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Selective and Stepwise Functionalization of the Pyridazine Scaffold by using Thio-substituted Pyridazine Building Blocks

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Erklärung

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C. Hamze, J. Brossier, K. Karaghiosoff, E. Godineau, P. Knochel, *Chem. Eur. J.* **2023**, e202302156.

Review:

"Preparation of Polyfunctional Zinc and Magnesium Organometallic Species"

F. Danton, C. Hamze, A. Desaintjean, P. Knochel, *L'Act. Chim.* **2020**, 22.

Poster Presentation "Preparation of fully substituted pyridazine":

1) *19th Austrian Chemistry Days*, **2022**, Vienna, Austria.

2) *23rd Tetrahedron Symposium*, **2023**, Gothenburg, Sweden.

Abbreviations:

°C	degree Celsius
Å	Ångström
Ac	acetyl
aq.	*aqueous*
Ar	undefined aryl substituent
ATR	attenuated total reflection
Bu	butyl
C	concentration
calcd.	calculated
CCDC	Cambridge crystallographic data center
CIPE	complex induced proximity effect
cm	centimeter
conc.	concentrated
d	doublet
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
D*o*M	directed *ortho* metalation
EI	electron impact ionization
equiv	equivalents
Et	ethyl
Et_2O	diethylether
Et_3N	triethylamine
EtOAc	ethyl acetate

eV	electronvolt
E-X	electrophile
FG	functional group
g	gram
GC	gas chromatography
h	hour
Hal	halogen
Het	undefined heteroaryl substituent
HRMS	high resolution mass spectra
Hz	hertz
i	*iso*
IR	infrared spectroscopy
J	coupling constant
kg	kilogram
kV	kilovolt
L	liter
LDA	lithium diisopropylamide
m	meter
M	molarity
m	multiplet
m. p.	melting point
Me	methyl
M	undefined metal
mg	milligram

MHz	mega hertz
min	minute
mL	milliliter
mmol	millimol
MS	mass spectra
NMR	nuclear magnetic resonance spectroscopy
o	*ortho*
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet
R	undefined organic substituent
s	second
s	singulet
sat.	*saturated*
T	temperature
t	time
t	triplet
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMPH	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TP	typical procedure
V	volume

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A. INTRODUCTION

1. OVERVIEW

From 2013 to 2022, the United States Food and Drug Administration's Center for Drug Evaluation and Research (FDA, CDER) approved an average of 43 new drugs per year. Last year, 37 novel drugs were approved by CDER, including 19 small-molecule drugs.[1] Among small-molecule drugs, the most common ones on the market are those containing nitrogen aromatic heterocycles such as pyridine, pyridazine, pyrimidine or triazole. In 2022, around two-thirds of the small-molecules (13 out of 19) contain these chemical moieties. Several of these drugs are kinase-related. The pyridazine containing Deucravacitinib is an allosteric tyrosine kinase 2 (TYK2) inhibitor for moderate-to-severe plaque psoriasis. Pacritinib is a kinase inhibitor used for the treatment of myelofibrosis. Daridorexant is a dual orexin receptor blocker (OX_1/OX_2) for insomnia (Figure 1).

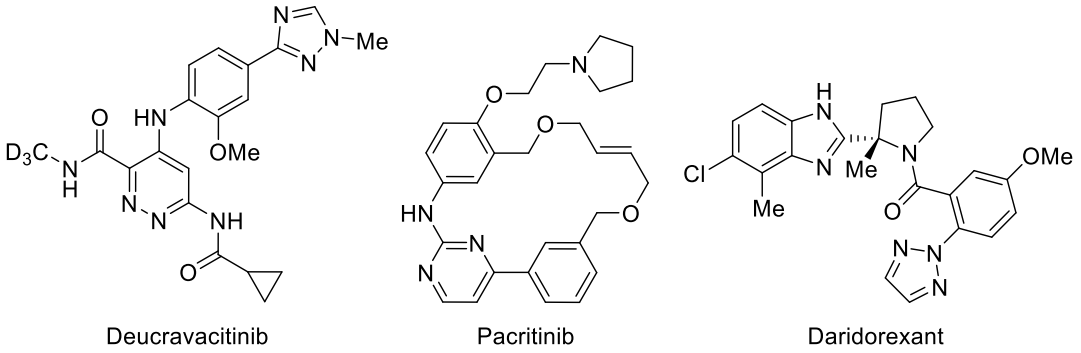
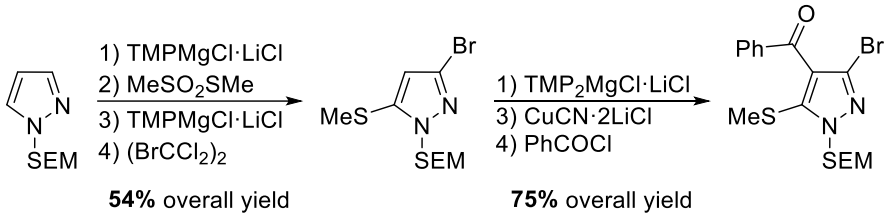


Figure 1. Novel drugs approved by the FDA's CDER in 2022.

Over the years, organometallic chemistry has proven to be an important tool for the synthesis of new compounds, particularly for the formation of new carbon-carbon bonds or carbon-heteroatom bonds. Organometallic synthesis is widely used for the functionalization of N-heterocycles (Scheme 1).[2]



Scheme 1. Synthesis of fully substituted pyrazoles via regio- and chemoselective metalations.

[1] B. G. de la Torre, F. Albericio, *Molecules* **2023**, *28*.
[2] C. Despotopoulou, L. Klier, P. Knochel, *Org. Lett.* **2009**, *11*, 3326.

2. ORGANOMETALLIC CHEMISTRY

Organometallic compounds are molecules containing at least one carbon-metal bond. Their reactivity depends on the bond polarization between the partial negatively charged carbon atom and the partial positively charged metal. The polarity of the carbon-metal bond is mainly determined by the electronegativity of the metal atom (Figure 2).[3] The less electronegative metal leads to a strong polarization of the carbon-metal bond, thus a high reactivity of the organometallic compound. A highly reactive metal species can react with a wide range of electrophiles. However, a high reactivity often means lower stability and functional group tolerance.[4]

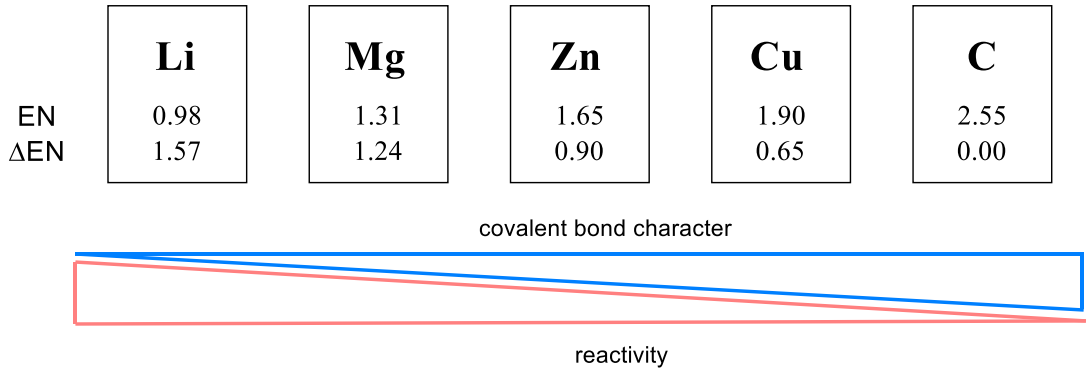
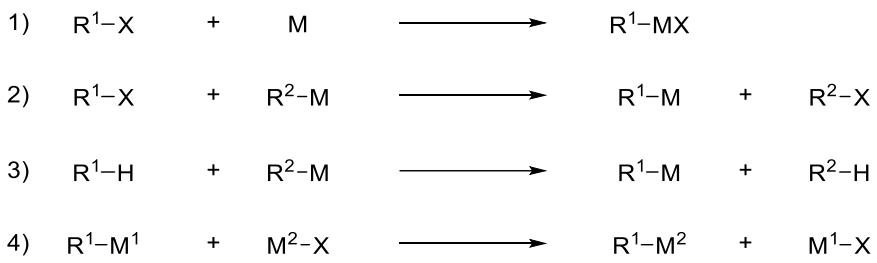


Figure 2. Correlation between EN-values according to Pauling and the reactivity and stability of the C–M bond.

There are four common pathways to obtain organometallic compounds: 1) Oxidative insertion; 2) Halogen-Metal exchange; 3) Directed metalation 4) Transmetalation (Scheme 2).



Scheme 2. Common pathways for the synthesis of organometallic compounds: 1) Oxidative insertion; 2) Halogen-Metal exchange; 3) Directed metalation; 4) Transmetalation.

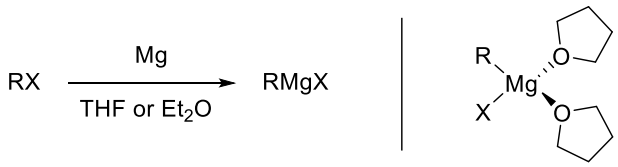
[3] A. L. Allred, *Journal of Inorganic and Nuclear Chemistry* **1961**, *17*, 215.
[4] a) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem. Int. Ed.* **2000**, *39*, 4414; b) C. Elschenbroich, F. Hensel, H. Hopf, *Organometallchemie, Vol. 6*, Teubner Verlag, Wiesbaden, **2008**.

2.1 Oxidative Insertion

The direct insertion of a metal into a carbon-halogen bond is highly attractive, as it provides a quick access to organometallics reagents in an inexpensive and environmentally friendly way due to its high atom economy.[5] The first oxidative insertion was realized by Frankland in 1849 who reported the preparation of diethylzinc using zinc dust with ethyl iodide.[6] Later, Grignard achieved the first synthesis of organomagnesium compound by reaction of methyl iodide with magnesium turnings in diethyl ether.[7] For this work, he was awarded the Nobel Prize in 1912, and organomagnesium reagents are known as Grignard reagents.[8]

2.1.1 Magnesium insertion

In general, Grignard reagents can be prepared using an excess of magnesium in the presence of a halide (Scheme 3). The reactivity order of the organohalide toward the magnesium is RI > RBr >> RCl (RF is inert). Often, the magnesium turnings need to be activated due to a passivation layer of magnesium oxide or magnesium hydroxide which might cover the metal surface. The activation can either be mechanically (by stirring or ultrasounds) or chemically for instance by using I_2, diisobutylaluminum hydride or 1,2-dibromoethane.[9] In order to stabilize the organomagnesium species, anhydrous coordinent solvents such as Et_2O or THF are used. The reaction is exothermic and high temperature (30-60°C) are usually needed for the insertion to occur.[10]



Scheme 3. General preparation of Grignard reagents.

The mechanism of the magnesium insertion into an organohalide bond occurs through the transfer of two electrons from the same metallic center by a double Singlet Electron Transfer (SET, Scheme 4).[11]

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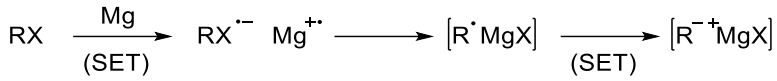
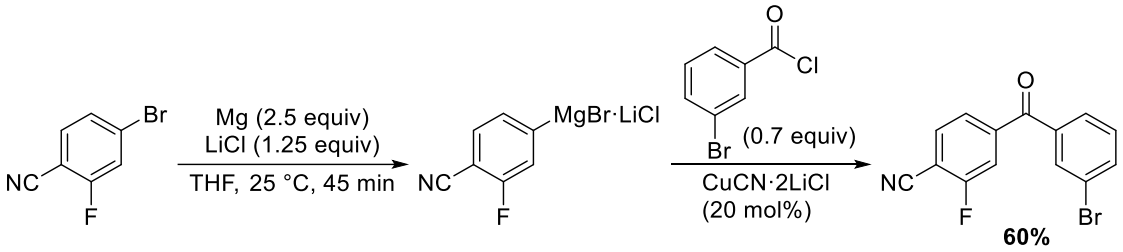
[5] L. Huck, A. de la Hoz, A. Díaz-Ortiz, J. Alcázar, *Org. Lett.* **2017**, *19*, 3747.
[6] a) E. Frankland, *J. Chem. Soc.* **1848**, *2*, 263; b) E. Frankland, *Liebigs Ann. Chem.* **1849**, *71*, 171.
[7] a) V. Grignard, *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322; b) V. Grignard, *Ann. Chem.* **1901**, *24*, 433.
[8] The Nobel Prize in Chemistry 1912. NobelPrize.org. Nobel Prize Outreach AB 2023. Thu. 24 Aug 2023. <https://www.nobelprize.org/prizes/chemistry/1912/summary/>
[9] a) D. E. Pearson, D. Cowan, J. D. Beckler, *J. Org. Chem.* **1959**, *24*, 504; b) Y.-H. Lai, *Synthesis* **1981**, *1981*, 585; c) U. Tilstam, H. Weinmann, *Org. Process Res. Dev.* **2002**, *6*, 906.
[10] H. E. Ramsden, A. E. Balint, W. R. Whitford, J. J. Walburn, R. Cserr, *J. Org. Chem.* **1957**, *22*, 1202.
[11] G. P. M. van Klink, H. J. R. de Boer, G. Schat, O. S. Akkerman, F. Bickelhaupt, A. L. Spek, *Organometallics* **2002**, *21*, 2119.



Scheme 4. Radical mechanism for the magnesium insertion.

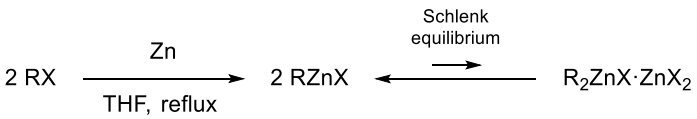
In the 2000s, Knochel reported the preparation of functionalized aromatic and heteroaromatic organomagnesium species in the presence of LiCl at low temperature (Scheme 5). The use of LiCl allows a better solubility of the Grignard reagent and provides a constantly clean metal surface leading to faster reactions. Moreover, sensitive functional groups can be tolerated since the need of high temperature is reduced.[12]



Scheme 5. Preparation of functionalized Grignard reagent via insertion in the presence of LiCI and subsequent electrophile quench.

2.1.2 Zinc insertion

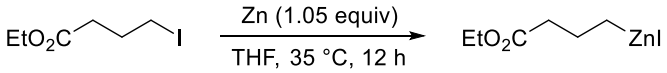
The zinc insertion into an organohalide is shown in Scheme 6. The reactivity order of the zinc toward an organohalide is the same as observed for magnesium. Nevertheless, zinc is a much less reductive metal and the insertion reaction into carbon-chloride bonds is rather difficult: RI >> RBr (RCl almost inert).[13] Moreover, the insertion works better with tertiary iodides. The use of high temperatures and polar solvents such as THF or DMF is a common requirement. Due to the poor reactivity of the zinc powder a treatment with TMSCl or 1,2-dibromoethane is mandatory in order to activate the metal.[14] The mechanism of the zinc insertion is the same as described for the magnesium insertion (see Scheme 4).



Scheme 6. General preparation of organozinc reagents.

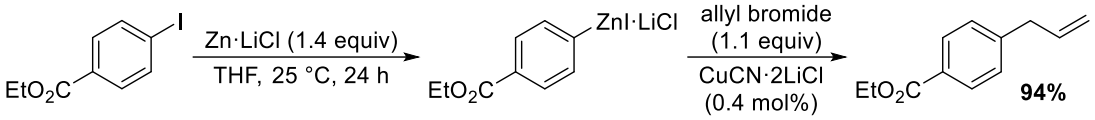
[12] a) F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 6802; b) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.
[13] P. Klein, V. D. Lechner, T. Schimmel, L. Hintermann, *Chem. Eur. J.* **2020**, *26*, 176.
[14] Q. Cao, J. L. Howard, E. Wheatley, D. L. Browne, *Angew. Chem. Int. Ed.* **2018**, *57*, 11339.

Due to the covalent nature of the zinc-carbon bond, organozinc reagents have a low reactivity and a high functional group tolerance which even includes highly reactive carbonyls. Thus, the preparation of highly functionalized organozinc species is easier than in the case of magnesium (Scheme 7).[15]



Scheme 7. Preparation of functionalized alkyl zinc species via zinc insertion.

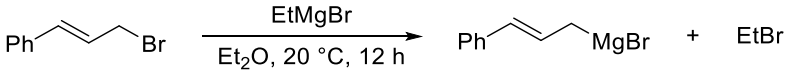
As mentioned previously, the use of LiCl salts in the preparation of organometallic reagents is a powerful tool. In fact, the presence of LiCl allows the synthesis of organozinc species starting from aryl iodides and primary alkyl bromides (Scheme 8).[16]



Scheme 8. Preparation of functionalized organozinc reagent via insertion in the presence of LiCI and subsequent electrophile quench.

2.2 Halogen-Metal Exchange

In 1931, Prévost reported the first halogen-magnesium exchange using cinnamyl bromide and ethyl magnesium bromide in diethyl ether (Scheme 9).[17]

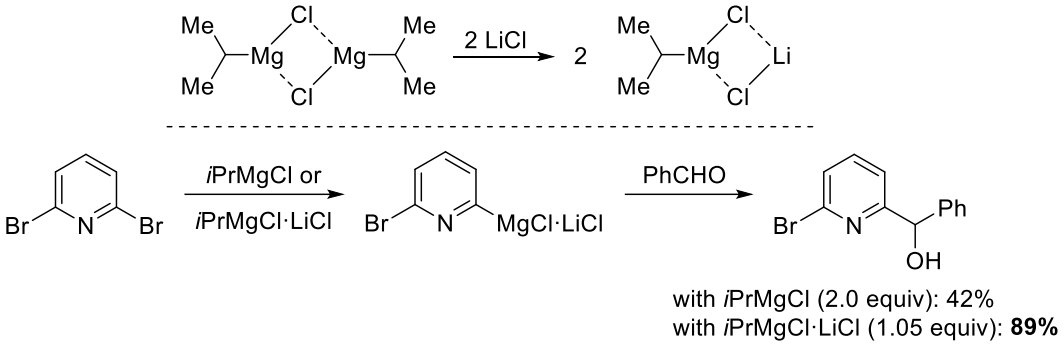


Scheme 9. First reported bromine-magnesium exchange.

The halogen-magnesium exchange is an equilibrium process. The driving force of the reaction is the formation of a more stable organometallic species compared to the exchange reagent itself. The stability of the organometallic compound follows the according order: $C(sp) > C(sp^2_{vinyl}) > C(sp^2_{aryl}) > C(sp^3_{primary}) > C(sp^3_{secondary}) > C(sp^3_{tertiary})$.[18]

[15] a) N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358; b) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107; c) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771.
[16] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.
[17] C. Prévost, *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[18] a) D. E. Applequist, D. F. O'Brien, *J. Am. Chem. Soc.* **1963**, *85*, 743; b) D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733.

Inspired by the pioneering work of Prévost and Villieras,[19] Knochel demonstrated that the addition of a stoechiometric amount of LiCl to *i*PrMgCl led to a better exchange reagent *i*PrMgCl·LiCl, often referred to as Turbo Grignard. The addition of LiCl prevents the aggregation of *i*PrMgCl, thereby increasing its solubility and reactivity. The formation of the ate-complex intermediate speeds up the Br/Mg exchange, using fewer equivalents and may generate the desired product in higher yield (Scheme 10). [20]



Scheme 10. Effect of the addition of LiCl on the Grignard reagent *i*PrMgCl.

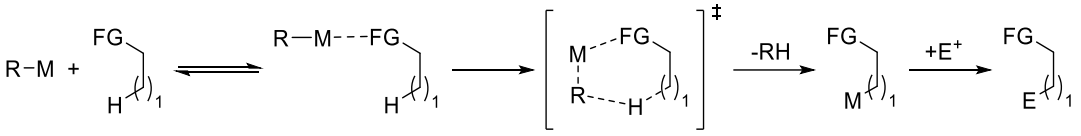
The use of Turbo Grignard allows the preparation of a wide range of functionalized aryl and heteroaryl compounds bearing sensitive groups such as esters or nitriles in excellent yields.[21] The efficiency of the halogen-metal exchange depends on the electron-deficiency of the aromatic halide used. The effect of electron-withdrawing substituents decreases with distance. The reaction velocity also depends on the nature of the halogen atom I> Br> Cl>> F.[22]

2.3 Directed Metalation

Besides oxidative insertion and halogen-metal exchange, another pathway to synthesize functionalized organometallic compound is the directed metalation using organometal (R-M) or metal amide (R_1R_2N-M) bases.[23] This method does not require the use of an organohalide reagent. The deprotonation can only occur if the C-H bond is more acidic than the newly

[19] 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.
[20] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[21] 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; d) C. Sämann, B. Haag, P. Knochel, *Chem. Eur. J.* **2012**, *18*, 16145.
[22] a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; b) C. Sämann, B. Haag, P. Knochel, *Chem. Eur. J.* **2012**, *18*, 16145.
[23] B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.

formed bond between the base and the proton.[24] Directed metalations can be seen as two-step mechanisms: First, the metal base coordinates to a Lewis basic functional group, then the proton next to the directing group is replaced by the corresponding metal in the base. The formation of this premetalation complex, which facilitates deprotonation, is called the complex-induced proximity effect (CIPE) (Scheme 11).[25]

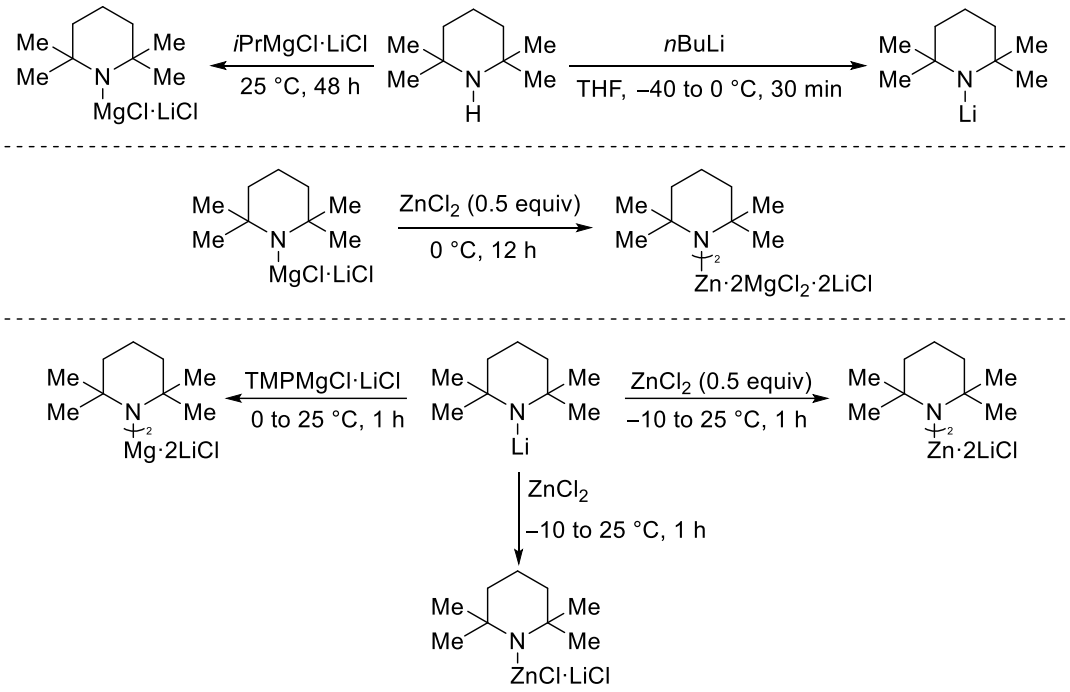


Scheme 11. Reaction mechanism of a functional group (FG) directed metalation via CIPE.

Strong bases such as alkyl lithium reagents (RLi, like *n*BuLi) or lithium amides (R_2NLi; like LDA) are commonly used for the directed *ortho* metalation (D*o*M) reactions.[26] Nevertheless, organolithium reagents often lead to undesirable side reactions, due to their high reactivity and low functional group tolerance. Another major drawback is their low stability in THF at room temperature, often requiring low temperatures of –78 to –100°C.[27] A major improvement in this area was reported by Knochel with the development of mixed Mg/Li bases like TMPMgCl·LiCl[28] or $TMP_2Mg·2LiCl$.[29] One again, the addition of a stoichiometric amount of LiCl enhance the solubility and avoid the use of a large excess of the bases. Moreover, in order to improve the metalation of sensitive substrates as well as the functional group tolerance, TMP-zinc bases such as TMPZnCl·LiCl,[30] $TMP_2Zn·2LiCl$[31] and $TMP_2Zn·2MgCl_2·2LiCl$[32]

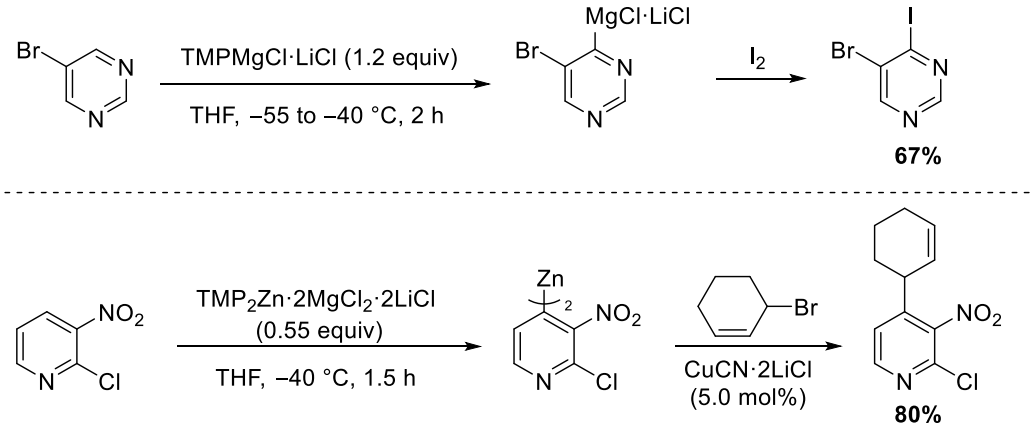
[24] M. Schlosser, P. Knochel, T. Hiyama, H.-J. Knölker, S. Bräse, *Organometallics in Synthesis - Third Manual*, John Wiley & Sons, Inc., Hoboken, **2013**.
[25] M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.
[26] a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; b) J. Clayden, *Organolithiums: Selectivity for Synthesis, Vol. 1*, Pergamon, Kidlington, Oxford, **2002**.
[27] J. Clayden, *Organolithiums: Selectivity for Synthesis, Vol. 1*, Pergamon, Kidlington, Oxford, **2002**.
[28] a) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; b) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; c) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[29] a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681; b) M. Mosrin, N. Boudet, P. Knochel, *Org. Biomol. Chem.* **2008**, *6*; c) M. Mosrin, M. Petrera, P. Knochel, *Synthesis* **2008**, *2008*, 3697; d) C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem. Int. Ed.* **2008**, *47*, 1503; e) A. Unsinn, C. J. Rohbogner, P. Knochel, *Adv. Synth. Catal.* **2013**, *355*, 1553.
[30] a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; b) M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615; c) T. Bresser, M. Mosrin, G. Monzon, P. Knochel, *J. Org. Chem.* **2010**, *75*, 4686; d) A. Unsinn, M. J. Ford, P. Knochel, *Org. Lett.* **2013**, *15*, 1128; e) M. Balkenhohl, H. Jangra, I. S. Makarov, S. M. Yang, H. Zipse, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 14992.
[31] K. Schwärzer, C. P. Tüllmann, S. Graßl, B. Górski, C. E. Brocklehurst, P. Knochel, *Org. Lett.* **2020**, *22*, 1899.
[32] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) S. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705; c) S. Wunderlich, P. Knochel, *Chem. Commun.* **2008**, 6387.

were also developed allowing the directed metalation of electron-poor heterocycles like pyridazines and triazoles. The preparation of all these TMP-bases is shown in Scheme 12, relatively stable and easy to synthesise, they are powerful tool for the metalation of various substrates.



Scheme 12. Preparation of the different TMP bases starting from TMPH.

Thus, several functionalized arenes and heteroaromatic compound were regioselectively metalated using these bases (Scheme 13).[33]

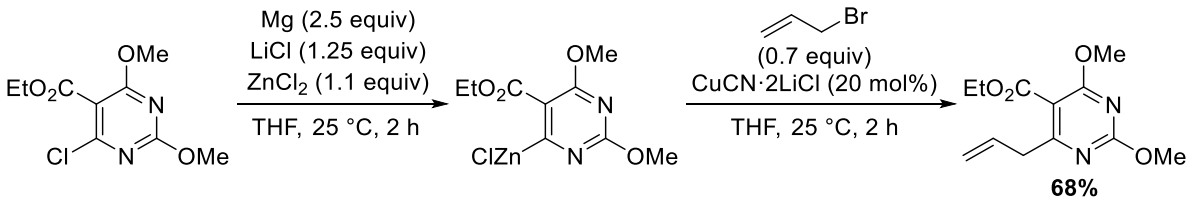


Scheme 13. Functionalization of heterocycles via metalation with TMPMgCl·LiCl or $TMP_2Zn·2MgCl_2·2LiCl$.

[33] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; b) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.

2.4 Transmetalation

Transmetalation reactions are used to adjust the reactivity of organometallic reagents to the electrophile and avoid side reactions. They are key transformations in synthetic organic chemistry. The most common transmetalation pathway is the treatment of an organometallic R^1-M^1 with a metal salt M^2-X_n, leading to a new organometallic species R^1-M^2. As mentioned for directed metalation and halogen-metal exchange, the driving force of the reaction is the formation of a stronger carbon-metal bond that possesses higher covalent character.[34] Transmetalation reactions are a useful tool for the preparation of sensitive reagents and allow the metalation of certain scaffolds with new selectivities.[35] Moreover, transmetalations are widely used for many reactions with electrophiles such as cross-coupling, acylation or allylation reactions where the organometallic species must be either an organozinc or an organocopper species in order to avoid over addition. Therefore, most highly reactive organometallic species such as organolithium or organomagnesium can be transmetalated to the corresponding organozinc as well as organocopper reagent by treatment with the appropriate metal salt, for instance $ZnCl_2$ or CuCN·2LiCl. Additionally, Knochel reported an *in situ* trapping pathway where the oxidative magnesium insertion into aryl-halide bonds is achieved in the presence of $ZnCl_2$ (Scheme 14).[36] Owing to this method, several functional groups like esters or nitriles can be tolerated during the magnesium insertion process. In fact, the transmetalation proceeds faster than the possible attack by the formed organomagnesium species. Furthermore, this *in situ* trapping allows the use of rather unreactive halides with low reactivity toward zinc insertion, and thus broadening the scope of organozinc reagents. In fact, the magnesium insertion is far more efficient and rapid than the zinc insertion.[37]



Scheme 14. Preparation and subsequent trapping of organozinc reagents via oxidative magnesium insertion in the presence of $ZnCl_2$.

[34] a) S. C. Rasmussen, *ChemTexts* **2020**, *7*, 1; b) K. Osakada, in *Current Methods in Inorganic Chemistry, Vol. 3* (Eds.: H. Kurosawa, A. Yamamoto), Elsevier, **2003**, pp. 233.
[35] a) F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192; b) A. Frischmuth, M. Fernández, N. M. Barl, F. Achrainer, H. Zipse, G. Berionni, H. Mayr, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7928.
[36] F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.
[37] P. Klein, V. D. Lechner, T. Schimmel, L. Hintermann, *Chem. Eur. J.* **2020**, *26*, 176.

3. CROSS-COUPLING REACTIONS WITH ORGANOMETALLIC REAGENTS

In organic chemistry, cross-couplings are defined as reactions in which two reagents are connected with each other using a transition metal catalyst. Cross-coupling reactions are one of the most versatile and successful way to create new carbon-carbon bonds as well as carbon-heteroatom bonds.[38] Pioneering works by Heck, Negishi and Suzuki led to the expansion of this field and was awarded with the Nobel Prize in Chemistry in 2010 for palladium-catalyzed cross-coupling reactions.[39]

3.1 Overview

Transition-metal catalyzed carbon-carbon bond-forming reactions are among the most powerful methods of organic synthesis and play an important role in medicinal chemistry and material science.[40] One of the main classes of cross-couplings is the reaction of a nucleophilic organometallic reagent (R^1-M) with an electrophilic organohalide or sulfonate (R-X) under transition-metal catalysis (Scheme 15).[41] Different types of organometallic reagents can be used: Suzuki-Miyaura cross-couplings use boronic acids as coupling partner,[42] Stille employs organotin compounds,[43] Hiyama utilizes organosilanes.[44] While Kumada[45] and Negishi[46] describe the use of organomagnesium and organozinc reagents respectively. Regarding the electrophilic coupling partner R-X, X mainly refers to the leaving group as iodide, bromide, chloride or triflate, cross-coupling reactions are only scarcely described with fluorides.[47]

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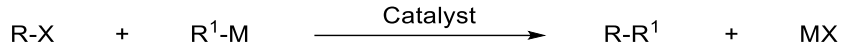
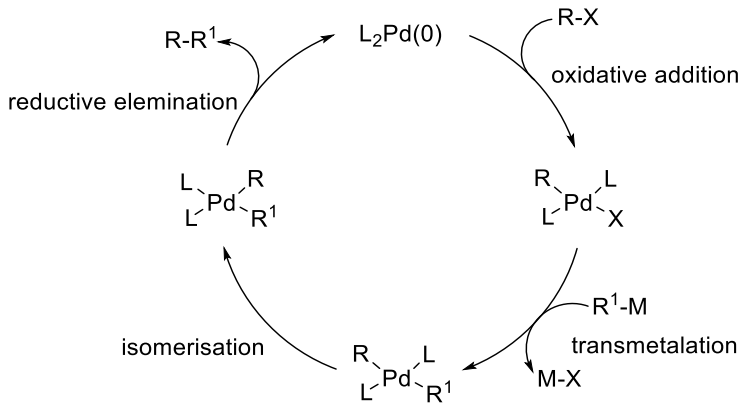
[38] A. Biffis, P. Centomo, A. Del Zotto, M. Zecca, *Chem. Rev.* **2018**, *118*, 2249.
[39] The Nobel Prize in Chemistry **2010**. NobelPrize.org. Nobel Prize Outreach AB 2023. Thu. 27 Jul 2023. <https://www.nobelprize.org/prizes/chemistry/2010/summary/>
[40] J. F. Hartwig, *Organotransition metal chemistry: From bonding to catalysis, Vol. 2010th edition*, University Science Books, Mill Valley, **2010**.
[41] F. A. Carey, R. J. Sundberg, in *Advanced Organic Chemistry: Part B: Reactions and Synthesis* (Eds.: F. A. Carey, R. J. Sundberg), Springer US, Boston, MA, **2007**, pp. 675.
[42] a) N. Miyaura, A. Suzuki, *J. Chem. Soc., Chem. Commun.* **1979**, 866; b) F. Bellina, A. Carpita, R. Rossi, *Synthesis* **2004**, *2004*, 2419.
[43] a) D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1979**, *101*, 4992; b) C. Cordovilla, C. Bartolomé, J. M. Martínez-Ilarduya, P. Espinet, *ACS Catal.* **2015**, *5*, 3040.
[44] a) Y. Hatanaka, T. Hiyama, *J. Org. Chem.* **1988**, *53*, 918; b) T. Komiyama, Y. Minami, T. Hiyama, *ACS Catal.* **2017**, *7*, 631.
[45] a) R. J. P. Corriu, J. P. Masse, *J. Chem. Soc., Chem. Commun.* **1972**, 144; b) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374; c) K. Tamao, Y. Kiso, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 9268.
[46] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; b) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540.
[47] a) H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119; b) F. Zhu, Z.-X. Wang, *J. Org. Chem.* **2014**, *79*, 4285.

Palladium and nickel are the two commonly used metal catalyst. However, Pd-catalysis leads in general to higher yields and better functional group tolerance and thus more widely used.[48]



Scheme 15. General equation for cross-coupling reactions between organohalides and organometallic reagents using transition-metal catalysis.

Palladium-catalyzed cross-coupling reactions of organohalides or triflates (R-X) with organometallic reagents (R^1-M) follow a general mechanistic cycle (Scheme 16). Once the active 14-electron Pd(0) catalyst is generated, the catalytic cycle goes through a four-step sequence. First, the electrophile R-X undergoes an oxidative addition to the Pd(0) leading to the 16-electron Pd(II) intermediate. The oxidative addition step pursues the following rate: I>OTf>Br>>Cl. Then, the transmetalation step occurs between the organometallic reagents R^1-M and the previously formed intermediate resulting in a new organo-Pd(II)-complex. An isomerization step from the trans-intermediate to the syn-intermediate is necessary to carry on the catalytic cycle. Finally, the reductive elimination step produces the coupling adduct R-R^1, regenerating the Pd(0) catalyst and thus leading to the closure of the catalytic cycle.[49]

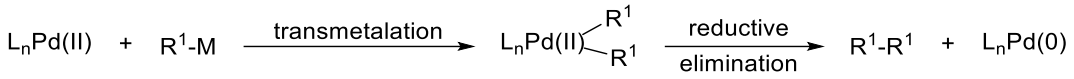


Scheme 16. General mechanism for cross-coupling reactions of organohalides with organometallic reagents.

As mentioned before, a Pd(0) catalyst needs to be generated to initiate the catalytic cycle of the cross-coupling reaction. However, rather unstable and expensive, Pd(0) sources are less used than Pd(II) sources.[50] For this reason, the Pd(II) precatalyst has to be transformed into a Pd(0) catalyst. In the case of cross-coupling reactions using organometallic species, the active Pd(0) catalyst is obtained after reduction of the Pd(II) species by the organometallic reagent R^1-M. The transmetalation step is followed by a reductive elimination leading to the homocoupling

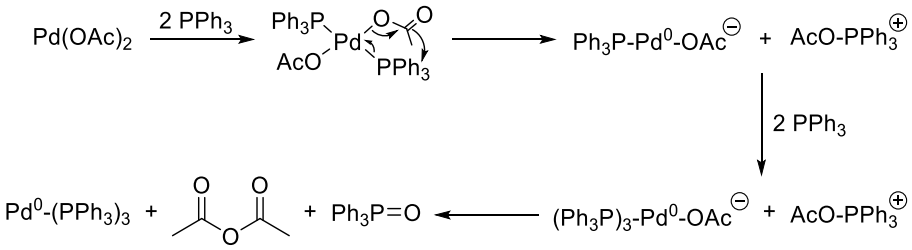
[48] A. Biffis, P. Centomo, A. Del Zotto, M. Zecca, *Chem. Rev.* **2018**, *118*, 2249.
[49] J. F. Hartwig, *Organotransition metal chemistry: From bonding to catalysis, Vol. Vol. 2010th edition*, University Science Books, Mill Valley, **2010**.
[50] S. J. Firsan, V. Sivakumar, T. J. Colacot, *Chem. Rev.* **2022**, *122*, 16983.

product R^1-R^1 as well as the Pd(0) species. The formation of homocoupling products is part of the reason why organometallic reagents are often used in excess in comparison of the organohalides (Scheme 17).[51]



Scheme 17. Formation of the Pd(0) catalyst from Pd(II) source.

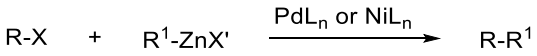
When using a Pd(II) precatalyst like $Pd(OAc)_2$ in the presence of a phosphine ligand such as PPh_3, the reduction to Pd(0) could also follow the mechanism shown in Scheme 18.[52]



Scheme 18. Reduction of the Pd(II) precatalyst using phosphine ligands.

3.2 Negishi Cross-Coupling

Published in 1977, the Negishi cross-coupling[53] was the first reaction allowing the preparation of unsymmetrical biaryls in good yields. The Negishi cross-coupling is the reaction of an organohalide or sulfonate with an organozinc reagent leading to the coupled product using palladium or nickel catalysis (Scheme 19). Organozinc reagents are less reactive than other organometallic compounds and are compatible with sensitive functional groups such as ketones, esters, amines and cyano groups. Moreover, the transmetalation of organozinc reagents to palladium is faster compared to the different organometallic species.[54]



Scheme 19. General equation of the Negishi cross-coupling. R, R^1 = alkenyl, aryl, allyl, alkynyl, propargyl; X, X' = Cl, Br, I or triflate, L = Ligand.

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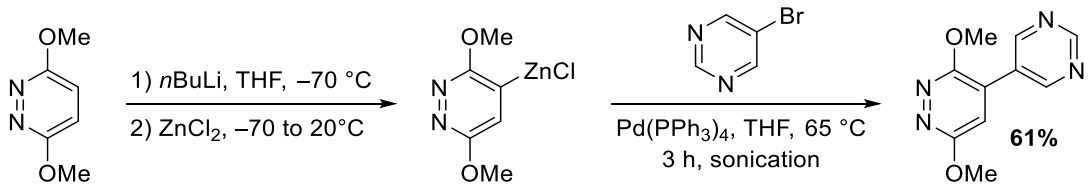
[51] J. F. Hartwig, *Organotransition metal chemistry: From bonding to catalysis, Vol. Vol. 2010th edition*, University Science Books, Mill Valley, **2010**.
[52] C. Amatore, E. Carre, A. Jutand, M. A. M'Barki, *Organometallics* **1995**, *14*, 1818.
[53] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[54] D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540.

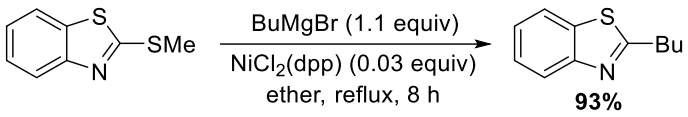
The higher stability of organozinc reagents in comparison to organolithium and organomagnesium species allows the Negishi cross-coupling reactions to be carried out at elevated temperatures. For instance, the organozinc reagent, derived from 3,6-dimethoxypyridazine, obtained by *ortho*-lithiation and subsequent transmetalation using $ZnCl_2$, was cross-coupled with 5-bromopyrimidine under Pd-catalyzed conditions leading to 3,6-dimethoxy-4-(pyrimidin-5-yl)pyridazine in 61% yield.[55] The use of high temperature and sonication enabled shorter reaction time and improved the reaction yield (Scheme 20).



Scheme 20. Negishi cross-coupling reaction.

3.3 Cross-Coupling Reactions of Unsaturated Thioethers

In 1979, Takei[56] and Wenkert[57] described for the first time the conversion of a carbon-sulfur bond into a carbon-carbon bond. The cross-coupling reactions were performed between unsaturated thioethers or thiols and Grignard reagents under nickel catalysis (Scheme 21). This discovery allowed a variation of the cross-coupling reactions that were so far limited to organohalides as coupling partners.



Scheme 21. Cross-coupling reaction of unsaturated thioether with Grignard reagent using Ni-catalysis.

The mechanism of this type of reactions follows the same pattern as the one described for the Pd-catalyzed version using halides as leaving group (see Scheme 16). The Ni(II) catalyst is first reduced to Ni(0). Then the catalytic circle starts with the oxidative addition step, followed by the transmetalation. Finally, the reductive elimination occurs leading to the coupling adduct Ar-R^1 (Scheme 22).[57c]

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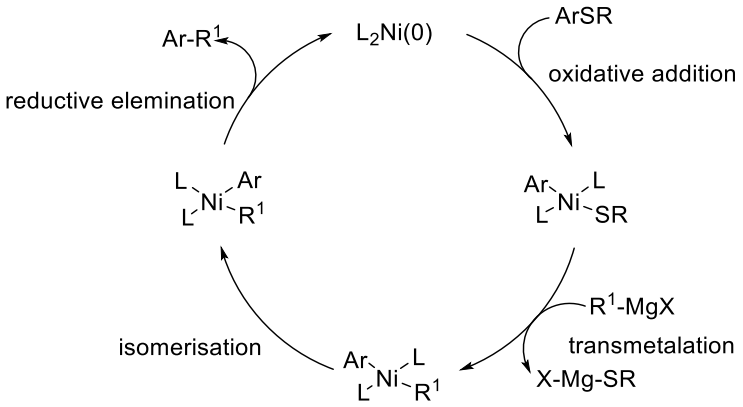
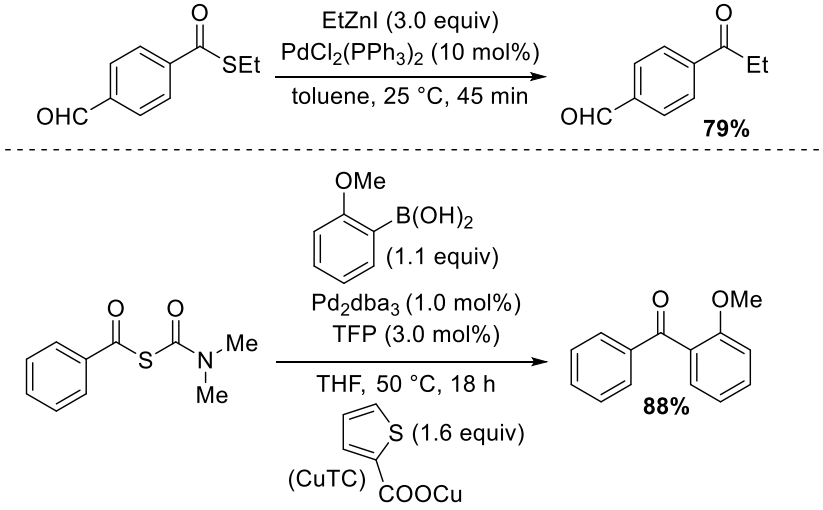
[55] A. Turck, N. Plé, A. Leprêtre-Gaquère, G. Quéguiner, *Heterocycles* **1998**, *49*, 205.
[56] a) H. Okamura, M. Miura, H. Takei, *Tetrahedron Lett.* **1979**, *20*, 43; b) H. Takei, M. Miura, H. Sugimura, H. Okamura, *Chem. Lett.* **1979**, *8*, 1447.
[57] a) E. Wenkert, T. W. Ferreira, E. L. Michelotti, *J. Chem. Soc., Chem. Commun.* **1979**, 637; b) E. Wenkert, T. W. Ferreira, *J. Chem. Soc., Chem. Commun.* **1982**, 840; c) E. Wenkert, M. E. Shepard, A. T. McPhail, *J. Chem. Soc., Chem. Commun.* **1986**, 1390; d) E. Wenkert, D. Chianelli, *J. Chem. Soc., Chem. Commun.* **1991**, 627.



Scheme 22. General mechanism for the cross-coupling between unsaturated thioether and Grignard reagent with Ni-catalyst.

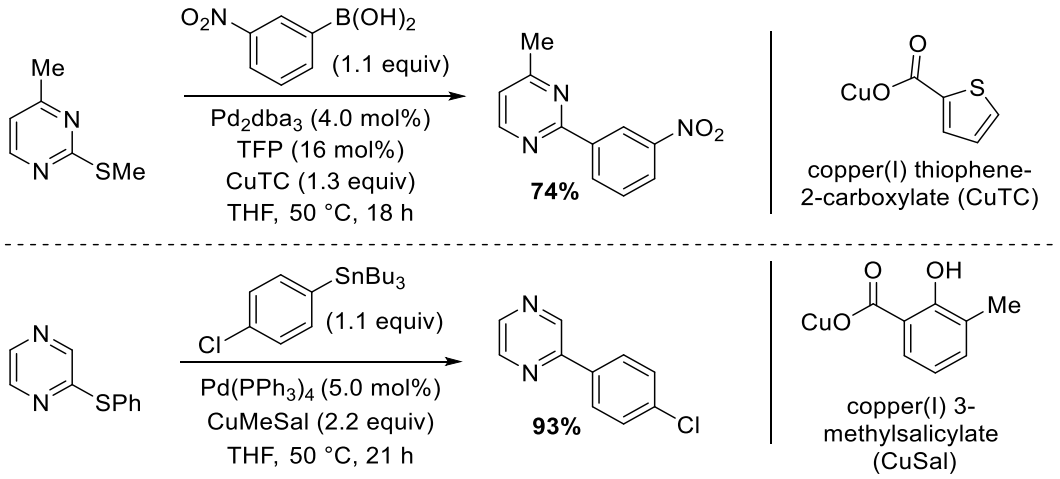
In the 2000s, inspired by these pioneering works, Fukuyama[58] and Liebeskind[59] extended the scope of this cross-coupling reaction using thioesters which led to a general ketone synthesis. Fukuyama reported the reaction between functionalized thioesters and organozinc reagents under palladium catalysis. While Liebeskind used boronic acids under Pd-catalyzed conditions with a stoichiometric amount of copper 2-thiophene carboxylate (CuTC, Scheme 23).[58,59]



Scheme 23. Ketone synthesis starting from thioesters by Fukuyama and Liebeskind.

[58] H. Tokuyama, S. Yokoshima, T. Yamashita, T. Fukuyama, *Tetrahedron Lett.* **1998**, *39*, 3189.
[59] a) J. Srogl, G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1997**, *119*, 12376; b) L. S. Liebeskind, J. Srogl, *J. Am. Chem. Soc.* **2000**, *122*, 11260; c) C. Savarin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2000**, *2*, 3229; d) C. L. Kusturin, L. S. Liebeskind, W. L. Neumann, *Org. Lett.* **2002**, *4*, 983; e) Y. Yu, L. S. Liebeskind, *J. Org. Chem.* **2004**, *69*, 3554; f) J. M. Villalobos, J. Srogl, L. S. Liebeskind, *J. Am. Chem. Soc.* **2007**, *129*, 15734; g) L. S. Liebeskind, H. Yang, H. Li, *Angew. Chem. Int. Ed.* **2009**, *48*, 1417.

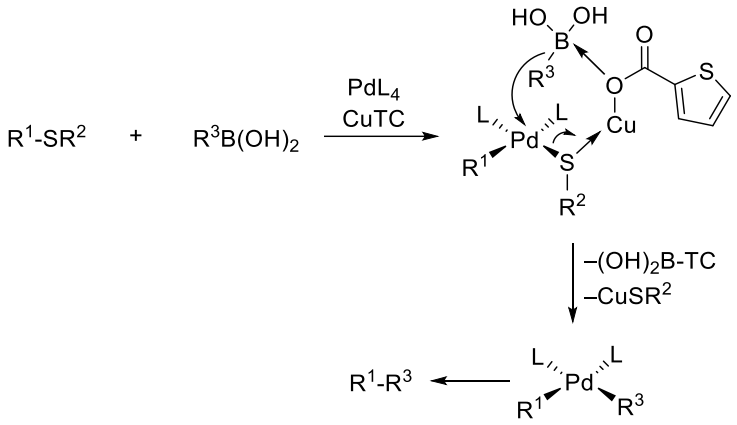
Additionally, Liebeskind described later the use of organostannanes[60] and organoindium[61] compounds as nucleophilic partners for the synthesis of ketones starting from the corresponding thioesters. Modifications of this method allowed the reaction of thioethers with organoboronic acids[62] or organostannanes[63] under Pd-catalysis (Scheme 24). This new cross-coupling reaction requires the use of a stoichiometric amount of Cu(I) carboxylate. In fact, no coupling adduct was obtained when copper(I) halide or CuCN were employed for these kind of reactions. The commercially available, cheap and relatively air stable copper(I) thiophene-2-carboxylate (CuTC) and copper(I) 3-methylsalicylate (CuMeSal) are the two copper reagents that are the most suitable.



Scheme 24. Cross-coupling reactions between organometallic reagents and thioethers under copper mediated Pd-catalyzed conditions.

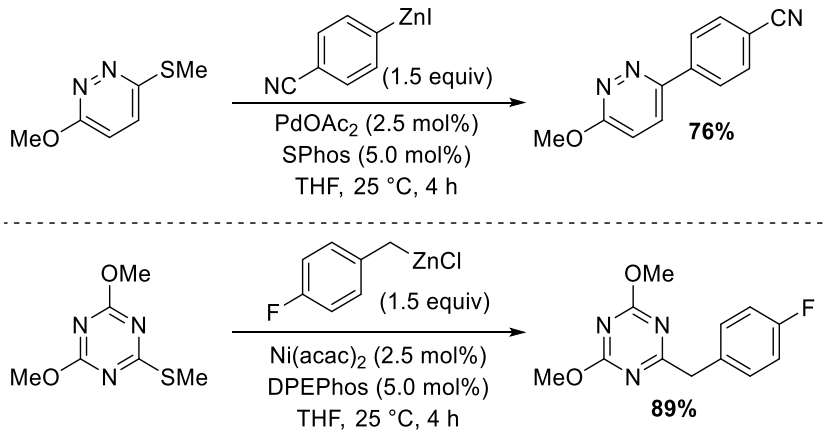
The mechanism for the Cu(I)-mediated Pd(0)-catalyzed cross-coupling reaction begins with the oxidative addition of the thioether to the Pd(0) catalyst. Then, the copper(I) carboxylate plays a dual role in the transition state. First, it polarizes the Pd-S bond owing to a coordination of the Cu^{I} to the sulfur center. In addition, it simultaneously activates the trivalent boron compound by coordination of the carboxylate to the boron center as such it facilitates the transmetalation step (Scheme 25).[62d]

[60] R. Wittenberg, J. Srogl, M. Egi, L. S. Liebeskind, *Org. Lett.* **2003**, *5*, 3033.
[61] B. W. Fausett, L. S. Liebeskind, *J. Org. Chem.* **2005**, *70*, 4851.
[62] a) C. Savarin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2001**, *3*, 91; b) L. S. Liebeskind, J. Srogl, *Org. Lett.* **2002**, *4*, 979; c) C. Kusturin, L. S. Liebeskind, H. Rahman, K. Sample, B. Schweitzer, J. Srogl, W. L. Neumann, *Org. Lett.* **2003**, *5*, 4349; d) H. Prokopcova, C. O. Kappe, *Angew. Chem. Int. Ed.* **2009**, *48*, 2276.
[63] M. Egi, L. S. Liebeskind, *Org. Lett.* **2003**, *5*, 801.



Scheme 25. Proposed mechanism for the Liebeskind-Srogl reaction.

More recently, Knochel reported the cross-coupling reactions between unsaturated heterocyclic and alkyl thioethers with organozinc reagents under Pd- and Ni-catalysis (Scheme 26). [64]



Scheme 26. Cross-couplings reactions between unsaturated heterocyclic thioethers and organozinc reagents under Pd- or Ni-catalysis.

[64] a) A. Metzger, L. Melzig, C. Despotopoulou, P. Knochel, *Org. Lett.* **2009**, *11*, 4228; b) L. Melzig, A. Metzger, P. Knochel, *J. Org. Chem.* **2010**, *75*, 2131; c) P. Knochel, A. Metzger, L. Melzig, *Synthesis* **2010**, *2010*, 2853; d) L. Melzig, A. Metzger, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 2948.

4. CHEMISTRY OF PYRIDAZINES[65]

4.1 General Properties of Diazines[66]

Diazines are six-membered aromatic heterocycles containing two sp^2-hybridized nitrogen atoms. They are structurally derived from benzene and pyridine by substitution of one or two CH groups by nitrogens. Pyridazine (1,2-diazine), pyrimidine (1,3-diazine) and pyrazine (1,4-diazine) are the three diazine isomers (Figure 3). These compounds are stable, colorless and soluble in water. They are rarely used as starting materials for the synthesis of their derivatives. In fact, they are not readily available and thus rather expensive.

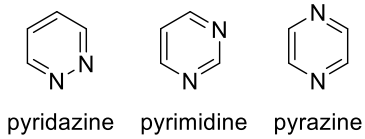


Figure 3. Structure of pyridazine, pyrimidine and pyrazine.

Diazines are 6π-electron heteroaromatic compounds. The inductive effect of the nitrogen atoms induces a partially positive charge on the carbon atoms. For this reason, diazines are electron-deficient heteroaromatic compounds. The π-electron density can be calculated for each isomers and compared to the values of pyridine (Figure 4). The lower π-electron density indicates that diazines have a lack of reactivity regarding electrophiles and would react better with nucleophiles.

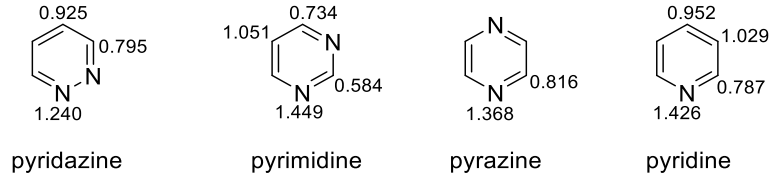


Figure 4. Comparison of the π-electron density of pyridazine, pyrimidine and pyrazine with pyridine values.

Pyridazine and pyrimidine both possess a planar slightly distorted hexagonal geometry, whereas pyrazine is planar with D_{2h} symmetry. X-ray diffraction and microwave spectroscopy studies allowed the calculation of the bond lengths and the internal bond angles (Figure 5).

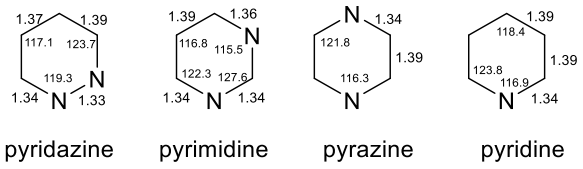


Figure 5. Bond lengths (Å) and internal bond angles (°) of pyridazine, pyrimidine, pyrazine and pyridine.

