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# Synthesis of (Hetero)arylated Pyridazin-3(2*H*)-ones via Negishi Reaction Involving Zincated Pyridazin-3(2*H*)-ones

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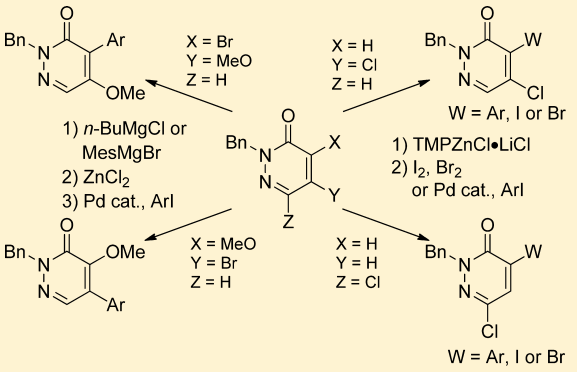
Supporting Information

**ABSTRACT:** Zincated pyridazin-3(2*H*)-ones generated via bromine−magnesium exchange followed by transmetalation using $ZnCl_2$ or via lactam-directed *ortho* C4-H zincation with TMPZnCl·LiCl have been synthesized. These in situ created organometallics can be used in Negishi reactions with iodo(hetero)arenes delivering a new approach toward (hetero)arylpyridazin-3(2*H*)-ones.




## INTRODUCTION

Pyridazin-3(2*H*)-ones are an important subclass of the pyridazine family. The pyridazin-3(2*H*)-one core can be found in a wide variety of launched pesticides (e.g., chloridazon, norflurazon, oxapyrazon, flufenpyr, dimidazon, diclomezine, pyridaphenthion, pyridaben) and drugs for human (e.g., azelastine, emorfazone) and veterinary use (e.g., pimobendan).[1] Although there was historically less interest for this nucleus for material science applications, this has changed in recent years.[2] Remarkably the available synthetic methods to selectively C-functionalize the pyridazin-3(2*H*)-one core are rather limited.[1a,b,e,h] Our group has a history of research on this privileged core, primarily in generating synthetic tools to selectively introduce substituents onto the 4 and 5 positions.[3] Classically, C-substituted pyridazin-3(2*H*)-ones have been constructed via a ring buildup.[1a,b,e,h] Alternatively, in some specific cases a regioselective nucleophilic substitution with carbon nucleophiles on halopyridazin-3(2*H*)-ones has been used.[1b,h] The introduction of palladium-catalyzed reactions, however, has transformed the reaction of carbon nucleophiles with halopyridazin-3(2*H*)-ones into a main route for the synthesis of C-functionalized pyridazin-3(2*H*)-ones (alkyl, alkenyl, alkynyl, (hetero)aryl, alkoxycarbonyl).[1g,h] In order to extend the arsenal of C-functionalization procedures, our group investigated the synthesis of magnesiated pyridazin-3(2*H*)-ones via reaction of Grignard reagents and magnesium amides with halopyridazin-3(2*H*)-ones.[3p−r] Quenching of these species with electrophiles allowed the direct introduction of an even wider variety of functional groups. In some substrates, the Grignard reagent interestingly acted as a nucleophile rather than as a halogen-magnesium exchange reagent allowing to perform double (C-4 and C-5) functionalizations of the pyridazin-3(2*H*)-one core in one step.[3p,q] As a continuation of this research program, we report here the synthesis of zincated pyridazin-3(2*H*)-ones which can be used as reagents to introduce (hetero)aryl groups via a Pd-catalyzed cross-coupling protocol. Interestingly, there are hitherto no reports in the literature on the synthesis and use in Negishi reactions of zincated pyridazin-3(2*H*)-ones.[4,5] The more covalent character of a carbon zinc in comparison with a carbon−magnesium bond is an advantage as it will deliver synthetic protocols with a wider functional group compatibility. Moreover, our previous research on magnesiated pyridazin-3(2*H*)-ones revealed that some representatives are unstable (even at lower temperature), which might simply prevent to perform cross-coupling reactions with these species.[3q,r] This was confirmed in our group by a preliminary unsuccessful Kumada type cross-coupling reaction of (2-benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)(halo)magnesium halide (**A**) (Table 1) with 2-iodopyridine and iodobenzene using iron, nickel, and palladium catalysis.[6,7] The interest for and importance of 4-, 5-, 4,5-di-, and 4,6-di(hetero)arylated pyridazin-3(2*H*)-ones is highlighted by the substantial number of publications and patents which appeared in the last 5 years describing both pharmaceutical and agrochemical applications [4-(hetero)arylpyridazin-3(2*H*)-ones: cathepsin S inhibitors,[8] herbicides,[9] P2X7 receptor inhibitors (rheumatoid arthritis),[10] serine protease inhibitors as treatment

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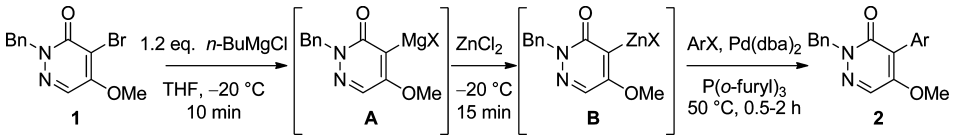
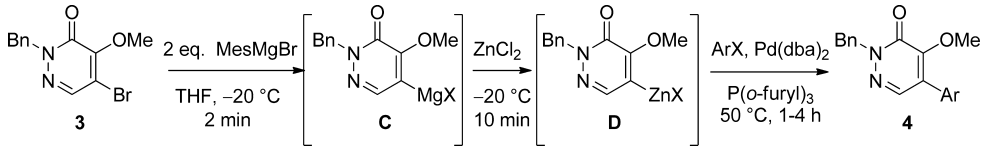
**Table 1. Bromine−Magnesium Exchange on 2-Benzyl-4-bromo-5-methoxypyridazin-3(2*H*)-one (1) Followed by Transmetalation using $ZnCl_2$ and Negishi Reaction**




| entry | ArX | 2 | yield[a] (%) |
|---|---|---|---|
| 1 | *p*-$EtOOCC_6H_4I$ | **2a** | 80 |
| 2 | *p*-$CH_3OC_6H_4I$ | **2b** | 72 |
| 3 | *p*-$CH_3OC_6H_4Br$ | **2b** | 0 |
| 4 | *o*-$ClC_6H_4I$ | **2c** | 34 |
| 5 | *m*-$ClC_6H_4I$ | **2d** | 73 |
| 6 | *p*-$ClC_6H_4I$ | **2e** | 74 |
| 7 | *m*-$CF_3C_6H_4I$ | **2f** | 69 |
| 8 | *p*-$CF_3C_6H_4I$ | **2g** | 90 |
| 9 | 2-iodopyridine | **2h** | 82 |
| 10 | 3-iodopyridine | **2i** | 86 |
| 11 | 2-iodopyrazine | **2j** | 78 |
| 12 | 2-iodothiophene | **2k** | 64 |

[a] **1** (1.0 mmol), 0.6 mL of 2 M *n*-BuMgCl solution in THF (1.2 equiv), THF (4.0 mL), −20 °C, 10 min; 2.86 mL of 0.7 M $ZnCl_2$ solution in THF (2.0 equiv), −20 °C, 15 min; ArX (4.0 equiv), $Pd(dba)_2$ (5 mol %), P(*o*-furyl)$_3$ (10 mol %), 50 °C, 30−120 min.

**Table 2. Bromine−Magnesium Exchange on 2-Benzyl-5-bromo-4-methoxypyridazin-3(2*H*)-one (3) Followed by Transmetalation Using $ZnCl_2$ and Negishi Reaction**




| entry | ArX | 4 | yield[a] (%) |
|---|---|---|---|
| 1 | *p*-$EtOOCC_6H_4I$ | **4a** | 45 |
| 2 | *p*-$CH_3OC_6H_4I$ | **4b** | 74 |
| 3 | *p*-$CH_3OC_6H_4Br$ | **4b** | 0 |
| 4 | *o*-$ClC_6H_4I$ | **4c** | 46 |
| 5 | *m*-$ClC_6H_4I$ | **4d** | 73 |
| 6 | *p*-$ClC_6H_4I$ | **4e** | 46 |
| 7 | *p*-$CF_3C_6H_4I$ | **4f** | 63 |
| 8 | 2-iodopyridine | **4g** | 10 (79)[b] |
| 9 | 3-iodopyridine | **4h** | 0 (0)[b] |
| 10 | 2-iodopyrazine | **4i** | 63 |
| 11 | 2-iodothiophene | **4j** | 78 |

[a] **3** (1.0 mmol), 2.0 mL of 1 M MesMgBr solution in THF (2.0 equiv), THF (4.0 mL), −20 °C, 2 min; 4.29 mL of 0.7 M $ZnCl_2$ solution in THF (3.0 equiv), −20 °C, 10 min; ArX (4.0 equiv), $Pd(dba)_2$ (5 mol %), P(*o*-furyl)$_3$ (10 mol %), 50 °C, 1−4 h. [b] 3.00 mL of 2.24 M LiCl solution in DMF and 1.0 mL of DMF were added to the catalyst solution.

for hepatitis C infection,[11] NS5B polymerase inhibitors,[12] histamine H3 inhibitors,[13] $\alpha$4 integrin receptor agonists,[14] cholinesterase inhibitors;[15] 5-(hetero)arylpyridazin-3(2*H*)-ones: human A1 adenosine receptor ligands,[16] $\beta$-secretase inhibitors,[17] HCV NS5B polymerase inhibitors,[18] mGluR5 modulators,[19] MCH antagonists,[20] inhibition of the production of PAI-1,[21] histamine H3 inhibitors,[13] CB1 antagonists[22] and $\alpha$2/$\alpha$3 subtype selective GABA-A agonists;[23] 4,5-di(hetero)arylpyridazin-3(2*H*)-ones: fungicides,[24] antimicrobial agents,[25] cannabinoid receptor modulators;[26] 4,6-di(hetero)arylpyridazin-3(2*H*)-ones: antimicrobial agents,[27] serine protease inhibitors as treatment for hepatitis C infection,[28,11a,b] histamine H3 inhibitors,[13] for the treatment of pain,[29] cholinesterase inhibitors[15]].

