particularly those involving palladium.[41d] Thus, various polycyclic aromatic hydrocarbons have been prepared through palladium-catalyzed co-cyclization of arynes.

1.2.2 Generation of arynes

Because of their extreme reactivity, arynes must be generated *in situ*. The generation-methods most widely used are summarized in Scheme 13. A halide **8** can be treated with a strong base, such as lithium amide,[17] to remove the *o*-aromatic proton and generate benzyne *via* an anion. The use of strong bases which may act as nucleophiles can be avoided by treatment of *o*-dihalosubstituted benzenes **9** with a metal (magnesium) to give the desired aryne by elimination.[43] Aryl triflates **10** can be used to generate arynes *via* other routes, and for example, a fluoride ion displacement of a trimethylsilyl group provides a convenient route to benzyne under mild conditions.[44] On the other hand, oxidation of aminotriazole **11** often produces benzyne in good yield, but has the disadvantage of requiring the presence of an

[40] a) F. C. Gozzo, M. N. Eberlin, *J. Org. Chem.* **1999**, *64*, 2188; b) W. Langenaeker, F. De Proft, P. Geerlings, *J. Phys. Chem. A* **1998**, *102*, 5944.
[41] a) T. L. Gilchrist, *The Chemistry of Functional Groups Supplement C* (Eds: S. Patai, Z. Rappoport), Wiley, Chichester, **1983**, 383; b) H. Hart, *The Chemistry of Triple-bonded Functional Groups Supplement C2* (Eds: S. Patai), Wiley, New York, **1994**, 1017; c) L. Castedo, E. Guitian, in *Studies in Natural Products Chemistry*, *Vol. 3*, *Part B*, (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1989**, p. 417; d) E. Guitián, D. Pérez; D. Peña, *Topics in Organometallic Chemistry, Vol. 14,* (Ed.: Springer), Berlin / Heidelberg, **2005**, 109.
[42] D. Peña, D. Pérez, E. Guitián, *Angew. Chem.* **2006**, *118*, 3659; *Angew. Chem., Int. Ed.* **2006**, *45*, 3579.
[43] G. Wittig, *Org. Synth.* **1959**, *39*, 75.
[44] Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211.

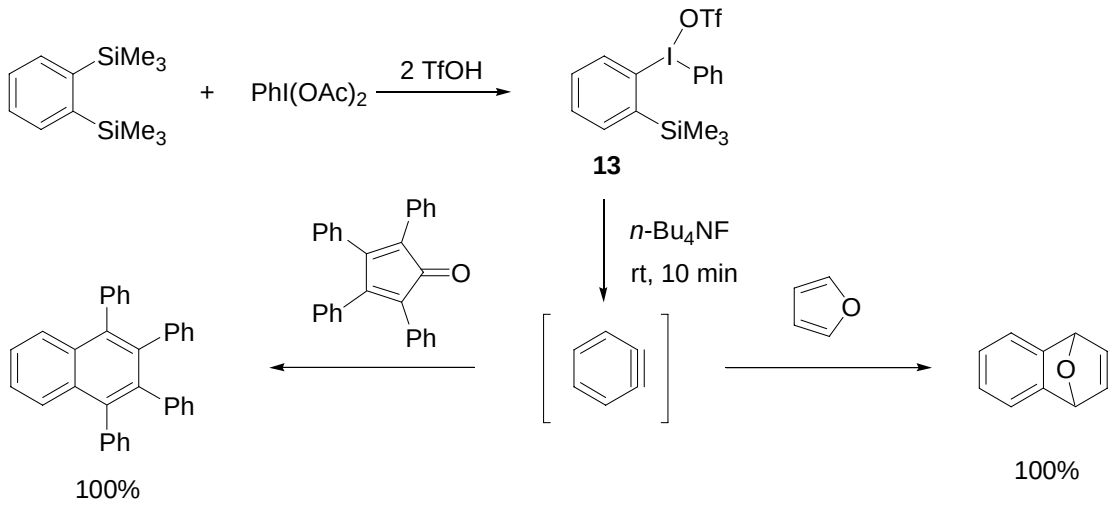
oxidant such as lead tetraacetate in the reaction medium.[45a] The use of NBS was also developed by Campbell.[45] Instead of NBS, Knight reported that NIS can also be an oxidant to convert aminotriazole derivatives into arynes.[46] Arynes may also be obtained from anthranilic acid, by decomposition of the internal benzenediazonium-2-carboxylate **12**.[47]



Scheme 13. General methods for the generation of arynes.

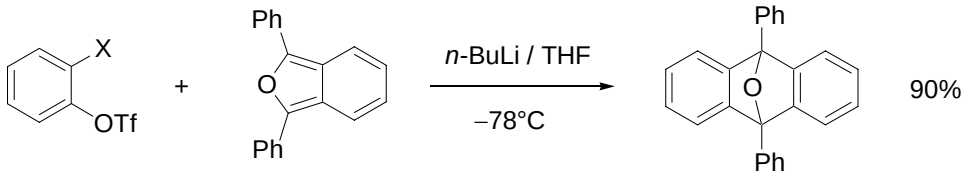
(Phenyl)[*o*-(trimethylsilyl)phenyl]iodonium triflate (**13**), readily prepared from *o*-bis(trimethylsilyl)benzene and $PhI(OAc)_2$, was reported to be a new and efficient precursor of benzyne by Kitamura in 1995.[48] Mild and neutral conditions provided adducts with typical trapping agents (Scheme 14).

[45] a) C. D. Campbell, C. W. Rees, *J. Chem. Soc. (C)* **1969**, 742; b) C. D. Campbell, C. W. Rees, *J. Chem. Soc. (C)* **1969**, 748, see also pp 752-756.
[46] M. A. Birkett, D. W. Knight and M. B. Mitchell, *Synlett* **1994**, 253.
[47] a) L. Friedman, F.M. Logullo, *J. Am. Chem. Soc.* **1963**, *85*, 1549; b) F. M. Logullo, A. H. Seitz and L. Friedman, *Org. Synth.* **1968**, *48*, 12; c) for a mechanistic study, see: P. C. Buxton, M. Fensome, H. Heaney, K. G. Mason, *Tetrahedron* **1995**, *51*, 2959. Please also see: references 34 and 41.
[48] T. Kitamura, M. Yamane, *J. Chem. Soc., Chem. Commun.* **1995**, 983.



Scheme 14. Generation of benzyne from (phenyl)[*o*-(trimethylsilyl)phenyl]iodonium triflate.

The lithium-halogen-exchange on *o*-halotriflates occurs with *n*-BuLi (−78°C) followed by the elimination of LiOTf to produce benzyne, which was reacted with 1,3-diphenyl-isobenzofuran affording the desired cycloaddition product in 90 % yield (Scheme 15).[49]



Scheme 15. Generation of benzyne from *o*-halotriflates.

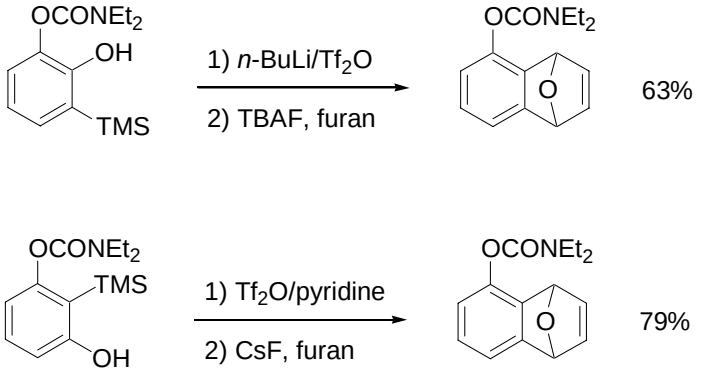
1.2.3 Diels–Alder reactions of arynes

The pericyclic reactions of arynes can include Diels–Alder reactions occurring in an inter- or intramolecular mode, the [2+2] cycloadditions, the 1,3-dipolar cycloadditions, the 1,4-dipolar cycloadditions, and the ene reactions. These reactions have been well reviewed by Pellissier.[50] Herein, Diels–Alder reactions are particularly selected as an introduction to our further research study.

The Diels–Alder reaction is one of the most important reactions of arynes and is used both as a means of detecting arynes and as a synthetic tool. Because of the highly electrophilic character of arynes, their reactions are observed with a very wide range of dienes including simple benzene derivatives or other benzenoid aromatic compounds. The reactions of benzyne

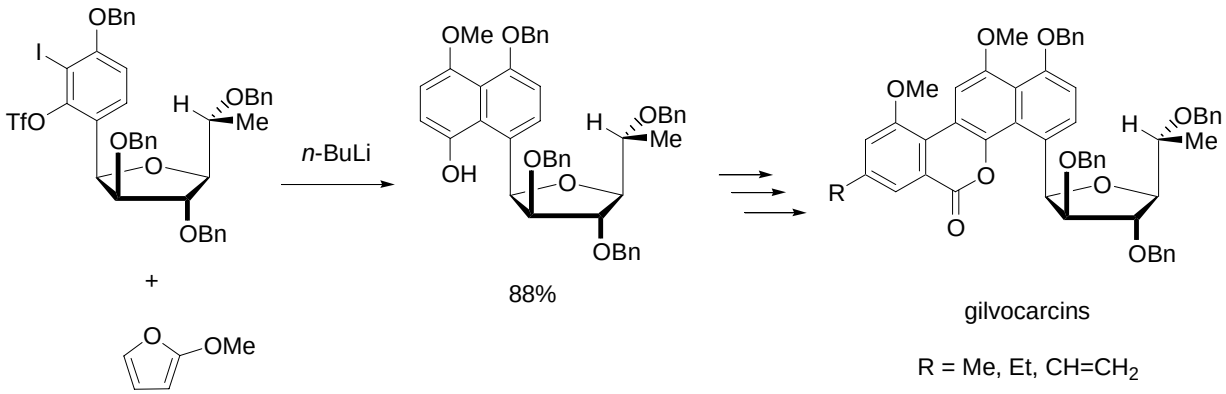
[49] T. Matsumoto, T. Hosoya, M. Katsuki, K. Suzuki, *Tetrahedron Lett.* **1991**, *32*, 6735.
[50] H. Pellissier, M. Santelli, *Tetrahedron* **2003**, *59*, 701.

with various classes of heterocyclic compounds have been reviewed.[51] Dienes of aromatic five-membered heterocycles, particularly furan and its derivatives, have been widely used to intercept arynes, and their [4+2] cycloadducts are useful intermediates in the synthesis of naphthalenes because the endoxide-bridge can be readily cleaved by acids. One recent example is the preparation of the benzamide benzyne intermediate generated from *o*-TMS-aryl triflate precursors affording the cycloadduct in good yield (Scheme 16).[13c]



Scheme 16. Diels–Alder reaction of a carbamate benzyne with furan.

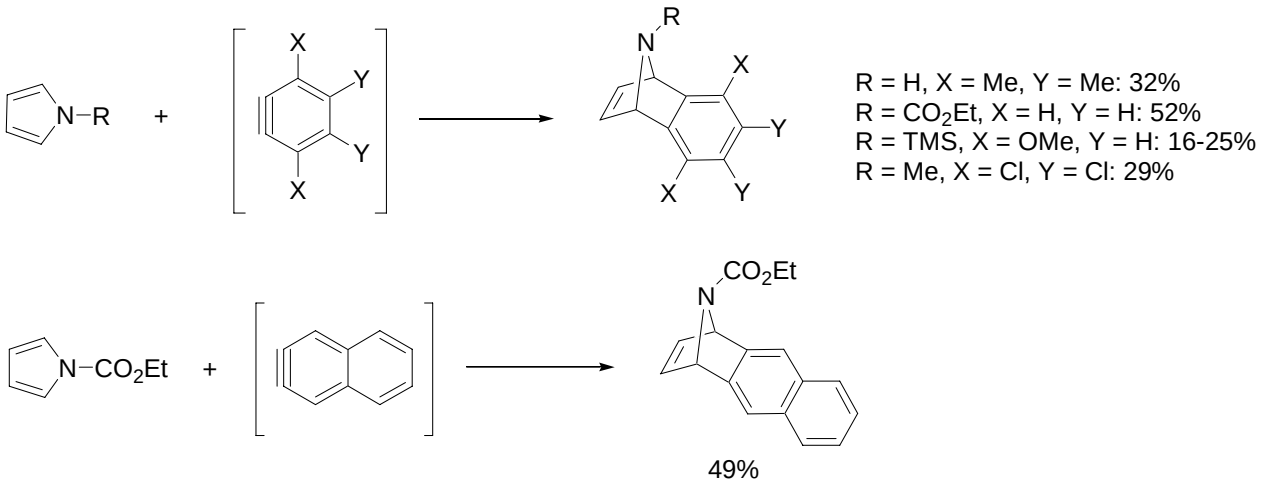
Another example using a functionalized furan as a trapping reagent is found in the total synthesis of the gilvocarcins *via* a regioselective [4+2] cycloaddition of a sugar-bearing benzyne derivative with 2-methoxyfuran (Scheme 17).[52]



Scheme 17. Synthesis of gilvocarcins *via* Diels–Alder reactions of arynes with 2-methoxyfuran.

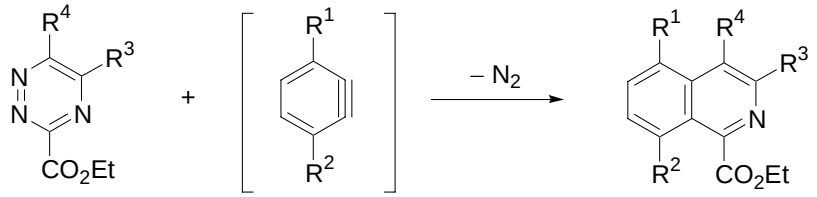
[51] M. R. Bryce, J. M. Vernon, *Advances in Heterocyclic Chemistry*, *Vol. 28*, (Eds: A. R. Katritsky, A. J. Boulton), Academic Press, New York, **1981**, p. 183-229.
[52] a) T. Matsumoto, T. Hosoya, K. Suzuki, *J. Am. Chem. Soc.* **1992**, *114*, 3568; b) T. Hosoya, E. Takashiro, T. Matsumoto, K. Suzuki, *J. Am. Chem. Soc.* **1994**, *116*, 1004.

Derivatives of pyrrole, which are less efficient trapping reagents than the derivatives of furan, can react with functionalized arynes leading to various 1,4-dihydro-1,4-iminonaphthalenes or the corresponding anthracenes (Scheme 18).[53]



Scheme 18. Diels–Alder reactions of arynes with the derivatives of pyrrole.

A route to isoquinolines bearing electron-withdrawing substituents has been developed starting from the derivatives of 1,2,4-triazine, which were used as trapping reagents for arynes (Scheme 19).[54]



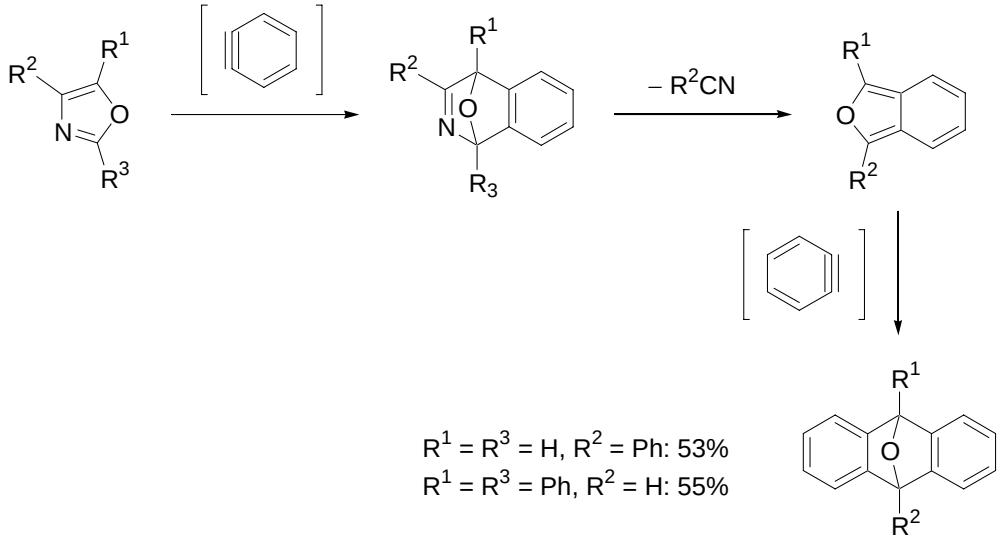
R^1 = H, R^2 = H, R^3 = Ph, R^4 = Ph: 77%
R^1 = Me, R^2 = H, R^3 = Ph, R^4 = H: 30%
R^1 = H, R^2 = Me, R^3 = Ph, R^4 = Ph: 61%

Scheme 19. Preparation of polyfunctionalized isoquinolines *via* Diels–Alder reactions of arynes with derivatives of the 1,2,4-triazine followed by the retro-Diels–Alder expulsion of nitrogen.

Polysubstituted oxazoles can be used as trapping reagents. They react with benzyne giving rise to the bis(benzyne) adducts. This transformation requires each of the following steps: (a)

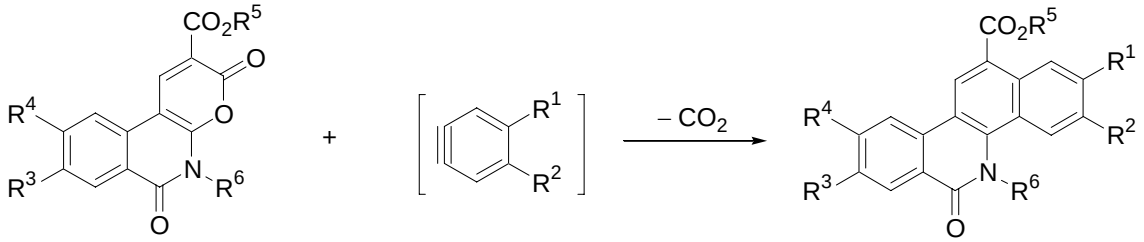
[53] J. W. Davies, M. L. Durrant, M. P. Walker, D. Belkacemi, J. R. Malpass, *Tetrahedron* **1992**, *48*, 861.
[54] A. M. A. Rocha Gonsalves, T. M. V. D. Pinho e Melo, T. L. Gilchrist, *Tetrahedron* **1992**, *48*, 6821.

a Diels–Alder reaction of benzyne with the polysubstituted oxazole; (b) the retro-Diels–Alder expulsion of a nitrile; and (c) a Diels–Alder reaction of benzyne with the isobenzofuran (Scheme 20).[55]



Scheme 20. Preparation of bis(benzyne) adducts *via* Diels–Alder reactions of benzyne with polysubstituted oxazoles followed by the retro-Diels–Alder expulsion of a nitrile and further Diels–Alder reactions with benzyne.

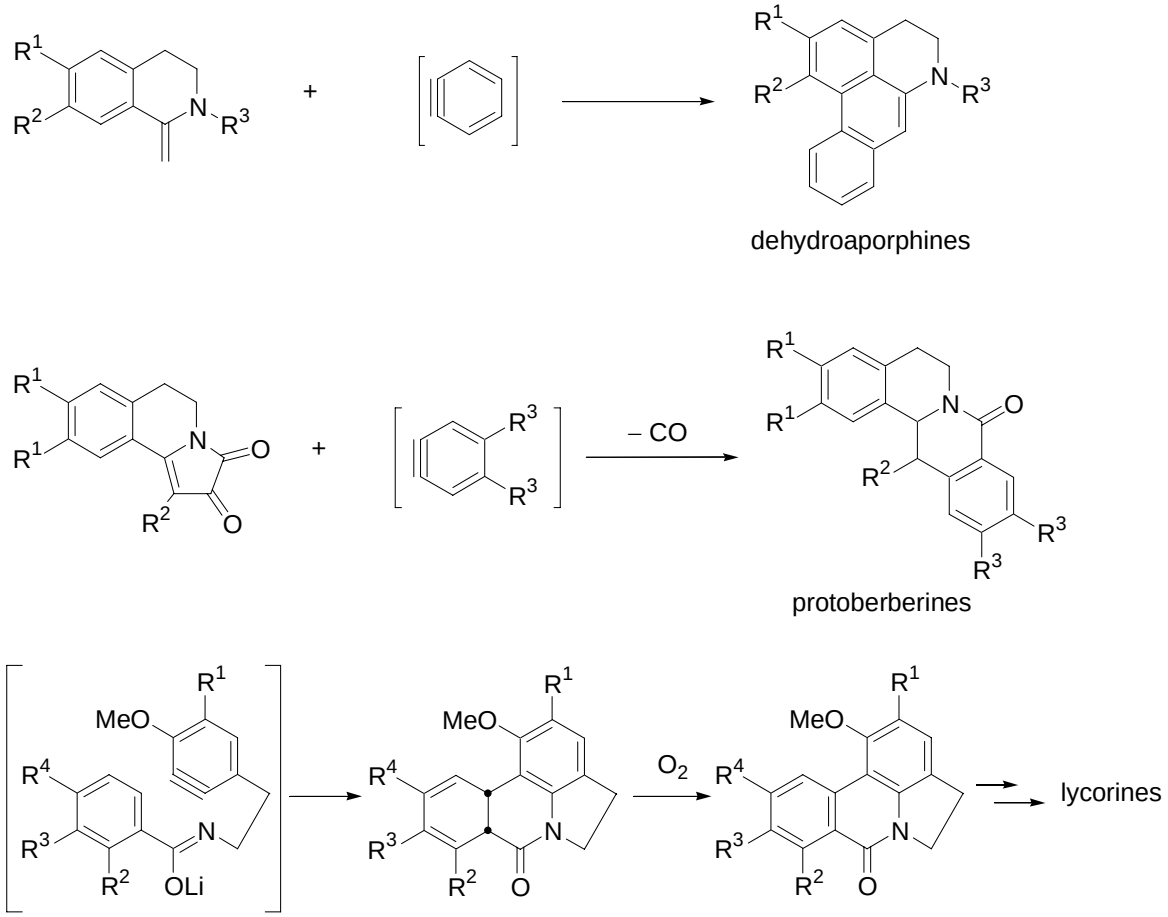
A new approach to antitumor benzophenanthridines was reported by Castedo et al. by using *α*-pyrone derivatives as trapping reagents for arynes (Scheme 21).[56]



Scheme 21. Preparation of antitumour benzophenanthridines *via* Diels–Alder reactions of arynes with *α*-pyrone derivatives followed by the retro-Diels–Alder expulsion of CO_2.

[55] S. E. Whitney, M. Winters, B. Rickborn. *J. Org. Chem.* **1990**, *55*, 929.
[56] D. Pérez, E. Guitián, L. Castedo, *J. Org. Chem.* **1992**, *57*, 5911.

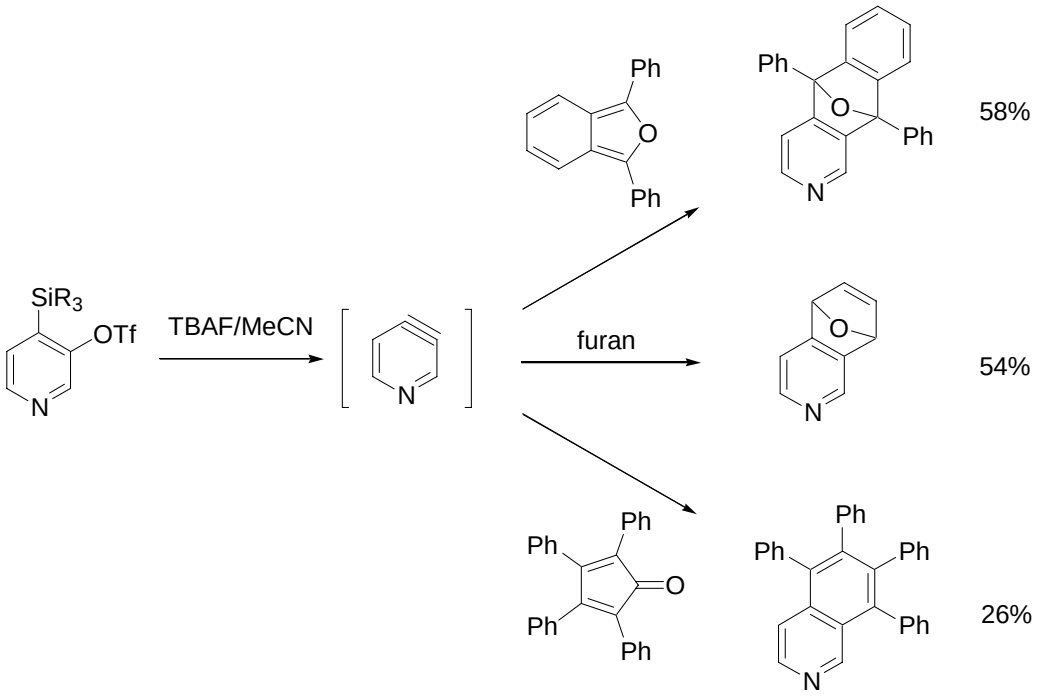
There are also some other examples of natural products synthesized *via* inter- or intramolecular aryne reactions of the Diels–Alder type including dehydroaporphines[57], protoberberines[58], and other types of alkaloids such as lycorines[59] (Scheme 22).



Scheme 22. Preparation of dehydroaporphines, protoberberines, and lycorines *via* Diels–Alder reactions of arynes with dienes.

In the field of heteroaryne[60] chemistry, 3,4-pyridyne has attracted considerable theoretical and synthetic interest. The most recent method for generating 3,4-pyridynes was to use 4-trialkylsilyl-3-pyridyl triflates as precursors. This type of precursors after treating with fluoride generated the expected pyridynes which were trapped with several dienes (Scheme 23).[61]

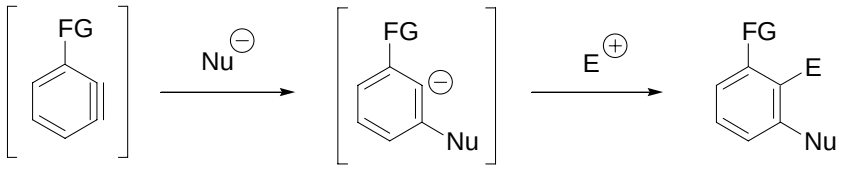
[57] N. Atanes, L. Castedo, E. Guitián, C. Saá, J. M. Saá, R. Suau, *J. Org. Chem.* **1991**, *56*, 2984.
[58] A. Cobas, E. Guitián, L. Castedo, *J. Org. Chem.* **1992**, *57*, 6765.
[59] C. González, D. Pérez, E. Guitián, L. Castedo, *J. Org. Chem.* **1995**, *60*, 6318.
[60] M. G. Reinecke, *Tetrahedron* **1982**, *38*, 427.
[61] M. Tsukazaki, V. Snieckus, *Heterocycles* **1992**, *33*, 533.



Scheme 23. Preparation of 3,4-pyridyne followed by trapping with a diene *via* the Diels–Alder reaction.

1.2.4 Nucleophilic additions to arynes

The addition of nucleophiles to arynes is highly regioselective when the position adjacent to the triple bond bears a functional group (FG) capable of stabilizing the negative charge acquired (Scheme 24).

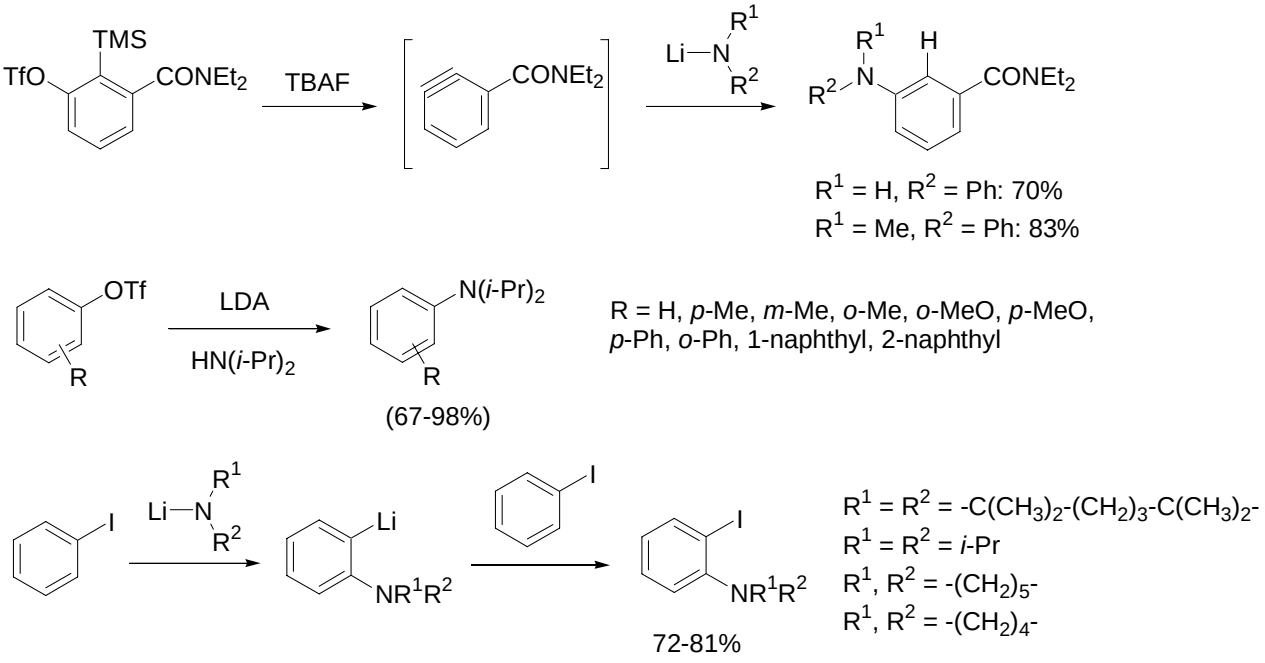


Scheme 24. The addition reactions of nucleophiles to arynes.

1.2.4.1 The addition of nitrogen nucleophiles

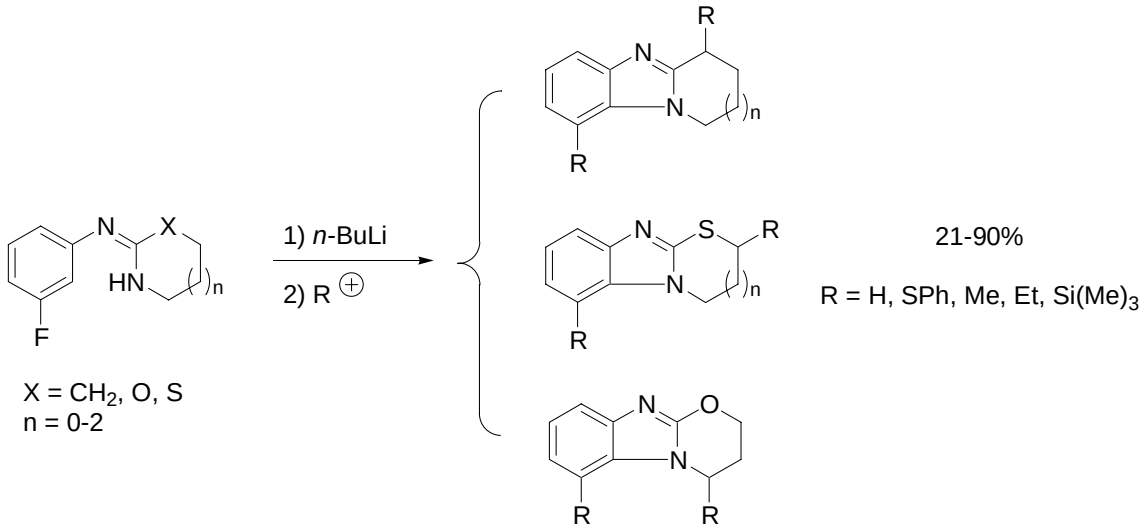
The reaction of arynes with primary and secondary amines provides a convenient route to alkylated anilines.[34,41a] Various precursors of arynes such as TMS-phenols,[13c] aryl triflates[62] or iodobenzenes have been involved in this kind of reaction (Scheme 25).[63]

[62] a) P. P. Wickham, K. H. Hazen, H. Guo, G. Jones, K. H. Reuter, W. J. Scott, *J. Org. Chem.* **1991**, *56*, 2045; b) K. H. Reuter, W. J. Scott, *J. Org. Chem.* **1993**, *58*, 4722.



Scheme 25. The addition reaction of lithium amides to arynes.

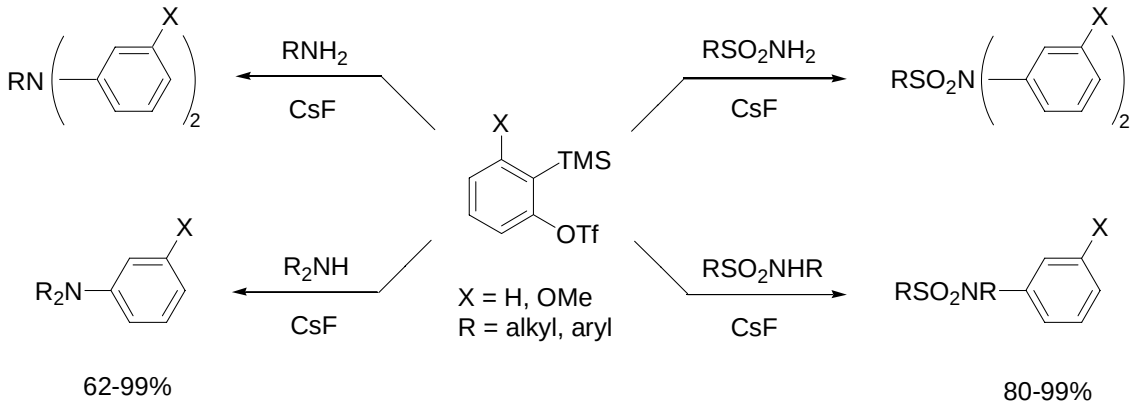
Interestingly, an intramolecular trapping of arynes generated from amidines could be applied on the preparation of 1,2-annulated benzimidazoles. Some electrophiles can trap the newly formed carbanions from the addition of nitrogen nucleophiles to arynes (Scheme 26).[64]



Scheme 26. Preparation of 1,2-annulated benzimidazoles *via* the intramolecular addition of nitrogen nucleophiles to arynes followed by quenching with electrophiles.

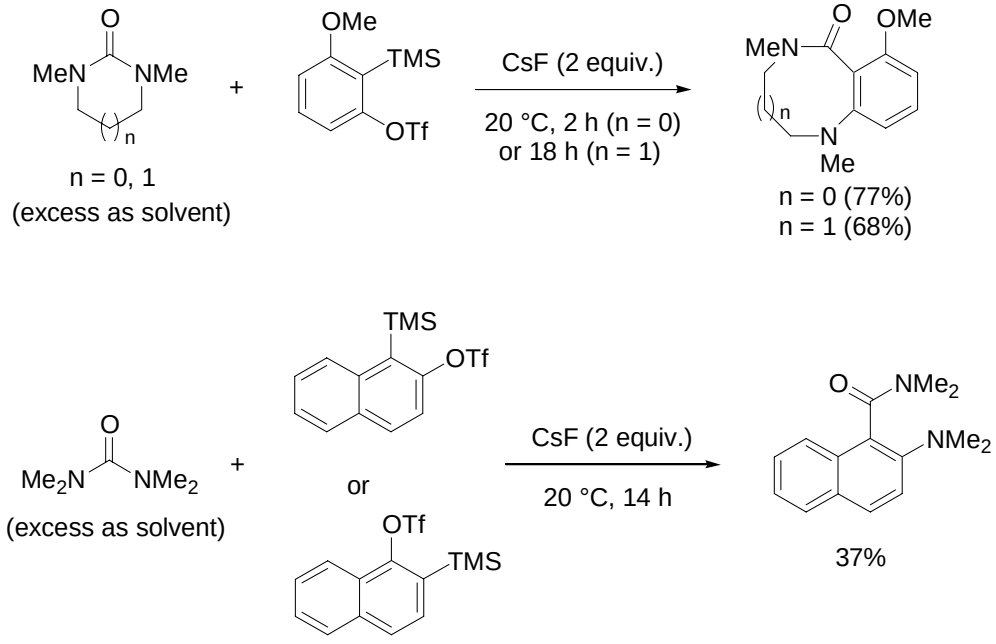
[63] S. Tripathy, R. LeBlanc, T. Durst, *Org. Lett.* **1999**, *1*, 1973.
[64] J. M. Caroon, L. E. Fisher, *Heterocycles* **1991**, *32*, 459.

In 2003, Larock reported a facile *N*-arylation procedure for amines and sulfonamides by using aryl triflates as aryne precursors. It affords the corresponding arylated products in good to excellent yields and high regioselectivity under very mild reaction conditions (Scheme 27).[65]



Scheme 27. The addition of amines or sulfonamides to arynes.

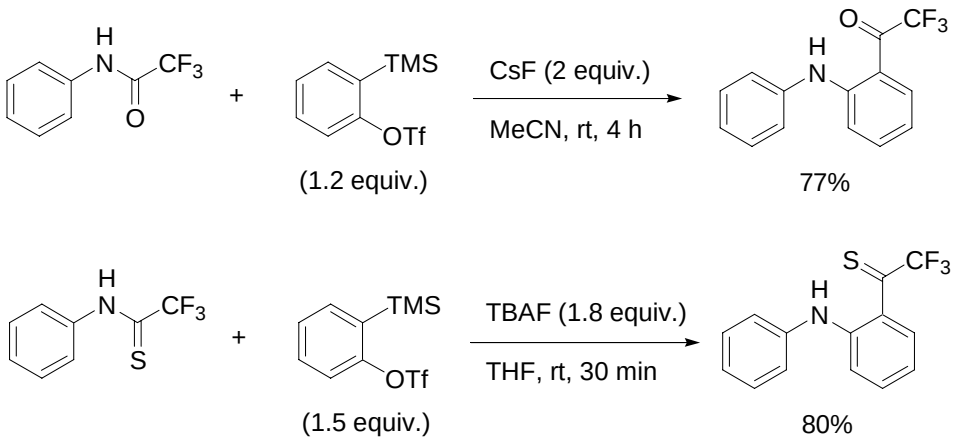
Even the N-CO bond of urea derivatives can add to arynes to give 1-amino-2-(aminocarbonyl)arenes in good yield (Scheme 28).[66]



Scheme 28. The addition of urea derivatives to arynes.

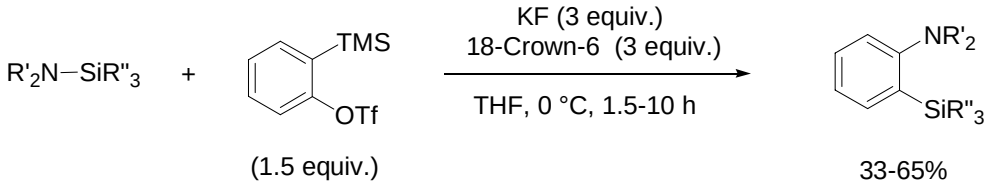
In 2005, Larock reported an efficient intermolecular C-N addition of amides or S-N addition of sulfinamides to arynes (Scheme 29).[67]

[65] Z. Liu, R. C. Larock, *Org. Lett.* **2003**, *5*, 4673.
[66] H. Yoshida, E. Shirakawa, Y. Honda, T. Hiyama, *Angew. Chem.* **2002**, *114*, 3381; *Angew. Chem., Int. Ed.* **2002**, *41*, 3247.



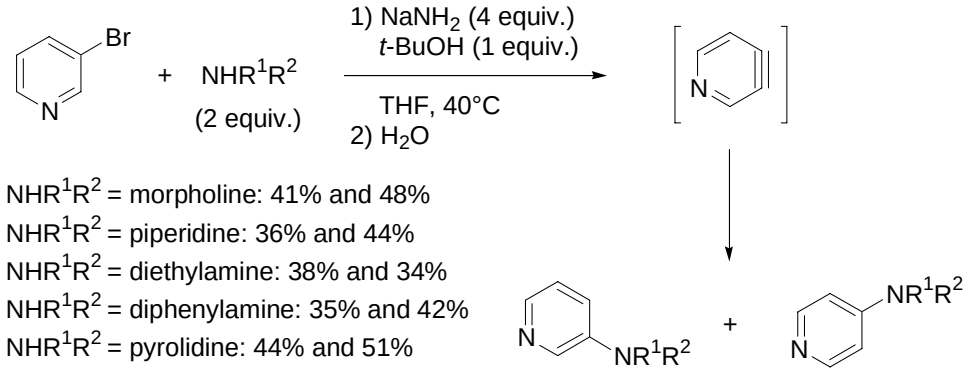
Scheme 29. The addition of a C-N or S-N bond to benzyne.

An addition of a N-Si bond to benzyne could also be achieved. 2-Silylaniline derivatives were obtained by means of this method in average yields (Scheme 30).[68]



Scheme 30. The addition of a Si-N bond to benzyne.

The nucleophilic condensation of 3,4-pyridyne could also be carried out, which led to a mixture of two products in good yields (Scheme 31).[69]

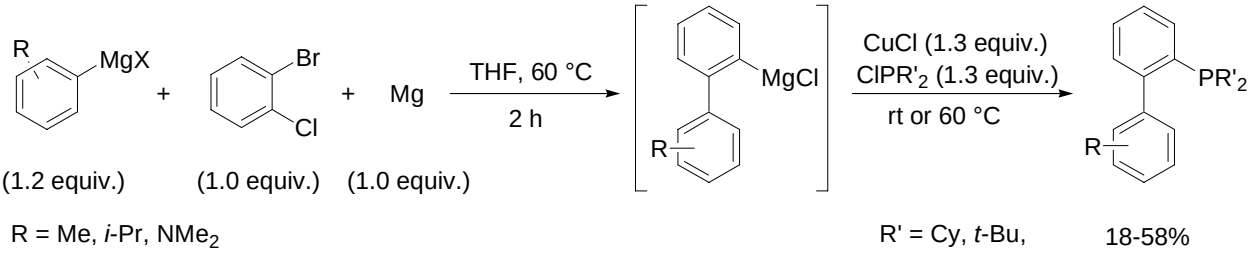


Scheme 31. The addition of an amine to 3,4-pyridyne.

[67] Z. Liu, R. C. Larock, *J. Am. Chem. Soc.* **2005**, *127*, 13112.
[68] H. Yoshida, T. Minabe, J. Ohshita, A. Kunai, *Chem. Commun.* **2005**, 3454.
[69] B. Jamart-Gregoire, C. Leger, P. Caubere, *Tetrahedron Lett.* **1990**, *31*, 7599.

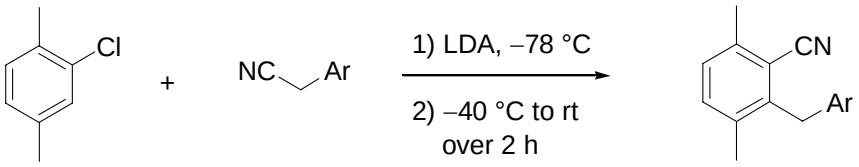
1.2.4.2 The addition of carbon nucleophiles

One of the most popular methods for the generation of carbon-carbon bond to produce biphenyls is *via* the addition of arylmagnesium halide or aryllithium to benzyne. For example, Buchwald reported an easy way to produce functionalized biphenyl-based phosphine ligands in *one-pot* procedure *via* the addition of arylmagnesium halide to benzyne followed by quenching with a chlorodialkylphosphine (Scheme 32).[70]



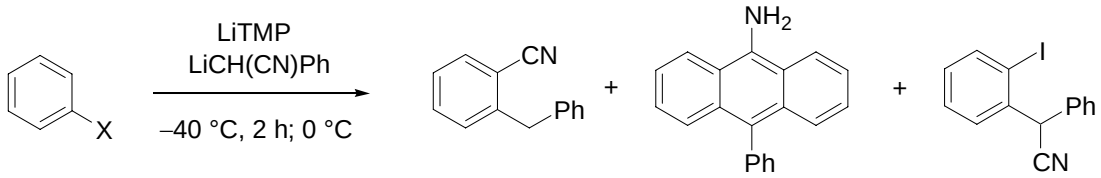
Scheme 32. Synthesis of electron-rich phosphine ligands with biphenyl backbones *via* the addition of arylmagnesium halide to benzyne followed by quenching with a chlorodialkylphosphine.

Lithioacetonitrile derivatives can also be used as carbon nucleophiles to add to arynes. [71] A *o*-benzylated aryl nitrile can be obtained from the unusual pathway when a 3-methyl- or a 3-methoxyaryne, generated from an appropriate haloanisole possessing at least one electron-releasing group, was used in combination with a 2-aryl-2-lithioacetonitrile.[71a] Interestingly, (2-iodo-phenyl)-phenyl-acetonitrile was isolated as the major product if the reaction of benzyne with 2-lithio-2-phenylacetonitrile was carried out in the presence of iodobenzene (Scheme 33).[71b]



Ar = Ph: 40%
Ar = 1-naphthyl: 51%
Ar = 3-FC_6H_4: 80%
Ar = 4-FC_6H_4: 78%
Ar = 3-$MeOC_6H_4$: 70%
Ar = 3,4-$(MeO)_2C_6H_3$: 48%
Ar = 3,4,5-$(MeO)_3C_6H_2$: 66%

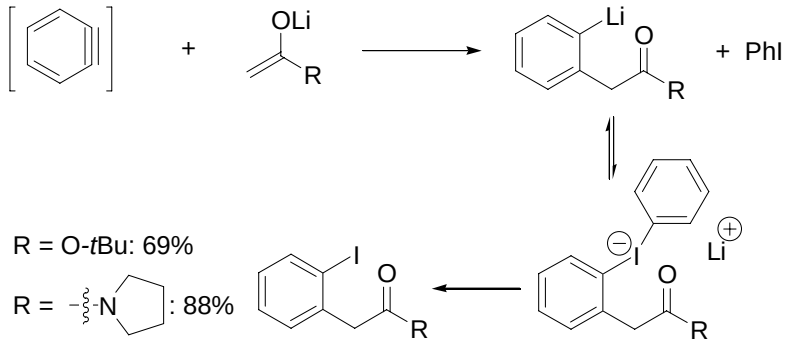
[70] H. Tomori, J. M. Fox, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 5334.
[71] a) J. H. Waggenspack, L. Tran, S. Taylor, L. K. Yeung, M. Morgan, A. R. Deshmukh, S. P. Khanapure, E. R. Biehl, *Synthesis* **1992**, 765; b) S. Tripathy, H. Hussain, T. Durst, *Tetrahedron Lett.* **2000**, *41*, 8401.



X = Br	35%	12%	0%
X = I	35%	15%	7%
X = I and 2,6-dimethoxyiodobenzene	8%	7%	37%

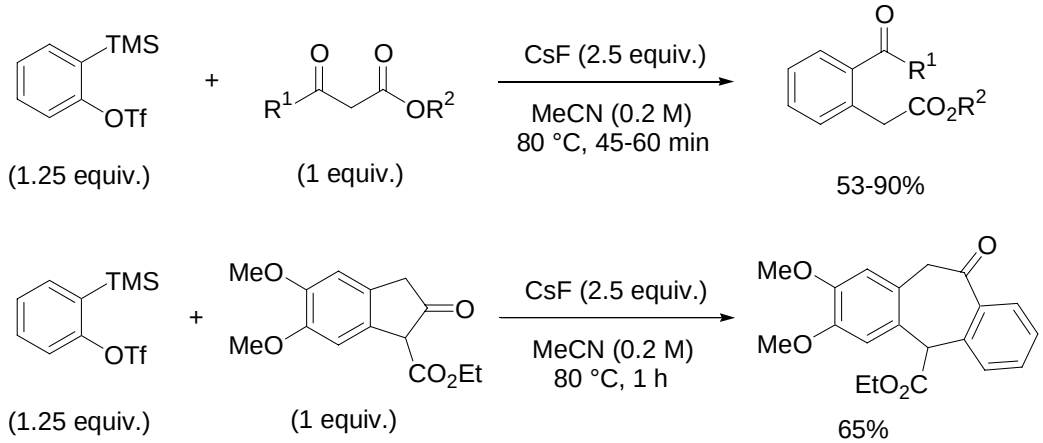
Scheme 33. Unexpected reaction between an aryne and an 2-aryl-2-lithioacetonitrile.

An ester or amide lithium enolate successfully added to benzyne as well. In the presence of excess iodobenzene, the intermediates, 2-lithioaromatics, underwent iodine transfer from iodobenzene furnishing 2-iodo derivatives in good yields (Scheme 34).[63]



Scheme 34. Reactivity of benzyne with an enolate in the presence of iodobenzene.

An efficient and mild acyl-alkylation of arynes has been developed recently. It was used to synthesize medium-sized carbocycles by the ring-expansion of cyclic *ß*-ketoesters (Scheme 35).[72]



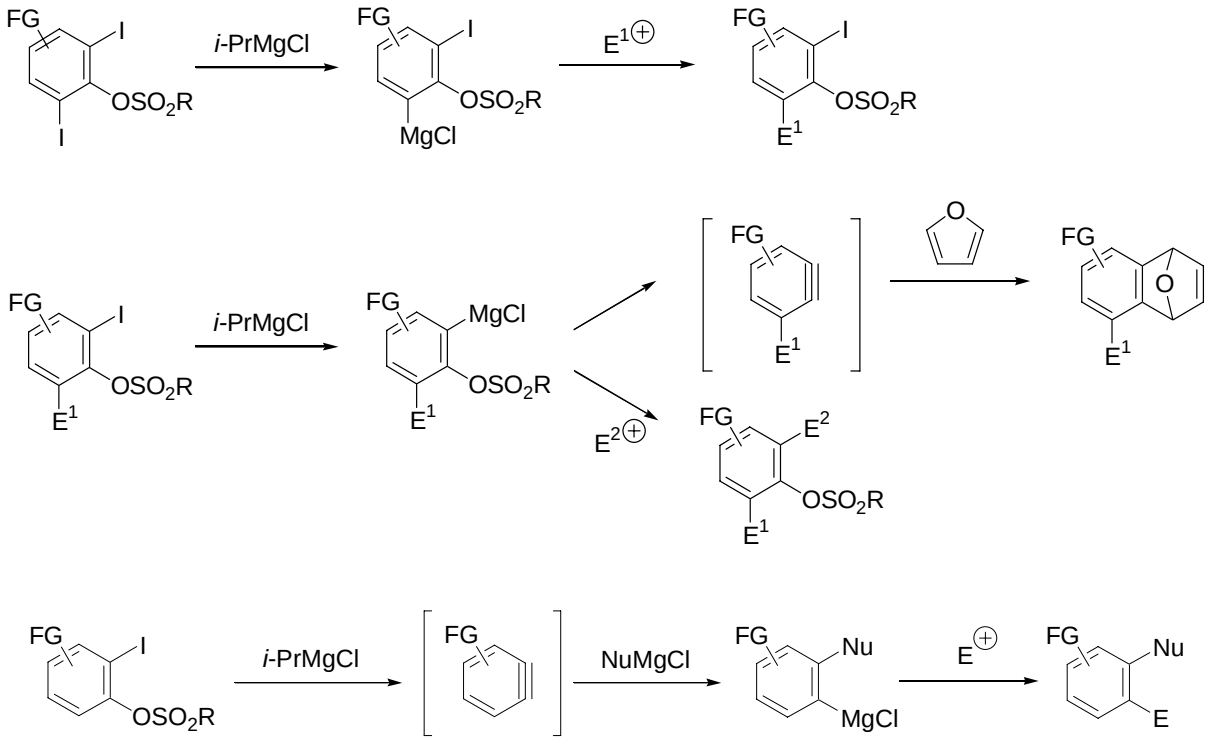
Scheme 35. An acyl-alkylation of benzyne.

[72] U. K. Tambar, B. M. Stoltz, *J. Am. Chem. Soc.* **2005**, *127*, 5340.

2. Objectives

Because of the successful development of a mild and selective I/Mg- or Br/Mg-exchange reaction, it was interesting to apply this methodology to aryne or heteroaryne chemistry (Scheme 36). The objectives were:

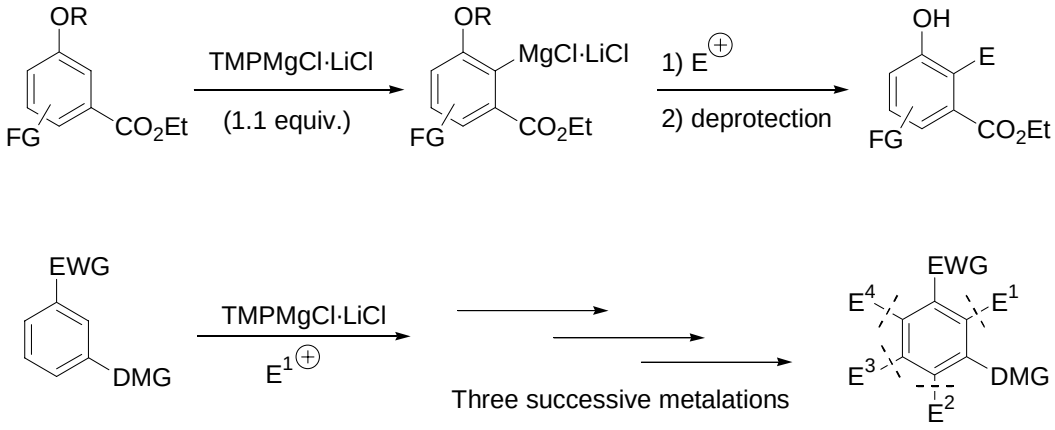
- an easy access to polyfunctionalized arynes and their precursors bearing sensitive groups.
- application of aryne chemistry to the Diels–Alder reaction with furan.
- application of aryne chemistry to the addition reaction of different nucleophiles followed by quenching with electrophiles.



Scheme 36. Generation and trapping of functionalized arynes.

The second project involved the application of the direct and selective metalation reaction of arenes by using TMPMgCl·LiCl as a base with the help of a directing group (Scheme 37). The objectives in this area were:

- an easy access to polyfunctionalized Grignard reagents *via* direct magnesiation followed by quenching with electrophiles and further deprotection leading to polyfunctionalized phenols.
- preparation of *hexa*-substituted benzenes *via* successive magnesiations with TMPMgCl·LiCl and quenching with electrophiles.



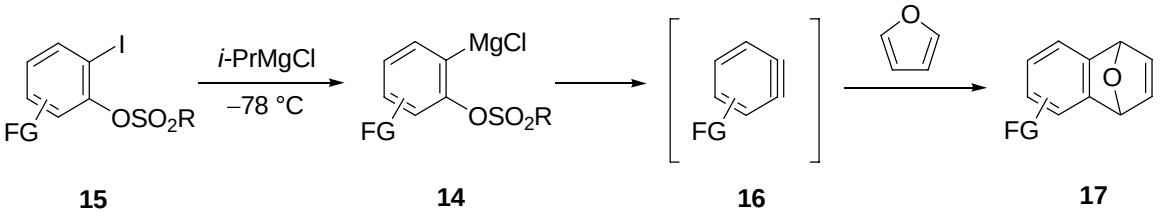
Scheme 37. Preparation of polyfunctionalized benzenes *via* direct magnesiation.

3. Preparation of Polyfunctionalized Arynes and Heteroarynes *via* 2-Magnesiated Diaryl Sulfonates

3.1 Introduction

Arynes are highly reactive intermediates which have found numerous applications in organic synthesis. Due to the strained nature of the ring (ca. 63 kcal/mol),[73] arynes react with a broad range of reagents (nucleophiles in addition reactions, alkenes in cyclo-additions or ene-reactions) having therefore a high synthetic potential. Whereas a number of methods for the generation of benzyne itself are known, the preparation of functionalized arynes is often incompatible with the harsh basic conditions necessary for their generation.

Recently, we have developed a new method allowing the generation of polyfunctional arylmagnesium compounds using an iodine-magnesium-exchange.[74] We envisioned the preparation of a range of 2-magnesiated aryl sulfonates of type **14** starting from the corresponding 2-iodo derivates of type **15**. After the elimination of RSO_3MgCl, arynes of type **16** would be formed and trapped with furan, furnishing the cycloadducts of type **17** (Scheme 38).



15 **14** **16** **17**

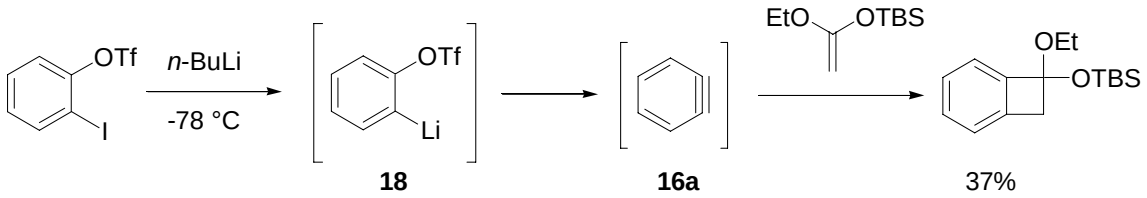
Scheme 38. Generation and trapping of functionalized arynes **16**.

3.2 Preparation of polyfunctionalized arynes

3.2.1 The preliminary study for the formation of arynes using a TsO-group as the leaving group

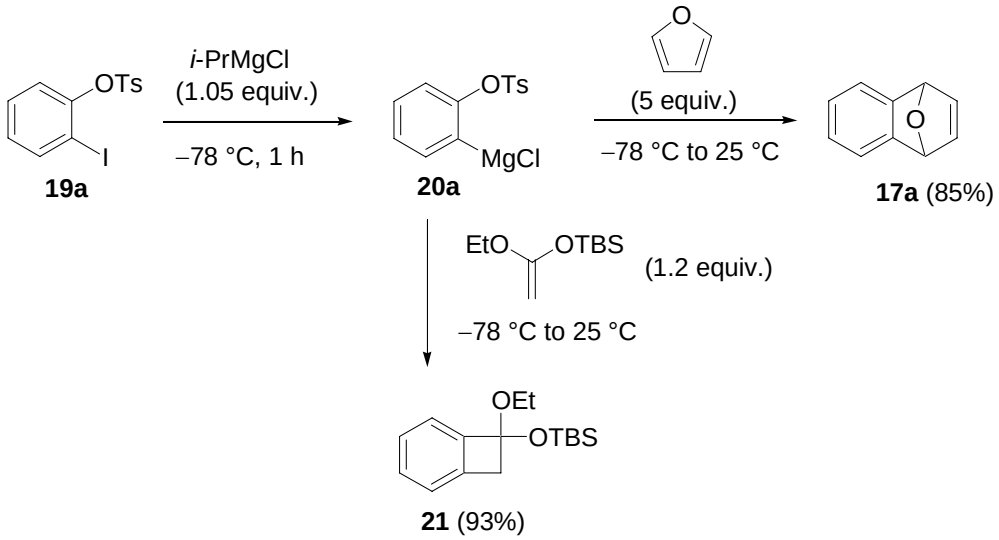
[73] C. Wentrup, *Reactive Molecules*, Wiley, New York, **1984**, 288.
[74] a) A. Staubitz, W. Dohle, P. Knochel, *Synthesis* **2003**, 233; b) A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu, P. Knochel, *Synthesis* **2002**, 565; c) N. Gommermann, C. Koradin, P. Knochel *Synthesis* **2002**, 2143; d) I. Sapountzis, P. Knochel, *Angew. Chem.* **2004**, *116*, 915; *Angew. Chem. Int. Ed.* **2004**, *43*, 897; e) please also see: references 25, 26, and 28.

K. Suzuki and co-workers reported the formation of benzyne, when treating 2-iodophenyltriflate with *n*-BuLi in THF. Benzyne intermediate **16a** was able to be trapped by several silyl enol ethers in a [2+2] cycloaddition reaction (Scheme 39).[75]



Scheme 39. Generation of **16a** through the I/Li-exchange.

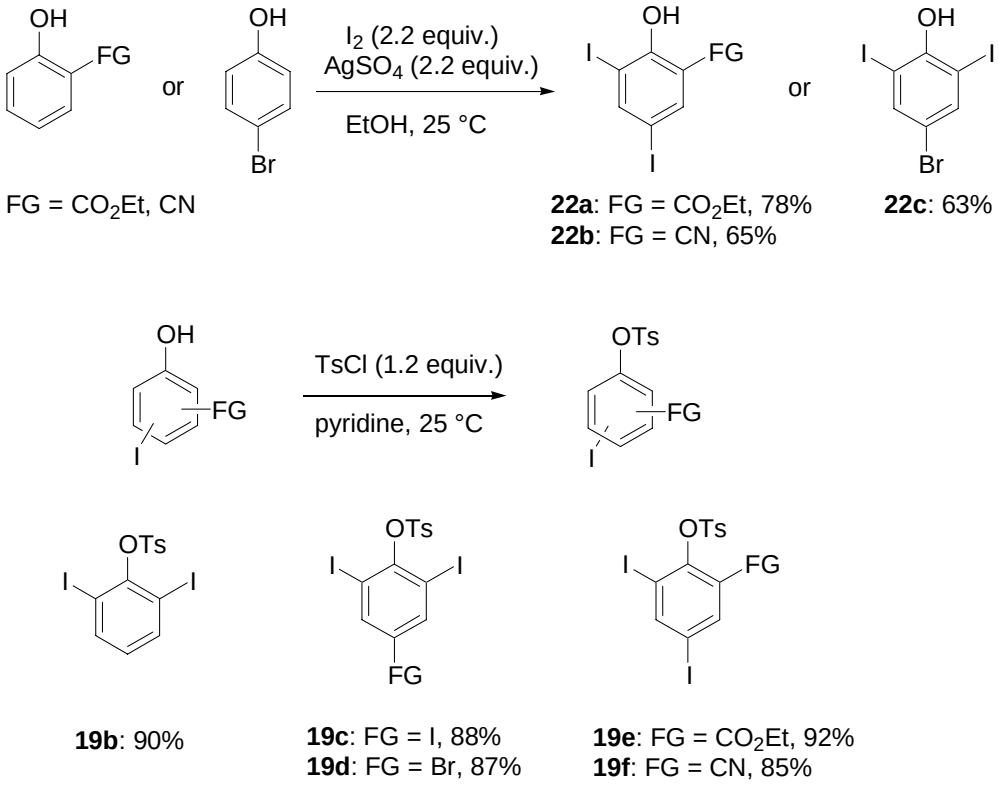
One of the disadvantages of the above mentioned method was the low tolerance of sensitive functional groups of aromatic rings. The second was that the elimination of OTf from **18** was very fast even at −78 °C that the trapping reagents such as silyl enol ethers ought to be in the reaction media before the I/Li-exchange took place. Therefore, a tosyl group, which should be less prone to undergo elimination at low temperature, was used as the leaving group. The exchange reaction of toluene-4-sulfonic acid 2-iodo-phenyl ester (**19a**) with *i*-PrMgCl was considerably slower and required 1 h at −78 °C to reach full conversion to **20a**, which was determined by GC-analysis of reaction aliquots. After the addition of furan or *tert*-butyl-(1-ethoxy-vinyloxy)-dimethyl-silane followed by warming to 25 °C, benzyne (**16a**) was formed and led to products **17a** or **21** in 85 % or 93 % yield, respectively (Scheme 40).



[75] T. Matsumoto, T. Sohma, H. Yamaguchi, S. Kurata, K. Suzuki, *Synlett* **1995**, 263. Please also see: a) T. Hamura, Y. Ibusuki, K. Sato, T. Matsumoto, Y. Osamura, K. Suzuki, *Org. Lett.* **2003**, *5*, 3551; b) T. Hosoya, T. Hamura, Y. Kuriyama, M. Miyamoto, T. Matsumoto, K. Suzuki, *Synlett* **2000**, 520; c) T. Hamura, T. Hosoya, H. Yamaguchi, Y. Kuriyama, M. Tanabe, M. Miyamoto, Y. Yasui, T. Matsumoto, K. Suzuki, *Helv. Chim. Acta* **2002**, *85*, 3589.

Scheme 40. Syntheses of compounds **17a** and **21**.

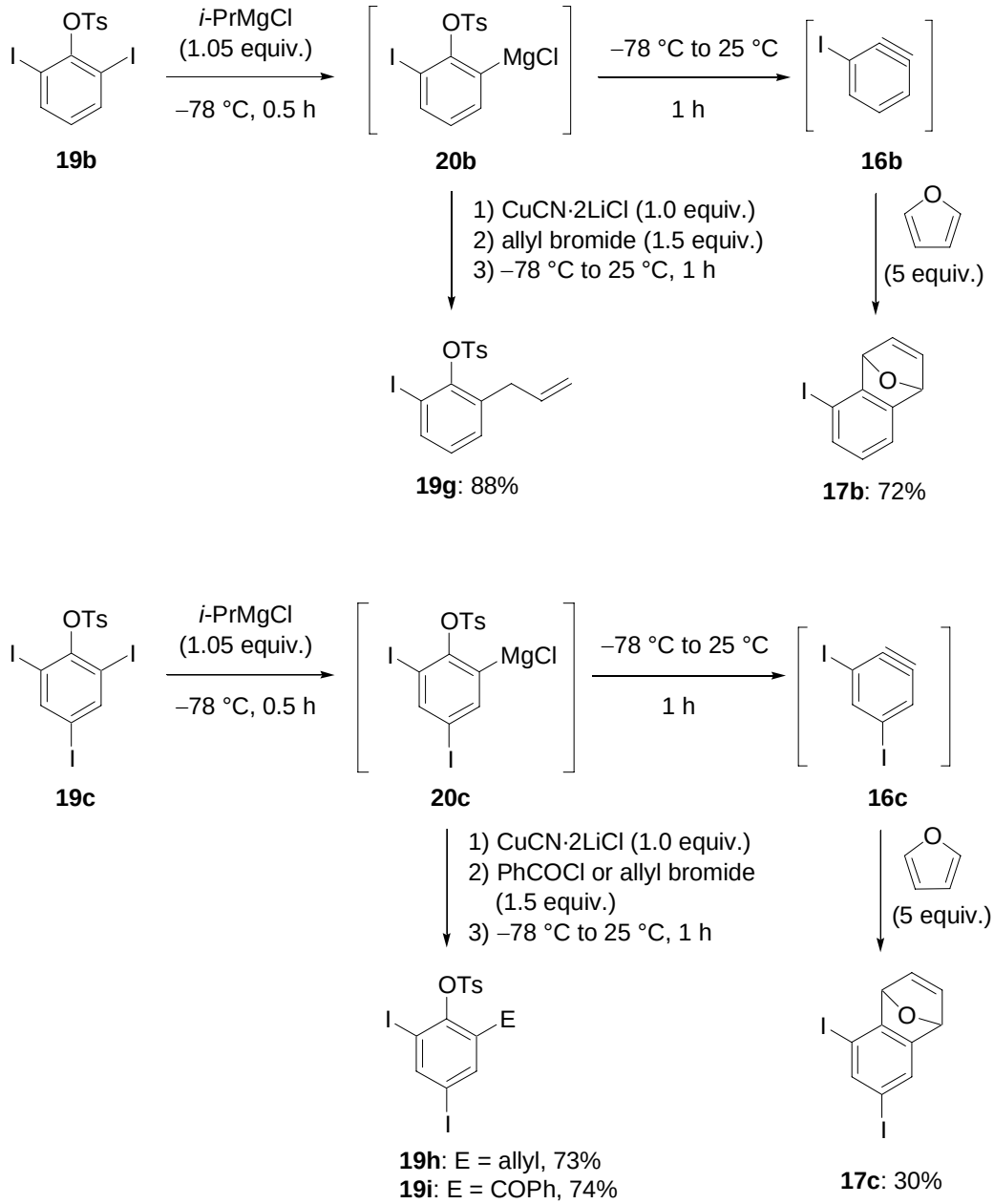
With these results in hand, the functional group tolerance of this transformation was studied. Several functionalized 2-iodophenols, **22a-c**, were synthesized according to the reported procedure.[76] The tosyl sulfonates **19b-f** were prepared from the corresponding phenols (Scheme 41).



Scheme 41. Syntheses of aromatic diiodides **19b-e**.

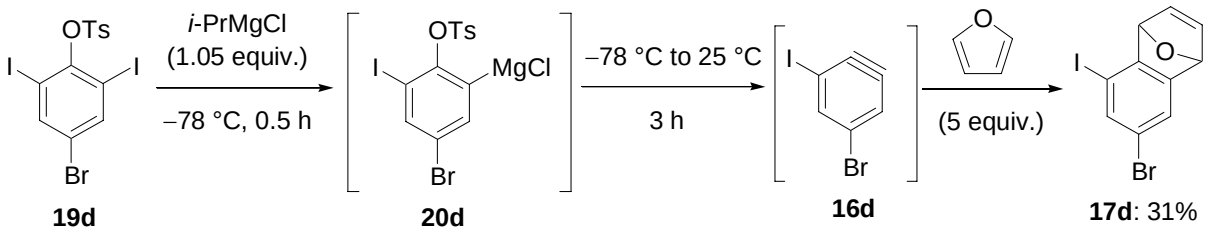
The observed results showed that iodine-magnesium-exchange on **19b-f** was fast (0.5 h at −78 °C) due to the electron-withdrawing properties and the strong chelating effect of the OTs group (Scheme 41-45). Furthermore, the resulting Grignard reagents **20b** and **20c** were stable at −78 °C for long time. Thus **20b-c** were further reacted with allyl bromide or benzoyl chloride in the presence of CuCN·2LiCl[77] (1.0 equiv.), leading to the corresponding compounds **19g-i** in 73-88 % yields. On the other hand, in the presence of furan, the Grignard reagent **20b** or **20c** furnished the Diels–Alder cycloadduct **17b** or **17c** in 30 % or 72 % yield, respectively, when the reaction was carried out by warming to room temperature. It indicated the formation of the functionalized arynes **16b-c** (Schemes 42).

[76] W.-W. Sy, *Synth. Comm.* **1992**, *22*, 3215.
[77] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.



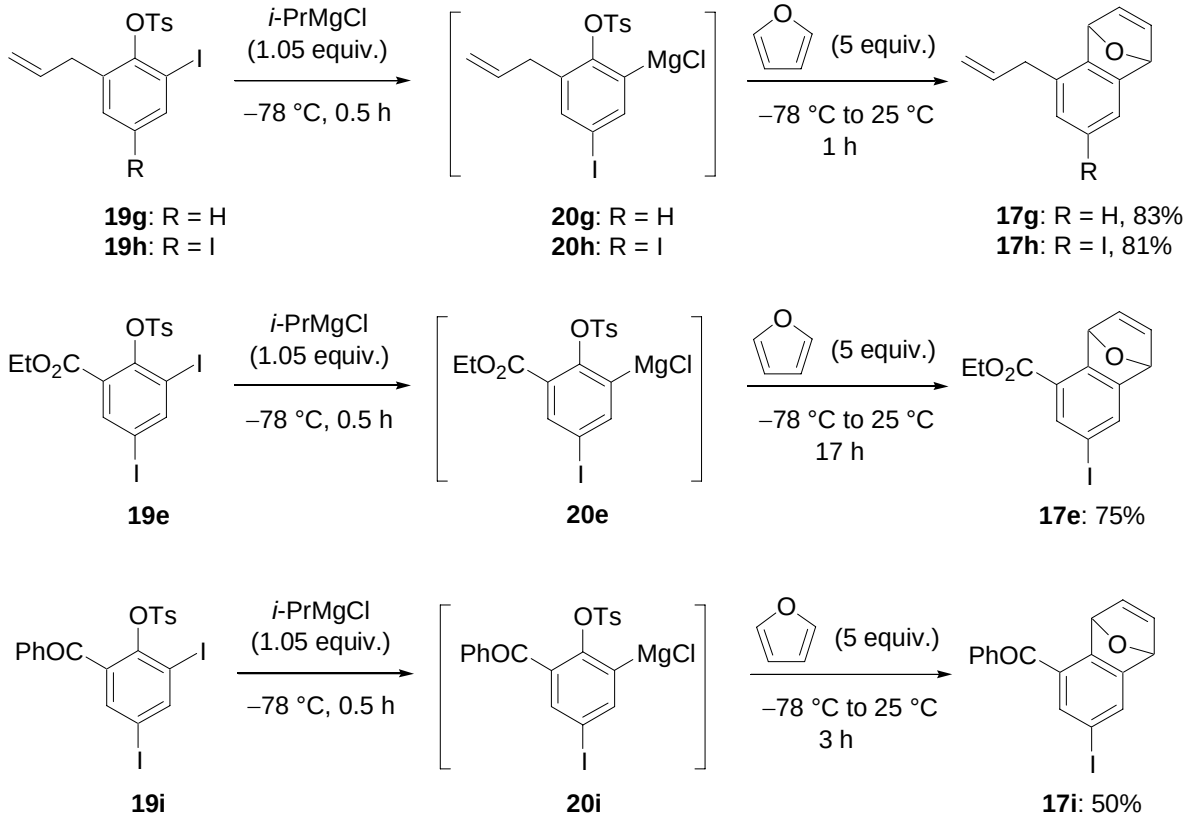
Scheme 42. Syntheses of compounds **17b-c** and **19g-i**.

The results showed above also indicated that the aryne bearing two iodines was trapped by furan less efficiently compared to the one bearing only one iodine. The aryne bearing two halogens (Br and I), **16d**, was also examined when it was trapped with furan. A similar result was observed (31 % yield of **17d**) showing that having more than one halogen as substituents complicated the reaction (Scheme 43).



Scheme 43. Syntheses of compound **17d**.

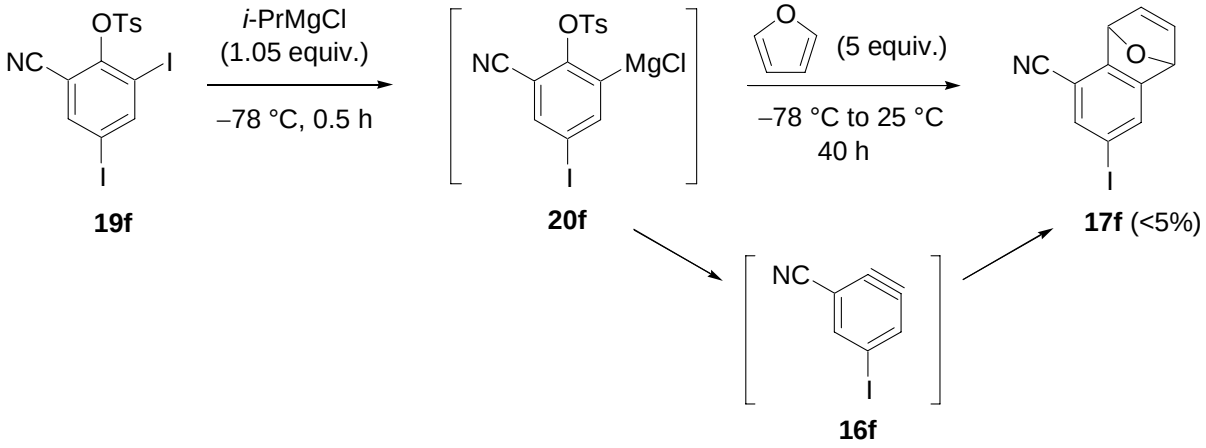
Other functionalities on the aromatic ring were also examined. An allyl, ester, and even ketone functional groups can be tolerated in the formation of functionalized arynes **17e** and **17g-i** in 50-83 % yields (Scheme 44). As we observed, an electron-withdrawing group on the aromatic ring, such as an ester group, can stabilize the Grignard reagent **20e** which after a very slow elimination of the tosylate group afforded the polyfucntionalized aryne **16e** (17 h, 25 °C) (Scheme 44).



Scheme 44. Syntheses of compounds **17e** and **17g-i**.

In the presence of a cyano group as a substituent, the Grignard reagent **20f** was stabilized by its strong electron-withdrawing effect. It was consumed after 40 h at 25 °C giving only trace

amounts of the Diels–Alder cycloaddition product **17f** as observed by GC and GC-MS analysis upon the reaction with furan (Scheme 45).



Scheme 45. Formation of an aryne bearing a nitrile function in the *ortho*-position (**16f**).

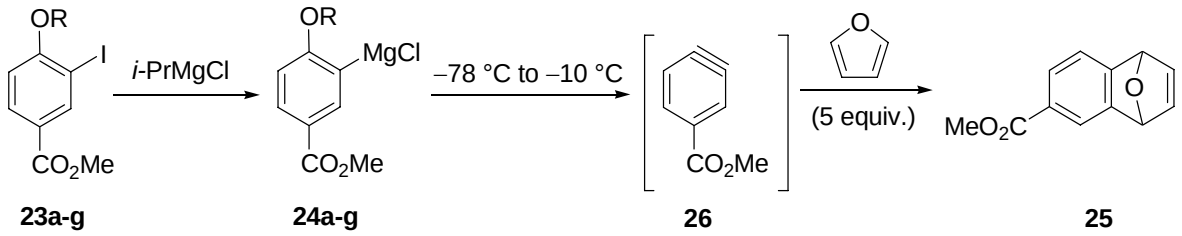
3.2.2 Optimization of the reaction conditions

Based on the preliminary study, a better leaving group, showing also good stability as the substrates of type **20** at low temperature but with a higher tendency to eliminate at higher temperature, was desired. We found that the leaving group ability of a sulfonate group (OSO_2R) was essential for the fine-tuning of the reaction conditions and thus optimizing the yields. The sulfonate moiety exerts a strong inductive effect so that the I/Mg-exchange was complete at −78 °C within 15 min. After the addition of furan (5 equiv.), the reaction mixture was allowed to warm up to −10 °C. Thus, we have prepared various sulfonates (**23a-g**) derived from methyl 4-hydroxy-3-iodobenzoate, generated the corresponding Grignard reagent (**24a-g**), added furan and have isolated the product **25** in variable yields. We have noticed that the decomposition of **24a** (R = SO_2CF_3) was too fast and led to aryne formation immediately at −78 °C hampering any reaction control. No product **25** was isolated in this case (Table 1, entry 1).[78] On the other hand, the corresponding mesylate **24b** required a reaction time of ca. 30 h for achieving a full conversion at 20 °C and gave the expected product **25** in 72 %, showing that a mesylate was a moderate leaving group. We have systematically varied the electron-withdrawing ability of the leaving group OSO_2R. Whereas the tosylate **24d** afforded the product **25** in 90 % yield, it still required a reaction time of 30 h. The 2,5-dichlorobenzene sulfonate **24e** and the 3,5-ditrifluoromethylbenzene sulfonate **24f**

[78] Unfortunately the magnesium derivative of methyl 4-pivaloxy-3-iodobenzoate proves also not to be stable and readily decomposes at −78 °C; please see: I. Sapountzis, Ph.D. Thesis, LMU, Munich **2004**.

gave fast aryne formation, but allowed to isolate **25** in only 87 % and 78 % yields, respectively (entries 5 and 6). The best result was obtained with the 4-chlorobenzene sulfonate **24g** in the presence of furan at −10 °C for 4 h leading to **25** in 93 % isolated yield.[79]

Table 1. Optimization of the nature of the leaving group for the generation of the aryne **26**.[78,79]



23a-g **24a-g** **26** **25**

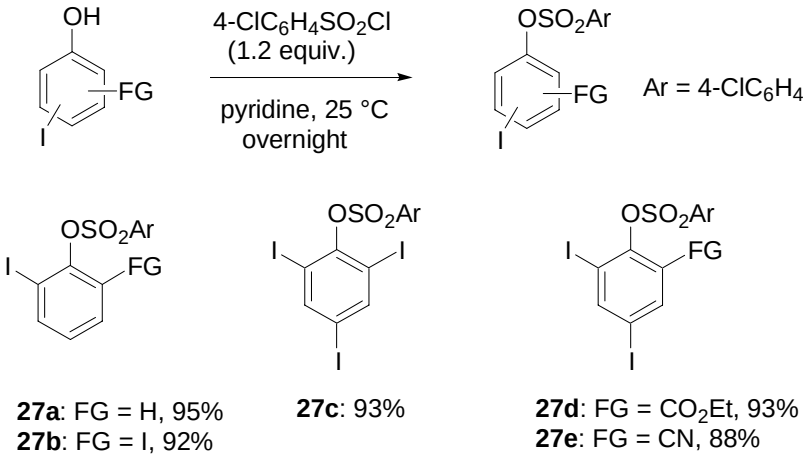
Entry	Sulfonate (R)	Reaction time (h)	Product **25** (%)[a]
1	CF_3SO_2 **24a**	-	0
2	CH_3SO_2 **24b**	30[b]	72
3	$CF_3CH_2SO_2$ **24c**	-	0
4	4-$MeC_6H_4SO_2$ **24d**	30[b]	90
5	2,5-$Cl_2C_6H_3SO_2$ **24e**	1	87
6	3,5-$(CF_3)_2C_6H_3SO_2$ **24f**	1	78
7	4-$ClC_6H_4SO_2$ **24g**	4	93

[a] Isolated yield of analytically pure compounds. [b] The reaction mixture was warmed to 25 °C.

3.2.3 Preparation of arene derivatives as the starting materials *via* iodination and protection

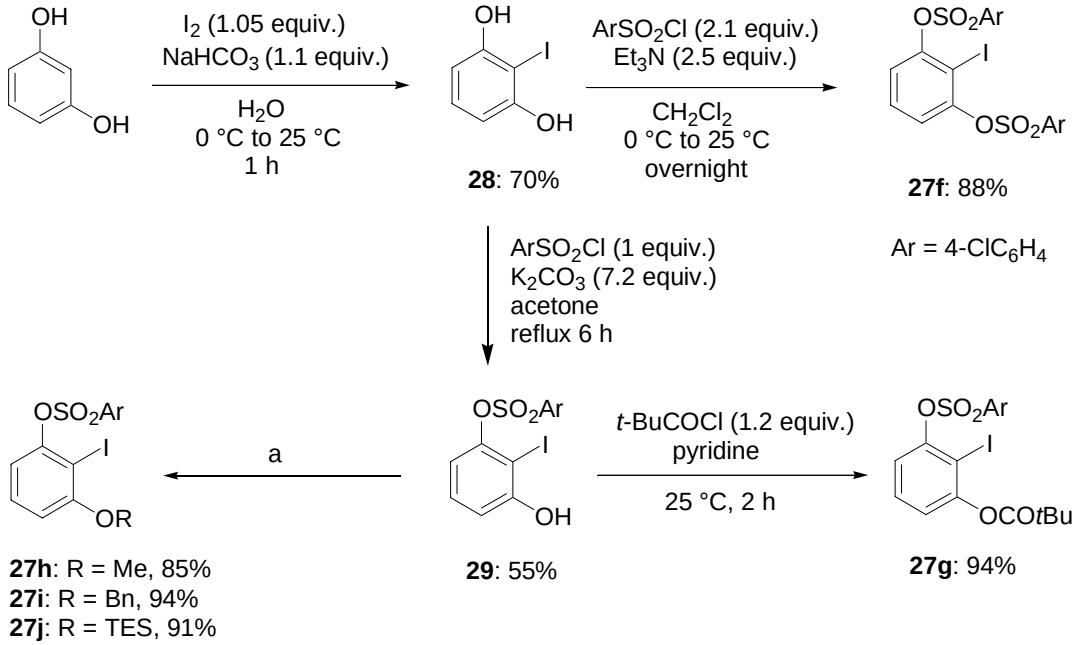
With these results in hand, having established the best leaving group for our purpose, the functional group tolerance of the transformation was studied. The starting materials **27a-e** were synthesized in excellent yields from the reaction of the corresponding phenols with 4-chloro-benzenesulfonyl chloride in pyridine at 25 °C overnight (Scheme 46).

[79] I. Sapountzis, W. Lin, M. Fischer, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 4364; *Angew. Chem.* **2004**, *116*, 4464; please also see: I. Sapountzis, Ph.D. Thesis, LMU, Munich **2004**.



Scheme 46. Syntheses of compounds **27a-e**.

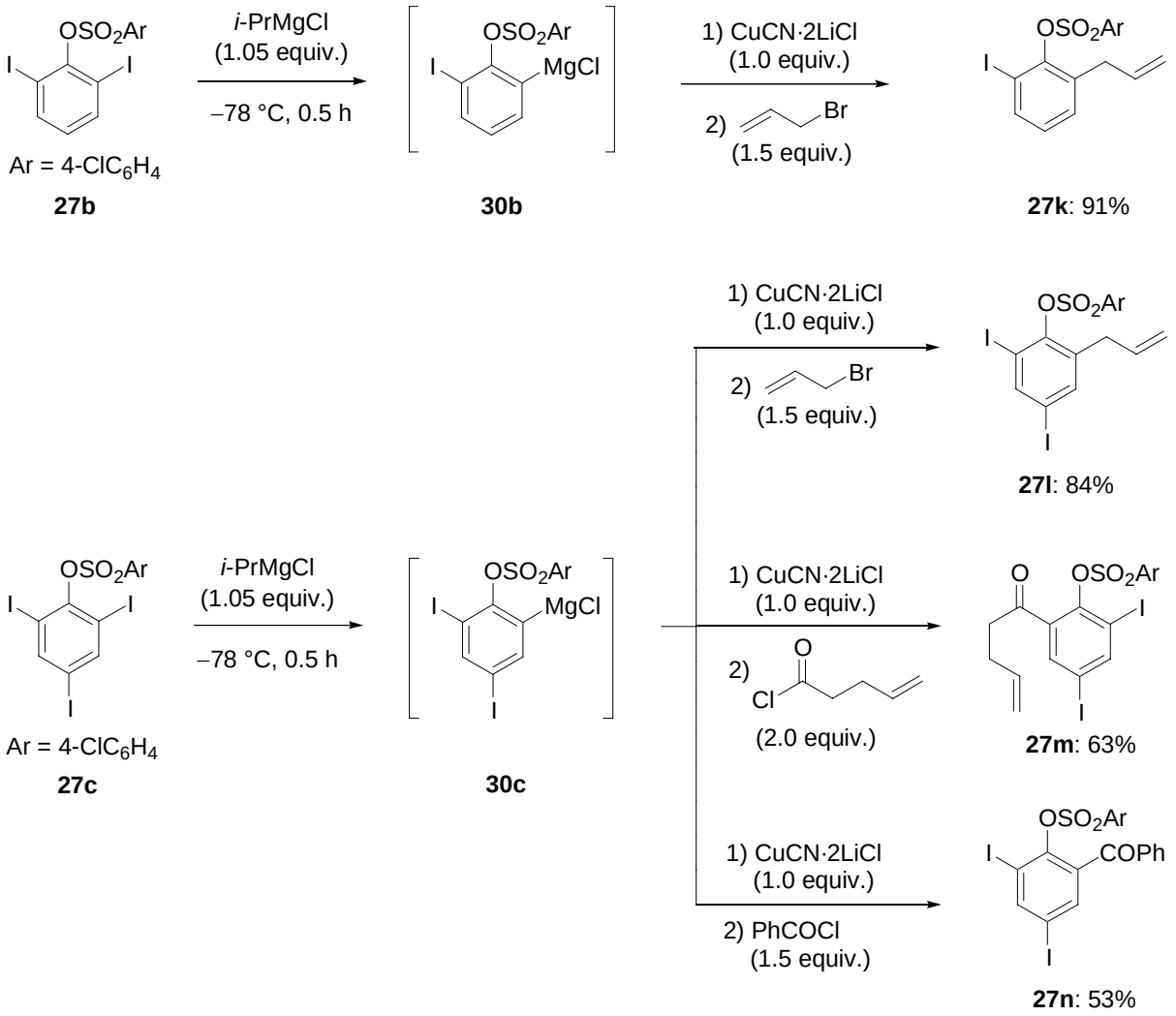
4-Chlorophenyl sulfonates **27f-j** were synthesized from 2-iodoresorcinol (**28**), which was prepared according to the literature procedure.[75c] In the presence of Et_3N (2.5 equiv.), **28** was reacted with 4-chloro-benzenesulfonyl chloride (2.1 equiv.) to give **27f** in 88 % yield. The compound **29** could be obtained in 55 % yield from the reaction of **28**, 4-chloro-benzenesulfonyl chloride (1.0 equiv.) and potassium carbonate (7.2 equiv.) in refluxing acetone for 6 h. Compounds **27g-j** were prepared from **29** with the corresponding protecting reagents under typical reaction conditions in 85-94 % yield (Scheme 47).