[65] M. Tišler, B. Stanovnik, in *Advances in Heterocyclic Chemistry Volume 9*, **1968**, pp. 211.
[66] M.-P. Cabal, in *Modern Heterocyclic Chemistry*, **2011**, pp. 1683.

Diazines are compounds that are less aromatic than benzene or pyridine because of lower resonance energy. The degree of aromaticity can also be determined with the aromaticity index that is expressed as a percentage. The structural index of aromaticity is calculated based on the bond lengths (Table 1).

Table 1 : Resonance energies and aromaticity index of diazines in comparison to benzene and pyridine.

	Resonance energies (kJ/mol)	Aromaticity index (%)
Benzene	150	100
Pyridine	117	82
Pyridazine		65
Pyrimidine	110	67
Pyrazine	100	75

The pyridazine N-N bond has a strong single bond character. Even though two resonance structures can be drown, experimental data indicate that the N-N single bond is the prevalent one (Figure 6).

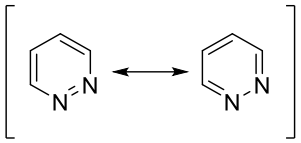


Figure 6. Resonance structure of pyridazine.

Pyridazine is a colorless liquid, soluble in water and alcohols but insoluble in hydrocarbons. Diazines are less basic than pyridine (pK_a = 5.2), the nitrogen atoms are more difficult to protonate. Pyridazine has the highest basicity (pK_a = 2.3), followed by pyrimidine (pK_a = 1.3) then pyrazine (pK_a = 0.4). Pyridazines dipolar moment is higher than the one of pyrimidine. Whereas pyrazine is a symmetrical compound and has no dipole moment. Calculation of the enthalpies of formation show that pyridazine is 83 kJ/mol more stable than pyrimidine and pyrazine (Table 2).

Table 2. Physical properties of diazines versus pyridine.

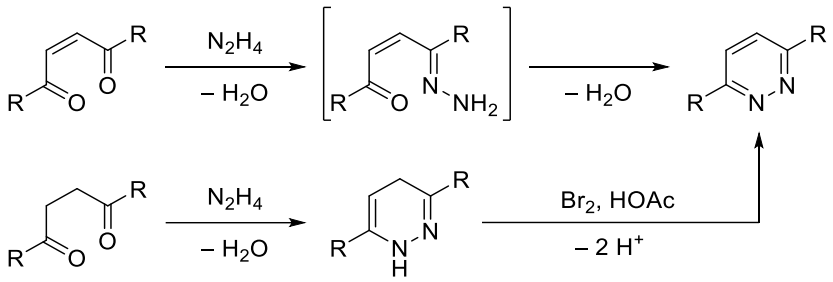
Property	Pyridazine	Pyrimidine	Pyrazine	Pyridine
Mp (°C)	–8	22.5	57	–42
Bp (°C/760 mmHg)	208	124	116	115
pK_a	2.3	1.3	0.4	5.2
Dipole moment (μ, D)	4.22	2.33	0	2.22
ΔH° (kJ/mol)	4397.8	4480.2	4480.6	

4.2 Preparation and Synthesis of the Pyridazine Ring

Fischer reported in 1886 the first synthesis of pyridazine.[67] Nevertheless, pyridazine chemistry had only been explored in more detail since the 1950s. The late interest of 1,2-diazine can result from the fact that these compounds rarely occur as natural product. However, many pyridazines possess biological activity, for that manner synthesis method need to be developed which make differently substituted pyridazines accessible. Pyridazines can be obtained by various pathways.[68] The most common ones are cyclocondensation and cycloaddition reactions.

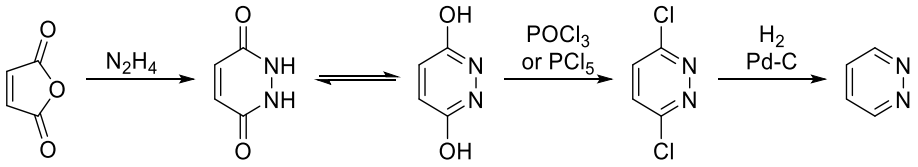
4.2.1 Cyclocondensation Reactions

Cyclocondensation of saturated or α,β-unsaturated 1,4-dicarbonyl using hydrazine leads to 1,4-dihydropyridazine or pyridazine.[69] Dehydrogenation of dihydropyridazine is for instance achieved using Br_2 in glacial acetic acid (Scheme 27). Cyclocondensation reactions are carried out in the presence of mineral acids in order to avoid the competing formation of N-aminopyrroles.



Scheme 27. Preparation of pyridazine via cyclocondensation of 1,4-dicarbonyl with hydrazine.

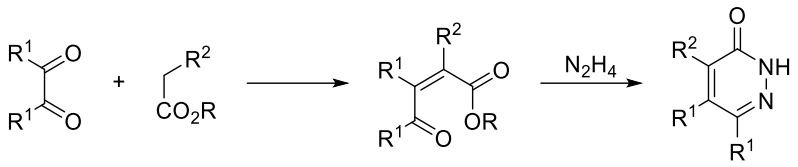
Pyridazine itself can be prepared from maleic anhydride and hydrazine. This reaction leads to maleic hydrazide which reacts with $POCl_3$ or PCl_5 to form 3,6-dichloropyridazine. This step is possible owing to an azinone-hydroxyazine tautomerism. Pyridazine is obtain by dehalogenation using H_2/Pd-C (Scheme 28).[70]



Scheme 28. Synthesis of pyridazine itself from maleic anhydride and hydrazine.

[67] E. Fisher, *Ann. Chem.* **1886**, *236*, 174.
[68] P. G. Sergeev, V. G. Nenajdenko, *Russ. Chem. Rev*. **2020**, *89*, 393.
[69] a) J. A. Hirsch, A. J. Szur, *J. Heterocycl. Chem.* **1972**, *9*, 523; b) C. Altomare, S. Cellamare, L. Summo, M. Catto, A. Carotti, U. Thull, P.-A. Carrupt, B. Testa, H. Stoeckli-Evans, *J. Med. Chem.* **1998**, *41*, 3812.
[70] R. Mizzoni, P. E. Spoerri, *J. Am. Chem. Soc*. **1951**, *73*, 1873.

1,2-diketone compounds are also used as precursor for the synthesis of 1,2-diazines.[71] A three component cyclocondensation of 1,2-diketones, reactive α-methylene esters and hydrazine leads, often in one-pot procedure, to pyridazine-3-(2H)ones. First, the 1,2-diketone undergoes aldol condensation with the α-CH_2 acidic ester giving a intermediate which is cyclized by N_2H_4 (Scheme 29).

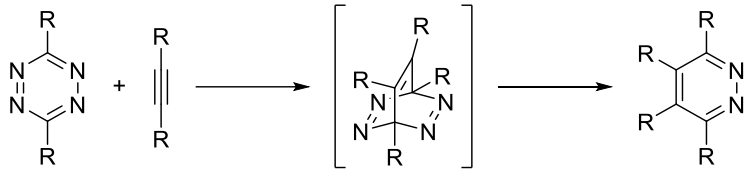


Scheme 29. Three-component cyclocondensation leading to pyridazin-3(2H)-ones.

4.2.2 Cycloadditions Reactions

[4+2] cycloaddition reactions between suitable dienes and dienophiles is one of the most versatile method for the synthesis of functionalized pyridazines.

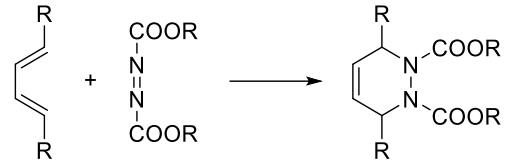
The inverse-electron-demand (LUMO diene-controlled) Diels-Alder reaction between 1,2,4,5-tetrazine and an alkene or alkyne-type dienophile, followed by the elimination of dinitrogen, is a common pathway to provide a broad range of substituted pyridazines (Scheme 30).[72] In order to achieve suitable reaction conditions, the dienophile needs to be electron-rich and the tetrazine should bear electron-withdrawing substituents.



Scheme 30. Diels-Alder reaction between 1,2,4,5-tetrazine and alkyne leading to pyridazine.

Tetrahydropyridazines can also be prepared using Diels-Alder reactions of 1,3-dienes with azodicarboxylic ester (Scheme 31). The usual stereochemical and substituent effects of these reactions follow the Woodward-Hoffmann considerations. [73]

[71] P. Schmidt, J. Druey, *Helv. Chim. Acta* **1954**, *37*, 134.
[72] a) R. A. Carboni, R. V. Lindsey, Jr., *J. Am. Chem. Soc.* **1959**, *81*, 4342; b) D. L. Boger, *Chem. Rev.* **1986**, *86*, 781; c) A. Hamasaki, R. Ducray, D. L. Boger, *J. Org. Chem.* **2006**, *71*, 185.
[73] E. Fahr, H. Lind, *Angew. Chem. Int. Ed.* **1966**, *5*, 372.



Scheme 31. [4+2] cycloaddition of 1,3-butadiene with azodicarboxylic ester giving tetrahydropyridazines.

4.3 Biological Activity of Pyridazines

Only a few pyridazines have been isolated from natural sources, unlike other heterocycles that are found in many important natural products. Pyridazomycin is an antifungal antibiotic produced by the soil bacteria *Streptomyces violaceoniger sp. griseofuscus* (strain Tü 2557), it was the first natural product known containing a pyridazine ring.[74] Then, phthalazinone meroterpenoid azamerone was isolated from the marine sediment-derived bacterium *Streptomyces* sp. CNQ-766 (Figure 7).[75] N-N bonds are of great importance because of their properties and the enzymes responsible for its formation could be a valuable biocatalyst.

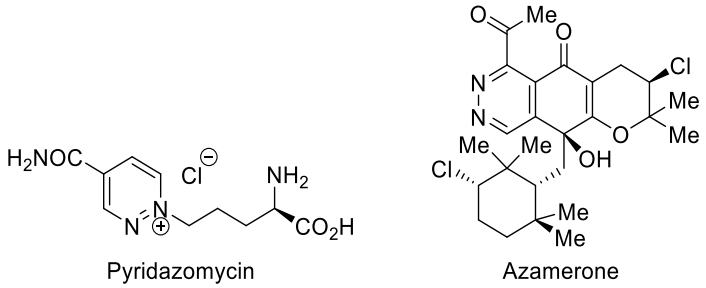


Figure 7. Structure of the two known natural products containing pyridazine ring: Pyridazomycin and Azamerone.

Pyridazine derivatives have a wide range of applications in pharmaceutical and agrochemical industries owing to their biological activities.[76] In crop sciences, 1,2-diazines are used as pesticides, for instance Norflurazon as a herbicide, Diclomezine as a fungicide and Pyridaben as an insecticide (Figure 8).[77]

[74] a) R. Grote, Y. Chen, A. Zeeck, Z. Chen, H. Zähner, P. Mischnick-Lübbecke, W. A. König, *J. Antibiot.* **1988**, *41 5*, 595; b) H. Bockholt, J. M. Beale, J. Rohr, *Angew. Chem. Int. Ed.* **1994**, *33*, 1648.
[75] a) J. Y. Cho, H. C. Kwon, P. G. Williams, P. R. Jensen, W. Fenical, *Org. Lett.* **2006**, *8*, 2471; b) J. M. Winter, A. L. Jansma, T. M. Handel, B. S. Moore, *Angew. Chem. Int. Ed.* **2009**, *48*, 767.
[76] a) J. Svete, *J. Heterocycl. Chem.* **2005**, *42*, 361; b) C. G. Wermuth, *MedChemComm* **2011**, *2*, 935; c) I. Mohd, A. Mohammad, *Russ. J. Bioorganic Chem.* **2020**, *46*, 745; d) I. Mohd, A. Mohammad, *Russ. J. Bioorganic Chem.* **2020**, *46*, 726.
[77] C. Lamberth, *J. Heterocycl. Chem.* **2017**, *54*, 2974.

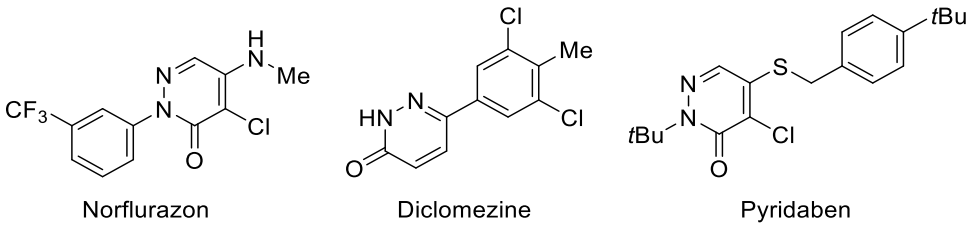


Figure 8. Structure of herbicide Norflurazon, fungicide Diclomezine and insecticide Pyridaben.

Pyridazine derivatives possess various therapeutic interests such as anti-inflammatory[78], anticancer[79], or antimicrobial[80] activities. In addition, a plethora of marketed drugs contain pyridazine core like minaprine (anti-depressant), hydralazine (anti-hypertensive) or azelastine (antihistamine, Figure 9).[81]

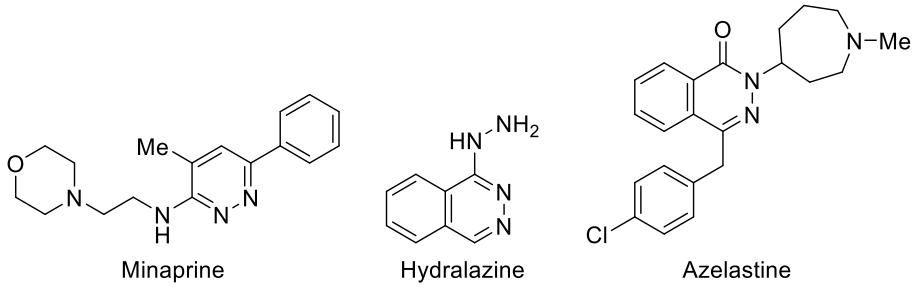


Figure 9. Structure of minaprine, hydralazine and azelastine.

In fact, 1,2-diazines are often used as bioisosteres of benzene or pyridine,[82] the substitution of one or two CH groups by nitrogens might provide better properties for drug's discovery. An interesting use of pyridazines is to increase the water solubility of an overly lipophilic drug candidate. For example, replacing the phenyl ring of diazepam with the isosteric pyridazine ring results in a decrease in log P of about two units (Figure 10).[83]

[78] a) A. K. Tewari, A. Mishra, *Bioorg. Med. Chem.* **2001**, *9*, 715; b) M. M. Saeed, N. A. Khalil, E. M. Ahmed, K. I. Eissa, *Arch. Pharm. Res.* **2012**, *35*, 2077; c) Y. Zaoui, Y. Ramli, S. L. Tan, E. R. T. Tiekink, L. Chemlal, J. T. Mague, J. Taoufik, M. E. A. Faouzi, M. H. Ansar, *J. Mol. Struct.* **2021**, *1234*.
[79] a) C. Kim, S. B. Kim, M. S. Park, *Arch. Pharm. Res.* **2014**, *37*, 452; b) S. Elmeligie, E. M. Ahmed, S. M. Abuel-Maaty, S. A.-B. Zaitone, D. S. Mikhail, *Chem. Pharm. Bull.* **2017**, *65*, 236; c) C. Kim, M.-S. Park, *Bull. Korean Chem. Soc.* **2017**, *38*, 1327; d) Z. X. He, Y. P. Gong, X. Zhang, L. Y. Ma, W. Zhao, *Eur. J. Med. Chem.* **2021**, *209*, 112946.
[80] a) R. M. Butnariu, M. D. Caprosu, V. Bejan, I. I. Mangalagiu, M. Ungureanu, A. Poiata, C. Tuchilus, M. Florescu, *J. Heterocycl. Chem.* **2007**, *44*, 1149; b) N. G. Kandile, M. I. Mohamed, H. Zaky, H. M. Mohamed, *Eur. J. Med. Chem.* **2009**, *44*, 1989; c) N. M. Abd El-Salam, M. S. Mostafa, G. A. Ahmed, O. Y. Alothman, *J. Chem.* **2013**, *2013*, 890617.
[81] N. A. Meanwell, *Med. Chem. Res.* **2023**.
[82] a) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529; b) M. A. M. Subbaiah, N. A. Meanwell, *J. Med. Chem.* **2021**, *64*, 14046.
[83] C. G. Wermuth, *MedChemComm* **2011**, *2*, 935.

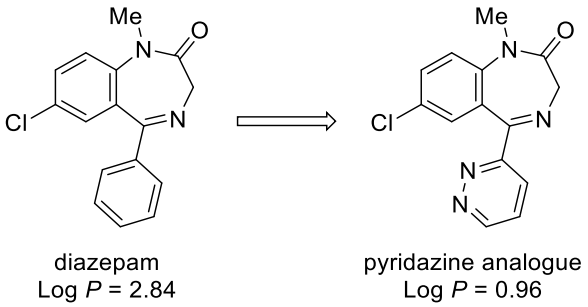


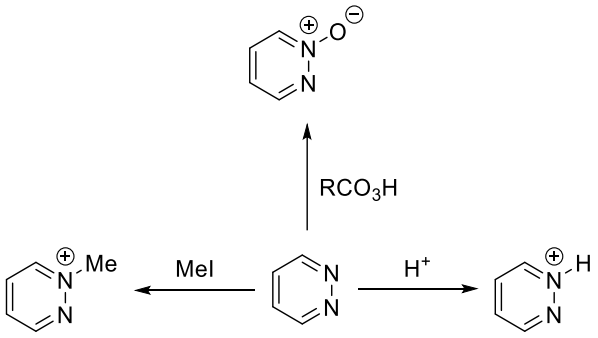
Figure 10. Replacement of the phenyl ring of diazepam by the isosteric pyridazine ring produces an approximately two-unit decrease in the log P (calculated values).

4.4 Reactivity of 1,2-diazines

As mentioned before, pyridazines are electro-deficient heteroaromatic compounds because of the presence of the two adjacent nitrogen atoms on the ring. The inductive effect of the nitrogens provides positively charged carbon atoms. For this manner, reactivity of 1,2-diazines is poor regarding electrophiles and is better with nucleophiles.

4.4.1 Reactions with electrophiles

Electrophilic additions most likely occur at the N-atoms, for instance in protonation, alkylation and oxidation reactions (Scheme 32).[84] Electrophilic substitutions at the ring C-atoms are difficult to carry out and must first break the aromaticity of the π-system. Even in the presence of activating substituents, the deactivation by the two electro-negative nitrogen atoms is still strong.

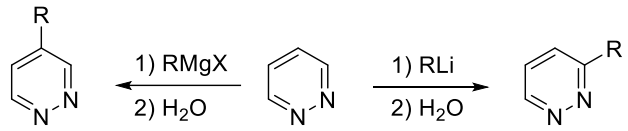


Scheme 32. Typical reaction of pyridazine with electrophiles.

[84] M. R. Grimmett, B. R. T. Keene, in *Advances in Heterocyclic Chemistry Volume 43*, **1988**, pp. 127.

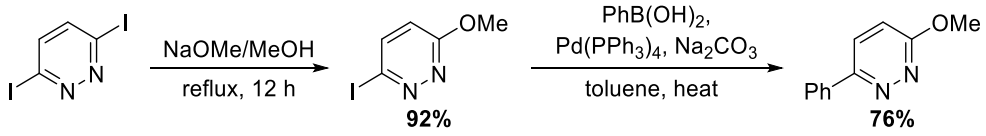
4.4.2 Reactions with nucleophiles

The presence of an extra nitrogen atom makes diazines more reactive to nucleophilic addition in comparison to pyridine. Pyridazine reacts easily with alkyl and aryl lithium and Grignard reagent, but the regioselectivity of the reaction differs depending on the metal used. In fact, a Grignard reagent is added in the 4-position, whereas an organolithium is reacting in the 3-position (Scheme 33).[85]



Scheme 33. Reaction of pyridazine with Grignard reagent and alkyl and aryl lithium.

Nucleophilic aromatic substitution (S_NAr) reactions of halopyridazines with nucleophiles proceed smoothly. For instance, unsymmetrical 3,6-disubstituted pyridazines can be prepared from commercially available 3,6-diiodopyridazine through nucleophilic substitution followed by palladium-catalyzed Suzuki cross-coupling reaction (Scheme 34).[86]



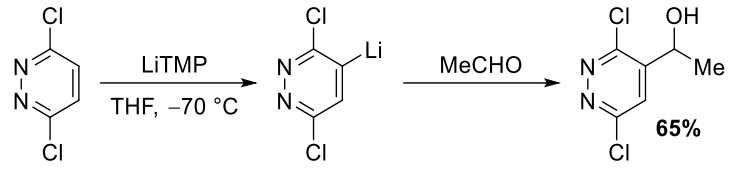
Scheme 34. Preparation of 3,6-disubstituted pyridazine using S_NAr reaction and Suzuki cross-coupling.

4.4.3 Metalation of the pyridazine scaffold

Because of their lower LUMO energies, diazines are more difficult to *ortho*-metalate than pyridine and are sensitive to nucleophilic additions. For this reason, the non-nucleophilic lithium 2,2,6,6-tetramethylpiperidin-1-ide (LiTMP) is a better reagent for *ortho*-metalation than alkyl or aryl lithium. Nevertheless, the formed heteroaryllithium species are very unstable and can dimerize easily. The use of shorter reaction time and *in situ* electrophilic trapping enable to overcome these undesirable effects. Hence, Quéguiner described for the first time in

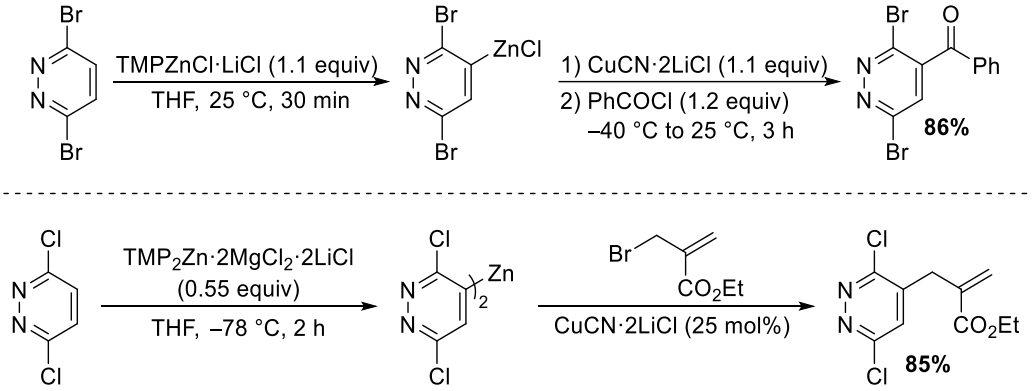
[85] T. Holm, *Acta Chem. Scand.* **1990**, *44*, 279.
[86] T. L. Draper, T. R. Bailey, *J. Org. Chem.* **1995**, *60*, 748.

the 1990s, the directed lithiation of pyridazine derivatives using mostly LiTMP as a base (Scheme 35).[87]



Scheme 35. Directed lithiation of the 3,6-dichloropyridazine using LiTMP.

Later, Knochel reported directed zincation of pyridazine derivatives using TMPZnCl·LiCl or TMPZnCl·LiCl (Scheme 36).[88]



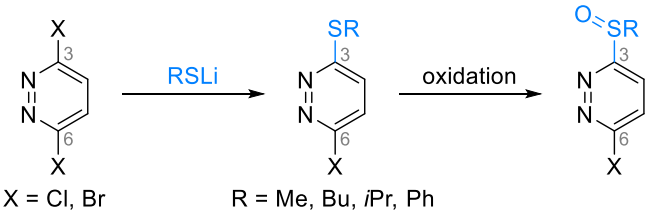
Scheme 36. Zincation of 3,6-dihalopyridazine using TMPZnCl·LiCl and TMPZnCl·LiCl.

[87] a) A. Turck, N. Plé, L. Mojovic, G. Quéguiner, *J. Heterocycl. Chem.* **1990**, *27*, 1377; b) A. Turck, N. Plé, B. Ndzi, G. Quéguiner, N. Haider, H. Schuller, G. Heinisch, *Tetrahedron* **1993**, *49*, 599; c) N. Plé, A. Turck, K. Couture, G. Quéguiner, *J. Org. Chem.* **1995**, *60*, 3781; d) L. Mojovic, A. Turck, N. Plé, M. Dorsy, B. Ndzi, G. Quéguiner, *Tetrahedron* **1996**, *52*, 10417; e) A. Turck, N. Plé, P. Pollet, G. Quéguiner, *J. Heterocycl. Chem.* **1998**, *35*, 429; f) P. Pollet, A. Turck, N. Plé, G. Quéguiner, *J. Org. Chem.* **1999**, *64*, 4512; g) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489.

[88] a) S. Wunderlich, P. Knochel, *Chem. Commun.* **2008**, 6387; b)M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; c) A. Unsinn, M. J. Ford, P. Knochel, *Org. Lett.* **2013**, *15*, 1128; d) T. Bresser, M. Mosrin, G. Monzon, P. Knochel, *J. Org. Chem.* **2010**, *75*, 4686; e) M. Balkenhohl, H. Jangra, T. Lenz, M. Ebeling, H. Zipse, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 9244.

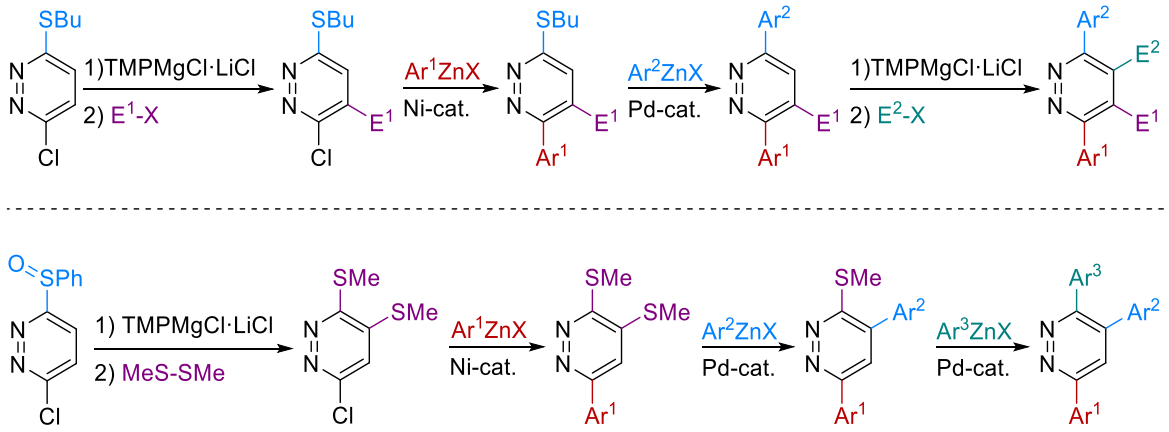
5. OBJECTIVES

As N-heterocycles are of great importance for the pharmaceutical industry in particular, it is necessary to develop synthetic methods for the functionalization of these compounds. Pyridazine is probably one of the least studied N-heterocycles and its functionalization is generally obtained by cyclocondensation or cycloaddition reactions. The aim of this project is to develop a synthetic method for the functionalization of pyridazine using substituted pyridazines as starting material. The idea was to use commercially available 3,6-dihalopyridazines and achieve its desymmetrization by implementing a thioether or sulfoxide group which should furthermore stabilize the organometallic intermediate (Scheme 37).



Scheme 37. Preparation of non-symmetrical pyridazine starting from commercially available 3,6-dihalopyridazines.

Thus, 3,6-disubtituted pyridazines were used and their functionalization was envisioned by performing selective metalations using TMPMgCl·LiCl and cross-coupling reactions with arylzinc halides (Scheme 38).



Scheme 38. Tri- and tetrafunctionalization of the pyridazine scaffold starting from 3,6-disubstituted pyridazines by performing selective metalation using TMPMgCl·LiCl and cross-coupling reactions with arylzinc halides.

B. RESULTS AND DISCUSSION

1. Selective and Stepwise Functionalization of the Pyridazine Scaffold[89]

1.1 Introduction

Diazines are an important class of N-heterocycles because of their numerous applications in agrochemical and pharmaceutical industries.[90] In fact, heteroaromatic rings are often used as phenyl bioisosteres.[91] The selective preparation and further functionalization of these heterocyclic scaffolds is an important current synthetic goal.[92] Although the preparation of substituted pyrimidines and pyrazines was well studied,[93] the synthesis of selectively substituted pyridazines remained a challenge. Pioneering works of Quéguiner in 1990 demonstrated that 3,6-dichloropyridazine (**1a**) may be lithiated at –70 °C in THF in fair yields.[94] Also, unsymmetrical amino-chloropyridazines have been regioselectively lithiated.[95] Pyridazine itself was lithiated and *bis*-lithiated using TMPLi (TMP = 2,2,6,6-tetramethyl-piperidin-1-yl).[96] The regioselective lithiation of unsymmetrical pyridazines such as 3-chloro-6-methoxypyridazine and sulfonyl- derivatives was moderately successful and a reliable and robust metalation of alternative disubstituted pyridazines would

[89] Adapted with permission from C. Hamze, J. Brossier, K. Karaghiosoff, E. Godineau, P. Knochel, *Chem. Eur. J.* **2023**, *n/a*, e202302156.. Copyright 2023 Chemistry – A European Journal published by Wiley-VCH. https://chemistry-europe.onlinelibrary.wiley.com/doi/abs/10.1002/chem.202302156.

[90] a) C. G. Wermuth, *MedChemComm* **2011**, *2*, 935; b) S. Dubey, P. A. Bhosle, *Med. Chem. Res.* **2015**, *24*, 3579; c) S. Elmeligie, E. M. Ahmed, S. M. Abuel-Maaty, S. A.-B. Zaitone, D. S. Mikhail, *Chem. Pharm. Bull.* **2017**, *65*, 236; d) E. M. Flefel, W. A. Tantawy, W. I. El-Sofany, M. El-Shahat, A. A. El-Sayed, D. N. Abd-Elshafy, *Molecules* **2017**, *22*; e) I. Mohd, A. Mohammad, *Russ. J. Bioorganic Chem.* **2020**, *46*, 726; f) I. Mohd, A. Mohammad, *Russ. J. Bioorganic Chem.* **2020**, *46*, 745; g) Z. X. He, Y. P. Gong, X. Zhang, L. Y. Ma, W. Zhao, *Eur. J. Med. Chem.* **2021**, *209*, 112946.

[91] a) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529; b) M. A. M. Subbaiah, N. A. Meanwell, *J. Med. Chem.* **2021**, *64*, 14046.

[92] a) A. Turck, N. Plé, F. Mongin, G. Quéguiner, *Tetrahedron* **2001**, *57*, 4489; b) F. Mongin, L. Mojovic, B. Guillamet, F. Trécourt, G. Quéguiner, *J. Org. Chem.* **2002**, *67*, 8991; c) F. Chevallier, F. Mongin, *Chem. Soc. Rev.* **2008**, *37*, 595; d) E. Horkel, in *Metalation of Azines and Diazines*, **2013**, pp. 223; e) H. Bel Abed, O. Mammoliti, O. Bande, G. Van Lommen, P. Herdewijn, *J. Org. Chem.* **2013**, *78*, 7845; f) T. D. Neubert, Y. Schmidt, E. Conroy, D. Stamos, *Org. Lett.* **2015**, *17*, 2362; g) P. G. Sergeev, V. G. Nenajdenko, *Russ. Chem. Rev.* **2020**, *89*, 393; h) L. Duan, X. Wang, Y. Gu, Y. Hou, P. Gong, *Org. Chem. Front.* **2020**, *7*, 2307; i) A. Kremsmair, A. S. Sunagatullina, L. J. Bole, P. Mastropierro, S. Grassl, H. R. Wilke, E. Godineau, E. Hevia, P. Knochel, *Angew. Chem. Int. Ed.* **2022**, *61*, e202210491.

[93] a) C. Gosmini, J. Y. Nédélec, J. Périchon, *Tetrahedron Lett.* **2000**, *41*, 201; b) M. Mosrin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 1468; c) M. Mosrin, T. Bresser, P. Knochel, *Org. Lett.* **2009**, *11*, 3406; d) L. G. Xie, S. Niyomchon, A. J. Mota, L. Gonzalez, N. Maulide, *Nat. Commun.* **2016**, *7*, 10914.

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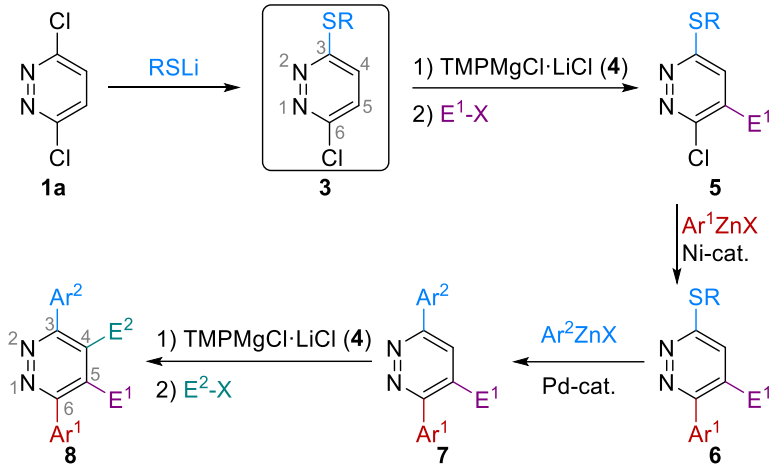
[95] A. Turck, N. Plé, B. Ndzi, G. Quéguiner, N. Haider, H. Schuller, G. Heinisch, *Tetrahedron* **1993**, *49*, 599.

[96] N. Plé, A. Turck, K. Couture, G. Quéguiner, *J. Org. Chem.* **1995**, *60*, 3781.

be desirable.[97] Recently, we have reported directed zincations[98] using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**2a**)[99] or $BF_3 \cdot OEt_2$ assisted zincations[100] using TMPZnCl·LiCl (**2b**)[101] in order to improve the metalation regioselectivity on pyridazines. Herein, we describe a new approach using readily available disubstituted chloropyridazyl thioethers of type **3** as versatile building blocks. They were easily prepared from commercial 3,6-dichloropyridazine (**1a**).[102] We will demonstrate that **3** may be regioselectively magnesiated with TMPMgCl·LiCl (**4**)[103] and trapped with various electrophiles (E^1-X) providing pyridazines of type **5**. Selective Ni-catalyzed cross-couplings[104] of the 6-chloro substituent of **5** with an arylzinc reagent (Ar^1ZnX) provided trisubstituted pyridazines of type **6**, which were subsequently cross-coupled with a range of different arylzinc halides (Ar^2ZnX) using Pd-catalysis[105] to furnish tri-functionalized compounds of type **7**. Magnesiation with TMPMgCl·LiCl (**4**)[103] followed by addition of an electrophile (E^2-X) selectively led to tetra-functionalized pyridazines of type **8** (Scheme 39).

[97] a) L. Mojovic, A. Turck, N. Plé, M. Dorsy, B. Ndzi, G. Quéguiner, *Tetrahedron* **1996**, *52*, 10417; b) A. Turck, N. Plé, P. Pollet, G. Quéguiner, *J. Heterocycl. Chem.* **1998**, *35*, 429.
[98] a) S. Wunderlich, P. Knochel, *Chem. Commun.* **2008**, 6387; b) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; c) A. Unsinn, M. J. Ford, P. Knochel, *Org. Lett.* **2013**, *15*, 1128; d) T. Bresser, M. Mosrin, G. Monzon, P. Knochel, *J. Org. Chem.* **2010**, *75*, 4686.
[99] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) S. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705.
[100] M. Balkenhohl, H. Jangra, T. Lenz, M. Ebeling, H. Zipse, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2019**, *58*, 9244.
[101] M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615.
[102] a) S.-K. Kwon, A. Moon, *Arch. Pharm. Res.* **2005**, *28*, 391; b) C. Kim, S. B. Kim, M. S. Park, *Arch. Pharm. Res.* **2014**, *37*, 452; c) C. Kim, M.-S. Park, *Bull. Korean Chem. Soc.* **2016**, *37*, 1858; d) C. Kim, M.-S. Park, *Bull. Korean Chem. Soc.* **2017**, *38*, 1327.
[103] a) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; b) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; c) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[104] a) C. Gosmini, S. Lasry, J.-Y. Nédélec, J. Périchon, *Tetrahedron* **1998**, *54*, 1289; b) C. Gosmini, J. Y. Nédélec, J. Périchon, *Tetrahedron Lett.* **2000**, *41*, 5039; c) E. Nicolas, A. Ohleier, F. D'Accriscio, A. F. Pecharman, M. Demange, P. Ribagnac, J. Ballester, C. Gosmini, N. Mezailles, *Chem. Eur. J.* **2015**, *21*, 7690; d) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540.
[105] a) V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner, P. Knochel, *Tetrahedron* **2002**, *58*, 4429; b) D. S. Chekmarev, A. E. Stepanov, A. N. Kasatkin, *Tetrahedron Lett.* **2005**, *46*, 1303; c) A. Metzger, L. Melzig, C. Despotopoulou, P. Knochel, *Org. Lett.* **2009**, *11*, 4228; d) L. Melzig, A. Metzger, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 2948.



Scheme 39. Selective stepwise tetra-functionalization of the pyridazine building block of type **3** providing fully substituted pyridazines of type **8**.

Alternatively, we also prepared the dithio-building block, 6-chloro-3,4-*bis*(methylthio)pyridazine (**9a**) in three steps from 3,6-dichloropyridazine (**1a**). This dithio-derivative **9a** was selectively cross-coupled with arylzinc halides (Ar^1ZnX) at position 6 using Ni-catalysis[106] providing 3,4-*bis*(methylthio)-6-aryl pyridazines of type **10**. A subsequent Pd-catalysis[107] allowed a selective cross-coupling with Ar^2ZnX at position 4 leading to *bis*-aryl pyridazines of type **11**. Switching the Pd-catalytic system for Pd-PEPPSI-SiPr[108] further promoted arylation at position 3, providing various 3,4,6-*tris*-arylated pyridazines of type **12** (Scheme 40).

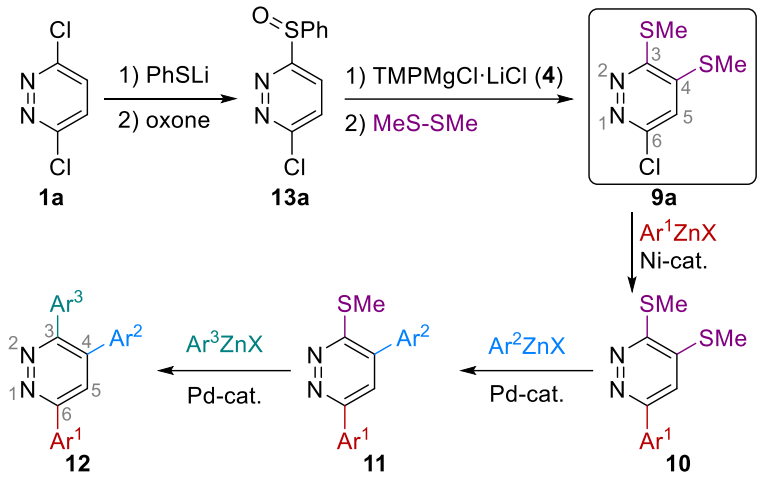
Thus, we report two alternative functionalizations of the pyridazine scaffold allowing to regioselectively prepare various tri- or tetra-functionalized pyridazines. Furthermore, we also show that some fused bicyclic heterocycles such as thieno[2,3-*c*]pyridazines and

[106] a) C. Gosmini, S. Lasry, J.-Y. Nédélec, J. Périchon, *Tetrahedron* **1998**, *54*, 1289; b) C. Gosmini, J. Y. Nédélec, J. Périchon, *Tetrahedron Lett.* **2000**, *41*, 5039; c) E. Nicolas, A. Ohleier, F. D'Accriscio, A. F. Pecharman, M. Demange, P. Ribagnac, J. Ballester, C. Gosmini, N. Mezailles, *Chem. Eur. J.* **2015**, *21*, 7690; d) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540.

[107] a) V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner, P. Knochel, *Tetrahedron* **2002**, *58*, 4429; b) D. S. Chekmarev, A. E. Stepanov, A. N. Kasatkin, *Tetrahedron Lett.* **2005**, *46*, 1303; c) A. Metzger, L. Melzig, C. Despotopoulou, P. Knochel, *Org. Lett.* **2009**, *11*, 4228; d) L. Melzig, A. Metzger, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 2948.

[108] a) C. J. O'Brien, E. A. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743; b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749;c) M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, J. O'Brien C, C. Valente, *Chem. Eur. J.* **2007**, *13*, 150; d) M. Organ, G. Chass, D.-C. Fang, A. Hopkinson, C. Valente, *Synthesis* **2008**, *2008*, 2776; e) M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. Kantchev, C. J. O'Brien, M. Sayah, C. Valente, *Chem. Eur. J.* **2008**, *14*, 2443; f) C. Valente, S. Baglione, D. Candito, C. J. O'Brien, M. G. Organ, *Chem. Commun.* **2008**, 735; g) C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* **2010**, *2010*, 4343; h) C. Valente, M. Pompeo, M. Sayah, M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 180; i) S. Otsuka, D. Fujino, K. Murakami, H. Yorimitsu, A. Osuka, *Chem. Eur. J.* **2014**, *20*, 13146.

1*H*-pyrazolo[3,4-*c*]pyridazines can be prepared from the newly synthesized substituted pyridazines. The structures of several new pyridazines have been confirmed by X-ray analysis.



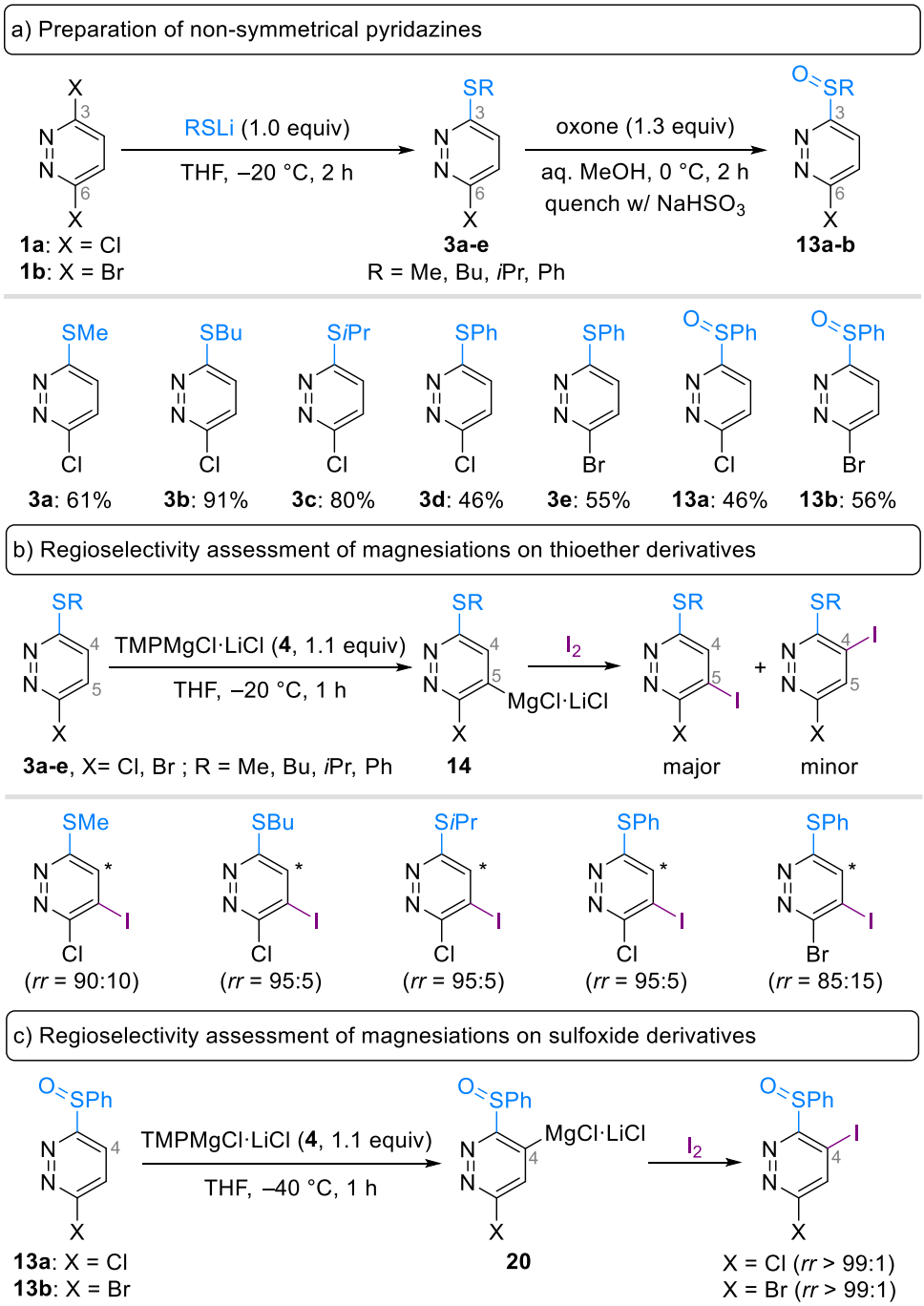
Scheme 40. Selective stepwise *tris*-arylation of the pyridazine building block **9a** providing trisubstituted pyridazines of type **12**.

1.2 Preparation of non-symmetrical pyridazines

In order to evaluate the regioselectivity of magnesiation with TMPMgCl·LiCl (**4**),[109] pyridazines substituted with thioethers and sulfoxides were prepared. Thus, commercial dichloro- (**1a**) and dibromo- (**1b**) pyridazines were reacted with various lithium thiolates (RSLi, 1.0 equiv) in THF affording the mono-thioether pyridazines of type **3** in 46-91% yield (Scheme 41a). Additionally sulfoxides of type **13** were generated by subsequent oxidation of the corresponding thioethers with oxone (46-56% yield).[110] In preliminary experiments, the metalation regioselectivity using TMPMgCl·LiCl (**4**)[109] was studied on pyridazines of type **3** (Scheme 41b). A general trend for magnesiation at position 5 was observed for pyridazines **3a-d** (regioselectivity ratio: *rr* > 90:10), providing 5-iodopyridazines structures after iodolysis. While the brominated pyridazine **3e** led to a lower selectivity (*rr* = 85:15). Interestingly, a switch of regioselectivity was observed for sulfoxide derivatives **13a** and **13b** giving, after metalation with TMPMgCl·LiCl (**4**)[109] and iodolysis, the iodinated compounds at position 4 selectively (*rr* > 99:1, Scheme 41c). The new regioselectivity is a result of the better complexation power of the sulfoxide group in the intermediate complex prior to the metalation

[109] a) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; b) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; c) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[110] R. V. Kupwade, S. S. Khot, U. P. Lad, U. V. Desai, P. P. Wadgaonkar, *Res. Chem. Intermed.* **2017**, *43*, 6875.

step.[111] The unstability of all these iodinated pyridazines precludes an isolation. However, quenchings with other electrophiles confirm these regioselectivities (see Schemes 42 and 48).



Scheme 41. Preparation of non symmetrical pyridazine thioethers (3a-e) and sulfoxides (13a-b) and preliminary optimization of their metalation using TMPMgCl·LiCl (4) followed by iodolysis. Regioselectivity ratio (rr) determined by GC analysis of water quenched aliquots; all iodinated products were not isolated due to their unstability.

[111] M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.

1.3 Regioselective metalation of pyridazines of type 3

With these regioselective metalation tools in hands, we started exploring the scope of the functionalization at position 5 of pyridazines of type **3** using TMPMgCl·LiCl[112] (**4**, 1.1 equiv, –20 °C, THF, 1 h) and subsequent electrophilic trapping (Scheme 42). Thus, bromination and copper-catalyzed allylation[113] reactions proceeded smoothly, giving compounds **5a-c** in 83-86% yield and *rr* = 95:5. Addition of ethyl cyanoformate also gave the heterocyclic ester **5d** in 85% yield. Acylations were performed by trapping the organomagnesium species **14** with acyl chlorides in the presence of CuCN·2LiCl[113] providing the carbonyl derivatives **5e-h** in 51-75% yield. Similarly, reactions with aldehydes or ketones furnished secondary and tertiary alcohols **5i-k**[114] in 61-84% yield. Transmetalation to the corresponding zinc species with $ZnCl_2$ and subsequent Negishi cross-coupling[115] using 5 mol% $Pd(dba)_2$ and 10 mol% tri(2-furyl)phosphine as catalytic system[116] led to arylated products **5l** and **5m** in 82-84% yield. The metalated species **14** could also be aminomethylated using Tietze salt[117] giving the aminomethyl pyridazine **5n** in 60% yield. Similar transformations were also conducted on the thiomethyl-substituted pyridazine **3a** and the thiophenyl derivative **3d**, expanding the reaction scope to diversely substituted pyridazines **5o-r**, however slightly decreased yields were obtained (33-76%). In addition, the bromo-substituted pyridazine **3e** led to the desired products **5s-t** in lower yields (44-46%) and decreased regioselectivity (*rr* = 85:15). This lower regioselectivity precludes the use of **3e** for further functionalizations. Thus, the best precursor is certainly **3b** based on the reaction yields and regioselectivities.

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[112] a) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; b) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; c) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.

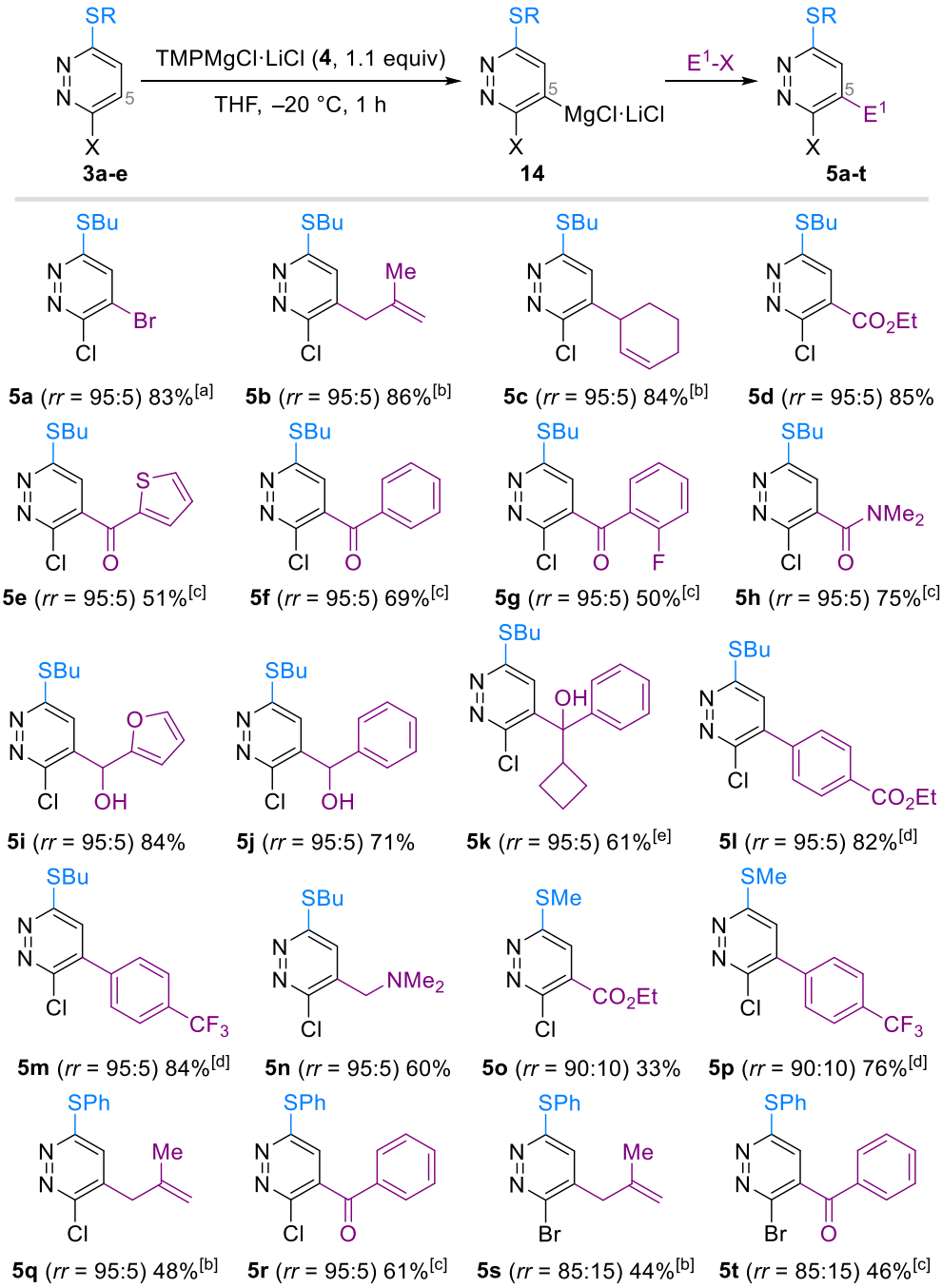
[113] a) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; b) F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

[114] The struture was confirmed by X-ray analysis, see supporting information. Deposition Numbers <url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/###.20220XXX"> 2267441 (for **5k**), 2278594 (for **6d**), 2267440 (for **7a**), 2267439 (for **7b**), 2267438 (for **9a**), 2278597 (for **12a**), 2278595 (for **12b**), 2278596 (for **15**), 2278593 (for **22e**), and 2270626 (for **23c**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <url href="http://www.ccdc.cam.ac.uk/structures">Access Structures service</url>.

[115] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.

[116] M. Rottländer, P. Knochel, *Synlett* **1997**, *1997*, 1084.

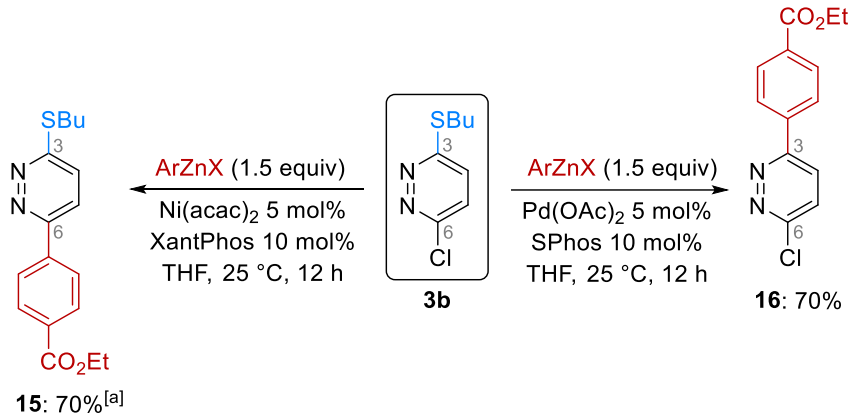
[117] a) G. Kinast, L.-F. Tietze, *Angew. Chem. Int. Ed.* **1976**, *15*, 239; b) M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed.* **1998**, *37*, 1044; c) N. Millot, C. Piazza, S. Avolio, P. Knochel, *Synthesis* **2000**, *2000*, 941; d) N. Gommermann, C. Koradin, P. Knochel, *Synthesis* **2002**, *2002*, 2143; e) V. Werner, M. Ellwart, A. J. Wagner, P. Knochel, *Org. Lett.* **2015**, *17*, 2026; f) M. Ellwart, G. Höfner, A. Gerwien, K. Wanner, P. Knochel, *Synthesis* **2017**, *49*, 5159.



Scheme 42. Regioselective magnesiation of pyridazines of type **3** using TMPMgCl·LiCl (**4**) and subsequent electrophile quench at position 5. [a](BrCCl$_2$)$_2$ was used as electrophile; [b]CuCN·2LiCl (10 mol%) and an allyl bromide were used; [c]CuCN·2LiCl (1.1 equiv) and an acyl chloride were used; [d]transmetalation with ZnCl$_2$ (1.2 equiv), followed by Pd-catalyzed cross-coupling with substituted iodobenzenes: Pd(dba)$_2$ (5 mol%) and tri(2-furyl)phosphine (10 mol%) was used; [e]The structure was confirmed by X-ray analysis.

1.4 Regioselective Negishi cross-coupling reactions

Then, Negishi cross-coupling[118] reactions were envisioned for the functionalization at position 3 and 6 of the resulting pyridazines of type **5**. Indeed both chloride and thioether undergo selective cross-coupling reactions. Pd- or Ni-catalyzed Negishi type cross-coupling reactions with unsaturated thioethers were previously reported.[119] Nevertheless, such cross-couplings were so far only described using thiomethyl- or thiophenyl-substituted heterocycles. Preliminary studies[120] on compound **3b** led to selective conditions for the Negishi cross-coupling[118] reactions: Substitution of the chlorine group using Ni-catalysis[121] gave compound **15**[122] in 70% yield and replacement of the butylthio substituent using Pd-catalysis[123] led to product **16** in 70% yield (Scheme 43).



