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Reliable Functionalization of 5,6-Fused Bicyclic N-Heterocycles Pyrazolopyrimidines and Imidazopyridazines via Zinc and Magnesium Organometallics

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Dedicated to our colleague Professor Anja Hoffmann-Röder on the occasion of her 50th birthday.

Abstract: DFT-calculations allow prediction of the reactivity of uncommon N-heterocyclic scaffolds of pyrazolo[1,5-*a*]pyrimidines and imidazo[1,2-*b*]pyridazines and considerably facilitate their functionalization. The derivatization of these N-heterocycles was realized using Grignard reagents for nucleophilic additions to 5-chloropyrazolo[1,5-*a*]pyrimidines and $TMP_2Zn \cdot 2\,MgCl_2 \cdot 2\,LiCl$ allowed regioselective zincations. In the case of 6-chloroimidazo[1,2-*b*]pyridazine, bases such as $TMP_2Zn \cdot MgCl_2 \cdot 2\,LiCl$, in the presence or absence of $BF_3 \cdot OEt_2$, led to regioselective metalations at positions 3 or 8. Subsequent functionalizations were achieved with $TMPMgCl \cdot LiCl$, producing various polysubstituted derivatives (up to penta-substitution). X-ray analysis confirmed the regioselectivity for key functional heterocycles.

Introduction

N-Heterocycles are key scaffolds for various applications, especially in pharmaceutical and agrochemical research.[1] Monocyclic N-heterocycles, including pyridines, pyrimidines, pyridazines, pyrroles, imidazoles and pyrazoles, as well as benzo-derivatives of these skeletons such as indoles and quinolines, have found numerous applications.[2] The synthesis of new N-heterocyclic cores are being actively investigated; the interest being, triggered by their potential new physicochemical and medicinal properties and favorable pharmacokinetics.[3] Two promising isomeric N-heterocycles, containing three nitrogen atoms embedded in a [4.3.0]-ring system, are pyrazolo[1,5-*a*]pyrimidines (**1a**) and imidazo[1,2-*b*]pyridazines (**2a**). These systems have been chosen based on the potential high impact of the pyrazolo[1,5-*a*]pyrimidine scaffold for pharmaceutical applications.[4] Thus, pyrazolo[1,5-*a*]pyrimidines such as zaleplon (**3**), a sedative and hypnotic agent,[5] the pain regulator larotrectinib **4**,[6] and the kinase inhibitor **5**,[7] are representative biomolecules of this important class of bicyclic N-heterocycles.[8] The antiplasmodial imidazopyridazine **6**[9] is also representative for this second class of bicyclic N-heterocycles (Figure 1).

The predictive decoration of these new heterocyclic scaffolds is an important synthetic challenge. The principle of predictive functionalization has been successfully applied to various N-heterocycles using theoretical computational methods such as molecular mechanics (MM) and density-functional theory (DFT).[10] Such approaches may allow a differentiation of all possible ring positions and an assessment of the electrophilicity of each carbon as well as the acidity of each ring proton. To facilitate such reactivity differences, we choose to start with the mono-chloro-substituted compounds **1b** and **2b**, assuming that the chlorine substituent can be readily replaced with various functional groups at a later stage.[11]

Herein, we report a range of selective functionalizations of the isomeric N-heterocycles **1b** and **2b** with the help of theoretical investigations. Remarkably, this study led to a new nucleophilic addition procedure on heterocycles derived from pyrazolo[1,5-*a*]pyrimidine (**1a**). This nucleophilic addition considerably expands the functionalization opportunities of scaffold **1a** and complements metalations of **1a** with TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl). In the case of N-heterocycles of type **2a**, calculations showed that successive metalations should allow their full regioselective decoration. These successful functionalizations of **1b** and **2b** are described below.

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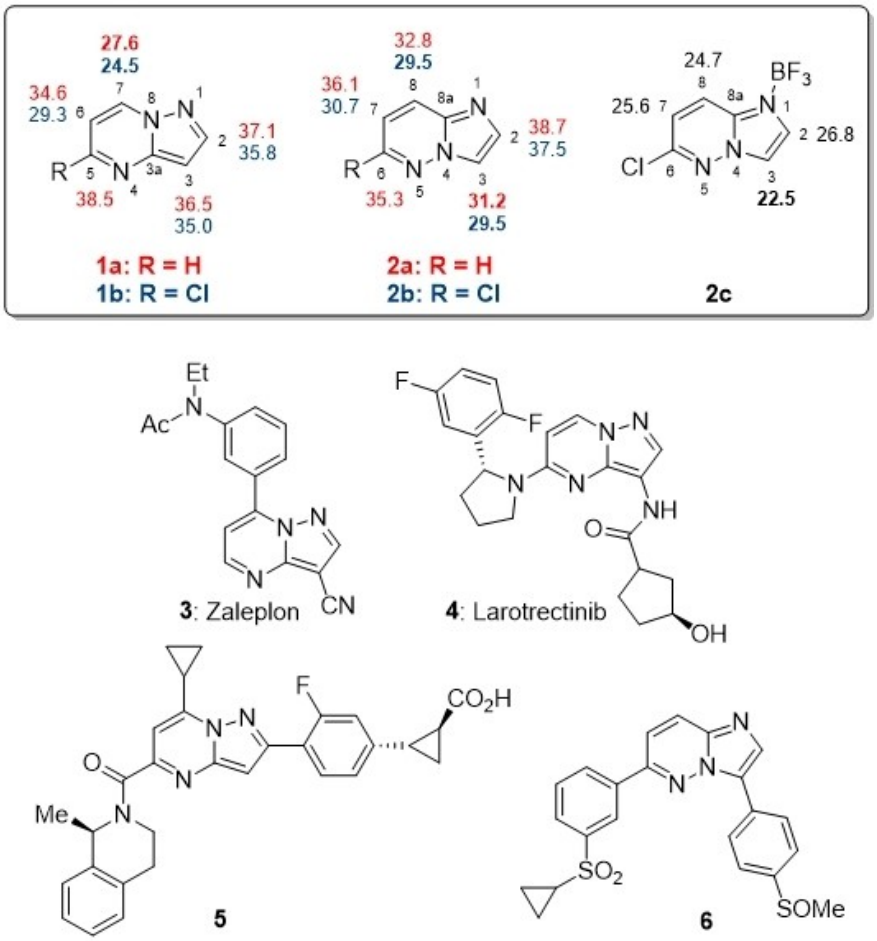


Figure 1. General structures of pyrazolo[1,5-*a*]pyrimidines **1 a** and imidazo[1,2-*b*]pyridazines **2 a** as well as chloro-derivatives **1 b** and **2 b** including calculated pK_a-values (DMSO), as well as drugs or drug candidates of these N-heterocycle classes.

