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Organometallic Reagents of Lithium, Magnesium, Zinc and Zirconium for the Functionalization of Aromatics, S-Heterocycles and Silylated Cyanohydrins

von

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Erklärung

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Eidesstattliche Versicherung

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A els meus pares

i a Joan

"Solo una ardiente paciencia hará del logro una espléndida felicidad"

-Pablo Neruda-

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A. Introduction

1. OVERVIEW

In 2012, according to the International Agency for Research on Cancer (IARC), an estimated 14.1 million new cases of cancer occurred worldwide.[1] By 2030, the global burden is expected to grow to 21.7 million new cancer cases simply due to the growth and aging of the population. The tremendous expansion of cancer together with other terminal illness or epidemic diseases produce the necessity of developing new drugs that can cure these diseases or at least halt the devastating effects in the human body.

Particularly, chemistry and especially organic chemistry has been and is searching for efficient solutions in the area of medicinal chemistry as well as in many other areas. In this context, in the agrochemical industry, the development of fertilizers, herbicides, fungicides and insecticides has helped to increase the crop yields in the harvested area due to more efficient cultivation and multiple cropping.[2] In addition, new technologies in materials science have been used for heat insulation, solar energy or to prepare organic LEDs (OLED), which have allowed to reduce the energy consumption.

However, this huge progress in the chemical sector has increased concerns about climate change and environmental degradation creating new targets for the scientific community. At this point, green chemistry has emerged to ensure that the chemical processes are efficient, environmentally benign, and economical- and energy-saving.[3] Consequently, chemical reactions must proceed with a high atom economy[4] by reducing the waste production and a low E-factor.[5] In addition, unnecessary reaction steps such as protection/deprotection or interconversions of functional groups should be avoided.[6] Thereby, organometallic chemistry has already shown its potential in the development of green chemistry.[7]

Indeed, organometallics have turned out to be important tools in the formation of complex molecules, allowing transformations which were not accessible using conventional synthetic methods. According to the Nobel Prize laureate E.-I. Negishi, "*Nowadays, it is not only unwise but rather difficult to accomplish an efficient and*

[1] L. A. Torre, F. Bray, R. L. Siegel, J. Ferlay, J. Lortet-Tieulent, *CA Cancer J. Clin.* **2015**, *65*, 87.
[2] Food and Agriculture Organization of the United Nations (FAO), *World Agriculture Towards 2030/2050*. The 2012 Revision.
[3] a) P. T. Anastas, J. C. Warner, *Green Chemistry, Theory and Practice*, Oxford University Press, Oxford, **1998**; b) R. Noyori, *Green Chem.* **2003**, *5*, G37; c) M. Lancaster, *Green Chemistry: An Introductory Text,* RCS Publishing, London, **2010**.
[4] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259; c) R. A. Sheldon, *Pure Appl. Chem.* **2000**, *72*, 1233.
[5] a) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273; b) R. A. Sheldon, I. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, **2007**.
[6] T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, *75*, 4657.
[7] R. H. Crabtree, *Organometallics* **2011**, *30*, 17.

selective multiple synthesis without using organometallics".[8] Since the first preparation of organometallic species in 1760 by Louis-Claude Cadet de Gassicourt[9], they have proven to be excellent nucleophilic intermediates in the formation of new carbon-carbon and carbon-heteroatom bonds. Over the years, considerable progress has been achieved in this field. Nowadays practically every metal in the periodic table has been used in synthetic organic chemistry and each one possesses a unique reactivity.[10]

The reactivity of organometallic reagents is determined by the polarity of the carbon-metal bond. On one hand, very reactive organometallics, such as organo-lithium or -sodium species show a high ionic character of the carbon-metal bond leading to an excellent reactivity towards electrophiles[11]. But this reactivity excludes the presence of many functional groups. On the other hand, magenium, zinc and copper reagents present a better compatibility with functional groups and a higher stability due to their more covalent carbon-metal bond.[12] Organocopper reagents have a well-balanced reactivity, but they present a main drawback as being thermally instable. Organozinc reagents possess a higher stability compared to Grignard reagents but less reactivity toward standard electrophiles. However, zinc reagents react much better in transition metal-catalyzed cross-coupling reactions. In the case of organo-titanium and -zirconium, they have the combination of the transition metal behavior such as the coordination of a carbon-carbon multiple bond, oxidative addition, reductive elimination, addition reactions and the behavior of classical σ-carbanion towards electrophiles.[13]

[8] E.-I. Negishi, *Organometallics in Organic Synthesis*, Wiley-VCH, Weinheim, **1980**.
[9] D. Seyferth, *Organometallics* **2001**, *20*, 1488.
[10] For recent reviews on organometallic reagents see: a)T. Klatt, J. T. Markiewicz, C. Sämann, P. Knochel, *J. Org. Chem.* **2014**, *79*, 4253; b) G. Dagousset, C. François, T. León, R. Blanc, E. Sansiaume-Dagousset, P. Knochel, *Synthesis* **2014**, *46*, 3133; c) J. H. Kim, Y. O. Ko, J. Bouffard, S.-G. Lee, *Chem. Soc. Rev.* **2015**, *44*, 2489; d) A. D. Benischke, M. Ellwart, M. R. Becker, P. Knochel, *Synthesis* **2016**, *48*, 1101; e) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540; f) M. Westerhausen, A. Koch, H. Görls, S. Krieck, *Chem. Eur. J.* **2017**, *23*, 1456; g) Y.-H. Chen, M. Ellwart, V. Malakhov, P. Knochel, *Synthesis* **2017**, DOI: 10.1055/s-0036-1588843.
[11] J. Clayden, *Organolithiums: Selectivity for Synthesis* (Ed. J.E. Baldwin), Pergamon Press, Oxford, **2002**.
[12] *Handbook of Functionalized Organometallics* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**.
[13] I. Marek, *Titanium and Zirconium in Organic Synthesis*, Wiley-VCH, Weinheim, **2002**.

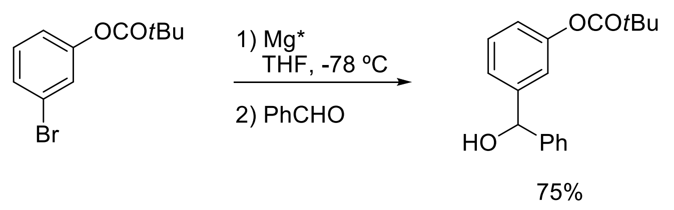
2. PREPARATION OF LITHIATED, MAGNESIATED AND ZINCATED ARYL AND HETEROARYL COMPOUNDS

2.1 OXIDATIVE INSERTION

Pioneered by Frankland, the first insertion of a metal into a carbon-halogen bond through an oxidative addition was performed in 1849.[14] He synthesized dialkylzinc species by using zinc metal and alkyliodides. However, the most widely used method for the direct insertion of a metal into a carbon-halogen bond arrived about 50 years later by Victor Grignard.[15] He prepared for the very first time organomagnesium compouds *via* insertion of elemental magnesium into a carbon-halide bond in diethyl ether.

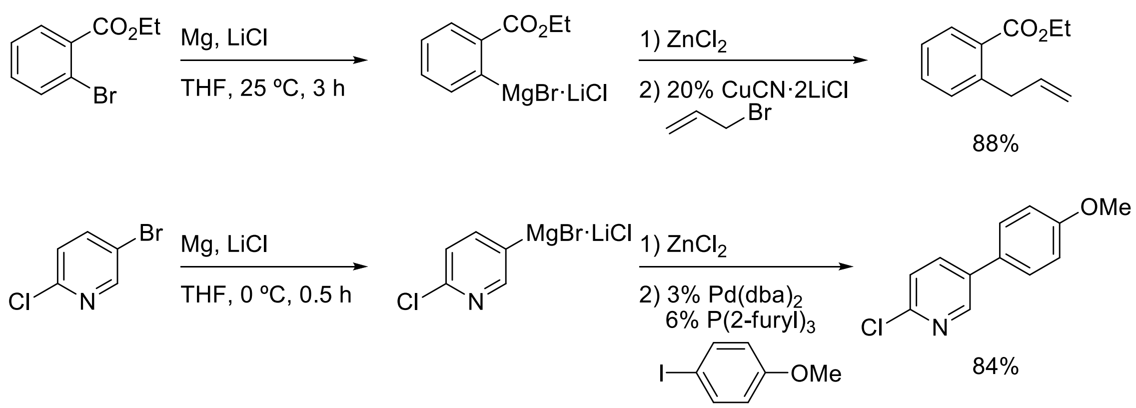
Grignard reagents (RMgX) became an important tool in organic synthesis to prepare new carbon-carbon bonds. The exact mechanism for the magnesium insertion is still not clear, but radical pathways are generally accepted.[16] Usually, magnesium metal needs to be activated due to a passivation layer of magnesium oxide or magnesium hydroxide that stays on the metal surface. Different activation ways including the use of 1,2-dibromoethane,[17] iodine,[18] transition metal catalysis of $FeCl_2$[19] and DIBAL-H[20] have been developed. The problem of the moisture on the surface of the magnesium was also faced by using highly reactive metal species, known as Rieke metals. The Rieke magnesium (Mg*) can be prepared by reduction of magnesium halides with sodium, potassium, or lithium and allows the preparation of highly functionalized organomagnesium reagents at low temperature (Scheme 1).[21]

[14] a) E. Frankland, *Ann. Chem.* **1849**, *71*, 171; b) E. Frankland, *Ann. Chem.* **1849**, *71*, 213.
[15] V. Grignard, *Compt. Rend. Acad. Sci. Paris*, **1900**, *130*, 1322.
[16] a) H. M. Walborsky, *Acc. Chem. Res.* **1990**, *23*, 286; b) J. F. Garst, *Acc. Chem. Res.* **1991**, *24*, 95; c) J. F. Garst, M. P. Soriaga, *Coord. Chem. Rev.* **2004***, 248*, 623.
[17] W. E. Lindsell, *Comprehensive Organometallic Chemistry I* (Eds. G. Wilkinson, F. G. S. Stone and G. E. Ebel), Vol. 1 , Chap. 3, Pergamon Press, Oxford, **1982**, pp. 155-252 and references therein.
[18] H. Gold, M. Larhed, P. Nilsson, *Synlett* **2005**, 1596.
[19] B. Bogdanovic, M. Schwickardi, *Angew. Chem. Int. Ed.* **2000**, *39*, 4610.
[20] U. Tilstam, H. Weinmann, *Org. Process Res. Dev.* **2002**, *6*, 906.
[21] a) R. D. Rieke, L.-C. Chao, *Syn. React. Inorg. Metal-Org. Chem.* **1974**, *4*, 101; b) R. D. Rieke, *Acc. Chem. Res.* **1977**, *10*, 301; c) R. D. Rieke, *Science* **1989**, *246*, 1260; d) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991**, *56*, 1445; e) R. D. Rieke, M. V. Hanson, *Tetrahedron* **1997**, *53*, 1925; f) R. D. Rieke, *Aldrichim. Acta* **2000**, *33*, 52; g) J. Lee, R. Velarde-Ortiz, A. Guijarro, J. R. Wurst, R. D. Rieke, *J. Org. Chem.* **2000**, *65,* 5428.



Scheme 1: Functionalization of Grignard reagents using highly reactive Rieke-Mg.

In 2008, Knochel *et al.* reported the preparation of aryl and heteroaryl organometallics from aryl and heteroaryl halides by direct metal insertion in the presence of LiCl (Scheme 2).[22] This methodology allowed to overcome the drawbacks from Rieke metals where the reagent needed to be freshly prepared, often at low temperatures, while presenting a large limitation in functional group tolerance.



Scheme 2: Preparation of aromatic and heteroaromatic organomagnesium reagents using Mg in the presence of LiCl.

2.2 HALOGEN-METAL EXCHANGE

A more practical method for the preparation of organometallics is the halogen-metal exchange. The bromine-lithium exchange reaction was discovered by Wittig[23] and Gilman[24], and many theories about the mechanism have been discussed. Beak proposed an intermediate based on a trigonal bipyramid with equatorial lone electron pairs and apical ligands (Figure 1).[25] This intermediate has been characterized at low

[22] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192; c) A. Metzger, F. M. Piller, P. Knochel, *Chem. Commun*. **2008**, 5824.
[23] G. Wittig, U. Pockels, H. Dröge, *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 1903.
[24] H. Gilman, W. Langham, Y. Jacoby, *J. Am. Chem. Soc.* **1939**, *61*, 106.
[25] a) P. Beak, D. J. Allen, *J. Am. Chem. Soc.* **1990**, *112*, 1629; b) P. Beak, D. J. Allen, *J. Am. Chem. Soc.* **1992**, *114*, 3420.

temperature in THF/HMPA for the ate complex lithium diphenyliodate ($Ph_2I^-Li^+$), formed from iodobenzene and phenyllithium.[26]

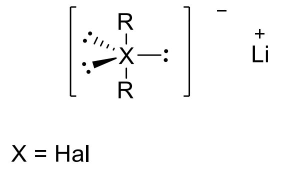
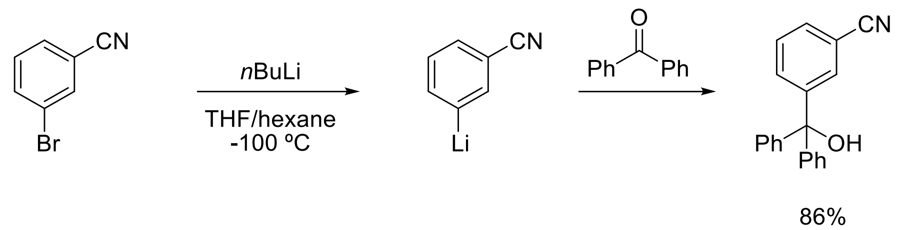


Figure 1: Intermediate formed in the halogen-lithium exchange reaction.

Polyfunctional organic molecules can be synthesized by lithium-halogen exchange using different commercially available reagents where *tert*-butyllithium is the most reactive and methyllithium the least one of alkyllithium reagents, but still superior to phenyllithium. The extremely ionic character of the prepared lithium-carbon bond makes organolithium compounds highly reactive but also instable. However, by lowering the temperature, even sensitive functional groups such as a nitrile group can be tolerated (Scheme 3). The bromine-lithium exchange can be performed at -100 ºC in THF/hexane leading to the corresponding lithium species that can further be trapped with benzophenone providing the expected alcohol in 86%.[27]

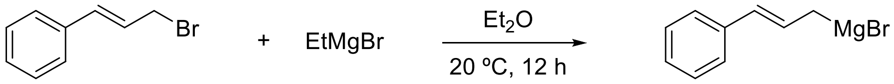


Scheme 3: Preparation and further functionalization of 2-cyanoaryl lithium.

The stability of prepared organolithiums depends on three factors. The compatibility with the functional groups is the most important one and sometimes these groups need to be protected. The hybridization of the carbon attached to the lithium influences in the stability of organometallic species ($C_{sp^3 secondary} < C_{sp^3 primary} < C_{sp^2 aryl} < C_{sp^2 vinyl} < C_{sp}$).[28] The relative position of the functionality and the carbanionic center is also important, for example β-functionalized derivatives are the least stable and β-elimination to produce olefin is favored.

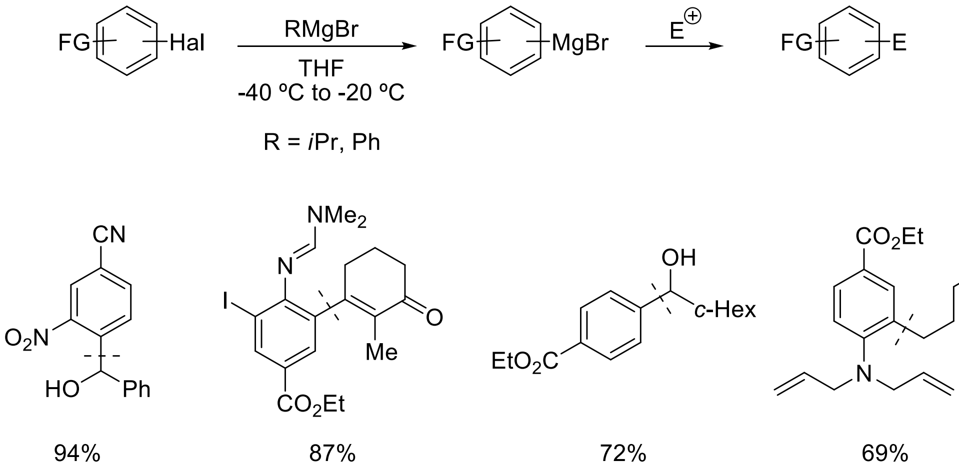
[26] a) H. J. Reich, D. P. Green, N. H. Phillips, *J. Am. Chem. Soc.* **1991**, *113*, 1414; b) K. B. Wiberg, S. Skelenak, W. F. Bailey, *J. Org. Chem.* **2000**, *65*, 2014.
[27] a) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 1187; b) W. E. Parham, L. D. Jones, *J. Org. Chem.* **1976**, *41*, 2704.
[28] D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.

These drawbacks can be relatively reduced by using magnesium-halogen exchange. This exchange produces more stable organometallic species. The first example of a bromine-magnesium exchange was reported by Prévost in 1931. In this case, cinnamyl bromide was converted into cinnamylmagnesium bromide using EtMgBr (Scheme 4).[29] The mechanism for this exchange is still not completely known, however a halogen ate complex is thought to be the intermediate in this process.



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

Based on the pioneered work of Prévost and Villieras[30], Knochel *et al.*, published in 1998, the first iodine-magnesium exchange by using *i*PrMgBr showing how useful this exchange was in the preparation of novel functionalized Grignard reagents.[31] Compering to halogen-lithium exchange, more sensitive groups, such as nitro, esters, or imines, were tolerated and higher temperatures could be used (Scheme 5).[32]

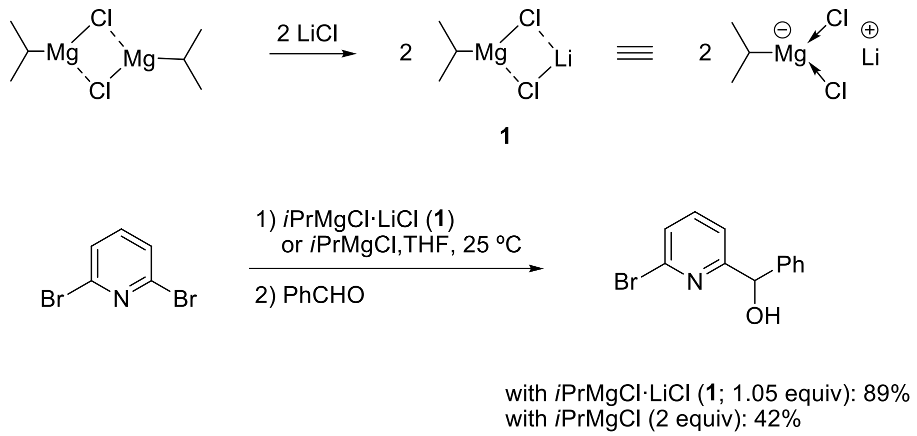


Scheme 5: Synthesis of functionalized aromatic compounds using a halogen-magnesium exchange.

The corresponding halogen-magnesium exchange rate was still a remaining limitation. This issue was overcome with the addition of a stoechiometric amount of LiCl to

[29] C. Prévost, *Bull. Soc. Chem. Fr.* **1931**, *49*, 1372.
[30] a) J. Villiéras, *Bull. Soc. Chim. Fr.* **1967**, *5*, 1520; b) J. Villiéras, B. Kirschleger, R. Tarhouni, M. Rambaud, *Bull. Soc. Chim. Fr.* **1986**, *24*, 470.
[31] L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1701.
[32] a) W. Dohle, D. M. Lindsay, P. Knochel, *Org. Lett.* **2001**, *3*, 2871; b) A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu, P. Knochel, *Synthesis* **2002**, 565; c) G. Varchi, C. Kofink, D. M. Lindsay, A. Ricci, P. Knochel, *Chem. Commun.* **2003**, 396.

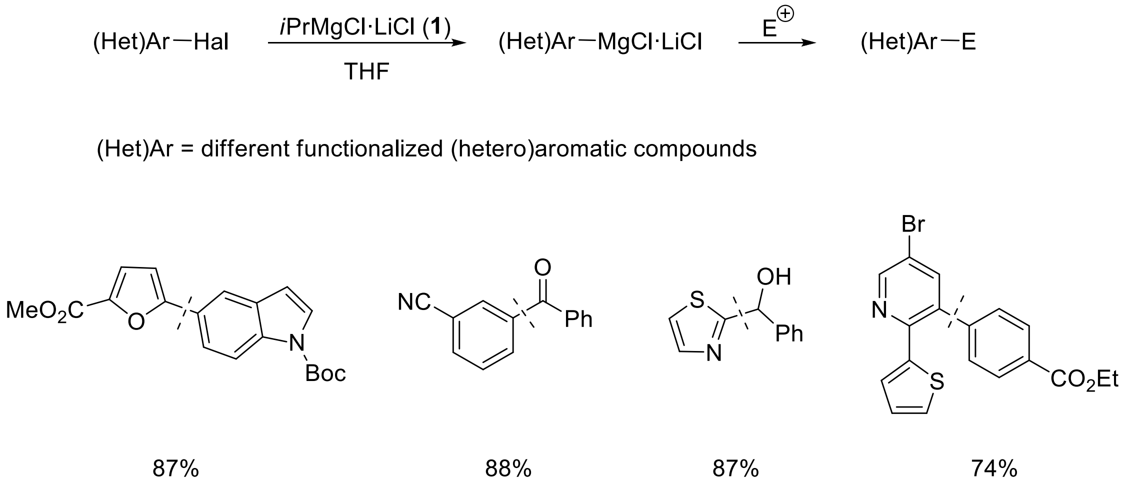
*i*PrMgCl forming the better exchange reagent *i*PrMgCl·LiCl (**1**), called Turbo Grignard.[33] The addition of LiCl breaks the aggregates of *i*PrMgCl and consequently enhances its solubility and reactivity (Scheme 6). The new organomagnesium species (**1**) allows a faster Br/Mg exchange by using less equivalents and generating the desired product in higher yield.



Scheme 6: Effect of LiCl on the Grignard reagent *i*PrMgCl.

A wide range of polyfunctionalized arenes and heteroaromatics bearing an ester, cyano and other sensitive groups could be then prepared by using the Turbo Grignard reagent in excellent yields (Scheme 7).[34] This halogen-magnesium exchange has proven to depend on the electron-deficiency of the aromatic halide. The effect of electron-withdrawing substituents decreased with the distance and also depends on the nature of the halogen atom: I> Br> Cl>> F.[35]

[33] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[34] a) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543; b) C.-Y. Liu, H. Ren, P. Knochel, *Org. Lett.* **2006**, *8*, 617; c) E. Demory, V. Blandin, J. Einhorn, P. Y. Chavant, *Org. Process Res. Dev.* **2011**, *15*, 710; c) C. Sämann, B. Haag, P. Knochel, *Chem. Eur. J.* **2012**, *18*, 16145.
[35] For reviews concerning the turbo Grignard, see: a) P. Knochel, N. M. Barl, V. Werner, C. Sämann, Heterocyles, **2014**, *88*, 827; b) R. L.-Y. Bao, R. Zhao, L. Shi, *Chem. Commun.* **2015**, *51*, 6884.



Scheme 7: Synthesis of functionalized organomagnesium species by halogen-magnesium exchange.

2.3 DIRECTED METALATION

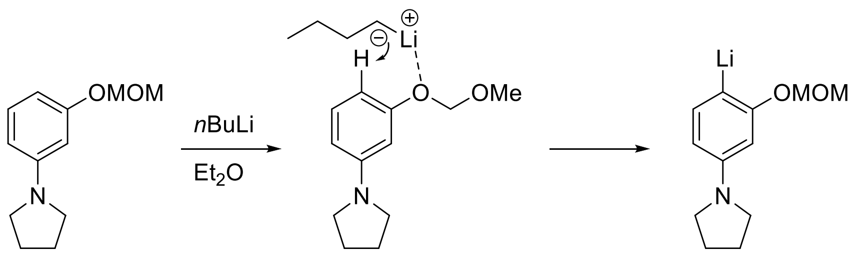
Metalation of arenes and heteroaromatics using alkyl metals or metal amide bases is the third major way to prepare organometallic reagents. Contrary to direct insertion and metal-halogen exchange, the presence of a halogen-carbon bond in the molecule is not required, and the organometallic is formed directly from a hydrogen-carbon bond.

The first organometallic deprotonation was the reaction of fluorene with EtLi, performed by Schlenk in 1928.[36] This reaction let to look for different metallic bases and alternative methodologies. In particular, the independent discovery by Gilman and Bebb[37] and Wittig and Fuhrmanm[38] of the *ortho*-deprotonation of anisole using *n*BuLi was remarkable. This pioneering result became the base for the directed *ortho*-metalation (D*o*M) and subsequently Break and Snieckus extensively investigated this kind of metalation using lithium bases and the complex-induced proximity effect (CIPE).[39]

The process of D*o*M generally requires a directed metalation group (DMG) in the aromatic system that ensures regioselective deprotonation, usually in the proximity of the DMG (Scheme 8). These DMGs usually coordinate the lithium bases and they are poor electrophilic centers avoiding their attack by the lithium species. For example,

[36] W. Schlenk, E. Bergmann, *Ann. Chem.* **1928**, *463*, 98.
[37] H. Gilman, R. L. Bebb, *J. Am. Chem. Soc.* **1939**, *61*, 109.
[38] G. Wittig, G. Fuhrmann, *Chem. Ber.* **1940**, *73*, 1197.
[39] For an overview, see: a) P. Beak, A. I. Meyers, *Acc. Chem. Res*. **1986**, *19*, 356; b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; c) M. C. Whisler, S. MacNeil, P. Beak, V. Snieckus, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; d) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827; e) M. Schlosser, F. Mongin, Chem. *Soc. Rev.* **2007**, *36*, 1161.

amides, carbamides, oxazolines, sulfonamides, esters, cyanides, phosphorous-containing substituents, sulfoxides or sulfones are good DMGs compared to ethers or amines. The deprotonation will depend of course on the nature of this DMG by either its capacity to coordinate or its inductive electron-withdrawing ability but also on the nature of the base and the reaction conditions. For this reason, in some cases the regioselectivity of the directed metalation can be unpredictable. If arenes possess more than one DMG, it may be that the effect of one substitutent cancels the effect of the other one or that they contribute in an equal way producing regioisomers in the metalation.[39b-e]



Scheme 8: Regioselective lithiation of a protected alcohol.

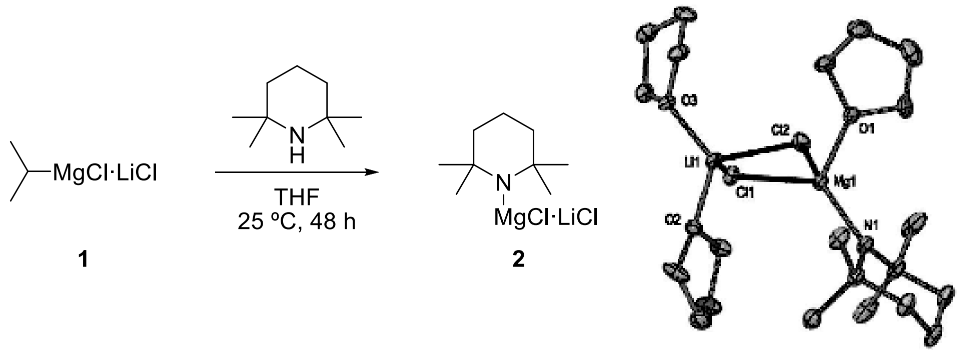
Typically powerful lithium amides (LDA, TMPLi) and alkyl-lithium bases (*t*BuLi, *s*BuLi, *n*BuLi) have been widely used for these metalations. These alkyl-lithium bases exist as various aggregates in solution and normally amine additives, like TMEDA, can be used to break them down and accelerate their reactivity by increasing their basicity. Theses bases are commercially available and they are good soluble in ether and alkane solutions. However, the use of these lithiated bases can lead to undesirable byproducts due to their low functional group tolerance and their strong nucleophilicity. Additionally, the metalation of aromatics and heteroaromatics with lithium bases usually need to be performed between -78 ºC and -100 ºC, which is unpractical as well for upscaling.

Therefore, alternative metalation methodologies have been developed. In 1947, Hauser and Walker reported magnesium amide bases of type R_2NMgX and $(R_2N)_2Mg$, known as Hauser bases.[40] Since then, these novel bases have attracted interest. Eaton[41] started working with the bis-amide TMP_2Mg for the magnesiation of arenes and later Mulzer[42] and co-workers reported the use of TMPMgCl in the functionalization of

[40] C. R. Hauser, H. G. Walker, *J. Am. Chem. Soc.* **1947**, *69*, 295.
[41] a) P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc*. **1989**, *111*, 8016; b) P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc*. **1993**, *115*, 11375; c) Y. Kondo, A. Yoshida, T. Sakamoto, *J. Chem. Soc., Perkin Trans 1,* **1996**, 2331; d) M.-X. Zhang, P. E. Eaton, *Angew. Chem. Int. Ed.* **2002**, *41*, 2169.
[42] a) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *J. Org. Chem.* **1995**, *60*, 8414; b) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Liebigs Ann. Chem.* **1995**, 1441; c) W. Schlecker, A. Huth, E. Ottow, J. Mulzer, *Synthesis* **1995**, 1225.

aromatic compounds. However, these Hauser bases had still some limitations. The low solubility required a large excess of the amide base (2-12 equivalentes) to achieve high conversion and high reaction rates. Furthermore, magnesium diamide reagents could also act as reducing agents in non-solvating media reducing carbonyl, nitro and azo substituents during the metalation.[42a-b]

A breakthrough in the Hauser bases was the introduction of LiCl to magnesium amide bases. Similarly to the classic Grignard reagents, LiCl helps to break the aggregates and increases the solubility of the magnesium amide. These facts led to prepared highly chemoselective TMP-metal/lithium chloride bases such as TMPMgCl·LiCl (**2**).[43] The main advantages of these novel bases are their excellent kinetic basicity, their good solubility and their excellent thermal stability in THF, which allows their storage for long term. TMPMgCl·LiCl (**2**) has been crystallized as a monomeric species, confirmed by Mulvey *et al.* (Scheme 9).[44]

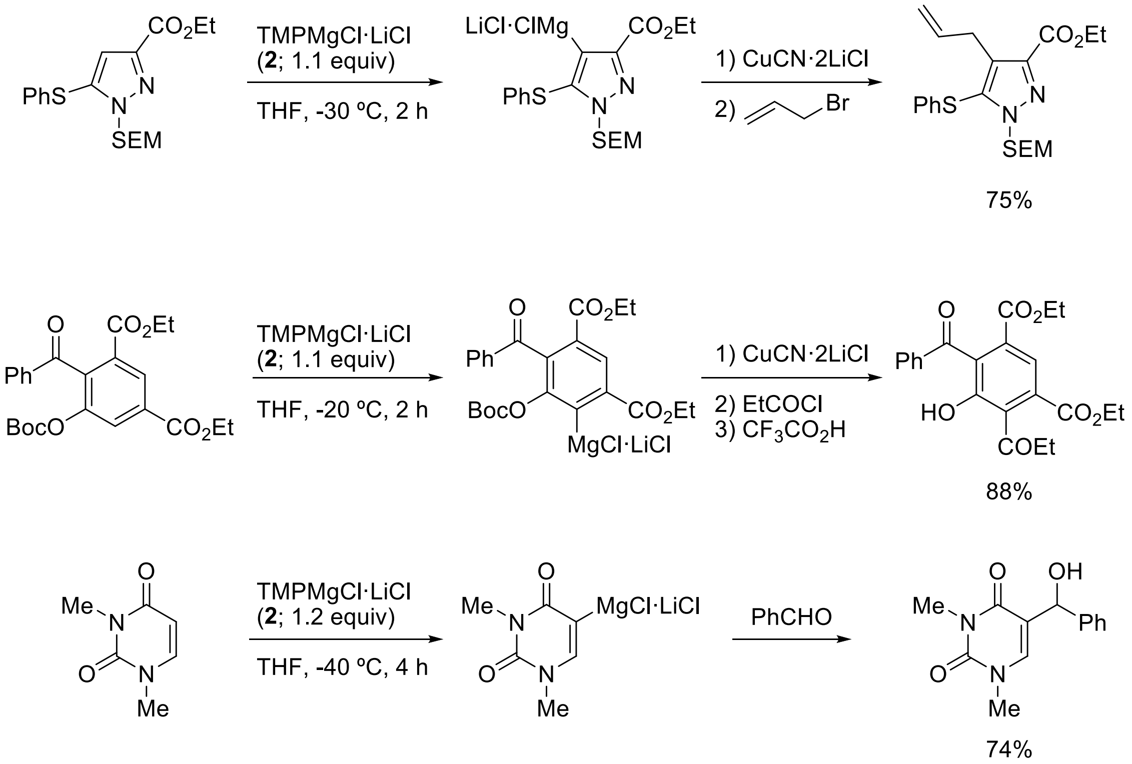


Scheme 9: Preparation and structure of TMPMgCl·LiCl (**2**).

Therefore, TMPMgCl·LiCl (**2**) can be used for mild metalation at convenient temperatures allowing the magnesiation of numerous arene and heteroaromatics in high conversion rates and with excellent regio- and chemoselectivity (Scheme 10).[45] Thus, the treatment of pyrazole with TMPMgCl·LiCl (**2**) at -30 ºC for 2 hours led to the corresponding metalated reagent that was trapped with allyl bromide.[46] Furthermore, the regio- and chemoselectivity of TMPMgCl·LiCl (**2**) was also proven in the deprotonation of a diester in the less sterical position providing a highly functionalized

[43] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
[44] P. García-Álvarez, D. V. Graham, E. Hevia, A. R. Kennedy, J. Klett, R. E. Mulvey, C. T. O'Hara, S. Weatherstone, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.
[45] a) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794; b) M. A. Ganiek, M. R. Becker, M. Ketels, P. Knochel, *Org. Lett.* **2017**, *19*, 360; c) M. Balkenhohl, C. François, D. Sustac-Roman, P. Quinio, P. Knochel, *Org. Lett.* **2017**, *19*, 536.
[46] C. Despotopoulou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326.

magnesium species that was acylated using propionyl chloride.[47] Besides, the regioselective functionalization of uracil derivatives has been successfully performed using TMPMgCl·LiCl (**2**) at -40 °C for 4 h.[48]

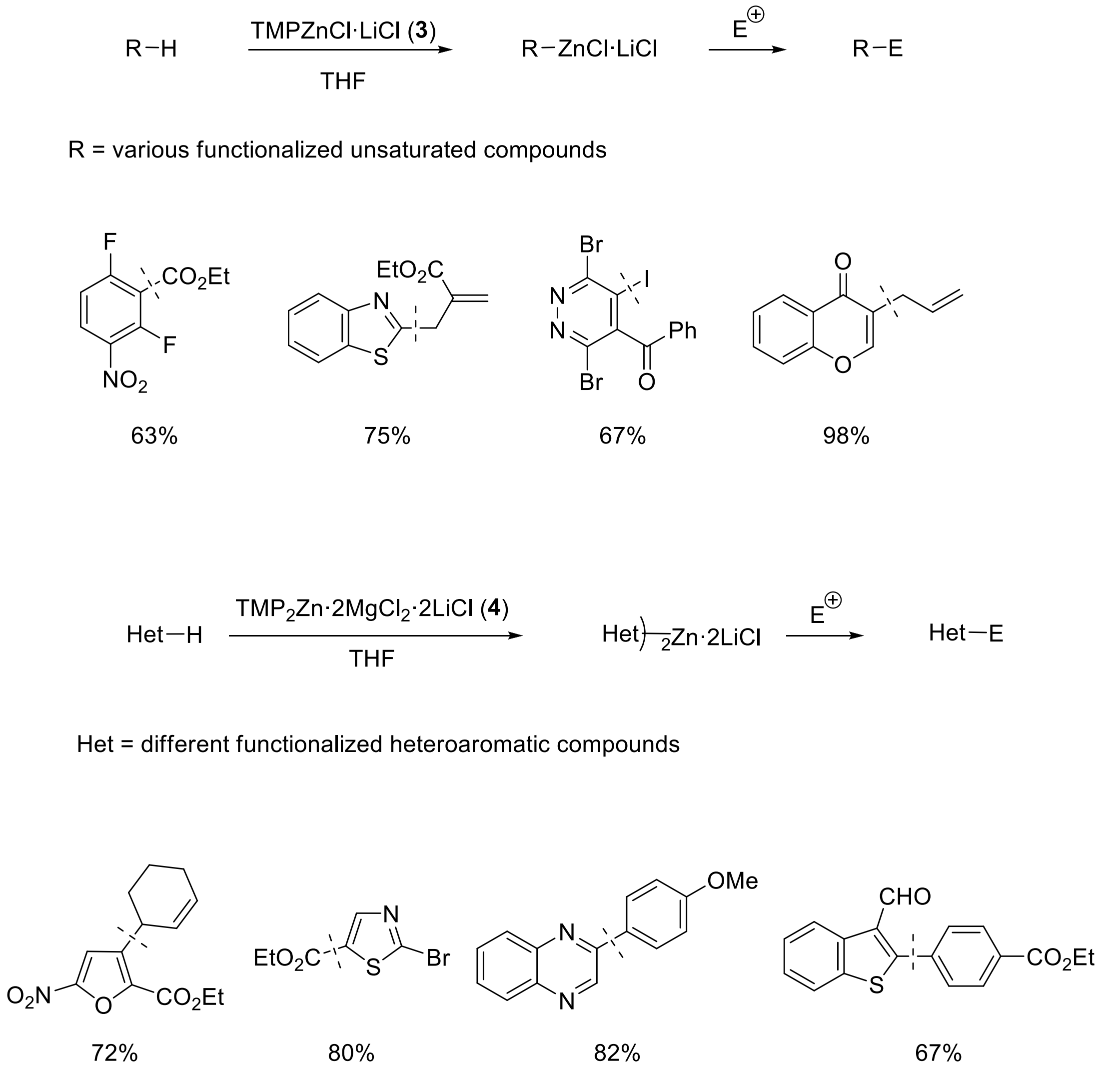


Scheme 10: Synthesis of organomagnesium reagents and subsequent functionalization.

The successful magnesium amide TMPMgCl·LiCl (**2**) is a great progress for the preparation of organometallic species under mild conditions, but there are still some functional groups such as nitro groups or aldehydes that are not tolerated. Besides, sensitive heterocycles, for example 1,3- and 1,2-oxazoles require metalation by a milder base due to ring opening reactions or degradation of the metal species. Knochel *et al.* developed the mild and chemoselective bases TMPZnCl·LiCl[49] (**3**) and $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$[50] (**4**). They are easily prepared by transmetalating TMPLi and TMPMgCl·LiCl (**2**) with $ZnCl_2$, respectively.

[47] W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673.
[48] L. Klier, E. Aranzamendi, D. Ziegler, J. Nickel, K. Karaghiosoff, T. Carell, P. Knochel, *Org. Lett.* **2016**, *18*, 1068.
[49] a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; b) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406; c) M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615.
[50] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) S. H. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705.

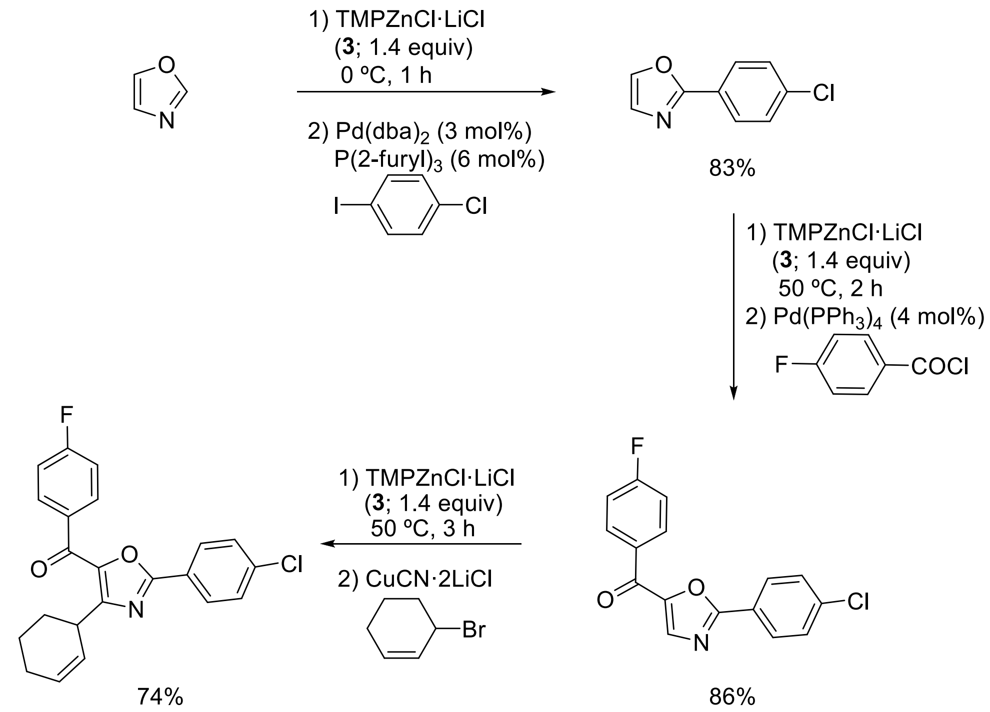
Since organozinc species have a excellent compatibility towards sensitive functional groups, it is possible to deprotonate a broad range of arenes and heteroarenes using different reaction conditions (Scheme 11).[49-51] This metalation is useful to functionalize electron-poor heterocycles such as pyridazines or thiazole, which lithium or magnesium species are not stable. Zinc-amide bases also offer the advantage that once the compounds are zincated, they can undergo palladium-catalyzed cross-coupling reactions with aromatic halides.



Scheme 11: Synthesis of organozinc reagents using TMPZnCl·LiCl (**3**) or $TMP_2Zn\cdot 2MgCl\cdot 2LiCl$ (**4**) and subsequent functionalization.

[51] a) S. H. Wunderlich, C. J. Rohbogner, A. Unsinn, P. Knochel, *Org. Process. Res. Dev.* **2010**, *14*, 339; b) C. Dunst, P. Knochel, *J. Org. Chem.* **2011**, *76*, 6972; c) D. Haas, D. Sustac-Roman, S. Schwarz, P. Knochel, *Org. Lett.* **2016**, *18*, 6380; d) L. Klier, D. S. Ziegler, R. Rahimoff, M. Mosrin, P. Knochel, *Org. Process. Res. Dev.* **2017**, *21*, 660.

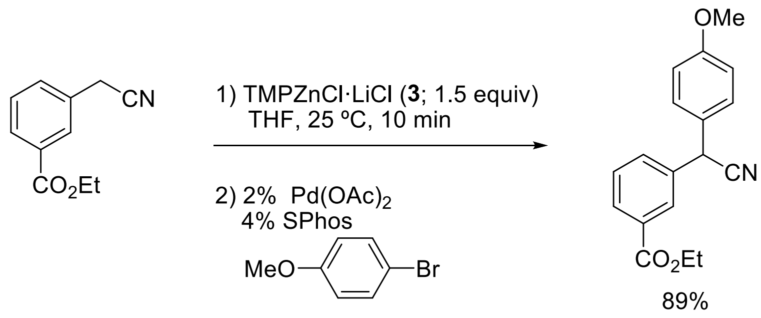
This methodology has been successfully extended to fully functionalize sensitive heteroaromatic systems such as oxazole through successive direct zincation (Scheme 12).[52]



Scheme 12: Succesive regio- and chemoselective zincation of oxazole.

Recently, Knochel *et al.* have also reported that these kinetically highly active TMP-bases can be also useful in benzylic metalations.[53] The zincation of the benzylic position in various aromatic scaffolds bearing sensitive functional groups has been successfully perfomed. Herein, TMPZnCl·LiCl (**3**, 1.5 equiv, 25 ºC, 10 min) allowed a smooth metalation of functionalized benzylic nitriles (Scheme 13).[54]

[52] D. Haas, M. Mosrin, P. Knochel, *Org. Lett.* **2013**, *15*, 6162.
[53] a) S. Duez, A. K. Steib, S. M. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 7686; b) S. Duez, A. K. Steib, P. Knochel, *Org. Lett.* **2012**, *14*, 1951; c) P. Quinio, C. François, A. Escribano Cuesta, A. K. Steib, F. Achrainer, H. Zipse, K. Karaghiosoff, P. Knochel, *Org. Lett.* **2015**, *17*, 1010.
[54] S. Duez, S. Bernhardt, J. Heppekausen, F. F. Fleming, P. Knochel, *Org. Lett.* **2011**, *13*, 1690.



Scheme 13: Metalation of functionalized benzylic nitriles.

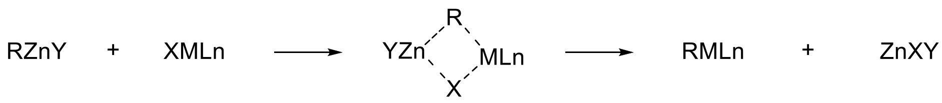
2.4 *VIA* TRANSMETALATION

Many organometallics bearing a carbon-metal bond are easily transmetalated into another metal modifying the reactivity and the selectivity of the carbon-metal bond.

The compatibility of lithium species in organic substrates is limited. Organolithium are highly reactive reagents and they need to be prepared at very low temperatures. The interconversion of a carbon-lithium bond with magnesium, zinc, manganese, titanium, zirconium, cerium, boron or aluminium salts reduces the basicity of the organometallic species without eliminating it completely. This conversion allows to handle more stable organometallic reagents bearing a more covalent carbon-metal. Transmetalation occurs through the formation of a lithium-metal ate complex followed by lithium-metal exchange.

The formation of organozinc reagents through transmetalation has been broadly used. The stability of the zinc compounds makes the transmetalation very attractive. Normally, organozinc species are much more stable at higher temperatures for which the corresponding organolithium and organomagnesium compounds decompose. This is attributed to the presence of empty low-lying *p*-orbitals in zinc species. Their interaction with the *d*-orbitals of many transition metal salts leads to intermediates such as organocopper[55] that react easily *via* acylation or allylation, or palladium compounds[56] *via* Negishi cross-coupling reactions[57] (Scheme 14).

[55] a) P. Knochel, *Synlett* **1995**, 393; b) P. Knochel, S. Vettel, C. Eisenberg, *Appl. Organomet. Chem*. **1995**, *9*, 175; c) P. Knochel, P. Jones, *Organozinc reagents. A Practical Approach*, Oxford University Press, **1999**; d) P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React*. **2001**, *58*, 417; e) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed*. **2000**, *39*, 4415.
[56] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc*. **1980**, *102*, 3298; b) M. Kobayashi, E. Negishi, *J. Org. Chem*. **1980**, *45*, 5223; c) E. Negishi, *Acc. Chem. Res*. **1982**, *15*, 340.
[57] A. O. King, N. Okukado, E. Negishi, *J. Chem. Soc., Chem. Commun.* **1977**, 683.

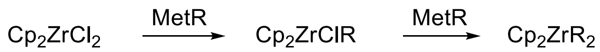


Scheme 14: Transmetalation of zinc reagents.

3. PREPARATION OF ORGANOZIRCONIUM REAGENTS

Wilkinson reported in 1954 the structure of Cp_2ZrCl_2, being one of the first organozirconium reagent described in the literature.[58] However, the use of organozirconium in organic chemistry was generalized in the mid-1970s with Schwartz and his investigation in hydrozirconation.[59] Afterwards, the expansion of organozirconium in organic chemistry was developed with the discoveries of the Ni- or Pd-catalyzed cross-coupling with alkenylzirconocene chlorides[60] and the Zr-catalyzed alkyne carboalumination.[61]

The most widely used method for the preparation of $ZrCp_2$ derivatives is *via* transmetalation (Scheme 15). This is expected to be favorable only with organometals containing highly electropositive metals. Indeed, organolithiums react easily with Cp_2ZrCl_2 giving mono- or dialkylation derivatives.[62] In the case of sterically hindered Grignard reagents only monoalkylation is observed and with aluminum, one carbon group can be transferred from zirconium to aluminum or vice versa.[63]

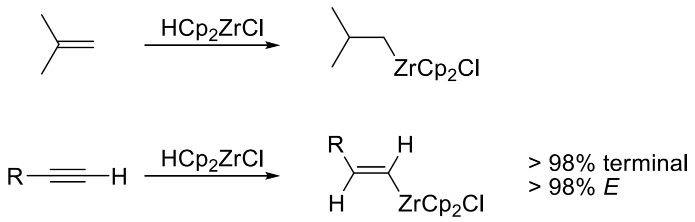


Scheme 15: Synthesis of mono- and diorganylzirconocene chlorides by transmetalation.

A second and effective method in the synthesis of organozirconium is the hydrozirconation of alkenes and alkynes that converts them into alkyl- and alkenylzirconium derivatives, respectively by mostly using $HZrCp_2Cl$ (Scheme 16). This reagent can be prepared by treating Cp_2ZrCl_2 with various aluminum hydrides or mixing

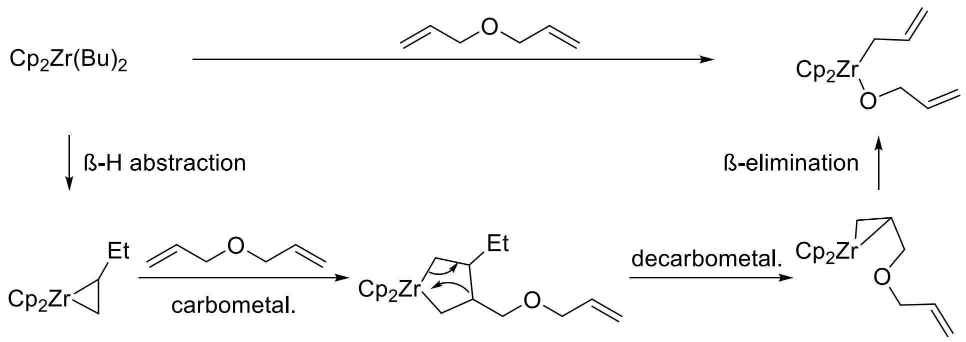
[58] G. Wilkinson, J. M. Birmingham, *J. Am. Chem. Soc.* **1954**, *76*, 4281.
[59] a) D. W. Hart, J. Schwartz, *J. Am. Chem. Soc.* **1974**, *96*, 8115; b) C. A. Bertelo, J. Schwartz, *J. Am. Chem. Soc.* **1976**, *98*, 262; c) J. Schwartz, J. A. Labinger, *Angew. Chem. Int. Ed.* **1976**, *15*, 333.
[60] a) E. Negishi, D. E. Van Horn, *J. Am. Chem. Soc.* **1977**, *99*, 3168; b) N. Okukado, D. E. Van Horn, W. L. Klima, E. Negishi, *Tetrahedron Lett.* **1978**, *19*, 1027; c) E. Negishi, N. Okukado, A. O. King, D. E. Van Horn, B. I. Spiegel, *J. Am. Chem. Soc.* **1978**, *100*, 2254.
[61] D. E. Van Horn, E. Negishi, *J. Am. Chem. Soc.* **1978**, *100*, 2252.
[62] D. Y. Kondakov, E. Negishi, *J. Chem. Soc., Chem. Commun.* **1996**, 963.
[63] L. D. Boardman, E. Negishi, *Tetrahedron Lett.* **1982**, *23*, 3327.

*i*BuZrCp$_2$Cl with aluminum chlorides, followed by trapping of the Al-byproduct.[64] Hydrozirconation with HZrCp$_2$Cl involves a concerted four-center process generating a *syn* addition where zirconium is placed at the least substituted carbon atom.[65]



Scheme 16: Preparation of monoorganylzirconocene chlorides by hydrozirconation.

Due to that the generation of 14-electron Cp$_2$Zr(II) by a reductive elimination has never been proven, the oxidative addition in the synthesis of organic derivatives of ZrCp$_2$ is not observed like in the late transition metals (such as Ni or Pd). Instead, it is thought that this "oxidative addition" occurs through some indirect processes that involve a 16-electron species (Scheme 17).[66]



Scheme 17: Preparation of monoorganylzirconocene chlorides by "oxidative addition" *via* a four-step mechanism.

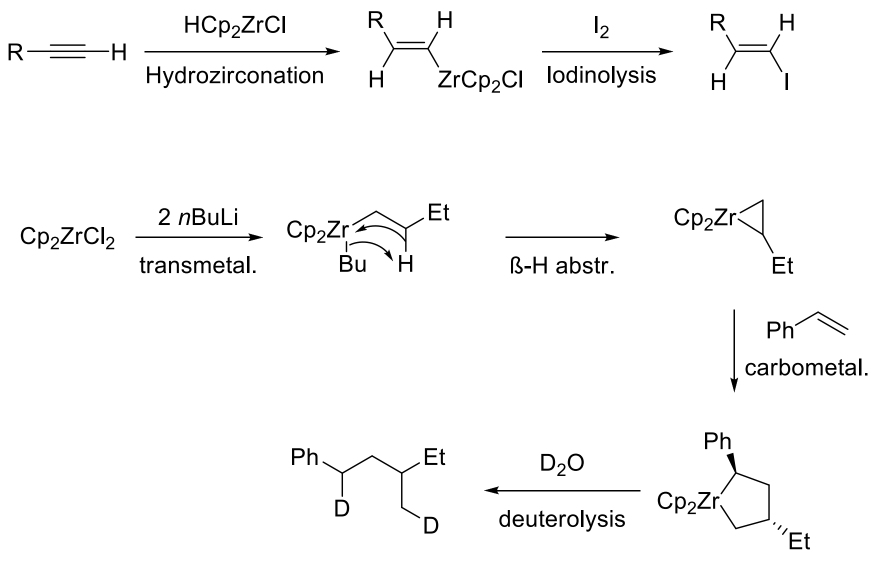
Dichlorozirconocene and its derivatives (Cp$_2$ZrXY) are 16-electron d^0 Zr(IV) complexes and, since they present an empty orbital, most of the reactions may occur by the interaction of this empty orbital with electron donors.

The relatively low nucleophilicity of organozirconium reagents compared to the corresponding organomagnesium or organolithium derivatives contributes to perform alkylation reactions in a highly chemo-, regio- and stereoselective manner.

[64] a) P. C. Wailes, H. Weigold, *J. Organomet. Chem.* **1970**, *24*, 405; b) D. B. Carr, J. Schwartz, *J. Am. Chem. Soc.* **1979**, *101*, 3521.
[65] D. W. Hart, T. F. Blackburn, J. Schwartz, *J. Am. Chem. Soc.* **1975**, *97*, 679.
[66] D. R. Swanson, C. J. Rousset, E. Negishi, T. Takahashi, T. Seki, M. Saburi, Y. Uchida, *J. Org. Chem.* **1989**, *54*, 3521.

Polyalkylated zirconium compounds show better reactivity in comparison with the monoalkylated analogues in nucleophilic additions to the carbonyl group.

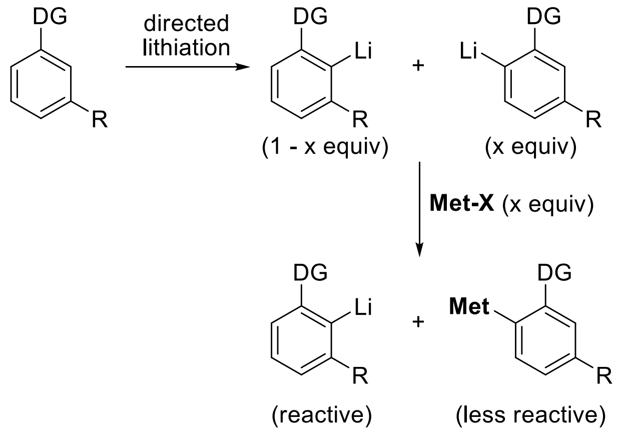
The presence of organozirconium in organic synthesis can be summarized in two types. The first one involves the formation of C-Zr reagent, followed by C-Zr bond cleavages for example by iodolysis, and the second category implicates that after forming the C-Zr bond, there is an interconversion and subsequent C-Zr bond cleavage (Scheme 18).[13]



Scheme 18: Two types of organic syntheses using organozirconium derivatives.

4. OBJECTIVES

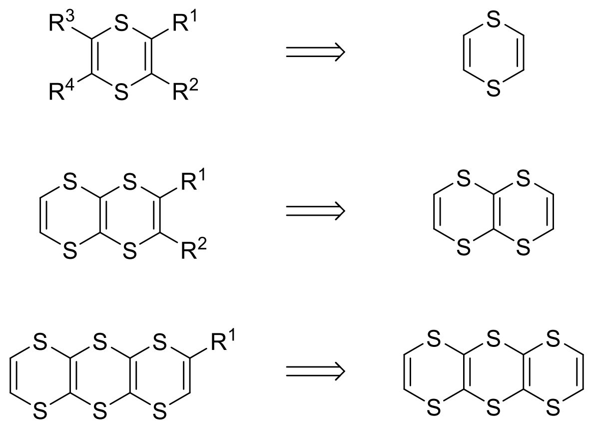
The functionalization of aromatic compounds is an important aspect in organic synthesis. There are cases where the metalation of arenes is not selective, giving for example regioisomeric mixtures of aryllithiums. A general method for the regioselective transmetalation of these mixtures with a metallic salt was the aim of the first project. This method would allow the least sterically hindered regioisomeric aryllithium to selectively be transmetalated to the corresponding metallic-species, producing a less reactive organometallic reagent, and leaving the more hindered aryllithium untouched. The aryllithium would be then ready for various reactions with electrophiles and subsequently, the least reactive species could also react with different electrophiles.[67]



Scheme 19: Metalation of arenes and subsequent transmetalation with a metallic salt.

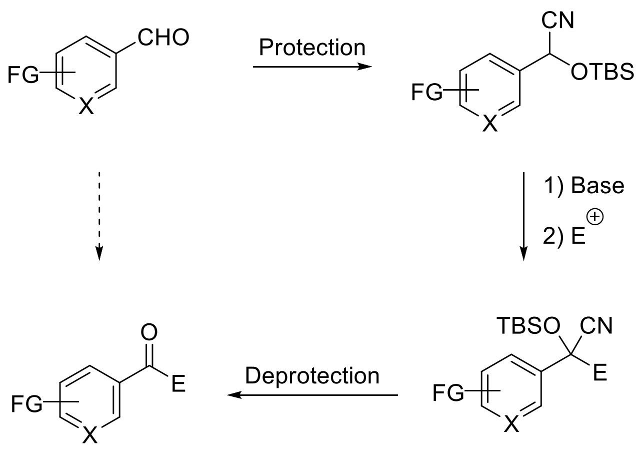
Also, 1,4-dithiins have attracted interest due to their electronical and structural properties. Their functionalization remained still a challenge since the lithiation of these scaffolds used resulted in undesired ring opening reactions. For this reason, a methodology for a mild metalation of the dithiin ring by direct metalation is highly desirable. Correspondingly, these metalation procedures could also be extended to the dithiin condensed analogues, TTN and HTA heterocycles.[68]

[67] This project was developed in cooperation with Dr. S. A. Herbert and Dr. T. León.
[68] This project was developed in cooperation with J. Nafe (see: Dissertation, LMU-München, **2015**), K. Higashida.



Scheme 20: Functionalization of 1,4-dithiin scaffold and condensed derivatives.

Furthermore, protected silylated cyanohydrins are important compounds in organic chemistry. When a benzylic carbonyl group is protected into a cyanohydrin, the carbon of the carbonyl group is converted from being an electrophile to a nucleophile after deprotonation. The versatility of converting carbonyl groups into an acyl anion, known as synthons with umpolung, is useful in the preparation of complex organic molecules. So far, the functionalization of these silylated cyanohydrins has been performed only by using lithium bases, limiting the presence of sensitive functional group and heterocyclic scaffolds. Consequently, a methodology allowing the metalation at the benzylic position in protected silylated cyanohydrins bearing highly sensitive functional groups should be developed.



Scheme 21: Nucleophilic acylation with aromatic and heteroaromatic aldehydes.