Scheme 43. Optimized conditions for Negishi cross-coupling at position 3 using Pd-catalysis and at position 6 using Ni-catalysis on compound **3b**. [a]The structure was confirmed by X-ray analysis.

However, for substituted pyridazines of type **5** containing an additional substituent at position 5, the previously developed Pd-catalyzed conditions[123] for the thioether cross-coupling were not selective anymore. Therefore, the best conditions for selective stepwise cross-couplings require first to perform Ni-catalyzed cross-coupling[121] at position 6. Thus, pyridazines of type **5** were selectively cross-coupled with arylzinc reagents (Ar^1ZnX, 1.5 equiv) using 5 mol%

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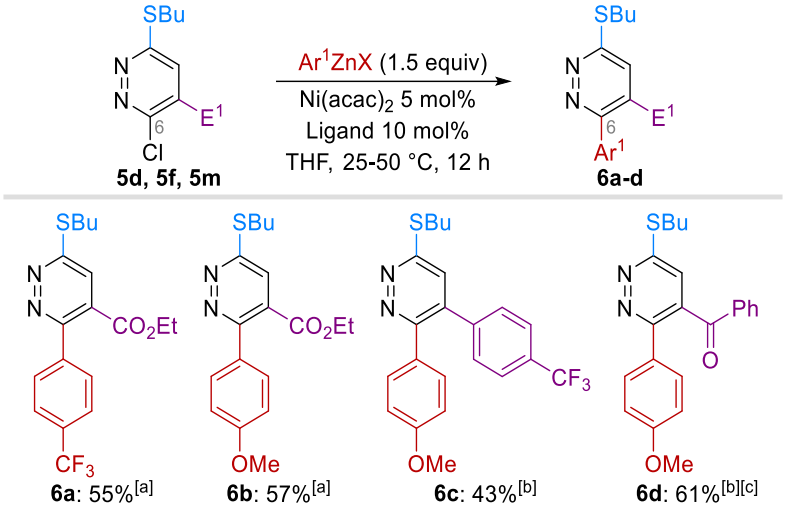
[118] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[119] a) A. Metzger, L. Melzig, C. Despotopoulou, P. Knochel, *Org. Lett.* **2009**, *11*, 4228; b) L. Melzig, A. Metzger, P. Knochel, *J. Org. Chem.* **2010**, *75*, 2131; c) P. Knochel, A. Metzger, L. Melzig, *Synthesis* **2010**, *2010*, 2853; d) L. Melzig, A. Metzger, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 2948.
[120] For optimization studies see experimental part.
[121] L. Melzig, T. Dennenwaldt, A. Gavryushin, P. Knochel, *J. Org. Chem.* **2011**, *76*, 8891.
[122] The structure was confirmed by X-ray analysis, see experimental part.
[123] a) J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028; b) R. A. Altman, S. L. Buchwald, *Nat. Protoc.* **2007**, *2*, 3115; c) T. E. Barder, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 5096.

$Ni(acac)_2$ and 10 mol% phosphine ligands[124] as catalytic system (Scheme 44). Depending on the functional group in ortho position of the chlorine group, either DPE- or Xant-phos[124] were used. The chloropyridazine **5d** gave upon reaction with para-substituted arylzinc species the trisubstituted pyridazines (**6a-b**, 55-57% yield) using Xantphos as a ligand. Whereas the chloropyridazines **5f** and **5m** gave better results using DPEPhos. Negishi cross-coupling[125] with (4-methoxyphenyl)zinc chloride resulted in the desired products **6c** and **6d**[126] in 43-61% yield. After this cross-coupling step, the minor regioisomer present in 5% (*rr* = 95:5) in the pyridazines of type **5** was eliminated affording regioisomerically pure products of type **6**.

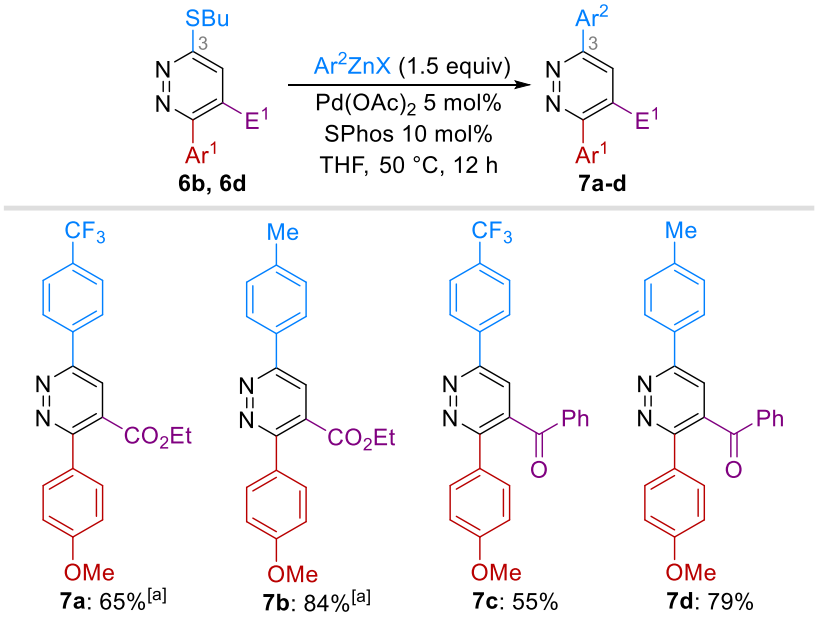


Scheme 44. Functionalization at position 6 via Negishi cross-coupling reactions of pyridazines of type **5** with arylzinc species (Ar^1ZnX) using $Ni(acac)_2$ and phosphine ligands. [a]Xantphos was used as ligand [b] DPEPhos was used as ligand. [c]The structure was confirmed by X-ray analysis.

Position 3 was subsequently functionalized using Pd-catalysis.[127] Thus, butylthio-substituted pyridazines of type **6** reacted with arylzinc species (Ar^2ZnX, 1.5 equiv) in THF at 50 °C using 5 mol% $Pd(OAc)_2$ and 10 mol% SPhos[128] as catalytic system (Scheme 45). Cross-coupling of the ester-substituted pyridazine **6b** gave the *bis*-arylated products **7a**[129] and **7b**[129] in 65-84%

[124] M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, *Organometallics* **1995**, *14*, 3081.
[125] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[126] The structure was confirmed by X-ray analysis, see experimental part.
[127] a) V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner, P. Knochel, *Tetrahedron* **2002**, *58*, 4429; b) D. S. Chekmarev, A. E. Stepanov, A. N. Kasatkin, *Tetrahedron Lett.* **2005**, *46*, 1303; c) A. Metzger, L. Melzig, C. Despotopoulou, P. Knochel, *Org. Lett.* **2009**, *11*, 4228; d) L. Melzig, A. Metzger, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 2948.
[128] a) J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028; b) R. A. Altman, S. L. Buchwald, *Nat. Protoc.* **2007**, *2*, 3115; c) T. E. Barder, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 5096.
[129] The structure was confirmed by X-ray analysis, see experimental part.

isolated yield. Pyridazines **6d** with a ketone moiety in position 5 reacted similarly and led to **7c** and **7d** in 55-79% yield.

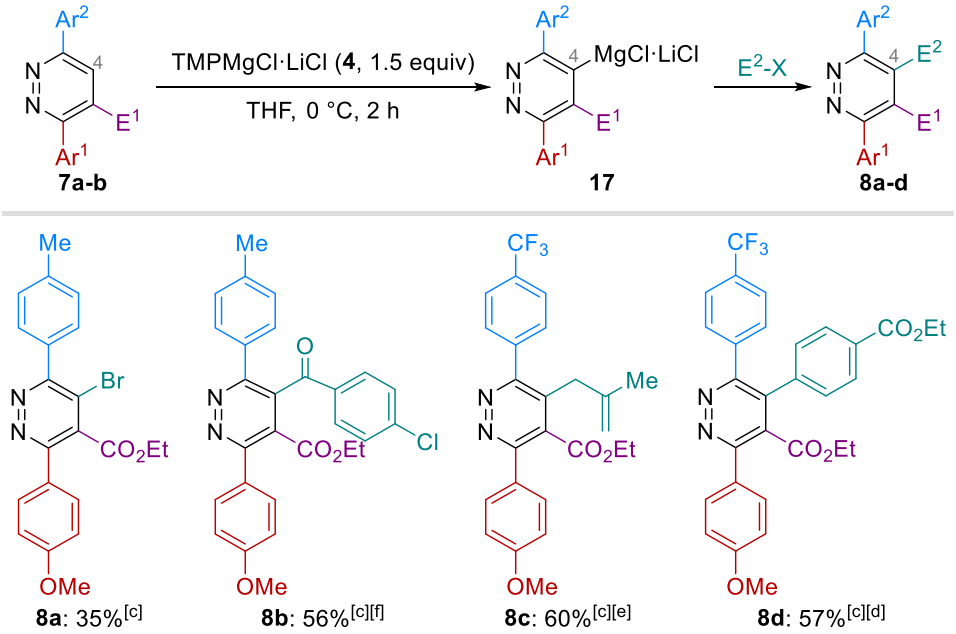


Scheme 45. Functionalization at position 3 via Negishi cross-coupling reactions of pyridazines of type **6** with arylzinc species (Ar^2ZnX) using $Pd(OAc)_2$ and SPhos. [a]The structure was confirmed by X-ray analysis.

1.5 Functionalization at position 4 of the pyridazine derivatives

The remaining position 4 of the pyridazine core was magnesiated using TMPMgCl·LiCl[130] (**4**, 1.5 equiv, 0 °C, THF, 2 h). The resulting magnesiated intermediates **17** were trapped with various electrophiles (E^2-X, Scheme 46). Thus, after bromination using $(BrCCl_2)_2$ or copper-mediated acylation,[131] the trisubstituted pyridazine **7b** furnished the fully functionalized pyridazines **8a** and **8b** in 35% and 56% yield respectively. Similarly, CuCN·2LiCl catalyzed allylation[131] of **7a** with methallyl bromide resulted in the tetra-functionalized pyridazine **8c** (60% yield). Moreover, the magnesiated pyridazine of type **17** derived from pyridazine **7a** was transmetalated using $ZnCl_2$ to the corresponding zinc species which underwent Pd-catalyzed cross-coupling[132] with ethyl 4-iodobenzoate leading to **8d** in 57% yield.

[130] a) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; b) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; c) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[131] a) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; b) F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.
[132] a) V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner, P. Knochel, *Tetrahedron* **2002**, *58*, 4429; b) D. S. Chekmarev, A. E. Stepanov, A. N. Kasatkin, *Tetrahedron Lett.* **2005**, *46*, 1303; c) A. Metzger, L. Melzig, C.



Scheme 46. Functionalization at position 4 via metalation and electrophilic trapping. [a]TMPZnCl·LiCl (**2b**, 1.1 equiv) was used, [b]$TMP_2Zn·2MgCl_2·2LiCl$ (**2a**, 1.2 equiv) was used, [c]TMPMgCl·LiCl (**4**, 1.5 equiv) was used, [d]obtained by Pd-catalyzed cross-coupling: $Pd(dba)_2$ (5 mol%) and tri(2-furyl)phosphine (10 mol%), [e]CuCN·2LiCl (10 mol%) was used, [f]CuCN·2LiCl (1.1 equiv) was used.

Functionalization of position 4 was also possible at earlier stages of the synthetic pathway. For instance, directed zincation of the ketone substituted 3-(butylthio)-6-chloropyridazine **5f** (see Scheme 42) using TMPZnCl·LiCl[133] (**2b**, 1.1 equiv, 25 °C, THF, 2 h) followed by a copper mediated[134] quenching with acyl chlorides or allyl bromides gave the diketones **18a-b** as well as the allylated compounds **18c-d** in 53-72% yield. Ester and aryl-substituted butylthio-chloropyridazines **5d** and **5m** were zincated with either TMPZnCl·LiCl[133] (**2b**, 1.1 equiv, 25 °C, THF, 2 h) or $TMP_2Zn·2MgCl_2·2LiCl$[135] (**2a**, 1.2 equiv, 25 °C, THF, 12 h). The resulting zinc species **19** were subsequently functionalized by brominations, copper-catalyzed allylations[136] and Pd-catalyzed cross-coupling reactions[137] (**18e-g**, 58-70%

Despotopoulou, P. Knochel, *Org. Lett.* **2009**, *11*, 4228; d) L. Melzig, A. Metzger, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 2948.

[133] M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615.

[134] a) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; b) F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

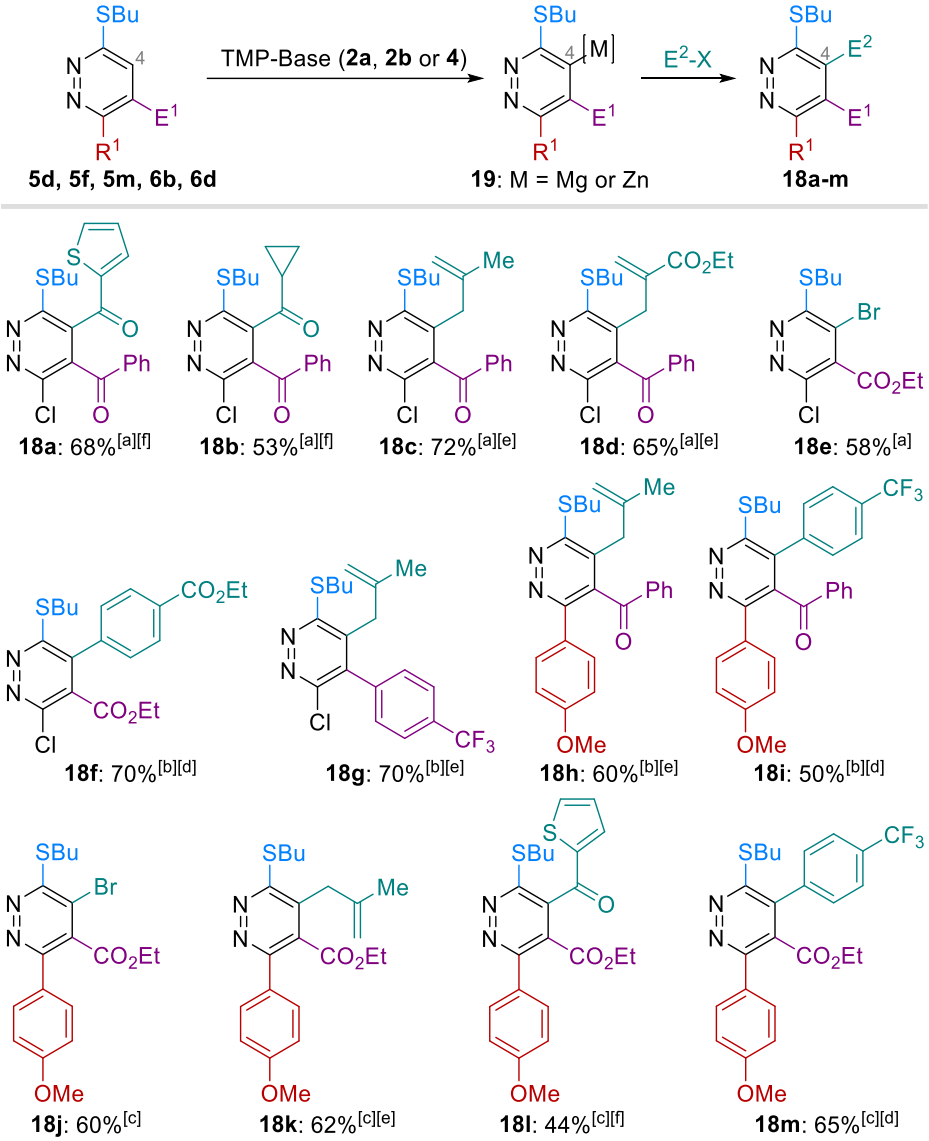
[135] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) S. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705.

[136] a) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; b) F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

[137] a) V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner, P. Knochel, *Tetrahedron* **2002**, *58*, 4429; b) D. S. Chekmarev, A. E. Stepanov, A. N. Kasatkin, *Tetrahedron Lett.* **2005**, *46*, 1303; c) A. Metzger, L. Melzig, C. Despotopoulou, P. Knochel, *Org. Lett.* **2009**, *11*, 4228; d) L. Melzig, A. Metzger, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 2948.

yield). Similarly, the 3-butylthio-subsituted pyridazines of type **6** were transformed into the respective metal species **19** via treatment with various TMP bases. Thus, the products **18h-i** (50-60% yield) were obtained after metalation of **6d** with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[138] (**2a**, 1.2 equiv, 25 °C, THF, 12 h) and electrophilic trapping. In addition, the ester substituted pyridazine **6b** was magnesiated with TMPMgCl·LiCl[139] (**4**, 1.5 equiv, –20 °C, THF, 6 h). The resulting Grignard reagent **19** reacted with $(BrCCl_2)_2$, allyl bromides or acyl chlorides leading to **18j-l** in 44-62% yield. Furthermore, a Negishi cross-coupling[140] with 1-iodo-4-(trifluoromethyl)benzene was successful after transmetalation with $ZnCl_2$ giving **18m** in 65% yield (Scheme 47). After these functionalizations, the minor regioisomer present in 5% (*rr* = 95:5) in the pyridazines of type **5** was separated affording regioisomerically pure products of type **18**.

[138] a) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; b) S. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705.
[139] a) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; b) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; c) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[140] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.



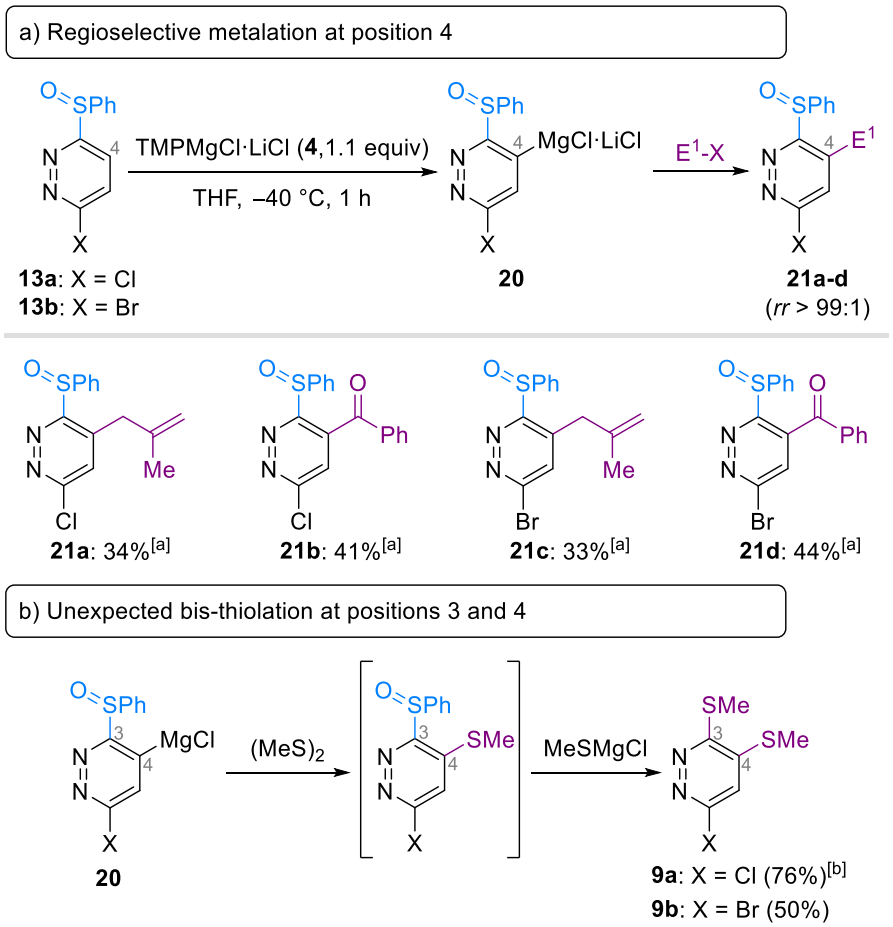
Scheme 47. Functionalization at position 4 via metalation and electrophilic trapping. [a]TMPZnCl·LiCl (**2b**, 1.1 equiv) was used, [b]$TMP_2Zn·2MgCl_2·2LiCl$ (**2a**, 1.2 equiv) was used, [c]TMPMgCl·LiCl (**4**, 1.5 equiv) was used, [d]obtained by Pd-catalyzed cross-coupling: $Pd(dba)_2$ (5 mol%) and tri(2-furyl)phosphine (10 mol%), [e]CuCN·2LiCl (10 mol%) was used, [f]CuCN·2LiCl (1.1 equiv) was used.

1.6 Regioselective metalation at position 4 of sulfoxides of type 13

Following the reaction pathway described in Scheme 40, the sulfoxides **13a** and **13b** were treated with TMPMgCl·LiCl[141] (**4**, 1.1 equiv, –40 °C, THF, 1 h) resulting in a regioselective magnesiation at position 4 (Scheme 48a). Copper-catalyzed allylations and acylations[142] of the

[141] a) W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, *8*, 5673; b) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958; c) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[142] a) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; b) F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

Grignard intermediate **20** provided the trisubstituted pyridazines **21a-d** in 33-44% yield. Interestingly, electrophile quench using dimethyl disulfide led to the unexpected *bis*-thiomethyl products **9a-b**[143] in 50-76% yield (Scheme 48b).[144]



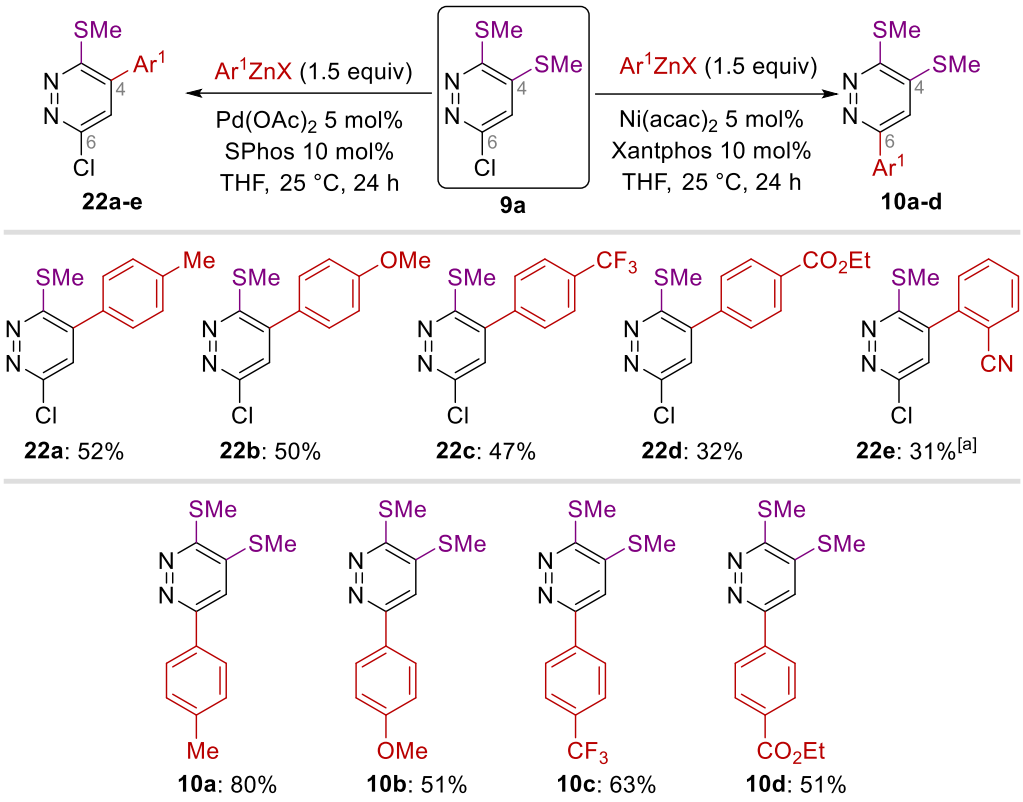
Scheme 48. Regioselective magnesiation of pyridazine of type **13** with TMPMgCl·LiCl (**4**) and subsequent electrophile quench at position 4. [a]CuCN·2LiCl (10 mol%) was used. [b]The structure was confirmed by X-ray analysis.

1.7 Selective preparation of tris-arylated pyridazines of type 12

It turns out that 6-chloro-3,4-*bis*(methylthio)pyridazine (**9a**) was a valuable scaffold since the choice of the catalytic system in cross-coupling reactions allowed either a substitution of the methylthio groups (at positions 3 or 4) or of the chlorine substituent (at position 6). Clearly, the observed regioselectivity was triggered by the nature of the metal catalyst and the chosen ligand. Under the reported conditions, these cross-couplings were fully regioselective. Thus, the treatment of **9a** with electron-rich as well as electron-deficient arylzinc halides (Ar^1ZnX)

[143] The structure was confirmed by X-ray analysis, see experimental part.
[144] S. Oae, T. Kawai, N. Furukawa, *Tetrahedron Lett.* **1984**, *25*, 69.

in the presence of 5 mol% $Pd(OAc)_2$ and 10 mol% SPhos[145] led to 4-arylated pyridazines of type **22**[146] in 31-52% yield. Alternatively, the reaction of **9a** with Ar^1ZnX in the presence of 5 mol% $Ni(acac)_2$ and 10 mol% Xantphos[147] provided 6-arylated pyridazines of type **10** in 51-80% yield (Scheme 49).

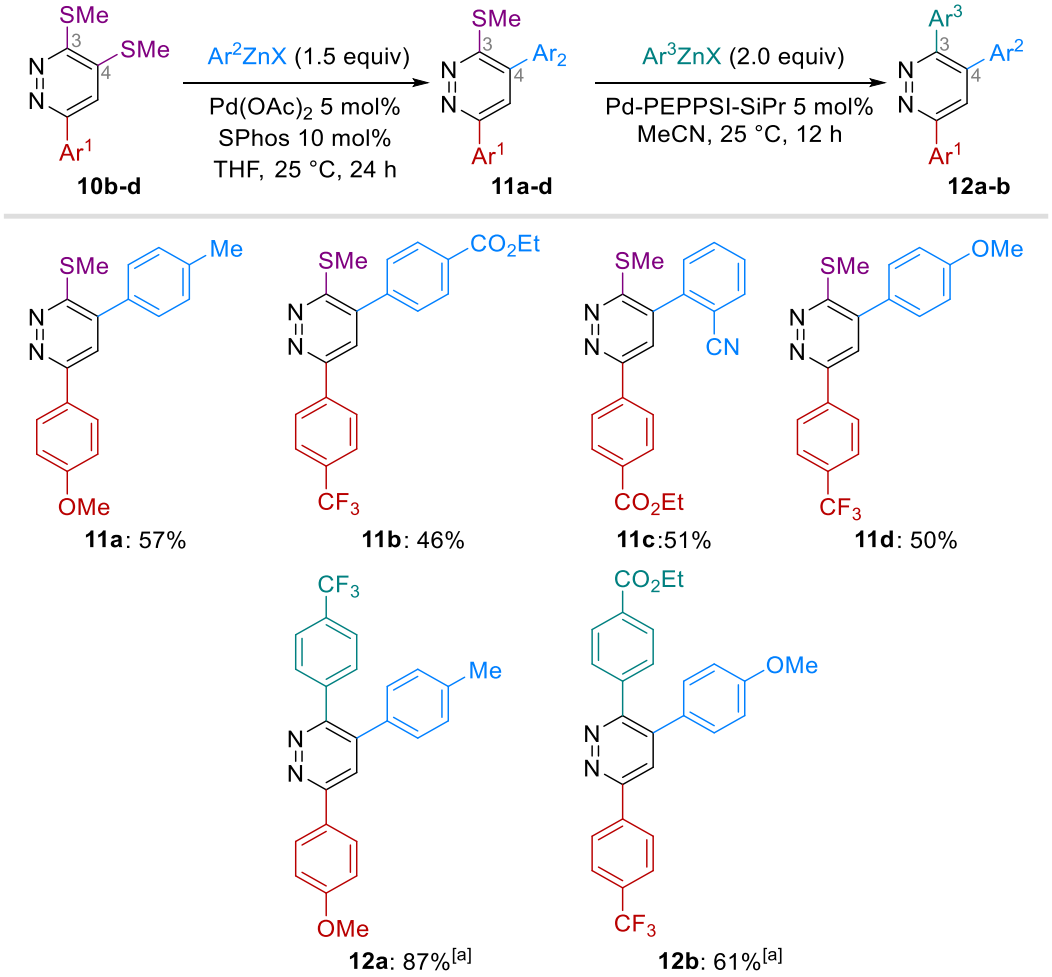


Scheme 49. Regioselective Negishi cross-couplings with Ar^1ZnX at position 4 or 6 depending on the nature of the catalytic system (Pd or Ni). [a]The structure was confirmed by X-ray analysis

These 6-arylated pyridazines of type **10** were submitted to a second Negishi cross-coupling[148] with Ar^2ZnX (5 mol% $Pd(OAc)_2$ and 10 mol% SPhos)[145] to give regioselectively the 4,6-*bis*-arylated pyridazines **11a-d** in 46-57% yield. Furthermore, the remaining 3-methylthio group reacted with different arylzinc halides (Ar^3ZnX) using a more powerful Pd-catalyst

[145] a) J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028; b) R. A. Altman, S. L. Buchwald, *Nat. Protoc.* **2007**, *2*, 3115; c) T. E. Barder, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 5096.
[146] The structure was confirmed by X-ray analysis, see experimental part.
[147] M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, *Organometallics* **1995**, *14*, 3081.
[148] a) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821; b) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; c) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.

system (5 mol% Pd-PEPPSI-SiPr[149] in MeCN, 25 °C, 12 h), leading to the *tris*-arylated pyridazines **12a-b**[150] in 61-87% yield (Scheme 50).



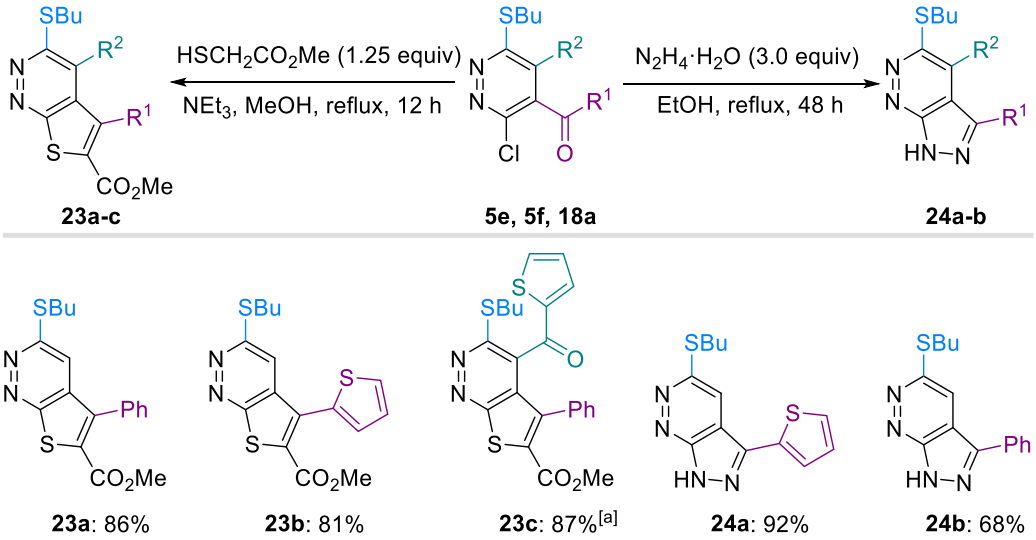
Scheme 50. Regioselective preparation of *tris*-arylated pyridazines of type **12** via Pd-catalyzed Negishi cross-couplings with two different arylzinc halides (Ar^2ZnX and Ar^3ZnX). [a]The tructure was confirmed by X-ray analysis.

[149] a) C. J. O'Brien, E. A. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743; b) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749; c) M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, J. O'Brien C, C. Valente, *Chem. Eur. J.* **2007**, *13*, 150; d) M. Organ, G. Chass, D.-C. Fang, A. Hopkinson, C. Valente, *Synthesis* **2008**, *2008*, 2776; e) M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. Kantchev, C. J. O'Brien, M. Sayah, C. Valente, *Chem. Eur. J.* **2008**, *14*, 2443; f) C. Valente, S. Baglione, D. Candito, C. J. O'Brien, M. G. Organ, *Chem. Commun.* **2008**, 735; g) C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* **2010**, *2010*, 4343; h) C. Valente, M. Pompeo, M. Sayah, M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 180; i) S. Otsuka, D. Fujino, K. Murakami, H. Yorimitsu, A. Osuka, *Chem. Eur. J.* **2014**, *20*, 13146.

[150] The structure was confirmed by X-ray analysis, see experimental part.

1.7 Preparation of annelated N-heterocycles

Additionally, various annelated N-heterocycles of type **23** and **24** were prepared from tri- or tetra-substituted pyridazines (**5e**, **5f**, **18a**). Thus, pyridazines **5e-f** and **18a** reacted with $HSCH_2CO_2Me$[151] in the presence of NEt_3, after refluxing for 12 h in MeOH, the thieno[2,3-*c*]pyridazines **23a-c**[152] were isolated in 81-87% yield. Similarly, the ketones **5e** and **5f** were treated with hydrazine hydrate[153] giving the corresponding 1*H*-pyrazolo[3,4-*c*]pyridazines **24a** and **24b** in 68-92% yield (Scheme 51).



Scheme 51. Preparation of annelated N-heterocycles such as thieno[2,3-*c*]pyridazine **23** and 1*H*-pyrazolo[3,4-*c*]pyridazine **24** starting from pyridazines **5e**,**5f** and **18a**. [a]The structure was confirmed by X-ray analysis.

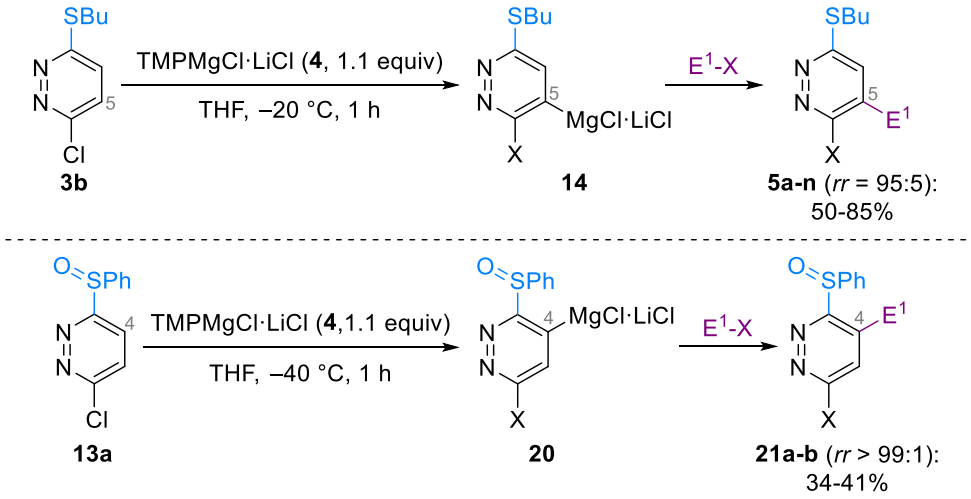
1.8 Conclusion

In summary, we have described a regioselective tri- and tetra-functionalization of the pyridazine scaffold using two readily available building blocks: 3-alkylthio-6-chloropyridazine **3** (Scheme 39) and 3,4-*bis*(methylthio)-6-chloropyridazine (**9a**) (Scheme 40) by performing selective metalations with TMPMgCl·LiCl (**4**) and catalyst-tuned Negishi cross-coupling reactions. Several of the resulting pyridazines were converted into more elaborated N-heterocycles such as thieno[2,3-*c*]pyridazines **23** and 1*H*-pyrazolo[3,4-*c*]pyridazines **24** (Scheme 51). The structures of several new pyridazines have been confirmed by X-ray analysis. Furthermore, extensions of this work are underway.

[151] L. K. A. Rahman, R. M. Scrowston, *J. Chem. Soc., Perkin trans. 1* **1984**, 385.
[152] The structure was confirmed by X-ray analysis, see experimental part.
[153] T. A. Eichhorn, S. Piesch, W. Ried, *Helv. Chim. Acta* **1988**, *71*, 988.

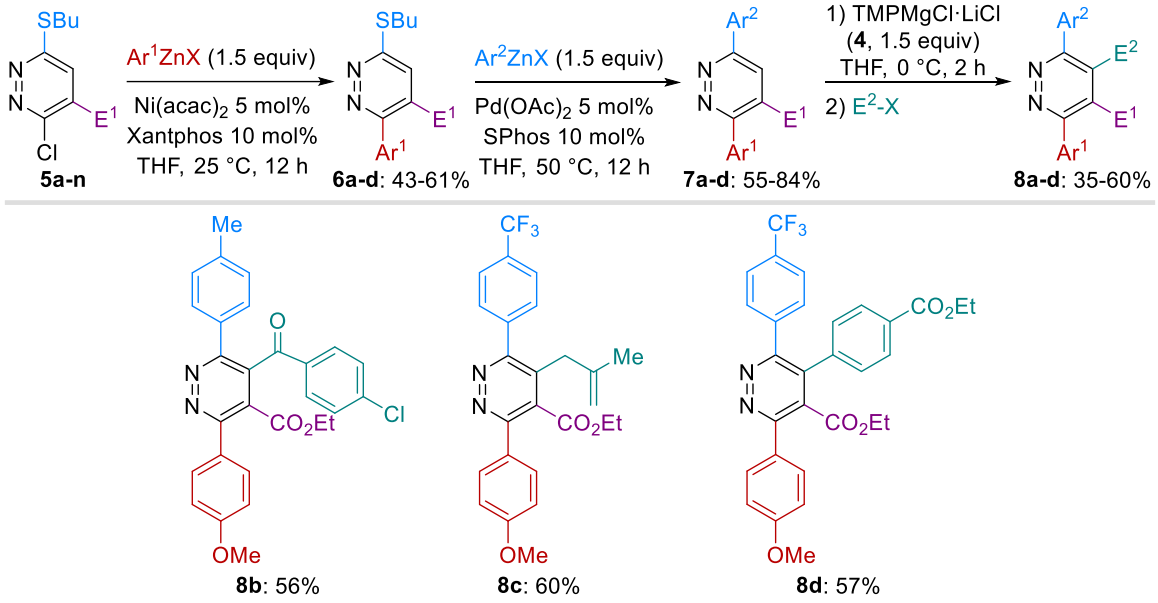
2. SUMMARY

During the course of this study, the full functionalization of the biologically interesting pyridazine scaffold was achieved. Starting from commercially available 3,6-dichloropyridazine (**1a**), desymmetrization of the pyridazine scaffold led to thioether substituted pyridazines (**3b**) as well as sulfoxide derivatives (**13a**). The directed magnesiation of these scaffolds using TMPMgCl·LiCl (**4**) gave different regioselectivities, whereas the sulfides were predominantly metalated in 5 position, the metalation of the sulfoxide occurred selectively in ortho position to the sulfoxide owing to the higher complexation power of the sulfoxide group. The formed organomagnesium species were successfully quenched with various electrophiles (Scheme 52).



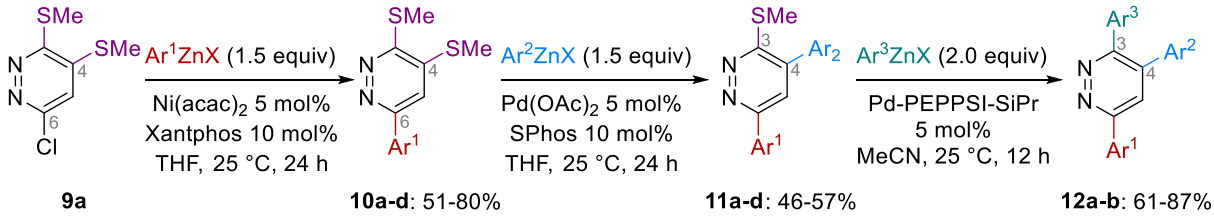
Scheme 52. Regioselective magnesiation of pyridazines **3b** and **13a** using TMPMgCl·LiCl (**4**) and subsequent electrophile quench.

The further functionalization of the pyridazine scaffold was achieved by performing selective metalations with TMPMgCl·LiCl (**4**) and catalyst-tuned Negishi cross-coupling reactions. Starting from the substituted pyridazine of type **5**, selective Ni-catalyzed cross-couplings of the 6-chloro substituent with an arylzinc reagent (Ar^1ZnX) provided trisubstituted pyridazines of type **6**, which were subsequently cross-coupled with a range of different arylzinc halides (Ar^2ZnX) using Pd-catalysis to furnish tri-functionalized compounds of type **7**. Finally, directed magnesiation with TMPMgCl·LiCl (**4**) followed by addition of an electrophile (E^2-X) selectively led to tetra-functionalized pyridazines of type **8** (Scheme 53).



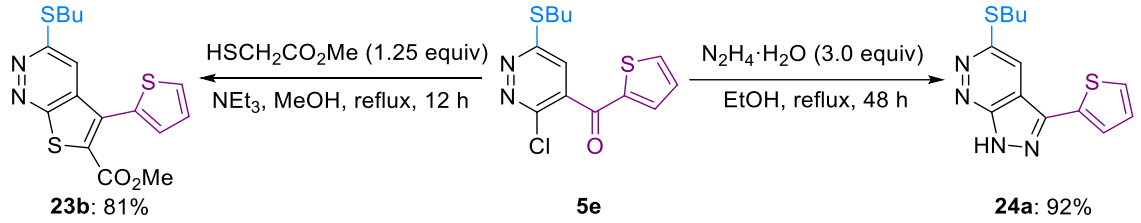
Scheme 53. Selective stepwise tetra-functionalization of the pyridazine scaffold providing fully substituted pyridazines of type **8**.

Alternatively, the readily available building block 3,4-*bis*(methylthio)-6-chloropyridazine (**9a**) allowed the preparation of *tris*-arylated pyridazines of type **12** by using a succession of Negishi cross-coupling reactions. The appropriate choice of catalysts and ligands led to fully regioselective cross-coupling reactions (Scheme 54).



Scheme 54. Selective stepwise *tris*-arylation of the pyridazine building block **9a** providing trisubstituted pyridazines of type **12.**

Additionally, several of the resulting pyridazines were converted into more elaborated fused N-heterocycles such as thieno[2,3-*c*]pyridazines **23** and 1*H*-pyrazolo[3,4-*c*]pyridazines **24** in good yields (Scheme 55).



Scheme 55. Preparation of annelated N-heterocycles such as thieno[2,3-*c*]pyridazine **23** and 1*H*-pyrazolo[3,4-*c*]pyridazine **24** starting from pyridazines **5e**.

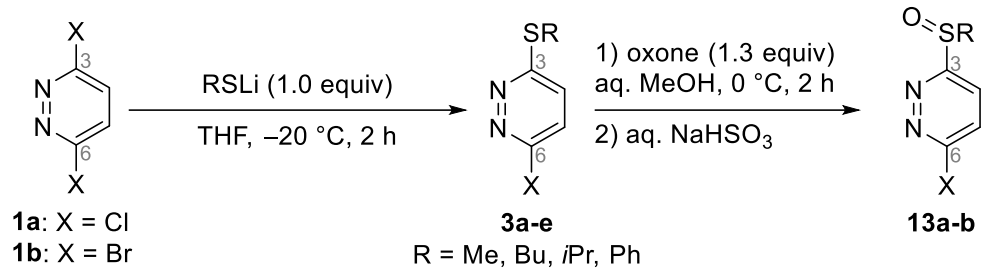
C. EXPERIMENTAL PART

1. GENERAL INFORMATION

All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone under nitrogen and stored over molecular sieves. Ethyl acetate was purchased from Sigma-Aldrich with a purity of 99% and used without destillation or drying prior to use. Yields refer to isolated yields of compounds estimated to be >95% purity as determined by ^{1}H-NMR (25 °C) and capillary gas-chromatographical analyses. Column chromatographical purifications were performed using SiO_2 (0.040-0.063 mm, 230-400 mesh ASTM) from Merck.

Melting points were measured using a Büchi B-540 apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ and chemical shifts are reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s = singlet; d = doublet; t = triplet; q = quartet; p = quintet; hep = sextet, m = multiplet. Mass spectra and high resolution mass spectra (HRMS) were recorded using electron ionization (EI) except otherwise noted. Gas-chromatographical analyses were performed on machines of the types hewlett-Packard 6890 or 5890 Series II (Hewlett Packard, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm; film thickness: 0.25 μm). All reagents not listed in the experimental part were obtained from commercial sources.

2. PREPARATION OF NON-SYMMETRICAL PYRIDAZINES



Scheme 56. Preparation of non-symmetrical pyridazine thioethers (**3a-e**) and sulfoxides (**13a-b**)

Preparation of Lithium Alkylthiolate solution (RSLi):

A dry and argon flushed Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with the desired thiol (5.0 mmol, 1.0 equiv) in dry THF (5 mL). This solution was cooled to 0 °C and *n*-BuLi (2.60 M in hexane, 5.0 mmol, 1.0 equiv) was added dropwise. After the addition was completed, the reaction mixture was stirred for 30 min at 0 °C. The resulting solution was used as it was for the following step.

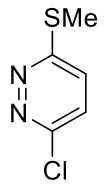
Preparation of 3-(alkylthio)-6-chloropyridazines (3a-d) and 3-bromo-6-(phenylthio)pyridazine (3e) (TP1):

A dry and argon flushed Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with 3,6-dichloropyridazine (**1a**, 745 mg, 5.0 mmol, 1.0 equiv) or 3,6-dibromopyridazine (**1b**, 1.2 g, 5.0 mmol, 1.0 equiv) in dry THF (5 mL). This solution was cooled to the appropriate temperature and the solution of lithium alkylthiolate (5.0 mmol, 1.0 equiv) was added dropwise. After the addition was completed, the reaction mixture was stirred for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) or recrystallization in cold MeOH provided the desired compounds **3a-d** and **3e** as white solids (46-84% yield).

Generale procedure for the oxidation of pyridazines of type 3[154] (TP2):

A round bottom flask, equipped with a magnetic stirrer was charged with the corresponding pyridazine **3a-e** (5.0 mmol, 1.0 equiv) in MeOH (5 mL). Then, oxone (4.0 g, 6.5 mmol, 1.3 equiv) in H_2O (10 mL) was added at 0 °C. The resulting mixture was stirred for 2 h. The reaction mixture was quenched with sat. aq. $NaHSO_3$ solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 80:20) provided the desired compounds **13a-b** as white solids (46-56% yield).

3-Chloro-6-(methylthio)pyridazine (3a)



According to **TP1**, 3,6-dichloropyridazine (**1a**, 745 mg, 5.0 mmol, 1.0 equiv) was treated with the solution of lithium methanethiolate (5.0 mmol, 1.0 equiv) at 0 °C for 2 h. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) afforded the title compound **3a** as a white solid (490 mg, 3.0 mmol, 61% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.29 (d, J = 9.0 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 2.70 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.3, 153.7, 128.0, 127.2, 13.6.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3037, 1566, 1387, 1312, 1161, 1146, 1127, 1035, 1027, 1017, 970, 962, 844, 776, 629.

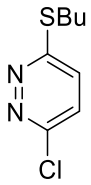
MS (EI, 70 eV): *m/z* (%) = 162 (34), 161 (11), 160 (100), 159 (32), 125 (52), 115 (9), 98 (25), 79 (14), 73 (10), 72 (9).

HRMS (EI): *m/z*: [M] calc. for [$C_5H_5ClN_2S$]: 159.9862; found 159.9855.

m. p. (°C): 107.

[154] R. V. Kupwade, S. S. Khot, U. P. Lad, U. V. Desai, P. P. Wadgaonkar, *Res. Chem. Intermed.* **2017**, *43*, 6875.

3-(Butylthio)-6-chloropyridazine (3b)



According to **TP1**, 3,6-dichloropyridazine (**1a**, 745 mg, 5.0 mmol, 1.0 equiv) was treated with the solution of lithium butanethiolate (5.0 mmol, 1.0 equiv) at 0 °C for 2 h. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) afforded the title compound **3b** as a white solid (924 mg, 4.6 mmol, 91% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.24 (d, J = 1.2 Hz, 2H), 3.32 (t, J = 7.4 Hz, 2H), 1.79 – 1.69 (m, 2H), 1.53 – 1.42 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.2, 153.5, 128.4, 127.2, 31.1, 30.2, 22.2, 13.8.

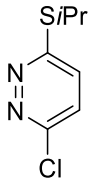
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2960, 2926, 2871, 2860, 1564, 1465, 1389, 1360, 1304, 1159, 1144, 1128, 1057, 1035, 1025, 1017, 845, 776, 728, 629.

MS (EI, 70 eV): *m/z* (%) = 173 (22), 160 (27), 155 (25), 148 (34), 147 (28), 146 (100), 125 (15), 111 (12), 102 (11).

HRMS (EI): *m/z*: [M+H$^+$] calc. for [$C_8H_{12}ClN_2S^+$]: 203.0404; found 203.0403.

m. p. (°C): 57.

3-Chloro-6-(isopropylthio)pyridazine (3c)



According to **TP1**, 3,6-dichloropyridazine (**1a**, 745 mg, 5.0 mmol, 1.0 equiv) was treated with the solution of lithium isopropylthiolate (5.0 mmol, 1.0 equiv) at 0 °C for 2 h. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) afforded the title compound **3c** as a white solid (716 mg, 3.8 mmol, 76% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.26 – 7.19 (m, 2H), 4.23 (hept, J = 6.8 Hz, 1H), 1.45 (d, J = 6.8 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.5, 153.5, 128.6, 127.3, 36.0, 23.0 (2C).

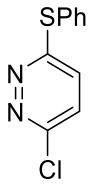
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2962, 2923, 1561, 1459, 1387, 1364, 1238, 1160, 1144, 1127, 1054, 1033, 1016, 994, 844, 775, 648, 626.

MS (EI, 70 eV): *m/z* (%) = 173 (11), 157 (11), 155 (33), 148 (35), 146 (100), 119 (10), 111 (12), 102 (10).

HRMS (EI): *m/z*: [M] calc. for [$C_7H_9ClN_2S$]: 188.0175; found 188.0168.

m. p. (°C): 62.

3-Chloro-6-(phenylthio)pyridazine (3d)



According to **TP1**, 3,6-dichloropyridazine (**1a**, 745 mg, 5.0 mmol, 1.0 equiv) was treated with the solution of lithium phenylthiolate (5.0 mmol, 1.0 equiv) at –40 °C for 2 h. Purification by recristallyzation in cold MeOH afforded the title compound **3d** as a white solid (511 mg, 2.3 mmol, 46% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.56 – 7.52 (m, 2H), 7.42 – 7.38 (m, 3H), 7.17 (d, J = 9.0 Hz, 1H), 6.91 (d, J = 9.0 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.4, 153.9, 135.5 (2C), 130.3 (3C), 128.7, 128.3, 127.1.

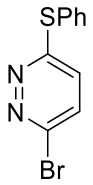
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1550, 1522, 1475, 1438, 1372, 1309, 1292, 1162, 1140, 1092, 1067, 1041, 1024, 999, 978, 834, 774, 754, 706, 689.

MS (EI, 70 eV): *m/z* (%) = 223 (37), 222 (10), 221(100), 160 (6), 134 (5), 115 (4).

HRMS (EI): *m/z*: [M-H^+] calc. for [$C_{10}H_6ClN_2S^-$]: 220.9946; found 220.9935.

m. p. (°C): 77.

3-Bromo-6-(phenylthio)pyridazine (3e)



According to **TP1**, 3,6-dibromopyridazine (**1b**, 1.2 g, 5.0 mmol, 1.0 equiv) was treated with the solution of lithium phenylthiolate (5.0 mmol, 1.0 equiv) at –40 °C for 2 h. Purification by recristallyzation in cold MeOH afforded the title compound **3e** as a white solid (745 mg, 2.8 mmol, 55% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.63 – 7.59 (m, 2H), 7.49 – 7.44 (m, 3H), 7.36 (d, *J* = 9.0 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.8, 144.8, 135.5 (2C), 131.5, 130.3, 130.3 (2C), 128.6, 126.8.

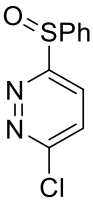
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1553, 1474, 1436, 1371, 1328, 1155, 1146, 1115, 1090, 1066, 1023, 1014, 999, 989, 980, 912, 829, 760, 746, 704, 686.

MS (EI, 70 eV): *m/z* (%) = 267 (100), 266 (10), 265(97), 186 (29), 159 (6), 134 (8), 115 (9), 109 (9).

HRMS (EI): *m/z*: [M-H$^+$] calc. for [$C_{10}H_6BrN_2S^-$]: 264.9441; found 265.9415.

m. p. (°C): 97.

3-Chloro-6-(phenylsulfinyl)pyridazine (13a)



According to **TP2**, 3-chloro-6-(phenylthio)pyridazine (**3d**, 1.1 g, 5.0 mmol, 1.0 equiv) was treated with oxone (4.0 g, 6.5 mmol, 1.3 equiv). Purification by flash column chromatography (pentane/ethyl acetate, 80:20) afforded the title compound **13a** as a white solid (549 mg, 2.3 mmol, 46% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.13 (d, J = 8.9 Hz, 1H), 7.87 – 7.78 (m, 2H), 7.68 (d, J = 8.9 Hz, 1H), 7.54 – 7.45 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 169.8, 158.3, 142.8, 131.9, 130.5, 129.7 (2C), 124.5 (2C), 124.3.

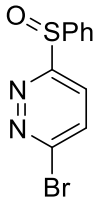
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3029, 1534, 1526, 1444, 1375, 1330, 1303, 1154, 1118, 1081, 1070, 1048, 1041, 1019, 996, 967, 849, 766, 756, 744, 697, 686.

MS (EI, 70 eV): *m/z* (%) = 223 (36), 222 (10), 221(100), 207 (8), 205 (23), 175 (7), 155 (15).

HRMS (EI): *m/z*: [M] calc. for [$C_{10}H_7ClN_2OS$]: 237.9968; found 237.9969.

m. p. (°C): 121.

3-Bromo-6-(phenylsulfinyl)pyridazine (13b)



According to **TP2,** 3-bromo-6-(phenylthio)pyridazine (**3e**, 1.3 g, 5.0 mmol, 1.0 equiv) was treated with oxone (4.0 g, 6.5 mmol, 1.3 equiv). Purification by flash column chromatography (pentane/ethyl acetate, 80:20) afforded the title compound **13b** as a white solid (793 mg, 2.8 mmol, 56% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.02 (d, J = 8.8 Hz, 1H), 7.85 – 7.80 (m, 3H), 7.49 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 170.2, 149.6, 142.7, 133.8, 131.9, 129.7 (2C), 124.5 (2C), 123.9.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1537, 1475, 1443, 1372, 1337, 1330, 1305, 1180, 1173, 1152, 1144, 1132, 1109, 1079, 1068, 1048, 1029, 1016, 997, 981, 853, 850, 841, 833, 775, 752, 738, 717, 693, 683, 667.

MS (EI, 70 eV): *m/z* (%) = 267 (98), 265 (100), 251 (21), 259 (24), 155 (26), 125 (55), 97 (61), 77 (43).

HRMS (EI): *m/z*: [M] calc. for [$C_{10}H_7BrN_2OS$]: 281.9462; found 281.9456.

m. p. (°C): 130.

3. PREPARATION OF THE REAGENTS

Preparation of the reagent TMPMgCl·LiCl (4):

A dry and argon flushed 250 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with freshly titrated *i*PrMgCl·LiCl (1.23 M in THF, 100 mL, 123 mmol, 1.0 equiv). 2,2,6,6-Tetramethylpiperidine (TMPH, 17.8 g, 126 mmol, 1.02 equiv) was added dropwise at 25 °C. The reaction mixture was stirred at 25 °C until gas evolution was completed (ca. - 48 h). The freshly prepared TMPMgCl·LiCl (**4**) solution was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)-diphenylamine as indicator. A concentration of 1.03 M in THF was obtained.

Preparation of the reagent TMPZnCl·LiCl (2b):

A dry and argon flushed 250 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with freshly distilled 2,2,6,6-Tetramethylpiperidine (TMPH, 10.22 mL, 60 mmol, 1.0 equiv) in dry THF (60 mL). This solution was cooled to –40 °C and *n*-BuLi (2.40 M in hexane, 25 mL, 60 mmol, 1.0 equiv) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm slowly to –10 °C for 1 h. $ZnCl_2$ (1.00 M in THF, 66 mL, 66 mmol, 1.1 equiv) was added dropwise and the resulting solution was stirred for 30 min at –10 °C and then for 30 min at 25 °C. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved. The freshly prepared TMPZnCl·LiCl (**2b**) solution was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.35 M in THF was obtained.

Preparation of the reagent $TMP_2Zn·2MgCl_2·2LiCl$ (2a):

A dry and argon flushed 250 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 50 mL, 50 mmol,

1.0 equiv) and cooled to 0 °C. Then, $ZnCl_2$ (1.00 M in THF, 25 mL, 25 mmol, 0.5 equiv) was added dropwise. The resulting solution was stirred for 12 h at 25 °C. The freshly prepared $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**2a**) solution was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.41 M in THF was obtained.