## RESULTS AND DISCUSSION

As a first approach we investigated the synthesis of zincated pyridazin-3(2*H*)-ones via transmetalation on the corresponding magnesium species. (2-Benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)(halo)magnesium (**A**) and (1-benzyl-5-methoxy-6-oxo-1,6-dihydropyridazin-4-yl)(halo)magnesium (**C**) were selected as test compounds (Table 1 and 2). We previously reported the synthesis of these species starting from 2-benzyl-4-bromo-5-methoxypyridazin-3(2*H*)-one (**1**) and 2-benzyl-5-bromo-4-methoxypyridazin-3(2*H*)-one (**3**) via bromine−magnesium exchange with *n*-BuMgCl and MesMgBr, respectively. The use of MesMgBr for substrate **3** is essential as with *n*-BuMgCl only nucleophilic substitution of the methoxy group occurs. Transmetalation on **A** and **C** with $ZnCl_2$ at −20 °C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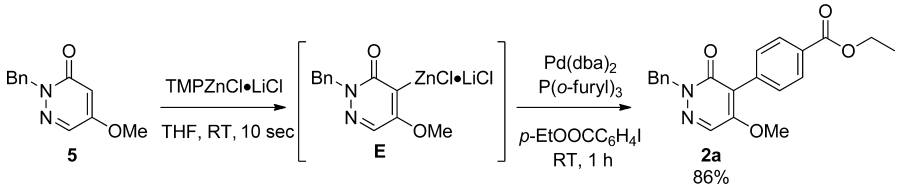
**Scheme 1. Lactam-Directed *Ortho* C−H Zincation of 2-Benzyl-5-methoxypyridazin-3(2*H*)-one (5) using TMPZnCl·LiCl Followed by Negishi Reaction**




generated the zinc halides (2-benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)(halo)zinc (**B**) and (1-benzyl-5-methoxy-6-oxo-1,6-dihydropyridazin-4-yl)(halo)zinc (**D**) (Table 1 and 2).[30] With the optimized protocol for the synthesis of the zincated methoxypyridazin-3(2*H*)-ones **B** and **D** in hand, attention was turned to developing the Negishi cross-coupling methodology. A set of triphenylphosphine-based palladium precatalysts were assessed ($Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$), but a combination of $Pd(dba)_2$ and P(*o*-furyl)$_3$ as a ligand was identified as optimal.[31] At room temperature, no cross-coupling occurred so we increased the reaction temperature to 50 °C. With this bromine−magnesium exchange/transmetalation/Negishi reaction protocol in place it was possible to couple **1** and **3** with aryl iodides with both electron-releasing and -withdrawing substituents (Tables 1 and 2). Substituents in the *meta* and *para* positions on the aryl iodide were well tolerated, while an *ortho* substituent seemed to work less as exemplified by *o*-chloroiodobenzene (Table 1, entry 4; Table 2, entry 4). The use of aryl iodides was found to be crucial as exemplified by the use of 1-iodo-4-methoxybenzene in comparison with 1-bromo-4-methoxybenzene. While a good yield was obtained with the former, no reaction product was formed with the latter substrate (Table 1, entries 2 and 3; Table 2, entries 2 and 3). Even with a very electron-deficient system like 4-bromobenzonitrile no cross-coupled reaction product could be isolated starting from **1**. Iodoheteroarenes were subsequently screened as substrates. Both representatives of six- (2-iodopyridine, 3-iodopyrazine) and five-membered (2-iodothiophene) ring systems gave moderate to good yields (Table 1, entries 9−12; Table 2, entries 10 and 11). An exception is the coupling of **3** with 2-iodopyridine, which gave only 10% yield (Table 2, entry 8). Based on a recent report of our research group in which we described two new rate-accelerating halide effects of LiCl in Stille reactions, we tried adding LiCl to the reaction mixture. These halide effects proved especially useful to speed up slow cross-coupling reactions with $\alpha$-halogenated azines and diazines.[32] Gratifyingly, when dry LiCl in DMF was added to the catalyst solution, the target compound 2-benzyl-4-methoxy-5-pyridin-2-ylpyridazin-3(2*H*)-one (**4g**) was obtained in 79% yield (Table 2, entry 8).[32] Negishi reaction of 3-iodopyridine with **D**, in the absence or presence of LiCl, gave no reaction product (Table 2, entry 9). Generally, yields of the bromine−magnesium exchange/transmetalation/cross-coupling protocol are higher starting from **1** than those obtained with regioisomer **3**.

Recently, our group described the lactam directed *ortho* C4-H magnesiation of pyridazin-3(2*H*)-ones with TMPMgCl·LiCl as base.[3r] Via a subsequent reaction with electrophiles, a direct functionalization was achieved. Based on this earlier research, we wondered whether a similar approach could be used to perform regioselective direct C4-H zincation utilizing zinc amide bases. Subsequent Negishi reaction would deliver an attractive alternative synthetic approach for 4-(hetero)-arylpyridazin-3(2*H*)-ones. 2-Benzyl-5-methoxypyridazin-3(2*H*)-one (**5**) was selected as test substrate. With $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[4a] (even at −78 °C) metalation unfortunately did not proceed, but changing the base to TMPZnCl·LiCl was successful.[4,5] Metalation on **5** is complete upon dropwise addition of the pyridazinone solution to the TMPZnCl·LiCl complex solution over 1 min at room temperature (Scheme 1). Upon completion of the zincation, Negishi reaction with ethyl 4-iodobenzoate using the $Pd(dba)_2$/P(*o*-furyl)$_3$ catalyst system was tried which gave **2a** in 86% yield. In this case, the reaction could be performed at room temperature. Compound **2a** is equal to the one obtained starting from 2-benzyl-4-bromo-5-methoxypyridazin-3(2*H*)-one (**1**) (Table 1, entry 1), and similar yields were obtained. This also proves the regioselectivity of the direct zincation protocol.

A substituent at C5 which can be directly substituted by $S_NAE$- and Pd-catalyzed cross-coupling reactions, and which is stable under the C4 zincation reaction conditions, would be more interesting than a methoxy group since it allows a wide range of further functionalization possibilities.[3q] 2-Benzyl-5-chloropyridazin-3(2*H*)-one (**6**), which can be easily synthesized *via* a two step synthesis from commercially available products, was selected as a candidate for this purpose.[33] Adding a solution of pyridazinone **6** dropwise to a TMPZnCl·LiCl solution over 1 min followed by a further 1 min stirring at room temperature, was optimal for complete C4 zincation as determined by quenching with $D_2O$ and MS analysis. We wondered whether the same procedure could also be used on 2-benzyl-6-chloropyridazin-3(2*H*)-one (**8**) allowing to access a regioisomeric 6-chloro-4-(hetero) substitution pattern with the same post functionalization possibilities. The decreased stability of (2-benzyl-6-chloro-3-oxo-2,3-dihydropyridazin-4-yl)(di-$\mu$-chloro)lithium zinc (**G**) versus (2-benzyl-5-chloro-3-oxo-2,3-dihydropyridazin-4-yl)(di-$\mu$-chloro)lithium zinc (**F**) (vide supra) required rapid addition of a solution of pyridazinone **8** to the TMPZnCl·LiCl solution, followed by stirring for 10 s at room temperature. With the optimized direct zincation protocols for **6** and **8** in hand we tested subsequent Negishi reaction under the conditions used for **E**. *Meta*- and *para*-substituted aryl iodides with both electron-donating and -withdrawing groups could be successfully coupled in moderate to good yields (Table 3, 4). As exemplified by 1-chloro-2-iodobenzene, *ortho* substitution was again found to be troublesome. Although we were able to produce **9c** from **8** in 61% yield, no reaction product could be isolated in a coupling reaction starting from regioisomer **6** (Table 3, entry 4, and Table 4, entry 4). Similarly as observed for reactions involving **B** and **D** no reaction occurred when coupling **F** and **G** with 1-bromo-4-methoxybenzene, while Negishi reaction involving 1-iodo-4-methoxybenzene worked smoothly (Table 3, entries 2 and 3, Table 4, entries 2 and 3). Also with a less electron-rich bromoarene no cross-coupling took place (Table 3, entry 7, Table 4, entry 7). It was possible to couple iodoheteroarenes


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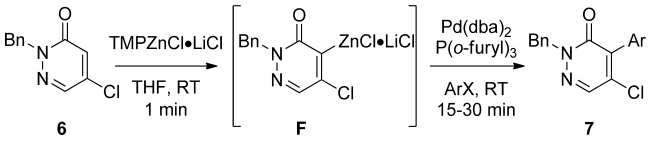
**Table 3. Lactam-Directed *Ortho* C−H Zincation of 2-Benzyl-5-chloropyridazin-3(2*H*)-one (6) Using TMPZnCl·LiCl Followed by Negishi Reaction**

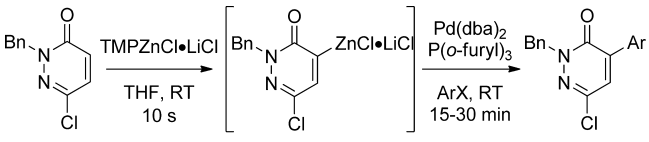



6 F 7

| entry | ArX | 7 | yield[a] (%) |
|---|---|---|---|
| 1 | *p*-EtOOCC$_6$H$_4$I | **7a** | 80 |
| 2 | *p*-CH$_3$OC$_6$H$_4$I | **7b** | 65 |
| 3 | *p*-CH$_3$OC$_6$H$_4$Br | **7b** | 0 |
| 4 | *o*-ClC$_6$H$_4$I | **7c** | 0 |
| 5 | *m*-ClC$_6$H$_4$I | **7d** | 44 |
| 6 | *p*-ClC$_6$H$_4$I | **7e** | 74 |
| 7 | *p*-ClC$_6$H$_4$Br | **7e** | 0 |
| 8 | *m*-CF$_3$C$_6$H$_4$I | **7f** | 51 |
| 9 | *p*-CF$_3$C$_6$H$_4$I | **7g** | 44 |
| 10 | 2-iodopyridine | **7h** | 0 (0)[b] |
| 11 | 3-iodopyridine | **7i** | 0 (30)[b] |
| 12 | 2-iodopyrazine | **7j** | 0 (0)[b] |
| 13 | 2-iodothiophene | **7k** | 40 |

[a]**6** (1.0 mmol), 1.81 mL of 0.55 M TMPZnCl·LiCl solution in THF (1.0 equiv), THF (4.0 mL), rt, 1 min; ArX (2.0 equiv), Pd(dba)$_2$ (5 mol %), P(*o*-furyl)$_3$ (10 mol %), rt, 15−30 min. [b]3.00 mL of 2.24 M LiCl solution in DMF and 1.0 mL of DMF were added to the catalyst solution.

**Table 4. Lactam-Directed *Ortho* C−H Zincation of 2-Benzyl-6-chloropyridazin-3(2*H*)-one (8) Using TMPZnCl·LiCl Followed by Negishi Reaction**




8 G 9

| entry | ArX | 9 | yield[a] (%) |
|---|---|---|---|
| 1 | *p*-EtOOCC$_6$H$_4$I | **9a** | 91 |
| 2 | *p*-CH$_3$OC$_6$H$_4$I | **9b** | 85 |
| 3 | *p*-CH$_3$OC$_6$H$_4$Br | **9b** | 0 |
| 4 | *o*-ClC$_6$H$_4$I | **9c** | 61 |
| 5 | *m*-ClC$_6$H$_4$I | **9d** | 77 |
| 6 | *p*-ClC$_6$H$_4$I | **9e** | 96 |
| 7 | *p*-ClC$_6$H$_4$Br | **9e** | 0 |
| 8 | *m*-CF$_3$C$_6$H$_4$I | **9f** | 97 |
| 9 | *p*-CF$_3$C$_6$H$_4$I | **9g** | 95 |
| 10 | 2-iodopyridine | **9h** | 87 |
| 11 | 3-iodopyridine | **9i** | 71 |
| 12 | 2-iodopyrazine | **9j** | 86 |
| 13 | 2-iodothiophene | **9k** | 78 |

[a]**8** (1.0 mmol), 1.81 mL of 0.55 M TMPZnCl·LiCl solution in THF (1.0 equiv), THF (4.0 mL), rt, 10 s; ArX (2.0 equiv), Pd(dba)$_2$ (5 mol %), P(*o*-furyl)$_3$ (10 mol %), rt, 15−30 min.

but only with limited success for Negishi reactions involving **F** (Table 3, entries 11 and 13). For the cross-coupling of **F** with 3-iodopyridine it was necessary to add LiCl in DMF, as was used in the synthesis of **4g**, but even in this case the yield was only 30%.[32] Unfortunately, for the coupling of **F** with 2-iodopyridine and 2-iodopyrazine this did not improve the yield as still no 4-(hetero)arylpyridazin-3(2*H*)-ones were formed (Table 3, entries 10 and 12). The cross-coupling with 2-iodothiophene gave **7k** in 40% yield (Table 3, entry 13). In sharp contrast, all Negishi reactions of **8** with the same heteraryl iodides gave very good yields (Table 4, entries 10−13). Actually, this is a general trend as the yields of the zincation/cross-coupling protocol with aryl iodides starting from chloropyridazin-3(2*H*)-one **8** are generally higher than those obtained with regioisomer **6**.