B. Results and Discussion

1. FUNCTIONALIZATIONS OF MIXTURES OF REGIOISOMERIC ARYLLITHIUM COMPOUNDS BY SELECTIVE TRAPPING WITH DICHLOROZIRCONOCENE

1.1 INTRODUCTION

Organolithiums are important organometallic intermediates in organic synthesis playing an important role in the preparation of pharmaceuticals and agrochemicals.[69] The most convenient preparation of aryllithiums involves a halogen-lithium exchange or a directed metalation using alkyllithium or lithium amides.[70] Substituted aromatics with directed metalation groups (DMGs) usually ensure lithiation at the *ortho*-position. This reaction is the most efficient way to synthesize isomerically pure *ortho*-substituted aromatics, and it plays a significant role in organic chemistry.

The deprotonation in systems with DMG occurs though the coordination between the DMG and the lithium reagent making that the organolithium gets closer to the *ortho*-proton, which is then selectively removed.

However in cases where arenes bears two competing DMGs or they are unsymmetrical substrates (Figure 2), the position of the deprotonation will depend on different factors. The inductive effects, the ability of coordination and the steric effects will affect the aggregation and complexation of alkyllithium reagents as well as the formation of the *ortho*-lithiated species.

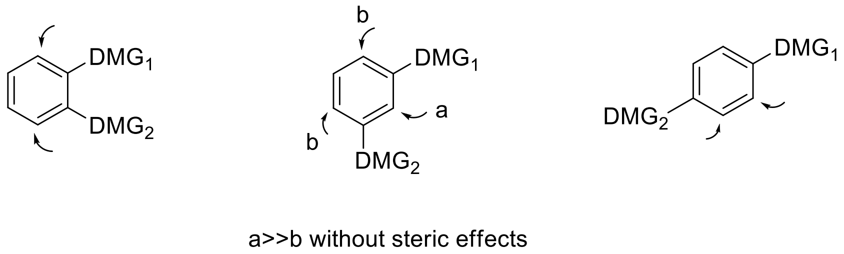
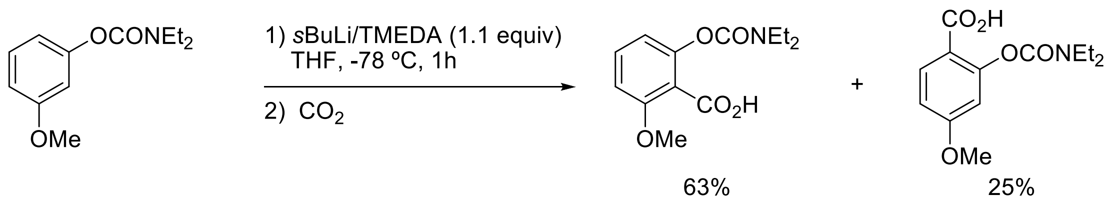


Figure 2: Expected metalation position for bis-DMG benzenoid system.

69 a) D. Hoppe, T. Hense, *Angew. Chem. Int. Ed.* **1997**, *36*, 2282; b) C. Nájera, J. M. Sansano, M. Yus, *Tetrahedron* **2003**, *59*, 9255; c) M. Yus, F. Foubelo, *Handbook of Functionalized Organometallics*, *Vol.1* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**, pp. 7-44; d) G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596; e) P. C. Gros, Y. Fort, *Eur. J. Org. Chem.* **2009**, *25*, 4199; f) Z. Xi, *Acc. Chem. Res.* **2010**, *43*, 1342; g) H. J. Reich, *Chem. Rev.* **2013**, *113*, 7130; h) *Lithium Compounds in Organic Synthesis – From Fundamentals to Applications* (Eds.: R. Luisi, V. Capriati), Wiley-VCH, Weinheim, **2014**; i) V. Capriati, F. M. Perna, A. Salomone, *J. Chem. Soc., Dalton Trans.* **2014**, *43*, 14204; j) W.-X. Zhang, Z. Xi, *Org. Chem. Front.* **2014**, *1*, 1132; k) S. Zhang, W.-X. Zhang, Z. Xi, *Top. Organomet. Chem.* **2014**, *47*, 1.

70 a) *Organolithiums: Selectivity for Synthesis*, *Vol. 23* (Eds.: J. Clayden), Pergamon, London, **2002**; b) R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470; c) M. A. Perry, S. D. Rychnovsky, *Nat. Prod. Rep.* **2015**, *32*, 517.

There are cases where the metalation of these disubstituted arenes may produce a mixture of regioisomeric aryllithiums (Scheme 22).[71,39b-e] In the case of an unsymmetrical carbamate, the metalation with *s*BuLi using TMEDA produces a non-selective *ortho*-deprotonation giving, after quenching with carbon dioxide, the two isomeric carboxylic acids in 63% and 25% isolated yields.[72] The formation of such mixtures hampers synthetic applications.



Scheme 22: Non-selective ortho-lithiation of substituted aryl carbamate.

In the past years, optimal conditions to regioselectively metalate these unsymmetrical arenes have been broadly studied. Apart from the nature of the substituents, the selectivity of the metalation also depends on the metal bases, the temperature and the solvents used.

Based on these factors, a convenient and general method solving the lack of regioselectivity in the metalation of unsymmetrically substituted arenes or aromatic systems with more than one DMG was envisioned.

1.2 REGIOSELECTIVE TRANSMETALATION OF ISOMERIC MIXTURES OF ARYLLITHIUMS

1.2.1 Mixtures of aryllithiums formed by directed metalation

The treatment of unsymmetrical substituted arenes of type **5** with a variety of lithium bases usually leads to the corresponding mixture of two regioisomers **6** and **7** (Scheme 23). Therefore, a selective transmetalation of the less sterically hindered aryllithium **7** with an appropriate metallic salt (Met-X) was envisioned. This produces selectively the new metalated arene **8**, leaving the more sterically hindered aryllithium **6** untouched. The lithium reagent (**6**) still remaining in the reaction mixture is then available to react with an electrophile E^{1+} leading to the 1,2,3-trisubstituted arenes of type **9**. On the other hand, the

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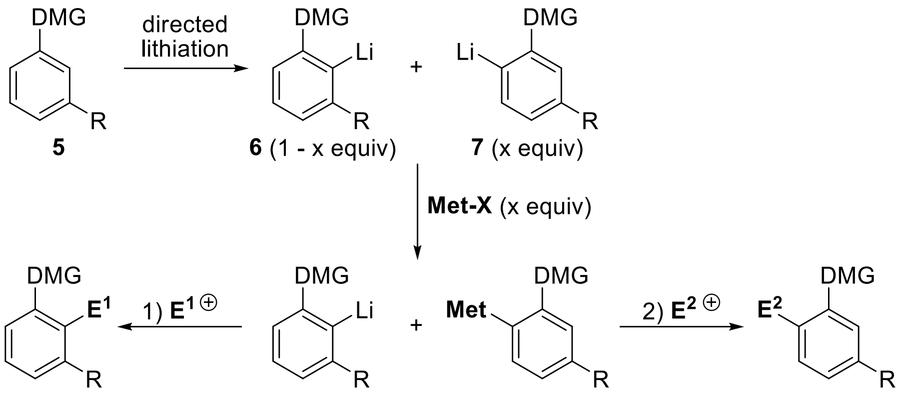
[71] a) A. J. Bridge, A. Lee, E. C. Maduakor, C. E. Schwartz, *Tetrahedron Lett.* **1992**, *33*, 7499; b) M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376; c) M. Dąbrowski, J. Kubicka, S. Luliński, J. Serwatowski, *Tetrahedron Lett.* **2005**, *46*, 4175; d) F. Chevallier, F. Mongin, *Chem. Soc. Rev.* **2008**, *37*, 595; e) L. Gupta, A. C. Hoepker, K. J. Singh, D. B. Collum, *J. Org. Chem.* **2009**, *74*, 2231; f) D. W. Slocum, S. Wang, C. B. White, P. E. Whitley, *Tetrahedron* **2010**, *66*, 4939; g) A. C. Hoepker, L. Gupta, Y. Ma, M. F. Faggin, D. B. Collum, *J. Am. Chem. Soc.* **2011**, *133*, 7135; h) M. Zenzola, L. Degennaro, P. Trinchera, L. Carroccia, A. Giovine, G. Romanazzi, P. Mastrorilli, R. Rizzi, L. Pisano, R. Luisi, *Chem. Eur. J.* **2014**, *20*, 12190.
[72] M. P. Sibi, V. Snieckus, *J. Org. Chem.* **1983**, *48*, 1935.

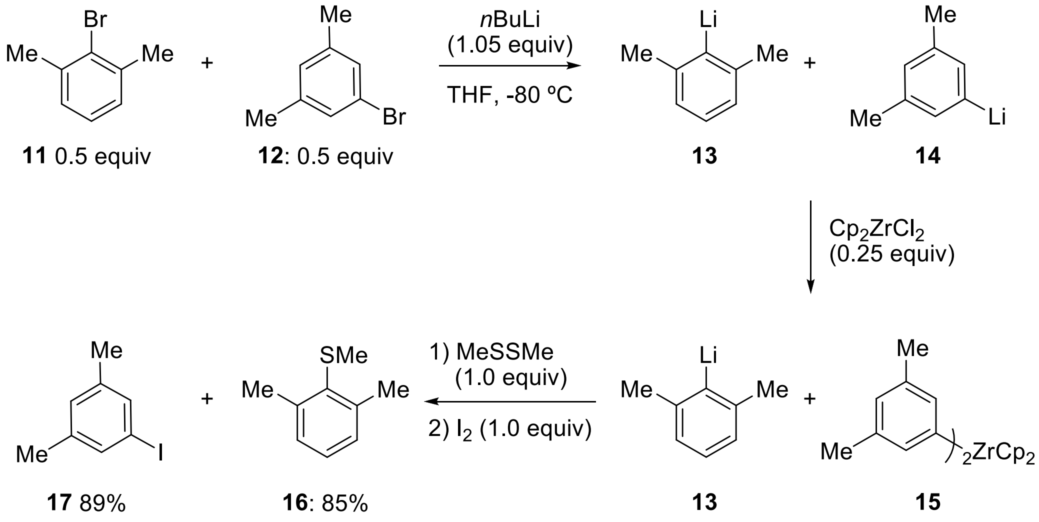
organometallic species (**8**) produced after the transmetalation step should have a significantly less reactive carbon-metal bond than the carbon-lithium bond of **6**. It may then be trapped by a second different electrophile E^{2+} producing the regioisomeric 1,3,6-trisubstituted arene of type **10**.



Scheme 23: Non-selective metalation of unsymmetrical arene of type **5** followed by selective transmetalation.

Preliminary experiments were performed in order to find the appropriate metallic salt (Met-X) that could solve this regioselectivity problem in such arene lithiations. The search for a successfully selective transmetalations was performed on 1:1 mixtures of 2-bromo-*m*-xylene (**11**, 0.5 equiv) and 5-bromo-*m*-xylene (**12**, 0.5 equiv, Scheme 24). After lithium-bromine exchange with *n*BuLi (1.05 equiv, -80 ºC), the mixture produced the regioisomeric 2,6-dimethylphenyllithium (**13**) and 3,5-dimethylphenyllithium (**14**) after 0.5 h. The transmetalation with various Zn, Mg, Cu, Ti or Sn salts gave no selective transmetalation. However, Cp_2ZrCl_2[73] (0.25 equiv, -80 ºC, 1 h) led to a preferential reaction with 3,5-dimethylphenyllithium **14** leaving **13** untouched and ready for a selective reaction with dimethyl disulfide (1.0 equiv, -80 ºC, 1 h). Subsequent addition of iodine (1.0 equiv, -80 ºC to 25 ºC, 1 h) proved that only the less sterically hindered aryllithium **14** reacted with Cp_2ZrCl_2 leading to a less reactive diarylzirconium species (**15**) that reacted with the added iodine. The isolated products were in 85% yield (2,6-dimethylphenyl)(methyl)sulfane (**16**) and in 89% yield 1-iodo-3,5-dimethylbenzene (**17**). They were obtained in more than 97:3 regioisomeric ratio as shown by crude ^{1}H NMR.

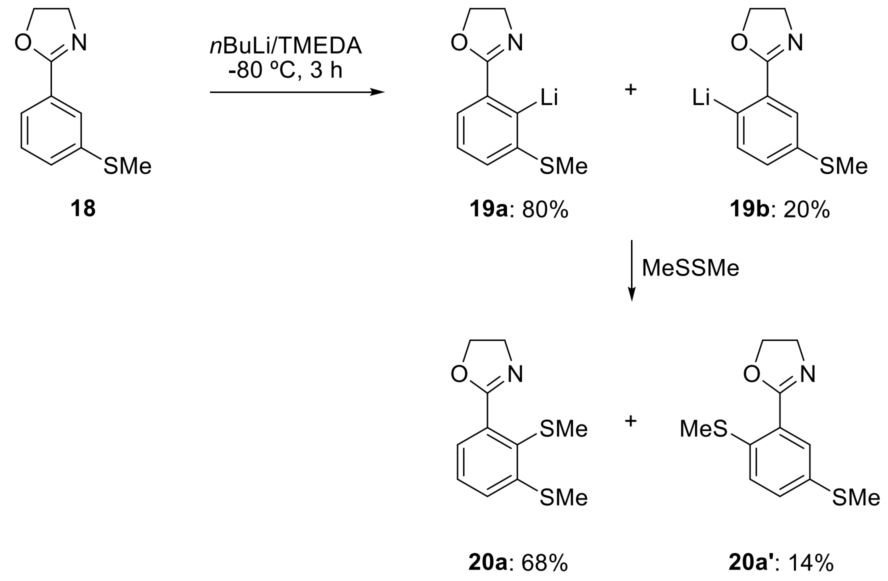
[73] a) G. Erker, *Angew. Chem. Int. Ed.***1989**, *28*, 397; b) T. Takahashi, Z. Xi, A. Yamazaki, Y. Liu, K. Nakajima, M. Kotora, *J. Am. Chem. Soc.* **1998,** *120*, 1672; c) I. Marek, N. Chinkov, A. Levin, *Synlett* **2006**, *2006*, 501; d) W.-X. Zhang, S. Zhang, Z. Xi, *Acc. Chem. Res.*, **2011**, *44*, 541.



Scheme 24: Chemoselective transmetalation using Cp_2ZrCl_2.

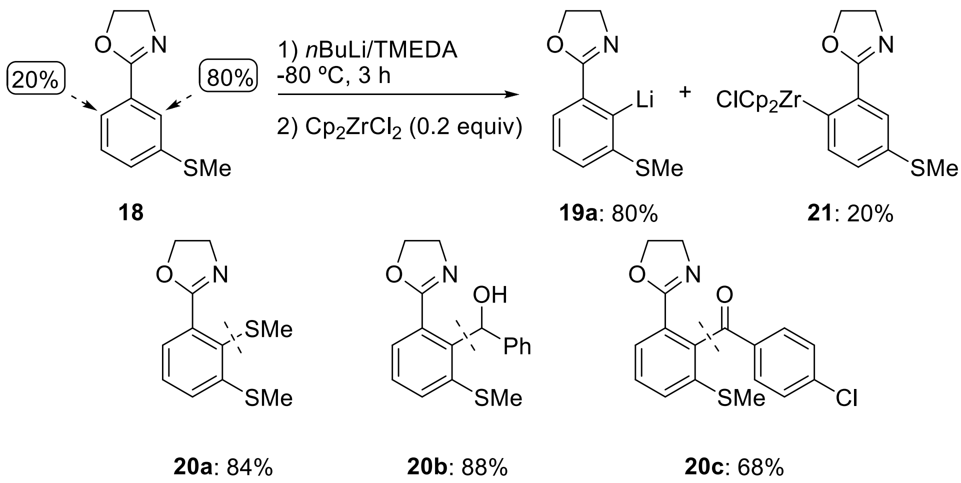
These encouraging results led us to examine the lithiation of various substrates of type **5**. Since oxazolines are important directing groups for *ortho*-lithiations[74], we first studied the lithiation of **18** with *n*BuLi-TMEDA (1.1 equiv, -80 ºC, Scheme 25). The reaction produced after 3 h a 4:1 mixture of the regioisomeric 2- and 6-lithio derivatives (**19a** and **19b**). In absence of a treatment with Cp_2ZrCl_2, the quenching with MeSSMe (0.8 equiv) led respectively to 2-thiomethyl isomer (**20a**) and 6-thiomethyl isomer (**20a'**) in 68% and 14% isolated yield.

[74] a) P. Break, R. A. Brown, *J. Org. Chem.* **1982**, *47*, 34; b) P. Beak, V. Snieckus, *Acc. Chem. Res.* **1982**, *15*, 306; c) P. D. Pansegrau, W. F. Rieker, A. I. Meyers, *J. Am. Chem. Soc.* **1988**, *110*, 7178; d) P. A. Evans, J. D. Nelson, A. L. Stanley, *J. Org. Chem.* **1995**, *60*, 2298.



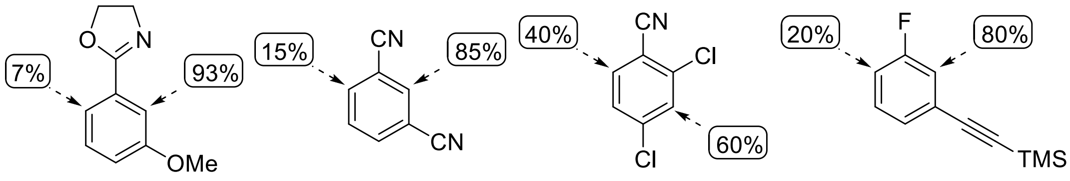
Scheme 25: Unselective metalation of oxazoline (**18**) affording a mixture of regioisomers.

Therefore, the addition of Cp_2ZrCl_2 (0.2 equiv, -80 ºC, 1 h) to the formed regioisomeric mixture of lithiated oxazolines (**19a**-**b**) achieved a completely selective transmetalation of the sterically less hindered 6-lithio derivative of **18**, providing the zirconium species **21** and leaving the lithiated arene (**19a**) untouched (Scheme 26). Thus, treatment of the mixture of **19a** and **21** with MeSSMe (0.8 equiv, -80 ºC, 1 h) and subsequent quenching with water produced only the trisubstituted arene (**20a**) in 84% isolated yield and the regeneration of the starting material **18**. Similarly, the addition of PhCHO (0.8 equiv, -80 ºC, 1 h) afforded the corresponding alcohol (**20b**) in 88% yield and quenching with 4-chlorobenzoyl chloride provided ketone **20c** in 68% yield.



Scheme 26: Regioselective functionalization of oxazoline (**18**).

The study was then extended to unsymmetrical arenes **22**-**25** (Figure 3). Thus, the methoxy-substituted oxazoline **22** produced after lithiation with *n*BuLi-TMEDA (1.1 equiv, -80 ºC, 3 h) a 93:7 mixture, checked by GC analysis of reaction aliquots quenched with iodine in dry THF as well as by analysis of crude ^{1}H NMR of the iodinated regioisomers. Similarly, 1,3-dicyanobenzene (**23**) afforded after metalation with TMPLi (1.05 equiv, -80 ºC, 0.5 h) a 85:15 mixture, and benzonitrile **24** gave a 60:40 mixture with TMPLi (1.0 equiv, -80 ºC, 20 min). Alkynylbenzene **25** also furnished a 80:20 mixture after lithiation with TMPLi (1.0-1.1 equiv, -80 ºC, 1 h).



22 **23** **24** **25**

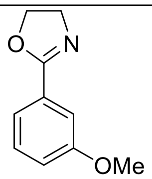
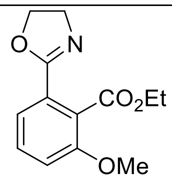
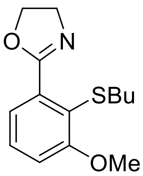
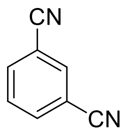
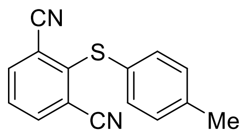
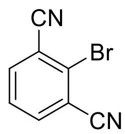
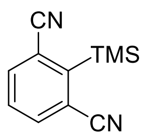
Figure 3: Unsymmetrical arenes that present non-selective metalation.

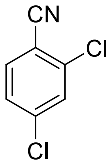
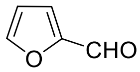
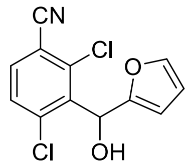
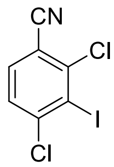
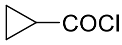
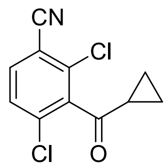
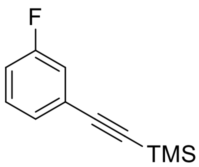
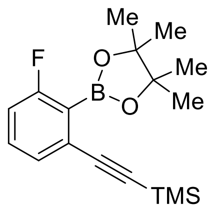
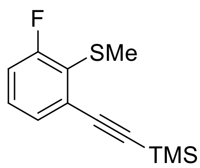
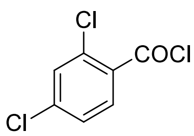
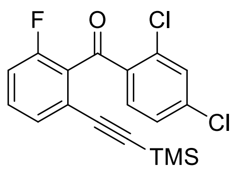
Treatment of these aryllithium mixtures with the appropriate amount of Cp_2ZrCl_2 allowed selective transmetalation of the less sterically hindered aryllithium to a less reactive arylzirconium species, leaving the major aryllithium reagent ready to react with various electrophiles and producing >97% regioisomerically pure products of type **26**-**29** (Table 1). In a typical experiment, the lithiated aryloxazolines derived from **22** were treated with Cp_2ZrCl_2 (0.1 equiv, -80 ºC, 1 h) followed by the addition of ethyl chloroformate (0.9 equiv, -80 ºC, 1 h) providing the 2-carbomethoxy arene (**26a**) free of any regioisomeric by-product in 85% yield (entry 1). Similarly, the thioether **26b** was produced in 83% isolated yield by adding BuSSBu (entry 2). The 85:15 mixture of the lithiated species **23** was also treated with Cp_2ZrCl_2 (0.15 equiv, -80 ºC, 0.5 h), followed by quenching with $(p\mathrm{TolS})_2$, which produced the expected thiocresol **27a** in 73% yield (entry 3). Adding various electrophiles, such as $(BrCCl_2)_2$ or TMSCl, also furnished regioisomerically pure 1,2,3-trisubstituted dinitriles **27b**-**c** in 66-75% yields (entries 4-5). The same strategy was applied to arene **24**. After the addition of Cp_2ZrCl_2 (0.35-0.4 equiv, -80 ºC, 0.5 h), the remaining more sterically hindered 3-lithio-isomer reacted with furfural, giving the corresponding regioisomerically pure alcohol **28a** in 75% (entry 6) and the reaction with $(ICH_2)_2$ produced the iodinated product **28b** in 78% (entry 7). Acylation was also performed using cyclopropanecarbonyl chloride in the presence of 10% $Sc(OTf)_3$[75,53a] producing the regioisomerically pure product **28c** in 61% yields (entry 8).

[75] S. Kobayashi, I. Hachiya, M. Araki, H. Ishitani, *Tetrahedron Lett.* **1993**, *34*, 3755.

Moreover, the regioisomeric mixture of aryllithium species of **25** led by addition of Cp_2ZrCl_2 (0.25 equiv, -80 ºC, 0.5 h) to the selective trasmetalation. The remaining 2-lithio-isomer reacted with various electrophiles. The addition of *i*PrOBpin produced the boronate ester **29a** in 90% yield (entry 9). Similarly, adding MeSSMe to the mixture of the 2-lithio-isomer and the 4-zirconium-isomer afforded the 2-methylthio product **29b** in 87% (entry 10). Acylation of the lithio-isomer was also possible by using 2,4-dichlorobenzoyl chloride, affording the isomerically pure product **29c** in 77% yield (entry 11).

Table 1: Regioselective functionalization of unsymmetric arenes.

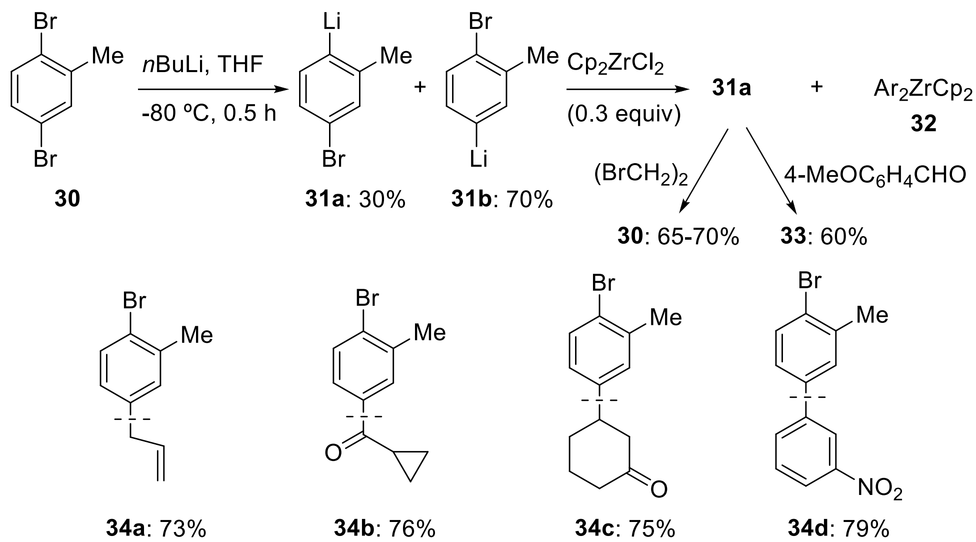
Entry	Substrate	Electrophile	Product[a], Yield[b]
1	 **22**	$ClCO_2Et$	 **26a**: 85%
2	**22**	BuSSBu	 **26b**: 83%
3	 **23**	$(p\text{TolS})_2$	 **27a**: 73%
4	**23**	$(BrCCl_2)_2$	 **27b**: 75%
5	**23**	TMSCl	 **27c**: 66%

Entry	Substrate	Electrophile	Product[a], Yield[b]
6	 **24**		 **28a**: 75%
7	**24**	$(ICH_2)_2$	 **28b**: 78%
8	**24**		 **28c**: 61%[c]
9	 **25**	*i*PrOBpin	 **29a**: 90%
10	**25**	MeSSMe	 **29b**: 87%
11	**25**		 **29c**: 77%

[a] Regioisomerically pure products (crude ratio >97:3). [b] Yield of analytically pure product (>99%) based on the electrophile added. [c] $Sc(OTf)_3$ was added.

1.2.2 Mixtures of aryllithiums formed by bromine/lithium exchange

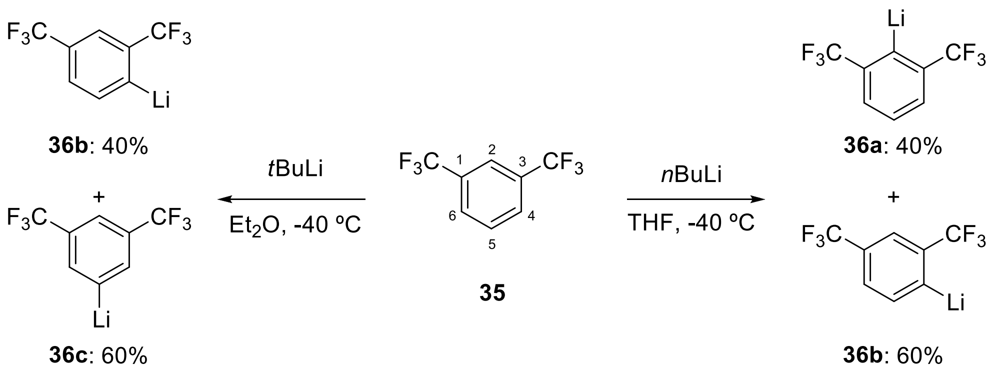
This methodology was also successfully applied to regioisomeric mixtures of aryllithiums obtained by a Br/Li-exchange. Indeed, the lithiation of 2,5-dibromotoluene (**30**) with *n*BuLi (1.0 equiv, -80 ºC, 0.5 h) in THF produced low selective bromine-lithium exchange after 0.5 h giving a 40:60 mixture of the two regioisomeric lithium species (**31a**-**b**, Scheme 27), which was checked by GC analysis of reaction aliquots quenched with iodine in dry THF and by iodination of the aryllithium mixtures and subsequent analysis of crude ^{1}H NMR. In this case, the major regioisomer (**31b**) was the less sterically hindered and was converted into the corresponding diarylzirconocene **32** by adding Cp_2ZrCl_2 (0.3 equiv, -80 ºC, 1.5 h). Then, the remaining aryllithium **31a** was quenched with $(BrCH_2)_2$ or 4-$MeOC_6H_4CHO$ (0.4-0.45 equiv, -80 ºC, 0.5-1 h), which generated the starting material (**30**) in 65-70% yield or the corresponding alcohol **33** in 60%, leaving the zirconocene species **32** untouched and ready to react with a range of electrophiles. Consequently, the addition of allyl bromide in presence of 20% CuCN·2LiCl produced the allylated product **34a** in 73%. Acylation was performed after the transmetalation of the zirconium species **32** into a zinc species using $ZnCl_2$, and subsequently to the copper species by using CuCN·2LiCl. Quenching of the copper species with cyclopropanecarbonyl chloride produced the expected product **34b** in 76%. 1,4-Addition was also performed using cyclohex-2-enone in presence of trimethylsilyl chloride and catalytic amount of rhodium producing the product **34c** in 75%. Moreover, palladium-catalyzed cross-coupling allowed the arylation of the zirconocene **32** providing the desired product **34d** in 79% yield.



Scheme 27: Regioselective functionalization of 2,5-dibromotoluene (**30**).

1.3 FURTHER APPLICATION USING SELECTIVE TRANSMETALATION

CF_3-substituted aromatics are very important pharmaceutical targets and much recent work on the selective preparation of CF_3-substituted molecules has been reported.[76] The lithiation of 1,3-bis(trifluoromethyl)benzene (**35**) has been observed to proceed without any appreciable regiocontrol (Scheme 28).[77] By using *n*BuLi in THF, the metalation produces a 40:60 mixture of the 2- and 4-lithio derivatives (**36a**-**b**). Alternatively, the use of *t*BuLi in ether leads to a 40:60 mixture of the 4- and 5-lithio derivatives (**36b**-**c**). The production of regioisomeric mixtures in 1,3-bis(trifluoromethyl)benzene (**35**) has reduced the use of these lithiations.

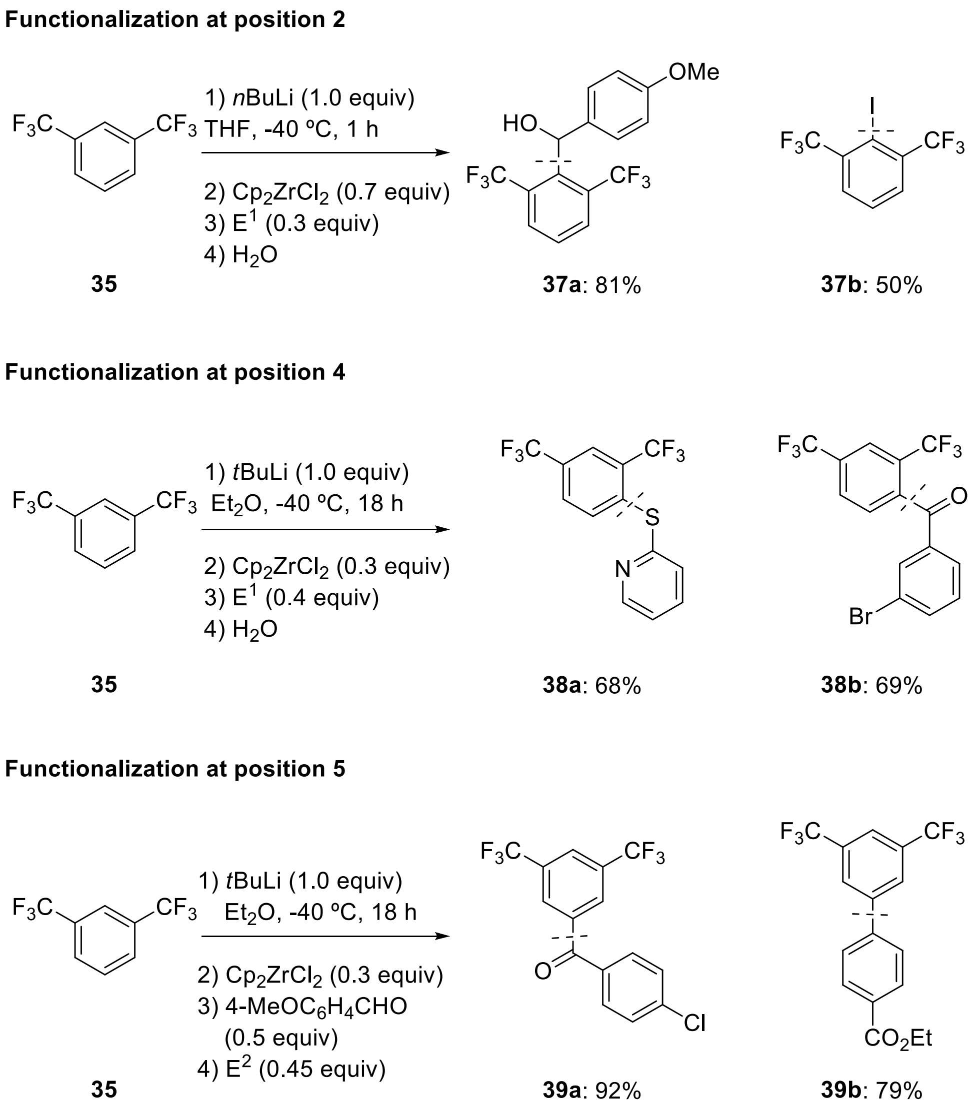


Scheme 28: Unselective 2-, 4- or 5- lithiation of 1,3-bis(trifluoromethyl)benzene (**35**).

However, the use of zirconium transmetalation made the regioselective functionalization of the three positions of **35** possible. Selective lithiation at position 2 was achieved by treating **35** with *n*BuLi (THF, 1.0 equiv, -40 ºC, 1 h), followed by subsequent addition of Cp_2ZrCl_2 (0.7 equiv, -80 ºC, 1.5 h) converting **36b** into the corresponding zirconium species and leaving **36a** as the sole remaining lithiated reagent. Its reaction with 4-$MeOC_6H_4CHO$ furnished the corresponding alcohol **37a** in 81% yield (Scheme 29). The lithium species **36a** was also quenched with $(ICH_2)_2$ producing the expected iodinated product **37b** in 50% yield. The selective functionalization at position 4 was possible using *t*BuLi (Et_2O, 1.0 equiv, -40 ºC, 18 h) followed by the addition of Cp_2ZrCl_2 (0.3 equiv, -80 ºC, 1-1.5 h) to the 40:60 mixture of **36b**-**c**. In this case, **36c** was transmetalated into the corresponding zirconium species and the lithium reagent (**36b**) was quenched with $(2\text{-PyrS})_2$ affording the corresponding product **38a** in 68% yield. Organolithium **36b** was also treated with 3-bromobenzoyl chloride leading

[76] a) M. Schlosser, *Angew. Chem. Int. Ed.* **2006**, *45*, 5432; b) A. Studer, *Angew. Chem. Int. Ed*. **2012**, *51*, 8950; c) J. Charpentier, N. Fruh, A. Togni, *Chem. Rev*. **2015**, *115*, 650.
[77] a) P. Aeberli, W. J. Houlihan, *J. Organomet. Chem.* **1974**, *67*, 321; b) H. J. Kroth, H. Schumann, H. G. Kuivila, C. D. Jr. Schaeffer, J. J. Zuckerman, *J. Am. Chem. Soc.* **1975**, *97*, 1754; c) L. Heuer, P. G. Jones, R. Schmutzler, *J. Fluorine Chem.* **1990**, *46*, 243.

to **38b** with 69% yield. On the other hand, lithiation with *t*BuLi in ether has also been used to functionalize the position 5, but in this case the mixture **36b-c** was treated with Cp_2ZrCl_2 (0.3 equiv, -80 ºC, 1.5 h) followed by the addition of 4-MeOC_6H_4CHO (0.5 equiv, -80 ºC, 1 h), which reacted exclusively with the lithio-species (**36b**). The zirconium species reacted with subsequently introduced electrophiles, such as 4-chlorobenzoyl chloride or ethyl 4-iodobenzoate, to produce the expected acylated and arylated products **39a-b** in 79-92% yields.

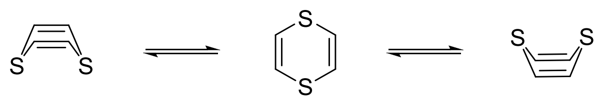


Scheme 29: Selective 2-, 4- or 5- functionalization of 1,3-bis(trifluoromethyl)benzene (**35**).

2. SELECTIVE METALATIONS OF 1,4-DITHIINS AND CONDENSED ANALOGUES USING TMP-MAGNESIUM AND -ZINC BASES

2.1 INTRODUCTION

Sulfur-heterocycles are important building blocks for applications in medicinal chemistry[78] and materials science.[79] Especially, 1,4-dithiins (**40**) have attracted attention due to their unique electronic and conducting properties, as well as their ability to act as electron donors[80] and their use for the preparation of other sulfur heterocycles.[81] Structural studies on 1,4-dithiin derivatives have also been the subject of several publications, as to whether or not 1,4-dithiins (**40**) are flat and to understand the electronic delocalization.[82] It has been concluded that this 8 π electron system has a non-planar boat conformation[83] with an angle of 132º, and that in solution[84] and vapor phase[85] the dithiin ring rapidly oscillates between the boat and planar structures (Scheme 30).



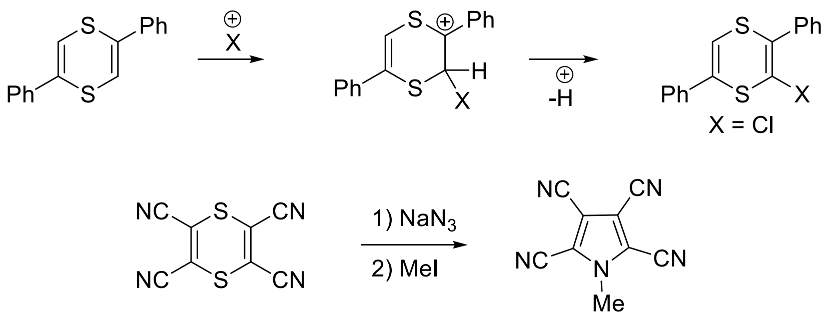
40

Scheme 30: Non-planar configuration of 1,4-dithiin (**40**).

The chemistry of sulfur-containing heterocycles has also been studied in the last years.[78] Due to the small ionization energy of their HOMO, they are susceptible to oxidation. Dithiins

[78] a) P. Metzner, A. Thuillier, In *Sulfur Reagents in Organic Synthesis*; A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds.; Academic Press: London, **1994**; b) M. Carmack, *Sulfur Reports* **1995**, *16*, 299; c) A. Senning, *Sulfur Reports* **2003**, *24*, 191; d) P. Bichler, J. Love, In *Topics of Organometallic Chemistry*; A. Vigalok, Ed.; Springer: Heidelberg, **2010**; Vol. 31, pp 39-64; e) Y. Hu, C.-Y. Li, X.-M. Wang, Y.-H. Yang, H.-L. Zhu, *Chem. Rev.* **2014**, *114*, 5572.
[79] a) M. Gingras, J.-M. Raimundo, Y. M. Chabre, *Angew. Chem. Int. Ed.* **2006**, *45*, 1686; b) W. Wu, Y. Liu, D. Zhu, *Chem. Soc. Rev.* **2010**, *39*, 1489; c) H. Ito, D. Watanabe, T. Yamamoto, N. Tsushima, H. Muraoka, S. Ogawa, *Chem. Lett.* **2013**, *42*, 646; d) D. A. Boyd, *Angew. Chem. Int. Ed.* **2016**, *55*, 15486.
[80] a) J. Kao, A. C. Lilly, *J. Am. Chem. Soc.* **1987**, *109*, 4149; b) M. R. Bryce, A. Chesney, A. K. Lay, A. S. Batsanov, J. A. K. Howard, *J. Chem. Soc., Perkin Trans. 1*, **1996**, 2451; c) G. Guillaumet, F. Suzenet, In *Comprehensive Heterocyclic Chemistry III*; A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, Eds.; Elsevier: Oxford, **2008**; Vol. 8, pp 857- 905; d) M. F. Peintinger, J. Beck, T. Bredow, *Phys. Chem. Chem. Phys.* **2013**, *15*, 18702.
[81] a) W. E. Parham, In *Organic Sulfur Compounds*, N. Kharasch, Ed.; Pergamon Press: New York, **1961**; Vol. 1, pp 248-256; b) K. Kobayashi, C. L. Gajurel, *Sulfur Reports* **1986**, *7*, 123.
[82] a) S. Saebo, L. Radom, G. L. D. Ritchie, *J. Mol. Struct.* **1984**, *17*, 59; b) O. Y. Borbulevych, O. V. Shishkin, *J. Mol. Struct.* **1998**, *446*, 11; c) S. Pelloni, F. Faglioni, A. Soncini, A. Ligabue, P. Lazzeretti, *Chem. Phys. Lett.* **2003**, *375*, 583; d) E. Vessally, *Bull. Chem. Soc. Ethiop.* **2008**, *22*, 465; e) A. R. Ilkhani, W. Hermoso, I. B. Bersuker, *Chem. Phys.* **2015**, *460*, 75.
[83] D. S. Sappenfield, M. Kreevoy, *Tetrahedron* **1963**, *19*, 157.
[84] a) R. C. Long, J. H. Goldstein, *J. Mol. Spectros.* **1971**, *40*, 632; b) J. Russell, *J. Org. Magn. Reson.* **1972**, *4*, 433.
[85] F. P. Colonna, G. Distefano, V. Galasso, *J. Electron Spectrosc. Relat. Phenom.* **1980**, *18*, 75.

with electron-withdrawing substituents facilitate the oxidation of the sulfur next to the substituent, making the flap angle larger and consequently the molecular geometry flatter. In addition, both electrophilic substitutions, such as formylation, nitration or sulfenylation, and nucleophilic substitutions resulting in the formation of a variety of 5-membered ring can occur at the carbon or at the sulfur center (Scheme 31).[86] 1,4-Dithiins can also undergo thermal reactions such as Diels-Alder,[87] and they are thermally stable and can be distilled at 190 ºC without decomposition although some substituted 1,4-dithiins can suffer ring contraction to thiophene.[81a]



Scheme 31: Electrophilic and nucleophilic substitution reactions in 1,4-dithiin derivatives.

Nevertheless, the preparation of functionalized 1,4-dithiins remains a challenge since the metalation of theses scaffolds has been scarcely studied. The reaction of 1,4-dithiin (**40**) with *n*BuLi leads to a ring-opening reaction unless this lithiation is performed at -110 ºC (Scheme 32).[88,39c] Also, the treatment of 2,5-diphenyl-1,4-dithiine with *t*BuOK gives a skeleton rearrangement affording 1,4-dithiafulvenes derivative due to the harsh reaction conditions.[89]

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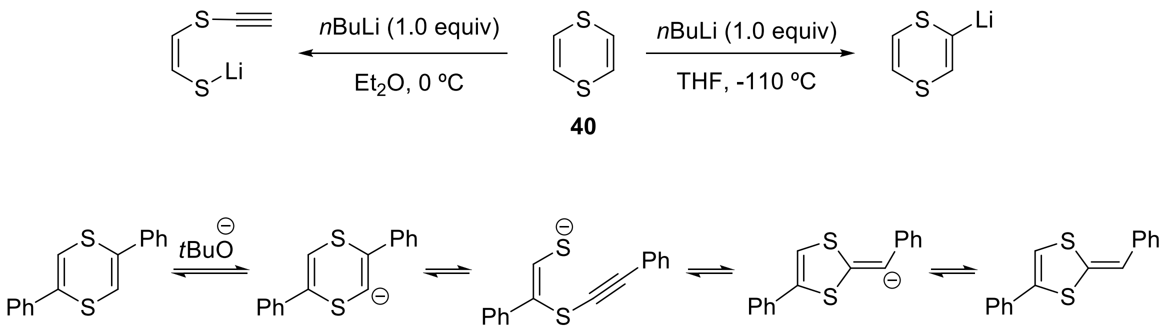
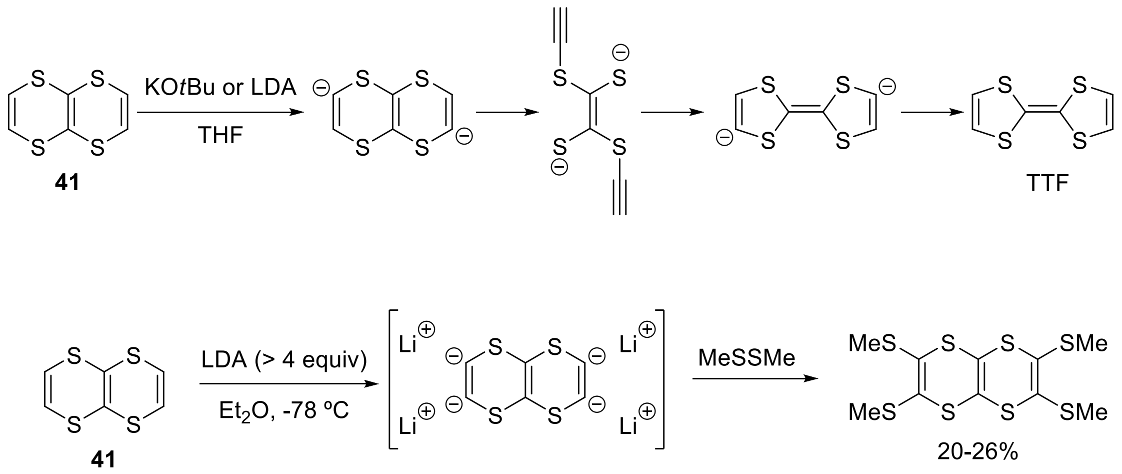
[86] a) M. Oki, K. Kobayashi, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 687; b) H. E. Simmons, R. D. Vest, S. A. Vladuchick, O. W. Webster, *J. Org. Chem.* **1980**, *45*, 5113.
[87] K. Kobayashi, K. Mutai, *Chem. Lett.* **1977**, *6*, 1149.
[88] a) M. Schoufs, J. Meyer, P. Vermeer, L. Brandsma, *Rec. Trav. Chim. Pays-Bas* **1977**, *96*, 259. For other selective metalation of heterocycles see: b) E. J.-G. Anctil, V. Snieckus, *J. Organomet. Chem.* **2002**, *653*, 150; c) R. Chinchilla, C. Nájera, M. Yus, *Tetrahedron* **2005**, *61*, 3139; d) G. Pelletier, L. Constantineau-Forget, A. B. Charette, *Chem. Commun.* **2014**, *50*, 6883.
[89] R. Andreu, J. Garín, J. Orduna, J. M. Royo, *Tetrahedron Lett.* **2001**, *42*, 875.



Scheme 32: Deprotonation of 1,4-dithiin derivatives.

Similarly, the deprotonation of condensed 1,4,5,8-tetrathianaphthalene (TTN, **41**) with an excess of *t*BuOK or LDA in THF leads through an intramolecular rearrangement to the more thermodynamic stable tetrathiafulvalene (TTF, Scheme 33).[90] This rearrangement made the functionalization of TTN (**41**) *via* metalation impossible unless diethyl ether was used as solvent. This solvent allowed the contact of the ion pair between the carbanion and lithium ion, which was not possible with THF, retaining the configuration of **41**. The tetralithio derivative of TTN generated by using LDA (> 4 equiv, Et_2O) was treated with dimethyl disulfide to produce the desired tetrakis(methylthio) derivative in just 21-26% yield.[91] The functionalization of TTN (**41**) using this metalation condition was still limited due to the low stabilization of the formed tetralithio species, and consequently the low yield of the isolated product.



Scheme 33: Metalation of TTN (**41**) producing the intramolecular rearrangement to TTF and a tetrasubstituted TTN.

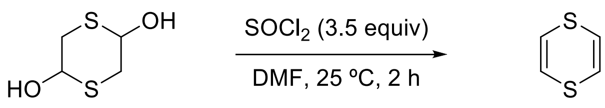
[90] a) S. Seong, D. S. Marynick, *J. Phys. Chem.* **1994**, *98*, 13334; b) R. L. Meline, R. L. Elsenbaumer, *Synthetic Metals*, **1997**, *86*, 1845.; c) R. L. Meline, R. L. Elsenbaumer, *J. Chem. Soc.*, *Perkin Trans*. 1 **1998**, 2467.
[91] S. Nakatsuji, Y. Amano, H. Kawamura, H. Anzai, *J. Chem. Soc., Chem. Commun.* **1994**, 841.

Therefore, a selective functionalization of 1,4-dithiin (**40**) and the condensed analogue TTN (**41**) is still remaining a challenge. Smooth reaction conditions should be investigated in order to avoid the ring opening or rearrangement described above.

2.2 FUNCTIONALIZATION OF 1,4-DITHIIN (40)

2.2.1 Preparation of 1,4-dithiin (**40**)

1,4-Dithiin (**40**) was synthesized by the reaction of 1,4-dithiane-2,5-diol (**42**, 1.0 equiv) with thionyl chloride (3.5 equiv, DMF, 25 ºC, 2 h).[92] Co-destillation of the crude product with DMF, followed by extraction afforded 1,4-dithiin (**40**) in 81% yield (Scheme 34).

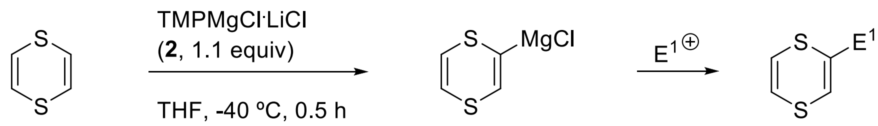


42 **40**: 81%

Scheme 34: Preparation of 1,4-dithiin (**40**).

2.2.2 Preparation of monosubtituted 1,4-dithiin derivatives

Preliminary experiments showed that the metalation of 1,4-dithiin (**40**) only proceeds using *n*BuLi at very low temperatures (-110 ºC).[88a] Since more stable metalated species wanted to be handled in order to avoid the ring opening and low temperatures, the main focus layed on the use of TMP-bases. Thus, it was found that the smooth metalation of **40** with TMPMgCl·LiCl (**2**) produced the magnesiated 1,4-dithiin (**43**) at -40 ºC within 0.5 h. The obtained magnesiated reagent **43** has proven to be highly reactive and could be quenched with various electrophiles leading to monosubstituted 1,4-dithiins of type **44** without side products being observed (Scheme 35).



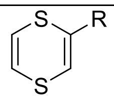
40 **43** **44**

Scheme 35: Magnesiation of 1,4-dithiin (**40**) using TMPMgCl·LiCl (**2**) and subsequent quenching with various electrophiles.

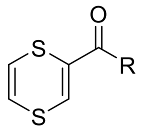
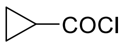
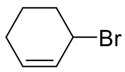
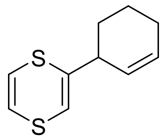
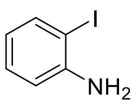
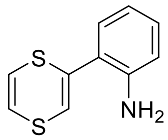
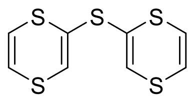
[92] A. S. Grant, S. Faraji-Dana, E. Graham, *J. Sulfur Chem.* **2009**, *30*, 135.

Thus, the magnesiated 1,4-dithiin (**43**) was readily halogenated using iodine, tetrachlorodibromoethane or benzenesulfonyl chloride leading to the 2-halo-1,4-dithiins (**44a**-**c**) in 56-78% yield (Table 2, entries 1-3). Cyanation of the magnesiated species **43** led to the corresponding product **44d** in 60% (entry 4). Similarly, aminomethylation using Tietze's reagent[93] was readily achieved giving the adduct **44e** in 58% yield (entry 5). Quenching of **43** with PhCHO afforded the alcohol **44f** in 97% yield (entry 6). The reaction of **43** with ethyl cyanoformate produced the ester **44g** in 89% yield (entry 7). Acylation was also performed after transmetalation of **43** to the zincated species with $ZnCl_2$, using catalytic amount of CuCN·2LiCl, and quenching with benzoyl chloride and cyclopropylcarbonyl chloride to provide the keto-substituted 1,4-dithiins (**44h**-**i**, 65-78%, entries 8-9). Copper-catalyzed allylation furnished the product **44j** in 73% yield (entry 10). Transmetalation of magnesiated species **43** using $ZnCl_2$ allowed the reaction of the corresponding organozinc in a Pd-catalyzed Negishi cross-coupling reaction[56,57] furnishing the coupling products (**44k**) in 94% yield (entry 11). Finally, the reaction of **43** with bis(phenylsulfonyl)sulfide[94] (0.5 equiv) produced the pentathio-derivative (**44l**) in 75% yield (entry 12).

Table 2: Preparation of 2-substituted 1,4-dithiins of type **44** by magnesiation of 1,4-dithiin (**40**) with TMPMgCl·LiCl (**2**).

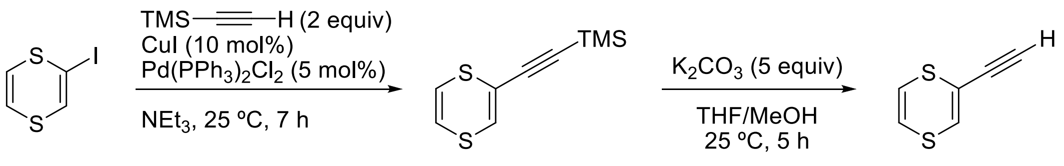
Entry	**Electrophile**	**Product, Yield**[a]
1	I_2	 **44a**: R = I, 75%
2	$(BrCCl_2)_2$	**44b**: R = Br, 78%
3	$C_6H_5SO_2Cl$	**44c**: R = Cl, 56%
4	TsCN	**44d**: R = CN, 60%
5	$Me_2NCH_2OCOCF_3$	**44e**: R = CH_2NMe_2, 58%
6	PhCHO	**44f**: R = CHOHPh, 97%

[93] a) G. Kinast, L.-F. Tietze, *Angew. Chem. Int. Ed.* **1976**, *15*, 239; b) V. Werner, M. Ellwart, A. J. Wagner, P. Knochel, *Org. Lett.* **2015**, *17*, 2026.
[94] a) M. Dötze, G. Klar, *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *84*, 95; b) S. Kerverdo, X. Fernandez, S. Poulain, M. Gingras, *Tetrahedron Lett.* **2000**, *41*, 5841; c) S. Kerverdo, M. Gingras, *Tetrahedron Lett.* **2000**, *41*, 6053.

Entry	Electrophile	Product, Yield[a]
		
7	$NCCO_2Et$	**44g**: R = OEt, 89%
8	PhCOCl	**44h**: R = Ph, 78%[b]
9		**44i**: R = *c*Pr, 65%[b]
10		 **44j**: 73%[b]
11		 **44k**: 94%[c]
12	$(PhSO_2)_2S$	 **44l**: 75%

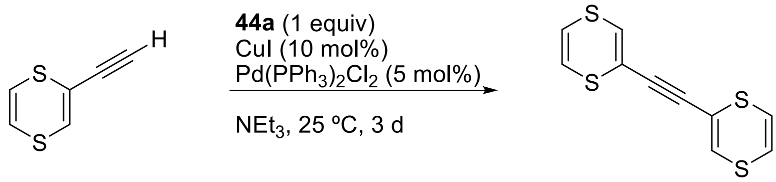
[a]Yield of isolated, analytically pure product. [b]Obtained after transmetalation with $ZnCl_2$ (1.2 equiv, -40 ºC, 15 min) and CuCN·2LiCl (1.2 equiv, -40 ºC, 15 min). [c]Obtained after transmetalation with $ZnCl_2$ (1.2 equiv, -40 ºC, 15 min) using 3 mol% $Pd(dba)_2$ and 6 mol% $P(2\text{-furyl})_3$.

The preparation of monosubtituted 1,4-dithiin was also investigated using Pd-catalyzed Sonogashira cross-coupling. Therefore, the previous synthesized dithiin **44a** reacted with trimethylsilylacetylene (2.0 equiv) in the presence of 10 mol% CuI and 5 mol% $Pd(PPh_3)_2Cl_2$ (NEt_3, 25 ºC, 7 h) leading to the alkyne **45** in 87% yield (Scheme 36). Cleavage of the trimethylsilyl group was successfully performed using potassium carbonate in THF/MeOH (1:1) at 25 ºC affording 2-ethynyl-1,4-dithiine (**46**) in 63% yield.



Scheme 36: Synthesis of 2-ethynyl-1,4-dithiine (**46**).

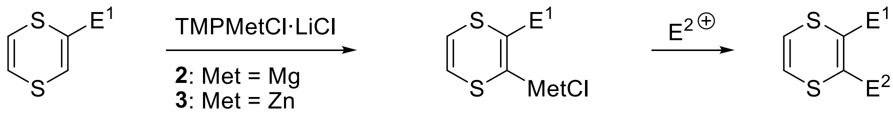
Afterwards, the synthesized ethynyl dithiin **46** was submitted to a second Sonogashira-coupling reaction with 2-iodo-1,4-dithiin (**44a**, 1.0 equiv), in the presence of 10 mol% CuI and 5 mol% $Pd(PPh_3)_2Cl_2$ (NEt_3, 25 ºC, 3 d) producing the symmetric alkyne **47** in 54% yield (Scheme 37).



Scheme 37: Cross-coupling reaction to synthesize the symmetric alkyne **47**.

2.2.3 Preparation of disubstituted 1,4-dithiin derivatives

Further functionalization of **44** could be achieved either with TMPMgCl·LiCl (**2**) or TMPZnCl·LiCl (**3**) depending on the nature of the substituent E^1 leading to the regioselectively metalated 2,3-disubstituted 1,4-dithiins of type **48** (Scheme 38). Subsequent quenching of the metal species with various eletrophiles produced a range of 2,3-disubstituted 1,4-dithiins **49**.

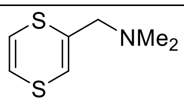
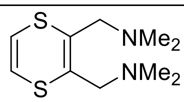
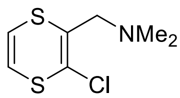
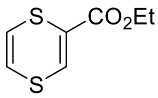
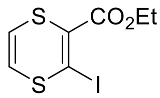
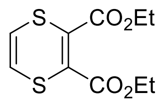


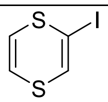
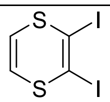
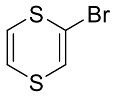
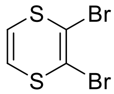
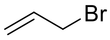
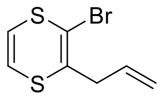
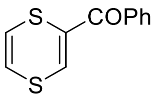
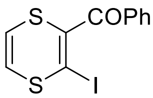
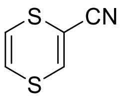
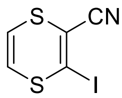
Scheme 38: Deprotonation and functionalization of the monosubstituted 1,4-dithiin derivatives **49**.

Thus, in the case of less sensitive substituents E^1 a magnesiation with TMPMgCl·LiCl (**2**, 1.05-1.1 equiv) was readily performed at -78 ºC (in only 0.5 h). That was the case for 1,4-diithin **44e**, where the magnesiated species was quenched with Tietze's reagent[93] leading to the symmetric dithiin **49a** in 64% yield (Table 3, entry 1) or halogenated with C_2Cl_6

producing the chloro-substituted **49b** in 43% (entry 2). The ester **44g** was also magnesiated, and its iodination afforded the corresponding product **49c** in 62% yield (entry 3), whereas the quenching with ethyl cyanoformate led to the 2,3-disubstituted 1,4-dithiin **49d** in 90% (entry 4). Similarly, the zincation of the more sensitive 1,4-dithiin **44a** was performed with TMPZnCl·LiCl (**3**, 1.1 equiv, 0.5 h) at -40 ºC and the quenching with iodine produced the expected product **49e** in 68% yield (entry 5). The same conditions were used to obtain the zincated species of **44b** and subsequent reaction with $(BrCCl_2)_2$ or copper-catalyzed allylation led to the 2,3-disubstituted 1,4-dithiins (**49f**-**g**) in 50-74% yield (entries 6-7). Similarly, the corresponding zincated species of **44h** was iodinated leading to dithiin **49h** in 78% yield (entry 8). The metalation of **44d** was achieved using TMPZnCl·LiCl (**3**, 1.1 equiv, 0.5 h) at 0 ºC and the reaction of the metallic species with iodine afforded the expected dithiin **49i** in 86% yield (entry 9).

Table 3: Preparation of disubstituted 1,4-dithiin-derivatives of type **49** by metalation of dithiins of type **44** using Mg- and Zn-TMP-Bases (**2** and **3**).