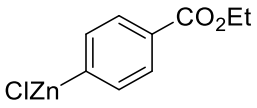
Preparation of CuCN·2LiCl solution:

A dry and argon flushed 250 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with CuCN (7.2 g, 80.0 mmol, 1.0 equiv) and LiCl (6.8 g, 160 mmol, 2.0 equiv). The mixture was heated under vacuum at 140 °C for 5 h. After cooling to 25 °C, 80 mL dry THF were added and stirring was continued until the salts were dissolved, providing a 1.00 M solution.

Preparation of $ZnCl_2$ solution:

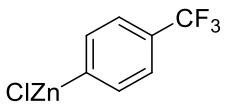
A dry and argon flushed 250 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with $ZnCl_2$ (13.6 g, 100 mmol). The flask was heated under vacuum at 140 °C for 5 h. After cooling to 25 °C, 100 mL dry THF were added and stirring was continued until the salt was dissolved, providing a 1.00 M solution.

Preparation of (4-(ethoxycarbonyl)phenyl)zinc chloride:



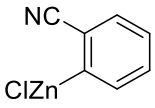
A dry and argon flushed Schlenk flask equipped with a magnetic stirrer and a septum was charged with ethyl 4-iodobenzoate (5.5 g, 20 mmol, 1.0 equiv) and dry THF (5 mL). The reaction mixture was cooled to –30 °C, and *i*PrMgCl·LiCl (1.23 M in THF, 18 mL, 22 mmol, 1.1 equiv) was added dropwise. After 1 h, the progress of the halogen-magnesium exchange was monitored by GC-analysis of reaction aliquots quenched with aq. sat. NH_4Cl solution. Upon completion of the exchange, $ZnCl_2$ (1.00 M in THF, 24 mL, 24 mmol, 1.2 equiv) was added as a solution in THF at –20 °C and the mixture was allowed to slowly warm to 25 °C. Titration with iodine gave a concentration of 0.30 mmol/mL active zinc species.

Preparation of (4-(trifluoromethyl)phenyl)zinc chloride:



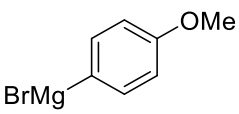
A dry and argon flushed Schlenk flask equipped with a magnetic stirrer and a septum was charged with 1-iodo-4-(trifluoromethyl)benzene (5.4 g, 20 mmol, 1.0 equiv) and dry THF (40 mL). The reaction mixture was cooled to –20 °C, and *i*PrMgCl·LiCl (1.23 M in THF, 18.0 mL, 22.0 mmol, 1.1 equiv) was added dropwise. After 4 h, the progress of the halogen-magnesium exchange was monitored by GC-analysis of reaction aliquots quenched with aq. sat. NH_4Cl solution. Upon completion of the exchange, $ZnCl_2$ (1.00 M in THF, 24 mL, 24 mmol, 1.2 equiv) was added at –20 °C and stirred for 1 h. After that, titration with iodine gave a concentration of 0.39 mmol/mL active zinc species.

Preparation of (2-cyanophenyl)zinc chloride:



A dry and argon flushed Schlenk flask equipped with a magnetic stirrer and a septum was charged with 2-iodobenzonitrile (4.6 g, 20 mmol, 1.0 equiv) and dry THF (40 mL). The reaction mixture was cooled to –40 °C, and *i*PrMgCl·LiCl (1.23 M in THF, 18 mL, 22 mmol, 1.1 equiv) was added dropwise. After 2 h, the progress of the halogen-magnesium exchange was monitored by GC-analysis of reaction aliquots quenched with aq. sat. NH_4Cl solution. Upon completion of the exchange, $ZnCl_2$ (1.00 M in THF, 24 mL, 24 mmol, 1.2 equiv) was added at –20 °C and stirred for 1 h. After that, titration with iodine gave a concentration of 0.41 mmol/mL active zinc species.

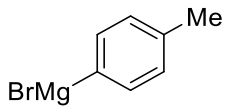
Preparation of (4-methoxyphenyl)magnesium bromide:



A dry and argon flushed Schlenk flask equipped with a magnetic stirrer and a septum was charged with LiCl (5.1 g, 120 mmol, 1.2 equiv). The flask was heated to 450 °C using a heat

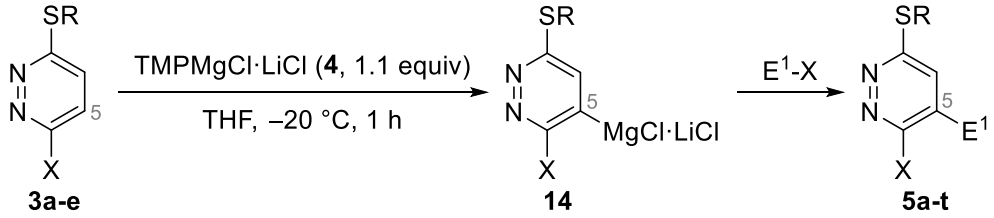
gun for 30 min under vacuum. After cooling to 25 °C, dry THF (80 mL) was added, and the mixture was stirred until the salts completely dissolved. Then, magnesium (2.9 g, 120 mmol, 1.2 equiv) was added and the solution was cooled to 0 °C. 1-Bromo-4-methoxybenzene (12.5 mL, 100 mmol, 1.0 equiv) was added dropwise and the mixture was stirred for 5 h. Titration with iodine gave a concentration of 0.93 mmol/mL in THF.

Preparation of *p*-tolylmagnesium bromide:



A dry and argon flushed Schlenk flask equipped with a magnetic stirrer and a septum was charged with LiCl (5.1 g, 120 mmol, 1.2 equiv). The flask was heated to 450 °C using a heat gun for 30 min under vacuum. After cooling to 25 °C, dry THF (80 mL) was added, and the mixture was stirred until the salts completely dissolved. Then, magnesium (2.9 g, 120 mmol, 1.2 equiv) was added and the solution was cooling to 0 °C. 4-Bromotoluene (17.1 g, 100 mmol, 1.0 equiv) was added dropwise and the mixture was stirred for 5 h. Titration with iodine gave a concentration of 0.79 mmol/mL in THF.

4. REGIOSELECTIVE METALATION OF PYRIDAZINES OF TYPE 3



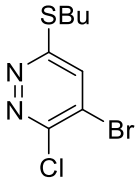
Scheme 57. Regioselective magnesiation of pyridazines of type **3** using TMPMgCl·LiCl (**4**) and subsequent electrophile quench at position 5.

General procedure for the magnesiation of pyridazines of type 3 using TMPMgCl·LiCl (TP3):

A dry and argon flushed flask, equipped with a magnetic stirrer and a septum, was charged with a solution of the corresponding pyridazine **3a-e** (0.5 mmol, 1.0 equiv) in dry THF (1 mL).

Then, TMPMgCl·LiCl (**4**, 0.55 mmol, 1.1 equiv) was added dropwise at –20 °C. After 1 h, the completion of the metalation was monitored by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

4-Bromo-6-(butylthio)-3-chloropyridazine (5a)



According to **TP3**, 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. $(BrCl_2C)_2$ (244 mg, 0.75 mmol, 1.5 equiv) in dry THF (1 mL) was then added dropwise and the resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 98:2) provided the title compound **5a** as an orange oil (117 mg, 0.42 mmol, 83% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.58 (s, 1H), 3.31 (t, J = 7.4 Hz, 2H), 1.79 – 1.69 (m, 2H), 1.52 – 1.42 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

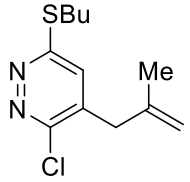
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.6, 153.3, 131.0, 126.9, 31.0, 30.5, 22.1, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2928, 2870, 1535, 1463, 1456, 1336, 1301, 1262, 1145, 1133, 1066, 882, 852, 843, 822, 726.

MS (EI, 70 eV): *m/z* (%) = 253 (22), 240 (29), 238 (24), 235 (23), 233 (19), 228 (25), 227 (19), 226 (100), 224 (76), 145 (24).

HRMS (EI): *m/z*: [M] calc. for $[C_8H_{10}BrClN_2S]$: 279.9437; found 279.9432.

6-(Butylthio)-3-chloro-4-(2-methylallyl)pyridazine (5b)



According to **TP3,** 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. Methallyl bromide (81 mg, 0.6 mmol, 1.2 equiv) and CuCN·2LiCl[155] (1.00 M solution in THF, 0.05 mL, 0.05 mmol, 10 mol%) were added and the resulting mixture was stirred for 12 h at – 20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 98:2) provided the title compound **5b** as a yellow oil (110 mg, 0.43 mmol, 86% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.12 (s, 1H), 4.99 (s, 1H), 4.70 (s, 1H), 3.35 – 3.28 (m, 4H), 1.78 – 1.70 (m, 5H), 1.52 – 1.42 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.3, 155.1, 140.1, 138.2, 127.8, 115.2, 40.2, 31.2, 30.2, 22.6, 22.2, 13.8.

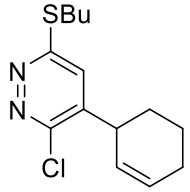
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2929, 2871, 1571, 1464, 1454, 1446, 1443, 1433, 1356, 1304, 1271, 1135, 1099, 895, 764, 758, 730, 724.

MS (EI, 70 eV): *m/z* (%) = 209 (100), 200 (84), 199 (62), 185 (88), 179 (56), 167 (57), 165 (40), 164 (70).

HRMS (EI): *m/z*: [M+H$^+$] calc. for [$C_{12}H_{18}ClN_2S^+$]: 257.0874; found 257.0873.

[155] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

6-(Butylthio)-3-chloro-4-(cyclohex-2-en-1-yl)pyridazine (5c)



According to **TP3,** 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. 3-Bromocyclohexene (97 mg, 0.6 mmol, 1.2 equiv) and CuCN·2LiCl[156] (1.00 M solution in THF, 0.05 mL, 0.05 mmol, 10 mol%) were added and the resulting mixture was stirred for 12 h at – 20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 98:2) provided the title compound **5c** as a colourless oil (118 mg, 0.42 mmol, 84% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.14 (s, 1H), 6.11 – 6.05 (m, 1H), 5.58 – 5.52 (m, 1H), 3.72 – 3.66 (m, 1H), 3.30 (t, *J* = 7.3 Hz, 2H), 2.15 – 2.06 (m, 3H), 1.78 – 1.70 (m, 2H), 1.68 – 1.53 (m, 3H), 1.51 – 1.42 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.3, 154.5, 143.8, 132.0, 126.9, 125.7, 37.1, 31.2, 30.2, 28.6, 24.9, 22.2, 19.9, 13.8.

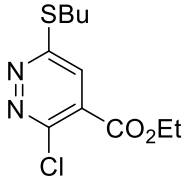
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2954, 2928, 2870, 2860, 1568, 1455, 1446, 1357, 1341, 1324, 1307, 1296, 1272, 1131, 1098, 1073, 1056, 1043, 908, 880, 760, 748, 724.

MS (EI, 70 eV): *m/z* (%) = 240 (35), 235 (96), 228 (36), 226 (100), 225 (51), 193 (45), 191 (50), 165 (35), 147 (60).

HRMS (EI): *m/z*: [M+H$^+$] calc. for [$C_{14}H_{20}ClN_2S^+$]: 283.1030; found 283.1030.

[156] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

Ethyl 6-(butylthio)-3-chloropyridazine-4-carboxylate (5d)



According to **TP3,** 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. Then, ethyl cyanoformate (60 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) provided the title compound **5d** as a yellow oil (118 mg, 0.43 mmol, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.60 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.34 (t, *J* = 7.3 Hz, 2H), 1.79 – 1.71 (m, 2H), 1.53 – 1.44 (m, 2H), 1.41 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).

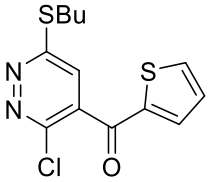
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.1, 162.8, 149.9, 129.1, 128.0, 63.2, 31.0, 30.5, 22.2, 14.2, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2931, 2872, 1739, 1496, 1464, 1369, 1347, 1318, 1301, 1273, 1242, 1178, 1141, 1085, 1011, 913, 858, 778, 763.

MS (EI, 70 eV): *m/z* (%) = 273 (49), 258 (62), 246 (33), 230 (39), 219 (34), 218 (49), 217 (100), 146 (30).

HRMS (EI): *m/z*: [M] calc. for [$C_{11}H_{15}ClN_2O_2S$]: 274.0543; found 274.0528.

(6-(Butylthio)-3-chloropyridazin-4-yl)(thiophen-2-yl)methanone (5e)



According to **TP3,** 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. CuCN·2LiCl[157] (1.00 M solution in THF, 0.55 mL, 0.55 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 15 min. Then, 2-thiophenecarbonyl chloride (88 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 90:10) provided the title compound **5e** as a colourless solid (80 mg, 0.26 mmol, 51% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.88 (d, J = 4.7 Hz, 1H), 7.45 (d, J = 3.6 Hz, 1H), 7.30 (s, 1H), 7.19 (dd, J = 4.9, 3.9 Hz, 1H), 3.37 (t, J = 7.4 Hz, 2H), 1.82 – 1.74 (m, 2H), 1.55 – 1.45 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 182.3, 162.8, 148.9, 141.8, 137.7, 136.8, 136.4, 129.0, 125.5, 31.0, 30.5, 22.2, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2950, 2933, 2867, 1648, 1509, 1491, 1465, 1406, 1364, 1355, 1341, 1324, 1313, 1307, 1273, 1263, 1256, 1233, 1227, 1216, 1140, 1099, 1085, 1054, 1043, 1025, 958, 931, 917, 904, 864, 859, 848, 805, 790, 755, 742, 732, 724, 695, 682, 678, 670, 656.

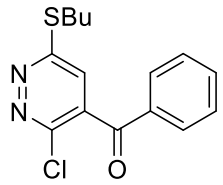
MS (EI, 70 eV): *m/z* (%) = 283 (10), 270 (18), 267 (9), 265 (27), 258 (20), 257 (11), 256 (50), 223 (26), 111 (100).

HRMS (EI): *m/z*: [M] calc. for [$C_{13}H_{13}ClN_2OS_2$]: 312.0158; found 312.0151.

m. p. (°C): 84.

[157] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

(6-(Butylthio)-3-chloropyridazin-4-yl)(phenyl)methanone (5f)



According to **TP3,** 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. CuCN·2LiCl[158] (1.00 M solution in THF, 0.55 mL, 0.55 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 15 min. Then, benzoyl chloride (84 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) provided the title compound **5f** as a colourless solid (106 mg, 0.35 mmol, 69% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.82 – 7.78 (m, 2H), 7.72 – 7.67 (m, 1H), 7.56 – 7.51 (m, 2H), 7.27 (s, 1H), 3.39 (t, *J* = 7.4 Hz, 2H), 1.84 – 1.76 (m, 2H), 1.56 – 1.46 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.6, 162.9, 149.0, 137.0, 135.2, 134.6, 130.2 (2C), 129.3 (2C), 125.7, 31.0, 30.5, 22.2, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2950, 2929, 2868, 1676, 1670, 1594, 1578, 1487, 1449, 1342, 1324, 1306, 1272, 1257, 1242, 1216, 1191, 1179, 1141, 1101, 1024, 999, 969, 904, 820, 800, 748, 708, 703, 683, 670, 658, 624, 615.

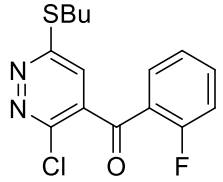
MS (EI, 70 eV): *m/z* (%) = 277 (13), 264 (26), 261 (11), 259 (36), 252 (23), 251 (14), 250 (67), 217 (28), 105 (100), 77 (34).

HRMS (EI): *m/z*: [M] calc. for [$C_{15}H_{15}ClN_2OS$]: 306.0594; found 306.0587.

m. p. (°C): 95.

[158] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

(6-(Butylthio)-3-chloropyridazin-4-yl)(2-fluorophenyl)methanone (5g)



According to **TP3,** 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. CuCN·2LiCl[159] (1.00 M solution in THF, 0.55 mL, 0.55 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 15 min. Then, 2-fluorobenzoyl chloride (95 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) provided the title compound **5g** as a colourless solid (80 mg, 0.25 mmol, 50% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.91 (td, *J* = 7.5, 1.9 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.37 – 7.32 (m, 1H), 7.26 (s, 1H), 7.15 (dd, *J* = 10.5, 8.6 Hz, 1H), 3.36 (t, *J* = 7.3 Hz, 2H), 1.81 – 1.73 (m, 2H), 1.54 – 1.44 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 187.7, 163.1, 162.3 (d, *J* = 258.8 Hz), 148.2 (d, *J* = 2.7 Hz), 138.3, 137.0 (d, *J* = 9.2 Hz), 131.3, 125.2 (d, *J* = 3.3 Hz), 125.2, 123.9 (d, *J* = 9.9 Hz), 117.1 (d, *J* = 22.0 Hz), 31.0, 30.5, 22.2, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3060, 2956, 2927, 2871, 2858, 1683, 1669, 1662, 1606, 1573, 1478, 1464, 1454, 1429, 1345, 1324, 1307, 1276, 1240, 1209, 1186, 1143, 1106, 1098, 1025, 973, 966, 912, 839, 803, 785, 754, 746, 685, 646, 622.

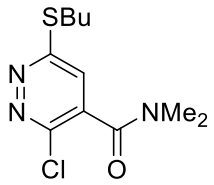
MS (EI, 70 eV): *m/z* (%) = 282 (14), 277 (17), 270 (14), 268 (40), 124 (8), 123 (100).

HRMS (EI): *m/z*: [M] calc. for [$C_{15}H_{14}ClFN_2OS$]: 324.0499; found 324.0491.

m. p. (°C): 73.

[159] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

6-(Butylthio)-3-chloro-*N*,*N*-dimethylpyridazine-4-carboxamide (5h)



According to **TP3,** 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. CuCN·2LiCl[160] (1.00 M solution in THF, 0.55 mL, 0.55 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 15 min. Then, *N*,*N*-dimethylcarbamyl chloride (65 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 80:20) provided the title compound **5h** as a white solid (104 mg, 0.38 mmol, 75% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.20 (s, 1H), 3.37 – 3.29 (m, 2H), 3.13 (s, 3H), 2.90 (s, 3H), 1.79 – 1.70 (m, 2H), 1.53 – 1.43 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.9, 163.0, 149.0, 135.0, 125.2, 38.1, 34.9, 31.0, 30.4, 22.2, 13.8.

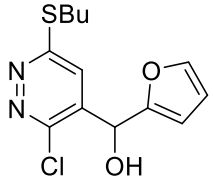
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2934, 2928, 2873, 2860, 1649, 1508, 1496, 1465, 1456, 1450, 1408, 1399, 1351, 1306, 1151, 1077, 915, 828.

MS (EI, 70 eV): *m/z* (%) = 244 (19), 231 (29), 228 (14), 226 (45), 219 (35), 218 (24), 217 (100), 182 (33), 165 (20), 160 (17), 153 (19), 123 (38), 96 (13), 72 (11).

HRMS (EI): *m/z*: [M] calc. for [$C_{11}H_{16}ClN_3OS$]: 273.0703; found 273.0696.

[160] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

(6-(Butylthio)-3-chloropyridazin-4-yl)(furan-2-yl)methanol (5i)



According to **TP3,** 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. Then, furfural (58 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 90:10) provided the title compound **5i** as a colourless solid (126 mg, 0.42 mmol, 84% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.73 (d, J = 0.8 Hz, 1H), 7.38 (dd, J = 1.8, 0.7 Hz, 1H), 6.33 (dd, J = 3.3, 1.9 Hz, 1H), 6.21 (d, J = 3.3 Hz, 1H), 5.98 (s, 1H), 3.31 (td, J = 7.2, 1.5 Hz, 2H), 3.27 (s, 1H),1.79 – 1.70 (m, 2H), 1.53 – 1.43 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.2, 151.9, 151.6, 143.5, 139.0, 125.8, 110.8, 109.5, 65.2, 31.0, 30.3, 22.2, 13.8.

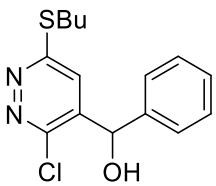
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3275, 2959, 2931, 2872, 1663, 1575, 1461, 1378, 1352, 1313, 1274, 1226, 1179, 1137, 1043, 1013, 787, 758, 743.

MS (EI, 70 eV): *m/z* (%) = 256 (43), 251 (51), 244 (34), 242 (100), 213 (34), 147 (45), 146 (31), 97 (36), 65 (40).

HRMS (EI): *m/z*: [M+H$^+$] calc. for [$C_{13}H_{16}ClN_2O_2S^+$]: 299.0616; found 299.0614.

m. p. (°C): 64.

(6-(Butylthio)-3-chloropyridazin-4-yl)(phenyl)methanol (5j)



According to **TP3,** 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. Then, benzaldehyde (64 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 90:10) provided the title compound **5j** as a yellow oil (110 mg, 0.36 mmol, 71% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.73 (d, J = 0.9 Hz, 1H), 7.35 – 7.25 (m, 5H), 5.88 (s, 1H), 3.74 (s, 1H), 3.27 (t, J = 7.3 Hz, 2H), 1.77 – 1.69 (m, 2H), 1.52 – 1.42 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

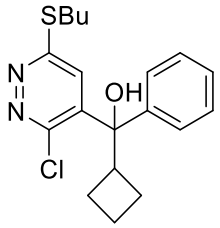
^{3}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.1, 152.0, 141.8, 139.5, 128.9 (2C), 128.9, 127.7 (2C), 125.4, 71.6, 31.0, 30.2, 22.1, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3292, 2959, 2930, 2872, 1572, 1494, 1455, 1431, 1408, 1351, 1306, 1274, 1225, 1187, 1133, 1078, 1042, 1026, 1003, 937, 907, 827, 729, 697, 668.

MS (EI, 70 eV): *m/z* (%) = 266 (28), 261 (30), 254 (17), 252 (49), 149 (14), 147 (44), 146 (12), 105 (100), 79 (14), 77 (20).

HRMS (EI): *m/z*: [M+H$^+$] calc. for [$C_{15}H_{18}ClN_2OS^+$]: 309.0823; found 309.0823.

(6-(Butylthio)-3-chloropyridazin-4-yl)(cyclobutyl)(phenyl)methanol (5k)



According to **TP3,** 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. Then, cyclobutyl phenyl ketone (96 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the

solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) provided the title compound **5k** as a colourless solid (110 mg, 0.30 mmol, 61% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.78 (s, 1H), 7.33 – 7.28 (m, 3H), 7.18 (dd, *J* = 7.7, 1.9 Hz, 2H), 3.59 (q, *J* = 8.5 Hz, 1H), 3.38 – 3.30 (m, 2H), 2.69 (s, 1H), 2.32 – 2.23 (m, 1H), 2.08 – 2.02 (m, 1H), 2.01 – 1.95 (m, 1H), 1.93 – 1.84 (m, 1H), 1.82 – 1.74 (m, 3H), 1.73 – 1.65 (m, 1H), 1.53 – 1.46 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.6, 152.0, 142.5, 142.4, 128.7 (2C), 128.2, 126.7 (2C), 126.0, 40.4, 31.2, 30.3, 23.4, 22.5, 22.3 (2C), 17.4, 13.8.

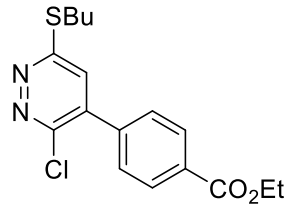
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2980, 2951, 2937, 2925, 2902, 2860, 1559, 1492, 1464, 1446, 1347, 1337, 1308, 1293, 1272, 1222, 1140, 1134, 1097, 1074, 1050, 997, 973, 926, 921, 912, 908, 801, 765, 759, 748, 716, 702, 694, 648, 618, 613, 607, 602.

MS (EI, 70 eV): *m/z* (%) = 320 (31), 315 (51), 306 (74), 252 (38), 251 (71), 218 (59), 105 (100), 77 (29).

HRMS (EI): *m/z*: [M] calc. for [$C_{19}H_{23}ClN_2OS$]: 362.1220; found 362.1217.

m. p. (°C): 118.

Ethyl 4-(6-(butylthio)-3-chloropyridazin-4-yl)benzoate (5l)



According to **TP3,** 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. Then, $ZnCl_2$ (1.00 M in THF, 0.6 mL, 0.6 mmol, 1.2 equiv) was added. In another dry and argon flushed flask, $Pd(dba)_2$ (9 mg, 0.025 mmol, 5 mol%), *P*(o-furyl)$_3$[161] (7 mg, 0.05 mmol, 10 mol%) and ethyl 4-iodobenzoate (166 mg, 0.6 mmol, 1.2 equiv) were dissolved in dry THF

[161] M. Rottländer, P. Knochel, *Synlett* **1997**, *1997*, 1084.

(1 mL). The resulting arylzinc species was added to the previously prepared reagent solution. The resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) provided the title compound **5l** as solid (144 mg, 0.41 mmol, 82% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.16 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.25 (s, 1H), 4.42 (q, J = 7.1 Hz, 2H), 3.36 (t, J = 7.4 Hz, 2H), 1.82 – 1.74 (m, 2H), 1.55 – 1.45 (m, 2H), 1.42 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.9, 162.7, 151.9, 138.6 (2C), 131.7, 130.0 (2C), 129.1 (2C), 127.7, 61.5, 31.1, 30.3, 22.2, 14.5, 13.8.

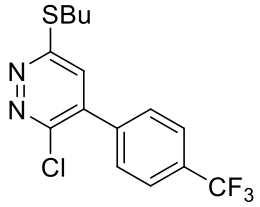
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2930, 1707, 1566, 1466, 1451, 1405, 1367, 1350, 1333, 1310, 1304, 1291, 1273, 1242, 1230, 1182, 1145, 1139, 1122, 1112, 1102, 1049, 1016, 963, 937, 866, 840, 775, 750, 733, 720, 704, 638.

MS (EI, 70 eV): *m/z* (%) = 310 (13), 308 (34), 303 (33), 296 (36), 294 (100), 266 (26), 249 (23), 181 (13).

HRMS (EI): *m/z*: [M] calc. for [$C_{17}H_{19}ClN_2O_2S$]: 350.0856; found 350.0851.

m. p. (°C): 66.

6-(Butylthio)-3-chloro-4-(4-(trifluoromethyl)phenyl)pyridazine (5m)



According to **TP3,** 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. Then, $ZnCl_2$ (1.00 M in THF, 0.6 mL, 0.6 mmol, 1.2 equiv) was added. In another dry and

argon flushed flask, $Pd(dba)_2$ (9 mg, 0.025 mmol, 5 mol%), *P*(o-furyl)$_3$[162] (7 mg, 0.05 mmol, 10 mol%) and 4-iodobenzotrifluoride (163 mg, 0.6 mmol, 1.2 equiv) were dissolved in dry THF (1 mL). The resulting arylzinc species was added to the previously prepared reagent solution. The resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 98:2) provided the title compound **5m** as white solid (145 mg, 0.42 mmol, 84% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.76 (d, *J* = 8.1 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.24 (s, 1H), 3.37 (t, *J* = 7.3 Hz, 2H), 1.83 – 1.74 (m, 2H), 1.53 – 1.45 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.8, 151.9, 138.1, 138.0 – 137.9 (m), 131.9 (q, *J* = 32.9 Hz), 129.6 (2C), 127.8, 125.9 (q, *J* = 3.8 Hz, 2C), 123.4 (q, *J* = 272.8 Hz), 31.1, 30.3, 22.2, 13.8.

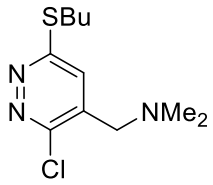
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2970, 2933, 2865, 1568, 1408, 1350, 1328, 1286, 1194, 1169, 1133, 1116, 1069, 1016, 904, 858, 844, 836.

MS (EI, 70 eV): *m/z* (%) = 317 (12), 306 (10), 304 (29), 299 (27), 292 (36), 290 (100), 246 (14), 217 (14), 203 (14), 183 (11), 182 (11).

HRMS (EI): *m/z*: [M] calc. for [$C_{15}H_{14}ClF_3N_2S$]: 346.0518; found 346.0511.

m. p. (°C): 72.

1-(6-(Butylthio)-3-chloropyridazin-4-yl)-*N*,*N*-dimethylmethanamine (5n)



According to **TP3**, 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL,

[162] M. Rottländer, P. Knochel, *Synlett* **1997**, *1997*, 1084

0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. Another dry and argon flushed flask equipped with a magnetic stirrer and a septum was charged with *N*,*N*,*N*',*N*'-tetramethyl-methanediamine (0.1 mL, 1.0 mmol, 2.0 equiv) and anhydrous DCM (1 mL). After cooling to 0 °C, trifluoroacetic anhydride (0.1 mL, 1.0 mmol, 2.0 equiv) was added dropwise and the solution was stirred for 30 min at this temperature.[163] The previously prepared methylene(dimethyl)iminium trifluoroacetate was than added dropwise to the previously prepared reagent solution at –20 °C. The resulting mixture was stirred for 12 h at – 20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 80:20) provided the title compound **5n** as a yellow oil (78 mg, 0.30 mmol, 60% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.47 – 7.46 (m, 1H), 3.45 (s, 2H), 3.31 (t, *J* = 7.3 Hz, 2H), 2.32 (s, 6H), 1.78 – 1.70 (m, 2H), 1.53 – 1.42 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

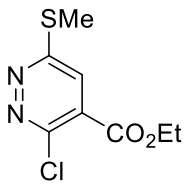
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.7, 153.8, 137.7, 127.2, 59.0, 45.8 (2C), 31.2, 30.2, 22.2, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2932, 2872, 2826, 2776, 1574, 1463, 1455, 1364, 1328, 1313, 1272, 1174, 1137, 1124, 1099, 1040, 974, 923, 900, 764, 736, 724.

MS (EI, 70 eV): *m/z* (%) = 214 (14), 205 (10), 203 (30), 181 (11), 172 (17), 168 (24), 160 (21), 127 (32), 115 (11), 76 (14), 58 (100).

HRMS (EI): *m/z*: [M+H$^+$] calc. for [$C_{11}H_{19}ClN_3S^+$]: 260.0983; found 260.0984.

Ethyl 3-chloro-6-(methylthio)pyridazine-4-carboxylate (5o)



According to **TP3,** 3-(methylthio)-6-chloropyridazine (**3a**, 80 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL,

[163] G. Kinast, L.-F. Tietze, *Angew. Chem. Int. Ed.* **1976**, *15*, 239; M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed.* **1998**, *37*, 1044; N. Millot, C. Piazza, S. Avolio, P. Knochel, *Synthesis* **2000**, *2000*, 941; N. Gommermann, C. Koradin, P. Knochel, *Synthesis* **2002**, *2002*, 2143.

0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. Then, ethyl cyanoformate (60 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 98:2) provided the title compound **5o** as a yellow oil (40 mg, 0.17 mmol, 33% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.64 (s, 1H), 4.44 (q, J = 7.1 Hz, 2H), 2.73 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H).

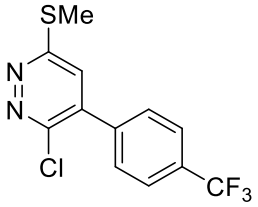
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.0, 162.8, 150.1, 129.1, 127.6, 63.2, 14.2, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1741, 1498, 1388, 1370, 1352, 1323, 1312, 1246, 1180, 1145, 1087, 1014, 780.

MS (EI, 70 eV): *m/z* (%) = 234 (22), 232 (63), 206 (35), 204 (100), 203 (30), 125 (77), 123 (14), 116 (17), 98 (10), 81 (15).

HRMS (EI): *m/z*: [M] calc. for [$C_8H_9ClN_2O_2S$]: 232.0073; found 232.0067.

3-Chloro-6-(methylthio)-4-(4-(trifluoromethyl)phenyl)pyridazine (5p)



According to **TP3,** 3-(methylthio)-6-chloropyridazine (**3a**, 80 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. Then, $ZnCl_2$ (1.00 M in THF, 0.6 mL, 0.6 mmol, 1.2 equiv) was added. In another dry and argon flushed flask, $Pd(dba)_2$ (9 mg, 0.025 mmol, 5 mol%), P(o-furyl)$_3$[164] (7 mg, 0.05 mmol, 10 mol%) and 4-iodobenzotrifluoride (163 mg, 0.6 mmol, 1.2 equiv) were dissolved in dry THF (1 mL). The resulting arylzinc species was added to previously prepared reagent solution. The resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with

[164] M. Rottländer, P. Knochel, *Synlett* **1997**, *1997*, 1084.

sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 90:10) provided the title compound **5p** as a white solid (116 mg, 0.38 mmol, 76% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.79 – 7.75 (m, 2H), 7.63 – 7.58 (m, 2H), 7.28 (s, 1H), 2.76 (s, 3H).

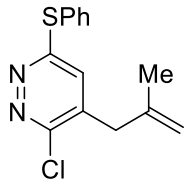
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.8, 152.0, 138.1, 137.9 – 137.8 (m), 132.0 (q, J = 32.8 Hz), 129.6 (2C), 127.4, 125.9 (q, J = 3.6 Hz, 2C), 125.0 (q, J = 272.8 Hz), 13.7.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1350, 1333, 1316, 1173, 1147, 1112, 1072, 855, 833.

MS (EI, 70 eV): *m/z* (%) = 306 (36), 304 (100), 303 (30), 269 (31), 236 (16), 217 (31), 203 (65), 182 (14), 176 (13).

HRMS (EI): *m/z*: [M] calc. for [$C_{12}H_8ClF_3N_2S$]: 304.0049; found 304.0042.

3-Chloro-4-(2-methylallyl)-6-(phenylthio)pyridazine (5q)



According to **TP3,** 3-(phenylthio)-6-chloropyridazine (**3d**, 111 mg, 0.5 mmol, 1.0 equiv) in THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. Methallyl bromide (81 mg, 0.6 mmol, 1.2 equiv) and CuCN·2LiCl[165] (1.00 M solution in THF, 0.05 mL, 0.05 mmol, 10 mol%) were added and the resulting mixture was stirred for 12 h at – 20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5) provided the title compound **5q** as a light orange solid (66 mg, 0.24 mmol, 48% yield).

[165] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.61 – 7.58 (m, 2H), 7.46 – 7.43 (m, 3H), 6.87 (s, 1H), 4.89 (s, 1H), 4.58 (s, 1H), 3.27 (s, 2H), 1.65 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.0, 155.4, 139.9, 139.3, 135.3 (2C), 130.1 (2C), 130.0, 129.2, 126.9, 115.1, 40.3, 22.5.

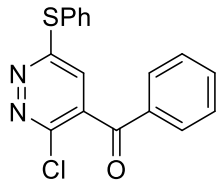
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1355, 1139, 903, 723, 692.

MS (EI, 70 eV): *m/z* (%) = 278 (5), 277 (35), 276 (14), 275 (100), 239 (12), 225 (5), 224 (8), 199 (5), 109 (4).

HRMS (EI): *m/z*: [M-H$^+$] calc. for [$C_{14}H_{12}ClN_2S^-$]: 275.0415; found 275.0406.

m. p. (°C): 60.

3-Chloro-6-(phenylthio)pyridazin-4-yl)(phenyl)methanone (5r)



According to **TP3,** 3-(phenylthio)-6-chloropyridazine (**3d**, 111 mg, 0.5 mmol, 1.0 equiv) in THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. CuCN·2LiCl[166] (1.00 M solution in THF, 0.55 mL, 0.55 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 15 min. Then, benzoyl chloride (0.07 mL, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5) provided the title compound **5r** as a yellow solid (101 mg, 0.31 mmol, 61% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 – 7.61 (m, 5H), 7.53 – 7.44 (m, 5H), 6.97 (s, 1H).

[166] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.5, 166.0, 149.2, 138.0, 135.5 (2C), 135.3, 134.4, 130.5, 130.4 (2C), 130.1 (2C), 129.3 (2C), 127.9, 124.2.

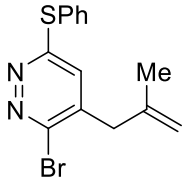
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1677, 1674, 1671, 1594, 1474, 1448, 1442, 1330, 1321, 1306, 1280, 1243, 1167, 1135, 1113, 1099, 1085, 1075, 1067, 1036, 1026, 999, 971, 901, 816, 800, 750, 716, 704, 700, 691, 684, 658.

MS (EI, 70 eV): *m/z* (%) = 328 (7), 327 (35), 326 (18), 325 (100), 221 (6), 105 (7), 77 (11).

HRMS (EI): *m/z*: [M-H$^+$] calc. for [$C_{17}H_{10}ClN_2OS^-$]: 325.0208 found; 325.0200.

m. p. (°C): 137.

3-Bromo-4-(2-methylallyl)-6-(phenylthio)pyridazine (5s)



According to **TP3,** 3-(phenylthio)-6-bromopyridazine (**3e**, 134 mg, 0.5 mmol, 1.0 equiv) in THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. Methallyl bromide (81 mg, 0.6 mmol, 1.2 equiv) and CuCN·2LiCl[167] (1.00 M solution in THF, 0.05 mL, 0.05 mmol, 10 mol%) were added and the resulting mixture was stirred for 12 h at – 20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5) provided the title compound **5s** as a light orange solid (71 mg, 0.22 mmol, 44% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.61 – 7.58 (m, 2H), 7.47 – 7.43 (m, 3H), 6.82 (s, 1H), 4.90 (s, 1H), 4.57 (s, 1H), 3.26 (s, 2H), 1.65 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.4, 148.9, 141.3, 140.0, 135.3 (2C), 130.1 (2C), 129.5, 129.0, 126.5, 115.2, 42.4, 22.6.

[167] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

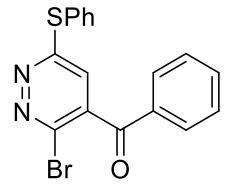
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1352, 1129, 903, 723.

MS (EI, 70 eV): *m/z* (%) = 322 (15), 321 (100), 320 (15), 319 (97), 239 (26), 225 (23), 224 (9), 199 (8), 109 (8).

HRMS (EI): *m/z*: [M-H^+] calc. for [$C_{14}H_{12}BrN_2S^-$]: 318.9910 found; 318.9899.

m. p. (°C): 71.

(3-Bromo-6-(phenylthio)pyridazin-4-yl)(phenyl)methanone (5t)



According to **TP3,** 3-(phenylthio)-6-bromopyridazine (**3e**, 134 mg, 0.5 mmol, 1.0 equiv) in THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 1 h. CuCN·2LiCl[168] (1.00 M solution in THF, 0.55 mL, 0.55 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 15 min. Then, benzoyl chloride (84 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5) provided the title compound **5t** as a yellow solid (85 mg, 0.23 mmol, 46% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.75 – 7.61 (m, 5H), 7.53 – 7.49 (m, 2H), 7.48 – 7.44 (m, 3H), 6.90 (s, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.0, 166.2, 140.3, 135.5 (2C), 135.4, 135.3, 134.2, 130.6, 130.4 (2C), 130.2 (2C), 129.3 (2C), 127.8, 123.6.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1677, 1675, 1595, 1476, 1449, 1440, 1323, 1305, 1242, 1130, 1091, 815, 796, 749, 709, 705, 699, 693, 690, 688.

[168] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

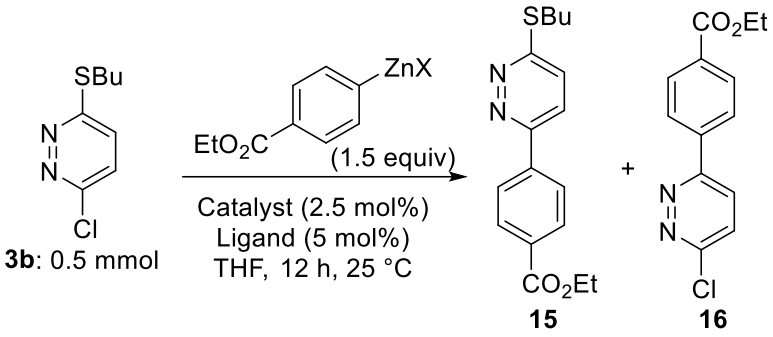
MS (EI, 70 eV): *m/z* (%) = 372 (19), 371 (99), 370 (18), 369 (100), 261 (34), 207 (19), 158 (14), 109 (14), 105 (18), 77 (27).

HRMS (EI): *m/z*: [M-H$^+$] calc. for [$C_{17}H_{10}BrN_2OS^-$]: 368.9703 found; 368.9692.

m. p. (°C): 141.

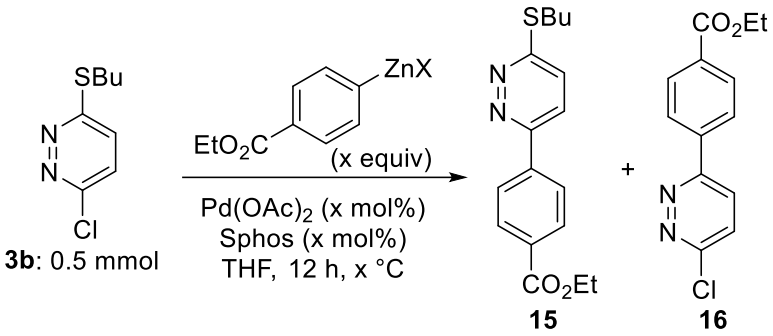
5. OPTIMIZATION OF NEGISHI CROSS-COUPLINGS

Table 3. Optimization of the catalytic system for the cross-couplinf of **3b** with (4-(ethoxycarbonyl)phenyl)zinc chloride.



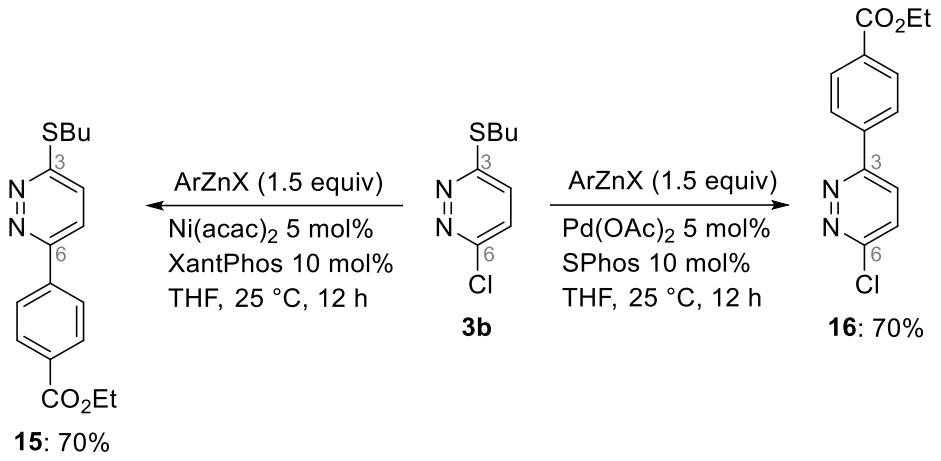
	Catalyst	Ligand	GC-Yield for 15 [%]	GC-Yield for 16 [%]	Conversion [%]
1	**$Pd(OAc)_2$**	**SPhos**	**0**	**72**	**83**
2	$Pd(OAc)_2$	XPhos	12	11	56
3	$Pd(OAc)_2$	RuPhos	3	74	86
4	$Pd(OAc)_2$	DPEPhos	59	3	100
5	$Pd(OAc)_2$	Xantphos	44	0	82
6	$Pd(OAc)_2$	P(*o*-furyl)$_3$	3	0	27
7	$Pd(OAc)_2$	Binap	43	4	89
8	$Pd(OAc)_2$	Davephos	3	35	63
9	$Pd(OAc)_2$	dppe	30	4	63
10	$Pd(OAc)_2$	dppf	57	4	100
11	$Pd(dba)_2$	SPhos	2	58	72
12	$Pd(dba)_2$	XPhos	10	10	48
13	$Pd(dba)_2$	RuPhos	3	60	79
14	$Pd(dba)_2$	DPEPhos	38	3	61
15	$Pd(dba)_2$	Xantphos	24	2	39
16	$Pd(dba)_2$	P(*o*-furyl)$_3$	2	1	18
17	$Pd_2(dba)_3$	SPhos	5	61	100
18	$Pd_2(dba)_3$	RuPhos	7	55	100
19	$Pd_2(dba)_3$	Binap	34	7	70
20	$Pd_2(dba)_3$	Davephos	5	50	68
21	$Pd_2(dba)_3$	Dppe	25	5	59
22	$Pd_2(dba)_3$	dppf	57	3	100
23	$PdCl_2(PPh_3)_2$	Sphos	5	19	39
24	$PdCl_2(PPh_3)_2$	RuPhos	4	27	49
25	$PdCl_2(PPh_3)_2$	Binap	40	3	94
26	$PdCl_2(PPh_3)_2$	Davephos			
27	$PdCl_2(PPh_3)_2$	dppe	22	2	37
28	$Pd(PPh_3)_2$	-	13	4	28
29	$PdCl(Ph)(PPh_3)_2$	-	6	7	27
30	$Pd(4\text{-}MeOC_6H_4)(PPh_3)_2$	-	4	3	25
31	PEPPSI	-	5	34	71
32	$Ni(acac)_2$	SPhos	34	1	54
33	$Ni(acac)_2$	XPhos	27	1	44
34	$Ni(acac)_2$	RuPhos	23	1	33
35	$Ni(acac)_2$	DPEPhos	38	1	71
36	**$Ni(acac)_2$**	**Xantphos**	**75**	**1**	**95**
37	$Ni(acac)_2$	P(*o*-furyl)$_3$	34	1	58

Table 4. Optimization of the cross-couplinf of **3b** with (4-(ethoxycarbonyl)phenyl)zinc chloride using $Pd(OAc)_2$ and phosphine ligands.



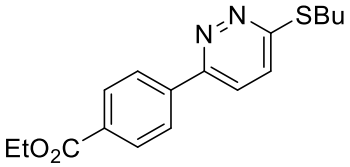
	$Pd(OAc)_2$ [mol%]	Ligand	ArZnX [equiv]	Temperature [°C]	GC-Yield for 15 [%]	GC-Yield for 16 [%]	Conversion [%]
1	2.5	SPhos (5 mol%)	1.5	25	0	72	83
2	2.5	SPhos (5 mol%)	1.5	50	2	55	95
3	2.5	SPhos (5 mol%)	1.5	0	0	72	83
4	2.5	SPhos (5 mol%)	1.2	25	1	74	84
5	2.5	SPhos (5 mol%)	2.0	25	0	4	100
6	**5**	**SPhos (10 mol%)**	**1.5**	**25**	**2**	**74**	**100**
7	2.5	RuPhos (5 mol%)	1.5	25	3	74	86
8	2.5	RuPhos (5 mol%)	1.5	50	7	38	97
9	2.5	RuPhos (5 mol%)	2.0	25	1	4	100
10	5	RuPhos (10 mol%)	1.5		7	56	99

The use of SPhos and RuPhos led to approximatly the same results, but RuPhos is a more expensive ligand, so we decide to use SPhos. We also made the choice to use 5 mol% $Pd(OAc)_2$ and 10% SPhos leading to full conversion to avoid separation problems for the purification step.



Scheme 58. Optimized conditions for Negishi cross-coupling at position 3 using Pd-catalysis and at position 6 using Ni-catalysis on compound **3b**.

Ethyl 4-(6-(butylthio)pyridazin-3-yl)benzoate (15)



A dry and argon flushed flask, equipped with a magnetic stirrer and a septum, was charged with 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL). $Ni(acac)_2$ (6.4 mg, 0.025 mmol, 5 mol%) and Xantphos (29 mg, 0.05 mmol, 10 mol%) were added to the solution. Then, a (4-(ethoxycarbonyl)phenyl)zinc chloride solution (0.30 M, 2.5 mL, 0.75 mmol, 1.5 equiv) was added dropwise to the mixture at 25 °C. The resulting reaction mixture was stirred at this temperature for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) provided the title compound **15** as white crystals (111 mg, 0.35 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.22 – 8.15 (m, 2H), 8.15 – 8.09 (m, 2H), 7.69 (d, *J* = 9.1 Hz, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.42 (t, *J* = 7.4 Hz, 2H), 1.84 – 1.76 (m, 2H), 1.55 – 1.47 (m , 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.4, 162.1, 155.0, 140.3, 131.6, 130.3 (2C), 126.7, 126.6 (2C), 123.4, 61.4, 31.3, 30.1, 22.3, 14.5, 13.8.

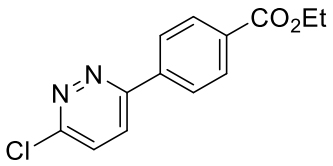
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2962, 2932, 1704, 1607, 1464, 1415, 1387, 1368, 1362, 1318, 1293, 1270, 1226, 1192, 1165, 1143, 1123, 1105, 1021, 1004, 865, 850, 828, 793, 777, 751, 732, 697.

MS (EI, 70 eV): *m/z* (%) = 274 (22), 269 (25), 261 (13), 260 (100), 232 (22), 215 (18), 159 (13), 129 (14).

HRMS (EI): *m/z*: [M] calc. for [$C_{17}H_{20}N_2O_2S$]: 316.1245; found: 316.1237.

m. p. (°C): 117.

Ethyl 4-(6-chloropyridazin-3-yl)benzoate (16)



A dry and argon flushed flask, equipped with a magnetic stirrer and a septum, was charged with 3-(butylthio)-6-chloropyridazine (**3b**, 101 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL). $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol%) and SPhos (27 mg, 0.05 mmol, 10 mol%) were added to the solution. Then, a (4-(ethoxycarbonyl)phenyl)zinc chloride solution (0.30 M, 2.5 mL, 0.75 mmol, 1.5 equiv) was added dropwise to the mixture at 25 °C. The resulting reaction mixture was stirred at this temperature for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 90:10) provided the title compound **16** as an orange solid (92 mg, 0.35 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.20 (d, *J* = 8.5 Hz, 2H), 8.13 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.1, 157.8, 156.3, 139.1, 132.3, 130.4 (2C), 128.8, 127.1 (2C), 126.5, 61.5, 14.4.

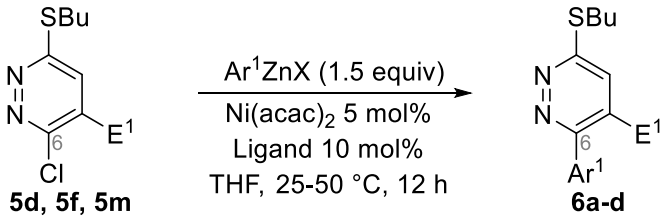
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1712, 1414, 1398, 1365, 1293, 1273, 1257, 1166, 1152, 1141, 1121, 1106, 1094, 1031, 1019, 1005, 871, 838, 778, 749, 702, 694.

MS (EI, 70 eV): *m/z* (%) = 262 (24), 234 (55), 219 (32), 217 (100), 189 (41), 146 (24), 129 (29).

HRMS (EI): *m/z*: [M] calc. for [$C_{13}H_{11}ClN_2O_2$]: 262.0509; found: 262.0504.

m. p. (°C): 174.

6. FUNCTIONALIZATION AT POSITION 6 OF PYRIDAZINES OF TYPE 5



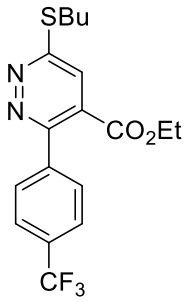
Scheme 59. Functionalization at position 6 via Negishi cross-coupling reactions of pyridazines of type **5** with arylzinc species (Ar^1ZnX) using $Ni(acac)_2$ and phosphine ligands.

General procedure for the cross-coupling of the chlorine substituent of pyridazines of type 5 (TP4):

A dry and argon flushed flask, equipped with a magnetic stirrer and a septum, was charged with the corresponding pyridazine of type **5** (0.5 mmol, 1.0 equiv) in dry THF (1 mL), $Ni(acac)_2$ (5 mol%) and the phosphine ligand[169] (10 mol%). The arylzinc halide Ar^1ZnX (0.75 mmol, 1.5 equiv) was added dropwise at 25 °C. After strirring 12 h at the appropriate temperature, the completion of the cross-coupling was monitored by GC-analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution.

[169] M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, *Organometallics* **1995**, *14*, 3081.

Ethyl 6-(butylthio)-3-(4-(trifluoromethyl)phenyl)pyridazine-4-carboxylate (6a)



According to **TP4**, ethyl 6-(butylthio)-3-chloropyridazine-4-carboxylate (**5d**, 137 mg, 0.5 mmol, 1.0 equiv), $Ni(acac)_2$ (6 mg, 0.025 mmol, 5 mol%) and Xantphos (29 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Then, (4-(trifluoromethyl) phenyl)zinc chloride solution (0.39 M in THF, 1.9 mL, 0.75 mmol, 1.5 equiv) was added dropwise. The resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 98:2 → 95:5) provided the title compound **6a** as a beige solid (105 mg, 0.28 mmol, 55% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.75 – 7.69 (m, 4H), 7.65 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.42 (t, J = 7.4 Hz, 2H), 1.84 – 1.75 (m, 2H), 1.56 – 1.45 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.5, 162.9, 154.2, 140.2 – 140.1 (m), 131.4 (q, J = 32.6 Hz), 129.3 (2C), 129.1, 126.1, 125.4 (q, J = 3.8 Hz, 2C), 124.2 (q, J = 272.4 Hz), 62.7, 31.1, 30.3, 22.2, 13.8, 13.8.

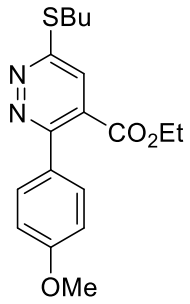
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2961, 2932, 1734, 1408, 1388, 1370, 1325, 1295, 1242, 1167, 1128, 1109, 1103, 1068, 1019, 848.

MS (EI, 70 eV): *m/z* (%) = 342 (26), 337 (36), 329 (13), 328 (100), 327 (10), 314 (11), 309 (14), 299 (92), 226 (16), 207 (13), 183 (56), 182 (26), 173 (17), 145 (13).

HRMS (EI): *m/z*: [M] calc. for $[C_{18}H_{19}F_3N_2O_2S]$: 384.1119; found 384.1106.

m. p. (°C): 103.

Ethyl 6-(butylthio)-3-(4-methoxyphenyl)pyridazine-4-carboxylate (6b)



According to **TP4,** ethyl 6-(butylthio)-3-chloropyridazine-4-carboxylate (**5d**, 137 mg, 0.5 mmol, 1.0 equiv), $Ni(acac)_2$ (6 mg, 0.025 mmol, 5 mol%) and Xantphos (29 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Another dry and argon flushed flask was charged with (4-methoxyphenyl)magnesium bromide (0.93 M in THF, 0.81 mL, 0.75 mmol, 1.5 equiv) then $ZnCl_2$ (1.00 M in THF, 0.83 mL, 0.83 mmol) was added dropwise at 0 °C and stirred for 30 min. The resulting arylzinc species was added dropwise to the solution of **5d**. The resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5 → 90:10) provided the title compound **6b** as a yellow oil (98 mg, 0.28 mmol, 57% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.60 – 7.54 (m, 2H), 7.52 (s, 1H), 7.01 – 6.95 (m, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.40 (t, *J* = 7.4 Hz, 2H), 1.84 – 1.72 (m, 2H), 1.57 – 1.41 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).

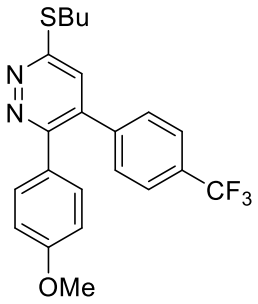
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.5, 161.1, 160.8, 154.7, 130.2 (2C), 129.2, 128.9, 125.7, 114.0 (2C), 62.5, 55.5, 31.3, 30.2, 22.2, 13.9, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2934, 1730, 1609, 1522, 1464, 1385, 1369, 1324, 1297, 1253, 1237, 1177, 1101, 1033, 1017, 837, 792.

MS (EI, 70 eV): *m/z* (%) = 304 (23), 299 (41), 291 (16), 290 (100), 286 (14), 275 (11), 271 (11), 261 (86), 173 (20), 145 (16), 145 (13), 132 (16).

HRMS (EI): *m/z*: [M] calc. for [$C_{18}H_{22}N_2O_3S$]: 346.1351; found 346.1343.