Scheme 47. a) Cs_2CO_3, MeI, in DMF, 25 °C, overnight (R = Me); K_2CO_3, $PhCH_2Br$, in DMF, 25 °C, overnight (R = Bn); Et_3N, Et_3SiCl, in CH_2Cl_2, 0 °C to 25 °C, overnight (R = TES).

3.2.4 Preparation of arene derivatives as starting materials *via* an iodine-magnesium-exchange reaction

The intermediate Grignard reagents of type **30** are stable at low temperature and can be quenched with electrophiles. Thus, the polyfunctional aryl sulfonate **27b** or **27c** was converted to the Grignard reagent **30b** or **30c** (*i*-PrMgCl, −78 °C, 30 min) and reacted with allyl bromide or an acid chloride (1.5 equiv.) in the presence of CuCN·2LiCl (1.0 equiv.) leading to the products **27k-n** in 53-91 % yields (Scheme 48).



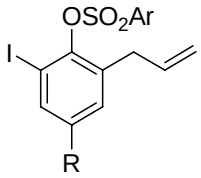
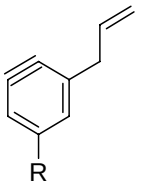
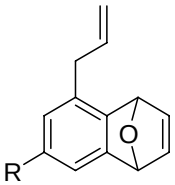
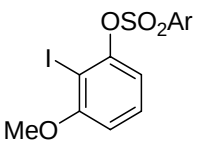
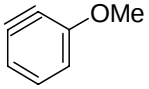
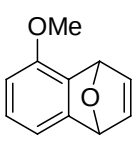
Scheme 48. Syntheses of compounds **27k-n**.

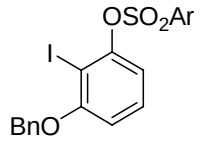
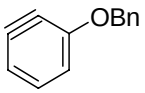
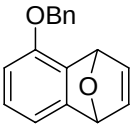
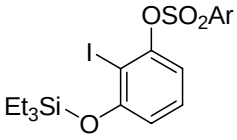
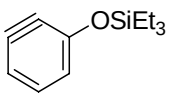
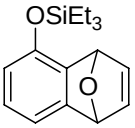
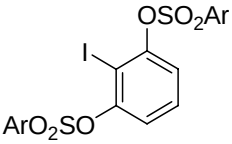
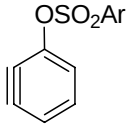
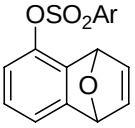
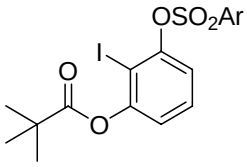
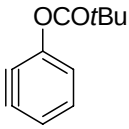
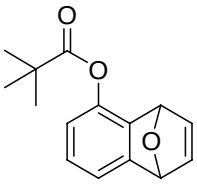
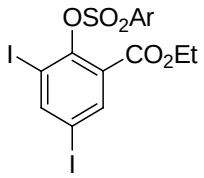
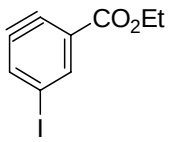
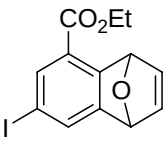
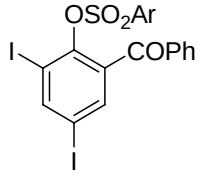
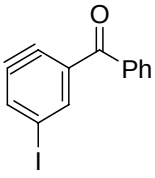
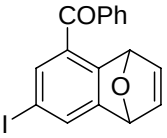
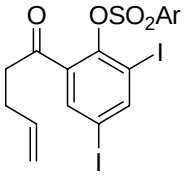
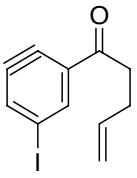
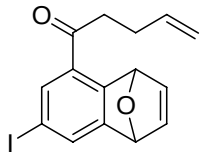
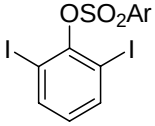
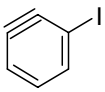
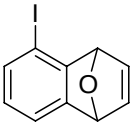
3.2.5 Preparation of polyfunctionalized arynes *via* an iodine-magnesium-exchange reaction

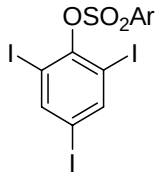
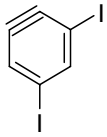
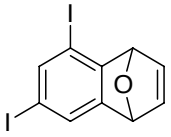
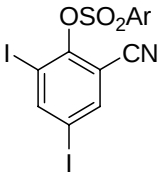
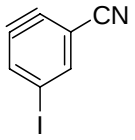
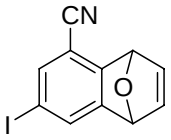
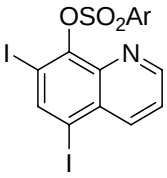
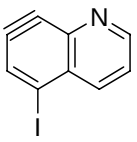
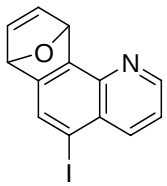
4-Chlorobenzenesulfonate as the leaving group was advantageously used for the preparation of various functionalized arynes **16b-c**, **16e-o**, and the heteroaryne **16p**, which were trapped

with an excess of furan providing the expected products **17b-c** and **17e-p** (Table 2). Thus, various functionalities like an iodine (entries 2, 8, 9, 10, 11, 12, 13, and 14), an alkoxy (entries 3-5), a sulfonate (entry 6), a pivalate (entry 7), and an ester (entry 8) were readily tolerated on the aryne intermediates. Interestingly, sensitive functionalities like a ketone function or even a ketone bearing *α*-acidic hydrogens (entries 9 and 10) were perfectly compatible with this method. We also observed that more than one halogen substituents on the aryne changed its reactivity and made the reaction complicated. When there was only one iodine on the aryne such as **16b**, its Diels–Alder reaction with furan went smoothly giving rise to **17b** in 78 % yield (entry 11). If there were two iodines on the aryne like **16c**, its reaction with furan led to **17c** only in 26 % yield owing to the side reactions (entry 12). Also, the electron-deficiency of the aromatic ring in aryne intermediate increased its reactivity so that the reaction of aryne with trapping reagents led to a low yield due to the competition with the side reactions. For example, when a nitrile function was on the *meta*-position of the aryne, good yield (78 %) was obtained by trapping with furan.[79] However, when a nitrile function was on the *ortho*-postion of aryne **16f**, its reation with furan furnished **17f** only in 23 % yield (entry 13). Instead of a cyano group, a weaker electron-withdrawing group such as an ester or a ketone function on the *ortho*-position of the aryne (**16e**, **16i**, or **16o**) reacting with furan led to **17e**, **17i**, or **17o** in 68-83 % yield (entries 8-10). Finally, the chinolinyl sulfonate **27o** was readily converted to the corresponding Grignard reagent (**30o**), which provided, *via* the heteroaryne (**16p**), the desired trapping product **17p** in 77 % yield (entry 14).

Table 2. Generation of polyfunctionalized arynes of type **16** and their trapping with furan.

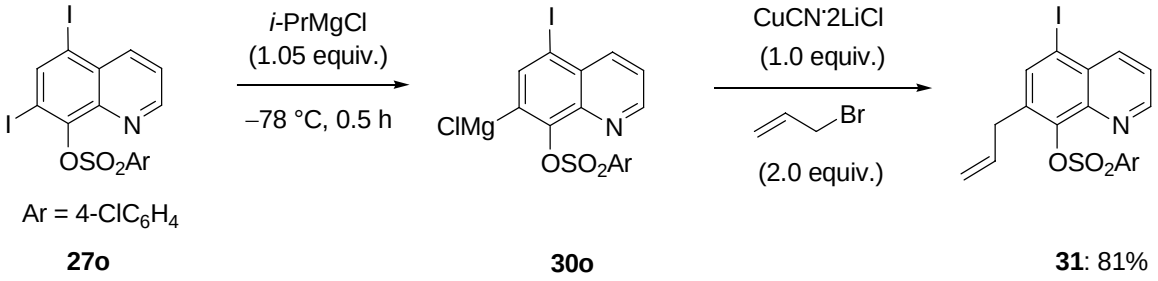
Entry	Precursor[a]	Aryne	Product of type **17**[a]	Yield (%)[b]
1	 **27k**: R=H	 **16g**: R=H (1 h[c])	 **17g**: R=H	83
2	**27l**: R=I	**16h**: R=I (1 h[c])	**17h**: R=I	88
3	 **27h**	 **16j** (1 h[c])	 **17j**	80

4	 **27i**	 **16k** (1 h[c])	 **17k**	83
5	 **27j**	 **16l** (1 h[c])	 **17l**	68
6	 **27f**	 **16m** (6 h[c])	 **17m**	72
7	 **27g**	 **16n** (3 h[c])	 **17n**	68
8	 **27d**	 **16e** (2 h[c])	 **17e**	83
9	 **27n**	 **16i** (1 h[c])	 **17i**	68
10	 **27m**	 **16o** (1 h[c])	 **17o**	71
11	 **27b**	 **16b** (1 h[c])	 **17b**	78

12	 **27c**	 **16c** (1 h[c])	 **17c**	26
13	 **27e**	 **16f** (2 h[c])	 **17f**	23
14	 **27o**	 **16p** (1 h[c])	 **17p**	77

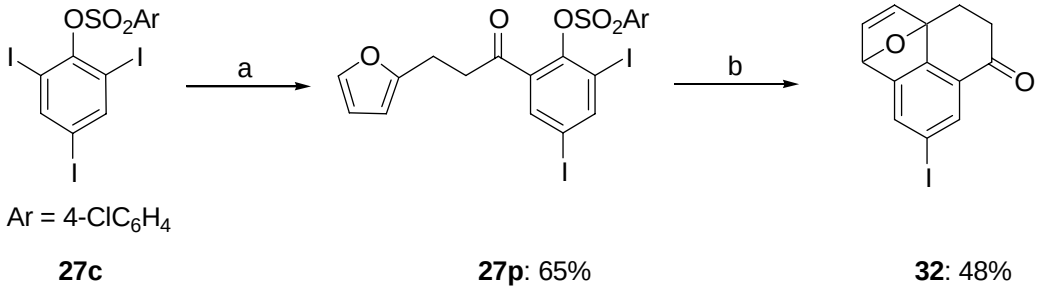
[a] Ar= 4-ClC_6H_4. [b] Isolated yield of analytically pure product. [c] Reaction time for the formation of heteroaryne at room temperature using furan (5.0 equiv.) as trapping reagents.

The presence of an *ortho*-arylsulfonate group exerted a strong inductive effect and allowed to perform the I/Mg-exchange of the *ortho*-iodide of the precursors of type **30** under very mild conditions showing a great functional group compatibility. Importantly, the careful choice of the *p*-chlorobenzenesulfonate group as a leaving group allowed to tune the rate of the aryne formation, which avoided the generation of the aryne at a temperature where the cycloadditon with the desired reaction partner (diene, electron-rich alkene) was too slow and thus led only to the decomposition of the intermediate aryne. Furthermore, the intermediate Grignard reagent of type **30** was stable at low temperature and could be quenched with electrophiles. Thus, the heterocyclic sulfonate **27o** was converted to the Grignard reagent **30o** (*i*-PrMgCl, −78 °C, 30 min) and was reacted with allyl bromide (2.0 equiv.) in the presence of CuCN·2LiCl (1.0 equiv.) leading to the product **31** in 81 % yield. This indicated the great versatility of the magnesiated sulfonates and demonstrated the tunable nature of their decomposition to arynes (Scheme 49; also see Scheme 48).



Scheme 49. Trapping of the heterocylic magnesiated sulfonate **30o** with allyl bromide.

Our method allowed an expeditive functionalization of the starting triiodoaryl sulfonate **27c** for the performance of intramolecular trapping reactions of functionalized arynes. Thus, the magnesiation of **27c** with *i*-PrMgCl followed by transmetallation with CuCN·2LiCl provided a copper intermediate which was acylated with 3-(2-furyl)propionyl chloride[80] (−78 °C to −25 °C, 1 h) leading to the iodoketone **27p** in 65 % yield (Scheme 50). This compound underwent an I/Mg-exchange at −78 °C with *i*-PrMgCl. By warming up to ambient temperature, the resulting aryne underwent an intramolecular cyclization with the furan moiety providing the condensed polycyclic iodoketone **32** in 48 % yield. As a side reaction we have observed a competitive protonation of the magnesium intermediate.[81]



Scheme 50. Intramolecular trapping of a functionalized aryne: (a) *i*-PrMgCl (1.1 equiv.), −78 °C, 0.5 h; CuCN·2LiCl (1.0 equiv.), −78 °C, 10 min; 3-(2-furyl)propionyl chloride (2.0 equiv.), −78 °C to 25 °C, 1 h. (b) *i*-PrMgCl (1.0 equiv.), −78 °C, 0.5 h; then −78 °C to 25 °C, 1 h.

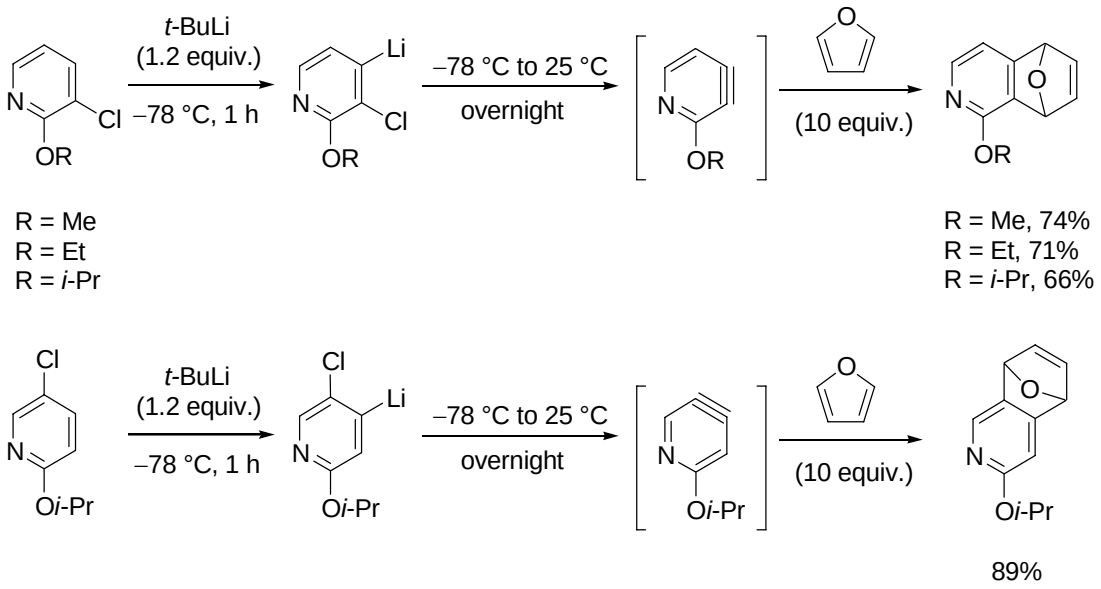
[80] For the preparation of 3-(2-furyl)propionyl chloride, we have used literature procedures starting from furfural: a) M. Takeuchi, T. Taniguchi, K. Ogasawara, *Synthesis* **1999**, 341; b) A. Robertson, D. Philip, N. Spencer, *Tetrahedron* **1999**, *55*, 11365; c) A. Padwa, T. J. Wisnieff, E. J. Walsh, *J. Org. Chem.* **1989**, *54*, 298.

[81] Besides the formation of **32** in 48 %, we have also observed an iodoketone (2-[3-(2-furyl)propanoyl]-4-iodophenyl 4-chlorobenzenesulfonate) tentatively resulting from protonation of the corresponding Grignard reagent.

3.3 Introduction of preparation of functionalized pyridynes

3.3.1 Introduction

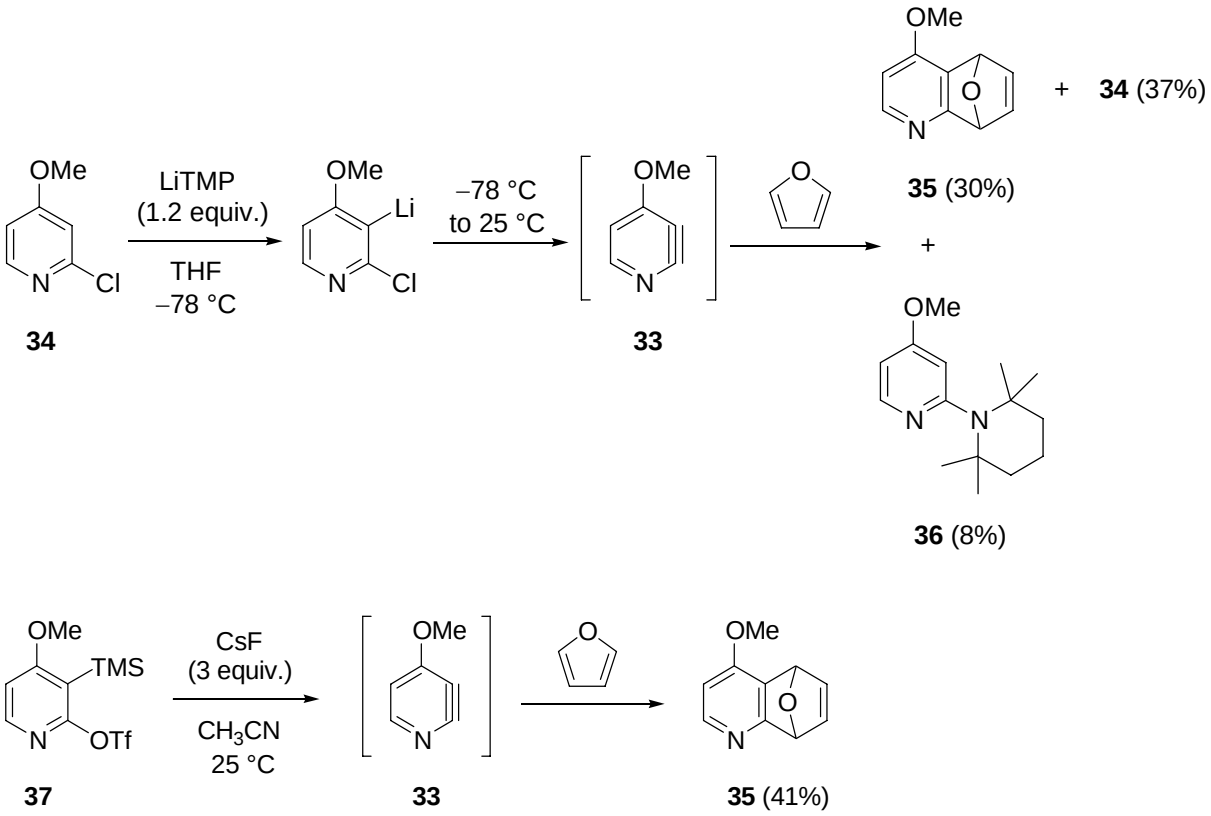
There are less applications of pyridynes than those of arynes due to the difficulty of trapping reactive pyridynes. For example, Hegarty reported the preparation of substituted 3,4-pyridynes and showed that the stabilization of 3,4-pyridynes by an alkoxy group adjacent to the ring nitrogen was essential to lead to the Diels–Alder cycloaddition products in good yields (66-89 %) after trapping with furan *in situ* (Scheme 51).[82]



Scheme 51. Preparation of 2-alkoxy-3,4-pyridynes.

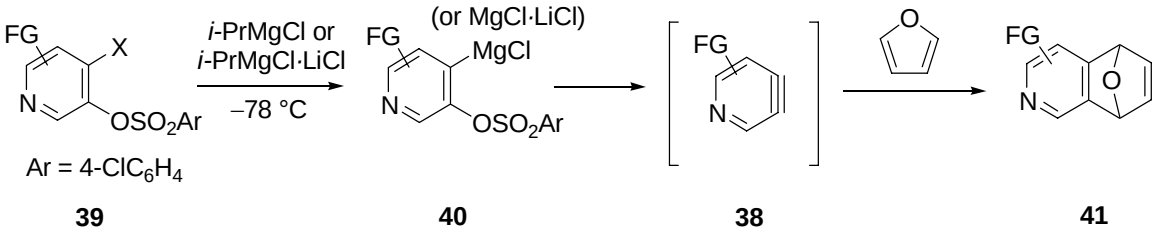
A substituted 2,3-pyridyne, such as 4-methoxy-2,3-pyridyne (**33**), can be prepared by metalating 2-chloro-4-methoxy-pyridine (**34**) with LiTMP (1.2 equiv.) followed by an elimination of LiCl and trapping with furan to furnish epoxyquinoline **35** in 30 % yield. However, the piperidine addition product **36** and unreacted **34** were also isolated in 8 % and 37 % yield, respectively. Instead of **34** as the precursor of **33**, compound **37** can be treated with 3 equiv. CsF (flame-dried under vacuum) in the presence of furan (44 equiv.) in acetonitrile at 25 °C affording **35** in 41 % yield (Scheme 52).[83]

[82] S. J. Connon, A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1245.
[83] a) M. A. Walters, J. J. Shay, *Tetrahedron Lett.* **1995**, *36*, 7575; b) M. A. Walters, J. J. Shay, *Syn. Commun.* **1997**, *27*, 3573.



Scheme 52. Preparation of 4-methoxy-1,2-pyridyne (**33**).

Based on the success of the preparation of functionalized arynes using 4-chlorobenzenesulfonate as a good leaving group, it should be possible to apply the same methodology to prepare the functionalized 3,4-pyridynes **38** (Scheme 53).

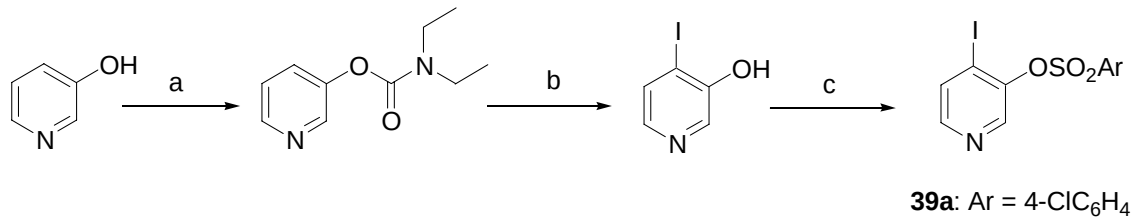


Scheme 53. Preparation of functionalized 3,4-pyridyne **38**.

3.3.2 Preparation of pyridine derivatives as the starting materials *via* iodination and protection or further iodine-magnesium-exchange reaction

Diethyl-carbamic acid 4-iodo-pyridin-3-yl ester can be easily prepared from the protection of 3-hydroxy-pyridine with an ethylcarbamoyl group followed by *ortho*-lithiation with *n*-BuLi

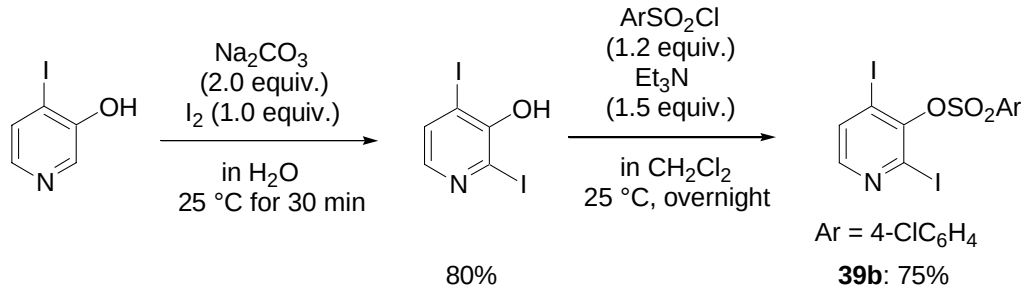
and further quenching with iodine.[84] After the deprotection, the obtained 3-hydroxy-4-iodopyridine was treated with 4-chlorobenzenesulfonyl chloride in the presence of Et_3N in CH_2Cl_2 at 25 °C overnight leading to 4-chloro-benzenesulfonic acid 4-iodo-pyridin-3-yl ester (**39a**) in 81 % yield (Scheme 54).



39a: Ar = 4-ClC_6H_4

Scheme 54. (a) Et_2NCOCl (1.2 equiv.), Et_3N (1.5 equiv.), toluene, 80 °C, overnight (92 %). (b) 1) *n*-BuLi (1.15 equiv.), TMEDA (1.21 equiv.), −78 °C, 30 min; I_2 (1.31 equiv.), −78 °C, 30 min; then 25 °C, 1 h (76 %); 2) 2N NaOH, MeOH, reflux, overnight (63 %). (c) Et_3N (1.5 equiv.), 4-chlorobenzenesulfonyl chloride (1.2 equiv.), CH_2Cl_2, 0 °C to 25 °C, overnight (81 %).

3-Hydroxy-4-iodopyridine can be further iodinated according to a modified procedure from that reported in the literature.[85] After reacting with 4-chlorobenzenesulfonyl chloride in the presence of Et_3N in CH_2Cl_2 at 25 °C overnight, 3-hydroxy-2,4-diiodopyridine was transformed into 4-chloro-benzenesulfonic acid 2,4-diiodo-pyridin-3-yl ester (**39b**) in 75 % yield (Scheme 55).

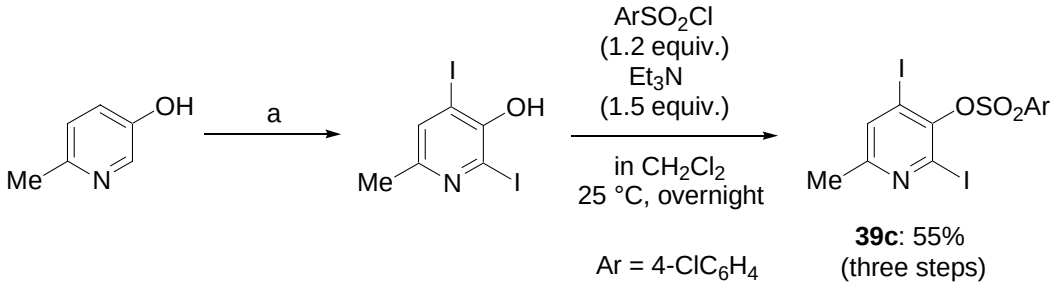


Scheme 55. Preparation of 4-chloro-benzenesulfonic acid 2,4-diiodo-pyridin-3-yl ester (**39b**).

4-Chloro-benzenesulfonic acid 2,4-diiodo-6-methyl-pyridin-3-yl ester (**39c**) (55 % yield over three steps) could also be obtained from 6-methyl-pyridin-3-ol by the procedure mentioned above. The 6-methyl-pyridin-3-ol was necessary to be iodinated in two separate steps rather

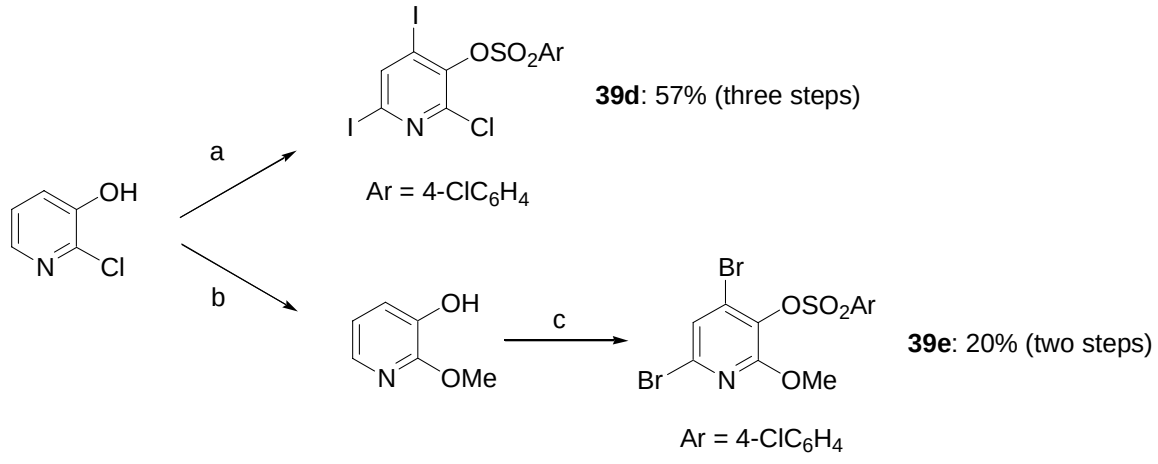
[84] a) O. E. Millner, Jr., J. W. Stanley, W. P. Purcell, *J. Med. Chem.* **1974**, *17*, 13; b) S. Lindström, L. Ripa, A. Hallberg, *Org. Lett.* **2000**, *2*, 2291.
[85] V. Koch, S. Schnatterer, *Synthesis* **1990**, *6*, 497.

than a double iodination in *one-pot* to furnish 2,4-diiodo-6-methyl-pyridin-3-ol in good yield (Scheme 56).



Scheme 56. (a) 1) Na_2CO_3 (2.0 equiv.), I_2 (1.0 equiv.), H_2O, 25 °C, 0.5 h; 2) Na_2CO_3 (2.0 equiv.), I_2 (1.0 equiv.), H_2O, 25 °C, overnight.

Similiarly, 4-chloro-benzenesulfonic acid 2-chloro-4,6-diiodo-pyridin-3-yl ester (**39d**) was prepared from 2-chloro-pyridin-3-ol according to the same procedure in 57 % yield over three steps. 2-Chloro-pyridin-3-ol was protected with a Bn group, followed by substitution of the chloride atom with a methoxy group and further deprotection, giving rise to 2-methoxy-pyridin-3-ol.[86] 2-Methoxy-pyridin-3-ol was brominated with NBS in CCl_4 at 25 °C for 3 days[87] and was then reacted with 4-chlorobenzenesulfonyl chloride in the presence of Et_3N in CH_2Cl_2 at 25 °C overnight furnishing 4-chloro-benzenesulfonic acid 4,6-dibromo-2-methoxy-pyridin-3-yl ester (**39e**) in 20 % yield (Scheme 57).

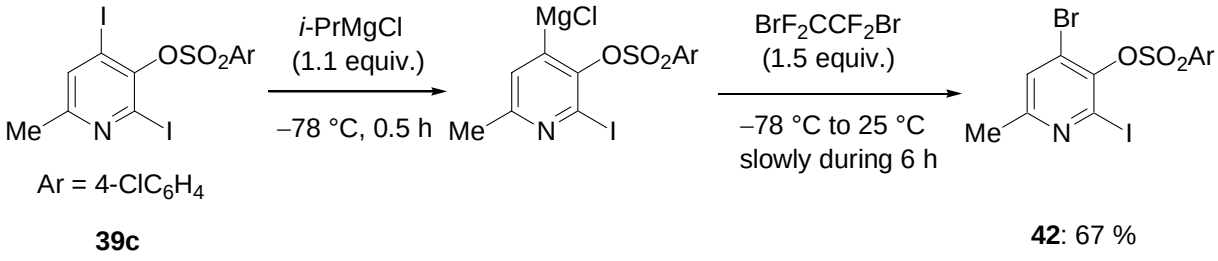


Scheme 57. (a) 1) Na_2CO_3 (2.0 equiv.), I_2 (1.0 equiv.), H_2O, 25 °C, 0.5 h; 2) Na_2CO_3 (2.0 equiv.), I_2 (1.0 equiv.), H_2O, 25 °C, overnight; 3) Et_3N (1.5 equiv.), 4-chlorobenzenesulfonyl

[86] S. Lazar, M. Soukri, J. M. Leger, C. Jarry, M. Akssira, R. Chirita, I. C. Grig-Alexa, A. Finaru, G. Guillaumet, *Tetrahedron* **2004**, *60*, 6461.
[87] V. Cañibano, J. F. Rodríguez, M. Santos, M. A. Sanz-Tejedor, M. C. Carreño, G. González, J. L. García-Ruano, *Synthesis* **2001**, *17*, 2175.

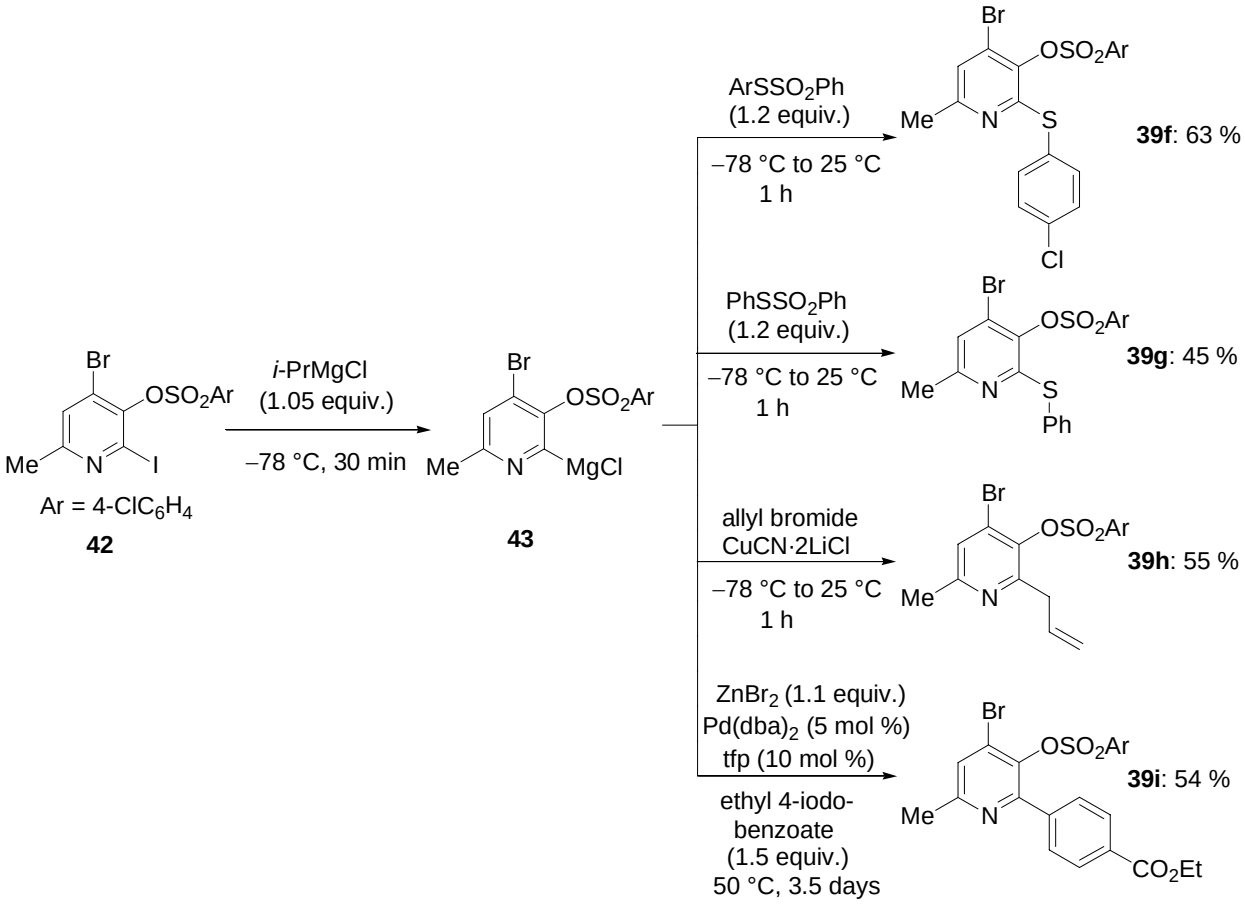
chloride (1.2 equiv.), CH_2Cl_2, 0 °C to 25 °C, overnight. (b) 1) NaH (1.1 equiv.), DMF, $PhCH_2Br$ (1.2 equiv.), 25 °C, overnight, 91 %; 2) MeONa (1.3 equiv.), DMF, 80 °C, 3 days, 92%; 3) H_2 (1 atom), Pd/C 10%, MeOH, 25 °C, 3 days, 85 %. c) NBS (2.1 equiv.), CCl_4, 25 °C, 3 days; Et_3N (1.5 equiv.), 4-chlorobenzenesulfonyl chloride (1.2 equiv.), CH_2Cl_2, 0 °C to 25 °C, overnight.

When treating **39c** with *i*-PrMgCl in THF at −78 °C, the I/Mg-exchange was complete in 30 min. The corresponding Grignard reagent was reacted with 1,2-dibromotetrafluoroethane (1.5 equiv.) followed by slowly warming to 25 °C during 6 h, and finally was leading to 4-chloro-benzenesulfonic acid 4-bromo-2-iodo-6-methyl-pyridin-3-yl ester (**42**) in 67 % yield (Scheme 58).



Scheme 58. Preparation of 4-chloro-benzenesulfonic acid 4-bromo-2-iodo-6-methyl-pyridin-3-yl ester (**42**).

4-Chloro-benzenesulfonic acid 4-bromo-2-iodo-6-methyl-pyridin-3-yl ester (**42**) could undergo a selective I/Mg-exchange (*i*-PrMgCl, −78 °C, 30 min) giving rise to the corresponding Grignard reagent **43** as the major product. The intermediate Grignard reagent **43** was reacted with *S*-phenyl arenethiosulfonates (1.2 equiv.) leading to the products **39f-g** in 45-63 % yields. In addition, **43** was reacted with allyl bromide (2.0 equiv.) in the presence of CuCN·2LiCl (1.0 equiv.) furnishing the product **39h** in 55 % yield. After transmetalation with $ZnBr_2$ (1.1 equiv.), **43** was reacted with ethyl 4-iodobenzoate (1.5 equiv.) in the presence of 5 mol % $Pd(dba)_2$ and 10 mol % *tri*-(2-furyl)phosphine at 50 °C for 3.5 days giving rise to the product **39i** in 54 % yield (Scheme 59).



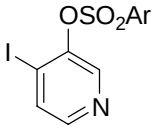
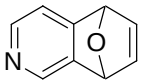
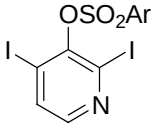
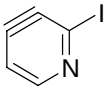
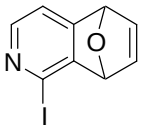
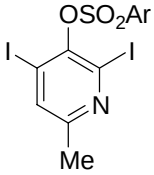
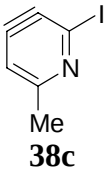
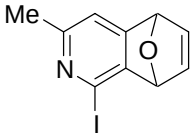
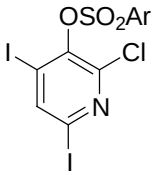
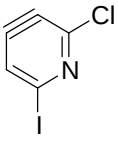
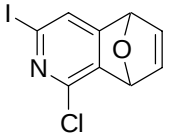
Scheme 59. Preparation of **39f-i** from **42** *via* an I/Mg-exchange with *i*-PrMgCl followed by quenching with an electrophile.

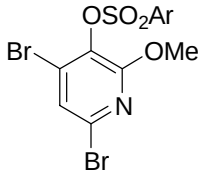
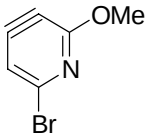
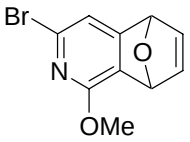
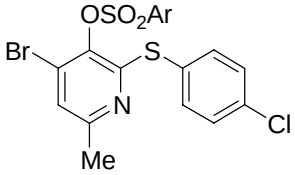
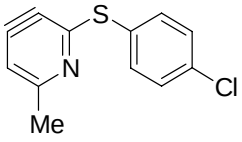
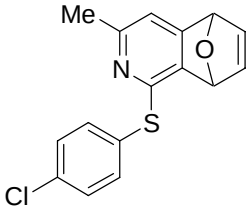
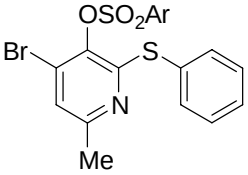
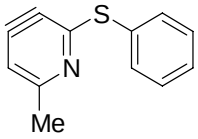
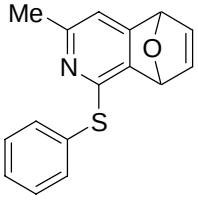
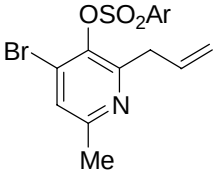
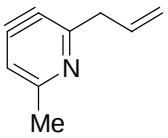
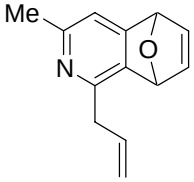
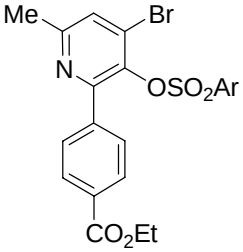
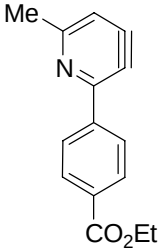
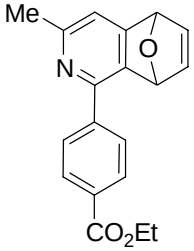
3.3.3 Preparation of polyfunctionalized 3,4-pyridynes *via* the halogen-magnesium-exchange reaction

Compounds **39a-i** were treated with *i*-PrMgCl or *i*-PrMgCl·LiCl, and the reactions were complete at −78 °C within 0.5 to 6 h to give rise to the corresponding Grignard reagents **40a-i**. After warming to 25 °C within 1-16 h, functionalized pyridynes **38a-i** were formed and trapped with furan leading to **41a-i** in 32-88 % yields (Table 3). Various functionalities like an iodine (or bromine or chlorine) (Table 3, entries 2, 3, 4 and 5), a methoxy (entry 5), an arylsulfide (entries 6 and 7), an allyl (entry 8), and an ester (entry 9) were readily tolerated on the pyridyne intermediates. We also observed that more than one halogen substituent on the pyridyne changed its reactivity and complicated its reaction. When there was only one halogen on pyridynes such as **38b-c** and **38e**, their Diels–Alder reactions with furan went smoothly giving rise to **41b-c** and **41e** in 45-78 % yields (entries 2-3 and 5). Instead, if there were two halogens on a pyridyne like **38d**, its reaction with furan only led to **41d** in 32 %

yield and the reaction did not go further to completion even after 16 h at 25 °C (entry 4). Also, a functionalized 3,4-pyridyne with one substituent on 6-position seemed to influence its stability owing to the increasing steric hindrance near the nitrogen atom. For instance, **38c** was reacted with furan leading to **41c** in 75 % yield, while **38b** was trapped with furan giving rise to **41b** in 45 % yield probably due to the further nucleophilic addition of the nitrogen atom of **38b** to itself (entries 2-3). The stabilization of 3,4-pyridynes by an alkoxy group or a sulfide function in 2-position was essential to afford the Diels–Alder cycloaddition products **41e-g** in good yields (78-88 %) after trapping *in situ* the intermediates **38e-g** with furan (entries 5-7). Alkyl groups have little electron-donating properties to contribute to the stabilization of 3,4-pyridynes. Therefore, **38h**, for instance, was reacted with furan furnishing the product **41h** in 57 % yield (entry 8). Finally, a 3,4-pyridine with an aryl group bearing an ester function, such as **38i**, was trapped with furan *in situ* giving rise to **41i** in 76 % yield (entry 9).

Table 3. Generation of polyfunctionalized pyridynes of type **38** and their trapping with furan.

Entry	Precursor[a]	3,4-Pyridyne of type **38**	Product of type **41**	Yield (%)[b]
1	 **39a**	 **38a** (0.5 h[c]; 2.5 h[d])	 **41a**	54
2	 **39b**	 **38b** (0.5 h[c]; 1.5 h[d])	 **41b**	45
3	 **39c**	 **38c** (0.5 h[c]; 6 h[d])	 **41c**	75
4	 **39d**	 **38d** (0.5 h[c]; 16 h[d])	 **41d**	32

		 **38e**		
5	**39e**	(0.5 h[e]; 4 h[d])	**41e**	78
		 **38f**		
6	**39f**	(0.5 h[e]; 1 h[d])	**41f**	88
		 **38g**		
7	**39g**	(0.5 h[e]; 1 h[d])	**41g**	85
		 **38h**		
8	**39h**	(2 h[e]; 1 h[d])	**41h**	57
		 **38i**		
9	**39i**	(6 h[e]; 1 h[d])	**41i**	76

[a] Ar= 4-ClC_6H_4. [b] Isolated yield of analytically pure product. [c] Reaction time for the I/Mg-exchange using *i*-PrMgCl at −78 °C. [d] Reaction time for the formation of heteroaryne at room temperature using furan (5.0 equiv.) as a trapping reagent. [e] Reaction time for the Br/Mg-exchange using *i*-PrMgCl·LiCl at −78 °C.

4. Preparation of Functionalized Arylmagnesium Reagents by the Addition of Magnesium Aryl Thiolates, Amides and Selenides to Arynes and Heteroarynes

4.1 Introduction

The functionalization of aromatic rings is an important synthetic task. A potential approach is the addition reaction of nucleophiles to intermediate arynes. The addition of heteroatom-metal bonds (Nu-Met; Nu= OR, NR_2, SR or PR_2) to alkynes of type **44** is usually a difficult process due to the high energy of the Nu-Met bond and to the high nucleophilicity of the resulting C-Met in the adduct **45** which is prone to polymerization and other side reactions.[88] The use of a catalytic amount of a metal catalyst allows the addition of various heteroatom-hydrogen bonds to triple bonds.[88,89] However, in this case, the reactivity of the C-Met bond of **45** cannot be exploited. By using a very reactive alkyne, such as an aryne **46**, the addition of nucleophiles should be facilitated and should afford useful aryl organometallics of type **47** which should react with various electrophiles leading to products **48** (Scheme 60). Although the addition of various nitrogen nucleophiles to arynes has been reported,[90] the successful trapping of the intermediates with electrophiles has only been reported in a few cases.[63,64,91]

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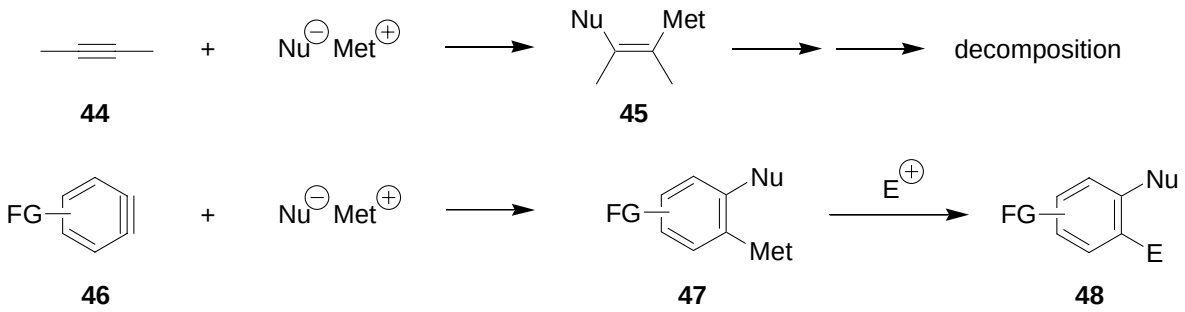
[88] a) R. Taube, in *Applied Homogeneous Catalysis with Organometallic Compounds,* (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, New York, **1996**, p. 507-520; b) T. E. Müller, M. Beller, in *Transition Metals for Organic Synthesis,* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim **1998**, p. 316-330; c) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675.

[89] a) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem.* **1998**, *110*, 1475; *Angew. Chem. Int. Ed.* **1998**, *37*, 1415; b) M. Beller, M. Eichberger, H. Trauthwein, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2225; c) M. Beller, C. Breindl, T. H. Riermeier, M. Eichberger, H. Trauthwein, *Angew. Chem.* **1998**, *110*, 3571; *Angew. Chem. Int. Ed.* **1998**, *37*, 3389; d) G. A. Molander, J. A. C. Romero, *Chem. Rev.* **2002**, *102*, 2161; e) M. Nobis, B. Driessen-Hoelscher, *Angew. Chem.* **2001**, *113*, 4105; *Angew. Chem. Int. Ed.* **2001**, *40*, 3983; f) F. Pohki, S. Doye, *Chem. Soc. Rev.* **2003**, *32*, 104; g) P. W. Roesky, T. E. Mueller, *Angew. Chem.* **2003**, *115,* 2812; *Angew. Chem. Int. Ed.* **2003**, *42,* 2708; h) S. Doye, *Synlett* **2004**, 1653.

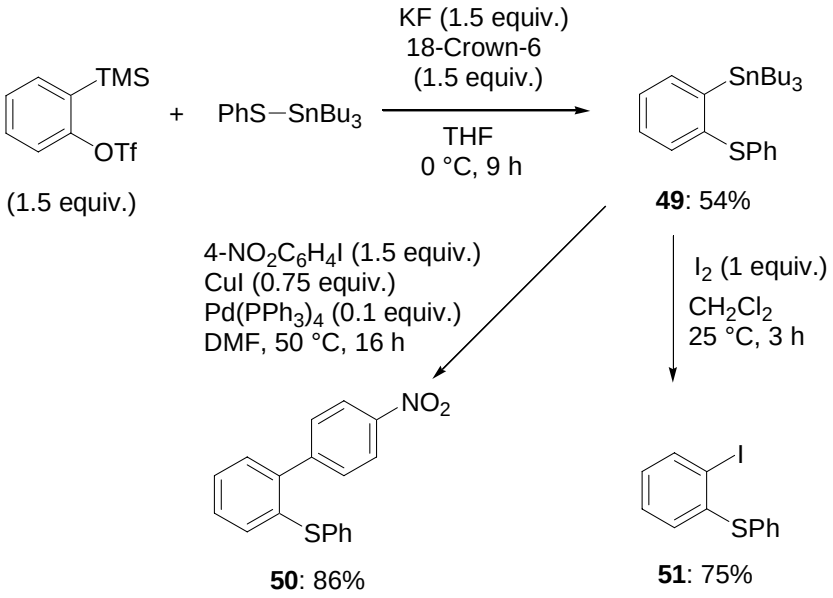
[90] a) S. V. Kessar, in *Comprehensive Organic Synthesis*, *Vol. 4*, (Eds.: B. M. Trost, I. Fleming, H. F. Semmelhack), Pergamon, Oxford, **1991**, p. 483; b) R. F. C. Brown, F. W. Eastwood, *Synlett* **1993**, 9; c) W. Sander, *Acc. Chem. Res.* **1999**, *32*, 669; d) M. Beller, C. Breindl, T. H. Riermeier, A. Tillack, *J. Org. Chem.* **2001**, *66*, 1403; e) P. Maurin, M. Ibrahim-Ouali, M. Santelli, *Tetrahedron Lett.* **2001**, *42*, 8147; f) H. Yoshida, Y. Honda, E. Shirakawa, T. Hiyama, *Chem. Commun.* **2001**, 1880; g) D. Peña, S. Escudero, D. Pérez, E. Guitián, L. Castedo, *Angew. Chem.* **1998**, *110*, 2804; *Angew. Chem. Int. Ed.* **1998**, *37*, 2659; h) J.-M. Becht, A. Gissot, A. Wagner, C. Mioskowski, *Chem. Eur. J.* **2003**, *9*, 3209; i) M. Paz, C. Saa, E. Guitian, L. Castedo, J. M. Saa, *Heterocycles* **1993**, *36*, 1217; j) I. Fleming, M. Woolias, *J. Chem. Soc. Perkin Trans 1* **1979**, 827; k) please also see: references 63-65.

[91] a) A. I. Meyers, P. D. Pansegrau, *J. Chem. Soc. Chem. Commun.* **1985**, 690; b) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356.



Scheme 60. The addition of heteroatom-metal bonds to unsaturated bonds.

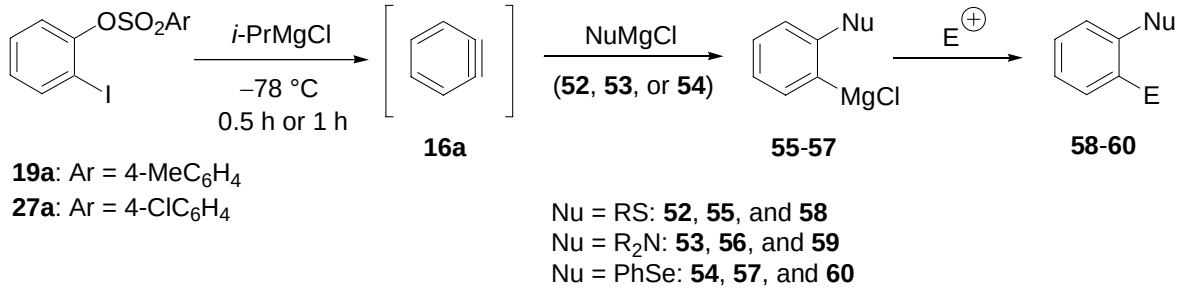
In 2004, Yoshida and his coworkers reported the successful addition of a S-Sn bond to benzyne (**16a**). The corresponding aryltin compound **49** could be further applied in the Stille coupling reaction with 4-iodo-nitrobenzene furnishing the functionalized diaryl compound **50** (86 % yield) or could be quenched with iodine to give rise to 2-iodophenyl phenyl sulfide (**51**) (75 % yield) (Scheme 61).[92]



Scheme 61. Preparation of the aryltin compound **49** *via* the addition of a S-Sn bond to **16a**.

We have showed a new preparation of polyfunctionalized arynes *via* the elimination of 2-magnesiated diaryl sulfonates of type **16**. Herein, we wish to apply the selective addition of magnesiated thiols of type **52**, amines of type **53**, or phenylselenol (**54**) to **16a**, generated by our procedure, to provide 2-thio- (**55**), 2-amino- (**56**), or 2-seleno-substituted arylmagnesium species (**57**). In contrast to previous methods, these arylmagnesium reagents **55-57** can be trapped by a range of electrophiles giving rise to thioethers of type **58**, arylamines of type **59**, and selenoethers of type **60** (Scheme 62).

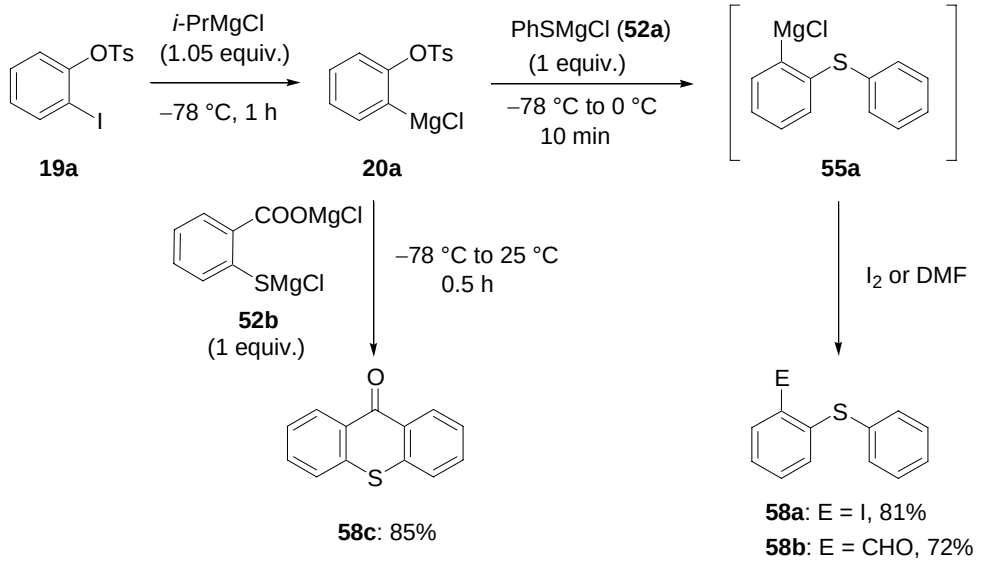
[92] H. Yoshida, T. Terayama, J. Ohshita, A. Kunai, *Chem. Commun.* **2004**, 1980.



Scheme 62. Preparation of aryl thioethers **58**, arylamines **59**, and aryl selenoethers **60** *via* addition reactions to **16a** followed by quenching with electrophiles.

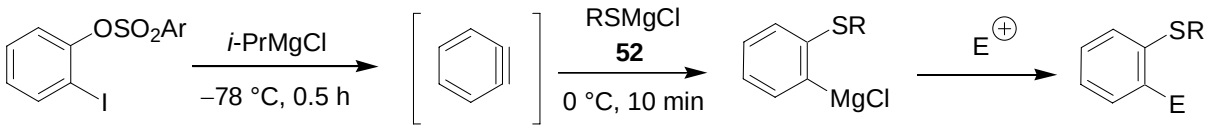
4.2 Preparation of functionalized arylmagnesium reagents by the addition of magnesium aryl thiolates to arynes and heteroarynes

In the preliminary study, tosylate was selected first as the leaving group for the formation of benzyne (**16a**). After the reaction conditions were optimized, it was found that **16a** can be trapped efficiently even in the presence of 1 equiv. of magnesium phenylthiolate **52a** in *one-pot* reaction. The corresponding newly formed Grignard reagent **55a** could be successfully utilized by quenching with typical electrophiles such as iodine or DMF furnishing **58a-b** in 72-81 % yields (Scheme 63). The magnesium thiolate **52b** bearing a carboxylate fucntion also added successfully to **16a**, and **58c** was formed after intramolecular condensation of the carboxylate function and the newly generated carbanion.



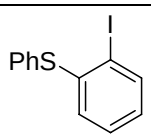
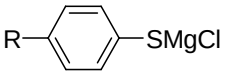
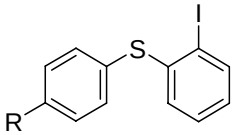
Scheme 63. Preparation of aryl thioethers **58a-c** *via* the addition of **52a** or **52b** to **16a** followed by quenching with electrophiles.

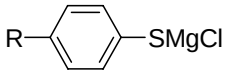
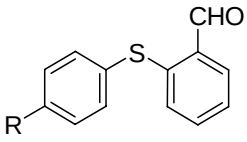
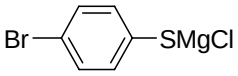
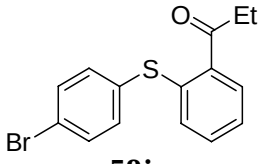
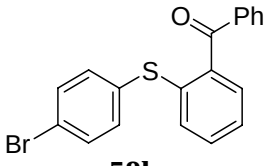
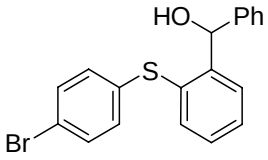
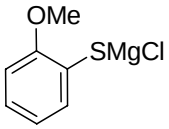
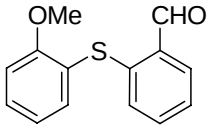
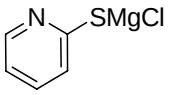
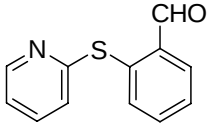
Although good results were obtained when TsO-group was used as a leaving group for the preparation of arynes, arenes bearing a better leaving group, such as the 4-$ClC_6H_4SO_3$- group, had a higher rate of the I/Mg-exchange than those bearing the TsO- group. Thus, the addition of *i*-PrMgCl (2.0 equiv.) to thiophenol (1.0 equiv.) in THF (−78 °C, 10 min) followed by the addition of 2-iodobenzenesulfonate (**27a**) (1.0 equiv.; −78 °C, 0.5 h) and subsequently warming up to 0 °C within 10 min led to the benzyne-addition product **55a** which, by quenching with iodine in THF at −78 °C, provided 2-iodophenyl phenyl sulfide (**58a**) in 83 % yield (Scheme 64, entry 1 of Table 4). Various substituted thiophenolates, such as **52c-e**, reacted in the same manner affording after iodolysis the 2-iodophenyl thioethers **58d-f** in 82-90 % yield (entries 2-4). Similarly, the intermediate Grignard reagents obtained after the addition of **52c-e** to benzyne could be formylated by reaction with DMF (2.5 equiv., −40 °C to 25 °C, 1 h) leading to aldehydes **58g-i** in 73-78 % yield (entries 5-7). Acid chlorides in the presence of CuCN·2LiCl and aldehydes were also excellent electrophiles leading respectively to ketones, such as **58j** and **58k** and to the benzylic alcohol **58l** in 85-90 % yield (entries 8-10). *Ortho*-substituted magnesium thiolates such as **52f** (entry 11) or a heterocyclic thiolate such as **52g** (entry 12) underwent the addition reaction followed by formylation with DMF giving rise to **58m-n** in 80-82 % yield.



27a: Ar = 4-ClC_6H_4 **16a** **55** **58**

Scheme 64 and **Table 4**. Thio-ethers of type **58** obtained by the addition of magnesium thiolates **52** to **16a** followed by the trapping of the intermediate Grignard reagents **55** with electrophiles.

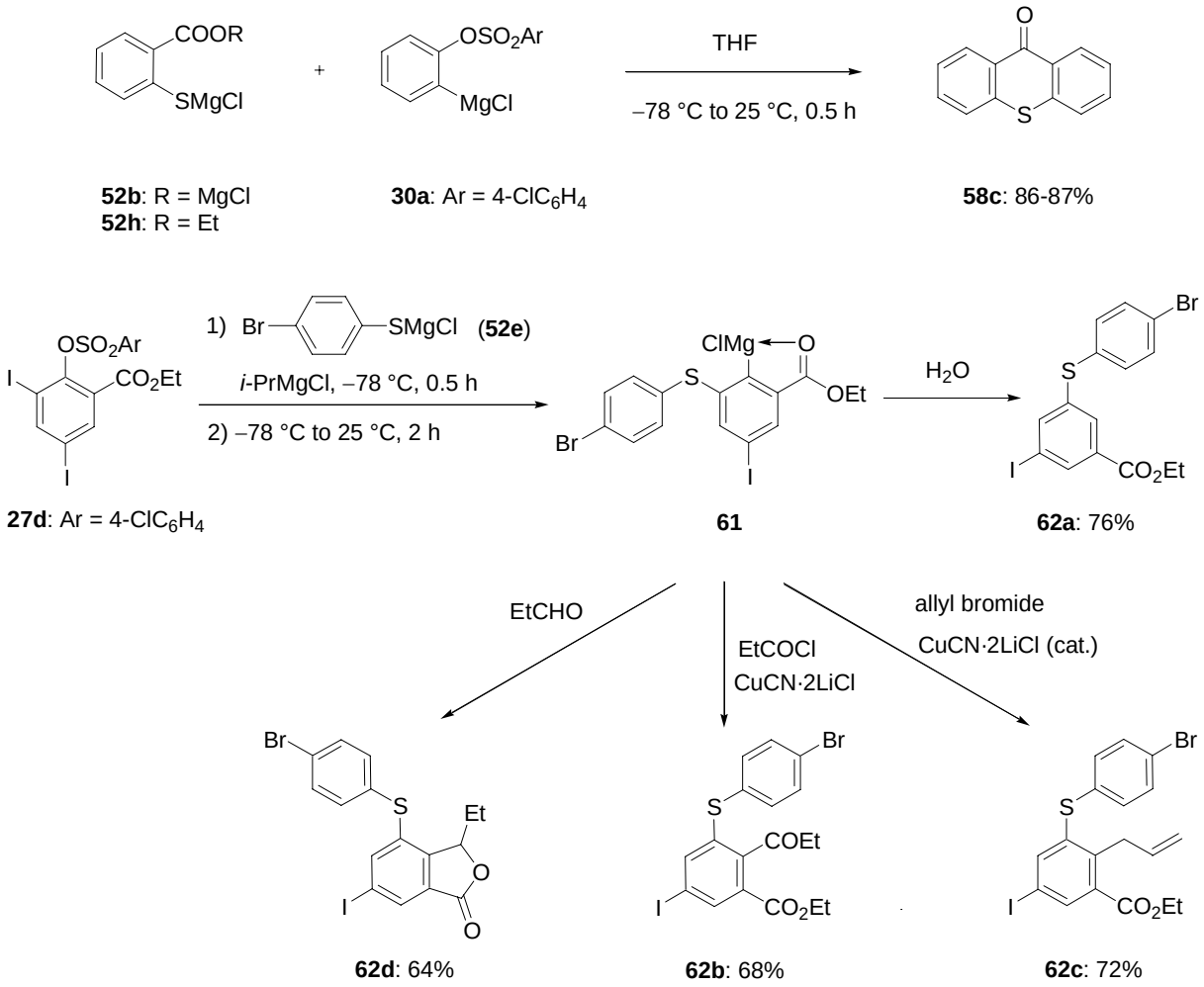
Entry	Mg-thiolate of type **52**	Electrophile	Thioether of type **58**	Yield (%)[a]
1	PhSMgCl **52a**	I_2	 **58a**	83
2 3 4	 **52c**: R=F **52d**: R=Cl **52e**: R=Br	I_2	 **58d**: R=F **58e**: R=Cl **58f**: R=Br	90 84 82

5 6 7	 **52c**: R=F **52d**: R=Cl **52e**: R=Br	DMF	 **58g**: R=F **58h**: R=Cl **58i**: R=Br	78 73 75
8	 **52e**	EtCOCl[b]	 **58j**	90
9	**52e**	PhCOCl[b]	 **58k**	88
10	**52e**	PhCHO	 **58l**	85
11	 **52f**	DMF	 **58m**	80
12	 **52g**	DMF	 **58n**	82

[a] Isolated yield of analytically pure product. [b] The reaction was performed with 1.0 equiv. CuCN·2LiCl.

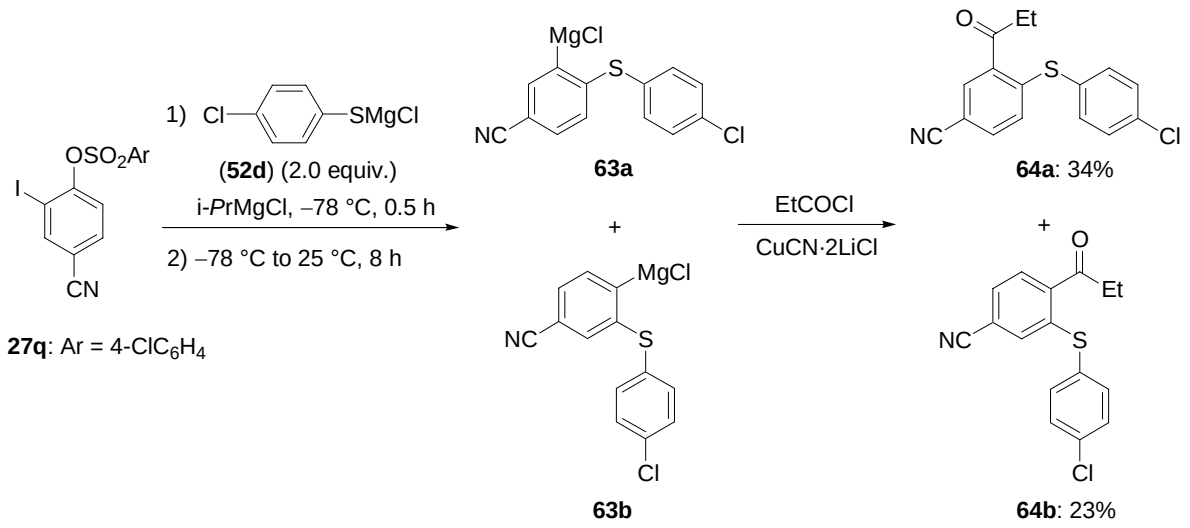
The high strain of the generated aryne ensures a smooth addition and an excellent functional group compatibility. Thus, the reaction of the magnesium thiolates **52b** and **52h** bearing a carboxylic acid or an ester function in position 2 with the 2-magnesiated benzenesulfonate (**30a**) provided the desired addition arylmagnesium species which reacted intramolecularly with the carbonyl group in *ortho*-position leading to thioxanthon (**58c**) in 86-87 % yield (Scheme 65). Functionalized arynes displayed remarkable regioselectivity in the addition step. Thus, the polyfunctional sulfonate **27d** was selectively magnesiated in the *α*-position to the sulfonate group (inductive activation of the *ortho*-carbon-iodine bond) and its reaction with the magnesium thiolate **52e** (2.0 equiv.) provided only the magnesium reagent **61** which was stabilized by chelation. The configuration of the regioselectivity was determined by

quenching with water to yield **62a** as one isomer in 76 % yield. Its reaction with various electrophiles, like an acid chloride or allyl bromide in the presence of CuCN·2LiCl, or an aldehyde furnished the tetrasubstituted thioethers **62b-d** in 64-72 % yield (Scheme 65).



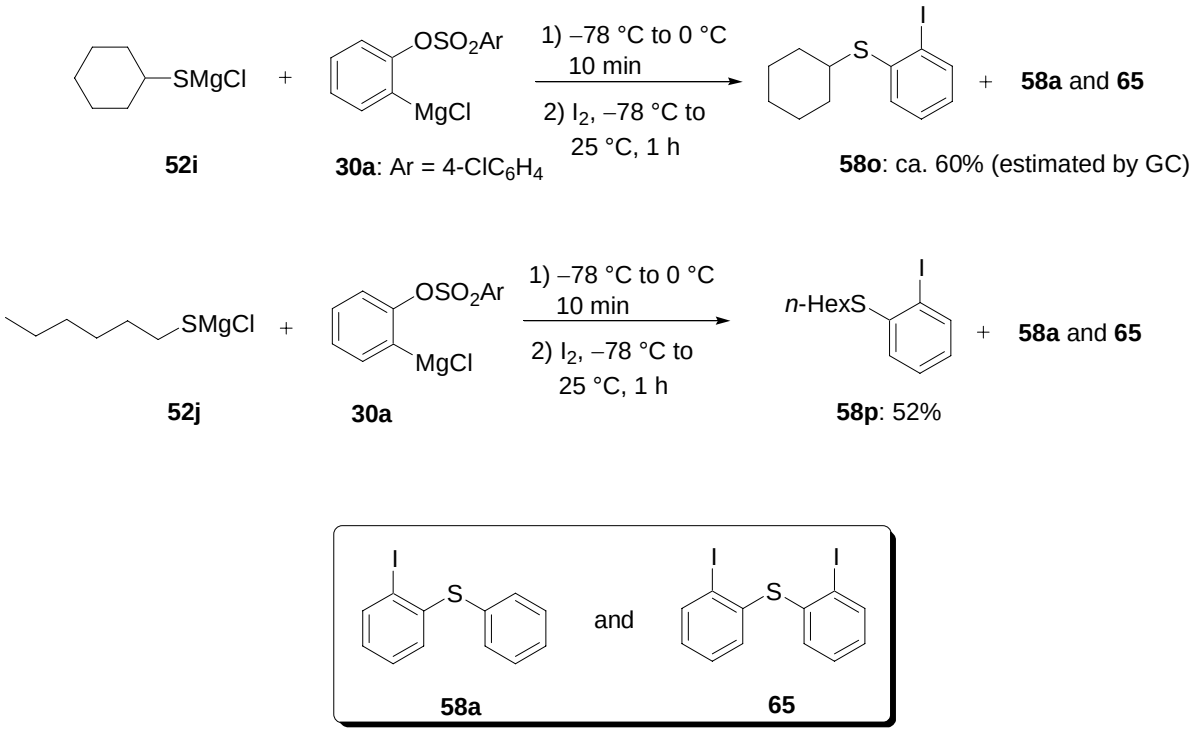
Scheme 65. Preparation of polyfunctionalized thioethers *via* the addition of magnesium thiolates to arynes followed by quenching with electrophiles.

When an aryne bears a nitrile function in the *meta*-position was employed, the addition of the magnesiated arylthiolate **52d** (2.0 equiv.) to the aryne led to a mixture of **63a** (38 % yield) and **63b** (25 % yield), and their configurations were confirmed by quenching with water. Compounds **63a** and **63b** could also be trapped with EtCOCl (in the presence of CuCN·2LiCl) furnishing **64a** and **64b** in 34 % and 23 % yields, respectively (Scheme 66).



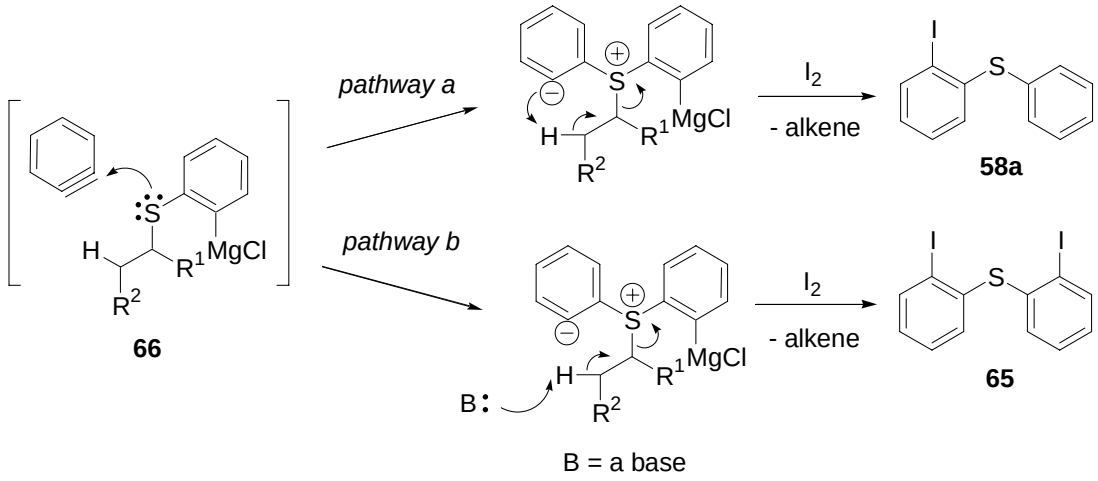
Scheme 66. Preparation of polyfunctionalized thioethers **64a-b** *via* the addition of the magnesium thiolate **52d** to aryne followed by quenching with EtCOCl (in the presence of CuCN·2LiCl).

Aliphatic thiolates (1.0 equiv.), such as **52i-j**, added to benzyne (**16a**) under the same reaction conditions followed by quenching with iodine affording alkyl 2-iodophenyl thioethers **58o-p** in 52-60 % yields (Scheme 67).



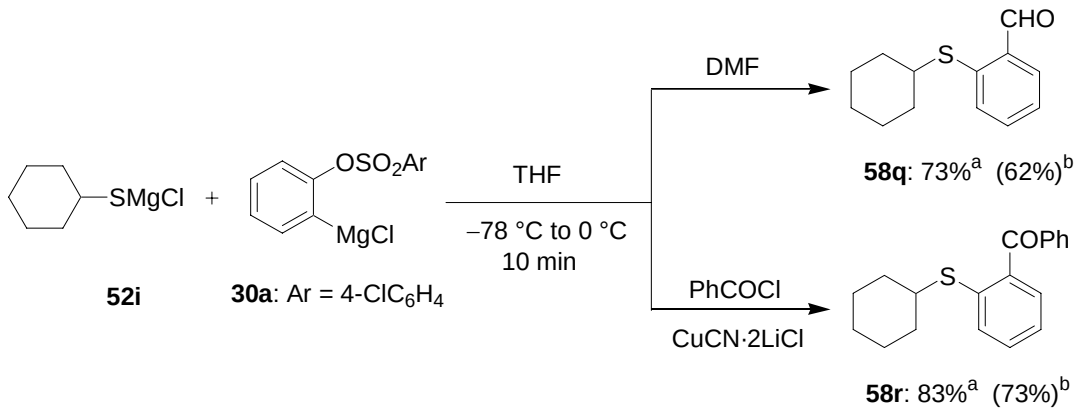
Scheme 67. Preparation of an aryl thioether **58o** or **58p** *via* the addition of **52i** or **52j** to **16a** followed by iodolysis.

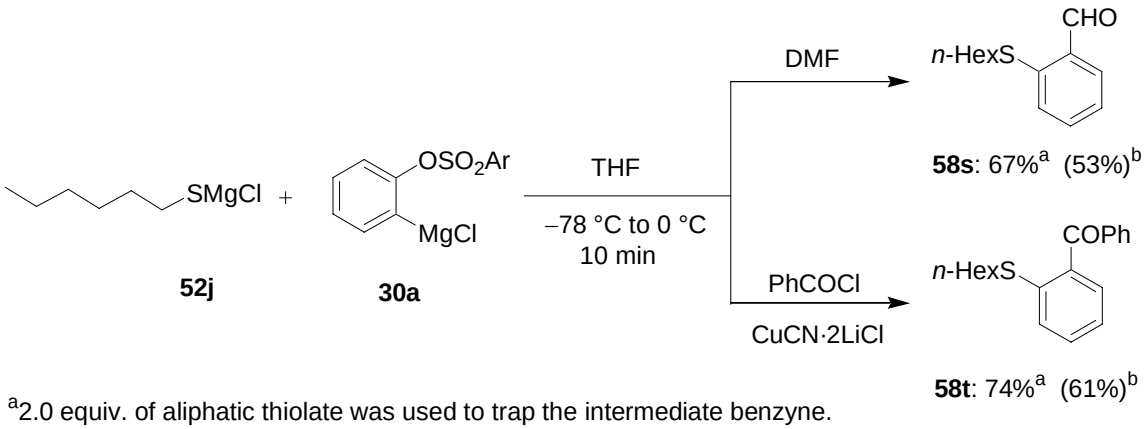
The same side products **58a** and **65** were observed when different aliphatic thiolates, like **52i** and **52j**, were used as trapping reagents of **16a**, respectively (Scheme 67). The two possible pathways in the mechanism for the formation of **58a** and **65** were proposed as following (Scheme 68).



Scheme 68. A possible reaction mechanism for the formation of **58a** and **65**.

In order to avoid the side reactions from the addition of the newly-formed Grignard reagents of type **66** to **16a**, **52i-j** (2.0 equiv.) were employed under the same reaction conditions. Their formylation with DMF or quenching with benzoyl chloride in the presence of CuCN·2LiCl, afforded the functionalized alkyl aryl thioethers **58q-t** in 67-83 % yields (Scheme 69).

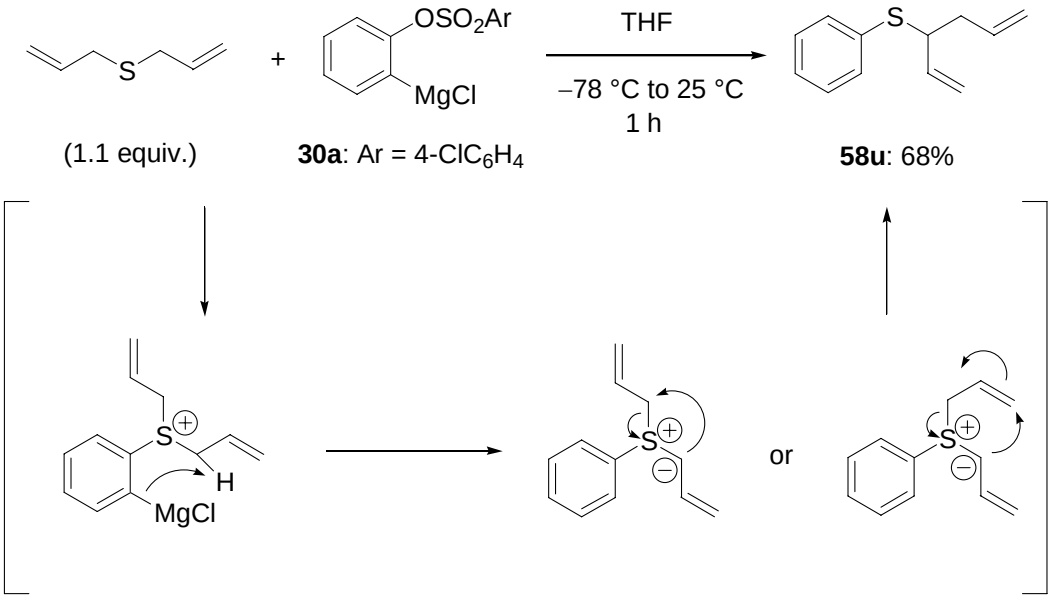




[a]2.0 equiv. of aliphatic thiolate was used to trap the intermediate benzyne.
[b]1.0 equiv. of aliphatic thiolate was used to trap the intermediate benzyne.

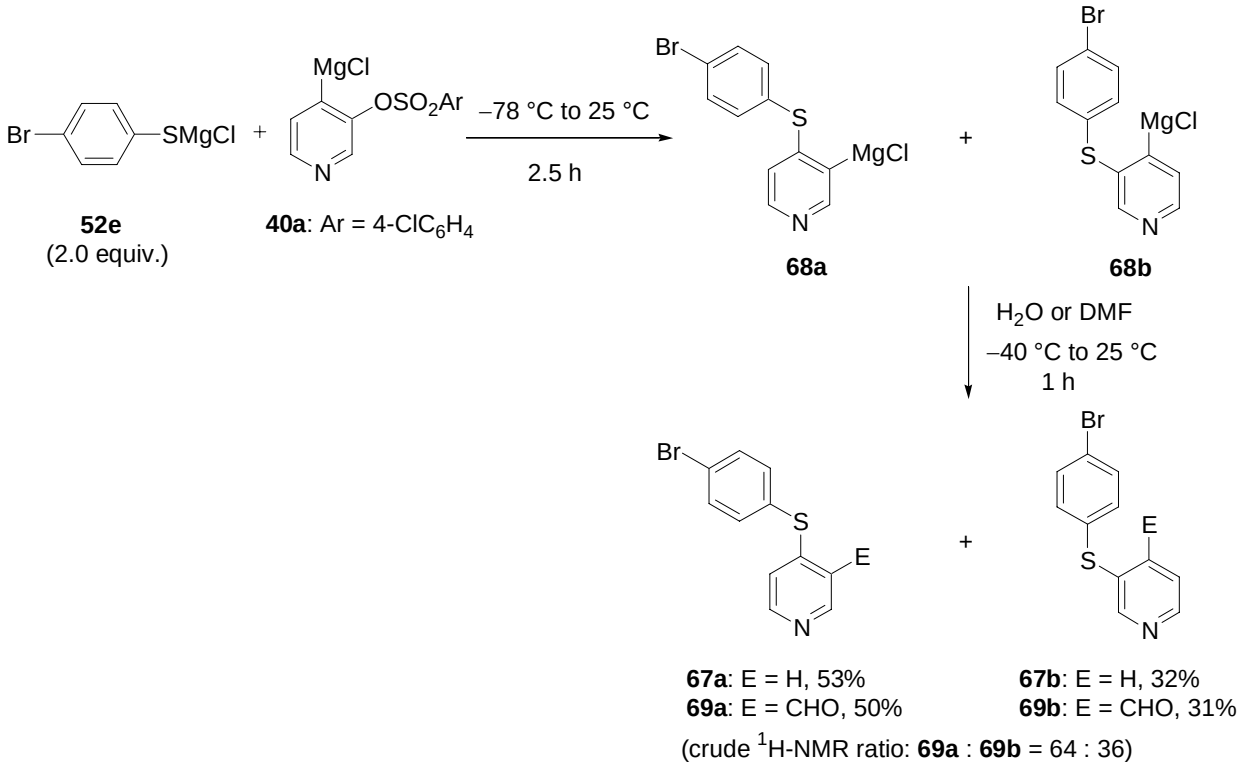
Scheme 69. Preparation of aryl thioethers **58q-t** *via* the addition of **52i** or **52j** to **16a** followed by quenching with electrophiles.

Due to the strong nucleophilicity of sulfur atom, even a neutral sulfide, such as diallylsulfide, could trap benzyne (**16a**) successfully to give rise to **58u** in 68 % yield (Scheme 70).



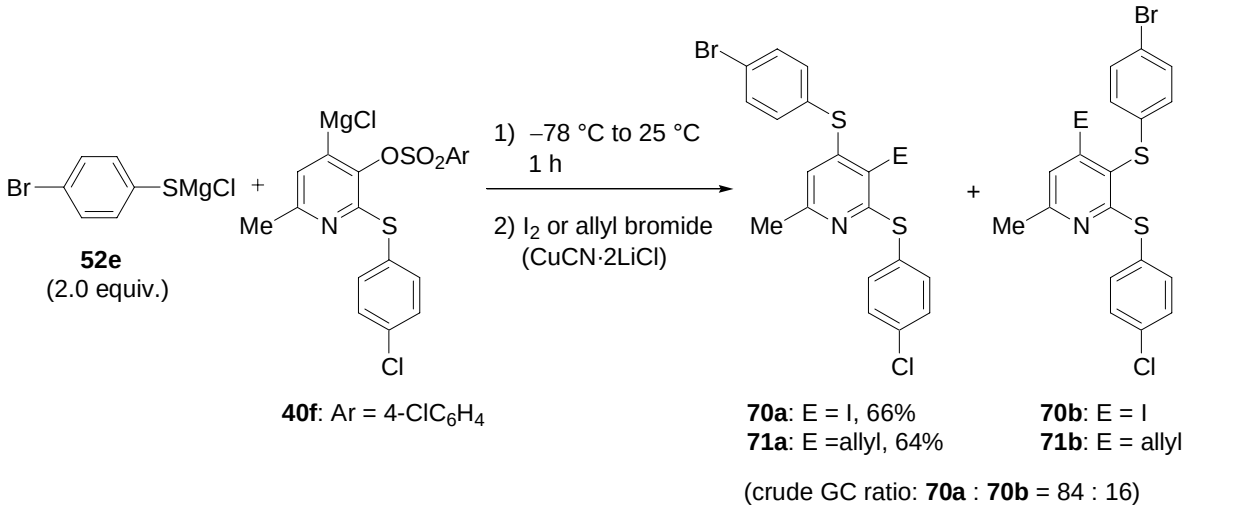
Scheme 70. The addition of diallylsulfide to **16a**.

Interestingly, the magnesium arylthiolate **52e** (2.0 equiv.) added successfully to 3,4-pyridyne (**38a**) followed by quenching with water leading to **67a** and **67b** in 53 % and 32 % yields, respectively. The Grignard reagents **68a** and **68b** could also be formylated with DMF furnishing **69a** and **69b** in 50 % and 31 % yields (crude ^{1}H-NMR ratio = **69a** : **69b** = 64 : 36) (Scheme 71).



Scheme 71. The addition of the magnesium arylthiolate **52e** to 3,4-pyridyne (**38a**).

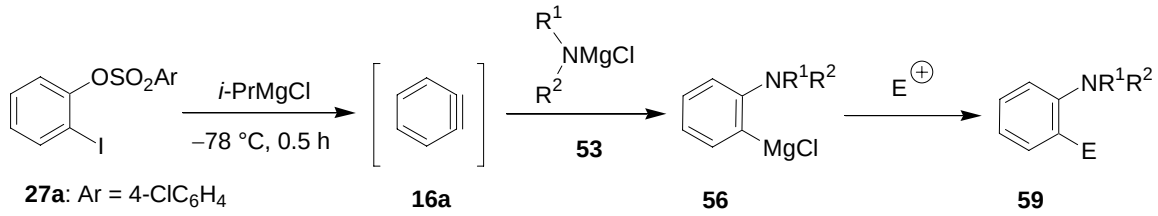
The magnesium arylthiolate **52e** (2.0 equiv.) also added to the functionalized 3,4-pyridyne **38f** followed by quenching with iodine leading to a mixture of **70a** and **70b** (crude GC ratio = **70a** : **70b** = 5.4 : 1), from which **70a** was isolated in 66 % yield. The corresponding Grignard reagents underwent allylation with allyl bromide in the presence of CuCN·2LiCl furnishing **71a** in 64 % yield (Scheme 72).



Scheme 72. The addition of the magnesium arylthiolate **52e** to the functionalized 3,4-pyridyne **38f**.