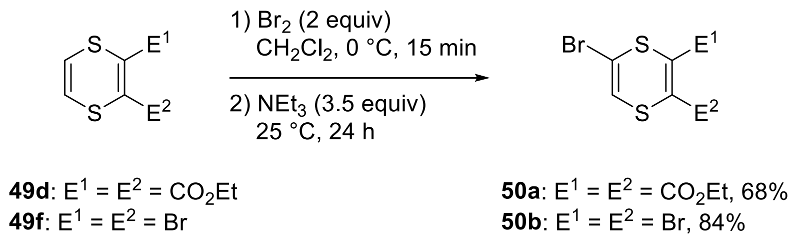
Entry	Substrate	Electrophile	Product, Yield[a]
1	 **44e**	$Me_2NCH_2OCOCF_3$	 **49a**: 64%[b]
2	**44e**	C_2Cl_6	 **49b**: 43%[b]
3	 **44g**	I_2	 **49c**: 62%[b]
4	**44g**	$NCCO_2Et$	 **49d**: 90%[b]

Entry	Substrate	Electrophile	Product, Yield[a]
5	 **44a**	I_2	 **49e**: 68%[c]
6	 **44b**	$(BrCCl_2)_2$	 **49f**: 50%[c]
7	**44b**		 **49g**: 74%[c]
8	 **44h**	I_2	 **49h**: 78%[c]
9	 **44d**	I_2	 **49i**: 86%[d]

[a]Yield of isolated, analytically pure product. [b]TMPMgCl·LiCl (1.05-1.1 equiv, -78 ºC, 0.5 h) was used. [c] TMPZnCl·LiCl (1.1 equiv, -40 ºC, 0.5 h) was used. [d]TMPZnCl·LiCl (1.1 equiv, 0 ºC, 0.5 h) was used.

2.2.4 Preparation of trisubstituted 1,4-dithiin derivatives

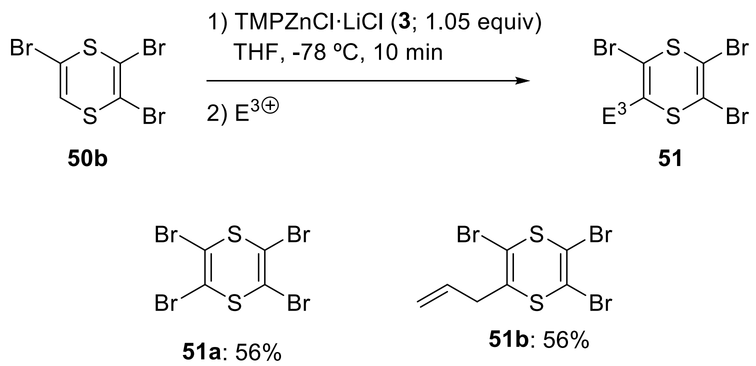
Then, the synthesis of trisubstituted 1,4-dithiins was successfully achieved by bromination. This reaction proceeded *via* an electrophilic addition of bromine to the 1,4-dithiin derivatives producing a bromonium intermediate. This intermediate was attacked by the bromide ion with a subsequent elimination of HBr by the base affording the brominated dithiin of type **50** (Scheme 39). Hence, the prepared diester 1,4-dithiin derivative (**49d**) was brominated by adding bromine, followed by the subsequent addition of trimethylamine, which produced the respective product **50a** in 68% yield. Similarly, the third position of 2,3-dibromo-1,4-dithiin (**49f**) was also brominated affording tribrominated dithiin **50b** in 84% yield.



Scheme 39: Bromination of disubstituted-1,4-dithiins (**49d** and **49f**).

2.2.5 Preparation of tetrasubstituted 1,4-dithiin derivatives

After the functionalization of the first, second and third position of 1,4-dithiins, the focus was put on the full functionalization of 1,4-dithins. The treatment of the trisubstituted dithiin **50b** with TMPZnCl·LiCl (**3**, 1.05 equiv) at -78 ºC for 10 min furnished the corresponding zinc reagent (Scheme 40). This zincated species was then quenched with $(BrCCl_2)_2$ affording the tetrabrominated product **51a** in 56% yield and the corresponding allylation in presence of 20% CuCN·2LiCl provided the expected dithiin **51b** in 56% yield.



Scheme 40: Synthesis of tetrafunctionalized 1,4-dithiin derivatives of type **51**.

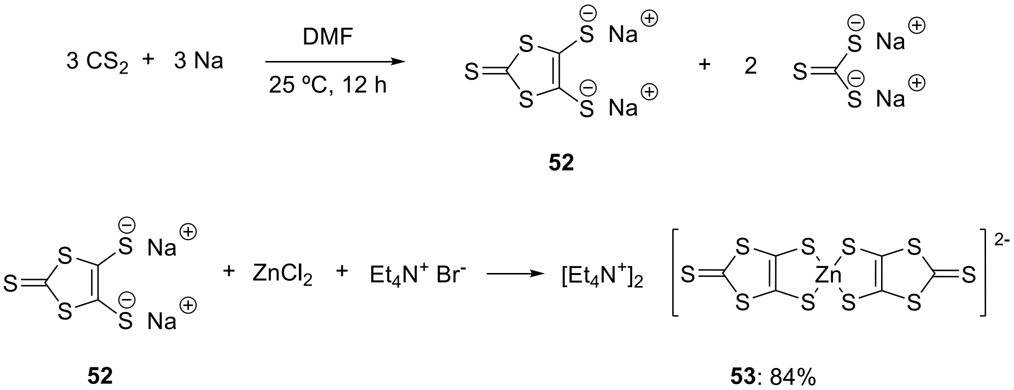
2.3 FUNCTIONALIZATION OF 1,4,5,8-TETRATHIANAPHTHALENE (TTN, 41)

2.3.1 Preparation of 1,4,5,8-tetrathianaphthalene (TTN, **41**)

First, 1,3-dithiole-2-thione-4,5-dithiolate was prepared as a tetralkylammonium salt of its zinc chelate (**53**).[95] Thus, sodium (1.0 equiv) reacted with carbon disulfide (3.0 equiv) in DMF (25 ºC, 12 h, Scheme 41) producing the dianion **52**. Then, methanol and water were added to the mixture followed by the addition of $ZnCl_2$ (0.15 equiv, in solution with ammonium hydroxide and methanol) and tetraethylammonium bromide (0.25 equiv, in water). After

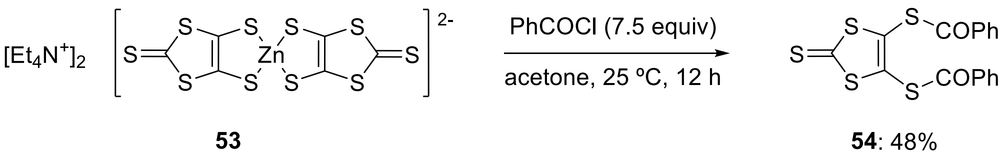
[95] T. K. Hansen, J. Becher, T. Joergensen, K. S. Varma, R. Khedekar, M. P. Cava, *Organic Syntheses*, **1996**, *73*, 270.

stirring for 12 h at 25 ºC, the precipitate salt provided the desired tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithiol) zincate (**53**) in 84% yield.



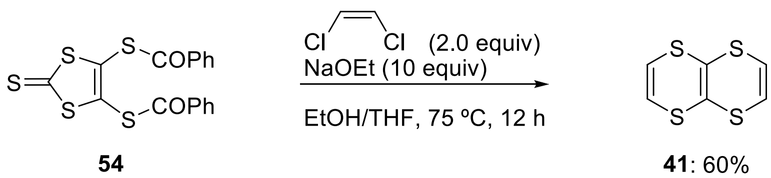
Scheme 41: Preparation of tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithiol) zincate (**53**).

Zincate **53** (1.0 equiv) was then reacted with benzoyl chloride (7.5 equiv) in acetone at 25 ºC for 12 h to produce 4,5-dibenzoylthio-1,3-dithiole-1-thione (**54**) in 48% yield (Scheme 42).



Scheme 42: Synthesis of 4,5-dibenzoylthio-1,3-dithiole-1-thione (**54**).

The synthesized 4,5-bis(benzoylthio)-1,3-dithiole-1-thione (**54**, 1.0 equiv, 0.16 M in THF) and *cis*-1,2-dichloroethylene (2.0 equiv, 0.34 M in THF) were then added simultaneously to a solution of sodium ethoxide (10 equiv) in THF.[90b] The reaction mixture was refluxed for 12 h to afford TTN (**41**) in 60% yield (Scheme 43).

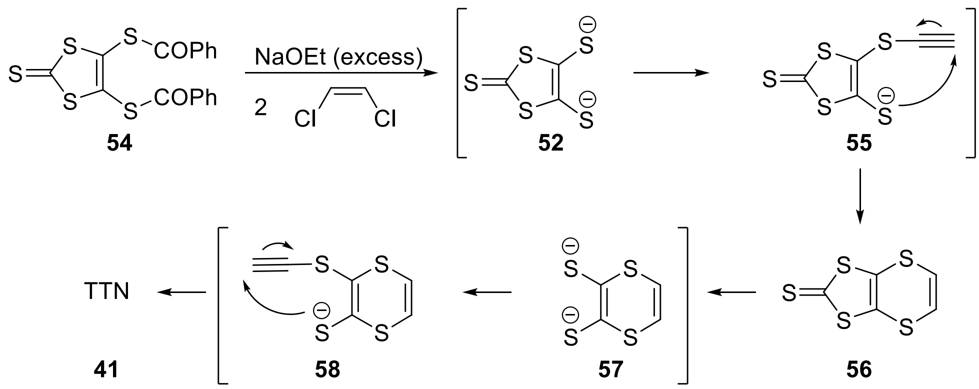


Scheme 43: Synthesis of 1,4,5,8-tetrathianaphthalene (**41**).

The mechanism of this cyclization was proposed by Garín *et al.* (Scheme 44).[96] They showed that the formation of TTN (**41**) occured through the formation of the dianion **52** (sodium

[96] R. Andreu, J. Garín, J. Orduna, J. M. Royo, *Tetrahedron Lett.* **2000**, *41*, 5207.

cations are omitted for simplification), which was generated quantitatively in the basic medium. Then, the addition of one thiolate group of **52** to chloroacetylene (formed from the dehydrohalogenation of *cis*-1,2-dichloroethylene due to sodium ethoxide) followed by *anti* elimination produced the ethynylthio compound **55**. Subsequent intramolecular addition of the remaining thiolate in **55** generated the intermediate **56**. This intermediate was rapidly cleaved in the basic medium to dianion **57** that reacted with chloroacetylene to form **58** and cyclized to TTN (**41**).

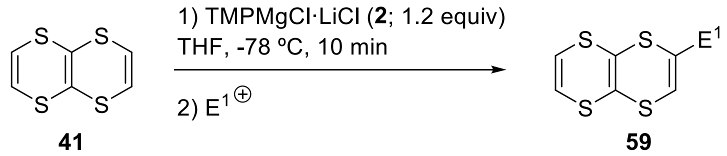


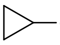
Scheme 44: Proposed mechanism for the synthesis of 1,4,5,8-tetrathianaphthalene (**41**).

2.3.2 Preparation of monosubstituted TTN

In order to functionalize the condensed S-containing heterocycle TTN (**41**), the same metalation procedure was applied using TMPMgCl·LiCl (**2**, 1.2 equiv), and avoiding the ring rearrangement into TTF. This magnesiation proceeded at -78 ºC in 10 min, and produced a magnesiated TTN that reacted smoothly with typical electrophiles. Iodination of the magnesiated species gave the corresponding product **59a** in 89% yield (Table 4, entry 1). Similarly, bromination with $(BrCl_2C)_2$ furnished the halogenated product **59b** in 89% yield (entry 2). Quenching of the magnesiated TTN with *p*-toluenesulfonyl cyanide led to the expected TTN **59c** in 73% yield (entry 3). Thiomethylation and carbonylation were also performed using $MeSO_2SMe$ and cyanoformate providing **59d**-**e** in 72-78% yield (entry 4-5). Acylation was also achieved by transmetalation of the magnesiated TTN to the zinc compound, and subsequent quenching with cyclopropanecarbonyl chloride using catalytic amounts of CuCN·2LiCl led to the keto-derivative **59f** in 65% yield (entry 6).

Table 4: Preparation of monosubstituted TTN by metalation of **41** using TMPMgCl·LiCl (**2**).



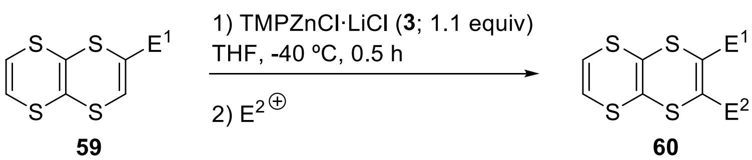
Entry	Electrophile	Product, Yield[a]
1	I_2	**59a**: E^1 = I, 89%
2	$(BrCCl_2)_2$	**59b**: E^1 = Br, 89%
3	TsCN	**59c**: E^1 = CN, 73%
4	$MeSO_2SMe$	**59d**: E^1 = SMe, 78%
5	$NCCO_2Et$	**59e**: E^1 = CO_2Et, 72%
6	 COCl	**59f**: E^1 = CO*c*Pr, 65%[b]

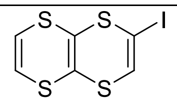
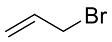
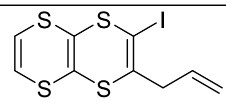
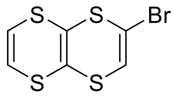
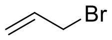
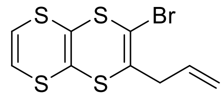
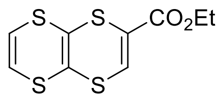
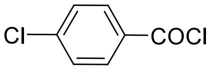
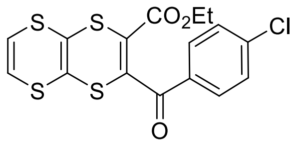
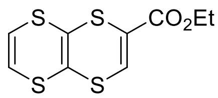
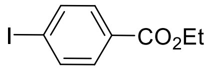
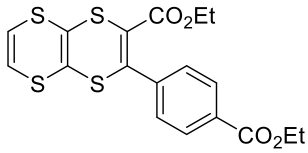
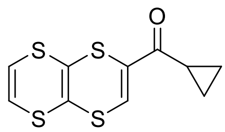
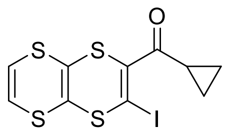
[a]Yield of isolated, analytically pure product. [b]CuCN·2LiCl was used.

2.3.3 Preparation of disubstituted TTN

A second successful metalation of monosubstituted TTN of type **59** was performed. This deprotonation was best achieved with TMPZnCl·LiCl (**3**, 1.1 equiv) at -40 ºC in 0.5 h, providing a metalated species that could readily react with a broad range of electrophiles affording disubstituted TTNs of type **60** (Table 5). Consequently, the Cu-catalyzed allylation of mono-halogenated TTNs **59a**-**b** furnished the expected products **60a**-**b** in 68-71% yield (entries 1-2). Acylation of **59e** was also performed using catalytic amount of copper and *p*-chlorobenzoyl chloride, affording the corresponding TTN **60c** in 55% yield (entry 3). Arylation of TTN **59e** was achieved *via* Negishi cross-coupling[56,57] using 6 mol% $Pd(dba)_2$ and 12 mol% $P(2\text{-furyl})_3$ as catalytic system, and ethyl 4-iodobenzoate as electrophile furnishing the corresponding arylated derivates **60d** in 74% yield (entry 4). Iodination of **59f** produced the desired product **60e** in 83% (entry 5).

Table 5: Synthesis of disubstituted TTN-derivatives of type **60** using TMPZnCl·LiCl (**3**).



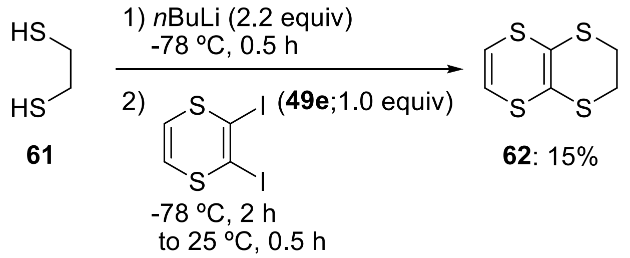
Entry	Substrate	Electrophile	Product, Yield[a]
1	 **59a**		 **60a**: 68%[b]
2	 **59b**		 **60b**: 71%[b]
3	 **59e**		 **60c**: 55%[b]
4	 **59e**		 **60d**: 74%[c]
5	 **59f**	I_2	 **60e**: 83%

[a]Yield of isolated, analytically pure product. [b]CuCN·2LiCl was used. [c]Pd(dba)$_2$ (6 mol%) and P(2-furyl)$_3$ (12 mol%) were used.

2.4 PREPARATION OF NEW S-HETEROCYCLES

Finally, these metalation procedures were extended to prepare new heterocycles, developing various strategies and using the previous functionalized 1,4-dithiins.

A convenient approach for the cyclization of the previous synthesized 2,3-diiodo-1,4-dithiine (**49e**) was investigated. Indeed, dithiin derivative **49e** was subjected to a reaction with lithium ethanedithiolate, which was formed from the double deprotonation of ethane-1,2-dithiol (**61**) with *n*BuLi (2.2 equiv, -78 ºC, 0.5 h, Scheme 45). The lithiated species reacted with the dithiin through an addition-elimination reaction affording 2,3-dihydro-[1,4]dithiino[2,3-*b*][1,4]dithiine (**62**) in 15% yield.[97]

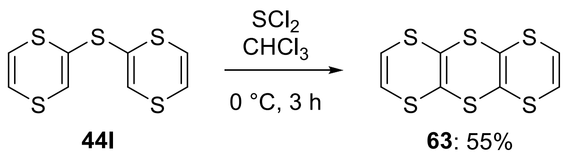


Scheme 45: Synthesis of 2,3-dihydro-[1,4]dithiino[2,3-*b*][1,4]dithiine (**62**) *via* nucleophilic substitution.

Screenings of different reaction conditions by changing solvent system or temperature were tested in order to improve the yield of this reaction, but those tests remained unsuccessful. Since lithium ethanedithiolate may not be stable due to polymerization side reactions, other ways of deprotonating ethane-1,2-dithiol (**61**) were developed. Consequently, several bases including inorganic salt such as Cs_2CO_3 or organic bases, like sodium ethoxide, as well as tin reagents (bis(triphenyltin) oxide or triphenyltin chloride)[98] in order to obtain the ditin derivative, were investigated. Unfortunately, better results could not be achieved and the desired product (**62**) was even not observable by GC-analysis of reaction aliquots. This may be due to the too weak strength of the bases used to deprotonate the dithiol substrate or to the low nucleophilicity of the dithiolate to attack 2,3-diiodo-1,4-dithiine (**49e**).

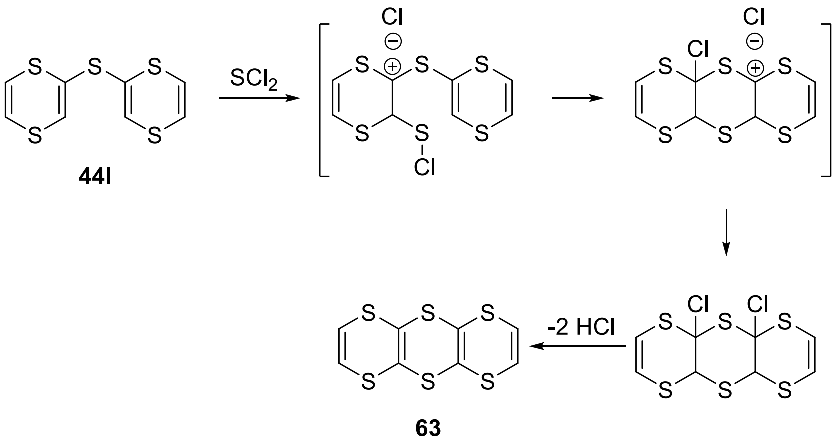
Consequently, the focus was put on the synthesis of a new S-heterocycle, called hexathiaanthracene **63** (HTA, Scheme 46). Since the electrophilic addition of sulfur dichloride to divinyl sulfide affording 2,6-dichloro-1,4-dithiane was known in the literature,[99] this addition was investigated in the previously described dithiin (**44l**). Thus, di(1,4-dithiin-2-yl)sulfane (**44l**) reacted with SCl_2 (2.0 equiv) in chloroform (0 ºC, 3 h) leading to the formation of HTA (**63**) in 55% yield.

[97] Due to small scale reaction, only ^{1}H-NMR was performed to characterize the product.
[98] a) D. N. Harpp, M. Gingras, *J. Am. Chem. Soc.* **1988**, *110*, 7737; b) M. Gingras, D. N. Harpp, *Tetrahedron Lett.* **1988**, *29*, 4669; c) T. Maruyama, M. Asada, T. Shiraishi, H. Egashira, H. Yoshida, T. Maruyama, S. Ohuchida, H. Nakai, K. Kondo, M. Toda, *Bioorg. Med. Chem,* **2002**, *10*, 975; d) C. Ma, Q. Wang, R. Zhang, *Heteroat. Chem.* **2009**, *20*, 50.
[99] S. V. Amosova, M. V. Penzik, V. A. Potapov, A. I. Albanov, *Chem. Heterocycl. Compd.* **2013**, *48*, 1716.



Scheme 46: Synthesis of 1,4,5,6,9,10-hexathiaanthracene (**63**).

The reaction could be explained by the electrophilic addition of sulfur dichloride to one of the double bonds followed by the subsequent intramolecular addition of the organosulfanyl chloride intermediates, obeying in both cases to the Markovnikov rule (Scheme 47). The final elimination of hydrochloric acid led to the desired hexathiaanthracene (**63**).



Scheme 47: Reaction path towards the synthesis of 1,4,5,6,9,10-hexathiaanthracene (**63**).

An X-ray analysis of this new synthesized compound confirmed the structure of the condensed S-heterocycle **63**, and demonstrated that this molecule was not planar but that its conformation was best viewed as fused boat system of three units linked together (Figure 4).

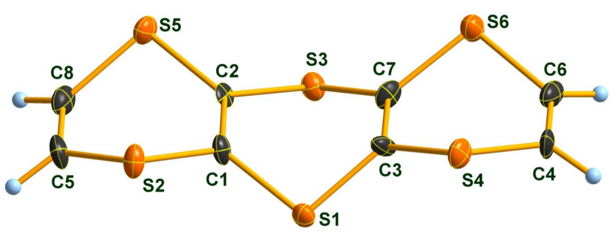
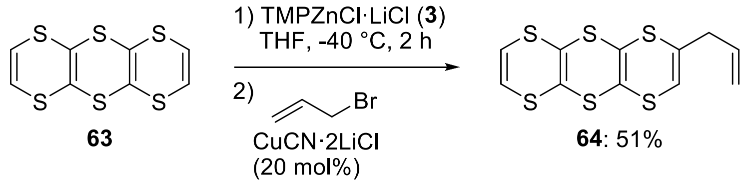


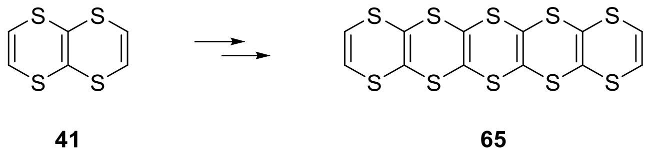
Figure 4: Crystal structure of HTA (**63**).

Remarkably, this metalation procedure could be extended to this new 3-ring S-heterocycle (**63**). The mild zinc-base TMPZnCl·LiCl (**3**, 1.1 equiv) provided after 2 hours at -40 ºC a zincated intermediate, which was readily allylated leading to the S-heterocycle **64** in 51% yield (Scheme 48).



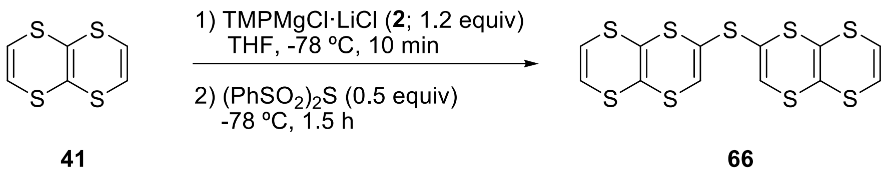
Scheme 48: Functionalization of 1,4,5,6,9,10-hexathiaanthracene (**63**).

Furthermore, after the successful synthesis and functionalization of the three ring dithiin derivative **63**, the scope of this procedure was extended in the same cyclization conditions to the condensed TTN (**41**) in order to prepare a five-ring dithiin (**65**, Scheme 49).



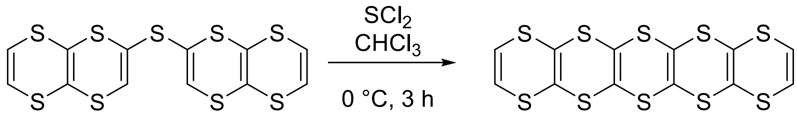
Scheme 49: Condesation of TTN (**41**).

Thus, the first step for the synthesis of this new S-heterocycle (**65**) was the preparation of di[1,4]dithiino[2,3-*b*][1,4]dithiin-2-ylsulfane (**66**, Scheme 50). The metalation of TTN (**41**) with TMPMgCl·LiCl (**2**, 1.2 equiv, -78 ºC, 10 min) and subsequent quenching with bis(phenylsulfonyl)sulfide provided the expected product **66**. Nonetheless, the purification of this new bis-tetrathianaphtalene (**66**) was not possible by column chromatography or by crystallization but the analysis of the crude ^{1}H NMR, proven the formation of the expected product (**66**) in 51% yield.



Scheme 50: Synthesis of di[1,4]dithiino[2,3-b][1,4]dithiin-2-ylsulfane (**66**).

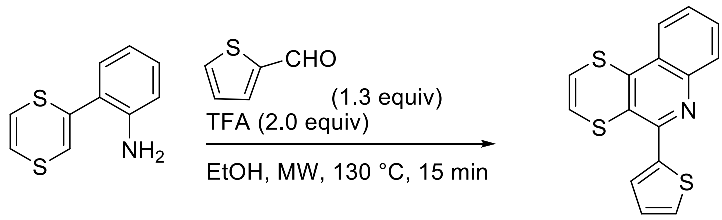
Then, the crude product of **66** was subjected to the cyclization condition by using sulfur dichloride (2.0 equiv) in chloroform (0 ºC, 3 h to 25 ºC, 12 h; Scheme 51). Unfortunately, in this case, due to side-polymerization only traces of 1,4,5,6,7,8,11,12,13,14-decathia-pentacene (**65**) were observed *via* GCMS analysis.



66 **65**

Scheme 51: Cyclization of di[1,4]dithiino[2,3-*b*][1,4]dithiin-2-ylsulfane (**66**).

Alternatively, two additional strategies were tested for the construction of more elaborated S-heterocycles. Consequently, the treatment of **44k** with 2-thiophenecarboxaldehyde (1.3 equiv) in the presence of trifluoroacetic acid (2.0 equiv) in EtOH under microwave irradiation (130 ºC, 15 min) afforded the tricyclic heterocycle **67** in 60% yield (Scheme 52).[100]

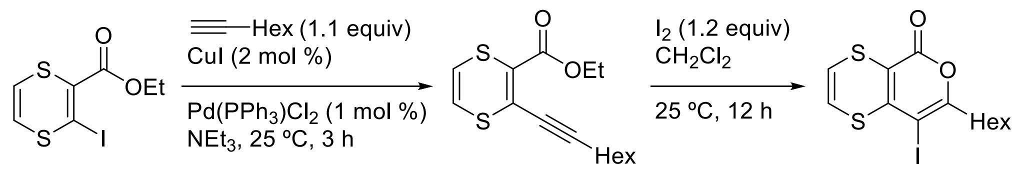


44k **67**: 60%

Scheme 52: Preparation of 1,4-dithiin-fused quinoline (**67**).

Moreover, the second approach included Pd-catalyzed Sonogashira cross-coupling of the 2,3-disubstituted dithiin **49c**. The reaction with 1-octyne (1.5 equiv) in the presence of 2 mol% CuI and 1 mol% $Pd(PPh_3)_2Cl_2$ (NEt_3, 25 ºC, 3 h) led to the alkyne **68** in 77% yield (Scheme 53). The treatment of the obtained 1,4-dithiin **68** with iodine in CH_2Cl_2 (25 ºC, 12 h) produced the endo-cyclization product **69** in 88% yield.[101]

[100] V. F. Vavsari, V. Dianati, S. Ramezanpour, S. Balalaie, *Synlett* **2015**, *26*, 1955.
[101] S. Mehta, J. P. Waldo, R. C. Larock, *J. Org. Chem.* **2009**, *74*, 1141.



49c **68**: 77% **69**: 88%

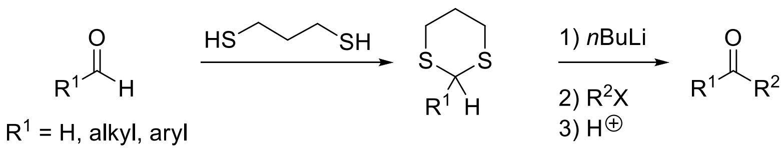
Scheme 53: Ring closure of **49c** leading to the S-heterocycle **69**.

3. ZINCATION AND MAGNESIATION OF FUNCTIONALIZED SILYLATED CYANOHYDRINS USING TMP-BASES

3.1 INTRODUCTION

Over the last few decades, the preparation of complex organic molecules has been rationalized by using retroanalysis involving synthons of opposite polarity.[102] In this respect, synthons with inverted polarity (synthons with umpolung)[103] are of special importance. It is clear that the species with umpolung reactivity such as acyl anion or enolate cations are not generally available. Thus, considerable studies have been made for the elaboration of synthetic equivalents of acyl anions.[104]

Metalated sulfur compounds such as S,S-acetals, 1,3-dithianes, and vinyl sulfides are examples that have been broadly used to provide masked reagents with carbonyl umpolung. The protected carbonyl groups for example with 1,3-propanedithiol could be metalated with *n*BuLi, quenched with an electrophile and later deprotected to get the carbonyl group back (Scheme 54).[103,104a-b]



Scheme 54: Umpolung of the reactivity of carbonyl compounds through sulfur-containing reagents.

Carbonyl umpolung with non-sulfur-reagents has also been studied. Benzoin condensation represents the beginning of the acyl anion equivalents of the cyanohydrin type (Scheme 55).[105] The addition of the cyanide ion to benzaldehyde creates an umpolung of the normal carbonyl charge affinity. This transformed the electrophilic aldehyde carbon into a

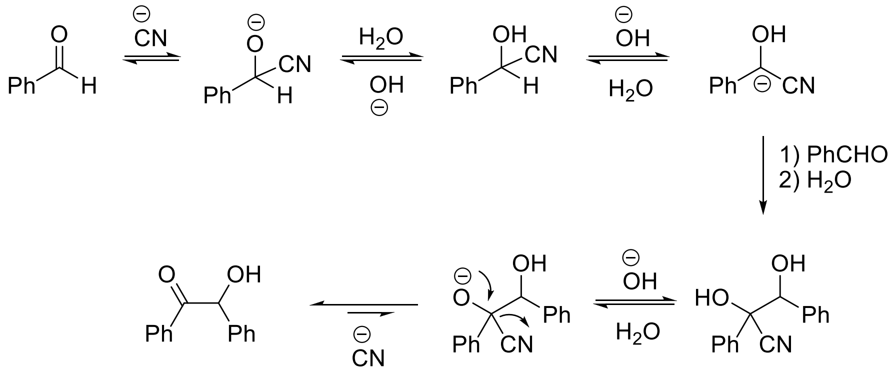
[102] a) E. J. Corey, *Pure Appl. Chem.* **1967**, *14*, 19; b) E. J. Corey, *Chem. Soc. Rev.* **1988**, *17*, 111; c) E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*; John Wiley: New York, **1989**; d) E. J. Corey, *Angew Chem. Int. Ed.* **1991**, *30*, 455; e) K. C. Nicolaou, S. A. Snyder, *Classics in Total Synthesis II: More Targets, Strategies, Methods*; Wiley-VCH: Weinheim; **2003**; f) S. Warren, P. Wyatt, *Organic Synthesis: The Disconnection Approach*, *2nd Edition*; Wiley, **2009**; g) T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, *75*, 4657.

[103] a) D. Seebach, *Angew. Chem. Int. Ed.* **1969**, *8*, 639; b) D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239.

[104] a) D. Seebach, E. J. Corey, *J. Org. Chem.* **1975**, *40*, 231; b) W. Lever, *Tetrahedron* **1976**, *32*, 1943; c) B. T. Gröbel, D. Seebach, *Synthesis* **1977**, 357; c) D. J. Ager, *Chem Soc. Rev*. **1982**, *11*, 493; d) J. D. Albright, *Tetrahedron* **1983**, *39*, 3207.

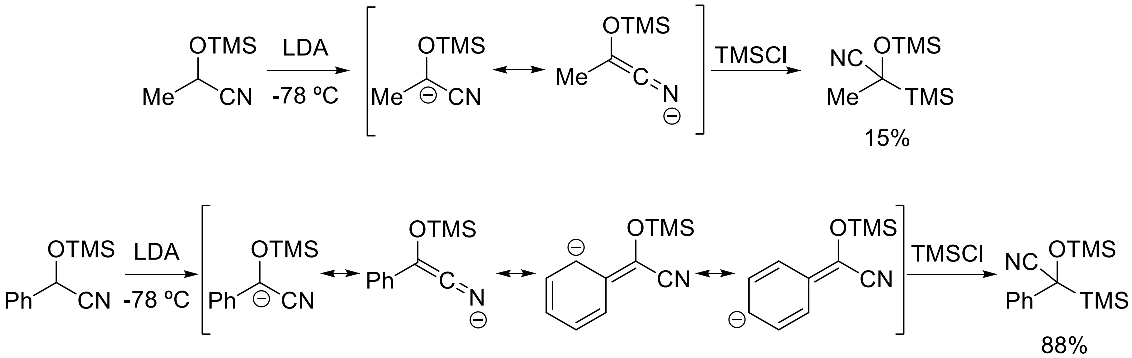
[105] a) A. Lapworth, *J. Chem. Soc., Trans.* **1904**, *85*, 1206; b) D. Enders, U. Kallfass, *Angew. Chem. Int. Ed.* **2002**, *41*, 1743; c) L. Baragwanath, C. A. Rose, K. Zeitler, S. J. Connon, *J. Org. Chem.* **2009**, *74*, 9214; d) S. M. Langdon, M. M. D. Wilde, K. Thai, M. Gravel, *J. Am. Chem. Soc.* **2014**, *136*, 7359.

nucleophilic center after deprotonation, attacking the benzaldehyde. The elimination of the cyano group regenerates the carbonyl compound at the end of the reaction.



Scheme 55: Mechanism of the benzoin condensation.

This deprotonation was extended by using silylated protected cyanohydrins. Pioneer work of Stork in 1971 demonstrated that 2-ethoxyethyl protected cyanohydrins could be metalated by using LDA.[106] West also performed a similar metalation procedure using LDA to deprotonate O-trimethylsilyl cyanohydrin synthesized from acetaldehyde. The formed anion was quenched with TMSCl affording the product in 15% yield (Scheme 56).[107] Following this procedure, Hünig in 1973 treated the protected benzaldehyde with LDA at -78 ºC affording a deprotonation in the benzylic position.[108] This anion was more stabilized than in the acetal derivative due to delocalization in the aromatic ring affording after quenching with trimethylsilyl chloride the product in high yield (88%).



Scheme 56: Metalation of silylated cyanohydrins.

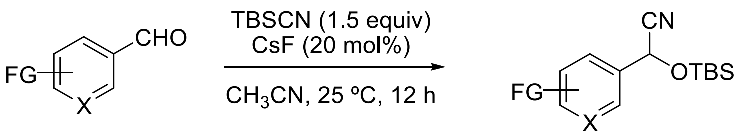
[106] G. Stork, L. Maldonado, *J. Am. Chem. Soc.* **1971**, *93*, 5286.
[107] A. Wright, R. West, *J. Am. Chem. Soc.* **1974**, *96*, 3214.
[108] a) K. Deuchert, U. Hertenstein, S. Hünig, *Synthesis* **1973**, 777; b) K. Deuchert, U. Hertenstein, S. Hünig, *Chem. Ber.* **1979**, *112*, 2045; c) R. F. Cunico, C. P. Kuan, *J. Org. Chem.* **1992**, *57*, 1202.

The functionalization of cyanohydrins was successful performed using LDA although the use of a highly reactive lithium base precluded the presence of sensitive functionalized groups in the protected cyanohydrins. Therefore, the use of the more chemoselective TMP-bases for milder metalations conditions was envisioned in order to deprotonate highly functionalized silylated cyanohydrins.

3.2 FUNCTIONALIZATION OF AROMATIC AND HETEROAROMATIC SILYLATED CYANOHYDRIN DERIVATIVES

3.2.1 Preparation of silylated cyanohydrin derivatives

In general, the silylated cyanohydrins of type **71** can be readily prepared by using TBSCN (1.5 equiv), CsF (20 mol%) in CH_3CN (25 ºC, 12 h) in good yields (50-98% yield), starting from the corresponding aldehydes (**70**, Scheme 57).[109,34b]



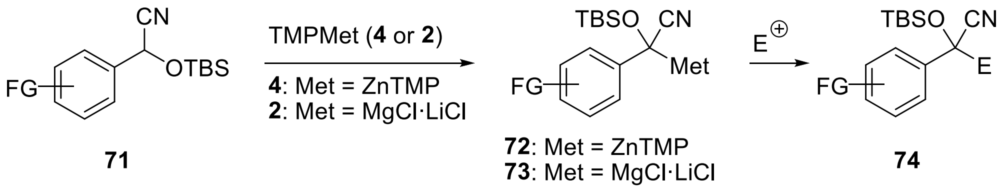
70 **71**

Scheme 57: Preparation of functionalized silylated cyanohydrins (**71**).

3.2.2 Metalation of aromatic silylated cyanohydrin derivatives

The synthesized silylated cyanohydrins bearing sensitive functional groups (**71**) could successfully be deprotonated at the benzylic position using smooth bases such as $TMP_2Zn·2MgCl_2·2LiCl$ (**4**, abbreviated TMP_2Zn) or TMPMgCl·LiCl (**2**, Scheme 58). The corresponding metalated cyanohydrins **72** (Met = ZnTMP) and **73** (Met = MgCl·LiCl) could be trapped with a range of electrophiles affording the corresponding polyfunctionalized cyanohydrin derivatives of type **74**.

[109] a) K. Tanaka, A. Mori, S. Inoue, *J. Org. Chem.* **1990**, *55*, 181; b) S. Kobayashi, Y. Tsuchiya, T. Mukaiyama, *Chem. Lett.* **1991**, 537; c) M. Hayashi, Y. Miyamoto, S. Inoue, N. Oguni, *J. Org. Chem.* **1993**, *58*, 1515; d) M. North, *Synlett* **1993**, 807; e) Y. Hanashima, D. Sawada, H. Nogami, M. Kanai, M. Shibasaki, *Tetrahedron* **2001**, *57*, 805; f) H. Deng, M. P. Ister, M. L. Snapper, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2002**, *41*, 3333; g) S. K. Tian, R. Hong, L. Deng, *J. Am. Chem. Soc.* **2003**, *125*, 9900; h) S. S. Kim, G. Rajagopal, D. H. Song, *J. Organomet. Chem.* **2004**, *689*, 1734.



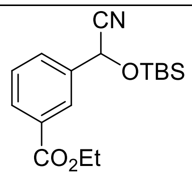
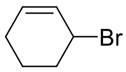
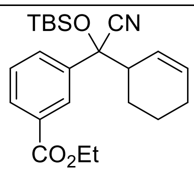
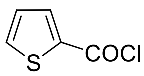
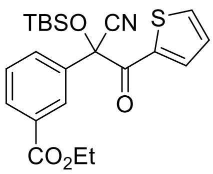
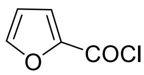
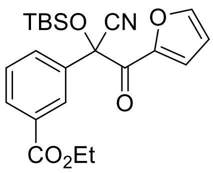
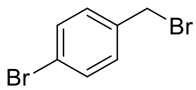
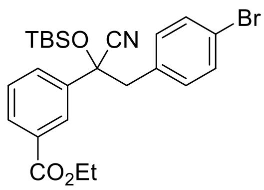
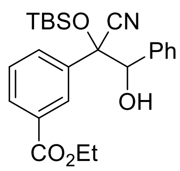
Scheme 58: Metalation of functionalized silylated (**71**) cyanohydrins and subsequent quenching with electrophiles.

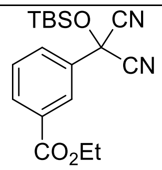
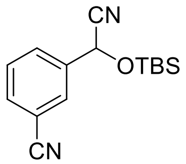
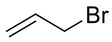
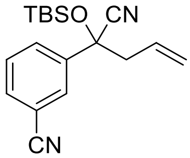
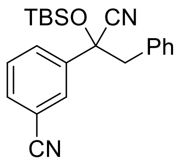
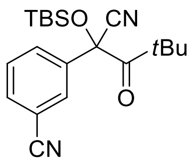
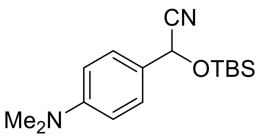
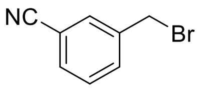
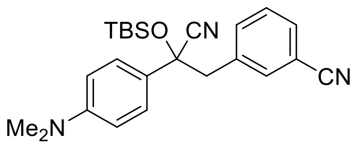
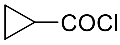
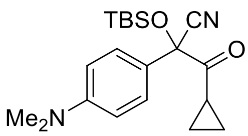
Thus, the silylated cyanohydrin (**71a**) was treated with TMP_2Zn (**4**, 1.1 equiv) in THF at -20 ºC. After 2 hours of reaction time, the complete zincation was achieved as indicated by TLC analysis of reaction aliquots by copper-catalyzed allylation in dry THF. The zincated cyanohydrin derivative of type **72** was allylated with 3-bromocyclohexene in the presence of 20% CuCN·2LiCl[110] leading to the allylated cyanohydrin (**74a**) in 54% yield (Table 6, entry 1). Acylations of zincated cyanohydrins were best performed in the presence of 20% CuCN·2LiCl and provided the keto-derivatives **74b**-**c** in 62-67% yield (entries 2 and 3). Also benzylation of **74a** was achieved using catalytic amount of CuBr leading to the corresponding product **74d** in 85% yield (entry 4). Quenching of the zinc intermediate of type **72** with less reactive electrophiles such as an aldehyde provided the product in low yield. However, the reaction of **71a** with TMPMgCl·LiCl (**2**, 1.3 equiv) in THF at -20 ºC for 2 h afforded the magnesiated cyanohydrin of type **73**. Its reaction with benzaldehyde or tosyl cyanide provided the expected products **74e**-**f** in 50-79% yield (entries 5-6). Similarly, the cyano-substituted silylated cyanohydrin **71b** was zincated with TMP_2Zn (**4**, 1.1 equiv, -20 ºC, 2 h), leading to the corresponding zinc derivatives of type **72**. Copper-catalyzed allylation reaction with allyl bromide furnished the expected product **74g** in 67% yield (entry 7). The benzylation was perfomed by using benzyl bromide and a catalytic amount of CuBr, yielding the product **74h** in 74% yield (entry 8). Acylation was also directly achieved by using pivaloyl chloride in presence of 20% CuCN·2LiCl leading to the desired cyanohydrin **74i** in 74% yield (entry 9). Also, silylated cyanohydrin bearing a dimethylamino-substituent (**71c**) was readily zincated with **4** (1.1 equiv, -20 ºC, 2 h) or magnesiated with base **2** (1.3 equiv, -20 ºC, 2 h) leading to the metalated **72** and **73** derivatives. The zincated species were reacted with 3-cyanobenzyl bromide and cyclopropanecarbonyl chloride in the presence of catalytic amount of copper providing the expected cyanohydrin deriatives **74j**-**k** in 83-85% yield (entries 10-11). In the case of the magnesiated derivative, the metal species was quenched with ethyl

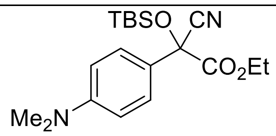
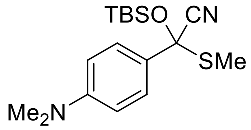
[110] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390.

cyanoformate and $MeSO_2SMe$ to provide the polyfunctional cyanohydrin deriatives **74l**-**m** in 89% and 74% yield (entries 12-13).

Table 6: Preparation of functionalized protected cyanohydrins of type **74**.

Entry	Substrate	Electrophile	Product, Yield[a]
1	 **71a**		 **74a**: 54%[b,c]
2	**71a**		 **74b**: 62%[b,c]
3	**71a**		 **74c**: 67%[b,c]
4	**71a**		 **74d**: 85%[b.e]
5	**71a**	PhCHO	 **74e**: 79%[d]

Entry	Substrate	Electrophile	Product, Yield[a]
6	**71a**	TsCN	 **74f**: 50%[d]
7	 **71b**		 **74g**: 67%[b,c]
8	**71b**	BnBr	 **74h**: 74%[b,e]
9	**71b**	*t*BuCOCl	 **74i**: 74%[b,c]
10	 **71c**		 **74j**: 83%[b,e]
11	**71c**		 **74k**: 85%[b,c]

Entry	Substrate	Electrophile	Product, Yield[a]
12	**71c**	$NCCO_2Et$	 **74l**: 89%[d]
13	**71c**	$MeSO_2SMe$	 **74m**: 74%[d]

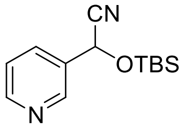
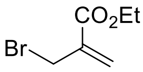
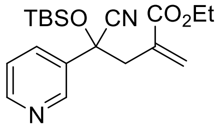
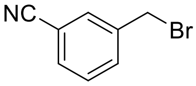
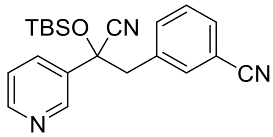
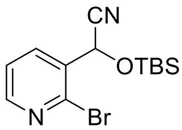
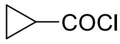
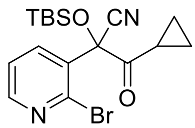
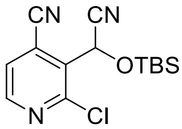
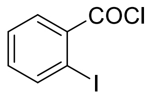
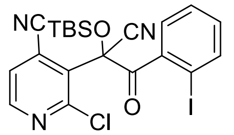
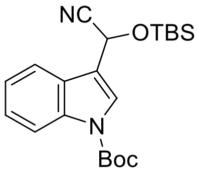
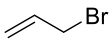
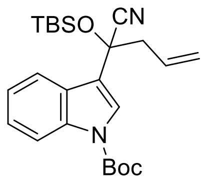
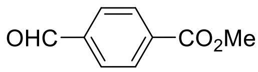
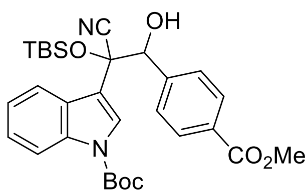
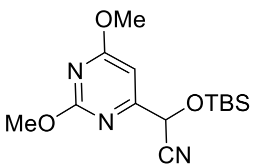
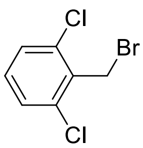
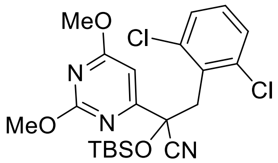
[a]Yield of isolated, analytically pure product. [b]TMP_2Zn (1.1 equiv, -20 ºC, 2 h) was used. [c]CuCN·2LiCl (20 mol%) was used. [d]TMPMgCl·LiCl (1.3 equiv, -20 ºC, 2 h) was used. [e]CuBr (10 mol%) was used.

3.2.3 Metalation of heteroaromatic silylated cyanohydrin derivatives

Then, heterocyclic silylated cyanohydrins were investigated. In this case, it was observed that only the use of the mild base TMP_2Zn (**4**) was successful to metalate the benzylic proton without decomposition of the starting material. Thus, the 3-pyridyl cyanohydrin derivative (**71d**) was smoothly zincated with TMP_2Zn (**4**, 1.1 equiv) at 0 ºC for 2 h (Table 7). Quenching with ethyl 2-(bromomethyl)acrylate[111] in the presence of 20% CuCN·2LiCl furnished the allylated product **74n** in 60% yield (entry 1). Copper-catalyzed benzylation with 3-cyanobenzyl bromide provided the cyanohydrin **74o** in 75% yield (entry 2). 2-Bromopyridine **71e** was also metalated using TMP_2Zn (**4**, 1.1 equiv) at 0 ºC for 2 h and the zincated species was quenched with cyclopropanecarbonyl chloride in the presence of 20% CuCN·2LiCl to give the keto-derivative **74p** in 91% yield (entry 3). Silylated cyanohydrin pyridine **71f** was readily metalated using TMP_2Zn (**4**, 1.1 equiv) at 0 ºC for 1 h. Its Cu-catalyzed acylation produced the expected product **74q** in 83% yield (entry 4). In the case of the protected indole **71g**, the zincation was performed using TMP_2Zn (**4**, 1.1 equiv, 0 ºC, 2 h) and the metalated species were quenched with allyl bromide in the presence of copper and with methy 4-formylbenzoate giving the respectively desired products **74r**-**s** in 63-72% yield (entries 5-6). Similarly, the protected uracil derivative **71h** was also deprotonated with TMP_2Zn (**4**, 1.1 equiv, -20 ºC, 2 h) and the corresponding benzylic metalated species were reacted with 2,6-dichlorobenzyl bromide using 10% CuBr affording **74t** in 79% yield (entry 7).

[111] J. Villieras, M. Rambaud, *Organic Syntheses* **1988**, *66*, 220.

Table 7: Synthesis of heterocyclic functionalized protected cyanohydrins of type **74**.

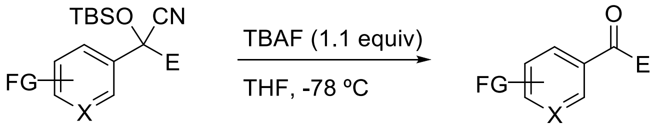
Entry	Substrate	Electrophile	Product, Yield[a]
1	 **71d**		 **74n**: 60%[b]
2	**71d**		 **74o**: 75%[c]
3	 **71e**		 **74p**: 91%[b]
4	 **71f**		 **74q**: 83%[b]
5	 **71g**		 **74r**: 72%
6	**71g**		 **74s**: 63%
7	 **71h**		 **74t**: 79%[c]

[a]Yield of isolated, analytically pure product. [b]CuCN·2LiCl (20 mol%) was used. [c]CuBr (10 mol%) was used.

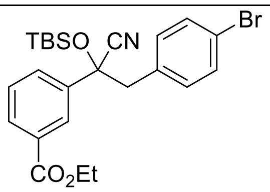
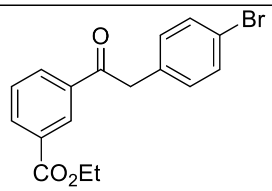
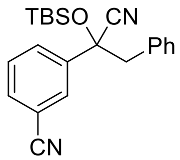
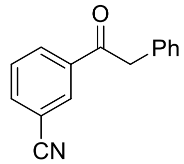
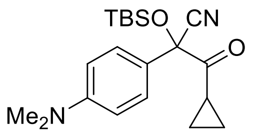
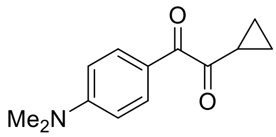
3.3 DEPROTECTION OF SILYLATED CYANOHYDRIN DERIVATIVES

In order to show the utility of this methodology to transform aldehydes (**70**) into the corresponding keto-derivatives, the polyfunctionalized silylated cyanohydrins (**74**) synthesized by benzylic metalation were then converted into the corresponding polyfunctional keto-derivatives **75** using TBAF (Table 8).[112] Thus, the treatment of silylated protected cyanohydrin derivatives **74d**,**h**,**k**,**l**,**m**,**n**,**o** (entries 1-7) with tetrabutylammonium fluoride (1.1 equiv, -78 ºC) in THF for 0.5 h, except for **74p** (entry 8) where the reaction time was 1.5 h, produced the corresponding keto-derivatives **75a**-**h** in 65-94% yield.

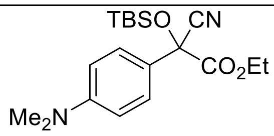
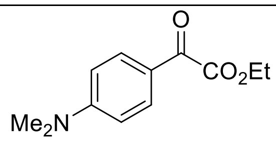
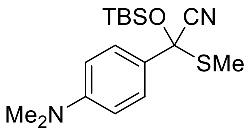
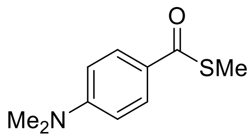
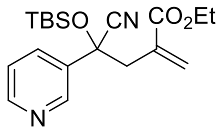
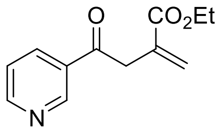
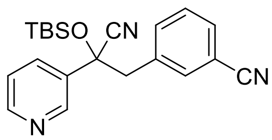
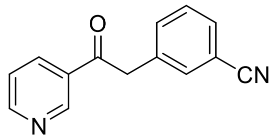
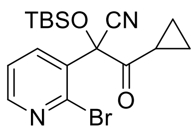
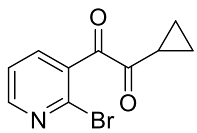
Table 8: Synthesis of polyfunctional keto-derivatives of Type **75**.



74 **75**

Entry	Substrate	Product, Yield[a]
1	 **74d**	 **75a**: 71%
2	 **74h**	 **75b**: 81%
3	 **74k**	 **75c**: 81%

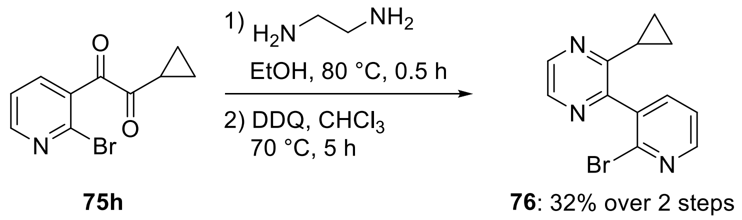
[112] A. Pelter, R. S. Ward, N. P. Storer, *Tetrahedron* **1994**, *50*, 10829.

Entry	Substrate	Product, Yield[a]
4	 **74l**	 **75d**: 86%
5	 **74m**	 **75e**: 94%
6	 **74n**	 **75f**: 83%
7	 **74o**	 **75g**: 65%
8	 **74p**	 **75h**: 90%

[a]Yield of isolated, analytically pure product.

3.4 FURTHER APPLICATION OF THE SYNTHESIZED KETO-DERIVATIVES

The previously synthesized 1,2-dione **75h** was then subjected to cyclization conditions in order to prepare a new heterocycle. Reaction with ethylenediamine (1.5 equiv) in EtOH at 80 ºC for 0.5 h gave the corresponding intermediate that was instantly oxidized with DDQ (2.0 equiv, 70 ºC, 5 h) in chloroform to afford the desired pyrazine **76** in 32% yield after 2 steps (Scheme 59).



Scheme 59: Synthesis of pyrazine (**76**) from the keto-derivate **75h**.

4. SUMMARY AND OUTLOOK

This work focused on the development of a general and convenient regioselective transmetalation procedure for isomeric mixtures of various aryllithiums, allowing the selective functionalization of regioisomeric mixture of aryllithiiums compounds.

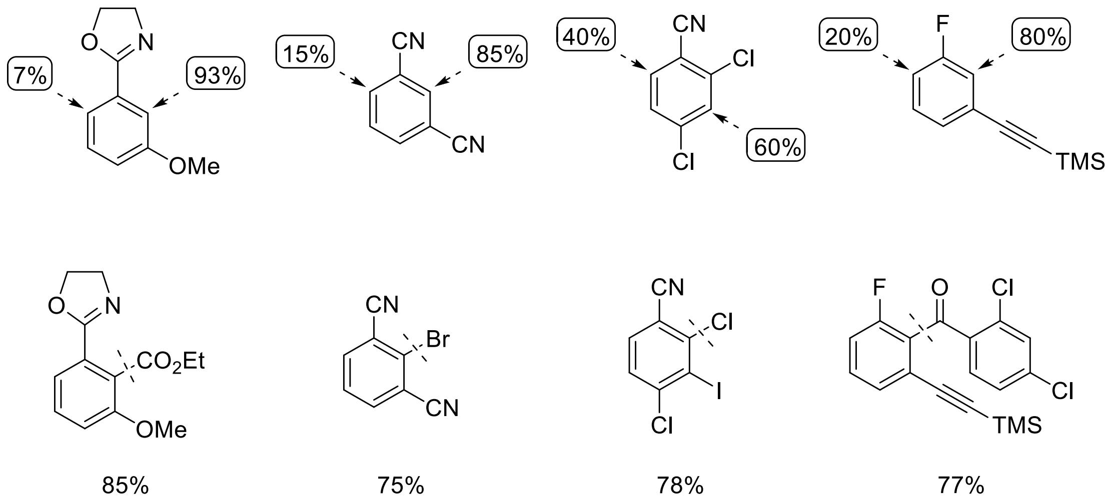
Besides, a methodology for the selective and predictable functionalization of all four positions of the 1,4-dithiin scaffold was disclosed *via* direct metalation and bromination. This method was also extended to the condensed S-heterocycles TTN and HTA permitting their functionalization.

Furthermore, the metalation of protected cyanohydrins as masked acyl anion equivalents bearing sensitive functional groups was developed.

4.1 FUNCTIONALIZATIONS OF MIXTURES OF REGIOISOMERIC ARYLLITHIUM COMPOUNDS BY SELECTIVE TRAPPING WITH DICHLOROZIRCONOCENE

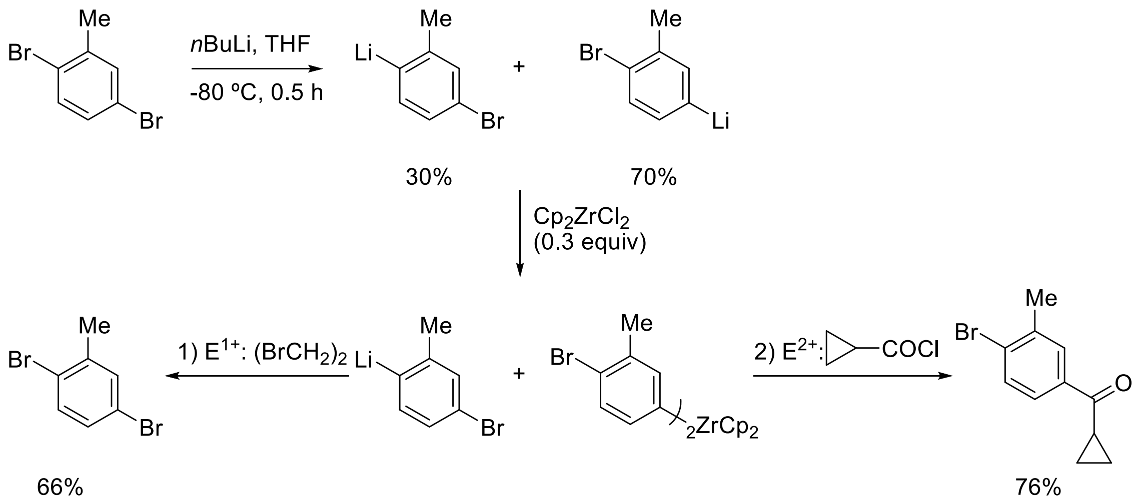
The lithiation of unsymmetrical substituted aromatics bearing one or more directed metalation group (DMG) can be non-selective, which leads to the mixture of regioisomeric aryllithiums. Therefore, a selective transmetalation of less sterically hindered aryllithium with Cp_2ZrCl_2 was investigated.

The reaction of regioisomeric mixtures of aryllithiums obtained by directed lithiation with sub-stoiechiometric amounts of Cp_2ZrCl_2 proceeds with high regioselectivity. The least sterically hindered regioisomeric aryllithium is selectively transmetalated to the corresponding arylzirconium-species leaving the more hindered aryllithium ready for various reactions with electrophiles (Scheme 60).



