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Access to 4-Alkylaminopyridazine Derivatives via Nitrogen-Assisted Regioselective Pd-Catalyzed Reactions

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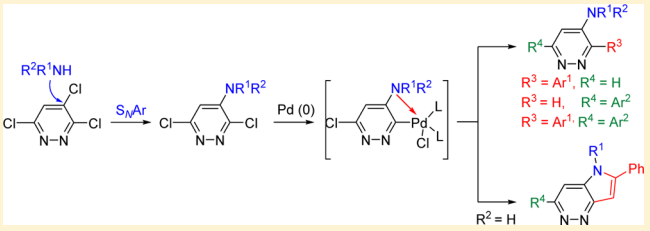
Supporting Information

ABSTRACT: 3-Substituted, 6-substituted, and unsymmetrical 3,6-disubstituted 4-alkylaminopyridazines were prepared from a sequence of three chemo- and regioselective reactions combining amination and palladium-catalyzed cross-coupling reactions, such as reductive dehalogenation and Suzuki–Miyaura reactions. Extension of the methodology to Sonogashira reaction yielded a novel class of 3-substituted pyrrolopyridazines.



INTRODUCTION

Pyridazines constitute a family of compounds that presents an increasing interest in modern drug design and discovery.[1] An important number of publications dealing with biologically active pyridazine derivatives belonging to almost all therapeutic classes have been published since 1970, which have led to constantly increasing number of reports, especially in the past decade. In particular, considerable attention has been devoted to various 6-substituted 3-aminopyridazines because of their synthetic versatility[2] and their response profiles.[3] Pyridazine derivatives have provided some preclinical candidates and several FDA-approved drugs,[4] including the antidepressant drug minaprine[5] and its metabolite moxiraprine as an anti-Parkinson drug[6] (Figure 1). However, the displacement of the amino group from position 3 to position 4 remains largely unexplored. Only a few examples of relatively unsubstituted 4-aminopyridazine derivatives are related in the literature (Figure 1).[7,8] One of the reasons for the smaller representation of 4-aminopyridazines in comparison to 3-aminopyridazines in the literature is the absence of high-yielding and reliable methods for their synthesis.[9−12]

To our knowledge, the most straightforward procedure reported for the preparation of aryl-substituted 4-alkylamino pyridazines (R^3 = R^4 = Ar; method A, Scheme 1) involves an inverse electron demand Diels–Alder reaction in the presence of 1,2,4,5-tetrazine derivatives **1**.[9] Despite the many advantages of this reaction (high atom economy, high level of regioselectivity), this approach relies heavily on the availability

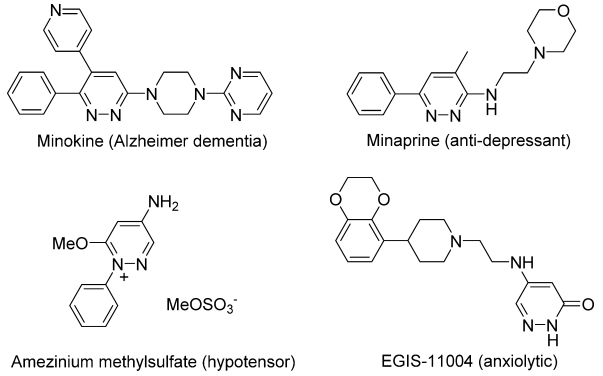


Figure 1. Examples of the pharmacologically relevant 3-aminopyridazines minokine (Alzheimer dementia) and minaprine (antidepressant) and 4-aminopyridazines amezinium methylsulfate (antihypotensive)[7] and 5-aminopyridazinone EGIS-11004 (anxiolytic).[8]

of the starting material and consequently suffers from important limitations in the substitution patterns (R^3, R^4 = Ar).

Several other classical ways have been developed for the preparation of 4(5)-*N*-substituted pyridazinones **2** and **3**. These derivatives may constitute the precursors of choice for the synthesis of 4-alkylaminopyridazines, since the activation of the amide function may open a route to additional substitutions on the pyridazine backbone. However, methods for preparation of

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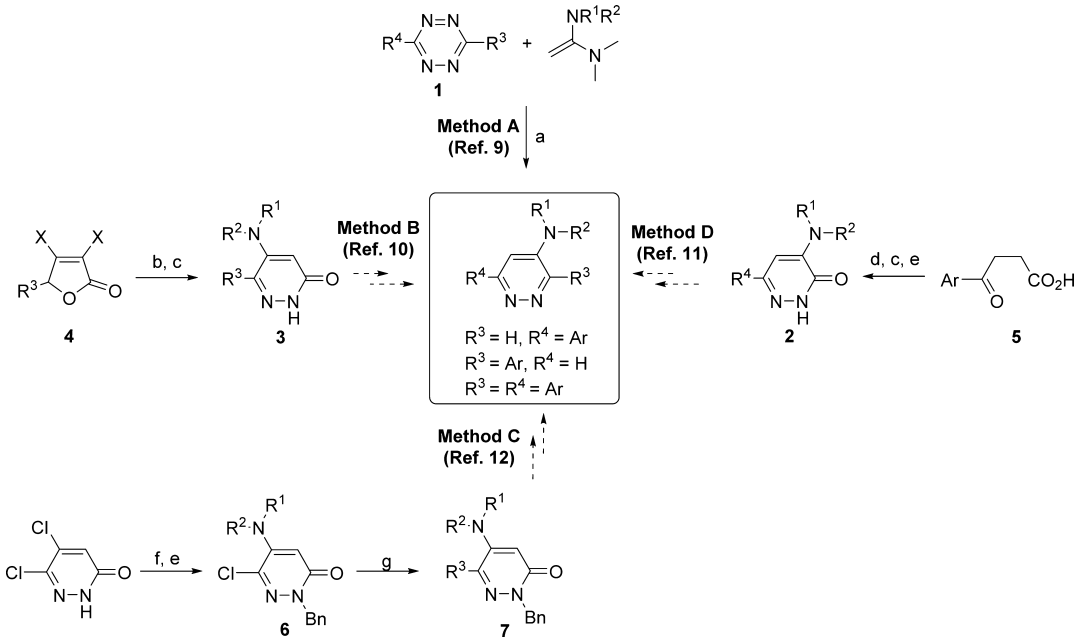
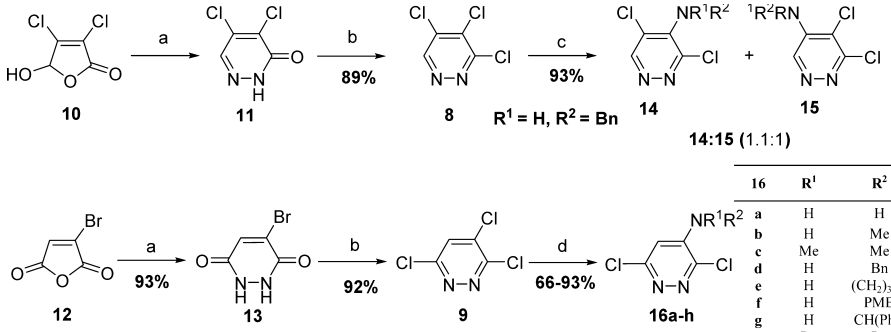
Scheme 1. Reported Synthesis of 4-Aminopyridazines and Their Precursors 2 and 3[a]



[a]Reagents and conditions: (a) DCM, room temperature (22−100%); (b) $AlCl_3$ (60%); (c) NH_2NHBn; (d) $POCl_3/PCl_5$; (e) NHR^1R^2 (60−79%); (f) TMG, BnBr, (98%); (g) $R^3B(OH)_2$, $Pd_2(dba)_3$/S-Phos (5 mol %), KF, dioxane, 135−140 °C, 30 min, μw (quanitative)

Scheme 2. Reactivity of 8 and 9 toward Amination Reactions[a]



16	R^1	R^2	Yields (%)[a]
a	H	H	86
b	H	Me	88
c	Me	Me	93
d	H	Bn	90
e	H	$(CH_2)_3Ph$	89
f	H	PMB	87
g	H	$CH(Ph)_2$	80
h	Bn	Bn	66

[a]Reaction conditions: (a) $N_2H_4.H_2SO_4$, H_2O, 100 °C, 12 h; (b) $POCl_3$, 120 °C, 5 h; (c) $BnNH_2$, *i*-PrOH, 120 °C, 20 min, μw; (d) NHR^1R^2, see the Experimental Section.

intermediates **2** and **3** (methods B−D) suffer from limitations such as the availability of the corresponding butenolides **4**[10] (method B) and 1,4-keto acids **5** (method D) or the need for drastic conditions.[11] More recently, a palladium-catalyzed Suzuki−Miyaura cross-coupling (SMCC) reaction of 6-chloro-5-*N*-substituted pyridazinones **6** has been carried out, leading to 5-piperidino-6-aryl-*N*-benzylpyridazin-3-ones **7** (method C).[12] This synthetic route allowed the introduction of chemical diversity at the C-6 position. Unfortunately, it suffered from moderate yields when piperidine was replaced by other secondary amines and the scope of the reaction could not be extended to primary alkylamines (R^2 = H).

The elaboration of novel versatile approaches leading to 4-aminopyridazines offering the largest structural diversity and thus allowing efficient structural optimization (R^3, R^4 = H, aryl, alkyl, aralkyl, others) around the pyridazine core is therefore of importance for drug design. The aim of this work was to investigate a general strategy starting from easily available materials, such as the highly electrophilic trichloropyridazines **8** and **9**. Herein we report the efficient synthesis of differently substituted 4-*N*-alkyl- or 4-*N*,*N*-dialkylaminopyridazines by regioselective palladium-catalyzed reactions.

RESULTS AND DISCUSSION

We first checked the reactivity of the two different trichloropyridazines 3,4,5-trichloropyridazines **8** and 3,4,6-trichloropyridazines **9**. Both could be prepared on a large scale, as previously described in the literature.[13,14] Hydrazinolysis of the commercially available mucochloric acid **10** and bromomaleic anhydride **12** yielded the 4,5-dichloropyridazinone **11** and the 4-bromo-1,2-dihydropyridazine-3,6-dione **13**, respectively. Activation of the amide functions of **11** and **13** with $POCl_3$ afforded **8** and **9** in nearly quantitative yield (Scheme 2).