There seems to be a link between the stability of the zincated pyridazin-3(2*H*)-ones and their successful use in Negishi reactions, irrespective of the way they are synthesized. The more stable zincated pyridazin-3(2*H*)-ones (**D** and **F**) are less reactive in cross-coupling reactions than the less stable ones (**B** and **G**) leading to lower yields and poorer performance, especially with the more challenging heteroaromatic substrates. The stability of the zincated pyridazin-3(2*H*)-ones was evaluated by looking at the percentage remaining organozinc compound in function of time (in the absence of substrate and catalyst). Time point zero was chosen as the moment when the (hetero)aryl iodide coupling partner and catalyst are normally added. The percentage remaining zincated pyridazin-3(2*H*)-one after a certain elapsed time can be determined by quenching aliquots of the organozinc solution with $D_2O$ and subsequently analyze the amount of D incorporation versus H with MS (after 10 min at rt: **B** 24%, **D** 61%, **F** 64%, **G** 10%).

The complete regioselectivity for C4 over C6 metalation in **6** and C4 over C5 metalation in **8** was determined by hydrogenolysis ($H_2$, Pd/C) of the reaction products of the zincation/cross-coupling protocol (2-benzyl-5-chloro-4-(4-methoxyphenyl)pyridazin-3(2*H*)-one (**7b**) and 2-benzyl-6-chloro-4-(4-methoxyphenyl)pyridazin-3(2*H*)-one (**9b**)) yielding the same reaction product 2-benzyl-4-(4-methoxyphenyl)-pyridazin-3(2*H*)-one (**10**) (Scheme 2). Moreover, the coupling constant of 4.3 Hz in **10** is very typical for a $J_{5-6}$ (3−6 Hz) in $^1$H NMR.[34]

The methoxy group in the 4-(hetero)aryl (**2**) and 5-(hetero)aryl (**4**) reaction products has been shown to be easily transformable into a triflate group allowing subsequent arylation via a Pd-catalyzed cross-coupling reaction.[3c,m] In this way, 4,5-di(hetero)arylated pyridazin-3(2*H*)-ones with two different (hetero)aryl groups can be obtained. Such compounds have been synthesized from 4,5-dihalopyridazin-3(2*H*)-ones with two different halogen atoms via two consecutive Pd-catalyzed cross-coupling reactions (e.g., 5-chloro-4-iodo- and 4-chloro-5-iodo-2-methylpyridazin-3(2*H*)-one).[1h,35a,35b] The selectivity is based on the different reactivity of the two halogens in an oxidative addition reaction. 4,5-Dihalopyridazin-3(2*H*)-ones containing two chlorine atoms (e.g., 4,5-dichloro-2-methylpyridazin-3(2*H*)-one) have shown to allow C-5 regioselective arylation. The selectivity is however very sensitive to the applied cross-coupling conditions, requiring a thorough optimization for each 2-substituted 4,5-dichloropyridazin-3(2*H*)-one and arylboronic acid combination, which unfortunately does not provide a generally applicable synthetic protocol for library synthesis.[35a] 4,6-Di(hetero)arylated pyridazin-3(2*H*)-ones have also been obtained via consecutive Pd-catalyzed cross-reactions. In this case 1-substituted 5-bromo-6-oxo-1,6-dihydropyridazin-3-yl tosylate was used as substrate in consecutive Suzuki reactions.[36] The oldest and classical route to synthesize both 4,6- as well as 4,5-di(hetero)arylated pyridazin-3(2*H*)-ones is via diazinone ring construction.[1b,h] Our new synthetic protocol starting from a 5-chloropyridazin-3(2*H*)-one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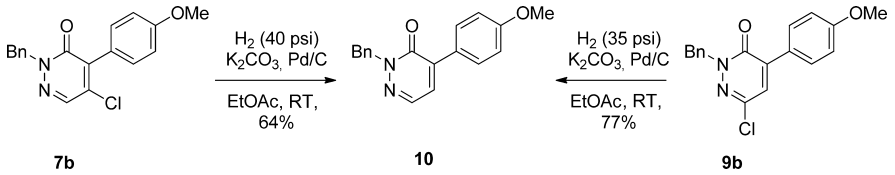
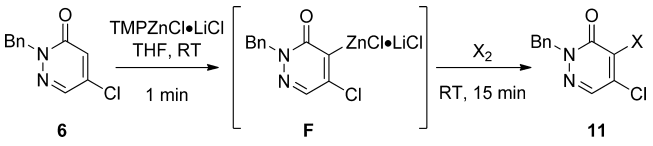
**Scheme 2. Hydrogenolysis ($H_2$, Pd/C) of the Reaction Products 2-Benzyl-5-chloro-4-(4-methoxyphenyl)pyridazin-3(2*H*)-one (7b) and 2-Benzyl-6-chloro-4-(4-methoxyphenyl)pyridazin-3(2*H*)-one (9b)**




and a 6-chloropyridazin-3(2*H*)-one provides a new approach for 5-chloro- and 6-chloro-4-(hetero)arylpyridazin-3(2*H*)-ones, respectively. Via a subsequent Pd-catalyzed cross-coupling an alternative synthetic route for 4,5-di- and 4,6-di(hetero)-arylpyridazin-3(2*H*)-ones with two different (hetero)aryl groups is achieved. The 5-chloro- and 6-chloro-4-(hetero)-arylpyridazin-3(2*H*)-one compound classes are very interesting on themselves as the chlorine allows further decoration of the pyridazinone core via $S_NAE$ and other Pd-catalyzed cross-coupling reactions than arylations, hereby also giving access to a new protocol for a variety of 5- and 6-substituted 4-(hetero)arylpyridazin-3(2*H*)-ones. The main advantage of our new approach to introduce a (hetero)aryl substituent in C4 of the pyridazinone nucleus is that it is based on a metalated pyridazinone and a halogenated (hetero)arene rather than on a halopyridazinone and a metalated (hetero)arene as coupling partners. After all, the (commercial) availability of metalated (hetero)arenes, especially the heteroarenes, is still rather limited and often there are stability issues. In addition, protodemetalation of these species in transition metal catalyzed cross-coupling reactions is a well-known competitive process.

As it has previously been shown that pyridazin-3(2*H*)-ones with two different halogens can be used in selective Pd-catalyzed cross-coupling reactions and these are not always so easily accessible (vide supra), we wondered whether quenching of the zincated chloropyridazin-3(2*H*)-ones with iodine and bromine would allow a simpler access to such compounds. Interestingly this worked smoothly and 2-benzyl-4-bromo-5-chloro- (**11a**),[37] 2-benzyl-5-chloro-4-iodo- (**11b**),[38] 2-benzyl-4-bromo-6-chloro- (**12a**),[39] and 2-benzyl-6-chloro-4-iodopyridazin-3(2*H*)-one (**12b**) were obtained in high yields (Tables 5 and 6). Scale-up of these reactions to 10.0 mmol were tried without any drop-off in yield. Interestingly, no 6-chloro-4-iodopyridazin-3(2*H*)-ones have hitherto been described in literature.

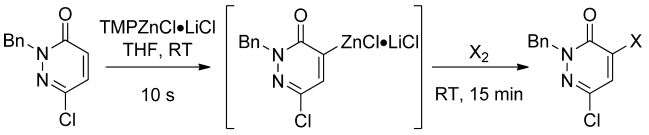
**Table 5. Lactam-Directed *Ortho* C−H Zincation of 2-Benzyl-5-chloropyridazin-3(2*H*)-one (6) Using TMPZnCl·LiCl Followed by Reaction with Halogens**




| entry | $X_2$ | X | **11** | yield[a] (%) |
|---|---|---|---|---|
| 1 | $Br_2$ | Br | **11a** | 76 |
| 2 | $I_2$ | I | **11b** | 73 |

[a] **6** (1.0 mmol), 1.81 mL of 0.55 M TMPZnCl·LiCl solution in THF (1.0 equiv), THF (4.0 mL), rt, 1 min; $X_2$ (2.0 equiv), rt, 15 min.

**Table 6. Lactam-Directed *Ortho* C−H Zincation of 2-Benzyl-6-chloropyridazin-3(2*H*)-one (8) Using TMPZnCl·LiCl Followed by Reaction with Halogens**




| entry | $X_2$ | X | **12** | yield[a] (%) |
|---|---|---|---|---|
| 1 | $Br_2$ | Br | **12a** | 91 |
| 2 | $I_2$ | I | **12b** | 91 |

[a] **8** (1.0 mmol), 1.81 mL of 0.55 M TMPZnCl·LiCl solution in THF (1.0 equiv), THF (4.0 mL), rt, 10 s; $X_2$ (2.0 equiv), rt, 15 min.

## CONCLUSION

In this paper, the synthesis of hitherto unknown zincated pyridazin-3(2*H*)-ones is presented. Both transmetalation with $ZnCl_2$ on C4 and C5 magnesiated pyridazin-3(2*H*)-ones, previously synthesized in our group, and lactam-directed C4 deprotonation with a Zn amide base can be used to prepare these zincated pyridazin-3(2*H*)-ones. We showed that these compounds can be used in Negishi reactions with iodo-(hetero)arenes providing a new way to access C4 and C5 (hetero)arylated pyridazin-3(2*H*)-ones in moderate to good yields. The directed C4 zincation of 2-benzyl-5-chloro- and 2-benzyl-6-chloropyridazin-3(2*H*)-one is especially interesting as the chlorine present in the substrate provides a tool for post functionalization via $S_NAE$ and Pd-catalyzed cross-coupling reactions. The (2-benzyl-chloro-3-oxo-2,3-dihydropyridazin-4-yl)(di-$\mu$-chloro)lithiumzinc compounds can also be used in a reaction with iodine and bromine providing a smooth access to 4,5- and 4,6-dihalogenated pyridazin-3(2*H*)-ones. These can be used as substrates for selective $S_NAE$ and palladium catalyzed reactions. The presented synthetic protocols further expand the limited functionalization procedures of the pyridazin-3(2*H*)-one scaffold hitherto available.