Results and Discussion

We have initiated our investigations by calculating the pK_a-values of all ring protons in compounds **1 a**, **1 b**, **2 a** and **2 b** as well as the BF_3-complex **2 c** using previously developed computational protocol[10e] (Figure 1). These pK_a-values clearly indicated that position 7 of the pyrazolo[1,5-*a*]pyrimidines **1 b** is the most acidic and should be selectively metalated. On the other hand, in the case of the chlorinated imidazo[1,2-*b*]pyridazine **2 b** the predicted pK_a-values of H3 and H8 were identical. Thus, thermodynamic considerations will not allow a differentiation of these positions. However, kinetic considerations involving the complex-induced proximity effect (CIPE) introduced by Snieckus and Beak[12] clearly favor position 8 for a first metalation due to the preferred coordination of the metallic base to the most basic N(1)-atom. We have also examined the coordination of a strong Lewis acid such as $BF_3 \cdot OEt_2$ to the nitrogen atoms of **2 b** in order to induce a pK_a change and have explored the impact of this change on the metalation regioselectivity. Initial calculations indicated that the thermodynamically preferred site for Lewis acid coordination is N1 (see structure **2 c**, Figure 1).

This coordination lowered the pK_a-values of all protons in the Lewis acid adduct. However, the position 3 was clearly most acidified, indicating that a regioselectivity switch of the metalation might be induced through a coordination with $BF_3 \cdot OEt_2$ before the addition of the TMP-base.[13] Finally, we have calculated the electrophilicity of the various ring positions by using methyl anion affinities (MAA)[14] as indicated in Figure 2. Thus, the MAA of various positions for **1 b** and **2 b** have been determined, showing that position 7 of **1 b** was highly activated towards a nucleophilic attack (MAA(C7) = −102.0 kJ/mol). On the other hand, for the imidazo[1,2-*b*]pyridazine **2 b** the corresponding position C8 was significantly less electrophilic (MAA(C8) = −80.3 kJ/mol). In summary, the pyrazolo[1,5-*a*]pyrimidine **1 b** is expected to coordinate metallic bases such as TMPMetX (Met=Zn, Mg; X=Hal), or organometallic reagents RMetX preferentially at N (1) allowing both metalations or nucleophilic addition via primary complexes **A** or **B** (Scheme 1).

After metalation or nucleophilic addition, the organometallic intermediate **7** or **8** should be obtained. Reaction with an electrophile (E–X) or oxidative workup would yield functionalized pyrazolo[1,5-*a*]pyrimidines of type **9** or **10**. Concerning 6-chloroimidazo[1,2-*b*]pyridazine (**2 b**), a complexation of either

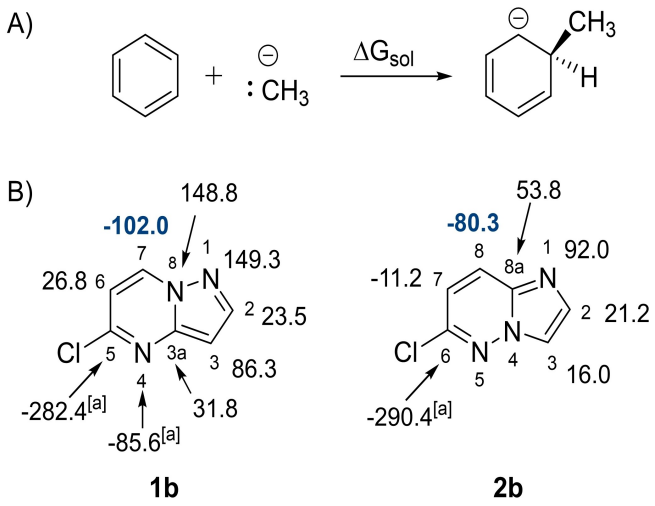
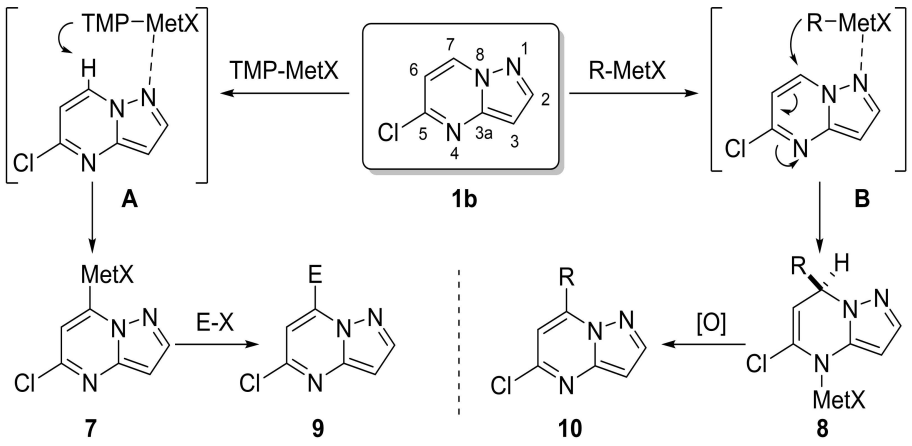


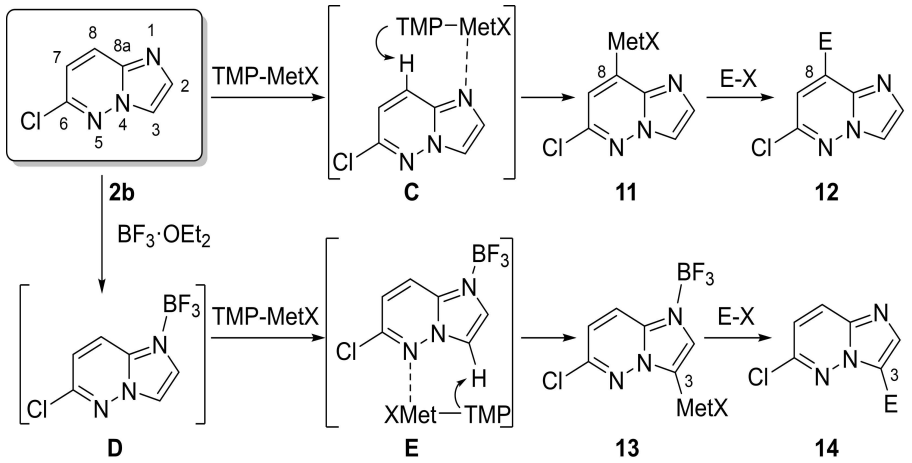
Figure 2. Methyl anion affinity values (MAA, in kJ/mol) calculated at SMD-(DMSO)/B3LYP/6-311 + + G(3df,2pd) //B3LYP/6-31G(d,p) level of theory. [a] Addition of methyl anion leads to Cl elimination.