The S_NAr-type amination reactions performed with 3-chloropyridazines needs generally relatively drastic experimental conditions: in particular, heating at high temperatures[15] and use of acid as the catalyst and a large excess of amine

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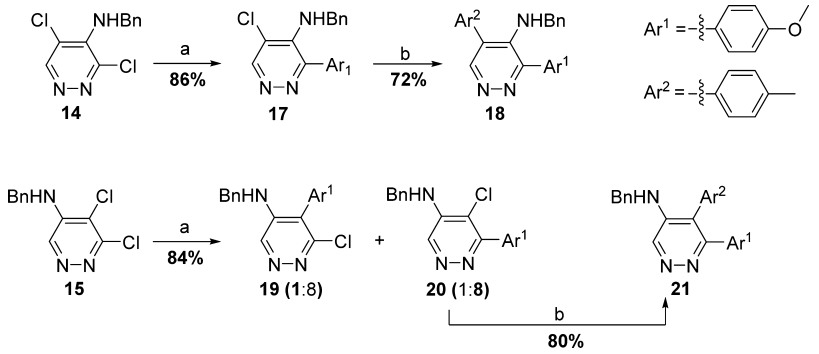
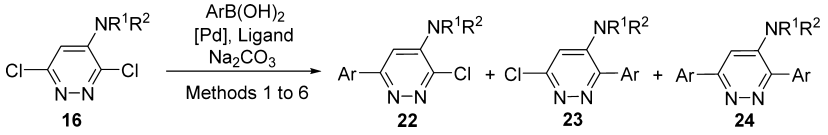
Scheme 3. SMCC Reactions with 14 and 15[a]



[a]Reaction conditions: (a) $Pd(PPh_3)_4$ (5 mol %), 4-MeOPhB$(OH)_2$ (1.05 equiv), Na_2CO_3 (2 equiv), toluene/EtOH/H_2O (3/1/1), 100 °C, 3 h; (b) $Pd(OAc)_2$ (2 mol %), XPhos (2.4 mol %), 4-MePhB$(OH)_2$ (1.5 equiv), CsOH.H_2O (1.7 equiv), *n*-BuOH/H_2O (4/1), 50 °C, 1 h.

Table 1. SMCC Reaction Conditions Leading to 3-Aryl-4-aminopyridazines 23[a]



								yield[b,d] (%)			
entry	**16**	R^1	R^2	Ar	catalytic system	method	product	**22**[c]	**23**	**24**[c]	**16**[c]
1[e]	**a**	H	H	Ph	$Pd(PPh_3)_4$	1	**a**		78	<5	
2[e]	**a**	H	H	4-ClPh	$Pd(PPh_3)_4$	1	**b**		85	<5	
3[e]	**a**	H	H	2-MeOPh	$Pd(PPh_3)_4$	1	**c**		84	<5	
4[e]	**a**	H	H	4-MeOPh	$Pd(PPh_3)_4$	1	**d**		86 (85)[f]	<5	
5[f]	**b**	H	Me	4-MeOPh	$Pd(PPh_3)_4$	2	**e**		76	<10	
6[f]	**c**	Me	Me	4-MeOPh	$Pd(PPh_3)_4$	2	**f**		84	<10	
7[f]	**e**	H	$(CH_2)_3Ph$	4-MeOPh	$Pd(PPh_3)_4$	2	**g**	<5	56	15	25
8[g]	**e**	H	$(CH_2)_3Ph$	4-MeOPh	$Pd_2(dba)_3{\cdot}CHCl_3$	3	**g**				100
9[h]	**e**	H	$(CH_2)_3Ph$	4-MeOPh	$Pd(OAc)_2$/S-Phos	4	**g**		35	15	39
10[i]	**e**	H	$(CH_2)_3Ph$	4-MeOPh	$Pd(CH_3CN)_2Cl_2$/BDPB	5	**g**	10	52	10	28
11[j]	**e**	H	$(CH_2)_3Ph$	4-MeOPh	$Pd(PPh_3)_4$	6	**g**		83	6	
12[j]	**d**	H	CH_2Ph	4-MeOPh	$Pd(PPh_3)_4$	6	**h**		77	8	
13[j]	**g**	H	$CH(Ph)_2$	4-MeOPh	$Pd(PPh_3)_4$	6	**i**		79	6	
14[j]	**h**	CH_2Ph	CH_2Ph	4-MeOPh	$Pd(PPh_3)_4$	6	**j**		61	9	8

[a]Reactions were performed in a solvent/H_2O mixture except for entry 8. [b]Yields refer to isolated, chromatographically purified materials. [c]Yield determined by NMR using CH_2I_2 as internal standard. [d]Unpublished products **23** were fully characterized by NMR 1D and 2D and HR-MS data. [e]Method 1: reaction conditions $Pd(PPh_3)_4$ (5 mol %), ArB$(OH)_2$ (1.1 equiv), Na_2CO_3 (2 equiv), DME/H_2O (3/1), 110 °C, 10 min, μw. [f]Method 2: reaction conditions $Pd(PPh_3)_4$ (5 mol %), ArB$(OH)_2$ (1.1 equiv), Na_2CO_3 (2 equiv), DME/H_2O (3/1), conventional heat 100 °C, 3 h. [g]Method 3: reaction conditions $Pd_2(dba)_3.CHCl_3$ (5 mol %), ArB$(OH)_2$ (1.1 equiv), K_2CO_3 (2 equiv), EtOH, 120 °C, 3 h. [h]Method 4: *r*eaction conditions $Pd(OAc)_2$ (2 mol %), S-Phos (4 mol %), ArB$(OH)_2$ (1 equiv), K_2CO_3 (2 equiv), MeCN/H_2O (3/1), 115 °C, 12 h. [i]Method 5: reaction conditions $Pd(CH_3CN)_2Cl_2$ (2 mol %), 1,2-bis(diphenylphosphino)benzene (BDPB, 4 mol %), ArB$(OH)_2$ (1.1 equiv), Na_2CO_3 (2 equiv), DME/H_2O (3/1), 120 °C, 5 h. [j]Method 6: reaction conditions $Pd(PPh_3)_4$ (5 mol %), ArB$(OH)_2$ (1.1 equiv), Na_2CO_3 (2 equiv), DME/H_2O (3/1); reaction conditions $Pd(PPh_3)_4$ (5 mol %), ArB$(OH)_2$ (1.05 equiv), Na_2CO_3 (2 equiv), toluene/EtOH/H_2O (3/1/1), 100 °C, 3 h.

reagent.[5b,16] The presence of two vicinal nitrogens in the pyridazine ring is clearly associated in the literature with its poor electrophilicity, in comparison with other related systems (pyrimidine, pyrazine).[17] However, in comparison to 3-chloropyridazines, 3,6-dichloropyridazines presented an increased electrophilic character, and thus better reactivity toward S_NAr amination reactions.[18,14b] Interestingly, the 3,4,5- and 3,4,6-trichloropyridazines **8** and **9** both possess an aryl chloride with different electrophilic character toward amination reactions. Finally, when **8** and **9** were submitted to reaction with benzylamine, the following occurred. (i) 3,4,5-Trichloropyridazine **8** yielded a mixture of 3,5-dichloro- (**14**) and 5,6-dichloro-4-benzylaminopyridazines (**15**) in equal amounts (see Scheme 2). (ii) No trace of reaction was observed on the 3-iminochloride, even after changing the solvent. (iii) 3,4,6-trichloropyridazine **9** gave a single isomer, the 3,6-dichloro-4-aminopyridazine (**16d**), as already described in the literature.[20] (iv) In both cases the aryl chloride function was the most reactive toward S_NAr amination reactions.

This amination reaction on pyridazine **9** was extended to various primary and secondary amines, as illustrated in Scheme 2. The reaction conditions were a function of the amine reactivity and steric hindrance (see the Supporting Information).[19] The dichloropyridazines **14**–**16** appeared to be excellent platforms for palladium-catalyzed cross-coupling reactions (PCCRs), affording new 4-aminopyridazines.

The selectivity of the PCCR of heteroarenes bearing multiple identical halogens is mainly determined by the relative ease of

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oxidative addition. On the basis of recent theoretical calculations, the C−Cl bond α to nitrogen of pyridazine requires less energy to break, suggesting that the order of reactivity for 3,5- or 5,6-dichloropyridazines **14** and **15** is C3(6) > C5.[22] In agreement with literature data we observed with dichloropyridazine **14** a chemoselective monosubstitution occurring at position 3 (**17**). Finally, by performing a second Suzuki−Miyaura cross-coupling (SMCC) reaction on compound **20** with a different catalytic system ($Pd(OAc)_2$/XPhos),[23] we prepared in good yield the 3,5-disubstituted 4-aminopyridazine **18**, bearing two different aryl groups at positions 3 and 5 (Scheme 3). The other isomer **15** behaved similarly and gave the expected 3-aryl pyridazine **20** as the major isomer in a ratio of 8:1. A second SMCC reaction afforded the 5,6-diaryl 4-aminopyridazine **21** in good yield.

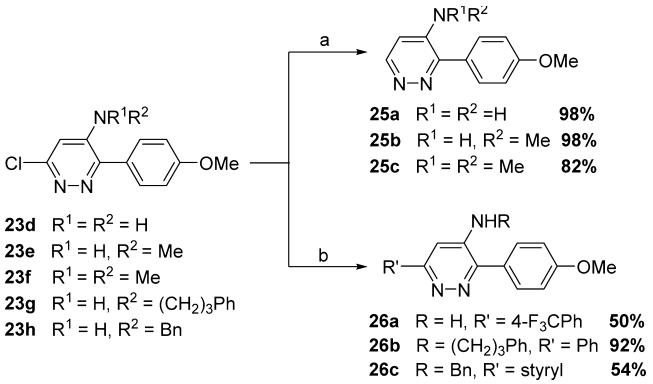
For the SMCC reactions of 3,6-dichloro 4-aminopyridazines **16** we envisioned to control regioselectivity of the two nearly identical imino chlorides. In addition, we could hypothesize that steric hindrance induced by the substituted amino group may favor formation of the 6-aryl 4-amino pyridazine **22**, but this effect may be counterbalanced by the fact that position 6 is slightly more electron enriched by the electron donor effect of the amino group. Interestingly, with the primary amine **16a**, under our conditions ($Pd(PPh_3)_4$, Na_2CO_3, microwave irradiation; see entry 1 in Table 1), the reaction occurred regioselectively at the most hindered position 3, leading to the monoadduct **23a**. Only traces (<5%) of 3,6-diadduct **24a** were observed by HPLC. The reaction was still efficient with other boronic acids bearing electron-withdrawing (entry 2) or electron-donating groups (entries 3 and 4). The position of the substituent on the boronic acid had no effect on the regioselectivity, as the reaction with the 2-MeO-phenylboronic acid proceeded efficiently (entry 3). The structure of **23d** was assigned using 2D NMR spectroscopic tools. In particular, the position of the aryl group was characterized by the presence of a NOESY correlation between the NH proton and the protons in an ortho position of the 4-methoxyphenyl ring. Compounds **23a−d** were obtained in similar yields (>78%). Moreover, reaction under classical heat (3 h, 100 °C) was also efficient, affording compounds **23d−f** in yields equivalent to those for microwave heating (entries 4−6).

