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Hot Paper

Selective and Stepwise Functionalization of the Pyridazine Scaffold by Using Thio-Substituted Pyridazine Building Blocks

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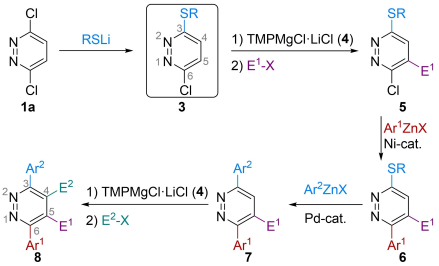
We described a regioselective tri- and tetra-functionalization of the pyridazine scaffold using two readily available building blocks: 3-alkylthio-6-chloropyridazine and 3,4-*bis*(methylthio)-6-chloropyridazine by performing selective metalations with TMPMgCl·LiCl and catalyst-tuned cross-coupling reactions with arylzinc halides. Several of the resulting pyridazines were converted into more elaborated N-heterocycles such as thieno[2,3-*c*]pyridazines and 1*H*-pyrazolo[3,4-*c*]pyridazines.

Introduction

Diazines are an important class of N-heterocycles because of their numerous applications in agrochemical and pharmaceutical industries.[1] In fact, heteroaromatic rings are often used as phenyl bioisosteres.[2] The selective preparation and further functionalization of these heterocyclic scaffolds is an important current synthetic goal.[3] Although the preparation of substituted pyrimidines and pyrazines was well studied,[4] 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.[5] Also, unsymmetrical amino-chloropyridazines have been regioselectively lithiated.[6] Pyridazine itself was lithiated and *bis*-lithiated using TMPLi (TMP = 2,2,6,6-tetramethyl-piperidin-1-yl).[7] 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 be desirable.[8] Recently, we have reported directed zincations[9] using $TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (**2a**)[10] or $BF_3\cdot OEt_2$ assisted zincations[11] using TMPZnCl·LiCl (**2b**)[12] 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**).[13] We will demonstrate that **3** may be regioselectively magnesiated with TMPMgCl·LiCl (**4**)[14] and trapped with various electrophiles (E^1-X) providing pyridazines of type **5**. Selective Ni-catalyzed cross-couplings[15] 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[16] to furnish tri-functionalized compounds of type **7**. Magnesiation with TMPMgCl·LiCl (**4**)[14] followed by addition of an electrophile (E^2-X) selectively led to tetra-functionalized pyridazines of type **8** (Scheme 1).

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[15d] providing 3,4-*bis*(methylthio)-6-aryl pyridazines of type **10**. A subsequent Pd-catalysis[16c,d] 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[17] further promoted arylation at position 3, providing various 3,4,6-*tris*-arylated pyridazines of type **12** (Scheme 2).

Thus, we report two alternative functionalizations of the pyridazine scaffold allowing to regioselectively prepare various tri- or tetra-functionalized pyridazines. Furthermore, we also



Scheme 1. Selective stepwise tetra-functionalization of the pyridazine building block of type **3** providing fully substituted pyridazines of type **8**.

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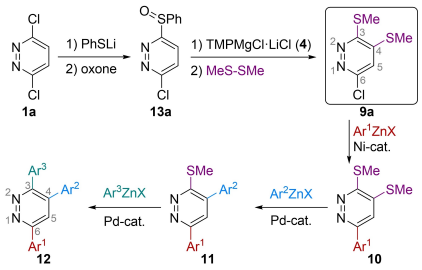