## EXPERIMENTAL SECTION

**General Methods.** All melting points reported are determined on a melting point apparatus and are uncorrected. The $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a 400 MHz spectrometer in the solvent indicated with TMS as the internal standard. *J* values are given in Hz, and the chemical shifts are given in ppm. For high-resolution mass-spectrometric analysis, samples were dissolved in $CH_3OH$/$CH_3CN$ 50/50 containing 0.1% formic acid and diluted to a concentration of approximately $10^{-5}$ mol/L. A 2 $\mu$L portion was injected using a CapLC system and electrosprayed through the nanoelectrospray source. The nanoelectrospray source was operated in positive ion mode at an electrospray potential of 1.7 kV. The eluent used was 30% A ($H_2O$ 0.1% formic acid) and 70% B (ACN/$H_2O$ 95/5 0.1% formic acid) at a flow rate of 6 $\mu$L/min. Samples were injected with an interval of 3 min. Before analysis and after each seventh sample a 2 $\mu$L volume of a 0.025% $H_3PO_4$ solution (50/50 MeOH/$H_2O$) was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injected that could be used as lock mass. The MS was calibrated prior to use with a 0.015% $H_3PO_4$ solution. The spectra were lock mass corrected using the known mass of the nearest $H_3PO_4$ cluster. Flash column chromatography was performed on Kieselgel 60 or using an automated chromatography system with Silica Flash Cartridges. Dry THF on molecular sieves was bought from a commercial source. The Grignard reagents *n*-BuMgCl and mesitylmagnesium bromide were bought from a commercial source as solutions in THF.

**General Procedure 1 for the Functionalization of 2-Benzyl-4-bromo-5-methoxypyridazin-3(2*H*)-one (1).** 2-Benzyl-4-bromo-5-methoxypyridazin-3(2*H*)-one (**1**) (0.295 g, 1.0 mmol)[3p] was brought in a dry 25 mL double-necked flask and was placed under argon atmosphere using a Schlenck apparatus. Subsequently, THF (4 mL) was added, and the solution was cooled to −20 °C (ice−salt bath). *n*-BuMgCl (0.6 mL, 2 M solution) was quickly added via a syringe. The mixture was stirred for 10 min, after which time $ZnCl_2$ (2.86 mL, 0.7 M solution) was added via a syringe and the mixture stirred for 15 min at −20 °C. In another 10 mL dry flask $Pd(dba)_2$ (0.029 g, 0.05 mmol) and tri(2-furyl)phosphine (0.023 g, 0.10 mmol) were weighed out, and 1 mL of THF was added under an argon flow. This solution was stirred for 5 min. The catalyst solution and (hetero)aryl iodide (4.00 mmol) were added simultaneously to the reaction mixture, which was placed in an oil bath at 50 °C and stirred until the reaction was completed. The resulting mixture was quenched with aq. $NH_4Cl$ and extracted with EtOAc (3 × 50 mL) and subsequently dried over $MgSO_4$. The organic phase was evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using a silica flash cartridge applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethyl acetate in 25 min, 25 mL/min).

**Ethyl 4-(2-Benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)benzoate (2a).** The general procedure 1 was followed using ethyl 4-iodobenzoate (0.670 mL, 4.00 mmol). The reaction time was 30 min. Compound **2a** was obtained in 80% (0.292 g) yield.

A dry 50 mL double-necked flask placed under argon atmosphere using a Schlenck apparatus was charged with TMPZnCl·LiCl[4] (1.818 mL, 0.55 *M* solution in THF). 2-Benzyl-5-methoxypyridazin-3(2*H*)-one (**5**) (0.216 g, 1.0 mmol)[3p] was brought in a second dry 25 mL double-necked flask and placed under argon atmosphere using a Schlenck apparatus. Subsequently, THF (2 mL) was added. In a third dry 25 mL double-necked flask $Pd(dba)_2$ (0.029 g, 0.05 mmol) and tri(2-furyl)phosphine (0.023 g, 0.10 mmol) were weighed out, and 1 mL of THF was added under an argon flow. Ethyl 4-iodobenzoate (0.335 mL, 2.00 mmol) was added to this solution after which it was stirred for 5 min. The pyridazin-3(2*H*)-one solution was added dropwise to the TMP solution (1 min) after which it was stirred for 10 s; subsequently, the catalyst solution was immediately added to this solution. The reaction mixture was stirred at room temperature for 60 min. The resulting mixture was quenched with aq $NH_4Cl$ and extracted with EtOAc (3 × 50 mL) and subsequently dried over $MgSO_4$. The organic phase was evaporated to dryness under reduced pressure, and the residue separated with an automated chromatography system using a silica flash cartridge applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethyl acetate in 25 min, 25 mL/min). Compound **2a** was obtained in 86% (0.315 g) yield: orange solid; mp 87−88 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.06 (d, 2H, $J$ = 8.61 Hz), 7.91 (s, 1H), 7.59 (d, 2H, $J$ = 8.66 Hz), 7.45 (m, 2H), 7.33−7.25 (m, 3H), 5.35 (s, 2H), 4.37 (q, 2H, $J$ = 7.19 Hz), 3.87 (s, 3H), 1.38 (t, 3H, $J$ = 7.17 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.3, 160.5, 155.0, 136.3, 135.1, 130.5, 129.0, 128.9, 128.6, 128.6, 127.9, 127.7, 120.4, 60.9, 57.2, 55.6, 14.3; HRMS (ESI) for $C_{21}H_{20}N_2O_4$ $[M + H]^+$ calcd 365.1496, found 365.1461.

**2-Benzyl-5-methoxy-4-(4-methoxyphenyl)pyridazin-3(2*H*)-one (2b).** The general procedure 1 was followed using 4-iodoanisole (0.936 g, 4.00 mmol). The reaction time was 30 min. Compound **2b** was obtained in 72% (0.232 g) yield: orange oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.87 (s, 1H), 7.50 (m, 2H), 7.46 (m, 2H), 7.30 (m, 3H), 6.93 (d, 2H, $J$ = 9.02 Hz), 5.35 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 161.0, 159.5, 154.4, 136.6, 131.8, 128.9, 128.5, 128.1, 127.8, 122.4, 121.2, 113.3, 57.1, 55.5, 55.2; HRMS (ESI) for $C_{19}H_{18}N_2O_3$ $[M + H]^+$ calcd 323.1390, found 323.1388.

**2-Benzyl-4-(2-chlorophenyl)-5-methoxypyridazin-3(2*H*)-one (2c).** The general procedure 1 was followed using 1-chloro-2-iodobenzene (0.489 mL, 4.00 mmol). The reaction time was 90 min. Compound **2c** was obtained in 34% (0.111 g) yield: yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.86 (s, 1H), 7.47−7.41 (m, 3H), 7.32−7.23 (m, 6H), 5.38 (d, 1H, $J$ = 13.65 Hz), 5.32 (d, 1H, $J$ = 13.65), 3.81 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.4, 155.7, 136.5, 134.1, 131.9, 130.2, 129.7, 129.5, 129.0, 128.9, 128.6, 128.6, 127.9, 126.6, 57.2, 55.3; HRMS (ESI) for $C_{18}H_{15}ClN_2O_2$ $[M + H]^+$ calcd 327.0895, found 327.0891.

**2-Benzyl-4-(3-chlorophenyl)-5-methoxypyridazin-3(2*H*)-one (2d).** The general procedure 1 was followed using 1-chloro-3-iodobenzene (0.496 mL, 4.00 mmol). The reaction time was 1 h. Compound **2d** was obtained in 73% (0.239 g) yield: orange oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.89 (s, 1H), 7.50 (s, 1H), 7.47−7.23 (m, 8H), 5.34 (s, 2H), 3.87 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.5, 154.9, 136.3, 133.6, 132.0, 130.4, 129.0, 128.9, 128.7, 128.6, 128.4, 127.9, 127.6, 120.0, 57.2, 55.6; HRMS (ESI) for $C_{18}H_{15}ClN_2O_2$ $[M + H]^+$ calcd 327.0895, found 327.0892.

**2-Benzyl-4-(4-chlorophenyl)-5-methoxypyridazin-3(2*H*)-one (2e).**[40] The general procedure 1 was followed using 1-chloro-4-iodobenzene (0.954 g, 4.00 mmol). The reaction time was 2 h. Compound **2e** was obtained in 74% (0.242 g) yield: orange oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.87 (s, 1H), 7.49−7.41 (m, 4H), 7.36−7.21 (m, 5H), 5.33 (s, 2H), 3.81 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.6, 154.8, 136.4, 134.1, 131.9, 128.9, 128.8, 128.6, 128.0, 128.0, 127.8, 120.2, 57.2, 55.6; HRMS (ESI) for $C_{18}H_{15}ClN_2O_2$ $[M + H]^+$ calcd 327.0895, found 327.0889.

**2-Benzyl-5-methoxy-4-[3-(trifluoromethyl)phenyl]-pyridazin-3(2*H*)-one (2f).** The general procedure 1 was followed using 1-iodo-3-(trifluoromethyl)benzene (0.588 mL, 4.00 mmol). The reaction time was 40 min. Compound **2f** was obtained in 69% (0.249 g) yield: yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.92 (s, 1H), 7.79 (s, 1H), 7.71 (d, 1H, $J$ = 7.81 Hz), 7.57 (d, 1H, $J$ = 7.84 Hz), 7.50 (d, 1H, $J$ = 7.79 Hz), 7.45 (m, 2H), 7.29 (m, 3H), 5.36 (s, 2H), 3.87 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.5, 155.0, 136.3, 133.9, 131.1, 130.2 (q, $J$ = 32.3 Hz), 128.9, 128.6, 128.2, 128.0, 127.6, 127.4 (q, $J$ = 3.8 Hz),125.0 (q, $J$ = 3.6 Hz), 124.0 (q, $J$ = 273.4), 119.8, 57.2, 55.6; HRMS (ESI) for $C_{19}H_{15}F_3N_2O_2$ $[M + H]^+$ calcd 361.1158, found 361.1158.

**2-Benzyl-5-methoxy-4-[4-(trifluoromethyl)phenyl]-pyridazin-3(2*H*)-one (2g).** The general procedure 1 was followed using 1-iodo-4-(trifluoromethyl)benzene (0.588 mL, 4.00 mmol). The reaction time was 90 min. Compound **2g** was obtained in 90% (0.324 g) yield: orange oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.91 (s, 1H), 7.63 (m, 4H), 7.45 (m, 2H), 7.28 (m, 3H), 5.34 (s, 2H), 3.84 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.5, 155.0, 136.6, 134.3, 130.9, 130.0 (q, $J$ = 33.0 Hz), 128.9, 128.6, 128.0, 127.6, 124.7 (q, $J$ = 3.7 Hz), 124.2 (q, $J$ = 271.9 Hz), 119.8, 57.2, 55.7; HRMS (ESI) for $C_{19}H_{15}F_3N_2O_2$ $[M + H]^+$ calcd 361.1158, found 361.1158.

**2-Benzyl-5-methoxy-4-(pyridin-2-yl)pyridazin-3(2*H*)-one (2h).** The general procedure 1 was followed using 2-iodopyridine (0.425 mL, 4.00 mmol). The reaction time was 60 min. Compound **2h** was obtained in 82% (0.241 g) yield: yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 8.73 (d, 1H, $J$ = 4.96 Hz), 7.96 (s, 1H), 7.77 (td, 1H, $J$ = 7.81, 1.78 Hz), 7.53 (d, 1H, $J$ = 8.03 Hz), 7.45 (m, 2H), 7.30 (m, 4H), 5.36 (s, 2H), 3.87 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 161.0, 156.3, 150.4, 149.4, 136.6, 136.1, 128.8, 128.6, 128.5, 128.0, 126.6, 123.2, 119.6, 57.6, 55.6; HRMS (ESI) for $C_{17}H_{15}N_3O_2$ $[M + H]^+$ calcd 294.1237, found 294.1235.