TMPMetX or $BF_3 \cdot OEt_2$ at the most basic N(1)-nitrogen atom should provide the complexes **C** and **D**. This complex **C** will readily lead to the metalation of position 8 affording the organometallic species **11** which after reaction with an electrophile E–X will afford 8-functionalized 6-chloroimidazo[1,2-*b*]pyridazine of type **12**. Alternatively, the complexation with $BF_3 \cdot OEt_2$ leading to the adduct **D**, will complex TMPMetX at the next basic nitrogen atom N(5), providing the complex **E**. By proximity, complex **E** will lead to a metalation at position 3 furnishing the organometallic species **13**, which after subsequent quenching with an electrophile E–X will give 3-functionalized imidazopyridazines of type **14** (Scheme 2).

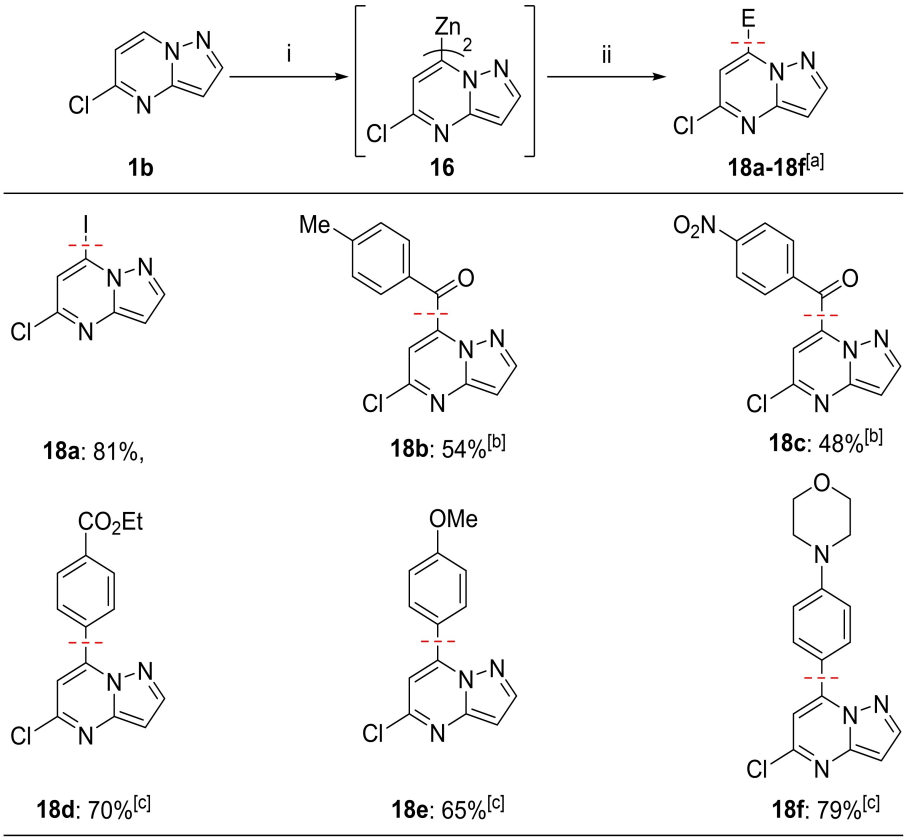
According to these predictions, we first investigated the metalation of the pyrazolo[1,5-*a*]pyrimidine **1b** and have found that $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$[15] (**15**) in THF led to a selective zincation at the predicted 7-position at −40 °C within 10 min, affording the diheteroarylzinc derivative **16**. The use of TMPMgCl·LiCl[16] (**17**) and other related bases were much less satisfactory.[17] The quenching of the organozinc intermediate **16** with various electrophiles provided disubstituted pyrazolo[1,5-*a*]pyrimidines **18a-18f** in 48–81 % isolated yield



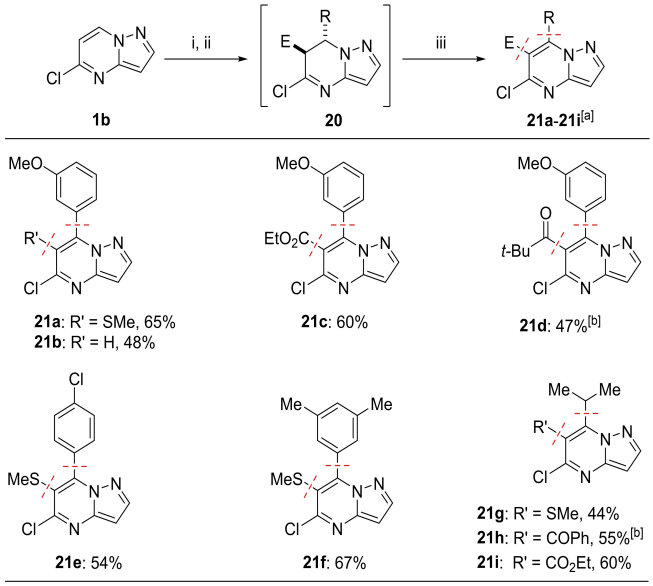
Scheme 1. Predicted reactivity of the 5,6-fused bicyclic heterocycle 5-chloropyrazolo[1,5-*a*]pyrimidine **1b**. Met=Zn, Mg.



Scheme 2. Predicted reactivity of the 5,6-fused bicyclic heterocycle 6-chloroimidazo[1,2-*b*]pyridazine **2b**. Met=Zn, Mg.



Scheme 3. The selective metalation of the pyrazolo[1,5-*a*]pyrimidine **1 b** at position 7 using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**15**). Reagents and conditions: (i) $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**15**, 0.55 equiv.), THF, −40 °C, 10 min; (ii) E–X, [b] THF, 25 °C, 2 h, the acylation was mediated by CuCN·2LiCl (50 mol%). [c] THF, 40 °C, 2 h, the cross-coupling was catalyzed by $Pd(dba)_2$ (5 mol%) and tfp (10 mol%). [a] Isolated yields of analytically pure product.



Scheme 4. 5,6,7-Trisubstituted pyrazolo[1,5-*a*]pyrimidines **21 a**–**21 i** prepared by the nucleophilic addition of organomagnesium halides (**19**) to the pyrazolo-[1,5-*a*]pyrimidine **1 b**, followed by electrophilic quenching reactions and DDQ oxidation. Reagents and conditions: (i) RMgX·LiCl (**19**, 1.2 equiv.), THF, −20 °C, 10 min; (ii) E–X; aqueous work-up; (iii) DDQ (1.2 equiv.), THF, 40 °C 5–7 h. [a] Isolated yield of analytically pure compounds. [b] The acylation was mediated by CuCN·2LiCl (50 mol%).