However, when the 4-amino group was substituted by a more sterically hindered phenylpropyl group (**16e**), the resulting steric hindrance led to a less reactive system under our standard conditions (25% recovery of starting material **16e**) and resulted in the formation of a significant amount of 3,6-disubstituted derivative **24g** (Table 1, entry 7). Following an optimization process, different sources of palladium catalysts and ligands were reacted at different temperatures in various solvents (entries 8−11). When $Pd_2(dba)_3{\cdot}CHCl_3$ was used,[24] no reaction occurred at all (entry 8). With other catalytic systems ($Pd(OAc)_2$/SPhos[25] and $Pd(CH_3CN)_2$/BDPB[26]) we still recovered a significant amount of starting material **16e**, the 6-aryl regioisomer **22g**, and the disubstituted pyridazine **24g** (entries 9 and 10). Finally, performing the Suzuki−Miyaura reaction in a 3/1/1 mixture of toluene, EtOH, and water gave the desired 3-aryl pyridazine **23g** in good yield and regioselectivity (entry 11).

These optimized experimental conditions were applied for further preparation of various 3-aryl-6-chloro-4-alkylaminopyridazines **23h−j** (Table 1, entries 12−14). The compounds were recovered in good yields and excellent regioselectivity, even for the bulky amino derivatives **16g,h**. For all of these examples, only small amounts of the diaryl derivatives **24h−j** (<10%) were observed.

Finally, imino chlorides **23d−f** were efficiently hydrogenated using Pearlman's catalyst ($Pd(OH)_2/C$), providing access to the valuable intermediates 3-aryl-4-alkylaminopyridazine **25a−c** (Scheme 4). In addition, **23d,g,h** were also reacted in a second SMCC reaction, affording the corresponding 3,6-diarylaminopyridazines **26a−c**, as illustrated in Scheme 4.

Scheme 4. Access to 3-Aryl-4-alkylaminopyridazines 25a−c and 3,6-Bis(aryl)-4-alkylaminopyridazines 26a−c[a]



[a]Reagents and conditions: (a) Pd/C or $Pd(OH)_2/C$, MeOH, room temperature, 60 psi, 6−12 h; (b) $Pd(OAc)_2$ (2 mol %), XPhos (2.4 mol %), $ArB(OH)_2$ (1.5 equiv), $CsOH{\cdot}H_2O$ (1.7 equiv), *n*-BuOH/H_2O (4/1), 50 °C, 1−12 h.

The regioselectivity of the Suzuki−Miyaura reaction might be associated with the presence of an electron-donating group ($-NR^1R^2$). In particular, the free doublet on the nitrogen atom might be able to coordinate the vicinal palladium and, thus, promote a regioselective attack at the 3-imino chloride system. In order to validate our working hypothesis, we further performed a similar Suzuki−Miyaura reaction in the case of compound **16** with *N*-Boc-pyridazine derivatives **27a,b** (Table 2).

The introduction of the *tert*-butylcarbamate on intermediates **16b,f** was easily achieved with $(Boc)_2O$ in the presence of a catalytic amount of DMAP, and **27a,b** were obtained in nearly quantitative yields. When the corresponding *N*-Boc derivatives **27a,b** were submitted to an SMCC reaction using our optimized experimental conditions (toluene/EtOH/H_2O), a partial deprotection of the *N*-Boc group was observed, leading to a complex mixture in HPLC. However, when the same reaction was performed in a DME/H_2O mixture, we isolated the corresponding 6-substituted 4-aminopyridazines **28a,b**, as the major compounds (>60%). Unfortunately, the presence of a significant amount of the diadducts **30a,b** (between 15 and 20% yield) was not satisfying, even if the results are in good agreement with our mechanistic hypothesis.

We thus examined whether the regioselectivity was similarly modulated by an alkoxy group in place of the amine moiety. The alkoxy group as an electron-donating group may mimic at least a part of the electronic effects of the amino function. The 4-OMe and 4-OBn pyridazine derivatives (**31a,b**, respectively) were synthesized following a previously reported method.[27] However, starting from **31a**, the SMCC reaction appeared to be favored at position 6. In addition to the 6-adduct **32a**, we observed a significant amount of the second regioisomeric pyridazine **33a** along with 14% of the bis-arylated product **34a**

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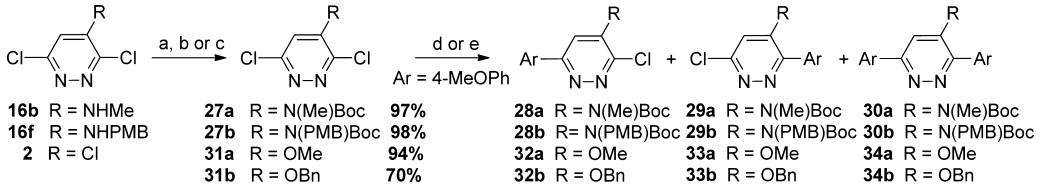
Table 2. SMCC Reactions Starting from 4-NRBoc 27 and 4-Alkoxypyridazine Derivatives 31[a]



				product (yield (%))[b,c]		
entry	R	method	starting material (amt (%))	6-adduct	3-adduct	3,6-diadduct
1	NMeBoc	2	**27a** (−)	**28a** (63)	**29a** (−)	**30a** (19)
2	NPMBBoc	2	**27b** (−)	**28b** (67)	**29b** (−)	**30b** (15)
3[d]	OMe	2	**31a** (30)	**32a** (45)	**33a** (15)	**34a** (10)
4[d]	OMe	6	**31a** (−)	**32a** (60)	**33a** (20)	**34a** (14)
5[d]	OBn	6	**31b** (−)	**32b** (50)	**33b** (11)	**34b** (15)

[a]Reagents and conditions: (a) Boc_2O, TEA, DMAP, THF, room temperature, 2 h; (b) NaOMe, dry MeOH, room temperature, 1 h; (c) BnOH, NaH, dry THF, 0 °C to room temperature, 2 h; (d) method 2 reaction conditions $Pd(PPh_3)_4$ (5 mol %), $ArB(OH)_2$ (1.1 equiv), Na_2CO_3 (2 equiv), DME/H_2O (3/1), 110 °C, 3 h; (e) method 6 reaction conditions $Pd(PPh_3)_4$ (5 mol %), $ArB(OH)_2$ (1.05 equiv), Na_2CO_3 (2 equiv), toluene/EtOH/H_2O (3/1/1), 100 °C, 3 h. [b]Yields refer to isolated, chromatographically, purified materials. [c]Unpublished products were fully characterized by NMR 1D and 2D and HR-MS data. [d]yYelds were determined by NMR using CH_2I_2 as internal standard.

(entry 4). Even when the benzyloxy group was more hindered (**31b**, entry 5), similar results were obtained. This clearly demonstrated that the observed regioselectivity of the 4-alkylamino pyridazine derivatives **16** is not linked to any steric or electron-donating effects of the amino group and the observed regioselectivity can be explained with the formation of a palladacycle, in which the Pd is complexed by the amino group (Figure 2). This phenomenon of complexation of palladium by nitrogen has already been documented in the literature.[28]

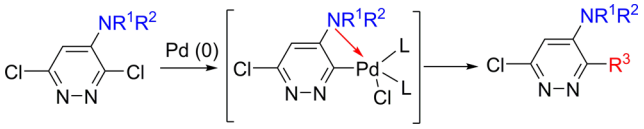
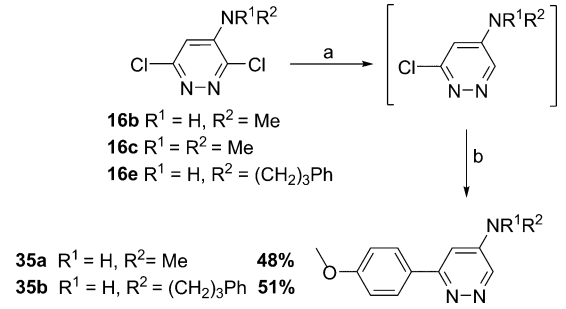


Figure 2. Suggested palladacycle for regioselective C−C bond formation.

We investigated whether the amino group would be able to direct a palladium-catalyzed dehalogenation at position 3 prior to the introduction of an aryl moiety at position 6 by an SMCC reaction (Scheme 5). For this purpose we used 3,6-dichloro pyridazines **16b−d** as substrates in halogen/metal exchange reactions in the presence of $Pd(PPh_3)_4$ and HCO_2H as reducing agent (see Scheme 5). After evaporation of the solvent, and without purification, the resulting mixture was directly used in a prototypical SMCC reaction in the presence of $Pd(OAc)_2$ and S-Phos. These conditions allowed access to the awaited 6-aryl 4-alkylaminopyridazines **35a−c** with a two-step cumulative yield ranging from 48% to 51%.

We next extended this regioselectivity to the Sonogashira reaction in order to access the pyrrolo[3,2-*c*]pyridazine derivative **37**. The efficiency of the method is clearly demonstrated by the results reported in Scheme 6. The cross-coupling reaction with phenylacetylene was successfully applied to **16a,d** to afford the corresponding expected monosubstituted adducts **36a,b**, respectively. Cyclization of **36a,b** was carried out in the presence of CuI to give the fused pyrrolo[3,2-*c*]pyridazines **37a,b** in 85% and 90% yields, respectively. Further SMCC on the imino chloride at position

Scheme 5. Regioselective Palladium-Catalyzed Hydrogenation: Access to 6-Arylpyridazin-4-amines 35a−c



[a]Reaction conditions: (a) $Pd(PPh_3)_4$ (4 mol %), HCO_2H (1 equiv), TEA (12 equiv), DMF, 100 °C, 45 min, μw; (b) $Pd(OAc)_2$ (2 mol %), SPhos (4 mol %), 4-MeOPhB$(OH)_2$ (1.5 equiv), K_2CO_3 (2.5 equiv), MeCN/H_2O (5/1), 115 °C, 12 h.

6 provided pyrrolo[3,2-*c*]pyridazine **38** in 59% yield. These new 3-substituted bicyclic pyridazine scaffolds have not been previously described in the literature.