6-(Butylthio)-3-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)pyridazine (6c)



According to **TP4,** 6-(butylthio)-3-chloro-4-(4-(trifluoromethyl)phenyl)pyridazine (**5m**, 173 mg, 0.5 mmol, 1.0 equiv), $Ni(acac)_2$ (6 mg, 0.025 mmol, 5 mol%) and DPEPhos (27 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Another dry and argon flushed flask was charged with (4-methoxyphenyl)magnesium bromide (0.93 M in THF, 0.81 mL, 0.75 mmol, 1.5 equiv) then $ZnCl_2$ (1.00 M in THF, 0.83 mL, 0.83 mmol) was added dropwise at 0 °C and stirred for 30 min. The resulting arylzinc species was added dropwise to the solution of **5m**. The resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5 → 90:10) provided the title compound **6c** as a yellow solid (90 mg, 0.22 mmol, 43% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.10 – 8.01 (m, 2H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.49 (s, 1H), 7.07 – 6.99 (m, 2H), 3.88 (s, 3H), 3.40 (t, *J* = 7.4, 2H), 1.81 – 1.69 (m, 2H), 1.48 (h, *J* = 14.7, 7.4 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.4, 158.9, 155.7, 139.5 – 139.4 (m), 138.4, 131.6 (q, *J* = 32.8 Hz), 129.3 (2C), 128.3, 128.1 (2C), 125.9 (q, *J* = 3.7 Hz, 2C), 124.0 (q, *J* = 272.9 Hz), 122.4, 114.6 (2C), 55.5, 31.0, 30.7, 22.3, 13.8.

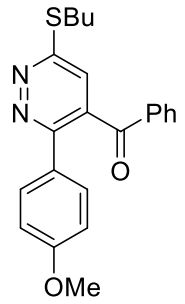
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1579, 1408, 1381, 1351, 1325, 1314, 1302, 1240, 1189, 1160, 1116, 1107, 1069, 1030, 1017, 996, 855, 841, 828.

MS (EI, 70 eV): *m/z* (%) = 376 (18), 375 (15), 371 (11), 362 (36), 361 (100), 358 (7), 357 (8), 132 (9), 117 (7), 89 (9).

HRMS (EI): *m/z*: [M] calc. for [$C_{22}H_{21}F_3N_2OS$]: 418.1327; found 418.1323.

m. p. (°C): 84.

(6-(Butylthio)-3-(4-methoxyphenyl)pyridazin-4-yl)(phenyl)methanone (6d)



According to **TP4,** (6-(butylthio)-3-chloropyridazin-4-yl)(phenyl)methanone (**5f**, 153 mg, 0.5 mmol, 1.0 equiv), $Ni(acac)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and DPEPhos (27 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Another dry and argon flushed flask was charged with (4-methoxyphenyl)magnesium bromide (0.93 M in THF, 0.81 mL, 0.75 mmol, 1.5 equiv) then $ZnCl_2$ (1.00 M in THF, 0.83 mL, 0.83 mmol) was added dropwise at 0 °C and stirred for 30 min. The resulting arylzinc species was added dropwise to the solution of **5f**. The resulting mixture was stirred for 12 h at 50 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5 → 90:10) provided the title compound **6d** as a brown solid (115 mg, 0.31 mmol, 61% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.71 – 7.64 (m, 2H), 7.60 – 7.48 (m, 3H), 7.41 – 7.32 (m, 2H), 7.30 (s, 1H), 6.84 – 6.75 (m, 2H), 3.75 (s, 3H), 3.43 (t, *J* = 7.4 Hz, 2H), 1.82 (q, *J* = 8.9, 6.8 Hz, 2H), 1.52 (h, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 194.9, 160.9, 160.7, 154.2, 135.9, 135.3, 134.5, 130.5 (2C), 130.0 (2C), 128.9 (2C), 128.3, 124.7, 114.2 (2C), 55.4, 31.3, 30.2, 22.3, 13.8.

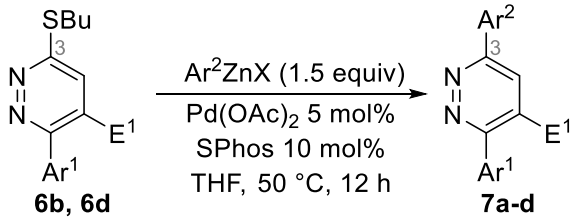
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2928, 1666, 1606, 1594, 1519, 1463, 1449, 1386, 1323, 1293, 1255, 1174, 1112, 1100, 1028, 968, 898, 837, 824, 807, 794, 772, 726, 710, 686.

MS (EI, 70 eV): *m/z* (%) = 336 (20), 332 (11), 331 (49), 323 (18), 322 (100), 318 (12), 307 (10), 294 (11), 293 (62), 245 (15), 173 (18), 159 (12), 145 (16), 105 (64), 77 (50).

HRMS (EI): *m/z*: [M] calc. for [$C_{22}H_{22}N_2O_2S$]: 378.1402; found 378.1395.

m. p. (°C): 74.

7. FUNCTIONALIZATION AT POSITION 3 OF PYRIDAZINES OF TYPE 6

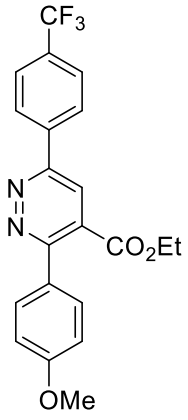


Scheme 60. Functionalization at position 3 via Negishi cross coupling reactions of pyridazines of type **6** with arylzinc species (Ar^2ZnX) using $Pd(OAc)_2$ and SPhos.

General procedure for the cross-coupling of the butylthio substituent[170] of pyridazines of type 6 (TP5):

A dry and argon flushed flask, equipped with a magnetic stirrer and a septum, was charged with the corresponding pyridazine of type **6** (0.5 mmol, 1.0 equiv) in dry THF (1 mL), $Pd(OAc)_2$ (5 mol%) and SPhos[171] (10 mol%). The arylzinc halide Ar^2ZnX (0.75 mmol, 1.5 equiv) was added dropwise at 25 °C. After stirring for 12 h at 50 °C, the completion of the cross-coupling was monitored by GC-analysis of reaction aliquots quenched with a sat. aq. NH_4Cl solution.

Ethyl 3-(4-methoxyphenyl)-6-(4-(trifluoromethyl)phenyl)pyridazine-4-carboxylate (7a)



[170] A. Metzger, L. Melzig, C. Despotopoulou, P. Knochel, *Org. Lett.* **2009**, *11*, 4228; L. Melzig, A. Metzger, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 2948.
[171] J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028; R. A. Altman, S. L. Buchwald, *Nat. Protoc.* **2007**, *2*, 3115; T. E. Barder, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 5096.

According to **TP5,** ethyl 6-(butylthio)-3-(4-methoxyphenyl)pyridazine-4-carboxylate (**6b**, 173 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Then, (4-(trifluoromethyl)phenyl)zinc chloride solution (0.39 M in THF, 1.9 mL, 0.75 mmol, 1.5 equiv) was added dropwise. The resulting mixture was stirred for 12 h at 50 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10 → 80:20) provided the title compound **7a** as a brown solid (131 mg, 0.33 mmol, 65% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.30 (d, J = 8.1 Hz, 2H), 8.12 (s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.73 – 7.65 (m, 2H), 7.07 – 7.01 (m, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.0, 161.3, 157.1, 156.2, 138.9 – 138.8 (m), 132.3 (q, J = 32.7 Hz), 130.6 (2C), 130.3, 128.6, 127.4 (2C), 126.3 (q, J = 3.7 Hz, 2C), 124.1 (q, J = 272.3 Hz), 123.6, 114.2 (2C), 62.7, 55.6, 14.0.

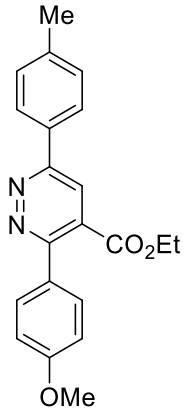
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1721, 1604, 1504, 1415, 1398, 1386, 1323, 1311, 1301, 1254, 1214, 1187, 1174, 1154, 1121, 1104, 1070, 1057, 1029, 1014, 976, 850, 840, 793, 761.

MS (EI, 70 eV): *m/z* (%) = 402 (11), 374 (13), 373 (69), 252 (24), 251 (13), 225 (16), 207 (20), 189 (27), 173 (15), 173 (35), 159 (20), 158 (15), 145 (24) 132 (100), 117 (14), 43 (15), 42 (42).

HRMS (EI): *m/z*: [M] calc. for [$C_{21}H_{17}F_3N_2O_3$]: 402.1191; found 402. 1187.

m. p. (°C): 126.

Ethyl 3-(4-methoxyphenyl)-6-(*p*-tolyl)pyridazine-4-carboxylate (7b)



According to **TP5,** ethyl 6-(butylthio)-3-(4-methoxyphenyl)pyridazine-4-carboxylate (**6a**, 173 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Another dry and argon flushed flask was charged with *p*-tolylmagnesium bromide (0.79 M in THF, 0.95 mL, 0.75 mmol, 1.5 equiv) then $ZnCl_2$ (1.00 M in THF, 0.83 mL, 0.83 mmol) was added dropwise at 0 °C and stirred for 30 min. The resulting arylzinc species was added dropwise to the solution of **6a**. The resulting mixture was stirred for 12 h at 50 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10 → 80:20) provided the title compound **7b** as a yellow solid (146 mg, 0.42 mmol, 84% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.09 – 8.06 (m, 2H), 8.05 (s, 1H), 7.69 – 7.65 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.04 – 7.00 (m, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 2.45 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 167.3, 161.0, 157.5, 156.3, 140.8, 132.7, 130.5 (2C), 130.1, 130.0 (2C), 129.1, 127.0 (2C), 123.0, 114.0 (2C), 62.5, 55.5, 21.6, 14.0.

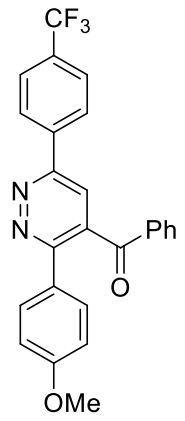
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2981, 1728, 1610, 1529, 1515, 1503, 1463, 1444, 1414, 1395, 1375, 1302, 1252, 1219, 1177, 1132, 1106, 1061, 1032, 1019, 838, 824, 795, 762.

MS (EI, 70 eV): *m/z* (%) = 348 (23), 320 (19), 319 (94), 247 (11), 203 (14), 202 (26), 189 (24), 159 (22), 132 (100), 119 (67), 117 (13), 115 (28), 89 (11).

HRMS (EI): *m/z*: [M] calc. for $[C_{21}H_{20}N_2O_3]$: 348.1474; found 348.1467.

m. p. (°C): 131.

(3-(4-Methoxyphenyl)-6-(4-(trifluoromethyl)phenyl)pyridazin-4-yl)(phenyl)methanone (7c)



According to **TP5,** (6-(butylthio)-3-(4-methoxyphenyl)pyridazin-4-yl)(phenyl) methanone (**6d**, 189 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Then, (4-(trifluoromethyl)phenyl)zinc chloride solution (0.39 M in THF, 1.9 mL, 0.75 mmol, 1.5 equiv) was added dropwise. The resulting mixture was stirred for 12 h at 50 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10 → 80:20) provided the title compound **7c** as a yellow solid (119 mg, 0.28 mmol, 55% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.31 (d, J = 8.1 Hz, 2H), 7.91 (s, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.74 – 7.63 (m, 4H), 7.59 – 7.50 (m, 1H), 7.38 (t, J = 7.8 Hz, 2H), 6.89 – 6.81 (m, 2H), 3.78 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.3, 161.2, 156.5, 155.9, 139.0 – 138.9 (m), 136.9, 135.2, 134.6, 132.3 (q, J = 32.7 Hz), 131.0 (2C), 130.0 (2C), 129.0 (2C), 128.1, 127.4 (2C), 126.3 (q, J = 3.8 Hz, 2C), 124.0 (q, J = 272.5 Hz), 123.0, 114.4 (2C), 55.4.

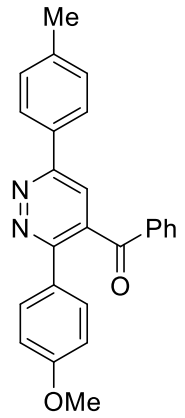
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2921, 1676, 1604, 1501, 1450, 1415, 1387, 1325, 1300, 1252, 1170, 1156, 1111, 1071, 1062, 1025, 1010, 959, 919, 868, 840, 828, 806, 798, 786, 768, 710, 686, 668.

MS (EI, 70 eV): *m/z* (%) = 434 (24), 405 (51), 281 (17), 253 (23), 233 (78), 225 (31), 218 (17), 208 (16), 207 (59), 193 (17), 189 (26), 159 (27), 105 (97), 77 (58), 44 (100), 42 (95).

HRMS (EI): *m/z*: [M] calc. for [$C_{25}H_{17}F_3N_2O_2$]: 434.1242; found 434.1234.

m. p. (°C): 204.

(3-(4-Methoxyphenyl)-6-(*p*-tolyl)pyridazin-4-yl)(phenyl)methanone (7d)



According to **TP5,** (6-(butylthio)-3-(4-methoxyphenyl)pyridazin-4-yl)(phenyl) methanone (**6d**, 189 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Another dry and argon flushed flask was charged with *p*-tolylmagnesium bromide (0.79 M in THF, 0.95 mL, 0.75 mmol, 1.5 equiv) then $ZnCl_2$ (1.00 M in THF, 0.83 mL, 0.83 mmol) was added dropwise at 0 °C and stirred for 30 min. The resulting arylzinc species was added dropwise to the solution of **6d**. The resulting mixture was stirred for 12 h at 50 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10 → 80:20) provided the title compound **7d** as a beige solid (150 mg, 0.40 mmol, 79% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.08 (d, J = 8.2 Hz, 2H), 7.84 (s, 1H), 7.72 – 7.69 (m, 2H), 7.67 – 7.63 (m, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.40 – 7.33 (m, 4H), 6.86 – 6.82 (m, 2H), 3.77 (s, 3H), 2.45 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.7, 160.9, 157.1, 155.6, 140.8, 136.8, 135.4, 134.4, 132.8, 130.8 (2C), 130.0 (2C), 130.0 (2C), 129.0 (2C), 128.5, 127.0 (2C), 122.3, 114.3 (2C), 55.4, 21.6.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2923, 1671, 1609, 1597, 1581, 1525, 1498, 1450, 1412, 1392, 1362, 1305, 1254, 1177, 1033, 1020, 964, 834, 824, 723.

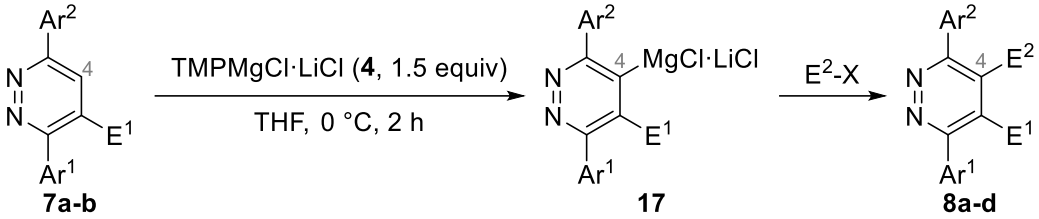
MS (EI, 70 eV): *m/z* (%) = 381 (27), 380 (100), 352 (16), 351 (54), 236 (14), 233 (14), 159 (17), 119 (22), 105 (27), 77 (13).

HRMS (EI): *m/z*: [M] calc. for [$C_{25}H_{20}N_2O_2$]: 380.1525; found 380.1524.

m. p. (°C): 166.

8. FUNCTIONALIZATION AT POSITION 4 VIA METALATION

8.1 Remaining functionalization via magnesiation

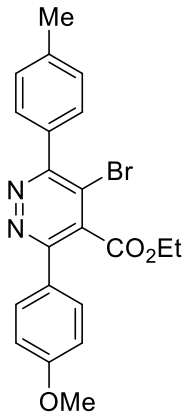


Scheme 61. Remaining functionalization at position 4 of pyridazines of type **7** using TMPMgCl·LiCl (**4**).

General procedure for the magnesiation using TMPMgCl·LiCl (TP6):

A dry and argon flushed flask, equipped with a magnetic stirrer and a septum, was charged with a solution of the corresponding pyridazine of type **7** (0.2 mmol, 1.0 equiv) in dry THF (1 mL). Then, TMPMgCl·LiCl (**4**, 0.3 mmol, 1.5 equiv) was added dropwise at 0 °C. The completion of the metalation was monitored after 2 h by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

Ethyl 5-bromo-3-(4-methoxyphenyl)-6-(*p*-tolyl)pyridazine-4-carboxylate (8a)



According to **TP6,** ethyl 3-(4-methoxyphenyl)-6-(*p*-tolyl)pyridazine-4-carboxylate (**7b**, 70 mg, 0.2 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.3 mL, 0.3 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred at this temperature for 2 h. $(BrCl_2C)_2$ (130 mg, 0.40 mmol, 2.0 equiv) in dry THF (1 mL) was then added dropwise and the resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10 → 80:20) provided the title compound **8a** as a yellow solid (30 mg, 0.07 mmol, 35% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.77 – 7.72 (m, 2H), 7.71 – 7.66 (m, 2H), 7.37 – 7.32 (m, 2H), 7.05 – 6.99 (m, 2H), 4.38 – 4.30 (m, 2H), 3.88 (s, 3H), 2.46 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.3, 161.4, 159.5, 155.4, 140.2, 134.8, 133.2, 130.5 (2C), 129.8 (2C), 129.1 (2C), 127.5, 125.1, 114.4 (2C), 63.0, 55.6, 21.6, 14.0.

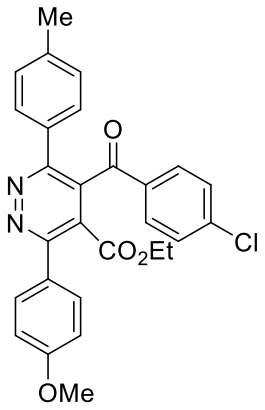
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2938, 1736, 1609, 1579, 1521, 1472, 1444, 1418, 1384, 1302, 1256, 1227, 1179, 1113, 1063, 1039, 1023, 837, 824, 770, 731.

MS (EI, 70 eV): *m/z* (%) = 428 (50), 426 (52), 399 (92), 397 (100), 356 (22); 354 (22), 247 (34), 246 (64), 234 (32), 231 (60), 203 (58), 202 (56).

HRMS (EI): *m/z*: [M] calc. for $[C_{21}H_{19}BrN_2O_3]$: 426.0579; found 426.0576.

m. p. (°C): 152.

Ethyl 5-(4-chlorobenzoyl)-3-(4-methoxyphenyl)-6-(*p*-tolyl)pyridazine-4-carboxylate (8b)



According to **TP6,** ethyl 3-(4-methoxyphenyl)-6-(*p*-tolyl)pyridazine-4-carboxylate (**7b**, 70 mg, 0.2 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.3 mL, 0.3 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred at this temperature for 2 h. CuCN·2LiCl[172] (1.00 M solution in THF, 0.4 mL, 0.4 mmol, 2.0. equiv) was added at –20 °C and the reaction mixture was stirred for 15 min. Then, 4-chlorobenzoyl chloride (70 mg, 0.4 mmol, 2.0 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10 → 80:20) provided the title compound **8b** as a white solid (55 mg, 0.11 mmol, 56% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 – 7.70 (m, 2H), 7.60 – 7.55 (m, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.29 (m, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.05 – 7.01 (m, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 2.30 (s, 3H), 0.98 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 193.3, 165.9, 161.3, 155.8, 155.5, 140.9, 140.3, 134.5, 134.1, 132.7, 130.8 (2C), 130.5 (2C), 129.6 (2C), 129.4 (2C), 129.3 (2C), 129.1, 128.3, 114.3 (2C), 62.8, 55.6, 21.5, 13.6.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2926, 1729, 1676, 1610, 1587, 1572, 1522, 1514, 1488, 1464, 1445, 1400, 1382, 1302, 1255, 1223, 1178, 1112, 1092, 1059, 1031, 1014, 964, 837, 826, 785, 749.

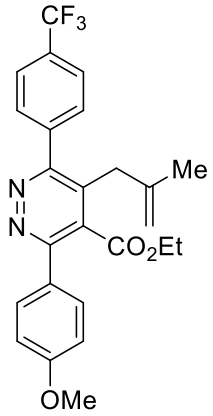
[172] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

MS (EI, 70 eV): *m/z* (%) = 457 (26), 281 (20), 231 (30), 225 (40), 207 (69), 203 (38), 202 (45), 140 (32), 139 (43), 138 (100), 132 (37), 119 (41).

HRMS (EI): *m/z*: [M] calc. for [$C_{28}H_{23}ClN_2O_4$]: 486.1346; found 486.1332.

m. p. (°C): 179.

Ethyl 3-(4-methoxyphenyl)-5-(2-methylallyl)-6-(4-(trifluoromethyl)phenyl)pyridazine-4-carboxylate (8c)



According to **TP6,** ethyl 3-(4-methoxyphenyl)-6-(4-(trifluoromethyl)phenyl)pyridazine-4-carboxylate (**7a**, 80 mg, 0.2 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.3 mL, 0.3 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred at this temperature for 2 h. Methallyl bromide (54 mg, 0.4 mmol, 2.0 equiv) and CuCN·2LiCl[173] (1.00 M solution in THF, 0.02 mL, 0.02 mmol, 10 mol%) were added at – 20 °C. The resulting mixture was stirred for 12 h at this temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10 → 80:20) provided the title compound **8c** as a yellow solid (55 mg, 0.12 mmol, 60% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.76 (s, 4H), 7.74 – 7.70 (m, 2H), 7.05 – 7.01 (m, 2H), 4.93 – 4.89 (m, 1H), 4.39 – 4.36 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.44 (s, 2H), 1.67 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H).

[173] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.8, 161.1, 159.9, 156.1, 142.4, 140.4 – 140.3 (m), 134.2, 132.2, 131.3 (q, J = 32.5 Hz), 130.3 (2C), 129.7 (2C), 128.9, 125.5 (q, J = 3.5 Hz, 2C), 125.2 (q, J = 272.4 Hz), 114.3 (2C), 114.1, 62.2, 55.6, 36.9, 23.6, 13.8.

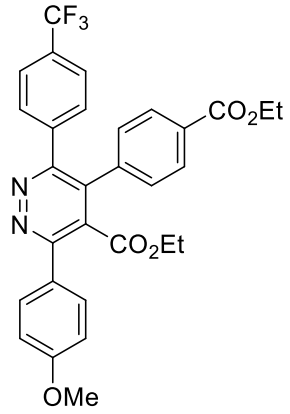
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2931, 1730, 1609, 1517, 1464, 1446, 1408, 1383, 1325, 1301, 1257, 1178, 1168, 1127, 1110, 1096, 1069, 1058, 1032, 1017, 838.

MS (EI, 70 eV): *m/z* (%) = 427 (35), 409 (17), 225 (35), 209 (16), 207 (43), 173 (39), 159 (32), 132 (100), 126 (35), 117 (16).

HRMS (EI): *m/z*: [M] calc. for [$C_{25}H_{23}F_3N_2O_3$]: 456.1661; found 456.1647.

m. p. (°C): 114.

Ethyl 5-(4-(ethoxycarbonyl)phenyl)-3-(4-methoxyphenyl)-6-(4-(trifluoromethyl)phenyl) pyridazine-4-carboxylate (8d)



According to **TP6,** ethyl 3-(4-methoxyphenyl)-6-(4-(trifluoromethyl)phenyl)pyridazine-4-carboxylate (**7a**, 80 mg, 0.2 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.3 mL, 0.3 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred at this temperature for 2 h. Then, $ZnCl_2$ (1.00 M in THF, 0.4 mL, 0.4 mmol, 2.0 equiv) was added. In another dry and argon flushed flask, $Pd(dba)_2$ (6 mg, 0.025 mmol, 5 mol%), P(o-furyl)$_3$[174] (5 mg, 0.05 mmol, 10 mol%) and ethyl 4-iodobenzoate (110 mg, 0.4 mmol, 2.0 equiv) were dissolved in dry THF (1 mL). The resulting arylzinc species was added to previously prepared reagent solution. The resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl

[174] M. Rottländer, P. Knochel, *Synlett* **1997**, *1997*, 1084.

acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 80:20) provided the title compound **8d** as a brown solid (63 mg, 0.11 mmol, 57% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 (d, *J* = 8.4 Hz, 2H), 7.79 – 7.74 (m, 2H), 7.56 – 7.48 (m, 4H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.06 – 7.01 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).z

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.9 (2C), 161.3, 156.5, 155.8, 139.7, 138.4, 135.3, 131.7, 131.2, 131.3 (q, *J* = 32.7 Hz), 130.5 (2C), 130.4 (2C), 129.9 (2C), 129.5 (2C), 128.2, 125.3 (q, *J* = 3.8 Hz, 2C), 125.2 (q, *J* = 272.4 Hz), 114.4 (2C), 62.4, 61.6, 55.5, 14.4, 13.7.

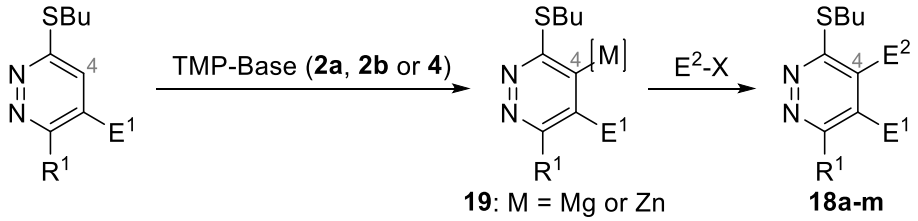
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2928, 1724, 1609, 1517, 1499, 1465, 1408, 1382, 1325, 1299, 1274, 1257, 1207, 1178, 1168, 1148, 1126, 1110, 1072, 1058, 1034, 1017, 849, 839, 767, 709.

MS (EI, 70 eV): *m/z* (%) = 550 (38), 521 (35), 508 (13), 495 (13), 380 (25), 355 (44), 352 (11), 351 (15), 339 (13), 270 (25), 269 (100), 132 (22), 112 (13), 110 (25), 100 (10), 98 (29), 97 (17), 96 (14).

HRMS (EI): *m/z*: [M] calc. for [$C_{30}H_{25}F_3N_2O_5$]: 550.1716; found 550.1717.

m. p. (°C): 140.

8.2 Functionalization via metalation and electrophilic trapping

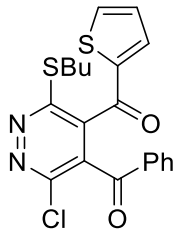


Scheme 62. Functionalization at position 4 via metalation and electrophilic trapping.

General procedure for the metalation of pyridazines of type 5 or 6 (TP7):

A dry and argon flushed flask, equipped with a magnetic stirrer and a septum, was charged with a solution of the corresponding pyridazine of type **5** or **6** (0.2 mmol, 1.0 equiv) in dry THF (1 mL). Then, the appropriate TMP-base **2a**, **2b** or **4** (0.3 mmol, 1.5 equiv) was added dropwise. The completion of the metalation was monitored by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

(5-Benzoyl-3-(butylthio)-6-chloropyridazin-4-yl)(thiophen-2-yl)methanone (18a)



According to **TP7**, (6-(butylthio)-3-chloropyridazin-4-yl)(phenyl)methanone (**5f**, 153 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPZnCl·LiCl (**2b**, 0.35 M in THF, 1.57 mL, 0.55 mmol, 1.1 equiv) at 25 °C. The reaction mixture was stirred at this temperature for 2 h and then cooled to –20 °C. CuCN·2LiCl[175] (1.0 M solution in THF, 0.55 mL, 0.55 mmol, 1.1 equiv) was added and the reaction mixture was stirred for 15 min. Then, 2-thiophenecarbonyl chloride (88 mg, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was allowed to warm slowly to 25 °C over 12 h while stirring continued. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) provided the title compound **18a** as a yellow solid (142 mg, 0.34 mmol, 68% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.83 (dd, J = 4.9, 1.1 Hz, 1H), 7.73 – 7.71 (m, 2H), 7.66 – 7.62 (m, 1H), 7.52 (dd, J = 3.9, 1.1 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.17 – 7.14 (m, 1H), 3.39 (t, J = 7.4 Hz, 2H), 1.77 – 1.69 (m, 2H), 1.49 – 1.38 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 190.1, 182.3, 159.7, 149.3, 141.5, 137.9, 137.6, 135.9, 135.3, 134.8, 134.4, 130.1 (2C), 129.2 (2C), 129.1, 31.1, 30.8, 22.2, 13.7.

[175] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

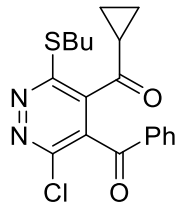
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2926, 1666, 1633, 1627, 1595, 1578, 1513, 1450, 1408, 1354, 1328, 1315, 1287, 1263, 1240, 1218, 1182, 1148, 1086, 1082, 1060, 1000, 982, 866, 859, 836, 803, 780, 754, 739, 731, 707, 680, 658, 628.

MS (EI, 70 eV): *m/z* (%) = 362 (36), 360 (90), 356 (18), 345 (15), 344 (45), 343 (42), 305 (51).

HRMS (EI): *m/z*: [M] calc. for [$C_{20}H_{17}ClN_2O_2S_2$]: 416.0420; found: 416.0414.

m. p. (°C): 109.

(5-Benzoyl-3-(butylthio)-6-chloropyridazin-4-yl)(cyclopropyl)methanone (18b)



According to **TP7,** (6-(butylthio)-3-chloropyridazin-4-yl)(phenyl)methanone (**5f**, 153 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPZnCl·LiCl (**2b**, 0.35 M in THF, 1.57 mL, 0.55 mmol, 1.1 equiv) at 25 °C. The reaction mixture was stirred at this temperature for 2 h and then cooled to –20 °C. CuCN·2LiCl[176] (1.00 M solution in THF, 0.55 mL, 0.55 mmol, 1.1 equiv) was added dropwise and the reaction mixture was stirred for 15 min at this temperature. Then, cyclopropanecarbonyl chloride (63 mg, 0.6 mmol, 1.2 equiv) was added dropwise and the resulting mixture was allowed to warm slowly to 25 °C over 12 h while stirring continued. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 98:2) provided the title compound **18b** as a yellow oil (101 mg, 0.27 mmol, 53% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.82 – 7.74 (m, 2H), 7.68 – 7.63 (m, 1H), 7.53 – 7.45 (m, 2H), 3.46 – 3.37 (m, 2H), 2.37 – 2.31 (m, 1H), 1.84 – 1.75 (m, 2H), 1.54 – 1.47 (m, 2H), 1.21 – 1.09 (m, 4H), 0.99 – 0.95 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 201.0, 190.9, 158.8, 149.4, 137.8, 135.2, 135.1, 134.2, 129.8 (2C), 129.2 (2C), 31.0, 31.0, 23.4, 22.3, 15.7 (2C), 13.8.

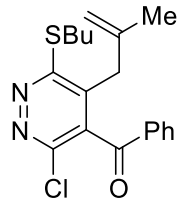
[176] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2929, 1674, 1596, 1449, 1379, 1322, 1242, 1192, 1182, 1172, 1067, 1047, 1017, 1000, 975, 885, 849, 818, 705, 690, 685, 664, 629.

MS (EI, 70 eV): *m/z* (%) = 305 (43), 290 (34), 289 (36), 287 (100), 261 (68), 257 (35), 77 (33).

HRMS (EI): *m/z*: [M+H^+] calc. for [$C_{19}H_{20}ClN_2O_2S^+$]: 375.0929; found: 375.0928.

(6-(Butylthio)-3-chloro-5-(2-methylallyl)pyridazin-4-yl)(phenyl)methanone (18c)



According to **TP7,** (6-(butylthio)-3-chloropyridazin-4-yl)(phenyl)methanone (**5f**, 153 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPZnCl·LiCl (**2b**, 0.35 M in THF, 1.57 mL, 0.55 mmol, 1.1 equiv) at 25 °C. The reaction mixture was stirred at this temperature for 2 h and then cooled to –20 °C. Methallyl bromide (81 mg, 0.6 mmol, 1.2 equiv) and CuCN·2LiCl[177] (1.00 M solution in THF, 0.05 mL, 0.05 mmol, 10 mol%) were added and the resulting mixture was allowed to warm slowly to 25 °C over 12 h while stirring continued. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 98:2) provided the title compound **18c** as a white solid (130 mg, 0.36 mmol, 72% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.78 – 7.75 (m, 2H), 7.69 – 7.64 (m, 1H), 7.52 – 7.48 (m, 2H), 4.76 – 4.75 (m, 1H), 4.41 (m, 1H), 3.38 (t, *J* = 7.4 Hz, 2H), 3.19 (s, 2H), 1.81 – 1.73 (m, 2H), 1.66 – 1.65 (m, 3H), 1.53 – 1.45 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.2, 164.1, 148.8, 139.1, 136.8, 136.7, 135.1, 135.0, 129.7 (2C), 129.3 (2C), 114.1, 37.2, 31.0, 30.7, 23.2, 22.3, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2965, 2955, 2935, 2911, 1676, 1653, 1592, 1578, 1503, 1464, 1448, 1430, 1334, 1317, 1308, 1293, 1252, 1246, 1218, 1203, 1186, 1178, 1163, 1100, 1072, 1040, 998, 982, 964, 939, 927, 907, 894, 803, 787, 775, 727, 711, 684.

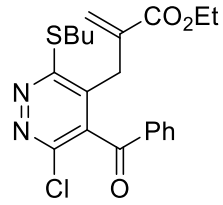
[177] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

MS (EI, 70 eV): *m/z* (%) = 305 (25), 304 (38), 303 (46), 291 (41), 290 (22), 289 (100), 271 (20), 105 (40), 77 (48).

HRMS (EI): *m/z*: [M] calc. for [$C_{19}H_{21}ClN_2OS$]: 360.1063; found: 360.1058.

m. p. (°C): 82.

Ethyl 2-((5-benzoyl-3-(butylthio)-6-chloropyridazin-4-yl)methyl)acrylate (18d)



According to **TP7,** (6-(butylthio)-3-chloropyridazin-4-yl)(phenyl)methanone (**5f**, 153 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPZnCl·LiCl (**2b**, 0.35 M in THF, 1.57 mL, 0.55 mmol, 1.1 equiv) at 25 °C. The reaction mixture was stirred at this temperature for 2 h and then cooled to –20 °C. Ethyl 2-(bromomethyl)acrylate (116 mg, 0.6 mmol, 1.2 equiv) and CuCN·2LiCl[178] (1.00 M solution in THF, 0.05 mL, 0.05 mmol, 10 mol%) were added and the resulting mixture was allowed to warm slowly to 25 °C over 12 h while stirring continued. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) provided the title compound **18d** as a yellow solid (138 mg, 0.33 mmol, 65% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 (d, *J* = 7.1 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 6.20 (s, 1H), 5.28 (d, *J* = 7.3 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.70 – 3.31 (m, 4H), 1.80 – 1.71 (m, 2H), 1.53 – 1.44 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 191.0, 165.8, 163.8, 148.7, 137.1, 135.8, 135.3, 134.8, 134.4, 129.7 (2C), 129.4 (2C), 127.5, 61.4, 31.4, 30.9, 30.7, 22.3, 14.2, 13.8.

[178] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

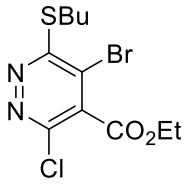
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2932, 1701, 1672, 1632, 1594, 1579, 1465, 1448, 1406, 1398, 1370, 1327, 1309, 1281, 1249, 1230, 1197, 1177, 1165, 1136, 1097, 1074, 1018, 1000, 953, 941, 932, 909, 860, 818, 801, 790, 764, 717, 704, 686, 672.

MS (EI, 70 eV): *m/z* (%) = 418 (1), 389 (2), 385 (3), 364 (2), 363 (7), 362 (5), 361 (20).

HRMS (EI): *m/z*: [M] calc. for [$C_{21}H_{23}ClN_2O_3S$]: 418.1118; found 418.1115.

m. p. (°C): 73.

Ethyl 5-bromo-6-(butylthio)-3-chloropyridazine-4-carboxylate (18e)



According to **TP7**, ethyl 6-(butylthio)-3-chloropyridazine-4-carboxylate (**5d**, 137 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPZnCl·LiCl (**2b**, 0.35 M in THF, 1.57 mL, 0.55 mmol, 1.1 equiv) at 25 °C. The reaction mixture was stirred at this temperature for 3 h and cooled to 0 °C. NBS (134 mg, 0.75 mmol, 1.5 equiv) in dry THF (2 mL) was added dropwise and the resulting mixture was allowed to warm slowly to 25 °C over 12 h while stirring continued. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 98:2) to provide the title compound **18e** as a yellow oil (101 mg, 0.29 mmol, 58% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 4.50 (q, *J* = 7.2 Hz, 2H), 3.34 – 3.31 (m, 2H), 1.79 – 1.72 (m, 2H), 1.54 – 1.46 (m, 2H), 1.43 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).

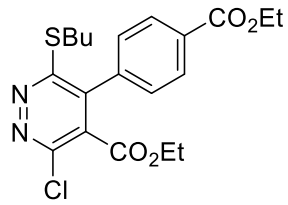
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.9, 162.1, 147.2, 134.1, 124.5, 63.7, 31.7, 30.5, 22.2, 14.1, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2930, 1741, 1464, 1368, 1317, 1262, 1236, 1181, 1093, 1060, 1007, 910, 902, 857, 820.

MS (EI, 70 eV): *m/z* (%) = 298 (100), 296 (74), 273 (31), 270 (46), 268 (36), 245 (35), 231 (80), 226 (39), 223 (32), 203 (39).

HRMS (EI): *m/z*: [M+H$^+$] calc. for [$C_{11}H_{15}BrClN_2O_2S^+$]: 352.9721; found: 352.9717.

Ethyl 6-(butylthio)-3-chloro-5-(4-(ethoxycarbonyl)phenyl)pyridazine-4-carboxylate (18f)



According to **TP7,** ethyl 6-(butylthio)-3-chloropyridazine-4-carboxylate (**5d**, 137 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**2a**, 0.41 M in THF, 1.5 mL, 0.6 mmol, 1.2 equiv) at 25 °C. The reaction mixture was stirred at this temperature for 12 h. In another dry and argon flushed flask, $Pd(dba)_2$ (9 mg, 0.025 mmol, 5 mol%), P(o-furyl)$_3$[179] (7 mg, 0.05 mmol, 10 mol%) and ethyl 4-iodobenzoate (166 mg, 0.6 mmol, 1.2 equiv) were dissolved in dry THF (1 mL). The resulting arylzinc species was added to previously prepared reagent solution. The resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 98:2) provided the title compound **18f** as a brown oil (148 mg, 0.35 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.27 (t, *J* = 7.4 Hz, 2H), 1.72 – 1.63 (m, 2H), 1.44 – 1.38 (m, 5H), 1.04 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.9, 162.9, 162.2, 148.8, 136.9, 136.0, 132.1, 131.0, 130.1 (2C), 128.8 (2C), 62.9, 61.6, 31.0, 30.6, 22.2, 14.4, 13.8, 13.8.

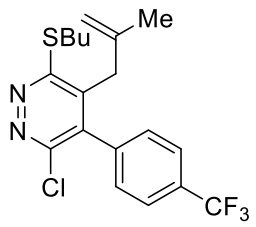
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2931, 1738, 1719, 1464, 1447, 1404, 1368, 1301, 1271, 1244, 1178, 1155, 1100, 1076, 1018, 1010, 912, 860, 835, 774, 761, 704.

MS (EI, 70 eV): *m/z* (%) = 380 (20), 365 (28), 347 (28), 339 (21), 337 (60), 309 (38), 295 (34), 293 (100), 265 (56).

HRMS (EI): *m/z*: [M] calc. for [$C_{20}H_{23}ClN_2O_4S$]: 422.1067; found 422.1057

[179] M. Rottländer, P. Knochel, *Synlett* **1997**, *1997*, 1084.

3-(Butylthio)-6-chloro-4-(2-methylallyl)-5-(4-(trifluoromethyl)phenyl)pyridazine (18g)



According to **TP7,** 6-(butylthio)-3-chloro-4-(4-(trifluoromethyl)phenyl)pyridazine (**5m**, 173 mg, 0.5 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**2a**, 0.41 M in THF, 1.5 mL, 0.6 mmol, 1.2 equiv) at 25 °C. The reaction mixture was stirred at this temperature for 12 h and then cooled to –20 °C. Methallyl bromide (81 mg, 0.6 mmol, 1.2 equiv) and $CuCN{\cdot}2LiCl$[180] (1.00 M solution in THF, 0.05 mL, 0.05 mmol, 10 mol%) were added and the resulting mixture was allowed to warm slowly to 25 °C over 12 h while stirring continued. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5) provided the title compound **18g** as a yellox oil (140 mg, 0.35 mmol, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.73 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.83 – 4.80 (m, 1H), 4.26 – 4.23 (m, 1H), 3.37 (t, J = 7.4 Hz, 2H), 3.07 (s, 2H), 1.81 – 1.71 (m, 2H), 1.67 (s, 3H), 1.48 (dt, J = 14.6, 7.4 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 163.7, 152.7, 140.8, 138.0, 137.7, 137.3 – 137.2 (m), 131.4 (q, J = 32.8 Hz), 129.1 (2C), 125.8 (q, J = 3.8 Hz, 2C), 123.9 (d, J = 272.5 Hz), 112.5, 37.6, 31.0, 30.7, 23.7, 22.3, 13.8.

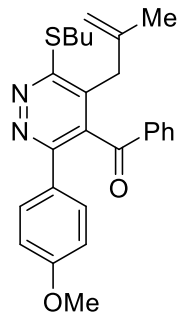
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2962, 2930, 1323, 1299, 1248, 1187, 1162, 1126, 1108, 1069, 1049, 1023, 934, 920, 906, 844, 824, 762.

MS (EI, 70 eV): *m/z* (%) = 345 (13), 344 (08), 343 (38), 332 (05), 331 (34), 330 (14), 329 (100), 328 (05), 325 (06), 314 (06), 313 (06), 311 (18), 297 (06), 199 (05).

HRMS (EI): *m/z*: [M] calc. for $[C_{19}H_{20}ClF_3N_2S]$: 400.0988; found: 400.0982.

[180] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

(6-(Butylthio)-3-(4-methoxyphenyl)-5-(2-methylallyl)pyridazin-4-yl)(phenyl)methanone (18h)



According to **TP7,** (6-(butylthio)-3-(4-methoxyphenyl)pyridazin-4-yl)(phenyl) methanone (**6d**, 76.0 mg, 0.20 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}LiCl$ (**2a**, 0.41 M in THF, 0.70 mL, 0.30 mmol, 1.2 equiv) at 25 °C. The reaction mixture was stirred at this temperature for 12 h. The solution was cooled to – 20 °C. Then, $CuCN{\cdot}2LiCl$[181] (1.00 M solution in THF, 0.02 mL, 0.02 mmol, 10 mol%) and methallyl bromide (32 mg, 0.24 mmol, 1.2 equiv) were added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5, 90:10) provided the title compound **18h** as a yellow solid (50 mg, 0.11 mmol, 58% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.58 – 7.54 (m, 2H), 7.54 – 7.49 (m, 2H), 7.49 – 7.42 (m, 1H), 7.32 – 7.26 (m, 2H), 6.79 – 6.74 (m, 2H), 4.77 – 4.71 (m, 1H), 4.42 (s, 1H), 3.73 (s, 3H), 3.51 – 3.15 (m, 4H), 1.85 – 1.75 (m, 2H), 1.68 (s, 3H), 1.59 – 1.46 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 195.2, 162.3, 160.5, 153.6, 140.0, 136.0, 135.8, 134.4, 134.3, 130.7 (2C), 129.5 (2C), 128.9, 128.8 (2C), 114.0 (2C), 113.6, 55.3, 36.8, 31.2, 30.6, 23.3, 22.4, 13.9.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2921, 1673, 1608, 1596, 1519, 1499, 1450, 1444, 1376, 1327, 1321, 1288, 1274, 1252, 1227, 1199, 1177, 1163, 1132, 1028, 904, 896, 836, 807, 798, 776, 716, 688, 654.

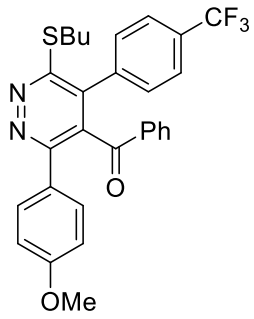
[181] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

MS (EI, 70 eV): *m/z* (%) = 432 (3), 389 (3), 385 (4), 376 (14), 375 (8), 363 (4), 362 (23), 361 (100), 347 (4), 343 (7), 329 (5), 327 (3).

HRMS (EI): *m/z*: [M] calc. for [$C_{26}H_{28}N_2O_2S$]: 432.1871; found 432.1869.

m. p. (°C): 122.

(6-(Butylthio)-3-(4-methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)pyridazin-4-yl) (phenyl)methanone (18i)



According to **TP7,** (6-(butylthio)-3-(4-methoxyphenyl)pyridazin-4-yl)(phenyl) methanone (**6d**, 76.0 mg, 0.20 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of $TMP_2Zn{\cdot}2MgCl_2{\cdot}LiCl$ (**2a**, 0.41 M in THF, 0.70 mL, 0.30 mmol, 1.2 equiv) at 25 °C. The reaction mixture was stirred at this temperature for 12 h. In another dry and argon flushed flask, $Pd(dba)_2$ (6.00 mg, 0.01 mmol, 5 mol%), *P*(o-furyl)$_3$[182] (5.00 mg, 0.02 mmol, 10 mol%) and 4-iodobenzotrifluoride (54.0 mg, 0.20 mmol, 1.2 equiv) were dissolved in dry THF (1 mL). The previously prepared reagent solution was added to the resulting arylzinc species. The resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5, 90:10) provided the title compound **18i** as a yellow oil (50 mg, 0.10 mmol, 50% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.59 – 7.54 (m, 2H), 7.49 – 7.44 (m, 2H), 7.44 – 7.40 (m, 2H), 7.28 – 7.22 (m, 5H), 6.83 – 6.78 (m, 2H), 3.75 (s, 3H), 3.53 – 3.32 (m, 2H), 1.81 – 1.70 (m, 2H), 1.52 – 1.41 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

[182] M. Rottländer, P. Knochel, *Synlett* **1997**, *1997*, 1084.

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 194.3, 160.7, 160.4, 153.8, 136.2, 136.2 –136.1 (m) 135.0, 134.9, 134.4, 131.4 (q, J = 32.8 Hz), 130.6 (2C), 129.3 (2C), 128.8 (2C), 128.4, 123.8 (q, J = 272.3 Hz), 114.2 (2C), 55.4, 31.0, 30.9, 22.3, 13.8.

Since the peaks attributed to the carbons on the CF_3 substituted ring were only of very low intensity, a ^{19}F-NMR was measured to proof the presense of the trifluoromethyl group.

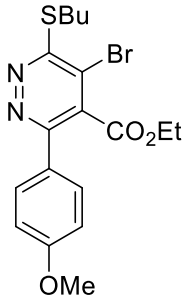
^{19}F-NMR (377 MHz, $CDCl_3$): –62.9.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2930, 1674, 1608, 1518, 1377, 1324, 1293, 1286, 1254, 1178, 1129, 1110, 1066, 1035, 1021, 838, 715.

MS (EI, 70 eV): *m/z* (%) = 466 (27), 465 (45), 281 (11), 262 (22), 253 (57), 251 (15), 250 (33), 236 (11), 225 (25), 209 (14), 207 (31), 105 (100), 77 (48), 53 (11), 44 (11), 43 (29), 42 (86).

HRMS (EI): *m/z*: [M] calc. for [$C_{29}H_{25}F_3N_2O_2S$]: 522.1589; found 522.1587.

Ethyl 5-bromo-6-(butylthio)-3-(4-methoxyphenyl)pyridazine-4-carboxylate (18j)



According to **TP7,** ethyl 6-(butylthio)-3-(4-methoxyphenyl)pyridazine-4-carboxylate (**6b**, 70.0 mg, 0.2 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.30 mL, 0.30 mmol, 1.5 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 6 h. Then, $(BrCl_2C)_2$ (130 mg, 0.40 mmol, 2.0 equiv) was added and stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 90:10, 80:20) provided the title compound **18j** as a brown oil (51 mg, 0.12 mmol, 60% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.67 – 7.61 (m, 2H), 7.01 – 6.94 (m, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 3.39 (t, *J* = 7.4 Hz, 2H), 1.86 – 1.74 (m, 2H), 1.52 (h, *J* = 14.7, 7.4 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H).

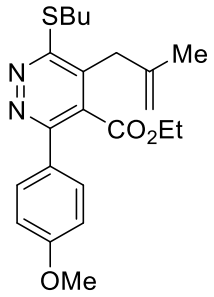
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.0, 161.9, 161.1, 153.4, 132.9, 130.1 (2C), 127.9, 124.3, 114.3 (2C), 62.9, 55.5, 31.5, 30.8, 22.3, 14.0, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2932, 1736, 1608, 1518, 1461, 1360, 1319, 1306, 1295, 1254, 1191, 1178, 1093, 1037, 1020, 836, 782.

MS (EI, 70 eV): *m/z* (%) = 317 (48), 303 (47), 230 (21), 188 (45), 187 (69), 173 (77), 172 (74), 145 (28), 145 (42), 144 (51), 135 (25).

HRMS (EI): *m/z*: [M] calc. for [$C_{18}H_{21}BrN_2O_3S$]: 424.0456; found 424.0451.

Ethyl 6-(butylthio)-3-(4-methoxyphenyl)-5-(2-methylallyl)pyridazine-4-carboxylate (18k)



According to **TP7,** ethyl 6-(butylthio)-3-(4-methoxyphenyl)pyridazine-4-carboxylate (**6b**, 70.0 mg, 0.20 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.30 mL, 0.30 mmol, 1.5 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 6 h. Then, CuCN·2LiCl[183] (1.00 M solution in THF, 0.02 mL, 0.02 mmol, 10 mol%) and methallyl bromide (32 mg, 0.24 mmol, 1.2 equiv) were added. The resulting mixture was strirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash

[183] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

column chromatography (hexane/ethyl acetate, 95:5 → 90:10) provided the title compound **18k** as a yellow oil (48 mg, 0.12 mmol, 62% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.66 – 7.59 (m, 2H), 7.03 – 6.93 (m, 2H), 4.86 (p, *J* = 1.5 Hz, 1H), 4.49 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 3.46 – 3.37 (m, 4H), 1.79 (s, 3H), 1.78 – 1.71 (m, 2H), 1.49 (h, *J* = 14.7, 7.4 Hz, 2H), 1.06 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H).

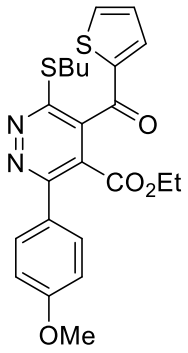
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.7, 161.9, 160.7, 153.5, 140.2, 134.0, 130.8, 129.9 (2C), 129.2, 114.1 (2C), 113.3, 62.1, 55.5, 36.8, 31.2, 30.6, 23.2, 22.3, 13.9, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2959, 2931, 1729, 1610, 1519, 1378, 1366, 1329, 1306, 1295, 1253, 1224, 1178, 1031, 837.

MS (EI, 70 eV): *m/z* (%) = 344 (13), 343 (27), 330 (18), 329 (100), 327 (15), 315 (19), 311 (10), 301 (37).

HRMS (EI): *m/z*: [M] calc. for [$C_{22}H_{28}N_2O_3S$]: 400.1821; found 400.1817.

Ethyl 6-(butylthio)-3-(4-methoxyphenyl)-5-(thiophene-2-carbonyl)pyridazine-4-carboxylate (18l)



According to **TP7,** ethyl 6-(butylthio)-3-(4-methoxyphenyl)pyridazine-4-carboxylate (**6b**, 70.0 mg, 0.20 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.30 mL, 0.30 mmol, 1.5 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 6 h. CuCN·2LiCl[184] (1.00 M solution in THF, 0.30 mL, 0.30 mmol, 1.5 equiv) was added and the reaction mixture was stirred for 15 min.

[184] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

Then, thiophene-2-carbonyl chloride (0.03 ml, 0.30 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 80:20) provided the title compound **18l** as a yellow oil (40 mg, 0.08 mmol, 44% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.84 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.67 – 7.59 (m, 2H), 7.46 (dd, *J* = 3.9, 1.2 Hz, 1H), 7.16 – 7.13 (m, 1H), 7.03 – 6.95 (m, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.41 (t, *J* = 7.4 Hz, 2H), 1.78 – 1.67 (m, 2H), 1.44 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H).

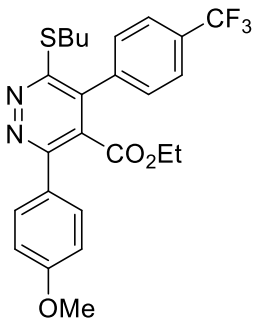
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 183.8, 165.3, 161.1, 157.4, 154.3, 142.3, 137.0, 136.3, 134.6, 130.1 (2C), 128.8, 128.3, 126.9, 114.3 (2C), 62.8, 55.5, 31.0, 30.9, 22.2, 13.8, 13.5.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2956, 2925, 2854, 1729, 1649, 1608, 1515, 1462, 1408, 1377, 1364, 1355, 1321, 1294, 1251, 1238, 1193, 1176, 1112, 1096, 1060, 1027, 1014, 859, 837, 824, 809, 799, 765, 728, 668.

MS (EI, 70 eV): *m/z* (%) = 371 (31), 345 (17), 299 (24), 187 (13), 173 (17), 171 (16), 145 (12), 144 (11), 135 (11), 111 (100).

HRMS (EI): *m/z*: [M] calc. for [$C_{23}H_{24}N_2O_4S_2$]: 456.1177; found 446.1168.

Ethyl 6-(butylthio)-3-(4-methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)pyridazine-4-carboxylate (18m)



According to **TP7,** ethyl 6-(butylthio)-3-(4-methoxyphenyl)pyridazine-4-carboxylate (**6b**, 70 mg, 0.2 mmol, 1.0 equiv) in dry THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.3 mL, 0.3 mmol, 1.5 equiv) at –20 °C. The reaction mixture was stirred at this temperature for 6 h. Then, $ZnCl_2$ (1.00 M in THF, 0.33 mL, 0.33 mmol, 1.1 equiv) was added. In another dry and argon flushed flask, $Pd(dba)_2$ (6.00 mg, 0.01 mmol, 5 mol%), P(o-furyl)$_3$[185] (5.00 mg, 0.02 mmol, 10 mol%) and 4-iodobenzotrifluoride (54.0 mg, 0.20 mmol, 1.2 equiv) were dissolved in dry THF (1 mL). The previously prepared reagent solution was added to the resulting arylzinc species. The resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 95:5 and NEt_3) provided the title compound **18m** as a yellow oil (64 mg, 0.13 mmol, 65% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 (d, *J* = 8.1 Hz, 2H), 7.69 – 7.65 (m, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.01 – 6.97 (m, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.36 (t, *J* = 7.3 Hz, 2H), 1.77 – 1.69 (m, 2H), 1.50 – 1.40 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.85 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.7, 161.0, 160.1, 153.5, 136.7 – 136.6 (m), 134.6, 131.8 (q, *J* = 32.8 Hz), 130.0 (2C), 129.9, 129.5 (2C), 128.5, 125.8 (q, *J* = 3.8 Hz, 2C), 124.0 (q, *J* = 272.7 Hz), 114.3 (2C), 62.2, 55.5, 31.0, 30.8, 22.3, 13.8, 13.6.

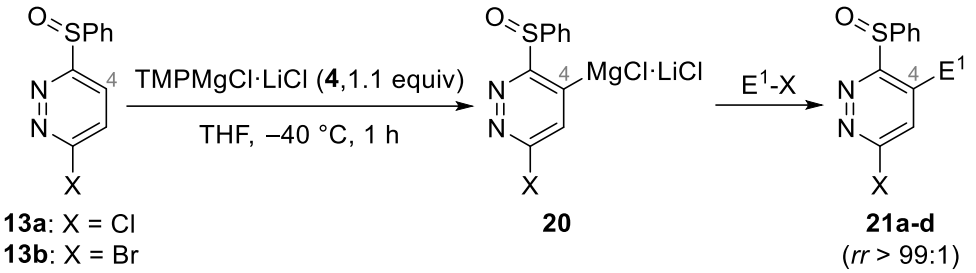
[185] M. Rottländer, P. Knochel, *Synlett* **1997**, *1997*, 1084.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2962, 1727, 1608, 1520, 1508, 1465, 1457, 1423, 1402, 1383, 1366, 1321, 1306, 1296, 1248, 1212, 1204, 1192, 1174, 1165, 1129, 1109, 1087, 1064, 1037, 1027, 1020, 1012, 918, 865, 858, 839, 830, 818, 808, 803, 793, 778, 764, 732.

MS (EI, 70 eV): *m/z* (%) = 448 (21), 443 (13), 435 (13), 434 (64); 433 (100), 430 (11), 429 (11), 405 (45), 317 (11), 289 (10), 225 (13), 176 (13), 135 (25), 132 (23), 43 (11).

HRMS (EI): *m/z*: [M] calc. for [$C_{25}H_{25}F_3N_2O_3S$]:490.1538; found 490.1530.

9. REGIOSELECTIVE METALATION AT POSITION 4 OF SULFOXIDES OF TYPE 13

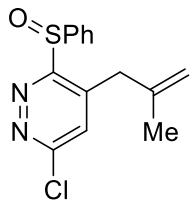


Scheme 63. Regioselective magnesiation of pyridazine of type **13** with TMPMgCl·LiCl (**4**) and subsequent electrophile quench at position 4.