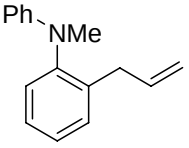
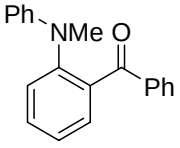
4.3 Preparation of functionalized arylmagnesium reagents by the addition of magnesium aryl amides to benzyne

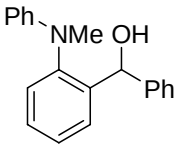
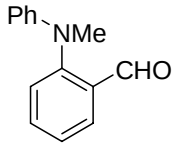
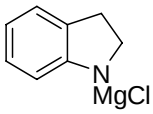
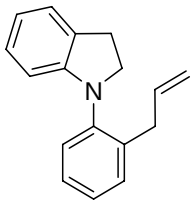
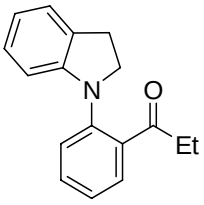
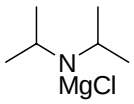
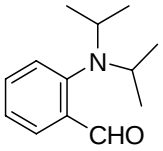
Remarkably, all the previous reactions involved the conversion of the magnesium-sulfur bond of **52** to the magnesium-carbon bond in **55**. We have also examined the addition of magnesium amides of type **53** to benzyne (**16a**) resulting in the conversion of a nitrogen-magnesium bond to a carbon-magnesium bond in the product **56** (Scheme 73). Thus, the reaction of magnesiated *N*-methylaniline (**53a**) with **16a** provided the desired addition product of type **56** (−78 °C, 30 min, then 0 °C for 10 min). After the addition of CuCN·2LiCl and allyl bromide, the desired product **59a** was obtained in 83 % yield (Table 5, entry 1). Typical electrophiles, such as benzoyl chloride, benzaldehyde, and DMF, reacted similarly furnishing the diarylamines **59b-d** in 74-85 % yields (entries 2-4). Related phenyl-substituted secondary magnesium amides, such as **53b** (entries 5-6) reacted in a similar way leading to the indolines **59e-f** (62-66 % yields). Sterically hindered aliphatic amides like *i*-Pr_2NMgCl (**53c**) were less prone to add to **16a** and gave rise to the desired product **59g** (after formylation) only in 25 % yield (entry 7).



27a: Ar = 4-ClC_6H_4 **16a** **53** **56** **59**

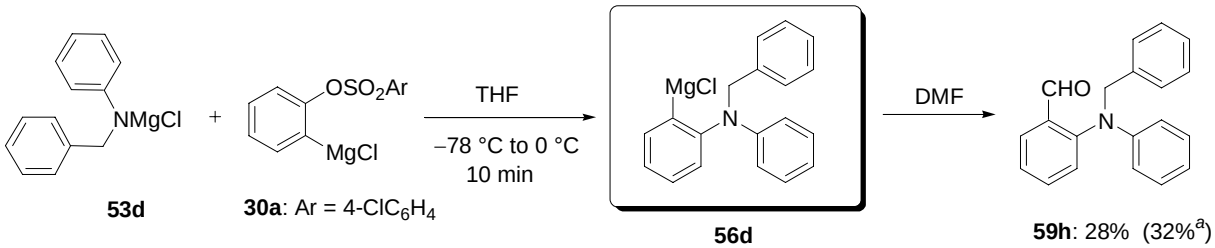
Scheme 73 and **Table 5**. Tertiary amines **59a-g** obtained by the addition of magnesium amides **53a-c** to **16a** followed by the trapping of the intermediate Grignard reagents **56a-c** with electrophiles.

Entry	Mg-amide of type **53**	Electrophile	Amine of type **59**	Yield (%)[a]
1	Ph(Me)NMgCl **53a**	Allyl bromide[b]	 **59a**	83
2	**53a**	PhCOCl[b]	 **59b**	85

3	**53a**	PhCHO	 **59c**	80
4	**53a**	DMF	 **59d**	74
5	 **53b**	Allyl bromide[b]	 **59e**	66
6	**53b**	EtCOCl[b]	 **59f**	62
7	 **53c**	DMF	 **59g**	25

[a] Isolated yield of analytically pure product. [b] The reaction was performed with 1.0 equiv. CuCN·2LiCl.

Highly sterically hindered phenyl-substituted secondary magnesium amides, such as **53d**, reacted in a similar way leading to the benzaldehyde **59h** only in 28 % yield (Scheme 74).

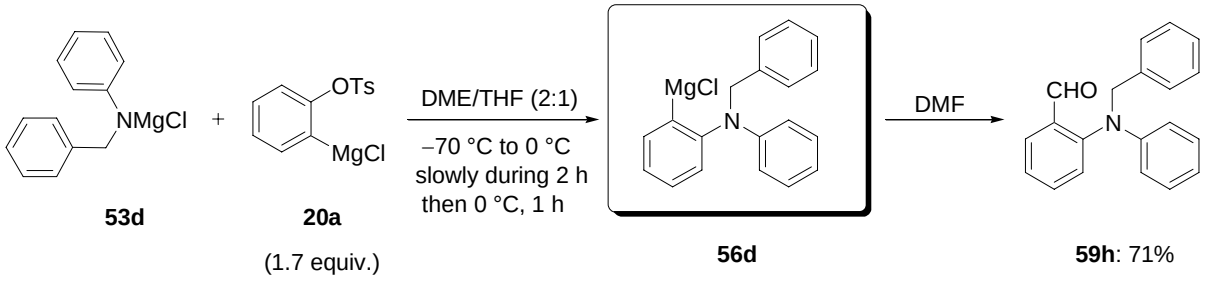


53d **30a**: Ar = 4-ClC$_6$H$_4$ **56d** **59h**: 28% (32%[a])

[a] 3.0 equiv. of **53d** was used to trap the intermediate benzyne.

Scheme 74. Preparation of the arylamine **59h** *via* the addition of **53d** to **16a** followed by formylation with DMF.

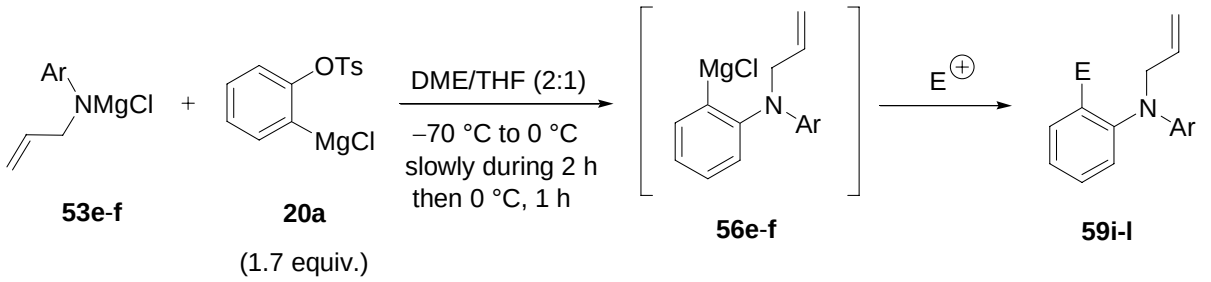
After screening different solvent systems for this reaction, it was found that the addition of DME as a cosolvent decreased the rate of formation of benzyne (**16a**). Therefore the low concentration of active **16a** avoided the occurance of the side reactions. In addition, the highly steric hindrance of the corresponding Grignard reagent **56d** hampered the addition of **56d** to **16a**. After optimization of the reaction conditions, compound **56d** could be formed followed by formylation with DMF giving rising to **59h** in 71 % yield (Scheme 75).



53d **20a** (1.7 equiv.) **56d** **59h**: 71%

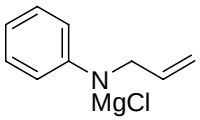
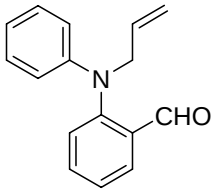
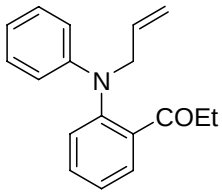
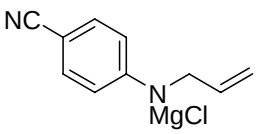
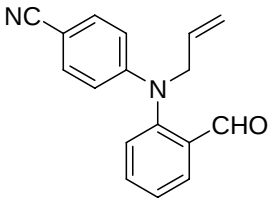
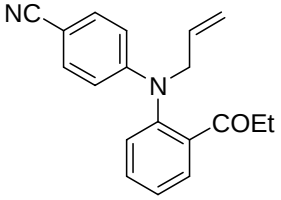
Scheme 75. Preparation of the arylamine **59h** *via* the addition of **53d** to **16a** followed by formylation with DMF.

A highly sterically hindered magnesium allylphenylamide **53e** or even a functionalized magnesium amide such as **53f** underwent the addition reaction to **16a** under the same reaction conditions providing polyfunctional arylmagnesium species **56e** or **56f**, which were efficiently trapped with DMF or EtCOCl furnishing the tertiary amines **59i-l** in 73-77 % yields (Scheme 76, Table 6).



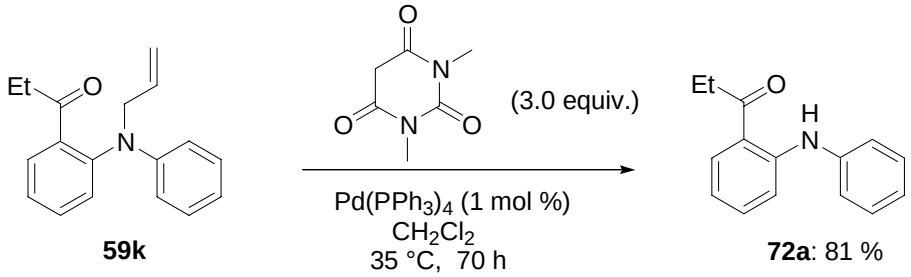
53e-f **20a** (1.7 equiv.) **56e-f** **59i-l**

Scheme 76 and **Table 6**. Tertiary amines **59i-l** obtained by the addition of magnesium amides **53e-f** to **16a** followed by the trapping of the intermediate Grignard reagents **56e-f** with electrophiles.

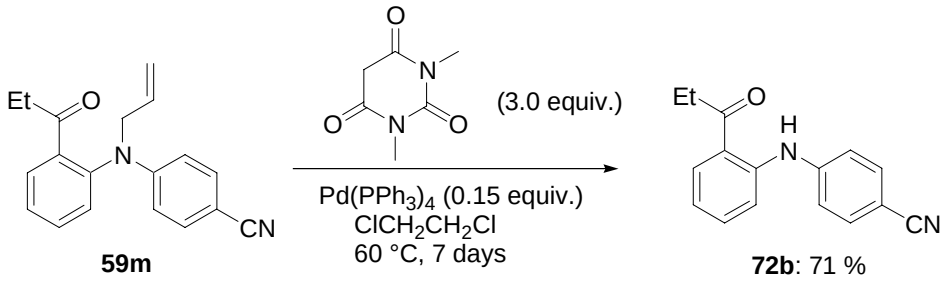
Entry	Mg-amide of type **53**	Electrophile	Amine of type **59**	Yield (%)[a]
1	 **53e**	DMF	 **59i**	75
2	**53e**	EtCOCl[b]	 **59j**	77
3	 **53f**	DMF	 **59k**	73
4	**53f**	EtCOCl[b]	 **59l**	76

[a] Isolated yield of analytically pure product. [b] The reaction was performed with 1.0 equiv. CuCN·2LiCl.

After deallylation according to a modified procedure from the literature[93], **59j** and **59l** were converted to the functionalized diarylamines **72a-b** in 71-81 % yields (Scheme 77).

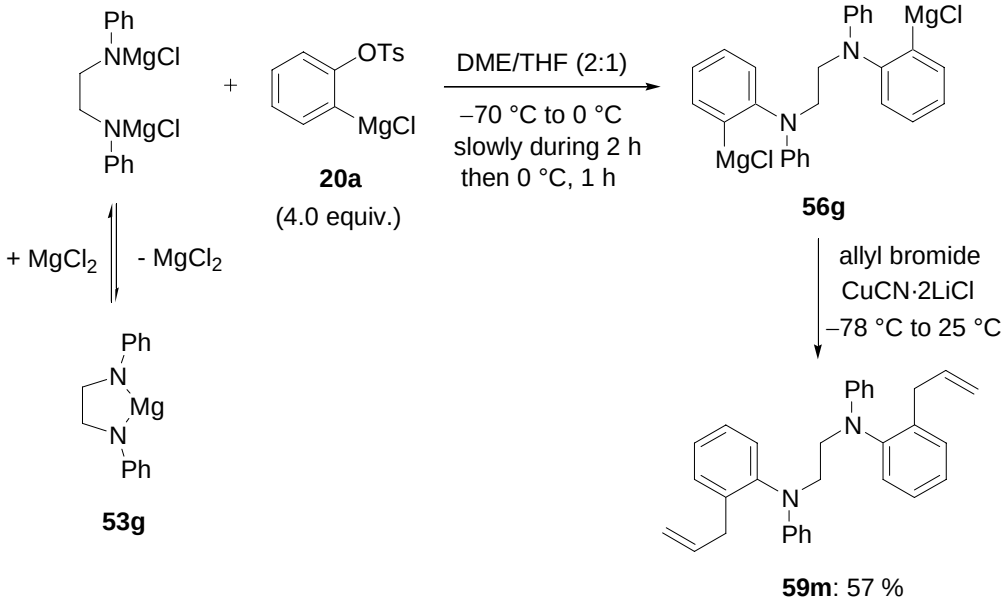


[93] F. Garro-Helion, A. Merzouk, F. Guibé, *J. Org. Chem.* **1993**, *58*, 6109.



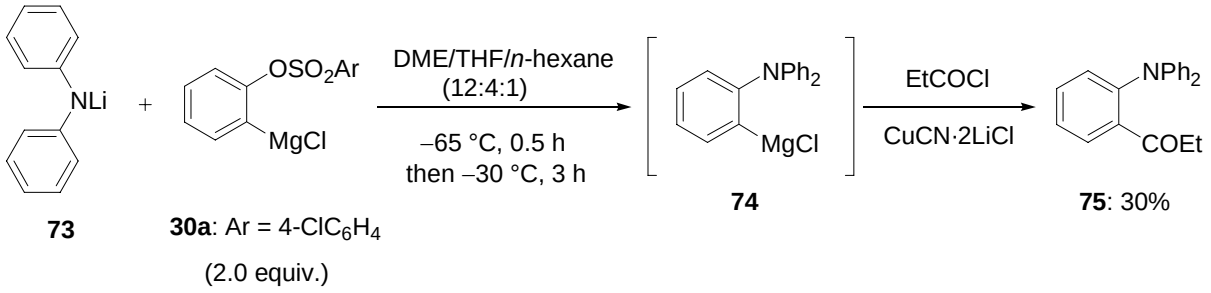
Scheme 77. Preparation of functionalized diarylamines **72a-b** *via* deallylation.

Magnesiated *N*,*N*′-diphenyl-ethane-1,2-diamine **53g** added to **16a** (4.0 equiv.) under the same reaction conditions providing the corresponding Grignard reagent **56g**. It was further reacted with allyl bromide (8.0 equiv.) in the presence of CuCN·2LiCl (1.0 equiv.) providing the tertiary amine **59m** in 57 % yield (Scheme 78).



Scheme 78. Preparation of the tertiary amine **59m** *via* the addition of **53g** to **16a** followed by allylation.

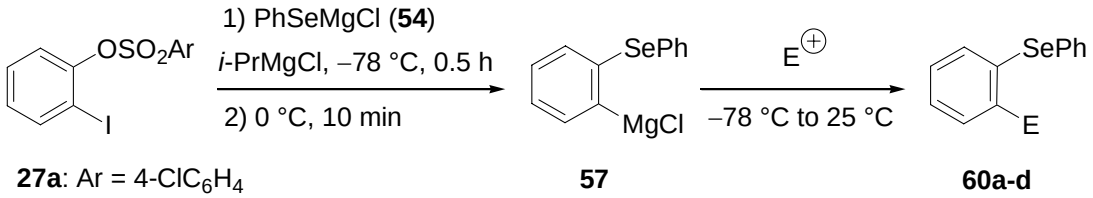
A weaker nitrogen nucleophile, such as lithium diphenylamide (**73**), was demonstrated to be a poor trapping reagent for **16a**. After optimization of the reaction conditions, the corresponding organometallic reagent **74**, resulting from the addition of **73** to **16a**, was quenched with propionyl chloride (2.0 equiv.) in the presence of CuCN·2LiCl (1.0 equiv.) leading to the functionalized triarylamine **75** in only 30 % yield (Scheme 79).



Scheme 79. Preparation of the functionalized triarylamine **75**.

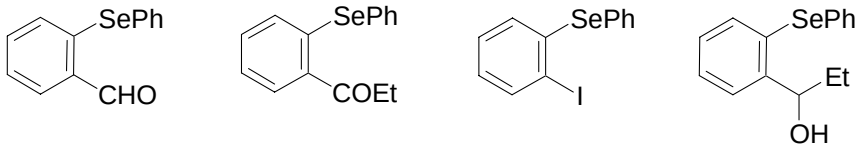
4.4 Preparation of functionalized arylmagnesium reagents by the addition of magnesium phenylselenide to arynes and heteroarynes

During this study, we realized that the rate of the addition to arynes strongly depended on the nucleophilicity of the magnesium reagent (Nu-MgX) as previously noticed by Huisgen.[32] Thus, whereas magnesium amides are basic reagents, magnesium thiolates are more nucleophilic and therefore add more readily. In addition, low steric hindrance was essential for an efficient addition reaction, since hindered amides add significantly less efficiently. Because arylselenoethers are useful compounds which can be further transformed,[94] we anticipated that highly nucleophilic reagents, like magnesium phenylselenide (**54**), would react well with benzyne (**16a**). Preliminary experiments confirmed this hypothesis. Thus, the products **60a-d** (75-87 % yields) were obtained *via* the addition of **54** to **16a** leading to the magnesiated intermediate **57**[95] under standard conditions followed by quenching with different electrophiles (Scheme 80).



[94] (a) D. Seebach, A. K. Beck, *Angew. Chem.* **1974**, *86*, 859; *Angew. Chem. Int. Ed.* **1974**, *13*, 806; (b) W. Dumont, A. Krief, *Angew. Chem.* **1976**, *88*, 184; *Angew. Chem. Int. Ed.* **1976**, *15*, 161; (c) A. Krief, W. Dumont, J. N. Denis, *Chem. Commun.* **1985**, 571.

[95] A. Krief, T. Van Wemmel, M. Redon, W. Dumont, C. Delmotte, *Angew. Chem. Int. Ed.* **1999**, *38*, 2245; *Angew. Chem. Int. Ed. Engl.* **1999**, *111*, 2389.

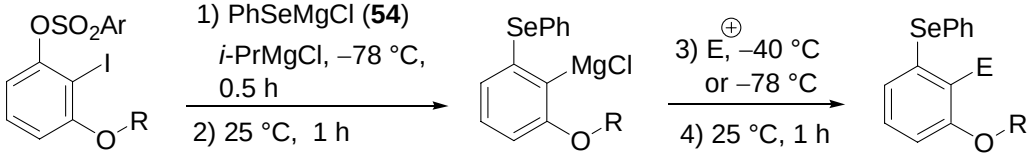


60a: 85% **60b**: 87% **60c**: 78% **60d**: 75%

Electrophile = DMF (**60a**); EtCOCl, CuCN·2LiCl (**60b**); I_2 (**60c**); EtCHO (**60d**).

Scheme 80. Preparation of aryl selenoethers **60a-d** *via* the addition of **54** to **16a** followed by quenching with electrophiles.

Herein, we also studied the regioselective addition of magnesium phenylselenide (**54**) to arynes **16j-l** generated by our procedure, providing 2-seleno-substituted arylmagnesium species of type **76**. The resulting arylmagnesium reagents **76** can be trapped by a range of electrophiles, yielding aryl selenoethers of type **77** (Scheme 81 and Table 7).



Ar = 4-ClC_6H_4

27h: R = Me
27i: R = Bn
27j: R = TES

76a: R = Me
76b: R = Bn
76c: R = TES

77a-j

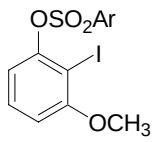
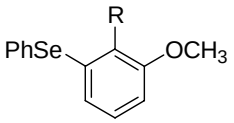
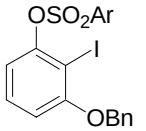
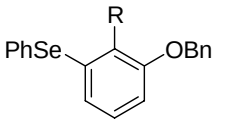
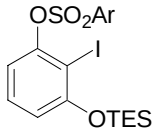
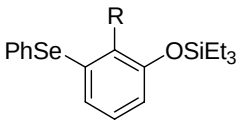
Scheme 81. Preparation of aryl selenoethers **77** *via* the addition of **54** to arynes followed by quenching with electrophiles.

Thus, the addition of *i*-PrMgCl (2.0 equiv.) to phenylselenol (1.0 equiv.) in THF (−78 °C, 0.5 h) followed by the addition of 2-iodo-3-methoxyphenyl 4-chlorobenzenesulfonate (**27h**) (1.0 equiv.; −78 °C, 0.5 h) and subsequent stirring at ambient temperature for 1 h led to the aryne-addition product **76a**, which upon quenching with water provided 1-methoxy-3-(phenylseleno)-benzene (**77a**) in 85 % isolated yield (Table 7, entry 1). Similarly, the intermediate Grignard reagent **76a** was formylated with DMF (1.5 equiv., –40 °C to 25 °C, 1 h), leading to 2-methoxy-6-(phenylseleno)-benzaldehyde (**77b**) in 70 % yield (entry 2). Allyl bromide and benzoyl chloride (in the presence of CuCN·2LiCl) also served as excellent electrophiles, yielding **77c** and **77d** in 82 % and 77 %, respectively (entries 3 and 4).

The intermediate Grignard reagent **76b**, which was formed from 2-iodo-3-benzyloxyphenyl 4-chlorobenzenesulfonate (**27i**) under the same reaction conditions as **76a**, was successfully

quenched with a range of electrophiles to give rise to the corresponding products **77e** (84 % yield), **77f** (72 % yield), **77g** (74 % yield), and **77h** (76 % yield), respectively (entries 5-8). Even the more sterically hindered Grignard reagent **76c** generated from 2-iodo-3-triethylsilanyloxyphenyl 4-chlorobenzenesulfonate (**27j**), was successfully trapped with iodine (1.5 equiv., −78 °C to 25 °C, 1 h) to give rise to **77i** in 51 % yield (entry 9). Furthermore, the reaction of **76c** with allyl bromide gave rise to the allylated selenoether **77j** in 45 % yield (entry 10).

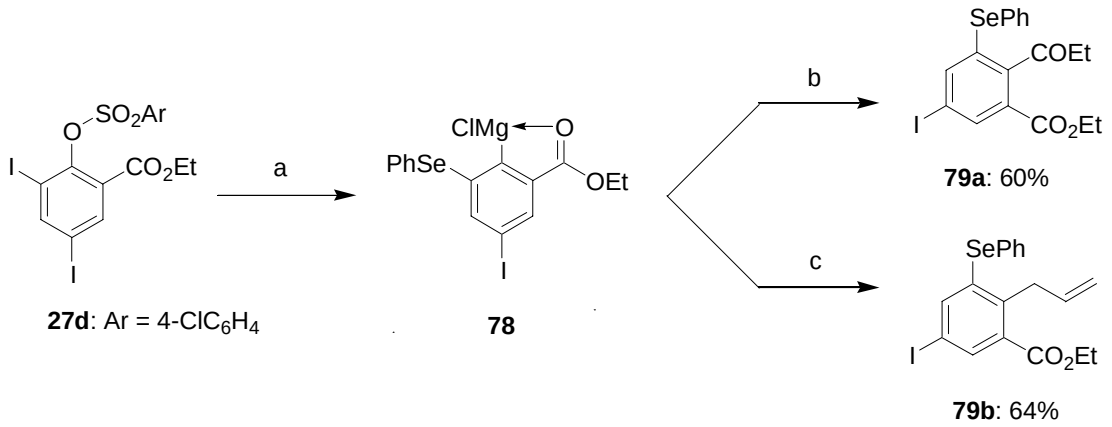
Table 7. Syntheses of selenoethers of type **77** *via* the addition of magnesium phenylselenide **54** to arynes followed by the trapping of the intermediate Grignard reagents **76** with electrophiles (see Scheme 81).

Entry	**27**	Electrophile	Product of type **77**	Yield (%)[a]
				
1		H_2O	**77a**: R = H	85
2		DMF	**77b**: R = CHO	70
3		Allyl bromide[b]	**77c**: R = allyl	82
4	**27h**	PhCOCl[c]	**77d**: R = COPh	77
				
5		H_2O	**77e**: R = H	84
6		DMF	**77f**: R = CHO	72
7		Allyl bromide[b]	**77g**: R = allyl	74
8	**27i**	PhCOCl[c]	**77h**: R = COPh	76
				
9		I_2	**77i**: R = I	51
10	**27j**	Allyl bromide[b]	**77j**: R = allyl	45

[a] Yield of analytically pure isolated product. [b] The reaction was performed with 0.5 equiv. CuCN·2LiCl. [c] The reaction was performed with 1.0 equiv. CuCN·2LiCl.

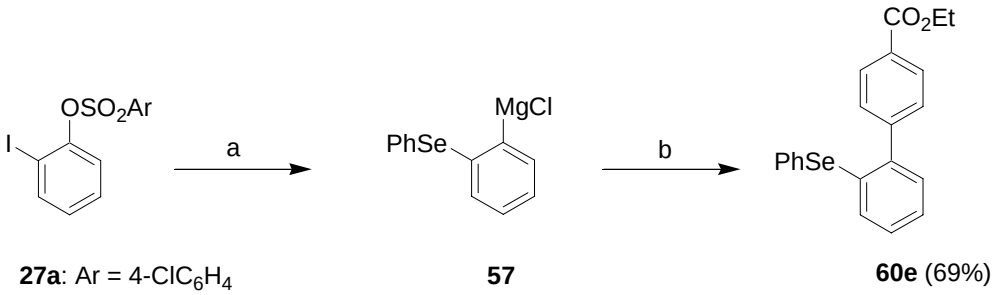
A functionalized aryne displayed a remarkable regioselectivity in the addition step. Thus the polyfunctional sulfonate **27d** was selectively magnesiated at the *ortho*-position of the sulfonate group, and its reaction with magnesium phenylselenide (**54**) provided selectively the magnesiated reagent **78**, which was stabilized by chelation. Its reaction with electrophiles, such as an acid chloride, or allyl bromide in the presence of CuCN·2LiCl, furnished the

tetrasubstituted selenoethers **79a** (60 % yield) and **79b** (64 % yield), respectively (Scheme 82).



Scheme 82. (a) THF, PhSeMgCl (**54**) (2.0 equiv.), *i*-PrMgCl (1.0 equiv.), −78 °C, 0.5 h; 25 °C, 2 h; (b) CuCN·2LiCl (1.0 equiv.), −78 °C, 10 min; EtCOCl (3.0 equiv.), −78 °C to 25 °C, 1 h; (c) CuCN·2LiCl (0.5 equiv.), −78 °C, 10 min; allyl bromide (3.0 equiv.), −78 °C to 25 °C, 1 h.

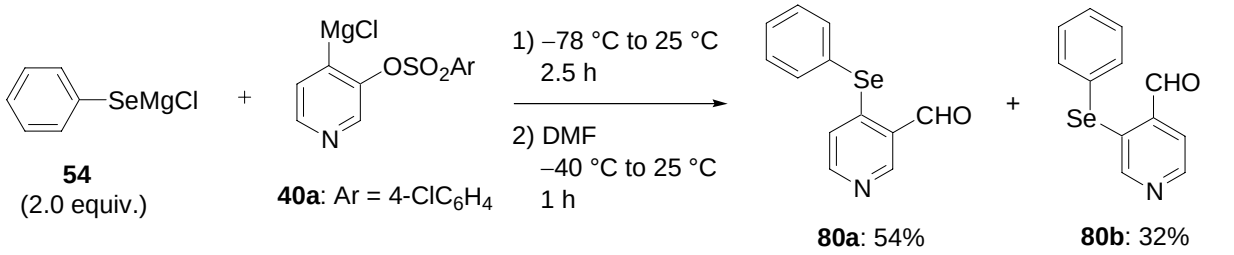
Furthermore, the arylmagnesium reagent **57**, which resulted from the reaction of **54** with **27a** under similar reaction conditions, could be subjected to a Negishi cross-coupling reaction. After transmetalation with $ZnBr_2$, the corresponding zinc reagents could react with an iodoarene, like ethyl iodobenzoate, under standard reaction conditions furnishing functionalized biaryl **60e** in 69 % yield (Scheme 83).[96]



Scheme 83. (a) THF, PhSeMgCl (**54**) (1.0 equiv.), *i*-PrMgCl (1.0 equiv.), −78°C, 0.5 h; 0 °C, 10 min; (b) $ZnBr_2$ (1.0 equiv.), −78 °C, 10 min; ethyl iodobenzoate (1.5 equiv.), $Pd(dba)_2$ (5 mol %), tfp (10 mol %), −40 °C to 25 °C, 5 h.

[96] W. Lin, F. Ilgen, P. Knochel, *Tetrahedron Lett.* **2006**, *47*, 1941; please also see: F. Ilgen, Diploma Thesis, LMU, Munich **2005**.

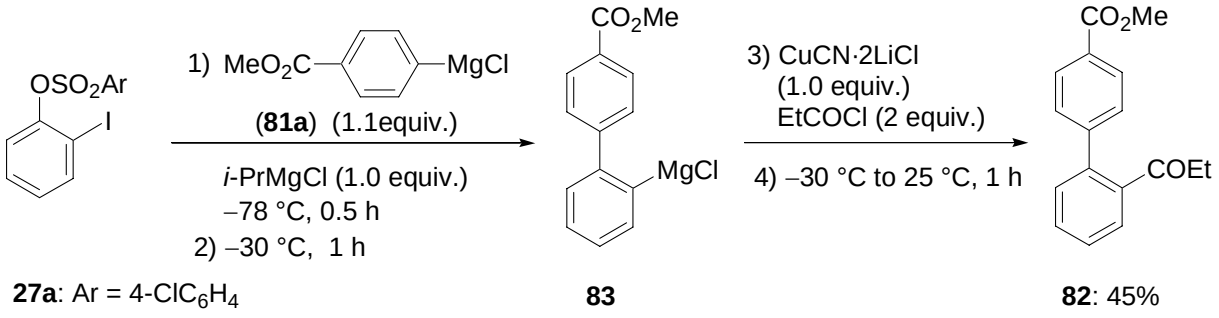
Interestingly, magnesium phenylselenide (**54**) also added successfully to 3,4-pyridyne (**38a**) followed by quenching with DMF leading to **80a** and **80b** in 54 % and 32 % yields (crude ^{1}H-NMR ratio = **80a** : **80b** = 62 : 38) (Scheme 84).



Scheme 84. The addition of magnesium phenylselenide (**54**) to 3,4-pyridyne (**38a**).

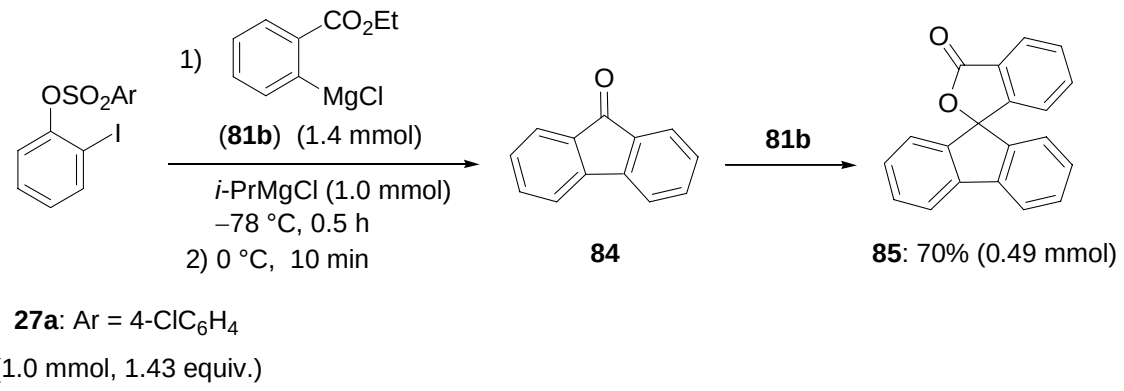
4.5 Preparation of functionalized arylmagnesium reagents by the addition of magnesium carbanions to benzyne

Carbon and oxygen nucleophiles were also examined on the addition reaction to arynes. The Grignard reagent **81a**, which was resulted from the reaction of methyl 4-iodobenzoate with *i*-PrMgCl *via* the I/Mg-exchange (30 min, −40 °C), added to benzyne (**16a**) followed by quenching with propionyl chloride (in the presence of CuCN·2LiCl) leading to the functionalized biaryl **82** in 45 % yield. The low yield was partly due to the side reaction resulting from the addition of **83** to **16a** (Scheme 85).



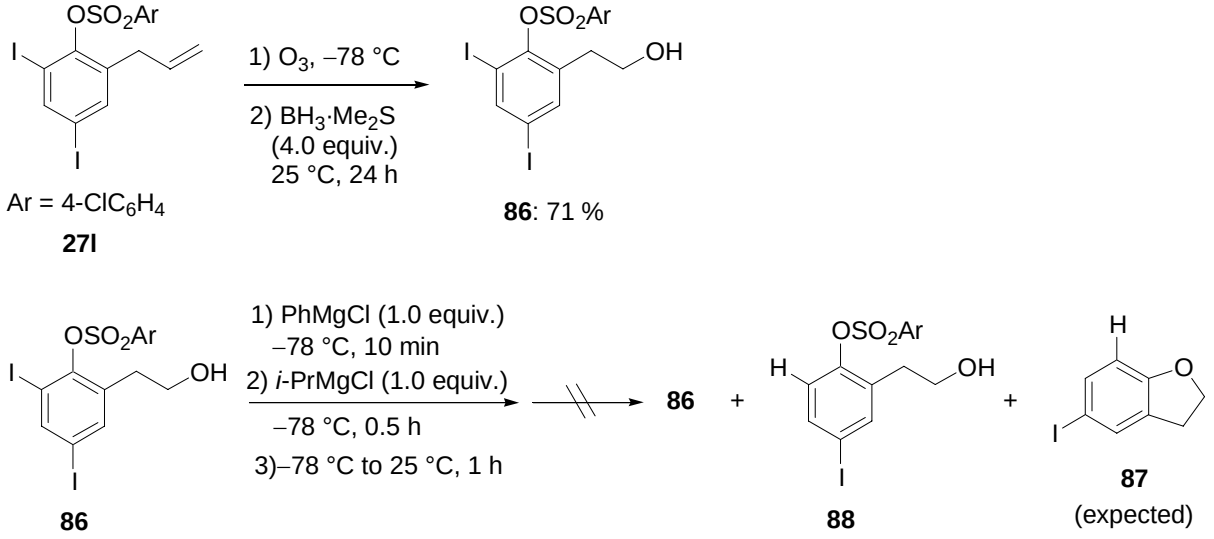
Scheme 85. Preparation of a functionalized biaryl **82**.

One the other hand, a carbon nucleophile, such as **81b**, bearing an ester group in the *ortho*-position, added to **16a** followed by an intramolecular cyclization leading to fluoren-9-one (**84**), which was reacted further with **81b** giving rise to **85** in 70 % yield (Scheme 86).



Scheme 86. The addition of the Grignard reagent **81b** to benzyne (**16a**).

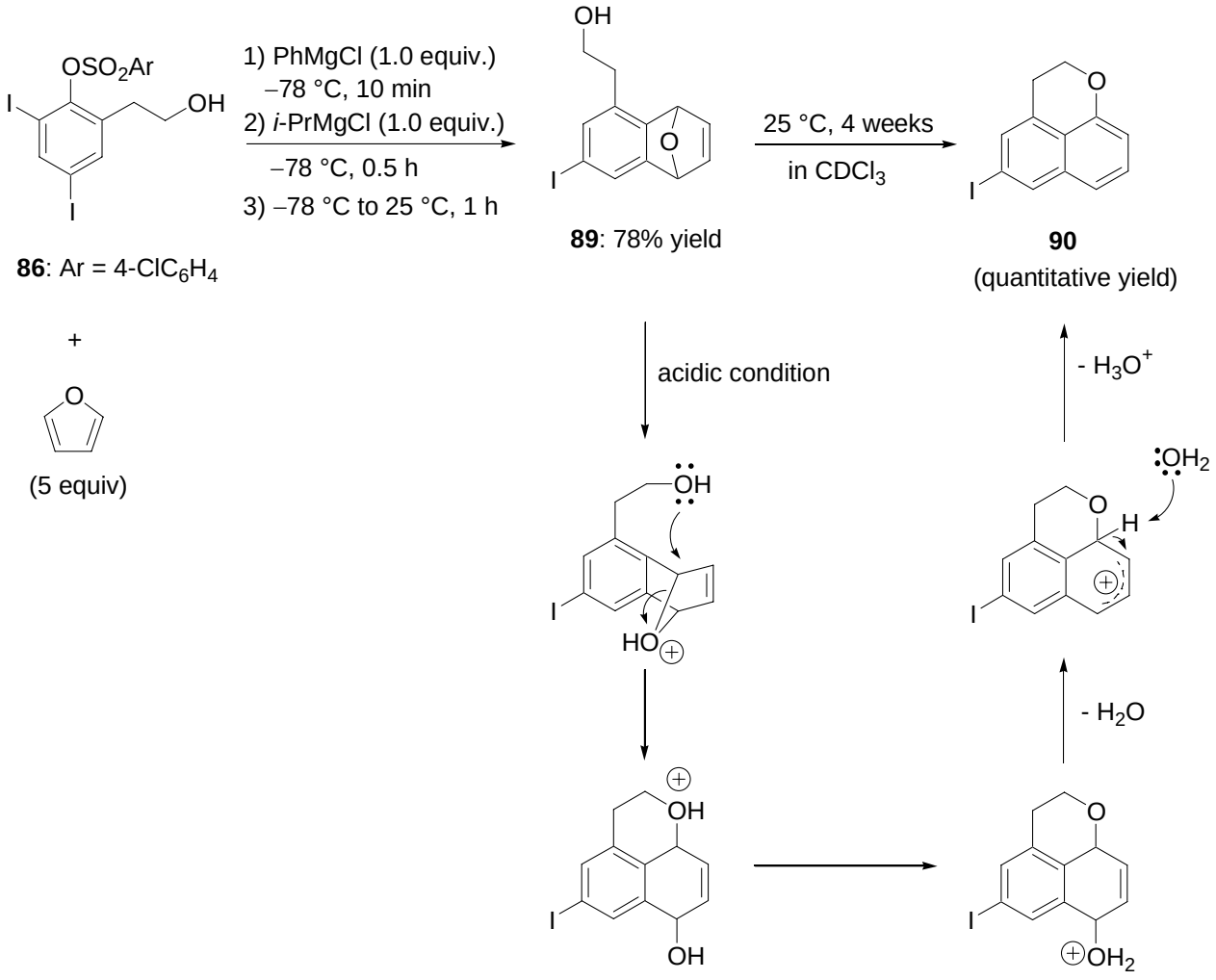
Various oxygen nucleophiles, including magnesium phenoxide and alkoxides, were examined. All of them failed to add to benzyne (**16a**) probably due to their low nucleophilicity to **16a**. The aryne precursor **86** was also prepared in order to examine if the aryne can be trapped more efficiently through an intramolecular nucleophilic addition of an oxygen nucleophile. **86** was prepared from ozonolysis of **27l** followed by reduction with $BH_3{\cdot}Me_2S$ (4.0 equiv.) in 71 % yield (Scheme 87). Then, **86** was reacted first with PhMgCl (1.0 equiv.; −78 °C, 10 min) followed by adding *i*-PrMgCl (1.0 equiv.; −78 °C, 30 min), and the reaction mixture was warmed to 25 °C for 1 h. The expected product **87** was not observed, as well as neither **86** nor **88** (Scheme 87).



Scheme 87. Preparation of **86** and a test of the addition reaction of an oxygen nucleophile to an aryne.

These results implied that the aryne was probably formed owing to the comsuption of **86** and **88**. Besides, the expected addition product **87** was not observed probably due to the too low

nucleophilicity of oxygen. In order to prove that the aryne was formed in the media, furan (5.0 equiv.) was used *in situ* as a trapping reagent. The compound **89** was formed from a Diels–Alder reaction of the resulting aryne with furan in 78 % yield. **89** was not stable in $CDCl_3$ and was slowly converted to **90** in quantitative yield (Scheme 88).



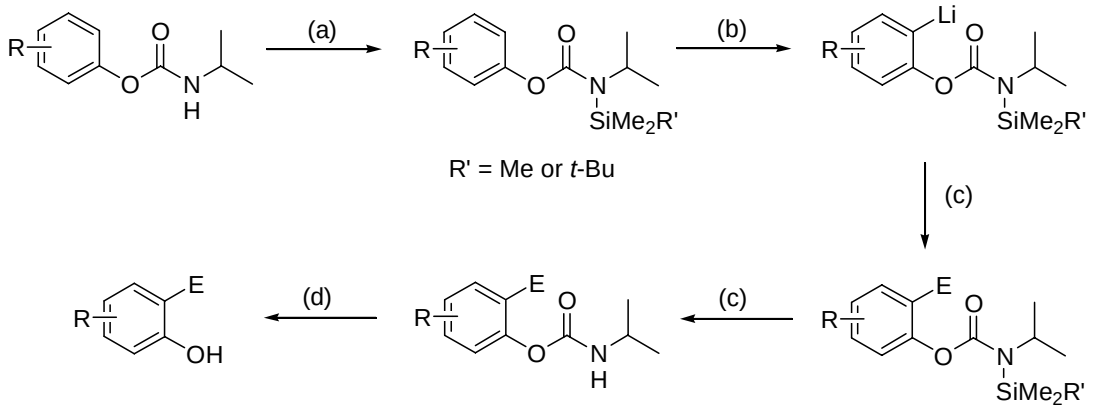
Scheme 88. Preparation of **89** *via* the formation of an aryne bearing an alkoxy side-chain.

5. Highly Functionalized Benzenes Syntheses by Directed Mono or Multiple Magnesiations Using TMPMgCl·LiCl

5.1 Introduction

After a brief allusion to the current status of synthetic aromatic chemistry, the Directed-*ortho*-Metalation (D*o*M) strategy is added to the armamentarium of the synthetic chemist as a general, regioselective, and effective strategy for the rational construction of polysubstituted aromatic or, even more commonly, heteroaromatic substances.[11b,11c, 97] Especially, while examination of alternative routes is undeniable, the approach to the construction of a key aromatic starting material by D*o*M is desirable. The strategy of D*o*M is frequently used in small-scale syntheses although it is also accepted in a higher-scale process routes to drug candidates and commercial pharmaceuticals and agrochemicals.

Aryllithiums can be readily obtained by directed lithiation combined with the D*o*M strategy. Although less sensitive functional groups on aryllithiums can be tolerated compared to those on arylmagnesium reagents, they have found wide applications. For example, in 2006, Hoppe reported the synthesis of functionalized phenols by directed *ortho*-lithiation of *in situ N*-silylated *O*-aryl *N*-isopropylcarbamates (Scheme 89).[11o,11p] Until now, arylmagnesium species prepared by using magnesium amides as bases have found fewer applications due to their lower basicity.



Scheme 89. Directed *ortho*-lithiation of *N*-silylated *O*-aryl *N*-isopropylcarbamates. Reagents and conditions: (a) TMSOTf or TBSOTf, TMEDA, Et_2O, rt, 30 min; (b) *n*- or *s*-

[97] For selective reviews, see: reference 11k and 13b.

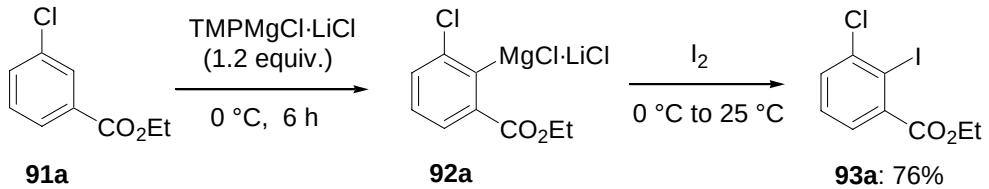
BuLi/TMEDA, −78 °C, 1 h; (c) an electrophile (E^+), −78 °C, 1 h; (d) 2 M HCl, −78 °C to rt; (e) 2 M NaOH, EtOH, rt, 2 h.

There is a renewed interest for the magnesium bases,[18,19,98] since it has been shown that arylmagnesium species are compatible with electrophilic functional groups such as an ester, a nitrile or even a ketone.[6,99] Recently, we have developed a new class of magnesium bases of type $R_2NMgCl{\cdot}LiCl$ (**2a** or **2b**) which, due to the presence of LiCl, display an excellent solubility in THF (up to 1.2 M for TMPMgCl·LiCl) as well as an enhanced kinetic basicity which has allowed a selective magnesiation of a broad range of functionalized heterocycles.[20] Accordingly, the use of these bases in combination with the directing group effect for the preparation of highly functionalized benzenes was studied.

5.2 Preparation of Boc-protected polyfunctionalized phenols *via* magnesiations using TMPMgCl·LiCl followed by trapping with electrophiles

5.2.1 Optimization of the nature of the protecting group for the generation of Grignard reagents

Although the *ortho*-magnesiation of ethyl benzoate with stoichiometric amounts of TMPMgCl·LiCl proved to be sluggish indicating that an ester group was only a moderately active directing group,[100] in the presence of a *meta*-chlorine atom, a smooth magnesiation of ethyl 3-chlorobenzoate (**91a**) took place at 0 °C within 6 h using TMPMgCl·LiCl (1.2 equiv.) as a base. The desired arylmagnesium species (**92a**) was obtained and furnished after iodolysis the expected aryl iodide (**93a**) in 76 % yield (Scheme 90). This experiment indicates that the electron-density of aromatic rings is also of importance and that electron-poor benzenes are more prone to magnesiation.



91a **92a** **93a**: 76%

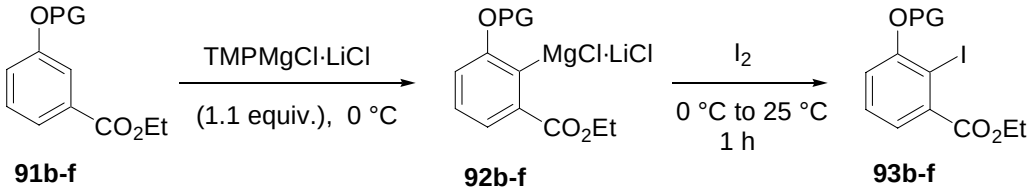
[98] a) P. C. Andrikopolous, D. R. Armstrong, D. V. Graham, E. Hevia, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, C. Talmard, *Angew. Chem.* **2005**, *117*, 3525; *Angew. Chem. Int. Ed.* **2005**, *44*, 3459; b) P. E. Eaton, M.-X. Zhang, N. Komiya, C.-G. Yang, I. Steele, R. Gilardi, *Synlett* **2003**, *9*, 1275.

[99] a) F. F. Kneisel, P. Knochel, *Synlett* **2002**, 1799; b) W. Lin, I. Sapountzis, P. Knochel, *Angew. Chem.* **2005**, *117*, 4330; *Angew. Chem. Int. Ed.* **2005**, *44*, 4258; c) C.-Y. Liu, H. Ren, P. Knochel, *Org. Lett.* **2006**, *8*, 617.

[100] a) The conversion of the starting material was very slow even at 25 °C and no desired magnesiated product was observed; see also: P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016.

Scheme 90. Magnesiation of ethyl 3-chlorobenzoate (**91a**) using TMPMgCl·LiCl followed by iodolysis.

Therefore, we have directed our attention toward various derivatives of ethyl 3-hydroxybenzoate such as the corresponding pivalate (**91b**), the *N*,*N*-dimethylcarbamate (**91c**), and the Boc-derivative (**91d**). These aromatics were submitted to a magnesiation using TMPMgCl·LiCl (1.1 equiv.) at 0 °C. The formation of the intermediate arylmagnesium reagents (**92b-d**) was monitored by GC-analysis of reaction aliquots. It was observed that the pivalate **91b** was only slowly metalated and led to the formation of significant amounts of side-products. After quenching with iodine, the expected aryl iodide (**93b**) was detected in only about 20 % yield by GC analysis (Scheme 91 and entry 1 of Table 8). The carbamate **91c** was magnesiated much more readily, but never led to a complete conversion. After iodolysis, the aryl iodide **93c** was obtained in 50 % yield (entry 2). However, by using the Boc-protected hydroxybenzoate (**91d**), a complete magnesiation was obtained at 0 °C within 3 h and led cleanly to the arylmagnesium reagent **92d**. After iodolysis, the aryl iodide **93d** was isolated in 86 % yield (entry 3).



91b-f **92b-f** **93b-f**

OPG = OCO*t*Bu **(91b)**, $OCONMe_2$ **(91c)**, OCO_2*t*Bu **(91d)**, OCO_2Me **(91e)**, OCO_2Et **(91f)**

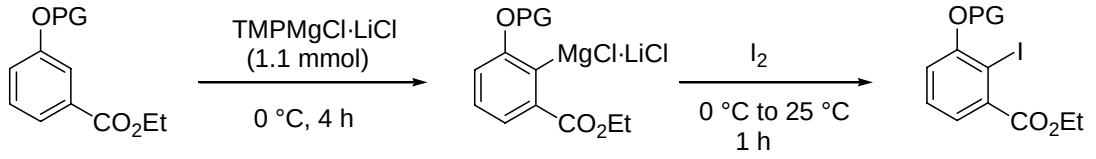
Scheme 91 and **Table 8**. Optimization of the nature of the protecting group for the generation of Grignard reagents **92b-f**.

Entry	Protecting group of **91**	Reaction time (h)	Product **93** (%)[a]
1	*t*-BuCO (**91b**)	20	**93b**, (20)[b]
2	Me_2NCO (**91c**)	3	**93c**, 50 (52)[c]
3	Boc (**91d**)	3	**93d**, 86
4	MeOCO (**91e**)	27	**93e**, (78)[d]

5	EtOCO (**91f**)	2	**93f**, 67

[a] Isolated yield of analytically pure compounds. [b] TMPMgCl·LiCl (1.2 equiv.) was used; there was less than 40 % conversion and the desired product was detected in ca. 20 % by GC analysis. [c] TMPMgCl·LiCl (1.1 equiv.) was used; there was 52 % conversion by GC analysis; the conversion did not increase even after 1 day reaction time and side products occurred by GC analysis. [d] TMPMgCl·LiCl (1.1 equiv.) was used and the reaction was performed at −20 °C; there was 78 % conversion and side products occurred by GC analysis.

This preliminary study indicates that a Boc-group is potentially an excellent directing group for the magnesiation of benzenes using TMPMgCl·LiCl. Competitive studies showed that the magnesiation rate was also several times faster with a Boc-directed group than with a Me_2NCO function (Scheme 92).



91d : **91c** = 1 : 1 (mmol)

91d : OPG = OBoc
91c : OPG = $OCONMe_2$

92d and **92c**

93d and **93c**

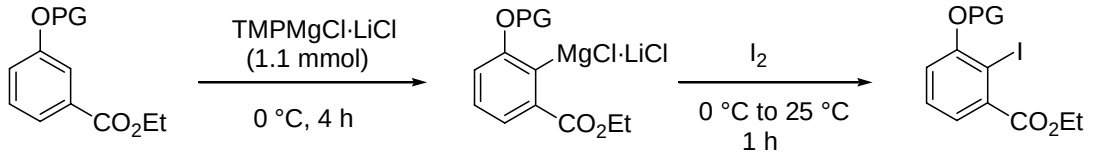
93d: 72% conversion[a]
93c: 20% conversion[a]

[a]The conversion of the starting material was determined by GC-analysis using tridecane as the internal standard.

Scheme 92. Comparisons of the rate of formation of **92c** and **92d** *via* metalation using TMPMgCl·LiCl as a base.

In order to understand the steric influence of the directing group on the metalation reaction, derivatives of ethyl 3-hydroxybenzoate like 3-methoxycarbonyloxy-benzoic acid ethyl ester (**91e**) and 3-ethoxycarbonyloxy-benzoic acid ethyl ester (**91f**) were submitted to a magnesiation using TMPMgCl·LiCl (1.1 equiv.) at 0 °C. The formation of the intermediate arylmagnesium reagents (**92d-f**) was monitored by GC-analysis of reaction aliquots. Not only the strong directing effect but also the high stability of the Boc-group was confirmed by the excellent yield in the preparation of **93d**. Although competitive studies showed that the magnesiation rate was faster with a MeOCO- or EtOCO-directed group than that with a Boc-directed group (Scheme 93), the arylmagnesium species **92e** was not stable at 0 °C and side products occurred before the completeness of the reaction (even when the reaction was performed at −20 °C, the side reaction happened and only 78% conversion was observed after

27 h.) (Table 8, entry 4). The arylmagnesium species **92f** seemed more stable than **92e**, but after iodolysis led to **93f** only in 67 % yield due to side reactions (entry 5).



A) **91d** : **91e** = 1 : 1 (mmol) — **92d** and **92e** — **93d** and **93e**

91d : OPG = OBoc
91e : OPG = OCO_2Me

93d: 35% conversion[a]
93e: 61% conversion[a]

B) **91d** : **91f** = 1 : 1 (mmol) — **92d** and **92f** — **93d** and **93f**

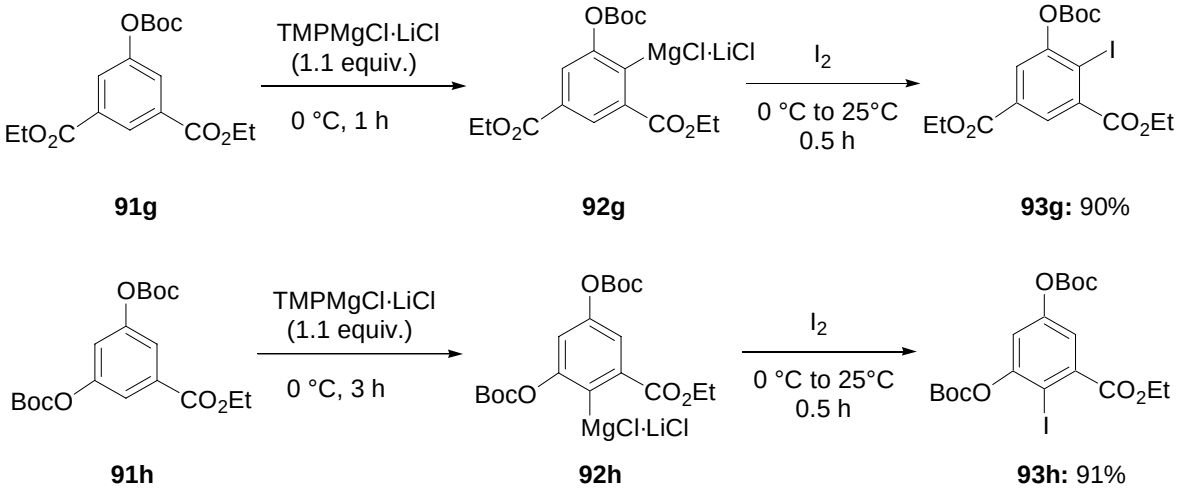
91d : OPG = OBoc
91f : OPG = OCO_2Et

93d: 33% conversion[a]
93f: 52% conversion[a]

[a]The conversion of the starting material was determined by GC-analysis using tridecane as the internal standard.

Scheme 93. Comparisons of the rate of formation of **92d** and **92e** or **92f** *via* metalation using TMPMgCl·LiCl as a base.

A highly regioselective metalation using the Boc-group can be approached. Compounds **91g** or **91f** were magnesiated with TMPMgCl·LiCl (1.1 equiv.) at 0 °C for 1 or 3 h after iodolysis leading to **93g** (90 % yield) or **93h** (91 % yield) as only one isomer, respectively (Scheme 94).

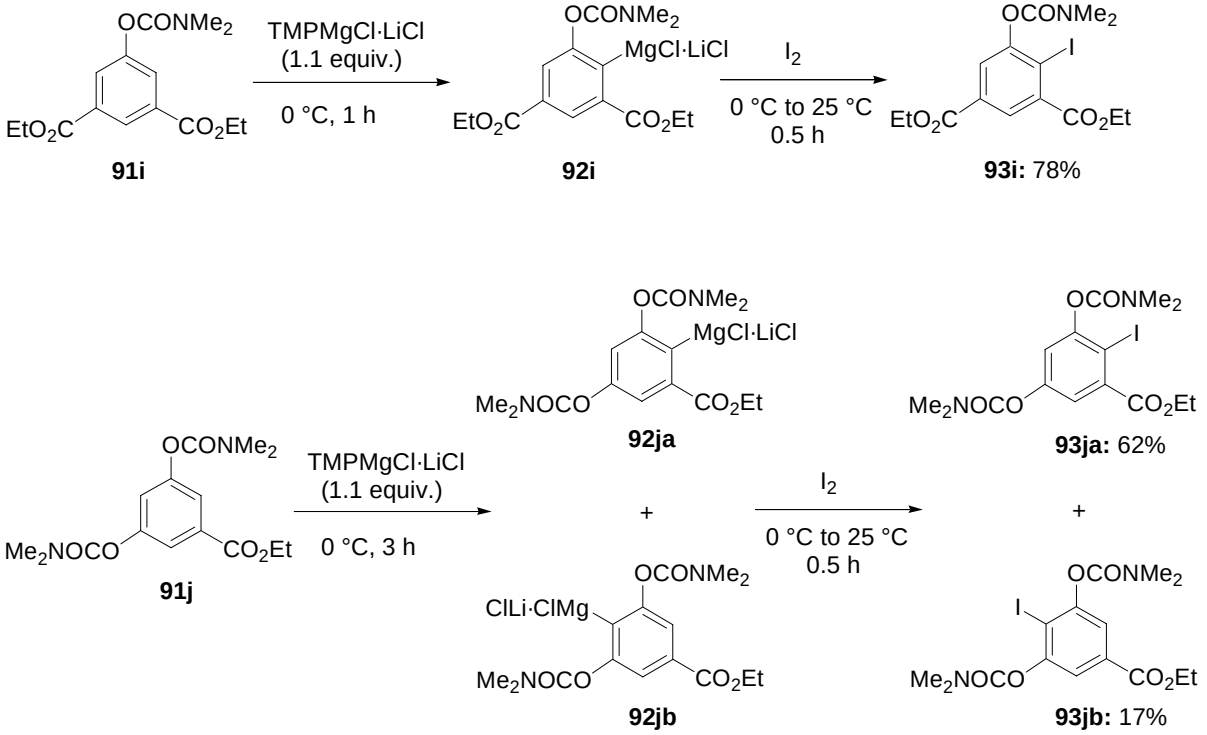


91g **92g** **93g:** 90%

91h **92h** **93h:** 91%

Scheme 94. Regioselective magnesiations of **91g** and **91h** using TMPMgCl·LiCl followed by iodolysis.

If the Me_2NCO-group was used as a directing group instead of the Boc-group, the low regioselectivity of magnesiation was observed. Although the compound **91i** could be magnesiated and furnished after iodolysis **93i** in 78 % yield as a single isomer, the two isomers **92ja** and **92jb** were formed after magnesiating the compound **91j** with TMPMgCl·LiCl, which after iodolysis gave rise to **93ja** and **93jb** in 62 % and 17 % yield, respectively (Scheme 95).

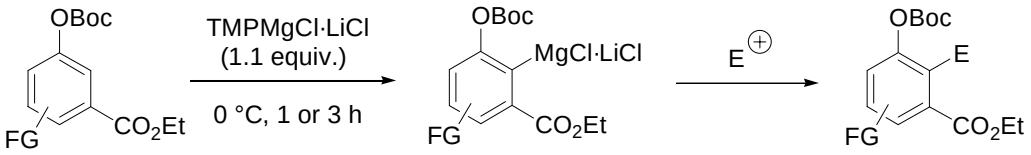


Scheme 95. Magnesiations of **91i** and **91j** using TMPMgCl·LiCl followed by iodolysis.

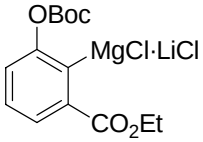
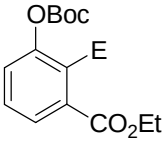
5.2.2 Boc-directed magnesiations of polyfunctionalized arenes followed by trapping with electrophiles.

A series of Boc-protected phenols **92g-m** were also prepared according to the standard procedure (Boc_2O, 1.2 equiv.; DMAP, 0.05 equiv.; CH_2Cl_2, 25 °C, overnight). The excellent directing ability of the Boc-group was confirmed by further studies summarized in Table 9 (Scheme 96). It showed that various Boc-protected phenols could be magnesiated leading to polyfunctional arylmagnesium derivatives **92d**, **92g-h** and, **92k-m** (Table 9, entries 1-22). In all cases, the metalations were completed within a few hours at 0 °C using TMPMgCl·LiCl (1.1 equiv.), and the quenching with various electrophiles proceeded with good yields. Thus, the benzoylation of the copper derivatives of **92d**, **92g-h** and **92k-m** (obtained by the reaction with CuCN·2LiCl) provided the corresponding ketones **94a**, **94d**, **94i**, **94l**, **94p**, and **94t** in 82-

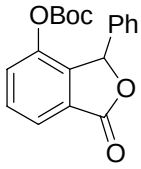
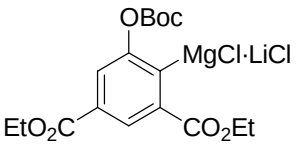
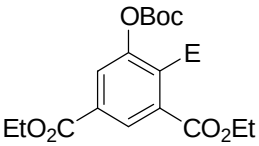
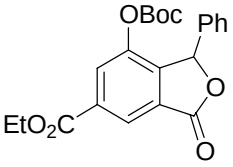
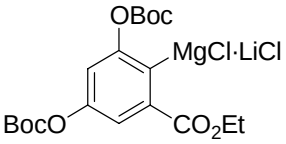
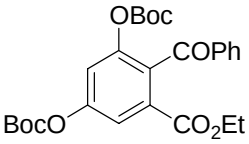
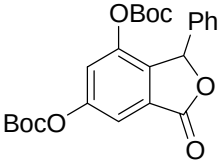
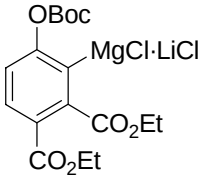
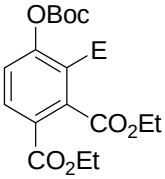
93 % yield (Table 9, entries 1, 4, 9, 12, 16, and 20). The arylmagnesium reagents **92k-m** after iodolysis gave rise to **94k**, **94o** and **94s** in 86-92 % yields (entries 11, 15, and 19). An ethyl carboxylation could be readily realized by the reaction with EtOCOCN (−40 °C to 25 °C, 0.5 h)[101] leading to the *di*- and *tri*-ester derivatives **94b**, **94e**, **94m**, and **94q** in 78-88 % yields (entries 2, 5, 13, and, 17). The cyanation of the arylmagnesium species **92g** with TsCN[102] led to the aromatic nitrile **94f** in 90 % yield (entry 6). A bromination was best performed by the reaction with $BrCl_2CCCl_2Br$. With this method, the magnesium derivative **92g** was smoothly converted to the brominated ester **94g** in 92 % yield (entry 7). The reaction of Grignard reagents **92d**, **92g**, **92h**, **92k**, **92l**, and **92m** with benzaldehyde provided, after spontaneous cyclization, the lactones **94c**, **94h**, **94j**, **94n**, **94r**, and **94v** in 77-91 % yield (entries 3, 8, 10, 14, 18 and, 22). A chlorination could also be achieved by a reaction with $PhSO_2Cl$.[103] By this method, the Grignard reagent **92m** afforded the ester **94u** in 78 % yield (entry 21).

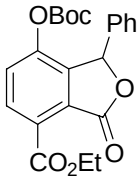
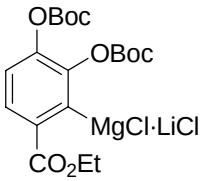
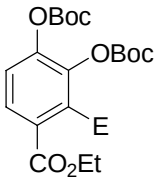
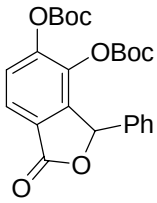
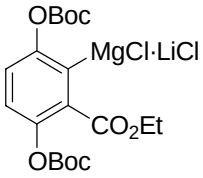
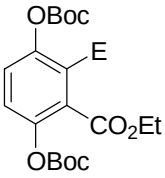
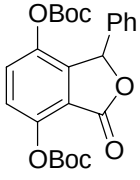


Scheme 96 and **Table 9**. Generation of magnesiated polyfunctionalized aryl derivatives of type **92** and their trapping with electrophiles leading to products of type **94**.

Entry	Grignard Reagent **92**[a]	Electrophile	Product of Type **94**	Yield (%)[b]
				
1	**92d** (3 h)	$PhCOCl$[c]	**94a**: E=COPh	90
2	**92d**	EtOCOCN	**94b**: E=CO_2Et	80

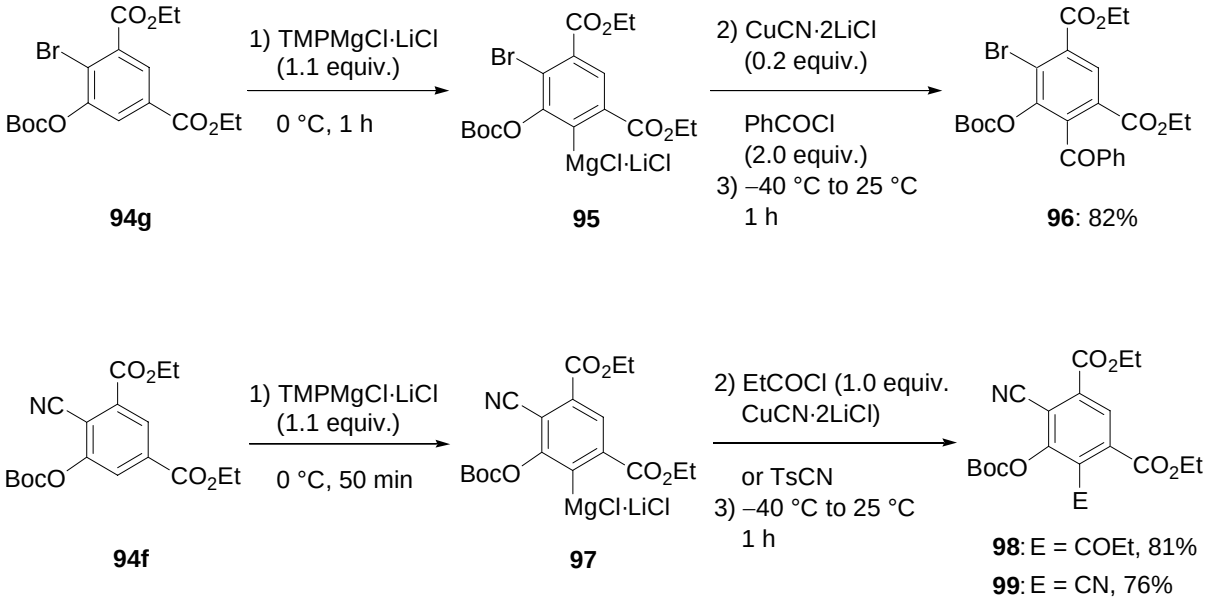
[101] T. Rho, Y. F. Abuh, *Synth. Commun.* **1994**, *24*, 253.
[102] a) J. M. Cox, R. Ghosh, *Tetrahedron Lett.* **1969**, *10*, 3351; b) D. Kahne, D. B. Collum, *Tetrahedron Lett.* **1981**, *22*, 5011; c) I. Klement, K. Lennick, C. E. Tucker, P. Knochel, *Tetrahedron Lett.* **1993**, *34*, 4623; d) K. J. Rutan, F. J. Heldrich, L. F. Bogers, *J. Org. Chem.* **1995**, *60*, 2948.
[103] a) I. Creton, H. Rezaeï, I. Marek, J. F. Normant, *Tetrahedron Lett.* **1999**, *40*, 1899; b) F. Chemla, I. Marek, J. F. Normant, *Synlett.* **1993**, *9*, 665; c) D. Gala, V. H. Dahanukar, J. M. Eckert, B. S. Lucas, D. P. Schumacher, I. A. Zavialov, *Org. Process Res. Dev.* **2004**, *8*, 754; see also the formation of sulfones: H. Gilman, R. E. Fothergill, *J. Am. Chem. Soc.* **1929**, *51*, 3501.

3	**92d**	PhCHO	 **94c**	83
4	 **92g** (1 h)	$PhCOCl^{[c]}$	 **94d**: E=COPh	91
5	**92g**	EtOCOCN	**94e**: E=CO_2Et	85
6	**92g**	TsCN	**94f**: E=CN	90
7	**92g**	$BrCl_2CCCl_2Br$	**94g**: E=Br	92
8	**92g**	PhCHO	 **94h**	78
9	 **92h** (3 h)	$PhCOCl^{[c]}$	 **94i**	93
10	**92h**	PhCHO	 **94j**	90
11	 **92k** (1 h)	I_2	 **94k**: E=I	86
12	**92k**	$PhCOCl^{[c]}$	**94l**: E=COPh	82
13	**92k**	EtOCOCN	**94m**: E=CO_2Et	78

14	**92k**	PhCHO	 **94n**	73
15	 **92l** (3 h)	I_2	 **94o**: E=I	92
16	**92l**	$PhCOCl$[c]	**94p**: E=COPh	90
17	**92l**	EtOCOCN	**94q**: E=CO_2Et	88
18	**92l**	PhCHO	 **94r**	91
19	 **92m** (3 h)	I_2	 **94s**: E=I	90
20	**92m**	$PhCOCl$[c]	**94t**: E=COPh	91
21	**92m**	$PhSO_2Cl$	**94u**: E=Cl	78
22	**92m**	PhCHO	 **94v**	77

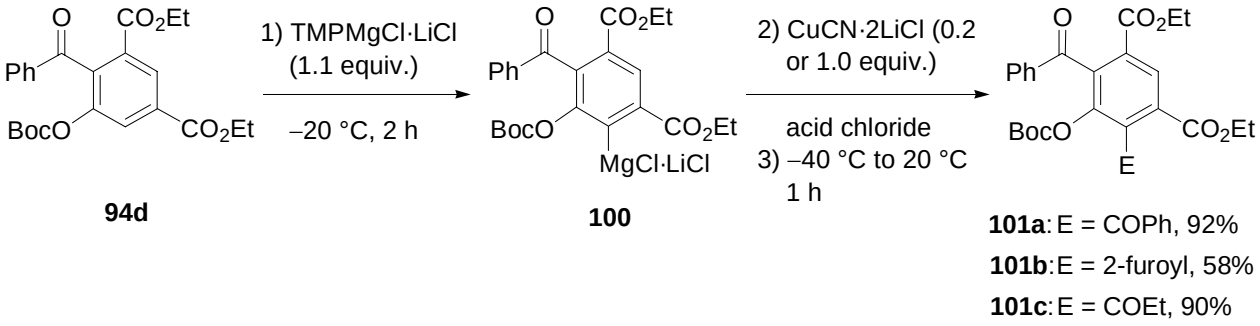
[a] Reaction time for the deprotonation using TMPMgCl·LiCl (1.1 equiv.) at 0 °C. [b] Isolated yield of analytically pure product. [c] The reaction was performed by using CuCN·2LiCl (0.2 equiv.).

The products of type **94** can be magnesiated again. Thus, the reaction of the Boc-protected bromophenol **94g** with TMPMgCl·LiCl provided the Grignard reagent **95** which underwent a smooth benzoylation with PhCOCl (2.0 equiv.) in the presence of CuCN·2LiCl (0.2 equiv.) affording the ketone **96** in 82 % yield. Similarly, the cyano-substituted diester (**94f**) was converted to the corresponding arylmagnesium derivative **97** using TMPMgCl·LiCl (1.1 equiv., 0 °C, 50 min). Its reaction with EtCOCl in the presence of CuCN·2LiCl provided the ketone **98** in 81 % yield (Scheme 97). The reaction of the Grignard reagent **97** with TsCN led to the dinitrile **99** in 76 % yield.



Scheme 97. Boc-directed magnesiations of polyfunctionalized bromoarene **94g** and benzonitrile **94f** followed by trapping with electrophiles.

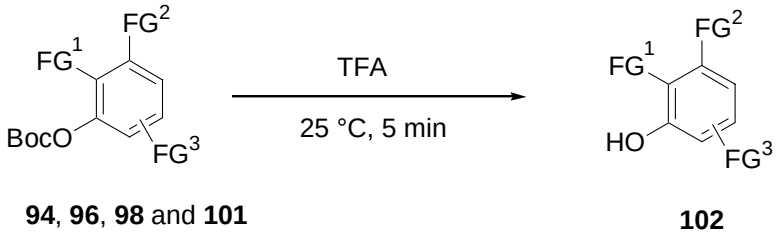
Interestingly, the functionalized benzophenone **94d** was readily magnesiated (−20 °C, 2 h) by using TMPMgCl·LiCl (1.1 equiv.) leading to the keto-substituted arylmagnesium reagent **100**. This remarkable functional group compatibility should be general and this magnesiation procedure may give an access to various arylketo-substituted arylmagnesium species. After the Cu-catalyzed acylation of **100** with acid chlorides, the polyfunctional *penta*-substituted Boc-protected phenols **101a-c** were obtained in 58-92 % yields (Scheme 98).



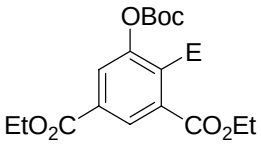
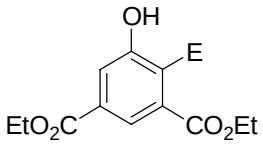
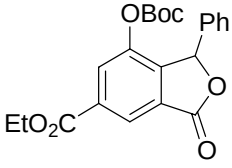
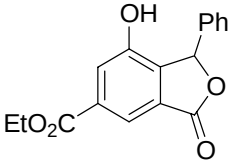
Scheme 98. The Boc-directed magnesiation of the polyfunctionalized benzophenone **94d** followed by a Cu-catalyzed acylation.

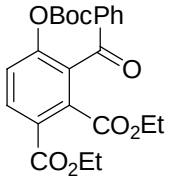
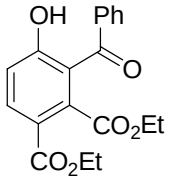
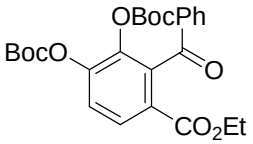
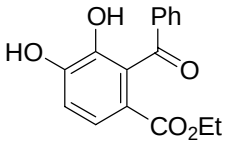
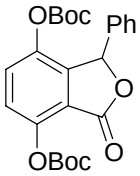
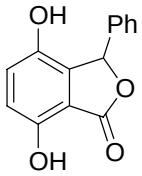
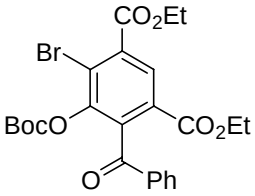
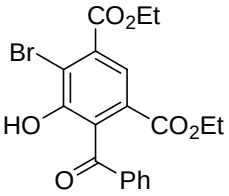
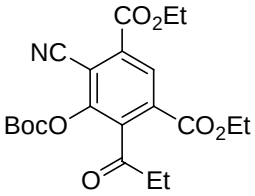
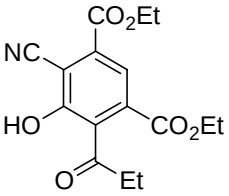
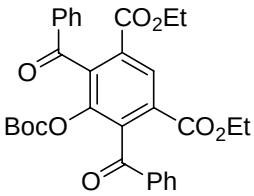
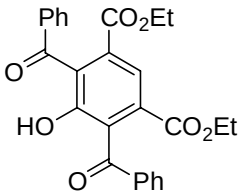
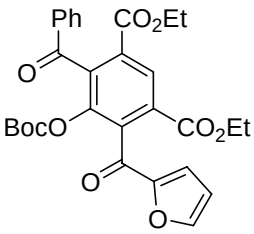
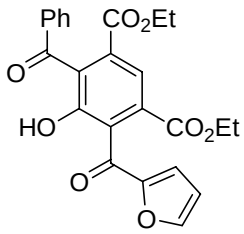
5.3 Preparation of polyfunctionalized phenols by deprotection of the Boc-group

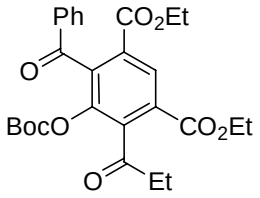
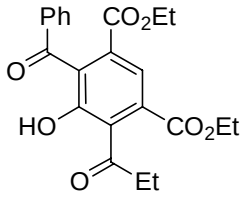
The Boc-deprotection could be easily performed under mild condition (TFA, 25 °C, 5 min), and the polyfunctional *tetra*- or *penta*-substituted phenols **102** were obtained in 90-98 % yields (Scheme 99 and Table 10).



Scheme 99 and **Table 10**. Formation of polyfunctionalized phenols of type **102** *via* deprotection of polyfunctionalized BocOAr (**94**, **96**, **98**, and **101**).

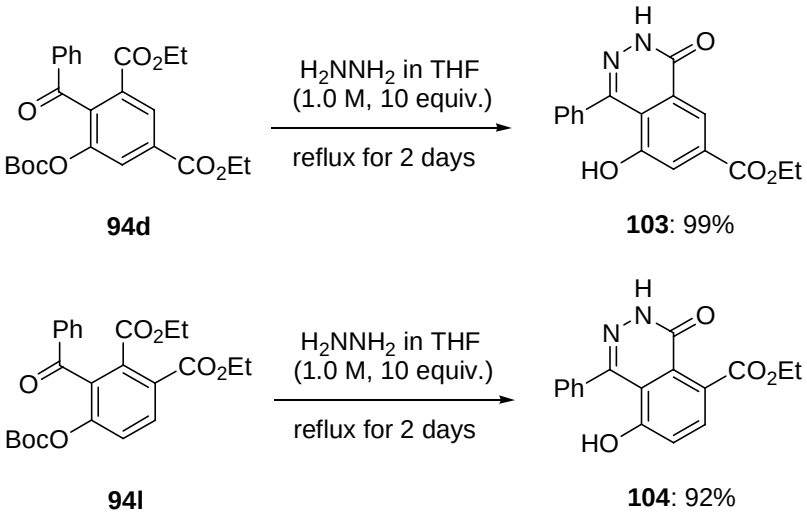
Entry	BocOAr **94**, **96**, **98**, **101**	Product of type **102**[a]	Yield (%)
1	 **94d**:E=COPh	 **102a**: E=COPh	98
2	**94f**:E=CN	**102b**: E=CN	98
3	 **94h**	 **102c**	99

4	 **94l**	 **102d**	98
5	 **94p**	 **102e**	99
6	 **94v**	 **102f**	98
7	 **96**	 **102g**	98
8	 **98**	 **102h**	96
9	 **101a**	 **102i**	97
10	 **101b**	 **102j**	90

11	 **101c**	 **102k**	98

[a] The reaction condition: BocOAr (0.4 mmol) in TFA (1 mL) at 25 °C for 5 min.

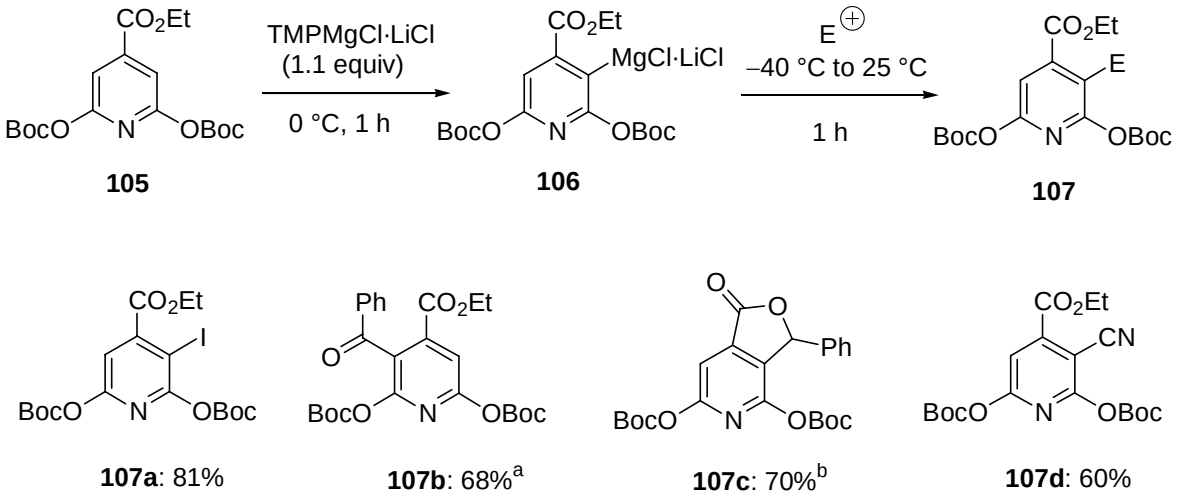
The Boc-protected polyfunctionalized phenols, such as **94d** and **94l**, bearing a ketone and an ester function, can react with hydrazine (10 equiv.) in refluxing THF furnishing the heterocycles **103** and **104** in 92-99 % yields (Scheme 100).



Scheme 100. Preparation of heterocyles **103** and **104**.

5.4 The Boc-directed magnesiation of a functionalized pyridine followed by trapping with an electrophile.

A pyridine bearing an ester function and the OBoc-directing group, such as **105**, was also readily magnesiated (0 °C, 1 h) by using TMPMgCl·LiCl (1.1 equiv.) leading to the arylmagnesium reagent **106**. After quenching with various electrophiles, **106** was converted to the *tetra*-substituted Boc-protected pyridine-2,6-diol derivatives **107a-d** in 60-81 % yields (Scheme 101).



Electrophile = I_2,1.5 equiv. (**107a**); PhCOCl, 2.0 equiv. (**107b**); PhCHO, 1.5 equiv. (**107c**); TsCN, 1.5 equiv. (**107d**).

a) in the presence of CuCN·2LiCl (0.2 equiv.)

b) PhCHO –40 °C, 3 h; $NH_4Cl_{(aq)}$ –40 °C to 25 °C.

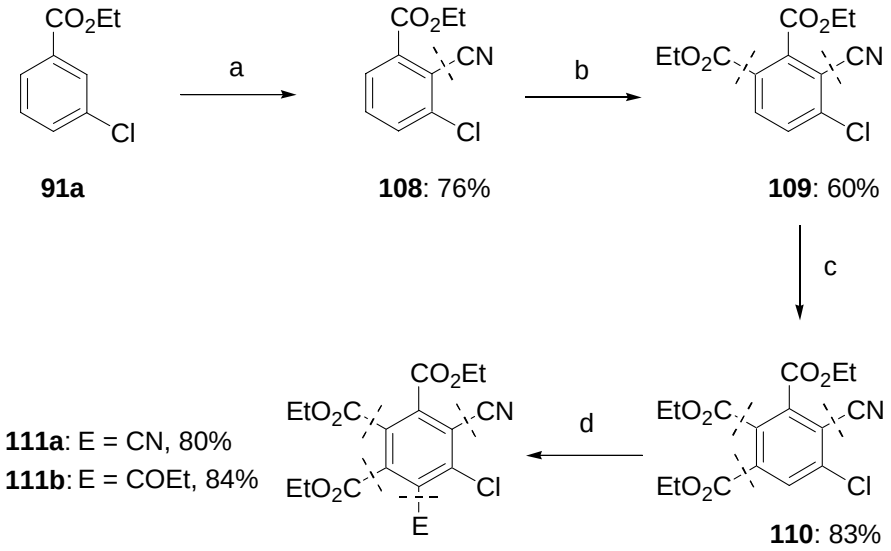
Scheme 101. The Boc-directed magnesiation of the functionalized pyridine **105** followed by trapping with electrophiles.

5.5 Preparation of *hexa*-substituted benzenes *via* successive magnesiations of ethyl 3-chlorobenzoate followed by trapping with electrophiles

Finally, a multiple functionalization of ethyl 3-chlorobenzoate (**91a**) could be achieved by successive magnesiations with TMPMgCl·LiCl and quenching with an electrophile leading to a *hexa*-substituted benzene (Scheme 102). Thus, the metalation of the ethyl ester **91a** with TMPMgCl·LiCl followed by an electrophilic cyanation with TsCN provided the nitrile **108** which by a further regioselective magnesiation at the α-position to the carboethoxy group afforded, after reaction with EtOCOCN (1.7 equiv.), the diester **109** in 60 % yield. The use of a solvent mixture THF/Et_2O (1:2) was essential for the control of the regioselectivity of the magnesiation (>95 % regioselectivity). By using only THF, a competitive metalation at the α-position to the chlorine-substituent of **108** was also observed (ca. 10 % relative to **109** by GC analysis). The treatment of **109** with TMPMgCl·LiCl (1.2 equiv., −50 °C, 30 min) followed by a transmetalation with $ZnCl_2$ and Pd(0)-catalyzed acylation with EtOCOCl[104] gave rise to the triester **110** in 83 % yield. The magnesiation of **110** with TMPMgCl·LiCl (1.2 equiv.,

[104] T. Sugihara, *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-I. Negishi), Wiley, New York, **2002**, *1*, 635.

−50 °C, 1.5 h) followed by the addition of trapping agents (TsCN or EtCOCl) furnished the *hexa*-substituted benzenes **111a** and **111b** in 80 % and 84 % yields, respectively (Scheme 102).



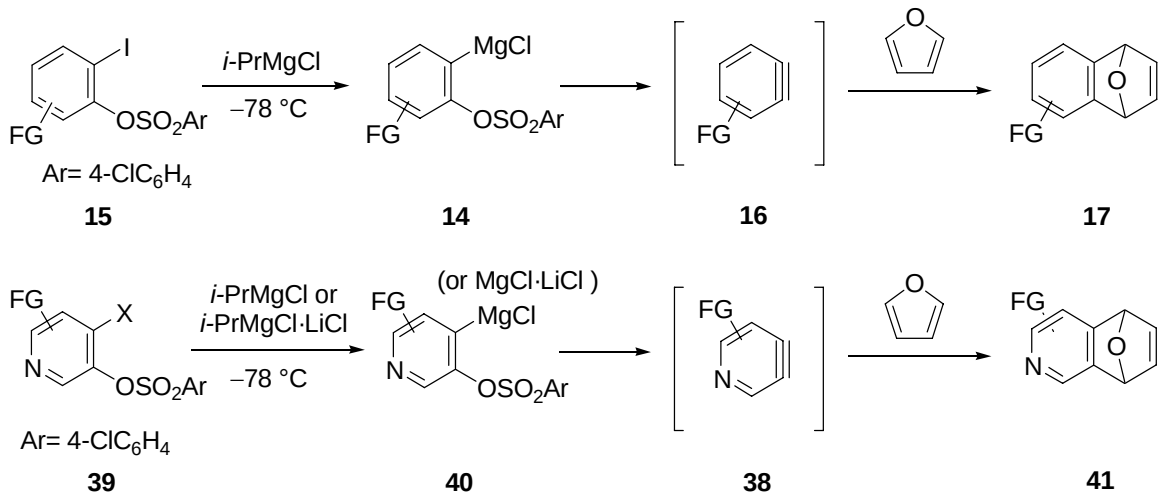
Scheme 102. Successive magnesiations of ethyl 3-chlorobenzoate (**91a**) followed by trapping with electrophiles leading to *hexa*-substituted benzenes of type **111**:

(a) TMPMgCl·LiCl (1.2 equiv.), 0 °C, 6 h, then TsCN (1.5 equiv.). (b) TMPMgCl·LiCl (1.5 equiv.), −20 °C, 5 h, THF/Et_2O (1:2), then EtOCOCN (1.7 equiv.), −40 °C to 25 °C, 1 h. (c) 1) TMPMgCl·LiCl (1.2 equiv.), −50 °C, 30 min, then $ZnCl_2$ (1.2 equiv.), −50 °C to −30 °C, 30 min; 2) $Pd(PPh_3)_4$ (2 mol %), EtOCOCl (1.5 equiv.), −30 °C to 25 °C, 24 h. (d) TMPMgCl·LiCl (1.2 equiv.), −50 °C, 1.5 h, then an electrophile.