CONCLUSION

In summary, we have described here a general method to aminopyridazines starting from the easily available trichloropyridazines **8** and **9**. A first chemoselective amination reaction led to the corresponding dichloro 4-aminopyridazines. Further regiocontrolled palladium-catalyzed cross-coupling reactions, i.e. Suzuki−Miyaura, dehalogenation, and Sonogashira reactions, highlighted a nitrogen-assisted regioselective SMCC reaction occurring at position 3. Finally, a unique strategy combining amination and two PCCR groups (SMCC and/or dehalogenation) allowed access to new 4-aminopyridazines and pyrrolo[3,2-*c*]pyridazines. The SMCC reaction was used here as a prototypical example, which could be extended to Sonogashira reactions with the same regioselectivity. Thus, generalization of the strategy described here allows a straightforward access to novel functionalized 4-aminopyridazines. Nitrogen-assisted regioselective substitution of vicinal chlorine by means of PCCR opens an avenue to other functionalized 4-aminopyridazines and thus to original

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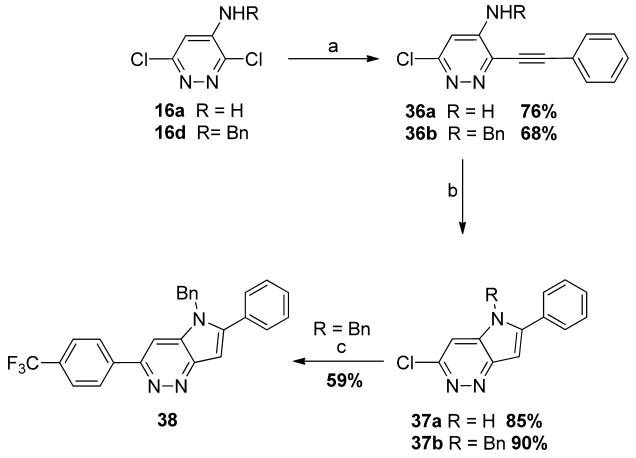
Scheme 6. Access to Pyrrolo[3,2-*c*]pyridazine Derivatives 36 and 38[a]



[a]Reaction conditions: (a) $PdCl_2(PPh_3)_2$ (3 mol %), CuI (6 mol %), phenylacetylene (1.1 equiv), TEA (5 equiv), MeCN, 60 °C, 6 h; (b) CuI (2 mol %), DMF, 120 °C, 12 h; (c) $Pd(PPh_3)_4$ (5 mol %), 4-$CF_3PhB(OH)_2$ (1.5 equiv), Na_2CO_3 (2 equiv), toluene/EtOH/H_2O (3/1/1), 100 °C, 3 h.

scaffolds, as illustrated by a first synthesis of novel functionalized scaffolds (pyrrolo[3,2-*c*]pyridazine **38**).

EXPERIMENTAL SECTION

General Considerations. Chemical reagents and solvents were used without further purification. All cross-coupling reactions were carried out under an argon atmosphere. Microwave irradiation was performed with a Biotage Initiator EXP (external sensor type). Analytical TLC was performed using silica gel plates, and plates were visualized by exposure to UV light at 254 and 356 nm. Column chromatography was performed over silica gel (particle size 0.040–0.063 mm). Yields refer to isolated compounds, estimated to be >97% pure as determined by ^{1}H NMR or HPLC. Melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 400 and 101 MHz, respectively, using deuterated chloroform ($CDCl_3$), methanol (MeOH-d_4), or dimethyl sulfoxide (DMSO-d_6) as a solvent. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constant values (J) are quoted in hertz (Hz). Multiplicity is represented as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Infrared analyses were performed by FT-IR, and wavenumbers are expressed in cm^{-1}. High-resolution mass spectra (HRMS) were recorded on a QTOF mass analyzer with electrospray ionization (ESI).

General Procedure for the Preparation of Trichloropyridazine Derivatives. *Method A (Preparation of Compounds **8** and **9**).* A suspension of the corresponding pyridazinone derivatives (1 equiv, 1 mmol, compound **11** or **12**) in $POCl_3$ (2.5 mL) was heated at 110 °C for 5 h. After it was cooled to room temperature, the yellow solution was evaporated to dryness. The crude residue was diluted with DCM and washed twice with ice–water. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using DCM/EtOAc 4/1 to give the expected products **8** and **9**.

General Procedures for the Preparation of 4-Alkylaminopyridazines. *Method B: General Procedure for the S_NAr Reaction under Microwave Irradiation (Preparation of Compounds **14**, **15**, and **16d–f**).* A microwave vial was charged with a solution of trichloropyridazine derivatives (1 equiv, 1 mmol, compound **8** or **9**) in *i*-PrOH (3.5 mL). The corresponding amine was added (3 equiv, 3 mmol), and then the reaction mixture was capped properly and heated by microwave irradiation at 120 °C until complete conversion of starting material. The reaction mixture was concentrated, and the crude mixture was purified by column chromatography on silica gel using EtOAc/heptane 1/2 to afford the expected products **14**, **15**, **16d–f**.

*Method C: General Procedure for the S_NAr Reaction using Hindered Amines (Preparation of Compounds **16g,h**).* A microwave vial was charged with a solution of the trichloropyridazine derivative (1 equiv, 1 mmol, compound **9**) in *i*-PrOH (3.5 mL). The corresponding amine was added (3 equiv, 3 mmol), and then the reaction mixture was capped properly and heated to 130 °C for 12 h. The reaction mixture was concentrated, and the crude mixture was purified by column chromatography on silica gel using EtOAc/heptane 1/1 to afford the expected products **16g,h**.

General Procedures for Pd(0)-Catalyzed Suzuki–Miyaura Reactions. *Method D: General Suzuki–Miyaura Procedure using $Pd(PPh_3)_4$ in DME/H_2O (Preparation of Compounds **23a–f** and **28a,b**).*[21d] A microwave vial (oven-dried and under nitrogen) was charged with the 4-alkylaminopyridazine derivative (1 equiv, 1 mmol, compound **16a–c**, **27a,b**, or **31a**), the corresponding boronic acid (1.1 equiv, 1.1 mmol), Na_2CO_3 (2 equiv, 2 mmol), and $Pd(PPh_3)_4$ (5 mol %). The reaction mixture was degassed, followed by the addition of a 3/1 DME/H_2O mixture (6.5 mL). The vial was capped properly, flushed with nitrogen, and heated by microwave irradiation (110 °C, 10 min) or conventional heating (110 °C, 3 h). After it was cooled, the suspension was concentrated and the crude residue extracted twice with EtOAc. The organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by chromatography on silica gel using EtOAc/heptane 30/70 to 70/30 to afford the expected products **23a–f** and **28a,b**.

*Method E: General Suzuki–Miyaura Procedure using $Pd(PPh_3)_4$ in Toluene/EtOH/H_2O (Preparation of Compounds **17**, **19**, **20**, and **23g–j**).*[21d] A microwave vial (oven-dried and under nitrogen) was charged with the corresponding 4-alkylaminopyridazine derivative (1 equiv, 1 mmol, compound **14**, **15**, **16d,e,g,h**, or **31a,b**), 4-methoxyphenylboronic acid (1.05 equiv, 1.05 mmol), Na_2CO_3 (2 equiv, 2 mmol), and $Pd(PPh_3)_4$ (5 mol %). The reaction mixture was degassed, followed by the addition of a 3/1/1 toluene/EtOH/H_2O mixture (12 mL). The vial was capped properly, flushed with nitrogen, and heated to 100 °C for 3 h. After it was cooled, the suspension was concentrated and the crude residue extracted twice with EtOAc. The organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by chromatography on silica gel using EtOAc/heptane 30/70 to 70/30 to afford the expected products **17**, **19**, **20**, and **23g–j**.

*Method F: General Suzuki–Miyaura Procedure using $Pd(OAc)_2$/X-Phos as the Catalytic System (Preparation of Compounds **18**, **21** and **26a–c**).*[23] A microwave vial (oven-dried and under nitrogen) was charged with the corresponding 4-alkylaminopyridazine 3(6)-aryl derivative (1 equiv, 1 mmol, compound **17**, **20**, or **23d,g,h**), the corresponding boronic acid (1.5 equiv, 1.5 mmol), X-Phos (2.4 mol %), and $Pd(OAc)_2$ (2 mol %). The reaction mixture was degassed, followed by the addition of *n*-BuOH (4 mL) and a solution of CsOH·H_2O (1.7 equiv, 1.7 mmol) in H_2O (1 mL). The vial was capped properly, flushed with nitrogen, and heated to 50 °C until complete conversion of the starting material. After it was cooled, the reaction mixture was concentrated and the crude residue was purified by chromatography on silica gel using 50/50 EtOAc/heptane to afford the expected products **18**, **21**, and **26a–c**.

General Procedure for Catalytic Hydrogenation of a Chlorinated Compound. *Method G: Pd-Catalyzed Reductive Dehalogenation in the Presence of H_2 (Preparation of Compounds **25a–c**).* A Paar flask was charged with a solution of corresponding 4-alkylaminopyridazine 3-aryl derivative (1 equiv, 1 mmol, compounds **23d–f**) in MeOH (24 mL). The solution was degassed, followed by the addition of $Pd(OH)_2$/C or Pd/C (10 mol %). The reaction mixture was hydrogenated in the Paar flask at a pressure of P = 60 psi for 12 h. The mixture was then filtered over Celite, and the filtrate was evaporated to dryness to afford the expected products **25a–c**.

*Method H: Pd-Catalyzed Reductive Dehalogenation with HCOOH (Preparation of Compounda **35a,b**).* To a solution of the corresponding 4-alkylaminopyridazine derivative (1 equiv, 1 mmol, compound **16b,e**) in dry DMF (7 mL) were added TEA (12 equiv, 12 mmol) and $Pd(PPh_3)_4$ (4 mol %). The vial was capped properly and

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degassed, and the contents were stirred at room temperature for 10 min. Then a solution of formic acid (1 equiv, 1 mmol) in dry DMF (0.4 mL) was added and the reaction mixture was heated by microwave irradiation at 100 °C for 45 min. After it was cooled, the reaction mixture was concentrated and the crude residue was submitted to a Suzuki−Miyaura reaction: a microwave vial (oven-dried and under nitrogen) was charged with the corresponding 4-alkylaminopyridazine 3-H derivative (1 equiv, 1 mmol), 4-methoxyphenylboronic acid (1.5 equiv, 1.5 mmol), K_2CO_3 (2.5 equiv, 2.5 mmol), S-Phos (4 mol %), and $Pd(OAc)_2$ (2 mol %). The reaction mixture was flushed with nitrogen, followed by the addition of a 5/1 CH_3CN/H_2O mixture (3.8 mL). The vial was capped properly, flushed with nitrogen, and heated to 115 °C for 12 h. After it was cooled, the reaction mixture was concentrated and the crude residue was purified by chromatography on silica gel using 80/20 EtOAc/MeOH to afford the expected products **35a,b**.

General Procedure for the Protection of Amines with a *tert*-Butyloxycarbonyl (Boc) Group. *Method I (Preparation of Compounds **27a,b**).* To a solution of corresponding the 4-alkylaminopyridazine derivative (1 equiv, 1 mmol, compound **16b,f**) in dry THF (3.5 mL) was added TEA (1.3 equiv, 1.3 mmol). The reaction mixture was stirred for 5 min at room temperature, and then a solution of di-*tert*-butyl dicarbonate (2.1 equi, 2.1 mmol) in dry THF (3 mL) was added dropwise. After an additional 15 min of stirring, DMAP (4 mol %) was added and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated to dryness, and the crude residue was diluted in water and extracted twice with EtOAc. The organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by chromatography on silica gel using 30/70 EtOAc/heptane to afford the expected products **27a,b**.