**2-Benzyl-5-methoxy-4-(pyridin-3-yl)pyridazin-3(2*H*)-one (2i).** The general procedure 1 was followed using 3-iodopyridine (0.820 g, 4.00 mmol). The reaction time was 60 min. Compound **2i** was obtained in 86% (0.252 g) yield: orange solid; mp 201−202 °C; $^1$H NMR ($CDCl_3$) $\delta$ 9.03 (s, 1H), 8.70 (d, 1H, $J$ = 4.72 Hz), 8.29 (d, 1H, $J$ = 8.10 Hz), 7.96 (s, 1H), 7.54 (m, 1H), 7.40 (m, 2H), 7.30 (m, 3H), 5.34 (s, 2H), 3.95 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.1, 155.6, 150.5, 147.4, 141.9, 135.9, 128.8, 128.7, 128.7, 128.1, 127.4, 124.5, 115.4, 57.5, 55.9; HRMS (ESI) for $C_{17}H_{15}N_3O_2$ $[M + H]^+$ calcd 294.1237, found 294.1237.

**2-Benzyl-5-methoxy-4-(pyrazin-2-yl)pyridazin-3(2*H*)-one (2j).** The general procedure 1 was followed using 2-iodopyrazine (0.395 mL, 4.00 mmol). The reaction time was 90 min. Compound **2j** was obtained in 78% (0.230 g) yield: yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 8.75 (d, 1H, $J$ = 1.51 Hz), 8.66 (dd, 1H, $J$ = 2.56, 1.51 Hz), 8.49 (d, 1H, $J$ = 2.56 Hz), 7.95 (s, 1H), 7.44 (m, 2H), 7.34−7.26 (m, 3H), 5.35 (s, 2H), 3.89 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.2, 156.6, 147.1, 147.0, 144.1, 143.4, 136.0, 128.9, 128.6, 128.0, 127.6, 117.3, 57.5, 55.5; HRMS (ESI) for $C_{16}H_{14}N_4O_2$ $[M + H]^+$ calcd 295.1190, found 295.1179.

**2-Benzyl-5-methoxy-4-(2-thienyl)pyridazin-3(2*H*)-one (2k).** The general procedure 1 was followed using 2-iodothiophene (0.422 mL, 4.00 mmol). The reaction time was 90 min. Compound **2k** was obtained in 64% (0.191 g) yield: orange solid; mp 129−130 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.25 (dd, 1H, $J$ = 3.97, 1.08 Hz), 7.87 (s, 1H), 7.48 (dd, 1H, $J$ = 5.24, 1.04 Hz), 7.43 (m, 2H), 7.32−7.23 (m, 3H), 7.12 (m, 1H), 5.41 (s, 2H), 4.03 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.7, 152.6, 136.4, 131.8, 131.0, 129.0, 128.7, 128.6, 127.9, 127.1, 126.3, 115.3, 57.0, 55.6; HRMS (ESI) for $C_{16}H_{14}N_2O_2S$ $[M + H]^+$ calcd 299.0849, found 299.0856.

**General Procedure 2 for the Functionalization of 2-Benzyl-5-bromo-4-methoxypyridazin-3(2*H*)-one (3).** 2-Benzyl-5-bromo-4-methoxypyridazin-3(2*H*)-one (**3**) (0.295 g, 1.0 mmol)[3p] was brought in a dry 25 mL double-necked flask and placed under argon atmosphere using a Schlenck apparatus. Subsequently THF (4 mL) was added and the solution was cooled to −20 °C (ice-salt bath). MesMgBr (2.00 mL, 1 *M* solution) was quickly added via a syringe. The mixture was stirred for 2 min after which $ZnCl_2$ (4.29 mL, 0.7 *M* solution) was added and the resulting mixture stirred for 10 min at −20 °C. In another 10 mL dry flask $Pd(dba)_2$ (0.029 g, 0.05 mmol) and tri(2-furyl)phosphine (0.023 g, 0.10 mmol) were weighed out, and 1 mL of THF was added under an argon flow. This solution was stirred for 5 min. The catalyst solution and (hetero)aryl iodide (4.00 mmol) were added simultaneously to the reaction mixture which was placed in an oil bath at 50 °C and stirred until the reaction was completed. The resulting mixture was quenched with aq $NH_4Cl$ and extracted with EtOAc (3 × 50 mL) and subsequently dried over $MgSO_4$. The organic phase was evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using a Silica Flash Cartridge applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethyl acetate in 25 min, 25 mL/min).

**Ethyl 4-(1-Benzyl-5-methoxy-6-oxo-1,6-dihydropyridazin-4-yl)benzoate (4a).** The general procedure 2 was followed using ethyl 4-iodobenzoate (0.670 mL, 4.00 mmol). The reaction time was 60 min. Compound **4a** was obtained in 45% (0.164 g) yield: orange oil; $^1$H NMR ($CDCl_3$) $\delta$ 8.11 (d, 2H, $J$ = 8.38 Hz), 7.78 (s, 1H), 7.56 (d, 2H, $J$ = 8.52 Hz), 7.48 (m, 2H), 7.30 (m, 3H), 5.35 (s, 2H), 4.40 (q, 2H, $J$ = 7.21 Hz), 4.11 (s, 3H), 1.40 (t, 3H, $J$ = 7.21 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.0, 158.0, 151.7, 137.9, 136.6, 136.2, 130.8, 129.7, 128.9, 128.8, 128.6, 128.0, 127.6, 61.2, 60.3, 55.3, 14.3; HRMS (ESI) for $C_{21}H_{20}N_2O_4$ $[M + H]^+$ calcd 365.1496, found 365.1485.

**2-Benzyl-4-methoxy-5-(4-methoxyphenyl)pyridazin-3(2*H*)-one (4b).**[41] The general procedure 2 was followed using 4-iodoanisole (0.936 g, 4.00 mmol). The reaction time was 40 min. Compound **4b** was obtained in 74% (0.238 g) yield: orange oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.79 (s, 1H), 7.47 (m, 4H), 7.36−7.24 (m, 3H), 6.97 (m, 2H), 5.34 (s, 2H), 4.06 (s, 3H), 3.83 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.2, 158.3, 151.0, 138.6, 136.4, 130.2, 128.8, 128.6, 128.6, 127.9, 124.4, 114.1, 60.0, 55.3, 55.1; HRMS (ESI) for $C_{19}H_{18}N_2O_3$ $[M + H]^+$ calcd 323.1390, found 323.1381.

**2-Benzyl-5-(2-chlorophenyl)-4-methoxypyridazin-3(2*H*)-one (4c).** The general procedure 2 was followed using 1-chloro-2-iodobenzene (0.489 mL, 4.00 mmol). The reaction time was 60 min. Compound **4c** was obtained in 46% (0.151 g) yield: yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.63 (s, 1H), 7.55−7.49 (m, 2H), 7.41−7.32 (m, 5H), 7.29−7.25 (m, 1H), 5.39 (s, 2H), 4.06 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.0, 152.3, 138.3, 136.2, 133.2, 131.6, 131.1, 130.2, 129.9, 128.9, 128.7, 128.0, 126.9, 126.0, 60.2, 55,4; HRMS (ESI) for $C_{18}H_{15}ClN_2O_2$ $[M + H]^+$ calcd 327.0895, found 327.0899.

**2-Benzyl-5-(3-chlorophenyl)-4-methoxypyridazin-3(2*H*)-one (4d).** The general procedure 2 was followed using 1-chloro-3-iodobenzene (0.497 mL, 4.00 mmol). The reaction time was 90 min. Compound **4d** was obtained in 73% (0.239 g) yield: yellow solid; mp 54−55 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.74 (s, 1H), 7.47 (m, 2H), 7.45−7.38 (m, 4H), 7.36−7.24 (m, 3H), 5.34 (s, 2H), 4.09 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.9, 151.6, 137.9, 136.2, 134.6, 134.0, 129.9, 129.0, 128.9, 128.8, 128.6, 128.0, 127.2, 127.0, 60.3, 55.3; HRMS (ESI) for $C_{18}H_{15}ClN_2O_2$ $[M + H]^+$ calcd 327.0895, found 327.0891.

**2-Benzyl-5-(4-chlorophenyl)-4-methoxypyridazin-3(2*H*)-one (4e).** The general procedure 2 was followed using 1-chloro-4-iodobenzene (0.954 g, 4.00 mmol). The reaction time was 60 min. Compound **4e** was obtained in 46% (0.151 g) yield: yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.74 (s, 1H), 7.49−7.44 (m, 3H), 7.39−7.24 (m, 6H), 5.34 (s, 2H), 4.11 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.0, 151.4, 138.0, 136.2, 135.1, 130.6, 130.2, 128.9, 128.8, 128.6, 128.0, 127.5, 60.2, 55.3; HRMS (ESI) for $C_{18}H_{15}ClN_2O_2$ $[M + H]^+$ calcd 327.0895, found 327.0884.

**2-Benzyl-4-methoxy-5-(4-(trifluoromethyl)phenyl)-pyridazin-3(2*H*)-one (4f).** The general procedure 2 was followed using 1-iodo-4-(trifluoromethyl)benzene (0.588 mL, 4.00 mmol). The reaction time was 90 min. Compound **4f** was obtained in 63% (0.227 g) yield: white solid; mp 87−88 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.76 (s, 1H), 7.70 (d, 2H, $J$ = 8.22 Hz), 7.60 (d, 2H, $J$ = 8.09 Hz), 7.48 (m, 2H), 7.36−7.26 (m, 3H), 5.35 (s, 2H), 4.13 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.9, 151.8, 137.8, 136.2, 136.0, 131.0 (q, $J$ = 32.7 Hz), 129.3, 128.9, 128.7, 128.1, 127.2, 125.6 (q, $J$ = 3.6 Hz), 124.0 (q, $J$ = 272.7 Hz), 60.4, 55.4; HRMS (ESI) for $C_{19}H_{15}F_3N_2O_2$ $[M + H]^+$ calcd 361.1158, found 361.1157.