General procedure for the magnesiation of pyridazines of type 13 using TMPMgCl·LiCl (TP8):

A dry and argon flushed flask, equipped with a magnetic stirrer and a septum, was charged with a solution of the corresponding pyridazine **13a-b** (0.5 mmol, 1.0 equiv) in dry THF (1 mL). Then, TMPMgCl·LiCl (**4**, 0.55 mmol, 1.1 equiv) was added dropwise at –40 °C. After 1 h, the completion of the metalation was monitored by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

6-Chloro-4-(2-methylallyl)-3-(phenylsulfinyl)pyridazine (21a)



According to **TP8,** 3-chloro-6-(phenylsulfinyl)pyridazine (**13a**, 119 mg, 0.5 mmol, 1.0 equiv) in THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –40 °C. The reaction mixture was stirred at this temperature for 1 h. Methallyl bromide (81 mg, 0.6 mmol, 1.2 equiv) and CuCN·2LiCl[186] (1.00 M solution in THF, 0.05 mL, 0.05 mmol, 10 mol%) were added and the resulting mixture was stirred for 12 h at –40 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 85:15) provided the title compound **21a** as a colourless oil (49 mg, 0.17 mmol, 34% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 – 7.71 (m, 2H), 7.50 – 7.46 (m, 3H,), 7.39 (s, 1H), 4.94 (s, 1H), 4.55 (s, 1H), 3.83 (d, *J* = 16.5 Hz, 1H), 3.53 (d, *J* = 16.5 Hz, 1H), 1.56 (s, 3H).

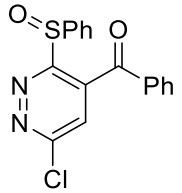
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.3, 158.5, 143.9, 142.0, 140.5, 131.5**,** 130.6, 129.5 (2C), 125.0 (2C), 116.2, 36.0, 22.3.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1650, 1553, 1475, 1443, 1419, 1361, 1319, 1292, 1204, 1135, 1083, 1053, 1021, 997, 914, 900, 898, 766, 747, 726, 694, 686, 667.

MS (EI, 70 eV): *m/z* (%) = 207 (229, 167 (21), 125 (44), 109 (16), 104 (19), 97 (61), 91 (16), 78 (36), 77 (100), 73 (17), 65 (20).

HRMS (EI): *m/z*: [M-H$^+$] calc. for [$C_{14}H_{12}ClN_2OS^-$]: 291.0364 found; 291.0341.

(6-Chloro-3-(phenylsulfinyl)pyridazin-4-yl)(phenyl)methanone (21b)



According to **TP8,** 3-chloro-6-(phenylsulfinyl)pyridazine (**13a**, 119 mg, 0.5 mmol, 1.0 equiv) in THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –40 °C. The reaction mixture was stirred at this temperature for 1 h.

[186] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

$CuCN \cdot 2LiCl$[187] (1.00 M solution in THF, 0.05 mL, 0.05 mmol, 10 mol%) was added and the reaction mixture was stirred for 15 min. Then, benzoyl chloride (0.07 mL, 0.6 mmol, 1.2 equiv) was added. The resulting mixture was stirred for 12 h at –40 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 80:20) provided the title compound **21b** as a white solid (72 mg, 0.21 mmol, 42% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm =7.79 – 7.76 (m, 2H), 7.74 – 7.70 (m, 2H), 7.69 – 7.64 (m, 1H), 7.53 – 7.50 (m, 2H), 7.49 – 7.46 (m, 3H), 7.44 (s, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 189.4, 166.9, 157.8, 141.8, 139.3, 135.7, 134.8, 132.0, 129.9 (2C), 129.6 (2C), 129.1 (2C), 127.9, 125.4 (2C).

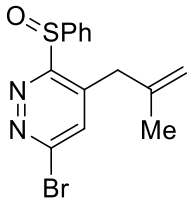
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1678, 1449, 1444, 1321, 1307, 1258, 1144, 1085, 1055, 822, 747, 709, 700, 688, 686.

MS (EI, 70 eV): *m/z* (%) = 325 (17), 251 (33), 249 (89), 125 (68), 105 (79), 97 (21), 78 (13), 77 (100), 51 (29).

HRMS (EI): *m/z*: [M] calc. for $[C_{17}H_{11}ClN_2O_2S]$: 342.0230 found; 342.0222.

m. p. (°C): 196.

6-Bromo-4-(2-methylallyl)-3-(phenylsulfinyl)pyridazine (21c)



According to **TP8,** 3-bromo-6-(phenylsulfinyl)pyridazine (**13b**, 142 mg, 0.5 mmol, 1.0 equiv) in THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –40 °C. The reaction mixture was stirred at this temperature for 1 h.

[187] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

Methallyl bromide (81 mg, 0.6 mmol, 1.2 equiv) and CuCN·2LiCl[188] (1.00 M solution in THF, 0.05 mL, 0.05 mmol, 10 mol%) were added and the resulting mixture was stirred for 12 h at –40 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 85:15) provided the title compound **21c** as a colourless oil (57 mg, 0.17 mmol, 33% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.74 – 7.70 (m, 2H), 7.53 (s, 1H), 7.51 – 7.46 (m, 3H), 4.94 (s, 1H), 4.55 (s, 1H), 3.81 (d, *J* = 16.5 Hz, 1H), 3.51 (d, *J* = 16.5 Hz, 1H), 1.57 (s, 3H).

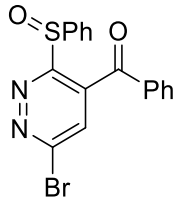
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.6, 150.0, 143.4, 141.9, 140.5, 134.0, 131.5, 129.5 (2C), 125.0 (2C), 116.2, 36.0, 22.3.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1665, 1662, 1659, 1652, 1545, 1475, 1443, 1358, 1316, 1127, 1082, 1053, 1023, 903, 748, 732, 728, 693, 688.

MS (EI, 70 eV): *m/z* (%) = 321 (88), 319 (70), 213 (94), 211 (97), 125 (78), 105 (38), 78 (53), 77 (100), 51 (43).

HRMS (EI): *m/z*: [M-H$^+$] calc. for [$C_{14}H_{12}BrN_2OS^-$]: 334.9859 found; 334.9851.

(6-Bromo-3-(phenylsulfinyl)pyridazin-4-yl)(phenyl)methanone (21d)



According to **TP8,** 3-bromo-6-(phenylsulfinyl)pyridazine (**13b**, 142 mg, 0.5 mmol, 1.0 equiv) in THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –40 °C. The reaction mixture was stirred at this temperature for 1 h. CuCN·2LiCl[189] (1.00 M solution in THF, 0.05 mL, 0.05 mmol, 10 mol%) was added and the reaction mixture was stirred for 15 min. Then, benzoyl chloride (0.07 mL, 0.6 mmol, 1.2 equiv)

[188] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.
[189] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; F. Dübner, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 379.

was added. The resulting mixture was stirred for 12 h at –40 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 80:20) provided the title compound **21d** as a white solid (85 mg, 0.22 mmol, 44% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.79 – 7.75 (m, 2H), 7.73 – 7.64 (m, 3H), 7.58 (s, 1H), 7.53 – 7.47 (m, 5H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 189.3, 167.2, 149.1, 141.7, 138.8, 135.8, 134.8, 132.0, 131.1, 129.9 (2C), 129.5 (2C), 129.1 (2C), 125.4 (2C).

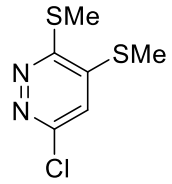
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1668, 1652, 1594, 1584, 1475, 1449, 1443, 1347, 1325, 1321, 1306, 1261, 1253, 1138, 1081, 1070, 1054, 1040, 1023, 998, 957, 911, 904, 811, 793, 760, 749, 743, 707, 699, 691, 684.

MS (EI, 70 eV): *m/z* (%) = 295 (64), 293 (63), 186 (17), 125 (69), 105 (97), 97 (20), 78 (11), 77 (100), 51 (29).

HRMS (EI): *m/z*: [M] calc. for [$C_{17}H_{11}BrN_2O_2S$]: 385.9725 found; 385.9721.

m. p. (°C): 195.

6-Chloro-3,4-*bis*(methylthio)pyridazine (9a)



According to **TP8,** 3-chloro-6-(phenylsulfinyl)pyridazine (**13a**, 119 mg, 0.5 mmol, 1.0 equiv) in THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –40 °C. The reaction mixture was stirred at this temperature for 1 h. Then, dimethyl disulphide (0.07 mL, 0.75 mmol, 1.5 equiv) was added. The resulting mixture was stirred for 12 h at –40 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10) provided the title compound **9a** as a white solid (79 mg, 0.38 mmol, 76% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 6.96 (s, 1H), 2.74 (s, 3H), 2.53 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.0, 152.8, 144.6, 119.2, 14.0, 14.0.

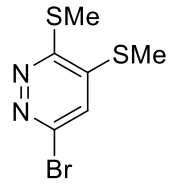
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1531, 1487, 1338, 1334, 1306, 1135, 861, 844.

MS (EI, 70 eV): *m/z* (%) = 206 (5), 193 (41), 192 (5), 191 (100), 173 (4), 156 (4), 148 (4), 119 (9), 116 (4), 103 (5).

HRMS (EI): *m/z*: [M] calc. for [$C_6H_7ClN_2S_2$]: 205.9739 found; 205.9733.

m. p. (°C): 123.

6-Bromo-3,4-*bis*(methylthio)pyridazine (9b)



According to **TP8,** 3-bromo-6-(phenylsulfinyl)pyridazine (**13b**, 142 mg, 0.5 mmol, 1.0 equiv) in THF (1 mL) was treated with a solution of TMPMgCl·LiCl (**4**, 1.03 M in THF, 0.5 mL, 0.55 mmol, 1.1 equiv) at –40 °C. The reaction mixture was stirred at this temperature for 1 h. Then, dimethyl disulphide (0.07 mL, 0.75 mmol, 1.5 equiv) was added. The resulting mixture was stirred for 12 h at –40 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10) provided the title compound **9b** as a yellow solid (63 mg, 0.25 mmol, 50% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.07 (s, 1H), 2.71 (s, 3H), 2.52 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.3, 144.3, 143.6, 122.1, 14.0, 13.9.

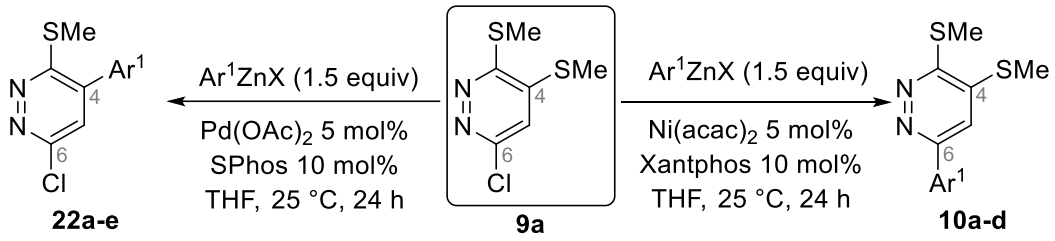
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1517, 1482, 1429, 1335, 1304, 1129, 1077, 904, 862, 822, 723.

MS (EI, 70 eV): *m/z* (%) = 239 (8), 237 (100), 235 (95), 156 (16), 128 (19), 127 (7), 103 (7), 84 (7).

HRMS (EI): *m/z*: [M] calc. for [$C_6H_7BrN_2S_2$]: 249.9234 found; 249.9229.

m. p. (°C): 114.

10. SELECTIVE PREPARATION OF TRIS-ARYLATED PYRIDAZINES OF TYPE 12



Scheme 64. Regioselective Negishi cross-couplings with Ar^1ZnX at position 4 or 6 depending on the nature of the catalytic system (Pd or Ni).

General procedure for the cross-coupling of the butylthio substituent[190] of pyridazines 9a and 10a-c (TP9):

A dry and argon flushed flask, equipped with a magnetic stirrer and a septum, was charged with the corresponding pyridazine **9a** or **10a-c** (0.5 mmol, 1.0 equiv) in dry THF (1 mL), $Pd(AOc)_2$ (5 mol%) and SPhos[191] (10 mol%). The arylzinc halide Ar^1ZnX (0.75 mmol, 1.5 equiv) was added dropwise at 25 °C. After 24 h, the completion of the cross-coupling was monitored by GC-analysis of reaction aliquots quenched with a sat. aq. NH_4Cl solution.

General procedure for the cross-coupling of the chlorine substituent of pyridazine 9a (TP10):

A dry and argon flushed flask, equipped with a magnetic stirrer and a septum, was charged with the corresponding pyridazine **9a** (0.5 mmol, 1.0 equiv) in dry THF (1 mL), $Ni(acac)_2$ (5 mol%) and Xantphos[192] (10 mol%). The arylzinc halide Ar^1ZnX (0.75 mmol, 1.5 equiv) was added dropwise at 25 °C. After 24 h, the completion of the cross-coupling was monitored by GC-analysis of reaction aliquots quenched with sat. aq. NH_4Cl solution.

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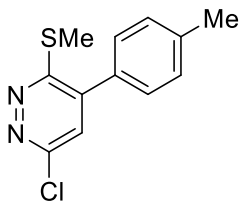
6-Chloro-3-(methylthio)-4-(*p*-tolyl)pyridazine (22a)



According to **TP9,** 6-chloro-3,4-*bis*(methylthio)pyridazine (**9a**, 103 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Another dry and argon flushed flask was charged with *p*-tolylmagnesium bromide (0.79 M in THF, 0.95 mL, 0.75 mmol, 1.5 equiv) then $ZnCl_2$ (1.00 M in THF, 0.83 mL, 0.83 mmol) was added dropwise at 0 °C and stirred for 30 min. The resulting arylzinc species was added dropwise to the solution of **9a**. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10) provided the title compound **22a** as a white solid (65 mg, 0.26 mmol, 52% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.36 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.18 (s, 1H), 2.65 (s, 3H), 2.43 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.4, 153.8, 142.0, 140.5, 131.1, 129.8 (2C), 128.5 (2C), 126.2, 21.6, 14.3.

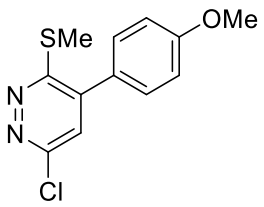
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3030, 2926, 2854, 1611, 1558, 1510, 1428, 1341, 1329, 1309, 1272, 1227, 1188, 1139, 1044, 898, 852, 818, 786, 721.

MS (EI, 70 eV): *m/z* (%) = 251 (35), 250 (40), 249 (100), 237 (30), 235 (88), 219 (22), 217 (71), 202 (23), 171 (23), 163 (31), 147 (27), 142 (29), 140 (23), 115 (52).

HRMS (EI): *m/z*: [M] calc. for $[C_{12}H_{11}ClN_2S]$: 250.0331; found 250.0330.

m. p. (°C): 117.

6-Chloro-4-(4-methoxyphenyl)-3-(methylthio)pyridazine (22b)



According to **TP9,** 6-chloro-3,4-*bis*(methylthio)pyridazine (**9a**, 103 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Another dry and argon flushed flask was charged with (4-methoxyphenyl)magnesium bromide (0.93 M in THF, 0.81 mL, 0.75 mmol, 1.5 equiv) then $ZnCl_2$ (1.00 M in THF, 0.83 mL, 0.83 mmol) was added dropwise at 0 °C and stirred for 30 min. The resulting arylzinc species was added dropwise to the solution of **9a**. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5) provided the title compound **22b** as a white solid (67 mg, 0.25 mmol, 50% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.45 – 7.41 (m, 2H), 7.26 (s, 1H), 7.03 – 6.99 (m, 2H), 3.87 (s, 3H), 2.66 (s, 3H).

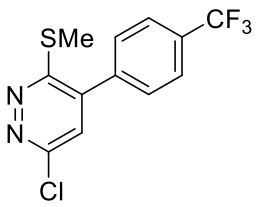
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.4, 161.1, 153.7, 141.8, 130.1 (2C), 126.2, 126.0, 114.5 (2C), 55.6, 14.4.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3044, 3005, 2958, 2930, 2838, 1607, 1576, 1557, 1511, 1460, 1442, 1387, 1343, 1331, 1311, 1288, 1254, 1181, 1139, 1116, 1048, 1027, 853, 833, 685.

MS (EI, 70 eV): *m/z* (%) = 267 (36), 266 (48), 265 (100), 253 (20), 251 (59), 233 (57), 218 (22), 179 (21), 173 (24), 163 (29), 158 (47), 114 (23).

HRMS (EI): *m/z*: [M] calc. for [$C_{12}H_{11}ClN_2OS$]: 266.0281; found 266.0278.

6-Chloro-3-(methylthio)-4-(4-(trifluoromethyl)phenyl)pyridazine (22c)



According to **TP9,** 6-chloro-3,4-*bis*(methylthio)pyridazine (**9a**, 103 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Then, (4-(trifluoromethyl)phenyl)zinc chloride solution (0.39 M in THF, 1.9 mL, 0.75 mmol, 1.5 equiv) was added dropwise. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5 → 90:10) provided the title compound **22c** as a white solid (72 mg, 0.24 mmol, 47% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.77 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H), 7.20 (s, 1H), 2.67 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 160.9, 153.8, 140.3, 137.6 – 137.5 (m), 132.2 (q, J = 33.0 Hz), 129.1 (2C), 126.3, 126.1 (q, J = 3.7 Hz, 2C), 123.8 (q, J = 272.1 Hz), 14.2.

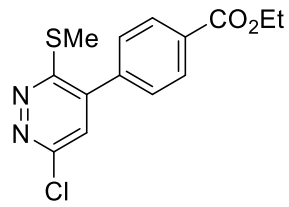
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3036, 2936, 2854, 1620, 1566, 1408, 1343, 1324, 1285, 1249, 1179, 1143, 1119, 1109, 1069, 1040, 1019, 971, 931, 908, 849, 837, 774, 764, 733.

MS (EI, 70 eV): *m/z* (%) = 306 (23), 305 (33), 304 (63), 303 (100), 289 (20), 273 (14), 271 (44), 270 (17), 269 (11), 217 (29), 203 (44), 201 (18), 182 (13), 176 (18), 157 (22).

HRMS (EI): *m/z*: [M] calc. for $[C_{12}H_8ClF_3N_2S]$: 304.0049; found 304.0052.

m. p. (°C): 148.

Ethyl 4-(6-chloro-3-(methylthio)pyridazin-4-yl)benzoate (22d)



According to **TP9,** 6-chloro-3,4-*bis*(methylthio)pyridazine (**9a**, 103 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Then, (4-(ethoxycarbonyl)phenyl)zinc chloride solution (0.30 M in THF, 2.5 mL, 0.75 mmol, 1.5 equiv) was added dropwise. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5 → 90:10) provided the title compound **22d** as a beige solid (48 mg, 0.16 mmol, 32% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.19 – 8.14 (m, 2H), 7.56 – 7.51 (m, 2H), 7.20 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.66 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 165.8, 160.9, 153.7, 140.8, 138.2, 132.0, 130.2 (2C), 128.7 (2C), 126.2, 61.5, 14.4, 14.2.

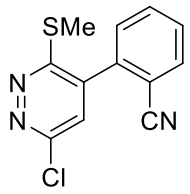
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3047, 2984, 2928, 1707, 1610, 1572, 1558, 1480, 1406, 1366, 1340, 1329, 1313, 1277, 1184, 1141, 1126, 1103, 1044, 1020, 964, 922, 859, 838, 775, 754, 727, 704.

MS (EI, 70 eV): *m/z* (%) = 310 (17), 309 (28), 308 (47), 307 (80), 281 (33), 279 (100), 275 (23), 265 (16), 263 (19), 247 (21), 246 (16), 237 (21), 235 (62), 229 (18), 202 (47), 181(32), 132 (17).

HRMS (EI): *m/z*: [M] calc. for $[C_{14}H_{13}ClN_2O_2S]$: 308.0386; found 308.0386.

m. p. (°C): 136.

2-(6-Chloro-3-(methylthio)pyridazin-4-yl)benzonitrile (22e)



According to **TP9,** 6-chloro-3,4-*bis*(methylthio)pyridazine (**9a**, 103 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Then, (2-cyanophenyl)zinc chloride solution (0.30 M in THF, 2.5 mL, 0.75 mmol, 1.5 equiv) was added dropwise. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5 → 90:10) provided the title compound **22e** as a brown solid (40 mg, 0.16 mmol, 31% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.85 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.74 (td, *J* = 7.7, 1.4 Hz, 1H), 7.63 (td, *J* = 7.7, 1.3 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.26 (s, 1H), 2.68 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.2, 153.6, 137.9, 137.1, 133.9, 133.2, 130.5, 129.9, 126.9, 116.7, 112.4, 14.1.

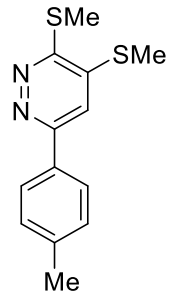
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 2928, 2854, 2229, 1598, 1565, 1482, 1444, 1429, 1381, 1339, 1329, 1314, 1282, 1234, 1190, 1140, 1050, 964, 910, 851, 769, 732, 693.

MS (EI, 70 eV): *m/z* (%) = 263 (36), 262 (12), 261 (100), 260 (25), 226 (11), 199 (16), 183 (15), 182 (34), 180 (36), 174 (20), 153 (33), 140 (15), 114 (17).

HRMS (EI): *m/z*: [M] calc. for [$C_{12}H_8ClN_3S$]: 261.0127; found 261.0123.

m. p. (°C): 150.

3,4-*Bis*(methylthio)-6-(*p*-tolyl)pyridazine (10a)



According to **TP10,** 6-chloro-3,4-*bis*(methylthio)pyridazine (**9a**, 103 mg, 0.5 mmol, 1.0 equiv), $Ni(acac)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and Xantphos (29 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Another dry and argon flushed flask was charged with *p*-tolylmagnesium bromide (0.79 M in THF, 0.95 mL, 0.75 mmol, 1.5 equiv) then $ZnCl_2$ (1.00 M in THF, 0.83 mL, 0.83 mmol) was added dropwise at 0°C and stirred for 30 min. The resulting arylzinc species was added dropwise to the solution of **9a**. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10) provided the title compound **10a** as a white solid (115 mg, 0.4 mmol, 80% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.95 – 7.90 (m, 2H), 7.32 – 7.28 (m, 3H), 2.80 (s, 3H), 2.57 (s, 3H), 2.41 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.9, 154.9, 142.2, 140.1, 133.3, 129.8 (2C), 126.8 (2C), 116.1, 21.5, 13.9, 13.8.

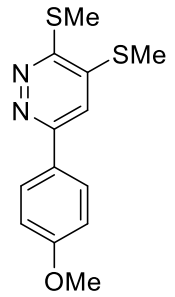
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3029, 2996, 2923, 2862, 1612, 1548, 1514, 1484, 1428, 1370, 1323, 1312, 1280, 1188, 1177, 1127, 1071, 1025, 962, 911, 875, 849, 819, 787, 729, 716, 687.

MS (EI, 70 eV): *m/z* (%) = 262 (10), 249 (09), 248 (12), 247 (100), 174 (06), 172 (18), 171 (19), 128 (08), 118 (07), 115 (09), 103 (13).

HRMS (EI): *m/z*: [M] calc. for [$C_{13}H_{14}N_2S_2$]: 262.0598; found 262.0591.

m. p. (°C): 101.

6-(4-Methoxyphenyl)-3,4-*bis*(methylthio)pyridazine (10b)



According to **TP10,** 6-chloro-3,4-*bis*(methylthio)pyridazine (**9a**, 103 mg, 0.5 mmol, 1.0 equiv), $Ni(acac)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and Xantphos (29 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Another dry and argon flushed flask was charged with (4-methoxyphenyl)magnesium bromide (0.93 M in THF, 0.81 mL, 0.75 mmol, 1.5 equiv) then $ZnCl_2$ (1.00 M in THF, 0.83 mL, 0.83 mmol) was added dropwise at 0 °C and stirred for 30 min. The resulting arylzinc species was added dropwise to the solution of **9a**. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10) provided the title compound **10b** as a white solid (72 mg, 0.26 mmol, 51% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 – 7.99 (m, 2H), 7.30 (s, 1H), 7.05 – 7.00 (m, 2H), 3.88 (s, 3H), 2.80 (s, 3H), 2.60 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.5, 157.7, 129.1, 128.6, 116.2, 114.8, 114.6 (4C), 55.6, 14.0 (2C).

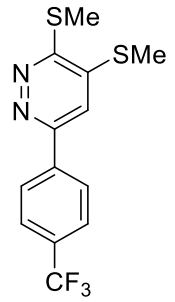
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3004, 2958, 2927, 2837, 1607, 1581, 1549, 1514, 1485, 1462, 1428, 1372, 1311, 1289, 1254, 1180, 1127, 1113, 1071, 1035, 962, 850, 834, 787, 730.

MS (EI, 70 eV): *m/z* (%) = 278 (14), 264 (12), 263 (100), 248 (09), 188 (20), 173 (27), 145 (14), 103 (12).

HRMS (EI): *m/z*: [M] calc. for $[C_{13}H_{14}N_2OS_2]$: 278.0548; found 278.0539.

m. p. (°C): 135

3,4-*Bis*(methylthio)-6-(4-(trifluoromethyl)phenyl)pyridazine (10c)



According to **TP10,** 6-chloro-3,4-*bis*(methylthio)pyridazine (**9a**, 103 mg, 0.5 mmol, 1.0 equiv), $Ni(acac)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and Xantphos (29 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Then, (4-(trifluoromethyl)phenyl)zinc chloride solution (0.39 M in THF, 1.9 mL, 0.75 mmol, 1.5 equiv) was added dropwise. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5 → 90:10) provided the title compound **10c** as a white solid (100 mg, 0.32 mmol, 63% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.33 (s, 1H), 2.81 (s, 3H), 2.60 (s, 3H).

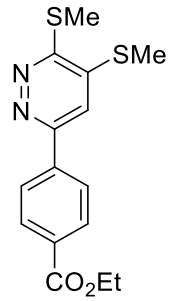
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 159.1, 153.7, 142.4, 140.1 – 139.6 (m), 131.6 (q, J = 32.6 Hz), 127.2 (2C), 126.0 (q, J = 3.8 Hz, 2C), 124.2 (q, J = 272.2 Hz), 116.1, 14.0, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 3000, 2927, 2854, 1617, 1583, 1547, 1487, 1431, 1407, 1371, 1321, 1311, 1288, 1249, 1163, 1120, 1109, 1067, 1022, 1015, 961, 911, 878, 843, 772, 733, 697, 678.

MS (EI, 70 eV): *m/z* (%) = 316 (11), 303 (09), 302 (12), 301 (100), 228 (06), 226 (12), 182 (05), 102 (09).

HRMS (EI): *m/z*: [M] calc. for [$C_{13}H_{11}F_3N_2S_2$]: 316.0316; found 316.0309.

Ethyl 4-(5,6-*bis*(methylthio)pyridazin-3-yl)benzoate (10d)



According to **TP10,** 6-chloro-3,4-*bis*(methylthio)pyridazine (**9a**, 103 mg, 0.5 mmol, 1.0 equiv), $Ni(acac)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and Xantphos (29 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Then, (4-(ethoxycarbonyl)phenyl)zinc chloride solution (0.30 M in THF, 2.5 mL, 0.75 mmol, 1.5 equiv) was added dropwise. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10 → 80:20) provided the title compound **10d** as a beige solid (82 mg, 0.26 mmol, 51% yield).

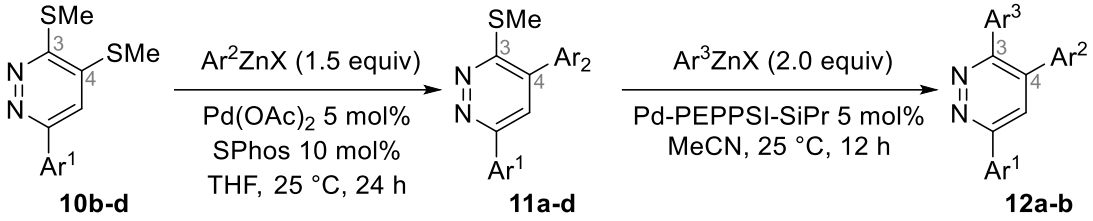
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.15 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.5 Hz, 2H), 7.34 (s, 1H), 4.40 (q, J = 7.1 Hz, 2H), 2.80 (s, 3H), 2.59 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.3, 158.9, 154.0, 142.3, 140.5, 131.5, 130.2 (2C), 126.7 (2C), 116.2, 61.3, 14.4, 14.0, 13.8.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2958, 2926, 2871, 2854, 1711, 1610, 1575, 1546, 1483, 1430, 1406, 1365, 1313, 1272, 1174, 1128, 1108, 1071, 1026, 961, 912, 856, 839, 776, 731, 699.

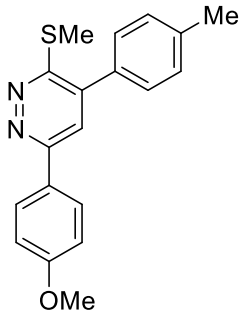
MS (EI, 70 eV): *m/z* (%) = 281 (42), 267 (11), 265 (10), 225 (23), 209 (10), 209 (12), 208 (13), 207 (100), 193 (10), 191 (19), 147 (14), 135 (18), 134 (22), 133 (12), 91 (15), 73 (20).

HRMS (EI): *m/z* calc. for [$C_{15}H_{16}N_2O_2S_2$]: 320.0653; found 320.1498.



Scheme 65. Regioselective preparation of *tris*-arylated pyridazines of type **12** via Pd-catalyzed Negishi cross-couplings with two different arylzinc halides (Ar^2ZnX and Ar^3ZnX).

6-(4-Methoxyphenyl)-3-(methylthio)-4-(*p*-tolyl)pyridazine (11a)



According to **TP9,** (6-(4-methoxyphenyl)-3,4-*bis*(methylthio)pyridazine (**10b**, 139 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Another dry and argon flushed flask was charged with *p*-tolylmagnesium bromide (0.79 M in THF, 0.81 mL, 0.75 mmol, 1.5 equiv) then $ZnCl_2$ (1.00 M in THF, 0.83 mL, 0.83 mmol) was added dropwise at 0 °C and stirred for 30 min. The resulting arylzinc species was added dropwise to the solution of **10b**. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10) provided the title compound **11a** as a beige solid (92 mg, 0.29 mmol, 57% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.10 – 8.05 (m, 2H), 7.52 (s, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.06 – 7.01 (m, 2H), 3.88 (s, 3H), 2.72 (s, 3H), 2.45 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.5, 159.8, 155.5, 140.0, 132.6, 129.7 (2C), 128.6 (2C), 128.4 (4C), 122.6, 114.6 (2C), 55.6, 21.6, 14.3.

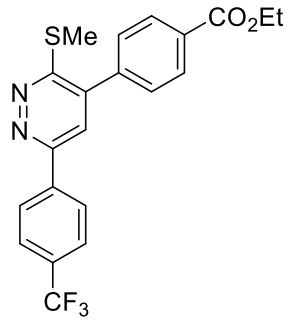
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2957, 2950, 2925, 2897, 2862, 2856, 2837, 1608, 1580, 1514, 1496, 1456, 1429, 1405, 1380, 1349, 1310, 1296, 1254, 1210, 1177, 1147, 1114, 1035, 835, 819.

MS (EI, 70 eV): *m/z* (%) = 323 (26), 322 (100), 321 (61), 307 (15), 289 (18), 288 (10), 235 (08), 162 (11), 147 (19).

HRMS (EI): *m/z*: [M] calc. for [$C_{19}H_{18}N_2OS$]: 322.1140; found 322.1134.

m. p. (°C): 175

Ethyl 4-(3-(methylthio)-6-(4-(trifluoromethyl)phenyl)pyridazin-4-yl)benzoate (11b)



According to **TP9,** 3,4-*bis*(methylthio)-6-(4-(trifluoromethyl)phenyl)pyridazine (**10c**, 158 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Then, (4-(ethoxycarbonyl)phenyl)zinc chloride solution (0.30 M in THF, 2.5 mL, 0.75 mmol, 1.5 equiv) was added dropwise. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5 → 90:10) provided the title compound **11b** as a yellow solid (96 mg, 0.23 mmol, 46% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.2 – 8.2 (m, 4H), 7.8 (d, *J* = 8.3 Hz, 2H), 7.6 – 7.6 (m, 3H), 4.4 (q, *J* = 7.1 Hz, 2H), 2.8 (s, 3H), 1.4 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.0, 160.8, 154.8, 139.5, 139.4 – 139.3 (m), 139.1, 131.8 (q, *J* = 32.6 Hz), 131.7, 130.2 (2C), 128.8 (2C), 127.0 (2C), 126.1 (q, *J* = 3.7 Hz, 2C), 124.1 (q, *J* = 272.5 Hz), 122.7, 61.5, 14.5, 14.2.

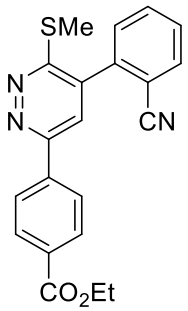
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2984, 2930, 1714, 1616, 1582, 1570, 1464, 1448, 1430, 1412, 1382, 1368, 1324, 1312, 1272, 1166, 1122, 1110, 1068, 1046, 1016, 912, 846, 776, 732, 706, 686.

MS (EI, 70 eV): *m/z* (%) = 419 (22), 418 (100), 417 (94), 390 (16), 389 (81), 385 (22), 375 (15), 357 (20), 356 (15), 345 (26), 312 (31), 175 (33), 132 (19).

HRMS (EI): *m/z*: [M] calc. for [$C_{21}H_{17}F_3N_2O_2S$]: 418.0963; found 418.0959.

m. p. (°C): 125.

Ethyl 4-(5-(2-cyanophenyl)-6-(methylthio)pyridazin-3-yl)benzoate (11c)



According to **TP9,** ethyl 4-(5,6-*bis*(methylthio)pyridazin-3-yl)benzoate (**10d**, 160 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Then, (2-cyanophenyl)zinc chloride solution (0.30 M in THF, 2.5 mL, 0.75 mmol, 1.5 equiv) was added dropwise. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 80:20 → 70:30) provided the title compound **11c** as a white solid (96 mg, 0.26 mmol, 51% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.20 – 8.15 (m, 4H), 7.87 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.67 (s, 1H), 7.64 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.61 – 7.57 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.77 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.3, 160.7, 155.1, 139.8, 138.5, 136.1, 133.9, 133.1, 131.8, 130.4 (2C), 130.2, 130.1, 126.8 (2C), 123.5, 117.1, 112.5, 61.4, 14.5, 14.1.

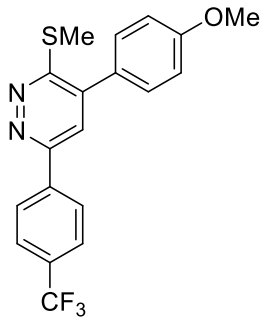
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2988, 2928, 2852, 2258, 2226, 1708, 1698, 1612, 1598, 1578, 1482, 1474, 1456, 1444, 1436, 1412, 1384, 1366, 1352, 1324, 1276, 1224, 1190, 1182, 1152, 1138, 1126, 1108, 1024, 970, 918, 902, 876, 860, 780, 768, 758, 730, 702, 686.

MS (EI, 70 eV): *m/z* (%) = 376 (12), 375 (56), 348 (19), 347 (100), 346 (15), 330 (06), 214 (08), 172 (08), 140 (25), 114 (10).

HRMS (EI): *m/z*: [M] calc. for [$C_{21}H_{17}N_3O_2S$]: 375.1041; found 375.1038.

m. p. (°C): 202.

4-(4-methoxyphenyl)-3-(methylthio)-6-(4-(trifluoromethyl)phenyl)pyridazine (11d)



According to **TP9,** 3,4-*bis*(methylthio)-6-(4-(trifluoromethyl)phenyl)pyridazine (**10c**, 158 mg, 0.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.0 mg, 0.025 mmol, 5 mol%) and SPhos (21 mg, 0.05 mmol, 10 mol%) were dissolved in dry THF (1 mL). Another dry and argon flushed flask was charged with (4-methoxyphenyl)magnesium bromide (0.93 M in THF, 0.81 mL, 0.75 mmol, 1.5 equiv) then $ZnCl_2$ (1.00 M in THF, 0.83 mL, 0.83 mmol) was added dropwise at 0 °C and stirred for 30 min. The resulting arylzinc species was added dropwise to the solution of **10c**. The resulting mixture was stirred for 24 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 95:5 → 90:10) provided the title compound **11d** as a yellow solid (94 mg, 0.25 mmol, 50% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.26 – 8.17 (m, 2H), 7.81 – 7.73 (m, 2H), 7.57 (s, 1H), 7.53 – 7.44 (m, 2H), 7.09 – 7.01 (m, 2H), 3.89 (s, 3H), 2.75 (s, 3H).

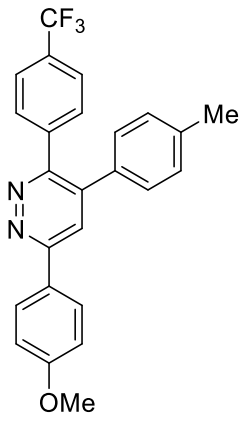
^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.3, 160.9, 154.8, 139.9, 139.8 – 139.6 (m), 131.7 (q, *J* = 32.6 Hz), 130.1 (2C), 127.4, 127.0 (2C), 126.1 (q, *J* = 3.7 Hz, 2C), 124.1 (q, *J* = 272.5 Hz), 122.7, 114.5 (2C), 55.6, 14.3.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2960, 2930, 2840, 1610, 1575, 1513, 1463, 1443, 1410, 1382, 1325, 1314, 1295, 1254, 1214, 1179, 1167, 1144, 1125, 1112, 1069, 1018, 848, 832, 702, 680.

MS (EI, 70 eV): *m/z* (%) = 377 (17), 376 (89), 375 (100), 362 (10), 361 (50), 343 (38), 342 (19), 341 (12), 163 (33).

HRMS (EI): *m/z*: [M] calc. for [$C_{19}H_{15}F_3N_2OS$]: 376.0857; found 376.0849.

6-(4-Methoxyphenyl)-4-(*p*-tolyl)-3-(4-(trifluoromethyl)phenyl)pyridazine (12a)



6-(4-Methoxyphenyl)-3-(methylthio)-4-(*p*-tolyl)pyridazine (**11a**, 161 mg, 0.5 mmol, 1.0 equiv) and Pd-PEPPSI-SiPr[193] (17 mg, 0.025 mmol, 5 mol%) were dissolved in dry MeCN (1 mL). Then, (4-(trifluoromethyl)phenyl)zinc chloride solution (0.39 M in THF, 2.6 mL, 1.0 mmol, 2.0 equiv) was added dropwise. The resulting mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10) provided the title compound **12a** as a beige solid (183 mg, 0.44 mmol, 87% yield).

[193] C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* **2010**, *2010*, 4343; S. Otsuka, D. Fujino, K. Murakami, H. Yorimitsu, A. Osuka, *Chem. Eur. J.* **2014**, *20*, 13146.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.18 – 8.13 (m, 2H), 7.80 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.15 – 7.11 (m, 2H), 7.09 – 7.04 (m, 2H), 3.89 (s, 3H), 2.39 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.6, 157.8, 156.5, 140.8 – 140.7 (m), 139.8, 139.3, 133.8, 130.5 (q, *J* = 32.4 Hz), 130.4 (2C), 129.8 (2C), 129.0 (2C), 128.6 (2C), 128.4, 125.2 (q, *J* = 3.8 Hz, 2C), 124.2 (q, *J* = 272.8 Hz), 124.2, 114.6 (2C), 55.6, 21.4.

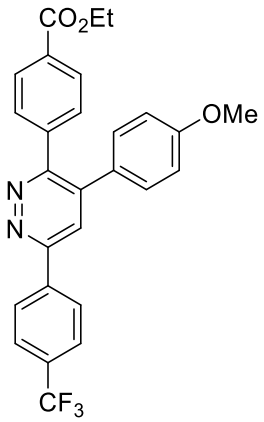
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2958, 2925, 2841, 1607, 1582, 1512, 1464, 1412, 1391, 1323, 1254, 1175, 1167, 1124, 1110, 1083, 1066, 1040, 1030, 1018, 910, 848, 836, 821, 733, 704.

MS (EI, 70 eV): *m/z* (%) = 421 (24), 420 (100), 419 (96), 405 (29), 281 (21), 261 (15); 260 (59), 259 (17), 207 (54), 189 (15), 132 (71), 69 (16), 44 (79), 43 (23).

HRMS (EI): *m/z*: [M] calc. for [$C_{25}H_{19}F_3N_2O$]: 420.1449; found 420.1446.

m. p. (°C): 146.

Ethyl 4-(4-(4-methoxyphenyl)-6-(4-(trifluoromethyl)phenyl)pyridazin-3-yl)benzoate (12b)



4-(4-Methoxyphenyl)-3-(methylthio)-6-(4-(trifluoromethyl)phenyl)pyridazine (**11d**, 188 mg, 0.5 mmol, 1.0 equiv) and Pd-PEPPSI-SiPr[194] (17 mg, 0.025 mmol, 5 mol%) were dissolved in dry MeCN (1 mL). Then, (4-(ethoxycarbonyl)phenyl)zinc chloride solution (0.30 M in THF, 3.3 mL, 1.0 mmol, 2.0 equiv) was added dropwise. The resulting mixture was stirred for 12 h

[194] C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* **2010**, *2010*, 4343; S. Otsuka, D. Fujino, K. Murakami, H. Yorimitsu, A. Osuka, *Chem. Eur. J.* **2014**, *20*, 13146.

at 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate, 90:10 → 80:20) provided the title compound **12b** as a yellow solid (145 mg, 0.31 mmol, 61% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.31 (d, *J* = 8.1 Hz, 2H), 8.03 – 7.99 (m, 2H), 7.88 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.61 – 7.57 (m, 2H), 7.20 – 7.15 (m, 2H), 6.90 – 6.85 (m, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.4, 160.5, 158.1, 156.8, 141.2, 139.7, 139.6 – 139.3 (m), 132.0 (q, *J* = 32.6 Hz), 130.7, 130.6 (2C), 130.1 (2C), 129.5 (2C), 128.4, 127.5 (2C), 126.1 (q, *J* = 3.8 Hz, 2C), 124.9, 124.1 (q, *J* = 272.5 Hz), 114.6 (2C), 61.3, 55.5, 14.4.

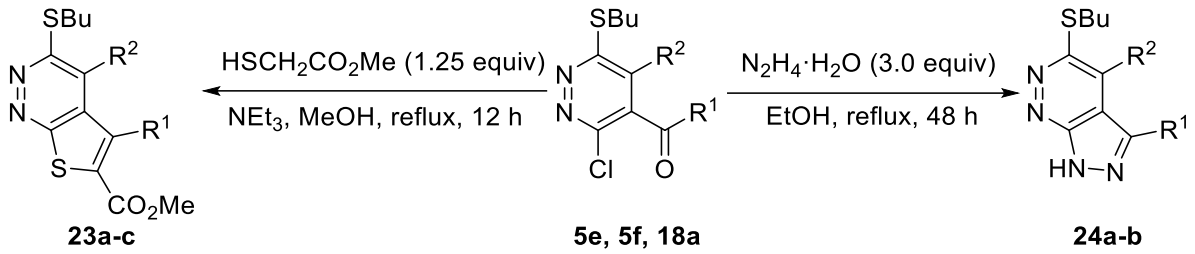
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2982, 2939, 2906, 2841, 2251, 1712, 1608, 1579, 1566, 1511, 1464, 1444, 1421, 1405, 1390, 1369, 1324, 1295, 1273, 1252, 1177, 1167, 1123, 1110, 1102, 1068, 1040, 1027, 1015, 909, 860, 848, 832, 799, 767, 730, 707, 666, 661.

MS (EI, 70 eV): *m/z* (%) = 478 (52), 477 (100), 449 (52), 447 (19), 280 (17), 252 (30), 237 (26), 235 (28), 209 (17), 164 (35), 163 (43), 132 (26).

HRMS (EI): *m/z*: [M-H$^+$] calc. for [$C_{27}H_{20}F_3N_2O_3^-$]: 477.1432; found 477.1421.

m. p. (°C): 156.

11. PREPARATION OF ANNELATED N-HETEROCYCLES



Scheme 66. Preparation of annelated N-heterocycles such as thieno[2,3-c]pyridazine **23** and 1*H*-pyrazolo[3,4-c]pyridazine **24** starting from pyridazines **5e**,**5f** and **18a**.

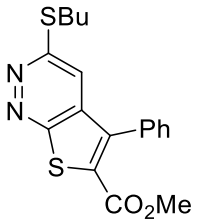
Preparation of thieno[2,3-c]pyridazines of type 23[195] (TP11):

A 50 mL round bottom flask, equipped with a magnetic stirrer was charged with a suspension of the corresponding pyridazine **5e-f** or **18a** (0.5 mmol, 1.0 equiv) in MeOH (5 mL). Then, $HSCH_2CO_2Me$[196] (0.625 mmol, 1.25 equiv) and NEt_3 (1.25 mmol, 2.5 equiv) were added in one portion. The resulting mixture was refluxed for 12 h. After cooling to 25 °C, DCM (25 mL) was added and the organic layer was washed with water (3 x 20 mL) and NaOH (2.00 M, 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate) provided the desired compound **23a-c** as yellow solids (80-87% yield).

Preparation of 1*H*-pyrazolo[3,4-c]pyridazines of type 24[195] (TP12):

A 50 mL round bottom flask, equipped with a magnetic stirrer was charged with a suspension of the corresponding pyridazine **5e-f** (0.5 mmol, 1.0 equiv) in EtOH (5 mL). Then, $N_2H_4 \cdot H_2O$[197] (1.5 mmol, 3.0 equiv) was added in one portion. The resulting mixture was refluxed for 2 days. After cooling to 25 °C, DCM (25 mL) was added and the organic layer was washed with water (3 x 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Purification by flash column chromatography (pentane/ethyl acetate) provided the desired compound **24a-b** as yellow solids (68-92% yield).

Methyl 3-(butylthio)-5-phenylthieno[2,3-c]pyridazine-6-carboxylate (23a)



According to **TP11**, (6-(butylthio)-3-chloropyridazin-4-yl)(phenyl)methanone (**5f**, 153 mg, 0.5 mmol, 1.0 equiv) was treated with $HSCH_2CO_2Me$ (0.06 mL, 0.625 mmol, 1.25 equiv) and NEt_3 (0.17 mL, 1.25 mmol, 2.5 equiv) in MeOH (5 mL). Purification by flash column

[195] S. Wunderlich, P. Knochel, *Chem. Commun.* **2008**, 6387.
[196] L. K. A. Rahman, R. M. Scrowston, *J. Chem. Soc., Perkin trans. 1* **1984**, 385.
[197] T. A. Eichhorn, S. Piesch, W. Ried, *Helv. Chim. Acta* **1988**, *71*, 988.

chromatography (pentane/ethyl acetate, 95:5) provided the title compound **23a** as a yellow solid (155 mg, 0.43 mmol, 86% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = δ 7.52 – 7.33 (m, 6H), 3.84 (s, 3H), 3.38 (t, *J* = 7.4 Hz, 2H), 1.81 – 1.67 (m, 2H), 1.56 – 1.33 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 162.0, 161.5, 158.1, 139.8, 135.5, 134.4, 131.9, 129.5 (2C), 129.2, 128.7 (2C), 120.4, 53.1, 31.4, 30.9, 22.2, 13.8.

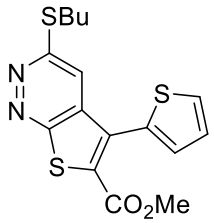
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1728, 1563, 1466, 1444, 1430, 1334, 1290, 1282, 1247, 1212, 1196, 1183, 1157, 1141, 1106, 1099, 1077, 1071, 1042, 937, 892, 845, 763, 735, 724, 694.

MS (EI, 70 eV): *m/z* (%) = 329 (22), 325 (7), 317 (7), 316 (44), 315 (22), 311 (33), 303 (13), 302 (100), 297 (8), 214 (14), 171 (14), 170 (20), 169 (10).

HRMS (EI): *m/z*: [M] calc. for [$C_{18}H_{18}N_2O_2S_2$]: 358.0810 found; 358.0802.

m. p. (°C): 89.

Methyl 3-(butylthio)-5-(thiophen-2-yl)thieno[2,3-c]pyridazine-6-carboxylate (23b)



According to **TP11**, (6-(butylthio)-3-chloropyridazin-4-yl)(thiophen-2yl)methanone (**5e**, 156 mg, 0.5 mmol, 1.0 equiv) was treated with $HSCH_2CO_2Me$ (0.06 mL, 0.625 mmol, 1.25 equiv) and NEt_3 (0.17 mL, 1.25 mmol, 2.5 equiv) in MeOH (5 mL). Purification by flash column chromatography (pentane/ethyl acetate, 95:5) provided the title compound **23b** as a yellow solid (148 mg, 0.40 mmol, 81% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.65 (s, 1H), 7.56 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.24 – 7.19 (m, 2H), 3.90 (s, 3H), 3.42 – 3.36 (m, 2H), 1.81 – 1.71 (m, 2H), 1.56 – 1.45 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 161.8, 160.9, 158.4, 135.6, 135.4, 131.8, 131.2, 129.7, 128.1, 127.5, 120.4, 53.2, 31.4, 30.9, 22.2, 13.8.

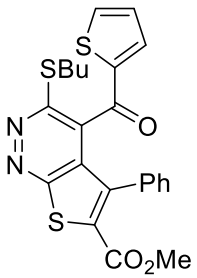
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 2955, 1728, 1564, 1449, 1435, 1335, 1277, 1251, 1212, 1172, 1159, 1143, 1099, 1081, 1067, 1040, 926, 884, 857, 839, 791, 766, 722, 680, 674.

MS (EI, 70 eV): *m/z* (%) = 335 (22), 322 (46), 321 (23), 317 (34), 310 (12), 308 (100), 221 (13), 220 (14), 207 (13), 177 (14), 176 (15).

HRMS (EI): *m/z*: [M] calc. for [$C_{16}H_{16}N_2O_2S_3$]: 364.0374 found; 364.0369.

m. p. (°C): 98.

Methyl 3-(butylthio)-5-phenyl-4-(thiophene-2-carbonyl)thieno[2,3-c]pyridazine-6-carboxylate (23c)



According to **TP11**, (5-benzoyl-3-(butylthio)-6-chloropyridazin-4-yl)(thiophen-2-yl) methanone (**18a**, 208 mg, 0.5 mmol, 1.0 equiv) was treated with $HSCH_2CO_2Me$ (0.06 mL, 0.625 mmol, 1.25 equiv) and NEt_3 (0.17 mL, 1.25 mmol, 2.5 equiv) in MeOH (5 mL). Purification by flash column chromatography (pentane/ethyl acetate, 90:10) provided the title compound **23c** as a yellow solid (203 mg, 0.43 mmol, 87% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.65 – 7.62 (m, 1H), 7.35 (s, 1H), 7.25 – 7.21 (m, 1H), 7.20 – 7.15 (m, 1H), 7.02 (dd, *J* = 3.8, 1.2 Hz, 1H), 6.97 (dd, *J* = 4.8, 3.9 Hz, 1H), 6.85 – 6.78 (m, 1H), 6.62 – 6.58 (m, 1H), 3.76 (s, 3H), 3.43 – 3.36 (m, 2H), 1.73 – 1.62 (m, 2H), 1.45 – 1.36 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 182.8, 161.6, 161.4, 154.5, 143.4, 139.9, 136.3, 136.1, 135.1, 131.7, 131.7, 130.8, 130.1, 129.7, 128.7, 128.2, 128.1, 127.0, 53.1, 31.8, 31.3, 22.1, 13.8.

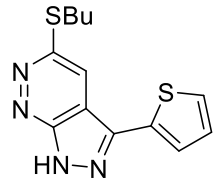
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1699, 1647, 1522, 1510, 1432, 1408, 1361, 1284, 1254, 1238, 1183, 1155, 1141, 1082, 1058, 987, 915, 867, 818, 769, 756, 733, 695, 683, 661.

MS (EI, 70 eV): *m/z* (%) = 412 (31), 393 (53), 383 (45), 369 (31), 365 (21), 357 (100), 300 (41), 269 (29), 169 (20), 111 (81), 97 (32).

HRMS (EI): *m/z*: [M] calc. for [$C_{23}H_{20}N_2O_3S_3$]: 468.0636 found; 468.0630.

m. p. (°C): 168.

5-(Butylthio)-3-(thiophen-2-yl)-1*H*-pyrazolo[3,4-c]pyridazine (24a)



According to **TP12**, (6-(butylthio)-3-chloropyridazin-4-yl)(thiophen-2-yl)methanone (**5e**, 156 mg, 0.5 mmol, 1.0 equiv) was treated with $N_2H_4 \cdot H_2O$ (0.07 mL, 1.5 mmol, 3.0 equiv) in EtOH (5 mL). Purification by flash column chromatography (pentane/ethyl acetate, 90:10) provided the title compound **24a** as a yellow solid (133 mg, 0.46 mmol, 92% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 12.00 (s, 1H), 8.02 (s, 1H), 7.65 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.46 – 7.43 (m, 1H), 7.20 (dd, *J* = 5.1, 3.6 Hz, 1H), 3.46 – 3.41 (m, 2H), 1.81 – 1.74 (m, 2H), 1.55 – 1.49 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 154.8, 154.3, 139.3, 134.0, 128.1, 126.7, 125.8, 118.7, 115.5, 32.1, 31.6, 22.2, 13.9.

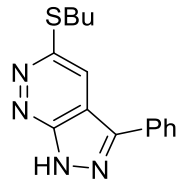
IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1422, 1289, 1125, 1062, 1047, 930, 848, 801, 741, 692.

MS (EI, 70 eV): *m/z* (%) = 290 (30), 261 (30), 257 (11), 249 (11), 248 (70), 247 (11), 243 (27), 235 (16), 234 (100), 230 (12), 146 (10), 52 (19).

HRMS (EI): *m/z*: [M] calc. for [$C_{13}H_{14}N_4S_2$]: 290.0660 found; 290.0656.

m. p. (°C): 164.

5-(Butylthio)-3-phenyl-1*H*-pyrazolo[3,4-c]pyridazine (24b)



According to **TP12**, (6-(butylthio)-3-chloropyridazin-4-yl)(phenyl)methanone (**5f**, 153 mg, 0.5 mmol, 1.0 equiv) was treated with $N_2H_4 \cdot H_2O$ (0.07 mL, 1.5 mmol, 3.0 equiv) in EtOH (5 mL). Purification by flash column chromatography (pentane/ethyl acetate, 85:15) provided the title compound **24b** as a yellow solid (97 mg, 0.34 mmol, 68% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 11.53 (s, 1H), 8.05 (s, 1H), 7.97 – 7.94 (m, 2H), 7.57 – 7.53 (m, 2H), 7.50 – 7.46 (m, 1H), 3.45 – 3.41 (m, 2H), 1.81 – 1.74 (m, 2H), 1.55 – 1.49 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 155.1, 154.2, 143.9, 131.8, 129.4, 129.4 (2C), 127.1 (2C), 118.9, 115.8, 32.1, 31.6, 22.2, 13.9.

IR (Diamond-Atr, neat): $\tilde{\nu}$ / cm^{-1} = 1459, 1392, 1138, 1068, 932, 800, 752, 679.

MS (EI, 70 eV): *m/z* (%) = 255 (27), 242 (77), 241(25), 237 (42), 228 (100), 224 (15), 168 (20), 140 (21).

HRMS (EI): *m/z*: [M] calc. for [$C_{15}H_{16}N_4S$]: 284.1096 found; 284.1090.

m. p. (°C): 156.

12. SINGLE CRYSTAL X-RAY DIFFRACTION STUDIES

(6-(Butylthio)-3-chloropyridazin-4-yl)(cyclobutyl)(phenyl)methanol (5k)

Single crystals of compound **5k**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM 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 and data reduction were performed with the CrysAlisPro software.[198] Absorption correction using the multiscan method[198] was applied. The structures were solved with SHELXS-97,[199] refined with SHELXL-97[200] and finally checked using PLATON.[201] Details for data collection and structure refinement are summarized in Table 5.

CCDC-2267441 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[198] Program package 'CrysAlisPro 1.171.40.82a (Rigaku OD, 2020)'.
[199] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[200] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[201] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 5. Details for X-ray data collection and structure refinement for compound **5k**.