General Procedures for Pd(0)-Catalyzed Sonogashira Reactions. *Method J: General Sonogashira Procedure using $PdCl_2(PPh_3)_2$/CuI (Preparation of Compounds **37a,b**).* A microwave vial (oven-dried and under nitrogen) was charged with the corresponding 4-alkylaminopyridazine derivative (1 equiv, 1 mmol, compound **16a,d**), TEA (5 equiv, 5 mmol), $PdCl_2(PPh_3)_2$ (3 mol %), and CuI (6 mol %). After CH_3CN was added (6.3 mL), the vial was capped properly and the reaction mixture was degassed. Phenylacetylene (1.05 equiv, 1.05 mmol) was added after 10 min of stirring at room temperature. The reaction mixture was heated to 60 °C for 5 h. After it was cooled, the suspension was concentrated and the crude residue extracted twice with EtOAc. The organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by chromatography on silica gel using 30/70 EtOAc/heptane to afford the expected products **37a,b**.

3,4,5-Trichloropyridazine (8). Following general method A and starting from 4,5-dichloro-2,3-dihydropyridazin-3-one (1 g, 6.06 mmol), **8** was obtained as a white solid (984 mg, 5.36 mmol, 89%): mp 56−58 °C; IR (neat; cm^{-1}) 3063, 1519, 1266, 1028, 823; ^1H NMR (300 MHz, $CDCl_3$; δ (ppm)) 9.09 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 155.8, 150.6, 137.7, 136.0.

3,4,6-Trichloropyridazine (9). Following general method A and starting from 4-bromo-1,2-dihydropyridazine-3,6-dione (**13**; 2 g, 10.47 mmol), **9** was obtained as a white solid (1.8 g, 9.64 mmol, 92%): ^1H NMR (400 MHz, DMSO-d_6; δ (ppm)) 8.58 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 155.1, 154.3, 138.6, 130.9. See ref 12 for other physical characteristics.

4-Bromo-1,2-dihydropyridazine-3,6-dione (13). Hydrazine sulfate (3.7 g, 28.26 mmol) was added to a solution of bromomaleic anhydride (5 g, 28.26 mmol) in water (25 mL). The reaction mixture was heated to 100 °C for 12 h and then cooled to room temperature. The resulting precipitate was filtered off and washed with water (20 mL) to afford **13** as a white solid (4.9 g, 26.16 mmol, 93%): mp 271−273 °C; IR (neat; cm^{-1}) 1633; ^1H NMR (400 MHz, DMSO-d_6; δ (ppm)) 12.33 (br s, 1H), 11.14 (br s, 1H), 7.60 (s, 1H); HRMS (ESI-TOF) m/z calcd for $C_4H_4BrN_2O_2$ $[M + H^+]$ 190.9450, found 190.9449.

***N*-Benzyl-3,5-dichloropyridazin-4-amine (14).** Following general method B and starting from 3,4,5-trichloropyridazine (**8**; 900 mg, 4.91 mmol) and benzylamine (1.6 mL, 14.72 mmol) under microwave irradiation (20 min), **14** was obtained as a white solid (603 mg, 2.37 mmol, 48%): mp 71−73 °C; IR (neat; cm^{-1}) 3236, 3030, 2946, 1553; ^1H NMR (400 MHz, $CDCl_3$; δ (ppm)) 8.49 (s, 1H), 7.30−7.19 (m, 5H), 5.34 (br s, 1H), 4.84 (d, J = 6.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 151.4, 145.5, 140.1, 137.8, 129.1, 128.2, 127.3, 117.9, 49.4; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{10}Cl_2N_3$ $[M + H^+]$ 254.0246, found 254.0248.

***N*-Benzyl-5,6-dichloropyridazin-4-amine (15).** Following general method B and starting from 3,4,5-trichloropyridazine (**8**; 900 mg, 4.91 mmol) and benzylamine (1.6 mL, 14.72 mmol) under microwave irradiation (20 min), **15** was obtained as a light white solid (563 mg, 2.21 mmol, 45%): mp 160−162 °C; IR (neat; cm^{-1}) 3242, 3025, 2915, 1575; ^1H NMR (400 MHz, DMSO-d_6; δ (ppm)) 8.61 (s, 1H), 7.91 (t, J = 6.3 Hz, 1H), 7.38−7.25 (m, 5H), 4.62 (d, J = 6.5 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 152.7, 143.9, 138.2, 138.0, 129.1, 127.7, 127.4, 115.4, 45.6; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{10}Cl_2N_3$ $[M + H^+]$ 254.0246, found 254.0247.

3,6-Dichloropyridazin-4-amine (16a). A mixture of 3,4,6-trichloropyridazine (**9**; 600 mg, 3.27 mmol) and 30% ammonia/70% water (27 equiv, 11.6 mL) in dioxane (10 mL) was heated to 90 °C for 12 h. The reaction mixture was concentrated and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the expected product **16a** as a white solid (460 mg, 2.80 mmol, 86%): mp 185−187 °C; IR (neat; cm^{-1}) 3042, 1638, 1561; ^1H NMR (300 MHz, DMSO-d_6; δ (ppm)) 7.15 (br s, 1H), 6.82 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 154.1, 145.8, 111.3, 108.0; HRMS (ESI-TOF) m/z calcd for $C_4H_4Cl_2N_3$ $[M + H^+]$ 163.9776, found 163.9774.

3,6-Dichloro-*N*-methylpyridazin-4-amine (16b). A mixture of 3,4,6-trichloropyridazine (**9**; 200 mg, 1.09 mmol) and 40% methylamine/60% water (36 equiv, 3.4 mL) in dioxane (3 mL) was stirred at room temperature for 10 min. The reaction mixture was concentrated and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the expected product **16b** as a white solid (170 mg, 0.95 mmol, 88%): mp 153−155 °C; IR (neat; cm^{-1}) 3297, 2926, 1581; ^1H NMR (300 MHz, $CDCl_3$; δ (ppm)) 6.52 (s, 1H), 5.23 (br s, 1H), 2.97 (d, J = 5.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 155.7, 144.7, 144.1, 104.8, 29.2; HRMS (ESI-TOF) m/z calcd for $C_5H_6Cl_2N_3$ $[M + H^+]$ 177.9933, found 177.9932.

3,6-Dichloro-*N*,*N*-dimethylpyridazin-4-amine (16c). A mixture of 3,4,6-trichloropyridazine (**9**; 200 mg, 1.09 mmol) and 40% methylamine/60% water (36 equiv, 4.9 mL) in dioxane (1 mL) was stirred at 0 °C for 10 min. The reaction mixture was concentrated and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give the expected product **16c** as a white solid (194 mg, 1.01 mmol, 93%): mp 70−72 °C; IR (neat; cm^{-1}) 2873, 1557; ^1H NMR (300 MHz, $CDCl_3$; δ (ppm)) 6.71 (s, 1H), 3.10 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 155.2, 149.1, 146.5, 112.7, 41.9; HRMS (ESI-TOF) m/z calcd for $C_6H_8Cl_2N_3$ $[M + H^+]$ 192.0089, found 192.0088.

***N*-Benzyl-3,6-dichloropyridazin-4-amine (16d).** Following general method B and starting from 3,4,6-trichloropyridazine (**9**; 150 mg, 0.82 mmol) and benzylamine (268 μL, 2.45 mmol) under microwave irradiation (40 min), **16d** was obtained as a white solid (188 mg, 0.74 mmol, 90%): mp 84−86 °C; IR (neat; cm^{-1}) 3231, 2925, 1571; ^1H NMR (300 MHz, $CDCl_3$; δ (ppm)) 7.42−7.30 (m, 5H), 6.50 (s, 1H), 5.87 (br s, 1H), 4.45 (d, J = 5.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 155.6, 144.2, 143.7, 135.1, 129.3, 128.5, 127.3, 105.7, 46.8; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{10}Cl_2N_3$ $[M + H^+]$ 254.0246, found 254.0263.

3,6-Dichloro-*N*-(3-phenylpropyl)pyridazin-4-amine (16e). Following general method B and starting from 3,4,6-trichloropyridazine (**9**; 80 mg, 0.44 mmol) and 3-phenylpropan-1-amine (186 μL, 1.31 mmol) under microwave irradiation (20 min), **16e** was obtained as a white solid (109 mg, 0.39 mmol, 89%): mp 96−98 °C; IR (neat; cm^{-1}) 3278, 2935, 1577; ^1H NMR (400 MHz, $CDCl_3$; δ (ppm)) 7.34−7.18 (m, 5H), 6.40 (s, 1H), 5.06 (br s, 1H), 3.20 (q, J = 7.0 Hz, 2H), 2.76 (t, J = 7.3 Hz, 2H), 2.05 (q, J = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 155.6, 144.1, 143.6, 140.1, 128.8, 128.3, 126.6,

104.9, 41.9, 32.9, 29.6; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{14}Cl_2N_3$ [M + H$^+$] 282.0559, found 282.0562.

3,6-Dichloro-*N*-(4-methoxybenzyl)pyridazin-4-amine (16f). Following general method B and starting from 3,4,6-trichloropyridazine (**9**; 200 mg, 1.09 mmol) and 4-methoxybenzylamine (427 μL, 3.27 mmol) under microwave irradiation (40 min), **16f** was obtained as a white solid (268 mg, 0.94 mmol, 87%): mp 110−112 °C; IR (neat; cm^{-1}) 3241, 2921, 2834, 1577, 1513, 1253, 1036, 824; ^{1}H NMR (300 MHz, $CDCl_3$; δ (ppm)) 7.25 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 6.55 (s, 1H), 5.41 (br s, 1H), 4.35 (d, J = 5.3 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 159.7, 155.6, 143.5, 128.8, 128.7, 126.9, 114.7, 105.6, 55.4, 46.4; HRMS (ESI-TOF) m/z calcd for $C_{12}H_{12}Cl_2N_3O$ [M + H$^+$] 284.0351, found 284.0358.

***N*-Benzhydryl-3,6-dichloropyridazin-4-amine (16g).** Following general method C and starting from 3,4,6-trichloropyridazine (**9**; 70 mg, 0.38 mmol) and benzhydrylamine (198 μL, 1.14 mmol), **16g** was obtained as a colorless oil (100 mg, 0.30 mmol, 80%): IR (neat; cm^{-1}) 3408, 3029, 2923, 1585, 1494; ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)) 7.33−7.24 (m, 5H), 7.21−7.17 (m, 5H), 6.25 (s, 1H), 5.54−5.49 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 155.5, 144.3, 142.8, 139.1, 129.4, 128.6, 127.2, 106.9, 61.7; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{14}Cl_2N_3$ [M + H$^+$] 330.0559, found 330.0571.