**2-Benzyl-4-methoxy-5-(pyridin-2-yl)pyridazin-3(2*H*)-one (4g).** 2-Benzyl-5-bromo-4-methoxypyridazin-3(2*H*)-one (**3**) (0.295 g, 1.0 mmol)[3p] was brought in a dry 25 mL double-necked flask and placed under argon atmosphere using a Schlenck apparatus. Subsequently, THF (4 mL) was added, and the solution was cooled to −20 °C (ice−salt bath). MesMgBr (2.00 mL, 1 M solution) was quickly added via a syringe. The mixture was stirred for 2 min, after which $ZnCl_2$ (4.29 mL, 1 M solution) was added and the resulting mixture stirred for 10 min at −20 °C. In another 10 mL dry flask $Pd(dba)_2$ (0.029 g, 0.05 mmol), tri(2-furyl)phosphine (0.023 g, 0.10 mmol) and lithium chloride (3.00 mL, 2.24 *M* solution in DMF) were weighed out, and 1 mL of DMF was added under an argon flow. 2-Iodopyridine (0.820 g, 4.00 mmol) was added, and this solution was stirred for 5 min. The catalyst/2-iodopyridine solution was added to the reaction mixture which was placed in an oil bath at 50 °C and stirred for 90 min until the reaction was completed. The resulting mixture was quenched with aq $NH_4Cl$, extracted with EtOAc (3 × 50 mL), and subsequently dried over $MgSO_4$. The organic phase was evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using a silica flash cartridge applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethyl acetate in 25 min, 25 mL/min). Compound **4g** was obtained in 79% (0.23 g) yield: white solid; mp 100−101 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.70 (m, 1H), 8.39 (s, 1H), 7.94 (dt, 1H, $J$ = 8.0, 1.0 Hz), 7.74 (td, 1H, $J$ = 7.8, 1.8 Hz), 7.48−7.43 (m, 2H), 7.35−7.24 (m, 4H), 5.35 (s, 2H), 4.18 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.2, 152.2, 150.6, 149.6, 138.3, 136.4, 136.3, 128.6, 128.6, 127.9, 126.6, 125.9, 123.4, 60.2, 55.3; HRMS (ESI) for $C_{17}H_{15}N_3O_2$ $[M + H]^+$ calcd 294.1237, found 294.1228.

**2-Benzyl-4-methoxy-5-(pyrazin-2-yl)pyridazin-3(2*H*)-one (4i).** The general procedure 2 was followed using 2-iodopyrazine (0.395 mL, 4.00 mmol). The reaction time was 60 min. Compound **4i** was obtained in 63% (0.186 g) yield: yellow solid; mp 106−107 °C; $^1$H NMR ($CDCl_3$) $\delta$ 9.25 (s, 1H), 8.66 (s, 1H), 8.54 (d, 1H, $J$ = 2.4 Hz), 8.38 (s, 1H), 7.48−7.43 (m, 2H), 7.36−7.25 (m, 3H), 5.35 (s, 2H), 4.30 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.7, 152.5, 146.9, 146.9, 144.2, 143.9, 137.4, 136.1, 128.7, 128.6, 128.0, 123.3, 60.6, 55.4; HRMS (ESI) for $C_{16}H_{14}N_4O_2$ $[M + H]^+$ calcd 295.1190, found 295.1203.

**2-Benzyl-4-methoxy-5-(2-thienyl)pyridazin-3(2*H*)-one (4j).** The general procedure 2 was followed using 2-iodothiophene (0.442 mL,


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4.00 mmol). The reaction time was 60 min. Compound **4j** was obtained in 78% (0.232 g) yield: white solid; mp 92−94 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.09 (s, 1H), 7.55 (dd, 1H, $J$ = 3.9, 1.0 Hz), 7.46 (dd, 1H, $J$ = 5.1, 1.0 Hz), 7.45−7.41 (m, 2H), 7.35−7.23 (m, 3H), 7.10 (dd, 1H, $J$ = 5.1, 3.9 Hz), 5.31 (s, 2H), 4.24 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.8, 148.3, 136.3, 135.7, 133.1, 129.4, 128.7, 128.6, 127.9, 127.4, 127.1, 122.6, 59.6, 55.0; HRMS (ESI) for $C_{16}H_{14}N_2O_2S$ $[M + H]^+$ calcd 299.0849, found 299.0842.

**General Procedure 3 for the Functionalization of 2-Benzyl-5-chloropyridazin-3(2*H*)-one (6).** A dry 50 mL double-necked flask placed under argon atmosphere using a Schlenck apparatus was charged with TMPZnCl·LiCl[4] (1.818 mL, 0.55 M solution in THF). 2-Benzyl-5-chloropyridazin-3(2*H*)-one (**6**) (0.221 g, 1.0 mmol)[3q] was brought in a second dry 25 mL double-necked flask and was placed under argon atmosphere using a Schlenck apparatus. Subsequently, THF (2 mL) was added. In a third dry 25 mL double-necked flask $Pd(dba)_2$ (0.029 g, 0.05 mmol) and tri(2-furyl)phosphine (0.023 g, 0.10 mmol) were weighed out, and 1 mL THF was added under an argon flow. (Hetero)aryl iodide (2.00 mmol) was added to this solution after which it was stirred for 5 min. The pyridazin-3(2*H*)-one solution was added dropwise to the TMP solution (1 min) after which it was stirred for an additional 1 min; subsequently, the catalyst/(hetero)aryl iodide solution was immediately added to this solution and stirred until the reaction was completed. The resulting mixture was quenched with aq $NH_4Cl$, extracted with EtOAc (3 × 50 mL), and subsequently dried over $MgSO_4$. The organic phase was evaporated to dryness under reduced pressure, and the residue separated with an automated chromatography system using a silica flash cartridge applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethyl acetate in 25 min, 25 mL/min).

**Ethyl 4-(2-Benzyl-5-chloro-3-oxo-2,3-dihydropyridazin-4-yl)benzoate (7a).** The general procedure 3 was followed using ethyl 4-iodobenzoate (0.335 mL, 2.00 mmol). The reaction time was 15 min. Compound **7a** was obtained in 80% (0.295 g) yield: yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 8.12 (d, 2H, $J$ = 8.46 Hz), 7.86 (s, 1H), 7.52 (d, 2H, $J$ = 8.44 Hz), 7.47 (m, 2H), 7.36−7.27 (m, 3H), 5.32 (s, 2H), 4.39 (q, 2H, $J$ = 7.17 Hz), 1.40 (t, 3H, $J$ = 7.17 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.0, 158.6, 137.3, 137.1, 135.9, 135.7, 135.5, 131.2, 129.8, 129.3, 129.1, 128.7, 128.2, 61.1, 56.0, 14.3; HRMS (ESI) for $C_{20}H_{17}ClN_2O_3$ $[M + H]^+$ calcd 369.1000, found 369.0996.

**2-Benzyl-5-chloro-4-(4-methoxyphenyl)pyridazin-3(2*H*)-one (7b).** The general procedure 3 was followed using 4-iodoanisole (0.468 g, 2.00 mmol). The reaction time was 15 min. Compound **7b** was obtained in 65% (0.212 g) yield: yellow solid; mp 88−89 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.78 (s, 1H), 7.48−7.41 (m, 3H), 7.31−7.20 (m, 4H), 6.93 (m, 2H), 5.28 (s, 2H), 3.76 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.4, 159.3, 137.7, 136.0, 134.9, 131.4, 129.1, 128.1, 127.6, 126.6, 123.1, 113.6, 55.9, 55.1; HRMS (ESI) for $C_{18}H_{15}ClN_2O_2$ $[M + H]^+$ calcd 327.0895, found 327.0892. The structure was unambiguously confirmed by single-crystal XRD analysis; see the Supporting Information and CCDC 848578.

**2-Benzyl-5-chloro-4-(3-chlorophenyl)pyridazin-3(2*H*)-one (7d).** The general procedure 3 was followed using 1-chloro-3-iodobenzene (0.477 g, 2.00 mmol). The reaction time was 20 min. Compound **7d** was obtained in 44% (0.146 g) yield: yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.84 (s, 1H), 7.46 (m, 2H), 7.38 (m, 3H), 7.35−7.30 (m, 4H), 5.31 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.7, 137.1, 136.9, 136.0, 135.6, 134.2, 132.7, 129.7, 129.5, 129.5, 129.1, 128.7, 128.2, 127.9, 56.0; HRMS (ESI) for $C_{17}H_{12}Cl_2N_2O$ $[M + H]^+$ calcd 331.0399, found 331.0396.

**2-Benzyl-5-chloro-4-(4-chlorophenyl)pyridazin-3(2*H*)-one (7e).**[42] The general procedure 3 was followed using 1-chloro-4-iodobenzene (0.477 g, 2.00 mmol). The reaction time was 15 min. Compound **7e** was obtained in 74% (0.245 g) yield: orange solid; MP 122−123 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.83 (s, 1H), 7.46 (m, 2H), 7.41−7.38 (m, 4H), 7.34−7.27 (m, 3H), 5.30 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.8, 143.3, 137.2, 135.7, 131.2, 129.4, 129.1, 129.0, 128.7, 128.5, 128.2, 125.5, 56.0; HRMS (ESI) for $C_{17}H_{12}Cl_2N_2O$ $[M + H]^+$ calcd 331.0399, found 331.0396.

**2-Benzyl-5-chloro-4-(3-(trifluoromethyl)phenyl)pyridazin-3(2*H*)-one (7f).** The general procedure 3 was followed using 1-iodo-3-(trifluoromethyl)benzene (0.288 mL, 2.00 mmol). The reaction time was 20 min. Compound **7f** was obtained in 51% (0.186 g) yield: yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.92 (s, 1H), 7.79 (s, 1H), 7.71 (d, 1H, $J$ = 7.81 Hz), 7.57 (d, 1H, $J$ = 7.84 Hz), 7.50 (d, 1H, $J$ = 7.79 Hz), 7.45 (m, 2H), 7.29 (m, 3H), 5.36 (s, 2H), 3.87 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.5, 155.0, 136.3, 133.9, 131.1, 130.2 (q, $J$ = 32.3 Hz), 128.9, 128.6, 128.2, 128.0, 127.6, 127.4 (q, $J$ = 3.8 Hz),125.0 (q, $J$ = 3.6 Hz), 124.0 (q, $J$ = 273.4), 119.8, 57.2, 55.6; HRMS (ESI) for $C_{19}H_{15}F_3N_2O_2$ $[M + H]^+$ calcd 361.1158, found 361.1158.

**2-Benzyl-5-chloro-4-(4-(trifluoromethyl)phenyl)pyridazin-3(2*H*)-one (7g).** The general procedure 3 was followed using 1-iodo-4-(trifluoromethyl)benzene (0.288 mL, 2.00 mmol). The reaction time was 30 min. Compound **7g** was obtained in 44% (0.160 g) yield: yellow solid; mp 75−76 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.90 (s, 1H), 7.74 (d, 2H, $J$ = 7.7 Hz), 7.60 (d, 2H, $J$ = 7.7 Hz), 7.52−7.47 (m, 2H), 7.39−7.31 (m, 3H), 5.35 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.7, 137.2, 136.9, 136.2, 135.6, 134.7, 131.4 (q, $J$ = 32.7 Hz), 130.3, 129.2, 128.8, 128.4, 125.3 (q, $J$ = 3.8 Hz), 123.9 (q, $J$ = 272.5 Hz), 56.2; HRMS (ESI) for $C_{18}H_{12}F_3ClN_2O$ $[M + H]^+$ calcd 365.0663, found 365.0655; HRMS (ESI) for $C_{18}H_{12}F_3ClN_2O$ $[M + H]^+$ calcd 365.0663, found 365.0661.