6. Summary

6.1 Preparation of polyfunctionalized arynes and heteroarynes *via* 2-magnesiated diaryl sulfonates

The preparation of polyfunctionalized arynes as highly reactive intermediates has been achieved by the controlled elimination of readily generated 2-magnesiated aryl aryl sulfonates of type **14** or **40** obtained by a low temperature halogen/Mg-exchange starting from the corresponding iodides of type **15** or **39**. The most effective leaving group was found to be 4-chlorobenzenesulfonate (4-Cl-$C_6H_4SO_2O$-). It allowed the generation of various functionalized arynes of type **16** or pyridynes of type **38** with appropriate rates. After trapping with furan, good to excellent yields of the polyfunctionalized cyclo-adducts of type 1**7** or **41** were obtained. This method has a broad scope and tolerates a wide range of polyfunctionalized arynes **16** or pyridynes **38**, which are now for the first time available for many synthetic applications (Scheme 103).

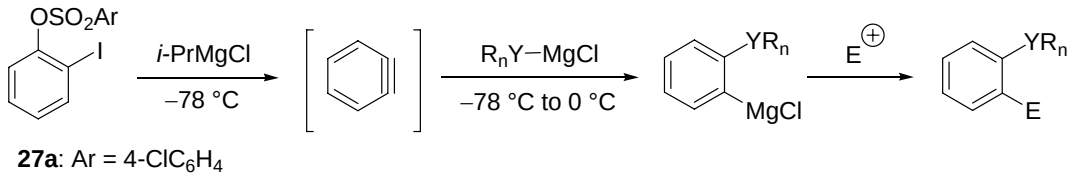


Scheme 103. Generation and trapping of functionalized arynes **16** and pyridynes **38**.

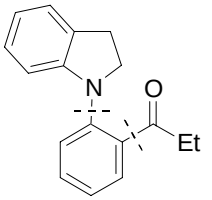
6.2 Preparation of functionalized arylmagnesium reagents by the addition of magnesium aryl thiolates, amides and selenides to arynes and heteroarynes

The functionalization of aromatic compounds is an important synthetic task. We have demonstrated the addition of various heteroatomic magnesium nucleophiles of the type RnY-MgX (Y=N, n=2; Y=S=Se, n=1) to arynes generated from *ortho*-magnesiated arylsulfonates. The resulting magnesium derivatives could in all cases be trapped by various electrophiles

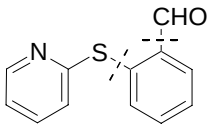
leading to polyfunctional products such as **59f**, **58n**, and **60a**. Similiarly, functionalized arynes generated by our method reacted with aryl thiolates or phenylselenide with high regioslectivity leading to highly functionalized *tri*- or *tetra*-substituted aromatic compounds like **62b** or **77a-j** (Scheme 104).



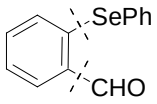
27a: Ar = 4-ClC_6H_4



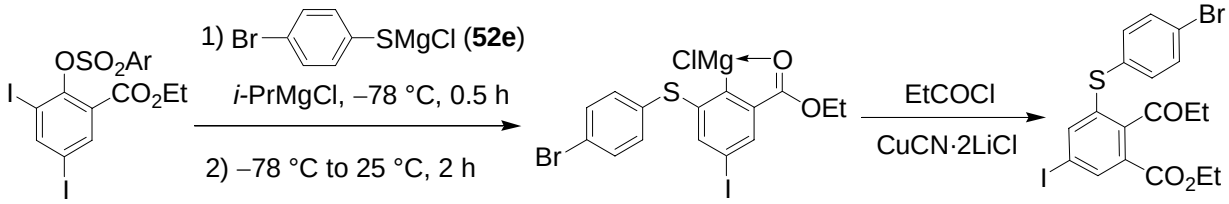
59f: 62 %



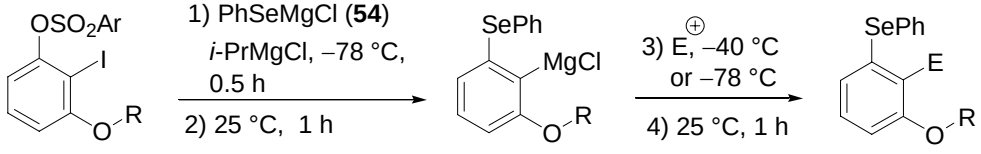
58n: 82 %



60a: 85 %



27d: Ar = 4-ClC_6H_4 **61** **62b**: 68 %



Ar = 4-ClC_6H_4

27h: R = Me
27i: R = Bn
27j: R = TES

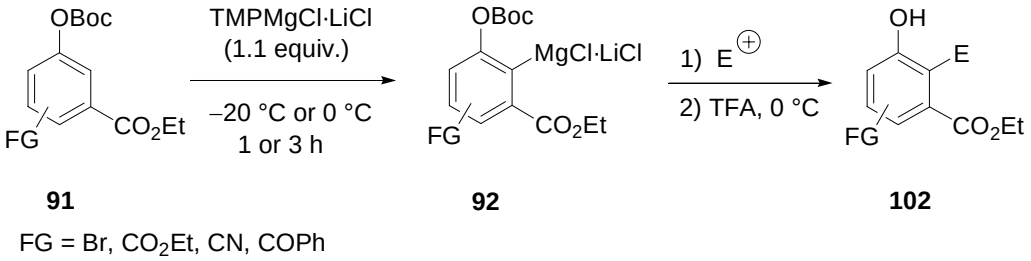
76a: R = Me
76b: R = Bn
76c: R = TES

77a-j

Scheme 104. Preparation of arylamines, aryl thioethers, and aryl selenoethers by addition reactions to arynes.

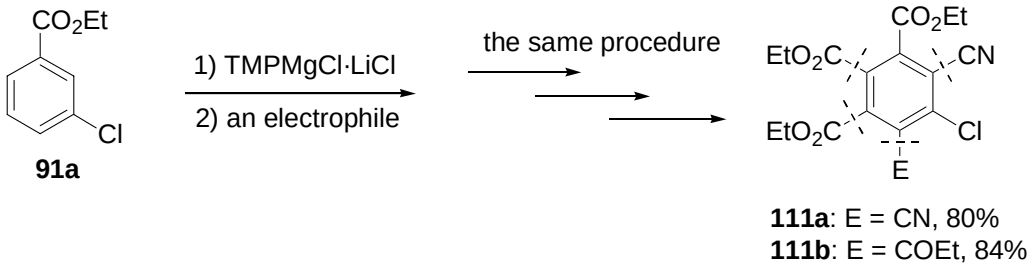
6.3 Highly functionalized benzenes syntheses by directed mono or multiple magnesiations using TMPMgCl·LiCl

The direct functionalization of aromatic rings *via* organometallic intermediates is an important method of a considerable industrial interest. Aryllithiums can be readily obtained by directed lithiation and have found many applications although less sensitive functional groups can be tolerated compared to arylmagnesium species. We have discovered that Boc-protected phenol derivatives were easily magnesiated using TMPMgCl·LiCl due to the strong directing and chelating effect of the OBoc group, and an ester, a nitrile or even a ketone function could be tolerated. Thus, various Boc-derivatives bearing an ester and (or) a nitrile function or even an aryl ketone (**91**) were readily magnesiated with TMPMgCl·LiCl at 0 °C or −20 °C within 1-3 h leading to the new magnesium derivatives **92** in high yields. Their reactions with electrophiles gave an entry to highly functionalized benzenes **102**. The easy introduction and removal of a Boc-group make this functionalization method of aromatics a useful complement to the well-known directed lithiation reaction (Scheme 105).



Scheme 105. Preparation of polyfunctionalized phenols **102** *via* magnesiations followed by quenching with electrophiles and then deprotection reactions.

A multiple magnesiation/electrophile quenching procedure could also be performed. Thus, ethyl 3-chlorobenzoate (**91a**) could be *ortho*-magnesiated and quenched with an electrophile four successive times with high yields and regioselectivity leading *via* successive products to the *hexa*-substituted benzene derivatives (**111a-b**) in good yields. This novel strategy for functionalizing aromatic rings gives a simple access to highly functionalized and substituted aromatics and should find considerable applications in material science and for the synthesis of biologically active compounds (Scheme 106).



Scheme 106. Successive magnesiations of ethyl 3-chlorobenzoate (**91a**) followed by trapping with electrophiles leading to *hexa*-substituted benzenes (**111a-b**).

EXPERIMENTAL PART

7. General Conditions

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

Solvents

Solvents were dried according to standard methods by distillation from drying agents as stated below and were stored under argon.

CH_2Cl_2 and **toluene** were predried over $CaCl_{2(s)}$ and distilled from $CaH_{2(s)}$.

Diethyl ether and **THF** were continueously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

1,2-dimethoxyethane (DME) was predried over $CaCl_{2(s)}$ and freshly distilled from sodium benzophenone ketyl under nitrogen.

Dimethylformamide (DMF) was heated to reflux for 14 h over $CaH_{2(s)}$ and distilled from $CaH_{2(s)}$.

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

Methanol was treated with magnesium turnings (20g/L) and sodium, heated to reflux for 6 h and distilled.

Pyridine and **triethylamine** were dried over $KOH_{(s)}$ and distilled from $KOH_{(s)}$.

Reagents

Reagents of >98% purity were used as obtained.

***n*-Butyllithium** was used as a 1.5 M solution in hexane purchased by Chemetall.

CuCN·2LiCl solution (1.0 M/THF) was prepared by drying CuCN (869 mg, 10 mmol) and LiCl (848 mg, 20 mmol) in a Schlenk flask under vacuum for 5 h at 140 °C. After cooling to room temperature, dry THF (10 mL) was added and stirred continuously until the salts were dissolved.

Phenylmagnesium chloride was used as a 2.0 M solution in THF purchased by Chemetall.

***i*-PrMgCl:** A dry three-necked flask equipped with an argon inlet, a dropping funnel and a thermometer was charged with magnesium turnings (110 mmol). A small amount of THF was added to cover the magnesium, and a solution of isopropyl chloride (100 mmol) in THF (50 mL) was added dropwise, keeping the temperature of the mixture below 30 °C (water bath). After the addition was complete, the reaction mixture was stirred for 12 h at room temperature. The grey solution of *i*-PrMgCl was cannulated to another flask under argon and removed in this way from excess of magnesium. A yield of ca. 95-98 % of *i*-PrMgCl was

obtained and the *i*-PrMgCl-solution was titrated prior to use according to reported literature.[105]

***i*-PrMgCl·LiCl:** A dry three-necked flask equipped with an argon inlet, a dropping funnel and a thermometer was charged with magnesium turnings (110 mmol) and anhydrous LiCl (100 mmol). A small amount of THF was added to cover the magnesium, and a solution of isopropyl chloride (100 mmol) in THF (50 mL) was added dropwise, keeping the temperature of the mixture below 30 °C (water bath). After the addition was complete, the reaction mixture was stirred for 12 h at room temperature. The grey solution of *i*-PrMgCl·LiCl was cannulated to another flask under argon and removed in this way from excess of magnesium. A yield of ca. 95-98 % of *i*-PrMgCl·LiCl was obtained and the *i*-PrMgCl·LiCl-solution was titrated prior to use according to reported literature.[105]

TMPMgCl·LiCl: A dry and nitrogen-flushed 250 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with freshly titrated *i*-PrMgCl·LiCl(100 mL, 1.2 M in THF, 120 mmol). 2,2,6,6-Tetramethylpiperidine (TMPH) (19.8 g, 126 mmol, 1.05 equiv.) was added dropwise at room temperature. The reaction mixture was stirred at room temperature until gas evolution was completed (ca. 24 h).[20] The concentration of the solution of TMPMgCl·LiCl was titrated by using benzoic acid in dry THF and 4-(phenylazo)diphenylamine as an indicator.

$ZnBr_2$ solution (1.0 M/THF) was prepared by drying $ZnBr_2$ (33.78 g, 150 mmol) under vacuum for 5 h at 150 °C. After cooling to room temperature, dry THF (150 mmol) was added and stirred continuously until the salts were dissolved.

$ZnCl_2$ solution (1.0 M/THF) was prepared by drying $ZnCl_2$ (20.45 g, 150 mmol) under vacuum for 5 h at 150 °C. After cooling to room temperature, dry THF (150 mmol) was added and stirred continuously until the salts were dissolved.

The following reagents were prepared according to literature procedures:

2,6-diiodophenol, [106] *tert*-butyl-(1-ethoxy-vinyloxy)-dimethyl-silane, [107] 2-iodo-benzene-1,3-diol (**28**),[75c] 3-hydroxy-4-iodopyridine,[84] 2-Methoxy-pyridin-3-ol,[86] 4-{[(4-chlorophenyl) sulfonyl]oxy}-3-iodobenzonitrile (**27q**),[79] allyl-phenyl-amine, [108] 4-(allylamino) benzonitrile,[108] palladium(II)bis(dibenzylidenacetone),[109] tri-(2-furyl)phosphine.[110]

Chromatography

Thin layer chromatography (TLC) was performed using aluminium plates coated with SiO_2 (Merck 60, F-254). The spots were visualized by UV light and/or by staining of the TLC plate with the solution bellow followed by heating with a heat gun:

- $KMnO_4$ (0.3 g), K_2CO_3 (20 g), KOH (0.3 g) in water (300 mL)

[105] (a) H. S. Lin, L. Paquette, *Synth. Commun.* **1994**, *24*, 2503; (b) A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 890.
[106] S. Adimurthy, G. Ramachandraiah, *Tetrahedron Lett.* **2004**, *45*, 5251.
[107] J. S. Nowick, R. L. Danheiser, *Tetrahedron* **1988**, *44*, 4113.
[108] S.-C. Yang, C.-W. Hung, *Synthesis* **1999**, 1747.
[109] Y. Takahashi, T. Ito, S. Sakai, *Chem. Comm.* **1970**, 1065.
[110] D. W. Allen, B. G. Hutley, M. T. J. Mellor, *J. Chem. Soc. Perkin Trans. II* **1972**, 63.

Flash column chromatography was performed using SiO_2 60 (0.04-0.063 mm, 230-400 mesh ASTM) from Merck. The diameters of the columns and the amount of silicagel were calculated according to the recommendation of W. C. Still.[111]

Analysis

Analytical data collection was done as follows:

- **Melting points** were uncorrected and measured on a Büchi B-540 apparatus.
- **NMR** spectra were recorded on a Bruker ARX 200, AC 300, WH 400, or AMX 600 instruments. Chemical shifts were given relative to $CDCl_3$ (7.26 ppm for ^1H NMR, 77.0 ppm for ^{13}C NMR), DMSO-d_6 (2.50 ppm for ^1H NMR, 39.4 ppm for ^{13}C NMR), acetone-d_6 (2.04 ppm for ^1H NMR, 29.3 ppm for ^{13}C NMR). For the characterization of the observed signal multiplicities the following abbreviations were applied: s (single), d (doublet), dd (double doublet), dt (double triplet), t (triplet), td (triple doublet), q (quartet), quint (quintet), m (multiplet), as well as br (broad).
- **IR** spectra were recorded from 4000-400 cm^{-1} on a Nicolet 510 FT-IR, a Perkin-Elmer 281 IR spectrometer, or a Perkin Elmer Spectrometer BX FT-IR-System with a Smith Dura sampl IR II ATR-unit. Samples were measured either as neat materials (neat) or as a film between potassium bromide plates (film) or as potassium bromide tablets (KBr). The absorption bands are reported in wave numbers (cm^{-1}). For the band characterization the following abbreviations were applied: br (broad), s (strong), m (medium), vs (very strong), w (weak).
- **Gas chromatography (GC)** was perfomed using a Hewlett-Packard 5890 Series II (Column A: 2.5 % phenylmethylpolysiloxane (HP Ultra 2) 12 m × 0.2 mm × 0.33 µm). The compounds were detected with a flame ionization detector.
- **Mass spectroscopy:** Mass spectra were recorded on a Varian MAT CH 7A for electron impact ionization (EI) and high resolution mass spectra (HRMS) on a Varian MAT 711 spectrometers. Fast atom bombardment (FAB) samples were recorded in either a 2-nitrobenzyl alcohol- or glycerine-matrix. Additionally, for the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890/MSD 5973 was used (Column B: 5 % phenylmethylpolysiloxane (HP 5) 30 m × 0.25 mm × 0.25 µm; Column C: 5 % phenylmethylpolysiloxane (HP 5) 15 m × 0.25 mm × 0.25 µm).
- **Elemental analysis** was carried out on a Heraeus CHN-Rapid-Elementanalyzer in the microanalytical laboratories of the Department Chemie und Biochemie, Ludwig-Maximilians Universität, Munich.

[111] W. C. Still, M. Khan, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

8. Typical procedures (TP)

8.1 Typical procedure for the iodination of arenes using silver sulfate (TP1)

A 250 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with iodine (11.18 g, 44.0 mmol) and silver sulfate (13.71 g, 44.0 mmol) in ethanol (100 mL). The corresponding aromatic compound (20 mmol) was then added and the mixture was stirred vigorously at 25 °C until TLC analysis indicated the end of the reaction. The reaction mixture was filtered through a glass sinter. The solids on the sinter were washed with ethyl acetate (2 × 200 mL) and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (200 mL), and the resulting mixture was washed with water (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Recrystallization from ethanol or flash chromatography on silica gel yielded the product (**22a-c**).

8.2 Typical procedure for the formation of aryl-sulfonates (19a-f, 27a-e, 27o) from the corresponding phenols (TP 2)

A 100 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with the corresponding phenol (20 mmol) dissolved in dry pyridine (20 mL). Then, the corresponding benzenesulfonyl chloride (24 mmol) was added portionwise and the reaction mixture was stirred at 25 °C overnight. Thereafter, pyridine was evaporated *in vacuo*. Water (50 mL) was added to the mixture residue, and this mixture was diluted with CH_2Cl_2 (100 mL). The organic phase was washed with saturated aqueous Na_2CO_3 (100 mL) and brine (100 mL), and then dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Recrystallization from CH_2Cl_2 and ethanol yielded the desired product (**19a-f**, **27a-e**, **27o**).

8.3 Typical procedure for the generation and trapping of functionalized arynes (16) with furan (TP 3)

(a) A dry and argon-flushed 10 mL Schlenk tube, equipped with a magnetic stirrer and a septum, was charged with a solution of the corresponding arylsulfonate **19** or **27** (0.5 mmol) in dry THF (3 mL). *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) was then added dropwise at –78 °C. After 0.5 or 1 h, furan (0.18 mL, 5 equiv.) was added slowly at –78 °C, and the resulting mixture was warmed to 25 °C and stirred for a few of hours. Or (b) a dry and argon-flushed 10 mL Schlenk tube, equipped with a magnetic stirrer and a septum, was charged with a solution of the corresponding arylsulfonate **19** or **27** (0.5 mmol) and furan (0.18 mL, 5 equiv.) in dry THF (3 mL). *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) was added dropwise at –78 °C. After 0.5 or 1 h, the resulting mixture was warmed to 25 °C and stirred for a few hours.

Saturated aqueous NH_4Cl solution (50 mL) was then added, and then the resulting mixture was extracted with CH_2Cl_2 (3 × 40 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated. Purification by flash chromatography furnished the product **17**.

Notice: Method (a) and method (b) made no difference in the results for most cases of **19** and **27**. Only the corresponding Grignard reagents **20a**, **20g-h**, **30a**, **30k-l** (**19a**, **19g-h**, **27a**, **27k-l** for the formation of arynes **16a**, **16g-h**) were not so stable above –70 °C, and therefore it was convenient to add furan before adding *i*-PrMgCl by using method (b).

8.4 Typical procedure for the formation of aryl-sulfonates from the corresponding 3-hydroxypyridine derivatives (39a-e) (TP 4)

A dry 250 mL round-bottomed flask, equipped with a magnetic stirrer and a septum, was charged with a solution of corresponding 3-hydroxypyridine derivative (50.0 mmol) in dry

CH_2Cl_2 (100 mL). After cooling to 0 °C, Et_3N (20.9 mL, 150 mmol) was added, and then 4-chlorobenzenesulfonyl chloride (12.7 g, 60.0 mmol) was added portionwise. After the addition was completed, the reaction mixture was stirred at 25 °C overnight. Then this mixture was diluted with 100 mL CH_2Cl_2. Saturated aqueous NH_4Cl solution (100 mL) was then added, and then the resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated. Purification by flash chromatography furnished the desired product (**39a-e**).

8.5 Typical procedure for the generation and trapping of functionalized 3,4-pyridynes (38) with furan (TP 5)

A dry and argon-flushed 10 mL Schlenk tube, equipped with a magnetic stirrer and a septum, was charged with a solution of the corresponding arylsulfonate **39** (1.0 mmol) in dry THF (3 mL). *i*-PrMgCl or *i*-PrMgCl·LiCl (1.1 equiv.) was then added dropwise at −78 °C. After 0.5 to 6 h, furan (0.36 mL, 5.0 equiv.) was added slowly at −78 °C, and the resulting mixture was warmed to 25 °C and stirred for 1 h. Saturated aqueous NH_4Cl solution (50 mL) was then added, and then the resulting mixture was extracted with CH_2Cl_2 (3 × 40 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated. Purification by flash chromatography furnished the product **41**.

8.6 Typical procedure for the generation of aryl thioethers (58a, 58d-f, 58o-p) by the addition of magnesium thiolates (52a, 52c-e, 52i-j) to benzyne followed by quenching with iodine (TP 6)

A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of the corresponding arylthiol (1.0 mmol) in dry THF (3 mL). After cooling to −78 °C, *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF) was added dropwise and stirred for 10 min. 2-Iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter, the resulting mixture was immediately warmed to 0 °C and stirred for 10 min. The reaction mixture was then added to a solution of iodine (508 mg, 2.0 equiv.) in dry THF (2 mL) at −78 °C. After the addition, the mixture was warmed to 25 °C and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution and 5 % aqueous $Na_2S_2O_3$ solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography furnished the desired product (**58a, 58d-f, 58o-p**).

8.7 Typical procedure for the generation of aryl thioethers (58b, 58g-i, 58m-n, 58q, 58s) by the addition of magnesium thiolates (52a, 52c-e, 52f-g, 52i-j) to benzyne followed by quenching with DMF (TP 7)

A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of the corresponding arylthiol (1.0 mmol) in dry THF (3 mL). After cooling to −78 °C, *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF) was added dropwise and stirred for 10 min. 2-Iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter, the resulting mixture was immediately warmed to 0 °C and stirred for 10 min. Then the reaction mixture was cooled to −40 °C and DMF (0.20 mL, 2.5 equiv.) was added. The mixture was warmed to 25 °C and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography furnished the desired product (**58b**, **58g-i**, **58m-n**, **58q**, **58s**).

8.8 Typical procedure for the generation of aryl thioethers (58j-k, 58r, 58t) by the addition of magnesium thiolates (52e, 52i-j) to benzyne followed by quenching with acid chloride or allyl bromide in the presence of CuCN·2LiCl (TP 8)

A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of the corresponding arylthiol (1.0 mmol) in dry THF (3 mL). After cooling to −78 °C, *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF) was added dropwise and stirred for 10 min. 2-Iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter, the resulting mixture was immediately warmed to 0 °C and stirred for 10 min. The reaction mixture was cooled to −78 °C, and then CuCN·2LiCl (1.0 M in THF, 1.0 mL, 1.0 equiv.) was added and stirred for 20 min. After acid chloride (2.5 equiv.) was added at −78 °C, the solution was allowed to warm to 25 °C and stirred for an additional 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography furnished the product (**58j-k**, **58r**, **58t**).

8.9 Typical procedure for the generation of polyfunctionalized aryl thioethers (62a-d) by the addition of magnesium thiolate (52e) to aryne (16e) followed by quenching with an electrophile (TP 9)

A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 4-bromothiophenol (190 mg, 1.0 mmol) in dry THF (2 mL). After cooling to −78 °C, *i*-PrMgCl (1.41 mL, 3.0 equiv., 1.07 M in THF) was added dropwise and stirred for 10 min. Ethyl 2-{[(4-chlorophenyl)sulfonyl]oxy}-3,5-diiodobenzoate (**27d**) (296 mg, 0.5 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter, the resulting mixture was warmed to 25 °C and stirred for 2 h. (a) The reaction mixture was quenched with water (procedure for **62a**); or (b) the reaction mixture was cooled to −78 °C, and propionaldehyde (0.15 mL, 4.0 equiv.) was added and the reaction mixture was warmed to 25 °C and kept stirring for 1 h (procedure for **62d**); or (c) the reaction mixture was cooled to −78 °C, and then CuCN·2LiCl (1.0 M in THF; 0.5 mL, 1.0 equiv. for **62b**; 0.25 mL, 0.5 equiv. for **62c**) was added and stirred for 20 min; propionyl chloride or allyl bromide (4.0 equiv.) was added at −78 °C, and the solution was allowed to warm to 25 °C and kept stirring for 1 h (procedure for **62b-c**).

The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography furnished the desired products (**62a-d**).

8.10 Typical procedure for the generation of tertiary amines (59a-g) by the addition reaction of magnesium amides (53a-c) to benzyne followed by quenching with an electrophile (TP 10)

A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of the corresponding secondary amine (1.0 mmol) in dry THF (3 mL). After cooling to −20 °C, *i*-PrMgCl (0.94 mL, 1.0 equiv., 1.07 M in THF) was added dropwise and stirred for 30 min. The reaction mixture was cooled to −78 °C and *i*-PrMgCl (0.94 mL, 1.0 equiv., 1.07 M in THF) was added. 2-Iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter the resulting mixture was immediately warmed to 0 °C and stirred for 10 min. (a) The reaction mixture was cooled to −78 °C, and then CuCN·2LiCl (1.0 M in THF; 0.5 mL, 0.5 equiv. for **59a** and **59e**; 1.0 mL, 1.0 equiv. for **59b** and **59f**) was added and stirred for 20 min; acid chloride or allyl bromide

(2.5 equiv.) was added at −78 °C, and the solution was allowed to warm to 25 °C and kept stirring for 1 h.; or (b) the reaction mixture was cooled to −78 °C, and benzaldehyde (0.12 mL, 1.2 mmol) was added and stirred for 3 h at the same temperature followed without warming to 25 °C. (procedure for **59c**); or (c) the reaction mixture was cooled to −40 °C and DMF (0.19 mg, 2.5 equiv.) was added followed by warming to 25 °C and stirring for 1 h.
The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography furnished the desired products (**59a-g**).

8.11 Typical procedure for the generation of tertiary amines (59h-l) by the addition reaction of magnesium amides (53d-f) to benzyne followed by quenching with an electrophile (TP 11)

A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of the corresponding secondary amine (1.0 mmol) in dry DME (4 mL). After cooling to −20 °C, *i*-PrMgCl (0.98 mL, 1.05 equiv., 1.07 M in THF) was added dropwise and stirred for 30 min. The reaction mixture was cooled to −70 °C and *i*-PrMgCl (1.60 mL, 1.70 equiv., 1.07 M in THF) was added. Toluene-4-sulfonic acid 2-iodophenyl ester (**19a**) (636 mg, 1.7 mmol) dissolved in dry DME (2 mL) was added and stirred vigorously for 2 h at the same temperature. Thereafter, the resulting mixture was warmed slowly to 0 °C during 2 h, and then stirred at the same temperature for 1 h. (a) The reaction mixture was cooled to −40 °C and DMF (0.19 mg, 2.5 equiv.) was added; or (b) the reaction mixture was cooled to −78 °C, and then CuCN·2LiCl (1.0 M in THF, 1.0 mL, 1.0 equiv.) was added and stirred for 20 min followed by the addition of propionyl chloride (0.44 mL, 5.0 mmol) at −78 °C.
Thereafter, the mixture was warmed to 25 °C and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography furnished the desired product (**59h-l**).

8.12 Typical procedure for the generation of aryl selenoethers (60a-d) by the addition of magnesium phenylselenide (54) to benzyne followed by quenching with an electrophile (TP 12)

A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of phenylselenol (157 mg, 1.0 mmol) in dry THF (3 mL). After cooling to −78 °C, *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF) was added dropwise and stirred for 30 min. 2-Iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter, the resulting mixture was immediately warmed to 0 °C and stirred for 10 min. (a) The reaction mixture was cooled to −40 °C and DMF (0.20 mL, 2.5 equiv.) was added (procedure for **60a**); or (b) the reaction mixture was cooled to −78 °C, CuCN·2LiCl (1.0 M in THF, 1.0 mL, 1.0 equiv.) was added followed by keeping stirring for 20 min, and propionyl chloride (0.22 mL, 2.5 mmol) was added at −78 °C (procedure for **60b**); or (c) the reaction mixture was added to a solution of iodine (508 mg, 2.0 equiv.) in dry THF (2 mL) at −78 °C (procedure for **60c**); (d) the reaction mixture was cooled to −78 °C, and propionaldehyde (145 mg, 2.5 mmol) was added (procedure for **60d**).
Thereafter, the mixture was warmed to 25 °C and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution (in the case of **60c**, 5 % aqueous $Na_2S_2O_3$ solution was also used to remove excess of iodine), extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography furnished the desired product (**60a-d**).

8.13 Typical procedure for the generation of aryl selenoethers (77a-j) by the addition of magnesium phenylselenide (54) to aryne followed by quenching with an electrophile (TP 13)

A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of phenylselenol (157 mg, 1.0 mmol) in dry THF (3 mL). After cooling to −78 °C, *i*-PrMgCl (1.88 mL, 2.01 equiv., 1.07 M in THF) was added dropwise and stirred for 30 min. The corresponding arylsulfonate (**27h-j**) (1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. The resulting mixture was immediately warmed to 25 °C and stirred for 1 h. (a) The reaction mixture was cooled to −40 °C and DMF (0.20 mL, 2.5 equiv.) was added (for **77b** and **77f**); or (b) the reaction mixture was cooled to −78 °C, CuCN·2LiCl (1.0 M in THF; 0.5 mL, 0.5 equiv. for **77c**, **77g** and **77j**; 1.0 mL, 1.0 equiv. for **77d** and **77h**) was added followed by keeping stirring for 20 min, and allyl bromide (0.20 mL, 2.5 mmol) or benzoyl chloride (211 mg, 1.5 mmol) was added at −78 °C; or (c) the reaction mixture was added to a solution of iodine (508 mg, 2.0 mmol) in dry THF (2 mL) at −78 °C (for **77i**).

Thereafter, the mixture was warmed to 25 °C and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution (in the case of **77i**, 5 % aqueous $Na_2S_2O_3$ solution was also used to remove excess of iodine), extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography furnished the desired product (**77a-j**).

8.14 Typical procedure for the generation of Boc-protected polyfunctionalized phenol derivatives (91d, 91g-h, 91k-m) *via* the protection with Boc_2O (TP 14)

A dry 100 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with a solution of the corresponding ArOH (15 mmol) in dry CH_2Cl_2 (50 mL). After cooling to 0 °C, DMAP (92 mg, 0.75 mmol) and Boc_2O (3.930 g, 18 mmol) was added and the reaction was warmed up to 25 °C and stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 100 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography furnished the desired product (**91d**, **91g-h**, **91k-m**).

8.15 Typical procedure for the generation of polyfunctionalized arenes (93, 94 and 107) magnesiated with TMPMgCl·LiCl followed by quenching with an electrophiles (TP 15)

A dry and nitrogen-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of **91** or **105** (1.0 mmol) in dry THF (3 mL). After cooling to 0 °C, TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF; in the case of **91a-b**: 1.00 mL, 1.2 equiv., 1.20 M in THF) was added dropwise and stirred for several hours. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry ether. (a) I_2 (381 mg, 1.5 equiv.) dissolved in dry THF (2 mL) was then added at 0 °C, and the resulting mixture was warmed to 25 °C and stirred for 1 h. Or (b) the reaction mixture was cooled to −40 °C, and CuCN·2LiCl (0.2 mL, 0.2 equiv., 1.0 M in THF) was added followed by stirring for 5 min. Benzoyl chloride (281 mg, 2.0 mmol) was added at −40 °C, and the reaction mixture was warmed to 25 °C and stirred for 1 h. Or (c) the reaction mixture was cooled to −40 °C, and ethyl cyanoformate (200 mg, 2.0 mmol) was added and stirred for 30 min. The resulting mixture was warmed to 25 °C and stirred for 30 min. Or (d) the reaction mixture was cooled to −40 °C, benzaldehyde (0.15 mL, 1.5 mmol) was added, and the resulting mixture was stirred for 3 h at the same temperature.

The reaction mixture was quenched with saturated aqueous NH_4Cl solution (or 5 % aqueous $Na_2S_2O_3$ solution when iodine was used as an electrophile), extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography furnished the desired product (**93**, **94**, **107**).

8.16 Typical procedure for the generation of polyfunctionalized phenols of type 102 *via* deprotection of polyfunctionalized BocOAr (94, 96, 98, and 101) (TP 16)

A dry 10 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with the corresponding Boc-protected arene (**94**, **96**, **98**, and **101**) (0.4 mmol) in trifluoroacetic acid (1.0 mL). After stirring at 25 °C for 5 min, excess trifluoroacetic acid was removed in *vacuo* without further purification yielded the product (**102**).

8.17 Comparison of the rate of formation of 92d and 92c (92e or 92f) *via* metalation using TMPMgCl·LiCl as a base (Scheme 92 and 93):

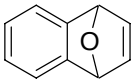
Procedure (for **92d** and **92c**): In order to compare the efficiency for the metalation reaction of these two protecting groups (Boc- and Me_2NCO-group), a dry and nitrogen-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of **91d** (266 mg, 1.0 mmol) and **91c** (237 mg, 1.0 mmol) in dry THF (6 mL). Tridecane (184 mg, 1.0 mmol) was added as the internal standard. After cooling to 0 °C, TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) was added dropwise and stirred for 4 h. The conversion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry ether. **91d** was observed as 72 % conversion as consumption, and **91c** was observed as 20 % conversion.

Procedure (for **92d** and **92e**): In order to compare the efficiency for the metalation reaction of these two protecting groups (Boc- and MeOCO-group), a dry and nitrogen-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of **91d** (266 mg, 1.0 mmol) and **91e** (224 mg, 1.0 mmol) in dry THF (6 mL). Tridecane (184 mg, 1.0 mmol) was added as the internal standard. After cooling to 0 °C, TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) was added dropwise and stirred for 4 h. The conversion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry ether. **91d** was observed as 35 % conversion as consumption, and **91e** was observed as 61 % conversion.

Procedure (for **92d** and **92f**): In order to compare the efficiency for the metalation reaction of these two protecting groups (Boc- and MeOCO-group), a dry and nitrogen-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of **91d** (266 mg, 1.0 mmol) and **91f** (224 mg, 1.0 mmol) in dry THF (6 mL). Tridecane (184 mg, 1.0 mmol) was added as the internal standard. After cooling to 0 °C, TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) was added dropwise and stirred for 4 h. The conversion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry ether. **91d** was observed as 33 % conversion as consumption, and **91f** was observed as 52 % conversion.

9. Preparation of polyfunctionalized arynes and heteroarynes *via* 2-magnesiated diaryl sulfonates

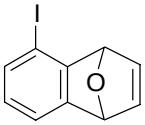
Synthesis of 1,4-dihydro-1,4-epoxynaphthalene (17a):



Prepared according to **TP 3** from 2-iodophenyl 4-methylbenzenesulfonate **(19a)** (748 mg, 2.0 mmol), *i*-PrMgCl (1.89 mL, 1.01 equiv., 1.07 M in THF) and furan (680 mg, 10.0 mmol). Reaction condition: −78 °C, 1 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane/ether = 20 : 1) yielded **17a** (59 mg, 85 %) as a colourless solid.

mp.: 52.2-53.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.17 (dd, ^3J(H,H) = 4.9 Hz, ^3J(H,H) = 3.1 Hz, 2H), 6.95 (m, 2H), 6.89 (dd, ^3J(H,H) = 4.9 Hz, ^3J(H,H) = 3.1 Hz, 2H), 5.63 (s, 2H).
MS (70 eV, EI) *m/z* (%): 144 (20) [M^+], 128 (15), 115 (100), 89 (9), 64 (3).
Spectral data match those reported in the literature and with compound **17a**.[112]

Synthesis of 1,4-dihydro-1,4-epoxy-5-iodonaphthalene (17b):



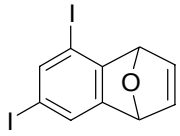
Prepared according to **TP 3** from toluene-4-sulfonic acid 2,6-diiodo-phenyl ester (**19b**) (500 mg, 1.0 mmol), *i*-PrMgCl (0.94 mL, 1.01 equiv., 1.07 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane/CH_2Cl_2 = 4 : 1) yielded **17b** (195 mg, 72 %) as a colourless oil.

Prepared according to **TP 3** from 4-chloro-benzenesulfonic acid 2,6-diiodo-phenyl ester (**27b**) (520 mg, 1.0 mmol), *i*-PrMgCl (0.94 mL, 1.01 equiv., 1.07 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane/CH_2Cl_2 = 4 : 1) yielded **17b** (211 mg, 78 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.25 (d, ^3J(H,H) = 8.1 Hz, 1H), 7.15 (d, ^3J(H,H) = 7.0 Hz, 1H), 7.08 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.7 Hz, 1H), 7.04 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.7 Hz, 1H), 6.99 (dd, ^3J(H,H) = 8.1 Hz, ^3J(H,H) = 7.0 Hz, 1H), 5.83-5.80 (m, 1H), 5.64-5.61 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 154.5, 151.1, 143.3, 142.4, 133.8, 127.1, 119.6, 86.3, 85.6, 83.5.
MS (70 eV, EI) *m/z* (%): 270 (48) [M^+], 244 (44), 242 (11), 241 (13), 115 (100), 114 (14).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3012 (w), 1576 (m), 1448 (m), 1406 (m), 1340 (w), 1280 (m), 1179 (w), 1110 (s), 995 (w), 882 (m), 871 (m), 851 (vs), 797 (w), 772 (m), 738 (m), 705 (m), 647 (m), 539 (w).
HRMS (EI) for **$C_{10}H_7OI$** (269.9542): found: 269.9552.

Synthesis of 1,4-dihydro-1,4-epoxy-5,7-diiodonaphthalene (17c):

[112] L. Shi, M. Wang, C.-A. Fan, F.-M. Zhang, Y.-Q. Tu, *Org. Lett.* **2003**, *5*, 3515.

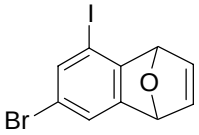


Prepared according to **TP 3** from toluene-4-sulfonic acid 2,4,6-triiodo-phenyl ester (**19c**) (626 mg, 1.0 mmol), *i*-PrMgCl (0.94 mL, 1.01 equiv., 1.07 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane/ether = 50 : 1) yielded **17c** (119 mg, 30 %) as a yellow oil.

Prepared according to **TP 3** from 4-chloro-benzenesulfonic acid 2,4,6-triiodo-phenyl ester (**27c**) (646 mg, 1.0 mmol), *i*-PrMgCl (0.94 mL, 1.01 equiv., 1.07 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane/ether = 50 : 1) yielded **17c** (103 mg, 26 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.63 (d, ^4J(H,H) = 1.2 Hz, 1H), 7.49-7.48 (m, 1H), 7.09 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.8 Hz, 1H), 7.02 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.8 Hz, 1H), 5.80 (dd, ^3J(H,H) = 1.8 Hz, ^4J(H,H) = 1.0 Hz, 1H), 5.59-5.57 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 154.9, 153.2, 142.9, 142.6, 141.1, 128.8, 90.9, 86.8, 85.5, 83.2.
MS (70 eV, EI) *m/z* (%): 396 (11) [M^+], 370 (9), 241 (37), 114 (15), 113 (7).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3065 (w), 3013 (w), 2923 (w), 2852 (w), 1732 (w), 1592 (m), 1558 (s), 1414 (m), 1369 (m), 1309 (w), 1278 (m), 1177 (w), 1104 (s), 1058 (m), 999 (w), 887 (m), 850 (vs), 802 (m), 772 (m), 736 (m), 711 (s), 662 (m), 642 (m), 574 (m), 550 (m).
HRMS (EI) for **$C_{10}H_6OI_2$** (395.8505): found: 395.8497.

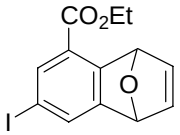
Synthesis of 7-bromo-1,4-dihydro-1,4-epoxy-5-iodonaphthalene (17d):



Prepared according to **TP 3** from toluene-4-sulfonic acid 4-bromo-2,6-diiodo-phenyl ester (**19d**) (579 mg, 1.0 mmol), *i*-PrMgCl (0.94 mL, 1.01 equiv., 1.07 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 3 h. Purification by flash chromatography (*n*-pentane/ether = 100 : 1) yielded **17d** (108 mg, 31 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.43 (d, ^4J(H,H) = 1.5 Hz, 1H), 7.31-7.29 (m, 1H), 7.10 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.8 Hz, 1H), 7.04 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.8 Hz, 1H), 5.81 (dd, ^3J(H,H) = 1.8 Hz, ^4J(H,H) = 1.0 Hz, 1H), 5.60-5.58 (m, 1H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 154.0, 152.9, 142.9, 142.6, 135.3, 123.5, 119.5, 86.0, 85.4, 83.4.
MS (70 eV, EI) *m/z* (%): 350 (6), 348 (6) [M^+], 324 (14), 322 (20), 241 (46), 195 (48), 193 (47), 114 (41), 113 (30), 63 (13), 57 (14), 43 (100), 42 (52), 41 (50).
IR (film) $\tilde{\nu}$ (cm^{-1}): 1596 (w), 1568 (m), 1417 (m), 1372 (w), 1278 (m), 1110 (m), 1060 (w), 853 (s), 806 (w), 775 (w), 714 (m), 672 (w), 644 (m), 578 (w), 554 (w).
HRMS (EI) for **$C_{10}H_6OI^{79}Br$** (347.8647): found: 347.8621.

Synthesis of 5-carbethoxy-1,4-dihydro-1,4-epoxy-7-iodonaphthalene (17e):

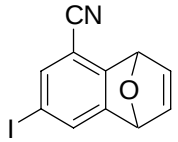


Prepared according to **TP 3** from 3,5-diiodo-2-(toluene-4-sulfonyloxy)-benzoic acid ethyl ester (**19e**) (572 mg, 1.0 mmol), *i*-PrMgCl (0.94 mL, 1.01 equiv., 1.07 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 17 h. Purification by flash chromatography (*n*-pentane/ether = 15 : 1) yielded **17e** (257 mg, 75 %) as a yellow oil.

Prepared according to **TP 3** from ethyl 2-{[(4-chlorophenyl)sulfonyl]oxy}-3,5-diiodobenzoate (**27e**) (593 mg, 1.0 mmol), *i*-PrMgCl (0.94 mL, 1.01 equiv., 1.07 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 2 h. Purification by flash chromatography (*n*-pentane/ether = 15 : 1) yielded **17e** (284 mg, 83 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.89 (d, ^4J(H,H) = 1.4 Hz, 1H), 7.67-7.66 (m, 1H), 7.06 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.8 Hz, 1H), 7.00 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.8 Hz, 1H), 6.32-6.30 (m, 1H), 5.68 (dd, ^3J(H,H) = 1.8 Hz, ^4J(H,H) = 0.9 Hz, 1H), 4.37 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.40 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 164.4, 152.6, 152.2, 143.2, 142.5, 133.7, 132.4, 125.4, 89.5, 82.5, 81.2, 61.3, 14.2.
MS (70 eV, EI) *m/z* (%): 342 (16) [M^+], 316 (22), 314 (31), 297 (17), 288 (24), 287 (26), 286 (34), 285 (16), 269 (12), 268 (14), 241 (29), 160 (14), 159 (100), 155 (18), 143 (50), 142 (12), 130 (11), 115 (37), 114 (43), 113 (36), 103 (20), 102 (21), 88 (12), 87 (11), 63 (15).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2980 (w), 1716 (s), 1590 (w), 1427 (w), 1400 (w), 1388 (w), 1367 (w), 1332 (m), 1261 (vs), 1238 (m), 1178 (m), 1159 (m), 1128 (m), 1008 (w), 868 (m), 845 (m), 806 (w), 781 (w), 715 (w), 644 (w).
HRMS (EI) for **$C_{13}H_{11}O_3I$** (341.9753): found: 341.9747.

Synthesis of 5-cyano-1,4-dihydro-1,4-epoxy-7-iodonaphthalene (17f):



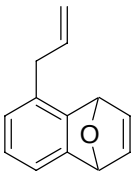
Prepared according to **TP 3** from toluene-4-sulfonic acid 2-cyano-4,6-diiodo-phenyl ester (**19f**) (525 mg, 1.0 mmol), *i*-PrMgCl (0.94 mL, 1.01 equiv., 1.07 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 40 h. Trace amount of **17f** was observed.

Prepared according to **TP 3** from 4-chloro-benzenesulfonic acid 2-cyano-4,6-diiodo-phenyl ester (**27e**) (546 mg, 1.0 mmol), *i*-PrMgCl (0.94 mL, 1.01 equiv., 1.07 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 2 h. Purification by flash chromatography (*n*-pentane/ether = 15 : 1) yielded **17f** (68 mg, 23 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.74-7.72 (m, 1H), 7.52 (d, ^4J(H,H) = 1.3 Hz, 1H), 7.08 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.8 Hz, 1H), 7.05 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.8 Hz, 1H), 5.90-5.88 (m, 1H), 5.75-5.73 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 154.4, 152.9, 143.2, 142.3, 135.0, 132.9, 115.2, 106.7, 90.0, 82.0, 81.3.

MS (70 eV, EI) *m/z* (%): 295 (8) [M^+], 279 (31), 269 (21), 267 (15), 152 (33), 140 (100), 139 (17), 127 (10), 113 (13), 85 (33), 83 (55).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2235 (w), 1328 (w), 1280 (w), 1016 (w), 856 (s), 827 (w), 728 (w), 643 (w).
HRMS (EI) for **$C_{11}H_6ONI$** (294.9494): found: 294.9504.

Synthesis of 5-allyl-1,4-dihydro-1,4-epoxynaphthalene (17g):

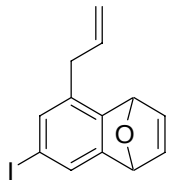


Prepared according to **TP 3** from toluene-4-sulfonic acid 2-allyl-6-iodo-phenyl ester (**19g**) (207 mg, 0.5 mmol), *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane : CH_2Cl_2 : ether = 200 : 50 : 1) yielded **17g** (78 mg, 83 %) as a colourless oil.

Prepared according to **TP 3** from 4-chloro-benzenesulfonic acid 2-allyl-6-iodo-phenyl ester (**27k**) (217 mg, 0.5 mmol), *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane : CH_2Cl_2 : ether = 200 : 50 : 1) yielded **17g** (78 mg, 83 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.17-7.10 (m, 1 H), 7.05-6.98 (m, 2 H), 6.96-6.90 (m, 1 H), 6.82-6.76 (m, 1 H), 6.02-5.86 (m, 1 H), 5.83 (bs, 1 H), 5.71 (brs, 1 H), 5.12-4.96 (m, 2 H), 3.52-3.32 (m, 2 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 148.8, 147.8, 143.0, 142.6, 137.0, 132.0, 126.0, 125.2, 118.3, 115.9, 82.3, 80.9, 37.3.
MS (70 eV, EI) *m/z* (%): 184 (20) [M^+], 165 (9), 156 (36), 155 (51), 154 (9), 153 (22), 152 (12), 141 (43), 129 (38), 128 (42), 127 (16), 116 (10), 115 (100), 77 (8).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3078 (m), 3055 (m), 3010 (m), 2977 (w), 1638 (m), 1610 (w), 1486 (w), 1470 (m), 1435 (m), 1420 (m), 1376 (m), 1280 (s), 1192 (m), 1180 (m), 1159 (w), 1081 (w), 1018 (m), 995 (m), 965 (w), 917 (m), 872 (s), 857 (s), 831 (s), 778 (s), 751 (s), 724 (s), 693 (m), 646 (m), 620 (w), 590 (w), 567 (m), 556 (m).
HRMS (EI) for **$C_{13}H_{12}O$** (184.0888): found: 184.0910.

Synthesis of 5-allyl-1,4-dihydro-1,4-epoxy-7-iodonaphthalene (17h):

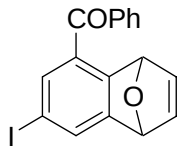


Prepared according to **TP 3** from toluene-4-sulfonic acid 2-allyl-4,6-diiodo-phenyl ester (**19h**) (270 mg, 0.5 mmol), *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane : CH_2Cl_2 : ether = 200 : 50 : 1) yielded **17h** (126 mg, 81 %) as a colourless oil.

Prepared according to **TP 3** from 4-chloro-benzenesulfonic acid 2-allyl-4,6-diiodo-phenyl ester (**27l**) (280 mg, 0.5 mmol), *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane : CH_2Cl_2 : ether = 200 : 50 : 1) yielded **17h** (137 mg, 88 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.46 (s, 1 H), 7.16 (d, ^4J(H,H) = 1.3 Hz, 1 H), 6.98 (m, 2 H), 5.95-5.81 (m, 1 H), 5.78-5.76 (m, 1 H), 5.67-5.65 (m, 1 H), 5.14-4.96 (m, 2 H), 3.44-3.24 (m, 2 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 151.6, 148.1, 142.6, 142.6, 136.1, 134.7, 134.1, 127.5, 116.6, 90.2, 81.8, 80.7, 36.9.
MS (70 eV, EI) *m/z* (%): 310 (77) [M^+], 282 (10), 281 (10), 241 (19), 165 (12), 156 (13), 155 (100), 154 (24), 153 (41), 152 (18), 129 (19), 128 (19), 127 (12).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3074 (w), 3016 (w), 2974 (w), 2910 (w), 1839 (w), 1723 (w), 1634 (m), 1607 (w), 1589 (m), 1560 (w), 1435 (m), 1406 (w), 1392 (w), 1331 (w), 1278 (m), 1220 (w), 1174 (w), 1134 (w), 1074 (w), 1012 (m), 962 (w), 942 (w), 919 (m), 890 (w), 855 (s), 830 (s), 801 (m), 726 (m), 690 (w), 654 (w), 641 (m), 591 (w), 579 (m), 554 (w).
HRMS (EI) for **$C_{13}H_{11}OI$** (309.9855): found: 309.9843.

Synthesis of 5-benzoyl-1,4-dihydro-1,4-epoxy-7-iodonaphthalene (17i):

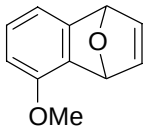


Prepared according to **TP 3** from toluene-4-sulfonic acid 2-benzoyl-4,6-diiodo-phenyl ester (**19i**) (302 mg, 0.5 mmol), *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 3 h. Purification by flash chromatography (*n*-pentane : ether = 40 : 1) yielded **17i** (94 mg, 50 %) as a pale yellow oil.

Prepared according to **TP 3** from 4-chloro-benzenesulfonic acid 2-benzoyl-4,6-diiodo-phenyl ester (**27n**) (312 mg, 0.5 mmol), *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane : ether = 40 : 1) yielded **17i** (128 mg, 68 %) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.80-7.71 (m, 3 H), 7.67-7.47 (m, 4 H), 7.14-7.08 (m, 1 H), 7.05-7.00 (m, 1 H), 5.83-5.80 (m, 1 H), 5.74-5.70 (m, 1 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 194.3, 152.9, 151.8, 143.1, 142.8, 136.9, 134.1, 133.2, 132.8, 132.0, 129.8, 128.6, 89.3, 82.3, 81.4.
MS (70 eV, EI) *m/z* (%): 374 (13) [M^+], 361 (12), 348 (23), 347 (11), 346 (53), 345 (69), 323 (8), 320 (9), 269 (12), 241 (12), 220 (19), 219 (100), 218 (57), 217 (8), 202 (18), 201 (9), 193 (21), 191 (29), 190 (32), 189 (86), 165 (44), 164 (12), 163 (15), 155 (92), 147 (20), 114 (25), 113 (22), 105 (90), 77 (59), 51 (12).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3060 (w), 2966 (w), 1657 (s), 1597 (m), 1448 (m), 1425 (w), 1381 (w), 1327 (m), 1271 (s), 1240 (w), 1198 (w), 1173 (m), 1088 (w), 1040 (m), 1023 (m), 866 (s), 853 (s), 811 (w), 754 (w), 725 (m), 716 (m), 695 (w), 676 (w), 641 (w), 662 (w), 625 (w), 579 (w), 549 (w).
HRMS (EI) for **$C_{17}H_{11}IO_2$** (373.9804): found: 373.9825.

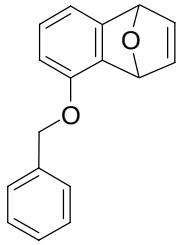
Synthesis of 5-methoxy-1,4-dihydro-1,4-epoxynaphthalene (17j):



Prepared according to **TP 3** from 4-chloro-benzenesulfonic acid 2-iodo-3-methoxy-phenyl ester (**27h**) (212 mg, 0.5 mmol), *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane : ether = 10 : 1) yielded **17j** (70 mg, 80 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.08 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.8 Hz, 1H), 7.03 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.8 Hz, 1H), 7.01-6.92 (m, 2H), 6.60 (dd, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 1.4 Hz, 1H), 5.97-5.95 (m, 1H), 5.72-5.70 (m, 1H), 3.84 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 152.9, 151.5, 143.0, 142.8, 135.0, 126.9, 113.7, 110.3, 82.5, 80.0, 55.7.
MS (70 eV, EI) *m/z* (%): 174 (28) [M^+], 159 (22), 147 (11), 146 (92), 131 (71), 116 (15), 115 (100), 105 (11), 103 (62), 102 (27), 77 (22), 76 (9), 63 (9), 50 (8).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3015 (w), 2938 (w), 2838 (w), 1617 (m), 1598 (m), 1480 (s), 1440 (m), 1280 (s), 1265 (vs), 1176 (w), 1092 (m), 1065 (m), 1000 (s), 922 (w), 877 (m), 856 (s), 822 (m), 792 (m), 771 (m), 738 (m), 721 (s), 666 (w), 624 (w).
HRMS (EI) for **$C_{11}H_{10}O_2$** (174.0681): found: 174.0713.

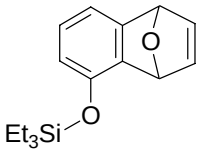
Synthesis of 5-benzyloxy-1,4-dihydro-1,4-epoxynaphthalene (17k):



Prepared according to **TP 3** from 4-chloro-benzenesulfonic acid 3-benzyloxy-2-iodo-phenyl ester (**27i**) (250 mg, 0.5 mmol), *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (pentane/diethyl ether = 20:1) yielded **17k** as a colourless oil (104 mg, 83 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.48-7.33 (m, 5H), 7.06-6.93 (m, 4H), 6.71-6.65 (m, 1H), 6.01-5.99 (m, 1H), 5.74-5.72 (m, 1H), 5.12 (s, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 152.1, 151.6, 142.9, 142.8, 137.0, 135.7, 128.5, 127.9, 127.3, 126.9, 114.0, 112.0, 82.5, 80.1, 70.7.
MS (70 eV, EI) *m/z* (%): 250 (1) [M^+], 222 (4), 131 (3), 92 (6), 91 (100), 77 (3), 65 (5), 51 (2).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3064 (w), 3028 (w), 1617 (m), 1596 (s), 1476 (s), 1465 (s), 1454 (m), 1280 (s), 1260 (vs), 1050 (w), 997 (s), 876 (m), 857 (s), 824 (m), 792 (m), 770 (m), 738 (s), 724 (s), 699 (s), 650 (w).
HRMS (EI) for **$C_{17}H_{14}O_2$** (250.0994): found: 250.0985.

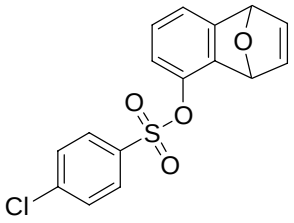
Synthesis of 5-triethylsilyl-1,4-dihydro-1,4-epoxynaphthalene (17l):



Prepared according to **TP 3** from 4-chloro-benzenesulfonic acid 2-iodo-3-triethylsilanyloxy-phenyl ester (**27j**) (262 mg, 0.5 mmol), *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (pentane/diethyl ether = 100:1) yielded **17l** as a colourless oil (94 mg, 68 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.05 (dd, ^3J(H,H) = 5.5 Hz, ^4J(H,H) = 1.7 Hz, 1H), 7.02 (dd, ^3J(H,H) = 5.5 Hz, ^4J(H,H) = 1.7 Hz, 1H), 6.93-6.83 (m, 2H), 6.48 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.1 Hz, 1H), 5.87-5.85 (m, 1H), 5.70-5.68 (m, 1H), 1.05-0.98 (m, 9H), 0.80-0.71 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 151.3, 148.6, 142.8, 142.7, 137.5, 126.5, 118.1, 114.1, 82.7, 79.9, 6.6, 5.1.
MS (70 eV, EI) *m/z* (%): 274 (32) [M^+], 248 (9), 246 (33), 245 (100), 229 (15), 218 (13), 217 (68), 215 (24), 199 (9).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3017 (w), 2957 (m), 2913 (m), 2878 (m), 1612 (m), 1599 (m), 1470 (s), 1414 (w), 1282 (s), 1261 (s), 1005 (m), 976 (s), 947 (m), 869 (m), 844 (vs), 808 (w), 776 (m), 739 (s), 719 (m), 685 (w).
HRMS (EI) for **$C_{16}H_{22}O_2{}^{28}Si$** (274.1389): found: 274.1371.

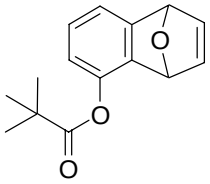
Synthesis of 4-chloro-benzenesulfonic acid 11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraen-3-yl ester (17m):



Prepared according to **TP 3** from **27f** (293 mg, 0.5 mmol), *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 6 h. Purification by flash chromatography (pentane/diethyl ether = 6:1) yielded **17m** as a colourless oil (121 mg, 72 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.64-7.59 (m, 2H), 7.42-7.37 (m, 2H), 7.03 (d, ^3J(H,H) = 7.0 Hz, 1H), 6.92-6.90 (m, 2H), 6.77 (dd, ^3J(H,H) = 8.1 Hz, ^3J(H,H) = 7.0 Hz, 1H), 6.24 (d, ^3J(H,H) = 8.1 Hz, 1H), 5.72 (*pseudo* s, 1H), 5.63 (*pseudo* s, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 152.7, 142.7, 142.5, 142.1, 141.9, 141.0, 133.4, 129.8, 129.5, 127.0, 119.3, 119.0, 82.4, 80.6.
MS (70 eV, EI) *m/z* (%): 334 (2) [M^+], 306 (11), 133 (30), 131 (100), 111 (17), 103 (37), 77 (13).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3093 (w), 1624 (w), 1587 (m), 1477 (m), 1462 (m), 1398 (m), 1380 (s), 1281 (m), 1185 (m), 1208 (s), 1132 (m), 1094 (s), 1015 (m), 965 (m), 941 (m), 874 (m), 866 (m), 838 (vs), 812 (s), 776 (s), 751 (m), 741 (m), 721 (m), 623 (m), 559 (m), 538 (m), 483 (m).
HRMS (EI) for **$C_{16}H_{11}SO_4{}^{35}Cl$** (334.0067): found: 334.0053.

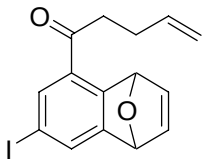
Synthesis of 5-pivalyl-1,4-dihydro-1,4-epoxynaphthalene (17n):



Prepared according to **TP 3** from **27g** (247 mg, 0.5 mmol), *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: –78 °C, 0.5 h; 25 °C, 3 h. Purification by flash chromatography (pentane/diethyl ether = 10:1) yielded **17n** as a yellow oil (83 mg, 68 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.15 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.8 Hz, 1H), 7.13-7.09 (m, 1H), 7.03 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.8 Hz, 1H), 6.99 (dd, ^3J(H,H) = 7.1 Hz, ^3J(H,H) = 7.0 Hz, 1H), 6.66 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 0.8 Hz, 1H), 5.75 (dd, ^3J(H,H) = 1.8 Hz, ^4J(H,H) = 0.9 Hz, 1H), 5.59-5.57 (m, 1H), 1.39 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 176.5, 151.3, 143.7, 142.7, 142.5, 140.1, 126.7, 118.4, 117.4, 82.4, 80.6, 39.1, 27.2.
MS (70 eV, EI) *m/z* (%): 244 (1) [M^+], 134 (9), 132 (38), 131 (25), 85 (9), 77 (10), 57 (100).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2975 (m), 2936 (w), 1748 (s), 1599 (w), 1480 (w), 1466 (m), 1398 (w), 1218 (m), 1120 (vs), 873 (m), 861 (m), 836 (m), 772 (w), 739 (w), 724 (m).
HRMS (EI) for **$C_{15}H_{16}O_3$** (244.1099): found: 244.1101.

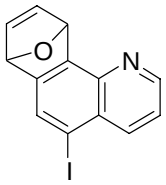
Synthesis of 5-(pent-4-enoyl)-1,4-dihydro-1,4-epoxy-7-iodonaphthalene (17o):



Prepared according to **TP 3** from 4-chloro-benzenesulfonic acid 2-(pent-4-enoyl)-6-iodo-phenyl ester **27m** (301 mg, 0.5 mmol), *i*-PrMgCl (0.47 mL, 1.01 equiv., 1.07 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane : ether = 20 : 1) yielded **17o** (125 mg, 71 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.73 (s, 1 H), 7.68 (s, 1 H), 7.12-7.06 (m, 1 H), 7.01-6.95 (m, 1 H), 6.30 (bs, 1 H), 5.95-5.79 (m, 1 H), 5.66 (brs, 1 H), 5.13-4.97 (m, 2 H), 3.03-2.93 (m, 2 H), 2.52-2.40 (m, 2 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 198.4, 153.2, 151.4, 143.0, 142.8, 136.7, 132.6, 132.4, 132.4, 115.6, 89.8, 82.6, 80.9, 38.3, 27.6.
MS (70 eV, EI) *m/z* (%): 352 (9) [M^+], 324 (11), 297 (23), 296 (9), 285 (31), 271 (14), 270 (16), 269 (100), 268 (50), 241 (36), 181 (9), 155 (11), 153 (10), 142 (11), 128 (17), 116 (15), 115 (30), 114 (40), 113 (23), 88 (11), 63 (13), 59 (12), 55 (19).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3076 (w), 3010 (w), 2977 (w), 2918 (w), 1685 (s), 1641 (w), 1588 (m), 1435 (w), 1410 (w), 1385 (w), 1322 (w), 1277 (m), 1243 (w), 1212 (m), 1175 (w), 1145 (w), 1097 (m), 1064 (m), 997 (w), 915 (m), 856 (s), 804 (w), 736 (w), 702 (w), 644 (m), 587 (w), 568 (w).
HRMS (EI) for **$C_{15}H_{13}IO_2$** (351.9960): found: 351.9927.

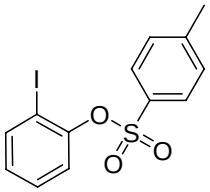
Synthesis of 5-iodo-7,10-dihydro-7,10-epoxy-benzo[h]quinoline (17p):



Prepared according to **TP 3** from 4-chloro-benzenesulfonic acid 5,7-diiodo-quinolin-8-yl ester (**27o**) (571 mg, 1.0 mmol), *i*-PrMgCl (0.94 mL, 1.01 equiv., 1.07 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane : ether = 4 : 1) yielded **17p** (248 mg, 77 %) as a yellow solid.

mp.: 138.0-139.0 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.82-8.77 (m, 1 H), 8.33-8.27 (m, 1 H), 8.13 (s, 1 H), 7.35-7.25 (m, 2 H), 7.17-7.13 (m, 1 H), 6.52-6.48 (m, 1 H), 5.91-5.88 (m, 1 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 154.4, 151.5, 150.6, 144.1, 144.1, 142.2, 140.6, 131.0, 127.9, 122.2, 94.9, 82.8, 81.2.
MS (70 eV, EI) *m/z* (%): 321 (27) [M^+], 295 (55), 294 (12), 293 (95), 281 (10), 207 (22), 183 (11), 168 (11), 167 (22), 166 (100), 165 (28), 164 (26), 140 (40), 139 (26), 138 (14), 116 (10), 113 (10), 75 (10), 73 (13), 63 (14), 59 (13), 55 (15), 41 (13).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3068 (w), 3016 (w), 2926 (w), 1635 (w), 1602 (m), 1558 (w), 1502 (m), 1440 (w), 1385 (w), 1327 (w), 1278 (w), 1240 (w), 1185 (w), 1139 (w), 1089 (w), 1052 (w), 1013 (m), 964 (w), 932 (w), 896 (m), 865 (s), 835 (m), 803 (w), 778 (m), 727 (m), 696 (w), 677 (w), 638 (w), 627 (m), 544 (w).
HRMS (EI) for **$C_{13}H_8INO$** (320.9651): found: 320.9621.

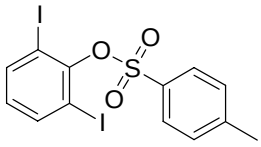
Synthesis of toluene-4-sulfonic acid 2-iodo-phenyl ester (19a):



Prepared according to **TP 2** from 2-iodophenol (4.40 g, 20 mmol) and 4-methyl-benzenesulfonyl chloride (4.58 g, 24 mmol). Recrystallization from ethanol yielded **19a** as a colourless solid (6.73 g, 90 %).

mp.: 85.0-86.0 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.79 (m, 3H), 7.33 (m, 4H), 6.97 (m, 1H), 2.46 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 150.0, 145.7, 140.1, 132.9, 129.8, 129.5, 128.8, 128.3, 123.0, 88.8, 21.7.
MS (70 eV, EI): *m/z* (%): 374 (83) [M^+], 155 (100), 91 (54).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1462 (s), 1377 (vs), 1199 (s), 1185 (s), 1170 (vs), 1090 (m), 943 (w), 868 (s), 858 (s), 812 (m), 766 (vs), 734 (s), 708 (s), 665 (s), 561 (vs), 549 (s).
HRMS (EI) for **$C_{13}H_{11}IO_3S$** (373.9474): found: 373.9507.

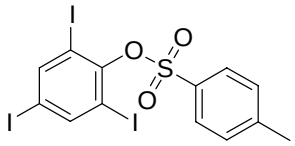
Synthesis of toluene-4-sulfonic acid 2,6-diiodo-phenyl ester (19b):



Prepared according to **TP 2** from 2,6-diiodophenol (3.46 g, 10 mmol) and 4-methyl-benzenesulfonyl chloride (2.29 g, 12 mmol). Recrystallization from ethanol yielded **19b** as a white solid (4.52 g, 90 %).

mp.: 149.4-149.8 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.94-7.90 (m, 2H), 7.81 (d, ^3J(H,H) = 7.9 Hz, 2H), 7.40-7.36 (m, 2H), 6.66 (t, ^3J(H,H) = 7.9 Hz, 1H), 2.48 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 151.5, 145.8, 140.8, 135.2, 129.9, 129.5, 129.1, 90.8, 21.8.
MS (70 eV, EI) *m/z* (%): 501 (19), 500 (84) [M^+], 373 (10), 346 (29), 218 (13), 207 (16), 156 (13), 155 (100).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1594 (m), 1556 (w), 1431 (w), 1410 (s), 1380 (vs), 1362 (w), 1216 (w), 1206 (m), 1187 (m), 1175 (vs), 1092 (m), 856 (s), 818 (m), 772 (m), 743 (s), 707 (s), 694 (s), 656 (m), 566 (s), 550 (m).
HRMS (EI) for **$C_{13}H_{10}O_3I_2S$** (499.8440): found: 499.8411.

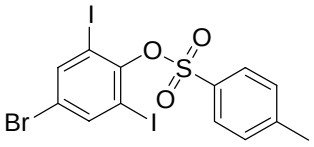
Synthesis of toluene-4-sulfonic acid 2,4,6-triiodo-phenyl ester (19c):



Prepared according to **TP 2** from 2,4,6-triiodophenol (9.44 g, 20 mmol) and 4-methyl-benzenesulfonyl chloride (4.58 g, 24 mmol). Recrystallization from ethanol yielded the **19c** as a white solid (11.02 g, 88 %).

mp.: 154.4-154.9 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.10 (s, 2H), 7.90 (d, ^3J(H,H) = 8.3 Hz, 2H), 7.38 (d, ^3J(H,H) = 8.3 Hz, 2H), 2.48 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 151.8, 148.2, 146.0, 134.9, 129.9, 129.1, 92.8, 91.8, 21.8.
MS (70 eV, EI) *m/z* (%): 626 (12) [M^+], 471 (10), 344 (11), 189 (14), 156 (11), 155 (100), 91 (67), 65 (16), 62 (21).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1595 (m), 1534 (m), 1528 (m), 1408 (s), 1377 (vs), 1306 (w), 1208 (m), 1190 (m), 1174 (vs), 1090 (m), 1044 (m), 852 (s), 816 (m), 743 (s), 714 (s), 701 (m), 664 (m), 636 (w), 573 (s), 551 (m).
HRMS (EI) for **$C_{13}H_9O_3I_3S$** (625.7407): found: 625.7427.

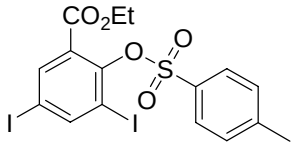
Synthesis of toluene-4-sulfonic acid 4-bromo-2,6-diiodo-phenyl ester (19d):



Prepared according to **TP 2** from 4-bromo-2,6-diiodophenol (4.25 g, 10 mmol) and 4-methyl-benzenesulfonyl chloride (2.29 g, 12 mmol). Recrystallization from ethanol yielded **19d** as a white solid (5.04 g, 87 %).

mp.: 135.2-135.9 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.93 (s, 2H), 7.92-7.88 (m, 2H), 7.41-7.37 (m, 2H), 2.47 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 151.1, 146.0, 142.6, 134.9, 129.9, 129.1, 121.2, 91.1, 21.8.
MS (70 eV, EI) *m/z* (%): 580 (12), 578 (12) [M^+], 155 (100), 139 (12), 91 (63), 65 (16).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1595 (w), 1541 (m), 1379 (s), 1408 (s), 1214 (m), 1173 (vs), 1087 (m), 1048 (w), 854 (s), 816 (m), 742 (s), 725 (s), 701 (w), 666 (s), 638 (w), 629 (w), 573 (s), 549 (m), 526 (w).
HRMS (EI) for **$C_{13}H_9O_3I_2S^{79}Br$** (577.7545): found: 577.7583.

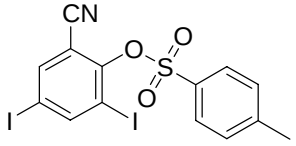
Synthesis of 3,5-diiodo-2-(toluene-4-sulfonyloxy)-benzoic acid ethyl ester (19e):



Prepared according to **TP 2** from 2-hydroxy-3,5-diiodo-benzoic acid ethyl ester (8.36 g, 20 mmol) and 4-methyl-benzenesulfonyl chloride (4.58 g, 24 mmol). Recrystallization from ethanol yielded **19e** as a yellow solid (10.53 g, 92 %).

mp.: 104.4-105.1 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.18-8.10 (m, 2H), 7.74-7.69 (m, 2H), 7.35-7.30 (m, 2H), 4.35 (q, ^3J(H,H) = 7.2 Hz, 2H), 2.45 (s, 3H), 1.41 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 163.6, 150.6, 147.8, 146.0, 140.3, 133.2, 130.0, 129.9, 128.9, 93.3, 91.7, 62.3, 21.7, 13.9.
MS (70 eV, EI) *m/z* (%): 572 (7) [M^+], 373 (14), 372 (100), 155 (44), 91 (42).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 1724 (vs), 1596 (m), 1538 (m), 1442 (w), 1420 (s), 1386 (vs), 1279 (vs), 1255 (m), 1203 (s), 1188 (s), 1177 (s), 1120 (w), 1108 (w), 1085 (m), 1018 (m), 866 (m), 847 (s), 814 (m), 787 (s), 739 (s), 711 (s), 668 (s), 652 (w), 583 (m), 572 (s), 548 (s).
HRMS (EI) for **$C_{16}H_{14}O_5I_2S$** (571.8651): found: 571.8671.

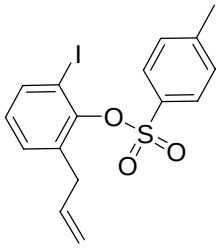
Synthesis of toluene-4-sulfonic acid 2-cyano-4,6-diiodo-phenyl ester (19f):



Prepared according to **TP 2** from 2-hydroxy-3,5-diiodo-benzonitrile (3.71 g, 10 mmol) and 4-methyl-benzenesulfonyl chloride (2.29 g, 12 mmol). Recrystallization from ethanol yielded **19f** as a white solid (4.47 g, 85 %).

mp.: 146.6-147.1 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.39 (d, ^4J(H,H) = 2.0 Hz, 1H), 7.94 (d, ^3J(H,H) = 8.3 Hz, 2H), 7.90 (d, ^4J(H,H) = 2.0 Hz, 1H), 7.42 (d, ^3J(H,H) = 8.3 Hz, 2H), 2.50 (s, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 152.6, 151.2, 146.8, 142.2, 132.7, 130.3, 129.1, 112.9, 111.3, 94.0, 91.5, 21.9.
MS (70 eV, EI) *m/z* (%): 525 (13) [M^+], 371 (13), 155 (84), 92 (17), 91 (100), 89 (11), 88 (19), 65 (27).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2236 (w), 1597 (w), 1537 (w), 1452 (w), 1428 (s), 1369 (s), 1219 (m), 1195 (s), 1179 (s), 1139 (m), 1087 (s), 880 (m), 863 (w), 819 (m), 754 (m), 723 (vs), 670 (m), 645 (m), 573 (s), 536 (m).
HRMS (EI) for **$C_{14}H_9O_3NSI_2$** (524.8393): found: 524.8421.

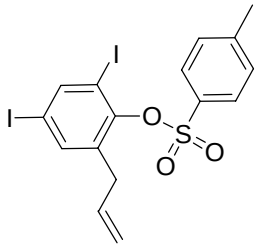
Synthesis of toluene-4-sulfonic acid 2-allyl-6-iodo-phenyl ester (19g):



A dry and argon-flushed 10 mL Schlenk tube, equipped with a magnetic stirrer and a septum, was charged with a solution of toluene-4-sulfonic acid 2,6-diiodo-phenyl ester (**19b**) (1.00 g, 2.0 mmol) in dry THF (5 mL). *i*-PrMgCl (0.92 M in THF, 2.4 mL, 1.1 equiv.) was added dropwise at −78 °C. After 30 min, CuCN·2LiCl (1.0 M in THF, 2.0 mL, 1.0 equiv.) was added slowly at −78 °C, and the resulting mixture was stirred at this temperature for 10 min. Then, allyl bromide (0.26 mL, 3.0 mmol, 1.5 equiv.) was added at −78 °C, and the resulting mixture was warmed to room temperature and stirred for 1 h. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 50 : 1) yielded **19g** (730 mg, 88 %) as a white solid.

mp.: 83.6-84.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.95-7.90 (m, 2H), 7.66 (dd, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.6 Hz, 1H), 7.40-7.35 (m, 2H), 7.27-7.23 (m, 1H), 6.93 (t, ^3J(H,H) = 7.8 Hz, 1H), 5.93-5.79 (m, 1H), 5.14-5.06 (m, 2H), 3.55-3.50 (m, 2H), 2.48 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 148.8, 145.5, 138.5, 136.5, 135.5, 134.5, 131.0, 129.8, 128.8, 128.4, 117.1, 91.2, 35.8, 21.7.
MS (70 eV, EI): *m/z* (%): 414 (7) [M^+], 259 (59), 257 (10), 155 (42), 133 (11), 132 (79), 131 (26), 104 (15), 103 (12), 91 (100), 77 (14), 65 (11).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1636 (w), 1097 (vs), 799 (w), 469 (m).
HRMS (EI) for **$C_{16}H_{15}IO_3S$** (413.9787): found: 413.9826.

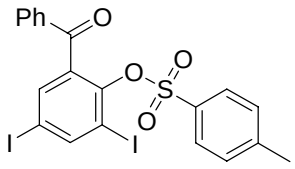
Synthesis of toluene-4-sulfonic acid 2-allyl-4,6-diiodo-phenyl ester (19h):



A dry and argon-flushed 50 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of toluene-4-sulfonic acid 2,4,6-triiodo-phenyl ester (**19c**) (5.008 g, 8.0 mmol) in dry THF (15.0 mL). *i*-PrMgCl (1.07 M in THF, 8.2 mL, 1.1 equiv.) was then added dropwise at −78 °C. After 30 min, CuCN·2LiCl (1.0 M in THF, 8.0 mL, 1.0 equiv.) was added slowly at −78 °C, and the resulting mixture was stirred at this temperature for 10 min. Then allyl bromide (1.02 mL, 12.0 mmol, 1.5 equiv.) was added at −78 °C, and the resulting mixture was warmed to room temperature and stirred for 1 hour. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 250: 1) yielded **19h** (3.155 g, 73 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.98 (d, ^4J(H,H) = 2.0 Hz, 1H), 7.90 (d, ^3J(H,H) = 8.4 Hz, 2H), 7.54 (d, ^4J(H,H) = 2.0 Hz, 1H), 7.38 (d, ^3J(H,H) = 8.4 Hz, 2H), 5.89-5.75 (m, 1H), 5.18-5.08 (m, 2H), 3.47-3.44 (m, 2H), 2.47 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 148.9, 145.9, 145.8, 139.8, 138.3, 134.6, 134.1, 129.8, 128.7, 117.9, 92.6, 92.5, 35.4, 21.7.
MS (70 eV, EI) *m/z* (%): 540 (24) [M^+], 385 (100), 258 (95), 257 (43), 155 (64), 131 (29), 91 (76), 65 (10).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3077 (w), 2979 (w), 2921 (w), 1639 (w), 1597 (m), 1568 (w), 1540 (m), 1494 (w), 1426 (s), 1380 (s), 1307 (w), 1294 (w), 1203 (s), 1188 (s), 1177 (vs), 1128 (s), 1088 (s), 995 (w), 923 (m), 862 (m), 835 (s), 813 (m), 755 (s), 727 (s), 667 (s), 577 (s), 542 (m).
HRMS (EI) for **$C_{16}H_{14}I_2O_3S$** (539.8753): found: 539.8747.

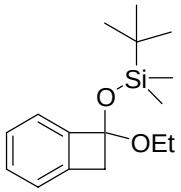
Synthesis of toluene-4-sulfonic acid 2-benzoyl-4,6-diiodo-phenyl ester (19i):



A dry and argon-flushed 50 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of toluene-4-sulfonic acid 2,4,6-triiodo-phenyl ester (5.171 g, 8.0 mmol) in dry THF (15.0 mL). *i*-PrMgCl (1.07 M in THF, 8.2 mL, 1.1 equiv.) was then added dropwise at −78 °C. After 30 min, CuCN·2LiCl (1.0 M in THF, 8.0 mL, 1.0 equiv.) was added slowly at −78 °C, and the resulting mixture was stirred at this temperature for 10 min. Then benzoyl chloride (1.39 mL, 12.0 mmol, 1.5 equiv.) was added at −78 °C, and the resulting mixture was warmed to room temperature and stirred for 1 h. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 20 : 1) yielded **19i** (3.576 g, 74 %) as a white solid.

mp.: 120.4-121.1 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C)) δ/ppm: 8.31 (d, ^4J(H,H) = 2.1 Hz, 1H), 7.77 (d, ^4J(H,H) = 2.1 Hz, 1H), 7.73-7.69 (m, 2H), 7.62-7.52 (m, 3H), 7.47-7.40 (m, 2H), 7.22-7.18 (m, 2H), 2.39 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 190.9, 150.2, 147.0, 145.9, 139.4, 136.3, 135.7, 133.5, 132.5, 130.2, 129.7, 128.7, 128.3, 94.6, 92.1, 21.7.
MS (70 eV, EI) *m/z* (%): 604 (7) [M^+], 450 (42), 449 (100), 448 (49), 322 (21), 195 (10), 155 (40), 139 (16), 105 (12), 91 (22), 77 (14).
IR (KBr): $\tilde{\nu}$ (cm^{-1}): 1677 (s), 1595 (m), 1543 (w), 1448 (w), 1417 (m), 1372 (s), 1314 (w), 1272 (s), 1242 (w), 1206 (s), 1187 (m), 1174 (vs), 1122 (w), 1086 (m), 952 (w), 872 (w), 856 (m), 814 (w), 802 (w), 775 (m), 750 (w), 731 (m), 707 (s), 666 (m), 571 (m), 550 (m).
HRMS (EI) for **$C_{20}H_{14}I_2O_4S$** (603.8702): found: 603.8741.

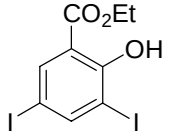
Synthesis of *tert*-butyl-(7-ethoxy-bicyclo[4.2.0]octa-1,3,5-trien-7-yloxy)-dimethyl-silane (21):



Prepared according to **TP 3** from 2-iodophenyl 4-methylbenzenesulfonate **(19a)** (748 mg, 2.0 mmol), *i*-PrMgCl (1.89 mL, 1.01 equiv., 1.07 M in THF) and *tert*-butyl-(1-ethoxy-vinyloxy)-dimethyl-silane (486 mg, 1.2 equiv.). Reaction condition: −78 °C, 1 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane/ether = 50 : 1) yielded **21** (516 mg, 93 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.29-7.14 (m, 4H), 3.86-3.75 (m, 1H), 3.74-3.63 (m, 1H), 3.50 (d, ^2J(H,H) = 13.7 Hz, 1H), 3.33 (d, ^2J(H,H) = 13.7 Hz, 1H), 1.20 (t, ^3J(H,H) = 7.1 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), -0.01 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 148.0, 141.1, 129.6, 126.7, 123.7, 121.0, 102.3, 59.8, 48.2, 25.7, 18.0, 15.3, -3.66, -3.74.
MS (70 eV, EI) *m/z* (%): 278 (6) [M^+], 277 (27), 263 (23), 233 (22), 222 (19), 221 (100), 207 (13), 193 (49), 179 (16), 177 (14), 163 (33), 149 (13), 147 (34), 119 (43), 118 (35), 103 (56), 91 (11), 90 (16), 75 (27), 73 (65).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2957 (m), 2930 (s), 2886 (w), 2858 (m), 1472 (w), 1469 (w), 1242 (vs), 1155 (m), 1141 (s), 1127 (m), 1112 (m), 1079 (m), 1057 (s), 996 (m), 949 (m), 901 (w), 837 (s), 778 (m), 758 (m), 717 (w).
HRMS (EI) for **$C_{16}H_{26}O_2Si$** (278.1702): found: 278.1651.
Spectral data match those reported in the literature with compound **21**.[113]

Synthesis of ethyl 2-hydroxy-3,5-diiodobenzoate (22a):

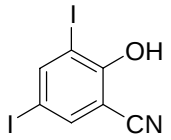


[113] T. Hosoya, T. Hasegawa, Y. Kuriyama, T. Matsumoto, K. Suzuki, *Synlett* **1995**, *2*, 177.

Prepared according to **TP 1** from 2-hydroxy-benzoic acid ethyl ester (3.32 g, 20 mmol), iodine (11.18 g, 44.0 mmol) and silver sulfate (13.71 g, 44.0 mmol). Recrystallization from ethanol yielded the final product as a pale yellow solid (6.52 g, 78 %).

mp.: 126.8-127.9°C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 11.67 (s, 1H), 8.17 (d, ^4J(H,H) = 2.2 Hz, 1H), 8.10 (d, ^4J(H,H) = 2.2 Hz, 1H), 4.42 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.42 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 168.4, 160.2, 151.9, 138.4, 114.4, 86.8, 80.6, 62.5, 14.1.
MS (70 eV, EI) *m/z* (%): 418 (71) [M^+], 373 (10), 372 (100), 246 (18), 245 (10), 91 (12), 72 (16), 63 (11), 62 (12), 59 (31), 55 (13), 45 (11), 43 (12), 41 (15).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1722 (w), 1665 (vs), 1589 (m), 1581 (m), 1472 (w), 1433 (m), 1416 (m), 1399 (s), 1371 (m), 1307 (vs), 1277 (m), 1234 (vs), 1183 (vs), 1103 (w), 1014 (s), 898 (w), 880 (m), 864 (w), 792 (s), 730 (m), 716 (m), 704 (w), 654 (m), 575 (w), 546 (w), 408 (w).
HRMS (EI) for **$C_9H_8I_2O_3$** (417.8563): found: 417.8599.

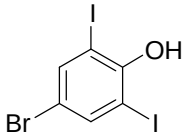
Synthesis of 2-hydroxy-3,5-diiodo-benzonitrile (22b):



Prepared according to **TP 1** from 2-hydroxy-benzonitrile (2.38 g, 20 mmol), iodine (11.18 g, 44.0 mmol) and silver sulfate (13.71 g, 44.0 mmol). Recrystallization from ethanol yielded **22b** as a white solid (4.83 g, 65 %).

mp.: 162.2-163.4°C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.16 (d, ^4J(H,H) = 2.0 Hz, 1H), 7.78 (d, ^4J(H,H) = 2.0 Hz, 1H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 156.8, 150.3, 141.5, 113.8, 101.5, 87.2, 82.0.
MS (70 eV, EI): *m/z* (%): 371 (100) [M^+], 245 (14), 244 (19).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3350 (brs), 3056 (m), 2230 (m), 1761 (w), 1572 (m), 1548 (w), 1451 (vs), 1384 (m), 1307 (s), 1273 (s), 1242 (m), 1194 (s), 1127 (s), 872 (m), 796 (w), 730 (w), 675 (m), 570 (w), 534 (m).
HRMS (EI) for **$C_7H_3I_2NO$** (370.8304): found: 370.8336.

Synthesis of 4-bromo-2,6-diiodo-phenol (22c):

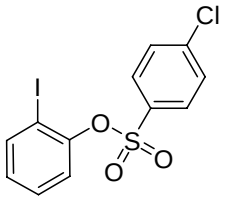


Prepared according to **TP 1** from 4-bromo-phenol (1.73 g, 10 mmol), iodine (5.59 g, 22.0 mmol) and silver sulfate (6.85 g, 22.0 mmol). Recrystallization from ethanol yielded **22c** as a pale yellow solid (2.68 g, 63 %).

mp.: 128.2-128.8 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.78 (s, 2H), 5.72 (s, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 153.1, 140.8, 113.6, 82.4.

MS (70 eV, EI) *m/z* (%): 426 (96), 424 (100) [M^+], 390 (10), 300 (11), 298 (11), 172 (14), 170 (12), 91 (12), 64 (75), 63 (18), 62 (14), 59 (18), 48 (32), 45 (33), 44 (16), 43 (13).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3464 (s), 1439 (vs), 1378 (m), 1308 (m), 1262 (w), 1231 (m), 1147 (m), 858 (m), 700 (m), 655 (w), 545 (w).
HRMS (EI) for **$C_6H_3I_2O^{79}Br$** (423.7457): found: 423.7449.