	5k
Empirical formula	$C_{19}H_{23}ClN_2OS$
Formula mass	362.90
T[K]	123(2)
Crystal size [mm]	0.35 × 0.20 × 0.15
Crystal description	colorless block
Crystal system	orthorhombic
Space group	*Pna*21
a [Å]	18.1974(3)
b [Å]	8.2624(2)
c [Å]	24.7335(5)
α [°]	90.0
β [°]	90.0
γ [°]	90.0
V [Å^3]	3718.79(13)
Z	8
$\rho_{calcd.}$ [g cm^{-3}]	1.296
μ [mm^{-1}]	0.326
F(000)	1536
Θ range [°]	2.23 – 25.24
Index ranges	$-22 \leq h \leq 22$
	$-10 \leq k \leq 10$
	$-30 \leq l \leq 30$
Reflns. collected	53277
Reflns. obsd.	7026
Reflns. unique	7601 (R_{int} = 0.0470)
R_1, wR_2 (2σ data)	0.0343, 0.0807
R_1, wR_2 (all data)	0.0382, 0.0824
GOOF on F^2	1.019
Peak/hole [e Å^{-3}]	0.353 / -0.152

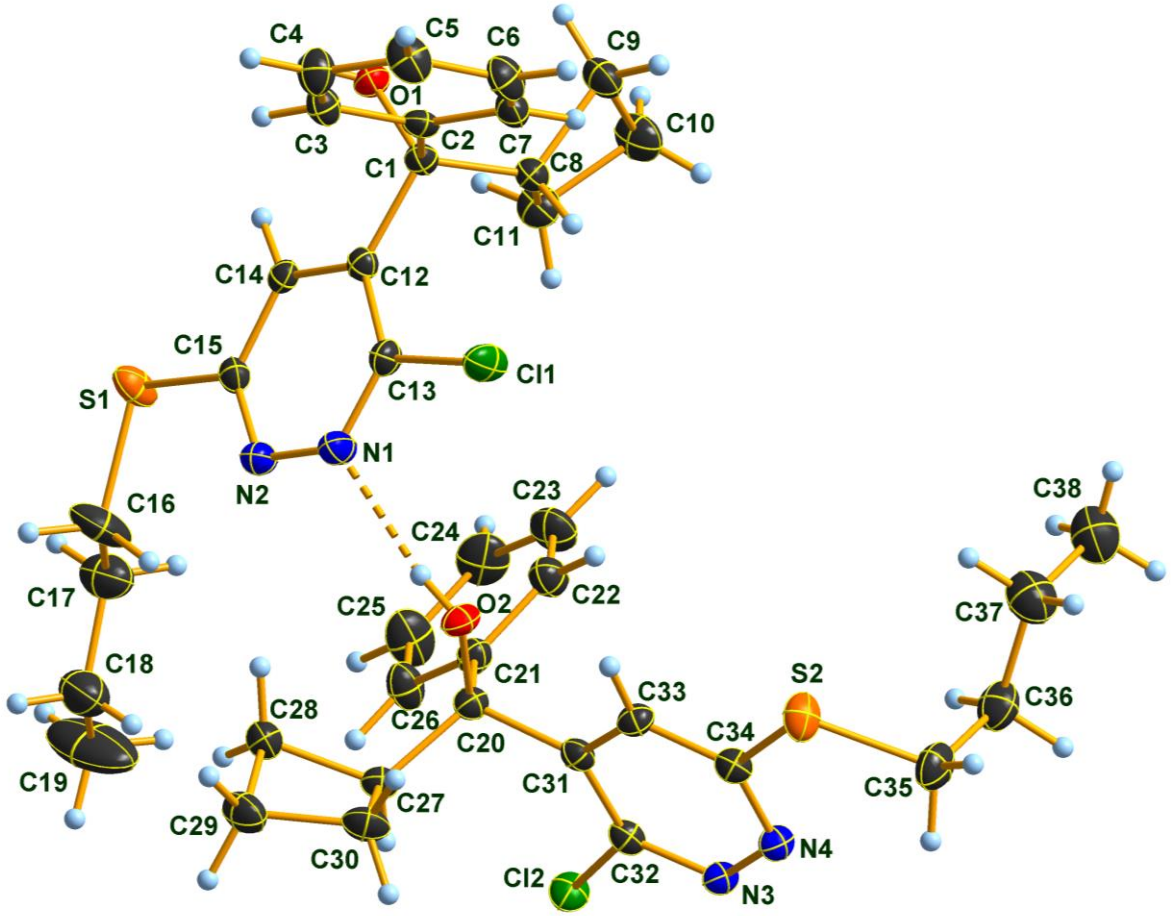


Figure 11 Molecular structure of compound **5k** in the crystal. DIAMOND[202] representation of the two crystallographically independent molecules; thermal ellipsoids are drawn at 50 % probability level.

Table 6. Selected bond lengths (Å) of compound **5k**.

Cl2 – C32	1.733(3)	C26 – C25	1.386(5)
O2 – C20	1.430(3)	C26 – C21	1.388(4)
N2 – C15	1.319(4)	C25 – C24	1.382(5)
N2 – N1	1.350(4)	C24 – C23	1.390(5)
C2 – C3	1.382(4)	C23 – C22	1.387(5)
C2 – C7	1.393(4)	C22 – C21	1.399(4)
C2 – C1	1.540(4)	C21 – C20	1.535(4)
S2 – C34	1.760(3)	C3 – C4	1.376(4)
S2 – C35	1.808(3)	N3 – N4	1.346(3)
Cl1 – C13	1.736(3)	C4 – C5	1.397(5)
O1 – C1	1.423(3)	C5 – C6	1.376(5)

[202] DIAMOND, Crystal Impact GbR., Version 3.2i.

N1 – C13	1.307(4)	C13 – C12	1.423(4)
C1 – C8	1.531(4)	C7 – C6	1.382(4)
C1 – C12	1.535(4)	C8 – C11	1.549(4)
S1 – C15	1.753(3)	C8 – C9	1.552(4)
S1 – C16	1.818(4)	C10 – C11	1.541(5)
C38 – C37	1.523(6)	C10 – C9	1.546(5)
C37 – C36	1.515(5)	C12 – C14	1.370(4)
C36 – C35	1.503(5)	C14 – C15	1.407(4)
C34 – N4	1.335(4)	C16 – C17	1.497(5)
C34 – C33	1.395(4)	C17 – C18	1.513(5)
C33 – C31	1.372(4)	C18 – C19	1.512(7)
C32 – N3	1.319(4)	C30 – C29	1.544(5)
C32 – C31	1.413(4)	C29 – C28	1.539(5)
C31 – C20	1.534(4)	C28 – C27	1.557(4)
C30 – C27	1.542(4)	C27 – C20	1.544(4)

Table 7. Selected bond angles (°) of compound **5k**.

C15 – N2 – N1	117.7(2)	C26 – C21 – C22	118.5(3)
C3 – C2 – C7	118.4(3)	C26 – C21 – C20	123.3(3)
C3 – C2 – C1	118.4(3)	C22 – C21 – C20	118.1(3)
C7 – C2 – C1	123.2(3)	C4 – C3 – C2	121.6(3)
C34 – S2 – C35	102.7(2)	C32 – N3 – N4	120.6(2)
C13 – N1 – N2	120.7(2)	C3 – C4 – C5	119.6(3)
O1 – C1 – C8	105.5(2)	C34 – N4 – N3	117.5(2)
O1 – C1 – C12	109.6(2)	C6 – C5 – C4	119.3(3)
C8 – C1 – C12	107.0(2)	N1 – C13 – C12	124.9(3)
O1 – C1 – C2	109.6(2)	N1 – C13 – Cl1	112.9(2)
C8 – C1 – C2	114.7(2)	C12 – C13 – Cl1	122.2(2)
C12 – C1 – C2	110.3(2)	C6 – C7 – C2	120.4(3)
C15 – S1 – C16	103.2(2)	C1 – C8 – C11	117.2(2)
C36 – C37 – C38	114.4(3)	C1 – C8 – C9	120.5(2)
C35 – C36 – C37	113.6(3)	C11 – C8 – C9	87.9(2)
C36 – C35 – S2	114.3(2)	C5 – C6 – C7	120.7(3)
N4 – C34 – C33	123.4(2)	C11 – C10 – C9	88.4(2)
N4 – C34 – S2	119.9(2)	C10 – C9 – C8	88.0(2)
C33 – C34 – S2	116.8(2)	C14 – C12 – C13	113.6(3)

C31 – C33 – C34	120.0(3)	C14 – C12 – C1	121.3(3)
N3 – C32 – C31	125.0(2)	C13 – C12 – C1	125.0(2)
N3 – C32 – Cl2	113.4(2)	C10 – C11 – C8	88.3(2)
C31 – C32 – Cl2	121.6(2)	C12 – C14 – C15	119.4(3)
C33 – C31 – C32	113.6(3)	N2 – C15 – C14	123.6(3)
C33 – C31 – C20	120.5(3)	N2 – C15 – S1	119.3(2)
C32 – C31 – C20	125.9(2)	C14 – C15 – S1	117.1(2)
C27 – C30 – C29	88.6(2)	C17 – C16 – S1	112.7(3)
C28 – C29 – C30	89.2(2)	C16 – C17 – C18	112.7(3)
C29 – C28 – C27	88.3(2)	C19 – C18 – C17	113.0(4)
C30 – C27 – C20	116.1(2)	O2 – C20 – C31	104.1(2)
C30 – C27 – C28	88.6(2)	O2 – C20 – C21	109.0(2)
C20 – C27 – C28	118.1(2)	C31 – C20 – C21	110.6(2)
C25 – C26 – C21	120.6(3)	O2 – C20 – C27	108.8(2)
C24 – C25 – C26	120.7(3)	C31 – C20 – C27	110.0(2)
C25 – C24 – C23	119.3(3)	C21 – C20 – C27	113.9(2)
C22 – C23 – C24	120.1(3)	C23 – C22 – C21	120.7(3)

Table 8. Selected torsion angles (°) of compound **5k**.

C15 – N2 – N1 – C13	1.1(4)	O1 – C1 – C8 – C9	47.5(3)
C3 – C2 – C1 – O1	60.0(3)	C12 – C1 – C8 – C9	164.1(3)
C7 – C2 – C1 – O1	-120.0(3)	C2 – C1 – C8 – C9	-73.2(3)
C3 – C2 – C1 – C8	178.5(3)	C4 – C5 – C6 – C7	1.2(5)
C7 – C2 – C1 – C8	-1.5(4)	C2 – C7 – C6 – C5	-1.9(5)
C3 – C2 – C1 – C12	-60.7(3)	C11 – C10 – C9 – C8	20.4(3)
C7 – C2 – C1 – C12	119.3(3)	C1 – C8 – C9 – C10	-140.9(3)
C38 – C37 – C36 – C35	-179.7(3)	C11 – C8 – C9 – C10	-20.3(3)
C37 – C36 – C35 – S2	71.4(4)	N1 – C13 – C12 – C14	-0.5(4)
C34 – S2 – C35 – C36	77.4(3)	Cl1 – C13 – C12 – C14	178.2(2)
C35 – S2 – C34 – N4	16.0(3)	N1 – C13 – C12 – C1	-178.0(3)
C35 – S2 – C34 – C33	-164.2(2)	Cl1 – C13 – C12 – C1	0.7(4)
N4 – C34 – C33 – C31	0.4(4)	O1 – C1 – C12 – C14	7.3(4)
S2 – C34 – C33 – C31	-179.4(2)	C8 – C1 – C12 – C14	-106.6(3)
C34 – C33 – C31 – C32	0.3(4)	C2 – C1 – C12 – C14	128.0(3)
C34 – C33 – C31 – C20	-178.5(3)	O1 – C1 – C12 – C13	-175.4(3)
N3 – C32 – C31 – C33	-1.0(4)	C8 – C1 – C12 – C13	70.7(3)

Cl2 – C32 – C31 – C33	-178.9(2)	C2 – C1 – C12 – C13	-54.7(4)
N3 – C32 – C31 – C20	177.7(3)	C9 – C10 – C11 – C8	-20.4(3)
Cl2 – C32 – C31 – C20	-0.2(4)	C1 – C8 – C11 – C10	143.8(3)
C27 – C30 – C29 – C28	-17.2(2)	C9 – C8 – C11 – C10	20.3(3)
C30 – C29 – C28 – C27	17.1(2)	C13 – C12 – C14 – C15	0.0(4)
C29 – C30 – C27 – C20	137.9(3)	C1 – C12 – C14 – C15	177.6(2)
C29 – C30 – C27 – C28	17.0(2)	N1 – N2 – C15 – C14	-1.6(4)
C29 – C28 – C27 – C30	-17.1(2)	N1 – N2 – C15 – S1	178.6(2)
C29 – C28 – C27 – C20	-136.2(3)	C12 – C14 – C15 – N2	1.1(4)
C21 – C26 – C25 – C24	-0.1(6)	C12 – C14 – C15 – S1	-179.2(2)
C26 – C25 – C24 – C23	1.3(6)	C16 – S1 – C15 – N2	-4.6(3)
C25 – C24 – C23 – C22	-1.9(6)	C16 – S1 – C15 – C14	175.6(2)
C24 – C23 – C22 – C21	1.3(5)	C15 – S1 – C16 – C17	-126.5(3)
C25 – C26 – C21 – C22	-0.5(5)	S1 – C16 – C17 – C18	176.8(3)
C25 – C26 – C21 – C20	177.8(3)	C16 – C17 – C18 – C19	-178.9(5)
C23 – C22 – C21 – C26	-0.1(5)	C33 – C31 – C20 – O2	3.0(3)
C23 – C22 – C21 – C20	-178.5(3)	C32 – C31 – C20 – O2	-175.7(3)
C7 – C2 – C3 – C4	1.1(4)	C33 – C31 – C20 – C21	119.9(3)
C1 – C2 – C3 – C4	-178.8(3)	C32 – C31 – C20 – C21	-58.7(4)
C31 – C32 – N3 – N4	0.9(4)	C33 – C31 – C20 – C27	-113.4(3)
Cl2 – C32 – N3 – N4	179.0(2)	C32 – C31 – C20 – C27	67.9(3)
C2 – C3 – C4 – C5	-1.8(5)	C26 – C21 – C20 – O2	-125.0(3)
C33 – C34 – N4 – N3	-0.5(4)	C22 – C21 – C20 – O2	53.2(3)
S2 – C34 – N4 – N3	179.3(2)	C26 – C21 – C20 – C31	121.1(3)
C32 – N3 – N4 – C34	-0.1(4)	C22 – C21 – C20 – C31	-60.6(3)
C3 – C4 – C5 – C6	0.7(5)	C26 – C21 – C20 – C27	-3.3(4)
N2 – N1 – C13 – C12	-0.1(5)	C22 – C21 – C20 – C27	174.9(3)
N2 – N1 – C13 – Cl1	-178.9(2)	C30 – C27 – C20 – O2	-52.1(3)
C3 – C2 – C7 – C6	0.7(4)	C28 – C27 – C20 – O2	51.3(3)
C1 – C2 – C7 – C6	-179.3(3)	C30 – C27 – C20 – C31	61.4(3)
O1 – C1 – C8 – C11	-57.3(3)	C28 – C27 – C20 – C31	164.8(2)
C12 – C1 – C8 – C11	59.4(3)	C30 – C27 – C20 – C21	-173.9(2)
C2 – C1 – C8 – C11	-178.0(2)	C28 – C27 – C20 – C21	-70.5(3)

(6-(Butylthio)-3-(4-methoxyphenyl)pyridazin-4-yl)(phenyl)methanone (6d)

Single crystals of compound **6d**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM 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 and data reduction were performed with the CrysAlisPro software.[203] Absorption correction using the multiscan method[203] was applied. The structures were solved with SHELXS-97,[204] refined with SHELXL-97[205] and finally checked using PLATON.[206] Details for data collection and structure refinement are summarized in Table 9.

CCDC-2278594 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[203] Program package 'CrysAlisPro 1.171.40.82a (Rigaku OD, 2020)'.
[204] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany
[205] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[206] 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 compound **6d**.

	6d
Empirical formula	$C_{22}H_{22}N_2O_2S$
Formula mass	378.47
T[K]	123(2)
Crystal size [mm]	0.30 × 0.20 × 0.15
Crystal description	yellow block
Crystal system	triclinic
Space group	*P*-1
a [Å]	8.5694(2)
b [Å]	9.9669(4)
c [Å]	12.2044(4)
α [°]	66.490(3)
β [°]	86.621(2)
γ [°]	79.229(2)
V [Å^3]	938.87(6)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.339
μ [mm^{-1}]	0.192
F(000)	400
Θ range [°]	2.27 – 25.24
Index ranges	$-12 \leq h \leq 12$
	$-14 \leq k \leq 14$
	$-17 \leq l \leq 17$
Reflns. collected	19157
Reflns. obsd.	4917
Reflns. unique	5724 (R_{int} = 0.0251)
R_1, wR_2 (2σ data)	0.0366, 0.0932
R_1, wR_2 (all data)	0.0445, 0.0986
GOOF on F^2	1.028
Peak/hole [e Å^{-3}]	0.423 / -0.198

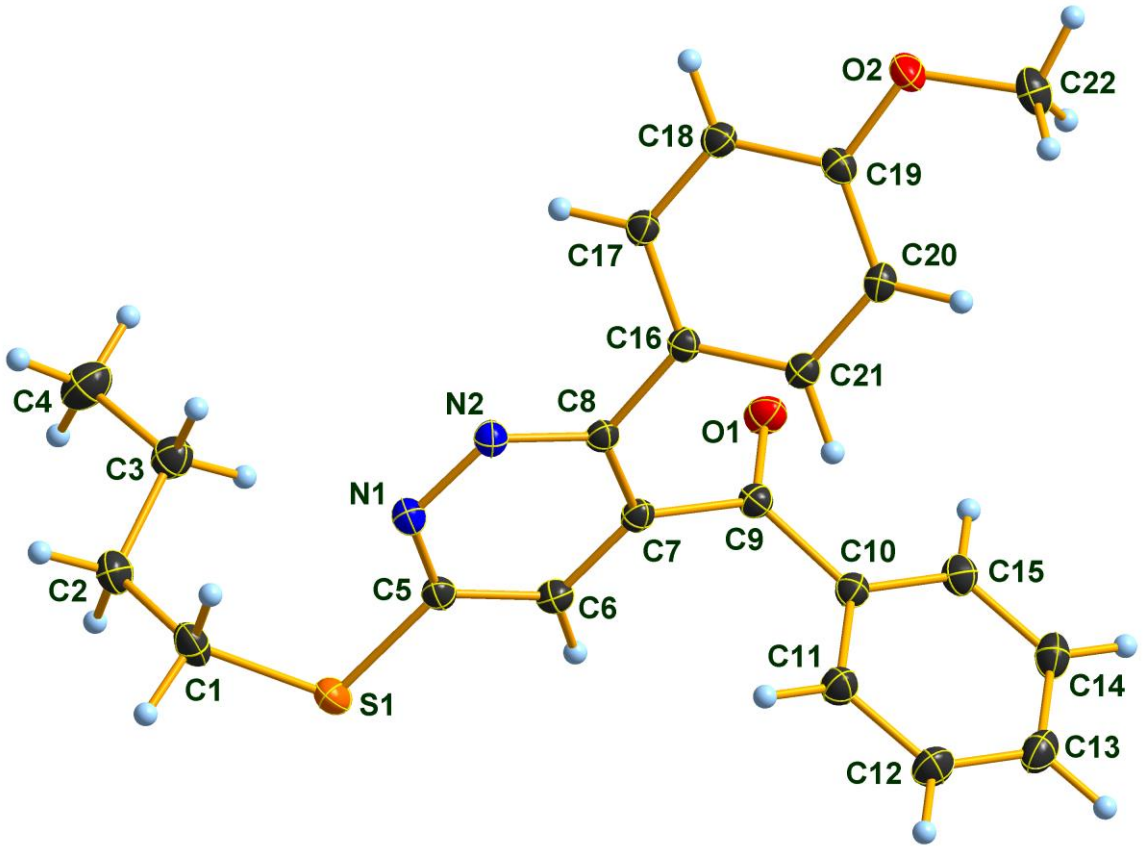


Figure 12. Molecular structure of compound **6d** in the crystal. DIAMOND[207] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 10. Selected bond lengths (Å) of compound **6d**.

S1 – C5	1.757(1)	C1 – C2	1.521(2)
S1 – C1	1.822(1)	C12 – C11	1.391(1)
C16 – C21	1.396(1)	C12 – C13	1.392(2)
C16 – C17	1.402(1)	C2 – C3	1.524(2)
C16 – C8	1.478(1)	C10 – C11	1.399(1)
O1 – C9	1.218(1)	C10 – C15	1.401(1)
N1 – C5	1.326(1)	C3 – C4	1.526(2)
N1 – N2	1.350(1)	C19 – C20	1.395(1)
N2 – C8	1.337(1)	C9 – C10	1.482(1)
C18 – C17	1.381(1)	C9 – C7	1.512(1)
C18 – C19	1.399(1)	C21 – C20	1.395(1)
O2 – C19	1.362(1)	C14 – C15	1.385(2)

[207] DIAMOND, Crystal Impact GbR., Version 3.2i.

O2 – C22	1.429(1)	C14 – C13	1.391(2)
C8 – C7	1.421(1)	C6 – C7	1.370(1)
C5 – C6	1.412(1)		

Table 11. Selected bond angles (°) of compound **6d**.

C5 – S1 – C1	103.5(1)	C1 – C2 – C3	114.8(1)
C21 – C16 – C17	118.4(1)	C14 – C13 – C12	120.2(1)
C21 – C16 – C8	121.6(1)	C11 – C10 – C15	119.9(1)
C17 – C16 – C8	120.1(1)	C11 – C10 – C9	121.6(1)
C5 – N1 – N2	120.2(1)	C15 – C10 – C9	118.5(1)
C8 – N2 – N1	120.6(1)	C6 – C7 – C8	118.2(1)
C17 – C18 – C19	120.1(1)	C6 – C7 – C9	119.7(1)
C19 – O2 – C22	117.8(1)	C8 – C7 – C9	121.5(1)
N2 – C8 – C7	121.0(1)	C14 – C15 – C10	119.9(1)
N2 – C8 – C16	116.4(1)	C21 – C20 – C19	119.5(1)
C7 – C8 – C16	122.6(1)	C2 – C3 – C4	112.0(1)
N1 – C5 – C6	122.2(1)	C12 – C11 – C10	119.7(1)
N1 – C5 – S1	120.2(1)	O1 – C9 – C7	117.4(1)
C6 – C5 – S1	117.6(1)	C10 – C9 – C7	119.8(1)
O2 – C19 – C20	124.6(1)	C20 – C21 – C16	121.2(1)
O2 – C19 – C18	115.7(1)	C15 – C14 – C13	120.2(1)
C20 – C19 – C18	119.8(1)	C7 – C6 – C5	117.7(1)
C18 – C17 – C16	121.0(1)	C2 – C1 – S1	114.0(1)
O1 – C9 – C10	122.8(1)	C11 – C12 – C13	120.1(1)

Table 12. Selected torsion angles (°) of compound **6d**.

C5 – N1 – N2 – C8	1.2(1)	C11 – C12 – C13 – C14	-0.4(2)
N1 – N2 – C8 – C7	-0.3(1)	O1 – C9 – C10 – C11	178.9(1)
N1 – N2 – C8 – C16	177.9(1)	C7 – C9 – C10 – C11	-2.7(2)
C21 – C16 – C8 – N2	136.9(1)	O1 – C9 – C10 – C15	0.4(2)
C17 – C16 – C8 – N2	-44.0(1)	C7 – C9 – C10 – C15	178.7(1)
C21 – C16 – C8 – C7	-45.0(1)	C5 – C6 – C7 – C8	1.5(1)
C17 – C16 – C8 – C7	134.2(1)	C5 – C6 – C7 – C9	-169.5(1)
N2 – N1 – C5 – C6	-0.7(2)	N2 – C8 – C7 – C6	-1.1(1)
N2 – N1 – C5 – S1	179.2(1)	C16 – C8 – C7 – C6	-179.1(1)
C1 – S1 – C5 – N1	10.7(1)	N2 – C8 – C7 – C9	169.8(1)

C1 – S1 – C5 – C6	-169.4(1)	C16 – C8 – C7 – C9	-8.3(1)
C22 – O2 – C19 – C20	8.0(2)	O1 – C9 – C7 – C6	101.3(1)
C22 – O2 – C19 – C18	-172.2(1)	C10 – C9 – C7 – C6	-77.1(1)
C17 – C18 – C19 – O2	178.0(1)	O1 – C9 – C7 – C8	-69.4(1)
C17 – C18 – C19 – C20	-2.2(2)	C10 – C9 – C7 – C8	112.2(1)
C19 – C18 – C17 – C16	-0.4(2)	C13 – C14 – C15 – C10	-0.4(2)
C21 – C16 – C17 – C18	2.4(2)	C11 – C10 – C15 – C14	0.3(2)
C8 – C16 – C17 – C18	-176.8(1)	C9 – C10 – C15 – C14	178.9(1)
C17 – C16 – C21 – C20	-1.8(2)	C16 – C21 – C20 – C19	-0.8(2)
C8 – C16 – C21 – C20	177.4(1)	O2 – C19 – C20 – C21	-177.4(1)
N1 – C5 – C6 – C7	-0.7(2)	C18 – C19 – C20 – C21	2.8(2)
S1 – C5 – C6 – C7	179.4(1)	C1 – C2 – C3 – C4	-176.2(1)
C5 – S1 – C1 – C2	99.7(1)	C13 – C12 – C11 – C10	0.3(2)
S1 – C1 – C2 – C3	-61.8(1)	C15 – C10 – C11 – C12	-0.3(2)
C15 – C14 – C13 – C12	0.4(2)	C9 – C10 – C11 – C12	-178.8(1)

Ethyl 3-(4-methoxyphenyl)-6-(4-(trifluoromethyl)phenyl)pyridazine-4-carboxylate (7a)

Single crystals of compound **7a**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM 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 and data reduction were performed with the CrysAlisPro software.[208] Absorption correction using the multiscan method[208] was applied. The structures were solved with SHELXS-97,[209] refined with SHELXL-97[210] and finally checked using PLATON.[211] Details for data collection and structure refinement are summarized in Table 13.

CCDC-2267440 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[208] Program package 'CrysAlisPro 1.171.40.82a (Rigaku OD, 2020)'.
[209] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[210] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[211] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 13. Details for X-ray data collection and structure refinement for compound **7a**.

	7a
Empirical formula	$C_{21}H_{17}F_3N_2O_3$
Formula mass	402.36
T[K]	123(2)
Crystal size [mm]	0.40 × 0.35 × 0.05
Crystal description	colorless platelet
Crystal system	triclinic
Space group	*P*-1
a [Å]	8.3213(4)
b [Å]	9.7458(6)
c [Å]	12.8825(8)
α [°]	72.027(5)
β [°]	72.801(4)
γ [°]	80.061(4)
V [Å^3]	945.51(10)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.413
μ [mm^{-1}]	0.115
F(000)	416
Θ range [°]	2.21 – 25.24
Index ranges	$-11 \leq h \leq 11$
	$-13 \leq k \leq 13$
	$-18 \leq l \leq 18$
Reflns. collected	19197
Reflns. obsd.	4443
Reflns. unique	5766 (R_{int} = 0.0297)
R_1, wR_2 (2σ data)	0.0482, 0.1232
R_1, wR_2 (all data)	0.0653, 0.1366
GOOF on F^2	1.025
Peak/hole [e Å^{-3}]	0.453 / -0.270

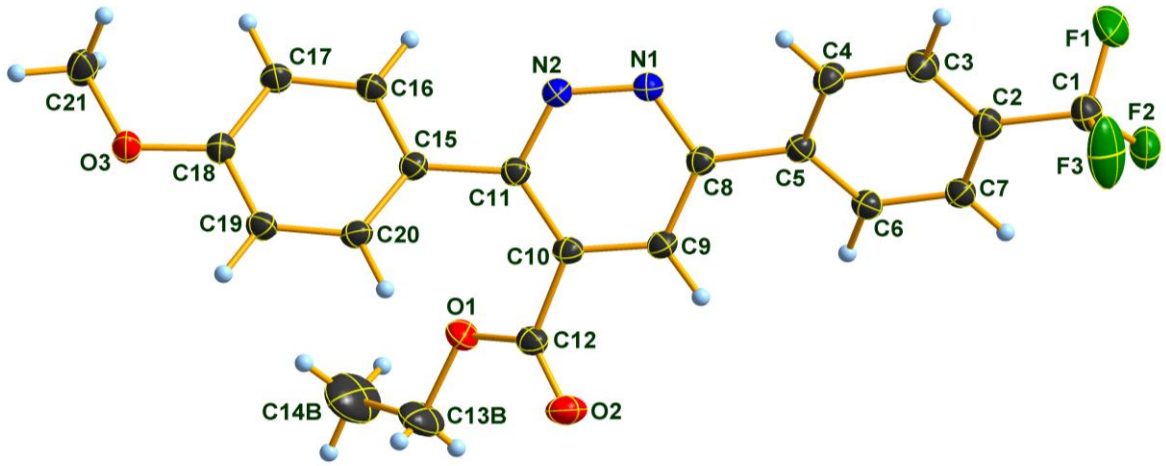


Figure 13. Molecular structure of compound **7a** in the crystal. DIAMOND[212] representation; thermal ellipsoids are drawn at 50 % probability level. The ethyl group is disordered over two positions; only one the higher populated position is shown.

Table 14. Selected bond lengths (Å) of compound **7a**.

N1 – N2	1.330(1)	C9 – C10	1.380(2)
N1 – C8	1.343(2)	C9 – C8	1.397(2)
C1 – F2	1.330(2)	C5 – C6	1.396(2)
C1 – F3	1.338(2)	C5 – C8	1.481(2)
C1 – F1	1.339(2)	C6 – C7	1.392(2)
C1 – C2	1.495(2)	C10 – C11	1.412(2)
C2 – C7	1.389(2)	C10 – C12	1.501(2)
C2 – C3	1.394(2)	C11 – C15	1.479(2)
C13B – O1	1.456(2)	O3 – C18	1.363(1)
C13B – C14B	1.497(5)	O3 – C21	1.434(2)
N2 – C11	1.351(2)	C20 – C19	1.383(2)
C4 – C3	1.384(2)	C20 – C15	1.402(2)
C4 – C5	1.401(2)	C15 – C16	1.395(2)
O2 – C12	1.209(2)	C16 – C17	1.393(2)
O1 – C12	1.331(2)	C17 – C18	1.395(2)
C18 – C19	1.397(2)		

[212] DIAMOND, Crystal Impact GbR., Version 3.2i.

Table 15. Selected bond angles (°) of compound **7a**.

N2 – N1 – C8	120.1(1)	C7 – C6 – C5	120.6(1)
F2 – C1 – F3	106.1(1)	C4 – C3 – C2	119.8(1)
F2 – C1 – F1	106.4(1)	C9 – C10 – C11	117.4(1)
F3 – C1 – F1	105.8(1)	C9 – C10 – C12	116.0(1)
F2 – C1 – C2	113.6(1)	C11 – C10 – C12	126.6(1)
F3 – C1 – C2	111.7(1)	N2 – C11 – C10	120.7(1)
F1 – C1 – C2	112.6(1)	N2 – C11 – C15	113.7(1)
C7 – C2 – C3	120.6(1)	C10 – C11 – C15	125.6(1)
C7 – C2 – C1	120.4(1)	C2 – C7 – C6	119.4(1)
C3 – C2 – C1	119.0(1)	N1 – C8 – C9	121.3(1)
O1 – C13B – C14B	108.6(2)	N1 – C8 – C5	115.9(1)
N1 – N2 – C11	121.4(1)	C9 – C8 – C5	122.9(1)
C3 – C4 – C5	120.3(1)	C18 – O3 – C21	117.0(1)
C12 – O1 – C13B	117.2(1)	O2 – C12 – O1	125.0(1)
C10 – C9 – C8	119.0(1)	O2 – C12 – C10	122.3(1)
C6 – C5 – C4	119.3(1)	O1 – C12 – C10	112.7(1)
C6 – C5 – C8	121.5(1)	C19 – C20 – C15	121.1(1)
C4 – C5 – C8	119.3(1)	C16 – C15 – C20	118.3(1)
O3 – C18 – C17	124.5(1)	C16 – C15 – C11	119.2(1)
O3 – C18 – C19	115.4(1)	C20 – C15 – C11	122.5(1)
C17 – C18 – C19	120.1(1)	C17 – C16 – C15	121.4(1)
C20 – C19 – C18	119.8(1)	C16 – C17 – C18	119.3(1)

Table 16. Selected torsion angles (°) of compound **7a.**

F2 – C1 – C2 – C7	24.4(2)	C10 – C9 – C8 – C5	178.1(1)
F3 – C1 – C2 – C7	-95.7(2)	C6 – C5 – C8 – N1	-153.0(1)
F1 – C1 – C2 – C7	145.5(1)	C4 – C5 – C8 – N1	27.5(2)
F2 – C1 – C2 – C3	-157.9(1)	C6 – C5 – C8 – C9	28.0(2)
F3 – C1 – C2 – C3	82.0(2)	C4 – C5 – C8 – C9	-151.5(1)
F1 – C1 – C2 – C3	-36.8(2)	C13B – O1 – C12 – O2	2.5(2)
C8 – N1 – N2 – C11	-2.6(2)	C13B – O1 – C12 – C10	-179.3(1)
C14B – C13B – O1 – C12	-172.8(3)	C9 – C10 – C12 – O2	34.5(2)
C3 – C4 – C5 – C6	-0.1(2)	C11 – C10 – C12 – O2	-146.7(1)
C3 – C4 – C5 – C8	179.4(1)	C9 – C10 – C12 – O1	-143.7(1)
C4 – C5 – C6 – C7	1.0(2)	C11 – C10 – C12 – O1	35.1(2)

C8 – C5 – C6 – C7	-178.5(1)	C19 – C20 – C15 – C16	2.1(2)
C5 – C4 – C3 – C2	-1.1(2)	C19 – C20 – C15 – C11	178.4(1)
C7 – C2 – C3 – C4	1.5(2)	N2 – C11 – C15 – C16	34.5(2)
C1 – C2 – C3 – C4	-176.2(1)	C10 – C11 – C15 – C16	-147.1(1)
C8 – C9 – C10 – C11	-3.1(2)	N2 – C11 – C15 – C20	-141.8(1)
C8 – C9 – C10 – C12	175.9(1)	C10 – C11 – C15 – C20	36.6(2)
N1 – N2 – C11 – C10	-1.5(2)	C20 – C15 – C16 – C17	-1.8(2)
N1 – N2 – C11 – C15	177.0(1)	C11 – C15 – C16 – C17	-178.2(1)
C9 – C10 – C11 – N2	4.2(2)	C15 – C16 – C17 – C18	0.0(2)
C12 – C10 – C11 – N2	-174.6(1)	C21 – O3 – C18 – C17	0.1(2)
C9 – C10 – C11 – C15	-174.1(1)	C21 – O3 – C18 – C19	179.5(1)
C12 – C10 – C11 – C15	7.2(2)	C16 – C17 – C18 – O3	-179.0(1)
C3 – C2 – C7 – C6	-0.7(2)	C16 – C17 – C18 – C19	1.6(2)
C1 – C2 – C7 – C6	177.0(1)	C15 – C20 – C19 – C18	-0.6(2)
C5 – C6 – C7 – C2	-0.6(2)	O3 – C18 – C19 – C20	179.3(1)
N2 – N1 – C8 – C9	3.7(2)	C17 – C18 – C19 – C20	-1.3(2)
N2 – N1 – C8 – C5	-175.3(1)	C10 – C9 – C8 – N1	-0.8(2)

Ethyl 3-(4-methoxyphenyl)-6-(*p*-tolyl)pyridazine-4-carboxylate (7b)

Single crystals of compound **7b**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM 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 and data reduction were performed with the CrysAlisPro software.[213] Absorption correction using the multiscan method[213] was applied. The structures were solved with SHELXS-97,[214] refined with SHELXL-97[215] and finally checked using PLATON.[216] Details for data collection and structure refinement are summarized in Table 17.

CCDC-2267439 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[213] Program package 'CrysAlisPro 1.171.40.82a (Rigaku OD, 2020)'.
[214] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[215] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[216] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands

Table 17. Details for X-ray data collection and structure refinement for compound **7b**.

	7b
Empirical formula	$C_{21}H_{20}N_2O_3$
Formula mass	348.39
T[K]	123(2)
Crystal size [mm]	0.40 × 0.35 × 0.10
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*-1
a [Å]	8.9589(5)
b [Å]	10.8215(6)
c [Å]	11.0233(8)
α [°]	116.015(6)
β [°]	106.668(5)
γ [°]	97.874(5)
V [Å^3]	876.15(10)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.321
μ [mm^{-1}]	0.089
F(000)	368
Θ range [°]	2.20 – 25.24
Index ranges	$-12 \leq h \leq 12$
	$-15 \leq k \leq 15$
	$-15 \leq l \leq 15$
Reflns. collected	17475
Reflns. obsd.	3818
Reflns. unique	5344 (R_{int} = 0.0380)
R_1, wR_2 (2σ data)	0.0559, 0.1454
R_1, wR_2 (all data)	0.0792, 0.1672
GOOF on F^2	1.021
Peak/hole [e Å^{-3}]	0.425 / -0.238

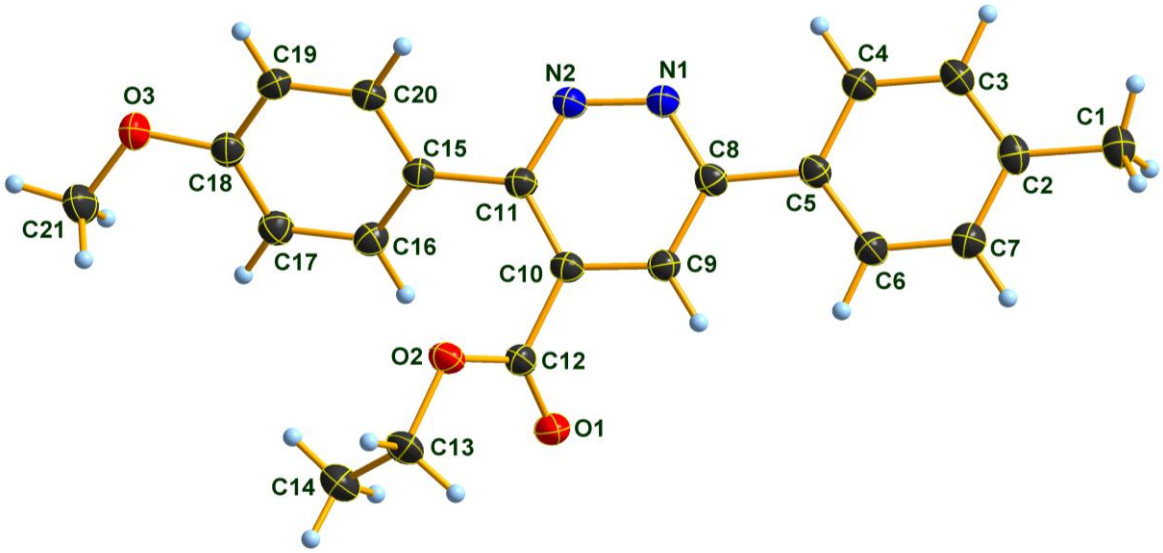


Figure 14. Molecular structure of compound **7b** in the crystal. DIAMOND[217] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 18. Selected bond lengths (Å) of compound **7b**.

O1 – C12	1.208(2)	C10 – C12	1.499(2)
C9 – C10	1.380(2)	C11 – N2	1.345(2)
C9 – C8	1.404(2)	C11 – C15	1.478(2)
C4 – C3	1.392(2)	N2 – N1	1.335(2)
C4 – C5	1.340(2)	C2 – C1	1.498(2)
C5 – C6	1.393(2)	C12 – O2	1.329(2)
C5 – C8	1.482(2)	C13 – O2	1.464(2)
C6 – C7	1.389(2)	C13 – C14	1.496(2)
C7 – C2	1.393(2)	C18 – C17	1.393(2)
C8 – N1	1.340(2)	C15 – C16	1.388(2)
O3 – C18	1.364(2)	C16 – C17	1.391(2)
O3 – C21	1.430(2)	C19 – C18	1.392(2)
C3 – C2	1.392(2)	C20 – C15	1.405(2)
C19 – C20	1.382(2)	C10 – C11	1.408(2)

[217] DIAMOND, Crystal Impact GbR., Version 3.2i.

Table 19. Selected bond angles (°) of compound **7b**.

C10 – C9 – C8	118.6(1)	O2 – C12 – C10	112.6(1)
C3 – C4 – C5	120.4(1)	O2 – C13 – C14	112.3(1)
C6 – C5 – C4	117.9(1)	N2 – N1 – C8	120.8(1)
C6 – C5 – C8	121.4(1)	C12 – O2 – C13	116.2(1)
C4 – C5 – C8	120.8(1)	O3 – C18 – C19	115.6(1)
C7 – C6 – C5	121.3(1)	O3 – C18 – C17	124.4(1)
C6 – C7 – C2	121.2(1)	C19 – C18 – C17	119.9(1)
N1 – C8 – C9	120.7(1)	C16 – C15 – C20	118.3(1)
N1 – C8 – C5	116.7(1)	C16 – C15 – C11	121.9(1)
C9 – C8 – C5	122.6(1)	C20 – C15 – C11	119.7(1)
C18 – O3 – C21	117.1(1)	C15 – C16 – C17	121.5(1)
C2 – C3 – C4	121.8(1)	C16 – C17 – C18	119.4(1)
C20 – C19 – C18	120.2(1)	C10 – C11 – C15	124.7(1)
C19 – C20 – C15	120.7(1)	N1 – N2 – C11	121.1(1)
C9 – C10 – C11	118.1(1)	C3 – C2 – C7	117.5(1)
C9 – C10 – C12	115.6(1)	C3 – C2 – C1	122.1(1)
C11 – C10 – C12	126.2(1)	C7 – C2 – C1	120.4(1)
N2 – C11 – C10	120.5(1)	O1 – C12 – O2	125.0(1)
N2 – C11 – C15	114.8(1)	O1 – C12 – C10	122.3(1)

Table 20. Selected torsion angles (°) of compound **7b**.

C3 – C4 – C5 – C6	0.1(2)	C9 – C10 – C12 – O1	-47.3(2)
C3 – C4 – C5 – C8	179.9(1)	C11 – C10 – C12 – O1	134.2(2)
C4 – C5 – C6 – C7	-0.2(2)	C9 – C10 – C12 – O2	129.2(1)
C8 – C5 – C6 – C7	180.0(1)	C11 – C10 – C12 – O2	-49.3(2)
C5 – C6 – C7 – C2	0.0(2)	C11 – N2 – N1 – C8	1.7(2)
C10 – C9 – C8 – N1	1.4(2)	C9 – C8 – N1 – N2	-2.9(2)
C10 – C9 – C8 – C5	-179.2(1)	C5 – C8 – N1 – N2	177.6(1)
C6 – C5 – C8 – N1	179.4(1)	O1 – C12 – O2 – C13	3.8(2)
C4 – C5 – C8 – N1	-0.4(2)	C10 – C12 – O2 – C13	-172.5(1)
C6 – C5 – C8 – C9	0.0(2)	C14 – C13 – O2 – C12	-80.5(2)
C4 – C5 – C8 – C9	-179.8(1)	C21 – O3 – C18 – C19	-169.6(1)
C5 – C4 – C3 – C2	0.2(2)	C21 – O3 – C18 – C17	10.4(2)
C18 – C19 – C20 – C15	-1.1(2)	C20 – C19 – C18 – O3	-178.7(1)
C8 – C9 – C10 – C11	1.2(2)	C20 – C19 – C18 – C17	1.3(2)

C8 – C9 – C10 – C12	-177.4(1)	C19 – C20 – C15 – C16	0.5(2)
C9 – C10 – C11 – N2	-2.4(2)	C19 – C20 – C15 – C11	178.0(1)
C12 – C10 – C11 – N2	176.1(1)	N2 – C11 – C15 – C16	140.8(1)
C9 – C10 – C11 – C15	176.3(1)	C10 – C11 – C15 – C16	-38.0(2)
C12 – C10 – C11 – C15	-5.2(2)	N2 – C11 – C15 – C20	-36.6(2)
C10 – C11 – N2 – N1	1.0(2)	C10 – C11 – C15 – C20	144.6(1)
C15 – C11 – N2 – N1	-177.9(1)	C20 – C15 – C16 – C17	0.0(2)
C4 – C3 – C2 – C7	-0.4(2)	C11 – C15 – C16 – C17	-177.5(1)
C4 – C3 – C2 – C1	180.0(1)	C15 – C16 – C17 – C18	0.1(2)
C6 – C7 – C2 – C3	0.3(2)	O3 – C18 – C17 – C16	179.2(1)
C6 – C7 – C2 – C1	179.9(1)	C19 – C18 – C17 – C16	-0.8(2)

6-Chloro-3,4-*bis*(methylthio)pyridazine (9a)

Single crystals of compound **9a**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM 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 and data reduction were performed with the CrysAlisPro software.[218] Absorption correction using the multiscan method[218] was applied. The structures were solved with SHELXS-97,[219] refined with SHELXL-97[220] and finally checked using PLATON.[221] Details for data collection and structure refinement are summarized in Table 21.

CCDC-2267438 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[218] Program package 'CrysAlisPro 1.171.40.82a (Rigaku OD, 2020)'.
[219] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[220] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[221] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 21. Details for X-ray data collection and structure refinement for compound **9a**.

	9a
Empirical formula	$C_6H_7ClN_2S_2$
Formula mass	206.71
T[K]	123(2)
Crystal size [mm]	0.40 × 0.40 × 0.03
Crystal description	colorless platelet
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	8.3151(5)
b [Å]	14.9774(9)
c [Å]	7.0165(5)
α [°]	90.0
β [°]	102.412(6)
γ [°]	90.0
V [Å^3]	853.40(10)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.609
μ [mm^{-1}]	0.869
F(000)	424
Θ range [°]	2.51 – 25.24
Index ranges	$-9 \leq h \leq 11$
	$-21 \leq k \leq 20$
	$-9 \leq l \leq 10$
Reflns. collected	7096
Reflns. obsd.	2150
Reflns. unique	2555 (R_{int} = 0.0365)
R_1, wR_2 (2σ data)	0.0420, 0.0928
R_1, wR_2 (all data)	0.0532, 0.0981
GOOF on F^2	1.107
Peak/hole [e Å^{-3}]	0.531 / -0.276

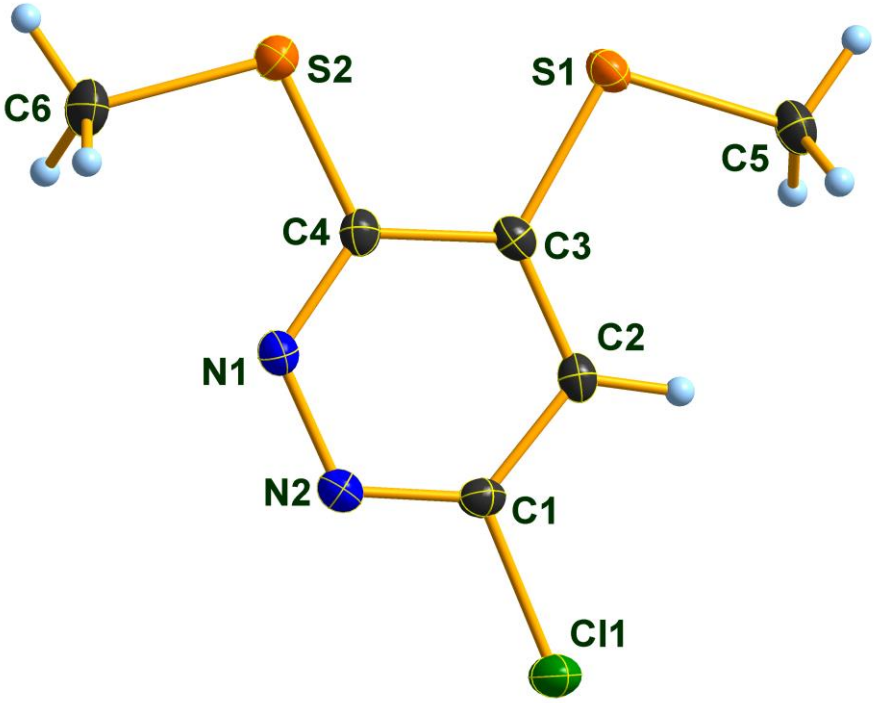


Figure 15. Molecular structure of compound **9a** in the crystal. DIAMOND[222] representation; thermal ellipsoids are drawn at 50 % probability level. In the crystal the molecule is disordered over two positions; only the position with the higher population (94 %) is shown.

Table 22. Selected bond lengths (Å) of compound **9a**.

S1 – C3	1.745(2)	C1 – C2	1.402(3)
S1 – C5	1.802(2)	N1 – C4	1.327(3)
Cl1 – C1	1.735(3)	N1 – N2	1.363(3)
S2 – C4	1.749(2)	C4 – C3	1.428(3)
S2 – C6	1.805(2)	C2 – C3	1.379(3)
C1 – N2	1.309(3)		

Table 23. Selected bond angles (°) of compound **9a**.

C3 – S1 – C5	103.6(1)	N1 – C4 – C3	123.1(2)
C4 – S2 – C6	101.3(1)	N1 – C4 – S2	119.0(2)
N2 – C1 – C2	126.5(2)	C3 – C4 – S2	117.9(1)
N2 – C1 – Cl1	115.3(2)	C3 – C2 – C1	116.3(2)
C2 – C1 – Cl1	118.2(2)	C2 – C3 – C4	116.4(2)
C4 – N1 – N2	120.5(2)	C2 – C3 – S1	125.6(1)

[222] DIAMOND, Crystal Impact GbR., Version 3.2i.

C1 – N2 – N1	117.3(2)	C4 – C3 – S1	118.0(1)

Table 24. Selected torsion angles (°) of compound **9a**.

C2 – C1 – N2 – N1	0.5(3)	C1 – C2 – C3 – C4	0.0(2)
Cl1 – C1 – N2 – N1	179.8(1)	C1 – C2 – C3 – S1	-179.6(1)
C4 – N1 – N2 – C1	-0.1(3)	N1 – C4 – C3 – C2	0.4(3)
N2 – N1 – C4 – C3	-0.3(3)	S2 – C4 – C3 – C2	-179.8(1)
N2 – N1 – C4 – S2	179.9(1)	N1 – C4 – C3 – S1	179.9(2)
C6 – S2 – C4 – N1	-0.4(2)	S2 – C4 – C3 – S1	-0.3(2)
C6 – S2 – C4 – C3	179.9(2)	C5 – S1 – C3 – C2	0.2(2)
N2 – C1 – C2 – C3	-0.4(3)	C5 – S1 – C3 – C4	-179.3(1)
Cl1 – C1 – C2 – C3	-179.7(1)		

6-(4-Methoxyphenyl)-4-(*p*-tolyl)-3-(4-(trifluoromethyl)phenyl)pyridazine (12a)

Single crystals of compound **12a**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM 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 and data reduction were performed with the CrysAlisPro software.[223] Absorption correction using the multiscan method[223] was applied. The structures were solved with SHELXS-97,[224] refined with SHELXL-97[225] and finally checked using PLATON.[226] Details for data collection and structure refinement are summarized in Table 25.

CCDC-2278597 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[223] Program package 'CrysAlisPro 1.171.40.82a (Rigaku OD, 2020)'.
[224] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[225] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[226] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 25. Details for X-ray data collection and structure refinement for compound **12a**.

	12a
Empirical formula	$C_{25}H_{19}F_3N_2O$
Formula mass	420.42
T[K]	123(2)
Crystal size [mm]	0.40 × 0.25 × 0.10
Crystal description	colorless block
Crystal system	monoclinic
Space group	*P*21/*c*
a [Å]	21.7913(7)
b [Å]	17.9713(4)
c [Å]	10.6536(3)
α [°]	90.0
β [°]	97.601(3)
γ [°]	90.0
V [Å^3]	4135.5(2)
Z	8
$\rho_{calcd.}$ [g cm^{-3}]	1.351
μ [mm^{-1}]	0.102
F(000)	1744
Θ range [°]	2.20 – 25.24
Index ranges	$-29 \leq h \leq 29$
	$-23 \leq k \leq 23$
	$-14 \leq l \leq 14$
Reflns. collected	74766
Reflns. obsd.	7113
Reflns. unique	10232 (R_{int} = 0.0572)
R_1, wR_2 (2σ data)	0.0528, 0.1144
R_1, wR_2 (all data)	0.0842, 0.1294
GOOF on F^2	1.030
Peak/hole [e Å^{-3}]	0.477 / -0.469

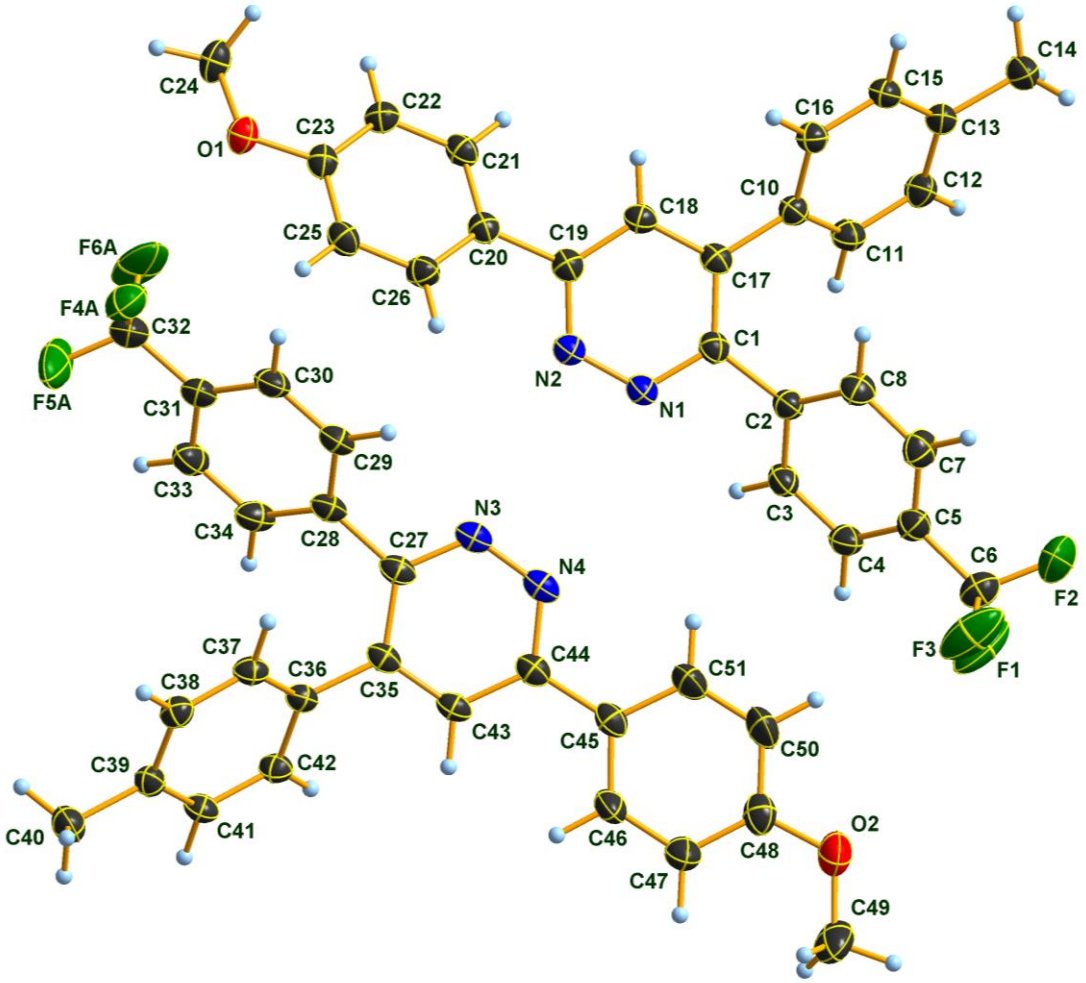


Figure 16. Molecular structure of compound **12a** in the crystal. DIAMOND[227] representation; thermal ellipsoids are drawn at 50 % probability level. The asymmetric unit contains two crystallographically independent molecules. The CF3 group of one of the molecules is disordered over two positions; only the highly populated position (64 %) is shown.

Table 26. Selected bond lengths (Å) of compound **12a**.

F1 – C6	1.327(2)	C13 – C14	1.510(2)
O1 – C23	1.365(2)	C27 – C28	1.484(2)
O1 – C24	1.431(2)	C15 – C16	1.388(2)
N1 – N2	1.334(2)	C18 – C17	1.380(2)
N1 – C1	1.342(2)	C18 – C19	1.398(2)
C1 – C17	1.417(2)	C19 – C20	1.481(2)
C1 – C2	1.493(2)	C20 – C21	1.392(2)
F2 – C6	1.329(2)	C20 – C26	1.403(2)

[227] DIAMOND, Crystal Impact GbR., Version 3.2i.