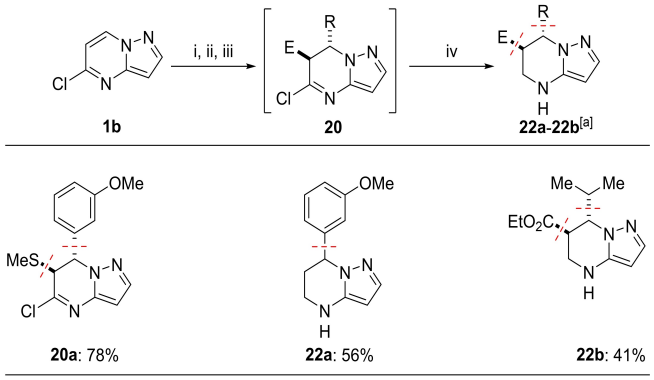
(Scheme 3). Thus, iodolysis of **16** gave the corresponding iodo-derivative **18 a** in 81% yield. Treatment of **16** with CuCN·2LiCl[18] (50 mol%) followed by the addition of benzoyl chloride derivatives (25 °C, 2 h) furnished the ketones **18 b** and **18 c** in 48–54% yield. Negishi cross-couplings[19] of the diheteroarylzinc derivative **16** with various aryl iodides in the presence of catalytic amounts of $Pd(dba)_2$ (5 mol%; dba = dibenzylideneacetone) and tfp[20] (10 mol%; tfp = tri(2-furyl)phosphine, 40 °C, 2 h) gave the arylated N-heterocycles **18 d**–**18 f** in 65–79% isolated yield.

Although the nucleophilic addition to electron-deficient heterocycles was reported previously,[21] only a few classes of N-heterocycles besides pyridines led to practical applications.[22] In addition, most reported nucleophilic addition reactions to N-heterocycles required either very harsh conditions or a preactivation via ionic intermediates such as pyridinium ions.[23] Based on the previously mentioned theoretical calculations (Figure 2), we treated pyrazolo[1,5-*a*]pyrimidine (**1 b**) with various organometallics, of which organomagnesium halides complexed with lithium chloride of type **19**[24] gave the best results (Scheme 4). Thus, the addition of 3-methoxyphenylmagnesium bromide-lithium chloride (**19 a**, 1.2 equiv. in THF) to chloropyrazolopyrimidine (**1 b**) at −20 °C was complete within 10 min. The intermediate magnesium species

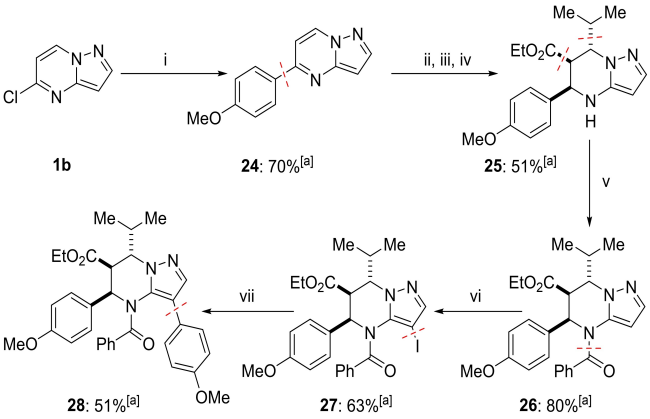
was then trapped with $PhSO_2SMe$[25] (1.2 equiv., 25 °C, 1 h) leading to a single *trans*-diastereomer of type **20**.[26] These partially saturated heterocycles proved not to be bench-stable and decomposed slowly over time. Therefore, these compounds were directly oxidized with DDQ (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 1.2 equiv., 40 °C, 5–7 h) in THF, furnishing the tri-substituted pyrazolo[1,5-*a*]pyrimidine **21 a** in 65% overall yield. An addition of **19 a** to **1 b** followed by an aqueous work-up and DDQ-oxidation, gave the di-substituted N-heterocycle **21 b** in 48% yield. This reaction sequence was also extended to other electrophiles. Thus, the addition of ethyl cyanoformate (2.0 equiv., 25 °C, 3 h) gave the polyfunctional N-heterocycle **21 c** in 60% yield. Also, copper-mediated acylation with pivaloyl chloride furnished the ketone **21 d** in 47% yield. Other arylmagnesium reagents such as 4-chlorophenyl-magnesium bromide (**19 b**) or 3,5-dimethylphenylmagnesium bromide (**19 c**) gave the expected pyrazolopyrimidine **21 e** and **21 f** in 54–67% yield after $PhSO_2SMe$ quench and rearomatization with DDQ. The nucleophilic addition of alkylmagnesium reagents was also possible, as demonstrated by use of *i*PrMgCl·LiCl. Various trapping reactions with $PhSO_2SMe$, PhCOCl and $NCCO_2Et$ followed by a DDQ oxidation gave the expected products **21 g**-**21 i** in 44–60% overall yield (Scheme 4).

As mentioned above, the partially reduced adducts of type **20** were moderately stable. However, we were able to isolate the 7,6-disubstituted product **20 a**, in 78% yield (Scheme 5).

This compound could be stored at 0 °C for 2–3 d. Considerably better stabilities were observed for the fully reduced pyrimidine ring products obtained by treating compounds of type **20** with $Na(CN)BH_3$ (2.0 equiv, 1 M HCl, H_2O: MeOH, 25 °C, 2 h) providing fused N-heterocycle **22 a** and diastereomerically pure *trans*-**22 b** in 41–56% isolated yield. Interestingly, the arylation of **1 b** with *p*-anisylzinc chloride[27] (**23**, 1.5 equiv.) in the presence of 2.5% $Pd(OAc)_2$ and 5% SPhos[28] (50 °C, 1.5 h) gave the fused heterocycle **24** in 70% yield (Scheme 6). This N-heterocycle **24** underwent the same sequence (nucleophilic addition, electrophilic quench and reduction) as outlined in Scheme 6, providing the bicyclic pyrazine **25** as a single diastereomer. The relative configuration was established using X-ray analysis[17] by converting **25** into the corresponding benzamide **26** (PhCOCl, 1.1 equiv.) in 80% yield.



Scheme 5. Nucleophilic addition of Grignard reagents **19** to the pyrazolo[1,5-*a*]pyrimidine (**1 b**) followed by reductive quenching leading to annulated pyrazines **20 a**, **22 a**-**22 b**. Reagents and conditions: (i) RMgX·LiCl (**19**, 1.2 equiv.), THF, −20 °C, 10 min; (ii) E–X; (iii) aqueous work-up; (iv) $Na(CN)BH_3$ (2 equiv.), MeOH, 25 °C, 1 M HCl, 2 h. [a] Isolated yield of analytically pure compounds.