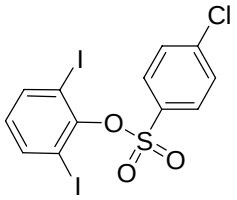
Synthesis of 2-iodophenyl 4-chlorobenzenesulfonate (27a):



Prepared according to **TP 2** from 2-iodophenol (4.40 g, 20 mmol) and 4-chlorobenzenesulfonyl chloride (5.22 g, 24 mmol). Recrystallization from ethanol yielded **27a** as a colourless solid (7.50 g, 95 %).

mp.: 89.3-90.2 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.85 (d, ^3J(H,H) = 8.9 Hz, 2H), 7.78-7.74 (m, 1H), 7.51 (d, ^3J(H,H) = 8.9 Hz, 2H), 7.37-7.33 (m, 2H), 7.03-6.95 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 149.8, 141.4, 140.2, 134.3, 130.3, 129.5, 128.6, 123.1, 112.6, 90.0.
MS (70 eV, EI) *m/z* (%): 394 (62) [M^+], 298 (4), 218 (20), 190 (17), 175 (100), 139 (4), 111 (66), 92 (42), 75 (27), 64 (32).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1584 (m), 1572 (m), 1462 (s), 1380 (vs), 1283 (m), 1199 (vs), 1174 (vs), 1085 (s), 866 (vs), 854 (vs), 774 (vs), 727 (vs), 619 (vs), 606 (vs), 557 (vs), 483 (m).
HRMS (EI) for **$C_{12}H_8{}^{35}ClIO_3S$** (393.8927): found: 393.8937.
$C_{12}H_8ClIO_3S$: calc.: C: 36.52; H: 2.04; found: C: 36.89; H: 2.08.

Synthesis of 4-chloro-benzenesulfonic acid 2,6-diiodo-phenyl ester (27b):

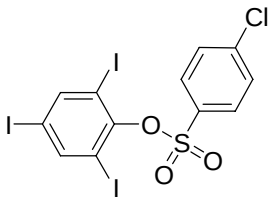


Prepared according to **TP 2** from 2,6-diiodophenol (2.422 g, 7.0 mmol) and 4-chloro-benzenesulfonyl chloride (1.78 g, 8.4 mmol). Recrystallization from ethanol yielded **27b** as a white solid (3.36 g, 92 %).

mp.: 127.4-127.8 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.00-7.94 (m, 2 H), 7.16 (d, ^3J(H,H) = 8.0 Hz, 2 H), 7.60-7.54 (m, 2 H), 6.67 (t, ^3J(H,H) = 8.0 Hz, 1 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 151.3, 141.3, 140.8, 136.5, 130.4, 129.8, 129.6, 90.6.
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3088 (w), 1929 (w), 1638 (w), 1586 (w), 1572 (w), 1556 (w), 1476 (w), 1431 (w), 1408 (m), 1388 (s), 1282 (w), 1210 (m), 1179 (s), 1092 (m), 1066 (w), 1037 (w),

1014 (w), 855 (s), 833 (w), 828 (w), 775 (m), 763 (s), 741 (m), 706 (m), 690 (m), 623 (m), 610 (m), 561 (m), 480 (w), 459 (w).
MS (70 eV, EI) *m/z* (%): 522 (20), 520 (55) [M^+], 345 (48), 317 (12), 218 (60), 190 (10), 177 (38), 175 (100), 159 (16), 113 (17), 111 (54), 75 (27), 63 (56), 62 (15).
HRMS (EI) for **$C_{12}H_7{}^{35}ClI_2O_3S$** (519.7894): found: 519.7848.

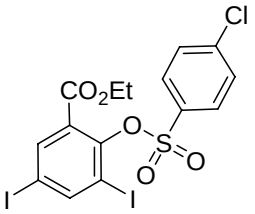
Synthesis of 4-chloro-benzenesulfonic acid 2,4,6-triiodophenyl ester (27c):



Prepared according to **TP 2** from 2,4,6-triiodophenol (9.44 g, 20 mmol) and 4-chlorobenzenesulfonyl chloride (5.22 g, 24 mmol). Recrystallization from ethanol yielded **27c** as a white solid (12.02 g, 93 %).

mp.: 123.8-124.7 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.10 (s, 2 H), 7.95 (d, ^3J(H,H) = 8.8 Hz, 2 H), 7.57 (d, ^3J(H,H) = 8.8 Hz, 2 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 151.6, 148.3, 141.5, 136.3, 130.4, 129.7, 93.1, 91.7.
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3085 (w), 3042 (w), 1916 (w), 1734 (w), 1636 (w), 1585 (m), 1533 (m), 1477 (m), 1409 (s), 1400 (s), 1383 (s), 1282 (w), 1210 (s), 1176 (s), 1092 (m), 1042 (m), 1016 (m), 967 (w), 855 (s), 830 (m), 761 (s), 739 (s), 714 (s), 700 (m), 632 (m), 618 (s), 565 (s), 516 (w), 481 (m), 471 (m).
MS (70 eV, EI) *m/z* (%): 648 (12), 646 (34) [M^+], 472 (10), 471 (100), 344 (22), 189 (17), 177 (10), 175 (28), 111 (15), 62 (14).
HRMS (EI) for **$C_{12}H_6{}^{35}ClI_3O_3S$** (645.6860): found: 645.6842.

Synthesis of ethyl 2-{[(4-chlorophenyl)sulfonyl]oxy}-3,5-diiodobenzoate (27d):

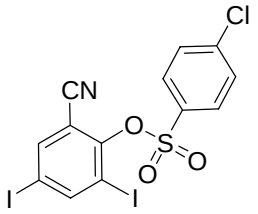


Prepared according to **TP 2** from ethyl 2-hydroxy-3,5-diiodobenzoate (4.18 g, 10 mmol) and 4-chlorobenzenesulfonyl chloride (2.61 g, 12 mmol). Recrystallization from ethanol yielded **27d** as a colourless solid (5.50 g, 93 %).

mp.: 96.8-97.5°C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.19 (d, ^4J(H,H) = 1.7 Hz, 1H), 8.15 (d, ^4J(H,H) = 1.7 Hz, 1H), 7.80 (d, ^3J(H,H) = 8.6 Hz, 2H), 7.53 (d, ^3J(H,H) = 8.6 Hz, 2H), 4.37 (q, ^3J(H,H) = 7.3 Hz, 2H), 1.42 (t, ^3J(H,H) = 7.3 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 163.4, 150.8, 147.7, 141.7, 140.5, 134.8, 130.3, 129.8, 129.8, 92.9, 92.1, 62.5, 13.9.

MS (70 eV, EI): *m/z* (%): 592 (10) [M^+], 417 (35), 373 (28), 372 (100), 262 (14), 245 (10), 189 (10), 177 (10), 175 (26), 111 (26).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3088 (w), 2983 (w), 1721 (vs), 1587 (w), 1570 (m), 1537 (w), 1478 (m), 1464 (w), 1446 (w), 1419 (s), 1385 (vs), 1300 (s), 1274 (vs), 1252 (s), 1212 (vs), 1202 (vs), 1180 (vs), 1106 (m), 1093 (s), 1082 (s), 1009 (s), 890 (w), 865 (s), 849 (s), 836 (m), 787 (s), 763 (vs), 736 (s), 711 (s), 652 (w), 624 (s), 567 (s), 485 (m).
HRMS (EI) for **$C_{15}H_{11}{}^{35}ClI_2O_5S$** (591.8105): found: 591.8127.

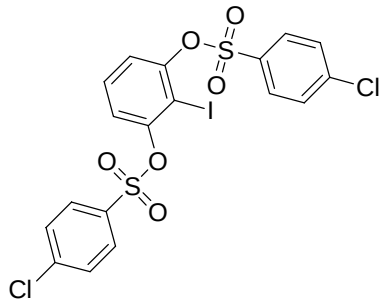
Synthesis of 4-chloro-benzenesulfonic acid 2-cyano-4,6-diiodo-phenyl ester (27e):



Prepared according to **TP 2** from 2-hydroxy-3,5-diiodobenzonitrile (3.71 g, 10 mmol) and 4-chlorobenzenesulfonyl chloride (2.61 g, 12 mmol). Recrystallization from ethanol yielded **27e** as a colourless solid (4.81 g, 88 %).

mp.: 141.6-142.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.40 (d, ^4J(H,H) = 2.1 Hz, 1H), 8.03-7.98 (m, 2H), 7.92 (d, ^4J(H,H) = 2.1 Hz, 1H), 7.63-7.58 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 152.7, 151.0, 142.3, 142.2, 134.2, 130.4, 130.0, 112.8, 111.1, 93.8, 91.8.
MS (70 eV, EI): *m/z* (%): 545 (16) [M^+], 371 (68), 245 (30), 244 (17), 177 (36), 175 (100), 114 (11), 113 (16), 112 (38), 111 (41), 88 (14).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3092 (w), 2235 (w), 1583 (w), 1476 (w), 1426 (s), 1397 (m), 1377 (vs), 1217 (m), 1192 (s), 1140 (m), 1083 (s), 1013 (w), 868 (m), 822 (m), 815 (m), 765 (s), 750 (m), 719 (s), 643 (w), 628 (s), 593 (m), 552 (m), 484 (m).
HRMS (EI) for **$C_{13}H_6{}^{35}ClI_2NO_3S$** (544.7846): found: 544.7848.

Synthesis of 3-{[(4-chlorophenyl)sulfonyl]oxy}-2-iodophenyl 4-chlorobenzenesulfonate (27f):

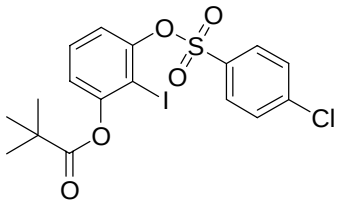


Prepared according to **TP 2** from 2-iodo-benzene-1,3-diol (**28**) (2.36 g, 10 mmol) and 4-chlorobenzenesulfonyl chloride (4.78 g, 22 mmol). Recrystallization from ethanol yielded **27f** as a white solid (5.15 g, 88 %).

mp.: 152.0-157.3 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.84-7.79 (m, 4H), 7.54-7.49 (m, 4H), 7.42 (dd, ^3J(H,H) = 9.3 Hz, ^3J(H,H) = 6.9 Hz, 1H), 7.34-7.30 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 151.1, 141.6, 134.0, 130.2, 130.1, 129.7, 121.5, 88.5.
MS (70 eV, EI): *m/z* (%): 586 (21), 584 (29) [M^+], 282 (13), 177 (39), 175 (100), 159 (14), 113 (19), 111 (53), 107 (13), 75 (11).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3090 (w), 1576 (m), 1476 (m), 1446 (s), 1398 (m), 1378 (s), 1360 (s), 1284 (w), 1231 (m), 1192 (vs), 1172 (s), 1090 (s), 1014 (m), 975 (vs), 837 (m), 808 (s), 769 (s), 733 (m), 708 (m), 676 (w), 642 (m), 610 (m), 570 (w), 554 (s), 486 (m), 474 (w).
HRMS (EI) for **$C_{18}H_{11}IO_6S_2{}^{35}Cl_2$** (583.8419): found: 583.8428.

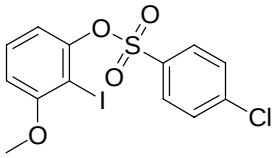
Synthesis of 2,2-dimethyl-propionic acid 3-(4-chloro-benzenesulfonyloxy)-2-iodo-phenyl ester (27g):



A 50 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with 4-chloro-benzenesulfonic acid 3-hydroxy-2-iodo-phenyl ester (**29**) (2.053 g, 5 mmol) and pivaloyl chloride (1.22 mL, 10 mmol) in pyridine (10 mL). The reaction mixture was stirred at room temperature overnight. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Recrystallization from ether and pentane yielded **27g** (2.525 g, 94 %) as a white solid.

mp.: 132.9-134.0 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.88-7.83 (m, 2H), 7.54-7.49 (m, 2H), 7.35 (t, ^3J(H,H) = 8.2 Hz, 1H), 7.21 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.4 Hz, 1H), 6.99 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.4 Hz, 1H), 1.38 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 175.6, 152.9, 150.8, 141.4, 134.1, 130.1, 129.6, 129.6, 121.3, 119.9, 88.2, 39.3, 27.2.
MS (70 eV, EI): *m/z* (%): 496 (4), 494 (9) [M^+], 412 (10), 410 (24), 346 (12), 177 (14), 175 (39), 111 (19), 85 (39), 57 (100), 41 (9).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2977 (m), 1748 (s), 1584 (m), 1575 (m), 1478 (m), 1449 (s), 1397 (m), 1377 (s), 1281 (w), 1220 (m), 1191 (s), 1173 (m), 1116 (vs), 1092 (s), 1028 (m), 1014 (m), 975 (s), 876 (w), 833 (s), 822 (m), 798 (s), 784 (m), 762 (m), 706 (w), 699 (w), 622 (m), 603 (m), 579 (w), 558 (m), 486 (m).
HRMS (EI) for **$C_{17}H_{16}IO_5S^{35}Cl$** (493.9452): found: 493.9451.

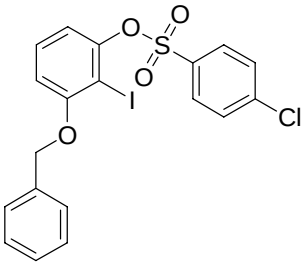
Synthesis of 4-chloro-benzenesulfonic acid 2-iodo-3-methoxy-phenyl ester (27h)



A 50 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with 4-chloro-benzenesulfonic acid 3-hydroxy-2-iodo-phenyl ester (**29**) (2.053 g, 5 mmol), cesium carbonate (2.28 g, 7 mmol) and iodomethane (6.54 mL, 105 mmol) in DMF (10 mL). The reaction mixture was stirred at room temperature overnight. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Recrystallization from ether and pentane yielded **27h** (1.807 g, 85 %) as a white solid.

mp.: 120.4-122.1 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.90-7.87 (m, 2H), 7.52-7.49 (m, 2H), 7.30 (t, ^3J(H,H) = 8.3 Hz, 1H), 7.00-6.97 (m, 1H), 6.73-6.70 (m, 1H), 3.86 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 159.8, 150.9, 141.2, 134.3, 130.2, 129.9, 129.5, 115.1, 109.2, 83.0, 56.8.
MS (70 eV, EI): *m/z* (%): 427 (5), 426 (37), 425 (14), 424 (100) [M^+], 249 (63), 233 (29), 221 (59), 206 (13), 177 (18), 175 (51), 122 (18), 113 (11), 111 (34), 107 (30), 79 (13).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1586 (m), 1468 (s), 1438 (w), 1398 (w), 1379 (vs), 1271 (m), 1187 (s), 1171 (m), 1092 (m), 1068 (s), 932 (w), 843 (w), 795 (s), 759 (w), 722 (w), 620 (m), 600 (m), 546 (m), 486 (m).
HRMS (EI) for **$C_{13}H_{10}IO_4S^{35}Cl$** (423.9033): found: 423.9034.

Synthesis of 4-chloro-benzenesulfonic acid 3-benzyloxy-2-iodo-phenyl ester (27i):

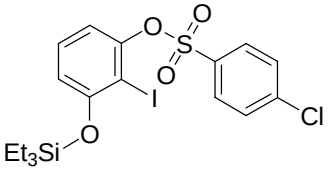


A 50 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with 4-chloro-benzenesulfonic acid 3-hydroxy-2-iodo-phenyl ester (**29**) (2.053 g, 5 mmol), potassium carbonate (0.691 g, 5 mmol) and benzyl bromide (1.026 g, 6 mmol) in DMF (10 mL). The reaction mixture was stirred at room temperature overnight. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane/ether = 20 : 1) yielded **27i** (2.357 g, 94 %) as a white solid.

mp.: 80.6-81.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.81-7.76 (m, 2H), 7.42-7.20 (m, 7H), 7.16 (t, ^3J(H,H) = 8.3 Hz, 1H), 6.90 (dd, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 1.0 Hz, 1H), 6.66 (dd, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 1.0 Hz, 1H), 5.02 (s, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 158.9, 150.9, 141.2, 135.8, 134.3, 130.8, 129.8, 129.4, 128.5, 128.0, 126.9, 115.4, 110.8, 83.9, 71.2.

MS (70 eV, EI): *m/z* (%): 502 (1), 500 (3) [M^+], 375 (1), 373 (3), 197 (5), 113 (2), 111 (5), 92 (6), 91 (100), 75 (2), 65 (4), 51 (2).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1582 (w), 1474 (w), 1450 (s), 1398 (w), 1378 (vs), 1266 (m), 1220 (w), 1186 (s), 1088 (m), 1048 (s), 1027 (m), 1014 (m), 948 (w), 828 (w), 810 (s), 788 (m), 760 (s), 748 (m), 727 (m), 696 (m), 617 (m), 569 (w), 488 (w).
HRMS (EI) for **$C_{19}H_{14}IO_4S^{35}Cl$** (499.9346): found: 499.9371.

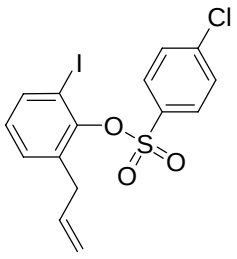
Synthesis of 4-chloro-benzenesulfonic acid 2-iodo-3-triethylsilanyloxy-phenyl ester (27j):



A 50 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with 4-chloro-benzenesulfonic acid 3-hydroxy-2-iodo-phenyl ester (**29**) (2.053 g, 5 mmol), triethylamine (2.79 mL, 20 mmol) and triethylsilyl chloride (1.67 mL, 10 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature overnight. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane/ether = 20 : 1) yielded **27h** (2.400 g, 91 %) as a yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.87-7.82 (m, 2H), 7.49-7.44 (m, 2H), 7.18 (t, ^3J(H,H) = 8.2 Hz, 1H), 7.00 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.3 Hz, 1H), 6.71 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.3 Hz, 1H), 0.99-0.92 (m, 9H), 0.82-0.71 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 157.2, 150.9, 141.1, 134.1, 130.3, 129.4, 129.3, 116.8, 115.4, 88.0, 6.6, 5.2.
MS (70 eV, EI): *m/z* (%): 496 (24), 495 (100), 321 (8), 320 (27), 185 (11), 111 (7), 87 (9), 59 (8).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2958 (m), 2912 (w), 2877 (m), 1584 (m), 1565 (w), 1477 (w), 1455 (vs), 1398 (m), 1384 (m), 1295 (m), 1217 (m), 1187 (s), 1088 (m), 1016 (s), 852 (m), 829 (w), 792 (m), 767 (s), 741 (s), 708 (m), 620 (m), 556 (w), 485 (w).
HRMS (EI) for **$C_{18}H_{22}IO_4SSi^{35}Cl$** (523.9741): found: 523.9709.

Synthesis of 4-chloro-benzenesulfonic acid 2-allyl-6-iodo-phenyl ester (27k):

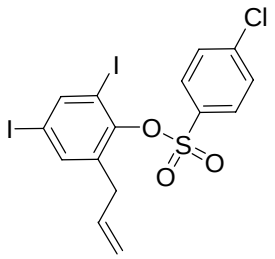


A dry and argon-flushed 10 mL Schlenk tube, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-chloro-benzenesulfonic acid 2,6-diiodo-phenyl ester (**27b**) (520 mg, 1.0 mmol) in dry THF (3 mL). *i*-PrMgCl (0.92 M in THF, 1.2 mL, 1.1 equiv.) was added dropwise at −78 °C. After 30 min, CuCN·2LiCl (1.0 M in THF, 1.0 mL, 1.0 equiv.) was added slowly at −78 °C, and the resulting mixture was stirred at this temperature for 10 min. Then, allyl bromide (0.13 mL, 1.5 mmol, 1.5 equiv.) was added at −78 °C, and the resulting

mixture was warmed to room temperature and stirred for 1 h. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 200 : 1) yielded **27k** (406 mg, 91 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.00-7.93 (m, 2 H), 7.63 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.8 Hz, 1 H), 7.57-7.51 (m, 2 H), 7.25 (d, ^3J(H,H) = 8.0 Hz, 1 H), 6.92 (t, ^3J(H,H) = 8.0 Hz, 1 H), 5.93-5.78 (m, 1 H), 5.15-5.06 (m, 2 H), 3.57-3.52 (m, 2 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 148.6, 141.1, 138.5, 136.4, 135.8, 135.2, 131.1, 130.2, 129.5, 128.6, 117.3, 90.8, 35.8.
MS (70 eV, EI) *m/z* (%): 436 (4), 434 (11) [M^+], 259 (35), 258 (13), 257 (14), 175 (15), 133 (10), 132 (100), 131 (50), 111 (19), 104 (23), 103 (17), 78 (11), 77 (15).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3090 (w), 2979 (w), 2918 (w), 1639 (w), 1586 (m), 1478 (m), 1452 (w), 1427 (s), 1398 (m), 1380 (s), 1281 (w), 1202 (s), 1186 (s), 1163 (m), 1112 (w), 1091 (s), 1070 (m), 1015 (m), 995 (w), 921 (m), 865 (s), 829 (s), 765 (s), 713 (s), 698 (m), 648 (s), 624 (m), 562 (s), 482 (m).
HRMS (EI) for **$C_{15}H_{12}{}^{35}ClIO_3S$** (433.9240): found: 433.9205.

Synthesis of 4-chloro-benzenesulfonic acid 2-allyl-4,6-diiodo-phenyl ester (27l):

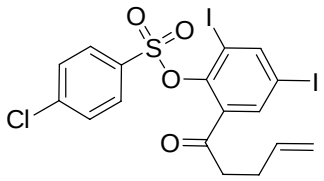


A dry and argon-flushed 50 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-chloro-benzenesulfonic acid 2,4,6-triiodo-phenyl ester (**27c**) (5.17 g, 8.0 mmol) in dry THF (15.0 mL). *i*-PrMgCl (1.07 M in THF, 8.2 mL, 1.1 equiv.) was then added dropwise at −78 °C. After 30 min, CuCN·2LiCl (1.0 M in THF, 8.0 mL, 1.0 equiv.) was added slowly at −78 °C, and the resulting mixture was stirred at this temperature for 10 min. Then allyl bromide (1.03 mL, 12.0 mmol, 1.5 equiv.) was added at −78 °C, and the resulting mixture was warmed to room temperature and stirred for 1 h. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 250 : 1) yielded **27l** (3.770 g, 84 %) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.00-7.94 (m, 3 H), 7.60-7.54 (m, 3 H), 5.92-5.76 (m, 1 H), 5.21-5.10 (m, 2 H), 3.54-3.47 (m, 2 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 148.8, 145.9, 141.4, 140.0, 138.3, 135.6, 134.4, 130.1, 129.6, 118.1, 92.9, 92.1, 35.4.
MS (70 eV, EI) *m/z* (%): 562 (6), 560 (17) [M^+], 386 (18), 385 (94), 258 (100), 257 (37), 175 (12), 159 (12), 131 (32), 111 (20), 77 (23), 76 (10), 75 (17).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3089 (m), 2978 (w), 2920 (w), 2563 (w), 1913 (w), 1731 (w), 1639 (m), 1589 (m), 1569 (m), 1540 (m), 1477 (m), 1425 (s), 1383 (s), 1282 (m), 1246 (w), 1204 (s), 1184 (s), 1127 (s), 1084 (s), 1014 (m), 995 (m), 923 (m), 862 (s), 835 (s), 765 (s), 723 (s), 675 (w), 645 (m), 625 (s), 568 (s), 522 (w), 481 (m).

HRMS (EI) for **$C_{15}H_{11}{}^{35}ClI_2O_3S$** (559.8207): found: 559.8246.

Synthesis of 4-chloro-benzenesulfonic acid 2-(pent-4-enoyl)-4,6-diiodo-phenyl ester (27m):

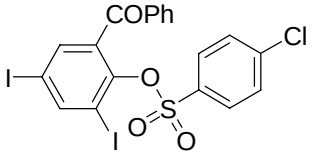


A solution containing 4-pentenoic acid (0.6 mL, 6.0 mmol) in 20 mL of CH_2Cl_2 was treated dropwise with oxalyl chloride (1.0 mL, 12.0 mmol). The mixture was stirred at room temperature for 12 h, and the solvent and the excess amount of oxalyl chloride was removed under reduced pressure. The resulting pent-4-enoyl chloride was dissolve in dry THF (5 mL) and was used without further purification.

A dry and argon-flushed 50 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-chloro-benzenesulfonic acid 2,4,6-triiodo-phenyl ester (1.939 g, 3.0 mmol) in dry THF (10 mL). *i*-PrMgCl (0.92 M in THF, 3.6 mL, 3.3 equiv.) was then added dropwise at −78 °C. After 30 min, CuCN·2LiCl (1.0 M in THF, 3.0 mL, 1.0 equiv.) was added slowly at −78 °C, and the resulting mixture was stirred at this temperature for 10 min. Then pent-4-enoyl chloride (6.0 mmol, 2.0 equiv.) in THF was added at −78 °C, and the resulting mixture was warmed to room temperature and stirred for 1 h. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 50 : 1) yielded **27m** (1.139 g, 63 %) as yellow solid.

mp.: 151.5-152.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.22-8.16 (m, 1 H), 7.86-7.76 (m, 3 H), 7.59-7.49 (m, 2 H), 5.91-5.75 (m, 1 H), 5.10-4.95 (m, 2 H), 3.04-2.94 (m, 2 H), 2.48-2.37 (m, 2 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 198.3, 150.1, 146.1, 142.0, 138.4, 137.8, 136.6, 133.7, 130.4, 129.8, 115.6, 93.7, 92.9, 40.9, 27.9.
MS (70 eV, EI) *m/z* (%): 602 (3) [M^+], 549 (11), 547 (23), 427 (64), 426 (14), 410 (75), 374 (10), 373 (100), 372 (22), 300 (14), 218 (12), 189 (10), 177 (15), 175 (47), 113 (12), 111 (35), 55 (17).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3087 (w), 3062 (w), 3044 (w), 1918 (w), 1856 (w), 1774 (w), 1703 (s), 1640 (m), 1585 (m), 1567 (m), 1537 (m), 1478 (m), 1449 (w), 1416 (s), 1400 (m), 1381 (m), 1352 (s), 1286 (m), 1270 (m), 1202 (s), 1178 (s), 1145 (s), 1085 (s), 1055 (w), 1014 (m), 1000 (m), 929 (m), 879 (m), 855 (s), 836 (m), 822 (m), 811 (m), 783 (m), 768 (s), 753 (s), 723 (s), 692 (w), 650 (m), 608 (m), 595 (m), 558 (s), 509 (m), 480 (m).
HRMS (EI) for **$C_{17}H_{13}{}^{35}ClI_2O_4S$** (601.8313): found: 601.8302.

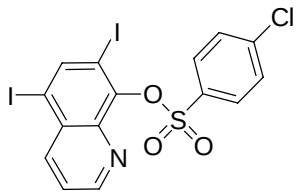
Synthesis of 4-chloro-benzenesulfonic acid 2-benzoyl-4,6-diiodo-phenyl ester (27n):



A dry and argon-flushed 50 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-chloro-benzenesulfonic acid 2,4,6-triiodo-phenyl ester (5.171 g, 8.0 mmol) in dry THF (15.0 mL). *i*-PrMgCl (1.07 M in THF, 8.2 mL, 1.1 equiv.) was then added dropwise at −78 °C. After 30 min, CuCN·2LiCl (1.0 M in THF, 8.0 mL, 1.0 equiv.) was added slowly at −78 °C, and the resulting mixture was stirred at this temperature for 10 min. Then benzoyl chloride (1.39 mL, 12.0 mmol, 1.5 equiv.) was added at −78 °C, and the resulting mixture was warmed to room temperature and stirred for 1 h. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 80 : 1) yielded **27n** (2.646 g, 53 %) as a white solid.

mp.: 184.2-185.1 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.33 (d, ^4J(H,H) = 2.2 Hz, 1 H), 7.77 (d, ^4J(H,H) = 2.2 Hz, 1 H), 7.72-7.67 (m, 2 H), 7.64-7.57 (m, 3 H), 7.49-7.41 (m, 2 H), 7.40-7.34 (m, 2 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 190.8, 150.2, 146.8, 141.5, 139.4, 136.1, 135.5, 134.0, 133.7, 130.2, 130.0, 129.5, 128.4, 94.4, 92.5.
MS (70 eV, EI) *m/z* (%): 624 (2) [M^+], 450 (29), 449 (100), 448 (31), 323 (9), 322 (38), 195 (11), 175 (12), 139 (15), 111 (14), 105 (18), 77 (27).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3088 (w), 3064 (w), 1908 (w), 1668 (s), 1593 (m), 1536 (m), 1477 (m), 1448 (m), 1420 (m), 1399 (m), 1384 (s), 1315 (w), 1274 (s), 1245 (m), 1211 (s), 1184 (s), 1121 (m), 1084 (s), 1014 (w), 950 (m), 898 (w), 858 (s), 826 (m), 804 (w), 778 (s), 760 (m), 729 (m), 707 (s), 652 (s), 618 (s), 565 (s), 521 (w), 510 (w), 482 (m), 472 (w).
HRMS (EI) for **$C_{19}H_{11}{}^{35}ClI_2O_4S$** (623.8156): found: 623.8199.

Synthesis of 4-chloro-benzenesulfonic acid 5,7-diiodo-quinolin-8-yl ester (27o):

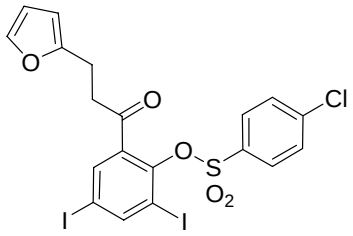


Prepared according to **TP 2** from 5,7-diiodo-quinolin-8-ol (7.939 g, 20 mmol) and 4-chlorobenzenesulfonyl chloride (5.22 g, 24 mmol). Recrystallization from ethanol yielded **27o** (9.488 g, 83 %) as a pale green solid.

mp.: 140.8 -141.6 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.70-8.64 (m, 1 H), 8.49 (s, 1 H), 8.33-8.26 (m, 1 H), 8.06-7.97 (m, 2 H), 7.58-7.44 (m, 3 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 151.3, 149.4, 145.5, 142.0, 140.7, 140.4, 136.6, 131.1, 130.3, 129.1, 123.8, 97.1, 92.9.
MS (70 eV, EI) *m/z* (%): 507 (100), 443 (60), 397 (93), 396 (83), 368 (33), 269 (68), 241 (44), 207 (36), 188 (33), 143 (19), 114 (60), 87 (24), 63 (20).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3087 (w), 1917 (w), 1586 (m), 1569 (m), 1546 (m), 1470 (m), 1443 (m), 1397 (m), 1378 (s), 1341 (m), 1282 (w), 1233 (w), 1208 (m), 1188 (s), 1173 (s), 1131 (w), 1090 (m), 1059 (s), 1040 (m), 1015 (m), 914 (w), 867 (w), 851 (w), 836 (m), 826 (m), 795 (s), 786 (s), 754 (m), 706 (m), 693 (m), 673 (m), 632 (m), 621 (m), 596 (w), 585 (m), 545 (w), 521 (m), 481 (m).

$C_{15}H_8ClI_2NO_3S$: calc.: C: 31.52; H: 1.41; N: 2.45; S: 5.61; found: C: 31.71; H: 1.39; N: 2.45; S: 5.87.

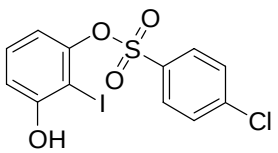
Synthesis of 4-chloro-benzenesulfonic acid 2-(3-furan-2-yl-propionyl)-4,6-diiodo-phenyl ester (27p):



A dry and argon-flushed 50 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-chloro-benzenesulfonic acid 2,4,6-triiodo-phenyl ester (**27c**) (1.939 g, 3.0 mmol) in dry THF (10 mL). *i*-PrMgCl (0.92 M in THF, 3.6 mL, 3.3 equiv.) was then added dropwise at −78 °C. After 30 min, CuCN·2LiCl (1.0 M in THF, 3.0 mL, 1.0 equiv.) was added slowly at −78 °C, and the resulting mixture was stirred at this temperature for 10 min. Then 3-furan-2-yl-propionyl chloride[80] (6.0 mmol, 2.0 equiv.) in THF was added at −78 °C, and the resulting mixture was warmed to room temperature and stirred for 1 h. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 200 : 1) yielded **27p** (1.287 g, 65 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.20 (d, ^4J(H,H) = 2.2 Hz, 1 H), 7.86-7.77 (m, 3 H), 7.58-7.51 (m, 2 H), 7.29 (dd, ^3J(H,H) = 2.2 Hz, ^4J(H,H) = 0.9 Hz, 1 H), 6.27 (dd, ^3J(H,H) = 3.1 Hz, ^3J(H,H) = 2.2 Hz, 1 H), 6.03 (dd, ^3J(H,H) = 3.1 Hz, ^4J(H,H) = 0.9 Hz, 1 H), 3.28-3.21 (m, 2 H), 3.08-3.01 (m, 2 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 197.8, 154.0, 150.3, 146.1, 142.1, 141.2, 138.4, 137.5, 133.7, 130.5, 129.9, 110.3, 105.6, 93.8, 92.8, 40.1, 22.6.
MS (70 eV, EI) *m/z* (%): 642 (M^+, 2), 516 (2), 468 (41), 467 (21), 450 (60), 374 (10), 373 (100), 342 (11), 341 (10), 324 (10), 247 (33), 218 (12), 114 (10), 112 (34), 111 (10), 95 (51), 94 (21).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2924 (w), 1700 (m), 1633 (m), 1416 (w), 1386 (m), 1206 (m), 1176 (m), 1148 (m), 1087 (m), 1013 (w), 860 (w), 830 (w), 767 (m), 722 (m), 623 (w), 566 (w).
HRMS (EI) for **$C_{19}H_{13}{}^{35}ClI_2O_5S$** (641.8262): found: 641.8279.

Synthesis of 4-chloro-benzenesulfonic acid 3-hydroxy-2-iodo-phenyl ester (29):

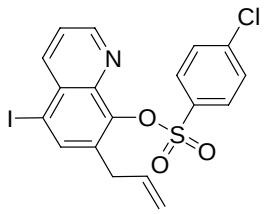


A 250 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with 2-iodo-benzene-1,3-diol (**28**)[76d] (7.08 g, 30 mmol), potassium carbonate (30.00 g) and 4-chlorobenzenesulfonyl chloride (6.52 g, 30 mmol) in acetone (100 mL). The reaction mixture was heated to refluxing and stirred vigorously for 6 h. The reaction mixture was filtered

through a glass sinter and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane/ether = 4:1 with 2% of CH_2Cl_2) yielded **29** (6.78 g, 55 %) as a white solid.

mp.: 119.0-120.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.88-7.85 (m, 2H), 7.53-7.50 (m, 2H), 7.22 (t, ^3J(H,H) = 8.2 Hz, 1H), 6.89 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.1 Hz, 1H), 6.86 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.1 Hz, 1H), 5.57 (s, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 156.7, 150.1, 141.4, 134.1, 130.2, 130.1, 129.6, 114.7, 113.6, 82.7.
MS (70 eV, EI): *m/z* (%): 412 (16), 410 (42) [M^+], 346 (17), 235 (17), 207 (21), 177 (34), 175 (100), 113 (18), 111 (56), 75 (13), 52 (13), 51 (10).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3480 (s), 3462 (s), 3096 (w), 1591 (m), 1572 (m), 1477 (m), 1461 (s), 1447 (s), 1398 (m), 1373 (s), 1320 (w), 1296 (m), 1284 (m), 1246 (m), 1228 (w), 1192 (s), 1174 (s), 1155 (s), 1088 (s), 1022 (s), 1014 (m), 979 (s), 815 (vs), 787 (m), 760 (s), 726 (m), 705 (m), 652 (w), 619 (s), 576 (m), 554 (m), 542 (m), 486 (m).
HRMS (EI) for **$C_{12}H_8IO_4S^{35}Cl$** (409.8877): found: 409.8873.

Synthesis of 4-chloro-benzenesulfonic acid 7-allyl-5-iodo-quinolin-8-yl ester (31):

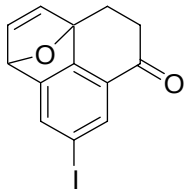


A dry and argon-flushed 10 mL Schlenk tube, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-chloro-benzenesulfonic acid 5,7-diiodo-quinolin-8-yl ester (**27o**) (571 mg, 1.0 mmol) in dry THF (5 mL). *i*-PrMgCl (0.92 M in THF, 1.20 mL, 1.1 equiv.) was then added dropwise at −78 °C. After 30 min, CuCN·2LiCl (1.0 M in THF, 1.0 mL, 1.0 equiv.) was added slowly at −78 °C, and the resulting mixture was stirred at this temperature for 10 min. Then allyl bromide (0.17 mL, 2.0 mmol, 2.0 equiv.) was added at −78°C, and the resulting mixture was warmed to room temperature and stirred for 1 h. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution; the mixture was then poured into water (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 200 : 1) yielded **31** (394 mg, 81 %) as a white solid.

mp.: 118.6-119.6 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.59-8.53 (m, 1 H), 8.29-8.21 (m, 1 H), 8.09-8.00 (m, 3 H), 7.56-7.46 (m, 2 H), 7.42-7.34 (m, 1 H), 6.06-5.89 (m, 1 H), 5.26-5.15 (m, 2 H), 3.76-3.67 (m, 2 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 150.7, 144.4, 142.1, 140.5, 140.0, 139.1, 136.2, 135.7, 134.5, 130.2, 129.8, 128.9, 122.8, 118.0, 96.4, 34.5.
MS (70 eV, EI): *m/z* (%): 423 (19), 422 (12), 421 (57), 408 (18), 407 (11), 406 (57), 311 (11), 310 (58), 294 (10), 184 (14), 183 (87), 182 (81), 155 (29), 154 (100), 153 (13), 128 (14), 127 (25), 111 (21), 77 (10), 75 (19).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3088 (w), 2977 (w), 1638 (w), 1609 (w), 1590 (m), 1575 (w), 1552 (w), 1477 (m), 1456 (w), 1379 (s), 1350 (m), 1298 (w), 1285 (m), 1236 (w), 1225 (m), 1202 (m), 1187 (s), 1179 (s), 1142 (m), 1089 (s), 1069 (s), 1044 (w), 1014 (m), 992 (m), 927 (m), 895

(w), 883 (w), 835 (m), 812 (m), 793 (s), 754 (m), 712 (m), 700 (w), 671 (w), 659 (m), 623 (s), 603 (m), 584 (m), 530 (m), 480 (m).
$C_{18}H_{13}ClINO_3S$: calc.: C: 44.51; H: 2.70; N: 2.88; S: 6.60; found: C: 44.66; H: 2.73; N: 2.84; S: 6.50.

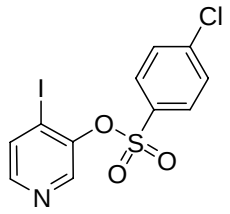
Synthesis of 8-iodo-2,3,3a,6-tetrahydro-3a,6-epoxy-1*H*-phenalen-1-one (32):



Prepared according to **TP 3** from 4-chloro-benzenesulfonic acid 2-(3-furan-2-yl-propionyl)-4,6-diiodo-phenyl ester **27p** (400 mg, 0.62 mmol) and *i*-PrMgCl (0.79 mL, 1.01 equiv., 0.79 M in THF). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane : ether = 50 : 1) yielded **32** (98 mg, 48 %) as a brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.75 (d, ^4J(H,H) = 0.9 Hz, 1 H), 7.71 (d, ^4J(H,H) = 0.9 Hz, 1 H), 7.16-7.08 (m, 2 H), 5.74 (d, ^3J(H,H) = 1.8 Hz, 1 H), 2.95-2.52 (m, 4 H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 194.2, 156.0, 151.8, 144.6, 141.5, 133.6, 129.0, 128.4, 91.1, 86.1, 82.2, 36.1, 26.3.
MS (70 eV, EI) *m/z* (%): 325 (11), 324 (M^+, 100), 323 (12), 168 (11), 141 (10), 139 (14).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3073 (w), 2957 (m), 2873 (w), 2249 (w), 1689 (s), 1588 (m), 1570 (w), 1453 (w), 1416 (m), 1337 (s), 1302 (m), 1277 (w), 1252 (s), 1217 (m), 1179 (m), 1088 (s), 1058 (w), 998 (m), 963 (m), 946 (m), 902 (m), 868 (s), 834 (w), 808 (m), 762 (w), 728 (s), 705 (m), 677 (m), 646 (m), 598 (m), 554 (m).
HRMS (EI) for **$C_{13}H_9IO_2$** (323.9647): found: 323.9645.

Synthesis of 4-iodopyridin-3-yl 4-chlorobenzenesulfonate (39a):

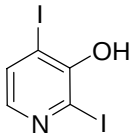


Prepared according to **TP 4** from 3-hydroxy-4-iodopyridine (11.1 g, 50.0 mmol), triethylamine (20.9 mL, 150 mmol), and 4-chlorobenzenesulfonyl chloride (12.7 g, 60.0 mmol). Recrystallization from ethanol yielded **39a** as a yellow solid (16.1 g, 81 %).

mp.: 135.3-136.1 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.40 (s, 1H), 8.10 (d, ^3J(H,H) = 5.1 Hz, 1H), 7.89-7.83 (m, 2H), 7.74 (d, ^3J(H,H) = 5.1 Hz, 1H), 7.58-7.51 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 148.7, 148.1, 144.3, 142.3, 135.3, 134.2, 131.0, 130.6, 102.2.
MS (70 eV, EI): m/z (%): 3103 (m), 3044 (w), 1586 (m), 1562 (s), 11478 (m), 1393 (vs), 1200 (s), 1174 (vs), 1087 (s), 864 (s), 767 (vs), 718 (s), 618 (s), 565 (s), 484 (m).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 395 (56) [M^+], 192 (4), 175 (100), 165 (12), 111 (65), 93 (14).

HRMS (EI) for **$C_{11}H_7{}^{35}ClINO_3S$** (394.8880): found 394.8846.

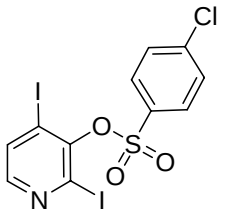
Synthesis of 2,4-diiodo-pyridin-3-ol :



To a soluion of 3-hydroxy-4-iodopyridyne (2.21 g, 10 mmol) and Na_2CO_3 (2.22 g, 21 mmol) in water was added iodine (2.54 g, 10 mmol) with stirring at 20 °C for 2 h. The $HCl_{(aq)}$ is added carefully until approximate pH 4. The solid is filtered off and dried to give 3-hydroxy-2,4-diiodopyridine as a brown solid (2.78 g, 80 %).

mp.: 179.0-180.3 °C.
^{1}H-NMR (300 MHz, CD_3SOCD_3, 25 °C) δ/ppm: 10.22 (s, 1H), 7.75 (d, ^3J(H,H) = 4.5 Hz, 1H), 7.54 (d, ^3J(H,H) = 4.5 Hz, 1H).
^{13}C-NMR (75 MHz, CD_3SOCD_3, 25 °C) δ/ppm: 153.5, 143.3, 133.7, 112.1, 97.1.
MS (70 eV, EI) *m/z* (%): 347 (100) [M^+], 221 (19), 220 (64), 165 (11); 127 (14), 93 (30), 66 (12), 65 (11), 64 (20).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3437 (brs), 1628 (w), 1524 (m), 1446 (m), 1409 (w), 1265 (w), 1149 (m), 1079 (w), 1061 (w), 812 (w), 706 (m).
HRMS (EI) for **$C_5H_3ONI_2$** (346.8304): found 346.8304.

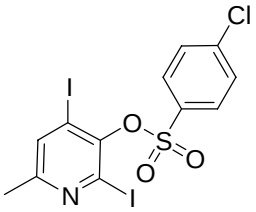
Synthesis of 2,4-diiodopyridin-3-yl 4-chlorobenzenesulfonate (39b):



Prepared according to **TP 4** from 2,4-diiodo-pyridin-3-ol (2.081 g, 6.0 mmol), 4-chlorobenzenesulfonyl chloride (1.520 g, 7.2 mmol), and triethylamine (1.26 mL, 9.0 mmol). Purification by flash chromatography (*n*-pentane : ether = 10 : 1) yielded **39b** as a white solid (2.354 g, 75 %).

mp.: 145.4-146.2 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.01-7.96 (m, 2H), 7.85 (d, ^3J(H,H) = 4.9 Hz, 1H), 7.73 (d, ^3J(H,H) = 4.9 Hz, 1H), 7.63-7.58 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 150.1, 148.4, 141.9, 136.1, 134.9, 130.5, 129.8, 114.3, 101.8.
MS (70 eV, EI) *m/z* (%): 523 (18), 521 (50) [M^+], 219 (25), 177 (34), 175 (100), 113 (12), 111 (40), 75 (11), 64 (14).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3096 (w), 1537 (m), 1520 (w), 1478 (w), 1425 (w), 1401 (m), 1382 (vs), 1353 (s), 1223 (m), 1200 (m), 1189 (s), 1178 (s), 1088 (m), 1078 (w), 1061 (w), 1015 (w), 850 (m), 830 (m), 762 (s), 718 (s), 690 (s), 617 (s), 566 (s), 481 (w).
HRMS (EI) for **$C_{11}H_6O_3NIS^{35}Cl_2$** (520.7846): found 520.7827.

Synthesis of 2,4-diiodo-6-methylpyridin-3-yl 4-chlorobenzenesulfonate (39c):



To a soluion of 3-hydroxy-6-methylpyridine (11.0 g, 100 mmol) and Na_2CO_3 (22.3g, 210 mmol) in water was added iodine (25.4 g, 100 mmol) with stirring at 20 °C. After 1 h, the iodine colour has disappeared. The $HCl_{(aq)}$ is added carefully until approximate pH 3. The solid is filtered off and dried to give 2-iodo-3-hydroxy 6-methylpyridine as a crude product (a yellow solid).

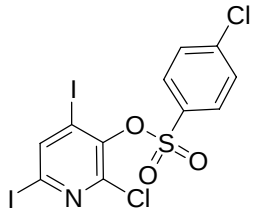
To a soluion of 2-iodo-3-hydroxy 6-methylpyridine (without further purification) and Na_2CO_3 (22.3g, 210 mmol) in water was added iodine (25.4 g, 100 mmol) with stirring at 20 °C overnight. The $HCl_{(aq)}$ is added carefully until approximate pH 6. Water was evaporated and 2,4-diiodo-3-hydroxy-6-methylpyridine was obtained as a crude product (a brown solid).

2,4-diiodo-3-hydroxy-6-methylpyridine:
mp.: 109.2-110.6 °C.
^{1}H-NMR (300 MHz, CD_3SOCD_3, 25 °C) δ/ppm: 7.61 (s, 1H), 2.29 (s, 3H).
^{13}C-NMR (75 MHz, CD_3SOCD_3, 25 °C) δ/ppm: 152.0, 151.2, 132.7, 111.0, 98.5, 21.5.
MS (70 eV, EI) *m/z* (%): 361 (100) [M^+], 235 (59), 234 (60), 108 (17), 107 (59), 79 (11), 78 (14), 52 (21), 51 (19).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3416 (brs), 1606 (w), 1562 (w), 1510 (w), 1430 (w), 1240 (w), 1211 (w), 714 (w).
HRMS (EI) for **$C_6H_5ONI_2$** (360.8461): found 360.8447.

A dry 250 mL round-bottomed flask, equipped with a magnetic stirrer and a septum, was charge with a solution of 2,4-diiodo-3-hydroxy-6-methylpyridine (crude product) in dry CH_2Cl_2 (100 mL). After cooling to 0 °C, Et_3N (18.8 mL, 135 mmol) was added, and then 4-chloro-benzenesulfonyl chloride (23.5 g, 108 mmol) was added portionwise. After addition was completed, the reaction mixture was stirred at room temperature overnight. Then this mixture was diluted with 100 mL CH_2Cl_2. Saturated aqueous NH_4Cl solution (100 mL) was then added, and then the resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL). The organic extracts were dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography (*n*-pentane : ether = 40 : 1) yielded **39c** (30.05 g, 55 %; the total yield over three steps) as a brown solid.

39c:
mp.: 119.4-121.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.00-7.95 (m, 2H), 7.61-7.56 (m, 3H), 2.48 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 158.8, 147.9, 141.8, 136.1, 134.4, 130.5, 129.8, 112.9, 101.7, 22.9.
MS (70 eV, EI) *m/z* (%): 537 (37), 535 (100) [M^+], 360 (85), 332 (19), 233 (90), 177 (28), 175 (77), 159 (20), 111 (38), 78 (26), 51 (19).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3086 (w), 1546 (m), 1504 (m), 1476 (w), 1402 (m), 1380 (s), 1320 (m), 1242 (m), 1200 (m), 1185 (s), 1176 (vs), 1088 (m), 1061 (m), 1015 (w), 870 (w), 846 (w), 814 (s), 759 (s), 742 (m), 703 (m), 683 (s), 624 (m), 617 (m).
HRMS (EI) for **$C_{12}H_8O_3NI_2S^{35}Cl$** (534.8003): found 534.7997.

Synthesis of 4-chloro-benzenesulfonic acid 2-chloro-4,6-diiodo-pyridin-3-yl ester (39d):



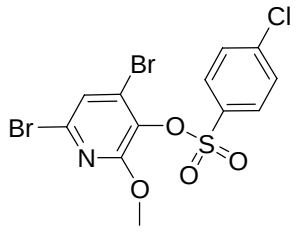
To a soluion of 2-chloro-3-hydroxypyridine (2.60 g, 20 mmol) and Na_2CO_3 (4.45 g, 42 mmol) in water was added iodine (5.33 g, 21 mmol) with stirring at 20 °C overnight. The $HCl_{(aq)}$ is added carefully until approximate pH 3. The solid is filtered off and dried to give 2-chloro-3-hydroxy-6-iodopyridine as a crude product (a yellow solid).

To a soluion of 2-chloro-3-hydroxy-6-iodopyridine (without further purification) and Na_2CO_3 (4.45 g, 42 mmol) in water was added iodine (5.33 g, 21 mmol) with stirring at 20 °C overnight. The $HCl_{(aq)}$ is added carefully until approximate pH 6. Water was evaporated and 4,6-diiodo-3-hydroxy-6-methylpyridine was obtained as a crude product (a brown solid).

A dry 250 mL round-bottomed flask, equipped with a magnetic stirrer and a septum, was charge with a solution of 4,6-diiodo-3-hydroxy-6-methylpyridine (crude product) in dry CH_2Cl_2 (100 mL). After cooling to 0 °C, Et_3N (4.18 mL, 30 mmol) was added, and then 4-chloro-benzenesulfonyl chloride (4.35 g, 20 mmol) was added portionwise. After addition was completed, the reaction mixture was stirred at room temperature overnight. Then this mixture was diluted with 100 mL CH_2Cl_2. Saturated aqueous NH_4Cl solution (100 mL) was then added, and then the resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL). The organic extracts were dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography (*n*-pentane : ether = 80 : 1) yielded **39d** (6.45 g, 57 %; the total yield over three steps) as a yellow solid.

mp.: 141.7-142.7 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.13 (s, 1H), 7.98-7.93 (m, 2H), 7.61-7.56 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 145.7, 144.4, 144.3, 141.9, 135.4, 130.0, 129.8, 112.0, 105.8.
MS (70 eV, EI) *m/z* (%): 557 (13) [M^+], 555 (21), 380 (10), 253 (16), 177 (37), 175 (100), 113 (13), 111 (42), 75 (12).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3085 (w), 1587 (w), 1527 (s), 1512 (s), 1395 (vs), 1381 (vs), 1309 (s), 1282 (w), 1231 (w), 1210 (m), 1187 (s), 1170 (m), 1086 (m), 1072 (m), 1014 (w), 867 (s), 823 (w), 779 (s), 758 (s), 728 (s), 656 (w), 625 (s), 580 (m), 481 (m).
HRMS (EI) for **$C_{11}H_5O_3NI_2S^{35}Cl_2$** (554.7457): found 554.7453.

Synthesis of 4-chloro-benzenesulfonic acid 4,6-dibromo-2-methoxy-pyridin-3-yl ester (39e):

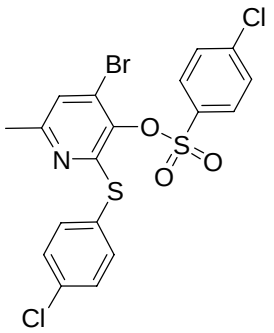


A 100 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with the 2-methoxy-pyridin-3-ol (2.501 g, 20 mmol) dissolved in CCl_4 (100 mL). *N*-Bromosuccinimide (7.476 g, 42 mmol) was added portionwise and the reaction mixture was stirred at room temperature for 72 h in darkness. The progress of the reaction was followed by GC and GC-MS spectroscopy. After the reaction was complete, the solvent was evaporated, diluted with CH_2Cl_2 (50 mL), washed with water (30 mL), extracted with CH_2Cl_2 (50 mL × 3) and ether (50 mL × 3), dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo* to obtain the crude product (4,6-dibromo-2-methoxy-pyridin-3-ol) for the next step.

Prepared according to **TP 4** from the crude 4,6-dibromo-2-methoxy-pyridin-3-ol, 4-chlorobenzenesulfonyl chloride (16.2 g, 74 mmol) and triethylamine (12.9 mL, 93 mmol). Filtration and then purification by flash chromatography (*n*-pentane : ether = 250 : 1) yielded **39e** as a white solid (1.83 g, 20 % for two steps).

mp.: 115.0-117.5 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.95-7.90 (m, 2H), 7.59-7.54 (m, 2H), 7.30 (s, 1H), 3.77 (s, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 157.0, 141.2, 135.6, 135.5, 132.2, 129.9, 129.8, 129.3, 124.5, 54.9.
MS (70 eV, EI) *m/z* (%): m/z (%): 459 (9), 457 (12), 455 (5) [M^+], 284 (46), 283 (7), 282 (100), 280 (48), 213 (9), 211 (6), 177 (5), 175 (14), 160 (5), 159 (9), 158 (5), 113 (6), 111 (19), 75 (9).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3088 (w), 1570 (m), 1473 (m), 1390 (m), 1321 (vs), 1283 (m), 1141 (s), 1090 (s), 1071 (s), 1009 (m), 830 (m), 820 (m), 752 (m), 745 (m), 702 (w).
HRMS (EI) for **$C_{12}H_8O_4N^{79}Br_2{}^{35}ClS$** (454.8229): found 454.8204.

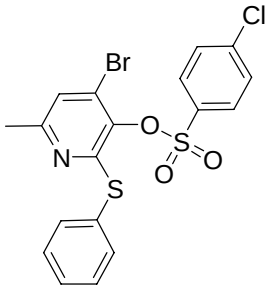
Synthesis of 4-chloro-benzenesulfonic acid 4-bromo-2-(4-chloro-phenylsulfanyl)-6-methyl-pyridin-3-yl ester (39f):



A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-bromo-2-iodo-6-methylpyridin-3-yl 4-chlorobenzenesulfonate (**42**) (2.409 g, 4.0 mmol) in dry THF (8.0 mL). *i*-PrMgCl (0.87 M/THF, 4.71 mL, 4.1 mmol.) was then added dropwise at −78 °C. After 30 min, benzenethiosulfonic acid S-(4-chloro-phenyl) ester (1.254 g, 4.4 mmol) in dry THF (3 mL) was added slowly at −78 °C, and the resulting mixture was warmed to room temperature and stirred for 1 h. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 50 : 1) yielded **39f** (1.273 g, 63 %) as a white solid.

mp.: 109.3-111.2 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.03-7.97 (m, 2H), 7.60-7.54 (m, 2H), 7.36-7.28 (m, 4H), 7.15 (s, 1H), 2.31 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 157.5, 153.8, 141.5, 139.6, 135.9, 135.5, 135.0, 130.1, 129.5, 129.0, 128.2, 127.6, 125.3, 23.5.
MS (70 eV, EI) *m/z* (%): 505 (10), 503 (6) [M^+], 443 (20), 442 (11), 441 (41), 440 (9), 439 (24), 332 (16), 331 (16), 330 (53), 329 (12), 328 (39), 296 (16), 295 (100), 294 (15), 293 (100), 267 (12), 265 (12), 251 (11), 249 (24), 248 (9), 186 (10), 111 (13), 108 (9), 51 (15).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3104 (w), 1572 (w), 1557 (w), 1537 (m), 1476 (m), 1414 (m), 1380 (vs), 1334 (m), 1262 (m), 1200 (w), 1177 (s), 1090 (s), 1071 (m), 1015 (w), 828 (s), 818 (m), 758 (s), 746 (m), 702 (m), 680 (m), 636 (m).
HRMS (EI) for **$C_{18}H_{12}O_3{}^{79}Br^{35}Cl_2S_2$** (502.8819): found 502.8816.

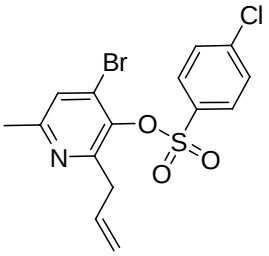
Synthesis of 4-chloro-benzenesulfonic acid 4-bromo-6-methyl-2-phenylsulfanyl-pyridin-3-yl ester (39g):



A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-bromo-2-iodo-6-methylpyridin-3-yl 4-chlorobenzenesulfonate (**42**) (1.466 g, 3.0 mmol) in dry THF (9.0 mL). *i*-PrMgCl (0.87 M/THF, 3.57 mL, 3.1 mmol) was then added dropwise at –78 °C. After 30 min, S-phenyl benzenethiosulfonate (875 mg, 3.5 mmol) in dry THF (3 mL) was added slowly at −78 °C, and the resulting mixture was warmed to room temperature and stirred for 1 hour. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 50: 1) and recrystallization (ethanol/acetone= 1 : 1) yielded **39g** (636 mg, 45 %) as a white solid.

mp.: 86.7-89.1 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.04-7.98 (m, 2H), 7.59-7.53 (m, 2H), 7.41-7.30 (m, 5H), 7.15 (s, 1H), 2.30 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 157.4, 154.1, 141.3, 139.7, 135.6, 134.4, 130.1, 129.8, 129.5, 128.8, 128.6, 127.6, 125.1, 23.5.
MS (70 eV, EI) *m/z* (%): 471(3), 469 (2) [M^+], 407 (20), 405 (15), 297 (35), 296 (100), 295 (35), 294 (94), 280 (14), 278 (15), 216 (11), 215 (21), 214 (13), 187 (18), 186 (21), 111 (10), 109 (11), 77 (12), 51 (21).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3098 (w), 1553 (m), 1538 (m), 1474 (m), 1442 (w), 1410 (m), 1383 (vs), 1330 (m), 1284 (w), 1262 (m), 1198 (w), 1180 (s), 1168 (s), 1093 (m), 1070 (m), 832 (s), 759 (s), 747 (m), 704 (m), 682 (s), 629 (m).
HRMS (EI) for **$C_{18}H_{13}O_3{}^{79}Br^{35}ClS_2$** (468.9209): found 468.9223.

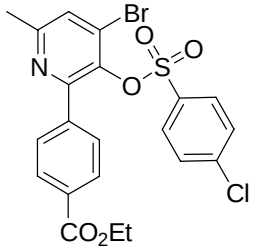
Synthesis of 2-allyl-4-bromo-6-methylpyridin-3-yl 4-chlorobenzenesulfonate (39h):



A dry and argon-flushed 50 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-bromo-2-iodo-6-methylpyridin-3-yl 4-chlorobenzenesulfonate (**42**) (1.466 g, 3.0 mmol) in dry THF (6.0 mL). *i*-PrMgCl (0.87 M in THF, 3.79 mL, 1.1 equiv.) was then added dropwise at −78 °C. After 30 min, CuCN·2LiCl (1.0 M in THF, 1.50 mL, 0.5 equiv.) was added slowly at −78 °C, and the resulting mixture was stirred at this temperature for 10 min. Then allyl bromide (0.43 mL, 5.0 mmol, 1.7 equiv.) was added at −78°C, and the resulting mixture was warmed to room temperature and stirred for 1 h. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 30 : 1) yielded **39h** (0.665 g, 55 %) as a colourless oil.

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.96-7.93 (m, 2H), 7.57-7.54 (m, 2H), 7.22 (s, 1H), 6.03-5.95 (m, 1H), 5.13-5.07 (m, 2H), 3.65-3.62 (m, 2H), 2.48 (s, 3H)
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 157.4, 155.4, 141.4, 140.7, 135.1, 133.9, 129.9, 129.6, 127.4, 126.3, 117.1, 38.1, 23.7.
MS (70 eV, EI) *m/z* (%): 403 (10), 402 (M^+, 18), 400 (14), 229 (19), 228 (99), 227 (27), 226 (100), 175 (12), 148 (11), 147 (22), 146 (15), 144 (12), 119 (23), 118 (22), 111 (24), 75 (12), 51 (20).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1586 (w), 1562 (s), 1476 (w), 1431 (m), 1373 (s), 1277 (w), 1205 (m), 1186 (vs), 1089 (s), 1014 (w), 910 (m), 844 (s), 806 (s), 758 (s), 730 (s), 706 (m), 676 (m), 645 (m).
HRMS (EI) for **$C_{15}H_{13}ClBrNO_3S$** (402.9488): found 402.9402.

Synthesis of 4-[4-bromo-3-(4-chloro-benzenesulfonyloxy)-6-methyl-pyridin-2-yl]-benzoic acid ethyl ester (39i):

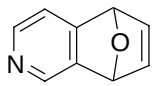


A dry and argon-flushed 250 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-bromo-2-iodo-6-methylpyridin-3-yl 4-chlorobenzenesulfonate (**42**) (4.885 g, 10.0 mmol) in dry THF (20.0 mL). *i*-PrMgCl (0.87 M/THF, 12.65 mL, 1.1 equiv.) was then added dropwise at −78 °C and stirred for 30 min. $ZnBr_2$ (1.0 M/THF, 11.00 mL, 1.1 equiv) was added to the magnesiated arene at −78 °C. Another dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with $Pd(dba)_2$ (290 mg, 5 mol %) and tris-*o*-furylphosphine (250 mg, 10 mol %) in dry THF (8.0 mL). The initial red color disappeared after 2 min leading to yellow

solution and ethyl 4-iodobenzoate (4.270 g, 15.0 mmol) was added. This solution was added *via* cannula after 10 min stirring to the reaction mixture at −78 °C. The reaction mixture was stirred at 50 °C for 4 days. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 50 : 1) yielded **39i** (2.759 g, 54 %) as a white solid.

mp.: 130.0-131.0 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.87-7.82 (m, 2H), 7.56-7.51 (m, 2H), 7.47 (s, 1H), 7.43-7.38 (m, 2H), 7.19-7.14 (m, 2H), 4.41 (q, ^3J(H,H) = 7.1 Hz, 2H), 2.58 (s, 3H), 1.44 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.9, 157.9, 152.0, 141.0, 141.0, 140.5, 134.9, 130.8, 130.0, 129.2, 129.2, 129.2, 127.8, 61.2, 23.9, 14.3.
MS (70 eV, EI) *m/z* (%): 511 (20), 509 (14) [M^+], 336 (24), 334 (24), 308 (25), 306 (25), 292 (45), 291 (27), 290 (53), 289 (21), 264 (93), 263 (21), 262 (98), 211 (50), 184 (14), 183 (100), 182 (42), 154 (23), 133 (20), 131 (20), 113 (14), 111 (32), 75 (19), 52 (18), 51 (41).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2984 (w), 1711 (vs), 1576 (w), 1556 (m), 1474 (w), 1431 (w), 1390 (s), 1271 (s), 1209 (m), 1184 (s), 1157 (m), 1107 (m), 1090 (m), 1062 (m), 1016 (w), 826 (s), 783 (m), 757 (m), 701 (m), 676 (m), 632 (m).
HRMS (EI) for **$C_{21}H_{18}O_5N^{79}Br^{35}ClS$**, [$M^+$+H] (509.9778): found 509.9771.

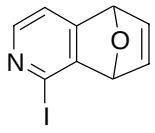
Synthesis of 11-oxa-4-aza-tricyclo[6.2.1.02,7]undeca-2(7),3,5,9-tetraene (41a):



Prepared according to **TP 5** from 4-iodopyridin-3-yl 4-chlorobenzenesulfonate (**39a**) (396 mg, 1.0 mmol), *i*-PrMgCl (1.21 mL, 1.05 mmol, 0.87 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25°C, 2.5 h. Purification by flash chromatography (*n*-pentane/diethyl ether = 2 : 1) yielded **41a** as a yellow oil (79 mg, 54 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.40 (s, 1H), 8.23 (d, ^3J(H,H) = 4.6 Hz, 1H), 7.18 (d, ^3J(H,H) = 4.6 Hz, 1H), 6.99 (dd, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 1.8 Hz, 1H), 6.93 (dd, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 1.8 Hz, 1H), 5.77-5.75 (m, 1H), 5.68-5.66 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 158.8, 147.2, 144.1, 143.3, 141.8, 139.6, 116.0, 81.5, 80.4.
MS (70 eV, EI) *m/z* (%): 145 (8) [M^+], 119 (21), 118 (9), 117 (100), 116 (20), 91 (8), 90 (39), 89 (40), 64 (7), 63 (18).
IR (film) $\tilde{\nu}$ (cm^{-1}): 1584 (w), 1414 (w), 1282 (w), 1126 (w), 1019 (w), 995 (w), 876 (w), 850 (s), 836 (m), 705 (m), 645 (w), 592 (w).
HRMS (EI) for **C_9H_7ON** (145.0528): found 145.0525.

Synthesis of 3-iodo-11-oxa-4-aza-tricyclo[6.2.1.02,7]undeca-2(7),3,5,9-tetraene (41b):

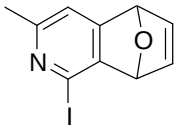


Prepared according to **TP 5** from 2,4-diiodopyridin-3-yl 4-chlorobenzenesulfonate (**39b**) (522 mg, 1.0 mmol), *i*-PrMgCl (1.21 mL, 1.05 mmol, 0.87 M in THF) and furan (340 mg,

5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1.5 h. Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **41b** as a white solid (123 mg, 45 %).

mp.: 91.8-93.8 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.03 (d, ^3J(H,H) = 4.7 Hz, 1H), 7.16 (d, ^3J(H,H) = 4.7 Hz, 1H), 7.14 (dd, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 1.84 Hz, 1H), 7.03 (dd, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 1.8 Hz, 1H), 5.85-5.82 (m, 1H), 5.61-5.58 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 160.4, 152.0, 148.8, 143.0, 142.5, 115.7, 107.1, 84.0, 83.0.
MS (70 eV, EI) *m/z* (%): 271 (22) [M^+], 245 (11), 243 (29), 144 (14), 118 (20), 117 (10), 116 (100), 115 (35), 89 (28), 63 (11).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1560, 1410, 1396, 1270, 1116, 856, 832, 731, 654.
HRMS (EI) for **C_9H_6ONI** (270.9494): found 270.9507.

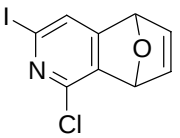
Synthesis of 3-iodo-5-methyl-11-oxa-4-aza-tricyclo[6.2.1.02,7]undeca-2(7),3,5,9-tetraene (41c):



Prepared according to **TP 5** from 2,4-diiodo-6-methylpyridin-3-yl 4-chlorobenzenesulfonate (**39c**) (536 mg, 1.0 mmol), *i*-PrMgCl (1.21 mL, 1.05 mmol, 0.87 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 6 h. Purification by flash chromatography (*n*-pentane/diethyl ether = 2 : 1) yielded **41c** as a yellow oil (214 mg, 75 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.09 (dd, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 1.88 Hz, 1H), 7.00 (s, 1H), 6.96 (dd, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 1.9 Hz, 1H), 5.77-5.75 (m, 1H), 5.54-5.52 (m, 1H), 2.44 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 160.6, 158.6, 148.7, 143.0, 142.0, 115.8, 105.8, 83.8, 82.9, 24.2.
MS (70 eV, EI) *m/z* (%): 285 (12) [M^+], 257 (20), 132 (14), 130 (100), 129 (28), 103 (35), 77 (13).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 1613 (w), 1549 (s), 1428 (m), 1322 (m), 1280 (m), 1180 (s), 1080 (s), 1004 (w), 910 (w), 865 (w), 851 (vs), 838 (s), 795 (m), 727 (m), 702 (s), 646 (m).
HRMS (EI) for **$C_{10}H_8ONI$** (284.9651): found 284.9633.

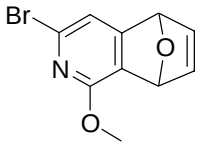
Synthesis of 3-chloro-5-iodo-11-oxa-4-aza-tricyclo[6.2.1.02,7]undeca-2(7),3,5,9-tetraene (41d):



Prepared according to **TP 5** from 4-chloro-benzenesulfonic acid 2-chloro-4,6-diiodo-pyridin-3-yl ester (**39d**) (556 mg, 1.0 mmol), *i*-PrMgCl (1.21 mL, 1.05 mmol, 0.87 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: –78 °C, 0.5 h; 25 °C 16 h. Purification by flash chromatography (*n*-pentane/diethyl ether = 30 : 1) yielded **41d** as a white solid (98 mg, 32 %).

mp.: 123.1-124.2 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.59 (s, 1H), 7.12 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.9 Hz, 1H), 6.99 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.9 Hz, 1H), 5.80-5.77 (m, 1H), 5.73-5.70 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 164.2, 143.9, 142.9, 141.9, 140.7, 126.6, 113.0, 81.9, 80.5.
MS (70 eV, EI) *m/z* (%): 307 (6), 305 (20) [M^+], 281 (7), 279 (23), 277 (12), 241 (9), 152 (44), 151 (13), 150 (100), 149 (12), 123 (12), 115 (7), 114 (25).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1598, 1553, 1402, 1300, 1284, 1204, 1134, 1054, 853, 814, 805, 728, 642.
HRMS (EI) for **$C_9H_5ON^{35}ClI$** (304.9104): found 304.9087.

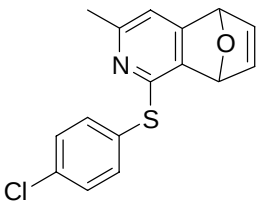
Synthesis of 5-bromo-3-methoxy-11-oxa-4-aza-tricyclo[6.2.1.02,7]undeca-2(7),3,5,9-tetraene (41e):



Prepared according to **TP 5** from 4-chloro-benzenesulfonic acid 4,6-dibromo-2-methoxy-pyridin-3-yl ester (**39e**) (229 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.51 mL, 0.51 mmol, 1.00 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 4 h. Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **41e** as a colourless oil (100 mg, 78 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.12-7.08 (m, 2H), 6.97 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.9 Hz, 1H), 5.84-5.81 (m, 1H), 5.67-5.64 (m, 1H), 3.93 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.2, 155.9, 143.6, 141.7, 135.7, 129.3, 115.0, 81.9, 79.3, 54.1.
MS (70 eV, EI) *m/z* (%): 255 (15), 253 (17) [M^+], 229 (29), 227 (52), 226 (99), 225 (34), 224 (100), 212 (15), 210 (17), 198 (29), 197 (18), 196 (23), 195 (13), 185 (29), 183 (27), 148 (26), 146 (20), 145 (19), 131 (21), 130 (41), 116 (19), 115 (17), 103 (15), 102 (13), 76 (19).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2950 (w), 1600 (m), 1572 (s), 1458 (m), 1411 (w), 1354 (vs), 1279 (m), 1079 (m), 1060 (m), 994 (m), 864 (m), 842 (m), 728 (w), 649 (w).
HRMS (EI) for **$C_{10}H_8O_2N^{79}Br$** (252.9738): found 252.9716.

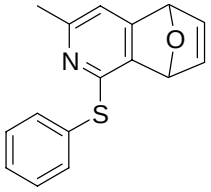
Synthesis of 3-(4-chloro-phenylsulfanyl)-5-methyl-11-oxa-4-aza-tricyclo[6.2.1.02,7] undeca-2(7),3,5,9-tetraene (41f):



Prepared according to **TP 5** from 4-chloro-benzenesulfonic acid 4-bromo-2-(4-chloro-phenylsulfanyl)-6-methyl-pyridin-3-yl ester (**39f**) (253 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.51 mL, 0.51 mmol, 1.00 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane/diethyl ether = 3 : 1) yielded **41f** as a yellow solid (134 mg, 88 %).

mp.: 98.1-101.2 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.29-7.20 (m, 4H), 6.92 (s, 1H), 6.82 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.9 Hz, 1H), 6.57 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.9 Hz, 1H), 5.57-5.54 (m, 1H), 5.34-5.31 (m, 1H), 2.41 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 160.7, 157.2, 146.4, 143.0, 142.7, 141.7, 133.8, 133.1, 132.4, 129.4, 114.9, 81.7, 80.5, 24.5.
MS (70 eV, EI) *m/z* (%): 303 (35) [M^+], 302 (23), 301 (88), 300 (20), 275 (43), 274 (63), 273 (70), 272 (100), 257 (24), 247 (29), 240 (34), 237 (31), 236 (23), 108 (29), 103 (31), 77 (42), 63 (20).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3077 (w), 2612 (w), 1558 (m), 1476 (s), 1443 (w), 1428 (m), 1390 (m), 1326 (w), 1282 (m), 1201 (m), 1086 (vs), 1007 (m), 860 (m), 848 (s), 826 (s), 810 (m), 750 (m), 709 (s), 649 (m).
HRMS (EI) for **$C_{16}H_{12}ON^{35}ClS$** (301.0328): found 301.0339.

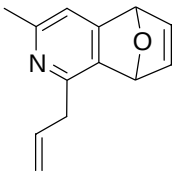
Synthesis of 5-methyl-3-phenylsulfanyl-11-oxa-4-aza-tricyclo[6.2.1.02,7]undeca-2(7),3,5,9-tetraene (41g):



Prepared according to **TP 5** from 4-chloro-benzenesulfonic acid 4-bromo-6-methyl-2-phenylsulfanyl-pyridin-3-yl ester (**39f**) (235 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.51 mL, 0.51 mmol, 1.00 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 0.5 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane/diethyl ether = 8 : 1) yielded **41g** as a yellow oil (114 mg, 85 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.46-7.40 (m, 2H), 7.37-7.29 (m, 3H), 6.95 (s, 1H), 6.83 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.9 Hz, 1H), 6.47 (dd, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 1.9 Hz, 1H), 5.58 (dd, ^3J(H,H) = 1.9 Hz, ^4J(H,H) = 0.9 Hz, 1H), 5.19 (dd, ^3J(H,H) = 1.9 Hz, ^4J(H,H) = 0.9 Hz, 1H), 2.48 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 160.6, 156.7, 147.8, 142.8, 142.6, 141.4, 133.6, 132.4, 129.3, 127.9, 114.5, 81.5, 80.4, 24.4.
MS (70 eV, EI) *m/z* (%): 267 (81) [M^+], 266 (23), 250 (37), 246 (30), 245 (25), 241 (20), 240 (35), 239 (57), 238 (100), 231 (27), 223 (36), 213 (25), 77 (25), 57 (24).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 1612 (w), 1555 (s), 1477 (m), 1440 (m), 1424 (s), 1324 (m), 1280 (m), 1204 (m), 1186 (w), 1086 (m), 1024 (w), 1007 (w), 890 (w), 845 (vs), 812 (m), 730 (s), 703 (s), 689 (s), 650 (s).
HRMS (EI) for **$C_{16}H_{13}ONS$** (267.0718): found 267.0694.

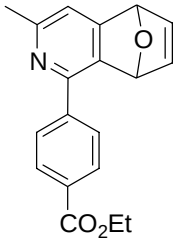
Synthesis of 3-allyl-5-methyl-11-oxa-4-aza-tricyclo[6.2.1.02,7]undeca-2(7),3,5,9-tetraene (41h):



Prepared according to **TP 5** from 2-allyl-4-bromo-6-methylpyridin-3-yl 4-chlorobenzenesulfonate (**39h**) (403 mg, 1.0 mmol), *i*-PrMgCl·LiCl (1.02 mL, 1.02 mmol, 1.00 M in THF) and furan (340 mg, 5.0 mmol). Reaction condition: −78 °C, 2 h; 25 °C, 1 h. Purification by flash chromatography (*n*-pentane/diethyl ether = 5 : 1) yielded **41h** as a yellow oil (114 mg, 57 %).

^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 6.98 (dd, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 1.9 Hz, 1H), 6.97 (s, 1H), 6.91 (dd, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 1.9 Hz, 1H), 6.03-5.92 (m, 1H), 5.82-5.81 (m, 1H), 5.64-5.63 (m, 1H), 5.11-5.01 (m, 2H), 3.62-3.46 (m, 2H), 2.47 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 159.6, 155.8, 148.7, 143.0, 141.6, 139.4, 135.7, 116.4, 114.4, 81.6, 80.3, 40.4, 24.5.
MS (70 eV, EI) *m/z* (%): 199 (55) [M^+], 198 (100), 173 (37), 172 (53), 171 (70), 170 (70), 169 (19), 168 (22), 155 (16), 154 (14), 145 (14), 144 (20), 130 (12), 128 (14), 115 (13), 103 (11), 77 (21), 63 (10), 51 (12).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 1616 (w), 1587 (m), 1433 (m), 1367 (w), 1280 (w), 845 (s), 700 (m), 647 (m).
HRMS (EI) for **$C_{13}H_{13}ON$**, $[M+H]^+$ (199.0997): found 199.0967.
HRMS (EI) for **$C_{13}H_{12}ON$** (198.0919): found 198.0904.

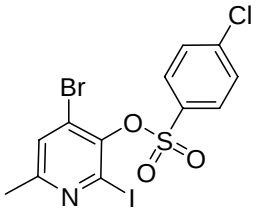
Synthesis of 4-(5-methyl-11-oxa-4-aza-tricyclo[6.2.1.02,7]undeca-2(7),3,5,9-tetraen-3-yl)-benzoic acid ethyl ester (41i):



Prepared according to **TP 5** from 4-[4-bromo-3-(4-chloro-benzenesulfonyloxy)-6-methyl-pyridin-2-yl]-benzoic acid ethyl ester (**39i**) (255 mg, 0.5 mmol), *i*-PrMgCl·LiCl (0.51 mL, 0.51 mmol, 1.00 M in THF) and furan (170 mg, 2.5 mmol). Reaction condition: −78 °C, 6 h; 25 °C, 1 h. Purification by flash chromatography (pentane/diethyl ether = 10 : 1) yielded **41i** as a pale yellow solid (117 mg, 76 %).

mp.: 148.6-150.1 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.18-8.13 (m, 2H), 7.74-7.69 (m, 2H), 7.20 (dd, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 1.8 Hz, 1H), 7.13 (s, 1H), 7.06 (dd, ^3J(H,H) = 5.6 Hz, ^3J(H,H) = 1.9 Hz, 1H), 5.93-5.91 (m, 1H), 5.74-5.72 (m, 1H), 4.41 (q, ^3J(H,H) = 7.1 Hz, 2H), 2.59 (s, 3H), 1.42 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.3, 160.0, 156.4, 147.3, 143.1, 142.8, 142.1, 139.2, 130.3, 129.9, 127.8, 115.6, 81.7, 81.3, 61.0, 24.7, 14.3.
MS (70 eV, EI) *m/z* (%): 307 (14) [M^+], 291 (13), 281 (35), 280 (23), 279 (100), 278 (17), 262 (27), 253 (14), 252 (12), 251 (96), 250 (24), 234 (17), 225 (13), 218 (20), 206 (22), 205 (17), 204 (24), 178 (11), 165 (14), 164 (11).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1708 (vs), 1610 (m), 1584 (w), 1404 (w), 1369 (w), 1278 (s), 1222 (w), 1108 (m), 1078 (w), 1016 (m), 862 (m), 843 (m), 816 (w), 761 (m), 718 (w), 704 (m), 650 (w).
HRMS (EI) for **$C_{19}H_{17}O_3N$** (307.1208): found 307.1222.

Synthesis of 4-bromo-2-iodo-6-methylpyridin-3-yl 4-chlorobenzenesulfonate (42):

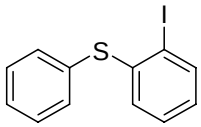


A dry and argon-flushed 250 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 2,4-diiodo-6-methylpyridin-3-yl 4-chlorobenzenesulfonate (16.07 g, 30 mmol) in dry THF (60 mL). *i*-PrMgCl (0.87 M/THF, 37.9 mL, 1.1 equiv.) was then added dropwise at −78 °C. After 30 min, 1,2-dibromotetrafluoroethane (13.3 g, 50 mmol) was added slowly at −78 °C, and the resulting mixture was warmed up slowly to room temperature during 6 h. Thereafter, the reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 100 mL). The organic fractions were dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane : ether = 50 : 1) yielded **42** (9.820 g, 67 %) as a yellow solid.

mp.: 112.6-113.8 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.99-7.94 (m, 2H), 7.60-7.55 (m, 2H), 7.34 (s, 1H), 2.50 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 159.1, 144.8, 141.7, 135.9, 130.3, 129.7, 128.1, 127.1, 114.4, 23.3.
MS (70 eV, EI) *m/z* (%): 491 (13), 489 (40), 487 (33) [M^+], 314 (29), 312 (28), 286 (17), 284 (17), 177 (41), 175 (100), 159 (14), 113 (12), 111 (41), 78 (19), 75 (14), 51 (16).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 1558 (m), 1513 (w), 1473 (w), 1390 (vs), 1325 (m), 1283 (w), 1244 (m), 1202 (w), 1183 (s), 1092 (m), 1064 (m), 1012 (w), 878 (w), 826 (m), 820 (s), 760 (m), 741 (w), 728 (m), 701 (m), 680 (m), 620 (m).
HRMS (EI) for **$C_{12}H_8O_3NIS^{79}Br^{35}Cl$** (486.8141): found 486.8141.

10. Preparation of functionalized arylmagnesium reagents by the addition of magnesium aryl thiolates, amides and selenides to arynes and heteroarynes

Synthesis of 2-iodophenyl phenyl sulfide (58a):

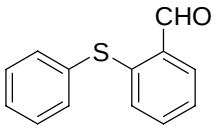


Prepared according to **TP 6** from thiophenol (111 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-methylbenzenesulfonate **(19a)** (374 mg, 1.0 mmol) and iodine (508 mg, 2.0 mmol). Reaction condition: −78 °C, 1 h (I/Mg-exchange reaction). Purification by flash chromatography (*n*-pentane) yielded **58a** as a white solid (253 mg, 81 %).

Prepared according to **TP 6** from thiophenol (111 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and iodine (508 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane) yielded **58a** as a white solid (260 mg, 83 %).

mp.: 55.6-56.6 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.86 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 7.48-7.35 (m, 5H), 7.21 (td, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 6.99 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 6.88 (td, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 142.2, 139.6, 133.9, 133.0, 129.6, 129.5, 128.7, 128.2, 127.4, 99.4.
MS (70 eV, EI) *m/z* (%): 312 (100) [M^+], 199 (11), 186 (16), 185 (32), 184 (84), 152 (11), 151 (9), 139 (8).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1552 (m), 1564 (w), 1474 (m), 1440 (s), 1421 (m), 1254 (m), 1009 (m), 999 (w), 743 (vs), 706 (m), 689 (m), 641 (w), 516 (w).
HRMS (EI) for **$C_{12}H_9IS$** (311.9470): found: 311.9463.
Spectral data match those reported in the literature.[91]

Synthesis of 2-phenylsulfanyl-benzaldehyde (58b):

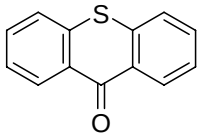


Prepared according to **TP 7** from thiophenol (111 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-methylbenzenesulfonate **(19a)** (374 mg, 1.0 mmol) and DMF (0.20 mL, 2.5 mmol). Reaction condition: −78 °C, 1 h (I/Mg-exchange reaction). Purification by washing with *n*-pentane yielded **58b** as a pale yellow solid (155 mg, 72 %).

mp.: 48.1-49.3 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.39 (s, 1H), 7.87 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.7 Hz, 1H), 7.45-7.28 (m, 7H), 7.10 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.7 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.3, 141.4, 134.0, 133.7, 133.2, 133.0, 131.7, 130.3, 129.6, 128.3, 126.2.
MS (70 eV, EI) *m/z* (%): 215 (14), 214 (100) [M^+], 213 (74), 186 (13), 185 (86), 184 (41), 136 (20).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3059 (w), 2852 (w), 2739 (w), 1694 (s), 1586 (m), 1558 (w), 1477 (w), 1459 (m), 1440 (m), 1396 (w), 1262 (w), 1198 (m), 845 (w), 751 (m), 691 (m).
HRMS (EI) for **$C_{13}H_{10}OS$** (214.0452): found: 214.0444.

Synthesis of thioxanthon (58c):

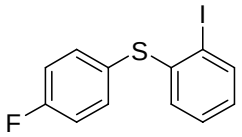


A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 2-mercapto-benzoic acid (154 mg, 1.0 mmol) in dry THF (3 mL). After cooling to −78 °C, *i*-PrMgCl (2.81 mL, 3.0 equiv., 1.07 M in THF) was then added dropwise and stirred for 10 min. (a) 2-Iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature; or (b) 2-iodophenyl 4-methylbenzenesulfonate **(19a)** (374 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 1 h at the same temperature. Thereafter, the resulting mixture was warmed to 25 °C and stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 150 : 1) yielded **58c** as a yellow solid (180-182 mg, 85-86 %).

A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 2-mercapto-benzoic acid ethyl ester (154 mg, 1.0 mmol) in dry THF (3 mL). After cooling to −78 °C, *i*-PrMgCl (1.87 mL, 2.0 equiv., 1.07 M in THF) was then added dropwise and stirred for 10 min. 2-Iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter, the resulting mixture was warmed to 25 °C and stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 150 : 1) yielded **58c** as a yellow solid (186 mg, 87 %).

mp.: 211.1-212.1 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.63-8.57 (m, 2H), 7.62-7.51 (m, 4H), 7.46 (ddd, ^3J(H,H) = 8.0 Hz, ^3J(H,H) = 6.6 Hz, ^4J(H,H) = 1.8 Hz, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 179.8, 137.2, 132.2, 129.8, 129.2, 126.2, 125.9.
MS (70 eV, EI) *m/z* (%): 212 (100) [M^+], 184 (45), 152 (9), 139 (12), 59 (9).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3061 (w), 1646 (s), 1592 (vs), 1568 (w), 1460 (w), 1436 (s), 1321 (vs), 1258 (w), 1170 (w), 1162 (m), 1124 (w), 1084 (w), 1074 (w), 1033 (w), 928 (w), 805 (w), 744 (m), 732 (vs), 666 (m), 626 (m), 482 (m).
HRMS (EI) for **$C_{13}H_8OS$** (212.0296): found: 212.0282.

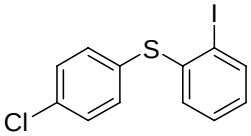
Synthesis of 4-fluorophenyl 2-iodophenyl sulfide (58d):



Prepared according to **TP 6** from 4-fluorothiophenol (128 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and iodine (508 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane) yielded **58d** as a white solid (297 mg, 90 %).

mp.: 93.7-94.7 °C.
^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.82 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.2 Hz, 1H), 7.49-7.42 (m, 2H), 7.19 (td, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.2 Hz, 1H), 7.13-7.06 (m, 2H), 6.89-6.82 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 163.0 (d, ^1J(F,C) = 249 Hz), 142.6, 139.7, 135.8 (d, ^3J(F,C) = 8 Hz), 128.9, 128.7, 128.6, 127.3, 116.9 (d, ^2J(F,C) = 22 Hz), 98.4.
MS (70 eV, EI) *m/z* (%): 331 (13), 330 (93) [M^+], 204 (10), 203 (58), 202 (100), 183 (17), 170 (14), 157 (9), 101 (9), 83 (8).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1589 (s), 1563 (w), 1490 (vs), 1466 (w), 1440 (s), 1422 (m), 1396 (w), 1256 (w), 1224 (s), 1154 (m), 1090 (w), 1036 (w), 1009 (s), 834 (s), 817 (w), 750 (vs), 704 (w), 644 (w), 634 (w), 527 (m).
HRMS (EI) for **$C_{12}H_8FIS$** (329.9375): found: 329.9370.