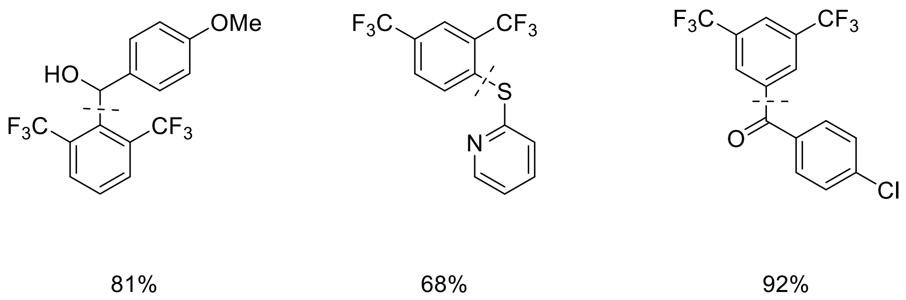
Scheme 60: Regioselective functionalization of unsymmetric arenes.

Mixtures of aryllithiums obtained by non-regioselective Br/Li-exchange with *n*BuLi were also studied. Following this new methodology, they could be regioselectively transmetalated to zirconium species allowing the most sterically hindered position to be available for a reaction with an electrophile (E^1). Afterwards, the remaining organozirconium could be trapped by a second and different electrophile (E^2, Scheme 61).



Scheme 61: Regioselective functionalization of 2,5-dibromotoluene.

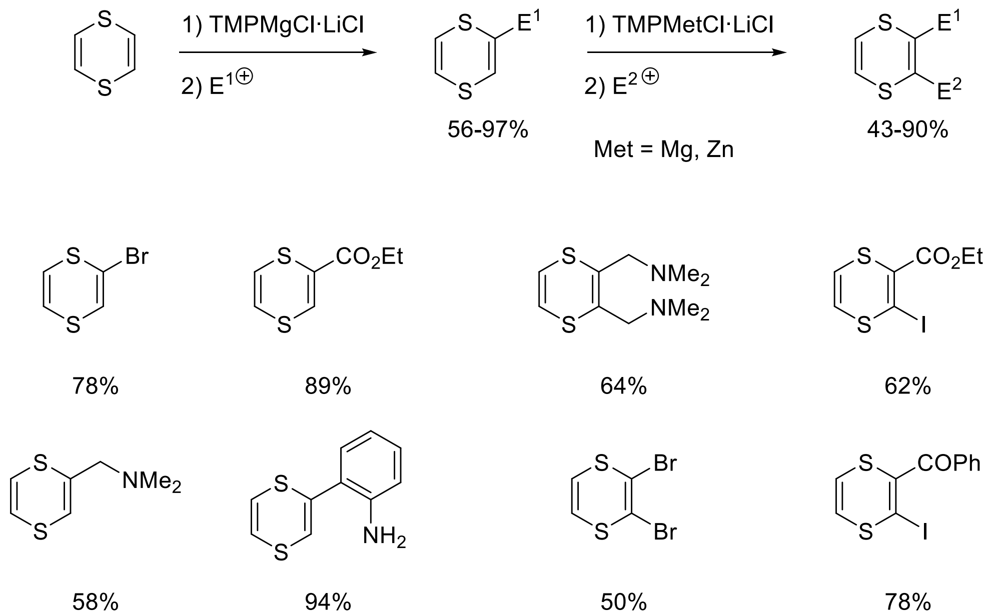
As an application, the regioselective transmetalation from lithium to zirconium species were used to prepare all three lithiated regioisomers of 1,3-bis(trifluoromethyl)benzene (Scheme 62).



Scheme 62: Selective 2-, 4-, and 5- functionalization of 1,3-bis(trifluoromethyl)benzene.

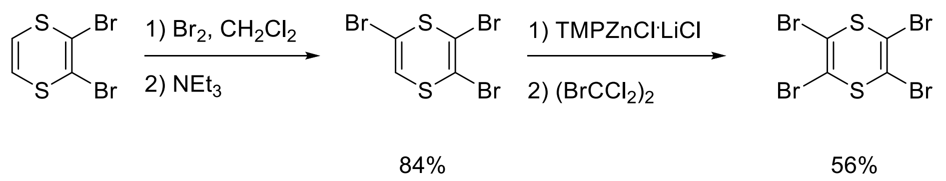
4.2 SELECTIVE METALATIONS OF 1,4-DITHIINS AND CONDENSED ANALOGUES USING TMP-MAGNESIUM AND -ZINC BASES

A convenient and mild protocol for the functionalization of 1,4-dithiins was developed. TMP-Bases allowed a facile metalation of the sensitive 1,4-dithiin scaffold furnishing after quenching with various electrophiles mono- and disubtituted derivatives (Scheme 63).



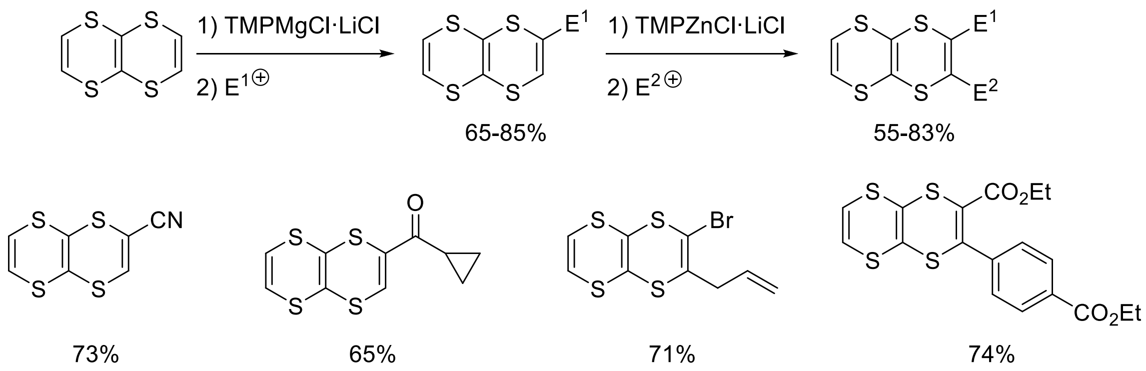
Scheme 63: Preparation of mono- and difunctionalized 1,4-dithiins.

Moreover, all four C-H bonds of the 1,4-dithiin core were functionalized. The treatment of dibromo-1,4-dithiin with bromine led to 2,3,5-tribromo-1,4-dithiin in 84% yield (Scheme 64). Subsequent metalation with TMPZnCl·LiCl and quenching with $(BrCCl_2)_2$ provided the tetra-substituted dithiin in 56% yield.



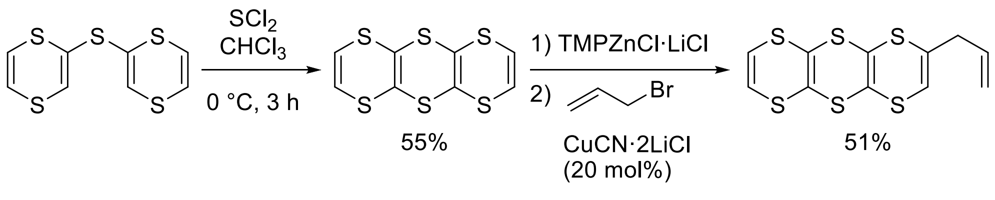
Scheme 64: Synthesis of tribrominated-1,4-dithiin and subsequent metalation *via* TMPZnCl·LiCl leading to the fully functionalized tetrasubstituted dithiin.

Interestingly, the metalation procedure could also be extended to the condensed TTN. The metalated species readily reacted with a broad variety of electrophiles giving to the mono- and disubstituted TTN (Scheme 65).



Scheme 65: Preparation of mono- and difunctionalized TTNs.

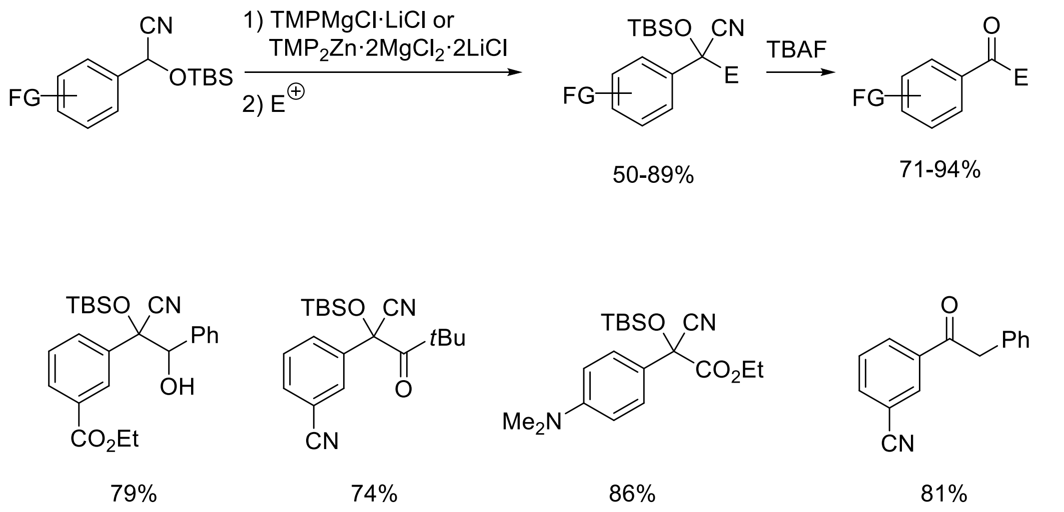
The resulting functionalized 1,4-dithiins were also employed for the synthesis of new S-heterocycles. In the case of di(1,4-dithiin-2-yl)sulfane, the condensation with sulfur dichloride provided hexathiaanthracene (HTA, Scheme 66). Remarkably, this new S-heterocycle could also be metalated with the mild zinc-base TMPZnCl·LiCl producing a zincated intermediate, which was allylated leading to the corresponding product in 51% yield.



Scheme 66: Synthesis of 1,4,5,6,9,10-hexathiaanthracene and subsequent functionalization by TMPZnCl·LiCl.

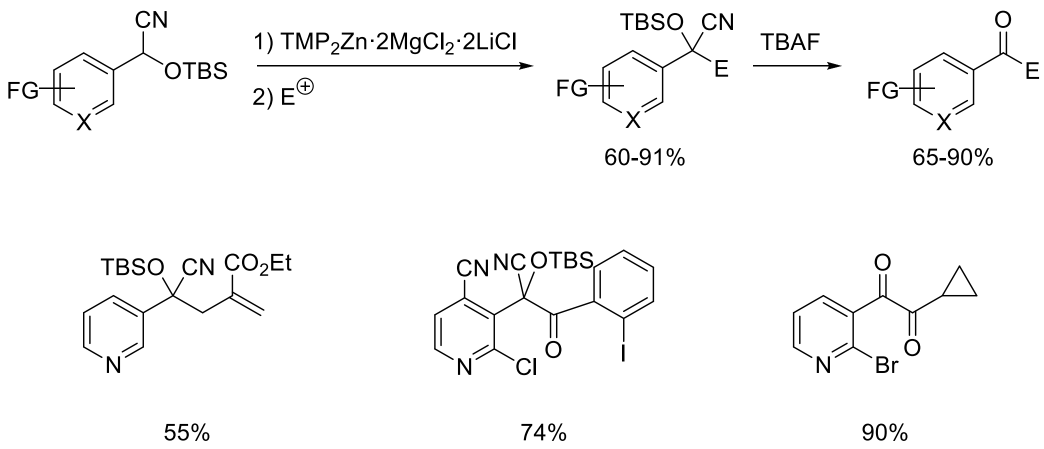
4.3 ZINCATION AND MAGNESIATION OF FUNCTIONALIZED SILYLATED CYANOHYDRINS USING TMP-BASES

Masked functional groups such as masked acyl anion equivalents have proven to be a powerful strategy in the formation of C-C or C-heteroatom bonds. Consequently, a mild and efficient method for the metalation of protected cyanohydrins with TMP-bases has been established (Scheme 67). The resulting benzylic metalated species could then react with different electrophiles such as aldehydes, acyl chlorides or ethyl cyanoformate, and subsequently deprotected with TBAF affording the corresponding keto-derivatives.



Scheme 67: Functionalization of silylated protected cyanohydrins using TMP-bases and subsequent deprotection with TBAF affording the keto-derivatives.

In addition, it was shown that these metalation conditions could be extended to heterocyclic functionalized protected cyanohydrins. These were metalated with $TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$, quenched with various electrophiles and subsequently deprotected using TBAF affording the corresponding their respective keto-compounds (Scheme 68).



Scheme 68: Synthesis of heterocyclic functionalized protected cyanohydrins using TMP-bases and subsequent deprotection with TBAF.

C. Experimental Section

1. GENERAL CONSIDERATIONS

All air and moisture sensitive reactions were carried out under argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. Unless otherwise indicated, all reagents were obtained from commercial sources. CuCN and LiCl were obtained from Merck.

1.1 SOLVENTS

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

CH_2Cl_2 was predried over CaH_2 and distilled from CaH_2.

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

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

Methanol was treated with magnesium turnings (10 g/L), heated to reflux and distilled.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

Triethylamine was dried over KOH and distilled.

1.2 REAGENTS

As not otherwise stated, all reagents were obtained from commercial sources. Reagents of >97% purity were used without purification, except technical grade tosyl cyanide (purity 95%) Liquid aldehydes were distilled prior to use. TMPH was distilled from CaH_2 and stored under argon.

The metal chlorides were purchased as follows:

$ZnCl_2$ (>99% purity): Merck

Cp_2ZrCl_2 (≥98% purity): Crompton GmbH.

Preparation of CuCN·2LiCl solution:[110]

CuCN·2LiCl solution (1.0 m in THF) was prepared by drying CuCN (7.17 g, 80 mmol) and LiCl (6.77 g, 160 mmol) in a Schlenk-flask under vacuum at 140 ºC for 5 h. After cooling, dry THF (80 mL) was added and stirring was continued until all salts were dissolved (24 h).

Preparation of $ZnCl_2$ solution:

$ZnCl_2$ solution (1.0 m in THF) was prepared by drying $ZnCl_2$ (136.3 g, 100 mmol) in a Schlenk-flask under vacuum at 140 ºC for 5 h. After cooling, dry THF (100 mL) was added and stirring was continued until all salts were dissolved (12 h).

Preparation of TMPMgCl·LiCl (2):[43]

In a dry and argon-flushed Schlenk-flask TMPH (2,2,6,6-tetramethylpiperidine, 14.8 g, 105 mmol) was added to *i*PrMgCl·LiCl (**1**) (71.4 mL, 1.40 M in THF, 100 mmol) at 23 ºC and the mixture was stirred for 3 days at 23 ºC. The freshly prepared TMPMgCl·LiCl (**2**) was titrated prior to use at 0 ºC with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

Preparation of TMPZn·LiCl (3):[49a]

A flame-dried and argon flushed Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, was charged with TMPH (2,2,6,6-tetramethylpiperidine, 10.2 mL, 60 mmol) dissolved in THF (60 mL). The solution was cooled to -40 ºC and *n*BuLi (25 mL, 60 mmol, 2.4 M in hexane) was added dropwise and the mixture was allowed to warm up to -10 ºC for 1 h. $ZnCl_2$ solution (66 mL, 66 mmol, 1.0 M in THF) was added dropwise and the resulting solution was stirred for 30 min at -10 ºC and then 30 min at 25 ºC. The solvents were removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added and the solution was stirred until all salts were completely dissolved. The freshly prepared TMPZnCl·LiCl (**3**) was titrated prior to use at 0 ºC with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

Preparation of $TMP_2Zn·2MgCl_2·2LiCl$ (4):[50a]

A flame-dried and argon flushed Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, was charged with TMPMgCl·LiCl (**2**, 348 mL, 400 mmol) and cooled to 0 ºC. Then, $ZnCl_2$ (200 mL, 200 mmol, 1.0 M in THF) was added over a period of 15 min. After stirring this mixture for 2 h at 0 ºC, the solution of $TMP_2Zn·2MgCl_2·2LiCl$ was concentrated in vacuo. Freshly distilled THF was then slowly added and the solution was stirred until all salts were completely dissolved. The freshly prepared $TMP_2Zn·2MgCl_2·2LiCl$ (**4**) was titrated prior to use at 0 ºC with benzoic acid using 4-(phenylazo)-diphenylamine as indicator.

Preparation of TMPLi solution:

TMPLi solution (0.6 M in THF) was prepared by slow addition of *n*BuLi (2.0 mL, 5.0 mmol, 2.5 M in hexanes) to a solution of TMPH (706 mg, 0.85 mL, 5.0 mmol) in THF (5 mL) at -40 ºC and stirred for 30 min at -40 ºC.

Preparation of *i*PrMgCl·LiCl (1):[33]

Magnesium turnings (110 mmol) and anhydrous LiCl (100 mmol) were placed in an Ar-flushed flask, and THF (50 mL) was added. A solution of *i*PrCl (100 mmol) in THF (50 mL) was slowly added at room temperature. The reaction started within a few minutes. After the addition, the reaction mixture was stirred for 12 h at 25 ºC. The gray solution of *i*PrMgCl·LiCl (**1**) was cannulated into another Ar-filled flask and removed in this way from excess magnesium. *i*PrMgCl·LiCl (**1**) was obtained in a yield of ca. 95–98 % and titrated against iodine prior to use.

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

***s*BuLi** was purchased as a solution in hexane from Rockwood Lithium GmbH.

***t*BuLi** was purchased as a solution in hexane from Rockwood Lithium GmbH.

The content of *n*BuLi, *s*BuLi and *t*BuLi was determined either by the method of *Paquette* using *i*PrOH and 1,10-phenanthroline as indicator.[113]

1.3 CHROMATOGRAPHY

Flash column chromatography was performed using SiO_2 (0.040–0.063 mm, 230–400 mesh) from Merck.

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

- Iodine absorbed on silica gel.

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

[113] H.-S. Lin, A. Paquette, *Synth. Commun.* **1994**, *24*, 2503.

1.4 ANALYTICAL DATA

NMR spectra were recorded on VARIAN MERCURY 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the solvent peak, i.e. chloroform-d (δ 7.26 ppm for ^{1}H-NMR and δ 77.0 ppm for ^{13}C-NMR), DMSO-d_6 (δ 2.50 ppm for ^{1}H-NMR and δ 39.5 ppm for ^{13}C-NMR). For the characterization of the observed signal multiplicities the following abbreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), spt (septet), m (multiplet), as well as br (broadened).

Mass spectroscopy: High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an ionization energy of 70 eV.

For coupled gas chromatography/mass spectrometry, a HEWLETT-PACKARD HP6890/MSD 5973 GC/MS system was used. Molecular fragments are reported starting at a relative intensity of 10%.

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

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

Microwave irradiation was performed in a Biotage Initiator™ Unit (Biotage, Uppsala, Sweden) in a closed-vessel system.

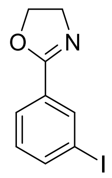
2. FUNCTIONALIZATIONS OF MIXTURES OF REGIOISOMERIC ARYLLITHIUM COMPOUNDS BY SELECTIVE TRAPPING WITH DICHLOROZIRCONOCENE

2.1 PREPARATION OF STARTING MATERIALS

Starting materials **11**, **12**, **23**, **24**, **25**, **30** and **35** are commercially available.

2.1.1 Preparation of 2-(3-(methylthio)phenyl)-4,5-dihydrooxazole (**18**)

2.1.1.1 Preparation of 2-(3-iodophenyl)-4,5-dihydrooxazole (**77**)



According to the literature,[114] 3-iodobenzoic acid (9.5 g, 38 mmol) was dissolved in dichloromethane (50 mL) and oxalyl chloride (10 mL, 121 mmol) followed by *N*,*N*-dimethylformamide (0.2 mL) was added at 0 ºC. The reaction mixture was stirred overnight at 25 ºC and after, concentrated under reduce pressure, the residue was dissolved in CH_2Cl_2. This was added to a mixture of ethanolamine (4.7 g, 77 mmol) and NEt_3 (21 mL, 153 mmol) in dichloromethane at 0 ºC and stirred for 10 h at 25 ºC. The mixture was then concentrated *in vacuo* and the residue was dissolved in dichloromethane (50 mL), and $SOCl_2$ (14 mL, 192 mmol) was added dropwise at 0 ºC. The reaction mixture was stirring for 20 h at 25 ºC and concentrated under reduce pressure. To the resulting residue saturated aqueous $NaHCO_3$ solution was added and stirred for 10 min. The product was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. Afterwards, the crude product was dissolved in methanol (40 mL) and NaOH (96 mL, 192 mmol, 2 M) was added at 0 ºC. After stirring for 12 h at 25 ºC, the reaction mixture was concentrated *in vacuo* and the product was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc 7:3) to afford the product **77** as a light yellow solid (8.2 g, 78%).

m.p.: 75 - 77 ºC.

[114] S. Chanthamath, K. Phomkeona, K. Shibatomi, S. Iwasa, *Chem. Commun.* **2012**, *48*, 7750.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.32 (s, 1 H), 7.91 (d, *J*=7.8 Hz, 1 H), 7.81 (d, *J*=7.8 Hz, 1 H), 7.16 (t, *J*=7.9 Hz, 1 H), 4.45 (t, *J*=9.5 Hz, 2 H), 4.07 (t, *J*=9.7 Hz, 2 H).

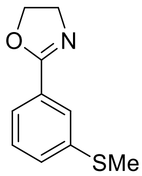
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 163.1, 140.1, 137.0, 129.9, 129.7, 127.2, 93.8, 67.7, 54.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2881, 1640, 1558, 1469, 1396, 1357, 1327, 1248, 1194, 1091, 1073, 1054, 990, 974, 937, 892, 795, 719, 645, 580, 566, 558.

MS (70 eV, EI) *m/z* (%): 273 (51), 243 (33), 231 (21), 149 (13), 146 (4), 97 (3), 89 (12), 83 (7), 82 (4), 76 (5), 71 (7), 70 (14), 69 (9), 67 (5), 61 (13), 50 (5), 45 (6), 44 (25), 43 (100), 41 (7).

HRMS (EI): *m/z* (M^+) for for C_9H_8INO: calcd. 272.9651; found 272.9639.

2.1.1.2 Preparation of 2-(3-(methylthio)phenyl)-4,5-dihydrooxazole (**18**)



According to the literature,[115] a solution of *i*PrMgCl·LiCl (**1**, 2.36 mL, 3.03 mmol, 1.28 M in THF) was added dropwise to a solution of 2-(3-iodophenyl)-4,5-dihydrooxazole (**77**, 750 mg, 2.75 mmol) in anhydrous THF (10 mL) at -80 ºC. The mixture was stirred for 1 h and then dimethyl disulfide (0.37 mL, 4.13 mmol) was added. The mixture was stirred allowing to warm up to 25 ºC over 5 h. After the completion of the reaction, the resulting mixture was quenched by addition of saturated aqueous NH_4Cl solution. The product was extracted with diethyl ether (2 x 20 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc 8:2) to provide the product **18** (440 mg, 83%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.83 (s, 1 H), 7.70 (d, *J*=7.3 Hz, 1 H), 7.30 - 7.38 (m, 2 H), 4.45 (t, *J*=9.5 Hz, 2 H), 4.08 (t, *J*=9.4 Hz, 2 H), 2.52 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 164.3, 139.1, 129.3, 128.7, 128.4, 125.6, 124.7, 67.7, 55.0, 15.6.

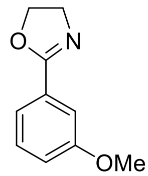
[115] R. L.-Y. Bao, R. Zhao, L. Shi, *Chem.Commun.* **2015**, *51*, 6884.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2877, 1648, 1587, 1570, 1474, 1425, 1358, 1325, 1276, 1196, 1086, 1062, 974, 944, 902, 878, 794, 762, 675, 562.

MS (70 eV, EI) *m/z* (%): 194 (8), 193 (100), 192 (25), 178 (9), 163 (45), 149 (15), 147 (27), 123 (20), 117 (6), 105 (6), 104 (6), 97 (13), 83 (11), 81 (14), 77 (11), 71 (14), 69 (12), 67 (7), 63 (7), 57 (16), 56 (7), 55 (11), 45 (6), 44 (10), 43 (12), 41 (15).

HRMS (EI): *m/z* (M$^+$) for $C_{10}H_{11}NOS$: calcd. 193.0561; found 193.0546.

2.1.2 Preparation of 2-(3-methoxyphenyl)-4,5-dihydrooxazole (**22**)



According to the literature,[113] 3-methoxybenzoic acid (2.6 g, 17 mmol) was dissolved in CH_2Cl_2 (20 mL) and oxalyl chloride (2.2 mL, 26 mmol) followed by *N*,*N*-dimethylformamide (0.05 mL) was added at 0 ºC. The reaction mixture was stirred at 0 ºC for 1 h and at 25 ºC for 2 h. Afterwards, the resulting mixture was concentrated under reduce pressure and the residue was dissolved in dichloromethane. This was added to a mixture of ethanolamine (2.1 g, 34 mmol) and trimethylamine (9.5 mL, 68 mmol) in dichloromethane at 0 ºC and stirred for 10 h at 25 ºC. The mixture was then concentrated under vacuum and the residue was dissolved in dichloromethane (50 mL) and $SOCl_2$ (6.2 mL, 85 mmol) was added dropwise at 0 ºC. The reaction was stirring for 20 h at 25 ºC and concentrated under reduce pressure. To the resulting residue saturated aqueous $NaHCO_3$ solution was added and stirred for 10 min. The product was extracted with dichloromethane (2 x 50 mL) and the combined organic phases were dried over sodium sulfate, filtered and concentrated. Afterwards, the crude product was dissolved in methanol (10 mL) and NaOH (43 mL, 85 mmol, 2 M) was added at 0 ºC. After stirring for 12 h at 25 ºC, the reaction mixture was concentrated *in vacuo* and the product was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc 7:3) to afford the product **22** as a light yellow solid (2.4 g, 80%).

m.p.: 59 - 61 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.54 (d, *J*=7.6 Hz, 1 H), 7.49 (s, 1 H), 7.32 (t, *J*=7.9 Hz, 1 H), 7.03 (d, *J*=8.1 Hz, 1 H), 4.44 (t, *J*=9.5 Hz, 2 H), 4.07 (t, *J*=9.4 Hz, 2 H), 3.85 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 164.6, 159.5, 129.4, 129.0, 120.6, 118.1, 112.4, 67.6, 55.4, 54.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2935, 2904, 2839, 1647, 1603, 1578, 1489, 1454, 1432, 1359, 1329, 1286, 1269, 1209, 1180, 1094, 1071, 1059, 994, 974, 945, 904, 823, 793, 681.

MS (70 eV, EI) *m/z* (%): 178 (11), 177 (83), 176 (29), 148 (18), 147 (100), 146 (5), 135 (10), 133 (6), 132 (5), 123 (5), 107 (9), 105 (5), 104 (6), 92 (8), 91 (5), 83 (4), 77 (21), 76 (4), 74 (5), 69 (4), 64 (5), 63 (6), 57 (5), 55 (4), 43 (11).

HRMS (EI): *m/z* (M^+) for $C_{10}H_{11}NO_2$: calcd. 177.0790; found 177.0784.

2.2 TYPICAL PROCEDURES

Typical Procedure 1 for the lithiation of arene of type (18) with *n*BuLi (TP1):

A dry and argon flushed Schlenk-flask was charged with a solution of the substrate **18** (1.0 equiv) and TMEDA (1.1 equiv) in dry THF (0.25 M). *n*BuLi (1.1 equiv) was added dropwise at -80 ºC and the reaction mixture was stirred for 3 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in dry THF. Cp_2ZrCl_2 (0.2 equiv) was added as a solid and the resulting mixture was stirring for a further 1 h at -80 ºC.

Typical Procedure 2 for the lithiation of arene of type (22) with *n*BuLi (TP2):

A dry and argon flushed Schlenk-flask was charged with a solution of the substrate **22** (1.0 equiv) and TMEDA (1.1 equiv) in dry THF (0.25 M). *n*BuLi (1.1 equiv) was added dropwise at -80 ºC and the reaction mixture was stirred for 3 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in dry THF. Cp_2ZrCl_2 (0.1 equiv) was added as a solid and the resulting mixture was stirring for a further 1 h at -80 ºC.

Typical Procedure 3 for the lithiation of arene of type (23) with TMPLi (TP3):

A dry and argon flushed Schlenk-flask was charged with a solution of the substrate **23** (1.0 equiv) in dry THF (0.25 M). TMPLi (1.05 equiv) was added dropwise at -80 ºC and the reaction mixture was stirred for 0.5 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in dry THF. Cp_2ZrCl_2 (0.15 equiv) was added as a solid and the resulting mixture was stirring for a further 0.5 h at -80 ºC.

Typical Procedure 4 for the lithiation of arene of type (24) with TMPLi (TP4):

A dry and argon flushed Schlenk-flask was charged with a solution of the substrate **24** (1.0 equiv) in dry THF (0.3-0.5 M). TMPLi (1.0 equiv) was added dropwise at -80 ºC and the reaction mixture was stirred for 20 min. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in dry THF. Cp_2ZrCl_2 (0.35-0.4 equiv) was added as a solid and the resulting mixture was stirring for a further 0.5 h at -80 ºC.

Typical Procedure 5 for the lithiation of heteroaromatic of type (25) with TMPLi (TP5):

A dry and argon flushed Schlenk-flask was charged with a solution of the substrate **25** (1.0 equiv) in dry THF (0.17-0.3 M). TMPLi (1.0-1.1 equiv) was added dropwise at -80 ºC and the reaction mixture was stirred for 0.5 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in dry THF. Cp_2ZrCl_2 (0.25 equiv) was added as a solid and the resulting mixture was stirring for a further 0.5 h at -80 ºC.

Typical Procedure 6 for the lithiation of arene of type (30) with *n*BuLi (TP6):

A dry and argon flushed Schlenk-flask was charged with a solution of 1,4-dibromo-2-methylbenzene (**30**, 1.0 equiv) in dry THF (0.2 M). *n*BuLi (1.0 equiv) was added dropwise at -80 ºC and the reaction mixture was stirred for 0.5 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in dry THF. Cp_2ZrCl_2 (0.3 equiv) was added as a solid and the resulting mixture was stirring for a further 1.5 h at -80 ºC.

Typical Procedure 7 for the lithiation of arene of type (35) with *n*BuLi (TP7):

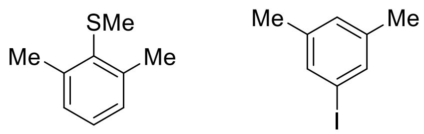
A dry and argon flushed Schlenk-flask was charged with a solution of 1,3-bis(trifluoromethyl)benzene (**35**, 1.0 equiv) in dry THF (0.4 M). *n*BuLi (1.0 equiv) was added dropwise at -40 ºC and the reaction mixture was stirred for 1 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in dry THF. Cp_2ZrCl_2 (0.7 equiv) was added as a solid at -80 ºC and the resulting mixture was stirring for a further 1.5 h at this temperature.

Typical Procedure 8 for the lithiation of arene of type (35) with *t*BuLi (TP8):

A dry and argon flushed Schlenk-flask was charged with a solution of 1,3-bis(trifluoromethyl)benzene (**35**, 1.0 equiv) in dry Et_2O (0.4 M). *t*BuLi (1.0 equiv) was added dropwise at -40 ºC and the reaction mixture was stirred for 18 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in dry THF. Cp_2ZrCl_2 (0.26-0.32 equiv) was added as a solid at -80 ºC and the resulting mixture was stirring for a further 1.5 h at this temperature.

2.3 PRELIMINARY EXPERIMENTS

2.3.1 Preparation of (2,6-dimethylphenyl)(methyl)sulfane (**16**) and 1-iodo-3,5-dimethylbenzene (**17**) through intermediates **13** and **15**



2-bromo-*m*-xylene (**11**, 92.5 mg, 0.50 mmol) and 5-bromo-*m*-xylene (**12**, 85.5 mg, 0.50 mmol) were dissolved in THF (3 mL) and *n*BuLi (0.42 mL, 1.05 mmol, 2.5 M in hexanes) was added dropwise at -80 ºC. The reaction mixture was stirred for 0.5 h and Cp_2ZrCl_2 (75 mg, 0.25 mmol, 98%) was added as a solid. Stirring was continued for a further 1 h at -80 ºC, after which dimethyl disulfide (94 mg, 1.00 mmol) was added and the mixture was stirred for a further 1 h at -80 ºC. Molecular iodine (254 mg, 1.00 mmol) was then added, the mixture warmed to 25 ºC, followed by the addition of a saturated aqueous NH_4Cl solution (2 mL). The product was extracted with diethyl ether (2 x 20 mL), followed by drying over $MgSO_4$ and removal of the solvent under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane) yielded the compounds **17**, 1-iodo-3,5-dimethylbenzene (103 mg, 89%), as a colorless oil, and **16**, 2,6-dimethylphenyl)(methyl)sulfane (65 mg, 85%), as a colorless oil as well.

1-Iodo-3,5-dimethylbenzene (17)

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.37 (s, 2 H), 6.96 (s, 1 H), 2.28 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 139.9, 135.0, 129.3, 94.3, 20.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2915, 2857, 1600, 1562, 1452, 1251, 1112, 1036, 985.

MS (70 eV, EI) *m/z* (%): 232 (100), 105 (48), 104 (5), 103 (16), 97 (2), 91 (3), 85 (3), 83 (3), 79 (25), 78 (6), 77 (20), 73 (2), 71 (5), 70 (4), 69 (4), 63 (6), 61 (5), 57 (8), 55 (4), 45 (5), 44 (12), 43 (37), 41 (6).

HRMS (EI): *m/z* (M$^+$) for for C_8H_9I: calcd. 231.9749; found 231.9743.

(2,6-Dimethylphenyl)(methyl)sulfane (16)

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.12 (s, 3 H), 2.57 (s, 6 H), 2.25 (s, 3 H).

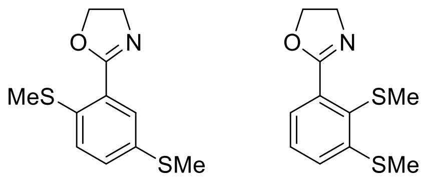
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 142.70, 135.15, 128.07, 128.03, 21.73, 18.24.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2952, 2919, 1459, 1434, 1375, 1313, 1056, 1031, 964, 722.

MS (70 eV, EI) *m/z* (%): 154 (5), 153 (11), 152 (100), 139 (3), 138 (7), 137 (71), 136 (2), 135 (7), 134 (3), 122 (2), 121 (4), 106 (2), 105 (15), 104 (5), 103 (9), 102 (2), 97 (2), 93 (7), 91 (12), 79 (3), 78 (5), 77 (8), 65 (2), 63 (2), 45 (6), 43 (3).

HRMS (EI): *m/z* (M$^+$) for for $C_9H_{12}S$: calcd. 152.0660; found 152.0647.

2.3.2. Preparation of 2-(2,5-bis(methylthio)phenyl)-4,5-dihydrooxazole (**20a'**) and 2-(2,3-bis(methylthio)phenyl)-4,5-dihydrooxazole (**20a**)[116]



An oven dried reaction flask was charged with the substrate (**18**, 193 mg, 1.00 mmol) and TMEDA (0.17 mL, 1.10 mmol) in THF (4 mL) and *n*BuLi (0.44 mL, 1.10 mmol, 2.5 M in hexanes) was added dropwise at -80 ºC. The reaction mixture was stirred for 3 h and dimethyl disulfide (75 mg, 0.80 mmol) was added. The mixture was stirred for a further 1 h at -80 ºC and the resulting mixture was allowed to warm up to 25 ºC. Saturated aqueous NH_4Cl solution (2 mL) was added and the product was extracted with diethyl ether (2 x 20 mL), followed by drying over $MgSO_4$ and removal of the solvent under reduced pressure. Purification by flash column chromatography on silica

[116] Experiment performed in absence of Cp_2ZrCl_2 to know the regioselectivity of the reaction.

gel (*i*hexane/EtOAc 7:3) yielded a white solid of the title compound **20a'** (26 mg, 14%) and the other regioisomer **20a** (130 mg, 68%).

2-(2,5-Bis(methylthio)phenyl)-4,5-dihydrooxazole (20a')

m.p.: 118 - 120 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.77 (s, 1 H), 7.33 (d, *J*=8.3 Hz, 1 H), 7.18 (d, *J*=8.3 Hz, 1 H), 4.39 (t, *J*=9.4 Hz, 2 H), 4.19 (t, *J*=9.4 Hz, 2 H), 2.49 (s, 3 H), 2.46 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 163.1, 137.7, 133.6, 129.7, 128.7, 125.2, 124.8, 66.7, 55.7, 16.3, 15.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2920, 2852, 1635, 1577, 1541, 1487, 1460, 1439, 1422, 1357, 1329, 1315, 1281, 1226, 1202, 1163, 1122, 1079, 1058, 1033, 978, 969, 961, 945, 907, 874, 738, 723, 673.

MS (70 eV, EI) *m/z* (%): 241 (11), 240 (15), 239 (100), 224 (70), 209 (17), 206 (43), 192 (12), 180 (12), 178 (27), 163 (26), 147 (13), 139 (23), 137 (18), 135 (11), 134 (24), 122 (13), 121 (26), 108 (15), 95 (23), 77 (21), 75 (12), 69 (35), 63 (27), 56 (13), 45 (38), 44 (30).

HRMS (EI): *m/z* (M^+) for $C_{11}H_{13}NOS_2$: calcd. 239.0439; found 239.0429.

2-(2,3-Bis(methylthio)phenyl)-4,5-dihydrooxazole (20a)

m.p.: 95 - 97 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.30 - 7.39 (m, 2 H), 7.19 (d, *J*=7.6 Hz, 1 H), 4.47 (t, *J*=9.5 Hz, 2 H), 4.10 (t, *J*=9.5 Hz, 2 H), 2.46 (s, 3 H), 2.41 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 165.1, 146.8, 135.7, 131.7, 128.9, 125.6, 125.2, 67.8, 55.4, 19.3, 15.6.

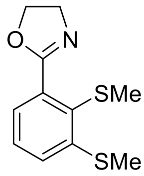
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2918, 2854, 1661, 1554, 1460, 1445, 1427, 1391, 1349, 1322, 1266, 1257, 1223, 1184, 1142, 1125, 1067, 1054, 979, 904, 765, 738, 574.

MS (70 eV, EI) *m/z* (%):239 (8), 226 (8), 225 (11), 224 (100), 192 (5), 182 (6), 181 (24), 180 (24), 178 (8), 153 (17), 147 (7), 139 (9), 134 (9), 122 (6), 121 (13), 117 (6), 116 (10), 107 (5), 91 (6), 89 (5), 77 (13), 76 (6), 75 (5), 63 (10), 56 (5), 45 (18).

HRMS (EI): *m/z* (M^+) for $C_{11}H_{13}NOS_2$: calcd. 239.0439; found 239.0419.

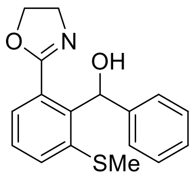
2.4 REGIOSELECTIVE FUNCTIONALIZATION OF UNSYMMETRICAL ARENE OF TYPE 18

2.4.1 Preparation of 2-(2,3-bis(methylthio)phenyl)-4,5-dihydrooxazole (**20a**)



According to **TP1**, the substrate (**18**, 193 mg, 1.00 mmol) and TMEDA (0.17 mL, 1.10 mmol) were dissolved in THF (4 mL) and *n*BuLi (0.44 mL, 1.10 mmol, 2.5 M in hexanes) was added dropwise at -80 ºC. The reaction mixture was stirred for 3 h and Cp_2ZrCl_2 (60 mg, 0.20 mmol, 98%) was added as a solid. Stirring was continued for a further 1 h at -80 ºC, after which dimethyl disulfide (75 mg, 0.80 mmol) was added and the mixture was stirred for a further 1 h at -80 ºC. The resulting mixture was allowed to warm up to 25 ºC and saturated aqueous NH_4Cl solution (2 mL) was added. The product was extracted with diethyl ether (2 x 20 mL), followed by drying over $MgSO_4$ and removal of the solvent under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane/EtOAc 7:3) yielded a white solid of the title compound **20a** (160 mg, 84%).

2.4.2 Preparation of (2-(4,5-dihydrooxazol-2-yl)-6-(methylthio)phenyl)(phenyl)-methanol (**20b**)



According to **TP1**, the substrate (**18**, 193 mg, 1.00 mmol) and TMEDA (0.17 mL, 1.10 mmol) were dissolved in THF (4 mL) and *n*BuLi (0.44 mL, 1.10 mmol, 2.5 M in hexanes) was added dropwise at -80 ºC. The reaction mixture was stirred for 3 h and Cp_2ZrCl_2 (60 mg, 0.20 mmol, 98%) was added as a solid. Stirring was continued for a further 1 h at -80 ºC, after which benzaldehyde (85 mg, 0.80 mmol) was added and the mixture was stirred for a further 1 h at -80 ºC. The resulting mixture was allowed to warm up to 25 ºC and saturated aqueous NH_4Cl solution (2 mL) was added. The product was extracted with diethyl ether (2 x 20 mL), followed by drying over $MgSO_4$ and removal of the solvent under reduced pressure. Purification by flash column chromatography on silica gel (EtOAc) yielded a white solid of the title compound **20b** (211 mg, 88%).

m.p.: 134 - 135 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.69 (d, *J*=7.6 Hz, 1 H), 7.47 (t, *J*=7.7 Hz, 1 H), 7.37 (d, *J*=4.4 Hz, 3 H), 7.29 (d, *J*=8.1 Hz, 1 H), 7.24 (d, *J*=4.4 Hz, 2 H), 6.29 (br. s., 1 H), 3.83 (br. s., 2 H), 3.57 - 3.70 (m, 2 H), 2.69 (br. s., 1 H), 2.33 (s, 3 H).

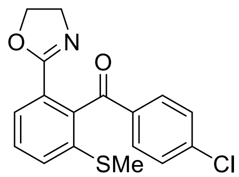
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 160.3, 143.7, 136.8, 133.9, 130.9, 129.9, 129.2, 128.7, 128.4, 128.0, 119.6, 85.3, 62.7, 49.3, 15.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3400, 2954, 2920, 2883, 2851, 1692, 1682, 1583, 1460, 1437, 1424, 1371, 1350, 1288, 1271, 1205, 1082, 1061, 1045, 1035, 1008, 992, 904, 884, 859, 840, 792, 773, 752, 730, 680.

MS (70 eV, EI) *m/z* (%): 229 (2), 270 (5), 269 (14), 268 (75), 252 (2), 240 (2), 239 (2), 238 (1), 225 (3), 224 (1), 222 (1), 196 (2), 195 (2), 178 (2), 166 (2), 165 (13), 164 (3), 163 (3), 153 (1), 152 (4), 151 (1), 139 (1), 120 (1), 115 (1), 104 (1), 103 (1), 97 (1), 92 (7), 91 (100), 89 (2), 77 (3), 76 (2), 75 (1), 63 (1), 45 (2).

HRMS (EI): *m/z* (M^+) for $C_{17}H_{17}NO_2S$: calcd. 299.0980; found 299.0984.

2.4.3 Preparation of (4-chlorophenyl)(2-(4,5-dihydrooxazol-2-yl)-6-(methylthio)phenyl)methanone (**20c**)



According to **TP1**, the substrate (**18**, 193 mg, 1.00 mmol) and TMEDA (0.17 mL, 1.10 mmol) were dissolved in THF (4 mL) and *n*BuLi (0.44 mL, 1.10 mmol, 2.5 M in hexanes) was added dropwise at -80 ºC. The reaction mixture was stirred for 3 h and Cp_2ZrCl_2 (60 mg, 0.20 mmol, 98%) was added as a solid. Stirring was continued for a further 1 h at -80 ºC, after which 4-chlorobenzoyl chloride (140 mg, 0.80 mmol) was added and the mixture was stirred for a further 1 h at -80 ºC. The resulting mixture was allowed to warm up to 25 ºC and saturated aqueous NH_4Cl solution (2 mL) was added. The product was extracted with diethyl ether (2 x 20 mL), followed by drying over $MgSO_4$ and removal of the solvent under reduced pressure. Purification by flash column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1) yielded a light grey solid of the title compound **20c** (179 mg, 68%).

m.p.: 159 - 160 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.83 (dd, *J*=7.6, 1.2 Hz, 1 H), 7.65 - 7.71 (m, 2 H), 7.53 (dd, *J*=7.8, 1.0 Hz, 1 H), 7.47 (t, *J*=7.7 Hz, 1 H), 7.35 - 7.40 (m, 2 H), 4.12 (t, *J*=9.5 Hz, 2 H), 3.78 (t, *J*=9.6 Hz, 2 H), 2.37 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 194.6, 162.5, 139.7, 139.0, 136.4, 135.9, 131.2, 130.2, 129.5, 128.7, 126.7, 126.1, 67.6, 54.9, 17.7.

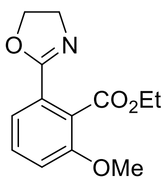
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2913, 1679, 1649, 1587, 1574, 1486, 1420, 1398, 1352, 1328, 1312, 1300, 1285, 1194, 1158, 1147, 1086, 1017, 977, 949, 906, 845, 830, 811, 763, 750, 736, 693, 688, 674.

MS (70 eV, EI) *m/z* (%): 333 (4), 332 (3), 331 (9), 330 (3), 304 (37), 302 (100), 288 (4), 287 (2), 286 (8), 258 (2), 257 (2), 256 (2), 245 (2), 227 (2), 222 (2), 220 (9), 206 (5), 195 (2), 177 (3), 166 (2), 151 (2), 150 (2), 139 (7), 138 (2), 126 (2), 125 (2), 121 (3), 111 (13), 104 (2), 89 (2), 77 (2), 76 (3), 75 (7), 63 (2), 50 (2), 45 (3).

HRMS (EI): *m/z* (M^+) for $C_{17}H_{14}ClNO_2S$: calcd. 331.0434; found 331.0433.

2.5 REGIOSELECTIVE FUNCTIONALIZATION OF UNSYMMETRICAL ARENE OF TYPE 22

2.5.1 Preparation of ethyl 2-(4,5-dihydrooxazol-2-yl)-6-methoxybenzoate (**26a**)



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According to **TP2**, the substrate (**22**, 177 mg, 1.00 mmol) and TMEDA (0.17 mL, 1.10 mmol) were dissolved in THF (4 mL) and *n*BuLi (0.44 mL, 1.10 mmol, 2.5 M in hexanes) was added dropwise at -80 ºC. The reaction mixture was stirred for 3 h and Cp_2ZrCl_2 (30 mg, 0.10 mmol, 98%) was added as a solid. Stirring was continued for a further 1 h at -80 ºC, after which ethyl chloroformate (98 mg, 0.90 mmol) was added and the mixture was stirred for a further 1 h at -80 ºC. The resulting mixture was allowed to warm up to 25 ºC and saturated aqueous NH_4Cl solution (2 mL) was added. The product was extracted with diethyl ether (2 x 20 mL), followed by drying over $MgSO_4$ and removal of the solvent under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane/EtOAc 7:3) yielded a white solid of the title compound **26a** (191 mg, 85%).

m.p.: 109 - 111 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.53 (d, *J*=8.1 Hz, 1 H), 7.39 (t, *J*=8.1 Hz, 1 H), 7.05 (d, *J*=8.3 Hz, 1 H), 4.34 - 4.45 (m, 4 H), 4.04 (t, *J*=9.5 Hz, 2 H), 3.86 (s, 3 H), 1.37 (t, *J*=7.1 Hz, 3 H).

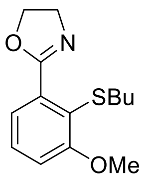
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 167.3, 162.9, 156.3, 130.4, 126.0, 124.3, 121.2, 113.8, 67.7, 61.4, 56.2, 55.2, 14.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2923, 1730, 1653, 1581, 1459, 1436, 1362, 1327, 1191, 1180, 1140, 1110, 1068, 1002, 978, 953, 912, 854, 828, 806, 744, 701.

MS (70 eV, EI) *m/z* (%): 250 (4), 249 (26), 220 (16), 205 (16), 204 (100), 202 (7), 190 (30), 179 (8), 178 (4), 177 (21), 176 (45), 163 (4), 160 (24), 159 (4), 148 (4), 147 (15), 134 (4), 133 (4), 120 (4), 119 (7), 117 (4), 105 (4), 104 (5), 77 (7), 76 (9), 43 (11).

HRMS (EI): *m/z* (M^+) for $C_{13}H_{15}NO_4$: calcd. 249.1001; found 249.0993.

2.5.2 Preparation of 2-(2-(butylthio)-3-methoxyphenyl)-4,5-dihydrooxazole (**26b**)



According to **TP2**, the substrate (**22**, 177 mg, 1.00 mmol) and TMEDA (0.17 mL, 1.10 mmol) were dissolved in THF (4 mL) and *n*BuLi (0.44 mL, 1.10 mmol, 2.5 M in hexanes) was added dropwise at -80 ºC. The reaction mixture was stirred for 3 h and Cp_2ZrCl_2 (30 mg, 0.10 mmol, 98%) was added as a solid. Stirring was continued for a further 1 h at -80 ºC, after which dibutyl disulfide (161 mg, 0.90 mmol) was added and the mixture was stirred for a further 1 h at -80 ºC. The resulting mixture was allowed to warm up to 25 ºC and saturated aqueous NH_4Cl solution (2 mL) was added. The product was extracted with diethyl ether (2 x 20 mL), followed by drying over $MgSO_4$ and removal of the solvent under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane/EtOAc 1:1) yielded an colorless oil of the title compound **26b** (198 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.31 (t, *J*=7.9 Hz, 1 H), 7.15 (d, *J*=7.6 Hz, 1 H), 6.97 (d, *J*=8.3 Hz, 1 H), 4.46 (t, *J*=9.5 Hz, 2 H), 4.09 (t, *J*=9.5 Hz, 2 H), 3.92 (s, 3 H), 2.85 (t, *J*=7.2 Hz, 2 H), 1.42 - 1.52 (m, 2 H), 1.33 - 1.42 (m, 2 H), 0.87 (t, *J*=7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 165.2, 160.1, 135.6, 129.0, 123.1, 121.8, 112.6, 67.8, 56.1, 55.3, 34.6, 31.6, 21.8, 13.6.

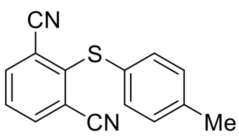
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2957, 2931, 2873, 1665, 1570, 1466, 1426, 1353, 1327, 1286, 1255, 1191, 1176, 1132, 1104, 974, 947, 912, 828, 790, 730, 705, 610.

MS (70 eV, EI) *m/z* (%): 265 (29), 236 (37), 235 (11), 232 (28), 223 (28), 222 (21), 209 (15), 208 (100), 203 (15), 193 (15), 190 (12), 189 (18), 177 (10), 176 (60), 166 (11), 164 (17), 148 (10), 147 (33), 136 (8), 133 (8), 123 (8), 109 (13), 108 (8), 104 (13), 56 (9), 41 (8).

HRMS (EI): *m/z* (M^+) for $C_{14}H_{19}NO_2S$: calcd. 265.1136; found 265.1142.

2.6 REGIOSELECTIVE FUNCTIONALIZATION OF UNSYMMETRICAL ARENE OF TYPE 23

2.6.1 Preparation of 2-(*p*-tolylthio)isophthalonitrile (**27a**)



According to **TP3**, to a solution of the substrate **23** (128 mg, 1.00 mmol) in THF (4 mL) was added TMPLi (1.75 mL, 1.05 mmol, 0.6 M in THF) dropwise at -80 ºC. The reaction mixture was stirred for 0.5 h, following which, Cp_2ZrCl_2 (45 mg, 0.15 mmol, 98%) was added as a solid. Then, after 0.5 h at -80 ºC, *p*-tolyl disulfide (209 mg, 0.85 mmol) was added and after 0.5 h the reaction was allowed to warm to 25 ºC. Dilute HCl (10 mL, 2.0 M) and diethyl ether (2 x 20 mL) were added, phases separated, the organic fraction dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc 8:2) furnishing the title compound **27a** (155 mg, 73%) as a pale yellow solid.

m.p.: 130 - 132 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.88 (d, *J*=7.7 Hz, 2 H), 7.54 (t, *J*=7.7 Hz, 1 H), 7.41 (d, *J*=8.3 Hz, 2 H), 7.16 (d, *J*=8.0 Hz, 2 H), 2.34 (s, 3 H).

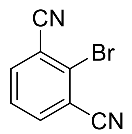
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 143.4, 139.2, 137.5, 132.6, 130.4, 129.2, 129.1, 120.1, 115.7, 21.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3069, 2922, 2852, 2239, 1570, 1490, 1451, 1419, 1397, 1305, 1235, 1210, 1182, 1117, 1103, 1085, 1043, 1014, 946, 732, 700.

MS (70 eV, EI) *m/z* (%): 252 (6), 251 (19), 250 (100), 249 (24), 248 (6), 234 (4), 224 (2), 223 (8), 222 (8), 218 (2), 217 (6), 190 (4), 125 (6), 124 (2), 123 (11), 121 (5), 92 (5), 91 (65), 90 (6), 89 (7), 79 (4), 78 (3), 77 (6), 65 (17), 63 (6), 45 (4).

HRMS (EI): *m/z* (M^+) for $C_{15}H_{10}N_2S$: calcd. 250.0565; found 250.0561.

2.6.2 Preparation of 2-bromoisophthalonitrile (**27b**)



According to **TP3**, to a solution of the substrate **23** (128 mg, 1.00 mmol) in THF (4 mL) was added TMPLi (1.75 ml, 1.05 mmol, 0.6 M in THF) dropwise at -80 ºC. The reaction mixture was stirred for 0.5 h, following which, Cp_2ZrCl_2 (45 mg, 0.15 mmol, 98%) was added as a solid. Then, after 0.5 h at -80 ºC, 1,2-dibromotetrachloroethane (277 mg, 0.85 mmol) was added and after 2 h the reaction was allowed to warm to 25 ºC. Dilute HCl (10 mL, 2.0 M) and diethyl ether (2 x 20 mL) were added, phases separated, the organic fraction dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc 8:2) furnishing the title compound **27b** (131 mg, 75%) as a pale yellow solid.

m.p.: 197 - 198 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.89 (d, *J*=7.8 Hz, 2 H), 7.61 (t, *J*=7.9 Hz, 1 H).

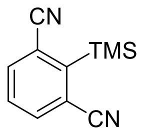
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 137.6, 128.8, 128.4, 118.2, 115.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3101, 3067, 2922, 2233, 1580, 1454, 1413, 1276, 1241, 1110, 1046, 1033, 989, 909, 885, 742.

MS (70 eV, EI) *m/z* (%): 218 (3), 208 (6), 206 (6), 204 (3), 185 (10), 181 (4), 121 (1), 105 (3), 88 (9), 84 (2), 83 (2), 81 (1), 73 (9), 71 (4), 70 (16), 69 (8), 67 (3), 61 (24), 57 (6), 55 (4), 45 (13), 44 (3), 43 (100), 42 (6), 41 (4).

HRMS (EI): *m/z* (M^+) for $C_8H_3BrN_2$: calcd. 205.9480; found 205.9461.

2.6.3 Preparation of 2-(trimethylsilyl)isophthalonitrile (**27c**)



According to **TP3**, to a solution of the substrate **23** (128 mg, 1.00 mmol) in THF (4 mL) was added TMPLi (1.75 mL, 1.05 mmol, 0.6 M in THF) dropwise at -80 ºC. The reaction mixture was stirred for 0.5 h, following which, Cp_2ZrCl_2 (45 mg, 0.15 mmol, 98%) was added as a solid. Then, after 0.5 h at -80 ºC, chlorotrimethylsilane (92 mg, 0.85 mmol) was added and after 2 h the reaction was allowed to warm to 25 ºC Dilute HCl (10 mL, 2.0 M) and diethyl ether (2 x 20 mL) were added, phases separated, the organic fraction dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc 8:2) furnishing the title compound **27c** (113 mg, 66%) as a pale yellow solid.

m.p.: 93 - 96 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.89 (d, *J*=7.7 Hz, 2 H), 7.56 (t, *J*=7.7 Hz, 1 H), 0.62 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 148.6, 137.7, 129.5, 119.4, 118.7, 0.3.

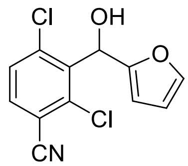
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2956, 2922, 2852, 2228, 1574, 1437, 1412, 1260, 1126, 1047, 761, 715, 694.

MS (70 eV, EI) *m/z* (%): 200 (1), 187 (5), 186 (19), 185 (100), 159 (1), 158 (1), 156 (1), 142 (1), 130 (3), 129 (1), 128 (1), 127 (1), 118 (1), 117 (2), 116 (2), 115 (1), 105 (1), 103 (1), 89 (1), 88 (4), 84 (1), 75 (1), 73 (4), 70 (5), 61 (4), 55 (1), 54 (2), 53 (1), 45 (3), 45 (1), 44 (29), 43 (3).

HRMS (EI): *m/z* (M^+) for $C_{11}H_{12}N_2Si$: calcd. 200.0770; found 200.0751.

2.7 REGIOSELECTIVE FUNCTIONALIZATION OF UNSYMMETRICAL ARENE OF TYPE 24

2.7.1 Preparation of 2,4-dichloro-3-(furan-2-yl(hydroxy)methyl)benzonitrile (**28a**)



According to **TP4**, TMPLi (1.70 mL, 1.00 mmol, 0.6 M in THF) was added dropwise to a solution of 2,4-dichlorobenzonitrile (**24**, 172 mg, 1.00 mmol) in THF (5 mL) at -80 ºC. The reaction mixture was stirred for 20 min and Cp_2ZrCl_2 (104 mg, 0.35 mmol, 98%) was added as a solid. After 0.5 h at -80 ºC, furfural (62 mg, 0.65 mmol) was added at -80 ºC. The mixture was stirred for a further 0.5 h at -80 ºC and saturated aqueous NH_4Cl solution (2 mL) was added. The product was extracted with diethyl ether (2 x 20 mL), followed by drying over $MgSO_4$ and removal of the solvent under reduced pressure. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc 9:1) furnishing the compound **28a** (131 mg, 75%) as a light orange solid.

m.p.: 84 - 86 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.62 (d, *J*=8.3 Hz, 1 H), 7.48 (d, *J*=8.3 Hz, 1 H), 7.40 (s, 1 H), 6.62 (d, *J*=8.3 Hz, 1 H), 6.39 (br. s., 1 H), 6.24 - 6.27 (m, 1 H), 3.36 (d, *J*=9.8 Hz, 1 H).

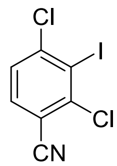
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 151.9, 142.7, 140.1, 137.7, 137.5, 133.5, 129.9, 115.3, 114.0, 110.7, 107.7, 67.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3487, 2925, 2238, 1572, 1553, 1444, 1396, 1319, 1296, 1253, 1220, 1180, 1144, 1100, 1070, 1051, 1000, 959, 923, 911, 884, 798, 768, 712, 665, 636, 614, 564, 556.

MS (70 eV, EI) *m/z* (%): 266 (10), 252 (14), 240 (10), 239 (52), 232 (10), 212 (9), 210 (13), 204 (26), 202 (11), 200 (55), 199 (13), 198 (86), 197 (9), 190 (9), 189 (8), 188 (10), 287 (21), 186 (8), 176 (14), 175 (9), 174 (9), 172 (9), 169 (26), 140 (23), 136 (13), 134 (9), 100 (23), 99 (12), 97 (100), 69 (33), 68 (11), 55 (20), 51 (8), 50 (8), 44 (18), 43 (35).

HRMS (EI): *m/z* for $C_{12}H_7Cl_2NO_2^+$: calcd 265.9776; found 265.9859.

2.7.2 Preparation of 2,4-dichloro-3-iodobenzonitrile (**28b**)



According to **TP4**, TMPLi (1.70 mL, 1.00 mmol, 0.6 M in THF) was added dropwise to a solution of 2,4-dichlorobenzonitrile (**24**, 172 mg, 1.00 mmol) in THF (3 mL) at -80 ºC. The reaction mixture was stirred for 20 min and Cp_2ZrCl_2 (119 mg, 0.40 mmol, 98%) was added as a solid. After 0.5 h at -80 ºC, 1,2-diiodoethane (169 mg, 0.60 mmol) was added at -80 ºC and stirred for 0.5 h. Saturated aqueous NH_4Cl solution (2 mL) was then added. The product was extracted with diethyl ether (2 x 20 mL), followed by drying over $MgSO_4$ and removal of the solvent under reduced pressure. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc 96:4) furnishing the compound **28b** (138 mg, 78%) as a light yellow solid.

m.p.: 119 - 120 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.62 (d, *J*=8.3 Hz, 1 H), 7.47 (d, *J*=8.3 Hz, 1 H).