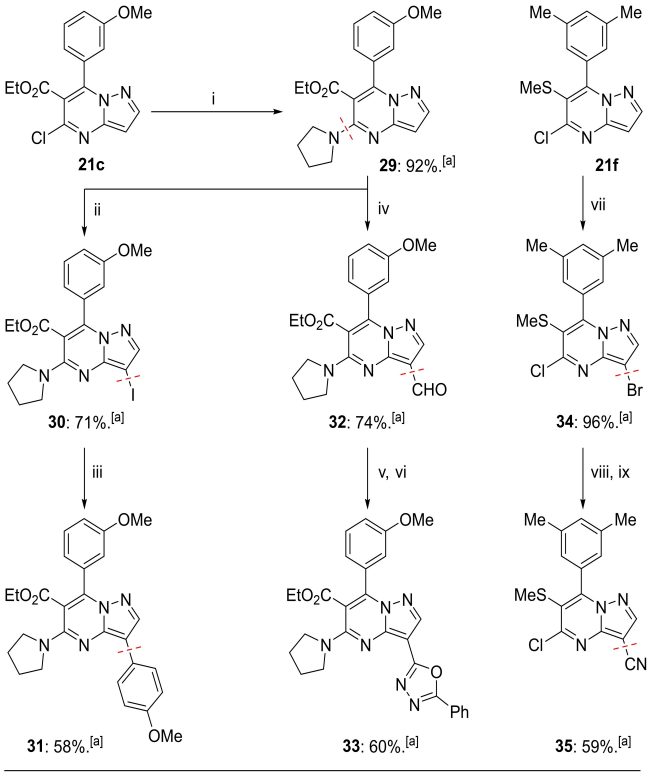


Scheme 6. Preparation of the bicyclic pyrazine **24** and derivatization to the corresponding benzoate for X-ray characterization and post-functionalization by iodination and *Negishi* cross-coupling affording the N-heterocycle **28**. Reagents and conditions: (i) **23**, $Pd(OAc)_2$ (2.5 mol%), SPhos (5 mol%), THF, 50 °C, 1.5 h; (ii) *i*PrMgBr·LiCl (1.2 equiv.), 0 °C, 20 min; (iii) $NCCO_2Et$ (2 equiv.) 25 °C, 2 h; (iv) $NaBH_3(CN)$, 25 °C, 2 h; (v) PhCOCl, Et_3N, CH_2Cl_2, 25 °C, 3 h; (vi) NIS (1.0 equiv.), MeCN, 25 °C,1 h; (vii) **23**, $Pd(OAc)_2$ (2.5 mol%), SPhos (5 mol%), THF, 50 °C, 1.5 h. [a] Isolated yield of analytically pure compounds.

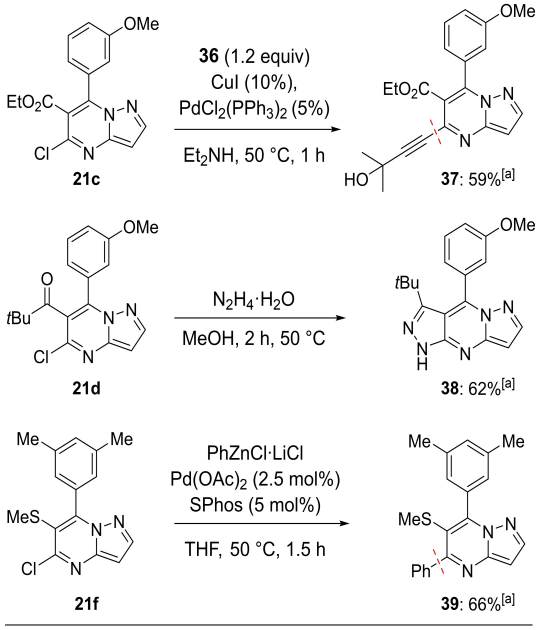
Furthermore, the post-functionalization of position 3 of the pyrazine ring of **26** was realized by iodination using NIS[29] (1.0 equiv.) in acetonitrile (25 °C, 1 h), affording the iodo N-heterocycle **27** in 63% yield. This iodide was readily arylated by a Negishi cross-coupling[19] with *p*-anisylzinc chloride **23** providing the 3-arylated heterocycle **28** in 51% yield (Scheme 6).

Furthermore, we have derivatized tri-substituted heterocycles **21 c** and **21 f** in order to prepare highly functionalized derivatives. Thus, treatment of **21 c** with pyrrolidine at 25 °C for 2 h provided by an addition-elimination reaction[30] the aminated product **29** in 92% yield. Iodination of **29** as described above with NIS gave the 3-iodinated pyrazine derivative **30** which after Negishi cross-coupling[19] provided the tetra-substituted pyrazolopyrimidine **31** in 58% yield. On another hand, formylation of **29** by *a* Vilsmeier–Haack reaction[29] using $POCl_3$ in DMF gave the 4-substituted heterocycle **32** in 74% yield. The structure of **32** was confirmed by X-ray analysis.[17] Conversion of **32** to the oxadiazole derivative **33** was achieved by a two-step sequence in an overall yield of 60% using benzohydrazide followed by oxidative cyclization.[31] Also, the bromination of **21 f** with NBS[32] gave the bromo-derivative **34** in 96% yield. Br/Mg-exchange of **34** with *i*PrMgCl·LiCl[33] gave an intermediate magnesium reagent, which was cyanated with TsCN[34] affording the nitrile **35** in 59% yield (Scheme 7).

The carbon-chloride bond of **21 c**, **21 d** and **21 f** was further used to increase the complexity of these heterocycles by straightforward derivatization. Thus, Sonogashira cross-coupling of **21 c** with propargylic alcohol (**36**) using a dual copper-



Scheme 7. Post-functionalization of the pyrazine ring of heterocycles **21 c** and **21 f** leading to tetra-substituted pyrazolo[1,5-*a*]pyrimidines **31**, **33** and **35**. Reagents and conditions: (i) Pyrrolidine (1.5 equiv.), THF, 25 °C, 2 h; (ii) NIS, MeCN, 25 °C, 1 h; (iii) **23**, $Pd(OAc)_2$ (2.5 mol%), SPhos (5 mol%), THF, 50 °C, 1.5 h; (iv) $POCl_3$, DMF, 25 °C, 12 h; (v) $PhCONHNH_2$, MeOH, 25 °C, 1 h; (vi) K_2CO_3, I_2, dioxane, 80 °C, 3 h; (vii) NBS, MeCN, 25 °C, 1 h; (viii) *i*PrMgCl·LiCl, THF, 0 °C, 30 min; (ix) TsCN, 25 °C, 3 h. [a] Isolated yield of analytically pure compounds.