O2 – C48	1.361(2)	C21 – C22	1.388(2)
O2 – C49	1.423(3)	C22 – C23	1.387(2)
N2 – C19	1.343(2)	C23 – C25	1.396(2)
C2 – C8	1.392(2)	C25 – C26	1.382(2)
C2 – C3	1.396(2)	C48 – C47	1.378(3)
N4 – N3	1.338(2)	C48 – C50	1.384(3)
N4 – C44	1.346(2)	C46 – C47	1.382(3)
C35 – C43	1.374(2)	C46 – C45	1.388(3)
C35 – C27	1.420(2)	C28 – C29	1.394(2)
C35 – C36	1.487(2)	C28 – C34	1.395(2)
C36 – C37	1.392(2)	C31 – C30	1.387(3)
C36 – C42	1.400(2)	C31 – C33	1.390(3)
C37 – C38	1.384(2)	C31 – C32	1.487(3)
C38 – C39	1.396(2)	C29 – C30	1.383(3)
F3 – C6	1.327(2)	C40 – C39	1.507(2)
N3 – C27	1.340(2)	C33 – C34	1.380(3)
C3 – C4	1.387(3)	C45 – C51	1.393(3)
C5 – C4	1.382(3)	C50 – C51	1.375(3)
C5 – C7	1.394(3)	C10 – C11	1.388(2)
C5 – C6	1.489(3)	C10 – C16	1.401(2)
F5A – C32	1.287(5)	C10 – C17	1.488(2)
F6A – C32	1.256(3)	C11 – C12	1.384(2)
F4A – C32	1.455(4)	C42 – C41	1.386(2)
C43 – C44	1.399(2)	C12 – C13	1.398(3)
C44 – C45	1.475(2)	C41 – C39	1.390(2)
C7 – C8	1.384(3)	C13 – C15	1.391(3)

Table 27. Selected bond angles (°) of compound **12a**.

C23 – O1 – C24	117.2(1)	C5 – C4 – C3	119.8(2)
N2 – N1 – C1	121.1(1)	C21 – C20 – C26	118.0(2)
N1 – C1 – C17	122.2(2)	C21 – C20 – C19	121.9(2)
N1 – C1 – C2	111.6(1)	C26 – C20 – C19	120.1(2)
C17 – C1 – C2	126.2(2)	C22 – C21 – C20	121.7(2)
C48 – O2 – C49	117.7(2)	C23 – C22 – C21	119.5(2)
N1 – N2 – C19	119.8(1)	O1 – C23 – C22	124.8(2)
C8 – C2 – C3	119.0(2)	O1 – C23 – C25	115.4(2)

C8 – C2 – C1	121.9(2)	C22 – C23 – C25	119.8(2)
C3 – C2 – C1	118.7(2)	C26 – C25 – C23	120.1(2)
N3 – N4 – C44	120.3(1)	C25 – C26 – C20	120.9(2)
C43 – C35 – C27	115.7(2)	O2 – C48 – C47	124.5(2)
C43 – C35 – C36	120.0(1)	O2 – C48 – C50	116.3(2)
C27 – C35 – C36	124.2(2)	C47 – C48 – C50	119.2(2)
C37 – C36 – C42	118.3(2)	C47 – C46 – C45	122.7(2)
C37 – C36 – C35	121.6(1)	C48 – C47 – C46	119.5(2)
C42 – C36 – C35	120.0(2)	C29 – C28 – C34	119.0(2)
C38 – C37 – C36	120.6(2)	C29 – C28 – C27	120.0(2)
C37 – C38 – C39	121.6(2)	C34 – C28 – C27	121.0(2)
N4 – N3 – C27	120.7(1)	C30 – C31 – C33	120.3(2)
C4 – C3 – C2	120.6(2)	C30 – C31 – C32	120.2(2)
C4 – C5 – C7	120.2(2)	C33 – C31 – C32	119.5(2)
C4 – C5 – C6	119.9(2)	C30 – C29 – C28	120.4(2)
C7 – C5 – C6	119.9(2)	C29 – C30 – C31	120.0(2)
F3 – C6 – F1	105.4(2)	F6A – C32 – F5A	114.2(4)
F3 – C6 – F2	105.4(2)	F6A – C32 – F4A	102.2(3)
F1 – C6 – F2	104.4(2)	F5A – C32 – F4A	100.9(3)
F3 – C6 – C5	113.3(2)	F6A – C32 – C31	113.9(2)
F1 – C6 – C5	113.6(2)	F5A – C32 – C31	114.4(3)
F2 – C6 – C5	113.8(2)	F4A – C32 – C31	109.5(2)
C35 – C43 – C44	120.4(2)	C41 – C39 – C38	117.5(2)
N4 – C44 – C43	120.6(2)	C41 – C39 – C40	121.7(2)
N4 – C44 – C45	116.9(2)	C38 – C39 – C40	120.9(2)
C43 – C44 – C45	122.4(2)	C34 – C33 – C31	119.5(2)
C8 – C7 – C5	119.8(2)	C33 – C34 – C28	120.8(2)
C7 – C8 – C2	120.6(2)	C46 – C45 – C51	116.5(2)
C11 – C10 – C16	118.2(2)	C46 – C45 – C44	121.9(2)
C11 – C10 – C17	121.8(2)	C51 – C45 – C44	121.6(2)
C16 – C10 – C17	120.0(2)	C51 – C50 – C48	120.6(2)
C12 – C11 – C10	121.0(2)	C50 – C51 – C45	121.7(2)
C41 – C42 – C36	120.5(2)	C15 – C16 – C10	120.8(2)
C11 – C12 – C13	120.9(2)	C17 – C18 – C19	120.3(2)
C42 – C41 – C39	121.6(2)	N2 – C19 – C18	121.0(2)
C15 – C13 – C12	118.3(2)	N2 – C19 – C20	114.8(1)
C15 – C13 – C14	120.6(2)	C18 – C19 – C20	124.2(2)

C12 – C13 – C14	121.1(2)	C18 – C17 – C1	115.5(2)
N3 – C27 – C35	122.1(2)	C18 – C17 – C10	121.1(2)
N3 – C27 – C28	114.9(1)	C1 – C17 – C10	123.5(2)
C35 – C27 – C28	123.0(2)	C16 – C15 – C13	120.8(2)

Table 28. Selected torsion angles (°) of compound **12a**.

N2 – N1 – C1 – C17	-2.7(3)	C16 – C10 – C17 – C1	-136.0(2)
N2 – N1 – C1 – C2	174.0(2)	C7 – C5 – C4 – C3	-1.3(3)
C1 – N1 – N2 – C19	-1.7(3)	C6 – C5 – C4 – C3	178.3(2)
N1 – C1 – C2 – C8	-129.3(2)	C2 – C3 – C4 – C5	0.2(3)
C17 – C1 – C2 – C8	47.3(3)	N2 – C19 – C20 – C21	-150.6(2)
N1 – C1 – C2 – C3	43.5(2)	C18 – C19 – C20 – C21	27.7(3)
C17 – C1 – C2 – C3	-139.9(2)	N2 – C19 – C20 – C26	27.5(2)
C43 – C35 – C36 – C37	130.8(2)	C18 – C19 – C20 – C26	-154.2(2)
C27 – C35 – C36 – C37	-45.4(2)	C26 – C20 – C21 – C22	-0.9(2)
C43 – C35 – C36 – C42	-45.0(2)	C19 – C20 – C21 – C22	177.3(2)
C27 – C35 – C36 – C42	138.8(2)	C20 – C21 – C22 – C23	0.8(3)
C42 – C36 – C37 – C38	-0.3(2)	C24 – O1 – C23 – C22	8.1(2)
C35 – C36 – C37 – C38	-176.2(2)	C24 – O1 – C23 – C25	-172.7(2)
C36 – C37 – C38 – C39	-0.9(3)	C21 – C22 – C23 – O1	179.2(2)
C44 – N4 – N3 – C27	2.5(2)	C21 – C22 – C23 – C25	0.1(2)
C8 – C2 – C3 – C4	1.5(3)	O1 – C23 – C25 – C26	179.9(2)
C1 – C2 – C3 – C4	-171.6(2)	C22 – C23 – C25 – C26	-0.9(3)
C4 – C5 – C6 – F3	-100.4(2)	C23 – C25 – C26 – C20	0.8(3)
C7 – C5 – C6 – F3	79.2(2)	C21 – C20 – C26 – C25	0.1(3)
C4 – C5 – C6 – F1	19.9(3)	C19 – C20 – C26 – C25	-178.1(2)
C7 – C5 – C6 – F1	-160.5(2)	C49 – O2 – C48 – C47	-1.4(3)
C4 – C5 – C6 – F2	139.2(2)	C49 – O2 – C48 – C50	176.9(2)
C7 – C5 – C6 – F2	-41.3(3)	O2 – C48 – C47 – C46	177.8(2)
C27 – C35 – C43 – C44	4.6(2)	C50 – C48 – C47 – C46	-0.4(3)
C36 – C35 – C43 – C44	-171.9(2)	C45 – C46 – C47 – C48	0.9(3)
N3 – N4 – C44 – C43	0.4(2)	N3 – C27 – C28 – C29	-47.5(2)
N3 – N4 – C44 – C45	-175.6(2)	C35 – C27 – C28 – C29	132.8(2)
C35 – C43 – C44 – N4	-4.1(3)	N3 – C27 – C28 – C34	132.6(2)
C35 – C43 – C44 – C45	171.7(2)	C35 – C27 – C28 – C34	-47.1(2)
C4 – C5 – C7 – C8	0.7(3)	C34 – C28 – C29 – C30	1.6(3)

C6 – C5 – C7 – C8	-178.9(2)	C27 – C28 – C29 – C30	-178.3(2)
C5 – C7 – C8 – C2	1.0(3)	C28 – C29 – C30 – C31	-0.7(3)
C3 – C2 – C8 – C7	-2.0(3)	C33 – C31 – C30 – C29	-1.0(3)
C1 – C2 – C8 – C7	170.7(2)	C32 – C31 – C30 – C29	-179.9(2)
C16 – C10 – C11 – C12	2.0(3)	C30 – C31 – C32 – F6A	79.4(4)
C17 – C10 – C11 – C12	-179.2(2)	C33 – C31 – C32 – F6A	-99.5(3)
C37 – C36 – C42 – C41	1.0(2)	C30 – C31 – C32 – F5A	-146.8(4)
C35 – C36 – C42 – C41	176.9(2)	C33 – C31 – C32 – F5A	34.4(4)
C10 – C11 – C12 – C13	0.8(3)	C30 – C31 – C32 – F4A	-34.3(3)
C36 – C42 – C41 – C39	-0.5(3)	C33 – C31 – C32 – F4A	146.8(2)
C11 – C12 – C13 – C15	-2.6(3)	C42 – C41 – C39 – C38	-0.8(3)
C11 – C12 – C13 – C14	176.6(2)	C42 – C41 – C39 – C40	179.6(2)
N4 – N3 – C27 – C35	-1.8(2)	C37 – C38 – C39 – C41	1.4(3)
N4 – N3 – C27 – C28	178.5(1)	C37 – C38 – C39 – C40	-178.9(2)
C43 – C35 – C27 – N3	-1.7(2)	C30 – C31 – C33 – C34	1.8(3)
C36 – C35 – C27 – N3	174.6(2)	C32 – C31 – C33 – C34	-179.3(2)
C43 – C35 – C27 – C28	177.9(2)	C31 – C33 – C34 – C28	-0.9(3)
C36 – C35 – C27 – C28	-5.7(3)	C29 – C28 – C34 – C33	-0.8(3)
C12 – C13 – C15 – C16	1.4(3)	C27 – C28 – C34 – C33	179.1(2)
C14 – C13 – C15 – C16	-177.7(2)	C47 – C46 – C45 – C51	-0.6(3)
C13 – C15 – C16 – C10	1.4(3)	C47 – C46 – C45 – C44	-176.6(2)
C11 – C10 – C16 – C15	-3.1(2)	N4 – C44 – C45 – C46	173.6(2)
C17 – C10 – C16 – C15	178.0(2)	C43 – C44 – C45 – C46	-2.4(3)
N1 – N2 – C19 – C18	3.8(3)	N4 – C44 – C45 – C51	-2.2(3)
N1 – N2 – C19 – C20	-177.8(2)	C43 – C44 – C45 – C51	-178.2(2)
C17 – C18 – C19 – N2	-1.6(3)	O2 – C48 – C50 – C51	-178.7(2)
C17 – C18 – C19 – C20	-179.8(2)	C47 – C48 – C50 – C51	-0.3(3)
C19 – C18 – C17 – C1	-2.6(2)	C48 – C50 – C51 – C45	0.6(4)
C19 – C18 – C17 – C10	177.1(2)	C46 – C45 – C51 – C50	-0.2(3)
N1 – C1 – C17 – C18	4.7(2)	C44 – C45 – C51 – C50	175.8(2)
C2 – C1 – C17 – C18	-171.5(2)	C11 – C10 – C17 – C18	-134.4(2)
N1 – C1 – C17 – C10	-174.9(2)	C16 – C10 – C17 – C18	44.4(2)
C2 – C1 – C17 – C10	8.9(3)	C11 – C10 – C17 – C1	45.2(2)

Ethyl 4-(4-(4-methoxyphenyl)-6-(4-(trifluoromethyl)phenyl)pyridazin-3-yl)benzoate (12b)

Single crystals of compound **12b**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM 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 and data reduction were performed with the CrysAlisPro software.[228] Absorption correction using the multiscan method[228] was applied. The structures were solved with SHELXS-97,[229] refined with SHELXL-97[230] and finally checked using PLATON.[231] Details for data collection and structure refinement are summarized in Table 29.

CCDC-2278595 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[228] Program package 'CrysAlisPro 1.171.40.82a (Rigaku OD, 2020)'.
[229] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[230] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[231] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 29. Details for X-ray data collection and structure refinement for compound **12b**.

	12b
Empirical formula	$C_{27}H_{21}F_3N_2O_3$
Formula mass	478.46
T[K]	123(2)
Crystal size [mm]	0.35 × 0.30 × 0.03
Crystal description	colorless platelet
Crystal system	triclinic
Space group	*P*-1
a [Å]	10.3898(5)
b [Å]	10.7684(5)
c [Å]	10.9143(5)
α [°]	104.629(4)
β [°]	94.360(4)
γ [°]	102.941(4)
V [Å^3]	1140.07(10)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.394
μ [mm^{-1}]	0.108
F(000)	496
Θ range [°]	1.95 – 25.24
Index ranges	$-13 \leq h \leq 13$
	$-14 \leq k \leq 14$
	$-14 \leq l \leq 14$
Reflns. collected	20358
Reflns. obsd.	3452
Reflns. unique	5641 (R_{int} = 0.0506)
R_1, wR_2 (2σ data)	0.0603, 0.1296
R_1, wR_2 (all data)	0.1103, 0.1526
GOOF on F^2	1.025
Peak/hole [e Å^{-3}]	0.393 / -0.316

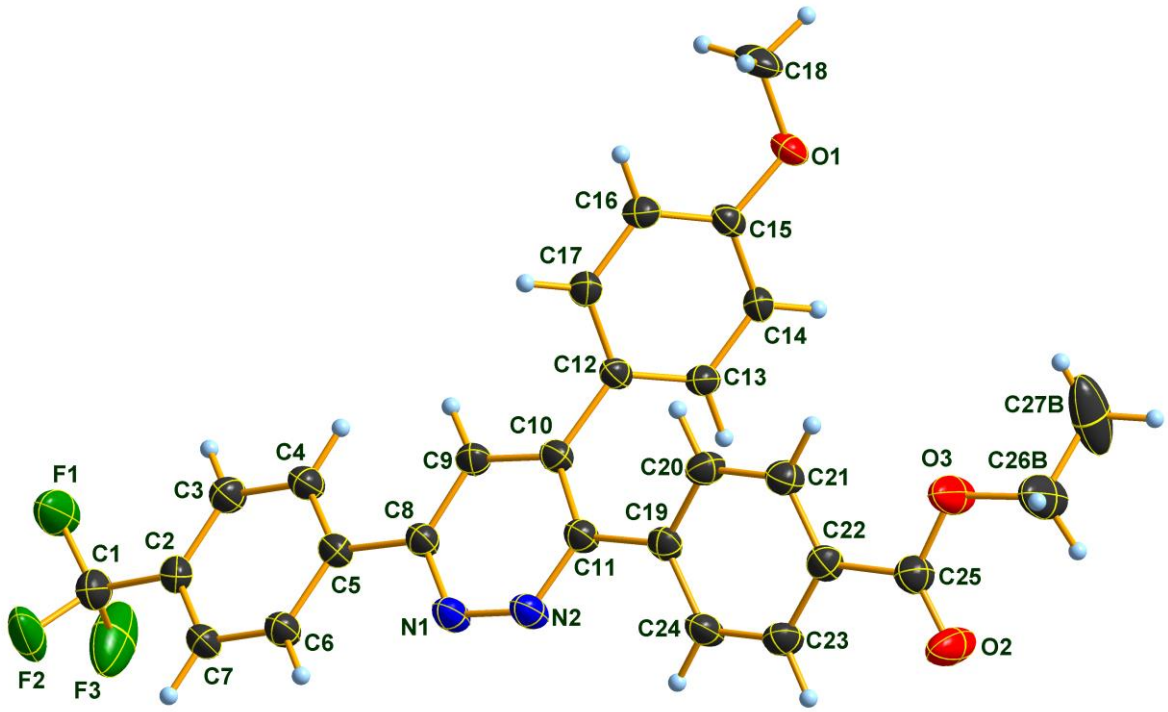


Figure 17. Molecular structure of compound **12b** in the crystal. DIAMOND[232] representation; thermal ellipsoids are drawn at 50 % probability level. The ethyl group is disordered over two positions; only the higher populated position (70 %) is shown.

Table 30. Selected bond lengths (Å) of compound **12b**.

F1 – C1	1.321(3)	C8 – C9	1.392(3)
O1 – C15	1.377(2)	C9 – C10	1.375(3)
O1 – C18	1.427(3)	C10 – C11	1.423(3)
N1 – C8	1.337(2)	C10 – C12	1.488(3)
N1 – N2	1.341(2)	C19 – C20	1.396(3)
C1 – F2	1.327(3)	C19 – C24	1.397(3)
C1 – F3	1.329(3)	C19 – C11	1.485(3)
C1 – C2	1.493(3)	C12 – C17	1.383(3)
N2 – C11	1.338(2)	C12 – C13	1.392(3)
C2 – C3	1.385(3)	C13 – C14	1.377(3)
C2 – C7	1.386(3)	C14 – C15	1.384(3)
O3 – C25	1.323(3)	C15 – C16	1.385(3)
O3 – C26B	1.458(3)	C16 – C17	1.390(3)
C3 – C4	1.384(3)	C20 – C21	1.378(3)

[232] DIAMOND, Crystal Impact GbR., Version 3.2i.

C4 – C5	1.391(3)	C21 – C22	1.390(3)
C5 – C6	1.396(3)	C22 – C23	1.383(3)
C5 – C8	1.490(3)	C22 – C25	1.490(3)
C26B – C27B	1.432(4)	O2 – C25	1.197(3)
C6 – C7	1.384(3)	C23 – C24	1.382(3)

Table 31. Selected bond angles (°) of compound **12b**.

C15 – O1 – C18	116.6(2)	C9 – C8 – C5	122.6(2)
C8 – N1 – N2	119.7(2)	C10 – C9 – C8	119.8(2)
F1 – C1 – F2	106.1(2)	C9 – C10 – C11	116.3(2)
F1 – C1 – F3	106.0(2)	C9 – C10 – C12	119.8(2)
F2 – C1 – F3	105.9(2)	C11 – C10 – C12	123.9(2)
F1 – C1 – C2	113.4(2)	C20 – C19 – C24	118.0(2)
F2 – C1 – C2	112.3(2)	C20 – C19 – C11	122.7(2)
F3 – C1 – C2	112.5(2)	C24 – C19 – C11	119.3(2)
C11 – N2 – N1	121.4(2)	N2 – C11 – C10	121.2(2)
C3 – C2 – C7	119.5(2)	N2 – C11 – C19	114.4(2)
C3 – C2 – C1	120.2(2)	C10 – C11 – C19	124.4(2)
C7 – C2 – C1	120.2(2)	C17 – C12 – C13	119.0(2)
C25 – O3 – C26B	117.3(2)	C17 – C12 – C10	120.8(2)
C4 – C3 – C2	120.2(2)	C13 – C12 – C10	120.3(2)
C3 – C4 – C5	120.8(2)	C14 – C13 – C12	120.7(2)
C4 – C5 – C6	118.6(2)	C13 – C14 – C15	119.8(2)
C4 – C5 – C8	121.4(2)	O1 – C15 – C14	115.6(2)
C6 – C5 – C8	120.0(2)	O1 – C15 – C16	124.0(2)
C27B – C26B – O3	108.7(2)	C14 – C15 – C16	120.4(2)
C7 – C6 – C5	120.5(2)	C15 – C16 – C17	119.3(2)
C6 – C7 – C2	120.4(2)	C12 – C17 – C16	120.8(2)
N1 – C8 – C9	121.5(2)	C21 – C20 – C19	121.0(2)
N1 – C8 – C5	115.9(2)	C20 – C21 – C22	120.4(2)
C23 – C24 – C19	120.7(2)	C23 – C22 – C21	119.1(2)
O2 – C25 – O3	123.0(2)	C23 – C22 – C25	119.3(2)
O2 – C25 – C22	124.7(2)	C21 – C22 – C25	121.6(2)
O3 – C25 – C22	112.3(2)	C24 – C23 – C22	120.6(2)

Table 32. Selected torsion angles (°) of compound **12b**.

C8 – N1 – N2 – C11	-3.4(3)	C20 – C19 – C11 – C10	27.9(3)
F1 – C1 – C2 – C3	-25.2(3)	C24 – C19 – C11 – C10	-153.0(2)
F2 – C1 – C2 – C3	-145.5(2)	C9 – C10 – C12 – C17	61.5(3)
F3 – C1 – C2 – C3	95.1(3)	C11 – C10 – C12 – C17	-121.0(2)
F1 – C1 – C2 – C7	158.3(2)	C9 – C10 – C12 – C13	-117.5(2)
F2 – C1 – C2 – C7	38.0(3)	C11 – C10 – C12 – C13	59.9(3)
F3 – C1 – C2 – C7	-81.4(3)	C17 – C12 – C13 – C14	1.3(3)
C7 – C2 – C3 – C4	-0.3(3)	C10 – C12 – C13 – C14	-179.7(2)
C1 – C2 – C3 – C4	-176.8(2)	C12 – C13 – C14 – C15	0.5(3)
C2 – C3 – C4 – C5	1.1(3)	C18 – O1 – C15 – C14	177.9(2)
C3 – C4 – C5 – C6	-1.6(3)	C18 – O1 – C15 – C16	-2.1(3)
C3 – C4 – C5 – C8	177.2(2)	C13 – C14 – C15 – O1	178.8(2)
C25 – O3 – C26B – C27B	150.0(3)	C13 – C14 – C15 – C16	-1.3(3)
C4 – C5 – C6 – C7	1.3(3)	O1 – C15 – C16 – C17	-179.9(2)
C8 – C5 – C6 – C7	-177.5(2)	C14 – C15 – C16 – C17	0.2(3)
C5 – C6 – C7 – C2	-0.5(3)	C13 – C12 – C17 – C16	-2.4(3)
C3 – C2 – C7 – C6	0.0(3)	C10 – C12 – C17 – C16	178.6(2)
C1 – C2 – C7 – C6	176.5(2)	C15 – C16 – C17 – C12	1.7(3)
N2 – N1 – C8 – C9	2.4(3)	C24 – C19 – C20 – C21	3.3(3)
N2 – N1 – C8 – C5	179.5(2)	C11 – C19 – C20 – C21	-177.6(2)
C4 – C5 – C8 – N1	-169.6(2)	C19 – C20 – C21 – C22	-1.4(3)
C6 – C5 – C8 – N1	9.2(3)	C20 – C21 – C22 – C23	-1.9(3)
C4 – C5 – C8 – C9	7.5(3)	C20 – C21 – C22 – C25	175.6(2)
C6 – C5 – C8 – C9	-173.7(2)	C21 – C22 – C23 – C24	3.2(3)
N1 – C8 – C9 – C10	1.8(3)	C25 – C22 – C23 – C24	-174.3(2)
C5 – C8 – C9 – C10	-175.1(2)	C22 – C23 – C24 – C19	-1.3(3)
C8 – C9 – C10 – C11	-4.7(3)	C20 – C19 – C24 – C23	-1.9(3)
C8 – C9 – C10 – C12	172.9(2)	C11 – C19 – C24 – C23	178.9(2)
N1 – N2 – C11 – C10	0.2(3)	C26B – O3 – C25 – O2	2.6(4)
N1 – N2 – C11 – C19	179.6(2)	C26B – O3 – C25 – C22	-175.2(2)
C9 – C10 – C11 – N2	3.8(3)	C23 – C22 – C25 – O2	-5.9(4)
C12 – C10 – C11 – N2	-173.7(2)	C21 – C22 – C25 – O2	176.6(2)
C9 – C10 – C11 – C19	-175.5(2)	C23 – C22 – C25 – O3	171.9(2)
C12 – C10 – C11 – C19	7.0(3)	C21 – C22 – C25 – O3	-5.7(3)
C20 – C19 – C11 – N2	-151.5(2)	C24 – C19 – C11 – N2	27.6(3)

Ethyl 4-(6-(butylthio)pyridazin-3-yl)benzoate (15)

Single crystals of compound **15**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM 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 and data reduction were performed with the CrysAlisPro software.[233] Absorption correction using the multiscan method[233] was applied. The structures were solved with SHELXS-97,[234] refined with SHELXL-97[235] and finally checked using PLATON.[236] Details for data collection and structure refinement are summarized in Table 33.

CCDC-2278596 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[233] Program package 'CrysAlisPro 1.171.40.82a (Rigaku OD, 2020)'.
[234] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[235] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[236] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 33. Details for X-ray data collection and structure refinement for compound **15**.

	15
Empirical formula	$C_{17}H_{20}N_2O_2S$
Formula mass	316.41
T[K]	123(2)
Crystal size [mm]	0.40 × 0.40 × 0.06
Crystal description	colorless platelet
Crystal system	monoclinic
Space group	*C*2
a [Å]	16.0804(5)
b [Å]	5.58770(10)
c [Å]	35.8175(9)
α [°]	90. 0
β [°]	98.578(3)
γ [°]	90.0
V [Å^3]	3182.29(14)
Z	8
$\rho_{calcd.}$ [g cm^{-3}]	1.321
μ [mm^{-1}]	0.212
F(000)	1344
Θ range [°]	2.54 – 25.24
Index ranges	$-20 \leq h \leq 20$
	$-6 \leq k \leq 6$
	$-44 \leq l \leq 44$
Reflns. collected	22986
Reflns. obsd.	6115
Reflns. unique	6459 (R_{int} = 0.0529)
R_1, wR_2 (2σ data)	0.0525, 0.1212
R_1, wR_2 (all data)	0.0555, 0.1230
GOOF on F^2	1.121
Peak/hole [e Å^{-3}]	0.486 / -0.291

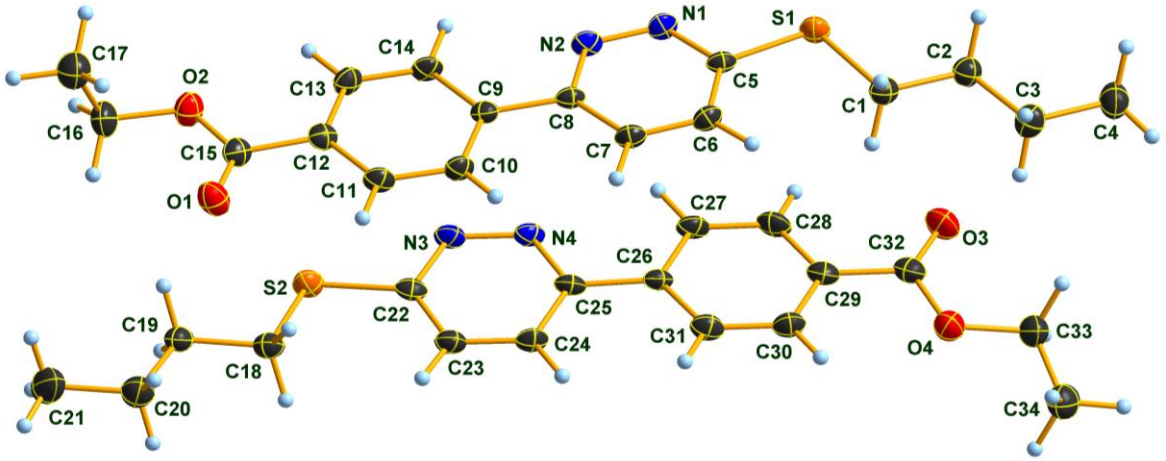


Figure 18. Molecular structure of compound **15** in the crystal. DIAMOND[237] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 34. Selected bond lengths (Å) of compound **15**.

S1 – C5	1.752(4)	N2 – C8	1.341(5)
S1 – C1	1.799(4)	C2 – C3	1.519(6)
S2 – C22	1.753(4)	C2 – C1	1.531(5)
S2 – C18	1.803(4)	C14 – C13	1.372(6)
O1 – C15	1.209(5)	C12 – C13	1.401(6)
C9 – C10	1.401(5)	C3 – C4	1.520(6)
C9 – C14	1.402(6)	C27 – C28	1.376(6)
C9 – C8	1.483(5)	C34 – C33	1.496(7)
N3 – N4	1.344(5)	C20 – C21	1.519(7)
N3 – C22	1.347(5)	C16 – C17	1.499(6)
O4 – C32	1.345(5)	C19 – C20	1.508(6)
O4 – C33	1.450(5)	C19 – C18	1.519(6)
N4 – C25	1.335(5)	C32 – O3	1.217(5)
C23 – C24	1.370(6)	C26 – C27	1.396(6)
C23 – C22	1.389(6)	C26 – C25	1.486(5)
O2 – C15	1.341(5)	N1 – N2	1.339(5)
O2 – C16	1.447(5)	N1 – C5	1.340(5)
C31 – C30	1.386(6)	C5 – C6	1.398(5)
C31 – C26	1.389(6)	C11 – C12	1.382(6)
C7 – C6	1.362(6)	C11 – C10	1.384(6)
C7 – C8	1.407(5)	C24 – C25	1.408(5)

[237] DIAMOND, Crystal Impact GbR., Version 3.2i.

C15 – C12	1.494(6)	C29 – C32	1.483(6)
C29 – C28	1.392(7)	C29 – C30	1.394(6)

Table 35. Selected bond angles (°) of compound **15**.

C5 – S1 – C1	104.2(2)	C2 – C3 – C4	113.5(4)
C22 – S2 – C18	104.0(2)	C7 – C6 – C5	117.4(4)
C10 – C9 – C14	118.3(4)	C31 – C30 – C29	120.4(4)
C10 – C9 – C8	121.3(3)	C14 – C13 – C12	120.4(4)
C14 – C9 – C8	120.4(3)	C28 – C27 – C26	121.2(4)
N4 – N3 – C22	119.4(4)	C2 – C1 – S1	107.4(3)
C32 – O4 – C33	116.3(4)	C27 – C28 – C29	120.5(4)
C25 – N4 – N3	120.5(3)	C19 – C20 – C21	112.4(4)
C24 – C23 – C22	117.7(4)	O2 – C16 – C17	111.8(4)
C15 – O2 – C16	116.9(4)	O4 – C33 – C34	107.4(4)
N3 – C22 – C23	122.6(4)	N4 – C25 – C26	115.6(3)
N3 – C22 – S2	111.7(3)	C24 – C25 – C26	122.8(4)
C23 – C22 – S2	125.7(3)	C12 – C11 – C10	120.8(4)
C30 – C31 – C26	120.9(4)	N1 – N2 – C8	120.0(3)
C6 – C7 – C8	118.7(4)	C11 – C10 – C9	120.5(4)
O1 – C15 – O2	123.6(4)	C3 – C2 – C1	111.5(4)
O1 – C15 – C12	123.8(4)	N2 – C8 – C7	121.5(4)
O2 – C15 – C12	112.6(4)	N2 – C8 – C9	115.7(3)
C28 – C29 – C30	118.8(4)	C7 – C8 – C9	122.8(3)
C28 – C29 – C32	118.7(4)	C13 – C14 – C9	121.0(4)
C30 – C29 – C32	122.4(4)	C11 – C12 – C13	119.0(4)
C23 – C24 – C25	118.2(4)	C11 – C12 – C15	118.8(4)
C20 – C19 – C18	113.0(4)	C13 – C12 – C15	122.2(4)
O3 – C32 – O4	123.2(4)	C19 – C18 – S2	107.2(3)
O3 – C32 – C29	124.5(4)	N2 – N1 – C5	120.1(3)
O4 – C32 – C29	112.4(4)	N1 – C5 – C6	122.4(4)
C31 – C26 – C27	118.3(4)	N1 – C5 – S1	111.8(3)
C31 – C26 – C25	121.2(4)	C6 – C5 – S1	125.7(3)
C27 – C26 – C25	120.6(4)	N4 – C25 – C24	121.5(4)

Table 36. Selected torsion angles (°) of compound **15**.

C22 – N3 – N4 – C25	0.7(5)	C6 – C7 – C8 – N2	-0.6(6)
N4 – N3 – C22 – C23	0.6(6)	C6 – C7 – C8 – C9	-178.7(3)
N4 – N3 – C22 – S2	-178.0(3)	C10 – C9 – C8 – N2	179.0(3)
C24 – C23 – C22 – N3	-1.1(6)	C14 – C9 – C8 – N2	-1.8(5)
C24 – C23 – C22 – S2	177.2(3)	C10 – C9 – C8 – C7	-2.8(5)
C18 – S2 – C22 – N3	-170.1(3)	C14 – C9 – C8 – C7	176.4(4)
C18 – S2 – C22 – C23	11.4(4)	C10 – C9 – C14 – C13	0.1(6)
C16 – O2 – C15 – O1	1.3(6)	C8 – C9 – C14 – C13	-179.2(4)
C16 – O2 – C15 – C12	-179.2(3)	C10 – C11 – C12 – C13	0.6(6)
C22 – C23 – C24 – C25	0.4(6)	C10 – C11 – C12 – C15	179.5(4)
C33 – O4 – C32 – O3	-3.4(6)	O1 – C15 – C12 – C11	2.9(6)
C33 – O4 – C32 – C29	175.5(4)	O2 – C15 – C12 – C11	-176.6(3)
C28 – C29 – C32 – O3	5.6(7)	O1 – C15 – C12 – C13	-178.3(4)
C30 – C29 – C32 – O3	-176.4(4)	O2 – C15 – C12 – C13	2.2(5)
C28 – C29 – C32 – O4	-173.3(4)	C20 – C19 – C18 – S2	176.3(3)
C30 – C29 – C32 – O4	4.7(6)	C22 – S2 – C18 – C19	175.7(3)
C30 – C31 – C26 – C27	-2.1(6)	C1 – C2 – C3 – C4	-176.5(4)
C30 – C31 – C26 – C25	176.9(4)	C8 – C7 – C6 – C5	-0.4(6)
N2 – N1 – C5 – C6	0.7(6)	N1 – C5 – C6 – C7	0.4(6)
N2 – N1 – C5 – S1	-179.3(3)	S1 – C5 – C6 – C7	-179.7(3)
C1 – S1 – C5 – N1	-174.7(3)	C26 – C31 – C30 – C29	1.0(6)
C1 – S1 – C5 – C6	5.3(4)	C28 – C29 – C30 – C31	0.3(6)
N3 – N4 – C25 – C24	-1.3(6)	C32 – C29 – C30 – C31	-177.7(4)
N3 – N4 – C25 – C26	177.0(3)	C9 – C14 – C13 – C12	0.4(6)
C23 – C24 – C25 – N4	0.7(6)	C11 – C12 – C13 – C14	-0.8(6)
C23 – C24 – C25 – C26	-177.5(4)	C15 – C12 – C13 – C14	-179.6(4)
C31 – C26 – C25 – N4	178.4(3)	C31 – C26 – C27 – C28	2.0(6)
C27 – C26 – C25 – N4	-2.6(5)	C25 – C26 – C27 – C28	-176.9(4)
C31 – C26 – C25 – C24	-3.3(6)	C3 – C2 – C1 – S1	-179.4(3)
C27 – C26 – C25 – C24	175.7(4)	C5 – S1 – C1 – C2	174.3(3)
C5 – N1 – N2 – C8	-1.8(5)	C26 – C27 – C28 – C29	-0.8(6)
C12 – C11 – C10 – C9	-0.1(6)	C30 – C29 – C28 – C27	-0.4(6)
C14 – C9 – C10 – C11	-0.2(6)	C32 – C29 – C28 – C27	177.7(4)
C8 – C9 – C10 – C11	179.0(3)	C18 – C19 – C20 – C21	-179.0(4)
N1 – N2 – C8 – C7	1.7(5)	C15 – O2 – C16 – C17	85.4(5)
N1 – N2 – C8 – C9	179.9(3)	C32 – O4 – C33 – C34	-173.5(4)

2-(6-Chloro-3-(methylthio)pyridazin-4-yl)benzonitrile (22e)

Single crystals of compound **22e**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM 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 and data reduction were performed with the CrysAlisPro software.[238] Absorption correction using the multiscan method[238] was applied. The structures were solved with SHELXS-97,[239] refined with SHELXL-97[240] and finally checked using PLATON.[241] Details for data collection and structure refinement are summarized in Table 37.

CCDC-2278593 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[238] Program package 'CrysAlisPro 1.171.40.82a (Rigaku OD, 2020)'.
[239] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[240] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[241] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 37. Details for X-ray data collection and structure refinement for compound **22e**.

	22e
Empirical formula	$C_{12}H_8ClN_3S$
Formula mass	261.72
T[K]	123(2)
Crystal size [mm]	0.40 × 0.30 × 0.20
Crystal description	colorless block
Crystal system	triclinic
Space group	*P*-1
a [Å]	7.9221(5)
b [Å]	8.7886(5)
c [Å]	9.8552(4)
α [°]	66.992(5)
β [°]	87.109(4)
γ [°]	68.662(5)
V [Å^3]	584.90(6)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.486
μ [mm^{-1}]	0.483
F(000)	268
Θ range [°]	3.31 – 25.24
Index ranges	$-11 \leq h \leq 11$
	$-12 \leq k \leq 12$
	$-14 \leq l \leq 14$
Reflns. collected	11618
Reflns. obsd.	2994
Reflns. unique	3562 (R_{int} = 0.0223)
R_1, wR_2 (2σ data)	0.0336, 0.0848
R_1, wR_2 (all data)	0.0419, 0.0913
GOOF on F^2	1.044
Peak/hole [e Å^{-3}]	0.450 / -0.216

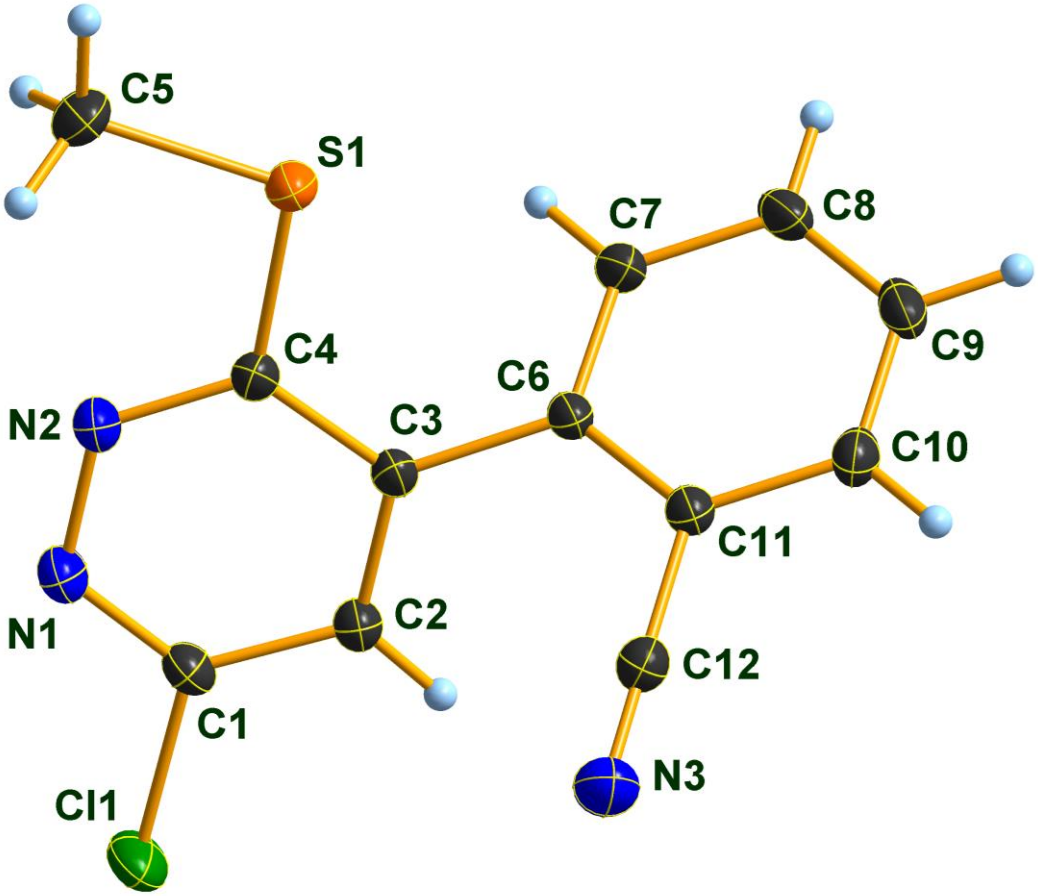


Figure 19. Molecular structure of compound **22e** in the crystal. DIAMOND[242] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 38. Selected bond lengths (Å) of compound **22e**.

S1 – C4	1.752(1)	C1 – C2	1.398(2)
S1 – C5	1.802(1)	N3 – C12	1.145(2)
Cl1 – C1	1.728(1)	C7 – C8	1.391(2)
C4 – N2	1.331(2)	C10 – C9	1.387(2)
C4 – C3	1.425(2)	C8 – C9	1.386(2)
N1 – C1	1.311(2)	C6 – C3	1.485(2)
N1 – N2	1.356(2)	C3 – C2	1.373(2)
C6 – C7	1.392(2)	C11 – C10	1.397(2)
C6 – C11	1.405(2)	C11 – C12	1.444(2)

[242] DIAMOND, Crystal Impact GbR., Version 3.2i.

Table 39. Selected bond angles (°) of compound **22e**.

C4 – S1 – C5	101.6(1)	C3 – C2 – C1	117.3(1)
N2 – C4 – C3	122.9(1)	C9 – C10 – C11	119.5(1)
N2 – C4 – S1	117.9(1)	N3 – C12 – C11	179.3(2)
C3 – C4 – S1	119.2(1)	C9 – C8 – C7	120.5(1)
C1 – N1 – N2	118.2(1)	C8 – C9 – C10	120.1(1)
C7 – C6 – C11	118.5(1)	C10 – C11 – C6	120.9(1)
C7 – C6 – C3	120.3(1)	C10 – C11 – C12	118.8(1)
C11 – C6 – C3	121.2(1)	C6 – C11 – C12	120.3(1)
C4 – N2 – N1	120.2(1)	N1 – C1 – C2	125.1(1)
C2 – C3 – C4	116.2(1)	N1 – C1 – Cl1	116.0(1)
C2 – C3 – C6	121.2(1)	C2 – C1 – Cl1	118.8(1)
C4 – C3 – C6	122.6(1)	C8 – C7 – C6	120.5(1)

Table 40. Selected torsion angles (°) of compound **22e**.

C5 – S1 – C4 – N2	0.1(1)	C7 – C6 – C11 – C12	180.0(1)
C5 – S1 – C4 – C3	-179.4(1)	C3 – C6 – C11 – C12	-1.9(2)
C3 – C4 – N2 – N1	2.7(2)	N2 – N1 – C1 – C2	-2.6(2)
S1 – C4 – N2 – N1	-176.8(1)	N2 – N1 – C1 – Cl1	177.9(1)
C1 – N1 – N2 – C4	0.1(2)	C11 – C6 – C7 – C8	-1.1(2)
N2 – C4 – C3 – C2	-2.8(2)	C3 – C6 – C7 – C8	-179.2(1)
S1 – C4 – C3 – C2	176.6(1)	C4 – C3 – C2 – C1	0.4(2)
N2 – C4 – C3 – C6	177.4(1)	C6 – C3 – C2 – C1	-179.8(1)
S1 – C4 – C3 – C6	-3.2(2)	N1 – C1 – C2 – C3	2.4(2)
C7 – C6 – C3 – C2	122.8(1)	Cl1 – C1 – C2 – C3	-178.2(1)
C11 – C6 – C3 – C2	-55.2(2)	C6 – C11 – C10 – C9	0.4(2)
C7 – C6 – C3 – C4	-57.4(2)	C12 – C11 – C10 – C9	-179.1(1)
C11 – C6 – C3 – C4	124.6(1)	C6 – C7 – C8 – C9	0.9(2)
C7 – C6 – C11 – C10	0.5(2)	C7 – C8 – C9 – C10	0.0(2)
C3 – C6 – C11 – C10	178.6(1)	C11 – C10 – C9 – C8	-0.6(2)

Methyl 3-(butylthio)-5-phenyl-4-(thiophene-2-carbonyl)thieno[2,3-c]pyridazine-6-carboxylate (23c)

Single crystals of compound **23c**, suitable for X-ray diffraction, were obtained by slow evaporation of DCM 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 and data reduction were performed with the CrysAlisPro software.[a)][243] Absorption correction using the multiscan method[243] was applied. The structures were solved with SHELXS-97,[244] refined with SHELXL-97[245] and finally checked using PLATON.[246] Details for data collection and structure refinement are summarized in Table 41.

CCDC-2270626 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[243] Program package 'CrysAlisPro 1.171.40.82a (Rigaku OD, 2020)'.
[244] Sheldrick, G. M. (1997) SHELXS-97: *Program for Crystal Structure Solution*, University of Göttingen, Germany.
[245] Sheldrick, G. M. (1997) SHELXL-97: *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[246] Spek, A. L. (1999) PLATON: *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands.

Table 41. Details for X-ray data collection and structure refinement for compound **23c**.

	23c
Empirical formula	$C_{23}H_{20}N_2O_3S_3$
Formula mass	468.59
T[K]	123(2)
Crystal size [mm]	0.30 × 0.30 × 0.10
Crystal description	yellow block
Crystal system	triclinic
Space group	*P*-1
a [Å]	9.7642(4)
b [Å]	9.8856(4)
c [Å]	11.1941(5)
α [°]	91.289(4)
β [°]	92.507(4)
γ [°]	100.086(4)
V [Å^3]	1062.29(8)
Z	2
$\rho_{calcd.}$ [g cm^{-3}]	1.465
μ [mm^{-1}]	0.378
F(000)	488
Θ range [°]	2.12 – 25.24
Index ranges	$-13 \leq h \leq 13$
	$-13 \leq k \leq 13$
	$-14 \leq l \leq 14$
Reflns. collected	18084
Reflns. obsd.	4505
Reflns. unique	5243 (R_{int} = 0.0238)
R_1, wR_2 (2σ data)	0.0324, 0.0790
R_1, wR_2 (all data)	0.0402, 0.0840
GOOF on F^2	1.026
Peak/hole [e Å^{-3}]	0.683 / -0.414

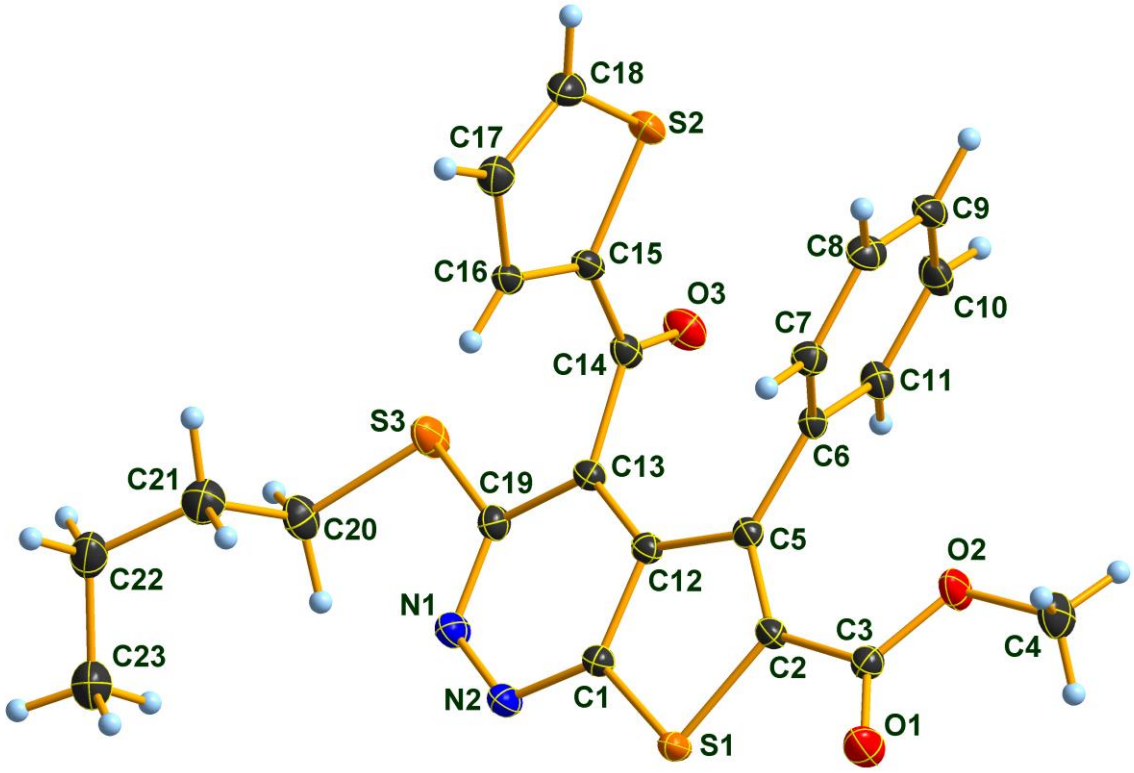


Figure 20. Molecular structure of compound **23c** in the crystal. DIAMOND[247] representation; thermal ellipsoids are drawn at 50 % probability level.

Table 42. Selected bond lengths (Å) of compound **23c**.

S1 – C1	1.732(1)	C6 – C11	1.392(2)
S1 – C2	1.741(1)	C6 – C7	1.394(2)
O1 – C3	1.206(2)	C7 – C8	1.388(2)
N1 – N2	1.341(2)	C8 – C9	1.387(2)
N1 – C19	1.344(2)	C9 – C10	1.386(2)
C1 – N2	1.326(2)	C10 – C11	1.391(2)
C1 – C12	1.417(2)	C19 – C13	1.413(2)
S2 – C18	1.700(2)	C12 – C13	1.392(2)
S2 – C15	1.722(1)	C13 – C14	1.514(2)
O2 – C3	1.326(2)	C21 – C20	1.517(2)
O2 – C4	1.446(2)	C21 – C22	1.535(2)
C2 – C5	1.366(2)	C22 – C23	1.515(2)
C2 – C3	1.487(2)	C16 – C17	1.415(2)
S3 – C19	1.758(1)	C17 – C18	1.364(2)

[247] DIAMOND, Crystal Impact GbR., Version 3.2i.

S3 – C20	1.812(2)	C5 – C12	1.449(2)
O3 – C14	1.219(2)	C5 – C6	1.485(2)
C15 – C16	1.392(2)	C15 – C14	1.453(2)

Table 43. Selected bond angles (°) of compound **23c**.

C1 – S1 – C2	90.1(1)	C9 – C10 – C11	120.1(1)
N2 – N1 – C19	119.9(1)	C10 – C11 – C6	120.3(1)
N2 – C1 – C12	126.5(1)	C17 – C18 – S2	112.6(1)
N2 – C1 – S1	121.2(1)	N1 – C19 – C13	124.1(1)
C12 – C1 – S1	112.4(1)	N1 – C19 – S3	118.6(1)
C18 – S2 – C15	91.6(1)	C13 – C19 – S3	117.3(1)
C3 – O2 – C4	116.5(1)	C13 – C12 – C1	115.1(1)
C1 – N2 – N1	117.7(1)	C13 – C12 – C5	132.9(1)
C5 – C2 – C3	130.8(1)	C1 – C12 – C5	112.0(1)
C5 – C2 – S1	115.2(1)	C12 – C13 – C19	116.6(1)
C3 – C2 – S1	114.1(1)	C12 – C13 – C14	123.7(1)
C19 – S3 – C20	103.3(1)	C19 – C13 – C14	119.7(1)
O1 – C3 – O2	125.3(1)	O3 – C14 – C15	124.4(1)
O1 – C3 – C2	122.1(1)	O3 – C14 – C13	119.8(1)
O2 – C3 – C2	112.6(1)	C15 – C14 – C13	115.8(1)
C16 – C15 – C14	127.7(1)	C20 – C21 – C22	112.9(1)
C16 – C15 – S2	111.6(1)	C23 – C22 – C21	115.2(1)
C14 – C15 – S2	120.7(1)	C21 – C20 – S3	113.0(1)
C15 – C16 – C17	111.3(1)	C11 – C6 – C5	120.2(1)
C18 – C17 – C16	112.9(1)	C7 – C6 – C5	120.5(1)
C2 – C5 – C12	110.5(1)	C8 – C7 – C6	120.2(1)
C2 – C5 – C6	125.6(1)	C9 – C8 – C7	120.3(1)
C12 – C5 – C6	124.0(1)	C10 – C9 – C8	119.9(1)
C11 – C6 – C7	119.3(1)		

Table 44. Selected torsion angles (°) of compound **23c**.

C2 – S1 – C1 – N2	-179.2(1)	C16 – C17 – C18 – S2	1.4(2)
C2 – S1 – C1 – C12	-0.6(1)	C15 – S2 – C18 – C17	-1.0(1)
C12 – C1 – N2 – N1	3.7(2)	N2 – N1 – C19 – C13	-2.0(2)
S1 – C1 – N2 – N1	-177.9(1)	N2 – N1 – C19 – S3	175.6(1)

C19 – N1 – N2 – C1	-1.9(2)	C20 – S3 – C19 – N1	10.9(1)
C1 – S1 – C2 – C5	1.3(1)	C20 – S3 – C19 – C13	-171.3(1)
C1 – S1 – C2 – C3	-177.4(1)	N2 – C1 – C12 – C13	-1.4(2)
C4 – O2 – C3 – O1	1.4(2)	S1 – C1 – C12 – C13	-179.9(1)
C4 – O2 – C3 – C2	-176.1(1)	N2 – C1 – C12 – C5	178.4(1)
C5 – C2 – C3 – O1	165.9(2)	S1 – C1 – C12 – C5	-0.2(2)
S1 – C2 – C3 – O1	-15.6(2)	C2 – C5 – C12 – C13	-179.2(2)
C5 – C2 – C3 – O2	-16.5(2)	C6 – C5 – C12 – C13	3.0(2)
S1 – C2 – C3 – O2	162.0(1)	C2 – C5 – C12 – C1	1.1(2)
C18 – S2 – C15 – C16	0.4(1)	C6 – C5 – C12 – C1	-176.7(1)
C18 – S2 – C15 – C14	-177.6(1)	C1 – C12 – C13 – C19	-2.5(2)
C14 – C15 – C16 – C17	178.1(1)	C5 – C12 – C13 – C19	177.9(1)
S2 – C15 – C16 – C17	0.4(2)	C1 – C12 – C13 – C14	179.5(1)
C15 – C16 – C17 – C18	-1.2(2)	C5 – C12 – C13 – C14	-0.2(2)
C3 – C2 – C5 – C12	176.9(1)	N1 – C19 – C13 – C12	4.3(2)
S1 – C2 – C5 – C12	-1.6(2)	S3 – C19 – C13 – C12	-173.4(1)
C3 – C2 – C5 – C6	-5.4(2)	N1 – C19 – C13 – C14	-177.6(1)
S1 – C2 – C5 – C6	176.2(1)	S3 – C19 – C13 – C14	4.7(2)
C2 – C5 – C6 – C11	113.6(2)	C16 – C15 – C14 – O3	169.5(1)
C12 – C5 – C6 – C11	-68.9(2)	S2 – C15 – C14 – O3	-13.0(2)
C2 – C5 – C6 – C7	-67.2(2)	C16 – C15 – C14 – C13	-10.9(2)
C12 – C5 – C6 – C7	110.2(2)	S2 – C15 – C14 – C13	166.6(1)
C11 – C6 – C7 – C8	1.7(2)	C12 – C13 – C14 – O3	97.8(2)
C5 – C6 – C7 – C8	-177.4(1)	C19 – C13 – C14 – O3	-80.2(2)
C6 – C7 – C8 – C9	-1.5(2)	C12 – C13 – C14 – C15	-81.9(2)
C7 – C8 – C9 – C10	0.3(2)	C19 – C13 – C14 – C15	100.2(2)
C8 – C9 – C10 – C11	0.8(2)	C20 – C21 – C22 – C23	61.0(2)
C9 – C10 – C11 – C6	-0.6(2)	C22 – C21 – C20 – S3	171.4(1)
C7 – C6 – C11 – C10	-0.6(2)	C19 – S3 – C20 – C21	78.6(1)
C5 – C6 – C11 – C10	178.5(1)		