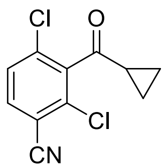
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 146.0, 143.2, 133.4, 127.5, 115.2, 111.8, 105.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2920, 2854, 2235, 1564, 1423, 1406, 1349, 1250, 1219, 1151, 1139, 1117, 848, 748, 714.

MS (70 eV, EI) *m/z* (%): 299 (5), 297 (8), 261 (11), 189 (7), 170 (4), 155 (4), 141 (5), 127 (8), 125 (4), 113 (10), 112 (5), 111 (8), 99 (15), 98 (6), 97 (14), 96 (4), 85 (46), 84 (9), 83 (23), 82 (7), 81 (7), 71 (62), 70 (16), 69 (29), 68 (6), 67 (8), 61 (4), 58 (5), 57 (100), 56 (20), 55 (33), 44 (9), 43 (61), 42 (7), 41 (31).

HRMS (EI): *m/z* (M^+) for $C_7H_2Cl_2IN$: calcd. 296.8609; found 296.8605.

2.7.3 Preparation of 2,4-dichloro-3-(cyclopropanecarbonyl)benzonitrile (**28c**)



According to **TP4**, TMPLi (1.70 mL, 1.00 mmol, 0.6 M in THF) was added dropwise to a solution of 2,4-dichlorobenzonitrile (**24**, 172 mg, 1.00 mmol) in THF (3 mL) at -80 ºC.

The reaction mixture was stirred for 20 min and Cp_2ZrCl_2 (119 mg, 0.40 mmol, 98%) was added as a solid. After 0.5 h at -80 ºC, $Sc(OTf)_3$ (25 mg, 0.05 mmol) followed by cyclopropanecarbonyl chloride (52 mg, 0.50 mmol) were added at -80 ºC. The mixture was stirred for a further 0.5 h at -80 ºC and saturated aqueous NH_4Cl solution (2 mL) was added. The product was extracted with diethyl ether (2 x 20 mL), followed by drying over $MgSO_4$ and removal of the solvent under reduced pressure. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc 96:4) furnishing the compound **28c** (73 mg, 61%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.64 (d, *J*=8.3 Hz, 1 H), 7.47 (d, *J*=8.3 Hz, 1 H), 2.20 (tt, *J*=7.9, 4.2 Hz, 1 H), 1.42 (quin, *J*=3.7 Hz, 2 H), 1.19 - 1.27 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 200.3, 141.7, 135.8, 134.2, 133.7, 128.9, 114.8, 112.9, 22.9, 13.7.

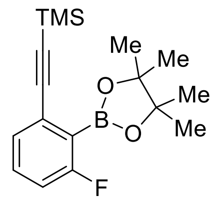
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3083, 2235, 1575, 1553, 1440, 1419, 1391, 1268, 1242, 1196, 1149, 1098, 1065, 986, 844, 781, 733, 680.

MS (70 eV, EI) *m/z* (%): 240 (6), 239 (26), 238 (4), 202 (11), 201 (6), 200 (63), 198 (100), 174 (3), 172 (10), 170 (14), 169 (4), 141 (2), 140 (5), 137 (2), 136 (5), 135 (4), 134 (12), 100 (6), 84 (3), 75 (2), 74 (2), 69 (26), 43 (2), 41 (18).

HRMS (EI): *m/z* (M$^+$) for $C_{11}H_7Cl_2NO$: calcd. 238.9905; found 238.9892.

2.8 REGIOSELECTIVE FUNCTIONALIZATION OF UNSYMMETRICAL ARENE OF TYPE 25

2.8.1 Preparation of ((3-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethynyl)trimethylsilane (**29a**)



According to **TP5**, TMPLi (0.92 mL, 0.55 mmol, 0.6 M in THF) was added dropwise to a solution of the substrate (**25**, 96 mg, 0.50 mmol) in THF (3 mL) at -80 ºC. The reaction mixture was stirred for 0.5 h following which Cp_2ZrCl_2 (39 mg, 98%, 0.13 mmol) was added as a solid. The reaction was stirred for a further 0.5 h at this temperature following by the addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.087 mL, 0.43 mmol). The resulting mixture was then warmed to 25 ºC and dilute HCl

(10 mL, 2.0 M) was added. The product was extracted with diethyl ether (2 x 20 mL), followed by driying the organic fraction over $MgSO_4$ and the removal of the solvent under reduced pressure. The crude product was purified flash column chromatography on silica gel (*i*hexane/EtOAc 3:1) furnishing the title compound **29a** (123 mg, 90%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.29 - 7.23 (m, 2 H), 7.01 - 6.91 (m, 1 H), 1.40 (s, 12 H), 0.23 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 165.2 (d, *J*=244.6 Hz), 131.1 (d, *J*=9.3 Hz), 128.7 (d, *J*=3.1 Hz), 128.2 (d, *J*=10.4 Hz), 115.2 (d, *J*=24.4 Hz), 104.1 (d, *J*=3.4 Hz), 96.0, 84.4, 24.8, -0.1.

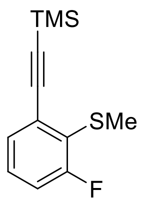
^{19}F NMR (280 MHz, $CDCl_3$) δ/ppm = -104.40 (m).

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3265, 2929, 2156, 1638, 1451, 1247, 992.

MS (70 eV, EI) *m/z* (%): 318 (20), 203 (100), 161 (40).

HRMS (EI): *m/z* (M^+) for $C_{17}H_{24}BFO_2Si$: calcd. 318.1623; found 318.1612.

2.8.2 Preparation of ((3-fluoro-2-(methylthio)phenyl)ethynyl)trimethylsilane (**29b**)



According to **TP5**, TMPLi (1.5 mL, 1.00 mmol, 0.6 M in THF) was added dropwise to a solution of the substrate (**25**, 192 mg, 1.00 mmol) in THF (3 mL) at -80 ºC. The reaction mixture was stirred for 0.5 h and a solution of Cp_2ZrCl_2 (75 mg, 0.25 mmol, 98%) in THF (1.5 mL) was added dropwise. After 0.5 h at -80 ºC, dimethyl disulfide (78 mg, 0.80 mmol) was added and the mixture stirred for a further 0.5 h. The resulting mixture was then warmed to 25 ºC and dilute HCl (10 mL, 2.0 M) was added. The product was extracted with diethyl ether (2 x 20 mL), followed by driying the organic fraction over $MgSO_4$ and the removal of the solvent under reduced pressure. The crude product was purified by flash column chromatography on silica gel (*i*hexane) furnishing the title compound **29b** (166 mg, 87%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.27 - 7.31 (m, 1 H), 7.16 (m, 1 H), 7.03 (ddd, *J*=9.5, 8.2, 1.4 Hz, 1 H), 2.54 (s, 3 H), 0.29 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 162.4 (d, *J* = 245.8 Hz) 129.1 (d, *J* = 2.9 Hz) 128.3 (d, *J* = 9.5 Hz) 128.2 (s) 126.7 (d, *J* = 18 Hz) 116.2 (d, *J* = 24.2 Hz) 102.1 (d, *J* = 4.4 Hz) 101.0, 17.9 (d, *J* = 4.4 Hz) -0.2.

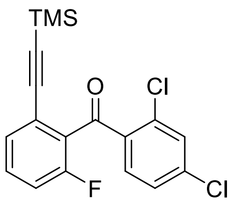
^{19}F NMR (280 MHz, $CDCl_3$) δ/ppm = -116.53 (m).

IR (Diamond-ATR, neat) $\tilde{\nu}$/cm^{-1}: 2959, 2928, 2155, 1591, 1556, 1455, 1421, 1317, 1249, 1161, 1055, 983, 965, 838, 786, 758, 716, 700, 665.

MS (70 eV, EI) *m/z* (%): 239 (11), 238 (26), 224 (16), 223 (29), 178 (14), 147 (15), 128 (11), 127 (11), 107 (13), 97 (16), 91 (50), 85 (13), 83 (18), 82 (21), 81 (17), 73 (19), 70 (21), 69 (37), 61 (26), 55 (27), 44 (30), 43 (100).

HRMS (EI): *m/z* (M^+) for $C_{12}H_{15}FSSi$: calcd. 238.0648; found 238.0648.

2.8.3 Preparation of (2,4-dichlorophenyl)(2-fluoro-6-((trimethylsilyl)ethynyl)-phenyl)methanone (**29c**)



According to **TP5**, TMPLi (0.92 mL, 0.55 mmol, 0.6 M in THF) was added dropwise to a solution of the substrate (**25**, 96 mg, 0.50 mmol) in THF (3 mL) at -80 ºC. The reaction mixture was stirred for 0.5 h, following which Cp_2ZrCl_2 (39 mg, 0.13 mmol, 98%) was added as a solid. After 0.5 h at -80 ºC, 2,4-dichlorobenzoyl chloride (0.056 mL, 0.40 mmol) was added and stirring was continued for a further 5 min. The resulting mixture was then warmed to 25 ºC and dilute HCl (10 mL, 2.0 M) was added. The product was extracted with diethyl ether (2 x 20 mL), followed by driying the organic fraction over $MgSO_4$ and the removal of the solvent under reduced pressure. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc 3:1) furnishing the title compound **29c** (112 mg, 77%) as an colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.57 (d, *J* = 8.4 Hz, 1 H), 7.46 - 7.44 (m, 1H), 7.42 - 7.28 (m, 3 H), 7.12 (m, 1 H), 0.07 - 0.05 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 189.9, 159.7 (d, *J* = 252.4 Hz), 138.7, 135.6, 134.5, 132.9, 131.7 (d, *J* = 9.3 Hz), 130.8, 130.2 (d, *J* = 16.3 Hz), 129.1 (d, *J* = 3.4 Hz), 127.2, 123.1 (d, *J* = 4.3 Hz), 116.6 (d, *J* = 21.8 Hz), 101.9, 100.3 (d, *J* = 3.9 Hz), -0.5.

^{19}F NMR (280 MHz, $CDCl_3$) δ/ppm = -114.46 (m).

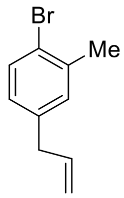
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2960, 1581, 1459, 1247, 994, 926, 798.

MS (70 eV, EI) *m/z* (%): 364 (1), 349 (100), 189 (2).

HRMS (EI): *m/z* (M+1) for $C_{18}H_{15}Cl_2FOSi$: calcd. 364.0253; found 364.0247.

2.9 REGIOSELECTIVE FUNCTIONALIZATION OF UNSYMMETRICAL ARENE OF TYPE 30

2.9.1 Preparation of 4-allyl-1-bromo-2-methylbenzene (**34a**)



According to **TP6**, 1,4-dibromo-2-methylbenzene (**30**, 250 mg, 1.00 mmol) was dissolved in THF (5 mL) and cooled to -80 ºC. *n*BuLi (0.40 mL, 1.00 mmol, 2.5 M in hexanes) was added dropwise and the resulting mixture stirred for a further 0.5 h. Cp_2ZrCl_2 (90 mg, 0.30 mmol, 98%) was added as a solid and reaction mixture stirred for 1.5 h, following which 4-methoxybenzaldehyde (57 mg, 0.42 mmol) was added and the reaction stirred for a further 0.5 h. The reaction mixture was warmed to -40 ºC, CuCN·2LiCl (0.2 mL, 0.2 mmol, 1.0 M in THF) and allylbromide (67 mg, 0.55 mmol) were introduced and stirring continued for 18 h. Saturated aqueous NH_4Cl solution (15 mL), was added, the layers separated, the organic phase extracted with EtOAc (2 x 20 mL), the organic fractions combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane), yielded a colourless oil **34a** (84 mg, 73%) and a pale yellow oil (**33**, 60%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.41 - 7.49 (m, 1 H), 7.08 (s, 1 H), 6.90 (d, *J*=8.3 Hz, 1 H), 5.86 - 6.04 (m, 1 H), 5.05 - 5.15 (m, 2 H), 3.33 (d, *J*=6.6 Hz, 2 H), 2.39 (s, 3 H).

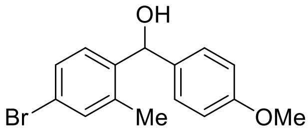
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 139.2, 137.7, 136.9, 132.2, 131.1, 127.6, 122.3, 116.1, 39.5, 22.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3079, 3009, 2978, 2911, 1638, 1474, 1432, 1379, 1229, 1161, 1145, 1026, 992, 912, 872, 812, 750, 703, 667.

MS (70 eV, EI) *m/z* (%): 212 (31), 210 (40), 183 (11), 132 (10), 131 (100), 130 (11), 129 (21), 128 (12), 116 (45), 115 (38), 97 (10), 91 (54), 88 (8), 77 (13), 69 (13), 57 (14), 55 (11), 51 (11), 15 (10), 43 (38).

HRMS (EI): *m/z* (M^+) for $C_{10}H_{11}Br$: calcd. 210.0044; found 210.0035.

(4-Bromo-2-methylphenyl)(4-methoxyphenyl)methanol (33)



^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.49 (d, *J*=8.1 Hz, 1 H), 7.39 (d, *J*=8.3 Hz, 1 H), 7.28 (br. s., 1 H), 7.20 (d, *J*=8.3 Hz, 2 H), 6.86 (d, *J*=8.3 Hz, 2 H), 5.88 (s, 1 H), 3.80 (s, 3 H), 2.16 (s, 3 H), 2.09 (br. s., 1 H).

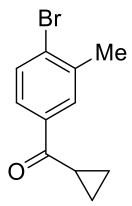
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 159.2, 140.6, 137.3, 134.5, 133.1, 129.0, 128.4, 127.6, 121.0, 113.9, 72.5, 55.2, 19.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3349, 2953, 2931, 2835, 1609, 1591, 1567, 1479, 1462, 1441, 1392, 1302, 1109, 1087, 908, 868, 795, 770, 731, 701, 664.

MS (70 eV, EI) *m/z* (%): 308 (45), 307 (17), 306 (46), 305 (10), 291 (13), 289 (12), 277 (8), 275 (10), 199 (51), 197 (49), 195 (9), 178 (8), 165 (12), 152 (8), 137 (61), 136 (21), 135 (87), 110 (8), 109 (100), 108 (30), 94 (11), 91 (14), 90 (10), 89 (9), 77 (18), 43 (8).

HRMS (EI): *m/z* (M^+) for $C_{15}H_{15}BrO_2$: calcd 306.0255; found 306.0253.

2.9.2 Preparation of (4-bromo-3-methylphenyl)(cyclopropyl)methanone (**34b**)



According to **TP6**, 1,4-dibromo-2-methylbenzene (**30**, 250 mg, 1.00 mmol) was dissolved in THF (5 mL) and cooled to -80 ºC. *n*BuLi (0.42 mL, 1.00 mmol, 2.4 M in hexanes) was added dropwise and the resulting mixture stirred for a further 0.5 h. Cp_2ZrCl_2 (90 mg, 0.30 mmol, 98%) was added as a solid and reaction mixture stirred for 1.5 h, following which 1,2-dibromoethane (75 mg, 0.40 mmol) was added and the mixture stirred for a further 1 h. The mixture was warmed to 25 ºC and $ZnCl_2$ (0.55 mL, 0.55 mmol, 1.0 M in THF) was added. The mixture was stirred for 15 min and then cooled down to -40 ºC. CuCN·2LiCl (0.55 mL, 0.55 mmol, 1.0 M in THF) and cyclopropanecarbonyl chloride (47 mg, 0.45 mmol) were introduced and stirring continued for 18 h. Then the reaction was warmed to 0 ºC and stirred for 48 h. Saturated aqueous NH_4Cl solution (15 mL), was added, the layers separated, the organic phase extracted with EtOAc (2 x 20 mL), the organic fractions combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane/EtOAc 99:1), yielded a light yellow oil **34b** (81 mg, 76%) and recovered starting material (**30**, 66%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.86 (br. s, 1 H), 7.68 (dd, *J*=8.3, 1.9 Hz, 1 H), 7.63 (d, *J*=8.3 Hz, 1 H), 2.57 - 2.67 (m, 1 H), 2.47 (s, 3 H), 1.21 - 1.28 (m, 3 H), 1.01 - 1.09 (m, 2 H).

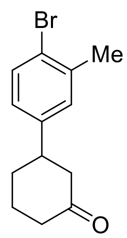
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 199.8, 138.3, 137.0, 132.5, 130.2, 130.1, 126.8, 23.0, 17.1, 11.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$/cm^{-1}: 3009, 2924, 1667, 1590, 1565, 1472, 1440, 1408, 1385, 1365, 1288, 1275, 1230, 1199, 1167, 1133, 1091, 1074, 991, 901, 873, 822, 742, 720, 689, 666.

MS (70 eV, EI) *m/z* (%): 241 (13), 238 (100), 200 (27), 198 (28), 170 (6), 169 (56), 158 (15), 144 (12), 130 (8), 115 (11), 105 (7), 91 (13), 90 (69), 89 (52), 77 (6), 71 (8), 69 (6), 64 (11), 63 (25), 62 (7), 57 (12), 55 (7), 43 (17), 41 (27).

HRMS (EI): *m/z* (M^+) for $C_{11}H_{11}BrO$: calcd. 237.9993; found 237.9963.

2.9.3 Preparation of 3-(4-Bromo-3-methylphenyl)cyclohexanone (**34c**)



According to **TP6**, 1,4-dibromo-2-methylbenzene (**30**, 250 mg, 1.00 mmol) was dissolved in THF (5 mL) and cooled to -80 ºC. *n*BuLi (0.40 mL, 1.00 mmol, 2.5 M in hexanes) was added dropwise and the resulting mixture stirred for a further 0.5 h. Cp_2ZrCl_2 (90 mg, 0.30 mmol, 98%) was added as a solid and reaction mixture stirred for 1.5 h, following which 1,2-dibromoethane (87 mg, 0.45 mmol) was added and the reaction mixture stirred for a further 0.5 h. The reaction was warmed to 25 ºC, and chloro(1,5-cyclooctadiene)rhodium(I) dimer (8 mg, 0.016 mmol), TMSCl (0.15 mL, 1.20 mmol) and cyclohex-2-enone (53 mg, 0.55 mmol) were introduced and stirring was continued for 18 h. Saturated aqueous NH_4Cl solution (15 mL), was added, the layers separated, the organic phase extracted with EtOAc (2 x 20 mL), the organic fractions combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane to *i*hexane/EtOAc 8:2), yielded the title compound **34c** as a colourless oil (110 mg, 75%) and recovered starting material (**30**, 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.47 (d, *J*=8.2 Hz, 1 H), 7.09 (d, *J*=2.4 Hz, 1 H), 6.91 (dd, *J*=8.2, 2.4 Hz, 1 H), 2.95 (dddd, *J*=15.6, 7.7, 4.1, 3.9 Hz, 1 H), 2.29 - 2.63 (m, 6 H), 1.98 - 2.20 (m, 2 H), 1.71 - 1.91 (m, 2 H).

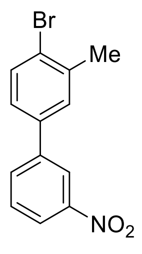
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 210.5, 143.6, 138.0, 132.5, 129.2, 125.5, 122.8, 48.8, 44.1, 41.1, 32.7, 25.4, 22.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$/cm^{-1}: 2935, 2865, 2360, 2340, 1707, 1559, 1477, 1457, 1419, 1379, 1351, 1277, 1250, 1221, 1181, 1078, 1055, 1026, 978, 937, 903, 881, 811, 759, 741, 709, 667.

MS (70 eV, EI) *m/z* (%): 269 (13), 268 (60), 266 (65), 225 (27), 223 (19), 212 (13), 211 (13), 187 (20), 185 (13), 131 (21), 130 (100), 129 (19), 117 (33), 116 (21), 115 (55), 91 (24), 83 (17), 70 (17), 43 (19).

HRMS (EI): *m/z* (M^+) for $C_{13}H_{15}OBr$: calcd. 266.0306; found 266.0303.

2.9.4 Preparation of 4-bromo-3-methyl-3'-nitro-1,1'-biphenyl (**34d**)



According to **TP6**, 1,4-dibromo-2-methylbenzene (**30**, 250 mg, 1.00 mmol) was dissolved in THF (5 mL) and cooled to -80 ºC. *n*BuLi (0.4 mL, 1.00 mmol, 2.5 M in hexanes) was added dropwise and the resulting mixture stirred for a further 0.5 h. Cp_2ZrCl_2 (90 mg, 0.30 mmol, 98%) was added as a solid and reaction mixture stirred for 1.5 h, following which 1,2-dibromoethane (85 mg, 0.45 mmol) was added and the reaction stirred for a further 0.5 h. The reaction was warmed to 25 ºC and Pd(dba)$_2$ (15 mg, 0.026 mmol), P(2-furyl)$_3$ (15 mg, 0.065 mmol) and 1-iodo-3-nitrobenzene (131 mg, 0.53 mmol) in THF (0.5 mL) where introduced and stirring continued for 18 h. Saturated aqueous NH_4Cl solution (15 mL), was added, the layers separated, the organic phase extracted with EtOAc (2 x 20 mL), the organic fractions combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane/EtOAc 95:5), yielded a solid **34d** (122 mg, 79%) and recovered starting material (**30**, 65%).

m.p.: 111 - 112 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.41 (m, 1 H), 8.21 (ddd, *J*=8.2, 2.3, 1.1 Hz, 1 H), 7.88 (ddd, *J*=7.7, 1.9, 1.1 Hz, 1 H), 7.55 - 7.67 (m, 2 H), 7.49 (d, *J*=1.9 Hz, 1 H), 7.30 (dd, *J*=8.3, 2.2 Hz, 1 H), 2.49 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 148.7, 141.8, 138.8, 137.8, 133.1, 132.8, 129.8, 129.4, 125.9, 125.4, 122.2, 121.7, 23.0.

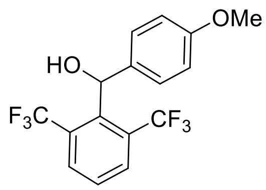
IR (Diamond-ATR, neat) $\tilde{\nu}$/cm^{-1}: 3087, 2920, 1578, 1559, 1521, 1487, 1465, 1381, 1351, 1294, 1100, 1060, 1026, 919, 902, 881, 846, 821, 796, 736, 704, 682.

MS (70 eV, EI) *m/z* (%): 292 (73), 246 (5), 235 (4), 167 (15), 166 (100), 165 (70), 164 (11), 163 (11), 139 (14), 82 (11), 69 (6), 63 (7), 51 (4).

HRMS (EI): *m/z* (M$^+$) for $C_{13}H_{10}O_2N^{81}Br$: calcd. 292.9874; found 292.9875.

2.10 REGIOSELECTIVE FUNCTIONALIZATION OF UNSYMMETRICAL ARENE OF TYPE 35 AT POSITION 2

2.10.1 Preparation of (2,6-bis(trifluoromethyl)phenyl)(4-methoxyphenyl)-methanol (37a)



According to **TP7**, 1,3-bis(trifluoromethyl)benzene (**35**, 214 mg, 1.00 mmol) was dissolved in THF (2.5 mL) and cooled to -40 ºC. *n*BuLi (0.40 mL, 1.00 mmol, 2.5 M in hexanes) was added dropwise and stirred for 1 h. Afterwards, it was cooled to -80 ºC and Cp_2ZrCl_2 (209 mg, 0.70 mmol, 98%) was added as a solid. Stirring was continued for a further 1.5 h, after which *p*-methoxybenzaldehyde (41 mg, 0.30 mmol) was added and the mixture stirred for a further 1 h. Saturated aqueous NH_4Cl solution (15 mL), was introduced, the layers separated, the organic phase extracted with EtOAc (2 x 20 mL), the organic fractions combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane/EtOAc 9:1), yielded a pale yellow oil of the title compound **37a** (85 mg, 81%).

^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.01 (d, *J*=8.0 Hz, 2 H), 7.64 (t, *J*=8.0 Hz, 1 H), 7.04 (d, *J*=8.5 Hz, 2 H), 6.84 (d, *J*=8.8 Hz, 2 H), 6.51 (d, *J*=7.1 Hz, 1 H), 3.80 (s, 3 H), 2.73 (d, *J*=7.1 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 158.7, 141.1, 134.5, 130.9 - 131.15 (m), 131.0 (q, *J*=30.9 Hz), 128.5, 127.0, 123.8 (q, *J*=274.3 Hz), 113.4, 70.5, 55.2.

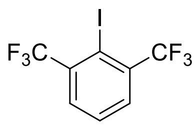
^{19}F NMR (280 MHz, $CDCl_3$) δ/ppm = -56.15.

IR (Diamond-ATR, neat) $\tilde{\nu}$/cm^{-1}: 3471, 1985, 1598, 1548, 1512, 1462, 1426, 1328, 1287, 1248, 1215, 1193, 1158, 1118, 1086, 1064, 1029, 937, 858, 819, 800, 778, 743, 702, 679, 658.

MS (70 eV, EI) *m/z* (%): 351 (14), 350 (67), 349 (14), 319 (12), 309 (28), 279 (30), 241 (25), 213 (14), 137 (100), 135 (10), 109 (72), 77 (13).

HRMS (EI): *m/z* (M$^+$) for $C_{16}H_{12}O_2F_6$: calcd. 350.0741; found 350.0720.

2.10.2 Preparation of 1-iodo-2,6-bis(trifluoromethyl)benzene (**37b**)



According to **TP7**, 1,3-bis(trifluoromethyl)benzene (**35**, 214 mg, 1.00 mmol) was dissolved in THF (2.5 mL) and cooled to -40 ºC. *n*BuLi (0.40 mL, 1.00 mmol, 2.5 M in hexanes) was added dropwise and stirred for 1 h. Afterwards, it was cooled to -80 ºC and Cp_2ZrCl_2 (209 mg, 0.70 mmol, 98%) was added as a solid. Stirring was continued for a further 1.5 h, after which 1,2-diiodoethane (85 mg, 0.30 mmol) was added and the mixture stirred for a further 1 h. Saturated aqueous NH_4Cl solution (15 mL), was introduced, the layers separated, the organic phase extracted with EtOAc (2 x 20 mL), the organic fractions combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (pentane) yielded a pale yellow solid of the title compound **37b** (51 mg, 50%).

m.p.: 72 - 74 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.83 (d, *J*=7.83 Hz, 2 H), 7.59 (t, *J*=8.10 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 136.7 (q, *J*=30.57 Hz), 130.5 (q, *J*=5.98 Hz), 128.3, 122.7 (q, *J*=275.40 Hz), 89.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -61.91.

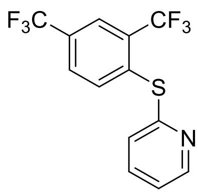
IR (Diamond-ATR, neat) $\tilde{\nu}$/cm^{-1}: 2959, 2930, 2873, 1584, 1465, 1416, 1379, 1328, 1289, 1202, 1186, 1070, 1016, 986, 911, 822, 806, 757, 723, 671.

MS (70 eV, EI) *m/z* (%): 385 (15), 340 (58), 229 (9), 215 (11), 213 (36), 194 (21), 163 (15), 159 (8), 113 (9), 97 (13), 95 (10), 85 (17), 83 (16), 81 (11), 71 (29), 70 (11), 69 (27), 57 (67), 56 (12), 55 (28), 45 (8), 44 (100), 43 (60), 40 (38).

HRMS (EI): *m/z* (M^+) for $C_8H_3F_6I$: calcd. 339.9184; found 339.9175.

2.11 REGIOSELECTIVE FUNCTIONALIZATION OF UNSYMMETRICAL ARENE OF TYPE 35 AT POSITON 4

2.11.1 Preparation of 2-((2,4-bis(trifluoromethyl)phenyl)thio)pyridine (**38a**)



According to **TP8**, 1,3-bis(trifluoromethyl)benzene (**35**, 214 mg, 1.00 mmol) was dissolved in diethyl ether (2.5 mL), cooled to -40 ºC and *t*BuLi (0.61 mL, 1.00 mmol, 1.6 M in hexanes) was added dropwise. The reaction mixture was held at this temperature for 18 h, after which time it was cooled to -80 ºC and Cp_2ZrCl_2 (95 mg, 0.32 mmol, 98%) was added as a solid. Stirring was continued for a further 1.5 h, after which 1,2-di(pyridin-2-yl)disulfane (88 mg, 0.37 mmol) in THF (1.5 mL) was added and the reaction stirred for a further 1 h. Saturated aqueous NH_4Cl solution (15 mL), was introduced, the layers separated, the organic phase extracted with EtOAc (2 x 20 mL), the organic fractions combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane/EtOAc 92:8), yielded a pale yellow oil of the title compound **38a** (81 mg, 68%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.45 - 8.50 (m, 1 H), 8.01 (s, 1 H), 7.75 (s, 2 H), 7.61 (td, *J*=7.9, 1.9 Hz, 1 H), 7.22 (d, *J*=7.9 Hz, 1 H), 7.12 - 7.19 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 157.1, 150.3, 137.3, 137.0, 136.8, 132.4 (q, *J* = 31.2 Hz), 130.3 (q, *J* = 33.7 Hz), 128.7 (m), 124.5, 124.2 (m), 123.2 (q, *J* = 272.5 Hz), 122.8 (q, *J* = 274.2 Hz) 121.7.

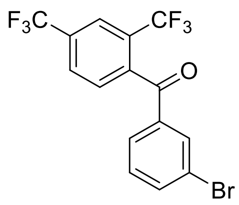
^{19}F NMR (280 MHz, $CDCl_3$) δ/ppm = -61.05, -63.05.

IR (Diamond-ATR, neat) $\tilde{\nu}$/cm^{-1}: 1619, 1574, 1592, 1480, 1451, 1419, 1341, 1294, 1275, 1259, 1173, 1125, 1079, 1040, 987, 911, 844, 760, 751, 721, 706, 663.

MS (70 eV, EI) *m/z* (%): 322 (24), 304 (9), 255 (10), 254 (100), 149 (6), 78 (7), 41 (5).

HRMS (EI): *m/z* (M^+) for $C_{13}H_6NF_6S$: calcd. 322.0203; found 322.0117.

2.11.2 Preparation of (2,4-bis(trifluoromethyl)phenyl)(3-bromophenyl)-methanone (**38b**)



According to **TP8**, 1,3-bis(trifluoromethyl)benzene (**35**, 214 mg, 1.00 mmol) was dissolved in diethyl ether (2.5 mL), cooled to -40 ºC and *t*BuLi (0.61 mL, 1.6 M in hexanes, 1.00 mmol) was added dropwise. The reaction mixture was held at this temperature for 18 h, after which time it was cooled to -80 ºC and Cp_2ZrCl_2 (90 mg, 0.30 mmol, 98%) was added as a solid. Stirring was continued for a further 1 h, after which 3-bromobenzoyl chloride (99 mg, 0.45 mmol) was added and the reaction stirred for a further 1 h at -80 ºC. Saturated aqueous NH_4Cl solution (15 mL), was introduced, the layers separated, the organic phase extracted with EtOAc (2 x 20 mL), the organic fractions combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane/EtOAc 95:5), yielded a pale yellow oil of the title compound **38b** (123 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.07 (s, 1 H), 7.91 - 7.97 (m, 2 H), 7.78 (ddd, *J*=7.1, 1.5, 1.4 Hz, 1 H), 7.65 (dt, *J*=8.0, 1.4 Hz, 1 H), 7.55 (d, *J*=8.0 Hz, 1 H), 7.37 (t, *J*=8.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 192.6, 141.0, 137.4, 137.2, 132.7, 132.6 (q, *J* = 33.9 Hz), 130.3, 129.3 (q, *J* = 33.4 Hz), 128.8, 128.63 (m), 124.1 123.2, 122.9 (q, *J* = 272.9 Hz), 122.7 (q, *J* = 274.6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -58.37, -63.14.

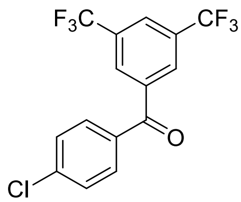
IR (Diamond-ATR, neat) $\tilde{\nu}$/cm^{-1}: 1681, 1627, 1582, 1567, 1503, 1468, 1424, 1343, 1302, 1269, 1175, 1126, 1079, 1059, 1000, 952, 942, 912, 852, 840, 808, 773, 752, 735, 686, 682, 671, 659.

MS (70 eV, EI) *m/z* (%): 399 (5), 398 (27), 396 (29), 221 (2), 214 (30), 185 (100), 183 (99), 157 (20), 155 (21), 76 (13), 50 (4).

HRMS (EI): *m/z* (M$^+$) for $C_{15}H_7O_{Br}F_6$: calcd. 395.9584; found 395.9602.

2.12 REGIOSELECTIVE FUNCTIONALIZATION OF UNSYMMETRICAL ARENE OF TYPE 35 AT POSITION 5

2.12.1 Preparation of (3,5-bis(trifluoromethyl)phenyl)(4-chlorophenyl)methanone (**39a**)



According to **TP8**, 1,3-bis(trifluoromethyl)benzene (**35**, 214 mg, 1.00 mmol) was dissolved in diethyl ether (2.5 mL), cooled to -40 ºC and *t*BuLi (0.61 mL, 1.6 M in hexanes, 1.00 mmol) was added dropwise. The reaction mixture was held at this temperature for 18 h, after which time it was cooled to -80 ºC and Cp_2ZrCl_2 (77 mg, 0.26 mmol, 98%) was added as a solid. Stirring was continued for a further 1.5 h, after which *p*-methoxybenzaldehyde (69 mg, 0.50 mmol) was added and the mixture stirred for a further 1 h. CuCN·2LiCl (0.1 mL, 0.1 mmol, 1.0 M in THF) was then introduced followed by 4-chlorobenzoylchloride (79 mg, 0.45 mmol) and the reaction warmed to -30 ºC and stirring was continued for a further 18 h. Saturated aqueous NH_4Cl solution (15 mL), was introduced, the layers separated, the organic phase extracted with EtOAc

(2 x 20 mL), the organic fractions combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane/EtOAc 9:1), yielded a pale yellow oil of the title compound **39a** (145 mg, 92%) and the alcohol **78** (98, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.22 (s, 2 H), 8.12 (s, 1 H), 7.71 - 7.84 (m, 2 H), 7.48 - 7.62 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 192.3, 140.3, 139.1, 134.2, 132. 2 (q, *J* = 34.1 Hz) 131.3, 129.6 (m), 129.3, 125.8 (spt, *J* = 3.65 Hz) 122.8 (q, *J* = 272.9 Hz).

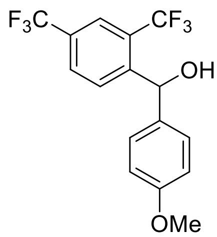
^{19}F NMR (280 MHz, $CDCl_3$) δ/ppm = -62.99.

IR (Diamond-ATR, neat) $\tilde{\nu}$/cm^{-1}: 1669, 1614, 1586, 1488, 1402, 1379, 1274, 1255, 1175, 1130, 1109, 1092, 1015, 977, 909, 850, 801, 759, 734, 705, 695, 680.

MS (70 eV, EI) *m/z* (%): 354 (11), 353 (5), 352 (31), 333 (9), 241 (18), 213 (18), 139 (100), 111 (21), 75 (10).

HRMS (EI): *m/z* (M^+) for $C_{15}H_7OF_6Cl$: calcd. 352.0090; found 352.0085.

(2,4-Bis(trifluoromethyl)phenyl)(4-methoxyphenyl)methanol (78)



^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.93 (d, *J*=8.31 Hz, 1 H), 8.89 (s, 1 H), 8.82 (d, *J*=8.07 Hz, 1 H), 8.23 (d, *J*=8.56 Hz, 2 H), 7.86 (d, *J*=8.31 Hz, 2 H), 4.78 (s, 3 H), 3.40 (br. s., 1 H).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 159.5, 146.7, 134.3, 130.3 (q, *J*=33.4 Hz), 130.3, 129.2 (m), 128.3 (q, *J*=31.4 Hz), 128.1, 123.6 (q, *J*=272.4 Hz), 123.4 (q, *J*=274.6 Hz), 123.1 (m), 114.2, 70.68 (m), 55.5.

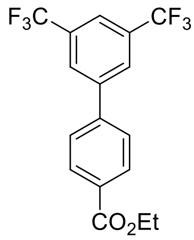
^{19}F NMR (282 MHz, $CDCl_3$) δ/ppm = -58.35, -62.94.

IR (Diamond-ATR, neat) $\tilde{\nu}$/cm^{-1}: 3365, 2959, 1628, 1612, 1586, 1512, 1464, 1443, 1345, 1300, 1273, 1251, 1166, 1083, 1057, 1031, 910, 870, 833, 789, 748, 706, 681, 670, 660.

MS (70 eV, EI) *m/z* (%): 351 (11), 350 (78), 333 (7), 329 (9), 311 (8), 309 (7), 299 (12), 279 (6), 241 (11), 213 (10), 195 (9), 138 (12), 137 (49), 135 (10), 110 (6), 109 (100), 94 (16), 92 (6), 77 (22).

HRMS (EI): *m/z* (M^+) for $C_{16}H_{12}F_6O_2$: calcd. 350.0741; found 350.0734.

2.12.2 Preparation of ethyl 3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylate (**39b**)



According to **TP8**, 1,3-bis(trifluoromethyl)benzene (**35**, 214 mg, 1.00 mmol) was dissolved in diethyl ether (2.5 mL), cooled to -40 ºC and *t*BuLi (0.61 mL, 1.6 M in hexanes, 1.00 mmol) was added dropwise. The reaction was held at this temperature for 18 h, after which time it was cooled to -80 ºC and Cp_2ZrCl_2 (77 mg, 0.26 mmol, 98%) was added as a solid. Stirring was continued for a further 1.5 h, after which *p*-methoxybenzaldehyde (68 mg, 0.50 mmol) was added and the reaction stirred for a further 1 h. Then $ZnCl_2$ (0.5 mL, 0.5 mmol, 1.0 M in THF) was added and after 5 min $Pd(dba)_2$ (10 mg, 0.017 mmol), P(2-furyl)$_3$ (10 mg, 0.043 mmol) and ethyl 4-iodobenzoate (124 mg, 0.45 mmol) were introduced, the reaction allowed to warm to 25 ºC and stirring was continued for 18 h. Saturated aqueous NH_4Cl solution (15 mL), was introduced, the layers separated, the organic phase extracted with EtOAc (2 x 20 mL), the organic fractions combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (*i*hexane/EtOAc 95:5), yielded a white solid of the title compound **39b** (129 mg, 79%) and the alcohol **78** (105 mg, 75%).

m.p.: 86 - 88 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.15 - 8.22 (m, 2 H), 8.05 (s, 2 H), 7.92 (s, 1 H), 7.66 - 7.72 (m, 2 H), 4.44 (q, *J*=7.1 Hz, 2 H), 1.44 (t, *J*=7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 166.0, 142.3, 142.2, 132.4 (q, *J* = 33.4 Hz), 130.8, 130.5, 127.4 (m), 127.2, 123.0 (q, *J* = 272.9 Hz), 121.7 (spt, *J* = 3.9 Hz), 61.3, 14.3.

^{19}F NMR (280 MHz, $CDCl_3$) δ/ppm = -62.92.

IR (Diamond-ATR, neat) $\tilde{\nu}$/cm^{-1}: 2989, 1714, 1611, 1514, 1466, 1453, 1402, 1382, 1370, 1309, 1277, 1257, 1170, 1126, 1105, 1054, 1018, 919, 874, 859, 846, 828, 773, 739, 727, 704, 682, 668.

MS (70 eV, EI) *m/z* (%): 364 (4), 365 (19), 269 (39), 220 (27), 219 (15), 201 (7), 170 (4), 149 (6), 125 (7), 124 (6), 45 (5).

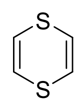
HRMS (EI): *m/z* (M^+) for $C_{16}H_7O_2F_2$: calcd. 362.0741; found 362.0746.

3. SELECTIVE METALATIONS OF 1,4-DITHIINS AND CONDENSED ANALOGUES USING TMP-MAGNESIUM AND -ZINC BASES

3.1 PREPARATION OF STARTING MATERIALS

43 is commercially available.

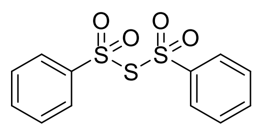
3.1.1 Preparation of 1,4-dithiin (**40**)



According to the literature,[92] thionyl chloride (18.5 g, 11.3 mL, 156 mmol) was added to a solution of 1,4-dithiane-2,5-diol (**42**, 6.77 g, 44.4 mmol) in dry DMF (250 mL) at 0 ºC. After the addition, the reaction mixture was stirred at 25 ºC for 2 h. The product which co-distills with DMF, was distilled under reduced pressure (100 ºC, 270 mbar). After reducing half of the volume, another dry DMF (100 mL) was added to the reaction flask and the distillation was continued until a black residue was left. The distilled DMF was extracted with water (150 mL) and Et_2O (400 mL). The organic phase was washed with water (3 x 150 mL), sat. aq. $NaHCO_3$ solution (2 x 100 mL) and sat. aq. NaCl solution (100 mL). The organic phase was dried over anhydrous $MgSO_4$ and, after filtration, the solvent was evaporated *in vacuo*. 1,4-dithiin (**40**) was obtained as yellow liquid (4.18 g, 81%) and was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.18 (s, 4H).

3.1.2 Preparation of bis(phenylsulfonyl)sulfide (**79**)



According to the literature,[117] sodium benzenesulfinate (41 g, 250 mmol) was suspended in dry Et_2O (300 mL) and a solution of sulfur dichloride (13 g, 125 mmol) in dry Et_2O (50 mL) was added dropwise. The mixture was stirred for 2 h at 40 ºC. Afterwards water was added and the insoluble product was filtered off. After

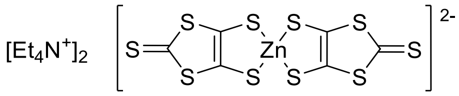
[117] a) F. Allared, J. Hellberg, T. Remonen, *Tetrahedron Lett.* 2002, **43**, 1553; b) C. Dostert, C. Wanstrath, W. Frank, T. J. J. Müller, *Chem. Commun.* **2012**, *48*, 7271.

recrystallization from acetone, bis(phenylsulfonyl)sulfide was obtained as white crystals (24 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.02 (d, *J*=7.6 Hz, 4 H), 7.71 (t, *J*=7.3 Hz, 2 H), 7.59 (t, *J*=7.8 Hz, 4 H).

3.1.3 Preparation of 1,4,5,8-tetrathianaphthalene (**41**)

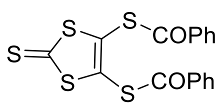
3.1.3.1 Synthesis of tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithiol) zincate (**53**)



According to the literature,[95] an oven-dried 1L round-bottomed flask, equipped with a mechanical stirrer, a 250-mL pressure-equalizing dropping funnel, and a gas inlet tube, was connected to nitrogen. The flask was charged with sodium (4.6 g, 200 mmol) and placed in an ice-water bath. Carbon disulfide (36 mL, 600 mmol) was introduced into the flask through the dropping funnel, after which 60 mL of DMF were added dropwise over 45 min. After the addition, the reaction mixture was allowed to warm to 25 ºC and stir overnight. Methanol (20 mL) was added slowly through the dropping funnel to the reaction mixture in an ice bath. Afterwards, a mixture of methanol (80 mL) and deionized water (100 mL), was then added rapidly through the dropping funnel. A solution of $ZnCl_2$ (4.1 g, 30 mmol) in concentrated aqueous ammonium hydroxide (150 mL) and methanol (100 mL) was then added through the dropping funnel. A solution of tetraethylammonium bromide (10.5 g, 50 mmol) in water (50 mL) was added dropwise *via* the dropping funnel with vigorous stirring over at least 45 min, and the solution was stirred 12 h. The precipitated was collected by suction on a Büchner funnel and washed with water (100 mL), isopropanol (80 mL) and diethyl ether (40 mL). The product was then dried in a desiccator under vacuum affording **53** as a red powder (15 g, 84%).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 209.4, 135.1, 52.0, 7.1.

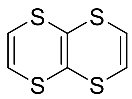
3.1.3.2 Synthesis of 4,5-dibenzoylthio-1,3-dithiole-1-thione (**54**).



According to the literature,[95] tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithio) zincate (**53**, 16 g, 22.0 mmol) was dissolved in acetone (400 mL) and benzoyl chloride (48.4 g, 345 mmol) was added dropwise. The reaction mixture was stirred for 12 h and the resulting yellow-light brown precipitate was collected by suction and washed with water (500 mL) and acetone (300 mL). This crude material was dissolved in chloroform (350 mL), Norit (0.5 g) was added and the mixture was heated under reflux for 10 min. The mixture was filtered while still hot, and washed with chloroform. The combined chloroform solutions were concentrated to 150 mL and the resulting mixture was warmed and methanol (50 mL) was added portionwise with stirring. The solution was then left overnight in the refrigerator. The resulting crystalline precipitate was collected by suction and air-dried, affording **54** (8.5 g, 48%).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 212.5, 185.6, 135.0, 134.9, 133.8, 129.3, 128.2.

3.1.3.3 Synthesis of 1,4,5,8-tetrathianaphthalene (**41**).



According to the literature,[90b] sodium (3.0 g, 130 mmol) was dissolved in ethanol (50 mL) under N_2 in a 3-necked 1L round bottom flask equiped with a stir bar and two 250 mL addition funnels. Then, THF (165 mL) was added and the solution was refluxed. At that moment, 4,5-bis(benzoylthio)-1,3-dithiole-1-thione (**54**, 5.3 g, 13.0 mmol in 80 mL of THF) and *cis*-1,2-dichloroethylene (2.6 g, 27.0 mmol in 80 mL of THF) were added simultaneously dropwise over 1 h to the sodium ethoxide solution. The reaction mixture was refluxed for 12 h. Water (130 mL) was added to dissolve the precipitate and then, the THF was removed under reduced pressure. The solid was collected and washed with water. The solid was purified by flash column chromatography on silica gel (*i*hexane) yielding **41** as yellow solid (1.6 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.46 (s, 4 H).

3.2 TYPICAL PROCEDURES

Typical Procedure 1 for the magnesiation of 1,4-dithiin (40) with TMPMgCl·LiCl (2) (TP1):

A dry and argon flushed Schlenk-flask was charged with a solution of 1,4-dithiin (**40**, 1.0 equiv) in dry THF (0.5 M). TMPMgCl·LiCl (**2**, 1.1 equiv) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in dry THF.

Typical Procedure 2 for the magnesiation or zincation of monofunctionalized 1,4-dithiin derivatives (44) withTMPMgCl·LiCl (2) or TMPZnCl·LiCl (3) (TP2):

A dry and argon flushed Schlenk-flask was charged with a solution of the corresponding monofunctionalized 1,4-dithiin derivative (**44**, 1.0 equiv) in dry THF (0.5 M). TMPMgCl·LiCl (**2**, 1.05 - 1.1 equiv) or TMPZnCl·LiCl (**3**, 1.1 equiv) was added dropwise at the indicated temperature and the reaction mixture was stirred for 0.5 h. The completion of the reaction was checked by TLC analysis of reaction aliquots quenched with iodine in dry THF.

Typical Procedure 3 for the zincation of trifunctionalized 1,4-dithiin (50b) with TMPZnCl·LiCl (3) (TP3):

A dry and argon flushed Schlenk-flask was charged with a solution of the corresponding monofunctionalized trifunctionalized 1,4-dithiin derivative (**50b**, 1.0 equiv) in dry THF (0.17 M). TMPZnCl·LiCl (**3**, 1.05 equiv) was added dropwise at -78 ºC and the reaction mixture was stirred for 10 min. The completion of the reaction was checked by TLC analysis of reaction aliquots quenched with iodine in dry THF.

Typical Procedure 4 for the magnesiation of 1,4,5,8-tetrathianaphthalene (41) with TMPMgCl·LiCl (2) (TP4):

A dry and argon flushed Schlenk-flask was charged with a solution of 1,4,5,8-tetrathianaphthalene (**41**, 1.0 equiv) in dry THF (0.13 M). TMPMgCl·LiCl (**2**, 1.2 equiv) was added dropwise at -78 ºC and the reaction mixture was stirred for 10 min. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in dry THF.

Typical Procedure 5 for the zincation of monofunctionalized 1,4,5,8-tetrathianaphthalene derivatives (59) with TMPZnCl·LiCl (3) (TP5):

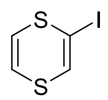
A dry and argon flushed Schlenk-flask was charged with a solution of the corresponding monofunctionalized 1,4,5,8-tetrathianaphthalene derivative (**59**, 1.0 equiv) in dry THF (0.13 M). TMPZnCl·LiCl (**3**, 1.1 equiv) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. The completion of the reaction was checked by TLC analysis of reaction aliquots quenched with iodine in dry THF.

Typical Procedure 6 for the zincation of 1,4,5,6,9,10-hexathiaanthracene (63) with TMPZnCl·LiCl (3) (TP6):

A dry and argon flushed Schlenk-flask was charged with a solution of 1,4,5,6,9,10-hexathiaanthracene (**63**, 1.0 equiv) in dry THF (0.03 M). TMPZnCl·LiCl (**3**, 1.1 equiv) was added dropwise at -40 ºC and the reaction mixture was stirred for 2 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with iodine in dry THF.

3.3 PREPARATION OF MONOFUNCTIONALIZED 1,4-DITHIIN DERIVATIVES

3.3.1 Preparation of 2-iodo-1,4-dithiine (**44a**)



According to **TP1**, 1,4-dithiin (**40**, 116 mg, 1.00 mmol) was dissolved in dry THF (2 mL). TMPMgCl·LiCl (**2**, 0.99 mL, 1.10 mmol, 1.11 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. The freshly prepared magnesium reagent was added to a solution of iodine (177 mg, 0.70 mmol) in dry THF (1 mL) at -78 ºC. The resulting solution was stirred at this temperature for 1 h and was then quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with Et_2O (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **44a** as yellow liquid (127 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.52 - 6.46 (m, 2H), 6.24 (d, *J* = 6.6, 1H).

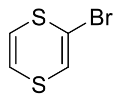
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 125.9, 122.7, 121.7, 72.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3025, 2921, 1678, 1598, 1554, 1534, 1513, 1469, 1273, 1217, 1134, 885, 839, 794, 768, 732, 668, 566.

MS (70 eV, EI) *m/z* (%): 242 (69), 115 (100), 89 (21), 71 (78), 57 (30), 45 (56).

HRMS (EI): *m/z* (M$^+$) for $C_4H_3IS_2$: calcd. 241.8721; found 241.8723.

3.3.2 Preparation of 2-bromo-1,4-dithiine (**44b**)



According to **TP1**, 1,4-dithiin (**40**, 116 mg, 5.00 mmol) was dissolved in dry THF (10 mL). TMPMgCl·LiCl (**2**, 4.95 mL, 5.50 mmol, 1.11 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. The freshly prepared magnesium reagent was added to a solution of 1,2-dibromotetrachloroethane (1.14 g, 3.50 mmol) in dry THF (5 mL) at -78 ºC. The resulting solution was stirred at this temperature for 2 h and was then quenched with sat. aq. NH_4Cl solution (10 mL), extracted with Et_2O (3 x 80 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **44b** as yellow liquid (529 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.40 (d, *J*=6.4 Hz, 1 H), 6.27 - 6.33 (m, 2 H).

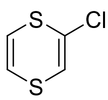
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 126.0, 122.8, 121.9, 73.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3031, 1563, 1555, 1524, 1503, 1493, 1468, 1446, 1413, 1322, 1275, 1218, 1188, 1135, 1091, 1070, 1031, 1011, 919, 886, 860, 827, 799, 773, 752, 701, 668.

MS (70 eV, EI) *m/z* (%): 196 (53), 194 (47), 115 (100), 71 (41), 57 (10), 45 (16).

HRMS (EI): *m/z* (M$^+$) for $C_4H_3BrS_2$: calcd. 193.8860; found 193.8840.

3.3.3 Preparation of 2-chloro-1,4-dithiine (**44c**)



According to **TP1**, 1,4-dithiin (**40**, 813 mg, 7.00 mmol) was dissolved in dry THF (14 mL). TMPMgCl·LiCl (**2**, 6.94 mL, 7.70 mmol, 1.11 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. The freshly prepared magnesium reagent was added to a solution of benzenesulfonyl chloride (865 mg, 4.90 mmol) in dry THF (5 mL) at -78 ºC. The resulting solution was stirred at this temperature for 2 h and was then quenched with sat. aq. NH_4Cl solution (10 mL), extracted with Et_2O (3 x 80 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **44c** as yellow liquid (413 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.37 (d, *J*=6.6 Hz, 1 H), 6.33 (d, *J*=6.6 Hz, 1 H), 6.16 (s, 1 H).

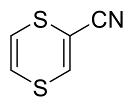
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 123.0, 122.6, 122.3, 117.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3035, 2922, 2179, 1601, 1579, 1548, 1528, 1455, 1402, 1278, 1206, 1136, 1065, 971, 928, 896, 818, 770, 668.

MS (70 eV, EI) *m/z* (%): 152 (21), 150 (52), 115 (87), 105 (13), 89 (14), 88 (17), 79 (12), 71 (45), 58 (23), 57 (52), 45 (100).

HRMS (EI): *m/z* (M$^+$) for $C_4H_3ClS_2$: calcd. 149.9365; found 149.9355.

3.3.4 Preparation of 1,4-dithiine-2-carbonitrile (**44d**)



According to **TP1**, 1,4-dithiin (**40**, 116 mg, 1.00 mmol) was dissolved in dry THF (2 mL). TMPMgCl·LiCl (**2**, 0.99 mL, 1.10 mmol, 1.11 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. The freshly prepared magnesium reagent was added to a solution of *p*-toluenesulfonyl cyanide (127 mg, 0.70 mmol) in dry THF (2 mL) at -60 ºC. The resulting solution was stirred at this temperature for 2 h and was then quenched with sat. aq. NH_4Cl solution (5 mL), extracted with Et_2O (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/Et_2O, 95:5) yielding **44d** as orange oil (59 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.13 (s, 1 H), 6.32 (d, *J*=6.6 Hz, 1 H), 6.28 (d, *J*=6.6 Hz, 1 H).

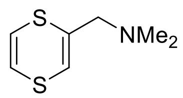
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 140.1, 122.0, 121.1, 114.5, 105.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3034, 2924, 2217, 1654, 1594, 1558, 1525, 1447, 1313, 1281, 1240, 1176, 1140, 1084, 1054, 999, 958, 932, 892, 851, 805, 785, 674, 661.

MS (70 eV, EI) *m/z* (%): 141 (100), 114 (19), 96 (13), 71 (27), 45 (33).

HRMS (EI): ***m/z*** **(M^+) for $C_5H_3NS_2$**: calcd. 140.9707; found 140.9694.

3.3.5 Preparation of 1-(1,4-dithiin-2-yl)-*N*,*N*-dimethylmethanamine (**44e**)



A dry and argon-flushed Schlenk-flask was charged with *N,N,N',N'*-tetramethyl-methanediamine (112 mg, 1.10 mmol) and anydrous CH_2Cl_2 (1.1 mL). Trifluoroacetic anhydride (231 mg, 1.10 mmol) was added dropwise and the solution was stirred for 15 min at 0 ºC.[93] In a second dry and argon-flushed Schlenk flask, according to **TP1**, 1,4-dithiin (**40**, 116 mg, 1.00 mmol) was dissolved in dry THF (2 mL). TMPMgCl·LiCl (**2**, 1.04 mL, 1.10 mmol, 1.06 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. Then, the previously prepared methylene(dimethyl)-iminium trifluoroacetate was added at -78 ºC to the magnesiated 1,4-dithiin solution. The reaction mixture was stirred for 3 h warming to 25 ºC. The crude mixture was quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with sat. aq. NaCl and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 8:2) yielding **44e** as orange oil (100 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.26 (d, *J*=7.0 Hz, 1 H), 6.24 (d, *J*=7.0 Hz, 1 H), 6.02 (s, 1 H), 3.10 (s, 2 H), 2.24 (s, 6 H).

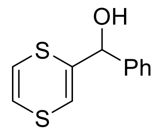
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 135.5, 122.3, 121.9, 117.3, 64.5, 45.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3025, 2973, 2942, 2853, 2817, 2771, 1538, 1464, 1450, 1351, 1262, 1225, 1174, 1147, 1091, 1042, 1023, 982, 890, 859, 834, 809, 782, 731, 668.

MS (70 eV, EI) *m/z* (%): 173 (23), 130 (6), 97 (8), 58 (100), 45 (11), 44 (6), 43 (18), 42 (11), 41 (7).

HRMS (EI): *m/z* (M^+) for $C_7H_{11}NS_2$: calcd. 173.0333; found 173.0322.

3.3.6 Preparation of (1,4-dithiin-2-yl)(phenyl)methanol (**44f**)



According to **TP1**, 1,4-dithiin (**40**, 58 mg, 0.50 mmol) was dissolved in dry THF (1 mL). TMPMgCl·LiCl (**2**, 0.50 mL, 0.55 mmol, 1.11 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. The freshly prepared magnesium reagent was added to a solution of benzaldehyde (37 mg, 0.35 mmol) in dry THF (1 mL) at -78 ºC. The resulting solution was stirred at this temperature for 2 h and was then quenched with sat. aq. NH_4Cl solution (5 mL), extracted with Et_2O (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 7:1) yielding **44f** as yellowish solid (75 mg, 97%).

m.p.: 64.9 - 68.3 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.31 - 7.42 (m, 6 H), 6.34 (d, *J*=6.8 Hz, 1 H), 6.28 (s, 1 H), 6.20 (d, *J*=6.8 Hz, 1 H), 5.36 (s, 1 H), 2.61 (br. s., 1 H).

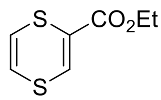
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 140.3, 139.6, 128.5, 128.3, 126.6, 123.7, 121.9, 118.3, 75.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3791, 3271, 3029, 3016, 2894, 2666, 1957, 1887, 1728, 1711, 1598, 1587, 1573, 1564, 1537, 1492, 1461, 1446, 1392, 1372, 1322, 1301, 1267, 1218, 1187, 1177, 1157, 1142, 1092, 1070, 1031, 1011, 919, 892, 859, 827, 794, 777, 748, 699, 687, 672.

MS (70 eV, EI) *m/z* (%): 223 (15), 222 (100), 116 (60), 107 (23), 105 (36), 103 (13), 79 (54), 77 (64), 71 (36), 58 (11), 45 (23).

HRMS (EI): *m/z* (M^+) for $C_{11}H_{10}OS_2$: calcd. 222.0173; found 222.0169.

3.3.7 Preparation of ethyl 1,4-dithiine-2-carboxylate (**44g**)



According to **TP1**, 1,4-dithiin (**40**, 697 mg, 6.00 mmol) was dissolved in dry THF (12 mL). TMPMgCl·LiCl (**2**, 5.95 mL, 6.60 mmol, 1.11 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. The freshly prepared magnesium reagent was added to a solution of ethyl cyanoformate (417 mg, 4.20 mmol) in dry THF (6 mL) at -60 ºC. The resulting solution was stirred at this temperature for 2 h and was then quenched with sat. aq. NH_4Cl solution (10 mL), extracted with Et_2O (3 x 70 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/Et_2O, 95:5) yielding **44g** as red oil (704 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.29 (s, 1 H), 6.19 (d, *J*=7.1 Hz, 1 H), 6.03 (d, *J*=7.1 Hz, 1 H), 4.26 (q, *J*=7.1 Hz, 2 H), 1.32 (t, *J*=7.1 Hz, 4 H).

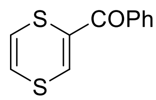
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 161.1, 133.8, 125.6, 122.0, 119.6, 62.0, 14.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3037, 2980, 2932, 2904, 1702, 1573, 1533, 1464, 1444, 1391, 1366, 1292, 1243, 1218, 1171, 1111, 1094, 1040, 994, 973, 889, 850, 830, 790, 731, 666.

MS (70 eV, EI) *m/z* (%): 190 (12), 189 (12), 188 (100), 162 (10), 160 (91), 143 (16), 142 (26), 115 (22), 114 (18), 111 (19).

HRMS (EI): *m/z* (M$^+$) for $C_7H_8O_2S_2$: calcd. 187.9966; found 187.9948.