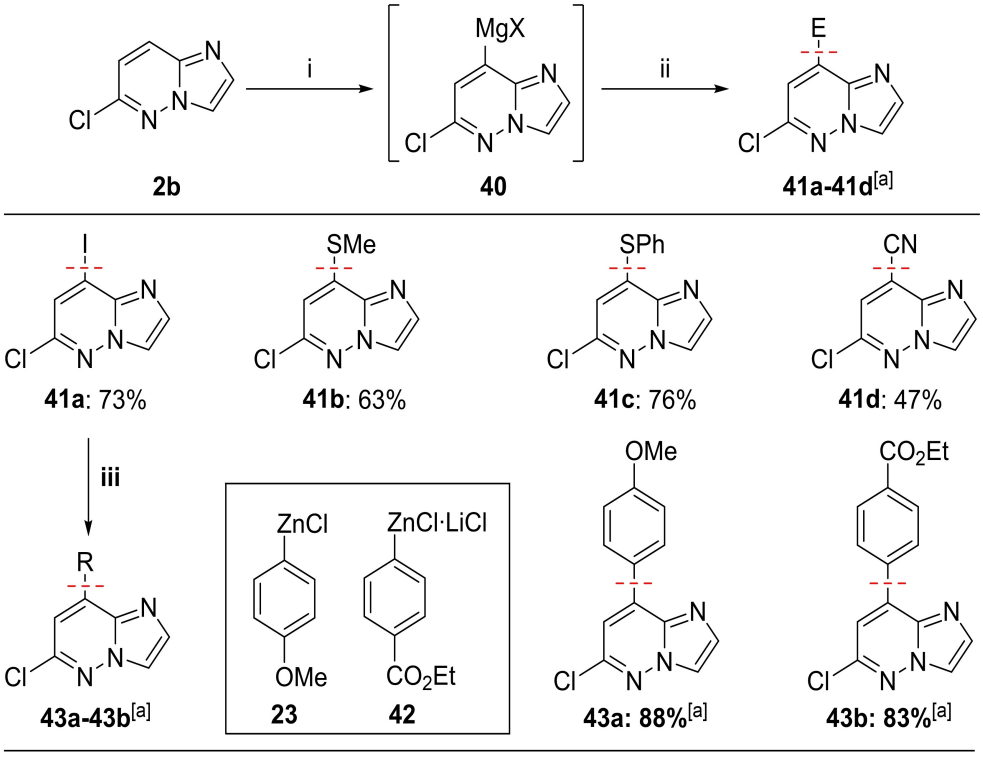
Scheme 8. Functionalization of the C–Cl bond of **21 c**, **21 d** and **21 f** providing the polyfunctionalized heterocycles **37**, **38** and **39**. [a] Isolated yield of analytically pure compounds.

palladium catalysis[35] provided the alkynylated product **37** in 59% yield (Scheme 8).

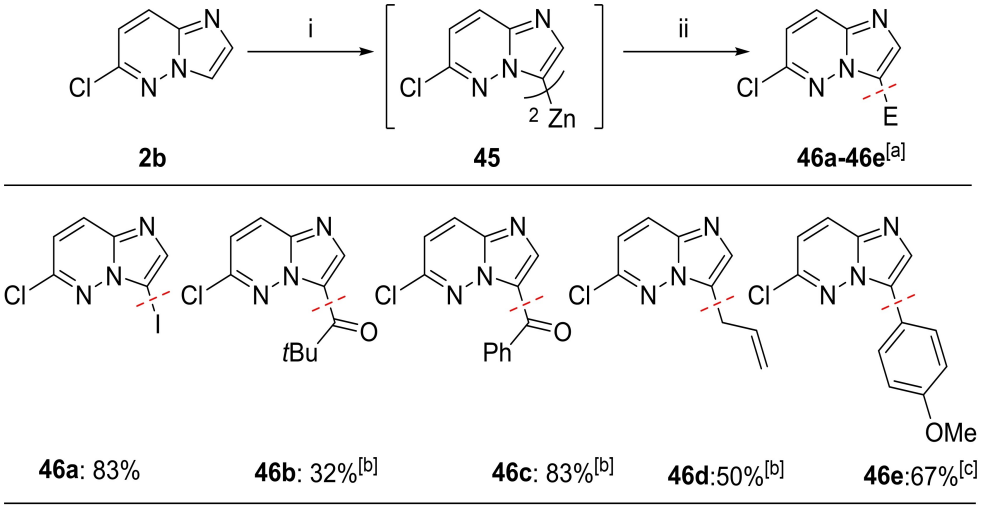
Treatment of **21 d** with hydrazine hydrate[36] provided the annulated heterocycle **38** in 62% yield. Finally, Negishi cross-coupling[19] of **21 f** with PhZnCl·LiCl furnished the phenylated product **39** in 66% yield. We turned then our attention to the functionalization of 6-chloroimidazo[1,2-*b*]pyridazine (**2 b**) according to the prediction depicted in Scheme 2. Thus, we have treated 6-chloroi-midazo[1,2-*b*]pyridazine (**2 b**) with TMPMgCl·LiCl (**17**)[16] in THF which led to a selective magnesiation at the predicted 8-position at −60 °C within 30 min, affording magnesiated species of type **40**. Thus, iodolysis of **40** afforded the corresponding iodo-derivative **41 a** in 73% yield (Scheme 9). Treatment of **40** with electrophiles such as $PhSO_2SMe$, $PhSO_2SPh$[25] gave sulfides **41 b**, and **41 c** in 63–76% yield whereas, treatment with commercially available TsCN gave cyano-compound **41 d** in 47% yield. Unfortunately, direct Kumada cross-coupling[37] of type **40** with aryl iodides gave an unsatisfactory result. We found that, iodide **41 a** was readily arylated with different arylzinc derivatives (*p*-anisylzinc chloride **23**, or *p*-carbethoxyphenylzinc chloride lithium chloride **42**) via Negishi cross-coupling[19] in the presence of catalytic amounts of $Pd(dba)_2$ (5 mol%) and tfp[20] (10 mol%, 25 °C, 0.5 h) giving the arylated N-heterocycles **43 a-43 b** in 83–88% isolated yield.