**2-Benzyl-5-chloro-4-(pyridin-3-yl)pyridazin-3(2*H*)-one (7i).** A dry 50 mL double-necked flask placed under argon atmosphere using a Schlenck apparatus was charged with TMPZnCl·LiCl[4] (1.818 mL, 0.55 M solution in THF). 2-Benzyl-5-chloropyridazin-3(2*H*)-one (**6**) (0.221 g, 1.0 mmol)[3q] was brought in a second dry 25 mL double-necked flask and placed under argon atmosphere using a Schlenck apparatus. Subsequently, THF (2 mL) was added. In a third dry 25 mL double-necked flask $Pd(dba)_2$ (0.029 g, 0.05 mmol), tri(2-furyl)-phosphine (0.023 g, 0.10 mmol), lithium chloride (3.00 mL, 2.24 M solution in DMF), and 3-iodopyridine (0.410 g, 2.00 mmol) were weighed out, and 1 mL of DMF was added under an argon flow; this solution was stirred for 5 min. The pyridazin-3(2*H*)-one solution was added dropwise to the TMP solution (1 min), after which it was stirred for an additional 1 min; subsequently, the catalyst/3-iodopyridine solution was immediately added to this solution and stirred for 20 min. The resulting mixture was quenched with aq $NH_4Cl$, extracted with EtOAc (3 × 50 mL), and subsequently dried over $MgSO_4$. The organic phase was evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using a silica flash cartridge applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethyl acetate in 25 min, 25 mL/min). Compound **7i** was obtained in 30% (0.089 g) yield: orange solid; mp 114−116 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.73 (d, 1H, $J$ = 1.4 Hz), 8.66 (dd, 1H, $J$ = 4.7, 1.2 Hz), 7.90 (s, 1H), 7.85 (dt, 1H, $J$ = 8.0, 1.9 Hz), 7.50−7.46 (m, 2H), 7.42−7.30 (m, 4H), 5.35 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.7, 150.2, 150.3, 137.5, 137.1, 136.3, 135.5, 135.0, 129.1, 128.7, 128.3, 127.3, 122.9, 56.1; HRMS (ESI) for $C_{16}H_{12}ClN_3O$ $[M + H]^+$ calcd 298.0742, found 298.0743.

**2-Benzyl-5-chloro-4-(2-thienyl)pyridazin-3(2*H*)-one (7k).** The general procedure 3 was followed using 2-iodothiophene (0.221 mL, 2.00 mmol). The reaction time was 15 min. Compound **7k** was obtained in 40% (0.121 g) yield: yellow solid; mp 75−77 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.24 (dd, 1H, $J$ = 3.99, 1.07 Hz), 7.83 (s, 1H), 7.69−7.65 (m, 1H), 7.45 (dd, 2H, $J$ = 8.20, 1.60 Hz), 7.35−7.23 (m, 3H), 7.17 (m, 1H), 5.36 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.1, 137.9, 135.7, 132.6, 131.6, 131.5, 131.3, 130.2, 128.9, 128.7, 128.1, 126.4, 56.1; HRMS (ESI) for $C_{15}H_{11}ClN_2OS$ $[M + H]^+$ calcd 303.0353, found 303.0353.

**General Procedure 4 for the Functionalization of 2-Benzyl-6-chloropyridazin-3(2*H*)-one (8).** A dry 50 mL double-necked flask placed under argon atmosphere using a Schlenck apparatus was charged with TMPZnCl·LiCl[4] (1.818 mL, 0.55 M solution in THF). 2-Benzyl-6-chloropyridazin-3(2*H*)-one (**8**) (0.221 g, 1.0 mmol)[3q] was brought in a second dry 25 mL double-necked flask and was placed under argon atmosphere using a Schlenck apparatus. Subsequently, THF (2 mL) was added. In a third dry 25 mL double-necked flask $Pd(dba)_2$ (0.029 g, 0.05 mmol) and tri(2-furyl)phosphine (0.023 g,


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0.10 mmol) were weighed out, and 1 mL of THF was added under an argon flow. (Hetero)aryl iodide (2.00 mmol) was added to this solution after which it was stirred for 5 min. The pyridazin-3(2*H*)-one solution was immediately added to the TMP solution (1 s) after which it was stirred for 10 s; subsequently, the catalyst/(hetero)aryl iodide solution was immediately added (1 s) to this solution. The reaction mixture was stirred at room temperature until the reaction was completed. The resulting mixture was quenched with aq $NH_4Cl$, extracted with EtOAc (3 × 50 mL), and subsequently dried over $MgSO_4$. The organic phase was evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using a silica flash cartridge applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethyl acetate in 25 min, 25 mL/min).

**Ethyl 4-(2-Benzyl-6-chloro-3-oxo-2,3-dihydropyridazin-4-yl)benzoate (9a).** The general procedure 4 was followed using ethyl 4-iodobenzoate (0.335 mL, 2.00 mmol). The reaction time was 20 min. Compound **9a** was obtained in 91% (0.226 g) yield: white solid; mp 102−103 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.09 (d, 2H, $J$ = 8.51 Hz), 7.83 (d, 2H, $J$ = 8.64 Hz), 7.50 (m, 2H), 7.37−7.27 (m, 4H), 5.33 (s, 2H), 4.40 (q, 2H, $J$ = 7.13 Hz), 1.40 (t, 3H, $J$ = 7.13 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 165.9, 158.2, 141.0, 137.6, 137.0, 135.5, 131.9, 130.2, 129.6, 129.1, 128.7, 128.7, 128.2, 61.3, 56.2, 14.3; HRMS (ESI) for $C_{20}H_{17}ClN_2O_3$ $[M + H]^+$ calcd 369.1000, found 369.0997.

**2-Benzyl-6-chloro-4-(4-methoxyphenyl)pyridazin-3(2*H*)-one (9b).**[3q] The general procedure 4 was followed using 4-iodoanisole (0.468 g, 2.00 mmol). The reaction time was 15 min. Compound **9b** was obtained in 85% (0.278 g) yield: yellow solid; mp 101−102 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.78 (m, 2H), 7.48 (m, 2H), 7.35−7.25 (m, 3H), 7.21 (s, 1H), 6.92 (m, 2H), 6.31 (s, 2H), 3.81 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 161.4, 158.7, 141.3, 137.8, 135.9, 130.4, 129.0, 128.6, 128.1, 127.9, 125.3, 114.0, 56.1, 55.4; HRMS (ESI) for $C_{18}H_{15}ClN_2O_2$ $[M + H]^+$ calcd 327.0895, found 327.0888.

**2-Benzyl-6-chloro-4-(2-chlorophenyl)pyridazin-3(2*H*)-one (9c).** The general procedure 4 was followed using 1-chloro-2-iodobenzene (0.245 mL, 2.00 mmol). The reaction time was 20 min. Compound **9c** was obtained in 61% (0.202 g) yield: orange solid; mp 108−109 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.51−7.44 (m, 3H), 7.37−7.27 (m, 6H), 7.22 (s, 1H), 5.32 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.9, 141.7, 137.0, 135.7, 133.0, 132.7, 132.1, 130.9, 130.7, 130.0, 129.1, 128.7, 128.2, 126.8, 56.1; HRMS (ESI) for $C_{17}H_{12}Cl_2N_2O$ $[M + H]^+$ calcd 331.0399, found 331.0392.

**2-Benzyl-6-chloro-4-(3-chlorophenyl)pyridazin-3(2*H*)-one (9d).** The general procedure 4 was followed using 1-chloro-3-iodobenzene (0.477 g, 2.00 mmol). The reaction time was 20 min. Compound **9d** was obtained in 77% (0.255 g) yield: white solid; mp 78−79 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.76 (d, 1H, $J$ = 1.84 Hz), 7.61 (m, 1H), 7.48 (m, 2H), 7.40−7.27 (m, 5H), 7.23 (s, 1H), 5.30 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.1, 140.4, 137.6, 135.6, 134.6, 134.5, 130.3, 129.9, 129.8, 129.0, 128.8, 128.7, 128.3, 126.9, 56.2; HRMS (ESI) for $C_{17}H_{12}Cl_2N_2O$ $[M + H]^+$ calcd 331.0399, found 331.0393.

**2-Benzyl-6-chloro-4-(4-chlorophenyl)pyridazin-3(2*H*)-one (9e).** The general procedure 4 was followed using 1-chloro-4-iodobenzene (0.477 g, 2.00 mmol). The reaction time was 15 min. Compound **9e** was obtained in 96% (0.318 g) yield: orange solid; mp 126−127 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.70 (m, 2H), 7.48 (m, 2H), 7.42−7.27 (m, 5H), 7.23 (s, 1H), 5.30 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.2, 140.5, 137.6, 136.4, 135.5, 131.2, 130.0, 129.3, 129.0, 128.7, 128.6, 128.2, 56.1; HRMS (ESI) for $C_{17}H_{12}Cl_2N_2O$ $[M + H]^+$, calcd 331.0399, found 331.0394. The structure was unambiguously confirmed by single-crystal XRD analysis; see the Supporting Information and CCDC 848579.

**2-Benzyl-6-chloro-4-(3-(trifluoromethyl)phenyl)pyridazin-3(2*H*)-one (9f).** The general procedure 4 was followed using 1-iodo-3-(trifluoromethyl)benzene (0.288 mL, 2.00 mmol). The reaction time was 20 min. Compound **9f** was obtained in 97% (0.354 g) yield: yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 8.01 (s, 1H), 7.93 (d, 1H, $J$ = 8.07 Hz), 7.67 (d, 1H, $J$ = 7.75 Hz), 7.52 (t, 1H, $J$ = 7.80 Hz), 7.48 (m, 2H), 7.34−7.27 (m, 4H), 5.32 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.1, 140.4, 137.6, 135.5, 133.6, 132.1, 131.0 (q, $J$ = 32.8 Hz), 130.1, 129.0, 129.0, 128.7, 128.3, 126.8 (q, $J$ = 3.7 Hz), 125.6 (q, $J$ = 4.0 Hz), 123.8 (q, $J$ = 273.4 Hz), 56.2; HRMS (ESI) for $C_{18}H_{12}F_3ClN_2O$ $[M + H]^+$ calcd 365.0663, found 365.0661.

**2-Benzyl-6-chloro-4-(4-(trifluoromethyl)phenyl)pyridazin-3(2*H*)-one (9g).** The general procedure 4 was followed using 1-iodo-4-(trifluoromethyl)benzene (0.294 mL, 2.00 mmol). The reaction time was 30 min. Compound **9g** was obtained in 95% (0.346 g) yield: yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.84 (d, 2H, $J$ = 8.27 Hz), 7.65 (d, 2H, $J$ = 8.31 Hz), 7.48 (m, 2H), 7.34−7.24 (m, 4H), 5.30 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.1, 140.5, 137.6, 136.4, 135.5, 131.9 (q, $J$ = 32.6 Hz), 130.3, 129.2, 129.1, 128.7, 128.3, 125.4 (q, $J$ = 3.8 Hz), 123.9 (q, $J$ = 273.1 Hz), 56.2; HRMS (ESI) for $C_{18}H_{12}F_3ClN_2O$ $[M + H]^+$ calcd 365.0663, found 365.0652. The structure was unambiguously confirmed by single-crystal XRD analysis; see the Supporting Information and CCDC 848580.