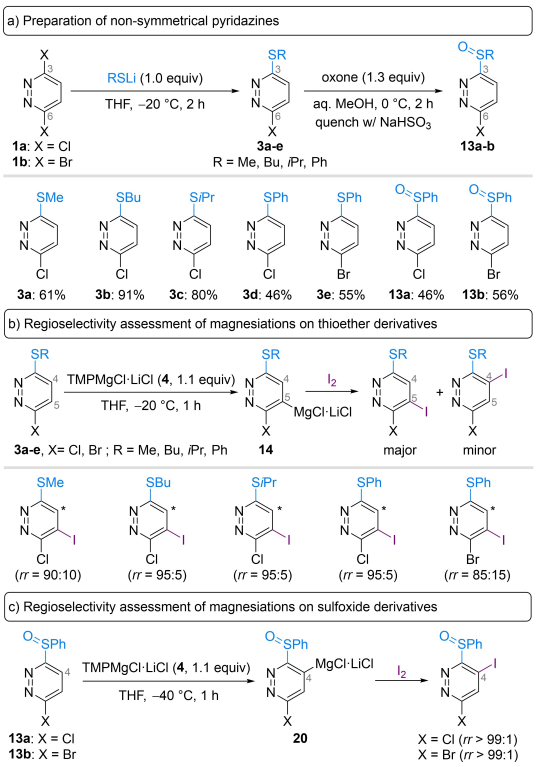
Scheme 2. Selective stepwise *tris*-arylation of the pyridazine building block **9a** providing trisubstituted pyridazines of type **12**.

show that some fused bicyclic heterocycles such as thieno[2,3-*c*]pyridazines and 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.

Results and Discussion

In order to evaluate the regioselectivity of magnesiation with TMPMgCl·LiCl (**4**),[14] 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 monothioether pyridazines of type **3** in 46–91% yield (Scheme 3a). Additionally sulfoxides of type **13** were generated by subsequent oxidation of the corresponding thioethers with oxone (46-56% yield).[18] In preliminary experiments, the metalation regioselectivity using TMPMgCl·LiCl (**4**)[14] was studied on pyridazines of type **3** (Scheme 3b). 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**)[14] and iodolysis, the iodinated compounds at position 4 selectively (*rr* > 99:1, Scheme 3c). The new regioselectivity is a result of the better complexation power of the sulfoxide group in the intermediate complex prior to the metalation step.[19] The unstability of all these iodinated pyridazines precludes an isolation. However, quenchings with other electrophiles confirm these regioselectivities (see Schemes 4 and 9).

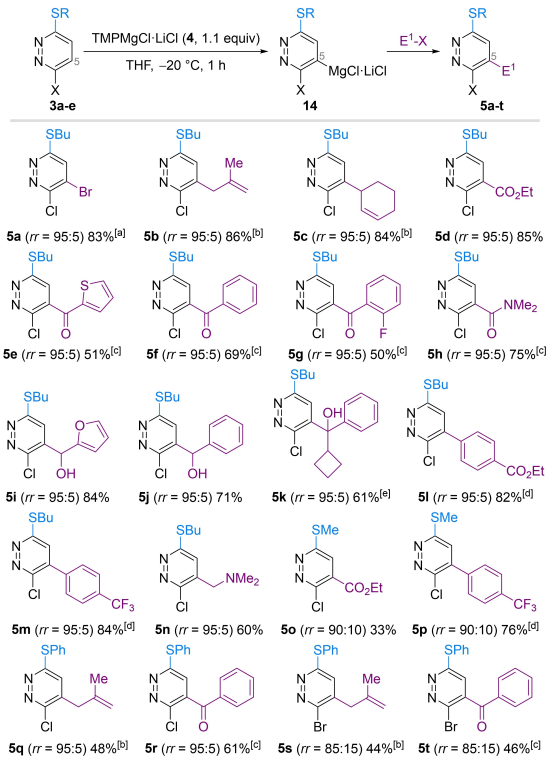
With these regioselective metalation tools in hands, we started exploring the scope of the functionalization at position 5 of pyridazines of type **3** using TMPMgCl·LiCl[14] (**4**, 1.1 equiv., −20 °C, THF, 1 h) and subsequent electrophilic trapping (Scheme 4). Thus, bromination and copper-catalyzed allylation[20] 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[20] providing the carbonyl derivatives **5e–h** in 51–75% yield.



Scheme 3. 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.