As described above in Scheme 2 a complexation of **2 b** with $BF_3 \cdot OEt_2$[13a] allowed a regioselectivity switch with $TMP_2Zn \cdot MgCl_2 \cdot 2LiCl$ (**44**) in THF at -20 °C within 20 min, affording zincated N-heterocycle of type **45** (Scheme 10). The quenching of **45** with various electrophiles provided the 3,6-disubstituted imidazo[1,2-*b*]pyridazines **46 a-46 e** in 32–83%. Thus, iodolysis of **45** provided the corresponding iodo-derivative **46 a** in 83% yield. Treatment of **45** with CuCN·2LiCl (20 mol%)[18] followed by addition of acyl chlorides, allyl bromide (25 °C, 2 h) furnished the ketones **46 b**, **46 c** and allylated N-heterocycle **46 d**. Negishi cross-couplings[19] of the diheteroarylzinc derivative **45** with *p*-iodoanisole in the presence of catalytic amounts of $Pd(PPh_3)_4$ (5 mol%, 40 °C, 2 h) gave the arylated N-heterocycle **46 e** in 67% isolated yield. The structure of **46 c** was confirmed by X-ray analysis.[17] A second metalation using TMPMgCl·LiCl (**17**) was also possible (Scheme 11). Treatment of 6-chloro-8-phenylthio-N-heterocycle **41 c** (from Scheme 9) with **17** (1.2 equiv., THF, −60 °C, 0.5 h) provided a full conversion to 3-magnesiated N-heterocycle **47**. This organometallic intermediate was successfully quenched with typical electrophiles providing 3,6-trisubstituted imidazo[1,2-*b*]pyridazines **48 a-48 e**.

Thus, iodolysis of **47** provided the corresponding iodo-derivative **48 a** in 69% yield. Treatment of **47** with pivaloyl chloride, allyl bromide in the presence of CuCN·2LiCl (20 mol%) or with benzoyl chloride (25 °C, 2 h) in the presence of $Pd(PPh_3)_4$ (5 mol%)[38] furnished the ketones **48 b**, **48 c** in 75–93% yield and allyl compound **48 d** in 70% yield. Whereas, quenching the



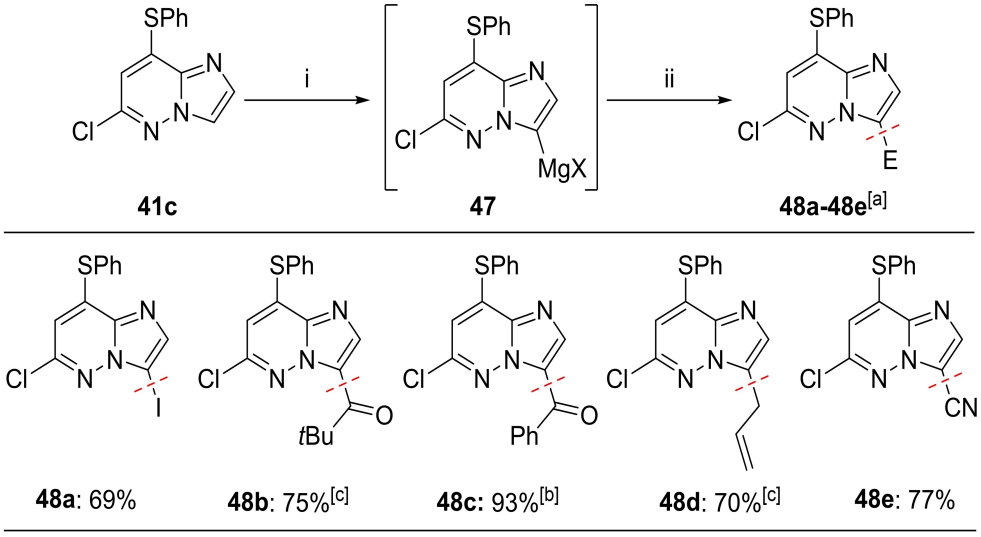
Scheme 9. Selective metalation of predicted 8-position of 6-chloroimidazo[1,2-*b*]pyridazine (**2b**) using TMPMgCl·LiCl (**17**) followed by electrophilic quenching. Reagents and conditions: (i) **17** (1.1 equiv.), THF, −60 °C, 30 min; (ii) E–X, THF, 25 °C, 0.1-2 h; (iii) **23** or **42** (1.5 equiv.), $Pd(dba)_2$ (5 mol%), tfp (10 mol%), THF, 25 °C, 30 min. [a] Isolated yield of analytically pure compounds.



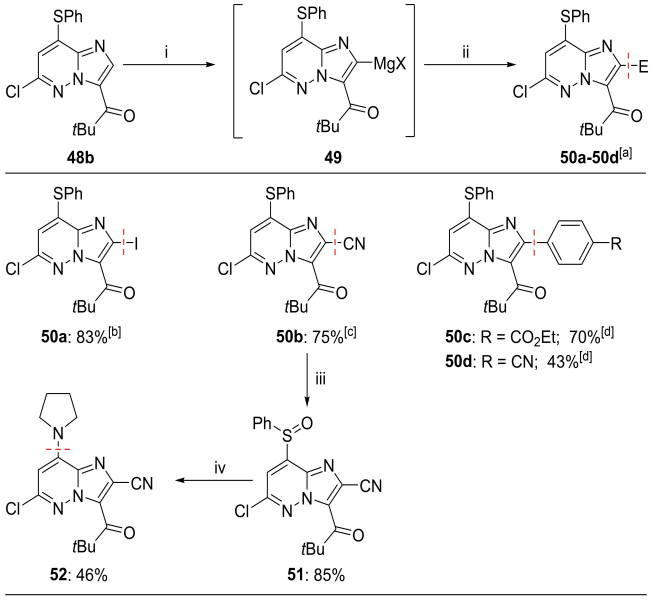
Scheme 10. Zincation in the presence of $BF_3 \cdot OEt_2$ leading to 3-substituted 6-chloroimidazo[1,2-*b*]pyridazine. Reagents and conditions: (i) $BF_3 \cdot OEt_2$ (1.0 equiv.), **44**, (0.6 equiv.); (ii) E–X, THF, 25 °C, 0.1-2 h. [a] Isolated yield of analytically pure compounds. [b] The acylation was mediated by CuCN·2LiCl (20 mol%). [c] The cross-coupling was catalyzed by $Pd(PPh_3)_4$ (5 mol%).

intermediate **47** with TsCN (1.5 equiv., 25 °C, 3 h) gave cyano-derivative **48e** in 77% yield.