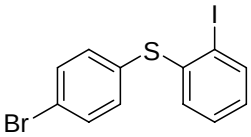
Synthesis of 4-chlorophenyl 2-iodophenyl sulfide (58e):



Prepared according to **TP 6** from 4-chlorothiophenol (145 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and iodine (508 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane) yielded **58e** as a white solid (291 mg, 84 %).

mp.: 89.0-90.0 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.83 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 7.32-7.28 (m, 4H), 7.20 (td, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 6.99 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 6.88 (td, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 141.3, 139.8, 134.3, 133.8, 132.8, 130.0, 129.7, 128.8, 127.9, 100.2.
MS (70 eV, EI) *m/z* (%): 348 (28), 346 (73) [M^+], 185 (14), 184 (100), 183 (18), 139 (15), 108 (11), 92 (15).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3085 (w), 1902 (w), 1639 (w), 1572 (w), 1562 (w), 1474 (s), 1440 (s), 1422 (s), 1386 (m), 1256 (m), 1172 (w), 1092 (s), 1036 (w), 1008 (s), 856 (w), 828 (m), 820 (s), 747 (vs), 702 (w), 642 (w), 510 (m).
HRMS (EI) for **$C_{12}H_8{}^{35}ClIS$** (345.9080): found: 345.9086.

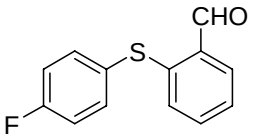
Synthesis of 4-bromophenyl 2-iodophenyl sulfide (58f):



Prepared according to **TP 6** from 4-bromothiophenol (190 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and iodine (508 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane) yielded **58f** as a white solid (321 mg, 82 %).

mp.: 88.1-88.8 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.85 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 7.51-7.45 (m, 2H), 7.26-7.20 (m, 3H), 7.04 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 6.91 (td, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 141.1, 139.9, 133.8, 133.6, 132.7, 130.3, 128.9, 128.1, 122.2, 100.5.
MS (70 eV, EI) *m/z* (%): 392 (17), 390 (16) [M^+], 185 (13), 184 (100), 139 (10), 92 (15).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3080 (w), 3053 (w), 1910 (w), 1654 (w), 1644 (w), 1564 (m), 1468 (s), 1439 (s), 1423 (s), 1386 (m), 1251 (w), 1174 (w), 1088 (w), 1071 (m), 1035 (w), 1007 (s), 950 (w), 834 (m), 821 (s), 748 (vs), 730 (m), 707 (m), 700 (m), 642 (w), 532 (w), 492 (m).
HRMS (EI) for **$C_{12}H_8{}^{79}BrIS$** (389.8575): found: 389.8561.

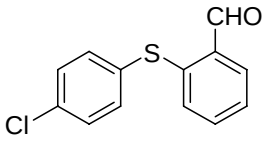
Synthesis of 2-[(4-fluorophenyl)sulfanyl]benzaldehyde (58g):



Prepared according to **TP 7** from 4-fluorothiophenol (128 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and DMF (0.20 mL, 2.5 mmol). Purification by washing with *n*-pentane yielded **58g** as a yellow solid (181 mg, 78 %).

mp.: 98.4-99.4 °C.
^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.32 (s, 1H), 7.84 (dd, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.5 Hz, 1H), 7.48-7.42 (m, 2H), 7.37 (td, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.5 Hz, 1H), 7.29 (td, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.2 Hz, 1H), 7.13-7.06 (m, 2H), 6.96 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 0.6 Hz, 1H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.3, 163.1 (d, ^1J(F,C) = 249 Hz), 142.1, 136.1 (d, ^3J(F,C) = 8 Hz), 133.9, 133.1, 132.5, 129.0, 127.7, 125.8, 116.9 (d, ^2J(F,C) = 22 Hz).
MS (70 eV, EI) *m/z* (%): 233 (16), 232 (100) [M^+], 231 (33), 204 (14), 203 (87), 202 (38), 183 (10), 170 (11), 136 (35), 104 (11).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3090 (w), 3065 (w), 3048 (w), 2855 (w), 2762 (w), 1696 (m), 1672 (vs), 1587 (m), 1554 (m), 1491 (s), 1457 (s), 1440 (m), 1399 (m), 1302 (m), 1258 (m), 1221 (s), 1191 (s), 1155 (m), 1126 (w), 1090 (w), 1066 (w), 1043 (w), 1014 (w), 846 (m), 832 (s), 814 (w), 766 (s), 674 (w), 658 (m), 635 (w), 527 (m), 499 (w).
HRMS (EI) for **$C_{13}H_9FOS$** (232.0358): found: 232.0370.

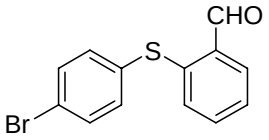
Synthesis of 2-[(4-chlorophenyl)sulfanyl]benzaldehyde (58h):



Prepared according to **TP 7** from 4-chlorothiophenol (145 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and DMF (0.20 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **58h** as a yellow solid (182 mg, 73 %).

mp.: 72.6-73.5 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.36 (s, 1H), 7.88 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.46-7.31 (m, 6H), 7.08 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.3 Hz, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.3, 140.9, 134.7, 134.4, 134.1, 133.7, 132.2, 131.8, 130.2, 129.9, 126.5.
MS (70 eV, EI) *m/z* (%): 250 (40), 249 (22), 248 (100) [M^+], 247 (22), 221 (10), 219 (28), 213 (31), 185 (33), 184 (70), 152 (10), 139 (14), 109 (14), 108 (15), 104 (22), 76 (12).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3079 (w), 2850 (w), 2755 (w), 1907 (w), 1693 (s), 1674 (vs), 1586 (m), 1572 (m), 1553 (m), 1476 (m), 1458 (s), 1438 (m), 1393 (m), 1300 (w), 1258 (w), 1199 (s), 1174 (w), 1126 (w), 1094 (m), 1083 (m), 1068 (w), 1042 (w), 1015 (m), 844 (m), 831 (m), 822 (s), 762 (s), 746 (m), 676 (m), 656 (m), 514 (w), 490 (w).
HRMS (EI) for **$C_{13}H_9{}^{35}ClOS$** (248.0063): found: 248.0043.

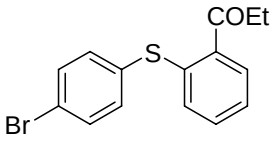
Synthesis of 2-[(4-bromophenyl)sulfanyl]benzaldehyde (58i):



Prepared according to **TP 7** from 4-bromothiophenol (190 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and DMF (0.20 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **58i** as a yellow solid (220 mg, 75 %).

mp.: 78.0-78.7 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.35 (s, 1H), 7.87 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 7.51-7.46 (m, 2H), 7.42 (td, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 7.34 (td, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 7.29-7.24 (m, 2H), 7.09 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.3, 140.5, 134.4, 134.1, 133.8, 132.8, 132.5, 132.1, 130.3, 126.6, 122.7.
MS (70 eV, EI) *m/z* (%): 294 (76), 293 (26), 292 (78) [M^+], 291 (14), 213 (43), 185 (33), 184 (100), 152 (16), 139 (14), 136 (64), 109 (14), 108 (16), 104 (13), 76 (14).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3079 (w), 2852 (w), 2829 (w), 2754 (m), 1976 (w), 1911 (w), 1674 (vs), 1587 (m), 1562 (m), 1464 (m), 1443 (w), 1404 (m), 1386 (m), 1301 (w), 1266 (w), 1204 (m), 1166 (w), 1130 (w), 1090 (w), 1069 (m), 1008 (m), 848 (m), 830 (m), 814 (m), 760 (s), 732 (w), 676 (m), 657 (w), 532 (w), 478 (w).
HRMS (EI) for **$C_{13}H_9{}^{79}BrOS$** (291.9557): found: 291.9568.

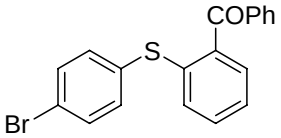
Synthesis of 1-{2-[(4-bromophenyl)sulfanyl]phenyl}-1-propanone (58j):



Prepared according to **TP 8** from 4-bromothiophenol (190 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), CuCN·2LiCl (1.0 mL, 1.0 equiv., 1.0 M in THF) and propionyl chloride (0.22 mL, 2.5 mmol). Purification by washing with *n*-pentane yielded **58j** as a yellow solid (288 mg, 90 %).

mp.: 121.2-122.0 °C.
^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.80 (dd, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.5 Hz, 1H), 7.53-7.49 (m, 2H), 7.37-7.33 (m, 2H), 7.26 (td, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.5 Hz, 1H), 7.19 (td, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.5 Hz, 1H), 6.93 (dd, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.5 Hz, 1H), 3.00 (q, ^3J(H,H) = 7.3 Hz, 2H), 1.24 (t, ^3J(H,H) = 7.3 Hz, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 202.1, 140.1, 136.0, 135.5, 133.0, 132.7, 131.8, 129.5, 128.8, 125.0, 123.0, 33.4, 8.3.
MS (70 eV, EI) *m/z* (%): 322 (28), 320 (27) [M^+], 293 (23), 291 (21), 213 (16), 212 (100), 184 (33), 139 (12), 137 (27).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3082 (w), 2984 (w), 2938 (w), 2901 (w), 1674 (vs), 1585 (m), 1564 (w), 1461 (m), 1431 (m), 1409 (w), 1388 (w), 1375 (w), 1349 (m), 1273 (w), 1216 (s), 1140 (w), 1098 (w), 1090 (w), 1065 (m), 1008 (s), 954 (m), 942 (m), 842 (m), 822 (m), 750 (s), 730 (m), 686 (w), 643 (w), 538 (w), 488 (w), 474 (w).
HRMS (EI) for **$C_{15}H_{13}{}^{79}BrOS$** (319.9870): found: 319.9881.

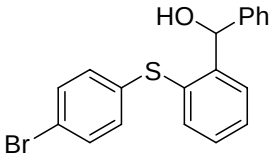
Synthesis of {2-[(4-bromophenyl)sulfanyl]phenyl}(phenyl)methanone (58k):



Prepared according to **TP 8** from 4-bromothiophenol (190 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), CuCN·2LiCl (1.0 mL, 1.0 equiv., 1.0 M in THF), and benzoyl chloride (0.17 mL, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **58k** as a yellow oil (324 mg, 88 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.78-7.73 (m, 2H), 7.59-7.52 (m, 1H), 7.45-7.30 (m, 6H), 7.29-7.23 (m, 2H), 7.19-7.13 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 196.2, 139.8, 137.2, 135.9, 134.2, 133.7, 133.2, 132.3, 131.9, 131.0, 130.0, 129.6, 128.4, 126.5, 121.9.
MS (70 eV, EI) *m/z* (%): 370 (62), 369 (16), 368 (100) [M^+], 213 (29), 212 (35), 207 (37), 197 (34), 185 (13), 184 (43), 152 (14), 139 (13), 105 (46), 97 (18), 77 (46), 57 (16), 55 (10), 41 (20).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3060 (m), 2970 (w), 2928 (w), 1905 (w), 1715 (w), 1668 (vs), 1596 (m), 1581 (m), 1472 (s), 1448 (s), 1433 (m), 1386 (m), 1315 (s), 1286 (s), 1268 (s), 1202 (m), 1176 (m), 1153 (m), 1089 (m), 1069 (m), 1009 (s), 927 (m), 899 (m), 815 (m), 764 (m), 743 (m), 729 (m), 701 (s), 686 (m), 637 (m), 530 (w), 476 (m).
HRMS (EI) for **$C_{19}H_{13}{}^{79}BrOS$** (367.9870): found: 367.9885.

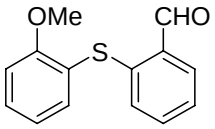
Synthesis of {2-[(4-bromophenyl)sulfanyl]phenyl}(phenyl)methanol (58l):



A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 4-bromothiophenol (190 mg, 1.0 mmol) in dry THF (3 mL). After cooling to −78 °C, *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF) was added dropwise and stirred for 10 min. 2-Iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter, the resulting mixture was immediately warmed to 0 °C and stirred for 10 min. The reaction mixture was cooled to −78 °C, then benzaldehyde (0.15 mL, 1.5 mmol) was added and the resulting mixture was stirred for 3 h at the this temperature. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **58l** as a yellow oil (315 mg, 85 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.62 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.39-7.18 (m, 10H), 6.98-6.92 (m, 2H), 6.31 (s, 1H), 2.42 (s, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 145.3, 142.7, 135.9, 134.4, 132.1, 131.7, 130.8, 128.8, 128.5, 128.4, 127.8, 127.5, 126.9, 120.3, 73.3.
MS (70 eV, EI) *m/z* (%): 372 (42), 370 (49) [M^+], 354 (11), 353 (22), 351 (19), 277 (19), 275 (17), 274 (11), 273 (39), 271 (14), 215 (16), 214 (70), 213 (100), 212 (23), 197 (65), 185 (10), 184 (39), 182 (28), 181 (81), 165 (36), 153 (14), 152 (30), 139 (12), 137 (21), 132 (14), 109 (19), 108 (10), 105 (52), 91 (10), 77 (51), 51 (14).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3392 (brm), 3060 (w), 3029 (w), 2921 (w), 1726 (w), 1588 (w), 1568 (w), 1494 (w), 1471 (vs), 1453 (m), 1439 (m), 1386 (m), 1180 (w), 1087 (m), 1069 (w), 1007 (vs), 811 (m), 758 (s), 699 (s), 648 (w), 601 (w), 478 (w).
HRMS (EI) for **$C_{19}H_{15}{}^{79}BrOS$** (370.0027): found: 370.0027.

Synthesis of 2-[(2-methoxyphenyl)sulfanyl]benzaldehyde (58m):

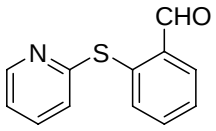


Prepared according to **TP 7** from 2-methoxythiophenol (140 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and DMF (0.20 mL, 2.5 mmol). Purification by washing with *n*-pentane yielded **58m** as a yellow solid (196 mg, 80 %).

mp.: 103.2-104.2 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.43 (s, 1H), 7.87 (dd, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 1.3 Hz, 1H), 7.40-7.25 (m, 4H), 7.08 (d, ^3J(H,H) = 7.3 Hz, 1H), 6.96-6.92 (m, 2H), 3.81 (s, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.6, 158.7, 140.6, 134.4, 134.1, 133.8, 131.4, 130.5, 130.2, 126.2, 121.5, 121.1, 111.3, 55.8.

MS (70 eV, EI) *m/z* (%): 245 (14), 244 (100) [M^+], 213 (13), 201 (11), 200 (12), 184 (17), 171 (11), 108 (27), 105 (11).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3010 (w), 2932 (w), 2848 (w), 2830 (w), 2754 (w), 1694 (m), 1676 (vs), 1585 (s), 1557 (s), 1476 (vs), 1461 (vs), 1442 (m), 1428 (m), 1399 (s), 1296 (m), 1274 (s), 1262 (m), 1250 (s), 1196 (s), 1162 (m), 1131 (m), 1068 (m), 1022 (s), 852 (m), 843 (m), 799 (m), 760 (vs), 686 (w), 676 (m), 656 (m).
HRMS (EI) for **$C_{14}H_{12}O_2S$** (244.0558): found: 244.0551.

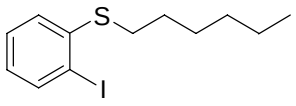
Synthesis of 2-(2-pyridinylsulfanyl)benzaldehyde (58n):



Prepared according to **TP 7** from pyridine-2-thiol (111 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and DMF (0.20 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether/methylene chloride = 10 : 1 : 2) yielded **58n** as a yellow oil (176 mg, 82 %).

^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.37 (s, 1H), 8.36 (d, ^3J(H,H) = 4.6 Hz, 1H), 8.01 (ddd, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.5 Hz, ^5J(H,H) = 0.9 Hz 1H), 7.61-7.47 (m, 4H), 7.07-7.00 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.6, 158.4, 149.7, 137.1, 136.9, 135.9, 134.4, 134.2, 129.5, 129.1, 122.3, 120.7.
MS (70 eV, EI) *m/z* (%): 215 (8) [M^+], 214 (10), 187 (18), 186 (100), 182 (12), 109 (11), 78 (10).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3061 (w), 2858 (w), 1695 (vs), 1651 (w), 1586 (m), 1574 (s), 1560 (m), 1450 (s), 1417 (s), 1383 (w), 1282 (w), 1262 (m), 1198 (s), 1114 (m), 1087 (w), 1059 (m), 1044 (w), 986 (w), 825 (m), 759 (s), 722 (m), 634 (w).
HRMS (EI) for **$C_{12}H_9NOS$** (215.0405): found: 215.0421.

Synthesis of 1-hexylsulfanyl-2-iodo-benzene (58p):

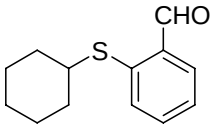


Prepared according to **TP 6** from hexane-1-thiol (118 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and iodine (508 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane) yielded **58p** as a colourless liquid (167 mg, 52 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.76 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.28-7.24 (m, 1H), 7.16 (d, ^3J(H,H) = 7.8 Hz, 1H), 6.82-6.78 (m, 1H), 2.87 (t, ^3J(H,H) = 7.4 Hz, 2H), 1.70-1.64 (m, 2H), 1.46-1.39 (m, 2H), 1.31-1.24 (m, 4H), 0.86 (t, ^3J(H,H) = 6.7 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 142.1, 139.5, 128.5, 126.9, 126.3, 99.3, 34.1, 31.3, 28.7, 28.3, 22.5, 14.0.
MS (70 eV, EI) *m/z* (%): 320 (46) [M^+], 236 (100), 122 (21), 109 (26), 108 (17), 55 (12), 43 (38).

IR (film) $\tilde{\nu}$ (cm^{-1}): 2954 (s), 2927 (vs), 2855 (m), 1569 (w), 1465 (w), 1443 (s), 1424 (m), 1252 (w), 1010 (m), 741 (s).
HRMS (EI) for **$C_{12}H_{17}IS$** (320.0096): found: 320.0107.

Synthesis of 2-(cyclohexylsulfanyl)benzaldehyde (58q):

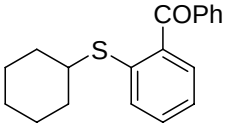


Prepared according to **TP 7** from cyclohexanethiol (161 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and DMF (0.40 mL, 5.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 100/1) yielded **58q** as a yellow oil (137 mg, 62 %).

Prepared according to **TP 7** from cyclohexanethiol (232 mg, 2.0 mmol), *i*-PrMgCl (2.81 mL, 3.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and DMF (0.40 mL, 5.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **58q** as a yellow oil (161 mg, 73 %).

^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.55 (s, 1H), 7.87-7.83 (m, 1H), 7.52-7.46 (m, 2H), 7.34-7.29 (m, 1H), 3.15-3.07 (m, 1H), 2.00-1.92 (m, 2H), 1.80-1.72 (m, 2H), 1.63-1.56 (m, 1H), 1.45-1.17 (m, 5H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 192.0, 139.9, 136.0, 133.7, 132.7, 129.8, 126.7, 47.3, 33.1, 25.9, 25.5.
MS (70 eV, EI) *m/z* (%): 220 (59) [M^+], 173 (20), 139 (18), 138 (100), 137 (40), 110 (14), 109 (18), 104 (25), 83 (11), 55 (21).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3368 (w), 3061 (w), 2930 (s), 2853 (m), 2734 (w), 1693 (vs), 1649 (w), 1587 (m), 1559 (w), 1458 (m), 1449 (m), 1397 (w), 1377 (w), 1340 (w), 1288 (w), 1260 (m), 1193 (m), 1061 (w), 997 (w), 844 (w), 824 (m), 758 (m), 714 (w), 635 (w).
HRMS (EI) for **$C_{13}H_{16}OS$** (220.0922): found: 220.0906.

Synthesis of [2-(cyclohexylsulfanyl)phenyl](phenyl)methanone (58r):

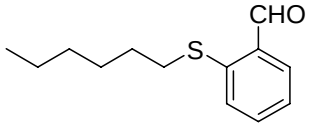


Prepared according to **TP 8** from cyclohexanethiol (116 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), CuCN·2LiCl (1.0 mL, 1.0 equiv., 1.0 M in THF), and benzoyl chloride (0.35 mL, 3.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **58r** as a yellow oil (216 mg, 73 %).

Prepared according to **TP 8** from cyclohexanethiol (232 mg, 2.0 mmol), *i*-PrMgCl (2.81 mL, 3.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), CuCN·2LiCl (1.0 mL, 1.0 equiv., 1.0 M in THF), and benzoyl chloride (0.35 mL, 3.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **58r** as a yellow oil (246 mg, 83 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.80-7.75 (m, 2H), 7.59-7.51 (m, 2H), 7.46-7.38 (m, 3H), 7.34-7.29 (m, 2H), 3.11-3.00 (m, 1H), 1.92-1.16 (m, 10H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 197.0, 142.5, 137.4, 133.7, 133.1, 132.9, 130.0, 129.9, 128.3, 128.2, 126.3, 47.3, 33.0, 25.9, 25.6.
MS (70 eV, EI) *m/z* (%): 296 (12) [M^+], 214 (33), 213 (100), 197 (10), 184 (14), 105 (10), 77 (10).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3325 (w), 3059 (w), 2930 (s), 2852 (m), 1720 (m), 1669 (vs), 1596 (m), 1582 (m), 1448 (s), 1433 (m), 1315 (m), 1285 (s), 1247 (m), 1178 (w), 1152 (w), 1065 (w), 1026 (w), 998 (w), 928 (m), 765 (m), 750 (m), 704 (s), 688 (m), 636 (m).
HRMS (EI) for **$C_{19}H_{20}OS$** (296.1235): found: 296.1250.

Synthesis of 2-(hexylsulfanyl)benzaldehyde (58s):

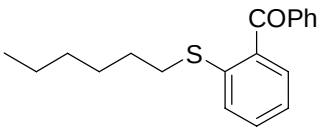


Prepared according to **TP 7** from hexane-1-thiol (118 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and DMF (0.40 mL, 5.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 50 : 1) yielded **58s** as a yellow oil (118 mg, 53 %).

Prepared according to **TP 7** from hexane-1-thiol (236 mg, 2.0 mmol), *i*-PrMgCl (2.81 mL, 3.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and DMF (0.40 mL, 5.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 50 : 1) yielded **58s** as a yellow oil (149 mg, 67 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.39 (s, 1H), 7.82 (d, ^3J(H,H) = 7.7 Hz, 1H), 7.50 (t, ^3J(H,H) = 7.7 Hz, 1H), 7.41 (d, ^3J(H,H) = 7.7 Hz, 1H), 7.28 (t, ^3J(H,H) = 7.7 Hz, 1H), 2.94 (t, ^3J(H,H) = 7.7 Hz, 2H), 1.72-1.65 (m, 2H), 1.48-1.42 (m, 2H), 1.33-1.26 (m, 4H), 0.88 (t, ^3J(H,H) = 7.3 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.4, 142.3, 134.0, 133.8, 131.8, 128.2, 125.2, 33.4, 31.3, 28.6, 28.5, 22.5, 14.0.
MS (70 eV, EI) *m/z* (%): 222 (55) [M^+], 161 (11), 151 (70), 148 (10), 147 (20), 139 (16), 138 (73), 137 (100), 135 (12), 134 (11), 123 (14), 110 (70), 109 (43), 104 (31), 77 (13), 65 (18), 55 (11), 45 (14), 43 (27), 41 (30).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2956 (m), 2928 (s), 2856 (m), 2733 (w), 1694 (vs), 1588 (m), 1560 (w), 1460 (m), 1440 (w), 1397 (w), 1261 (w), 1195 (m), 1128 (w), 845 (w), 825 (w), 751 (m), 680 (w), 657 (w), 636 (w).
HRMS (EI) for **$C_{13}H_{18}OS$** (222.1078): found: 222.1081.

Synthesis of (2-hexylsulfanyl-phenyl)-phenyl-methanone (58t):



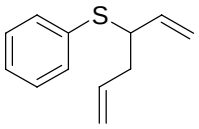
Prepared according to **TP 8** from hexane-1-thiol (118 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), CuCN·2LiCl (1.0 mL, 1.0 equiv., 1.0 M in THF), and benzoyl chloride (0.35 mL,

3.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **58t** as a yellow oil (182 mg, 61 %).

Prepared according to **TP 8** from hexane-1-thiol (236 mg, 2.0 mmol), *i*-PrMgCl (2.81 mL, 3.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), CuCN·2LiCl (1.0 mL, 1.0 equiv., 1.0 M in THF), and benzoyl chloride (0.35 mL, 3.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **58t** as a yellow oil (221 mg, 74 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.81-7.76 (m, 2H), 7.60-7.53 (m, 1H), 7.50-7.39 (m, 4H), 7.37-7.33 (m, 1H), 7.27-7.21 (m, 1H), 2.85 (t, ^3J(H,H) = 7.4 Hz, 2H), 1.61-1.50 (m, 2H), 1.38-1.17 (m, 6H), 0.85 (t, ^3J(H,H) = 6.8 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 196.8, 140.0, 137.4, 136.6, 133.0, 130.4, 130.0, 129.7, 129.0, 128.3, 125.2, 34.4, 31.2, 28.7, 28.4, 22.4, 13.9.
MS (70 eV, EI) *m/z* (%): 298 (15) [M^+], 214 (19), 213 (100), 184 (15), 105 (14), 91 (11), 77 (11).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2956 (m), 2928 (s), 2856 (m), 1721 (w), 1668 (vs), 1597 (w), 1583 (w), 1463 (w), 1449 (m), 1433 (w), 1315 (m), 1285 (vs), 1253 (m), 926 (m), 763 (w), 742 (m), 703 (m), 637 (m).
HRMS (EI) for **$C_{19}H_{22}OS$** (298.1391): found: 298.1406.

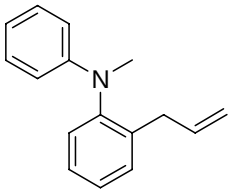
Synthesis of (1-vinyl-but-3-enylsulfanyl)-benzene (58u):



A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of diallylsulfide (128 mg, 1.1 mmol) and 4-chloro-benzenesulfonic acid 2-iodo-phenyl ester (**27a**) (394 mg, 1.0 mmol) in dry THF (3 mL). *i*-PrMgCl (1.22 mL, 1.1 equiv., 0.90 M in THF) was then added dropwise at −78 °C and stirred vigorously for 30 min at the same temperature. Thereafter the resulting mixture was warmed to RT and stirred for 1 h. Saturated aqueous NH_4Cl solution was then added, and then the resulting mixture was extracted with CH_2Cl_2 (3 × 40 mL), dried over anhydrous Na_2SO_4, and concentrated. Purification by flash chromatography (*n*-pentane) yielded **58u** as a colourless liquid (130 mg, 68 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.46-7.41 (m, 2H), 7.35-7.23 (m, 3H), 5.96-5.69 (m, 2H), 5.18-5.10 (m, 2H), 5.04-4.90 (m, 2H), 3.74-3.65 (m, 1H), 2.58-2.39 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 138.1, 135.0, 134.4, 132.8, 128.6, 127.1, 117.2, 115.9, 51.7, 38.6.
MS (70 eV, EI) *m/z* (%): 190 (18) [M^+], 150 (11), 149 (100), 147 (14), 134 (10), 116 (20), 115 (12), 110 (14), 109 (10), 79 (13).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3078 (m), 3005 (w), 2980 (w), 2923 (w), 1640 (m), 1584 (w), 1480 (m), 1438 (m), 1416 (w), 1091 (w), 1026 (w), 989 (m), 916 (vs), 746 (m), 692 (s).
HRMS (EI) for **$C_{12}H_{14}S$** (190.0816): found: 190.0804.

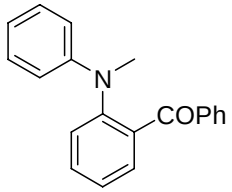
Synthesis of 2-allyl-*N*-methyl-*N*-phenylaniline (59a):



Prepared according to **TP 10** from *N*-methylaniline (107 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), CuCN·2LiCl (0.5 mL, 0.5 equiv., 1.0 M in THF), and allyl bromide (0.21 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane) yielded **59a** as a colourless oil (185 mg, 83 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.34-7.10 (m, 6H), 6.73-6.66 (m, 1H), 6.54-6.49 (m, 2H), 5.95-5.80 (m, 1H), 5.04-4.94 (m, 2H), 3.29-3.24 (m, 2H), 3.19 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 149.4, 146.6, 139.0, 137.0, 130.5, 128.9, 128.6, 128.0, 126.7, 116.9, 115.9, 112.9, 39.6, 35.5.
MS (70 eV, EI) *m/z* (%): 223 (100) [M^+], 222 (39), 221 (15), 208 (37), 207 (15), 194 (91), 193 (38), 180 (23), 167 (20), 165 (14), 155 (48), 147 (19), 120 (15), 115 (36), 111 (15), 107 (15), 106 (16), 97 (33), 95 (22), 91 (59), 85 (15), 83 (31), 82 (19), 81 (18), 77 (27), 74 (17), 73 (22), 71 (23), 70 (16), 69 (43), 67 (18), 59 (39), 57 (49), 56 (15), 55 (39), 45 (27), 43 (35), 42 (17), 41 (43).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3061 (w), 3024 (w), 2893 (w), 2810 (w), 1638 (w), 1603 (s), 1594 (s), 1576 (m), 1500 (vs), 1449 (m), 1430 (w), 1344 (m), 1300 (w), 1256 (m), 1187 (w), 1137 (w), 1114 (w), 991 (w), 915 (w), 870 (w), 774 (w), 748 (s), 692 (m).
HRMS (EI) for **$C_{16}H_{17}N$** (223.1361): found: 223.1376.

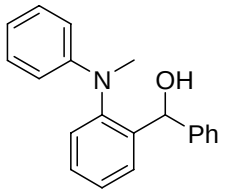
Synthesis of [2-(methylanilino)phenyl](phenyl)methanone (59b):



Prepared according to **TP 10** from *N*-methylaniline (107 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), CuCN·2LiCl (1.0 mL, 1.0 equiv., 1.0 M in THF), and benzoyl chloride (0.17 mL, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 200 : 1) yielded **59b** as a yellow oil (244 mg, 85 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.55-7.47 (m, 4H), 7.45-7.38 (m, 1H), 7.30-7.22 (m, 4H), 7.05-6.98 (m, 2H), 6.70-6.63 (m, 1H), 6.48-6.43 (m, 2H), 3.02 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 197.4, 148.4, 147.3, 137.7, 136.5, 132.5, 132.1, 130.3, 129.1, 128.6, 127.8, 126.8, 124.8, 118.7, 115.4, 40.5.
MS (70 eV, EI) *m/z* (%): 287 (75) [M^+], 271 (23), 270 (100), 210 (17), 167 (17), 105 (11), 91 (12), 77 (20).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3060 (w), 3027 (w), 2932 (w), 2887 (w), 2814 (w), 1730 (w), 1662 (s), 1593 (vs), 1579 (m), 1499 (vs), 1487 (vs), 1450 (s), 1426 (w), 1348 (s), 1316 (s), 1287 (s), 1258 (s), 1187 (w), 1153 (m), 1136 (m), 1113 (m), 1097 (m), 1070 (w), 1026 (w), 936 (m), 866 (w), 749 (s), 708 (s), 693 (s), 639 (s), 569 (w), 515 (w).
HRMS (EI) for **$C_{20}H_{17}NO$** (287.1310): found: 287.1300.

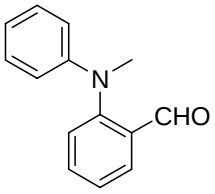
Synthesis of [2-(methylanilino)phenyl](phenyl)methanol (59c):



Prepared according to **TP 10** from *N*-methylaniline (107 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) and benzaldehyde (0.12 mL, 1.2 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **59c** as a yellow oil (232 mg, 80 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.61-7.56 (m, 1H), 7.33-7.02 (m, 10H), 6.75-6.68 (m, 1H), 6.53-6.47 (m, 2H), 5.86 (s, 1H), 2.85 (s, 3H), 2.62 (s, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 149.4, 146.1, 143.6, 142.4, 129.4, 129.0, 128.5, 128.2, 127.9, 127.3, 127.0, 126.7, 117.6, 113.4, 72.2, 39.7.
MS (70 eV, EI) *m/z* (%): 287 (75) [M^+], 271 (23), 270 (100), 210 (17), 167 (17), 105 (11), 91 (12), 77 (20).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3537 (m), 3392 (brm), 3061 (m), 3029 (m), 2883 (m), 2812 (w), 1602 (s), 1575 (m), 1499 (vs), 1451 (s), 1344 (s), 1299 (m), 1257 (m), 1182 (m), 1157 (w), 1137 (w), 1110 (w), 1088 (w), 1066 (w), 1032 (m), 1017 (m), 917 (w), 871 (w), 846 (w), 749 (s), 718 (m), 696 (s), 649 (w), 598 (w), 579 (w), 491 (w).
HRMS (EI) for **$C_{20}H_{19}NO$** (289.1467): found: 289.1450.

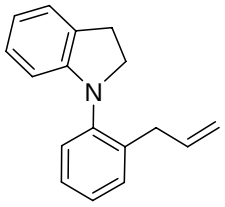
Synthesis of 2-(methylanilino)benzaldehyde (59d):



Prepared according to **TP 10** from *N*-methylaniline (107 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and DMF (0.20 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 250 : 1) yielded **59d** as a yellow oil (156 mg, 74 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.13 (s, 1H), 7.93 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.61 (td, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.35-7.28 (m, 1H), 7.26-7.15 (m, 3H), 6.83-6.77 (m, 1H), 6.74-6.69 (m, 2H), 3.35 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.2, 151.9, 150.0, 135.7, 132.7, 129.2, 128.9, 127.6, 125.9, 119.1, 115.1, 41.4.
MS (70 eV, EI) *m/z* (%): 211 (100) [M^+], 210 (14), 194 (32), 182 (36), 168 (38), 167 (37).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3064 (m), 3036 (w), 2925 (w), 2852 (w), 1693 (vs), 1593 (vs), 1498 (vs), 1485 (vs), 1454 (m), 1385 (m), 1343 (m), 1291 (m), 1268 (m), 1249 (m), 1190 (m), 1158 (w), 1132 (m), 1111 (w), 1065 (w), 1031 (w), 869 (w), 821 (m), 775 (m), 751 (s), 694 (m), 639 (w).
HRMS (EI) for **$C_{14}H_{13}NO$** (211.0997): found: 211.0989.

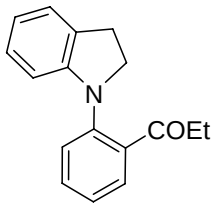
Synthesis of 1-(2-allylphenyl)indoline (59e):



Prepared according to **TP 10** from 2,3-dihydro-1H-indole (119 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), CuCN·2LiCl (0.5 mL, 0.5 equiv., 1.0 M in THF), and allyl bromide (0.21 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane) yielded **59e** as a colourless oil (155 mg, 66 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.32-7.11 (m, 5H), 6.99-6.92 (m, 1H), 6.66 (td, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.3 Hz, 1H), 6.18 (d, ^3J(H,H) = 7.5 Hz, 1H), 6.02-5.87 (m, 1H), 5.07-4.98 (m, 2H), 3.82-3.67 (m, 2H), 3.46-3.40 (m, 2H), 3.15-3.07 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 151.4, 143.8, 138.4, 137.4, 130.3, 130.0, 127.6, 127.1, 126.1, 125.2, 124.5, 117.8, 115.7, 108.1, 55.4, 35.6, 28.9.
MS (70 eV, EI) *m/z* (%): 235 (84) [M^+], 234 (53), 233 (22), 232 (22), 220 (51), 218 (77), 217 (36), 206 (100), 205 (65), 204 (87), 115 (22).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3073 (w), 3025 (w), 2976 (w), 2923 (w), 2847 (w), 1638 (w), 1608 (m), 1597 (m), 1580 (w), 1487 (vs), 1460 (m), 1373 (m), 1328 (w), 1290 (m), 1262 (m), 1224 (m), 1057 (w), 915 (m), 764 (m), 746 (s).
HRMS (EI) for **$C_{17}H_{17}N$** (235.1361): found: 235.1351.

Synthesis of 1-[2-(2,3-dihydro-1*H*-indol-1-yl)phenyl]-1-propanone (59f):

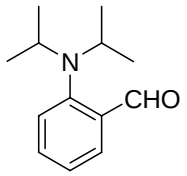


Prepared according to **TP 10** from 2,3-dihydro-1H-indole (119 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), CuCN·2LiCl (1.0 mL, 1.0 equiv., 1.0 M in THF), and propionyl chloride (0.22 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 200 : 1) yielded **59f** as a yellow oil (156 mg, 62 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.42 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.35 (td, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.27 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.12 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.09-7.04 (m, 1H), 6.90 (t, ^3J(H,H) = 7.5 Hz, 1H), 6.64 (td, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 0.9 Hz, 1H), 6.41 (d, ^3J(H,H) = 7.5 Hz, 1H), 3.70 (t, ^3J(H,H) = 8.4 Hz, 2H), 3.03 (t, ^3J(H,H) = 8.4 Hz, 2H), 2.77 (q, ^3J(H,H) = 7.1 Hz, 2H), 0.94 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 206.5, 149.4, 143.2, 137.3, 132.0, 130.5, 129.0, 127.2, 124.8, 124.7, 123.0, 119.1, 108.5, 55.4, 34.9, 28.8, 8.6.
MS (70 eV, EI) *m/z* (%): 251 (100) [M^+], 222 (60), 220 (15), 218 (23), 205 (13), 204 (57), 194 (20), 193 (13), 111 (14).

IR (film) $\tilde{\nu}$ (cm^{-1}): 3066 (w), 3027 (w), 2974 (w), 2936 (w), 2876 (w), 2849 (w), 1688 (s), 1606 (m), 1594 (m), 1572 (w), 1486 (vs), 1460 (s), 1447 (m), 1376 (m), 1334 (w), 1262 (m), 1209 (m), 947 (w), 744 (s).
HRMS (EI) for **$C_{17}H_{17}NO$** (251.1310): found: 251.1286.

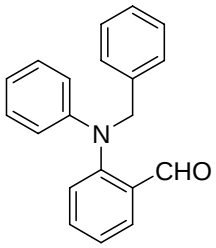
Synthesis of 2-(diisopropylamino)benzaldehyde (59g):



Prepared according to **TP 10** from diisopropylamine (304 mg, 3.0 mmol), *i*-PrMgCl (3.74 mL, 4.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and DMF (0.20 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 200 : 1) yielded **59g** as a yellow oil (51 mg, 25 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.66 (s, 1H), 7.86 (dd, ^3J(H,H) = 7.52 Hz, ^4J(H,H) = 1.77 Hz, 1H), 7.57-7.50 (m, 1H), 7.38-7.33 (m, 1H), 7.30-7.23 (m, 1H), 3.69-3.55 (m, 2H), 0.97 (d, ^3J(H,H) = 6.19 Hz, 12H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 193.9, 151.1, 137.0, 133.6, 129.7, 127.0, 125.4, 49.5, 21.2.
MS (70 eV, EI) *m/z* (%): 205 (16) [M^+], 190 (56), 155 (17), 154 (12), 148 (40), 144 (24), 132 (15), 130 (68), 120 (38), 118 (13), 97 (17), 95 (10), 92 (13), 91 (77), 85 (13), 83 (17), 81 (13), 78 (11), 77 (39), 71 (16), 69 (18), 65 (15), 57 (45), 56 (10), 55 (25), 51 (16), 43 (100), 42 (53), 41 (61).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2971 (m), 2930 (m), 2855 (w), 1690 (vs), 1651 (w), 1593 (m), 1480 (w), 1450 (w), 1382 (w), 1364 (w), 1270 (w), 1234 (w), 1179 (w), 824 (w), 770 (w), 747 (w).
HRMS (EI) for **$C_{13}H_{19}NO$** (205.1467): found: 205.1501.

Synthesis of 2-(benzylanilino)benzaldehyde (59h):



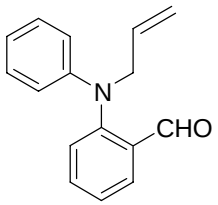
Prepared according to **TP 10** from benzyl-phenyl-amine (549 mg, 3.0 mmol), *i*-PrMgCl (3.76 mL, 4.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) and DMF (0.20 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 200 : 1) yielded **59h** as a yellow oil (92 mg, 32 %).

Prepared according to **TP 10** from benzyl-phenyl-amine (183 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) and DMF (0.20 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 200 : 1) yielded **59h** as a yellow oil (81 mg, 28 %).

Prepared according to **TP 11** from benzyl-phenyl-amine (183 mg, 1.0 mmol), *i*-PrMgCl (2.58 mL, 2.75 equiv., 1.07 M in THF), toluene-4-sulfonic acid 2-iodo-phenyl ester (**19a**) (636 mg, 1.7 mmol) and DMF (0.20 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 200 : 1) yielded **59h** as a yellow oil (204 mg, 71 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.11 (s, 1H), 7.89 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.57 (td, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.34-7.08 (m, 9H), 6.80-6.69 (m, 3H), 4.96 (s, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 190.8, 150.5, 149.9, 138.0, 135.7, 132.9, 129.3, 129.2, 128.6, 128.3, 127.2, 127.1, 126.1, 119.4, 115.7, 57.6.
MS (70 eV, EI) *m/z* (%): 287 (100) [M^+], 286 (16), 270 (37), 210 (16), 209 (28), 196 (40), 195 (12), 182 (12), 180 (17), 168 (17), 167 (41), 166 (11), 106 (13), 91 (95), 77 (15), 65 (10).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2871 (w), 2841 (w), 2748 (w), 1694 (vs), 1591 (s), 1574 (w), 1496 (vs), 1480 (m), 1452 (m), 1392 (m), 1375 (w), 1350 (m), 1291 (w), 1270 (m), 1253 (m), 1229 (w), 1186 (w), 820 (w), 782 (m), 750 (s), 736 (m), 694 (m), 591 (w).
HRMS (EI) for **$C_{20}H_{17}NO$** (287.1310): found: 287.1306.

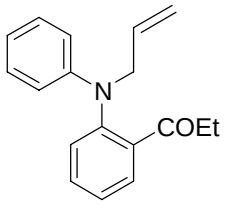
Synthesis of 2-(allyl-phenyl-amino)-benzaldehyde (59i):



Prepared according to **TP 11** from allyl-phenyl-amine (133 mg, 1.0 mmol), *i*-PrMgCl (2.58 mL, 2.75 equiv., 1.07 M in THF), toluene-4-sulfonic acid 2-iodo-phenyl ester (**19a**) (636 mg, 1.7 mmol), and DMF (0.20 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **59i** as a yellow oil (178 mg, 75 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.15 (s, 1H), 7.95 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.64 (td, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.38-7.32 (m, 1H), 7.29 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.0 Hz, 1H), 7.22-7.14 (m, 2H), 6.83-6.77 (m, 1H), 6.74-6.69 (m, 2H), 6.05-5.91 (m, 1H), 5.30-5.18 (m, 2H), 4.39-4.35 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.3, 150.6, 149.3, 135.7, 133.5, 133.1, 129.3, 129.0, 128.7, 126.2, 119.1, 117.8, 115.5, 56.2.
MS (70 eV, EI) *m/z* (%): 238 (17), 237 (95) [M^+], 236 (30), 220 (42), 210 (17), 209 (26), 208 (89), 196 (37), 195 (33), 194 (29), 193 (35), 180 (33), 168 (40), 167 (100), 166 (33), 132 (24), 117 (20), 115 (17), 77 (42), 51 (23).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3066 (w), 2852 (w), 1693 (vs), 1594 (vs), 1497 (vs), 1480 (m), 1454 (m), 1386 (w), 1364 (w), 1268 (m), 1248 (m), 1224 (m), 1190 (m), 924 (w), 820 (w), 749 (m), 694 (m).
HRMS (EI) for **$C_{16}H_{15}NO$** (237.1154): found: 237.1174.

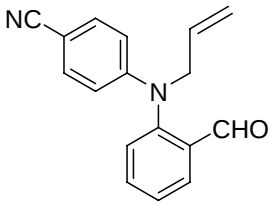
Synthesis of 1-[2-(allyl-phenyl-amino)-phenyl]-propan-1-one (59j):



Prepared according to **TP 11** from allyl-phenyl-amine (133 mg, 1.0 mmol), *i*-PrMgCl (2.58 mL, 2.75 equiv., 1.07 M in THF), toluene-4-sulfonic acid 2-iodo-phenyl ester (**19a**) (636 mg, 1.7 mmol), CuCN·2LiCl (1.0 M in THF, 1.0 mL, 1.0 equiv.) and propionyl chloride (0.44 mL, 5.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **59j** as a yellow oil (204 mg, 77 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.52-7.42 (m, 2H), 7.30-7.24 (m, 2H), 7.21-7.13 (m, 2H), 6.81-6.74 (m, 1H), 6.73-6.67 (m, 2H), 6.01-5.87 (m, 1H), 5.27-5.15 (m, 2H), 4.25-4.21 (m, 2H), 2.75 (q, ^3J(H,H) = 7.1 Hz, 2H), 0.97 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 205.9, 148.1, 145.4, 139.2, 133.7, 131.9, 129.1, 129.0, 128.9, 125.8, 118.6, 117.4, 115.5, 55.6, 35.0, 8.2.
MS (70 eV, EI) *m/z* (%): 265 (57) [M^+], 263 (16), 237 (19), 236 (100), 234 (31), 209 (17), 208 (77), 206 (26), 196 (17), 195 (23), 180 (22), 168 (19), 167 (36), 166 (16), 77 (31).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2979 (w), 2937 (w), 1689 (m), 1600 (m), 1592 (s), 1499 (vs), 1482 (s), 1445 (m), 1368 (m), 1346 (w), 1208 (w), 750 (m), 694 (m), 559 (w).
HRMS (EI) for **$C_{18}H_{19}NO$** (265.1467): found: 265.1476.

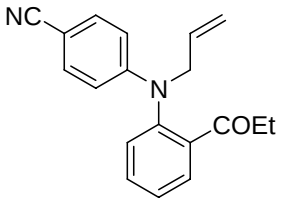
Synthesis of 4-(allyl-2-formylanilino)benzonitrile (59k):



Prepared according to **TP 11** from 4-allylamino-benzonitrile (158 mg, 1.0 mmol), *i*-PrMgCl (2.58 mL, 2.75 equiv., 1.07 M in THF), toluene-4-sulfonic acid 2-iodo-phenyl ester (**19a**) (636 mg, 1.7 mmol) and DMF (0.20 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 5 : 1) yielded **59k** as a yellow oil (191 mg, 73 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.00 (s, 1H), 7.98 (dd, ^3J(H,H) = 7.96 Hz, ^4J(H,H) = 1.77 Hz, 1H), 7.72 (td, ^3J(H,H) = 7.96 Hz, ^4J(H,H) = 1.77 Hz, 1H), 7.49 (td, ^3J(H,H) = 7.96 Hz, ^4J(H,H) = 1.77 Hz, 1H), 7.41-7.35 (m, 2H), 7.30 (dd, ^3J(H,H) = 7.96 Hz, ^4J(H,H) = 1.77 Hz, 1H), 6.62-6.56 (m, 2H), 6.00-5.86 (m, 1H), 5.30-5.21 (m, 2H), 4.37-4.32 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 190.0, 151.7, 147.5, 136.2, 133.4, 133.1, 131.7, 130.1, 129.8, 128.0, 119.7, 118.6, 113.5, 100.1, 55.8.
MS (70 eV, EI) *m/z* (%): 263 (18), 262 (100) [M^+], 261 (26), 245 (31), 235 (16), 234 (20), 233 (68), 221 (27), 220 (19), 219 (25), 218 (25), 205 (21), 193 (21), 192 (64), 191 (14), 132 (19), 117 (12), 102 (13), 77 (11).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2853 (w), 2217 (s), 1694 (s), 1606 (vs), 1594 (vs), 1511 (vs), 1482 (m), 1456 (m), 1379 (m), 1269 (w), 1256 (m), 1224 (w), 1178 (m), 823 (m), 775 (m), 741 (m), 546 (m).
HRMS (EI) for **$C_{17}H_{14}N_2O$** (262.1106): found: 262.1085.

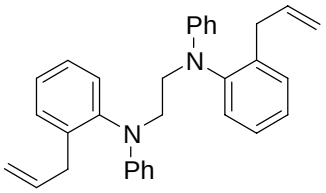
Synthesis of 4-(allyl-2-propionylanilino)benzonitrile (59l):



Prepared according to **TP 11** from 4-allylamino-benzonitrile (158 mg, 1.0 mmol), *i*-PrMgCl (2.58 mL, 2.75 equiv., 1.07 M in THF), toluene-4-sulfonic acid 2-iodo-phenyl ester (**19a**) (636 mg, 1.7 mmol), CuCN·2LiCl (1.0 M in THF, 1.0 mL, 1.0 equiv.) and propionyl chloride (0.44 mL, 5.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 5 : 1) yielded **59l** as a yellow solid (220 mg, 76 %).

mp.: 83.1-84.6 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.63 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.54 (td, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.8 Hz, 1H), 7.44-7.34 (m, 3H), 7.27-7.23 (m, 1H), 6.56-6.51 (m, 2H), 5.96-5.83 (m, 1H), 5.28-5.19 (m, 2H), 4.25-4.20 (m, 2H), 2.70 (q, ^3J(H,H) = 7.08 Hz, 2H), 0.98 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 203.7, 151.1, 143.0, 138.7, 133.2, 132.7, 132.3, 130.2, 129.5, 127.6, 120.0, 117.8, 113.4, 99.4, 55.5, 34.8, 8.0.
MS (70 eV, EI) *m/z* (%): 290 (44) [M^+], 262 (18), 261 (18), 234 (18), 233 (67), 220 (14), 218 (10), 205 (12), 192 (15), 102 (11), 57 (14).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2215 (s), 1683 (s), 1606 (vs), 1593 (m), 1510 (vs), 1483 (m), 1448 (m), 1376 (s), 1342 (m), 1253 (m), 1180 (m), 946 (w), 937 (m), 861 (w), 823 (m), 776 (m), 741 (m), 544 (m), 490 (m).
HRMS (EI) for **$C_{19}H_{18}N_2O$** (290.1419): found: 290.1390.

Synthesis of N,N'-bis-(2-allyl-phenyl)-N,N'-diphenyl-ethane-1,2-diamine (59m):

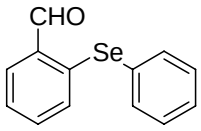


Prepared according to **TP 11** from *N,N'*-diphenyl-ethane-1,2-diamine (107 mg, 0.5 mmol), *i*-PrMgCl (3.62 mL, 6.0 equiv., 0.83 M in THF), toluene-4-sulfonic acid 2-iodo-phenyl ester (**19a**) (748 mg, 2.0 mmol), CuCN·2LiCl (0.5 mL, 0.5 equiv., 1.0 M in THF) and allyl bromide (0.34 mL, 4.0 mmol). Purification by flash chromatography (*n*-pentane) yielded **59m** as a white solid (130 mg, 57 %).

mp.: 113.3-114.1 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.38-7.24 (m, 6H), 7.19-7.14 (m, 2H), 7.12-7.04 (m, 4H), 6.69-6.63 (m, 2H), 6.42-6.36 (m, 4H), 5.89-5.75 (m, 2H), 5.02-4.91 (m, 4H), 3.87 (s, 4H), 3.23-3.18 (m, 4H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 148.4, 144.5, 139.1, 136.6, 130.9, 129.7, 129.1, 128.1, 127.0, 117.1, 116.3, 112.9, 49.0, 35.1.
MS (70 eV, EI) *m/z* (%): 444 (8) [M^+], 223 (15), 222 (100), 194 (12).

IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3064 (w), 3024 (w), 2976 (w), 2941 (w), 1641 (w), 1594 (s), 1574 (m), 1499 (vs), 1464 (w), 1448 (m), 1374 (m), 1340 (m), 1298 (m), 1255 (m), 1206 (m), 1189 (w), 1120 (w), 1069 (w), 990 (w), 915 (m), 761 (m), 747 (s), 693 (m), 582 (w).
HRMS (EI) for **$C_{32}H_{32}N_2$** (444.2565): found: 444.2570.

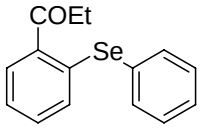
Synthesis of 2-(phenylselanyl)benzaldehyde (60a):



Prepared according to **TP 12** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.41 mL, 3.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) and DMF (0.20 mL, 2.5 equiv.). Purification by flash chromatography (*n*-pentane/diethyl ether = 50 : 1) yielded **60a** as a yellow solid (223 mg, 85 %).

mp.: 54.8-56.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.15 (s, 1H), 7.82-7.78 (m, 1H), 7.64-7.60 (m, 2H), 7.45-7.22 (m, 5H), 7.03-6.99 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 192.4, 139.4, 136.6, 134.9, 133.7, 133.6, 129.9, 129.7, 129.0, 128.1, 125.4.
MS (70 eV, EI) *m/z* (%): 262 (100) [M^+], 261 (26), 260 (45), 259 (23), 258 (18), 232 (17), 184 (28), 154 (43), 152 (18), 77 (14).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3064 (w), 2863 (w), 2742 (w), 1689 (m), 1666 (vs), 1581 (m), 1552 (m), 1477 (w), 1453 (s), 1439 (m), 1391 (m), 1301 (m), 1254 (w), 1200 (s), 1120 (w), 1034 (m), 1022 (w), 1000 (w), 842 (m), 759 (s), 736 (m), 688 (m), 660 (m), 650 (w), 479 (w).
HRMS (EI) for **$C_{13}H_{10}OSe$** (261.9897): found: 261.9894.

Synthesis of 1-[2-(phenylselanyl)phenyl]-1-propanone (60b):



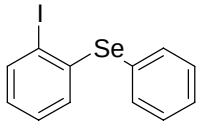
Prepared according to **TP 12** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.41 mL, 3.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), CuCN·2LiCl (1.0 M in THF, 1.0 mL, 1.0 equiv.) and propionyl chloride (0.22 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **60b** as a yellow oil (253 mg, 87 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.96-7.91 (m, 1H), 7.69-7.64 (m, 2H), 7.44-7.34 (m, 3H), 7.21-7.12 (m, 2H), 7.01-6.94 (m, 1H), 3.03 (q, ^3J(H,H) = 7.5 Hz, 2H), 1.26 (t, ^3J(H,H) = 7.5 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.3, 140.1, 137.2, 133.6, 132.2, 130.5, 129.6, 129.5, 129.5, 128.9, 124.5, 32.1, 8.2.
MS (70 eV, EI) *m/z* (%): 290 (73) [M^+], 288 (35), 287 (12), 286 (14), 263 (18), 262 (14), 261 (100), 259 (48), 258 (16), 257 (18), 232 (39), 230 (20), 213 (15), 185 (13), 153 (13), 152 (35), 77 (19).

IR (film) $\tilde{\nu}$ (cm^{-1}): 3056 (w), 2977 (w), 2937 (w), 1667 (vs), 1585 (m), 1557 (w), 1460 (m), 1434 (m), 1378 (w), 1351 (w), 1268 (w), 1219 (s), 1139 (w), 1034 (w), 1021 (w), 1012 (w), 954 (m), 743 (s), 695 (m).
HRMS (EI) for **$C_{15}H_{14}OSe$** (290.0210): found: 290.0215.

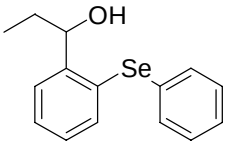
Synthesis of 2-iodophenyl phenyl selenide (60c):



Prepared according to **TP 12** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.41 mL, 3.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol), and iodine (508 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane) yielded **60c** as a white solid (281 mg, 78 %).

mp.: 77.4-78.0 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.78 (dd, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.4 Hz, 1H), 7.67-7.62 (m, 2H), 7.46-7.36 (m, 3H), 7.16-7.10 (m, 1H), 6.93-6.84 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 194.2, 140.6, 139.4, 135.8, 130.2, 129.8, 128.8, 128.7, 127.4, 99.5.
MS (70 eV, EI) *m/z* (%): 362 (17), 361 (12), 360 (100) [M^+], 358 (50), 357 (17), 356 (17), 234 (14), 233 (38), 232 (53), 231 (20), 230 (31), 229 (15), 153 (11), 152 (42), 77 (13), 51 (10).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1438 (s), 1419 (m), 1001 (m), 746 (s), 738 (s), 689 (m).
HRMS (EI) for **$C_{12}H_9ISe$** (359.8914): found: 359.8897.

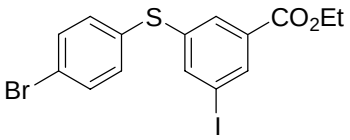
Synthesis of 1-(2-phenylselanyl-phenyl)-propan-1-ol (60d):



Prepared according to **TP 12** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.41 mL, 3.0 equiv., 1.07 M in THF), 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol) and propionaldehyde (145 mg, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 15 : 1) yielded **60d** as an orange oil (218 mg, 75 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.55 (dd, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.4 Hz, 1H), 7.47-7.25 (m, 7H), 7.14 (td, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.6 Hz, 1H), 5.18 (t, ^3J(H,H) = 6.2 Hz, 1H), 1.98 (s, 1H), 1.76 (dq, ^3J(H,H) = 6.2 Hz, ^3J(H,H) = 7.2 Hz, 2H), 0.96 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 146.4, 134.5, 132.6, 131.4, 129.5, 129.3, 128.1, 128.0, 127.2, 126.5, 74.4, 31.2, 10.3.
MS (70 eV, EI) *m/z* (%):292 (48) [M^+], 263 (10), 245 (9), 185 (100), 157 (31), 133 (14), 105 (21), 77 (35), 51 (11).
IR (film) $\tilde{\nu}$ (cm^{-1}): 4066 (w), 3057 (m), 2964 (s), 2931 (m), 1578 (m), 1477 (s), 1463 (s), 1438 (vs), 1021 (m), 975 (m), 754 (vs), 690 (s), 480 (m).
HRMS (EI) for **$C_{15}H_{16}OSe$** (292.0366): found: 292.0341.

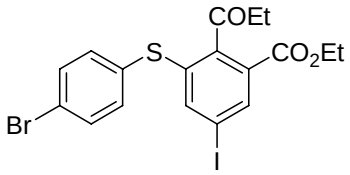
Synthesis ethyl 3-[(4-bromophenyl)sulfanyl]-5-iodo-benzoate (62a):



Prepared according to **TP 9** from 4-bromothiophenol (190 mg, 1.0 mmol), *i*-PrMgCl (1.41 mL, 3.0 equiv., 1.07 M in THF), ethyl 2-{[(4-chlorophenyl)sulfonyl]oxy}-3,5-diiodobenzoate (**27d**) (296 mg, 0.5 mmol). Purification by flash chromatography (*n*-pentane) yielded **62a** as a white solid (176 mg, 76 %).

mp.: 78.8-79.7 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.20 (t, ^4J(H,H) = 1.6 Hz, 1H), 7.90 (t, ^4J(H,H) = 1.6 Hz, 1H), 7.74 (t, ^4J(H,H) = 1.6 Hz, 1H), 7.49-7.44 (m, 2H), 7.26-7.21 (m, 2H), 4.35 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.37 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 164.3, 142.1, 138.7, 136.8, 133.5, 132.9, 132.8, 132.7, 130.2, 122.4, 94.3, 61.6, 14.2.
MS (70 eV, EI) *m/z* (%): 465 (17), 464 (100), 463 (15), 462 (93) [M^+], 436 (11), 434 (12), 419 (12), 417 (13), 310 (18), 228 (12), 284 (15), 183 (18), 139 (16), 75 (16).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1718 (s), 1708 (m), 1552 (m), 1472 (m), 1425 (w), 1362 (w), 1271 (vs), 1140 (w), 1024 (w), 1010 (m), 871 (w), 819 (w), 764 (m), 751 (w), 717 (w), 489 (w).
HRMS (EI) for **$C_{15}H_{12}{}^{79}BrIO_2S$** (461.8786): found: 461.8769.

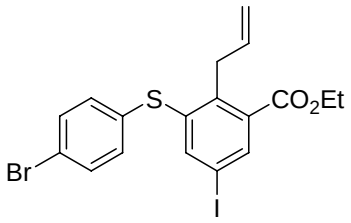
Synthesis of ethyl 3-[(4-bromophenyl)sulfanyl]-5-iodo-2-propionylbenzoate (62b):



Prepared according to **TP 9** from 4-bromothiophenol (190 mg, 1.0 mmol), *i*-PrMgCl (1.41 mL, 3.0 equiv., 1.07 M in THF), ethyl 2-{[(4-chlorophenyl)sulfonyl]oxy}-3,5-diiodobenzoate (**27d**) (296 mg, 0.5 mmol), CuCN·2LiCl (0.5 mL, 1.0 equiv., 1.0 M in THF) and propionyl chloride (0.17 mL, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 200 : 1) yielded **62b** as a yellow solid (176 mg, 68 %).

mp.: 134.4-135.7 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.26 (d, ^4J(H,H) = 1.8 Hz, 1H), 7.76 (d, ^4J(H,H) = 1.8 Hz, 1H), 7.46-7.40 (m, 2H), 7.17-7.11 (m, 2H), 4.33 (q, ^3J(H,H) = 7.1 Hz, 2H), 2.84 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.35 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.23 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 205.3, 163.8, 146.0, 145.3, 138.6, 133.5, 133.5, 132.6, 132.4, 129.6, 122.1, 94.0, 62.2, 37.3, 14.0, 7.5.
MS (70 eV, EI) *m/z* (%): 520 (46), 518 (43) [M^+], 492 (19), 491 (100), 490 (18), 489 (95), 474 (13), 463 (61), 462 (16), 461 (59), 446 (14), 445 (69), 444 (13), 443 (66), 382 (18), 365 (12), 338 (43), 335 (11), 318 (16), 317 (14), 316 (13), 183 (20), 182 (32), 139 (11), 57 (26).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 1716 (vs), 1698 (vs), 1558 (m), 1469 (m), 1283 (vs), 1257 (s), 1210 (m), 1129 (w), 1105 (w), 1069 (w), 1022 (w), 1010 (m), 948 (m), 820 (m), 792 (w), 772 (w).
HRMS (EI) for **$C_{18}H_{16}{}^{79}BrIO_3S$** (517.9048): found: 517.9089.

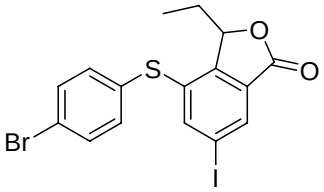
Synthesis of ethyl 2-allyl-3-[(4-bromophenyl)sulfanyl]-5-iodobenzoate (62c):



Prepared according to **TP 9** from 4-bromothiophenol (190 mg, 1.0 mmol), *i*-PrMgCl (1.41 mL, 3.0 equiv., 1.07 M in THF), ethyl 2-{[(4-chlorophenyl)sulfonyl]oxy}-3,5-diiodobenzoate (**27d**) (296 mg, 0.5 mmol), CuCN·2LiCl (0.25 mL, 0.5 equiv., 1.0 M in THF) and allyl bromide (0.17 mL, 2.0 mmol). Purification by flash chromatography (*n*-pentane) yielded **62c** as a yellow solid (181 mg, 72 %).

mp.: 54.1-55.2 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.00 (d, ^4J(H,H) = 1.8 Hz, 1H), 7.63 (d, ^4J(H,H) = 1.8 Hz, 1H), 7.47-7.41 (m, 2H), 7.15-7.09 (m, 2H), 5.96-5.82 (m, 1H), 5.05-4.89 (m, 2H), 4.35 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.90-3.86 (m, 2H), 1.38 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.2, 143.3, 140.4, 139.0, 138.0, 135.4, 134.2, 134.1, 132.6, 132.5, 121.7, 116.2, 91.3, 61.6, 34.6, 14.2.
MS (70 eV, EI) *m/z* (%): 504 (100), 502 (99) [M^+], 489 (51), 487 (49), 461 (31), 459 (29), 457 (27), 443 (87), 441 (82), 378 (59), 377 (32), 376 (50), 301 (72), 222 (41), 221 (61), 192 (65), 115 (62).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3078 (w), 2979 (w), 2933 (w), 1724 (vs), 1635 (w), 1556 (w), 1472 (m), 1433 (w), 1385 (w), 1365 (w), 1254 (s), 1185 (w), 1123 (w), 1096 (m), 1069 (w), 1009 (m), 915 (w), 817 (m), 784 (w).
HRMS (EI) for **$C_{18}H_{16}{}^{79}BrIO_2S$** (501.9099): found: 501.9115.

Synthesis of 4-[(4-bromophenyl)sulfanyl]-3-ethyl-6-iodo-2-benzofuran-1(3*H*)-one (62d):

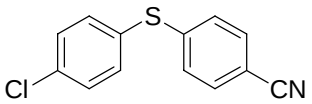


Prepared according to **TP 9** from 4-bromothiophenol (190 mg, 1.0 mmol), *i*-PrMgCl (1.41 mL, 3.0 equiv., 1.07 M in THF), ethyl 2-{[(4-chlorophenyl)sulfonyl]oxy}-3,5-diiodobenzoate (**27d**) (296 mg, 0.5 mmol), propionaldehyde (0.15 mL, 4.0 equiv.). Purification by flash chromatography (*n*-pentane/diethyl ether = 200 : 1) yielded **62d** as a yellow oil (152 mg, 64 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.08 (d, ^4J(H,H) = 1.3 Hz, 1H), 7.67 (d, ^4J(H,H) = 1.3 Hz, 1H), 7.54-7.49 (m, 2H), 7.25-7.19 (m, 2H), 5.26 (dd, ^3J(H,H) = 7.1 Hz, ^3J(H,H) = 3.1 Hz, 1H), 2.44-2.30 (m, 1H), 1.96-1.80 (m, 1H), 0.87 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 168.1, 147.9, 143.3, 133.5, 133.2, 133.2, 133.1, 130.8, 129.5, 123.1, 94.7, 82.2, 25.4, 8.5.
MS (70 eV, EI) *m/z* (%): 476 (69), 474 (67) [M^+], 447 (21), 445 (21), 419 (17), 417 (19), 367 (18), 366 (100), 365 (36), 338 (18), 183 (24), 182 (20), 139 (17).

IR (film) $\tilde{\nu}$ (cm^{-1}): 3065 (w), 2969 (m), 2934 (m), 2877 (w), 1770 (vs), 1588 (m), 1568 (m), 1472 (s), 1442 (m), 1385 (m), 1333 (m), 1276 (m), 1232 (m), 1173 (m), 1110 (m), 1087 (m), 1068 (s), 1008 (m), 969 (m), 868 (m), 817 (m), 779 (m), 729 (w), 481 (m).
HRMS (EI) for **$C_{16}H_{12}{}^{79}BrIO_2S$** (473.8786): found: 473.8790.

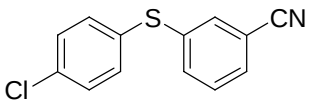
Synthesis of 4-(4-chloro-phenylsulfanyl)-benzonitrile (63a-H):



A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 4-chlorothiophenol (298 mg, 2.0 mmol) in dry THF (4 mL). After cooling to −78 °C, *i*-PrMgCl (4.0 mL, 3.0 equiv., 0.75 M in THF) was added dropwise and stirred for 10 min. 4-{[(4-Chlorophenyl)sulfonyl]oxy}-3-iodobenzonitrile (**27q**) (420 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter, the resulting mixture was warmed to 25 °C and stirred for 8 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane) yielded **63a-H** as a white solid (94 mg, 38 %) and **63b-H** as a white solid (61 mg, 25 %)

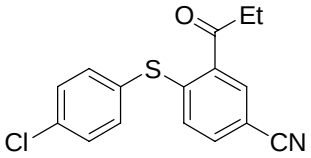
mp.: 87.8-89.2 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.52-7.47 (m, 2H), 7.46-7.36 (m, 4H), 7.20-7.15 (m, 2H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 144.9, 135.7, 135.5, 132.5, 130.1, 129.6, 127.6, 118.6, 109.2.
MS (70 eV, EI) *m/z* (%): 247 (33), 246 (16), 245 (100) [M^+], 210 (66), 209 (40), 183 (10), 108 (14), 75 (16).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2224 (vs), 1592 (s), 1571 (w), 1488 (m), 1474 (s), 1405 (w), 1390 (w), 1095 (m), 1084 (s), 1014 (m), 839 (w), 826 (m), 820 (m), 545 (m), 502 (m).
HRMS (EI) for **$C_{13}H_8{}^{35}ClNS$** (245.0066): found: 245.0079.

Synthesis of 3-(4-chloro-phenylsulfanyl)-benzonitrile (63b-H):



mp.: 86.1-87.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.49-7.41 (m, 3H), 7.40-7.34 (m, 5H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 139.2, 135.1, 134.4, 133.1, 131.9, 131.0, 130.0, 129.9, 129.7, 118.1, 113.5.
MS (70 eV, EI) *m/z* (%): 247 (42), 246 (19), 245 (100) [M^+], 244 (10), 211 (12), 210 (76), 209 (45), 183 (12), 108 (15).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2226 (s), 1592 (s), 1564 (m), 1488 (m), 1476 (vs), 1405 (w), 1390 (m), 1095 (m), 1084 (s), 1014 (s), 827 (s), 820 (s), 792 (m), 746 (w), 683 (m), 545 (m), 504 (m).
HRMS (EI) for **$C_{13}H_8{}^{35}ClNS$** (245.0066): found: 245.0075.

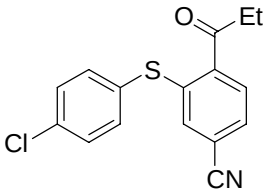
Synthesis of 4-(4-chloro-phenylsulfanyl)-3-propionyl-benzonitrile (64a):



A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 4-chlorothiophenol (298 mg, 2.0 mmol) in dry THF (4 mL). After cooling to −78 °C, *i*-PrMgCl (4.0 mL, 3.0 equiv., 0.75 M in THF) was added dropwise and stirred for 10 min. 4-{[(4-Chlorophenyl)sulfonyl]oxy}-3-iodobenzonitrile (**27q**) (420 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter, the resulting mixture was warmed to 25 °C and stirred for 8 h. The reaction mixture was cooled to −78 °C, and then CuCN·2LiCl (1.0 M in THF; 1.0 mL, 1.0 equiv.) was added and stirred for 20 min. Propionyl chloride (0.34 mL, 4.0 mmol, 4.0 equiv.) was added at −78 °C, and the solution was allowed to warm to 25 °C and kept stirring for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane) yielded **64a** as a pale yellow solid (103 mg, 34 %) and **64b** as a yellow solid (70 mg, 23 %).

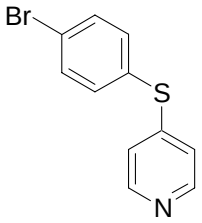
mp.: 101.0-101.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.11 (d, ^4J(H,H) = 1.8 Hz, 1H), 7.48-7.41 (m, 5H), 6.89 (d, ^3J(H,H) = 8.5 Hz, 1H), 3.03 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.27 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 199.8, 149.0, 136.8, 136.4, 134.0, 133.6, 133.4, 130.4, 129.7, 127.9, 117.9, 107.8, 33.0, 8.0.
MS (70 eV, EI) *m/z* (%): 303 (16), 301 (41) [M^+], 274 (38), 273 (17), 272 (100), 237 (28), 209 (37), 208 (11), 164 (17).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2941 (m), 2879 (m), 2229 (m), 1733 (vs), 1681 (m), 1597 (w), 1475 (w), 1462 (m), 1381 (w), 1352 (w), 1185 (s), 1116 (m), 1094 (m), 1084 (m), 1013 (w), 822 (w).
HRMS (EI) for **$C_{16}H_{12}{}^{35}ClNOS$** (301.0328): found: 301.0314.

Synthesis of 3-(4-chloro-phenylsulfanyl)-4-propionyl-benzonitrile (64b):



mp.: 82.8-84.2 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.85 (d, ^3J(H,H) = 8.0 Hz, 1H), 7.47-7.43 (m, 5H), 7.12 (d, ^4J(H,H) = 1.5 Hz, 1H), 3.02 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.27 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.2, 193.7, 143.0, 137.6, 136.4, 131.3, 130.5, 129.9, 129.7, 127.8, 117.6, 115.6, 33.7, 8.1.
MS (70 eV, EI) *m/z* (%): 303 (16), 301 (43) [M^+], 274 (38), 273 (16), 272 (100), 237 (25), 209 (34), 164 (16), 162 (16), 139 (16).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2919 (s), 2230 (w), 1732 (w), 1681 (m), 1463 (m), 1384 (m), 1213 (w), 1094 (m), 1014 (w), 827 (w).
HRMS (EI) for **$C_{16}H_{12}{}^{35}ClNOS$** (301.0328): found: 301.0302.

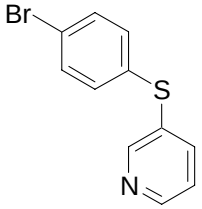
Synthesis of 4-(4-bromo-phenylsulfanyl)-pyridine (67a):



A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-bromothiophenol (380 mg, 2.0 mmol) in dry THF (5 mL). After cooling to −78 °C, *i*-PrMgCl (2.81 mL, 3.0 equiv., 1.07 M in THF) was then added dropwise and stirred for 10 min. 4-Chloro-benzenesulfonic acid 4-iodo-pyridin-3-yl ester (**39a**) (395 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter the resulting mixture was warmed to 25 °C and stirred for 2.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **67a** as a yellow solid (141 mg, 53 %) and **67b** as a yellow oil (85 mg, 32 %), respectively.

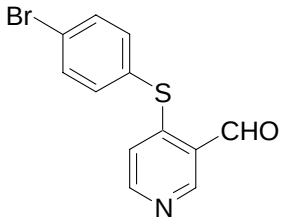
mp.: 70.5-71.8 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.34 (d, ^3J(H,H) = 5.3 Hz, 2H), 7.60-7.52 (m, 2H), 7.44-7.34 (m, 2H), 6.99-6.98 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 149.5, 149.4, 136.4, 133.1, 128.7, 124.2, 120.9.
MS (70 eV, EI) *m/z* (%): 265 (100) [M^+], 186 (60), 154 (5), 115 (14), 93 (10), 78 (7), 51 (4).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3044 (w), 1567 (m), 1472 (m), 1405 (m), 1386 (m), 1189 (w), 1086 (m), 1008 (m), 814 (m), 705 (m), 618 (m).
HRMS (EI) for **$C_{11}H_8{}^{79}BrNS$** (264.9561): found: 264.9586.

Synthesis of 3-(4-bromo-phenylsulfanyl)-pyridine (67b):



^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.58 (d, ^4J(H,H) = 1.9 Hz, 1H), 8.51 (dd, ^3J(H,H) = 4.9 Hz, ^4J(H,H) = 1.3 Hz, 1H), 7.66-7.59 (m, 1H), 7.51-7.42 (m, 2H), 7.29-7.20 (m, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 151.2, 148.1, 138.4, 133.4, 132.8, 132.5, 124.0, 121.9.
MS (70 eV, EI) *m/z* (%): 265 (100) [M^+], 240 (4), 186 (50), 154 (4), 115 (7), 93 (6).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3045 (w), 1630 (w) 1552 (vs), 1467 (s), 1404 (s), 1382 (m), 1087 (m), 1067 (m), 1008 (s), 818 (s), 805 (s), 699 (m), 528 (m), 491 (s).
HRMS (EI) for **$C_{11}H_8{}^{79}BrNS$** (264.9561): found: 264.9568.

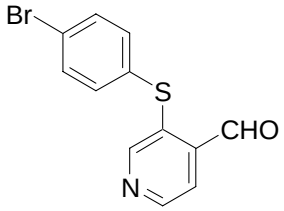
Synthesis of 4-(4-bromo-phenylsulfanyl)-pyridine-3-carbaldehyde (69a):



A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-bromothiophenol (380 mg, 2.0 mmol) in dry THF (5 mL). After cooling to −78 °C, *i*-PrMgCl (2.81 mL, 3.0 equiv., 1.07 M in THF) was then added dropwise and stirred for 10 min. 4-Chloro-benzenesulfonic acid 4-iodo-pyridin-3-yl ester (**39a**) (395 mg, 1.00 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter the resulting mixture was warmed to 25 °C and stirred for 2.5 h. The reaction mixture was cooled to −78 °C, added with DMF (219 mg, 3.00 mmol), warmed to 25 °C, and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 5 : 1) yielded **69a** as a pale yellow solid (147 mg, 50 %) and **69b** as a yellow solid (91 mg, 31 %), respectively.

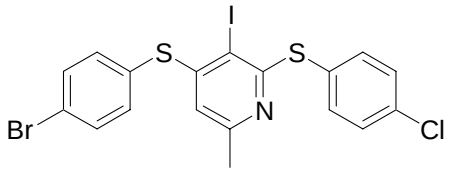
mp.: 89.8-91.0 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.22 (s, 1H), 8.90 (s, 1H), 8.37 (d, ^3J(H,H) = 5.8 Hz, 1H), 7.68-7.61 (m, 2H), 7.47-7.39 (m, 2H), 6.67 (d, ^3J(H,H) = 5.8 Hz, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 190.3, 154.9, 154.4, 152.1, 137.3, 133.6, 127.6, 125.4, 120.4, 112.6.
MS (70 eV, EI) *m/z* (%): 295 (76) [M^+], 266 (6), 185 (24), 137 (100), 105 (18), 77 (6), 50 (4).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3081 (w), 2849 (w), 2760 (w), 1684 (vs), 1576 (s), 1523 (s), 1466 (s), 1358 (s), 1256 (m), 1183 (s), 1066 (s), 1008 (vs), 816 (vs), 730 (m), 685 (m), 479 (m).
HRMS (EI) for **$C_{12}H_8{}^{79}BrNOS$** (294.9510): found: 294.9511.

Synthesis of 3-(4-bromo-phenylsulfanyl)-pyridine-4-carbaldehyde (69b):



mp.: 85.7-87.3 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.39 (s, 1H), 8.65 (d, ^3J(H,H) = 4.9 Hz, 1H), 8.43 (s, 1H), 7.66 (d, ^3J(H,H) = 4.9 Hz, 1H), 7.55-7.48 (m, 2H), 7.33-7.25 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 190.6, 152.1, 148.3, 138.9, 134.2, 133.1, 131.2, 123.3, 123.1, 112.6.
MS (70 eV, EI) *m/z* (%): 265 (100) [M^+], 266 (25), 214 (30), 185 (54), 137 (18), 109 (9).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3080 (w), 2843 (w), 2752 (w), 1925 (w), 1691 (vs), 1467 (s), 1387 (s), 1387 (m), 1204 (m), 1138 (m), 1067 (m), 1009 (s), 826 (s), 729 (m), 658 (m), 525 (m), 480 (m).
HRMS (EI) for **$C_{12}H_8{}^{79}BrNOS$** (294.9510): found: 294.9471.

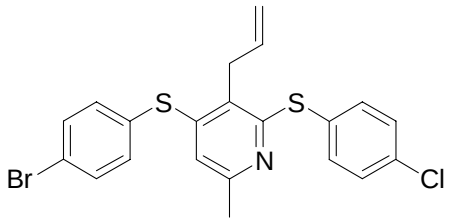
Synthesis of 4-(4-bromo-phenylsulfanyl)-2-(4-chloro-phenylsulfanyl)-3-iodo-6-methyl-pyridine (70a):



A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-bromothiophenol (190 mg, 1.0 mmol) in dry THF (1 mL). After cooling to −78 °C, *i*-PrMgCl·LiCl (1.41 mL, 3.0 equiv., 1.07 M in THF) was then added dropwise and stirred for 10 min. 4-Chloro-benzenesulfonic acid 4-bromo-2-(4-chloro-phenylsulfanyl)-6-methyl-pyridin-3-yl ester (**39f**) (253 mg, 0.5 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter the resulting mixture was warmed to 25 °C and stirred for 1 h. The reaction mixture was cooled to −78 °C, added with iodine (508 mg, 2.0 mmol), warmed to 25 °C, and stirred for 1 h. The reaction was quenched with 5 % aqueous $Na_2S_2O_3$ and saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 50 : 1) yielded **70a** as a white solid (182 mg, 66 %).

mp.: 216.1-217.7 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.63-7.58 (m, 2H), 7.47-7.38 (m, 4H), 7.37-7.32 (m, 2H), 6.02 (s, 1H), 2.08 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 161.3, 157.7, 155.4, 137.4, 136.5, 135.2, 133.8, 131.6, 130.1, 129.4, 125.2, 117.0, 89.7, 24.3.
MS (70 eV, EI) *m/z* (%): 551 (27), 550 (27), 549 (83) [M^+], 548 (44), 547 (56), 546 (23), 424 (25), 423 (30), 422 (83), 421 (52), 420 (100), 419 (29), 418 (39), 386 (17), 342 (19), 341 (16), 340 (38), 257 (22), 256 (22), 229 (20), 196 (22), 171 (21), 153 (29), 152 (17), 108 (31).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 1538 (m), 1502 (m), 1468 (m), 1434 (w), 1384 (m), 1309 (m), 1091 (m), 1084 (w), 1066 (w), 1010 (m), 992 (M), 817 (s), 786 (m), 745 (m), 730 (m), 718 (w).
HRMS (EI) for **$C_{18}H_{12}{}^{79}Br^{35}ClINS_2$** (546.8328): found: 546.8322.

Synthesis of 3-allyl-4-(4-bromo-phenylsulfanyl)-2-(4-chloro-phenylsulfanyl)-6-methyl-pyridine (71a):

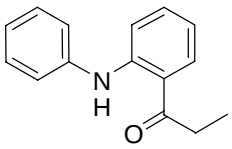


A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-bromothiophenol (190 mg, 1.0 mmol) in dry THF (1 mL). After cooling to −78 °C, *i*-PrMgCl·LiCl (1.41 mL, 3.0 equiv., 1.07 M in THF) was then added dropwise and stirred for 10 min. 4-Chloro-benzenesulfonic acid 4-bromo-2-(4-chloro-phenylsulfanyl)-6-methyl-pyridin-3-yl ester (**39f**) (253 mg, 0.5 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter the resulting mixture was warmed to 25 °C and stirred for 1 h. The reaction mixture was cooled to

−78 °C, and then CuCN·2LiCl (1.0 M in THF; 0.5 mL, 0.5 equiv.) was added and stirred for 20 min. Allyl bromide (0.17 mL, 2.0 mmol, 4.0 equiv.) was added at −78 °C, and the solution was allowed to warm to 25 °C and kept stirring for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 200 : 1) yielded **71a** as a white solid (149 mg, 64 %).

mp.: 163.2-164.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.58-7.53 (m, 2H), 7.42-7.27 (m, 6H), 6.36 (s, 1H), 6.01-5.87 (m, 1H), 5.16-5.07 (m, 2H), 3.74-3.69 (m, 2H), 2.19 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 156.4, 156.1, 149.0, 136.1, 134.6, 133.7, 133.2, 133.0, 131.1, 130.1, 128.8, 127.8, 123.8, 118.8, 116.8, 34.0, 24.0.
MS (70 eV, EI) *m/z* (%): 463 (9) [M^+], 462 (7), 461 (6), 450 (33), 449 (23), 448 (100), 447 (17), 446 (69), 368 (14), 97 (18), 95 (12), 85 (13), 83 (16), 71 (19), 69 (18), 57 (28), 55 (19), 43 (20).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 1557 (m), 1518 (m), 1471 (m), 1416 (m), 1385 (w), 1335 (m), 1174 (w), 1090 (s), 1167 (m), 1008 (s), 914 (m), 820 (vs), 802 (s), 777 (s), 746 (m), 730 (m).
HRMS (EI) for **$C_{21}H_{17}{}^{79}Br^{35}ClNS_2$** (460.9674): found: 460.9680.

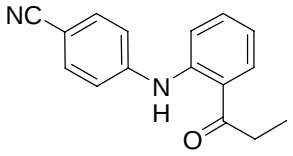
Synthesis of 1-(2-phenylamino-phenyl)-propan-1-one (72a):



A solution of the 1-[2-(allyl-phenyl-amino)-phenyl]-propan-1-one (**59j**) (152 mg, 0.57 mmol) in dry degassed CH_2Cl_2 (1.4 mL) was added with a syringe through a rubber septum cap in a Schlenk tube containing tetrakis(triphenylphosphine)palladium (6.6 mg, 0.0057 mmol, 1 mol %) and *N,N'*-dimethylbarbituric acid (267 mg, 1.71 mmol, 3 equiv.) under agron. The usually homogeneous mixture was stirred at 35 °C for 70 h. After cooling, the CH_2Cl_2 was removed under vacuum and replaced by ether. The ethereal mixture was extracted twice with small volumes of saturated aqueous Na_2CO_3 solution to remove the unreacted *N,N'*-dimethylbarbituric acid and its mono-*C*-allyl derivative. The organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **72a** as a yellow oil (105 mg, 81 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.6 (s, 1H), 7.83-7.79 (m, 1H), 7.34-7.20 (m, 6H), 7.09-7.03 (m, 1H), 6.74-6.65 (m, 1H), 3.01 (q, ^3J(H,H) = 7.3 Hz, 2H), 1.21 (t, ^3J(H,H) = 7.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 203.8, 147.7, 140.4, 134.2, 131.4, 129.3, 123.7, 122.8, 118.7, 116.5, 114.3, 32.5, 8.8.
MS (70 eV, EI) *m/z* (%): 225 (54) [M^+], 197 (14), 196 (100), 168 (10), 167 (27).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3264 (w), 2977 (w), 2937 (w), 1644 (s), 1591 (s), 1573 (s), 1516 (s), 1447 (vs), 1417 (w), 1377 (w), 1320 (m), 1304 (w), 1266 (w), 1243 (w), 1203 (s), 1164 (m), 952 (w), 745 (m), 695 (m).
HRMS (EI) for **$C_{15}H_{15}NO$** (225.1154): found: 225.1164.

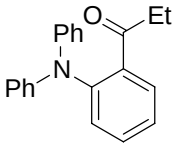
Synthesis of 4-(2-propionyl-phenylamino)-benzonitrile (72b):



A solution of the 4-(allyl-2-propionylanilino)benzonitrile (**59l**) (145 mg, 0.5 mmol) in dry degassed 1,2-dichloroethane (1 mL) was added with a syringe through a rubber septum cap in a Schlenk tube containing tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol, 10 mol %) and *N,N'*-dimethylbarbituric acid (234 mg, 1.5 mmol, 3 equiv.) under agron. The usually homogeneous mixture was stirred at 60 °C for 7 days. After cooling, 1,2-dichloroethane was removed under vacuum and replaced by ether. The ethereal mixture was extracted twice with small volumes of saturated aqueous Na_2CO_3 solution to remove the unreacted *N,N'*-dimethylbarbituric acid and its mono-*C*-allyl derivative. The organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **72b** as a yellow solid (95 mg, 71 %).

mp.: 89.0-89.7 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.7 (s, 1H), 7.89 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 7.56-7.50 (m, 2H), 7.47-7.36 (m, 2H), 7.26-7.21 (m, 2H), 6.91 (ddd, ^3J(H,H) = 8.0 Hz, ^3J(H,H) = 7.1 Hz, ^4J(H,H) = 1.3 Hz, 1H), 3.04 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.21 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 204.3, 145.3, 144.2, 134.1, 133.4, 131.5, 121.2, 119.4, 119.3, 119.2, 116.0, 104.3, 32.8, 8.4.
MS (70 eV, EI): *m/z* (%) 250 (45) [M^+], 222 (15), 221 (100), 192 (16).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3248 (brw), 3252 (w), 2985 (w), 2221 (s), 1643 (s), 1581 (vs), 1518 (vs), 1452 (s), 1412 (w), 1376 (w), 1317 (m), 1303 (m), 1206 (m), 1180 (m), 1162 (m), 953 (m), 851 (m), 751 (m), 551 (m).
HRMS (EI) for **$C_{16}H_{14}N_2O$** (250.1106): found: 250.1104.