Similarly, reactions with aldehydes or ketones furnished secondary and tertiary alcohols **5i–k**[21] in 61–84% yield. Transmetalation to the corresponding zinc species with $ZnCl_2$ and subsequent Negishi cross-coupling[22] using 5 mol% $Pd(dba)_2$ and 10 mol% tri(2-furyl)phosphine as catalytic system[23] led to arylated products **5l** and **5m** in 82–84% yield. The metalated species **14** could also be aminomethylated using Tietze salt[24] 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.

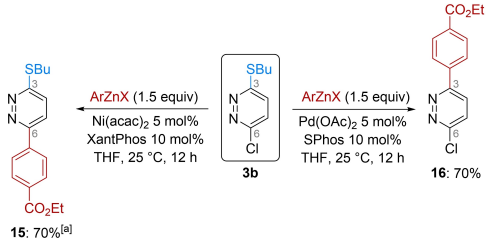
Then, Negishi cross-coupling[22] reactions were envisioned for the functionalization at position 3 and 6 of the resulting pyridazines of type **5**. Indeed both chloride and thioether undergo selective cross-coupling reactions. Pd- or Ni-catalyzed Negishi type cross-coupling reactions with unsaturated thioethers were previously reported.[16c,d] Nevertheless, such cross-couplings were so far only described using thiomethyl- or thiophenyl-substituted heterocycles. Preliminary studies[25] on



Scheme 4. 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.

compound **3b** led to selective conditions for the Negishi cross-coupling[22] reactions: Substitution of the chlorine group using Ni-catalysis[15d,26] gave compound **15**[27] in 70% yield and replacement of the butylthio substituent using Pd-catalysis[28] led to product **16** in 70% yield (Scheme 5).

However, for substituted pyridazines of type **5** containing an additional substituent at position 5, the previously developed Pd-catalyzed conditions[28] 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[15d,26] at position 6. Thus, pyridazines of

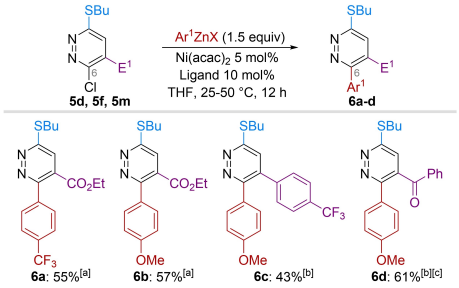


Scheme 5. Optimized conditions for Negishi cross-coupling at position 3 using Pd-catalysis and at position 6 using Ni-catalysis on compound **3b**. [a]The structure was confirmed by X-ray analysis.

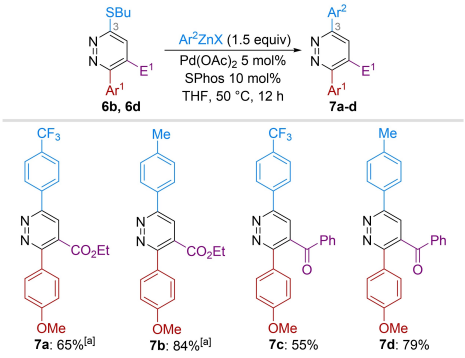
type **5** were selectively cross-coupled with arylzinc reagents (Ar^1ZnX, 1.5 equiv.) using 5 mol% $Ni(acac)_2$ and 10 mol% phosphine ligands[29] as catalytic system (Scheme 6). Depending on the functional group in ortho position of the chlorine group, either DPE- or Xant-phos[29] were used. The chloropyridazine **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[22] with (4-methoxyphenyl)zinc chloride resulted in the desired products **6c** and **6d**[27] 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**.

Position 3 was subsequently functionalized using Pd-catalysis.[28] 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[28] as catalytic system (Scheme 7). Cross-coupling of the ester-substituted pyridazine **6b** gave the *bis*-arylated products **7a**[27] and **7b**[27] in 65–84% isolated yield. Pyridazines **6d** with a ketone moiety in position 5 reacted similarly and led to **7c** and **7d** in 55–79% yield.