3.3.8 Preparation of (1,4-dithiin-2-yl)(phenyl)methanone (**44h**)



According to **TP1**, 1,4-dithiin (**40**, 1.16 g, 10.0 mmol) was dissolved in dry THF (20 mL). TMPMgCl·LiCl (**2**, 9.91 mL, 11.0 mmol, 1.11 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. $ZnCl_2$ solution (12.0 mL, 12.0 mmol, 1.0 M in THF) was added and the reaction mixture was allowed to stir for 15 min. CuCN·2LiCl solution (12.0 mL, 12.0 mmol, 1.0 M in THF) was added and the reaction mixture was allowed to stir for 15 min, before benzoyl chloride (984 mg, 7.0 mmol) was added. The reaction mixture was stirred at 25 ºC for 12 h and was then quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 50 mL), extracted with Et_2O (3 x 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/Et_2O, 94:6) yielding **44h** as red liquid (1.20 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.69 (d, *J*=7.6 Hz, 2 H), 7.56 (t, *J*=7.6 Hz, 1 H), 7.45 (t, *J*=7.6 Hz, 2 H), 6.96 (s, 1 H), 6.28 (d, *J*=7.6 Hz, 1 H), 6.10 (d, *J*=7.6 Hz, 1 H).

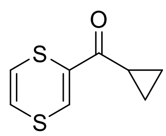
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 188.6, 137.0, 136.8, 134.2, 132.5, 129.1, 128.4, 122.6, 119.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3092, 3035, 2973, 2955, 2928, 2868, 2360, 1748, 1693, 1638, 1563, 1528, 1468, 1396, 1366, 1261, 1126, 1020, 938, 900, 872, 858, 770, 737, 666.

MS (70 eV, EI) *m/z* (%): 220 (40), 105 (100), 77 (63).

HRMS (EI): *m/z* (M^+) for $C_{11}H_8OS_2$: calcd. 220.0017; found 220.0014.

3.3.9 Preparation of cyclopropyl(1,4-dithiin-2-yl)methanone (**44i**)



According to **TP1**, 1,4-dithiin (**40**, 232 mg, 2.00 mmol) was dissolved in dry THF (4 mL). TMPMgCl·LiCl (**2**, 1.98 mL, 2.20 mmol, 1.11 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. $ZnCl_2$ solution (2.40 mL, 2.40 mmol, 1.0 M in THF) was added and the reaction mixture was allowed to stir for 15 min. CuCN·2LiCl solution (2.40 mL, 2.40 mmol, 1.0 M in THF) was added and the reaction mixture was allowed to stir for 15 min, before cyclopropanecarbonyl chloride (146 mg, 1.40 mmol) was added. The reaction mixture was stirred at 25 ºC for 20 h and was then quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 5 mL), extracted with Et_2O (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/Et_2O, 9:1) yielding **44i** as red oil (168 mg, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.31 (s, 1 H), 6.20 (d, *J*=7.4 Hz, 1 H), 6.06 (d, *J*=7.4 Hz, 1 H), 2.29 - 2.39 (m, 1 H), 1.08 - 1.15 (m, 2 H), 0.92 - 1.00 (m, 2 H).

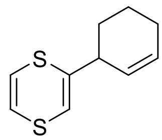
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 192.6, 135.2, 133.2, 122.3, 119.7, 17.3, 11.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3033, 2360, 2086, 1645, 1561, 1528, 1438, 1418, 1385, 1292, 1198, 1161, 1128, 1090, 1061, 1029, 984, 925, 878, 792, 718.

MS (70 eV, EI) *m/z* (%): 203 (98), 186 (12), 185 (13), 184 (100), 116 (51), 115 (20), 111 (10), 105 (12), 85 (11), 71 (30), 69 (88), 45 (32), 44 (13), 41 (61).

HRMS (EI): *m/z* (M$^+$) for $C_8H_8OS_2$: calcd. 184.0017; found 184.0014.

3.3.10 Preparation of 2-(cyclohex-2-en-1-yl)-1,4-dithiine (**44j**)



According to **TP1**, 1,4-dithiin (**40**, 58 mg, 0.50 mmol) was dissolved in dry THF (1 mL). TMPMgCl·LiCl (**2**, 0.50 mL, 0.55 mmol, 1.11 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. $ZnCl_2$ solution (0.6 mL, 0.6 mmol, 1.0 M in THF) was added and the reaction mixture was allowed to stir for 15 min. CuCN·2LiCl solution (0.6 mL, 0.60 mmol, 1.0 M in THF) was added and the reaction mixture was allowed to stir for 15 min, and afterwards, 3-bromocyclohexene (56 mg, 0.35 mmol) was added. The reaction mixture was stirred at 25 ºC for 12 h and was then quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 5 mL), extracted with Et_2O (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **44j** as yellow oil (50 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.35 (d, *J*=6.8 Hz, 1 H), 6.30 (d, *J*=6.8 Hz, 1 H), 5.92 (s, 1 H), 5.82 - 5.89 (m, 1 H), 5.56 - 5.63 (m, 1 H), 3.03 - 3.14 (m, 1 H), 1.96 - 2.08 (m, 2 H), 1.80 - 1.91 (m, 1 H), 1.62 - 1.74 (m, 2 H), 1.50 - 1.61 (m, 1 H).

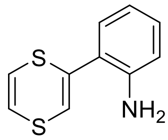
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 142.4, 129.8, 127.7, 123.4, 122.6, 115.6, 42.4, 28.6, 24.9, 20.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3019, 2926, 2856, 2831, 1720, 1647, 1584, 1535, 1444, 1429, 1343, 1212, 1159, 1134, 1086, 1045, 1019, 978, 964, 898, 887, 869, 805, 793, 784, 772, 734, 723, 708, 669, 652, 624, 612, 596, 587, 576, 571, 568, 564, 555.

MS (70 eV, EI) *m/z* (%): 196 (20), 79 (23), 77 (21), 53 (34), 52 (22), 45 (100).

HRMS (EI): *m/z* (M$^+$) for $C_{10}H_{12}S_2$: calcd. 196.0380; found 196.0386.

3.3.11 Preparation of 2-(1,4-dithiin-2-yl)aniline (**44k**)



According to **TP1**, 1,4-dithiin (**40**, 1.16 g, 10.0 mmol) was dissolved in dry THF (20 mL). TMPMgCl·LiCl (**2**, 9.91 mL, 11.0 mmol, 1.11 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. $ZnCl_2$ solution (12.0 mL, 12.0 mmol, 1.0 M in THF) was added and the reaction mixture was allowed to stir for 15 min. The freshly prepared zinc reagent was added over 1 h to a solution of 2-iodoaniline (1.75 g, 8.0 mmol), $Pd(dba)_2$ (173 mg, 0.3 mmol) and $P(2\text{-furyl})_3$ (139 mg, 0.6 mmol) in dry THF (7 mL) at 25 ºC. The reaction mixture was stirred at 25 ºC for 6 h and was then quenched with sat. aq. NH_4Cl solution (50 mL), extracted with Et_2O (3 x 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 14:1) yielding **44k** as yellow oil (1.56 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.10 - 7.20 (m, 2 H), 6.66 - 6.78 (m, 2 H), 6.46 (d, *J*=6.8 Hz, 1 H), 6.39 (d, *J*=6.8 Hz, 1 H), 6.20 (s, 1 H), 3.93 (br. s., 2 H).

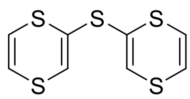
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 143.9, 135.0, 130.7, 129.7, 123.0, 122.8, 122.8, 119.1, 118.5, 116.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3435, 3352, 3204, 3024, 2923, 2853, 2620, 1936, 1669, 1611, 1575, 1533, 1486, 1450, 1365, 1302, 1281, 1256, 1211, 1157, 1138, 1054, 1032, 1007, 939, 910, 855, 792, 777, 746, 673, 655, 634, 577, 558.

MS (70 eV, EI) *m/z* (%): 207 (90), 190 (37), 174 (94), 173 (51), 130 (55), 117 (100), 90 (61), 89 (47), 77 (16), 63 (17), 58 (11), 57 (11), 45 (40), 43 (11).

HRMS (EI): *m/z* (M^+) for $C_{10}H_9NS_2$: calcd. 207.0176; found 207.0162.

3.3.12 Preparation of di(1,4-dithiin-2-yl)sulfane (**44l**)



According to **TP1**, 1,4-dithiin (**40**, 348 mg, 2.00 mmol) was dissolved in dry THF (4 mL). TMPMgCl·LiCl (**2**, 2.00 mL, 2.20 mmol, 1.10 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. Bis(phenylsulfonyl)sulfide (**79**, 314 mg, 1.00 mmol) in dry THF (2 mL) was added at -78 ºC and stirred for 12 h allowing to reach 25 ºC. The resulting solution was then quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 x 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/CH_2Cl_2, 9:1) yielding **44l** as brown solid (196 mg, 75%).

m.p.: 45.8 - 46.3 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.41 (s, 2 H), 6.28 - 6.36 (m, 4 H).

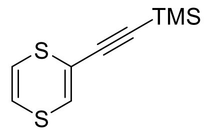
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 126.9, 124.2, 122.8, 122.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3026, 2921, 2850, 1680, 1573, 1512, 1276, 1261, 1215, 1134, 1090, 1020, 883, 812, 769.

MS (70 eV, EI) *m/z* (%): 262 (32), 147 (14), 103 (100), 71 (30), 45 (34), 44 (53).

HRMS (EI): *m/z* (M^+) for $C_8H_6S_5$: calcd. 261.9073; found 261.9068.

3.3.13 Preparation of ((1,4-dithiin-2-yl)ethynyl)trimethylsilane (**45**)



2-Iodo-1,4-dithiine (**44a**, 295 mg, 1.22 mmol), CuI (23 mg, 0.12 mmol), $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol) were dissolved in NEt_3 (3 mL). The mixture was then degassed and trimethylsilylacetylene (0.34 mL, 2.44 mmol) was added. The resulting mixture was stirred at 25 ºC for 7 h. The reaction was quenched by the addition of sat. aq. NH_4Cl solution (20 mL), extracted with EtOAc (3 x 40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **45** as yellow oil (226 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.51 (t, *J*=0.7 Hz, 1 H), 6.33 (dd, *J*=6.8, 0.7 Hz, 1 H), 6.23 (dd, *J*=6.8, 0.7 Hz, 1 H), 0.20 (s, 9 H).

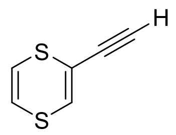
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 127.8, 122.7, 121.5, 117.0, 99.9, 95.7, -0.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3031, 2958, 2898, 1595, 1560, 1526, 1408, 1249, 1110, 1073, 1048, 960, 855, 835, 789, 757, 699.

MS (70 eV, EI) *m/z* (%): 213 (7), 212 (44), 199 (9), 198 (10), 197 (66), 151 (6), 107 (5), 73 (12), 43 (100).

HRMS (EI): *m/z* (M$^+$) for $C_9H_{12}S_2Si$: calcd. 212.0150; found 212.0138.

3.3.14 Preparation of 2-ethynyl-1,4-dithiine (**46**)



The synthesized ((1,4-dithiin-2-yl)ethynyl)trimethylsilane (**45**, 207 mg, 0.97 mmol) was dissolved in dry THF/MeOH (100 mL, 1:1) and K_2CO_3 (670 mg, 4.90 mmol) was added to the solution. The resulting mixture was stirred at 25 ºC for 5 h and concentrated afterwards in the rotary evaporator. Sat. aq. NH_4Cl solution (20 mL) was then added extracted with EtOAc (3 x 40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **46** as yellow oil (86 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.57 (s, 1 H), 6.34 (d, *J*=6.8 Hz, 1 H), 6.24 (d, *J*=6.8 Hz, 1 H), 3.04 (s, 1 H).

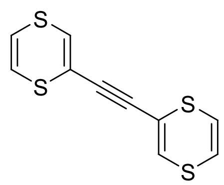
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 129.2, 121.6, 121.4, 114.0, 81.1, 79.5.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3282, 3029, 2919, 2850, 1592, 1526, 1463, 1376, 1281, 1221, 1138, 1069, 1036, 889, 838, 787, 669.

MS (70 eV, EI) *m/z* (%): 140 (39), 111 (11), 97 (15), 96 (22), 95 (10), 71 (22), 70 (10), 69 (21), 57 (29), 43 (100).

HRMS (EI): *m/z* (M$^+$) for $C_6H_4S_2$: calcd. 139.9754; found 139.9748.

3.3.15 Preparation of 2-ethynyl-1,4-dithiine (**47**)



The prepared 2-ethynyl-1,4-dithiine (**46**, 154 mg, 1.10 mmol), 2-iodo-1,4-dithiin (**44a**, 266 mg, 1.10 mmol), CuI (21 mg, 0.11 mmol), $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol) were dissolved in NEt_3 (2.8 mL) and the mixture was then degassed. The resulting mixture was stirred at 25 ºC for 3 days. The reaction was quenched by the addition of sat. aq. NH_4Cl solution (20 mL), extracted with EtOAc (3 x 40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane to *i*hexane/EtOAc 98:2) yielding **47** as red solid (151 mg, 54%).

m.p.: 61.9 - 64.5 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.53 (t, *J*=0.7 Hz, 2 H), 6.33 (dd, *J*=6.8, 0.7 Hz, 2 H), 6.25 (dd, *J*=6.8, 0.7 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 128.5, 122.5, 121.8, 116.1, 85.2.

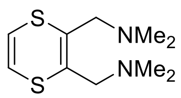
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3028, 2920, 2850, 1591, 1563, 1530, 1275, 1257, 1233, 1207, 1132, 1076, 961, 881, 852, 782, 735, 680.

MS (70 eV, EI) *m/z* (%): 256 (18), 255 (17), 254 (100), 222 (33), 221 (51), 209 (47), 177 (68), 164 (24), 120 (32), 93 (38), 59 (57), 45 (50), 41 (97).

HRMS (EI): *m/z* (M^+) for $C_{10}H_6S_4$: calcd. 253.9352; found 253.9338.

3.4 PREPARATION OF DIFUNCTIONALIZED 1,4-DITHIIN DERIVATIVES

3.4.1 Preparation of 1,1'-(1,4-dithiine-2,3-diyl)bis(*N*,*N*-dimethylmethanamine) (**49a**)



A dry and argon-flushed Schlenk-flask was charged with *N,N,N',N'*-tetramethyl-methanediamine (45 mg, 0.44 mmol) and anydrous CH_2Cl_2 (0.44 mL). Trifluoroacetic anhydride (92 mg, 0.44 mmol) was added dropwise and the solution was stirred for 15 min at 0 ºC.[93] In a second dry and argon-flushed Schlenk flask, according to **TP2**, 1-(1,4-dithiin-2-yl)-*N*,*N*-dimethylmethanamine (**44e**, 69 mg, 0.40 mmol) was dissolved in dry THF (0.8 mL). TMPMgCl·LiCl (**2**, 0.40 mL, 0.40 mmol, 1.00 M in THF) was added dropwise at -78 ºC and the reaction mixture was stirred for 0.5 h. Then, the previously prepared methylene(dimethyl)iminium trifluoroacetate was added at -78 ºC to the magnesiated 1-(1,4-dithiin-2-yl)-*N*,*N*-dimethylmethanamine solution. The reaction mixture was stirred for 1 h at -78 ºC. The crude mixture was quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with sat. aq. NaCl and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 8:2) yielding **49a** as orange oil (59 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.43 (s, 2 H), 3.17 (s, 4 H), 2.27 (s, 12 H).

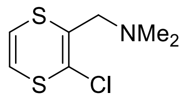
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 131.7, 124.3, 61.7, 45.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3388, 2973, 2941, 2853, 2817, 2767, 1609, 1536, 1453, 1344, 1260, 1175, 1135, 1096, 1041, 1029, 1007, 947, 911, 841, 804, 770, 731, 671.

MS (70 eV, EI) *m/z* (%): 230 (1), 185 (100), 141 (21), 140 (47), 129 (11), 94 (12), 58 (79), 42 (12).

HRMS (EI): *m/z* (M^+) for $C_{10}H_{18}N_2S_2$: calcd. 230.0911; found 230.0897.

3.4.2 Preparation of 1-(3-chloro-1,4-dithiin-2-yl)-*N*,*N*-dimethylmethanamine (**50b**)



According to **TP2**, 1-(1,4-dithiin-2-yl)-*N*,*N*-dimethylmethanamine (**44e**, 74 mg, 0.43 mmol) was dissolved in dry THF (0.9 mL). TMPMgCl·LiCl (**2**, 0.42 mL, 0.45 mmol, 1.07 M in THF) was added dropwise at -78 ºC and the reaction mixture was stirred for 0.5 h. Hexachloroethane (153 mg, 0.65 mmol) was added and the resulting solution was stirred for 12 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 8:2) yielding **49b** as orange oil (38 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.46 (d, *J*=6.4 Hz, 1 H), 6.40 (d, *J*=6.4 Hz, 1 H), 3.26 (s, 2 H), 2.28 (s, 6 H).

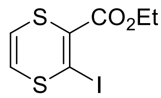
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 129.9, 124.4, 122.7, 119.2, 62.0, 45.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2974, 2943, 2856, 2820, 2772, 1587, 1562, 1535, 1453, 1348, 1262, 1174, 1156, 1095, 1042, 1027, 983, 888, 842, 801, 746, 673.

MS (70 eV, EI) *m/z* (%): 209 (9), 207 (23), 71 (4), 58 (100), 55 (5), 45 (5), 44 (7), 41 (5).

HRMS (EI): *m/z* (M^+) for $C_7H_{10}ClNS_2$: calcd. 206.9943; found 206.9941.

3.4.3 Preparation of ethyl 3-iodo-1,4-dithiine-2-carboxylate (**49c**)



According to **TP2**, ethyl 1,4-dithiine-2-carboxylate (**44g**, 1.09 g, 5.81 mmol) was dissolved in dry THF (20 mL). TMPMgCl·LiCl (**2**, 5.76 mL, 6.39 mmol, 1.11 M in THF) was added dropwise at -78 ºC and the reaction mixture was stirred for 0.5 h. The freshly prepared magnesium reagent was added to a solution of iodine (1.03 g, 4.07 mmol) in dry THF (6 mL) at -78 ºC. The resulting solution was stirred at this temperature for 1 h and was then quenched with sat. aq. $Na_2S_2O_3$ solution (50 mL), extracted with Et_2O (3 x 100 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/CH_2Cl_2, 2:1) yielding **49c** as orange oil (793 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.61 (d, *J* = 6.2 Hz, 1H), 6.25 (d, *J* = 6.2 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H).

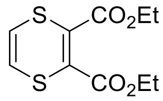
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 162.2, 126.6, 124.4, 123.5, 83.2, 62.5, 14.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3033, 2979, 2934, 1710, 1601, 1558, 1510, 1463, 1443, 1388, 1365, 1212, 1113, 1093, 1030, 889, 851, 795, 761, 676.

MS (70 eV, EI) *m/z* (%): 314 (100), 159 (69), 144 (10), 115 (16), 114 (20), 88 (21), 71 (13), 58 (10), 45 (14).

HRMS (EI): *m/z* (M^+) for $C_7H_7O_2IS_2$: calcd. 313.8932; found 313.8929.

3.4.4 Preparation of diethyl 1,4-dithiine-2,3-dicarboxylate (**49d**)



According to **TP2**, ethyl 1,4-dithiine-2-carboxylate (**44g**, 188 mg, 1.00 mmol) was dissolved in dry THF (2 mL). TMPMgCl·LiCl (**2**, 0.95 mL, 1.05 mmol, 1.11 M in THF) was added dropwise at -78 ºC and the reaction mixture was stirred for 0.5 h. Ethyl cyanoformate (149 mg, 1.50 mmol) was added and the resulting solution was stirred at this temperature for 3 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 8:2) yielding **49d** as orange oil (234 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.41 (s, 2 H), 4.28 (q, *J*=7.2 Hz, 4 H), 1.33 (t, *J*=7.1 Hz, 6 H).

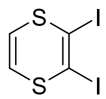
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 162.3, 133.3, 123.8, 62.6, 13.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3040, 2982, 2938, 2904, 1714, 1580, 1537, 1464, 1444, 1390, 1366, 1230, 1113, 1094, 1069, 1022, 965, 906, 853, 795, 765, 743, 680.

MS (70 eV, EI) *m/z* (%): 260 (100), 160 (36), 159 (25), 142 (34), 71 (19), 43 (35).

HRMS (EI): *m/z* (M$^+$) for $C_{10}H_{12}O_4S_2$: calcd. 260.0177; found 260.0174.

3.4.5 Preparation of 2,3-diiodo-1,4-dithiine (**49e**)



According to **TP2**, 2-iodo-1,4-dithiine (**44a**, 242 mg, 1.00 mmol) was dissolved in dry THF (2 mL). TMPZnCl·LiCl (**3**, 0.83 mL, 1.10 mmol, 1.33 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. The freshly prepared zinc reagent was added to a solution of iodine (177 mg, 0.70 mmol) in dry THF (1 mL) at -78 ºC. The resulting solution was stirred at this temperature for 1 h and was then quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with Et_2O (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*.

The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **49e** as yellow solid (175 mg, 68%).

m.p.: 84.9 - 86.4 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.43 (s, 2H).

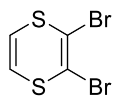
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 123.4, 84.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3024, 2962, 1592, 1544, 1485, 1260, 1092, 1020, 885, 872, 790, 757, 671.

MS (70 eV, EI) *m/z* (%): 368 (58), 241 (95), 127 (21), 114 (100), 88 (49), 61 (13), 45 (13), 43 (17).

HRMS (EI): *m/z* (M^+) for $C_4H_2I_2S_2$: calcd. 367.7687: found 367.7680.

3.4.6 Preparation of 2,3-dibromo-1,4-dithiine (**49f**)



According to **TP2**, 2-bromo-1,4-dithiine (**44b**, 969 mg, 5.00 mmol) was dissolved in dry THF (10 mL). TMPZnCl·LiCl (**3**, 6.4 mL, 5.50 mmol, 0.86 M in THF) was added dropwise at -40 ºC and the mixture was stirred for 0.5 h. 1,2-Dibromotetrachloroethane (2.4 g, 7.50 mmol) in dry THF (4 mL) was added and the resulting solution was stirred for 12 h and allowed to reach 25 ºC. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with EtOAc (3 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by HPLC yielding **49f** as light brown oil (680 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.47 (s, 2 H).

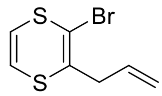
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 123.6, 108.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3032, 1594, 1548, 1523, 1275, 1258, 1128, 920, 883, 861, 803, 775, 754, 719, 669.

MS (70 eV, EI) *m/z* (%): 276 (23), 274 (33), 195 (78), 193 (64), 114 (38), 111 (29), 97 (33), 95 (63), 91 (58), 85 (39), 83 (47), 82 (29), 81 (27), 71 (67), 69 (57), 67 (28), 57 (100), 56 (27), 55 (64), 44 (55), 43 (62), 41 (51).

HRMS (EI): *m/z* (M^+) for $C_4H_2{}^{81}Br_2S_2$: calcd. 273.7965; found 273.7869.

3.4.7 Preparation of 2-allyl-3-bromo-1,4-dithiine (**49g**)



According to **TP2**, 2-bromo-1,4-dithiine (**44b**, 316 mg, 1.60 mmol) was dissolved in dry THF (3 mL). TMPZnCl·LiCl (**3**, 1.34 mL, 1.78 mmol, 1.33 M in THF) was added dropwise at -40 ºC and the reaction mixture was stirred for 0.5 h. CuCN·2LiCl solution (1.94 mL, 1.94 mmol, 1.0 M in THF) was added and the reaction mixture was allowed to stir for 15 min, before allyl bromide (137 mg, 1.10 mmol) was added. The reaction mixture was stirred at -40 ºC for 1 h and was then quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 5 mL), extracted with Et_2O (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **49g** as yellow liquid (191 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.47 (d, *J*=6.6 Hz, 1 H), 6.38 (d, *J*=6.6 Hz, 1 H), 5.77 (ddt, *J*=16.7, 10.2, 6.3, 6.0 Hz, 1 H), 5.10 - 5.21 (m, 2 H), 3.23 (d, *J*=6.0 Hz, 2 H).

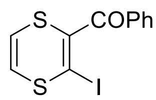
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 132.0, 132.0, 123.7, 123.4, 117.7, 103.2, 41.5.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3032, 3018, 2925, 2853, 2832, 1718, 1648, 1585, 1563, 1556, 1520, 1500, 1492, 1466, 1433, 1413, 1341, 1275, 1214, 1180, 1162, 1133, 1090, 1053, 1029, 1012, 979, 966, 915, 899, 885, 865, 822, 798, 780, 778, 741, 730, 705, 668, 654.

MS (70 eV, EI) *m/z* (%): 236 (78), 234 (75), 195 (16), 193 (16), 155 (28), 153 (11), 140 (14), 127 (13), 125 (10), 123 (19), 122 (100), 121 (38), 111 (23), 97 (20), 95 (11), 85 (14), 83 (14), 81 (10), 71 (22), 69 (32), 57 (28), 55 (16), 45 (27), 44 (14), 43 (28), 41 (21).

HRMS (EI): *m/z* (M^+) for $C_7H_7BrS_2$: calcd. 233.9171; found 233.9178.

3.4.8 Preparation of (3-iodo-1,4-dithiin-2-yl)(phenyl)methanone (**49h**)



According to **TP2**, (1,4-dithiin-2-yl)(phenyl)methanone (**44h**, 220 mg, 1.00 mmol) was dissolved in dry THF (2 mL). TMPZnCl·LiCl (**3**, 0.83 mL, 1.10 mmol, 1.33 M in THF) was added dropwise at 0 ºC and the reaction mixture was stirred for 0.5 h. The freshly prepared zinc reagent was added to a solution of iodine (178 mg, 0.70 mmol) in dry THF (1 mL) at -78 ºC. The resulting solution was stirred at this temperature for 1 h and was then quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with Et_2O (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/CH_2Cl_2, 2:1) yielding **49h** as orange oil (189 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.88 (d, *J*=7.8 Hz, 2 H), 7.65 (t, *J*=7.3 Hz, 1 H), 7.51 (t, *J*=7.6 Hz, 2 H), 6.66 (d, *J*=6.4 Hz, 1 H), 6.55 (d, *J*=6.4 Hz, 1 H).

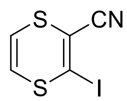
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 191.2, 134.4, 133.4, 133.0, 130.0, 128.9, 125.9, 122.4, 75.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3031, 2923, 1963, 1656, 1594, 1578, 1528, 1447, 1311, 1234, 1175, 1160, 1130, 1055, 1022, 999, 974, 935, 894, 806, 782, 727, 677.

MS (70 eV, EI) *m/z* (%): 348 (11), 347 (13), 346 (98), 220 (13), 219 (14), 191 (16), 190 (25), 147 (21), 105 (100), 77 (72), 51 (26), 43 (45).

HRMS (EI): *m/z* (M^+) for $C_{11}H_7OIS_2$: calcd. 345.8983; found 345.8976.

3.4.9 Preparation of 3-iodo-1,4-dithiine-2-carbonitrile (**49i**)



According to **TP2**, 1,4-dithiine-2-carbonitrile (**44d**, 93 mg, 0.66 mmol) was dissolved in dry THF (3 mL). TMPZnCl·LiCl (**3**, 0.55 mL, 0.73 mmol, 1.33 M in THF) was added dropwise at 0 ºC and the reaction mixture was stirred for 0.5 h. The freshly prepared zinc reagent was added to a solution of iodine (117 mg, 0.46 mmol) in dry THF (1 mL) at -78 ºC. The resulting solution was stirred at this temperature for 1 h and was then quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with Et_2O (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/CH_2Cl_2, 2:1) yielding **49i** as orange liquid (106 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.62 (d, *J*=6.2 Hz, 1 H), 6.31 (d, *J*=6.2 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 124.3, 122.1, 116.0, 109.0, 96.6.

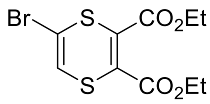
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3039, 3028, 2954, 2920, 2851, 2212, 1594, 1573, 1553, 1522, 1502, 1463, 1373, 1281, 1262, 1130, 1072, 1054, 1022, 892, 874, 841, 802, 791, 730, 679, 601, 557.

MS (70 eV, EI) *m/z* (%): 267 (84), 142 (10), 141 (14), 140 (100), 127 (13), 114 (10), 96 (61), 82 (10), 45 (15).

HRMS (EI): *m/z* (M^+) for $C_5H_2NIS_2$: calcd. 266.8673; found 266.8675.

3.5 PREPARATION OF TRIFUNCTIONALIZED 1,4-DITHIIN DERIVATIVES

3.5.1 Preparation of diethyl 5-bromo-1,4-dithiine-2,3-dicarboxylate (**50a**)



Diethyl 1,4-dithiine-2,3-dicarboxylate (**49d**, 52 mg, 0.20 mmol) was dissolved in dry CH_2Cl_2 (1 mL). Bromine (62 mg, 0.39 mmol) in dry CH_2Cl_2 (0.6 mL) was added dropwise at 0 ºC and 15 min later Et_3N (69 mg, 0.68 mmol) was added. The reaction was stirred for 24 h and allowed to reach 25 ºC. Then, the reaction mixture was quenched with aq. HCl solution (3 mL, 2.0 M) and sat. aq. $Na_2S_2O_3$ solution (3 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with water and brine and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 96:4) yielding **50a** as orange oil (46 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 6.42 (br. s, 1 H), 4.22 - 4.33 (m, 4 H), 1.32 (td, *J*=7.14, 1.10 Hz, 6 H).

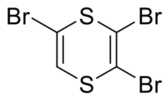
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 162.2, 161.1, 135.1, 132.6, 121.5, 110.3, 62.9, 62.8, 13.9, 13.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3039, 2982, 2937, 1715, 1585, 1550, 1463, 1444, 1390, 1366, 1232, 1113, 1094, 1068, 1022, 907, 864, 785, 766, 736, 686.

MS (70 eV, EI) *m/z* (%): 340 (100), 339 (13), 338 (93), 240 (17), 239 (18), 238 (14), 237 (17), 222 (35), 220 (31), 187 (16), 186 (18), 185 (33), 159 (41), 115 (13), 114 (17), 113 (14), 89 (15), 88 (22), 69 (27), 57 (16), 57 (17), 45 (20), 43 (17).

HRMS (EI): *m/z* (M+) for $C_{10}H_{11}{}^{81}BrO_4S_2$: calcd. 339.9282; found 339.9244.

3.5.2 Preparation of 2,3,5-tribromo-1,4-dithiine (**50b**)



2,3-dibromo-1,4-dithiine (**49f**, 213 mg, 0.78 mmol) was dissolved in dry CH_2Cl_2 (2 mL). Bromine (131 mg, 0.83 mmol) in dry CH_2Cl_2 (2 mL) and Et_3N (0.19 mL, 1.33 mmol) were added dropwise at 0 ºC. The reaction was stirred for 24 h and allowed to reach 25 ºC. Then, the reaction mixture was quenched with aq. HCl solution (5.0 mL, 2.0 M) and sat. aq. $Na_2S_2O_3$ solution (5 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with water and brine and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **50b** as white solid (230 mg, 84%).

m.p.: 92.5 - 94.4 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.52 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 122.0, 110.7, 110.2, 108.8.

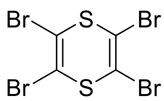
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3035, 2358, 1553, 1532, 1519, 1222, 1206, 1194, 917, 860, 809, 776, 757, 720, 712.

MS (70 eV, EI) *m/z* (%): 356 (2), 354 (7), 352 (6), 350 (2), 275 (10), 273 (19), 271 (9), 194 (11), 192 (11), 61 (16), 45 (15), 44 (2), 43 (100), 41 (5).

HRMS (EI): *m/z* (M+) for $C_4H^{79}Br_3S_2$: calcd. 349.7070; found 349.7066.

3.6 PREPARATION OF TETRAFUNCTIONALIZED 1,4-DITHIIN DERIVATIVES

3.6.1 Preparation of perbromo-1,4-dithiine (**51a**)



According to **TP3**, 2,3,5-tribromo-1,4-dithiine (**50b**, 517 mg, 1.50 mmol) was dissolved in dry THF (9 mL). TMPZnCl·LiCl (**3**, 1.81 mL, 1.60 mmol, 0.88 M in THF) was added dropwise at -78 ºC and the mixture was stirred for 15 min. 1,2-Dibromotetrachloroethane (723 mg, 2.20 mmol) in dry THF (1 mL) was added and the resulting solution was allowed to reach 25 ºC for 24 h, after which time it was warmed to 50 ºC and stirred for further 12 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **51a** as white solid (357 mg, 56%).

m.p.: 170.8 - 172.3 ºC.

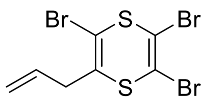
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 110.5.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3078, 3028, 2921, 2851, 1641, 1593, 1556, 1530, 1514, 1423, 1407, 1265, 1108, 1047, 985, 937, 914, 884, 848, 830, 798, 769, 676.

MS (70 eV, EI) *m/z* (%): 434 (18), 432 (25), 430 (18), 355 (35), 353 (100), 351 (94), 349 (29), 274 (36), 272 (69), 270 (32), 149 (24), 147 (23), 137 (31), 135 (29), 88 (39), 68 (30).

HRMS (EI): *m/z* (M^+) for $C_4Br_4S_2$: calcd. 427.6175; found 427.6178.

3.6.2 Preparation of 2-allyl-3,5,6-tribromo-1,4-dithiine (**51b**)



According to **TP3**, 2,3,5-tribromo-1,4-dithiine (**50b**, 35 mg, 0.10 mmol) was dissolved in dry THF (0.6 mL). TMPZnCl·LiCl (**3**, 0.12 mL, 0.11 mmol, 0.92 M in THF) was added dropwise at -78 ºC and the mixture was stirred for 15 min. CuCN·2LiCl (0.02 mL, 0.02 mmol, 1.0 M in THF) was then introduced followed by allyl bromide (18 mg, 0.15 mmol) and the reaction warmed to -40 ºC and stirring was continued for a further 18 h. The reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 5 mL), extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **51b** as light brown solid (22 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 5.76 (ddt, *J*=16.8, 10.3, 6.4 Hz, 1 H), 5.22 (dq, *J*=5.6, 1.2 Hz, 1 H), 5.20 (dq, *J*=12.5, 1.5 Hz, 1 H), 3.27 (dt, *J*=6.4, 1.5 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 135.1, 131.0, 118.8, 111.1, 109.9, 105.7, 40.5.

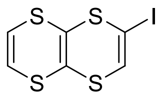
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3038, 3020, 2923, 2852, 1720, 1643, 1590, 1553, 1530, 1510, 1485, 1423, 1411, 1343, 1266, 1143, 1105, 1046, 991, 967, 914, 889, 848, 829, 771, 656.

MS (70 eV, EI) *m/z* (%): 392 (70), 390 (67), 312 (18), 310 (17), 281 (96), 279 (100), 202 (14), 200 (14), 121 (40), 97 (25), 85 (10).

HRMS (EI): *m/z* (M^+) for $C_7H_5Br_3S_2$: calcd. 389.7383; found 389.7370.

3.7 PREPARATION OF MONOSUBSTITUTED TTN

3.7.1 Preparation of 2-iodo-[1,4]dithiino[2,3-*b*][1,4]dithiine (**59a**)



According to **TP3**, 1,4,5,8-tetrathianaphthalene (**41**, 102 mg, 0.50 mmol) was dissolved in dry THF (4 mL). TMPMgCl·LiCl (**2**, 0.51 mL, 0.60 mmol, 1.18 M in THF) was added dropwise at -78 ºC and the mixture was stirred for 10 min. Iodine (191 mg, 0.75 mmol) in dry THF (1 mL) was added and the resulting solution was stirred at this temperature for 2 h. Then, the reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **59a** as yellow solid (147 mg, 89%).

m.p.: 94.8 - 96.5 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.70 (s, 1 H), 6.47 (d, *J*=6.6 Hz, 1 H), 6.44 (d, *J*=6.6 Hz, 1 H).

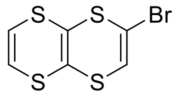
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 129.4, 125.7, 125.6, 121.0, 120.1, 78.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3025, 2926, 1607, 1568, 1533, 1510, 1470, 1366, 1260, 1213, 1128, 965, 906, 887, 864, 834, 801, 778, 759, 733.

MS (70 eV, EI) *m/z* (%): 330 (86), 285 (41), 203 (78), 159 (100), 146 (46), 127 (32), 88 (69), 69 (48), 57 (36), 45 (55).

HRMS (EI): *m/z* (M^+) for $C_6H_3IS_4$: calcd. 329.8162; found 329.8153.

3.7.2 Preparation of 2-bromo-[1,4]dithiino[2,3-*b*][1,4]dithiine (**59b**)



According to **TP4**, 1,4,5,8-tetrathianaphthalene (**41**, 102 mg, 0.50 mmol) was dissolved in dry THF (4 mL). TMPMgCl·LiCl (**2**, 0.51 mL, 0.60 mmol, 1.18 M in THF) was added dropwise at -78 ºC and the mixture was stirred for 10 min. 1,2-Dibromo-tetrachloroethane (244 mg, 0.75 mmol) in dry THF (1 mL) was added and the resulting solution was stirred at this temperature for 2 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **59b** as yellow solid (126 mg, 89%).

m.p.: 65.8 - 67.6 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.53 (s, 1 H), 6.43 - 6.48 (m, 2 H).

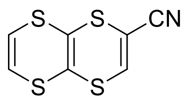
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 125.9, 125.6, 123.8, 121.8, 119.6, 112.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3032, 2923, 1551, 1538, 1517, 1280, 1263, 1208, 1135, 966, 904, 870, 850, 804, 782, 759, 701, 673.

MS (70 eV, EI) *m/z* (%): 284 (67), 282 (60), 239 (47), 237 (44), 203 (86), 159 (100), 127 (54), 88 (79), 69 (40), 45 (51).

HRMS (EI): *m/z* (M^+) for $C_6H_3{}^{81}BrS_4$: calcd. 283.8301; found 283.8278.

3.7.3 Preparation of [1,4]dithiino[2,3-*b*][1,4]dithiine-2-carbonitrile (**59c**)



According to **TP4**, 1,4,5,8-tetrathianaphthalene (**41**, 102 mg, 0.50 mmol) was dissolved in dry THF (4 mL). TMPMgCl·LiCl (**2**, 0.51 mL, 0.60 mmol, 1.18 M in THF) was added dropwise at -78 ºC and the mixture was stirred for 10 min. *p*-Tolylsulfonyl cyanide (136 mg, 0.75 mmol) in dry THF (1 mL) was added and the resulting solution was stirred for 12 h allowing to reach 25 ºC. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 96:4) yielding **59c** as orange solid (84 mg, 73%).

m.p.: 130.4 - 132.2 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.31 (s, 1 H), 6.49 (d, *J*=6.4 Hz, 1 H), 6.46 (d, *J*=6.4 Hz, 1 H).

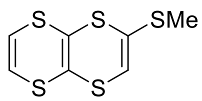
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 143.3, 125.7, 125.2, 120.0, 118.6, 113.7, 109.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3027, 2222, 1578, 1559, 1543, 1506, 1281, 1263, 1231, 1119, 1099, 1062, 966, 885, 862, 852, 803, 767, 678.

MS (70 eV, EI) *m/z* (%): 231 (4), 229 (20), 196 (4), 186 (4), 184 (29), 165 (8), 159 (8), 153 (6), 102 (6), 88 (10), 76 (7), 73 (4), 70 (8), 61 (14), 45 (13), 43 (100), 42 (5).

HRMS (EI): *m/z* (M^+) for $C_7H_3NS_4$: calcd. 228.9148; found 228.9144.

3.7.4 Preparation of 2-(methylthio)-[1,4]dithiino[2,3-*b*][1,4]dithiine (**59d**)



According to **TP4**, 1,4,5,8-tetrathianaphthalene (**41**, 41 mg, 0.20 mmol) was dissolved in dry THF (1.6 mL). TMPMgCl·LiCl (**2**, 0.21 mL, 0.24 mmol, 1.14 M in THF) was added dropwise at -78 ºC and the mixture was stirred for 10 min. *S*-Methyl thiomethanesulfonate (38 mg, 0.30 mmol) was added and the resulting solution was stirred for 12 h allowing to reach 25 ºC. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **59d** as light yellow solid (39 mg, 78%).

m.p.: 101.9 - 103.6 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.40 - 6.46 (m, 2 H), 6.08 (s, 1 H), 2.40 (s, 3 H).

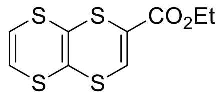
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 139.0, 125.6, 125.6, 123.4, 119.9, 116.2, 18.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3019, 2977, 2910, 2850, 1575, 1556, 1539, 1511, 1471, 1429, 1411, 1310, 1264, 1229, 1134, 968, 951, 904, 888, 857, 798, 766, 735.

MS (70 eV, EI) *m/z* (%): 250 (12), 159 (10), 70 (13), 61 (17), 45 (15), 43 (100).

HRMS (EI): *m/z* (M^+) for $C_7H_6S_5$: calcd. 249.9073; found 249.9068.

3.7.5 Preparation of ethyl [1,4]dithiino[2,3-*b*][1,4]dithiine-2-carboxylate (**59e**)



According to **TP4**, 1,4,5,8-tetrathianaphthalene (**41**, 612 mg, 3.00 mmol) was dissolved in dry THF (24 mL). TMPMgCl·LiCl (**2**, 3.30 mL, 3.60 mmol, 1.09 M in THF) was added dropwise at -78 ºC and the mixture was stirred for 10 min. Ethyl cyanoformate (446 mg, 4.50 mmol) was added and the resulting solution was stirred for 12 h allowing to reach 25 ºC. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/CH_2Cl_2, 8:2 to 7:3) yielding **59e** as orange solid (600 mg, 72%).

m.p.: 99.3 - 101.2 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.45 (s, 1 H), 6.49 (d, *J*=6.6 Hz, 1 H), 6.44 (d, *J*=6.6 Hz, 1 H), 4.25 (q, *J*=7.1 Hz, 2 H), 1.32 (t, *J*=7.1 Hz, 3 H).

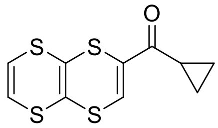
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 160.8, 136.7, 130.4, 125.8, 125.0, 120.4, 116.8, 62.3, 14.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3033, 2979, 1704, 1572, 1552, 1463, 1443, 1391, 1366, 1263, 1244, 1218, 1094, 1040, 997, 886, 856, 828, 805, 770, 731, 677.

MS (70 eV, EI) *m/z* (%): 295 (20), 276 (100), 231 (76), 221 (43), 207 (25), 203 (88), 159 (80), 147 (22), 146 (35), 103 (21), 91 (25), 88 (46), 85 (24), 81 (20), 76 (31), 71 (31), 70 (22), 69 (41), 69 (27), 57 (55), 55 (27), 44 (60), 43 (32), 40 (26).

HRMS (EI): *m/z* (M^+) for $C_9H_8O_2S_4$: calcd. 275.9407; found 275.9401.

3.7.6 Preparation of [1,4]dithiino[2,3-*b*][1,4]dithiin-2-yl(cyclopropyl)methanone (**59f**)



According to **TP4**, 1,4,5,8-tetrathianaphthalene (**41**, 102 mg, 0.50 mmol) was dissolved in dry THF (4 mL). TMPMgCl·LiCl (**2**, 0.51 mL, 0.60 mmol, 1.18 M in THF) was added dropwise at -78 ºC and the mixture was stirred for 10 min. CuCN·2LiCl (0.60 mL, 0.60 mmol, 1.0 M in THF) was then introduced followed by cyclopropanecarbonyl chloride (78 mg, 0.75 mmol) and the reaction warmed to -40 ºC and stirring was continued for a further 18 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 5 mL), extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 96:4) yielding **59f** as dark red solid (89 mg, 65%).

m.p.: 90.3 - 91.6 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.48 (s, 1 H), 6.50 (d, *J*=6.4 Hz, 1 H), 6.44 (d, *J*=6.6 Hz, 1 H), 2.29 - 2.36 (m, 1 H), 1.11 - 1.21 (m, 2 H), 0.95 - 1.06 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 192.5, 139.7, 135.6, 125.9, 124.8, 120.8, 116.8, 17.6, 12.3.

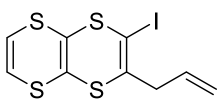
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3071, 3042, 3031, 3004, 2954, 2923, 2853, 1627, 1574, 1558, 1542, 1523, 1463, 1435, 1417, 1397, 1322, 1276, 1262, 1222, 1204, 1173, 1127, 1095, 1087, 1057, 1030, 959, 923, 890, 878, 847, 838, 827, 811, 800, 783, 769, 732, 719, 691, 674.

MS (70 eV, EI) *m/z* (%): 272 (100), 227 (63), 159 (59), 146 (19), 88 (21).

HRMS (EI): *m/z* (M^+) for $C_{10}H_8OS_4$: calcd. 271.9458; found 271.9452.

3.8 PREPARATION OF DISUBSTITUTED TTN

3.8.1 Preparation of 2-iodo-3-allyl-[1,4]dithiino[2,3-*b*][1,4]dithiine (**60a**)



According to **TP5**, 2-iodo-[1,4]dithiino[2,3-*b*][1,4]dithiine (**59a**, 99 mg, 0.30 mmol) was dissolved in dry THF (2.4 mL). TMPZnCl·LiCl (**3**, 0.41 mL, 0.33 mmol, 0.80 M in THF) was added dropwise at -40 ºC and the mixture was stirred for 0.5 h. CuCN·2LiCl (0.06 mL, 0.06 mmol, 1.0 M in THF) was then introduced followed by allyl bromide (54 mg, 0.45 mmol) and the reaction was stirred for 12 h allowing to reach 25 ºC. Then, the reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 5 mL), extracted with EtOAc (3 x 15 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **60a** as yellow oil (75 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.43 (d, *J*=6.6 Hz, 1 H), 6.42 (d, *J*=6.6 Hz, 1 H), 5.67 - 5.82 (m, 1 H), 5.19 (dd, *J*=13.9, 2.3 Hz, 2 H), 3.26 (d, *J*=6.6 Hz, 2 H).

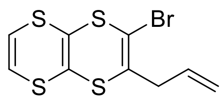
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 139.6, 131.4, 125.7, 125.7, 121.3, 121.0, 118.5, 45.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3078, 3028, 2977, 2905, 1636, 1580, 1549, 1516, 1419, 1279, 1262, 1093, 1037, 987, 969, 918, 887, 866, 821, 803, 768, 736, 671.

MS (70 eV, EI) *m/z* (%): 370 (100), 325 (67), 210 (49), 209 (31), 146 (47), 88 (31).

HRMS (EI): *m/z* (M^+) for $C_9H_7IS_4$: calcd. 369.8475; found 369.8464.

3.8.2 Preparation of 2-bromo-3-allyl-[1,4]dithiino[2,3-*b*][1,4]dithiine (**60b**)



According to **TP5**, 2-bromo-[1,4]dithiino[2,3-*b*][1,4]dithiine (**59b**, 56 mg, 0.20 mmol) was dissolved in dry THF (1.6 mL). TMPZnCl·LiCl (**3**, 0.28 mL, 0.22 mmol, 0.79 M in THF) was added dropwise at -40 ºC and the mixture was stirred for 0.5 h. CuCN·2LiCl (0.04 mL, 0.04 mmol, 1.0 M in THF) was then introduced followed by allyl bromide (36 mg, 0.30 mmol) and the reaction was stirred for 2 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 5 mL), extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane) yielding **60b** as yellow oil (46 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.37 - 6.48 (m, 2 H), 5.74 (ddt, *J*=17.5, 9.6, 6.4 Hz, 1 H), 5.11 - 5.24 (m, 2 H), 3.23 (d, *J*=6.4 Hz, 2 H).

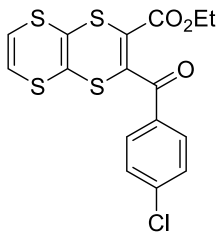
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 136.1, 131.3, 125.9, 125.7, 122.1, 120.7, 118.4, 108.1, 41.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3078, 3028, 2977, 2900, 1637, 1581, 1554, 1516, 1421, 1280, 1265, 987, 918, 887, 871, 841, 803, 769, 712.

MS (70 eV, EI) *m/z* (%): 324 (100), 322 (92), 279 (96), 277 (80), 210 (65), 167 (51), 146 (47), 88 (66), 69 (52), 57 (50), 45 (47).

HRMS (EI): *m/z* (M^+) for $C_9H_7BrS_4$: calcd. 321.8614; found 321.8610.

3.8.3 Synthesis of ethyl 3-(4-chlorobenzoyl)-[1,4]dithiino[2,3-*b*][1,4]dithiine-2-carboxylate (**60c**)



According to **TP5**, ethyl [1,4]dithiino[2,3-*b*][1,4]dithiine-2-carboxylate (**59e**, 83 mg, 0.30 mmol) was dissolved in dry THF (2.4 mL). TMPZnCl·LiCl (**3**, 0.41 mL, 0.33 mmol, 0.80 M in THF) was added dropwise at -40 ºC and the mixture was stirred for 0.5 h. CuCN·2LiCl (0.30 mL, 0.30 mmol, 1.0 M in THF) was then introduced followed by 4-chlorobenzoyl chloride (263 mg, 0.45 mmol) and the reaction was stirred for 2 h at the same temperature and further 12 h allowing to reach 25 ºC. Then, the reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 5 mL), extracted with EtOAc (3 x 15 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 96:4) yielding **60c** as orange oil (68 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.79 (d, *J*=8.4 Hz, 2 H), 7.48 (d, *J*=8.4 Hz, 2 H), 6.50 (d, *J*=6.6 Hz, 1 H), 6.43 (d, *J*=6.6 Hz, 1 H), 4.06 (q, *J*=7.0 Hz, 2 H), 1.05 (t, *J*=7.0 Hz, 3 H).

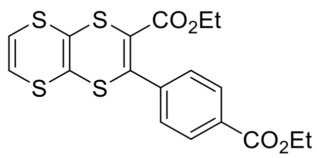
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 187.9, 160.1, 147.5, 140.8, 132.6, 131.3, 130.3, 129.4, 125.6, 125.1, 124.8, 117.7, 62.9, 13.5.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3036, 2958, 2925, 2854, 1714, 1672, 1585, 1572, 1552, 1485, 1463, 1444, 1399, 1366, 1297, 1243, 1172, 1092, 1023, 1011, 966, 907, 860, 837, 799, 769, 760, 739, 720, 678.

MS (70 eV, EI) *m/z* (%): 416 (15), 414 (34), 384 (13), 382 (44), 370 (11), 369 (15), 221 (9), 141 (23), 139 (100), 113 (10), 111 (48), 91 (15), 76 (9), 64 (13), 44 (76), 43 (18).

HRMS (EI): *m/z* (M$^+$) for $C_{16}H_{11}ClO_3S_4$: calcd. 413.9280; found 413.9269.

3.8.4 Preparation of ethyl 3-(4-(ethoxycarbonyl)phenyl)-[1,4]dithiino[2,3-*b*][1,4]dithiine-2-carboxylate (**60d**)



According to **TP5**, ethyl [1,4]dithiino[2,3-*b*][1,4]dithiine-2-carboxylate (**59e**, 55 mg, 0.20 mmol) was dissolved in dry THF (1.6 mL). TMPZnCl·LiCl (**3**, 0.41 mL, 0.33 mmol, 0.80 M in THF) was added dropwise at -40 ºC and the mixture was stirred for 0.5 h. A solution of ethyl 4-iodobenzoate (72 mg, 0.26 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol) and $P(2\text{-furyl})_3$ (6 mg, 0.024 mmol) in dry THF (1 mL) was added to the freshly prepared zinc reagent at -40 ºC. Then, the reaction mixture was stirred at 25 ºC for 12 h. The reaction was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 96:4) yielding **60d** as orange solid (63 mg, 74%).

m.p.: 125.9 - 127.1 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.03 (d, *J*=8.2 Hz, 2 H), 7.41 (d, *J*=8.2 Hz, 2 H), 6.47 (d, *J*=6.6 Hz, 1 H), 6.44 (d, *J*=6.6 Hz, 1 H), 4.40 (q, *J*=7.0 Hz, 2 H), 4.03 (q, *J*=7.2 Hz, 2 H), 1.41 (t, *J*=7.1 Hz, 3 H), 1.00 (t, *J*=7.1 Hz, 3 H).

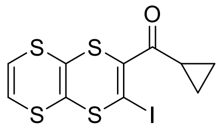
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 165.8, 162.8, 150.8, 140.2, 131.4, 129.5, 129.0, 125.8, 125.1, 124.4, 122.5, 120.4, 62.0, 61.2, 14.3, 13.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2980, 2934, 2902, 1709, 1606, 1573, 1499, 1463, 1444, 1403, 1365, 1269, 1202, 1177, 1102, 1045, 1018, 968, 917, 860, 805, 765, 733, 698, 678.

MS (70 eV, EI) *m/z* (%): 426 (12), 425 (11), 424 (57), 392 (14), 381 (16), 380 (22), 379 (100), 350 (20), 323 (16), 276 (10), 146 (10).

HRMS (EI): *m/z* (M^+) for $C_{18}H_{16}O_4S_4$: calcd. 423.9931; found 423.9916.

3.8.5 Preparation of cyclopropyl(3-iodo-[1,4]dithiino[2,3-*b*][1,4]dithiin-2-yl)-methanone (**60e**)



According to **TP5**, [1,4]dithiino[2,3-*b*][1,4]dithiin-2-yl(cyclopropyl)methanone (**59f**, 54 mg, 0.20 mmol) was dissolved in dry THF (1.6 mL). TMPZnCl·LiCl (**3**, 0.27 mL, 0.22 mmol, 0.81 M in THF) was added dropwise at -40 ºC and the mixture was stirred for 0.5 h. Iodine (76 mg, 0.30 mmol) in dry THF (1 mL) was added at -78 ºC and stirred for 2 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 96:4) yielding **60e** as orange solid (66 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.48 (d, *J*=6.7 Hz, 1 H), 6.43 (d, *J*=6.7 Hz, 1 H), 2.34 - 2.43 (m, 1 H), 1.27 (quin, *J*=3.8 Hz, 2 H), 1.12 (dq, *J*=7.5, 3.7 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 197.5, 137.0, 125.9, 125.4, 122.6, 121.1, 83.0, 20.8, 14.1.

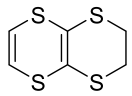
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3032, 2923, 1667, 1580, 1524, 1501, 1442, 1416, 1370, 1262, 1190, 1149, 1110, 1088, 1062, 1027, 976, 950, 925, 883, 864, 842, 803, 771, 734.

MS (70 eV, EI) *m/z* (%): 400 (20), 398 (100), 353 (50), 243 (19), 146 (52), 88 (35), 69 (80), 41 (58).

HRMS (EI): *m/z* (M^+) for $C_{10}H_7IOS_4$: calcd. 397.8424; found 397.8414.

3.9 PREPARATION OF NEW S-HETEROCYCLES

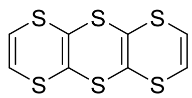
3.9.1 Preparation of 2,3-dihydro-[1,4]dithiino[2,3-*b*][1,4]dithiine (**62**)



1,2-Ethanedithiol (**61**, 9.4 mg, 0.10 mmol) was dissolved in THF (0.25 mL) and *n*BuLi (0.09 mL, 0.22 mmol, 2.44 M in hexane) was added dropwise at -78 ºC. After 0.5 h, a solution of 2,3-diiodo-1,4-dithiin (**49e**, 37 mg, 0.10 mmol) in THF (0.5 mL) was added and the resulting mixture was stirred at -78 ºC for 2 h. The temperature was increased to 25 ºC and stirring was continued for 0.5 h. The reaction was quenched by the addition of sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 15 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc 96:4) yielding **62** as yellow oil (3 mg, 15%).[97]

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.61 (s, 2H), 3.24 (s, 4H).

3.9.2 Preparation of 1,4,5,6,9,10-hexathiaanthracene (**63**)



Di(1,4-dithiin-2-yl)sulfane (**44l**, 52 mg, 0.20 mmol) was dissolved in dry $CHCl_3$ (20 mL). Sulfur dichloride (41 mg, 0.40 mmol) in dry $CHCl_3$ (3 mL) was added dropwise at 0 ºC over 15 min and the mixture was stirred for 3 h allowing to reach 25 ºC. Then, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (*i*hexane/CH_2Cl_2, 8:2) yielding **63** as light yellow solid (32 mg, 55%).

m.p.: 194.0 - 195.8 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.42 (s, 4 H).

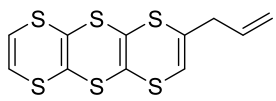
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 125.6, 123.5.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3029, 2916, 1583, 1552, 1514, 1278, 1264, 1132, 981, 882, 846, 806, 776, 672.

MS (70 eV, EI) *m/z* (%): 292 (100), 247 (42), 190 (55), 158 (39), 88 (61), 57 (36).

HRMS (EI): *m/z* (M+) for $C_8H_4S_6$: calcd. 291.8637; found 291.8636.

3.9.2.1 Preparation of 2-allyl-1,4,5,6,9,10-hexathiaanthracene (**64**)



According to **TP6**, 1,4,5,6,9,10-hexathiaanthracene (**63**, 29 mg, 0.10 mmol) was dissolved in dry THF (3 mL). TMPZnCl·LiCl (**3**, 0.14 mL, 0.11 mmol, 0.79 M in THF) was added dropwise at -40 ºC and the mixture was stirred for 2 h. CuCN·2LiCl (0.02 mL, 0.02 mmol, 1.0 M in THF) was then introduced followed by allyl bromide (22 mg, 0.15 mmol) and the reaction was stirred for 12 h allowing to reach 25 ºC. Then, the reaction mixture was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 5 mL), extracted with EtOAc (3 x 15 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by HPLC yielding **64** as yellow solid (17 mg, 51%).

m.p.: 119.2 - 121.4 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.42 (s, 2 H), 6.07 (s, 1 H), 5.77 (ddt, *J*=16.6, 10.3, 6.4 Hz, 1 H), 5.13 - 5.22 (m, 2 H), 3.07 (dd, *J*=6.4, 0.8 Hz, 2 H).

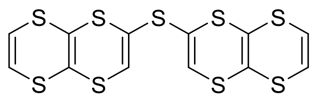
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 141.5, 132.9, 125.7, 124.2, 123.5, 123.5, 119.2, 118.8, 40.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3077, 3027, 2922, 2852, 1640, 1592, 1554, 1514, 1422, 1408, 1283, 1265, 1225, 1108, 1046, 985, 914, 883, 845, 805, 769, 732.

MS (70 eV, EI) *m/z* (%): 334 (24), 332 (100), 268 (17), 247 (24), 230 (20), 190 (25), 158 (21), 146 (22), 88 (37), 83 (20), 73 (22), 71 (25), 69 (30), 57 (42), 55 (33), 43 (37), 41 (29).

HRMS (EI): *m/z* (M+) for $C_{11}H_8S_6$: calcd. 331.8950; found 331.8953.

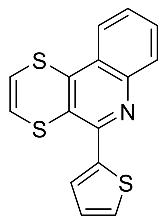
3.9.3 Preparation of di[1,4]dithiino[2,3-*b*][1,4]dithiin-2-ylsulfane (**66**)



According to **TP4**, 1,4,5,8-tetrathianaphthalene (**41**, 204 mg, 0.50 mmol) was dissolved in dry THF (4 mL). TMPMgCl·LiCl (**2**, 0.55 mL, 0.60 mmol, 1.09 M in THF) was added dropwise at -78 ºC and the mixture was stirred for 10 min. Bis(phenylsulfonyl)sulfide (**79**, 79 mg, 0.25 mmol) in dry THF (1 mL) was added at -78 ºC and stirred for 1.5 h. The resulting solution was then quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 x 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo* and no further purification was performed. The crude ^{1}H NMR shown that ca. 51% from the obtained oil was the desired product **66**.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.57 (s, 2 H), 6.46 (d, *J*=6.6 Hz, 2 H), 6.44 (d, *J*=6.6 Hz, 2 H).