***N,N*-Dibenzyl-3,6-dichloropyridazin-4-amine (16h).** Following general method C and starting from 3,4,6-trichloropyridazine (**9**; 110 mg, 0.60 mmol) and dibenzylamine (348 μL, 1.80 mmol), **16h** was obtained as a colorless oil (136 mg, 0.39 mmol, 66%): IR (neat; cm^{-1}) 1552; ^{1}H NMR (300 MHz, $CDCl_3$; δ (ppm)) 7.39−7.22 (m, 10H), 6.76 (s, 1H), 4.57 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 155.4, 148.5, 148.4, 135.2, 128.9, 128.1, 127.6, 116.7, 54.6; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{16}Cl_2N_3$ [M + H$^+$] 344.0715, found 344.0739.

***N*-Benzyl-5-chloro-3-(4-methoxyphenyl)pyridazin-4-amine (17).** Following general method E and starting from **14** (400 mg, 1.57 mmol) and 4-methoxyphenylboronic acid (251 mg, 1.65 mmol), **17** was obtained as a colorless oil (441 mg, 1.35 mmol, 86%): IR (neat; cm^{-1}) 2925, 1556, 1513, 1254, 1023, 840; ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)) 8.74 (s, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.29−7.27 (m, 3H), 7.06 (dd, J = 7.9 Hz, J = 2.1 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 4.87 (t, J = 5.6 Hz, 1H), 4.20 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 160.5, 151.6, 149.2, 141.3, 138.1, 130.2, 128.8, 128.4, 127.9, 127.3, 121.3, 114.3, 55.4, 49.9; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{17}ClN_3O$ [M + H$^+$] 326.1054, found 326.1062.

***N*-Benzyl-3-(4-methoxyphenyl)-5-(*p*-tolyl)pyridazin-4-amine (18).** Following general method F and starting from **17** (100 mg, 0.31 mmol) and *p*-tolylboronic acid (62.6 mg, 0.46 mmol) for 1 h, **18** was obtained as a white solid (87 mg, 0.225 mmol, 75%): mp 119−121 °C; IR (neat; cm^{-1}) 3383, 3027, 2930, 2836, 1609, 1509, 1249, 1176, 1031, 834, 731; ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)) 8.59 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.31−7.24 (m, 4H), 7.19−7.17 (m, 3H), 7.01 (d, J = 8.7 Hz, 2H), 6.84−6.82 (m, 2H), 4.71 (t, J = 6.0 Hz, 1H), 3.86 (s, 3H), 3.81 (d, J = 6.3 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 160.3, 152.4, 150.9, 142.0, 138.6, 138.2, 132.5, 130.3, 129.6, 128.8, 128.3, 127.6, 127.2, 123.9, 114.5, 55.4, 50.2, 21.3; HRMS (ESI-TOF) m/z calcd for $C_{25}H_{24}N_3O$ [M + H$^+$] 382.1914, found 382.1915.

***N*-Benzyl-6-chloro-5-(4-methoxyphenyl)pyridazin-4-amine (19).** Following general method E and starting from **15** (400 mg, 1.57 mmol) and 4-methoxyphenylboronic acid (251 mg, 1.65 mmol), **19** was obtained as a white solid (53 mg, 0.16 mmol, 10%): mp 186−188 °C; IR (neat; cm^{-1}) 3029, 2960, 2835, 1573, 1515, 1251, 1021, 841; ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)) 8.63 (s, 1H), 7.39−7.32 (m, 3H), 7.29−7.24 (m, 4H), 7.09 (d, J = 8.7 Hz, 2H), 4.78 (br s, 1H), 4.46 (d, J = 5.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 160.3, 154.8, 144.6, 137.2, 136.5, 130.6, 129.1, 128.1, 126.9, 122.8, 121.3, 115.3, 55.4, 47.0; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{17}ClN_3O$ [M + H$^+$] 326.1054, found 326.1061.

***N*-Benzyl-5-chloro-6-(4-methoxyphenyl)pyridazin-4-amine (20).** Following general method E and starting from **15** (400 mg, 1.57 mmol) and 4-methoxyphenylboronic acid (251 mg, 1.65 mmol), **20** was obtained as a white solid (382 mg, 1.17 mmol, 74%): mp 149−151 °C; IR (neat; cm^{-1}) 3029, 2960, 2835, 1573, 1515, 1251, 1021, 841; ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)) 8.59 (s, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.43−7.35 (m, 5H), 7.01 (d, J = 8.8 Hz, 2H), 5.44 (br s, 1H), 4.59 (d, J = 4.5 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 160.5, 157.1, 141.8, 136.4, 135.6, 131.0, 129.2, 128.3, 128.1, 127.3, 118.0, 113.6, 55.4, 47.1; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{17}ClN_3O$ [M + H$^+$] 326.1054, found 326.1061.

***N*-Benzyl-6-(4-methoxyphenyl)-5-(*p*-tolyl)pyridazin-4-amine (21).** Following general method F and starting from **20** (60 mg, 0.18 mmol) and *p*-tolylboronic acid (37.6 mg, 0.28 mmol) for 1 h, **21** was obtained as a white solid (56 mg, 0.146 mmol, 80%): mp 176−178 °C; IR (neat; cm^{-1}) 3225, 2918, 1555, 1515, 1246, 1174, 1028, 834, 813; ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)) 8.66 (s, 1H), 7.37−7.25 (m, 7H), 7.19 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.73 (d, J = 8.8 Hz, 2H), 4.80 (t, J = 5.4 Hz, 1H), 4.45 (d, J = 5.5 Hz, 2H), 3.76 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 159.5, 157.1, 143.0, 138.4, 137.1, 136.2, 131.3, 130.4, 129.7, 129.6, 129.0, 127.8, 126.9, 121.1, 113.2, 55.2, 46.9, 21.3; HRMS (ESI-TOF) m/z calcd for $C_{25}H_{24}N_3O$ [M + H$^+$] 382.1914, found 382.1917.

6-Chloro-3-phenylpyridazin-4-amine (23a). Following general method D and starting from **16a** (60 mg, 0.36 mmol) and phenylboronic acid (49 mg, 0.40 mmol) under microwave irradiation, **23a** was obtained as a yellow oil (58 mg, 0.28 mmol, 78%): IR (neat; cm^{-1}) 3060, 2918, 1641, 1563, 752; ^{1}H NMR (400 MHz, DMSO-d_6; δ (ppm)) 7.60−7.50 (m, 5H), 6.85 (s, 1H), 6.49 (br s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 153.6, 149.2, 146.3, 134.6, 129.0, 128.8, 128.4, 107.7; HRMS (ESI-TOF) m/z calcd for $C_{10}H_9ClN_3$ [M + H$^+$] 206.0479, found 206.0471.

6-Chloro-3-(4-chlorophenyl)pyridazin-4-amine (23b). Following general method D and starting from **16a** (50 mg, 0.30 mmol) and 4-chlorophenylboronic acid (51.6 mg, 0.33 mmol), **23b** was obtained as an orange solid (61 mg, 0.25 mmol, 85%): mp 246−248 °C; IR (neat; cm^{-1}) 3465, 1496, 1090, 1016, 837; ^{1}H NMR (400 MHz, DMSO-d_6; δ (ppm)) 7.63−7.58 (m, 4H), 6.85 (s, 1H), 6.59 (br s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 153.7, 148.2, 146.4, 133.7, 133.5, 130.3, 128.8, 107.9; HRMS (ESI-TOF) m/z calcd for $C_{10}H_8Cl_2N_3$ [M + H$^+$] 240.0089, found 240.0099.

6-Chloro-3-(2-methoxyphenyl)pyridazin-4-amine (23c). Following general method D and starting from **16a** (50 mg, 0.30 mmol) and 2-methoxyphenylboronic acid (50.8 mg, 0.33 mmol) under microwave irradiation, **23c** was obtained as a yellow solid (60 mg, 0.25 mmol, 84%): mp 194−196 °C; IR (neat; cm^{-1}) 3069, 2834, 1240, 755; ^{1}H NMR (400 MHz, DMSO-d_6; δ (ppm)) 7.49 (td, J = 8.7 Hz, J = 1.8 Hz, 1H), 7.25 (dd, J = 7.4 Hz, J = 1.6 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H), 7.08 (t, J = 7,4 Hz, 1H), 6.76 (s, 1H), 6.24 (br s, 2H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 156.9, 153.7, 148.6, 147.0, 130.9, 130.7, 123.4, 120.6, 111.7, 106.6, 55.3; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{11}ClN_3O$ [M + H$^+$] 236.0585, found 236.0589.

6-Chloro-3-(4-methoxyphenyl)pyridazin-4-amine (23d). Following general method D and starting from **16a** (60 mg, 0.36 mmol) and 4-methoxyphenylboronic acid (61 mg, 0.40 mmol) under microwave irradiation, **23d** was obtained as a yellow solid (74 mg, 0.31 mmol, 86%): mp 204−206 °C; IR (neat; cm^{-1}) 3042, 1507, 1244, 1036, 841; ^{1}H NMR (300 MHz, DMSO-d_6; δ (ppm)) 7.55−7.52 (m, 2H), 7.09−7.06 (m, 2H), 6.81 (s, 1H), 6.45 (br s, 2H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 159.8, 153.2, 149.0, 146.3, 129.7, 126.9, 114.2, 107.5, 55.2; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{11}ClN_3O$ [M + H$^+$] 236.0585, found 236.0591.

6-Chloro-3-(4-methoxyphenyl)-*N*-methylpyridazin-4-amine (23e). Following general method D and starting from **16b** (80 mg, 0.45 mmol) and 4-methoxyphenylboronic acid (75 mg, 0.49 mmol) under conventional heating, **23e** was obtained as a white solid (85 mg, 0.34 mmol, 76%): mp 153−155 °C; IR (neat; cm^{-1}) 3361, 1512, 1247, 1030, 836; ^{1}H NMR (300 MHz, $CDCl_3$; δ (ppm)) 7.47−7.44 (m, 2H), 6.98−6.95 (m, 2H), 6.49 (s, 1H), 4.99 (br s, 1H), 3.82 (s, 3H), 2.81 (d, J = 5.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 160.6, 155.1, 150.1, 146.1, 130.0, 126.1, 114.7, 103.9, 55.4, 29.7;

HRMS (ESI-TOF) m/z calcd for $C_{12}H_{13}ClN_3O$ [M + H$^+$] 250.0741, found 250.0748.

6-Chloro-3-(4-methoxyphenyl)-*N*,*N*-dimethylpyridazin-4-amine (23f). Following general method D and starting from **16c** (80 mg, 0.42 mmol) and 4-methoxyphenylboronic acid (70 mg, 0.46 mmol) under conventional heating, **23f** was obtained as a white solid (92 mg, 0.35 mmol, 84%): mp 99−101 °C; IR (neat; cm^{-1}) 2936, 2841, 1519, 1258, 1031, 832; ^{1}H NMR (300 MHz, $CDCl_3$; δ (ppm)) 7.63 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 6.77 (s, 1H), 3.86 (s, 3H), 2.71 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 160.2, 154.2, 151.9, 149.9, 130.2, 129.5, 114.1, 110.9, 55.3, 41.6; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{15}ClN_3O$ [M + H$^+$] 264.0898, found 264.0895.