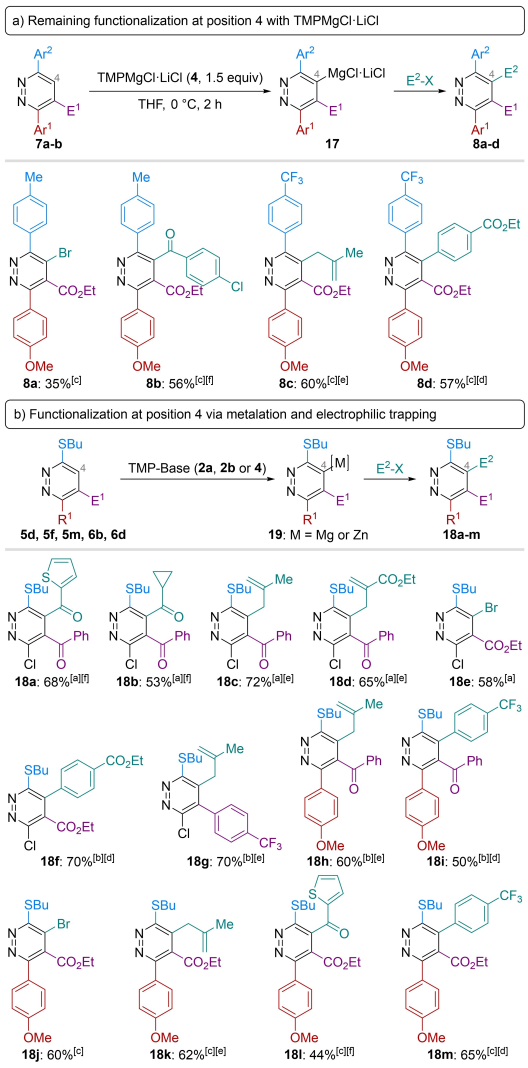
The remaining position 4 of the pyridazine core was magnesiated using TMPMgCl·LiCl[14] (**4**, 1.5 equiv., 0 °C, THF, 2 h). The resulting magnesiated intermediates **17** were trapped with various electrophiles (E^2-X, Scheme 8a). Thus, after bromi-



Scheme 6. 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.



Scheme 7. 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.



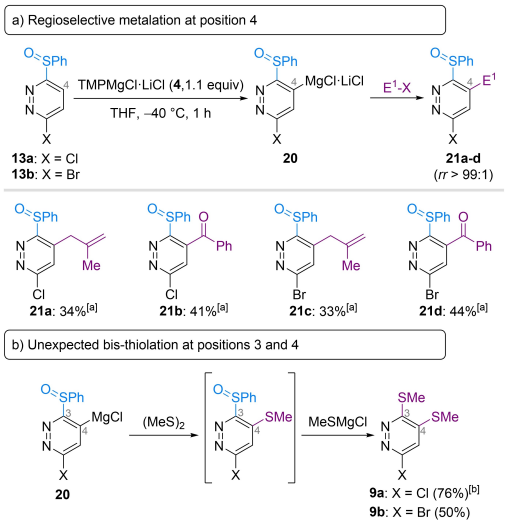
Scheme 8. Functionalization at position 4 via metalation and electrophilic trapping. [a] TMPZnCl·LiCl (**2b**, 1.1 equiv.) was used, [b] $TMP_2Zn·2MgCl_2·2LiCl$ (**2a**, 1.2 equiv.) was used, [c] TMPMgCl·LiCl (**4**, 1.5 equiv.) was used, [d] obtained by Pd-catalyzed cross-coupling: Pd(dba)2 (5 mol%) and tri(2-furyl)phosphine (10 mol%), [e] CuCN·2LiCl (10 mol%) was used, [f] CuCN·2LiCl (1.1 equiv.) was used.

nation using $(BrCCl_2)_2$ or copper-mediated acylation,[20] the trisubstituted pyridazine **7b** furnished the fully functionalized pyridazines **8a** and **8b** in 35% and 56% yield respectively. Similarly, CuCN·2LiCl catalyzed allylation[20] 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[23] with ethyl 4-iodobenzoate leading to **8d** in 57% yield.