3.9.4 Preparation of 5-(thiophen-2-yl)-[1,4]dithiino[2,3-*c*]quinoline (**67**)



According to the literature,[118] thiophene-2-carbaldehyde (73 mg, 0.65 mmol) was added to a solution of 2-(1,4-dithiin-2-yl)aniline (**44k**, 104 mg, 0.50 mmol) and TFA (114 mg, 1.00 mmol) in EtOH (0.2 mL) at 25 ºC. The reaction mixture was heated under microwave irradiation using a Biotage Initiator 2.5 system (130 ºC, 100 W, 15 min). The reaction mixture was allowed to cool to 25 ºC and was then quenched with sat. aq. NH_4Cl solution (5 mL), extracted with EtOAc (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc/NEt_3, 98:2:0.05) yielding **67** as yellow solid (90 mg, 60%).

m.p.: 128.8 - 131.2 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.28 (d, *J*=8.4 Hz, 1 H), 8.09 (d, *J*=8.4 Hz, 1 H), 7.94 (d, *J*=3.1 Hz, 1 H), 7.68 - 7.74 (m, 1 H), 7.51 - 7.60 (m, 2 H), 7.20 (dd, *J*=4.8, 4.0 Hz, 1 H), 6.71 (d, *J*=6.6 Hz, 1 H), 6.60 (d, *J*=6.6 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 149.8, 146.3, 142.6, 142.5, 130.0, 130.0, 129.5, 128.8, 127.4, 127.2, 126.6, 126.3, 125.9, 124.1, 123.5.

[118] S. W. Youn, J. H. Bihn, *Tetrahedron Lett.* **2009**, *50*, 4598.

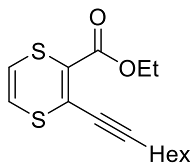
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3079, 3064, 3021, 2923, 2852, 1607, 1579, 1558, 1544, 1531, 1474, 1447, 1425, 1374, 1356, 1336, 1307, 1292, 1235, 1221, 1156, 1134, 1070, 1051, 971, 916, 894, 882, 858, 849, 836, 799, 774, 760, 743, 729, 706, 687, 656.

MS (70 eV, EI) *m/z* (%): 301 (14), 300 (25), 299 (100), 298 (46), 267 (14), 266 (45), 222 (10).

HRMS (EI): *m/z* (M^+) for $C_{15}H_9NS_3$: calcd. 298.9897; found 298.9889.

3.9.5 Preparation of 7-hexanoyl-8-iodo-5*H*-[1,4]dithiino[2,3-*c*]pyran-5-one (**69**)

3.9.5.1 Preparation of ethyl 3-(3-oxooct-1-yn-1-yl)-1,4-dithiine-2-carboxylate (**68**)



Ethyl 3-iodo-1,4-dithiine-2-carboxylate (**48c**, 1.13 g, 3.60 mmol) was added to a solution of 1-octyne (593 mg, 5.40 mmol), CuI (14 mg, 0.07 mmol) and $Pd(PPh_3)_2Cl_2$ (25 mg, 0.04 mmol) in NEt_3 (18 mL) at 25 ºC. The reaction mixture was stirred at this temperature for 4 h and was then quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 x 70 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1) yielding **68** as orange oil (817 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.38 (s, 2 H), 4.28 (q, *J*=7.0 Hz, 2 H), 2.44 (t, *J*=7.1 Hz, 2 H), 1.59 (quin, *J*=7.3 Hz, 2 H), 1.38 - 1.47 (m, 2 H), 1.27 - 1.36 (m, 6 H), 0.86 - 0.94 (m, 3 H).

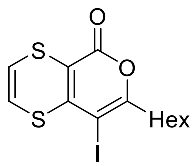
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 161.7, 128.5, 128.2, 123.7, 123.6, 102.7, 61.9, 31.3, 28.6, 28.1, 22.5, 20.1, 14.1, 14.0. (One signal not observed; possible coincidental isochronicity).

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3035, 2954, 2929, 2857, 2208, 1701, 1562, 1530, 1464, 1444, 1426, 1389, 1365, 1325, 1260, 1233, 1181, 1110, 1094, 1044, 1016, 960, 898, 864, 830, 797, 760, 723, 676.

MS (70 eV, EI) *m/z* (%): 298 (11), 297 (19), 296 (100), 198 (13), 197 (25), 171 (10), 153 (50), 143 (15), 43 (36), 41 (10).

HRMS (EI): *m/z* (M^+) for $C_{15}H_{20}O_2S_2$: calcd. 296.0905; found 296.0900.

3.9.5.2 Preparation of 7-hexanoyl-8-iodo-5*H*-[1,4]dithiino[2,3-*c*]pyran-5-one (**69**)



According to literature,[119] a solution of iodine (841 mg, 3.30 mmol) in dry CH_2Cl_2 (22 mL) was added dropwise to a solution of ethyl 3-(3-oxooct-1-yn-1-yl)-1,4-dithiine-2-carboxylate (**68**, 817 mg, 2.80 mmol) in dry CH_2Cl_2 (35 mL) at 25 ºC. The reaction mixture was stirred at this temperature for 2 h and was then quenched with sat. aq. $Na_2S_2O_3$ solution (5 mL), extracted with CH_2Cl_2 (3 x 10 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/CH_2Cl_2, 2:1) yielding **69** as red oil (972 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.32 (d, *J*=7.1 Hz, 1 H), 6.11 (d, *J*=7.1 Hz, 1 H), 2.78 - 2.85 (m, 2 H), 1.66 (quin, *J*=7.6 Hz, 2 H), 1.36 (quin, *J*=7.0 Hz, 2 H), 1.26 - 1.33 (m, 4 H), 0.89 (t, *J*=6.7 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 163.0, 156.8, 153.3, 125.2, 121.4, 113.9, 74.1, 37.2, 31.3, 28.7, 27.0, 22.4, 14.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3035, 2952, 2925, 2854, 1697, 1574, 1554, 1489, 1463, 1377, 1351, 1333, 1252, 1175, 1144, 1105, 1029, 977, 891, 858, 792, 745, 723, 673.

MS (70 eV, EI) *m/z* (%): 396 (10), 395 (17), 394 (100), 324 (34), 295 (10), 197 (24), 127 (23), 43 (23), 41 (10).

HRMS (EI): *m/z* (M^+) for $C_{13}H_{15}O_2IS_2$: calcd. 393.9558; found 393.9553.

[119] T. Yao, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 5936.

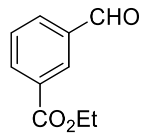
4. ZINCATION AND MAGNESIATION OF FUNCTIONALIZED SILYLATED CYANOHYDRINS USING TMP-BASES

4.1 PREPARATION OF STARTING MATERIALS

3-Formylbenzoic acid, 4-(dimethylamino)benzaldehyde, 2-chloro-3-iodopyridine and indole-3-carboxaldehyde are commercial available.

4.1.1 Preparation of ethyl 3-(((*tert*-butyldimethylsilyl)oxy)(cyano)methyl)-benzoate (**71a**)

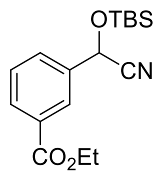
4.1.1.1 Preparation of ethyl 3-formylbenzoate (**80**)



According to the literature,[120] 3-formylbenzoic acid (751 mg, 5.00 mmol) was dissolved in DMF (50 mL) and K_2CO_3 (1.4 g, 10.0 mmol) and EtI (1.6 g, 10.0 mmol) were added to this solution. The reaction mixture was stirred at 60 ºC under nitrogen atmosphere for 14 h. The resulting solution was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with EtOAc (3 x 50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 96:4 to 9:1) yielding **80** as white solid (561 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 10.11 (s, 1H), 8.59 (s, 1H), 8.29 (d, J = 7.6 Hz, 1 H), 8.11 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 4.46 (q, J = 7.0 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H).

4.1.1.2 Preparation of ethyl 3-(((*tert*-butyldimethylsilyl)oxy)(cyano)methyl)-benzoate (**71a**)



[120] H. Horiuchi, M. Hosaka, H. Mashio, M. Terata, S. Ishida, S. Kyushin, T. Okutsu, T. Takeuchi, H. Hiratsuka, *Chem. Eur. J.* **2014**, *20*, 6054.

According to the literature,[34b] ethyl 3-formylbenzoate (**80**, 866 mg, 4.90 mmol), CsF (148 mg, 0.97 mmol) and *t*Bu$(CH_3)_2$SiCN (1.3 g, 7.3 mmol) were dissolved in dry CH_3CN (4.9 mL). The reaction was stirred at 25 ºC for 12 h. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 95:5 to 9:1) yielding **71a** as a colorless oil (1.4 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.15 (br. s, 1 H), 8.08 (d, *J*=7.6 Hz, 1 H), 7.69 (d, *J*=7.6 Hz, 1 H), 7.52 (t, *J*=7.6 Hz, 1 H), 5.58 (s, 1 H), 4.41 (q, *J*=7.0 Hz, 2 H), 1.42 (t, *J*=7.0 Hz, 3 H), 0.96 (s, 9 H), 0.26 (s, 3 H), 0.18 (s, 3 H).

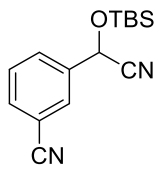
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 165.8, 136.9, 131.3, 130.4, 130.2, 129.1, 127.2, 118.9, 63.5, 61.3, 25.5, 18.2, 14.3, -5.1, -5.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2957, 2932, 2887, 2860, 1719, 1610, 1592, 1472, 1146, 1392, 1367, 1284, 1255, 1188, 1107, 1078, 1023, 1006, 914, 892, 837, 780, 746, 734, 698, 673.

MS (70 eV, EI) *m/z* (%): 304 (5), 262 (100), 219 (64), 207 (26), 202 (46), 191 (8), 163 (12), 133 (13), 75 (8).

HRMS (EI): *m/z* for $C_{16}H_{22}NO_3Si^+$: calcd. 304.1369; found 304.1364.

4.1.2 Preparation of 3-(((*tert*-butyldimethylsilyl)oxy)(cyano)methyl)benzonitrile (**71b**)



According to the literature,[34b] 3-cyanobenzaldehyde (525 mg, 4.00 mmol), CsF (122 mg, 0.8 mmol) and *t*Bu$(CH_3)_2$SiCN (848 mg, 6.00 mmol) were dissolved in dry CH_3CN (4 mL). The reaction was stirred at 25 ºC for 12 h. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1) yielding **71b** as a colorless oil (1.1 g, 98%).

m.p.: 40.6 - 42.0 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.78 (s, 1 H), 7.70 (d, *J*=8.2 Hz, 1 H), 7.73 (d, *J*=8.2 Hz, 1 H), 7.57 (t, *J*=8.2 Hz, 1 H), 5.56 (s, 1 H), 0.96 (s, 9 H), 0.27 (s, 3 H), 0.20 (s, 3 H).

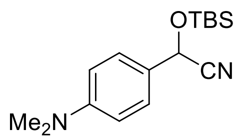
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 138.1, 132.8, 130.2, 129.8, 129.5, 118.3, 118.0, 113.2, 63.0, 25.4, 18.1, -5.2, -5.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2956, 2932, 2887, 2860, 2234, 1471, 1437, 1409, 1392, 1363, 1340, 1256, 1228, 1149, 1112, 1086, 1006, 957, 940, 902, 879, 835, 803, 781, 735, 688, 676.

MS (70 eV, EI) *m/z* (%): 272 (0.5), 246 (10), 215 (100), 147 (9), 84 (33), 73 (21), 57 (13), 41 (7).

HRMS (EI): *m/z* (M^+) for $C_{15}H_{20}N_2OSi$: calcd. 272.1345; found 272.1324.

4.1.3 Preparation of 2-((*tert*-butyldimethylsilyl)oxy)-2-(4-(dimethylamino)phenyl)-acetonitrile (**71c**)



According to the literature,[34b] 4-(dimethylamino)benzaldehyde (447 mg, 3.00 mmol), CsF (91 mg, 0.60 mmol) and *t*Bu$(CH_3)_2$SiCN (636 mg, 4.50 mmol) were dissolved in dry CH_3CN (3 mL). The reaction was stirred at 25 ºC for 12 h. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 96:4) yielding **71c** as a yellow oil (766 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.32 (d, *J*=8.6 Hz, 2 H), 6.73 (d, *J*=8.6 Hz, 2 H), 5.43 (s, 1 H), 2.99 (s, 6 H), 0.93 (s, 9 H), 0.20 (s, 3 H), 0.12 (s, 3 H).

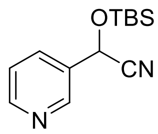
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 150.9, 127.5, 119.7, 112.2, 64.0, 40.4, 25.6, 18.1, -5.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2955, 2930, 2887, 2858, 1613, 1524, 1471, 1463, 1445, 1360, 1254, 1230, 1185, 1166, 1132, 1064, 1005, 940, 909, 835, 814, 778, 730, 672.

MS (70 eV, EI) *m/z* (%): 290 (11), 160 (15), 159 (100), 148 (12), 75 (7), 57 (9).

HRMS (EI): *m/z* (M$^+$) for $C_{16}H_{26}N_2OSi$: calcd. 290.1814; found 290.1818.

4.1.4 Preparation of 2-((*tert*-butyldimethylsilyl)oxy)-2-(pyridin-3-yl)acetonitrile (**71d**)



According to the literature,[34b] 3-pyridinecarboxaldehyde (428 mg, 4.00 mmol), CsF (122 mg, 0.80 mmol) and tBu(CH_3)$_2$SiCN (848 mg, 6.00 mmol) were dissolved in dry CH_3CN (4 mL). The reaction was stirred at 25 ºC for 12 h. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1 to 8:2 + 2% NEt_3) yielding **71d** as a colorless oil (903 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.69 (s, 1 H), 8.63 (d, *J*=4.5 Hz, 1 H), 7.81 (d, *J*=7.8 Hz, 1 H), 7.35 (dd, *J*=7.8, 4.5 Hz, 1 H), 5.56 (s, 1 H), 0.92 (s, 9 H), 0.24 (s, 3 H), 0.16 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 150.5, 147.6, 133.7, 132.3, 123.6, 118.3, 62.0, 25.4, 18.0, -5.2, -5.3.

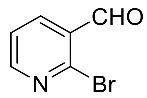
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2955, 2931, 2887, 2859, 1592, 1579, 1472, 1427, 1391, 1363, 1255, 1213, 1089, 1025, 1006, 960, 937, 920, 835, 780, 732, 709, 678, 662.

MS (70 eV, EI) *m/z* (%): 248 (2), 191 (100), 117 (7), 84 (24), 75 (9), 57 (4), 41 (3).

HRMS (EI): *m/z* (M$^+$) for $C_{13}H_{20}N_2OSi$: calcd. 248.1345; found 248.1345.

4.1.5 Preparation of 2-(2-bromopyridin-3-yl)-2-((*tert*-butyldimethylsilyl)oxy)-acetonitrile (**71e**)

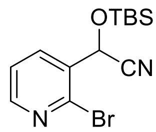
4.1.5.1 Preparation of 2-bromo-3-pyridinecarboxaldehyde (**81**)



According to the literature,[121] a dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with a solution of lithium diisopropylamide (30.0 mmol, 0.5 M in THF) and was cooled to -78 ºC. 2-Bromopyridine (7.9 g, 10.0 mmol) was added dropwise to the cooled solution. The resulting mixture was stirred for 1 h at -78 ºC. DMF (2.9 g, 40.0 mmol) was then added and stirred for 1 h at -78 ºC. The resulting solution was quenched with sat. aq. NH_4Cl solution (40 mL), extracted with EtOAc (3 x 80 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 8:2 + NEt_3 2%) yielding **81** as colorless oil (1.0 g, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 10.34 (1 H, s), 8.60 (dd, J = 4.5, 2.1 Hz, 1 H), 8.19 (dd, J = 7.9, 2.1 Hz, 1 H), 7.46 (dd, J = 7.9, 4.5 Hz, 1 H).

4.1.5.2 Preparation of 2-(2-bromopyridin-3-yl)-2-((*tert*-butyldimethylsilyl)oxy)-acetonitrile (**71e**)



According to the literature,[34b] 2-bromo-3-pyridinecarboxaldehyde (**81**, 430 mg, 2.30 mmol), CsF (70 mg, 0.46 mmol) and *t*Bu$(CH_3)_2$SiCN (492 mg, 3.5 mmol) were dissolved in dry CH_3CN (2.3 mL). The reaction was stirred at 25 ºC for 12 h. The resulting reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 30 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1) yielding **71e** as a colorless oil (670 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.43 (dd, *J*=4.8, 1.6 Hz, 1 H), 8.02 (dd, *J*=7.7, 1.6 Hz, 1 H), 7.41 (dd, *J*=7.7, 4.8 Hz, 1 H), 5.69 (s, 1 H), 0.95 (s, 9 H), 0.30 (s, 3 H), 0.20 (s, 3 H).

[121] P. Melnyk, J. Gasche, C. Thal, *Synth. Commun.* **1993**, *23*, 2727.

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 150.7, 140.9, 136.7, 133.4, 123.5, 117.5, 62.8, 25.5, 18.1, -5.2, -5.3.

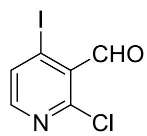
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2955, 2931, 2887, 2859, 1577, 1563, 1472, 1401, 1363, 1330, 1287, 1256, 1184, 1125, 1103, 1049, 1006, 938, 924, 835, 781, 739, 698, 674.

MS (70 eV, EI) *m/z* (%): 312 (1), 271 (100), 270 (15), 190 (51), 139 (29), 137 (31), 84 (13), 75 (15), 57 (20).

HRMS (EI): *m/z* for $C_{13}H_{19}BrN_2OSi^+$: calcd. 312.0294; found 312.0253.

4.1.6 Preparation of 3-((*tert*-butyldimethylsilyloxy)(cyano)methyl)-2-chloro-isonicotinonitrile (**71f**)

4.1.6.1 Preparation of 2-chloro-4-iodonicotinaldehyde (**82**)

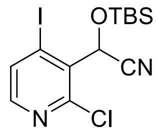


According to the literature,[122] a dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with a solution of lithium diisopropylamide (18.0 mmol, 1.0 M in THF) and was cooled to -78 ºC. 2-Chloro-3-iodopyridine (3.1 g, 13.0 mmol) was added dropwise to the cooled solution. The resulting mixture was stirred for 3 h at -78 ºC. Ethyl formate (2.5 g, 34.0 mmol) was then added and stirred for 1.5 h at -78 ºC. The resulting solution was quenched with sat. aq. NH_4Cl solution (80 mL), extracted with EtOAc (3 x 120 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1 to 8:2 + NEt_3 2%) yielding **82** as yellow solid (1.8 g, 52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 10.19 (s, 1 H), 8.07 (d, *J*=5.1 Hz, 1 H), 7.94 (d, *J*=5.1 Hz, 1 H).

4.1.6.2 Preparation of 2-(*tert*-butyldimethylsilyloxy)-2-(2-chloro-4-iodopyridin-3-yl)acetonitrile (**83**)

[122] T. Blench, S. Goodacre, Y. Lai, Y. Liang, C. MacLeod, S. Magnuson, V. Tsui, K. Williams, B. Zhang, La Roche A.-G., Switzerland, WO2012066061, **2012**.



According to the literature,[34b] 2-chloro-4-iodonicotinaldehyde (**82**, 989 mg, 3.70 mmol), CsF (112 mg, 0.74 mmol) and *t*Bu(CH_3)$_2$SiCN (784 mg, 5.60 mmol) were dissolved in dry CH_3CN (3.7 mL). The reaction was stirred at 25 ºC for 12 h. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 40 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1 + NEt_3 2%) yielding **83** as a light yellow solid (1.5 g, 98%).

m.p.: 83.4 - 85.2 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.99 (d, *J*=5.2 Hz, 1 H), 7.85 (d, *J*=5.2 Hz, 1 H), 6.24 (s, 1 H), 0.94 (s, 9 H), 0.31 (s, 3 H), 0.13 (s, 3 H).

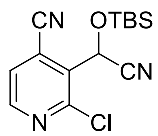
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 150.3, 149.9, 135.5, 132.5, 116.7, 110.3, 65.2, 25.4, 18.0, -4.9, -5.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2955, 2930, 2887, 2859, 1636, 1548, 1534, 1472, 1434, 1370, 1337, 1302, 1255, 1186, 1109, 1066, 1006, 939, 911, 833, 781, 760, 727.

MS (70 eV, EI) *m/z* (%): 353 (28), 351 (79), 323 (52), 296 (4), 226 (35), 224 (100), 209 (12), 150 (6), 93 (20).

HRMS (EI): *m/z* for $C_9H_9ClIN_2OSi^+$: calcd. 350.9217; found 350.9210.

4.1.6.3 Preparation of 3-((*tert*-butyldimethylsilyloxy)(cyano)methyl)-2-chloro-isonicotinonitrile (**71f**)



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with 2-(*tert*-butyldimethylsilyloxy)-2-(2-chloro-4-iodopyridin-3-yl)aceto-nitrile (**83**, 2.3 g, 5.70 mmol) in 23 mL THF and *i*PrMgCl·LiCl (**1**, 5.0 mL, 5.90 mmol, 1.20 M) was added at -60 ºC. After 0.5 h, GC-analysis of hydrolyzed reaction aliquot showed full consumption of the starting material. A solution of tosyl cyanide (1.6 g, 8.60 mmol) in THF (5 mL) was then added dropwise at -78 ºC and let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl solution (30 mL), extracted with EtOAc (3 x 60 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1 + NEt_3 2%) yielding **71f** as colorless oil (1.2 g, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.63 (d, *J*=4.9 Hz, 1 H), 7.65 (d, *J*=4.9 Hz, 1 H), 6.04 (s, 1 H), 0.96 (s, 9 H), 0.34 (s, 3 H), 0.21 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 151.0, 150.7, 132.1, 126.9, 122.7, 116.0, 113.6, 60.4, 25.4, 18.2, -5.3.

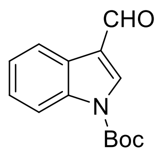
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2932, 2860, 1633, 1575, 1541, 1472, 1387, 1364, 1338, 1299, 1257, 1166, 1102, 1072, 1006, 940, 885, 839, 808, 783.

MS (70 eV, EI) *m/z* (%): 306 (1), 292 (7), 250 (100), 223 (12), 208 (19), 93 (20).

HRMS (EI): *m/z* for $C_{14}H_{17}ClN_3OSi^+$: calcd. 306.0829; found 306.0821.

4.1.7 Preparation of *tert*-butyl 3-((*tert*-butyldimethylsilyloxy)(cyano)methyl)-1*H*-indole-1-carboxylate (**71g**)

4.1.7.1 Preparation of *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate (**84**)

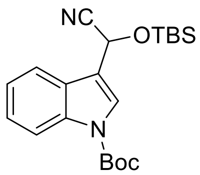


According to the literature,[123] di-*tert*-butyl dicarbonate (2.6 g, 12.0 mmol), NEt_3 (1.8 mL, 13.0 mmol) followed by DMAP (122 mg, 1.00 mmol) were added to a solution of indole-3-carboxaldehyde (1.5 g, 10.0 mmol) in dry CH_2Cl_2 (50 mL). The reaction mixture was then stirred at 25 ºC for 12 h. The resulting mixture was diluted with CH_2Cl_2 and washed with a saturated aqueous solution of NH_4Cl (50 mL). The product was extracted with CH_2Cl_2 (2 x 80 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1) yielding **84** as white solid (2.3 g, 96%).

[123] X.-L. Xu, J. Wang, C.-L. Yu, W. Chen, Y.-C. Li, Y. Li, H.-B. Zhang, X.-D. Yang, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4926.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 10.11 (s, 1H), 8.29-8.32 (m, 1H), 8.23 (s, 1H), 8.14 (d, J = 7.5 Hz, 1H), 7.45-7.30 (m, 2H), 1.71 (s, 9H).

4.1.7.2 Preparation of *tert*-butyl 3-((*tert*-butyldimethylsilyloxy)(cyano)methyl)-1*H*-indole-1-carboxylate (**71g**)



According to the literature,[34b] *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate (**84**, 2.4 g, 9.60 mmol), CsF (288 mg, 1.90 mmol) and *t*Bu$(CH_3)_2$SiCN (2.0 g, 14.4 mmol) were dissolved in dry CH_3CN (9.6 mL). The reaction was stirred at 25 ºC for 12 h. The resulting mixture was diluted with water (40 mL) and extracted with EtOAc (3 x 80 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 98:2 to 95:5) yielding **71g** as a colorless oil (3.6 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.18 (d, *J*=6.9 Hz, 1 H), 7.70 - 7.74 (m, 2 H), 7.37 - 7.41 (m, 1 H), 7.31 (t, *J*=7.4 Hz, 1 H), 5.75 (s, 1 H), 1.70 (s, 9 H), 0.95 (s, 9 H), 0.26 (s, 3 H), 0.19 (s, 3 H).

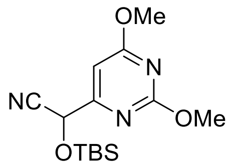
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 149.3, 135.8, 127.1, 125.2, 124.2, 123.1, 119.4, 118.5, 116.7, 115.5, 84.4, 57.9, 28.1, 25.5, 18.1, -5.1, -5.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2956, 2932, 2859, 1739, 1635, 1570, 1518, 1472, 1452, 1369, 1336, 1308, 1288, 1255, 1224, 1155, 1130, 1089, 1071, 1018, 909, 838, 800, 780, 767, 731, 676.

MS (70 eV, EI) *m/z* (%): 386 (11), 273 (56), 259 (17), 229 (100), 202 (29), 154 (23), 75 (55), 57 (41).

HRMS (EI): *m/z* (M^+) for $C_{21}H_{30}N_2O_3Si$: calcd. 386.2026; found 386.2024.

4.1.8 Preparation of 2-(*tert*-butyldimethylsilyloxy)-2-(2,6-dimethoxypyrimidin-4-yl)acetonitrile (**71h**)



According to the literature,[124] 2,4-dimethoxypyrimidine (71 mg, 0.50 mmol) was dissolved in dry THF (1 mL). TMPMgCl·LiCl (**2**, 0.46 mL, 0.55 mmol, 1.20 M in THF) was added dropwise at 25 ºC and the reaction mixture was stirred for 0.5 h. DMF (55 mg, 0.75 mmol) was then added at -78 ºC and let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The resulting oil containing the product, 2,6-dimethoxypyrimidine-4-carbaldehyde, and ca. 50% of the 2,4-dimethoxypyrimidine was dried on the high vacuum line and used in the next step without further purification.

According to the literature,[34b] the freshly synthesized 2,6-dimethoxypyrimidine-4-carbaldehyde CsF (7.6 mg, 0.05 mmol) and *t*Bu$(CH_3)_2$SiCN (53 mg, 0.38 mmol) were dissolved in dry CH_3CN (0.5 mL). The reaction was stirred at 25 ºC for 12 h. The resulting reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 20 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1) yielding **71h** as a white solid (37 mg, 26% over 2 steps).

m.p.: 90.0 - 90.9 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.61 (s, 1 H), 5.35 (s, 1 H), 3.98 (s, 3 H), 3.97 (s, 3 H), 0.95 (s, 9 H), 0.25 (s, 3 H), 0.19 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 172.6, 165.7, 165.2, 117.6, 98.0, 64.2, 55.0, 54.1, 25.4, 18.1, -5.3, -5.5.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2955, 2932, 2860, 1633, 1599, 1573, 1484, 1463, 1386, 1356, 1255, 1204, 1158, 1129, 1095, 1079, 1038, 942, 837, 783.

MS (70 eV, EI) *m/z* (%): 308 (1), 294 (3), 252 (100), 224 (1), 84 (2), 72 (2).

HRMS (EI): *m/z* for $C_{14}H_{22}N_3O_3Si^+$: calcd. 308.1430; found 308.1408.

[124] M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*, 3237.

4.2 GENERAL PROCEDURES

Typical Procedure for the zincation of protected cyanohydrins (71) with $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (4) (TP1):

A dry and argon flushed Schlenk-flask was charged with a solution of the protected cyanohydrins (**71**, 1.0 equiv) in dry THF (0.25 M). $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**4**, 1.1 equiv) was added dropwise at the indicated temperature and the reaction mixture was stirred for 1-2 h. The completion of the reaction was checked by TLC analysis of reaction aliquots quenched with iodine in dry THF.

Typical Procedure for the magnesiation of protected cyanohydrins (71) with TMPMgCl·LiCl (2) (TP2):

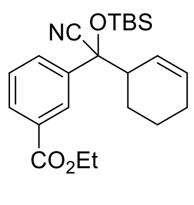
A dry and argon flushed Schlenk-flask was charged with a solution of the protected cyanohydrins (**71**, 1.0 equiv) in dry THF (0.25 M). TMPMgCl·LiCl (**2**, 1.3 equiv) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. The completion of the reaction was checked by TLC analysis of reaction aliquots quenched with allyl bromide in dry THF.

Typical Procedure for the deprotection of silylated cyanohydrins (74) with TBAF (TP3):

An argon flushed round-bottom flask with a magnetic stirring bar and a septum was charged with silylated cyanohydrin derivative (**74**, 1.0 equiv) in dry THF (0.07 M) at -78 ºC. TBAF (1.1 equiv, 1.0 M in THF) was added dropwise to the solution. The reaction mixture was then stirred at -78 ºC. The completion of the reaction was checked by TLC analysis of reaction aliquots.

4.3 SYNTHESIS OF AROMATIC FUNCTIONALIZED PROTECTED CYANOHYDRIN DERIVATIVES

4.3.1 Preparation of ethyl 3-((*tert*-butyldimethylsilyloxy)(cyano)(cyclohex-2-enyl)methyl)benzoate (**74a**)



According to **TP1**, ethyl 3-(((*tert*-butyldimethylsilyl)oxy)(cyano)methyl)benzoate (**71a**, 160 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (**4**, 1.62 mL, 0.55 mmol, 0.34 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. CuCN·2LiCl solution (0.10 mL, 0.10 mmol, 1.0 M in THF) was added at -40 ºC and stirred for 5 min. 3-Bromocyclohexene (72 mg, 0.45 mmol) was added and the reaction mixture was stirred at -40 ºC and let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by HPLC yielding **74a** as colorless oil (97 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.21 (s, 1 H), 8.06 (d, *J*=7.7 Hz, 1 H), 7.73 (d, *J*=7.7 Hz, 1 H), 7.48 (t, *J*=7.7 Hz, 1 H), 5.90 - 6.01 (m, 2 H), 4.33 - 4.48 (m, 2 H), 2.69 (br. s., 1 H), 1.94 - 2.03 (m, 2 H), 1.65 - 1.74 (m, 1 H), 1.35 - 1.46 (m, 4 H), 1.16 - 1.30 (m, 2 H), 0.95 (s, 9 H), 0.20 (s, 3 H), -0.19 (s, 3 H).

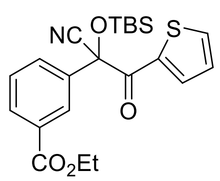
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 165.9, 140.3, 131.4, 130.9, 130.2, 129.9, 128.4, 126.8, 124.9, 119.4, 79.1, 61.2, 49.1, 25.7, 24.9, 24.6, 21.4, 18.3, 14.3, -3.8, -4.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3367, 2932, 2860, 1718, 1636, 1532, 1472, 1391, 1368, 1302, 1281, 1202, 1096, 1023, 908, 839, 781, 728, 674, 692.

MS (70 eV, EI) *m/z* (%): 399 (0.2), 356 (3), 318 (21), 315 (17), 296 (6), 177 (100), 149 (6), 73 (14).

HRMS (EI): *m/z* (M^+) for $C_{23}H_{33}NO_3Si$: calcd. 399.2230; found 399.2231.

4.3.2 Preparation of ethyl 3-(1-(*tert*-butyldimethylsilyloxy)-1-cyano-2-oxo-2-(thiophen-2-yl)ethyl)benzoate (**74b**)



According to **TP1**, ethyl 3-(((*tert*-butyldimethylsilyl)oxy)(cyano)methyl)benzoate (**71a**, 160 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (**4**, 1.62 mL, 0.55 mmol, 0.34 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. CuCN·2LiCl solution (0.10 mL, 0.10 mmol, 1.0 M in THF) was added at -40 ºC and stirred for 5 min. 2-Thiophenecarbonyl chloride (95 mg, 0.65 mmol) was added and the reaction mixture was stirred at -40 ºC and let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 95:5 to 9:1) yielding **74b** as a light yellow oil (133 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.42 (s, 1 H), 8.08 (d, *J*=7.7 Hz, 1 H), 7.81 (d, *J*=7.7 Hz, 1 H), 7.77 (d, *J*=4.0 Hz, 1 H), 7.67 (d, *J*=4.0 Hz, 1 H), 7.51 (t, *J*=7.7 Hz, 1 H), 7.04 (t, *J*=4.0 Hz, 1 H), 4.39 (qd, *J*=7.0, 1.9 Hz, 2 H), 1.40 (t, *J*=7.0 Hz, 3 H), 1.00 (s, 9 H), 0.32 (s, 3 H), 0.20 (s, 3 H).

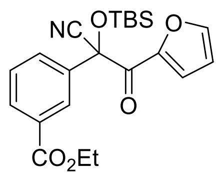
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 184.4, 165.5, 137.4, 136.3, 136.2, 136.0, 131.5, 130.8, 129.7, 129.3, 128.0, 126.3, 117.9, 80.6, 61.3, 25.8, 18.6, 14.2, -3.8, -3.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2957, 2932, 2886, 2860, 1720, 1668, 1606, 1588, 1514, 1500, 1472, 1464, 1444, 1409, 1392, 1367, 1353, 1300, 1253, 1186, 1140, 1105, 1082, 1039, 1022, 920, 889, 838, 784, 752, 731, 696, 669.

MS (70 eV, EI) *m/z* (%): 429 (0.3), 414 (8), 372 (70), 223 (4), 149 (8), 177 (72), 111 (100), 73 (18).

HRMS (EI): *m/z* (M$^+$) for $C_{22}H_{27}NO_4SSi$: calcd. 429.1430; found 429.1424.

4.3.2 Preparation of ethyl 3-(1-(*tert*-butyldimethylsilyloxy)-1-cyano-2-(furan-2-yl)-2-oxoethyl)benzoate (**74c**)



According to **TP1**, ethyl 3-(((*tert*-butyldimethylsilyl)oxy)(cyano)methyl)benzoate (**71a**, 160 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $TMP_2Zn·2MgCl_2·2LiCl$ (**4**, 1.62 mL, 0.55 mmol, 0.34 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. CuCN·2LiCl solution (0.10 mL, 0.10 mmol, 1.0 M in THF) was added at -40 ºC and stirred for 5 min. 2-Furoyl chloride (85 mg, 0.65 mmol) was added and the reaction mixture was stirred at -40 ºC and let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 95:5 to 9:1) yielding **74c** as a light yellow oil (139 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.38 (br. s, 1 H), 8.07 (d, *J*=7.9 Hz, 1 H), 7.81 (d, *J*=7.9 Hz, 1 H), 7.59 (s, 1 H), 7.50 (t, *J*=7.9 Hz, 1 H), 7.28 (d, *J*=3.3 Hz, 1 H), 6.49 (dd, *J*=3.3, 1.4 Hz, 1 H), 4.35 - 4.42 (m, 2 H), 1.40 (t, *J*=7.1 Hz, 3 H), 0.99 (s, 9 H), 0.25 (s, 3 H), 0.22 (s, 3 H).

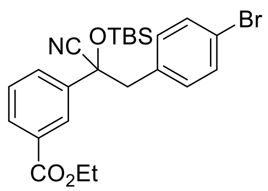
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 179.3, 165.5, 147.9, 147.6, 137.0, 131.4, 130.7, 129.8, 129.1, 126.5, 122.5, 117.6, 112.4, 79.4, 61.3, 25.6, 18.5, 14.2, -3.9, -4.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2958, 2932, 2887, 2860, 1720, 1682, 1607, 1588, 1561, 1460, 1391, 1368, 1266, 1231, 1188, 1169, 1143, 1082, 1021, 939, 917, 885, 839, 816, 783, 735, 698.

MS (70 eV, EI) *m/z* (%): 413 (0.3), 356 (68), 318 (30), 177 (100), 149 (14), 95 (46), 73 (96).

HRMS (EI): *m/z* (M$^+$) for $C_{22}H_{27}NO_5Si$: calcd. 413.1658; found 413.1655.

4.3.4 Preparation of ethyl 3-(2-(4-bromophenyl)-1-(*tert*-butyldimethylsilyloxy)-1-cyanoethyl)benzoate (**74d**)



According to **TP1**, ethyl 3-(((*tert*-butyldimethylsilyl)oxy)(cyano)methyl)benzoate (**71a**, 160 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $TMP_2Zn·2MgCl_2·2LiCl$ (**4**, 1.62 mL, 0.55 mmol, 0.34 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. CuBr (7 mg, 0.05 mmol) and 4-bromobenzyl bromide (150 mg, 0.60 mmol) were added as a solid at -78 ºC. The reaction mixture was stirred at -78 ºC for 1 h and at 50 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 95:5) yielding **74d** as a colorless oil (207 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.19 (s, 1 H), 8.06 (d, *J*=7.8 Hz, 1 H), 7.63 (d, *J*=7.8 Hz, 1 H), 7.46 (t, *J*=7.8 Hz, 1 H), 7.40 (d, *J*=7.6 Hz, 2 H), 7.02 (d, *J*=7.6 Hz, 2 H), 4.33 - 4.48 (m, 2 H), 3.21 (d, *J*=13.5 Hz, 1 H), 3.11 (d, *J*=13.5 Hz, 1 H), 1.41 (t, *J*=7.1 Hz, 3 H), 0.94 (s, 9 H), 0.02 (s, 3 H), -0.09 (s, 3 H).

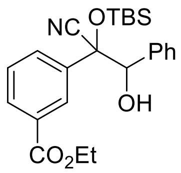
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 165.8, 140.9, 132.6, 131.1, 131.0, 130.0, 129.6, 128.6, 126.3, 121.8, 119.8, 75.5, 61.2, 51.6, 25.7, 18.3, 14.2, -3.8, -4.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2957, 2931, 2886, 2859, 2256, 1720, 1591, 1489, 1472, 1464, 1441, 1406, 1391, 1367, 1299, 1275, 1262, 1234, 1193, 1174, 1112, 1084, 1013, 949, 935, 910, 881, 826, 781, 754, 730, 706.

MS (70 eV, EI) *m/z* (%): 487 (0.2), 444 (5), 432 (24), 324 (27), 318 (100), 177 (84), 149 (11), 73 (36).

HRMS (EI): *m/z* (M^+) for $C_{24}H_{30}BrNO_3Si$: calcd. 487.1178; found 487.1166.

4.3.5 Preparation of ethyl 3-(1-(*tert*-butyldimethylsilyloxy)-1-cyano-2-hydroxy-2-phenylethyl)benzoate (**74e**)



According to **TP2**, ethyl 3-(((*tert*-butyldimethylsilyl)oxy)(cyano)methyl)benzoate (**71a**, 160 mg, 0.50 mmol) was dissolved in dry THF (2 mL). TMPMgCl·LiCl (**2**, 0.54 mL, 0.65 mmol, 1.20 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. Benzaldehyde (64 mg, 0.60 mmol) was added at -78 ºC and the reaction mixture let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl solution (10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 95:5) yielding **74e** as a colorless oil (124 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.80 (br. s, 1 H), 8.21 (d, *J*=7.8 Hz, 1 H), 8.17 (d, *J*=7.8 Hz, 1 H), 7.58 (d, *J*=7.6 Hz, 2 H), 7.46 (t, *J*=7.8 Hz, 1 H), 7.38 (t, *J*=7.6 Hz, 2 H), 7.27 - 7.31 (m, 1 H), 5.78 (br. s, 1 H), 4.41 (qd, *J*=7.1, 1.8 Hz, 2 H), 1.43 (t, *J*=7.1 Hz, 3 H), 0.94 (s, 9 H), 0.12 (s, 3 H), 0.05 (s, 3 H).

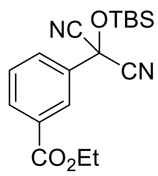
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 198.0, 165.8, 138.6, 134.6, 134.0, 133.6, 131.3, 130.6, 128.7, 128.3, 127.9, 125.6, 80.8, 61.2, 25.7, 18.2, 14.3, -5.0, -5.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2996, 2859, 2255, 1716, 1683, 1602, 1493, 1472, 1464, 1450, 1368, 1302, 1257, 1223, 1191, 1116, 1072, 1006, 907, 860, 837, 780, 757, 728, 698.

MS (70 eV, EI) *m/z* (%): 383 (5), 341 (55), 221 (100), 177 (5), 73 (78), 59 (8).

HRMS (EI): *m/z* for $C_{22}H_{27}O_4Si^+$: calcd. 383.1679; found 383.1646.

4.3.6 Preparation of ethyl 3-((*tert*-butyldimethylsilyloxy)dicyanomethyl)benzoate (**74f**)



According to **TP2**, ethyl 3-(((*tert*-butyldimethylsilyl)oxy)(cyano)methyl)benzoate (**71a**, 128 mg, 0.40 mmol) was dissolved in dry THF (1.6 mL). TMPMgCl·LiCl (**2**, 0.43 mL, 0.52 mmol, 1.21 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. A solution of tosyl cyanide (109 mg, 0.60 mmol) in dry THF (0.4 mL) was added at -78 ºC and the reaction mixture let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl solution (10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1) yielding **74f** as a colorless oil (69 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.38 (br. s, 1 H), 8.20 (d, *J*=7.8 Hz, 1 H), 7.87 (d, *J*=7.8 Hz, 1 H), 7.62 (t, *J*=7.8 Hz, 1 H), 4.43 (q, *J*=7.1 Hz, 2 H), 1.42 (t, *J*=7.1 Hz, 3 H), 1.00 (s, 9 H), 0.41 (s, 6 H).

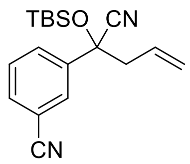
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 165.1, 135.3, 132.0, 132.0, 129.7, 129.3, 126.3, 114.8, 64.7, 61.6, 25.2, 18.2, 14.2, -4.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2958, 2934, 2888, 2862, 2244, 1723, 1609, 1590, 1472, 1465, 1444, 1393, 1367, 1300, 1268, 1190, 1105, 1081, 1041, 1022, 1004, 987, 940, 617. 882, 837, 786, 750, 738, 706, 688.

MS (70 eV, EI) *m/z* (%): 344 (1), 299 (19), 287 (100), 242 (15), 232 (23), 177 (96), 149 (11), 75 (10).

HRMS (EI): ***m/z*** **(M^+) for $C_{18}H_{24}N_2O_3Si$**: calcd. 344.1556; found 344.1551.

4.3.7 Preparation of 3-(1-(*tert*-butyldimethylsilyloxy)-1-cyanobut-3-enyl)-benzonitrile (**74g**)



According to **TP1**, 3-((*tert*-butyldimethylsilyloxy)(cyano)methyl)benzonitrile (**71b**, 136 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $TMP_2Zn·2MgCl_2·2LiCl$ (**4**, 1.57 mL, 0.55 mmol, 0.35 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. CuCN·2LiCl solution (0.10 mL, 0.10 mmol, 1.0 M in THF) was added at -40 ºC and stirred for 5 min. Allyl bromide (91 mg, 0.75 mmol) was added and the reaction mixture was stirred at -40 ºC and let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 96:4) yielding **74g** as a colorless oil (105 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.83 (br. s, 1 H), 7.78 (d, *J*=7.8 Hz, 1 H), 7.67 (d, *J*=7.8 Hz, 1 H), 7.54 (t, *J*=7.8 Hz, 1 H), 5.63 - 5.72 (m, 1 H), 5.21 (d, *J*=10.2 Hz, 1 H), 5.13 (d, *J*=17.0 Hz, 1 H), 2.78 (dd, *J*=13.7, 7.1 Hz, 1 H), 2.66 (dd, *J*=13.7, 7.1 Hz, 1 H), 0.95 (s, 9 H), 0.26 (s, 3 H), 0.00 (s, 3 H).

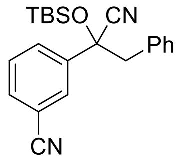
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 142.2, 132.4, 129.7, 129.6, 129.4, 128.9, 121.5, 119.5, 118.1, 112.9, 74.4, 50.1, 25.6, 18.3, -3.8, -3.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3083, 2956, 2931, 2887, 2859, 2233, 1472, 1464, 1428, 1391, 1362, 1287, 1257, 1160, 1108, 1096, 1039, 1005, 991, 920, 837, 802, 781, 733, 712, 689.

MS (70 eV, EI) *m/z* (%): 297 (1), 271 (25), 255 (26), 228 (100), 130 (43), 99 (30), 84 (15), 75 (39), 73 (55), 57 (24), 41 (17).

HRMS (EI): ***m/z*** **for $C_{18}H_{24}N_2OSi^+$**: calcd. 297.1423; found 297.1414.

4.3.8 Preparation of 3-(1-(*tert*-butyldimethylsilyloxy)-1-cyano-2-phenylethyl)-benzonitrile (**74h**)



According to **TP1**, 3-((*tert*-butyldimethylsilyloxy)(cyano)methyl)benzonitrile (**71b**, 82 mg, 0.30 mmol) was dissolved in dry THF (1.2 mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 1.03 mL, 0.33 mmol, 0.32 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. CuBr (4 mg, 0.03 mmol) and benzyl bromide (54 mg, 0.32 mmol) were added as a solid at -78 ºC. The reaction mixture was stirred at -78 ºC for 1 h and at 50 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 96:4) yielding **74h** as a white solid (80 mg, 74%).

m.p.: 97.7 - 98.7 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.73 (br. s, 1 H), 7.64 (d, *J*=7.8 Hz, 1 H), 7.66 (d, *J*=7.8 Hz, 1 H), 7.47 (t, *J*=7.8 Hz, 1 H), 7.23 - 7.27 (m, 3 H), 7.07 (d, *J*=6.6 Hz, 2 H), 3.22 (d, *J*=13.4 Hz, 1 H), 3.11 (d, *J*=13.4 Hz, 1 H), 0.91 (s, 9 H), 0.01 (s, 3 H), -0.08 (s, 3 H).

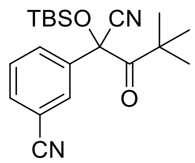
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 142.4, 133.0, 132.4, 130.9, 129.7, 129.3, 129.0, 128.1, 127.8, 119.5, 118.1, 112.7, 75.4, 52.1, 25.7, 18.3, -3.8, -4.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3034, 2957, 2931, 2887, 2859, 2255, 2233, 1498, 1472, 1464, 1456, 1424, 1391, 1362, 1256, 1149, 1112, 1094, 1032, 1005, 943, 908, 874, 839, 828, 782, 729, 699, 693.

MS (70 eV, EI) *m/z* (%): 362 (1), 305 (31), 271 (100), 265 (29), 255 (10), 130 (32), 90 (22), 84 (19), 75 (39), 73 (56), 41 (11).

HRMS (EI): *m/z* (M^+) for $C_{22}H_{26}N_2OSi$: calcd. 362.1814; found 362.1817.

4.3.9 Preparation of 3-(1-(*tert*-butyldimethylsilyloxy)-1-cyano-3,3-dimethyl-2-oxobutyl)benzonitrile (**74i**)



According to **TP1**, 3-((*tert*-butyldimethylsilyloxy)(cyano)methyl)benzonitrile (**71b**, 136 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $TMP_2Zn·2MgCl_2·2LiCl$ (**4**, 1.93 mL, 0.55 mmol, 0.28 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. CuCN·2LiCl solution (0.10 mL, 0.10 mmol, 1.0 M in THF) was added at -40 ºC and stirred for 5 min. Pivaloyl chloride (72 mg, 0.60 mmol) was added and the reaction mixture was stirred at -40 ºC and let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 95:5) yielding **74i** as a light yellow solid (131 mg, 74%).

m.p.: 59.1 - 60.9 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.85 (br. s, 1 H), 7.80 (d, *J*=7.8 Hz, 1 H), 7.71 (d, *J*=7.8 Hz, 1 H), 7.56 (t, *J*=7.8 Hz, 1 H), 1.28 (s, 9 H), 1.01 (s, 9 H), 0.33 (s, 3 H), 0.02 (s, 3 H).

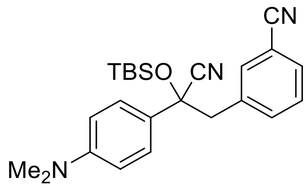
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 205.0, 139.0, 133.0, 130.7, 129.8, 129.7, 117.8, 117.8, 113.2, 79.8, 45.7, 27.3, 25.8, 18.5, -3.8, -3.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2959, 2933, 2861, 2233, 1719, 1480, 1472, 1425, 1393, 1363, 1258, 1226, 1151, 1124, 1095, 1045, 998, 937, 911, 886, 840, 814, 783, 760, 732, 688.

MS (70 eV, EI) *m/z* (%): 299 (42), 272 (32), 188 (7), 130 (25), 85 (13), 75 (38), 73 (29), 58 (100), 41 (17).

HRMS (EI): *m/z* for $C_{16}H_{19}N_2O_2Si^+$: calcd. 299.1216; found 299.1212.

4.3.10 Preparation of 3-(2-(*tert*-butyldimethylsilyloxy)-2-cyano-2-(4-(dimethylamino)phenyl)ethyl)benzonitrile (**74j**)



According to **TP1**, 2-(*tert*-butyldimethylsilyloxy)-2-(4-(dimethylamino)phenyl)acetonitrile (**71c**, 145 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**4**, 1.93 mL, 0.55 mmol, 0.28 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. CuBr (7 mg, 0.05 mmol) and 3-cyanobenzyl bromide (118 mg, 0.60 mmol) were added as a solid at -78 ºC. The reaction mixture was stirred at -78 ºC for 1 h and at 50 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1) yielding **74j** as a white solid (168 mg, 83%).

m.p.: 117.6 - 119.1 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.57 (d, *J*=7.6 Hz, 1 H), 7.43 - 7.50 (m, 2 H), 7.40 (t, *J*=7.6 Hz, 1 H), 7.32 (m, *J*=8.9 Hz, 2 H), 6.69 (m, *J*=8.9 Hz, 2 H), 3.28 (d, *J*=13.5 Hz, 1 H), 3.13 (d, *J*=13.5 Hz, 1 H), 3.00 (s, 6 H), 0.89 (s, 9 H), -0.02 (s, 3 H), -0.11 (s, 3 H).

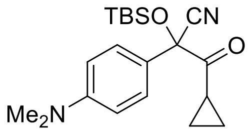
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 150.7, 136.2, 135.4, 134.7, 130.9, 128.7, 126.9, 126.3, 120.1, 118.7, 111.9, 111.7, 75.7, 51.7, 40.3, 29.7, 25.7, 18.3, -3.7, -4.4.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2955, 2929, 2895, 2857, 2230, 1611, 1521, 1483, 1471, 1463, 1445, 1360, 1325, 1254, 1226, 1192, 1165, 1088, 1045, 1007, 946, 910, 891, 830, 816, 804, 779, 754, 731, 694, 981.

MS (70 eV, EI) *m/z* (%): 405 (2), 378 (5), 289 (80), 274 (17), 262 (7), 247 (10), 148 (100), 73 (9), 57 (7).

HRMS (EI): *m/z* (M^+) for $C_{24}H_{31}N_3OSi$: calcd. 405.2236; found 405.2229.

4.3.11 Preparation of 2-(*tert*-butyldimethylsilyloxy)-3-cyclopropyl-2-(4-(dimethylamino)phenyl)-3-oxopropanenitrile (**74k**)



According to **TP1**, 2-(*tert*-butyldimethylsilyloxy)-2-(4-(dimethylamino)phenyl)acetonitrile (**71c**, 145 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**4**, 1.57 mL, 0.55 mmol, 0.35 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. CuCN·2LiCl solution (0.10 mL, 0.10 mmol, 1.0 M in THF) was added at -40 ºC and stirred for 5 min. Cyclopropanecarbonyl chloride (78 mg, 0.75 mmol) was added and the reaction mixture was stirred at -40 ºC and let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 98:2) yielding **74k** as a light yellow solid (152 mg, 85%).

m.p.: 73.3 - 75.1 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.41 (d, *J*=9.0 Hz, 2 H), 6.72 (d, *J*=9.0 Hz, 2 H), 2.99 (s, 6 H), 2.19 - 2.27 (m, 1 H), 1.02 - 1.12 (m, 2 H), 1.01 (s, 9 H), 0.91 - 0.97 (m, 2 H), 0.26 (s, 3 H), 0.17 (s, 3 H).

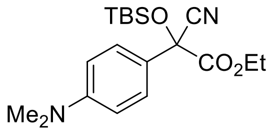
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 202.0, 151.0, 126.6, 122.7, 118.5, 112.1, 80.7, 40.2, 25.7, 18.4, 15.7, 13.1, 12.5, -4.0, -4.0.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2955, 2930, 2887, 2807, 1710, 1609, 1520, 1471, 1463, 1445, 1361, 1256, 1224, 1185, 1166, 1140, 1117, 1086, 1061, 1033, 1003, 976, 939, 921, 882, 837, 813, 781, 730, 707, 684, 670.

MS (70 eV, EI) *m/z* (%): 358 (1), 343 (2), 301 (16), 290 (15), 289 (66), 148 (100), 73 (9).

HRMS (EI): *m/z* (M^+) for $C_{20}H_{30}N_2O_2Si$: calcd. 358.2077; found 358.2087.

4.3.12 Preparation of ethyl 2-(*tert*-butyldimethylsilyloxy)-2-cyano-2-(4-(dimethyl-amino)phenyl)acetate (**74l**)



According to **TP2**, 2-(*tert*-butyldimethylsilyloxy)-2-(4-(dimethylamino)phenyl)acetonitrile (**71c**, 145 mg, 0.50 mmol) was dissolved in dry THF (2 mL). TMPMgCl·LiCl (**2**, 0.65 mL, 0.59 mmol, 0.91 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. Ethyl cyanoformate (59 mg, 0.60 mmol) was added at -78 ºC and the reaction mixture let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl solution (10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/CH_2Cl_2, 9:1) yielding **74l** as a light yellow solid (161 mg, 89%).

m.p.: 47.1 - 48.8 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.49 (d, *J*=8.4 Hz, 2 H), 6.71 (d, *J*=8.4 Hz, 2 H), 4.14 - 4.30 (m, 2 H), 2.99 (s, 6 H), 1.26 (t, *J*=7.1 Hz, 3 H), 0.98 (s, 9 H), 0.25 (s, 3 H), 0.15 (s, 3 H)**.**

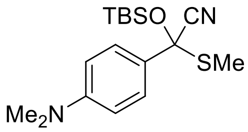
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 167.5, 151.1, 126.5, 123.6, 118.4, 111.8, 75.0, 63.0, 40.2, 25.6, 18.4, 13.8, -4.2, -4.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2956, 2929, 2895, 2858, 2253, 1759, 1741, 1714, 1610, 1521, 1472, 1463, 1445, 1361, 1253, 1234, 1218, 1186, 1166, 1149, 1122, 1047, 1017, 945, 911, 876, 841, 830, 813, 782, 732, 692, 673.

MS (70 eV, EI) *m/z* (%): 362 (1), 305 (22), 289 (33), 250 (11), 148 (100), 121 (34), 73 (14).

HRMS (EI): *m/z* (M^+) for $C_{19}H_{30}N_2O_3Si$: calcd. 362.2026; found 362.2029.

4.3.13 Preparation of 2-(*tert*-butyldimethylsilyloxy)-2-(4-(dimethylamino)phenyl)-2-(methylthio)acetonitrile (**74m**)



According to **TP2**, 2-(*tert*-butyldimethylsilyloxy)-2-(4-(dimethylamino)phenyl)acetonitrile (**71c**, 145 mg, 0.50 mmol) was dissolved in dry THF (2 mL). TMPMgCl·LiCl (**2**, 0.65 mL, 0.59 mmol, 0.91 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. *S*-Methyl methanethiosulfonate (95 mg, 0.75 mmol) was added at -78 ºC and the reaction mixture let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl solution (10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 98:2) yielding **74m** as a light yellow solid (124 mg, 74%).

m.p.: 52.8 - 53.7 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.54 (d, *J*=8.8 Hz, 2 H), 6.70 (d, *J*=8.8 Hz, 2 H), 3.00 (s, 6 H), 2.33 (s, 3 H), 0.96 (s, 9 H), 0.20 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 151.0, 126.8, 125.1, 118.5, 111.4, 78.9, 40.2, 25.6, 18.3, 14.7, -3.9, -4.2.

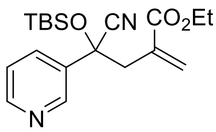
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2954, 2928, 2886, 2857, 2806, 2225, 1609, 1563, 1521, 1471, 1462, 1444, 1360, 1324, 1254, 1230, 1190, 1166, 1064, 1005, 996, 946, 910, 836, 810, 781, 765, 731, 673.

MS (70 eV, EI) *m/z* (%): 335 (0.2), 289 (40), 173 (7), 148 (100), 73 (17), 57 (8).

HRMS (EI): *m/z* for $C_{17}H_{28}N_2OSSi^+$: calcd. 335.1613; found 335.1601.

4.4 SYNTHESIS OF HETEROAROMATIC FUNCTIONALIZED PROTECTED CYANOHYDRINS

4.4.1 Preparation of ethyl 4-(*tert*-butyldimethylsilyloxy)-4-cyano-2-methylene-4-(pyridin-3-yl)butanoate (**74n**)



According to **TP1**, 2-(*tert*-butyldimethylsilyloxy)-2-(pyridin-3-yl)acetonitrile (**71d**, 186 mg, 0.75 mmol) was dissolved in dry THF (3 mL). $TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (**4**, 2.4 mL, 0.83 mmol, 0.35 M in THF) was added dropwise at 0 °C and the reaction mixture was stirred for 2 h. CuCN·2LiCl solution (0.15 mL, 0.15 mmol, 1.0 M in THF) was added at -40 °C and stirred for 5 min. Ethyl 2-(bromomethyl)acrylate (173 mg, 0.90 mmol) was added and the reaction mixture was stirred at -40 °C and let warm up to 25 °C for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 8:2) yielding **74n** as a light yellow oil (165 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.82 (dd, *J*=2.4, 0.8 Hz, 1 H), 8.62 (dd, *J*=4.8, 1.6 Hz, 1 H), 7.84 (ddd, *J*=8.0, 2.4, 1.6 Hz, 1 H), 7.33 (ddd, *J*=8.0, 4.8, 0.8 Hz, 1 H), 6.40 (d, *J*=1.2 Hz, 1 H), 5.77 (d, *J*=1.2 Hz, 1 H), 4.00 - 4.11 (m, 2 H), 3.17 (dd, *J*=13.6, 0.7 Hz, 1 H), 3.00 (dd, *J*=13.6, 0.7 Hz, 1 H), 1.22 (t, *J*=7.1 Hz, 3 H), 0.92 (s, 9 H), 0.22 (s, 3 H), -0.05 (s, 3 H).

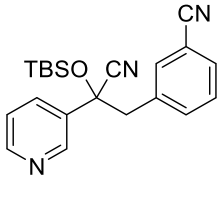
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 166.1, 150.2, 147.1, 135.8, 133.7, 133.2, 130.9, 123.0, 119.2, 74.0, 61.1, 46.2, 25.6, 18.2, 14.0, -3.7, -3.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2957, 2932, 2898, 2859, 1718, 1631, 1576, 1472, 1464, 1420, 1391, 1369, 1336, 1299, 1256, 1184, 1153, 1096, 1050, 1025, 991, 962, 943, 915, 833, 814, 781, 731, 711, 690, 667.

MS (70 eV, EI) *m/z* (%): 345 (3), 303 (100), 275 (96), 248 (52), 155 (14), 106 (67), 75 (42), 73 (48), 57 (9), 43 (27).

HRMS (EI): *m/z* for $C_{18}H_{25}N_2O_3Si^+$: calcd. 345.1634; found 345.1627.