Synthesis of 1-(2-diphenylamino-phenyl)-propan-1-one (75):

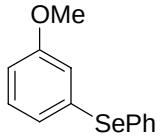


A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 2-Iodophenyl 4-chlorobenzenesulfonate (**27a**) (788 mg, 2.0 mmol) dissolved in dry DME (5 mL). After cooling to −65 °C, *i*-PrMgCl (2.67 mL, 0.75 M in THF) was added dropwise and stirred for 30 min. The other dry and argon-flushed 10 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of diphenylamine (173 mg, 1.0 mmol) in dry DME (2 mL). After cooling to −78 °C, *n*-BuLi (0.625 mL, 1.0 equiv., 1.6 M in *n*-hexane) was added dropwise and then stirred for 30 min leading to lithium diphenylamide. Fresh-prepared lithium diphenylamide was added *via cannula* to the reaction mixture (an additionl 1 mL DME was used to transfer lithium diphenylamide completely) at −65 °C, and the resulting mixture was warmed to −30 °C during 1 h. The reaction mixture was kept stirring at −30 °C for additional 3 h. Thereafter, the resulting mixture was slowly warmed to 0 °C during 2 h. The reaction mixture was cooled to −78 °C, CuCN·2LiCl (1.0 mL, 1.0 equiv., 1.0 M in THF) was added, and the reaction mixture was stirred for 20 min. Then propionyl chloride (0.44 mL, 5.0 mmol)

was added and the resulting mixture was warmed to 25 °C and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 200 : 1) yielded **75** as a yellow solid (90 mg, 30 %).

mp.: 113.3-114.1 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.51-7.45 (m, 2H), 7.35-7.22 (m, 6H), 7.12-7.03 (m, 6H), 2.82 (q, ^3J(H,H) = 7.2 Hz, 2H), 0.92 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 205.2, 147.6, 145.3, 138.3, 131.8, 129.2, 129.1, 128.6, 124.8, 122.9, 122.5, 34.7, 7.8.
MS (70 eV, EI) *m/z* (%): 302 (21), 301 (100) [M^+], 282 (10), 273 (16), 272 (84), 245 (12), 244 (34), 243 (16), 242 (14), 241 (19), 196 (41), 195 (11), 167 (23), 166 (27), 136 (13), 77 (25), 51 (20).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 1675 (m), 1587 (m), 1494 (m), 1479 (m), 1450 (w), 1442 (w), 1297 (m), 1274 (m), 1262 (m), 1206 (m), 950 (w), 772 (w), 751 (s), 737 (m), 696 (vs), 622 (m).
HRMS (EI) for **$C_{21}H_{19}NO$** (301.1467): found: 301.1465.

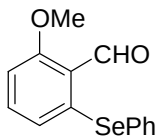
Synthesis of 1-methoxy-3-(phenylseleno)-benzene (77a):



Prepared according to **TP 13** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.01 equiv., 1.07 M in THF) and 2-iodo-3-methoxyphenyl 4-chlorobenzenesulfonate (**27h**) (424 mg, 1.0 mmol). Purification by flash chromatography (*n*-pentane) yielded **77a** as a colourless oil (224 mg, 85 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.53-7.50 (m, 2H), 7.32-7.28 (m, 3H), 7.20 (t, ^3J(H,H) = 8.0 Hz, 1H), 7.07-7.05 (m, 1H), 7.04-7.02 (m, 1H), 6.84-6.81 (m, 1H), 3.77 (s, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 160.0, 133.2, 132.2, 130.8, 130.0, 129.3, 127.4, 124.9, 118.0, 113.1, 55.2.
MS (70 eV, EI) *m/z* (%): 266 (11), 265 (9), 264 (59) [M^+], 262 (30), 261 (12), 260 (11), 185 (13), 184 (100), 169 (12), 154 (16), 141 (21), 77 (10).
IR (film) $\tilde{\nu}$ (cm^{-1}): 1587 (vs), 1574 (s), 1476 (vs), 1438 (m), 1423 (m), 1284 (m), 1244 (s), 1230 (s), 1040 (s), 1022 (m), 737 (m), 687 (m).
HRMS (EI) for **$C_{13}H_{12}OSe$** (264.0053): found: 264.0034.

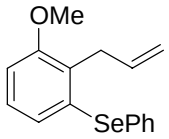
Synthesis of 2-methoxy-6-(phenylseleno)-benzaldehyde (77b):



Prepared according to **TP 13** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.01 equiv., 1.07 M in THF), 2-iodo-3-methoxyphenyl 4-chlorobenzenesulfonate (**27h**) (424 mg, 1.0 mmol) and DMF (0.12 mL, 1.5 equiv.). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **77b** as a yellow solid (207 mg, 70 %).

mp.: 77.4-79.9 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.65 (s, 1H), 7.70-7.66 (m, 2H), 7.46-7.37 (m, 3H), 7.15 (t, ^3J(H,H) = 8.2 Hz, 1H), 6.71 (d, ^3J(H,H) = 8.2 Hz, 1H), 6.47 (d, ^3J(H,H) = 8.2 Hz, 1H), 3.91 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 190.0, 164.0, 142.6, 137.4, 134.4, 129.6, 129.1, 128.6, 122.2, 120.9, 107.1, 55.8.
MS (70 eV, EI) *m/z* (%): 294 (20), 293 (20), 292 (100) [M^+], 291 (29), 290 (49), 289 (28), 288 (22), 215 (21), 214 (52), 212 (28), 135 (21), 134 (19), 77 (25), 76 (19).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2888 (w), 1650 (s), 1579 (s), 1564 (vs), 1463 (s), 1437 (m), 1396 (m), 1295 (w), 1267 (vs), 1212 (w), 1187 (w), 1033 (m), 827 (w), 776 (w), 743 (w), 693 (w).
HRMS (EI) for **$C_{14}H_{12}O_2Se$** (292.0002): found: 292.0027.

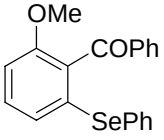
Synthesis of 2-allyl-1-methoxy-3-(phenylseleno)-benzene (77c):



Prepared according to **TP 13** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.01 equiv., 1.07 M in THF), 2-iodo-3-methoxyphenyl 4-chlorobenzenesulfonate (**27h**) (424 mg, 1.0 mmol), CuCN·2LiCl (1.0 M in THF, 0.5 mL, 0.5 equiv.) and allyl bromide (0.21 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane) yielded **77c** as a colourless oil (250 mg, 82 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.48-7.42 (m, 2H), 7.30-7.25 (m, 3H), 7.07 (t, ^3J(H,H) = 8.0 Hz, 1H), 6.95 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.0 Hz, 1H), 6.81 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.0 Hz, 1H), 6.02-5.88 (m, 1H), 5.05-5.01 (m, 1H), 5.00-4.97 (m, 1H), 3.84 (s, 3H), 3.70-3.65 (m, 2H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 157.7, 136.0, 133.6, 133.2, 131.3, 129.9, 129.3, 127.6, 127.2, 126.0, 115.1, 109.7, 55.7, 33.8.
MS (70 eV, EI) *m/z* (%): 306 (21), 305 (17), 304 (100) [M^+], 302 (49), 301 (19), 300 (18), 289 (50), 287 (23), 229 (11), 227 (62), 225 (34), 224 (14), 223 (13), 212 (26), 210 (15), 146 (18), 131 (22), 115 (35), 103 (20), 91 (19), 77 (26), 51 (13).
IR (film) $\tilde{\nu}$ (cm^{-1}): 1570 (s), 1476 (m), 1460 (s), 1435 (s), 1261 (vs), 1215 (m), 1042 (s), 1022 (m), 914 (w), 772 (m), 735 (m), 691 (m).
HRMS (EI) for **$C_{16}H_{16}OSe$** (304.0366): found: 304.0355.

Synthesis of (2-methoxy-6-phenylselanyl-phenyl)-phenyl-methanone (77d):

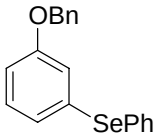


Prepared according to **TP 13** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.01 equiv., 1.07 M in THF), 2-iodo-3-methoxyphenyl 4-chlorobenzenesulfonate (**27h**) (424 mg, 1.0 mmol), CuCN·2LiCl (1.0 M in THF, 1.0 mL, 1.0 equiv.) and benzoyl chloride (211 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **77d** as a pale yellow solid (285 mg, 77 %).

mp.: 116.0-118.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.81-7.76 (m, 2H), 7.55-7.49 (m, 1H), 7.43-7.35 (m, 4H), 7.25-7.15 (m, 4H), 7.00 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 0.8 Hz, 1H), 6.85 (dd, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 0.7 Hz, 1H), 3.67 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 195.8, 157.1, 137.2, 133.8, 133.2, 131.8, 130.6, 130.3, 129.5, 129.2, 128.5, 127.7, 126.2, 110.0, 88.8, 55.8.
MS (70 eV, EI) *m/z* (%): 370 (20), 369 (20), 368 (100) [M^+], 366 (48), 291 (46), 289 (23), 276 (34), 275 (21), 105 (23), 77 (38).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1663 (vs), 1579 (m), 1566 (s), 1458 (s), 1448 (m), 1439 (m), 1429 (s), 1312 (m), 1269 (vs), 1257 (s), 1031 (s), 1021 (m), 928 (s), 836 (m), 778 (m), 742 (s), 706 (s), 694 (m), 655 (m).
HRMS (EI) for **$C_{20}H_{16}O_2Se$** (368.0315): found: 368.0340.

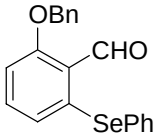
Synthesis of 1-(benzyloxy)-3-(phenylselanyl)benzene (77e):



Prepared according to **TP 13** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.01 equiv., 1.07 M in THF) and 4-chloro-benzenesulfonic acid 3-benzyloxy-2-iodo-phenyl ester (**27i**) (501 mg, 1.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 500 : 1) yielded **77e** as a colourless oil (286 mg, 84 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.55-7.48 (m, 2H), 7.45-7.27 (m, 8H), 7.24-7.18 (m, 1H), 7.12-7.06 (m, 2H), 6.90 (ddd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 2.5 Hz, ^4J(H,H) = 1.0 Hz, 1H), 5.02 (s, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 159.2, 136.6, 133.3, 132.3, 130.6, 130.0, 129.3, 128.5, 128.0, 127.5, 125.1, 118.8, 114.0, 70.0.
MS (70 eV, EI) *m/z* (%): 340 (25) [M^+], 338 (14), 91 (100).
IR (film) $\tilde{\nu}$ (cm^{-1}): 1585 (s), 1573 (s), 1476 (s), 1464 (m), 1455 (m), 1438 (m), 1411 (w), 1384 (m), 1311 (m), 1283 (w), 1242 (s), 1018 (s), 991 (w), 880 (w), 852 (w), 790 (s), 747 (s), 736 (vs), 670 (s).
HRMS (EI) for **$C_{19}H_{16}OSe$** (340.0366): found: 340.0378.

Synthesis of 2-benzyloxy-6-phenylselanyl-benzaldehyde (77f):

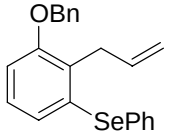


Prepared according to **TP 13** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.01 equiv., 1.07 M in THF), 4-chloro-benzenesulfonic acid 3-benzyloxy-2-iodo-phenyl ester (**27i**) (501 mg, 1.0 mmol) and DMF (0.12 mL, 1.5 equiv.). Purification by flash chromatography (*n*-pentane/diethyl ether = 5 : 1) yielded **77f** as a white solid (265 mg, 72 %).

mp.: 136.1-137.6 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.76 (s, 1H), 7.73-7.68 (m, 2H), 7.50-7.35 (m, 8H), 7.15 (t, ^3J(H,H) = 8.2 Hz, 1H), 6.79 (*pseudo* d, ^3J(H,H) = 8.2 Hz, 1H), 6.52-6.48 (m, 1H), 5.19 (s, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 190.0, 163.1, 142.8, 137.5, 135.9, 134.3, 129.6, 129.1, 128.7, 128.6, 128.3, 127.3, 122.5, 121.2, 108.5, 70.7.
MS (70 eV, EI) *m/z* (%): 368 (37) [M^+], 366 (19), 277 (18), 275 (10), 91 (100).
IR (film) $\tilde{\nu}$ (cm^{-1}): 1655 (vs), 1582 (m), 1570 (m), 1446 (m), 1260 (m), 1038 (m), 774 (m), 743 (m), 734 (m), 696 (m).
HRMS (EI) for **$C_{20}H_{16}O_2Se$** (368.0315): found: 368.0321.

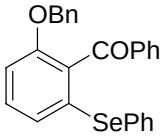
Synthesis of 2-allyl-1-(benzyloxy)-3-(phenylselanyl)benzene (77g):



Prepared according to **TP 13** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.01 equiv., 1.07 M in THF), 4-chloro-benzenesulfonic acid 3-benzyloxy-2-iodo-phenyl ester (**27i**) (501 mg, 1.0 mmol), CuCN·2LiCl (1.0 M in THF, 0.5 mL, 0.5 equiv.) and allyl bromide (0.21 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 500 : 1) yielded **77g** as a colourless oil (283 mg, 74 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.39-7.13 (m, 10H), 6.93 (t, ^3J(H,H) = 7.9 Hz, 1H), 6.85 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.3 Hz, 1H), 6.75 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.3 Hz, 1H), 5.94-5.80 (m, 1H), 4.99 (s, 2H), 4.96-4.88 (m, 2H), 3.65-3.61 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 156.8, 137.1, 135.9, 133.8, 133.3, 131.2, 130.2, 129.3, 128.5, 127.8, 127.6, 127.3, 127.1, 126.2, 115.4, 111.0, 70.3, 34.1.
MS (70 eV, EI) *m/z* (%): 380 (14) [M^+], 289 (13), 211 (13), 132 (14), 91 (100).
IR (film) $\tilde{\nu}$ (cm^{-1}): 1568 (s), 1476 (m), 1447 (vs), 1261 (s), 1214 (s), 1040 (m), 1021 (s), 915 (m), 771 (m), 735 (s), 693 (s).
HRMS (EI) for **$C_{22}H_{20}OSe$** (380.0679): found: 380.0688.

Synthesis of (2-benzyloxy-6-phenylselanyl-phenyl)-phenyl-methanone (77h):

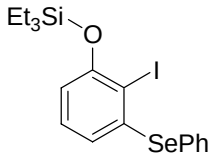


Prepared according to **TP 13** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.01 equiv., 1.07 M in THF), 4-chloro-benzenesulfonic acid 3-benzyloxy-2-iodo-phenyl ester (**27i**) (501 mg, 1.0 mmol), CuCN·2LiCl (1.0 M in THF, 1.0 mL, 1.0 equiv.) and benzoyl chloride (211 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether/CH_2Cl_2 = 50 : 1 : 1) yielded **77h** as a pale yellow solid (338 mg, 76 %).

mp.: 133.2-133.9 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.77-7.72 (m, 2H), 7.49-7.42 (m, 1H), 7.39-7.28 (m, 4H), 7.18-7.06 (m, 7H), 6.94-6.87 (m, 3H), 6.81-6.76 (m, 1H), 4.88 (s, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 195.9, 156.1, 137.4, 136.2, 134.1, 133.1, 131.8, 131.2, 130.6, 130.3, 129.4, 129.2, 128.4, 128.3, 127.8, 127.6, 126.6, 126.1, 111.2, 70.2.
MS (70 eV, EI) *m/z* (%): 446 (9), 445 (11), 444 (41) [M^+], 441 (8), 440 (7), 105 (25), 91 (100), 77 (10).

IR (neat) $\tilde{\nu}$ (cm^{-1}): 3051 (w), 2935 (w), 1639 (s), 1596 (w), 1656 (s), 1441 (s), 1388 (w), 1314 (w), 1279 (m), 1256 (vs), 1158 (w), 1013 (s), 937 (w), 925 (w), 912 (w), 869 (w), 772 (w), 740 (m), 722 (w), 693 (s), 643 (m).
HRMS (EI) for **$C_{26}H_{20}O_2Se$** (444.0628): found: 444.0638.

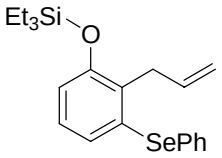
Synthesis of triethyl-(2-iodo-3-phenylselanyl-phenoxy)-silane (77i):



Prepared according to **TP 13** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.01 equiv., 1.07 M in THF), 4-chloro-benzenesulfonic acid 2-iodo-3-triethylsilanyloxy-phenyl ester (**27j**) (525 mg, 1.0 mmol) and iodine (508 mg, 2 mmol). Purification by flash chromatography (*n*-pentane) yielded **77i** as a colourless oil (250 mg, 51 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.60-7.54 (m, 2H), 7.34-7.25 (m, 3H), 6.86 (t, ^3J(H,H) = 7.9 Hz, 1H), 6.51 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.3 Hz, 1H), 6.30 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.3 Hz, 1H), 0.98-0.91 (m, 9H), 0.78-0.69 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 155.7, 142.6, 136.2, 130.7, 129.8, 129.2, 128.9, 122.2, 114.8, 95.3, 6.8, 5.3.
MS (70 eV, EI) *m/z* (%): 490 (44) [M^+], 488 (21), 463 (22), 462 (21), 461 (100), 459 (49), 458 (18), 457 (17), 305 (23).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2956 (m), 2876 (m), 1562 (s), 1440 (vs), 1396 (m), 1284 (s), 1011 (m), 942 (s), 772 (m), 742 (s), 691 (m).
HRMS (EI) for **$C_{18}H_{23}IOSeSi$** (489.9728): found: 489.9770.

Synthesis of (2-allyl-3-phenylselanyl-phenoxy)-triethyl-silane (77j):

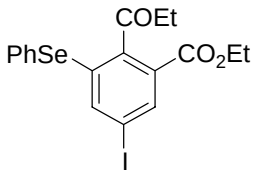


Prepared according to **TP 13** from phenylselenol (157 mg, 1.0 mmol), *i*-PrMgCl (1.88 mL, 2.01 equiv., 1.07 M in THF), 4-chloro-benzenesulfonic acid 2-iodo-3-triethylsilanyloxy-phenyl ester (**27j**) (525 mg, 1.0 mmol), CuCN·2LiCl (1.0 M in THF, 0.5 mL, 0.5 equiv.) and allyl bromide (0.21 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane) yielded **77j** as a light brown liquid (250 mg, 45 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm:7.36-7.30 (m, 2H), 7.19-7.12 (m, 3H), 6.88-6.80 (m, 2H), 6.66-6.61 (m, 1H), 5.90-5.75 (m, 1H), 4.94-4.85 (m, 2H), 3.56-3.51 (m, 2H), 0.95-0.88 (m, 9H), 0.74-0.65 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 154.0, 135.9, 133.7, 133.1, 132.0, 131.4, 129.2, 127.4, 127.1, 126.5, 117.3, 115.2, 34.3, 6.7, 5.3.
MS (70 eV, EI) *m/z* (%): 404 (81) [M^+], 402 (39), 375 (28), 327 (35), 297 (51), 189 (86), 161 (38), 115 (45), 113 (45), 97 (100), 91 (27), 83 (42), 78 (41), 77 (61), 69 (42).

IR (film) $\tilde{\nu}$ (cm^{-1}): 2957 (m), 2877 (m), 1579 (m), 1566 (m), 1451 (vs), 1438 (m), 1271 (s), 951 (s), 733 (s).
HRMS (EI) for **$C_{21}H_{28}OSeSi$** (404.1075): found: 404.1046.

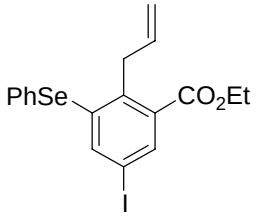
Synthesis of 5-iodo-3-phenylselanyl-2-propionyl-benzoic acid ethyl ester (79a):



A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of phenylselenol (158 mg, 1.0 mmol) in dry THF (2 mL). After cooling to −78 °C, *i*-PrMgCl (1.41 mL, 3.0 equiv., 1.07 M in THF) was then added dropwise and stirred for 10 min. Ethyl 2-{[(4-chlorophenyl)sulfonyl]oxy}-3,5-diiodobenzoate (**27d**) (296 mg, 0.5 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter the resulting mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was cooled to −78 °C, and then CuCN·2LiCl (1.0 M in THF; 0.5 mL, 1.0 equiv.) was added and stirred for 10 min. Thereafter, propionyl chloride (0.17 mL, 2.0 mmol) was added at −78 °C, warmed to 25 °C and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 200 : 1) yielded **79a** as a yellow solid (148 mg, 60 %).

mp.: 64.5-65.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.23 (d, ^4J(H,H) = 1.8 Hz, 1H), 7.82 (d, ^4J(H,H) = 1.8 Hz, 1H), 7.48-7.42 (m, 2H), 7.35-7.29 (m, 3H), 4.33 (q, ^3J(H,H) = 7.1 Hz, 2H), 2.85 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.36 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.26 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 206.0, 164.0, 146.1, 145.9, 138.0, 133.6, 130.3, 129.7, 129.6, 129.3, 128.4, 94.3, 62.1, 37.0, 14.0, 7.6.
MS (70 eV, EI) *m/z* (%): 488 (60) [M^+], 486 (29), 459 (59), 457 (26), 431 (30), 413 (26), 355 (23), 353 (100), 351 (51), 349 (20), 57 (20).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 2938 (w), 1723 (vs), 1700 (s), 1558 (m), 1543 (w), 1438 (w), 1366 (w), 1279 (s), 1253 (s), 1196 (m), 1113 (m), 1020 (w), 948 (w), 868 (w), 785 (w), 765 (w), 742 (m), 722 (w), 692 (m).
HRMS (EI) for **$C_{18}H_{17}IO_3Se$** (487.9388): found: 487.9415.

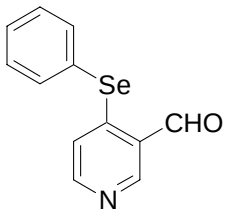
Synthesis of 2-allyl-5-iodo-3-phenylselanyl-benzoic acid ethyl ester (79b):



Prepared according to the same procedure for the preparation of **79a** from phenylselenol (158 mg, 1.0 mmol), *i*-PrMgCl (1.41 mL, 3.0 equiv., 1.07 M in THF), ethyl 2-{[(4-chlorophenyl)sulfonyl]oxy}-3,5-diiodobenzoate (**27d**) (296 mg, 0.5 mmol), CuCN·2LiCl (1.0 M in THF, 0.5 mL, 0.5 equiv.) and allyl bromide (0.21 mL, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 300 : 1) yielded **79b** as a yellow oil (152 mg, 64 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.98 (d, ^4J(H,H) = 1.9 Hz, 1H), 7.66 (d, ^4J(H,H) = 1.9 Hz, 1H), 7.50-7.44 (m, 2H), 7.36-7.30 (m, 3H), 5.99-5.84 (m, 1H), 5.09-4.93 (m, 2H), 4.35 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.92-3.87 (m, 2H), 1.38 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.3, 143.9, 140.1, 137.8, 137.5, 135.5, 134.0, 133.8, 129.7, 128.2, 116.3, 91.5, 61.5, 36.7, 14.2.
MS (70 eV, EI) *m/z* (%): 474 (18), 473 (21), 472 (100) [M^+], 470 (45), 469 (20), 468 (18), 425 (25), 411 (60), 409 (29), 408 (14), 349 (30), 347 814), 240 (25), 191 (19), 115 (39), 91 (15), 77 (16).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3073 (w), 2978 (w), 1718 (vs), 1544 (w), 1476 (w), 1438 (m), 1364 (w), 1243 (s), 1179 (m), 1091 (m), 1019 (m), 911 (w), 780 (w), 736 (m), 689 (m).
HRMS (EI) for **$C_{18}H_{17}IO_2Se$** (471.9438): found: 471.9430.

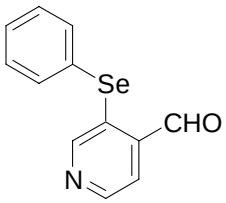
Synthesis of 4-phenylselanyl-pyridine-3-carbaldehyde (80a):



A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of phenylselenol (305 mg, 2.0 mmol) in dry THF (5 mL). After cooling to −78 °C, *i*-PrMgCl (2.81 mL, 3.0 equiv., 1.07 M in THF) was then added dropwise and stirred for 10 min. 4-chloro-benzenesulfonic acid 4-iodo-pyridin-3-yl ester (**39a**) (395 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred vigorously for 30 min at the same temperature. Thereafter the resulting mixture was warmed to 25 °C and stirred for 2.5 h. The reaction mixture was cooled to −78 °C, added with DMF (219 mg, 3.00 mmol), warmed to 25 °C, and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 5 : 1) yielded **80a** as a pale yellow solid (142 mg, 54 %) and **80b** as a yellow solid (84 mg, 32 %), respectively.

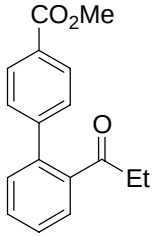
mp.: 94.7-98.2 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.18 (s, 1H), 8.84 (s, 1H), 8.23 (d, ^3J(H,H) = 5.5 Hz, 1H), 7.67-7.60 (m, 2H), 7.53-7.40 (m, 3H), 6.81 (d, ^3J(H,H) = 5.5 Hz, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.1, 155.7, 152.5, 151.9, 137.2, 130.1, 130.0, 129.3, 126.0, 123.3.
MS (70 eV, EI) *m/z* (%):263 (100) [M^+], 234 (17), 185 (58), 157 (16), 127 (6), 115 (9), 105 (15), 77 (19), 51 (16).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3068 (w), 2838 (w), 2745 (w), 1709 (m), 1683 (vs), 1571 (vs), 1524 (m), 1461 (m), 1389 (m), 1255 (m), 1188 (m), 1067 (m), 914 (w), 851 (s), 748 (m), 690 (m), 660 (m), 523 (w), 480 (w).
HRMS (EI) for **$C_{12}H_9NOSe$** (262.9849): found: 262.9846.

Synthesis of 3-phenylselanyl-pyridine-4-carbaldehyde (80b):



mp.: 38.8-41.0 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 10.24 (s, 1H), 8.59 (d, ^3J(H,H) = 4.9 Hz, 1H), 8.31 (s, 1H), 7.68-7.59 (m, 3H), 7.46-7.33 (m, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.9, 151.6, 147.2, 138.5, 136.1, 133.1, 130.0, 129.4, 126.7, 125.6.
MS (70 eV, EI) *m/z* (%):263 (100) [M^+], 234 (32), 185 (24), 155 (32), 127 (6), 115 (7), 105 (6), 77 (16), 51 (9).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 3068 (w), 2820 (w), 1686 (s), 1568 (w), 1466 (m), 1438 (m), 1404 (m), 1276 (m), 1229 (m), 1206 (m), 1156 (m), 1093 (m), 1020 (m), 916 (w), 856 (m), 818 (m9, 744 (m), 693 (m), 657 (m), 513 (w), 480 (m).
HRMS (EI) for **$C_{12}H_9NOSe$** (262.9849): found: 262.9859.

Synthesis of 2'-propionyl-biphenyl-4-carboxylic acid methyl ester (82):

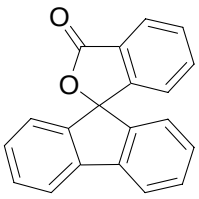


A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of methyl 4-iodobenzoate (294 mg, 1.1 mmol) in dry THF (3 mL). After cooling to −40 °C, *i*-PrMgCl (1.47 mL, 1.1 mmol, 0.75 M in THF) was added dropwise and stirred for 30 min. After cooling to −78 °C, *i*-PrMgCl (1.33 mL, 1.0 mmol, 0.75 M in THF) was added followed by adding 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1.0 mmol; in 2 mL dry THF), and the resulting mixture was stirred vigorously for 30 min at the same temperature. The resulting mixture was immediately warmed to −30 °C and stirred for 1 h. CuCN·2LiCl (1.0 M in THF, 1.0 mL, 1.0 equiv.) was added and stirred for 20 min. After propionyl chloride (0.17 mL, 2.0 mmol) was added at −30 °C, the solution was allowed to warm to 25 °C and stirred for an additional 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **82** as a colourless oil (121 mg, 45 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.10-8.05 (m, 2H), 7.54-7.36 (m, 6H), 3.93 (s, 3H), 2.33 (q, ^3J(H,H) = 7.3 Hz, 2H), 0.92 (t, ^3J(H,H) = 7.3 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 207.6, 166.7, 145.4, 140.7, 138.9, 130.5, 130.1, 129.8, 129.4, 128.7, 128.0, 127.7, 52.1, 36.1, 8.5.
MS (70 eV, EI) *m/z* (%): 268 (6) [M^+], 239 (33), 195 (37), 180 (19), 152 (18), 149 (13), 97 (11), 91 (15), 71 (10), 70 (14), 69 (12), 61 (16), 57 (18), 55 (13), 45 (14), 43 (100), 41 (11).
IR (film) $\tilde{\nu}$ (cm^{-1}): 2978 (w), 2952 (w), 1725 (s), 1693 (m), 1610 (w), 1436 (m), 1312 (w), 1281 (vs), 1213 (w), 1181 (w), 1113 (m), 1103 (m), 781 (w), 755 (m), 707 (w).

HRMS (EI) for **$C_{17}H_{16}O_3$** (268.1099): found: 268.1106.

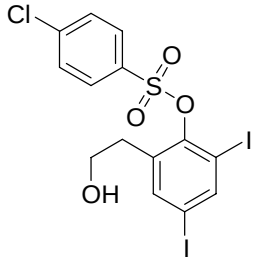
Synthesis of 2'-propionyl-biphenyl-4-carboxylic acid methyl ester (85):



A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of ethyl 2-iodobenzoate (394 mg, 1.4 mmol) in dry THF (3 mL). After cooling to −40 °C, *i*-PrMgCl (1.87 mL, 1.4 mmol, 0.75 M in THF) was added dropwise and stirred for 1 h. After cooling to −78 °C, *i*-PrMgCl (1.33 mL, 1.0 mmol, 0.75 M in THF) was added followed by adding 2-iodophenyl 4-chlorobenzenesulfonate (**27a**) (394 mg, 1 mmol; in 2 mL dry THF), and the resulting mixture was stirred vigorously for 30 min at the same temperature. Thereafter, the resulting mixture was immediately warmed to 25 °C and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **85** as a white solid (141 mg, 70 %).

mp.: 85.1-91.7 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.06-8.02 (m, 1H), 7.75-7.70 (m, 2H), 7.60-7.49 (m, 2H), 7.47-7.40 (m, 2H), 7.25-7.19 (m, 2H), 7.05-7.00 (m, 2H), 6.93-6.89 (m, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 170.5, 150.5, 142.7, 140.7, 134.7, 130.4, 129.5, 128.4, 126.0, 125.6, 124.5, 122.2, 120.5, 91.8.
MS (70 eV, EI) *m/z* (%): 285 (21), 284 (17) [M^+], 255 (15), 241 (14), 240 (83), 239 (86), 237 (18), 228 (16), 226 (12), 142 (11), 128 (10), 113 (15).
IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1763 (s), 1610 (w), 1467 (w), 1451 (w), 1288 (w), 1275 (w), 1230 (m), 1098 (m), 1082 (w), 981 (w), 937 (w), 761 (m), 751 (w), 735 (m), 692 (w).
HRMS (EI) for **$C_{20}H_{12}O_2$** (284.0837): found: 284.0842.

Synthesis of 4-chloro-benzenesulfonic acid 2-(2-hydroxy-ethyl)-4,6-diiodo-phenyl ester (86):

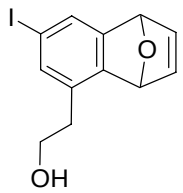


A dry 100 mL round-bottomed flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 4-chloro-benzenesulfonic acid 2-allyl-4,6-diiodo-phenyl ester (**27l**) (2.163 g, 3.86 mmol) in dry THF (40 mL). After cooling to −78 °C, ozone was bubbled through the solution of reaction mixture until the colour of the solution turned blue. N_2 was then bubbled through it to remove excess ozone until the colour of the solution turned colourless. Then the reaction mixture was warmed to 25 °C. BH_3·Me_2S (1.52 mL, 16.0 mmol) was added slowly and the reaction mixture was stirred at 25 °C for 24 h (similar procedure as

reported literature).[114] 1 mL 5 % $HCl_{(aq.)}$ was added, and the resulting mixture was stirred vigorously for 1 h. Solid $NaHCO_3$ was added until the resulting mixture was about pH 7. The reaction was extracted with CH_2Cl_2 (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 5 : 1) yielded **86** as a light brown oil (1.544 g, 71 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.01-7.96 (m, 3H), 7.69 (d, ^4J(H,H) = 2.1 Hz, 1H), 7.60-7.55 (m, 2H), 3.89 (t, ^3J(H,H) = 6.5 Hz, 2H), 3.03 (t, ^3J(H,H) = 6.5 Hz, 2H), 1.63 (s, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 149.4, 146.3, 141.5, 140.4, 137.2, 135.5, 130.2, 129.6, 92.9, 92.2, 61.9, 34.6.
MS (70 eV, EI) *m/z* (%): 564 (5) [M^+], 534 (6), 373 (6), 372 (100), 360 (5), 359 (72), 232 (5), 204 (4), 159 (4), 111 (8), 77 (6), 76 (8), 75 (6), 51 (4), 50 (4).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3370 (brw), 2944 (w), 2885 (w), 1586 (w), 1573 (w), 1540 (w), 1478 (m), 1427 (m), 1372 (s), 1282 (w), 1204 (s), 1186 (s), 1128 (m), 1085 (s), 1044 (m), 1014 (m), 864 (m), 841 (m), 808 (m), 765 (vs), 724 (s), 652 (w), 629 (m), 565 (m), 482 (m).
HRMS (EI) for **$C_{14}H_{11}I_2O_4S^{35}Cl$** (563.8156): found: 563.8137.

Synthesis of 2-(5-iodo-11-oxa-tricyclo[6.2.1.02,7]undeca-2(7),3,5,9-tetraen-3-yl)-ethanol (89):

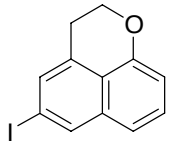


A dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of 4-chloro-benzenesulfonic acid 2-(2-hydroxy-ethyl)-4,6-diiodo-phenyl ester (**86**) (282 mg, 0.5 mmol) and furan (170 mg, 2.5 mmol) in dry THF (4 mL). After cooling to −78 °C, PhMgCl (0.32 mL, 0.52 mmol, 1.65 M in THF) was added dropwise and stirred for 10 min. *i*-PrMgCl (0.58 mL, 0.52 mmol, 0.90 M in THF) was added dropwise at −78 °C, and the resulting mixture was stirred for 30 min followed by warming to 25 °C and stirring for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 1 : 1) yielded **89** as a colourless oil (123 mg, 78 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.47 (*pseudo* s, 1H), 7.19 (*pseudo* s, 1H), 7.04-6.94 (m, 2H), 5.80-5.76 (m, 1H), 5.67-5.63 (m, 1H), 3.87-3.64 (m, 2H), 2.92-2.65 (m, 2H), 1.73 (s, 1H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 151.6, 148.5, 143.0, 142.4, 134.8, 133.4, 127.7, 90.3, 82.0, 81.0, 62.8, 35.8.
MS (70 eV, EI) *m/z* (%): 314 (55) [M^+], 288 (42), 283 (15), 268 (49), 257 (31), 255 (44), 159 (23), 141 (100), 131 (53), 129 (53), 128 (95), 127 (31), 115 (31), 102 (18), 51 (14).
IR (film) $\tilde{\nu}$ (cm^{-1}): 3413, 2944, 2874, 1589, 1433, 1279, 1040, 857, 728.
HRMS (EI) for **$C_{12}H_{11}O_2I$** (313.9804): found: 313.9804.
(Note: **89** was unstable in $CDCl_3$, and it was converted to **90** slowly.)

[114] L. A. Flippin, D. W. Gallagher, K. Jalali-Araghi, *J. Org. Chem.* **1989**, *54*, 1430-1432.

Synthesis of 5-iodo-2,3-dihydro-benzo[de]chromene (90):

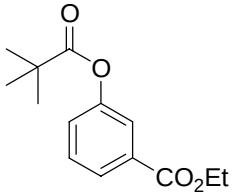


2-(5-Iodo-11-oxa-tricyclo[6.2.1.02,7]undeca-2(7),3,5,9-tetraen-3-yl)-ethanol **89** (in $CDCl_3$) Reaction condition: 25°C, 4 weeks. No further purification yielded **90** as a brown oil (quantitative yield).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.09 (d, ^4J(H,H) = 1.0 Hz, 1H), 7.44-7.42 (m, 1H), 7.37 (t, ^3J(H,H) = 7.8 Hz, 1H), 7.29 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 0.9 Hz, 1H), 6.94 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.1 Hz, 1H), 4.39 (t, ^3J(H,H) = 5.7 Hz, 2H), 3.19 (t, ^3J(H,H) = 5.7 Hz, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 153.4, 135.7, 134.5, 132.5, 130.5, 127.6, 120.4, 119.0, 110.4, 91.9, 65.8, 28.9.
MS (70 eV, EI) *m/z* (%): 297 (10), 296 (100) [M^+], 281 (21), 169 (7), 139 (5).
IR (film) $\widetilde{\nu}$ (cm^{-1}): 1618, 1588, 1272, 1222, 1115, 1074, 1023, 854, 806, 754.
HRMS (EI) for **$C_{12}H_9OI$** (295.9698): found: 295.9700.

11. Highly functionalized benzenes syntheses by directed mono or multiple magnesiations using TMPMgCl·LiCl

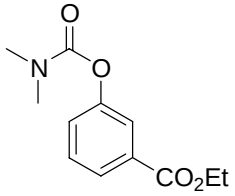
Synthesis of 3-(2,2-dimethyl-propionyloxy)-benzoic acid ethyl ester (91b)



A dry 100 mL round-bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with a solution of 3-hydroxy-benzoic acid ethyl ester (2.52 g, 15.0 mmol) in dry pyridine (5 mL). Pivaloyl chloride (2.20 mL, 18.0 mmol) was added and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was poured into 2 N $HCl_{(aq)}$ (50 mL), extracted with CH_2Cl_2 (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 5 : 1) yielded the product **91b** as a pale yellow oil (3.38 g, 90 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.88 (dt, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.2 Hz, 1H), 7.70-7.68 (m, 1H), 7.04 (t, ^3J(H,H) = 7.9 Hz, 1H), 7.22 (ddd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 2.4 Hz, ^4J(H,H) = 1.2 Hz, 1H), 4.35 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.36 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.34 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 176.6, 165.5, 150.9, 131.8, 129.1, 126.6, 126.0, 122.5, 61.1, 38.9, 26.9, 14.1.
MS (70 eV, EI) *m/z* (%): 250 (24) [M^+], 166 (74), 138 (44), 122 (11), 121 (52), 93 (11), 85 (29), 57 (100), 41 (16).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2977 (m), 1755 (m), 1720 (s), 1588 (w), 1481 (w), 1444 (w), 1367 (w), 1282 (m), 1263 (s), 1192 (m), 1106 (vs), 1075 (m), 1027 (m), 748 (m).
HRMS (EI) for **$C_{14}H_{18}O_4$** (250.1205): found: 250.1194.

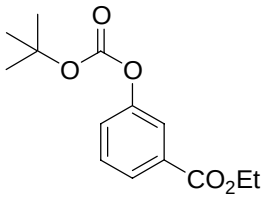
Synthesis of 3-dimethylcarbamoyloxy-benzoic acid ethyl ester (91c)



A dry 100 mL round-bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with a solution of 3-hydroxy-benzoic acid ethyl ester (2.52 g, 15.0 mmol), dimethylcarbamyl chloride (2.75 mL, 30.0 mmol), and triethylamine (5.23 mL, 37.5 mmol) in dry toluene (40 mL). The reaction mixture was stirred at 100 °C for 24 h. Toluene was evaporated, and then saturated aqueous NH_4Cl solution (30 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 2 : 1) yielded **91c** as a pale yellow oil (3.31 g, 93 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.87 (dt, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 1.3 Hz, 1H), 7.77 (t, ^4J(H,H) = 1.9 Hz, 1H), 7.41 (t, ^3J(H,H) = 7.9 Hz, 1H), 7.33-7.29 (m, 1H), 4.35 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.10 (s, 3H), 3.00 (s, 3H), 1.37 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.7, 154.5, 151.4, 131.7, 129.1, 126.3, 126.3, 122.8, 61.0, 36.7, 36.4, 14.2.
MS (70 eV, EI) *m/z* (%): 237 (22) [M^+], 192 (21), 72 (100).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 1713 (s), 1385 (w), 1280 (w), 1260 (m), 1200 (m), 1152 (m), 1098 (w), 750 (w).
HRMS (EI) for **$C_{12}H_{15}NO_4$** (237.1001): found: 237.1002.

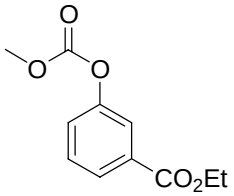
Synthesis of 3-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester (91d)



Prepared according to **TP 14** from 3-hydroxy-benzoic acid ethyl ester (2.52 g, 15 mmol), DMAP (92 mg, 0.75 mmol), and Boc_2O (3.930 g, 18 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **91d** as a yellow oil (3.80 g, 95 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.93-7.89 (m, 1H), 7.85-7.82 (m, 1H), 7.44 (td, ^3J(H,H) = 7.8 Hz, ^5J(H,H) = 0.4 Hz, 1H), 7.38-7.33 (m, 1H), 4.37 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.56 (s, 9H), 1.39 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.6, 151.6, 151.0, 132.0, 129.3, 126.9, 125.8, 122.5, 83.9, 61.2, 27.7, 14.3.
MS (70 eV, EI) *m/z* (%): 166 (44) [M−Boc]$^+$, 138 (13), 121 (38), 57 (100).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 1758 (m), 1719 (m), 1369 (w), 1241 (vs), 1207 (m), 1143 (s), 1099 (m), 1075 (w), 1025 (w), 732 (w).
$C_{14}H_{18}O_5$: calc.: C: 63.15; H: 6.81; found: C: 63.02; H: 6.80.

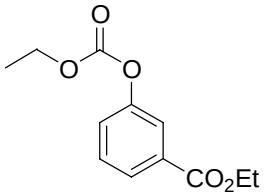
Synthesis of 3-methoxycarbonyloxy-benzoic acid ethyl ester (91e)



A dry 100 mL round-bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with a solution of 3-hydroxy-benzoic acid ethyl ester (2.52 g, 15.0 mmol) in dry CH_2Cl_2 (40 mL). After cooling to 0 °C, methyl chloroformate (1.74 mL, 22.5 mmol) and triethylamine (3.14 mL, 22.5 mmol) were added slowly. The reaction mixture was warmed to 25 °C and stirred overnight. Saturated aqueous NH_4Cl solution (30 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 5 : 1) yielded **91e** as a colourless liquid (3.28 g, 97 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.95-7.90 (m, 1H), 7.85-7.82 (m, 1H), 7.47-7.40 (m, 1H), 7.38-7.33 (m, 1H), 4.36 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.90 (s, 3H), 1.37 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.4, 153.9, 151.0, 132.1, 129.4, 127.1, 125.4, 122.2, 61.2, 55.4, 14.2.
MS (70 eV, EI) *m/z* (%): 225 (8), 224 (54) [M^+], 180 (17), 179 (42), 165 (15), 152 (44), 136 (20), 135 (100), 121 (10), 108 (10), 107 (19), 92 (11), 77 (8).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 1763 (m), 1717 (m), 1438 (w), 1295 (w), 1280 (w), 1230 (vs), 1207 (m), 1101 (w), 1075 (w), 945 (w), 761 (w).
HRMS (EI) for **$C_{11}H_{12}O_5$** (224.0685): found: 224.0676.

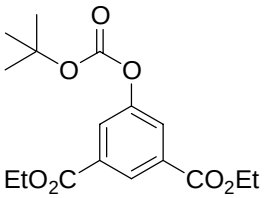
Synthesis of 3-ethoxycarbonyloxy-benzoic acid ethyl ester (91f)



Prepared according to the same procedure for the preparation of **91e** from 3-hydroxy-benzoic acid ethyl ester (2.52 g, 15 mmol), triethylamine (3.14 mL, 22.5 mmol), and ethyl chloroformate (2.15 mL, 22.5 mmol). No further purification yielded **91f** as a pale yellow oil (3.50 g, 98 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.95-7.91 (m, 1H), 7.86-7.84 (m, 1H), 7.45 (t, ^3J(H,H) = 7.9 Hz, 1H), 7.39-7.34 (m, 1H), 4.42-4.29 (m, 4H), 1.42-1.35 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.5, 153.4, 151.0, 132.1, 129.4, 127.1, 125.6, 122.3, 65.0, 61.2, 14.3, 14.2.
MS (70 eV, EI) *m/z* (%): 238 (2) [M^+], 193 (18), 166 (51), 151 (10), 138 (47), 122 (13), 121 (100), 93 (12).
IR (neat) $\tilde{\nu}$ (cm^{-1}) = 1760 (m), 1718 (m), 1368 (w), 1295 (w), 1281 (w), 1228 (vs), 1204 (s), 1099 (w), 1075 (w), 1060 (w), 1019 (w), 995 (w), 982 (w), 761 (w).
HRMS for **$C_{12}H_{14}O_5$** (238.0841): found: 238.0826.

Synthesis of 5-*tert*-butoxycarbonyloxy-isophthalic acid diethyl ester (91g)



Prepared according to **TP 14** from 5-hydroxy-isophthalic acid diethyl ester (3.574 g, 15 mmol), DMAP (92 mg, 0.75 mmol), and Boc_2O (3.930 g, 18 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded the product **91g** as a white solid (4.822 g, 95 %).

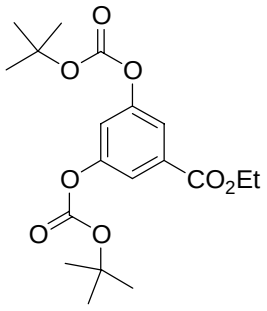
mp.: 71.2-73.4 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.55 (t, ^4J(H,H) = 1.5 Hz, 1H), 8.02 (d, ^4J(H,H) = 1.5 Hz, 2H), 4.41 (q, ^3J(H,H) = 7.2 Hz, 4H), 1.57 (s, 9H), 1.41 (t, ^3J(H,H) = 7.2 Hz, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 164.9, 151.3, 151.0, 132.3, 127.8, 126.7, 84.3, 61.6, 27.7, 14.3.
MS (70 eV, EI) *m/z* (%): 238 (23) $[M-Boc]^+$, 193 (39), 165 (10), 137 (9), 57 (100), 56 (9), 44 (11), 41 (21).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2979 (w), 1756 (m), 1718 (s), 1368 (w), 1232 (vs), 1144 (s), 1101 (m), 1051 (w), 1026 (m), 863 (w).
$C_{17}H_{22}O_7$: calc.: C: 60.35; H: 6.55; found: C: 60.34; H: 6.60.

Preparation of 5-hydroxy-isophthalic acid diethyl ester: A dry 1000 mL round-bottomed flask, equipped with a magnetic stirring bar and a condenser, was charged with a solution of 5-hydroxy-isophthalic acid (15 g, 80 mmol) in dry ethanol (400 mL). Concentrated $H_2SO_{4(l)}$ (1 mL) was added and the reaction mixture was refluxed overnight. Ethanol was evaporated, and then saturated aqueous NaCl solution (30 mL) was added. The reaction mixture was extracted with ether (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. No further purification furnished the desired product as a white solid (18.2 g, 95 %).
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.21 (t, ^4J(H,H) = 1.4 Hz, 1H), 7.81 (d, ^4J(H,H) = 1.4 Hz, 2H), 6.51 (s, 1H), 4.39 (q, ^3J(H,H) = 7.1 Hz, 4H), 1.39 (t, ^3J(H,H) = 7.1 Hz, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.2, 156.6, 131.9, 122.5, 121.0, 61.7, 14.2.
MS (70 eV, EI) *m/z* (%): 238 (32) $[M^+]$, 210 (12), 194 (15), 193 (100), 182 (13), 165 (33), 137 (21).
HRMS (EI) for **$C_{12}H_{14}O_5$** (238.0841): found: 238.0852.

Spectral data match those reported in the literature.[115]

Synthesis of 3,5-bis-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester (91h)



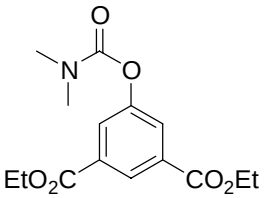
Prepared according to **TP 14** from 3,5-dihydroxy-benzoic acid ethyl ester (2.732 g, 15 mmol), DMAP (184 mg, 1.5 mmol), Et_3N (1 mL), and Boc_2O (7.200 g, 33 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded the product **91h** as a white solid (5.466 g, 95 %).

mp.: 75.9-77.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.72 (d, ^4J(H,H) = 2.2 Hz, 2H), 7.27 (d, ^4J(H,H) = 2.2 Hz, 1H), 4.37 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.55 (s, 18H), 1.38 (t, ^3J(H,H) = 7.2 Hz, 3H).

[115] Lakshmi, C.; Hanshaw, R. G.; Smith, B. D. *Tetrahedron* **2004**, *60*, 11307.

^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 164.8, 151.3, 151.0, 132.5, 119.7, 119.2, 84.1, 61.5, 27.6, 14.2.
MS (70 eV, EI) *m/z* (%): 337 (4), 267 (16), 183 (8), 182 (79), 177 (8), 138 (8), 137 (18), 57 (100), 41 (13).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2985 (w), 1759 (s), 1722 (m), 1370 (w), 1270 (w), 1244 (s), 1156 (w), 1125 (s), 1104 (m), 1052 (w), 1027 (w), 950 (w), 904 (w), 855 (w), 772 (w).
HRMS (EI) for **$C_{17}H_{21}O_7$**, $[M-C_2H_5O]^+$ (337.1287): found: 337.1294.
HRMS (EI) for **$C_9H_{10}O_4$**, $[M-C_{10}H_{16}O_4]^+$ (182.0579): found: 182.0592.
$C_{19}H_{26}O_8$: calc.: C: 59.68; H: 6.85; found: C: 59.62; H: 6.93.

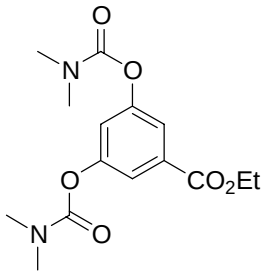
Synthesis of 5-dimethylcarbamoyloxy-isophthalic acid diethyl ester (91i)



Prepared according to the same procedure for the preparation of **91c** from 3,5-dihydroxy-benzoic acid ethyl ester (2.732 g, 15 mmol), dimethylcarbamyl chloride (2.75 mL, 30.0 mmol), and triethylamine (5.23 mL, 37.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 2 : 1) yielded **91i** as a white solid (4.40 g, 95 %).

mp.: 90.1-91.5 °C.
^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.52 (t, ^4J(H,H) = 1.4 Hz, 1H), 7.96 (d, ^4J(H,H) = 1.4 Hz, 2H), 4.39 (q, ^3J(H,H) = 7.1 Hz, 4H), 3.11 (s, 3H), 3.02 (s, 3H), 1.39 (t, ^3J(H,H) = 7.1 Hz, 6H).
^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.1, 154.2, 151.5, 132.0, 127.3, 127.2, 61.5, 36.8, 36.4, 14.3.
MS (70 eV, EI) *m/z* (%): 309 (26) [M^+], 264 (54), 72 (100).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 1724 (s), 1708 (s), 11458 (w), 1385 (m), 1365 (m), 1313 (m), 1246 (s), 1219 (s), 1168 (s), 1102 (m), 1022 (s), 952 (m), 914(m), 864 (m), 750 (s).
HRMS (EI) for **$C_{15}H_{19}NO_6$** (309.1212): found: 309.1206.

Synthesis of 3,5-bis-dimethylcarbamoyloxy-benzoic acid ethyl ester (91j)

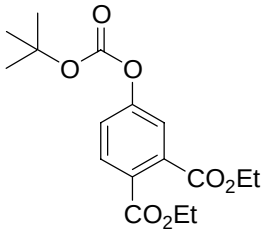


Prepared according to the same procedure for the preparation of **91c** from 3,5-dihydroxy-benzoic acid ethyl ester (2.732 g, 15 mmol), dimethylcarbamyl chloride (4.13 mL, 45.0 mmol), and triethylamine (5.23 mL, 37.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 2 : 1) yielded **91j** as a pale yellow solid (4.57 g, 94 %).

mp.: 66.1-67.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.62 (d, ^4J(H,H) = 2.2 Hz, 2H), 7.19 (t, ^4J(H,H) = 2.2 Hz, 1H), 4.33 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.06 (s, 6H), 2.98 (s, 6H), 1.35 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.1, 154.1, 151.6, 132.0, 120.2, 119.5, 61.2, 36.6, 36.3, 14.2.
MS (70 eV, EI) *m/z* (%): 324 (15) [M^+], 279 (8), 72 (100).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 1741 (m), 1711 (s), 1464 (w), 1436 (w), 1380 (m), 1365 (m), 1303 (s), 1270 (m), 1243 (m), 1158 (vs), 1104 (m), 1030 (s), 949 (w), 883 (w), 821 (w), 766 (s), 750 (m), 674 (w), 610 (w).
HRMS (EI) for **$C_{15}H_{20}N_2O_6$**, (324.1321): found: 324.1311.

Synthesis of 4-*tert*-butoxycarbonyloxy-phthalic acid diethyl ester (91k)



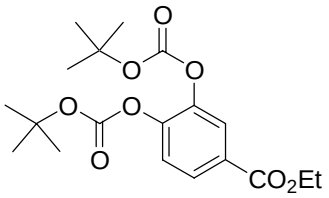
Prepared according to **TP 14** from 4-hydroxy-phthalic acid diethyl ester (3.574 g, 15 mmol), DMAP (92 mg, 0.75 mmol), and Boc_2O (3.930 g, 18 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **91k** as a yellow oil (4.822 g, 95 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.75 (d, ^3J(H,H) = 8.5 Hz, 1H), 7.51 (d, ^4J(H,H) = 2.4 Hz, 1H), 7.33 (dd, ^3J(H,H) = 8.5 Hz, ^4J(H,H) = 2.4 Hz, 1H), 4.37-4.32 (m, 4H), 1.55 (s, 9H), 1.36-1.32 (m, 6H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.7, 166.6, 152.8, 150.8, 134.2, 130.5, 129.0, 123.4, 121.6, 84.3, 61.8, 61.6, 27.6, 14.0, 14.0.
MS (70 eV, EI) *m/z* (%): 238 (13) [M−Boc]$^+$, 193 (25), 165 (60), 57 (100), 41 (9).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1760 (m), 1723 (s), 1369 (w), 1241 (vs), 1210 (m), 1146 (m), 1111 (s), 1069 (m), 1022 (m), 870 (w), 778 (w), 731 (w).
HRMS (EI) for **$C_{17}H_{23}O_7$**, $[M+H]^+$ (339.1444): found: 339.1458.
HRMS (FAB) for **$C_{17}H_{23}O_7$**, $[M+H]^+$ (339.1444): found: 339.1425.

Preparation of 4-hydroxy-phthalic acid diethyl ester: A dry 100 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with a solution of 4-hydroxyphthalic acid (4.60 g, 25 mmol) in dry ethanol (30 mL). Concentrated $H_2SO_{4(l)}$ (0.5 mL) was added and the reaction mixture was refluxed overnight. Ethanol was evaporated, and then saturated aqueous NaCl solution (30 mL) was added. The reaction mixture was extracted with ether (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. No further purification furnished the desired product as a yellow oil (5.89 g, 99 %).
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.71 (d, ^3J(H,H) = 8.6 Hz, 1H), 7.00 (d, ^4J(H,H) = 2.5 Hz, 1H), 6.90 (dd, ^3J(H,H) = 8.6 Hz, ^4J(H,H) = 2.5 Hz, 1H), 4.34 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.30 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.33 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.32 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 169.3, 167.0, 159.6, 135.7, 131.8, 121.5, 117.2, 115.3, 62.1, 61.5, 14.0, 13.9.
MS (70 eV, EI) *m/z* (%): 238 (13) [M^+], 193 (27), 166 (11), 165 (100).

IR (neat) $\tilde{\nu}$ (cm^{-1}): 3265 (brm), 2983 (w), 1698 (vs), 1614 (m), 1578 (m), 1372 (w), 1312 (m), 1286 (m), 1261 (s), 1210 (m), 1148 (m), 1135 (m), 1067 (m), 1018 (m), 780 (w).
HRMS (EI) for $\mathbf{C_{12}H_{14}O_5}$ (238.0841): found: 238.0829.

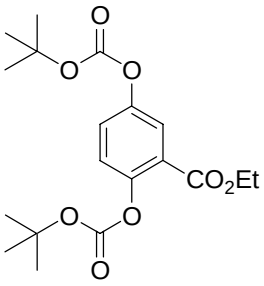
Synthesis of 3,4-bis-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester (91l)



Prepared according to **TP 14** from 3,4-dihydroxy-benzoic acid ethyl ester (2.732 g, 15 mmol), DMAP (184 mg, 1.5 mmol), Et_3N (1 mL), and Boc_2O (7.200 g, 33 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **91l** as a yellow oil (5.450 g, 95 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.94-7.91 (m, 2H), 7.34 (d, ^3J(H,H) = 9.0 Hz, 1H), 4.36 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.55 (s, 9H), 1.54 (s, 9H), 1.37 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.0, 150.4, 150.0, 146.2, 142.3, 128.8, 127.8, 124.6, 122.9, 84.2, 84.1, 61.3, 27.6, 27.6, 14.2.
MS (70 eV, EI) *m/z* (%):182 (31) $[M-2Boc]^+$, 137 (22), 57 (100), 41 (14).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 1764 (s), 1721 (m), 1370 (w), 1270 (m), 1246 (vs), 1152 (s), 1137 (s), 1112 (s), 1094 (s), 1046 (w), 1021 (w), 769 (w), 734 (w).
HRMS (FAB) for $\mathbf{C_{25}H_{42}O_8N}$, $[M+Et_3N+H]^+$ (484.2905): found: 484.2902.

Synthesis of 2,5-bis-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester (91m)

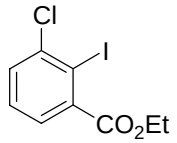


Prepared according to **TP 14** from 2,5-dihydroxy-benzoic acid ethyl ester (2.732 g, 15 mmol), DMAP (184 mg, 1.5 mmol), Et_3N (1 mL), and Boc_2O (7.200 g, 33 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 30 : 1) yielded **91m** as a white solid (5.335 g, 93 %).

mp.: 55.9-57.0 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.79 (d, ^4J(H,H) = 2.9 Hz, 1H), 7.35 (dd, ^3J(H,H) = 8.8 Hz, ^4J(H,H) = 2.9 Hz, 1H), 7.17 (d, ^3J(H,H) = 8.8 Hz, 1H), 4.34 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.55 (s, 18H), 1.36 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 163.7, 151.4, 151.3, 148.3, 148.0, 126.4, 124.7, 124.5, 124.2, 84.1, 83.9, 61.4, 27.7, 27.6, 14.2.
MS (70 eV, EI) *m/z* (%):182 (63) $[M-2Boc]^+$, 137 (13), 136 (59), 57 (100), 41 (17).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2980 (w), 1756 (s), 1712 (m), 1370 (w), 1277 (m), 1235 (m), 1125 (vs), 1075 (m), 1052 (w), 1020 (w), 897 (w), 811 (w), 777 (w), 727 (w).

HRMS (FAB) for $\mathbf{C_{25}H_{42}O_8N}$, $[M+Et_3N+H]^+$ (484.2905): found: 484.2895.

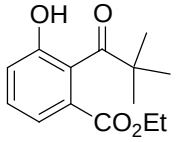
Synthesis of 3-chloro-2-iodo-benzoic acid ethyl ester (93a)



Prepared according to **TP 15** from ethyl 3-chlorobenzoate (**91a**) (185 mg, 1.0 mmol), TMPMgCl·LiCl (1.00 mL, 1.2 equiv., 1.2 M in THF) [reaction condition: 0 °C for 6 h], and iodine (381 mg, 1.5 mmol in 5 ml THF). Purification by flash chromatography (*n*-pentane, and then diethyl ether) yielded **93a** as a yellow oil (0.235 g, 76 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.56-7.54 (m, 1H), 7.44-7.42 (m, 1H), 7.34-7.31 (m, 1H), 4.41 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.41 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 167.3, 140.7, 140.6, 131.1, 129.0, 127.4, 98.0, 62.1, 14.1.
MS (70 eV, EI) *m/z* (%): 312 (17), 310 (52) [M^+], 282 (27), 265 (100), 110 (32), 75 (35).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2962 (w), 2935 (w), 1725 (vs), 1575 (w), 1443 (m), 1399 (m), 1366 (m), 1280 (vs), 1254 (vs), 1191 (s), 1149 (s), 1129 (s), 1088 (s), 1014 (vs), 884 (w), 860 (w), 791 (s), 757 (s), 731 (s), 687 (w).
HRMS (EI) for $\mathbf{C_9H_8{}^{35}ClIO_2}$, (309.9258): found: 309.9234.

Synthesis of 2-(2,2-dimethyl-propionyl)-3-hydroxy-benzoic acid ethyl ester

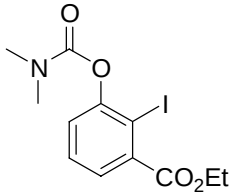


A dry and nitrogen-flushed 10 mL Schlenk tube, equipped with a magnetic stirring bar and a septum, was charged with a solution of **91b** (250 mg, 1.0 mmol) in dry THF (3 mL). After cooling to 0 °C, TMPMgCl·LiCl (1.0 mL, 1.2 equiv., 1.20 M in THF) was added dropwise and stirred for 20 h. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry ether. The GC-analysis was detected in less than 40 % conversion of starting material and the desired product **93b** was about 20 %. I_2 (381 mg, 1.5 equiv.) dissolved in dry THF (2 mL) was then added at 0 °C, and the resulting mixture was warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with 5 % aqueous $Na_2S_2O_3$ solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 3 : 2) yielded the side product as a yellow oil (33 mg, 13 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.49 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.0 Hz, 1H), 7.17 (t, ^3J(H,H) = 7.9 Hz 1H), 7.04 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.0 Hz, 1H), 6.50 (brs, 1H), 4.30 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.33 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.21 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 216.2, 166.2, 152.4, 129.9, 129.3, 128.9, 121.5, 121.4, 61.5, 45.6, 27.8, 14.2.
MS (70 eV, EI) *m/z* (%): 205 (4), 193 (47), 166 (11), 165 (100), 147 (16).

IR (neat) $\tilde{\nu}$ (cm^{-1}): 3257 (brw), 2960 (m), 2929 (m), 1714 (m), 1678 (m), 1585 (w), 1480 (w), 1460 (m), 1391 (w), 1366 (w), 1295 (s), 1261 (m), 1149 (w), 1031 (m), 959 (m), 755 (m), 747 (w).
HRMS (EI) for **$C_{12}H_{13}O_3$**, $[M-EtO]^+$ (205.0865): found: 205.0861.

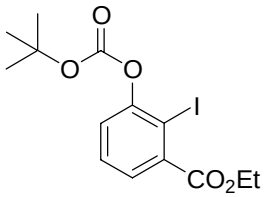
Synthesis of 3-dimethylcarbamoyloxy-2-iodo-benzoic acid ethyl ester (93c)



Prepared according to **TP 15** from **91c** (237 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h; the conversion: 52% by GC-analysis], and iodine (381 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 3 : 2) yielded **93c** as a yellow oil (182 mg, 50 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.55 (dd, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.7 Hz, 1H), 7.37 (t, ^3J(H,H) = 7.8 Hz 1H), 7.28 (dd, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 1.7 Hz, 1H), 4.39 (q, ^3J(H,H) = 7.2 Hz, 2H), 3.21 (s, 3H), 3.04 (s, 3H), 1.40 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.6, 153.5, 152.5, 138.0, 128.8, 127.4, 125.8, 91.9, 61.8, 36.9, 36.8, 14.2.
MS (70 eV, EI) *m/z* (%): 363 (1) [M^+], 318 (7), 237 (8), 236 (58), 72 (100).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2931 (w), 1718 (vs), 1384 (m), 1284 (m), 1253 (m), 1235 (m), 1138 (s), 1020 (m), 747 (w).
HRMS (EI) for **$C_{12}H_{14}INO_4$** (362.9968): found: 362.9941.

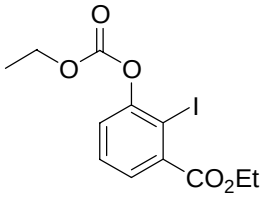
Synthesis of 3-*tert*-butoxycarbonyloxy-2-iodo-benzoic acid ethyl ester (93d)



Prepared according to **TP 15** from **91d** (266 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], and iodine (381 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **93d** as a yellow oil (338 mg, 86 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.57 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.38 (t, ^3J(H,H) = 7.8 Hz, 1H), 7.25 (d, ^3J(H,H) = 7.8 Hz, 1H), 4.39 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.56 (s, 9H), 1.39 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.4, 152.2, 150.8, 138.3, 129.1, 127.9, 125.2, 91.8, 84.4, 61.9, 27.7, 14.2.
MS (70 eV, EI) *m/z* (%): 292 (100) $[M-Boc]^+$, 264 (15), 247 (67), 57 (86), 41 (11).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2981 (w), 1759 (m), 1726 (m), 1369 (w), 1246 (m), 1227 (s), 1133 (vs), 1025 (w), 873 (w), 741 (w).
HRMS (EI) for **$C_{14}H_{17}IO_5$** (392.0121): found: 392.0102.

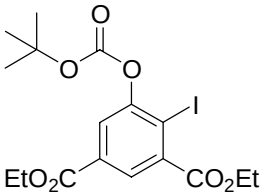
Synthesis of 3-ethoxycarbonyloxy-2-iodo-benzoic acid ethyl ester (93f)



Prepared according to **TP 15** from **91f** (238 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 2 h], and iodine (381 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 8 : 1) yielded **93f** as a yellow oil (245 mg, 67 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.60 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.7 Hz, 1H), 7.40 (t, ^3J(H,H) = 7.9 Hz, 1H), 7.29 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.7 Hz, 1H), 4.45-4.32 (m, 4H), 1.44-1.38 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.3, 152.5, 152.1, 138.4, 129.2, 128.1, 124.9, 91.3, 65.5, 61.9, 14.2, 14.1.
MS (70 eV, EI) *m/z* (%): 364 (10) [M^+], 319 (12), 292 (71), 264 (43), 248 (15), 247 (100), 246 (22), 218 (12), 136 (10), 119 (10), 92 (19), 63 (13).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 1762 (m), 1724 (m), 1368 (w), 1291 (w), 1246 (m), 1212 (vs), 1183 (m), 1141 (m), 1095 (w), 1016 (w), 997 (w), 980 (w), 761 (w).
HRMS (EI) for **$C_{12}H_{13}IO_5$** (363.9808): found: 363.9785.

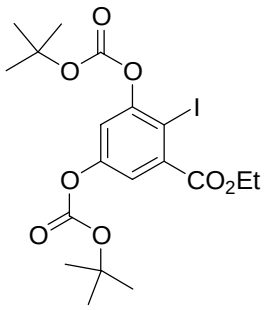
Synthesis of 5-*tert*-butoxycarbonyloxy-4-iodo-isophthalic acid diethyl ester (93g)



Prepared according to **TP 15** from **91g** (338 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 1 h], and iodine (381 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 100 : 1) yielded **93g** as a yellow oil (418 mg, 90 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.18 (d, ^4J(H,H) = 1.9 Hz, 1H), 7.86 (d, ^4J(H,H) = 1.9 Hz, 1H), 4.44-4.36 (m, 4H), 1.57 (s, 9H), 1.43-1.37 (m, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.8, 164.4, 152.5, 150.4, 138.6, 131.9, 128.3, 125.4, 98.0, 84.8, 62.2, 61.7, 27.6, 14.2, 14.1.
MS (70 eV, EI) *m/z* (%): 364 (33) [M−Boc]$^+$, 319 (25), 238 (32), 193 (100), 177 (39), 165 (30), 161 (31), 85 (23), 71 (33), 57 (85), 56 (27), 55 (24), 44 (33), 43 (28), 41 (58).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 1763 (m), 1723 (s), 1370 (w), 1324 (w), 1241 (vs), 1146 (s), 1113 (w), 1055 (w), 1018 (w), 863 (w), 754 (w).
HRMS (EI) for **$C_{17}H_{21}IO_7$** (464.0332): found: 464.0342.

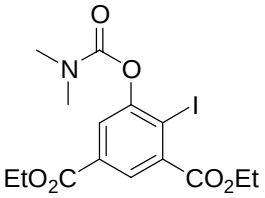
Synthesis of 3,5-bis-*tert*-butoxycarbonyloxy-2-iodo-benzoic acid ethyl ester (93h)



Prepared according to **TP 15** from **91h** (382 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], and iodine (381 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **93h** as a yellow oil (480 mg, 91 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.50 (d, ^4J(H,H) = 2.7 Hz, 1H), 7.23 (d, ^4J(H,H) = 2.7 Hz, 1H), 4.39 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.56 (s, 9H), 1.54 (s, 9H), 1.39 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.4, 152.5, 151.4, 150.4, 150.3, 138.0, 120.9, 118.5, 87.5, 84.6, 84.4, 62.0, 27.6, 27.6, 14.1.
MS (70 eV, EI) *m/z* (%): 309 (8), 308 (78) $[M-2Boc]^+$, 263 (14), 182 (17), 177 (8), 137 (9), 71 (7), 57 (100), 56 (7), 41 (15).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1761 (m), 1730 (m), 1370 (w), 1240 (s), 1151 (m), 1124 (vs), 1064 (w), 1019 (w), 910 (w), 853 (w), 729 (m).
HRMS (FAB) for **$C_{25}H_{41}O_8NI$**, $[M+Et_3N+H]^+$ (610.1877): found: 610.1858.
HRMS (EI) for **$C_{19}H_{26}O_8I$**, $[M+H]^+$ (509.0672): found: 509.0665.

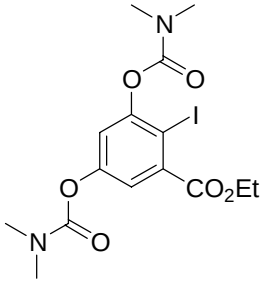
Synthesis of 5-dimethylcarbamoyloxy-4-iodo-isophthalic acid diethyl ester (93i)



Prepared according to **TP 15** from 5-dimethylcarbamoyloxy-isophthalic acid diethyl ester (**91i**) (309 mg, 1.0 mmol) [reaction condition: 0 °C for 1 h], TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF), and iodine (381 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 3 : 1) yielded **93i** as a yellow solid (340 mg, 78 %).

mp.: 66.0-67.1 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.15 (d, ^4J(H,H) = 2.0 Hz, 1H), 7.86 (d, ^4J(H,H) = 2.0 Hz, 1H), 4.40 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.36 (q, ^3J(H,H) = 7.2 Hz, 2H), 3.19 (s, 3H), 3.03 (s, 3H), 1.40 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.36 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.9, 164.5, 153.1, 152.8, 138.2, 131.6, 127.8, 125.9, 98.1, 62.1, 61.6, 36.9, 36.7, 14.2, 14.1.
MS (70 eV, EI) *m/z* (%): 390 (10), 309 (10), 308 (66), 72 (100).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 2938 (w), 1715 (s), 1382 (w), 1365 (w), 1311 (m), 1232 (s), 1151 (s), 1111 (m), 1027 (m), 1016 (m), 757 (m).
HRMS (EI) for **$C_{15}H_{18}INO_6$** (435.0179): found: 435.0186.

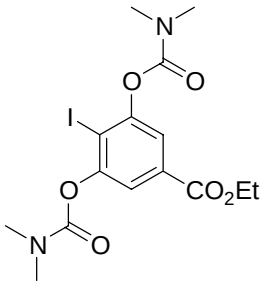
Synthesis of 3,5-bis-dimethylcarbamoyloxy-2-iodo-benzoic acid ethyl ester (93ja)



Prepared according to **TP 15** from 3,5-bis-dimethylcarbamoyloxy-benzoic acid ethyl ester (**91j**) (649 mg, 2.0 mmol), TMPMgCl·LiCl (2.0 mL, 1.1 equiv., 1.10 M in THF) [reaction condition: 0 °C for 3 h], and iodine (762 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 1 : 2) yielded **93ja** as a yellow oil (565 mg, 62 %) and **93jb** as a yellow solid (159 mg, 17 %).

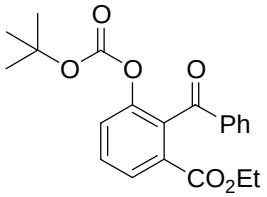
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.43 (d, ^4J(H,H) = 2.7 Hz, 1H), 7.20 (d, ^4J(H,H) = 2.7 Hz, 1H), 4.37 (q, ^3J(H,H) = 7.2 Hz, 2H), 3.18 (s, 3H), 3.06 (s, 3H), 3.02 (s, 3H), 2.99 (s, 3H), 1.38 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.7, 153.6, 153.2, 152.7, 151.7, 137.4, 120.9, 119.6, 86.8, 61.9, 36.8, 36.7, 14.1.
MS (70 eV, EI) *m/z* (%): 405 (5), 324 (16), 323 (91), 72 (100).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2935 (w), 1716 (vs), 1436 (w), 1375 (m), 1302 (m), 1264 (w), 1135 (s), 1016 (m).
HRMS (EI) for **$C_{15}H_{19}IN_2O_6$** (450.0288): found: 450.0261.

Synthesis of 3,5-bis-dimethylcarbamoyloxy-4-iodo-benzoic acid ethyl ester (93jb)



mp.: 98.3-99.9 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.68 (s, 2H), 4.34 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.18 (s, 6H), 3.04 (s, 6H), 1.36 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 164.8, 153.2, 152.8, 132.1, 120.8, 95.4, 61.5, 36.9, 36.7, 14.2.
MS (70 eV, EI) *m/z* (%): 405 (8), 324 (16), 323 (100), 72 (98).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2935 (w), 1716 (vs), 1368 (m), 1307 (m), 1230 (m), 1139 (s), 1105 (m), 1054 (m), 1020 (m).
HRMS (EI) for **$C_{15}H_{19}IN_2O_6$** (450.0288): found: 450.0282.

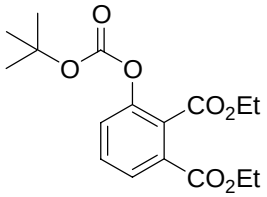
Synthesis of 2-benzoyl-3-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester (94a)



Prepared according to **TP 15** from **91d** (266 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], CuCN·2LiCl (0.20 mL, 0.2 equiv., 1.0 M in THF), and benzoyl choride (281 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94a** as a yellow solid (335 mg, 90 %).

mp.: 56.9-58.4 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.00 (d, ^3J(H,H) = 7.9 Hz, 1H), 7.79 (d, ^3J(H,H) = 7.9 Hz, 2H), 7.58-7.50 (m, 2H), 7.48-7.39 (m, 3H), 4.12 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.29 (s, 9H), 1.05 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 193.9, 165.0, 151.2, 148.4, 137.2, 134.9, 133.4, 130.6, 130.0, 129.3, 128.6, 128.2, 127.7, 84.2, 61.9, 27.5, 13.8.
MS (70 eV, EI) *m/z* (%): 270 (28) $[M-Boc]^+$, 269 (16), 225 (24), 224 (48), 223 (100), 165 (20), 105 (18), 77 (17), 57 (36), 41 (10).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2989 (w), 2918 (w), 1753 (s), 1725 (s), 1672 (s), 1596 (w), 1580 (w), 1449 (w), 1370 (w), 1259 (vs), 1224 (s), 1186 (m), 1146 (s), 1134 (s), 1051 (m), 1032 (m), 924 (w), 874 (w), 774 (w), 754 (m), 699 (m).
HRMS (FAB) for **$C_{27}H_{38}NO_6$**, $[M+Et_3N+H]^+$ (472.2699): found: 472.2697.

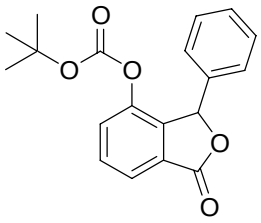
Synthesis of 3-*tert*-butoxycarbonyloxy-phthalic acid diethyl ester (94b)



Prepared according to **TP 15** from **91d** (266 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], and ethyl cyanoformate (200 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **94b** as a yellow oil (271 mg, 80 %).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.83 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 7.46 (t, ^3J(H,H) = 8.0 Hz, 1H), 7.38 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 1H), 4.38 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.32 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.51 (s, 9H), 1.35 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.32 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.5, 164.8, 151.0, 148.0, 130.0, 128.6, 127.3, 126.8, 84.0, 61.7, 61.6, 27.5, 14.0, 13.9.
MS (70 eV, EI) *m/z* (%): 238 (9) $[M-Boc]^+$, 192 (20), 164 (24), 120 (31), 111 (22), 97 (29), 95 (20), 85 (38), 83 (25), 71 (45), 69 (24), 57 (100), 55 (20), 44 (23), 43 (22), 41 (54).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1763 (m), 1723 (s), 1460 (w), 1369 (w), 1256 (s), 1229 (s), 1185 (w), 1142 (vs), 1106 (m), 1053 (m), 1032 (m), 878 (w), 735 (w).
HRMS (FAB) for **$C_{23}H_{38}NO_7$**, $[M+Et_3N+H]^+$ (440.2648): found: 440.2646.

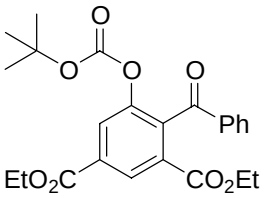
Synthesis of carbonic acid *tert*-butyl ester 1-oxo-3-phenyl-1,3-dihydro-isobenzofuran-4-yl ester (94c)



Prepared according to **TP 15** from **91d** (266 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], and benzaldehyde (159 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94c** as a white solid (271 mg, 83 %).

mp.: 115.5-116.5 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.86 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.59 (t, ^3J(H,H) = 7.8 Hz, 1H), 7.43 (d, ^3J(H,H) = 7.8 Hz, 1H), 7.38-7.32 (m, 3H), 7.23-7.20 (m, 2H), 6.46 (s, 1H), 1.37 (s, 9H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 169.6, 150.2, 146.0, 140.7, 134.7, 131.3, 129.8, 129.0, 128.6, 128.0, 127.9, 123.4, 84.6, 82.0, 27.7.
MS (70 eV, EI) *m/z* (%): 227 (55), 226 (100) $[M-Boc]^+$, 225 (43), 207 (12), 197 (13), 182 (10), 181 (27), 153 (12), 152 (27), 149 (26), 126 (11), 121 (74), 120 (29), 115 (11), 105 (59), 93 (14), 92 (12), 77 (21), 65 (12), 63 (13), 51 (14).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2990 (w), 1761 (vs), 1485 (w), 1456 (w), 1298 (w), 1280 (w), 1232 (m), 1139 (m), 1088 (m), 968 (m), 862 (w).
HRMS (FAB) for **$C_{25}H_{34}NO_5$**, $[M+Et_3N+H]^+$ (428.2437): found: 428.2430.

Synthesis of 4-benzoyl-5-*tert*-butoxycarbonyloxy-isophthalic acid diethyl ester (94d)

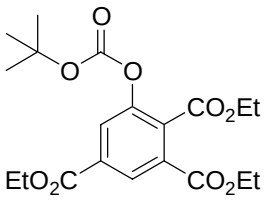


Prepared according to **TP 15** from 5-*tert*-butoxycarbonyloxy-isophthalic acid diethyl ester (**91g**) (338 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 1 h], CuCN·2LiCl (0.20 mL, 0.2 equiv., 1.0 M in THF), and benzoyl choride (281 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94d** as a yellow solid (405 mg, 91 %).

mp.: 77.3-79.0 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.63 (d, ^4J(H,H) = 1.4 Hz, 1H), 8.08 (d, ^4J(H,H) = 1.4 Hz, 1H), 7.76 (d, ^3J(H,H) = 7.4 Hz, 2H), 7.53 (t, ^3J(H,H) = 7.4 Hz, 1H), 7.40 (t, ^3J(H,H) = 7.4 Hz, 2H), 4.43 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.15 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.42 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.29 (s, 9H), 1.08 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 193.1, 164.6, 164.3, 150.9, 148.5, 138.8, 136.8, 133.7, 132.7, 131.0, 129.2, 129.1, 128.7, 128.5, 84.6, 62.2, 62.1, 27.5, 14.5, 13.8.
MS (70 eV, EI) *m/z* (%): 342 (31) $[M-Boc]^+$, 341 (13), 297 (25), 296 (51), 295 (100), 267 (11), 237 (17), 105 (24), 85 (11), 77 (16), 71 (14), 57 (46), 55 (12), 43 (13), 41 (15).

IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1761 (m), 1720 (s), 1682 (m), 1369 (w), 1237 (vs), 1144 (s), 1092 (m), 1053 (m), 1020 (m), 911 (w), 864 (w), 730 (m), 708 (m).
HRMS (FAB) for **$C_{24}H_{26}O_8Na$**, $[M+Na]^+$ (465.1525): found: 465.1519.

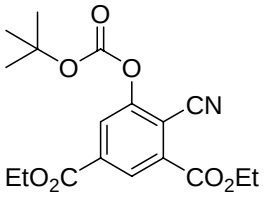
Synthesis of 6-*tert*-butoxycarbonyloxy-benzene-1,2,4-tricarboxylic acid triethyl ester (94e)



Prepared according to **TP 15** from **91g** (338 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 1 h], and ethyl cyanoformate (200 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94e** as a yellow oil (350 mg, 85 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.48 (d, ^4J(H,H) = 1.3 Hz, 1H), 8.04 (d, ^4J(H,H) = 1.3 Hz, 1H), 4.43-4.34 (m, 6H), 1.53 (s, 9H), 1.41-1.34 (m, 9H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.0, 164.2, 164.2, 150.7, 148.2, 132.5, 132.4, 130.3, 128.3, 127.7, 84.5, 62.0, 62.0, 61.8, 27.5, 14.2, 14.0, 14.0.
MS (70 eV, EI) *m/z* (%): 310 (28) $[M-Boc]^+$, 309 (17), 265 (51), 264 (96), 263 (11), 237 (56), 236 (42), 221 (11), 220 (36), 219 (12), 209 (24), 208 (100), 193 (14), 192 (94), 191 (34), 164 (27), 163 (21), 136 (12), 135 (12), 57 (68), 44 (14), 41 (21).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1765 (m), 1723 (s), 1370 (w), 1235 (vs), 1146 (m), 1120 (m), 1078 (m), 1056 (m), 1022 (m), 866 (w), 766 (w).
HRMS (FAB) for **$C_{26}H_{42}NO_9$**, $[M+Et_3N+H]^+$ (512.2860): found: 512.2849.

Synthesis of 3,5-di(ethoxycarbonyl)-2-cyanophenyl *tert*-butyl carbonate (94f)

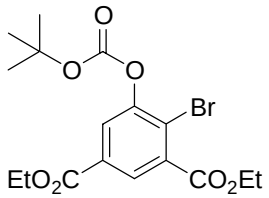


A dry and nitrogen-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of **91g** (1.015 g, 3.0 mmol) in dry THF (9 mL). After cooling to 0 °C, TMPMgCl·LiCl (2.75 mL, 1.1 equiv., 1.20 M in THF) was added dropwise and stirred for 1 h. The reaction mixture was cooled to −40 °C, and then tosyl cyanide (858 mg, 4.5 mmol) in dry THF (5 mL) was added and stirred for 30 min, warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 15 : 1) yielded **94f** as a colourless solid (985 mg, 90 %).

mp.: 92.0-94.2 °C.

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.61-8.60 (m, 1H), 8.12-8.11 (m, 1H), 4.49 (q, ^{3}J(H,H) = 7.1 Hz, 2H), 4.34 (q, ^{3}J(H,H) = 7.1 Hz, 2H), 1.59 (s, 9H), 1.46 (t, ^{3}J(H,H) = 7.1 Hz, 3H), 1.42 (t, ^{3}J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 163.5, 162.7, 154.2, 150.2, 135.2, 134.4, 128.8, 127.2, 112.5, 111.4, 86.0, 62.8, 62.4, 27.6, 14.2, 14.0.
MS (70 eV, EI) *m/z* (%): 264 (25), 263 (43) $[M-Boc]^+$, 236 (17), 235 (26), 219 (12), 218 (89), 207 (42), 191 (15), 190 (56), 163 (12), 162 (11), 57 (100), 56 (14), 44 (13), 41 (27).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2974 (m), 2940 (m), 2187 (m), 1766 (s), 1726 (vs), 1471 (w), 1369 (m), 1331 (m), 1271 (m), 1248 (s), 1210 (m), 1176 (m), 1147 (m), 1128 (m), 1093 (w), 1058 (w), 1037 (m), 1021 (m), 952 (w), 864 (w), 767 (m).
HRMS (EI) for **$C_{18}H_{22}NO_7$**, $[M+H]^+$ (364.1391): found: 364.1400.

Synthesis of 4-bromo-5-*tert*-butoxycarbonyloxy-isophthalic acid diethyl ester (94g)

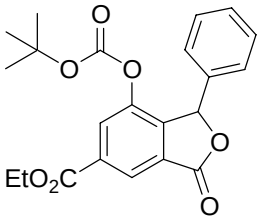


A dry and nitrogen-flushed 100 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of **91g** (3.384 g, 10 mmol) in dry THF (9 mL). After cooling to 0 °C, TMPMgCl·LiCl (9.20 mL, 1.1 equiv., 1.20 M in THF) was added dropwise and stirred for 1 h. The reaction mixture was cooled to −40 °C, and then 1,2-dibromotetrachloroethane (4.89 g, 15 mmol) was added and stirred for 30 min, warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **94g** as a yellow oil (4.065 g, 97 %).

In the case of **91g** (1.0 mmol) as the starting material with TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) and 1,2-dibromotetrachloroethane (0.489 g, 1.5 mmol), **94g** was obtained in 92 % yield according to the same reaction procedure.

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.26 (d, ^{4}J(H,H) = 2.1 Hz, 1H), 7.93 (d, ^{4}J(H,H) = 2.1 Hz, 1H), 4.42 (q, ^{3}J(H,H) = 7.2 Hz, 2H), 4.39 (q, ^{3}J(H,H) = 7.2 Hz, 2H), 1.57 (s, 9H), 1.41 (t, ^{3}J(H,H) = 7.2 Hz, 3H), 1.39 (t, ^{3}J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.1, 164.3, 150.4, 149.4, 134.9, 130.7, 129.0, 126.5, 121.8, 84.9, 62.2, 61.8, 27.6, 14.2, 14.2.
MS (70 eV, EI) *m/z* (%): 319 (9), 318 (51), 317 (10), 316 (51) $[M-Boc]^+$, 290 (14), 288 (14), 274 (9), 273 (60), 272 (10), 271 (60), 245 (23), 243 (23), 57 (100), 56 (10), 41 (19).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 1764 (m), 1723 (s), 1370 (w), 1235 (vs), 1181 (m), 1144 (s), 1114 (m), 1055 (m), 1020 (m), 862 (w), 754 (w).
HRMS (EI) for **$C_{17}H_{22}{}^{79}BrO_7$**, $[M+H]^+$ (417.0549): found: 417.0561.