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 4) using TMPZnCl·LiCl[9b,c, 12] (**2b**, 1.1 equiv., 25 °C, THF, 2 h) followed by a copper mediated[20] 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[9b,c,12] (**2b**, 1.1 equiv., 25 °C, THF, 2 h) or $TMP_2Zn·2MgCl_2·2LiCl$[10] (**2a**, 1.2 equiv., 25 °C, THF, 12 h). The resulting zinc species **19** were subsequently functionalized by brominations, copper-catalyzed allylations[20] and Pd-catalyzed cross-coupling reactions[23] (**18e–g**, 58–70% 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 $TMP_2Zn·2MgCl_2·2LiCl$[10] (**2a**, 1.2 equiv., 25 °C, THF, 12 h) and electrophilic trapping. In addition, the ester substituted pyridazine **6b** was magnesiated with TMPMgCl·LiCl[14] (**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[22–23] with 1-iodo-4-(trifluoromethyl)benzene was successful after transmetalation with $ZnCl_2$ giving **18m** in 65% yield (Scheme 8b). 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**.

Following the reaction pathway described in Scheme 2, the sulfoxides **13a** and **13b** were treated with TMPMgCl·LiCl[14] (**4**, 1.1 equiv., −40 °C, THF, 1 h) resulting in a regioselective magnesiation at position 4 (Scheme 9a). Copper-catalyzed allylations and acylations[20] of the 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**[27] in 50–76% yield (Scheme 9b).[30]

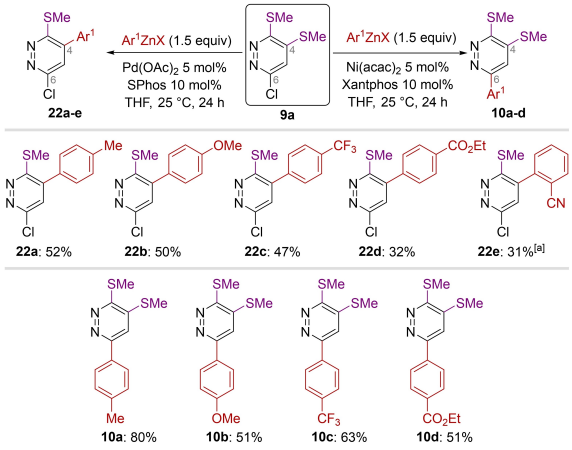
It turns out that 6-chloro-3,4-*bis*(methylthio)pyridazine (**9a**) was a valuable scaffold since the choice of the catalytic system in cross-coupling reactions allowed either a substitution of the



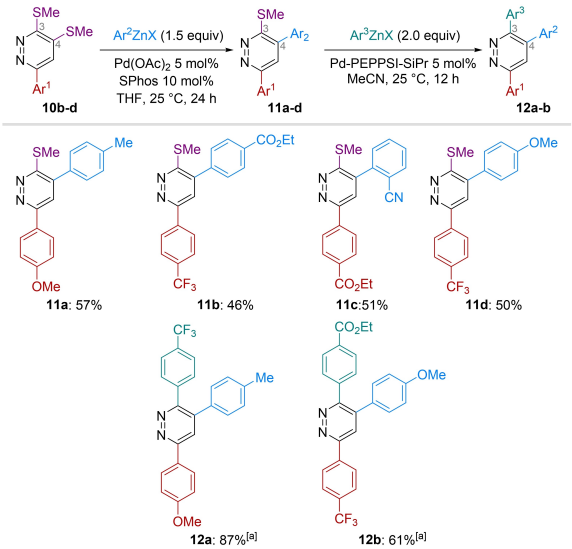
Scheme 9. Regioselective magnesiation of pyridazine of type **13** with TMPMgCl·LiCl (**4**) and subsequent electrophile quench at position 4. [a] CuCN·2LiCl (10 mol%) was used. [b] The structure was confirmed by X-ray analysis.