6-Chloro-3-(4-methoxyphenyl)-*N*-(3-phenylpropyl)-pyridazin-4-amine (23g). Following general method E and starting from **16e** (400 mg, 1.42 mmol) and 4-methoxyphenylboronic acid (226 mg, 1.49 mmol), **23g** was obtained as a yellow oil (417 mg, 1.18 mmol, 83%): IR (neat; cm^{-1}) 3280, 2928, 1565, 1249, 1033, 835; ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)) 7.47 (d, J = 8.7 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 7.20 (d, J = 7.3 Hz, 1H), 7.13 (d, J = 7.2 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.45 (s, 1H), 4.75 (br s, 1H), 3.86 (s, 3H), 3.11 (q, J = 7.2 Hz, 2H), 2.68 (t, J = 7.4 Hz, 2H), 1.93 (q, J = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 160.7, 155.1, 150.1, 144.9, 140.4, 129.9, 128.7, 128.3, 126.4, 126.1, 114.8, 104.2, 55.4, 41.8, 33.1, 29.8; HRMS (ESI-TOF) m/z calcd for $C_{20}H_{21}ClN_3O$ [M + H$^+$] 354.1367, found 354.1377.

***N*-Benzyl-6-chloro-3-(4-methoxyphenyl)pyridazin-4-amine (23h).** Following general method E and starting from **16d** (40 mg, 0.16 mmol) and 4-methoxyphenylboronic acid (25 mg, 0.17 mmol), **23h** was obtained as a colorless oil (39.5 mg, 0.12 mmol, 77%): IR (neat; cm^{-1}) 3031, 2929, 2837, 1561, 1246, 1062, 832; ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)) 7.56 (d, J = 8.5 Hz, 2H), 7.40−7.28 (m, 5H), 7.03 (d, J = 8.7 Hz, 2H), 6.54 (s, 1H), 5.25 (t, J = 5.1 Hz, 1H), 4.36 (d, J = 5.5 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 160.7, 155.1, 150.2, 144.9, 136.0, 130.0, 129.2, 128.1, 127.0, 126.1, 114.9, 104.9, 55.4, 46.8; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{17}ClN_3O$ [M + H$^+$] 326.1054, found 326.1059.

***N*-Benzhydryl-6-chloro-3-(4-methoxyphenyl)pyridazin-4-amine (23i).** Following general method E and starting from **16g** (80 mg, 0.24 mmol) and 4-methoxyphenylboronic acid (38.6 mg, 0.25 mmol), **23i** was obtained as a white solid (77 mg, 0.19 mmol, 79%): mp 151−153 °C; IR (neat; cm^{-1}) 2921, 2840, 1512, 1247, 1026, 842; ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)) 7.61 (d, J = 8.8 Hz, 2H), 7.37−7.28 (m, 6H), 7.25−7.22 (m, 4H), 7.02 (d, J = 8.8 Hz, 2H), 6.38 (s, 1H), 5.51 (d, J = 5.0 Hz, 1H), 5.35 (br d, J = 5.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 160.7, 154.9, 150.2, 143.9, 139.9, 129.9, 129.3, 128.3, 127.0, 126.0, 114.9, 106.1, 61.8, 55.4; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{21}ClN_3O$ [M + H$^+$] 402.1367, found 402.1372.

***N*,*N*-Dibenzyl-6-chloro-3-(4-methoxyphenyl)pyridazin-4-amine (23j).** Following general method E and starting from **16h** (80 mg, 0.23 mmol) and 4-methoxyphenylboronic acid (37 mg, 0.24 mmol), **23j** was obtained as a white solid (59 mg, 0.14 mmol, 61%): mp 146−148 °C; IR (neat; cm^{-1}) 3026, 2956, 2847, 1539, 1251, 1031, 831; ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)) 7.78 (d, J = 8.8 Hz, 2H), 7.34−7.28 (m, 6H), 7.04−7.00 (m, 6H), 6.79 (s, 1H), 4.12 (s, 4H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 160.5, 154.5, 153.4, 149.3, 135.7, 129.8, 129.6, 128.8, 128.1, 127.9, 115.0, 114.4, 55.4, 54.3; HRMS (ESI-TOF) m/z calcd for $C_{25}H_{23}ClN_3O$ [M + H$^+$] 416.1524, found 416.1527.

3-(4-Methoxyphenyl)pyridazin-4-amine (25a). Following general method G and starting from **23d** (30 mg, 0.13 mmol) and $Pd(OH)_2/C$ (10 wt %), **25a** was obtained as a white solid (25 mg, 0.12 mmol, 98%): mp 232−234 °C; IR (neat; cm^{-1}) 3307, 3075, 2838, 1608, 1515, 1253, 1020, 838; ^{1}H NMR (300 MHz, MeOD-d_4; δ (ppm)) 8.60 (d, J = 6.9 Hz, 1H), 7.60 (d, J = 8.9 Hz, 2H), 7.19 (d, J = 7.0 Hz, 1H), 7.12 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (101 MHz, MeOD-d_4; δ (ppm)) 161.7, 151.2, 149.7, 142.2, 129.7, 123.9, 114.5, 109.4, 54.6; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{12}N_3O$ [M + H$^+$] 202.0975, found 202.0971.

3-(4-Methoxyphenyl)-*N*-methylpyridazin-4-amine (25b). Following general method G and starting from **23e** (40 mg, 0.16 mmol) and $Pd(OH)_2/C$ (10 wt %), **25b** was obtained as a yellow solid (33 mg, 0.15 mmol, 98%): mp 106−108 °C; IR (neat; cm^{-1}) 2929, 2709, 1599, 1509, 1248, 1029, 831; ^{1}H NMR (300 MHz, MeOD-d_4; δ (ppm)) 7.68 (d, J = 7.0 Hz, 1H), 7.57 (d, J = 8.7 Hz, 2H), 7.14−7.09 (m, 3H), 3.88 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (101 MHz, MeOD-d_4; δ (ppm)) 163.1, 151.9, 151.3, 144.3, 131.3, 125.2, 115.9, 106.5, 56.1, 30.2; HRMS (ESI-TOF) m/z calcd for $C_{12}H_{14}N_3O$ [M + H$^+$] 216.1131, found 216.1134.

3-(4-Methoxyphenyl)-*N*,*N*-dimethylpyridazin-4-amine (25c). Following general method G and starting from **23f** (19 mg, 0.07 mmol) and Pd/C (10 wt %), **25c** was obtained as a yellow solid (13 mg, 0.06 mmol, 82%): mp 260−262 °C; IR (neat; cm^{-1}) 3055, 2991, 2632, 1556, 1506, 1243, 1023, 841; ^{1}H NMR (300 MHz, MeOD-d_4; δ (ppm)) 8.66 (d, J = 7.2 Hz, 1H), 7.54 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 7.2 Hz, 1H), 7.10 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H), 3.01 (s, 6H); ^{13}C NMR (101 MHz, MeOD-d_4; δ (ppm)) 161.2, 151.6, 149.9, 140.4, 129.4, 128.3, 114.0, 109.8, 54.6, 41.9; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{16}N_3O$ [M + H$^+$] 230.1288, found 230.1284.

3-(4-Methoxyphenyl)-6-(4-(trifluoromethyl)phenyl)-pyridazin-4-amine (26a). Following general method F and starting from **23d** (110 mg, 0.47 mmol) and 4-trifluoromethylphenylboronic acid (133 mg, 0.70 mmol) for 2 h, **26a** was obtained as a light yellow solid (81 mg, 0.23 mmol, 50%): mp 324−326 °C; IR (neat; cm^{-1}) 3015, 2924, 2845, 1643, 1582, 1505, 1320, 1249, 1108, 1069, 841; ^{1}H NMR (400 MHz, DMSO-d_6; δ (ppm)) 8.21 (d, J = 8.2 Hz, 2H), 7.91 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.30 (s, 1H), 7.11 (d, J = 8.8 Hz, 2H), 6.26 (br s, 2H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 160.1, 155.1, 148.7, 145.2, 141.6, 130.2, 128.3, 127.7, 126.3, 126.2, 114.7, 106.8, 55.7; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{15}F_3N_3O$ [M + H$^+$] 346.1162, found 346.1160.

3-(4-Methoxyphenyl)-6-phenyl-*N*-(3-phenylpropyl)-pyridazin-4-amine (26b). Following general method F and starting from **23g** (150 mg, 0.42 mmol) and phenylboronic acid (77.5 mg, 0.63 mmol) for 1 h, **26b** was obtained as a colorless oil (154 mg, 0.39 mmol, 92%); IR (neat; cm^{-1}) 3419, 3059, 2929, 2855, 1580, 1513, 1247, 1028, 836, 697; ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)) 8.03−8.01 (m, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.52−7.44 (m, 3H), 7.29 (t, J = 7.5 Hz, 2H), 7.21 (td, J = 7.3 Hz, 1H), 7.16 (d, J = 6.9 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 6.79 (s, 1H), 4.74 (t, J = 5.3 Hz, 1H), 3.88 (s, 3H), 3.22 (q, J = 7.3 Hz, 2H), 2.71 (t, J = 7.4 Hz, 2H), 1.97 (q, J = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 160.4, 157.7, 149.1, 143.8, 140.7, 137.6, 130.1, 129.4, 128.7, 128.6, 128.3, 127.3, 127.2, 126.3, 114.6, 101.7, 55.4, 41.7, 33.2, 30.0; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{26}N_3O$ [M + H$^+$] 396.2070, found 396.2082.

***(E)*-*N*-Benzyl-3-(4-methoxyphenyl)-6-styrylpyridazin-4-amine (26c).** Following general method F and starting from **23h** (80 mg, 0.24 mmol) and (*E*)-styrylboronic acid (72.7 mg, 0.49 mmol) for 12 h, **26c** was obtained as a light yellow solid (52 mg, 0.13 mmol, 54%): mp 203−205 °C; IR (neat; cm^{-1}) 3030, 2929, 2836, 1578, 1512, 1247, 1175, 835, 731; ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)) 7.65 (d, J = 8.8 Hz, 2H), 7.60−7.56 (m, 3H), 7.41−7.36 (m, 4H), 7.34−7.29 (m, 4H), 7.23 (d, J = 16.4 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 6.68 (s, 1H), 5.14 (br s, 1H), 4.43 (d, J = 5.4 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 160.4, 149.1, 143.5, 136.8, 136.4, 133.8, 130.1, 129.1, 128.7, 128.6, 127.9, 127.2, 127.1, 114.7, 102.4, 55.4, 46.8; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{24}N_3O$ [M + H$^+$] 394.1914, found 394.1910.