A third functionalization of the imidazo[1,2-*b*]pyridazines skeleton was demonstrated on the ketone **48b** (Scheme 12). Therefore, treating **48b** with TMPMgCl·LiCl (**17**) in THF at −40 °C within 20 min afforded selectively 2-magnesiated species of type **49**. The quenching of organomagnesium intermediates (**49**) with various electrophiles provided tetra-substituted imidazo[1,2-*b*]pyridazines **50a-50d**. Thus, iodolysis of **49** furnished the corresponding iodo-derivative **50a** in 83% yield. Treatment of **49** with TsCN (1.5 equiv., 25 °C, 2 h) gave cyano-derivative **50b** in 75% yield. Magnesiated species of type **49**



Scheme 11. Selective metalation of N-heterocycle **41 c** using TMPMgCl·LiCl followed by electrophilic quenching affording the N-heterocycles **48 a-48 e**. Reagents and conditions: (i) **17** (1.2 equiv.), THF, −60 °C, 30 min; (ii) E–X, THF, 25 °C, 0.1-3 h. [a] Isolated yield of analytically pure compounds. [b] The acylation was mediated by $Pd(PPh_3)_4$ (5 mol%). [c] The acylation was mediated by CuCN·2 LiCl (20 mol%).



Scheme 12. Metalation of the tri-substituted imidazopyridazines **48 c**, followed by various quenching reactions. Oxidation of sulfide **50 b** to sulfoxide **51** followed by nucleophilic substitution of the C-SOPh bond to give amine **52**. Reagents and conditions: (i) **17** (1.2 equiv.), THF, −40 °C, 20 min; (ii) E–X; [b] I_2, THF, 25 °C, 20 min; [c] TsCN, 25 °C, 2 h; [d] $Pd(OAc)_2$ (5 mol%), XantPhos (10 mol%), 40 °C, 4 h; (iii) *m*-CPBA (1.5 equiv.), 0 °C to 25 °C, 2 h; (iv) pyrrolidine (1.5 equiv.), 0 °C, 20 min. [a] Isolated yield of analytically pure compounds.

underwent transmetalation[39] with a 1 M THF solution of $ZnCl_2$ (1 equiv.) for 15 min giving a diheteroarylzinc species. The resulting zinc reagents were subjected to cross-coupling with various aryl iodides in the presence of catalytic amounts of $Pd(OAc)_2$ (5 mol%) and XantPhos[40] (10 mol%, 40 °C, 4 h) to give the arylated N-heterocycles **50 c-50 d** in 43–70 % isolated yield.

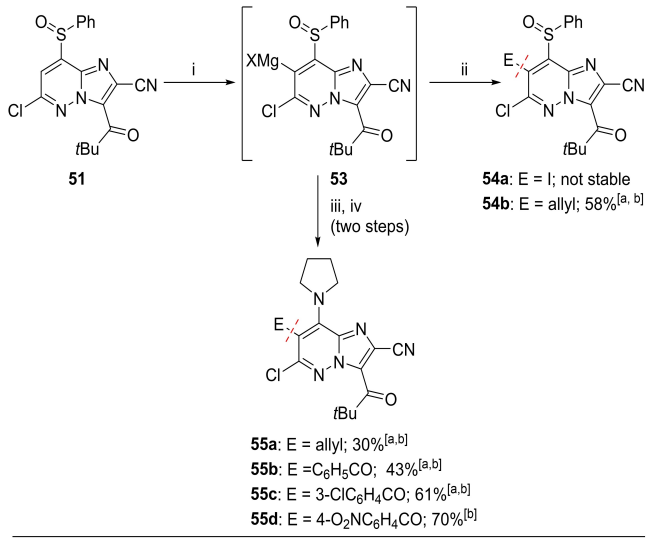
Furthermore, oxidation of sulfide **50 b** with *m*-CPBA (1.5 equiv., 25 °C, 2 h) afforded the sulfoxide **51** as a pure compound in 85 % yield. Reacting sulfoxide **51** with pyrrolidine (1.5 equiv., 0 °C, 20 min) led to a selective substitution of the sulfoxide moiety (and not a substitution of the chloride) giving amine **52** in 46 % yield. The structure of **52** was confirmed by X-ray analysis.[17]

In addition, magnesiation of sulfoxide **51** with TMPMgCl·LiCl (**17**) in THF (−60 °C, 1 min) led to a fast metalation at the 7-position **53** (Scheme 13). The iodolysis of **53** afforded an unstable iodo-derivative **54 a** which was characterized by mass spectrometry,[17] but was too unstable to record full analytical data. Therefore, we quenched **53** with allyl bromide (2 equiv., 25 °C, 0.5 h) in the presence of CuCN·2LiCl (50 mol%) and in this case we were able to isolate fully substituted **54 b** in 58 % yield. The structure of **54 b** was confirmed by X-ray analysis.[17]

We suspected that the sulfoxide moiety was responsible for the instability of these heterocycles. We overcame this problem by in situ treatment of sulfoxides with pyrrolidine[41] (5 equiv. 25 °C, 10 min) to give penta-substituted imidazo[1,2-*b*]pyridazines **55 a**–**55 d** in 30–70 %.

Conclusion

In summary, by using theoretical calculations of new N-heterocyclic scaffolds **1 b** and **2 b**, we were able to establish a reliable protocol for the functionalization of most positions of 5,6-fused bicyclic pyrazolopyrimidines of type **1 b** and imidazolopyridazines of type **2 b** combining nucleophilic addition of Grignard reagents (in the case of **1 b**) and successive metalations using various TMP-zinc and magnesium bases. This study allowed a straightforward and rational functionalization of the



Scheme 13. Magnesiation of imidazopyridazines **51** using TMPMgCl·LiCl (17) followed by quenching with electrophiles giving sulfoxides of type **54**. Or, by a two-step reaction sequence: quenching with electrophiles followed by subsequent nucleophilic substitution of the C-SOPh bond with pyrrolidine to give amines of type **55**. Reagents and conditions: (i) **17** (1.2 equiv.), THF, −60 °C, 1 min; (ii) E–X, THF, 25 °C, 1 h; (iii) E–X, THF, 25 °C, 1 h; (iv) Pyrrolidine (5 equiv.), THF, 10 min. [a] Isolated yield of analytically pure compounds. [b] The allylation and acylation was mediated by CuCN·2 LiCl (50 mol%).

two scaffolds of pyrazolo[1,5-*a*]pyrimidines (**1 a**) and imidazo[1,2-*b*]pyridazines (**2 a**). Further extensions of this approach with the help of theoretical calculations and consideration for organometallic functionalizations of other complex N-heterocycles are currently underway.

Experimental

Full details of materials, synthetic procedures and product analysis can be found in the Supporting Information.

Deposition Number(s) 2155748 (**26**), 2155751 (**32**), 2155749 (**46 c**), 2155750 (**52**), 2155752 (**54 b**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interest

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: DFT calculation · imidazopyridazines · magnesium · N-heterocycle · pyrazolopyrimidines

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