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) in the presence of 5 mol% $Pd(OAc)_2$ and 10 mol% SPhos[28] led to 4-arylated pyridazines of type **22**[27] 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[29] provided 6-arylated pyridazines of type **10** in 51–80% yield (Scheme 10).

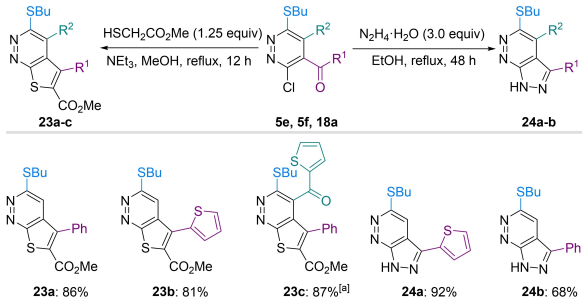
These 6-arylated pyridazines of type **10** were submitted to a second Negishi cross-coupling[22] with Ar^2ZnX (5 mol% $Pd(OAc)_2$ and 10 mol% SPhos)[28] to give regioselectively the 4,6-*bis*-arylated pyridazines **11a–d** in 46–57% yield. Furthermore, the



Scheme 10. 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.



Scheme 11. 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.



Scheme 12. 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.

remaining 3-methylthio group reacted with different arylzinc halides (Ar^3ZnX) using a more powerful Pd-catalyst system (5 mol% Pd-PEPPSI-SiPr[17] in MeCN, 25 °C, 12 h), leading to the *tris*-arylated pyridazines **12a–b**[27] in 61–87% yield (Scheme 11).

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 $HSCH_2CO_2Me$[31] in the presence of NEt_3, after refluxing for 12 h in MeOH, the thieno[2,3-*c*]pyridazines **23a–c**[27] were isolated in 81–87% yield. Similarly, the ketones **5e** and **5f** were treated with hydrazine hydrate[32] giving the corresponding 1*H*-pyrazolo[3,4-*c*]pyridazines **24a** and **24b** in 68–92% yield (Scheme 12).

Conclusions

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 1) and 3,4-*bis*(methylthio)-6-chloropyridazine (**9a**) (Scheme 2) 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 12). The structures of several new pyridazines have been confirmed by X-ray analysis. Furthermore, extensions of this work are underway.

Experimental Section

For experimental procedures, analytical data, and NMR spectra, see the Supporting Information.

General procedure for the magnesiation of pyridazine derivatives using TMPMgCl·LiCl: A dry and argon flushed flask, equipped with a magnetic stirrer and a septum, was charged with the pyridazine of type **3** (0.5 mmol, 1.0 equiv.) in dry THF (1 mL).The solution was treated with 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, the electrophilic quench was performed. The resulting mixture was stirred for 12 h at the appropriate

temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3×20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated in *vacuo*. Purification by flash column chromatography provided the product. For more details, please refer to the Supporting Information.

General procedure for the Negishi cross-coupling: A dry and argon flushed flask, equipped with a magnetic stirrer and a septum, was charged with the corresponding pyridazine (0.5 mmol, 1.0 equiv.) in dry THF (1 mL). The catalyst (5 mol%) and the ligand (10 mol%) were added to the solution. Then, the organozinc reagent solution (0.75 mmol, 1.5 equiv.) was added dropwise to the mixture at 25 °C. The resulting reaction mixture was stirred at the appropriate temperature for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with ethyl acetate (3×20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated in *vacuo*. Purification by flash column chromatography provided the product. For more details, please refer to the Supporting Information.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: cross-coupling · magnesium amides · metalation · N-heterocycles · pyridazine

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