4.4.2 Preparation of 3-(2-(*tert*-butyldimethylsilyloxy)-2-cyano-2-(pyridin-3-yl)ethyl)benzonitrile (**74o**)



According to **TP1**, 2-(*tert*-butyldimethylsilyloxy)-2-(pyridin-3-yl)acetonitrile (**71d**, 128 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (**4**, 1.60 mL, 0.55 mmol, 0.34 M in THF) was added dropwise at 0 ºC and the reaction mixture was stirred for 2 h. CuBr (7 mg, 0.05 mmol) and 3-cyanobenzyl bromide (118 mg, 0.60 mmol) were added as a solid at -78 ºC. The reaction mixture was stirred at -78 ºC for 1 h and at 50 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 8:2) yielding **74o** as a white solid (136 mg, 75%).

m.p.: 63.7 - 65.6 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.81 (br. s., 1 H), 8.68 (d, *J*=3.5 Hz, 1 H), 7.79 (dt, *J*=8.0, 1.8 Hz, 1 H), 7.59 - 7.64 (m, 1 H), 7.49 (s, 1 H), 7.40 - 7.47 (m, 2 H), 7.36 (dd, *J*=8.0, 4.8 Hz, 1 H), 3.31 (d, *J*=13.7 Hz, 1 H), 3.19 (d, *J*=13.7 Hz, 1 H), 0.92 (s, 9 H), -0.01 (s, 3 H), -0.08 (s, 3 H).

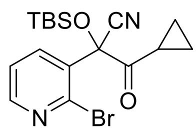
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 150.6, 146.9, 135.3, 134.9, 134.6, 132.9, 131.5, 129.0, 123.2, 118.9, 118.3, 112.4, 74.1, 51.5, 25.6, 18.3, -3.8, -4.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2957, 2931, 2887, 2859, 2231, 1712, 1576, 1472, 1464, 1420, 1391, 1362, 1256, 1220, 1097, 1047, 1025, 1005, 970, 939, 910, 891, 830, 807, 781, 730, 712, 694, 679.

MS (70 eV, EI) *m/z* (%): 348 (2), 306 (40), 279 (100), 247 (14), 106 (26), 73 (19).

HRMS (EI): *m/z* for $C_{20}H_{22}N_3OSi^+$: calcd. 348.1532; found 348.1531.

4.4.3 Preparation of 2-(2-bromopyridin-3-yl)-2-(*tert*-butyldimethylsilyloxy)-3-cyclopropyl-3-oxopropanenitrile (**74p**)



According to **TP1**, 2-(2-bromopyridin-3-yl)-2-(*tert*-butyldimethylsilyloxy)acetonitrile (**71e**, 326 mg, 1.00 mmol) was dissolved in dry THF (4 mL). $TMP_2Zn·2MgCl_2·2LiCl$ (**4**, 3.14 mL, 1.10 mmol, 0.35 M in THF) was added dropwise at 0 ºC and the reaction mixture was stirred for 2 h. CuCN·2LiCl solution (0.20 mL, 0.20 mmol, 1.0 M in THF) was added at -40 ºC and stirred for 5 min. Cyclopropanecarbonyl chloride (125 mg, 1.20 mmol) was added and the reaction mixture was stirred at -40 ºC and let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 20 mL) extracted with EtOAc (3 x 40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 8:2) yielding **74p** as a white solid (357 mg, 91%).

m.p.: 107.9 - 109.7 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.44 (dd, *J*=4.7, 1.7 Hz, 1 H), 8.19 (dd, *J*=7.8, 1.7 Hz, 1 H), 7.46 (dd, *J*=7.8, 4.7 Hz, 1 H), 1.94 - 2.02 (m, 1 H), 1.18 - 1.28 (m, 2 H), 1.00 - 1.08 (m, 2 H), 0.98 (s, 9 H), 0.28 (s, 3 H), 0.22 (s, 3 H).

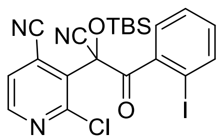
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 198.9, 150.7, 140.4, 136.9, 133.9, 123.0, 116.0, 78.6, 25.5, 18.4, 16.8, 14.2, 13.4, -4.1, -4.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2956, 2930, 2859, 1720, 1573, 1560, 1472, 1447, 1392, 1256, 1192, 1126, 1107, 1085, 1052, 1035, 976, 930, 915, 883, 837, 807, 783, 735, 687.

MS (70 eV, EI) *m/z* (%): 394 (0.3), 339 (34), 337 (35), 328 (20), 326 (22), 186 (7), 184 (9), 69 (100), 43 (15), 41 (30).

HRMS (EI): *m/z* (M^+) for $C_{17}H_{23}BrN_2O_2Si$: calcd. 394.0712; found 394.0703.

4.4.4 Preparation of 3-(1-(*tert*-butyldimethylsilyloxy)-1-cyano-2-(2-iodophenyl)-2-oxoethyl)-2-chloroisonicotinonitrile (**74q**)



According to **TP1**, 3-((*tert*-butyldimethylsilyloxy)(cyano)methyl)-2-chloroisonicotinonitrile (**71f**, 307 mg, 1.00 mmol) was dissolved in dry THF (4 mL). $TMP_2Zn·2MgCl_2·2LiCl$ (**4**, 3.14 mL, 1.10 mmol, 0.35 M in THF) was added dropwise at 0 ºC and the reaction mixture was stirred for 1 h. CuCN·2LiCl solution (0.20 mL, 0.20 mmol, 1.0 M in THF) was added at -40 ºC and stirred for 5 min. 2-Iodobenzyol chloride (400 mg, 1.50 mmol) was added and the reaction mixture was stirred at -40 ºC and let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 20 mL) extracted with EtOAc (3 x 40 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 8:2) yielding **74q** as a light yellow solid (446 mg, 83%).

m.p.: 163.3 - 164.7 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.50 (d, *J*=4.9 Hz, 1 H), 8.05 - 8.07 (m, 1 H), 7.73 (dd, *J*=7.8, 1.3 Hz, 1 H), 7.70 (d, *J*=4.9 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.09 (td, *J*=7.8, 1.3 Hz, 1 H), 0.96 (s, 9 H), 0.56 (s, 3 H), 0.50 (s, 3 H).

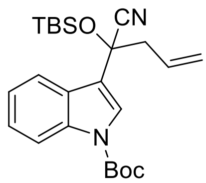
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 187.2, 150.8, 150.3, 143.4, 134.0, 133.7, 132.7, 129.2, 128.7, 126.9, 121.3, 115.2, 115.1, 97.0, 79.2, 26.2, 19.1, -3.0, -3.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2932, 2860, 1712, 1572, 1534, 1470, 1429, 1363, 1264, 1230, 1191, 1114, 1087, 1018, 951, 875, 845, 828, 790, 766, 745, 676.

MS (70 eV, EI) *m/z* (%): 522 (4), 480 (100), 232 (29), 203 (85), 104 (18), 73 (96), 57 (51).

HRMS (EI): *m/z* for $C_{20}H_{18}ClIN_3O_2Si^+$: calcd. 521.9901; found 521.9888.

4.4.5 Preparation of *tert*-butyl 3-(1-(*tert*-butyldimethylsilyloxy)-1-cyanobut-3-enyl)-1*H*-indole-1-carboxylate (**74r**)



According to **TP1**, *tert*-butyl 3-((*tert*-butyldimethylsilyloxy)(cyano)methyl)-1*H*-indole-1-carboxylate (**71g**, 77 mg, 0.20 mmol) was dissolved in dry THF (0.8 mL). $TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (**4**, 0.65 mL, 0.22 mmol, 0.34 M in THF) was added dropwise at 0 ºC and the reaction mixture was stirred for 2 h. CuCN·2LiCl solution (0.04 mL, 0.04 mmol, 1.0 M in THF) was added at -40 ºC and stirred for 5 min. Allyl bromide (36 mg, 0.30 mmol) was added at -40 ºC and the reaction mixture was stirred at -40 ºC and let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 5 mL) extracted with EtOAc (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 98:2) yielding **74r** as a colorless oil (61 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.21 (d, *J*=8.2 Hz, 1 H), 7.74 - 7.79 (m, 2 H), 7.34 - 7.40 (m, 1 H), 7.26 - 7.30 (m, 1 H), 5.81 (ddt, *J*=17.0, 10.2, 7.2 Hz, 1 H), 5.16 - 5.24 (m, 2 H), 3.06 (dd, *J*=13.9, 7.2 Hz, 1 H), 2.91 (dd, *J*=13.9, 7.2 Hz, 1 H), 1.70 (s, 9 H), 0.95 (s, 9 H), 0.28 (s, 3 H), -0.06 (s, 3 H).

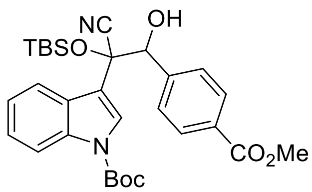
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 149.3, 136.3, 130.9, 126.3, 125.0, 123.7, 122.8, 120.7, 120.5, 120.5, 119.9, 115.5, 84.3, 71.0, 47.5, 28.1, 25.6, 18.4, -3.9.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2957, 2931, 2859, 1740, 1641, 1566, 1473, 1452, 1370, 1308, 1254, 1153, 1081, 1023, 962, 922, 836, 780, 746.

MS (70 eV, EI) *m/z* (%): 426 (2), 385 (35), 329 (100), 313 (10), 285 (43), 242 (11), 144 (59), 57 (40).

HRMS (EI): *m/z* (M$^+$) for $C_{24}H_{34}N_2O_3Si$: calcd. 426.2339; found 426.2337.

4.4.6 Preparation of *tert*-butyl 3-(1-(*tert*-butyldimethylsilyloxy)-1-cyano-2-hydroxy-2-(4-(methoxycarbonyl)phenyl)ethyl)-1*H*-indole-1-carboxylate (**74s**)



According to **TP1**, *tert*-butyl 3-((*tert*-butyldimethylsilyloxy)(cyano)methyl)-1*H*-indole-1-carboxylate (**71g**, 193 mg, 0.50 mmol) was dissolved in dry THF (2 mL). $TMP_2Zn·2MgCl_2·2LiCl$ (**4**, 1.62 mL, 0.55 mmol, 0.34 M in THF) was added dropwise at 0 ºC and the reaction mixture was stirred for 2 h. Methy 4-formylbenzoate (123 mg, 0.75 mmol) was added at -78 ºC and the reaction mixture was stirred at -78 ºC and let warm up to 25 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl solution (10 mL) extracted with EtOAc (3 x 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 96:4 to 9:1) yielding **74s** as a colorless oil (173 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.76 (s, 1 H), 8.40 (dd, *J*=6.6, 2.2 Hz, 1 H), 8.14 (d, *J*=7.4 Hz, 1 H), 8.04 (d, *J*=8.2 Hz, 2 H), 7.70 (d, *J*=8.2 Hz, 2 H), 7.32 - 7.38 (m, 2 H), 5.60 (s, 1 H), 3.89 (s, 3 H), 1.71 (s, 9 H), 1.00 (s, 9 H), 0.15 (s, 3 H), 0.12 (s, 3 H).

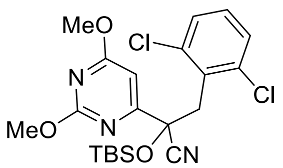
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 195.2, 166.7, 148.8, 144.6, 134.8, 134.7, 129.8, 129.5, 128.3, 125.4, 125.3, 124.4, 122.5, 115.0, 114.8, 85.1, 82.0, 52.0, 28.0, 25.8, 18.2, -4.9, -5.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2954, 2931, 2886, 2858, 2256, 1746, 1724, 1658, 1610, 1539, 1472, 1450, 1436, 1371, 1357, 1334, 1309, 1274, 1237, 1190, 1144, 1106, 1054, 1018, 968, 910, 868, 837, 770, 749.

MS (70 eV, EI) *m/z* (%): 523 (0.4), 492 (1), 366 (23), 279 (29), 244 (17), 188 (51), 144 (100), 73 (55), 57 (16).

HRMS (EI): *m/z* for $C_{29}H_{37}NO_6Si^+$: calcd. 523.2390; found 523.2346.

4.4.7 Preparation of 2-(*tert*-butyldimethylsilyloxy)-3-(2,6-dichlorophenyl)-2-(2,6-dimethoxypyrimidin-4-yl)propanenitrile (**74t**)



According to **TP1**, 2-(*tert*-butyldimethylsilyloxy)-2-(2,6-dimethoxypyrimidin-4-yl)acetonitrile (**71h**, 31 mg, 0.10 mmol) was dissolved in dry THF (2 mL). $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**4**, 0.31 mL, 0.11 mmol, 0.35 M in THF) was added dropwise at -20 ºC and the reaction mixture was stirred for 2 h. CuBr (1 mg, 0.01 mmol) and 2,6-dichlorobenzyl bromide (36 mg, 0.15 mmol) were added as a solid at -78 ºC. The reaction mixture was stirred at -78 ºC for 1 h and at 50 ºC for 12 h. The resulting solution was quenched with sat. aq. NH_4Cl/NH_3 solution (8:1, 5 mL) extracted with EtOAc (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1) yielding **74t** as a white solid (37 mg, 79%).

m.p.: 112.5 - 113.1 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.30 (d, *J*=8.0 Hz, 2 H), 7.15 (t, *J*=8.0 Hz, 1 H), 6.62 (s, 1 H), 4.00 (s, 3 H), 3.92 (s, 3 H), 3.75 - 3.87 (m, 2 H), 0.91 (s, 9 H), 0.19 (s, 3 H), 0.14 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 172.5, 169.5, 165.0, 137.5, 130.7, 129.1, 128.3, 119.3, 97.9, 74.6, 55.1, 54.2, 43.5, 25.8, 18.3, -3.6, -3.9.

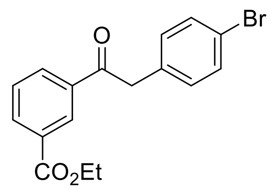
IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2955, 2859, 1633, 1596, 1571, 1483, 1461, 1436, 1384, 1355, 1297, 1256, 1206, 1161, 1126, 1094, 1050, 1007, 983, 945, 830, 780, 733.

MS (70 eV, EI) *m/z* (%): 467 (1), 412 (67), 410 (100), 307 (7), 251 (71), 167 (4).

HRMS (EI): *m/z* (M^+) for $C_{21}H_{27}Cl_2N_3O_3Si$: calcd. 467.1199; found 467.1195.

4.5 DEPROTECTION OF SILYLATED CYANOHYDRIN DERIVATIVES

4.5.1 Preparation of ethyl 3-(2-(4-bromophenyl)acetyl)benzoate (**75a**)



According to **TP3**, ethyl 3-(2-(4-bromophenyl)-1-(*tert*-butyldimethylsilyloxy)-1-cyanoethyl)benzoate (**74d**, 207 mg, 0.43 mmol) was dissolved in THF (6.5 mL) and TBAF (0.47 mL, 0.47 mmol, 1.0 M in THF) was added dropwise at -78 ºC. The reaction mixture was stirred for 0.5 h at -78 ºC and diluted with water (20 mL). The resulting solution was allowed to warm to 25 ºC and extracted with EtOAc (3 x 40 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 95:5 to 9:1) yielding **75a** as a colorless oil (104 mg, 71%).

m.p.: 62.2 - 64.0 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.65 (br. s, 1 H), 8.21 - 8.28 (m, 1 H), 8.13 - 8.19 (m, 1 H), 7.55 (t, *J*=7.7 Hz, 1 H), 7.45 (d, *J*=8.4 Hz, 2 H), 7.15 (d, *J*=8.4 Hz, 2 H), 4.42 (q, *J*=7.2 Hz, 2 H), 4.28 (s, 2 H), 1.42 (t, *J*=7.2 Hz, 3 H).

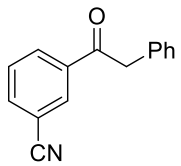
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 196.1, 165.6, 136.5, 134.0, 133.0, 132.4, 131.7, 131.2, 131.1, 129.5, 128.9, 121.0, 61.4, 44.8, 14.2.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2983, 2905, 1716, 1688, 1603, 1488, 1433, 1405, 1368, 1300, 1276, 1239, 1209, 1194, 1103, 1072, 1012, 1001, 907, 859, 802, 752, 710, 695, 682.

MS (70 eV, EI) *m/z* (%): 348 (1), 346 (1), 303 (4), 301 (4), 177 (100), 149 (13), 104 (7), 90 (5), 76 (8).

HRMS (EI): *m/z* (M^+) for $C_{17}H_{15}BrO_3$: calcd. 346.0205; found 346.0203.

4.5.2 Preparation of 3-(2-phenylacetyl)benzonitrile (**75b**)



According to **TP3**, 3-(1-(*tert*-butyldimethylsilyloxy)-1-cyano-2-phenylethyl)benzonitrile (**74h**, 68 mg, 0.19 mmol) was dissolved in THF (2.9 mL) and TBAF (0.21 mL, 0.21 mmol, 1.0 M in THF) was added dropwise at -78 ºC. The reaction mixture was stirred for 0.5 h at -78 ºC and diluted with water (10 mL). The resulting solution was allowed to warm to 25 ºC and extracted with EtOAc (3 x 30 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1) yielding **75b** as a white solid (34 mg, 81%).

m.p.: 76.6 - 78.2 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.26 (s, 1 H), 8.21 (d, *J*=7.8 Hz, 1 H), 7.81 (d, *J*=7.8 Hz, 1 H), 7.58 (t, *J*=7.8 Hz, 1 H), 7.31 - 7.37 (m, 2 H), 7.22 - 7.30 (m, 3 H), 4.28 (s, 2 H).

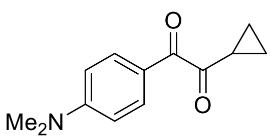
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 195.5, 137.2, 136.0, 133.4, 132.5, 132.2, 129.7, 129.3, 128.9, 127.3, 117.8, 113.2, 45.6.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3069, 3031, 2894, 2227, 1696, 1602, 1579, 1497, 1478, 1453, 1418, 1406, 1333, 1313, 1286, 1266, 1236, 1166, 1155, 1098, 1077, 1032, 1007, 998, 929, 894, 870, 802, 773, 720.

MS (70 eV, EI) *m/z* (%): 221 (6), 130 (100), 102 (20), 91 (25), 75 (3), 65 (9), 51 (4).

HRMS (EI): *m/z* (M^+) for $C_{15}H_{11}NO$: calcd. 221.0841; found 221.0841.

4.5.3 Preparation of 1-cyclopropyl-2-(4-(dimethylamino)phenyl)ethane-1,2-dione (**75c**)



According to **TP3**, 2-(*tert*-butyldimethylsilyloxy)-3-cyclopropyl-2-(4-(dimethylamino)phenyl)-3-oxopropanenitrile (**74k**, 42 mg, 0.12 mmol) was dissolved in THF (1.8 mL) and TBAF (0.13 mL, 0.13 mmol, 1.0 M in THF) was added dropwise at -78 ºC. The reaction mixture was stirred for 0.5 h at -78 ºC and diluted with water (5 mL). The resulting solution was allowed to warm to 25 ºC and extracted with EtOAc (3 x 20 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1) yielding **75c** as a yellow solid (21 mg, 81%).

m.p.: 121.4 - 123.2 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.89 (d, *J*=9.2 Hz, 2 H), 6.67 (d, *J*=9.2 Hz, 2 H), 3.09 (s, 6 H), 2.45 - 2.53 (m, 1 H), 1.26 - 1.32 (m, 2 H), 1.10 - 1.15 (m, 2 H).

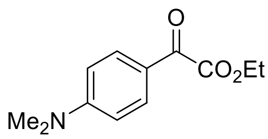
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 204.2, 190.7, 154.3, 132.6, 119.7, 110.9, 40.0, 18.8, 12.7.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3096, 3008, 2924, 2828, 2253, 1684, 1633, 1587, 1540, 1481, 1440, 1374, 1337, 1319, 1290, 1232, 1196, 1189, 1108, 1083, 1064, 1040, 998, 906, 882, 846, 822, 800, 774, 760, 728, 703, 670.

MS (70 eV, EI) *m/z* (%): 217 (7), 148 (100), 105 (5), 77 (4), 42 (4).

HRMS (EI): *m/z* (M^+) for $C_{13}H_{15}NO_2$: calcd. 217.1103; found 217.1093.

4.5.4 Preparation of ethyl 2-(4-(dimethylamino)phenyl)-2-oxoacetate (**75d**)



According to **TP3**, ethyl 2-(*tert*-butyldimethylsilyloxy)-2-cyano-2-(4-(dimethylamino)phenyl)acetate (**74l**, 107 mg, 0.30 mmol) was dissolved in THF (4.5 mL) and TBAF (0.33 mL, 0.33 mmol, 1.0 M in THF) was added dropwise at -78 ºC. The reaction mixture was stirred for 1.5 h at -78 ºC and diluted with water (10 mL). The resulting solution was allowed to warm to 25 ºC and extracted with EtOAc (3 x 30 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 9:1) yielding **75d** as a white solid (57 mg, 86%).

m.p.: 87.8 - 89.6 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.88 (d, *J*=9.2 Hz, 2 H), 6.65 (d, *J*=9.2 Hz, 2 H), 4.40 (q, *J*=7.0 Hz, 2 H), 3.08 (s, 6 H), 1.40 (t, *J*=7.0 Hz, 3 H).

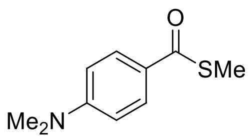
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 184.1, 165.0, 154.4, 132.4, 120.1, 110.8, 61.7, 39.9, 14.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2980, 2925, 1722, 1647, 1581, 1543, 1468, 1445, 1412, 1384, 1341, 1327, 1312, 1227, 1172, 1098, 1063, 1017, 967, 944, 862, 840, 823, 796, 783, 730, 686.

MS (70 eV, EI) *m/z* (%): 221 (8), 149 (9), 148 (100), 77 (7), 42 (7).

HRMS (EI): *m/z* (M^+) for $C_{12}H_{15}NO_3$: calcd. 221.1052; found 221.1046.

4.5.5 Preparation of *S*-methyl 4-(dimethylamino)benzothioate (**75e**)



According to **TP3**, 2-(*tert*-butyldimethylsilyloxy)-2-(4-(dimethylamino)phenyl)-2-(methylthio)acetonitrile (**74m**, 118 mg, 0.35 mmol) was dissolved in THF (5.3 mL) and TBAF (0.39 mL, 0.39 mmol, 1.0 M in THF) was added dropwise at -78 ºC. The reaction mixture was stirred for 0.5 h at -78 ºC and diluted with water (10 mL). The resulting solution was allowed to warm to 25 ºC and extracted with EtOAc (3 x 30 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 98:2 to 96:4) yielding **75e** as a white solid (64 mg, 94%).

m.p.: 102.2 - 104.0 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.88 (d, *J*=9.0 Hz, 2 H), 6.63 (d, *J*=9.0 Hz, 2 H), 3.04 (s, 6 H), 2.43 (s, 3 H).

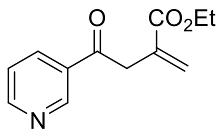
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 190.1, 153.5, 129.1, 124.7, 110.5, 39.9, 11.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2927, 2253, 1638, 1595, 1552, 1526, 1484, 1445, 1369, 1316, 1242, 1179, 1167, 1131, 1065, 1003, 946, 904, 820, 754, 725.

MS (70 eV, EI) *m/z* (%): 195 (1), 148 (12), 127 (11), 113 (14), 111 (11), 99 (13), 97 (16), 85 (42), 83 (20), 71 (51), 69 (29), 57 (100), 55 (23), 43 (37).

HRMS (EI): *m/z* (M^+) for $C_{10}H_{13}NOS$: calcd. 195.0718; found 195.0697.

4.5.6 Preparation of ethyl 2-methylene-4-oxo-4-(pyridin-3-yl)butanoate (**75f**)



According to **TP3**, ethyl 4-(*tert*-butyldimethylsilyloxy)-4-cyano-2-methylene-4-(pyridin-3-yl)butanoate (**74n**, 63 mg, 0.17 mmol) was dissolved in THF (2.6 mL) and TBAF (0.19 mL, 0.19 mmol, 1.0 M in THF) was added dropwise at -78 ºC. The reaction mixture was stirred for 0.5 h at -78 ºC and diluted with water (10 mL). The resulting solution was allowed to warm to 25 ºC and extracted with EtOAc (3 x 30 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 1:1) yielding **75f** as a colorless oil (32 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.20 (br. s., 1 H), 8.79 (d, *J*=4.4 Hz, 1 H), 8.25 (d, *J*=7.7 Hz, 1 H), 7.43 (dd, *J*=7.7, 4.4 Hz, 1 H), 6.43 (s, 1 H), 5.73 (s, 1 H), 4.20 (q, *J*=7.0 Hz, 2 H), 3.99 (s, 2 H), 1.25 (t, *J*=7.0 Hz, 3 H).

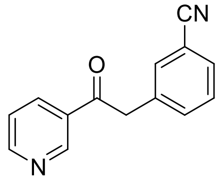
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 195.8, 166.1, 153.6, 149.8, 135.6, 134.2, 131.8, 128.9, 123.6, 61.1, 41.9, 14.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 2983, 2928, 1714, 1694, 1668, 1621, 1585, 1445, 1418, 1391, 1368, 1313, 1262, 1236, 1204, 1146, 1113, 1055, 1023, 973, 856, 806, 757, 703.

MS (70 eV, EI) *m/z* (%): 219 (4), 174 (10), 106 (100), 78 (34), 57 (6), 45 (5), 43 (18).

HRMS (EI): *m/z* (M^+) for $C_{12}H_{13}NO_3$: calcd. 219.0895; found 219.0894.

4.5.7 Preparation of 3-(2-oxo-2-(pyridin-3-yl)ethyl)benzonitrile (**75g**)



According to **TP3**, 3-(2-(*tert*-butyldimethylsilyloxy)-2-cyano-2-(pyridin-3-yl)ethyl)-benzonitrile (**74o**, 90 mg, 0.25 mmol) was dissolved in THF (3.7 mL) and TBAF (0.28 mL, 0.28 mmol, 1.0 M in THF) was added dropwise at -78 ºC. The reaction mixture was stirred for 0.5 h at -78 ºC and diluted with water (10 mL). The resulting solution was allowed to warm to 25 ºC and extracted with EtOAc (3 x 30 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 1:1) yielding **75g** as a light yellow solid (36 mg, 65%).

m.p.: 159.9 - 161.4 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.20 - 9.29 (m, 1 H), 8.83 (d, *J*=3.3 Hz, 1 H), 8.28 (d, *J*=8.0 Hz, 1 H), 7.55 - 7.64 (m, 2 H), 7.50 - 7.54 (m, 1 H), 7.44 - 7.50 (m, 2 H), 4.37 (s, 2 H).

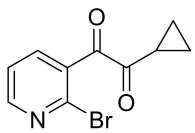
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 195.0, 154.0, 149.8, 135.7, 134.9, 134.2, 133.2, 131.5, 131.0, 129.5, 123.9, 118.5, 112.9, 44.8.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3055, 2925, 2231, 1690, 1585, 1483, 1419, 1338, 1266, 1225, 1194, 1116, 1096, 1044, 1026, 1005, 993, 910, 802, 782, 732, 700, 682.

MS (70 eV, EI) *m/z* (%): 222 (2), 116 (4), 106 (100), 89 (5), 78 (31), 51 (11).

HRMS (EI): *m/z* (M^+) for $C_{14}H_{10}N_2O$: calcd. 222.0793; found 222.0781.

4.5.8 Preparation of 1-(2-bromopyridin-3-yl)-2-cyclopropylethane-1,2-dione (**75h**)



According to **TP3**, 2-(2-bromopyridin-3-yl)-2-(*tert*-butyldimethylsilyloxy)-3-cyclopropyl-3-oxopropanenitrile (**74p**, 115 mg, 0.29 mmol) was dissolved in THF (4.4 mL) and TBAF (0.32 mL, 0.32 mmol, 1.0 M in THF) was added dropwise at -78 ºC. The reaction mixture was stirred for 0.5 h at -78 ºC and diluted with water (10 mL). The resulting solution was allowed to warm to 25 ºC and extracted with EtOAc (3 x 30 mL). The organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 8:2) yielding **75h** as a yellow oil (66 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.50 (dd, *J*=4.7, 1.8 Hz, 1 H), 7.84 (dd, *J*=7.6, 1.8 Hz, 1 H), 7.41 (dd, *J*=7.6, 4.7 Hz, 1 H), 2.70 - 2.79 (m, 1 H), 1.31 - 1.40 (m, 2 H), 1.24 - 1.31 (m, 2 H).

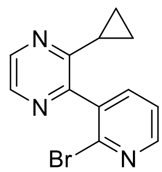
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 199.2, 191.4, 152.6, 139.4, 139.3, 134.1, 122.8, 17.5, 14.3.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3009, 1689, 1572, 1554, 1443, 1388, 1287, 1191, 1119, 1055, 1030, 917, 877, 842, 805, 756, 729, 688.

MS (70 eV, EI) *m/z* (%): 252 (1), 227 (19), 225 (15), 186 (35), 184 (39), 158 (24), 156 (26), 76 (36), 70 (15), 50 (22), 43 (22), 41 (100).

HRMS (EI): *m/z* (M^+) for $C_{10}H_8BrNO_2$: calcd. 252.9738; found 252.9719.

4.6 SYNTHESIS OF 2-(2-BROMOPYRIDIN-3-YL)-3-CYCLOPROPYLPYRAZINE (76)



1-(2-Bromopyridin-3-yl)-2-cyclopropylethane-1,2-dione (**75h**, 60 mg, 0.24 mmol) was dissolved in EtOH (2 mL) and ethylenediamine (21 mg, 0.36 mmol) was added dropwise. The reaction mixture was stirred at 80 ºC for 0.5 h and the solvents were evaporated in *vacuo*. The resulting oil was dissolved in $CHCl_3$ (2 mL), DDQ (109 mg, 0.48 mmol) was added and the mixture was stirred at 70 ºC for 5 h. Then, sat. aq. $NaHCO_3$ solution (10 mL) was added and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ solution (2 x 10 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (*i*hexane/EtOAc, 1:1) yielding **76** as a light brown solid (21 mg, 32% over 2 steps).

m.p.: 56.6 - 58.2 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.45 - 8.52 (m, 2 H), 8.40 (d, *J*=2.1 Hz, 1 H), 7.75 (dd, *J*=7.4, 2.1 Hz, 1 H), 7.44 (dd, *J*=7.4, 4.9 Hz, 1 H), 1.68 - 1.78 (m, 1 H), 0.84 - 1.30 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 157.0, 150.9, 150.1, 143.9, 142.5, 140.1, 139.3, 136.7, 122.8, 14.1.

IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm^{-1}: 3044, 3008, 2926, 2228, 1923, 1695, 1579, 1551, 1530, 1442, 1417, 1388, 1350, 1288, 1261, 1206, 1163, 1131, 1120, 1085, 1055, 1045, 1025, 1010, 902, 887, 854, 810, 800, 746, 733, 664.

MS (70 eV, EI) *m/z* (%): 276 (13), 274 (13), 196 (100), 169 (10), 142 (6), 76 (2).

HRMS (EI): *m/z* for $C_{12}H_9BrN_3^+$: calcd. 273.9980; found 273.9975.

D. Appendix

1. SINGLE CRYSTAL X-RAY DIFFRACTION STUDIES FOR COMPOUNDS 49E, 59C, 59D, 44L AND 63

Single crystals of compounds **49e**, **59c**, **59d**, **44l** and **63**, suitable for X-ray diffraction, were obtained by slow evaporation of hexane- and THF-, as well as CH_2Cl_2-solutions solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection was performed with the CrysAlis CCD software;[125] CrysAlis RED software[126] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method[127] was applied. The structures were solved with SHELXS-97,[128] refined with SHELXL-97[129] and finally checked using PLATON.[130] Details for data collection and structure refinement are summarized in Table 1 and Table 2.

CCDC 1518630 (**49e**), CCDC 1518626 (**59c**), CCDC 1518629 (**59d**), CCDC 1518628 (**44l**) and CCDC 1518627 (**63**) contain supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[125] CrysAlis CCD, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).

[126] CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.27p5 beta (release 01-04-2005 CrysAlis171.NET) (compiled Apr 1 2005, 17:53:34).

[127] SCALE3 ABSPACK – An Oxford Diffraction Program (1.0.4, gui:1.0.3) (C), Oxford Diffraction, Ltd., 2005.

[128] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.

[129] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.

[130] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 9: Details for X-ray data collection and structure refinement for compounds **49e**, **59c** and **59d**.

	49e	**59c**	**59d**
Empirical formula	$C_4H_2I_2S_2$	$C_7H_3NS_4$	$C_7H_6S_5$
Formula mass	367.98	229.34	250.42
T[K]	173(2)	173(2)	173(2)
Crystal size [mm]	0.15 × 0.10 × 0.02	0.35 × 0.10 × 0.01	0.25 × 0.15 × 0.02
Crystal description	yellow block	yellow platelet	yellow platelet
Crystal system	monoclinic	triclinic	Tetragonal
Space group	*P*21/*n*	*P*-1	*P*41212
a [Å]	12.9361(3)	3.9407(5)	7.89440(10)
b [Å]	7.6445(2)	7.3930(8)	7.89440(10)
c [Å]	16.4323(4)	15.5227(14)	31.4906(10)
α [º]	90	78.238(8)	90
β [º]	95.386(2)	87.991(8)	90
γ [º]	90	82.647(9)	90
V [$Å^3$]	1617.82(7)	439.08(8)	1962.54(8)
Z	8	2	8
$\rho_{calcd.}$ [g cm^{-3}]	3.022	1.735	1.695
μ [mm^{-1}]	8.194	1.016	1.119
F(000)	1312	232	1024
Θ range [º]	4.13 – 25.24	4.21 – 25.24	4.14 – 25.24
Index ranges	-18 ≤ *h* ≤ 18	-5 ≤ *h* ≤ 4	-10 ≤ *h* ≤ 10
	-10 ≤ *k* ≤ 10	-10 ≤ *k* ≤ 10	-10 ≤ *k* ≤ 11
	-23 ≤ *l* ≤ 23	-17 ≤ *l* ≤ 22	-36 ≤ *l* ≤ 43
Reflns. collected	31600	4284	18662
Reflns. obsd.	4117	1743	2257
Reflns. unique	4921 (R_{int} = 0.0344)	2689 (R_{int} = 0.0330)	2806 (R_{int} = 0.0652)
R_1, wR_2 (2σ data)	0.0241, 0.0480	0.0453, 0.0747	0.0367, 0.0654
R_1, wR_2 (all data)	0.0339, 0.0518	0.0841, 0.0914	0.0574, 0.0716
GOOF on F^2	1.057	1.031	1.036
Peak/hole [e $Å^{-3}$]	1.631 / -1.380	0.409 / -0.395	0.357 / -0.288

Table 10: Details for X-ray data collection and structure refinement for compounds **44l** and **63**.

	44l	**63**
Empirical formula	$C_8H_6S_5$	$C_8H_4S_6$
Formula mass	262.43	292.47
T[K]	173(2)	173(2)
Crystal size [mm]	0.40 × 0.35 × 0.04	0.15 × 0.01 × 0.01
Crystal description	yellow block	pale yellow rod
Crystal system	triclinic	orthorhombic
Space group	*P*-1	*Pna*21
a [Å]	6.1998(2)	19.0955(17)
b [Å]	9.3980(4)	3.9322(3)
c [Å]	10.0285(4)	14.6103(16)
α [º]	112.307(4)	90
β [º]	102.451(3)	90
γ [º]	90.518(3)	90
V [$Å^3$]	525.20(4)	1097.05(18)
Z	2	4
$\rho_{calcd.}$ [g cm^{-3}]	1.659	1.771
μ [mm^{-1}]	1.049	1.198
F(000)	268	592
Θ range [º]	4.20 – 25.24	4.30 – 25.24
Index ranges	$-8 \le h \le 8$	$-21 \le h \le 23$
	$-13 \le k \le 13$	$-4 \le k \le 4$
	$-14 \le l \le 14$	$-17 \le l \le 18$
Reflns. collected	10463	6517
Reflns. obsd.	2783	1560
Reflns. unique	3188 (R_{int} = 0.0222)	2186 (R_{int} = 0.0776)
R_1, wR_2 (2σ data)	0.0260, 0.0617	0.0715, 0.1640
R_1, wR_2 (all data)	0.0323, 0.0660	0.1037, 0.1908
GOOF on F^2	1.041	1.031
Peak/hole [e $Å^{-3}$]	0.358 / -0.344	2.244 / -0.652

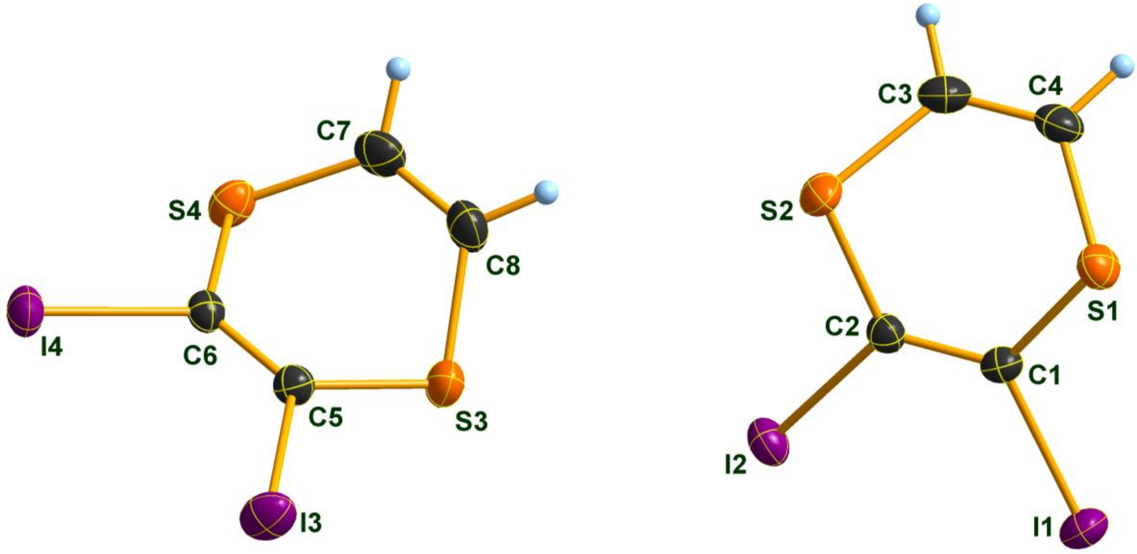


Figure 5: Molecular structure of compound **49e** in the crystal, DIAMOND[131] representation of the two crystallographically independent molecules; thermal ellipsoids are drawn at 50 % probability level.

Table 11: Selected bond lengths (Å) of compound **49e**.

I1 – C1	2.092(3)	S3 – C5	1.759(3)
I2 – C2	2.094(3)	S3 – C8	1.762(4)
I3 – C5	2.086(3)	C1 – C2	1.339(4)
I4 – C6	2.099(3)	C3 – C4	1.315(5)
S4 – C7	1.750(4)	C5 – C6	1.332(4)
S4 – C6	1.765(3)	C7 – C8	1.315(5)
S2 – C2	1.757(3)	S1 – C1	1.760(3)
S2 – C3	1.759(3)	S1 – C4	1.761(3)

Table 12: Selected bond angles (°) of compound **49e**.

C7 – S4 – C6	101.1(2)	C6 – C5 – S3	123.2(2)
C2 – S2 – C3	100.3(1)	C6 – C5 – I3	124.2(2)
C1 – S1 – C4	100.9(2)	S3 – C5 – I3	112.6(2)
C5 – S3 – C8	101.4(1)	C5 – C6 – S4	122.4(2)
C2 – C1 – S1	121.3(2)	C5 – C6 – I4	124.0(2)
C2 – C1 – I1	124.3(2)	S4 – C6 – I4	113.6(2)
S1 – C1 – I1	114.4(2)	C8 – C7 – S4	123.7(3)
C1 – C2 – S2	122.6(2)	C7 – C8 – S3	122.8(3)

[131] DIAMOND, Crystal Impact GbR., Version 3.2i.

C1 – C2 – I2	123.2(2)	C4 – C3 – S2	123.2(3)
S2 – C2 – I2	114.1(2)	C3 – C4 – S1	121.6(3)

Table 13: Selected torsion angles (º) of compound **49e**.

C4 – S1 – C1 – C2	-40.7(3)	C8 – S3 – C5 – C6	37.2(3)
C4 – S1 – C1 – I1	138.9(2)	C8 – S3 – C5 – I3	-143.7(2)
S1 – C1 – C2 – S2	-0.4(4)	S3 – C5 – C6 – S4	0.0(4)
I1 – C1 – C2 – S2	-179.9(2)	I3 – C5 – C6 – S4	-180.0(1)
S1 – C1 – C2 – I2	177.4(1)	S3 – C5 – C6 – I4	180.0(1)
I1 – C1 – C2 – I2	-2.1(4)	I3 – C5 – C6 – I4	1.0(4)
C3 – S2 – C2 – C1	40.4(3)	C7 – S4 – C6 – C5	-37.8(3)
C3 – S2 – C2 – I2	-137.5(2)	C7 – S4 – C6 – I4	142.3(2)
C2 – S2 – C3 – C4	-39.8(3)	C6 – S4 – C7 – C8	39.1(3)
S2 – C3 – C4 – S1	-1.2(5)	S4 – C7 – C8 – S3	-2.0(5)
C1 – S1 – C4 – C3	41.8(3)	C5 – S3 – C8 – C7	-36.3(3)

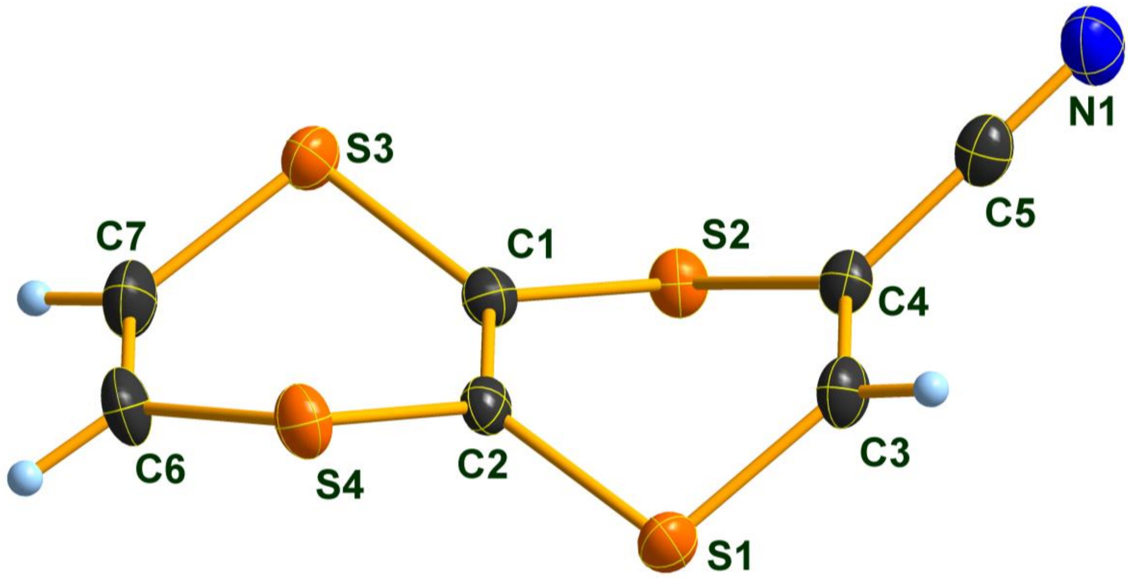


Figure 6: Molecular structure of compound **59c** in the crystal, DIAMOND[10] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 14: Selected bond lengths (Å) of compound **59c**.

S3 – C1	1.759(3)	C4 – C3	1.333(3)
S3 – C7	1.765(3)	C4 – C5	1.440(3)
S1 – C3	1.750(3)	N1 – C5	1.139(3)
S1 – C2	1.765(3)	C2 – C1	1.331(3)
S4 – C2	1.760(3)	C6 – C7	1.319(4)
S4 – C6	1.761(3)	S2 – C4	1.777(3)
S2 – C1	1.767(3)		

Table 15: Selected bond angles (º) of compound **59c**.

C1 – S3 – C7	99.7(1)	C2 – C1 – S2	121.7(2)
C3 – S1 – C2	99.6(1)	S3 – C1 – S2	114.9(1)
C2 – S4 – C6	99.8(1)	C4 – C3 – S1	121.8(2)
C1 – S2 – C4	98.2(1)	C7 – C6 – S4	123.0(2)
C3 – C4 – C5	121.2(2)	C6 – C7 – S3	124.3(2)
C3 – C4 – S2	123.1(2)	S4 – C2 – S1	113.2(1)
C5 – C4 – S2	115.7(2)	N1 – C5 – C4	178.8(3)
C1 – C2 – S4	123.5(2)	C2 – C1 – S3	123.5(2)
C1 – C2 – S1	123.2(2)		

Table 16: Selected torsion angles (º) of compound **59c**.

C1 – S2 – C4 – C3	44.1(3)	C7 – S3 – C1 – C2	-36.8(2)
C1 – S2 – C4 – C5	-133.8(2)	C7 – S3 – C1 – S2	143.3(2)
C6 – S4 – C2 – C1	39.3(2)	C4 – S2 – C1 – C2	-42.6(2)
C6 – S4 – C2 – S1	-143.0(2)	C4 – S2 – C1 – S3	137.4(2)
C3 – S1 – C2 – C1	41.3(2)	C5 – C4 – C3 – S1	175.1(2)
C3 – S1 – C2 – S4	-136.4(2)	S2 – C4 – C3 – S1	-2.7(3)
S4 – C2 – C1 – S3	-1.4(3)	C2 – S1 – C3 – C4	-39.9(3)
S1 – C2 – C1 – S3	-178.9(1)	C2 – S4 – C6 – C7	-38.8(3)
S4 – C2 – C1 – S2	178.5(1)	S4 – C6 – C7 – S3	0.7(4)
S1 – C2 – C1 – S2	1.1(3)	C1 – S3 – C7 – C6	37.4(3)

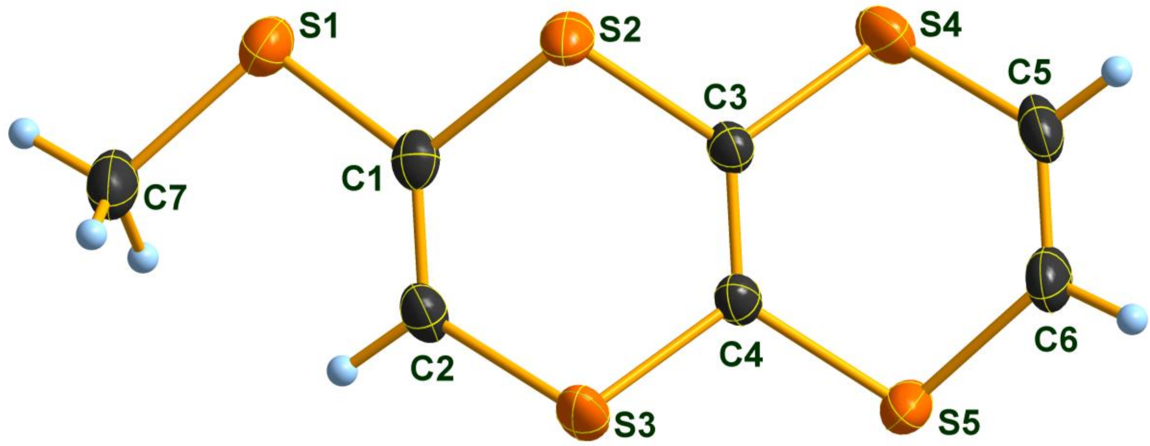


Figure 7: Molecular structure of compound **59d** in the crystal, DIAMOND[10] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 17: Selected bond lengths (Å) of compound **59d**.

S2 – C3	1.766(3)	C4 – C3	1.321(4)
S2 – C1	1.776(3)	C2 – C1	1.324(5)
S5 – C6	1.763(3)	C5 – C6	1.309(5)
S5 – C4	1.767(3)	S4 – C3	1.762(3)
S1 – C1	1.749(3)	S3 – C4	1.763(3)
S1 – C7	1.799(4)	S3 – C2	1.764(3)
S4 – C5	1.757(4)		

Table 18: Selected bond angles (º) of compound **59d**.

C3 – S2 – C1	100.3(2)	C4 – C3 – S2	122.9(2)
C6 – S5 – C4	99.6(2)	S4 – C3 – S2	114.4(2)
C1 – S1 – C7	103.0(2)	C6 – C5 – S4	123.3(3)
C5 – S4 – C3	99.7(2)	C5 – C6 – S5	123.0(3)
C4 – S3 – C2	100.6(2)	C2 – C1 – S1	128.7(3)
C3 – C4 – S3	122.8(2)	C2 – C1 – S2	121.5(3)
C3 – C4 – S5	122.9(2)	S1 – C1 – S2	109.9(2)
S3 – C4 – S5	114.3(2)	C4 – C3 – S4	122.6(2)
C1 – C2 – S3	124.0(3)		

Table 19: Selected torsion angles (º) of compound **59d**.

C2 – S3 – C4 – C3	36.8(3)	S3 – C4 – C3 – S4	-179.4(2)
C2 – S3 – C4 – S5	-144.3(2)	S5 – C4 – C3 – S4	1.7(4)
C6 – S5 – C4 – C3	38.7(3)	S3 – C4 – C3 – S2	3.5(4)
C6 – S5 – C4 – S3	-140.3(2)	S5 – C4 – C3 – S2	-175.5(2)
C4 – S3 – C2 – C1	-38.9(3)	C5 – S4 – C3 – C4	-40.8(3)
S3 – C2 – C1 – S1	180.0(2)	C5 – S4 – C3 – S2	136.6(2)
S3 – C2 – C1 – S2	0.3(4)	C1 – S2 – C3 – C4	-41.8(3)
C7 – S1 – C1 – C2	10.5(4)	C1 – S2 – C3 – S4	140.9(2)
C7 – S1 – C1 – S2	-170.8(2)	C3 – S4 – C5 – C6	39.6(4)
C3 – S2 – C1 – C2	39.5(3)	S4 – C5 – C6 – S5	0.9(5)
C3 – S2 – C1 – S1	-140.3(2)	C4 – S5 – C6 – C5	-40.2(4)

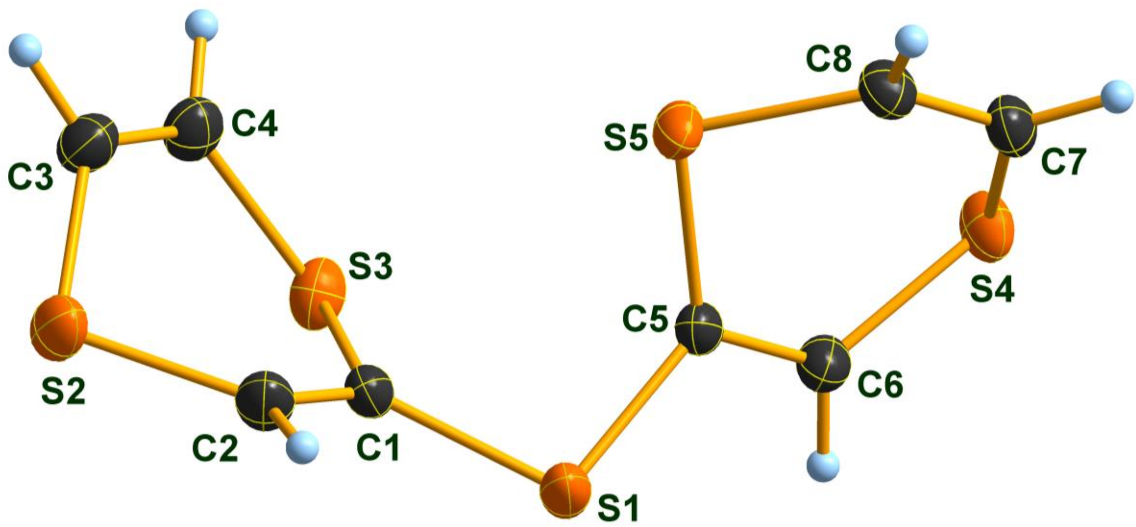


Figure 8: Molecular structure of compound **44l** in the crystal, DIAMOND[10] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 20: Selected bond lengths (Å) of compound **44l**.

S4 – C6	1.747(1)	C5 – C6	1.336(2)
S4 – C7	1.752(1)	C1 – C2	1.332(2)
S5 – C8	1.761(1)	C8 – C7	1.318(2)
S5 – C5	1.773(1)	C4 – C3	1.324(2)
S2 – C3	1.756(2)	S3 – C1	1.764(1)
S2 – C2	1.759(2)	S1 – C5	1.764(1)
S3 – C4	1.754(2)	S1 – C1	1.767(1)

Table 21: Selected bond angles (°) of compound **44l**.

C6 – S4 – C7	101.2(1)	C3 – C4 – S3	123.3(1)
C8 – S5 – C5	99.9(1)	C5 – C6 – S4	123.9(1)
C3 – S2 – C2	100.0(1)	C8 – C7 – S4	124.2(1)
C4 – S3 – C1	100.8(1)	C4 – C3 – S2	123.8(1)
C5 – S1 – C1	101.8(1)	C2 – C1 – S1	120.9(1)
C6 – C5 – S1	119.2(1)	S3 – C1 – S1	115.7(1)
C6 – C5 – S5	122.1(1)	C1 – C2 – S2	123.2(1)
S1 – C5 – S5	118.3(1)	C7 – C8 – S5	122.7(1)
C2 – C1 – S3	123.2(1)		

Table 22: Selected torsion angles (°) of compound **44l**.

C1 – S1 – C5 – C6	-139.0(1)	C3 – S2 – C2 – C1	-40.0(1)
C1 – S1 – C5 – S5	48.3(1)	C5 – S5 – C8 – C7	40.5(1)
C8 – S5 – C5 – C6	-41.4(1)	C1 – S3 – C4 – C3	-37.6(1)
C8 – S5 – C5 – S1	131.2(1)	S1 – C5 – C6 – S4	-167.7(1)
C4 – S3 – C1 – C2	35.3(1)	S5 – C5 – C6 – S4	4.7(2)
C4 – S3 – C1 – S1	-149.0(1)	C7 – S4 – C6 – C5	34.0(1)
C5 – S1 – C1 – C2	-130.8(1)	S5 – C8 – C7 – S4	-2.8(2)
C5 – S1 – C1 – S3	53.3(1)	C6 – S4 – C7 – C8	-35.3(1)
S3 – C1 – C2 – S2	3.7(2)	S3 – C4 – C3 – S2	0.5(2)
S1 – C1 – C2 – S2	-171.8(1)	C2 – S2 – C3 – C4	38.0(2)

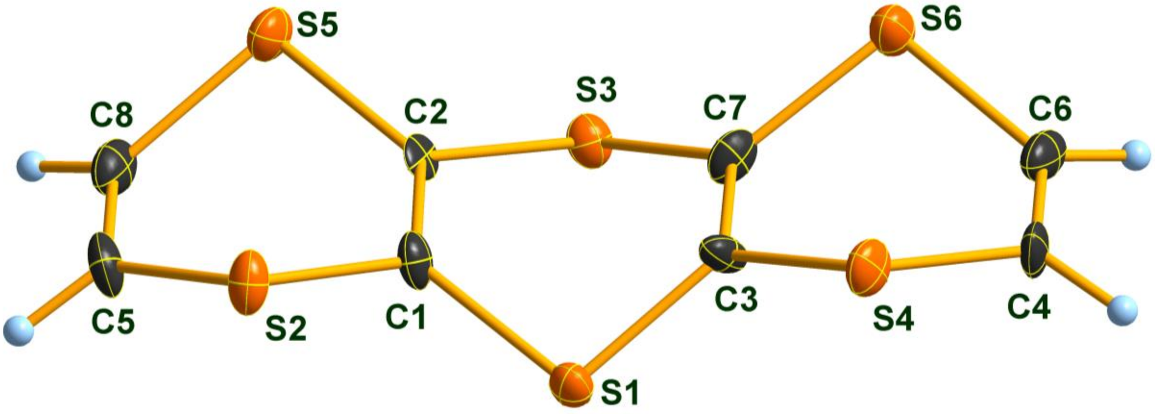


Figure 9: Molecular structure of compound **63** in the crystal, DIAMOND[10] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 23: Selected bond lengths (Å) of compound **63**.

S1 – C3	1.748(14)	S6 – C6	1.765(13)
S1 – C1	1.774(14)	S6 – C7	1.781(15)
S2 – C1	1.753(13)	C1 – C2	1.365(19)
S2 – C5	1.763(13)	C3 – C7	1.314(18)
S3 – C7	1.746(13)	C4 – C6	1.32(2)
S3 – C2	1.782(14)	C5 – C8	1.27(2)
S4 – C4	1.758(14)	S5 – C2	1.741(12)
S4 – C3	1.775(12)	S5 – C8	1.791(16)

Table 24: Selected bond angles (°) of compound **63**.

C3 – S1 – C1	98.8(6)	C6 – C4 – S4	122.9(11)
C1 – S2 – C5	99.9(7)	C8 – C5 – S2	123.5(12)
C7 – S3 – C2	100.1(6)	C4 – C6 – S6	123.4(12)
C4 – S4 – C3	100.3(7)	C3 – C7 – S3	122.9(11)
C2 – S5 – C8	98.2(6)	C3 – C7 – S6	123.3(10)
C6 – S6 – C7	99.3(7)	S3 – C7 – S6	113.8(8)
C2 – C1 – S2	121.6(10)	C5 – C8 – S5	124.2(11)
C2 – C1 – S1	122.5(10)	S5 – C2 – S3	115.4(8)

S2 – C1 – S1	115.9(7)	C7 – C3 – S1	123.6(10)
C1 – C2 – S5	123.8(10)	C7 – C3 – S4	122.6(11)
C1 – C2 – S3	120.8(9)	S1 – C3 – S4	113.8(8)

Table 25: Selected torsion angles (º) of compound **63**.

C5 – S2 – C1 – C2	38.5(11)	C4 – S4 – C3 – S1	138.1(8)
C5 – S2 – C1 – S1	-139.2(8)	C3 – S4 – C4 – C6	38.0(14)
C3 – S1 – C1 – C2	41.4(12)	C1 – S2 – C5 – C8	-40.0(14)
C3 – S1 – C1 – S2	-140.9(8)	S4 – C4 – C6 – S6	2.6(19)
S2 – C1 – C2 – S5	1.9(15)	C7 – S6 – C6 – C4	-40.8(14)
S1 – C1 – C2 – S5	179.5(7)	S1 – C3 – C7 – S3	2.7(17)
S2 – C1 – C2 – S3	-178.1(7)	S4 – C3 – C7 – S3	-179.5(7)
S1 – C1 – C2 – S3	-0.5(14)	S1 – C3 – C7 – S6	-176.6(7)
C8 – S5 – C2 – C1	-40.3(11)	S4 – C3 – C7 – S6	1.2(17)
C8 – S5 – C2 – S3	139.6(7)	C2 – S3 – C7 – C3	40.1(13)
C7 – S3 – C2 – C1	-40.4(11)	C2 – S3 – C7 – S6	-140.6(7)
C7 – S3 – C2 – S5	139.7(7)	C6 – S6 – C7 – C3	38.6(13)
C1 – S1 – C3 – C7	-43.5(13)	C6 – S6 – C7 – S3	-140.7(8)
C1 – S1 – C3 – S4	138.5(7)	S2 – C5 – C8 – S5	-0.1(19)
C4 – S4 – C3 – C7	-39.9(13)	C2 – S5 – C8 – C5	40.1(14)

2. LIST OF ABBREVIATIONS

Ar	aryl
aq.	aqueous
Bn	benzyl
Boc	*tertbutyl* carbonate
Bu	butyl
calc.	calculated
cat.	catalytic
CIPE	complex-induced proximity effect
conc.	concentrated
Cp	cyclopentadienyl
δ	chemical shifts in parts per million
d	doublet
dba	trans,trans-dibenzylideneacetone
DFT	discrete Fourier transform
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DG	directing group
DMG	direct metalation group
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
D*o*M	directed *ortho*-metalation
E	electrophile
EI	electron-impact ionization
equiv	equivalent
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
Het	heteroaryl
HRMS	high resolution mass spectroscopy
HTA	1,4,5,6,9,10-hexathiaanthracene
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
M	molarity
m	*meta*
m	multiplet
Me	methyl
Met	metal
min	minute
m.p.	Melting point
MS	mass spectroscopy
MW	microwave
*n*Bu	*n*-butyl
o	ortho
p	para
q	quartet
Ph	phenyl
R	organic substituent
RT	room temperature
s	singulet
sat.	saturated
*s*Bu	*sec*-butyl

TBAF	tetra-n-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidyl
TMS	trimethylsilyl
TP	typical procedure
Ts	*p*-toluenesulfonyl
TTF	tetrathiafulvalene
TTN	1,4,5,8-tetrathianaphthalene