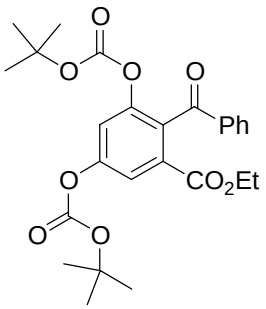
Synthesis of 7-*tert*-butoxycarbonyloxy-3-oxo-1-phenyl-1,3-dihydro-isobenzofuran-5-carboxylic acid ethyl ester (94h)



Prepared according to **TP 15** from **91g** (338 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 1 h], and benzaldehyde (159 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94h** as a yellow oil (312 mg, 78 %).

^{1}H-NMR (200 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.50 (d, ^4J(H,H) = 1.2 Hz, 1H), 8.09 (d, ^4J(H,H) = 1.2 Hz, 1H), 7.39-7.30 (m, 3H), 7.22-7.15 (m, 2H), 6.49 (s, 1H), 4.41 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.40 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.37 (s, 9H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 168.7, 164.4, 149.9, 145.9, 144.6, 134.6, 134.0, 130.0, 129.1, 129.0, 129.0, 128.0, 124.6, 85.0, 82.0, 62.1, 27.7, 14.5.
MS (70 eV, EI): *m/z* (%): 299 (24) $[M-Boc]^+$, 298 (58), 297 (15), 269 (10), 253 (25), 193 (40), 192 (13), 181 (10), 152 (13), 105 (38), 57 (100), 41 (12).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1760 (s), 1723 (s), 1370 (w), 1268 (w), 1245 (vs), 1217 (s), 1144 (s), 1108 (w), 1085 (m).
HRMS (FAB) for **$C_{28}H_{38}NO_7$**, $[M+Et_3N+H]^+$ (500.2648): found: 500.2643.

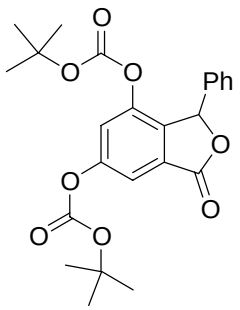
Synthesis of 2-benzoyl-3,5-bis-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester (94i)



Prepared according to **TP 15** from 3,5-bis-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester (**91h**) (382 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], CuCN·2LiCl (0.20 mL, 0.2 equiv., 1.0 M in THF), and benzoyl choride (281 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94i** as a yellow oil (453 mg, 93 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.83-7.81 (m, 1H), 7.79-7.76 (m, 2H), 7.53-7.49 (m, 1H), 7.41-7.37 (m, 2H), 7.37-7.36 (m, 1H), 4.10 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.56 (s, 9H), 1.28 (s, 9H), 1.04 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 192.9, 164.0, 151.3, 150.6, 150.4, 148.5, 136.9, 133.2, 131.8, 131.0, 129.0, 128.4, 120.7, 120.6, 84.4, 84.2, 61.8, 27.6, 27.2, 13.5.
MS (70 eV, EI) *m/z* (%): 313 (10), 287 (9), 286 (48) $[M-2Boc]^+$, 285 (38), 241 (16), 240 (30), 239 (51), 181 (15), 105 (18), 77 (8), 57 (100), 41 (14).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1761 (m), 1724 (m), 1682 (w), 1370 (w), 1238 (vs), 1143 (s), 1113 (s), 1055 (w), 1029 (w), 914 (w), 853 (w), 729 (w).
HRMS (FAB) for **$C_{32}H_{46}NO_9$**, $[M+Et_3N+H]^+$ (588.3173): found: 588.3150.
HRMS (FAB) for **$C_{26}H_{29}O_9$**, $[M-H]^+$ (485.1812): found: 485.1806.

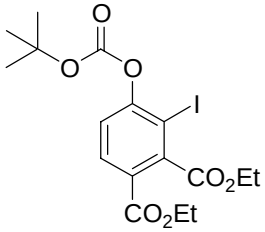
Synthesis of carbonic acid 7-*tert*-butoxycarbonyloxy-3-oxo-1-phenyl-1,3-dihydro-isobenzofuran-5-yl ester *tert*-butyl ester (94j)



Prepared according to **TP 15** from **91h** (382 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], and benzaldehyde (159 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94j** as a yellow solid (401 mg, 90 %).

mp.: 147.9-148.9 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.70 (d, ^4J(H,H) = 1.9 Hz, 1H), 7.39-7.33 (m, 3H), 7.32 (d, ^4J(H,H) = 1.9 Hz, 1H), 7.23-7.20 (m, 2H), 6.45 (s, 1H), 1.57 (s, 9H), 1.37 (s, 9H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 168.5, 152.7, 150.8, 149.5, 145.8, 137.4, 134.2, 129.6, 128.9, 128.8, 127.8, 121.3, 115.8, 84.7, 84.7, 81.7, 27.6, 27.4.
MS (70 eV, EI) *m/z* (%): 286 (16), 243 (12), 242 (49) $[M-2Boc]^+$, 241 (10), 137 (16), 105 (14), 57 (100), 56 (12), 44 (11), 41 (15).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2986 (w), 1767 (s), 1756 (vs), 1371(w), 1270 (m), 1243 (s), 1130 (s), 1098 (s), 983 (w), 951 (w), 848 (w), 778 (w).
HRMS (FAB) for **$C_{30}H_{42}O_8N$**, $[M+Et_3N+H]^+$ (544.2910): found: 544.2884.

Synthesis of 4-*tert*-butoxycarbonyloxy-3-iodo-phthalic acid diethyl ester (94k)

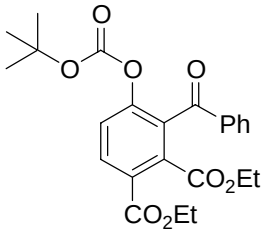


Prepared according to **TP 15** from 4-*tert*-butoxycarbonyloxy-phthalic acid diethyl ester (**91k**) (338 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 1 h], and iodine (381 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **94k** as a yellow oil (400 mg, 86 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.03 (d, ^3J(H,H) = 8.5 Hz, 1H), 7.24 (d, ^3J(H,H) = 8.5 Hz, 1H), 4.44 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.33 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.55 (s, 9H), 1.40 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.34 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 167.6, 163.5, 154.6, 149.9, 143.8, 131.6, 126.6, 122.7, 91.2, 84.9, 62.2, 61.9, 27.6, 14.1, 13.9.
MS (70 eV, EI) *m/z* (%): 364 (31) $[M-Boc]^+$, 319 (19), 291 (56), 71 (10), 57 (100), 41 (13).

IR (neat) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 1764 (w), 1723 (m), 1668 (w), 1588 (w), 1464 (w), 1368 (w), 1424 (s), 1142 (vs), 1024 (m).
HRMS (EI) for **$C_{17}H_{21}O_7I$** (464.0332): found: 464.0329.

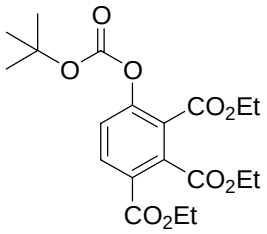
Synthesis of 3-benzoyl-4-*tert*-butoxycarbonyloxy-phthalic acid diethyl ester (94l)



Prepared according to **TP 15** from **91k** (338 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 1 h], CuCN·2LiCl (0.20 mL, 0.2 equiv., 1.0 M in THF), and benzoyl choride (281 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94l** as a white solid (364 mg, 82 %).

mp.: 115.7-117.1 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.99 (d, ^3J(H,H) = 8.6 Hz, 1H), 7.77 (d, ^3J(H,H) = 7.6 Hz, 2H), 7.55 (t, ^3J(H,H) = 7.6 Hz, 1H), 7.42 (t, ^3J(H,H) = 7.6 Hz, 2H), 7.39 (d, ^3J(H,H) = 8.6 Hz, 1H), 4.35 (q, ^3J(H,H) = 7.1 Hz, 2H), 4.08 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.35 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.29 (s, 9H), 1.06 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 192.8, 165.9, 165.4, 150.3, 150.1, 136.8, 134.8, 133.5, 132.5, 131.8, 129.4, 128.4, 128.3, 124.4, 84.4, 62.0, 61.9, 27.3, 14.0, 13.4.
MS (70 eV, EI) *m/z* (%): 342 (23) $[M-Boc]^+$, 297 (22), 296 (100), 295 (36), 267 (51), 251 (13), 224 (11), 223 (12), 207 (12), 191 (18), 139 (11), 105 (21), 77 (16), 57 (57), 41 (11).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2981 (w), 1764 (m), 1742 (m), 1721 (s), 1672 (s), 1583 (w), 1451 (w), 1420 (w), 1370 (w), 1299 (m), 1261 (m), 1223 (vs), 1141 (s), 1124 (s), 1051 (m), 981 (w), 883 (w), 775 (w), 713 (w).
HRMS (FAB) for **$C_{30}H_{42}NO_8$**, $[M+Et_3N+H]^+$ (554.2910): found: 554.2912.

Synthesis of 4-*tert*-butoxycarbonyloxy-benzene-1,2,3-tricarboxylic acid triethyl ester (94m)

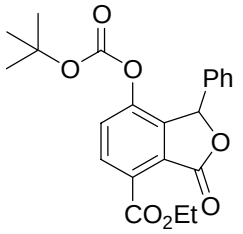


Prepared according to **TP 15** from **91k** (338 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 1 h], and ethyl cyanoformate (200 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **94m** as a yellow oil (321 mg, 78 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.03 (d, ^3J(H,H) = 8.6 Hz, 1H), 7.31 (d, ^3J(H,H) = 8.6 Hz, 1H), 4.38-4.30 (m, 6H), 1.53 (s, 9H), 1.34 (t, ^3J(H,H) = 7.2 Hz, 9H),

^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.5, 164.7, 163.8, 151.5, 150.4, 136.5, 133.2, 127.3, 125.4, 124.2, 84.6, 62.1, 61.9, 61.8, 27.5, 14.0, 13.9, 13.8.
MS (70 eV, EI) *m/z* (%): 310 (11) $[M-Boc]^+$, 265 (13), 264 (36), 263 (12), 208 (15), 192 (13), 191 (61), 190 (22), 164 (17), 120 (17), 119 (16), 57 (100), 41 (13).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1763 (m), 1726 (s), 1590 (w), 1466 (w), 1370 (w), 1225 (vs), 1145 (s), 1102 (m), 1052 (w), 1022 (m).
HRMS (EI) for **$C_{20}H_{26}O_9$** (410.1577): found: 410.1587.

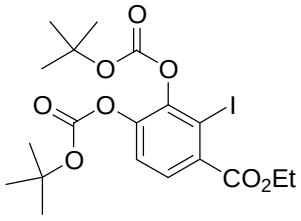
Synthesis of 7-*tert*-butoxycarbonyloxy-3-oxo-1-phenyl-1,3-dihydro-isobenzofuran-4-carboxylic acid ethyl ester (94n)



Prepared according to **TP 15** from **91k** (338 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 1 h], and benzaldehyde (159 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **94n** as a white solid (291 mg, 73 %).

mp.: 103.0-104.5 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.86 (d, ^3J(H,H) = 8.24 Hz, 1H), 7.48 (d, ^3J(H,H) = 8.24 Hz, 1H), 7.38-7.32 (m, 3H), 7.24-7.21 (m, 2H), 6.41 (s, 1H), 4.49 (q, ^3J(H,H) = 7.15 Hz, 2H), 1.44 (t, ^3J(H,H) = 7.15 Hz, 3H), 1.37 (s, 9H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.6, 165.4, 149.7, 147.6, 141.9, 134.5, 132.0, 129.9, 129.7, 129.0, 128.0, 127.4, 126.3, 85.0, 80.8, 62.5, 27.6, 14.3.
MS (70 eV, EI): *m/z* (%): 299 (7), 298 (16) $[M-Boc]^+$, 297 (6), 253 (11), 165 (5), 152 (5), 57 (100), 41 (7).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2981 (w), 1781 (s), 1764 (vs), 1735 (s), 1456 (w), 1368 (w), 1278 (m), 1268 (m), 1234 (s), 1224 (s), 1178 (m), 1139 (s), 1083 (m), 1020 (m), 999 (m), 871 (w), 844 (w), 769 (w), 691 (w).
HRMS (EI) for **$C_{22}H_{23}O_7$**, $[M+H]^+$ (399.1444): found: 399.1449.

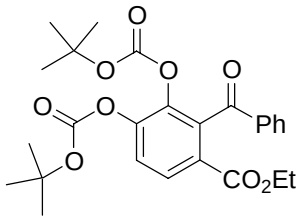
Synthesis of 3,4-bis-*tert*-butoxycarbonyloxy-2-iodo-benzoic acid ethyl ester (94o)



Prepared according to **TP 15** from 3,4-bis-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester (**91l**) (382 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], and iodine (381 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **94o** as a yellow oil (477 mg, 92 %).

^{1}H-NMR (200 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.70 (d, ^3J(H,H) = 8.6 Hz, 1H), 7.33 (d, ^3J(H,H) = 8.6 Hz, 1H), 4.38 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.56 (s, 9H), 1.53 (s, 9H), 1.38 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.5, 149.8, 149.4, 145.2, 144.3, 134.3, 128.6, 122.7, 93.2, 84.6, 84.5, 61.9, 27.6, 27.5, 14.1.
MS (70 eV, EI) *m/z* (%): 308 (32) $[M-2Boc]^+$, 263 (5), 137 (6), 57 (100), 41 (10).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 1766 (s), 1727 (m), 1370 (w), 1241 (vs), 1147 (s), 1114 (s), 1046 (w), 1026 (w).
HRMS (EI) for **$C_{19}H_{26}O_8I$**, $[M+H]^+$ (509.0672): found: 509.0653.

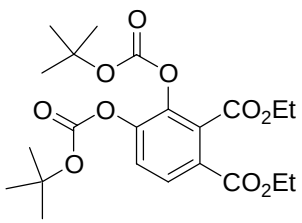
Synthesis of 2-benzoyl-3,4-bis-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester (94p)



Prepared according to **TP 15** from **91l** (382 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], CuCN·2LiCl (0.20 mL, 0.2 equiv., 1.0 M in THF), and benzoyl choride (281 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94p** as a white solid (438 mg, 90 %).

mp.: 144.3-145.2 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.03 (d, ^3J(H,H) = 8.6 Hz, 1H), 7.82-7.79 (m, 2H), 7.54-7.50 (m, 2H), 7.42-7.38 (m, 2H), 4.12 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.52 (s, 9H), 1.30 (s, 9H), 1.05 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 192.5, 164.3, 149.7, 149.6, 146.8, 139.7, 136.7, 136.5, 133.3, 129.2, 128.7, 128.4, 126.8, 123.6, 84.5, 84.2, 61.7, 27.5, 27.2, 13.6.
MS (70 eV, EI) *m/z* (%): 286 (35) $[M-2Boc]^+$, 241 (14), 240 (71), 239 (23), 105 (16), 57 (100), 41 (12).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2980 (w), 1779 (m), 1767 (m), 1726 (m), 1678 (m), 1454 (w), 1373 (w), 1302 (w), 1243 (vs), 1151 (s), 1126 (s), 1052 (w), 1028 (w), 845 (w), 769 (w), 692 (w).
HRMS (FAB) for **$C_{32}H_{46}NO_9$**, $[M+Et_3N+H]^+$ (588.3173): found: 588.3171.
HRMS (FAB) for **$C_{26}H_{30}O_9Na$**, $[M+Na]^+$ (509.1788): found: 509.1784.

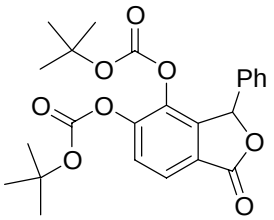
Synthesis of 3,4-bis-*tert*-butoxycarbonyloxy-phthalic acid diethyl ester (94q)



Prepared according to **TP 15** from **91l** (382 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], and ethyl cyanoformate (200 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 15 : 1) yielded **94q** as a yellow oil (402 mg, 88 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.87 (d, ^3J(H,H) = 8.6 Hz, 1H), 7.41 (d, ^3J(H,H) = 8.6 Hz, 1H), 4.38 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.31 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.51 (s, 9H), 1.50 (s, 9H), 1.36-1.30 (m, 6H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 164.7, 164.2, 149.6, 149.6, 146.5, 139.9, 130.6, 128.2, 126.4, 123.7, 84.5, 84.3, 61.8, 61.6, 27.4, 27.4, 14.0, 13.9.
MS (70 eV, EI) *m/z* (%): 254 (12) $[M-2Boc]^+$, 209 (12), 208 (72), 207 (11), 181 (13), 180 (55), 136 (15), 57 (100), 41 (17).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1770 (m), 1725 (m), 1370 (w), 1241 (vs), 1148 (s), 1123 (m), 1050 (m), 1028 (m), 877 (w), 729 (m).
HRMS (FAB) for **$C_{28}H_{46}NO_{10}$**, $[M+Et_3N+H]^+$ (556.3122): found: 556.3120.

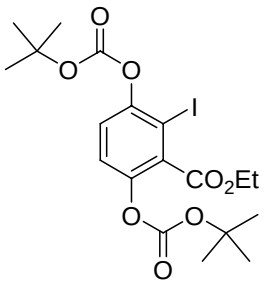
Synthesis of carbonic acid 4-*tert*-butoxycarbonyloxy-1-oxo-3-phenyl-1,3-dihydro-isobenzofuran-5-yl ester *tert*-butyl ester (94r)



Prepared according to **TP 15** from **91l** (382 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], and benzaldehyde (159 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94r** as a white solid (403 mg, 91 %).

mp.: 111.8-113.2 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.86 (d, ^3J(H,H) = 8.2 Hz, 1H), 7.49 (d, ^3J(H,H) = 8.2 Hz, 1H), 7.38-7.31 (m, 3H), 7.25-7.20 (m, 2H), 6.48 (s, 1H), 1.52 (s, 9H), 1.35 (s, 9H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 168.7, 149.7, 148.7, 147.6, 142.5, 137.6, 134.1, 129.6, 128.8, 127.8, 125.3, 124.9, 123.6, 84.7, 84.6, 81.4, 27.5, 27.3.
MS (70 eV, EI) *m/z* (%): 331 (8), 287 (6), 243 (8), 242 (30) $[M-2Boc]^+$, 241 (8), 164 (6), 137 (6), 57 (100), 41 (12).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2978 (w), 1761 (vs), 1484 (w), 1370 (w), 1298 (m), 1270 (m), 1254 (m), 1149 (m), 1129 (m), 1093 (m), 984 (w), 774 (w), 700 (w).
HRMS (FAB) for **$C_{30}H_{42}O_8N$**, $[M+Et_3N+H]^+$ (544.2910): found: 544.2899.

Synthesis of 3,6-bis-*tert*-butoxycarbonyloxy-2-iodo-benzoic acid ethyl ester (94s)

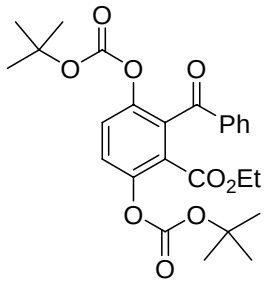


Prepared according to **TP 15** from 2,5-bis-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester (**91m**) (382 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction

condition: 0 °C for 3 h], and iodine (381 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94s** as a white solid (458 mg, 90 %).

mp.: 118.3-119.4 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.25 (d, ^3J(H,H) = 8.90 Hz, 1H), 7.22 (d, ^3J(H,H) = 8.90 Hz, 1H), 4.42 (q, ^3J(H,H) = 7.15 Hz, 2H), 1.56 (s, 9H), 1.52 (s, 9H), 1.40 (t, ^3J(H,H) = 7.14 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.0, 150.8, 150.5, 149.4, 145.5, 134.8, 123.8, 123.7, 90.0, 84.6, 84.4, 62.3, 27.7, 27.6, 14.1.
MS (70 eV, EI) *m/z* (%): 308 (49) $[M-2Boc]^+$, 263 (14), 262 (100), 57 (77), 56 (11), 44 (12), 41 (24).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2985 (w), 1764 (vs), 1726 (s), 1464 (w), 1371 (w), 1250 (m), 1216 (m), 1137 (s), 1097 (m), 1047 (w), 1025 (w), 1010 (w), 873 (w).
HRMS (FAB) for **$C_{19}H_{25}O_8INa$**, $[M+Na]^+$ (531.0492): found: 531.0459.

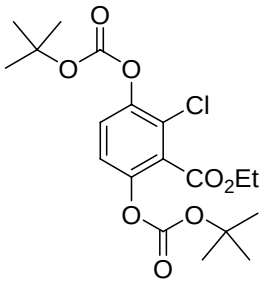
Synthesis of 2-benzoyl-3,6-bis-*tert*-butoxycarbonyloxy-benzoic acid ethyl ester (94t)



Prepared according to **TP 15** from **91m** (382 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], CuCN·2LiCl (0.20 mL, 0.2 equiv., 1.0 M in THF), and benzoyl choride (281 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94t** as a yellow oil (444 mg, 91 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.81-7.78 (m, 2H), 7.55-7.51 (m, 1H), 7.43-7.39 (m, 2H), 7.38 (d, ^3J(H,H) = 8.9 Hz, 1H), 7.31 (d, ^3J(H,H) = 8.9 Hz, 1H), 4.02 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.54 (s, 9H), 1.28 (s, 9H), 0.97 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 192.4, 163.2, 151.0, 150.6, 147.3, 145.4, 136.9, 134.6, 133.3, 130.1, 129.2, 128.4, 127.0, 125.1, 84.2, 84.1, 61.8, 27.6, 27.3, 13.3.
MS (70 eV, EI) *m/z* (%): 286 (28) $[M-2Boc]^+$, 241 (9), 240 (47), 239 (100), 105 (8), 77 (11), 56 (8), 44 (8), 41 (11).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2981 (w), 1760 (s), 1731 (m), 1684 (w), 1450 (w), 1370 (w), 1251 (m), 1217 (s), 1136 (s), 1125 (vs), 1054 (w), 1026 (w), 712 (w), 696 (w).
HRMS (FAB) for **$C_{26}H_{30}O_9Na$**, $[M+Na]^+$ (509.1788): found: 509.1750.

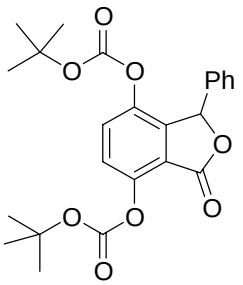
Synthesis of 3,6-bis-*tert*-butoxycarbonyloxy-2-chloro-benzoic acid ethyl ester (94u)



A dry and nitrogen-flushed 100 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of **91m** (3.824 g, 10.0 mmol) in dry THF (9 mL). After cooling to 0 °C, TMPMgCl·LiCl (9.20 mL, 1.1 equiv., 1.20 M in THF) was added dropwise and stirred for 1 h. The reaction mixture was cooled to −40 °C, and then $PhSO_2Cl$ (2.650 g, 15.0 mmol) was added, warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 25 : 1) yielded **94u** as a yellow solid (3.253 g, 78 %).

mp.: 60.3-62.2 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.28 (d, ^3J(H,H) = 8.9 Hz, 1H), 7.17 (d, ^3J(H,H) = 8.9 Hz, 1H), 4.41 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.55 (s, 9H), 1.53 (s, 9H), 1.38 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 163.1, 150.8, 150.4, 146.2, 145.2, 128.4, 125.6, 124.7, 122.0, 84.6, 84.4, 62.2, 27.6, 27.6, 14.1.
MS (70 eV, EI) *m/z* (%): 218 (11), 216 (34) $[M-2Boc]^+$, 172 (15), 171 (13), 170 (46), 57 (100), 41 (14).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 1762 (s), 1737 (m), 1470 (w), 1370 (w), 1272 (m), 1244 (m), 1219 (s), 1141 (vs), 1108 (s), 1049 (w), 1024 (w).
HRMS (FAB) for **$C_{25}H_{41}O_8N^{35}Cl$**, $[M+Et_3N+H]^+$ (518.2515): found: 518.2529.

Synthesis of carbonic acid 7-*tert*-butoxycarbonyloxy-3-oxo-1-phenyl-1,3-dihydro-isobenzofuran-4-yl ester *tert*-butyl ester (94v)

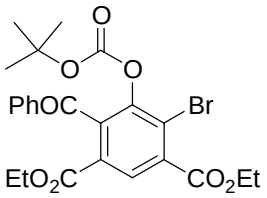


Prepared according to **TP 15** from **91m** (382 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) [reaction condition: 0 °C for 3 h], and benzaldehyde (159 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **94v** as a white solid (341 mg, 77 %).

mp.: 57.3-59.4 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.41 (d, ^3J(H,H) = 8.6 Hz, 1H), 7.37-7.31 (m, 3H), 7.27 (d, ^3J(H,H) = 8.6 Hz, 1H), 7.24-7.20 (m, 2H), 6.40 (s, 1H), 1.60 (s, 9H), 1.35 (s, 9H).

^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.2, 150.5, 149.8, 146.0, 142.9, 141.8, 134.1, 129.6, 129.1, 128.8, 127.8, 123.9, 119.9, 84.8, 84.4, 81.1, 27.6, 27.4.
MS (70 eV, EI) *m/z* (%): 243 (15), 242 (100) $[M-2Boc]^+$, 224 (11), 137 (35), 105 (10), 57 (67), 56 (10), 44 (10), 41 (18).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1758 (s), 1495 (w), 1371 (w), 1279 (m), 1219 (m), 1133 (vs), 1093 (m), 1048 (m), 1027 (m), 980 (w), 880 (w).
HRMS (FAB) for **$C_{30}H_{42}O_8N$**, $[M+Et_3N+H]^+$ (544.2910): found: 544.2916.

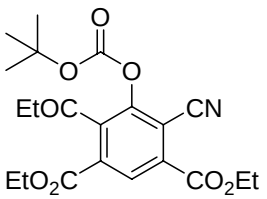
Synthesis of 4-benzoyl-6-bromo-5-*tert*-butoxycarbonyloxy-isophthalic acid diethyl ester (96)



A dry and nitrogen-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of **94g** (1.25 g, 3.0 mmol) in dry THF (9 mL). After cooling to 0 °C, TMPMgCl·LiCl (2.41 mL, 1.1 equiv., 1.37 M in THF) was added dropwise and stirred for 1 h. The reaction mixture was cooled to −40 °C, and then CuCN·2LiCl (0.6 mL, 1.0 M in THF) was added and stirred for 5 min. Thereafter, benzoyl choride (696 mg, 6.0 mmol) was added at −40 °C, warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 60 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **96** as a yellow oil (1.28 g, 82 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.37 (s, 1H), 7.77 (d, ^3J(H,H) = 7.7 Hz, 2H), 7.55 (t, ^3J(H,H) = 7.7 Hz, 1H), 7.42 (t, ^3J(H,H) = 7.7 Hz, 2H), 4.46 (q, ^3J(H,H) = 7.1 Hz, 2H), 4.14 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.44 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.31 (s, 9H), 1.05 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.7, 164.7, 163.6, 149.0, 146.7, 138.4, 136.0, 135.0, 133.7, 129.9, 129.3, 128.9, 128.5, 123.3, 84.9, 62.4, 62.2, 27.2, 14.2, 13.5.
MS (70 eV, EI) *m/z* (%): 422 (43) $[M-Boc]^+$, 421 (25); 420 (44), 419 (16), 377 (30), 376 (67), 375 (100), 374 (64), 373 (79), 317 (14), 315 (13), 105 (48), 77 (20), 57 (85), 41 (13).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1770 (m), 1723 (s), 1682 (m), 1451 (w), 1370 (w), 1324 (w), 1235 (vs), 1146 (s), 1120 (m), 1053 (m), 1022 (w).
HRMS (FAB) for **$C_{30}H_{41}O_8N^{79}Br$**, $[M+Et_3N+H]^+$ (622.2016): found: 622.2014.

Synthesis of 3,5-di(ethoxycarbonyl)-2-cyano-6-propionylphenyl *tert*-butyl carbonate (98)

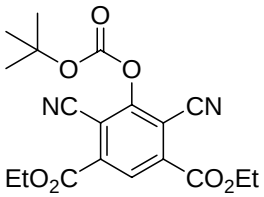


A dry and nitrogen-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of **94f** (363 mg, 1.0 mmol) in dry THF (3 mL). After

cooling to 0 °C, TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) was added dropwise and stirred for 50 min. The reaction mixture was cooled to −40 °C, and then CuCN·2LiCl (1.0 mL, 1.0 equiv., 1.0 M in THF) was added and stirred for 5 min. Thereafter, propionyl choride (231 mg, 2.5 mmol) was added at −40 °C, warmed to 25 °C and stirred for an additional hour. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 15 : 1) yielded **98** as a yellow solid (295 mg, 81 %).

mp.: 114.9-116.3 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.59 (s, 1H), 4.50 (q, ^3J(H,H) = 7.1 Hz, 2H), 4.39 (q, ^3J(H,H) = 7.1 Hz, 2H), 2.77 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.55 (s, 9H), 1.46 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.38 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.24 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.4, 163.2, 162.3, 150.5, 149.5, 141.5, 133.9, 132.1, 129.9, 112.8, 112.1, 86.5, 63.1, 62.9, 37.2, 27.4, 14.0, 14.0, 7.4.
MS (70 eV, EI) *m/z* (%): 291 (12), 290 (76), 274 (37), 273 (19), 263(13), 262 (100), 246 (11), 244 (20), 234 (76), 216 (31), 162 (13), 57 (44), 44 (10), 41 (17).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2990 (w), 1761 (s), 1717 (vs), 1373 (w), 1326 (m), 1240 (s), 1220 (m), 1139 (s), 1095 (w), 1052 (m), 1036 (m), 1018 (w), 860 (w).
HRMS (FAB) for **$C_{27}H_{41}O_8N_2$**, $[M+Et_3N+H]^+$ (521.2857): found: 521.2835.

Synthesis of 3,5-di(ethoxycarbonyl)-2,6-dicyanophenyl *tert*-butyl carbonate (99)

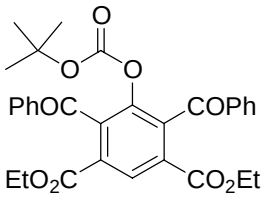


A dry and nitrogen-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of **94f** (363 mg, 1.0 mmol) in dry THF (3 mL). After cooling to 0 °C, TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) was added dropwise and stirred for 50 min. The reaction mixture was cooled to −40 °C, and then TsCN (286 mg, 1.5 mmol) in dry THF (2 mL) was added, stirred for 30 min, warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 8 : 1) yielded **99** as a yellow solid (296 mg, 76 %).

mp.: 90.0-90.9 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.67 (s, 1H), 4.53 (q, ^3J(H,H) = 7.2 Hz, 4H), 1.61 (s, 9H), 1.47 (t, ^3J(H,H) = 7.2 Hz, 6H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 161.5, 157.1, 148.9, 136.8, 129.9, 112.8, 111.1, 87.7, 63.6, 27.5, 13.9.
MS (70 eV, EI) *m/z* (%): 289 (14), 288 (36) $[M-Boc]^+$, 260 (27), 244 (12), 243 (80), 233 (11), 232 (51), 216 (18), 215 (52), 189 (18), 188 (25), 114 (11), 57 (100), 56 (12), 44 (12), 41 (21).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 1774 (s), 1728 (vs), 1374 (m), 1334 (w), 1242 (vs), 1215 (m), 1140 (vs), 1060 (m), 1028 (m), 942 (w), 858 (w), 766 (w).
HRMS (EI) for **$C_{14}H_{12}O_5N_2$**, $[M-C_5H_8O_2]^+$ (288.0746): found: 288.0739.
HRMS (FAB) for **$C_{14}H_{12}O_5N_2$**, $[M-C_5H_8O_2]^+$ (288.0746): found: 288.0714.
HRMS (FAB) for **$C_{14}H_{11}O_5N_2$**, $[M-C_5H_9O_2]^+$ (287.0668): found: 287.0674.

$C_{19}H_{20}N_2O_7$: calc.: C: 58.76; H: 5.19; N: 7.21. found: C: 58.62; H: 5.19; N: 7.17.

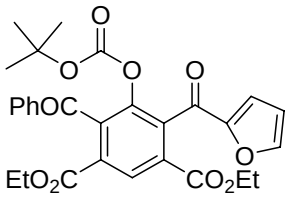
Synthesis of 4,6-dibenzoyl-5-*tert*-butoxycarbonyloxy-isophthalic acid diethyl ester (101a)



A dry and nitrogen-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of **94d** (443 mg, 1.0 mmol) in dry THF (3 mL). After cooling to −20 °C, TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF) was added dropwise and stirred for 2 h. The reaction mixture was cooled to −40 °C, and then CuCN·2LiCl (0.2 mL, 1.0 M in THF) was added and stirred for 5 min. Thereafter, benzoyl choride (281 mg, 2.0 mmol) was added at −40 °C, warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by *flash*-chromatography (*n*-pentane/diethyl ether = 5 : 1) yielded **101a** as a yellow solid (507 mg, 92 %).

mp.: 78.8-81.2 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.71 (s, 1H), 7.80-7.77 (m, 4H), 7.55-7.51 (m, 2H), 7.42-7.39 (m, 4H), 4.16 (q, ^3J(H,H) = 7.2 Hz, 4H), 1.08 (t, ^3J(H,H) = 7.2 Hz, 6H), 1.05 (s, 9H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.9, 163.7, 149.5, 145.6, 139.7, 136.1, 133.6, 131.2, 129.8, 129.2, 128.4, 84.5, 62.2, 26.8, 13.5.
MS (70 eV, EI) *m/z* (%): 447 (35), 446 (100) $[M-Boc]^+$, 445 (22), 402 (10), 401 (42), 400 (76), 399 (98), 372 (20), 371 (47), 355 (15), 354 (9), 327 (12), 299 (11), 295 (45), 293 (18), 223 (16), 105 (79), 97 (12), 83 (10), 77 (37), 71 (10), 69 (10), 57 (40), 55 (10), 41 (16).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1769 (m), 1720 (s), 1678 (m), 1599 (w), 1582 (w), 1449 (w), 1235 (vs), 1157 (m), 1138 (m), 1051 (m), 1036 (m), 917 (w), 701 (m).
HRMS (FAB) for **$C_{37}H_{46}O_9N$**, $[M+Et_3N+H]^+$ (648.3173): found: 648.3148.

Synthesis of diethyl 4-benzoyl-5-[(*tert*-butoxycarbonyl)oxy]-6-(2-furoyl)isophthalate (101b)

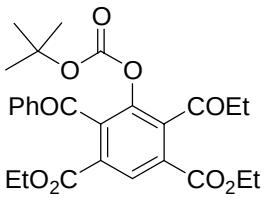


Prepared according to the same procedure for the preparation of **101a** from **94d** (443 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF), CuCN·2LiCl (0.20 mL, 0.2 equiv., 1.0 M in THF), and 2-furoyl choride (261 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 3 : 1) yielded **101b** as an orange solid (312 mg, 58 %).

mp.: 65.5-67.3 °C.

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.69 (s, 1H), 7.78 (d, ^3J(H,H) = 7.5 Hz, 2H), 7.58 (dd, ^3J(H,H) = 1.6 Hz, ^4J(H,H) = 0.8 Hz, 1H), 7.56-7.52 (m, 1H), 7.41 (t, ^3J(H,H) = 7.7 Hz, 2H), 7.06 (dd, ^3J(H,H) = 3.4 Hz, ^4J(H,H) = 0.8 Hz, 1H), 6.52 (dd, ^3J(H,H) = 3.6 Hz, ^3J(H,H) = 1.6 Hz, 1H), 4.23 (q, ^3J(H,H) = 7.1 Hz, 2H), 4.16 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.17 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.16 (s, 9H), 1.08 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.9, 179.0, 163.8, 163.7, 152.3, 149.8, 147.1, 146.0, 139.6, 137.9, 136.2, 133.6, 131.5, 131.4, 129.8, 129.3, 128.5, 119.2, 112.5, 84.7, 62.3, 27.0, 13.7, 13.5.
MS (70 eV, EI) *m/z* (%): 437 (31), 436 (100) $[M-Boc]^+$, 408 (46), 391 (26), 362 (66), 361 (85), 344 (30), 334 (37), 316 (26), 293 (33), 105 (47), 95 (27), 77 (29), 57 (30), 41 (32).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2984 (w), 1768 (m), 1723 (m), 1671 (m), 1568 (w), 1464 (m), 1371 (w), 1238 (s), 1141 (m), 1043 (m), 1024 (m), 910 (m), 727 (m).
HRMS (FAB) for **$C_{35}H_{44}O_{10}N$**, $[M+Et_3N+H]^+$ (638.2965): found: 638.2960.

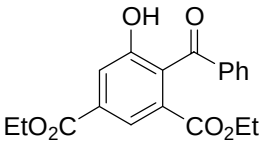
Synthesis of 4-benzoyl-5-*tert*-butoxycarbonyloxy-6-propionyl-isophthalic acid diethyl ester (101c)



Prepared according to the same procedure for the preparation of **101a** from **94d** (443 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF), CuCN·2LiCl (1.00 mL, 1.0 equiv., 1.0 M in THF), and propionyl choride (231 mg, 2.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 15 : 1) yielded **101c** as a pale yellow oil (450 mg, 90 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.61 (s, 1H), 7.78-7.74 (m, 2H), 7.55-7.51 (m, 1H), 7.42-7.38 (m, 2H), 4.38 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.12 (q, ^3J(H,H) = 7.2 Hz, 2H), 2.79 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.37 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.23 (s, 9H), 1.18 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.03 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 202.5, 192.0, 163.9, 163.6, 149.9, 144.5, 142.1, 139.7, 136.0, 133.6, 130.6, 129.9, 129.6, 129.3, 128.4, 84.9, 62.3, 62.2, 37.0, 27.0, 14.0, 13.4, 7.5.
MS (70 eV, EI) *m/z* (%): 398 (4) $[M-Boc]^+$, 370 (13), 369 (52), 353 (9), 352 (9), 307 (7), 306 (19), 296 (18), 295 (100), 278 (6), 223 (8), 105 (11), 77 (6), 57 (5), 41 (4).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1768 (m), 1721 (s), 1681 (m), 1451 (w), 1371 (w), 1324 (w), 1238 (vs), 1144 (s), 1094 (w), 1048 (m), 910 (m), 727 (s).
HRMS (FAB) for **$C_{33}H_{46}O_9N$**, $[M+Et_3N+H]^+$ (600.3173): found: 600.3166.

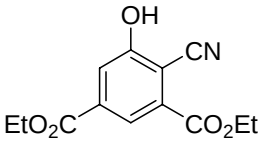
Synthesis of 4-benzoyl-5-hydroxy-isophthalic acid diethyl ester (102a)



Prepared according to **TP 16** from **94d** (177 mg, 0.4 mmol) in TFA (1.0 mL). Evaporate excess TFA in *vacuo* without further purification yielded **102a** as a yellow oil (134 mg, 98 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.14 (d, ^4J(H,H) = 1.5 Hz, 1H), 7.85 (d, ^4J(H,H) = 1.5 Hz, 1H), 7.74-7.70 (m, 2H), 7.58-7.52 (m, 1H), 7.45-7.39 (m, 2H), 4.41 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.90 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.41 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.02 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 197.3, 165.6, 165.2, 156.3, 137.8, 133.4, 132.4, 128.8, 128.6, 128.0, 122.5, 122.1, 61.9, 14.2, 13.5.
MS (70 eV, EI) *m/z* (%): 342 (25) [M^+], 297 (21), 296 (42), 295 (100), 237 (13), 105 (21), 77 (10).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3347 (brw), 2983 (w), 1718 (s), 1581 (w), 1422 (w), 1371 (w), 1326 (m), 1230 (vs), 1175 (w), 1095 (w), 1022 (m), 918 (w), 765 (w), 711 (w).
HRMS (EI) for **$C_{19}H_{18}O_6$** (342.1103): found: 342.1080.

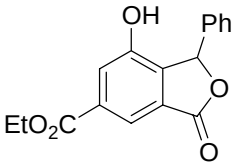
Synthesis of diethyl 4-cyano-5-hydroxybenzene-1,3-dioate (102b)



Prepared according to **TP 16** from **94f** (145 mg, 0.4 mmol) in TFA (1.0 mL). Evaporate excess TFA in *vacuo* without further purification yielded **102b** as a white solid (103 mg, 98 %).

mp.: 161.5-163.0 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.22 (s, 1H), 7.92 (s, 1H), 4.47 (q, ^3J(H,H) = 7.1 Hz, 2H), 4.42 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.45 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.41 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 164.6, 163.5, 160.2, 135.2, 133.7, 123.4, 121.2, 114.1, 103.1, 62.7, 62.4, 14.2, 14.1.
MS (70 eV, EI) *m/z* (%): 263 (54) [M^+], 235 (27), 218 (100), 207 (64), 191 (38), 190 (89), 163 (23), 145 (10), 89 (15).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3142 (brm), 2244 (w), 1719 (s), 1603 (w), 1430 (w), 1371 (m), 1323 (s), 1230 (vs), 1090 (m), 1025 (s), 989 (m), 760 (s).
HRMS (EI) for **$C_{13}H_{13}NO_5$** (263.0794): found: 263.0791.

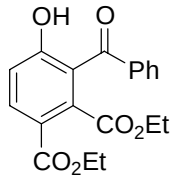
Synthesis of ethyl 1,3-dihydro-7-hydroxy-3-oxo-1-phenylisobenzofuran-5-carboxylate (102c)



Prepared according to **TP 16** from **94h** (159 mg, 0.4 mmol) in TFA (1.0 mL). Evaporate excess TFA in *vacuo* without further purification yielded **102c** as a white solid (118 mg, 99 %).

mp.: 222.9-224.0 °C.
^{1}H-NMR (400 MHz, CD_3COCD_3, 25 °C) δ/ppm: 9.74 (s, 1H), 7.98 (d, ^4J(H,H) = 1.0 Hz, 1H), 7.79 (d, ^4J(H,H) = 1.0 Hz, 1H), 7.42-7.32 (m, 5H), 6.62 (s, 1H), 4.39 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.39 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (100 MHz, CD_3COCD_3, 25 °C) δ/ppm: 170.9, 166.6, 154.7, 141.5, 137.7, 135.9, 130.9, 130.5, 130.2, 129.5, 122.6, 118.6, 83.2, 63.1, 15.5.
MS (70 eV, EI) *m/z* (%): 299 (33), 298 (84) [M^+], 269 (11), 253 (25), 225 (11), 194 (11), 193 (94), 192 (24), 181 (18), 152 (26), 105 (100), 77 (12).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3130 (brm), 2983 (w), 1726 (vs), 1715 (vs), 1610 (m), 1447 (m), 1289 (m), 1238 (s), 1216 (m), 1132 (m), 964 (m), 753 (m).
HRMS (EI) for **$C_{17}H_{14}O_5$** (298.0841): found: 298.0817.

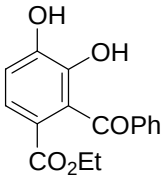
Synthesis of 3-benzoyl-4-hydroxy-phthalic acid diethyl ester (102d)



Prepared according to **TP 16** from **94l** (177 mg, 0.4 mmol) in TFA (1.0 mL). Evaporate excess TFA in *vacuo* without further purification yielded **102d** as a white solid (134 mg, 98 %).

mp.: 173.1-174.1 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 9.49 (s, 1H), 7.93 (d, ^3J(H,H) = 8.7 Hz, 1H), 7.67-7.64 (m, 2H), 7.58-7.55 (m, 1H), 7.44-7.40 (m, 2H), 7.15 (d, ^3J(H,H) = 8.7 Hz, 1H), 4.28 (q, ^3J(H,H) = 7.1 Hz, 2H), 3.56 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.32 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.04 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 199.2, 166.6, 165.9, 161.0, 137.9, 136.4, 134.8, 133.3, 129.4, 128.2, 122.4, 120.8, 119.0, 61.8, 61.6, 14.1, 13.3.
MS (70 eV, EI) *m/z* (%): 342 (6) [M^+], 313 (5), 298 (6), 297 (30), 296 (100), 295 (26), 269 (11), 268 (18), 267 (73), 252 (5), 251 (20), 239 (9), 224 (8), 223 (22), 196 (7), 195 (7), 191 (28), 168 (5), 139 (8), 119 (13), 105 (19), 77 (17).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3338 (s), 2990 (w), 2936 (w), 1738 (s), 1684 (s), 1665 (s), 1580 (vs), 1451 (w), 1365 (m), 1294 (vs), 1270 (m), 1250 (s), 1133 (m), 1018 (m), 988 (m).
HRMS (EI) for **$C_{19}H_{18}O_6$** (342.1103): found: 342.1091.

Synthesis of 2-benzoyl-3,4-dihydroxy-benzoic acid ethyl ester (102e)

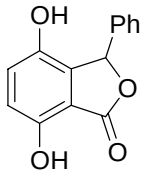


Prepared according to **TP 16** from **94p** (195 mg, 0.4 mmol) in TFA (1.0 mL). Evaporate excess TFA in *vacuo* without further purification yielded **102e** as a white solid (114 mg, 99 %).

mp.: 147.2-149.4 °C.

^{1}H-NMR (400 MHz, CD_3COCD_3, 25 °C) δ/ppm: 7.82-7.78 (m, 2H), 7.60-7.55 (m, 1H), 7.53 (d, ^3J(H,H) = 8.4 Hz, 1H), 7.50-7.45 (m, 2H), 7.05 (d, ^3J(H,H) = 8.4 Hz, 1H), 4.02 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.03 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (100 MHz, CD_3COCD_3, 25 °C) δ/ppm: 196.2, 167.0, 151.2, 144.6, 140.0, 134.3, 131.8, 130.5, 130.2, 124.7, 122.6, 116.5, 62.2, 15.1.
MS (70 eV, EI) *m/z* (%): 286 (35) [M^+], 241 (31), 240 (100), 239 (91), 212 (17), 105 (21), 77 (21).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3166 (brs), 2983 (w), 1695 (s), 1646 (s), 1605 (m), 1577 (s), 1501 (w), 1450 (w), 1370 (m), 1317 (m), 1287 (vs), 1272 (vs), 1195 (s), 1160 (s), 1125 (s), 1095 (m), 1002 (w) 958 (w).
HRMS (EI) for **$C_{16}H_{14}O_5$** (286.0841): found: 286.0820.

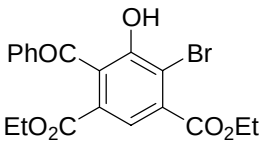
Synthesis of 4,7-dihydroxy-3-phenylisobenzofuran-1(3H)-one (102f)



Prepared according to **TP 16** from **94v** (177 mg, 0.4 mmol) in TFA (1.0 mL). Evaporate excess TFA in *vacuo* without further purification yielded **102f** as a white solid (95 mg, 98 %).

mp.: decompose above 250 °C.
^{1}H-NMR (400 MHz, CD_3COCD_3, 25 °C) δ/ppm: 8.15 (s, 2H), 7.42-7.32 (m, 5H), 7.07 (d, ^3J(H,H) = 8.6 Hz, 1H), 6.86 (d, ^3J(H,H) = 8.62 Hz, 1H), 6.51 (s, 1H).
^{13}C-NMR (100 MHz, CD_3COCD_3, 25 °C) δ/ppm: 172.0, 151.3, 146.8, 138.3, 136.3, 130.8, 130.4, 129.5, 125.6, 119.1, 113.8, 83.4.
MS (70 eV, EI) *m/z* (%): 243 (15), 242 (100) [M^+], 223 (11), 137 (55), 105 (13).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3215 (brm), 1716 (s), 1633 (w), 1502 (m), 1392 (w), 1368 (w), 1283 (m), 1250 (w), 1108 (w), 1024 (w), 935 (w), 819 (w), 690 (w).
HRMS (EI) for **$C_{14}H_{10}O_4$** (242.0579): found: 242.0580.

Synthesis of 4-benzoyl-6-bromo-5-hydroxy-isophthalic acid diethyl ester (102g)

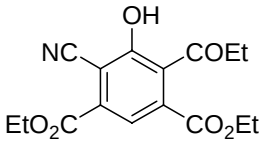


Prepared according to **TP 16** from **96** (209 mg, 0.4 mmol) in TFA (1.0 mL). Evaporate excess TFA in *vacuo* without further purification yielded **102g** as a yellow oil (166 mg, 98 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.05 (s, 1H), 7.77 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 1.3 Hz, 2H), 7.59-7.56 (m, 1H), 7.45 (t, ^3J(H,H) = 8.0 Hz, 2H), 7.00 (s, 1H), 4.46 (q, ^3J(H,H) = 7.1 Hz, 2H), 4.06 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.45 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.05 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 194.2, 164.8, 164.4, 151.5, 136.9, 134.0, 133.6, 129.8, 129.6, 128.9, 128.7, 124.1, 115.4, 62.3, 62.1, 14.2, 13.5.
MS (70 eV, EI) *m/z* (%): 422 (30), 421 (17), 420 (30) [M^+], 419 (11), 377 (25), 376 (54), 375 (100), 374 (51), 373 (76), 347 (13), 345 (12), 317 (19), 315 (18), 296 (10), 295 (20), 105 (62), 77 (31).

IR (neat) $\tilde{\nu}$ (cm^{-1}): 3421 (brw), 2986 (w), 1790 (w), 1718 (m), 1684 (m), 1597 (w), 1398 (w), 1374 (w), 1305 (w), 1250 (m), 1211 (m), 1155 (s), 1120 (m), 1023 (m), 965 (w), 922 (w), 713 (w), 685 (w).
HRMS (EI) for **$C_{19}H_{17}O_6{}^{79}Br$** (420.0209): found: 420.0190.

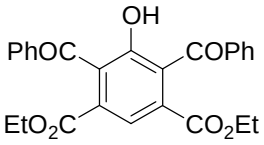
Synthesis of diethyl 4-cyano-5-hydroxy-6-propionylbenzene-1,3-dioate (102h)



Prepared according to **TP 16** from **98** (168 mg, 0.4 mmol) in TFA (1.0 mL). Evaporate excess TFA in *vacuo* without further purification yielded **102h** as a white solid (123 mg, 96 %).

mp.: 131.3-134.7 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.06 (s, 1H), 4.47 (q, ^3J(H,H) = 7.1 Hz, 2H), 4.40 (q, ^3J(H,H) = 7.1 Hz, 2H), 2.81 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.44 (t, ^3J(H,H) = 7.1 Hz, 3H) , 1.39 (t, ^3J(H,H) = 7.1 Hz, 3H) , 1.21 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 205.4, 164.9, 162.7, 158.8, 134.7, 134.2, 123.2, 113.2, 104.4, 62.9, 36.6, 14.0, 14.0, 8.0.
MS (70 eV, EI) *m/z* (%): 320 (21) [M^+], 370 (9), 369 (43), 353 (7), 352 (7), 307 (5), 306 (13), 296 (14), 295 (100), 278 (5), 223 (8), 105 (8), 77 (4).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3329 (brm), 2988 (w), 2944 (w), 2234 (w), 1730 (s), 1713 (vs), 1472 (w), 1414 (m), 1372 (m), 1330 (s), 1251 (m), 1220 (s), 1090 (m), 1069 (w), 1024 (s), 941 (w).
HRMS (EI) for **$C_{16}H_{18}O_6N$**, $[M+H]^+$ (320.1129): found: 320.1120.

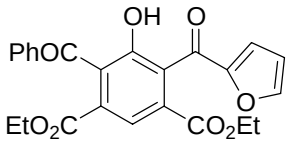
Synthesis of 4,6-dibenzoyl-5-hydroxy-isophthalic acid diethyl ester (102i)



Prepared according to **TP 16** from 4,6-dibenzoyl-5-*tert*-butoxycarbonyloxy-isophthalic acid diethyl ester (**101a**) (218 mg, 0.4 mmol) and TFA (1.0 mL). Evaporation of excess TFA in *vacuo* yielded without further purification **102i** as a yellow solid (175 mg, 98 %).

mp.: 155.7-157.4 °C.
^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.15 (s, 1H), 7.81-7.76 (m, 4H), 7.61-7.54 (m, 2H), 7.49-7.42 (m, 4H), 3.98 (q, ^3J(H,H) = 7.1 Hz, 4H), 1.06 (t, ^3J(H,H) = 7.1 Hz, 6H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 195.7, 164.7, 155.3, 137.4, 133.6, 133.3, 129.4, 128.8, 128.7, 122.6, 62.1, 13.5.
MS (70 eV, EI) *m/z* (%): 447 (25), 446 (94) [M^+], 445 (19), 401 (32), 400 (71), 399 (100), 372 (18), 371 (44), 355 (14), 354 (10), 327 (11), 295 (47), 293 (18), 223 (15), 105 (58), 77 (30).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3286 (brw), 2990 (w), 1725 (s), 1708 (s), 1681 (s), 1646 (s), 1595 (m), 1580 (m), 1468 (w), 1448 (m), 1291 (m), 1248 (vs), 1202 (m), 1158 (m), 1024 (m), 916 (m), 706 (s), 683 (m).
HRMS (EI) for **$C_{26}H_{22}O_7$** (446.1366): found: 446.1371.

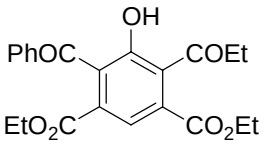
Synthesis of 4-benzoyl-6-(furan-2-carbonyl)-5-hydroxy-isophthalic acid diethyl ester (102j)



Prepared according to **TP 16** from **101b** (214 mg, 0.4 mmol) in TFA (1.0 mL). Evaporate excess TFA in *vacuo* without further purification yielded **102j** as a yellow oil (157 mg, 90 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 9.00 (s, 1H), 8.18 (s, 1H), 7.81-7.78 (m, 2H), 7.62-7.61 (m, 1H), 7.60-7.56 (m, 1H), 7.45 (t, ^3J(H,H) = 7.7 Hz, 2H), 7.21 (d, ^3J(H,H) = 3.5 Hz, 1H), 6.59 (dd, ^3J(H,H) = 3.5 Hz, ^4J(H,H) = 1.6 Hz, 1H), 4.13 (q, ^3J(H,H) = 7.1 Hz, 2H), 4.05 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.15 (t, ^3J(H,H) = 7.1 Hz, 3H), 1.07 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 195.0, 182.6, 165.2, 164.4, 155.4, 152.8, 147.4, 137.2, 133.6, 133.4, 133.2, 131.1, 128.8, 128.7, 126.6, 122.8, 119.5, 113.0, 62.3, 62.2, 13.7, 13.6.
MS (70 eV, EI) *m/z* (%): 437 (28), 436 (100) [M^+], 409 (11), 408 (42), 391 (26), 390 (18), 389 (25), 363 (17), 362 (67), 361 (93), 345 (15), 344 (28), 334 (39), 333 (17), 317 (20), 316 (28), 295 (18), 294 (13), 293 (40), 289 (14), 285 (13), 213 (16), 105 (58), 95 (23), 77 (33).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3298 (brm), 2988 (m), 1718 (s), 1680 (m), 1634 (m), 1598 (w), 1563 (m), 1459 (m), 1371 (w), 1333 (m), 1220 (m), 1150 (w), 1024 (m).
HRMS (EI) for **$C_{24}H_{20}O_8$** (463.1158): found: 463.1136.

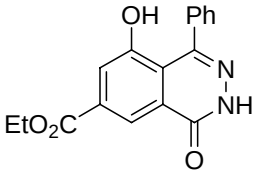
Synthesis of 4-benzoyl-5-hydroxy-6-propionyl-isophthalic acid diethyl ester (102k)



Prepared according to **TP 16** from 4-benzoyl-5-*tert*-butoxycarbonyloxy-6-propionyl-isophthalic acid diethyl ester (**101c**) (199 mg, 0.4 mmol) and TFA (1.0 mL). Evaporation of excess TFA in *vacuo* yielded without further purification **102k** as a yellow oil (156 mg, 98 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.02 (s, 1H), 7.74-7.71 (m, 2H), 7.59-7.55 (m, 1H), 7.46-7.42 (m, 2H), 4.40 (q, ^3J(H,H) = 7.2 Hz, 2H), 3.89 (q, ^3J(H,H) = 7.2 Hz, 2H), 2.86 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.40 (t, ^3J(H,H) = 7.2 Hz, 3H) , 1.23 (t, ^3J(H,H) = 7.2 Hz, 3H) , 1.01 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 206.0, 196.3, 165.2, 164.9, 154.6, 137.6, 133.6, 133.1, 132.6, 131.9, 128.8, 128.7, 128.2, 122.4, 62.5, 62.1, 36.9, 14.0, 13.5, 8.0.
MS (70 eV, EI) *m/z* (%): 398 (3) [M^+], 370 (9), 369 (43), 353 (7), 352 (7), 307 (5), 306 (13), 296 (14), 295 (100), 278 (5), 223 (8), 105 (8), 77 (4).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3390 (brw), 2982 (w), 1717 (s), 1678 (m), 1597 (w), 1449 (w), 1372 (w), 1330 (m), 1238 (vs), 1163 (m), 1092 (m), 1047 (w), 1024 (m), 919 (w), 718 (w), 688 (w).
HRMS (EI) for **$C_{22}H_{22}O_7$** (398.1366): found: 398.1367.

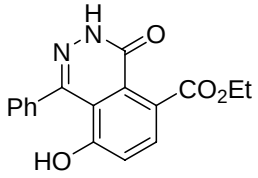
Synthesis of ethyl 3,4-dihydro-8-hydroxy-4-oxo-1-phenylphthalazine-6-carboxylate (103)



A 10 mL round-bottomed flask, equipped with a condenser and a magnetic stirring bar, was charged with a solution of **94e** (221 mg, 0.5 mmol) and $H_2N{\cdot}NH_2$ (5 mL, 10 equiv., 1.00 M in THF). The reaction mixture was heated to reflux and stirred for 48 h. The resulting mixture was added with saturated aqueous NH_4Cl solution and 2 N $HCl_{(aq)}$, extracted with ether (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. No further purification yielded **103** as an orange solid (155 mg, 99 %).

mp.: decomposed above 240 °C.
^{1}H-NMR (200 MHz, CD_3COCD_3, 25 °C) δ/ppm: 11.98 (s, 1H), 9.82 (s, 1H), 8.51 (d, ^4J(H,H) = 1.7 Hz, 1H), 7.86 (d, ^4J(H,H) = 1.7 Hz, 1H), 7.52-7.35 (m, 5H), 4.41 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.40 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (100 MHz, CD_3COCD_3, 25 °C) δ/ppm: 164.9, 158.9, 155.0, 145.3, 139.6, 133.9, 130.6, 129.1, 127.8, 127.3, 120.9, 119.4, 118.5, 61.5, 13.8.
MS (70 eV, EI) *m/z* (%): 311 (19), 310 (100) [M^+], 309 (65), 281 (27), 265 (14).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3379 (brs), 2984 (m), 2903 (m), 1696 (s), 1654 (vs), 1614 (s), 1587 (m), 1418 (m), 1278 (s), 1246 (s), 1026 (m), 771 (m), 747 (m), 696 (m).
HRMS (EI) for **$C_{17}H_{14}O_4N_2$** (310.0954): found: 310.0966.

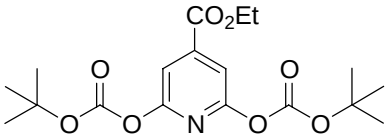
Synthesis of ethyl 3,4-dihydro-8-hydroxy-4-oxo-1-phenylphthalazine-5-carboxylate (104)



Prepared according to the same procedure for the preparation of **103** from **94l** (221 mg, 0.5 mmol), and $H_2N{\cdot}NH_2$ (5 mL, 10 equiv., 1.00 M in THF). Recrystallization from ether/ethanol yielded **104** as a white solid (143 mg, 92 %).

mp.: 242.6-243.5 °C.
^{1}H-NMR (400 MHz, CD_3COCD_3, 25 °C) δ/ppm: 11.83 (s, 1H), 9.55 (s, 1H), 7.59 (d, ^3J(H,H) = 8.2 Hz, 1H), 7.49-7.45 (m, 2H) ,7.40-7.35 (m, 3H), 7.32 (d, ^3J(H,H) = 8.2 Hz, 1H), 4.34 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.32 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (100 MHz, CD_3COCD_3, 25 °C) δ/ppm: 170.8, 159.7, 157.1, 147.1, 141.6, 133.0, 130.7, 129.4, 129.0, 128.8, 128.2, 121.0, 120.9, 62.7, 15.4.
MS (70 eV, EI) *m/z* (%): 311 (25), 310 (100) [M^+], 309 (13), 281 (12), 266 (22), 265 (99), 264 (12), 263 (32), 239 (14), 238 (75), 237 (69), 236 (10), 152 (17), 77 (14).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 3211 (brm), 2995 (m), 1688 (s), 1638 (s), 1587 (vs), 1368 (w), 1280 (s), 1230 (w), 1148 (m), 770 (w), 694 (w).
HRMS (EI) for **$C_{17}H_{14}O_4N_2$** (310.0954): found: 310.0930.

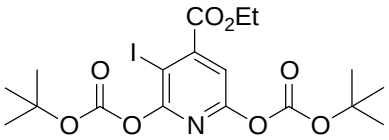
Synthesis of 2,6-bis-*tert*-butoxycarbonyloxy-isonicotinic acid ethyl ester (105)



A 100 mL round-bottomed flask, equipped with a condenser and a magnetic stirring bar, was charged with a solution of 2,6-dihydroxyisonicotinic acid (6.204 g, 40 mmol) in presence of cat. $H_2SO_{4(conc.)}$ in ethanol (50 mL). The reaction mixture was heated to reflux and stirred for 3 days. After the removal of ethanol, the crude mixture was dissolved in Et_3N (30 mL) and CH_2Cl_2 (30 mL). DMAP (244 mg, 2 mmol) and Boc_2O (10.476 g, 48 mmol) was then added and stirred at 25 °C overnight. Purification by flash chromatography (*n*-pentane/diethyl ether = 40 : 1) yielded **105** as a colourless solid (1.534 g, 10 %).

mp.: 44.1-45.3 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.60 (s, 2H), 4.42 (q, ^3J(H,H) = 7.13 Hz, 2H), 1.55 (s, 18H), 1.40 (t, ^3J(H,H) = 7.13 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 163.3, 156.9, 150.1, 144.7, 113.4, 84.7, 62.3, 27.6, 14.1.
MS (70 eV, EI) *m/z* (%): 184 (14), 183 (42) $[M-2Boc]^+$, 138 (7), 57 (100), 41 (13).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 1763 (m), 1731 (m), 1370 (m), 1268 (m), 1237 (s), 1130 (vs), 1078 (s), 1025 (m), 855 (m), 773 (m), 756 (m).
HRMS (EI) for **$C_{18}H_{26}O_8N$**, $[M+H]^+$ (384.1653): found: 384.1661.
HRMS (FAB) for **$C_{18}H_{25}O_8NNa$**, $[M+Na]^+$ (406.1478): found: 406.1446.

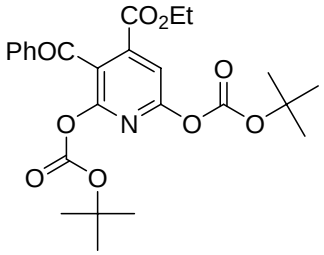
Synthesis of 2,6-bis-*tert*-butoxycarbonyloxy-3-iodo-isonicotinic acid ethyl ester (107a)



Prepared according to **TP 15** from **105** (383 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF), and iodine (381 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 30 : 1) yielded **107a** as a colourless oil (414 mg, 81 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.33 (s, 1H), 4.42 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.55 (s, 9H), 1.53 (s, 9H), 1.40 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 164.3, 157.2, 156.9, 150.4, 149.5, 149.1, 114.3, 85.1, 85.0, 80.8, 62.8, 27.6, 27.5, 14.0.
MS (70 eV, EI) *m/z* (%): 310 (12), 309 (100) $[M-2Boc]^+$, 254 (48), 183 (13), 156 (11), 155 (22), 140 (10), 138 (29), 127 (11), 112 (40), 84 (25), 64 (14), 57 (90), 56 (40), 55 (12), 44 (39), 41 (52).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (w), 1765 (s), 1737 (m), 1589 (w), 1370 (m), 1221 (s), 1130 (vs), 1076 (s), 1015 (m), 856 (w).
HRMS (FAB) for **$C_{18}H_{24}O_8INa$**, $[M+Na]^+$ (532.0444): found: 532.0414.
HRMS (FAB) for **$C_{24}H_{40}O_8N_2I$**, $[M+Et_3N+H]^+$ (611.1829): found: 611.1822.

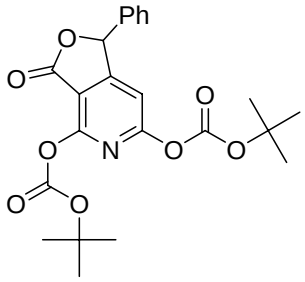
Synthesis of 3-benzoyl-2,6-bis-*tert*-butoxycarbonyloxy-isonicotinic acid ethyl ester (107b)



Prepared according to **TP 15** from **105** (383 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF), CuCN·2LiCl (0.20 mL, 0.2 equiv., 1.0 M in THF), and benzoyl choride (281 mg, 2.0 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **107b** as a yellow oil (332 mg, 68 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.81-7.78 (m, 2H), 7.70 (s, 1H), 7.58-7.54 (m, 1H), 7.45-7.41 (m, 2H), 4.16 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.57 (s, 9H), 1.32 (s, 9H), 1.06 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 191.3, 162.8, 156.9, 153.7, 149.7, 149.2, 143.5, 136.4, 133.7, 129.2, 128.6, 125.6, 114.2, 85.1, 84.8, 62.7, 27.6, 27.3, 13.4.
MS (70 eV, EI) *m/z* (%): 288 (15), 287 (77) $[M-2Boc]^+$, 286 (46), 242 (22), 241 (50), 240 (23), 213 (11), 182 (14), 105 (53), 77 (23), 57 (100), 56 (14), 44 (16), 41 (25).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2983 (m), 1766 (s), 1732 (m), 1680 (m), 1598 (w), 1371 (w), 1225 (vs), 1144 (m), 1104 (vs), 1065 (m).
HRMS (FAB) for $\mathbf{C_{31}H_{45}O_9N_2}$, $[M+Et_3N+H]^+$ (589.3125): found: 589.3125.

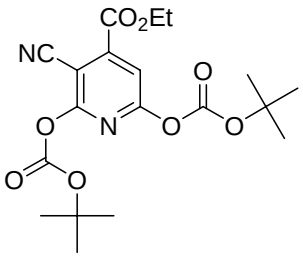
Synthesis of carbonic acid 6-*tert*-butoxycarbonyloxy-3-oxo-1-phenyl-1,3-dihydro-furo[3,4-c]pyridin-4-yl ester *tert*-butyl ester (107c)



Prepared according to **TP 15** from **105** (383 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF), and benzaldehyde (159 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **107c** as a white solid (311 mg, 70 %).

mp.: 219.6-220.0 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.62 (s, 1H), 7.42-7.35 (m, 3H), 7.24-7.21 (m, 2H), 6.51 (s, 1H), 1.57 (s, 9H), 1.36 (s, 9H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 166.6, 157.4, 151.0, 149.9, 148.5, 141.6, 133.0, 131.9, 130.1, 129.0, 127.8, 109.8, 85.3, 85.2, 82.0, 27.6, 27.4.
MS (70 eV, EI) *m/z* (%): 288 (15), 287 (77) $[M-2Boc]^+$, 286 (46), 242 (22), 241 (50), 240 (23), 213 (11), 182 (14), 105 (53), 77 (23), 57 (100), 56 (14), 44 (16), 41 (25).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2989 (w), 1786 (m), 1773 (s), 1753 (vs), 1371 (m), 1272 (m), 1238 (s), 1135 (s), 1092 (s), 1070 (s), 987 (w), 838 (w), 776 (m), 699 (w).
$\mathbf{C_{23}H_{25}NO_8}$: calc.: C: 62.30; H: 5.68; N: 3.16; found: C: 62.14; H: 5.65; N: 3.14.

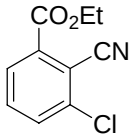
Synthesis of 2,6-bis-*tert*-butoxycarbonyloxy-3-cyano-isonicotinic acid ethyl ester (107d)



Prepared according to **TP 15** from **105** (383 mg, 1.0 mmol), TMPMgCl·LiCl (0.92 mL, 1.1 equiv., 1.20 M in THF), and tosyl cyanide (286 mg, 1.5 mmol). Purification by flash chromatography (*n*-pentane/diethyl ether = 20 : 1) yielded **107d** as a white solid (246 mg, 60 %).

mp.: 110.5-111.8 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.72 (s, 1H), 4.50 (q, ^3J(H,H) = 7.1 Hz, 2H), 1.57 (s, 9H), 1.56 (s, 9H), 1.45 (t, ^3J(H,H) = 7.1 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 161.3, 159.4, 159.0, 148.7, 148.6, 146.5, 114.2, 111.8, 99.2, 86.3, 85.9, 63.5, 27.5, 27.5, 13.9.
MS (70 eV, EI) *m/z* (%): 209 (20), 208 (18) $[M-2Boc]^+$, 180 (12), 163 (10), 57 (100), 56 (15), 44 (15), 41 (25).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2982 (w), 1763 (s), 1740 (m), 1599 (w), 1394 (w), 1369 (m), 1231 (s), 1160 (s), 1103 (vs), 1070 (s), 1024 (s), 1012 (s), 956 (m), 855 (s), 787 (m), 771 (s).
HRMS (FAB) for **$C_{25}H_{40}O_8N_3$**, $[M+Et_3N+H]^+$ (510.2815): found: 510.2782.
$C_{19}H_{24}O_8N_2$: calc.: C: 55.88; H: 5.92; N: 6.86; found: C: 56.03; H: 5.93; N: 6.73.

Synthesis of 3-chloro-2-cyano-benzoic acid ethyl ester (108)

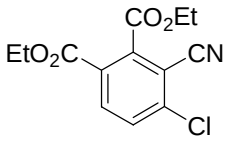


A dry and nitrogen-flushed 50 mL Schlenk tube, equipped with a magnetic stirring bar and a septum, was charged with a solution of **91a** (1.846 g, 10.0 mmol) in dry THF (10 mL). After cooling to 0°C, TMPMgCl·LiCl (9.6 mL, 12.0 mmol, 1.25 M in THF) was added dropwise and the reaction mixture was stirred for 6 h. TsCN (2.718 g, 15.0 mmol) in dry THF (5 mL) was added and stirred for 30 min. The resulting mixture was warmed to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/Et_2O, 10 : 1) yielded **108** as a colourless solid (1.589 g, 76 %).

mp.: 97.0-97.9 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.03-8.01 (m, 1H), 7.72-7.70 (m, 1H), 7.62-7.59 (m, 1H), 4.48-4.44 (m, 2H), 1.45-1.42 (m, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 163.3, 139.3, 135.1, 133.4, 132.8, 129.2, 114.2, 113.4, 62.7, 14.0.
MS (70 eV, EI) *m/z* (%): 211 (7), 209 (22) $[M^+]$, 183 (13), 164 (100), 137 (33), 100 (16), 75 (5).

IR (neat) $\tilde{\nu}$ (cm^{-1}): 3088 (w), 3066 (w), 2988 (w), 2230 (w), 1724 (vs), 1582 (w), 1567 (w), 1480 (w), 1437 (m), 1371 (w), 1272 (s), 1207 (s), 1168 (m), 1109 (w), 1024 (m), 902 (w), 829 (w), 762 (m), 729 (w), 710 (w).
HRMS (EI) for **$C_{10}H_8{}^{35}ClNO_2$** (209.0244): found: 209.0248.

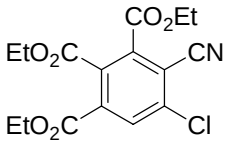
Synthesis of 4-chloro-3-cyano-phthalic acid diethyl ester (109)



A dry and nitrogen-flushed 50 mL Schlenk tube, equipped with a magnetic stirring bar and a septum, was charged with a solution of **108** (629 mg, 3.0 mmol) in dry THF (3.5 mL) and dry ether (15 mL). After cooling to –20 °C, TMPMgCl·LiCl (4.1 mL, 1.5 equiv., 1.10 M in THF) was added dropwise and the reaction mixture was stirred for 6 h. Ethyl cyanoformate (506 mg, 5.1 mmol) was added and stirred for 30 min. Then the reaction mixture was warmed to 25 °C and stirred for 1 h. The resulting mixure was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 60 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 25 : 1) yielded **109** as a yellow solid (507 mg, 60 %).

mp.: 48.0-49.6 °C.
^{1}H-NMR ($CDCl_3$, 600 MHz, 25 °C) δ/ppm: 8.13 (d, ^3J(H,H) = 8.6 Hz, 1H), 7.64 (d, ^3J(H,H) = 8.6 Hz, 1H), 4.51 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.38 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.44 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.38 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 150 MHz, 25 °C) δ/ppm: 165.0, 163.3, 141.4, 140.9, 134.7, 130.7, 127.8, 113.1, 112.6, 63.1, 62.5, 14.0, 13.9.
MS (70 eV, EI) *m/z* (%): 283 (<1), 281 (2) [M^+], 253 (11), 236 (16), 210 (35), 208 (100), 136 (18), 100 (5).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2982 (m), 2240 (w), 1722 (vs), 1574 (m), 1480 (w), 1449 (w), 1412 (w), 1389 (w), 1370 (w), 1266 (s), 1206 (w), 1179 (m), 1145 (m), 1103 (m), 1011 (m), 946 (w), 890 (w), 859 (w), 844 (w), 783 (m), 731 (w), 715 (w).
HRMS (EI) for **$C_{13}H_{12}{}^{35}ClNO_4$** (281.0455): found: 281.0451.

Synthesis of 5-chloro-4-cyano-benzene-1,2,3-tricarboxylic acid triethyl ester (110)

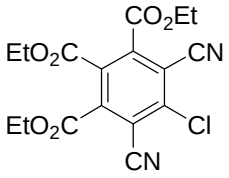


A dry and nitrogen-flushed 50 mL Schlenk tube, equipped with a magnetic stirring bar and a septum, was charged with a solution of **109** (0.930 g, 3.3 mmol) in dry THF (12 mL). After cooling to −50 °C, TMPMgCl·LiCl (3.60 mL, 1.2 equiv., 1.1 M in THF) was added dropwise and the reaction mixture was stirred for 0.5 h. $ZnCl_2$ (4.00 mL, 1.2 equiv., 1.0 M in THF) was then added and the reaction was warmed up to −30 °C and stirred for 0.5 h. Ethyl chloroformate (0.537 g, 4.95 mmol) and $Pd(PPh_3)_4$ (76 mg, 0.033 mmol) in dry THF (1 mL) was added, and the reaction mixture was warmed up to 25 °C and stirred for 24 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 60 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in*

vacuo. Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **110** as a yellow oil (0.970 g, 83 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.13 (s, 1H), 4.47 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.40 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.38 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.43 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.39 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.36 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 165.0, 163.1, 163.0, 139.5, 136.7, 134.4, 133.8, 132.8, 115.7, 113.0, 63.6, 63.0, 62.7, 14.0, 13.8, 13.8.
MS (70 eV, EI) *m/z* (%):355 (2), 353 (4) [M^+], 308 (46), 280 (49), 252 (48), 234 (100), 208 (8), 162 (17).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2985 (w), 1726 (vs), 1031 (m), 1274 (m), 1228 (s), 1176 (m), 1154 (m), 1128 (m), 1017 (m).
HRMS (EI) for **$C_{16}H_{16}{}^{35}ClNO_6$** (353.0666): found: 353.0680.

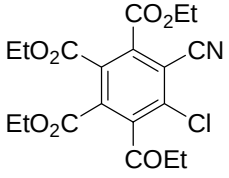
Synthesis of 5-chloro-4,6-dicyano-benzene-1,2,3-tricarboxylic acid triethyl ester (111a)



A dry and nitrogen-flushed 10 mL Schlenk tube, equipped with a magnetic stirring bar and a septum, was charged with a solution of **110** (0.177 g, 0.5 mmol) in dry THF (2 mL). After cooling to −50 °C, TMPMgCl·LiCl (0.55 mL, 1.2 equiv., 1.1 M in THF) was added dropwise and the reaction mixture was stirred for 1.5 h. TsCN (143 mg, 0.75 mmol) in dry THF (1 mL) was added and the resulting mixture was stirred at −50 °C for 0.5 h, followed by warming up to 25 °C, and then stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **111a** as a yellow solid (153 mg, 80 %).

mp.: 75.0-76.3 °C.
^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 4.49 (q, ^3J(H,H) = 7.2 Hz, 4H), 4.35 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.43 (t, ^3J(H,H) = 7.2 Hz, 6H), 1.34 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 162.5, 162.4, 143.3, 141.1, 130.8, 115.4, 111.6, 64.1, 63.5, 13.7, 13.6.
MS (70 eV, EI) *m/z* (%): 380 (2), 378 (6) [M^+], 335 (15), 333 (45), 307 (18), 306 (11), 305 (53), 279 (25), 278 (12), 277 (83), 261 (32), 260 (22), 259 (100), 234 (12), 232 (11), 187 (19).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2987 (w), 1736 (vs), 1552 (w), 1465 (w), 1412 (w), 1367 (w), 1309 (m), 1235 (m), 1203 (s), 1097 (w), 1017 (m), 854 (w).
HRMS (EI) for **$C_{17}H_{15}O_6N_2{}^{35}Cl$** (378.0619): found: 378.0600.

Synthesis of 5-chloro-4-cyano-6-propionyl-benzene-1,2,3-tricarboxylic acid triethyl ester (111b)



A dry and nitrogen-flushed 10 mL Schlenk tube, equipped with a magnetic stirring bar and a septum, was charged with a solution of **110** (0.177 g, 0.5 mmol) in dry THF (2 mL). After cooling to −50 °C, TMPMgCl·LiCl (0.55 mL, 1.2 equiv., 1.1 M in THF) was added dropwise and the reaction mixture was stirred for 1.5 h. CuCN·2LiCl (0.50 mL, 1.0 equiv., 1.0 M in THF) was added, followed by the addition of propionyl chloride (0.11 mL, 1.25 mmol), and the reaction mixture was warmed up to 25 °C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (3 × 40 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (*n*-pentane/diethyl ether = 10 : 1) yielded **111b** as a pale yellow oil (172 mg, 84 %).

^{1}H-NMR (600 MHz, $CDCl_3$, 25 °C) δ/ppm: 4.47 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.33 (q, ^3J(H,H) = 7.2 Hz, 2H), 4.30 (q, ^3J(H,H) = 7.2 Hz, 2H), 2.92 (q, ^3J(H,H) = 7.2 Hz, 2H), 1.43 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.34 (t, ^3J(H,H) = 7.2 Hz, 3H) 1.31 (t, ^3J(H,H) = 7.2 Hz, 3H), 1.24 (t, ^3J(H,H) = 7.2 Hz, 3H).
^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C) δ/ppm: 201.5, 164.1, 163.6, 162.9, 143.9, 137.4, 135.1, 133.9, 132.7, 115.5, 112.4, 63.7, 63.4, 62.9, 37.0, 13.7, 13.7, 13.6, 7.2.
MS (70 eV, EI) *m/z* (%): 382 (16), 380 (46), 364 (13), 352 (17), 324 (12), 308 (10), 306 (19), 290 (14), 280 (30), 279 (11), 278 (100), 47 (9).
IR (neat) $\tilde{\nu}$ (cm^{-1}): 2984 (w), 1731 (vs), 1409 (w), 1299 (m), 1233 (m), 1199 (s), 1099 (m), 1016 (m).
HRMS (EI) for **$C_{19}H_{21}NO_7{}^{35}Cl$**, $[M+H]^+$ (410.1007): found: 410.1019.

12. Curriculum Vitae

Name: Wenwei Lin
Date of Birth: October, 18th 1975
Nationality: Taiwanese
Place of birth: I-Lan, Taiwan
Marital Status: Single
Mother language: Chinese. Other language: English.

EDUCATION

Aug./2003- Nov./2006	**Ludwig-Maximilians-Universität (München)** **Department Chemie und Biochemie** Ph.D. under the supervision of Prof. Dr. Paul Knochel	Germany
Sep./1998 - Jun./2000	**National Taiwan Normal University** **Department of Chemistry** Master of Science Degree under the supervision of Prof. Dr. Ching-Fa Yao	Taipei, Taiwan
Sep./1994 - Jun./1998	**National Taiwan Normal University** **Department of Chemistry** Bachelor of Science Degree in Chemistry Graduated with Honor. Overall GPA: 3.96/4.0 Ranked first in a class of twenty-eight students	Taipei, Taiwan
Sep./1991 - Jun./1994	**Taipei Municipal Chienkuo Senior High school** Graduated with Honor	Taipei, Taiwan

EXPERIENCE

Dec./2003 - Feb./2006	*Coworker with Dr. Kurt Polborn*, **Department Chemie und Biochemie, Ludwig-Maximilians-Universität (München)** Engaged in the operation of X-ray (single crystal diffraction) instrument
Mar./2002 - Jul./2003	*Teaching Assistant*, **Department of Chemistry, NTNU** Employed by National Taiwan Normal University with the engagement in teaching courses and experiments including: Organic Chemistry, Inorganic Chemistry, and Physical Chemistry.
Jul./2000 - Mar./2002	*Second Lieutenant of Infantry Troops* (by the compulsory military service), **The Army of R.O.C., Taiwan** Engaged in the training and education of the students in the military school.

PUBLICATIONS

1. W. Lin, O. Baron, P. Knochel, "Highly Functionalized Benzene Syntheses by Directed Mono or Multiple Magnesiations Using TMPMgCl·LiCl", *Org. Lett.* **2006**, *accepted.*
2. W. Lin, F. Ilgen, P. Knochel, "Preparation of Highly Functionalized Arylmagnesium Reagents by the Magnesium Phenylselenide to Arynes", *Tetrahedron Lett.* **2006**, *47*, 1941-1944.

3. W. Lin, I. Sapountzis, P. Knochel, "Preparation of Functionalized Aryl Magnesium Reagents by the Magnesium Aryl Thiolates and Amides to Arynes", *Angew. Chem. Int. Ed.* **2005**, *44*, 4258-4261; *Angew. Chem.* **2005**, *117*, 4330-4333.
4. I. Sapountzis, W. Lin, C. C. Kofink, C. Despotopoulou, P. Knochel, "Iron-Catalyzed Aryl-Aryl Cross-Couplings with Magnesium-Derived Copper Reagents", *Angew. Chem. Int. Ed.* **2005**, *44*, 1654-1657; *Angew. Chem.* **2005**, *117*, 1682-1685.
5. I. Sapountzis, W. Lin, M. Fischer, P. Knochel, "Preparation of Polyfunctional Arynes via 2-Magnesiated Diaryl sulfonates", *Angew. Chem. Int. Ed.* **2004**, *43*, 4364-4366; *Angew. Chem.* **2004**, *116*, 4464-4466.
6. J.-Y. Liu, Y.-J. Jang, W.-W. Lin, J.-T. Liu, C.-F. Yao, "Triethylaluminum or Triethylborane-Induced Free-Radical Reaction of Alkyl Iodides and *α,β*-Unsaturated Compounds", *J. Org. Chem.* **2003**, *68*, 4030-4038.
7. Y.-J. Jang, W.-W. Lin, Y.-K. Shih, J.-T. Liu, M.-H. Hwang, C.-F. Yao, "An Easy One-Pot Method for the Synthesis of 2,2-Disubstituted 1-Nitroalkenes", *Tetrahedron* **2003**, *59*, 4979-4992.
8. W.-W. Lin, Y.-J. Jang, Y. Wang, J.-T. Liu, S.-R. Hu, L.-Y. Wang, C.-F. Yao, "An Improved and Easy Method for the Preparation of 2,2-Disubstituted 1-Nitroalkenes", *J. Org. Chem.* **2001**, *66*, 1984-1991.
9. J.-T. Liu, W.-W. Lin, Y.-J. Jang, J.-Y. Liu, M.-C. Yan, C. Hung, K.-H. Kao, Y. Wang, C.-F. Yao, "One-pot synthesis of six- or five-membered carbocycles through intramolecular cycloadditions by the use of ethyl chloroformate", *Tetrahedron* **1999**, *55*, 7115-7128.
10. M.-C. Yan, J.-Y. Liu, W.-W. Lin, K.-H. Kao, J.-T Liu, J.-J. Jang, C.-F. Yao, "One-Pot Synthesis of Five-Membered Cyclic Thioethers or Ethers via Intramolecular Nitrile Oxide-Olefin Cycloaddition (INOC) or Intramolecular Alkoxycarbonyl Nitronate-Olefin Cycloaddition (IAOC) by the use of Methyl Chloroformate", *Tetrahedron* **1999**, *55*, 12493-12514.
11. J.-Y. Liu, M.-C. Yan, W.-W. Lin, L. Y. Wang, C.-F. Yao, "An improved, easy and efficient method for the generation of nitrile oxides from nitronates for in situ 1,3-dipolar cycloaddition", *J. Chem. Soc. Perkin Trans.1* **1999**, 1215-1218.
12. K.-H. Kao, R.-S. Sheu, Y.-S. Chen, W.-W. Lin, J.-T. Liu, C.-F. Yao, "Face selectivity in the reactions of Grignard reagents with 5-substituted-2-dicyano methylene adamantanes", *J. Chem. Soc. Perkin Trans. 1* **1999**, 2383-2390.
13. C.-M. Chu, J.-T. Liu, W.-W. Lin, C.-F. Yao, "Free radical reactions to generate alkenes and/or ionic reactions to generate hydroximoyl halides when *β*-nitrostyrenes react with triethylaluminium or diethylaluminium chloride", *J. Chem. Soc. Perkin Trans. 1* **1999**, 47-52.
14. K.-H. Kao, C.-S. Yang, J.-T Liu, W.-W. Lin, H.-Y. Fang, C.-F. Yao, K. Chen, "One-Pot Synthesis of the Hydroximoyl Chlorides and [3.3.0]Bicyclic Compounds from the Reactions of *β*-Nitrostyrenes with Stabilized Nucleophiles", *Tetrahedron* **1998**, *54*, 13997-14014.
15. C.-F. Yao, K.-H. Kao, J.-T. Liu, C.-M. Chu, Y. Wang, W.-C. Chen, Y.-M. Lin, W.-W. Lin, M.-C. Yan, J.-Y. Liu, M.-C. Chuang, J.-L. Shiue, "Generation of Nitroalkanes, Hydroximoyl Halides and Nitrile Oxides from the Reactions of *β*-Nitrostyrenes with Grignard or Organolithium Reagents", *Tetrahedron* **1998**, *54*, 791-822.

CONFERENCES

1. **"***Preparation of Functionalized Arylmagnesium Reagents by the Addition of Magnesium Aryl Thiolates and Amides to Arynes***";** Poster P-353, 13th IUPAC International Symposium on Organometallic Chemistry directed toward Organic Synthesis (OMCOS-13), Geneva, Switzerland, 17th-21th, July, 2005.
2. **"***Iron-Catalyzed Aryl-Aryl Cross-Couplings Using Magnesium-Derived Copper Reagents***";** Poster P-250, 13th IUPAC International Symposium on Organometallic Chemistry directed toward Organic Synthesis (OMCOS-13), Geneva, Switzerland, 17th-21th, July, 2005.

München, den 30.09.2006