**2-Benzyl-6-chloro-4-(pyridin-2-yl)pyridazin-3(2*H*)-one (9h).** The general procedure 4 was followed using 2-iodopyridine (0.213 mL, 2.00 mmol). The reaction time was 30 min. Compound **9h** was obtained in 87% (0.259 g) yield: white solid; mp 131−132 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.68 (m, 1H), 8.64 (m, 1H), 8.19 (s, 1H), 7.74 (td, 1H, $J$ = 7.80, 1.81 Hz), 7.47 (m, 2H), 7.35−7.26 (m, 4H), 5.35 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.5, 149.7, 149.6, 138.4, 138.3, 136.6, 135.7, 131.2, 128.8, 128.7, 128.2, 125.4, 124.8, 56.1; HRMS (ESI) for $C_{16}H_{12}ClN_3O$ $[M + H]^+$ calcd 298.0742, found 298.0739.

**2-Benzyl-6-chloro-4-(pyridin-3-yl)pyridazin-3(2*H*)-one (9i).** The general procedure 4 was followed using 3-iodopyridine (0.410 g, 2.00 mmol). The reaction time was 15 min. Compound **9i** was obtained in 71% (0.211 g) yield: orange solid; mp 115−116 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.88 (d, 1H, $J$ = 2.10 Hz), 8.66 (dd, 1H, $J$ = 4.89, 1.54 Hz), 8.21 (td, 1H, $J$ = 8.03, 1.98 Hz), 7.49 (m, 2H), 7.40−7.28 (m, 5H), 5.33 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.2, 151.0, 149.0, 139.0, 137.6, 136.4, 135.4, 129.8, 129.0, 128.7, 128.3, 123.1, 56.2 (only 13 of 14 carbons resolved); HRMS (ESI) for $C_{16}H_{12}ClN_3O$ $[M + H]^+$ calcd 298.0742, found 298.0742.

**2-Benzyl-6-chloro-4-(pyrazin-2-yl)pyridazin-3(2*H*)-one (9j).** The general procedure 4 was followed using 2-iodopyrazine (0.197 mL, 2.00 mmol). The reaction time was 15 min. Compound **9j** was obtained in 86% (0.284 g) yield: white solid; mp 125−126 °C; $^1$H NMR ($CDCl_3$) $\delta$ 9.92 (s, 1H), 8.62 (s, 2H), 8.19 (s, 1H), 7.49 (m, 2H), 7.37−7.27 (m, 3H), 5.38 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.0, 146.2, 145.7, 145.6, 144.2, 138.1, 136.6, 135.4, 131.9, 128.9, 128.7, 128.3, 56.2; HRMS (ESI) for $C_{15}H_{11}ClN_4O$ $[M + H]^+$ calcd 299.0694, found 299.0694.

**2-Benzyl-6-chloro-4-(2-thienyl)pyridazin-3(2*H*)-one (9k).** The general procedure 4 was followed using 2-iodothiophene (0.221 mL, 2.00 mmol). The reaction time was 15 min. Compound **9k** was obtained in 78% (0.288 g) yield: yellow solid; mp 182−183 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.83 (dd, 1H, $J$ = 3.86, 1.09 Hz), 7.57 (dd, 1H, $J$ = 5.11, 1.04 Hz), 7.50−7.46 (m, 2H), 7.45 (s, 1H), 7.35−7.27 (m, 3H), 7.12 (m, 1H), 5.35 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.3, 137.9, 135.6, 134.9, 133.6, 132.3, 129.0, 128.9, 128.6, 128.2, 127.4, 123.8, 56.1; HRMS (ESI) for $C_{15}H_{11}ClN_2OS$ $[M + H]^+$ calcd 303.0353, found 303.0346.

**2-Benzyl-4-(4-methoxyphenyl)pyridazin-3(2*H*)-one (10).** In a Pyrex Parr flask 2-benzyl-5-chloro-4-(4-methoxyphenyl)pyridazin-3(2*H*)-one (**7b**) (0.163 g, 0.5 mmol) was weighed out and dissolved in 6 mL of EtOAc. Palladium on carbon (0.053 g, 10%) and potassium carbonate (0.138 g, 1.0 mmol) were added to the pyridazin-3(2*H*)-one-solution under an argon flow. The reaction mixture was placed under 40 psi of hydrogen gas and stirred overnight. The resulting mixture was filtered through a path of Celite and concentrated under vacuum. The residue was separated with an automated chromatography system using a silica flash cartridge applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethyl acetate in 25 min, 25 mL/min). Compound **10** was obtained in 64% (0.094 g) yield.

In a Pyrex Parr flask 2-benzyl-6-chloro-4-(4-methoxyphenyl)-pyridazin-3(2*H*)-one (**9b**) (0.163 g, 0.5 mmol) was weighed out and dissolved in 6 mL of EtOAc. Palladium on carbon (0.053 g, 10%) and potassium carbonate (0.138 g, 1.0 mmol) were added to the pyridazin-3(2*H*)-one solution under an argon flow. The reaction mixture was

placed under 35 psi of hydrogen gas for 4 h. The resulting mixture was filtered through a path of Celite and concentrated under vacuum. The residue was separated with an automated chromatography system using a silica flash cartridge applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethyl acetate in 25 min, 25 mL/min). Compound **10** was obtained in 77% (0.113 g) yield: white solid; mp 119−121 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.85−7.80 (m, 3H), 7.54−7.48 (m, 2H), 7.38−7.27 (m, 3H), 7.24 (d, 1H, $J$ = 4.3 Hz), 6.99−6.94 (m, 2H), 5.42 (s, 2H), 3.86 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.8, 160.2, 139.5, 136.5, 136.5, 130.2, 128.9, 128.6, 127.9, 126.3, 126.2, 113.9, 55.9, 55.4; HRMS (ESI) for $C_{18}H_{16}N_2O_2$ $[M + H]^+$ calcd 293.1285, found 293.1278.

**General Procedure 5 for the Functionalization of 2-Benzyl-5-chloropyridazin-3(2*H*)-one (6).** A dry 50 mL double-necked flask placed under argon atmosphere using a Schlenck apparatus was charged with TMPZnCl·LiCl[4] (1.818 mL, 0.55 M solution in THF). 2-Benzyl-5-chloropyridazin-3(2*H*)-one (**6**) (0.221 g, 1.0 mmol)[3q] was brought in a second dry 25 mL double-necked flask and placed under argon atmosphere using a Schlenck apparatus. Subsequently, THF (4 mL) was added. The pyridazin-3(2*H*)-one solution was added dropwise to the TMP solution (1 min) after which it was stirred for 1 min; subsequently, the electrophile (2 mmol) was immediately added to this solution and stirred until the reaction was completed. The resulting mixture was quenched with aq $NH_4Cl$, and aq $NaHSO_3$ was added. The aqueous phase was extracted with EtOAc (3 × 50 mL) and subsequently dried over $MgSO_4$. The organic phase was evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using a silica flash cartridge applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethyl acetate in 25 min, 25 mL/min).

**2-Benzyl-4-bromo-5-chloropyridazin-3(2*H*)-one (11a).** The general procedure 5 was followed using bromine (0.077 mL, 2.00 mmol). The reaction time was 15 min. Compound **11a** was obtained in 76% (0.219 g) yield: yellow solid; mp 118−119 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.70 (s, 1H), 7.43 (m, 2H), 7.36−7.28 (m, 3H), 5.32 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 156.8, 139.5, 135.5, 135.1, 129.1, 128.7, 128.4, 127.5, 56.6; HRMS (ESI) for $C_{11}H_8BrClN_2O$ $[M + H]^+$ calcd 298.9581, found 298.9575.

**2-Benzyl-5-chloro-4-iodopyridazin-3(2*H*)-one (11b).** The general procedure 5 was followed using iodine (0.381 g, 2.00 mmol) dissolved in 1 mL of THF. The reaction time was 15 min. Compound **11b** was obtained in 73% (0.263 g) yield: yellow solid; mp 127−129 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.58 (s, 1H), 7.44 (m, 2H), 7.35−7.28 (m, 3H), 5.33 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 158.2, 145.0, 135.2, 134.9, 129.1, 128.7, 128.4, 109.6, 56.8; HRMS (ESI) for $C_{11}H_8ClIN_2O$ $[M + H]^+$ calcd 346.9443, found 346.9438. The structure was unambiguously confirmed by single-crystal XRD analysis; see the Supporting Information and CCDC 848581.

**General Procedure 6 for the Functionalization of 2-Benzyl-6-chloropyridazin-3(2*H*)-one (8).** A dry 50 mL double-necked flask placed under argon atmosphere using a Schlenck apparatus was charged with TMPZnCl·LiCl[4] (1.818 mL, 0.55 M solution in THF). 2-Benzyl-6-chloropyridazin-3(2*H*)-one (**8**) (0.221 g, 1.0 mmol)[3q] was brought in a second dry 25 mL double-necked flask and placed under argon atmosphere using a Schlenck apparatus. Subsequently THF (4 mL) was added. The pyridazin-3(2*H*)-one solution was immediately added to the TMP solution (1 s) after which it was stirred for 10 s; subsequently, electrophile (2 mmol) was immediately added to this solution. The reaction mixture was stirred at room temperature until the reaction was completed. The resulting mixture was quenched with aq $NH_4Cl$, and aq $NaHSO_3$ was added. The aqueous phase was extracted with EtOAc (3 × 50 mL) and subsequently dried over $MgSO_4$. The organic phase was evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using a silica flash cartridge applying a heptane-ethyl acetate gradient (from 100% heptane to 100% ethyl acetate in 25 min, 25 mL/min).

**2-Benzyl-4-bromo-6-chloropyridazin-3(2*H*)-one (12a).** The general procedure 6 was followed using bromine (0.077 mL, 2.00 mmol). The reaction time was 15 min. Compound **12a** was obtained in 91% (0.273 g) yield: yellow solid; mp 118−119 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.55 (s, 1H), 7.46 (m, 2H), 7.37−7.28 (m, 3H), 5.27 (s, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 156.2, 136.3, 135.0, 135.0, 130.6, 129.2, 128.7, 128.5, 57.0; HRMS (ESI) for $C_{11}H_8BrClN_2O$ $[M + H]^+$ calcd 298.9581, found 298.9576.

**2-Benzyl-6-chloro-4-iodopyridazin-3(2*H*)-one (12b).** The general procedure 6 was followed using iodine (0.381 g, 2.00 mmol) dissolved in 1 mL of THF. The reaction time was 15 min. Compound **12b** was obtained in 91% (0.315 g) yield: yellow solid; mp 127−128 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.79 (s, 1H), 7.45 (m, 2H), 7.35−7.25 (m, 3H), 5.27 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 157.0, 142.1, 136.6, 135.0, 129.1, 128.7, 128.4, 109.3, 57.2; HRMS (ESI) for $C_{11}H_8ClIN_2O$ $[M + H]^+$ calcd 346.9443, found 346.9434. The structure was unambiguously confirmed by single-crystal XRD analysis; see the Supporting Information and CCDC 848582.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Copies of NMR spectra of all compounds. X-ray structural data of compounds **7b**, **9e,g**, **11b**, and **12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) **A** was reacted with iodobenzene or 2-iodpyridine using $FeF_2$, $FeCl_3$, $Fe(acac)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $Pd(dba)_2/P(2\text{-furyl})_3$, and $NiCl_2(dppp)$ as catalyst systems. Temperatures were varied from −20 to +50 °C. No desired reaction products were formed.

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