***tert*-Butyl(3,6-dichloropyridazin-4-yl)methylcarbamate (27a).** Following general method I and starting from **16b** (70 mg, 0.30 mmol), **27a** was obtained as a white solid (109 mg, 0.39 mmol, 99%): mp 108−110 °C; IR (neat; cm^{-1}) 1717, 1557, 1386, 1364, 1127; ^{1}H NMR (300 MHz, DMSO-d_6; δ (ppm)) 8.25 (s, 1H), 3.17 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 155.7, 154.8, 151.8, 143.7, 128.1, 81.8, 36.0, 27.5; HRMS (ESI-TOF) m/z calcd for $C_{10}H_{14}Cl_2N_3O_2$ [M + H$^+$] 278.0457, found 278.0459.

***tert*-Butyl(3,6-dichloropyridazin-4-yl)(4-methoxybenzyl)-carbamate (27b).** Following general method I and starting from **16f** (265 mg, 0.93 mmol), **27b** was obtained as a colorless oil (351 mg,

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0.91 mmol, 98%): IR (neat; cm^{-1}) 2979, 2934, 1717, 1560, 1513, 1395, 1369, 1248, 1157, 1070, 847; ^1H NMR (400 MHz, $CDCl_3$; δ (ppm)) 7.10 (d, J = 8.5 Hz, 2H), 7.06 (s, 1H), 6.83 (d, J = 8.7 Hz, 2H), 4.73 (br s, 2H), 3.79 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 159.5, 155.8, 155.6, 142.1, 129.7, 128.3, 127.8, 114.3, 83.2, 55.3, 51.9, 28.0; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{20}Cl_2N_3O_3$ [M + H^+] 384.0876, found 384.0895

***tert*-Butyl(3-chloro-6-(4-methoxyphenyl)pyridazin-4-yl)-methylcarbamate (28a).** Following general method D and starting from **27a** (80 mg, 0.29 mmol) and 4-methoxyphenylboronic acid (48.1 mg, 0.32 mmol) under conventional heating, **28a** was obtained as a white solid (63 mg, 0.18 mmol, 63%): mp 160−162 °C; IR (neat; cm^{-1}) 2974, 2930, 1716, 1576, 1519, 1343, 1250, 1148, 1021, 838; ^1H NMR (400 MHz, $CDCl_3$; δ (ppm)) 8.02 (d, J = 8.9 Hz, 2H), 7.67 (s, 1H), 7.04 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H), 3.25 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 161.8, 159.6, 153.4, 142.2, 128.6, 127.2, 123.1, 114.6, 82.3, 55.5, 36.5, 28.1; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{21}ClN_3O_3$ [M + H^+] 350.1266, found 350.1269.

***tert*-Butyl(3-chloro-6-(4-methoxyphenyl)pyridazin-4-yl)(4-methoxybenzyl)carbamate (28b).** Following general method D and starting from **27b** (80 mg, 0.21 mmol) and 4-methoxyphenylboronic acid (34.8 mg, 0.23 mmol) under conventional heating, **28b** was obtained as a colorless oil (64 mg, 0.14 mmol, 67%): IR (neat; cm^{-1}) 2927, 2838, 1710, 1608, 1513, 1366, 1247, 1157, 1032, 835; ^1H NMR (400 MHz, $CDCl_3$; δ (ppm)) 7.83 (d, J = 8.9 Hz, 2H), 7.23 (br s, 1H), 7.14 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 4.75 (br s, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 161.7, 159.5, 159.2, 154.2, 153.0, 140.4, 130.0, 128.7, 128.5, 127.2, 124.2, 114.5, 114.2, 82.4, 55.5, 55.3, 51.9, 28.1; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{27}ClN_3O_4$ [M + H^+] 456.1685, found 456.1675.

3,6-Dichloro-4-methoxypyridazine (31a). Sodium methanolate (170 mg, 3.15 mmol) was added to a solution of 3,4,6-trichloropyridazine (**9**; 650 mg, 3.54 mmol) in dry methanol (20 mL). The reaction mixture was stirred at room temperature for 1 h and then evaporated to dryness. The crude residue was diluted in water and extracted twice with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness to afford **31a** as a white solid (596 mg, 3.33 mmol, 94%): mp 109−111 °C; IR (neat; cm^{-1}) 1556, 1123, 861; ^1H NMR (300 MHz, $CDCl_3$; δ (ppm)) 6.93 (s, 1H), 4.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 156.1, 155.7, 148.1, 109.5, 56.7; HRMS (ESI-TOF) m/z calcd for $C_5H_5Cl_2N_2O$ [M + H^+] 178.9773, found 178.9765.

4-(Benzyloxy)-3,6-dichloropyridazine (31b). In a flame-dried two-neck round-bottom flask containing Na_2SO_4, benzylic alcohol (60 μL, 0.60 mmol) was dissolved in dry THF (5 mL). When the solution was cooled to 0 °C, NaH (16 mg, 0.65 mmol) was added portionwise and the reaction mixture was stirred for 15 min. 3,4,6-Trichloropyridazine (**9**; 100 mg, 0.55 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h. After evaporation to dryness, the crude residue was diluted in water and extracted twice with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness to afford **31b** as a white solid (98 mg, 0.38 mmol, 70%): mp 144−146 °C; IR (neat; cm^{-1}) 3062, 1552, 1363, 1121; ^1H NMR (300 MHz, $CDCl_3$; δ (ppm)) 7.26−7.21 (m, 5H), 6.83 (s, 1H), 5.01 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 155.9, 154.7, 148.4, 133.3, 129.2, 129.1, 127.4, 110.6, 71.6; HRMS (ESI-TOF) m/z calcd for $C_{11}H_9Cl_2N_2O$ [M + H^+] 255.0092, found 255.0084.

6-(4-Methoxyphenyl)-*N*-methylpyridazin-4-amine (35a). Following general method H and starting from **16b** (200 mg, 1.12 mmol), **35a** was obtained as a yellow solid (116 mg, 0.54 mmol, 48%): mp 168−170 °C; IR (neat; cm^{-1}) 3232, 3051, 2924, 1601, 1519, 1245, 1031, 832; ^1H NMR (400 MHz, $CDCl_3$; δ (ppm)) 8.57 (d, J = 2.8 Hz, 1H), 7.95 (d, J = 8.9 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 2.8 Hz, 1H), 5.01 (br d, J = 4.0 Hz, 1H), 3.86 (s, 3H), 2.94 (d, J = 5.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 161.0, 157.9, 146.9, 139.6, 128.6, 114.2, 101.7, 55.4, 28.9; HRMS (ESI-TOF) m/z calcd for $C_{12}H_{14}N_3O$ [M + H^+] 216.1131, found 216.1127.

6-(4-Methoxyphenyl)-*N*-(3-phenylpropyl)pyridazin-4-amine (35b). Following general method H and starting from **16e** (150 mg, 0.53 mmol), **35b** was obtained as a yellow oil (86 mg, 0.27 mmol, 51%): IR (neat; cm^{-1}) 3229, 2946, 1595, 1245, 1027, 838; ^1H NMR (400 MHz, DMSO-d_6; δ (ppm)) 8.52 (d, J = 2.6 Hz, 1H), 7.98 (d, J = 8.9 Hz, 2H), 7.32−7.18 (m, 5H), 7.15 (br t, J = 5.3 Hz, 1H), 7.05 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 2.6 Hz, 1H), 3.83 (s, 3H), 3.22 (q, J = 6.8 Hz, 2H), 2.70 (t, J = 7.3 Hz, 2H), 1.88 (q, J = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 160.9, 156.9, 146.8, 142.0, 129.9, 128.8, 128.6, 126.3, 114.5, 55.7, 41.2, 32.9, 30.4; HRMS (ESI-TOF) m/z calcd for $C_{20}H_{22}N_3O$ [M + H^+] 320.1757, found 320.1766.

6-Chloro-3-(phenylethynyl)pyridazin-4-amine (36a). Following general method J and starting from **16a** (100 mg, 0.61 mmol), **36a** was obtained as a light white solid (106 mg, 0.46 mmol, 76%): mp 202−204 °C; IR (neat; cm^{-1}) 3456, 3054, 2924, 2216, 1633, 1557, 1271, 1143, 752; ^1H NMR (400 MHz, DMSO-d_6; δ (ppm)) 7.78−7.75 (m, 2H), 7.50−7.48 (m, 3H), 6.85 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 149.2, 135.6, 132.5, 130.2, 129.2, 126.5, 117.7, 107.1, 82.7; HRMS (ESI-TOF) m/z calcd for $C_{12}H_9ClN_3$ [M + H^+] 230.0479, found 230.0480.

***N*-Benzyl-6-chloro-3-(phenylethynyl)pyridazin-4-amine (36b).** Following general method J and starting from **16d** (80 mg, 0.31 mmol), **36b** was obtained as a colorless oil (68 mg, 0.21 mmol, 68%): IR (neat; cm^{-1}) 3239, 3062, 2207, 1565, 1490, 1275, 1132, 689; ^1H NMR (400 MHz, DMSO-d_6; δ (ppm)) 7.80−7.74 (m, 3H), 7.51−7.50 (m, 3H), 7.37−7.36 (m, 4H), 7.29−7.25 (m, 1H), 6.81 (s, 1H), 4.58 (d, J = 6.3 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 154.0, 148.0, 137.9, 136.3, 132.6, 130.4, 129.2, 129.1, 127.6, 127.3, 121.5, 104.5, 98.4, 82.5, 45.1; HRMS (ESI-TOF) m/z calcd for $C_{19}H_{15}ClN_3$ [M + H^+] 320.0942, found 320.0945.

3-Chloro-6-phenyl-5*H*-pyrrolo[3,2-*c*]pyridazine (37a). To a solution of **36a** (20 mg, 0.09 mmol) in dry DMF (1 mL) was added CuI (20 mol %). The reaction mixture was heated to 130 °C for 12 h. After it was cooled, the reaction mixture was diluted in ice−water and filtered under reduced pressure to afford **37a** as a brown solid (17 mg, 0.07 mmol, 85%): mp 295−297 °C; IR (neat; cm^{-1}) 3076, 2928, 1622, 1416, 1141, 742; ^1H NMR (400 MHz, DMSO-d_6; δ (ppm)) 12.49 (s, 1H), 8.03 (d, J = 7.5 Hz, 2H), 7.72 (s, 1H), 7.59−7.45 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 130.3, 129.7, 126.8, 108.2, 98.1; HRMS (ESI-TOF) m/z calcd for $C_{12}H_9ClN_3$ [M + H^+] 230.0479, found 230.0485.

5-Benzyl-3-chloro-6-phenyl-5*H*-pyrrolo[3,2-*c*]pyridazine (37b). To a solution of **36b** (150 mg, 0.65 mmol) in dry DMF (6 mL) was added CuI (20 mol %). The reaction mixture was heated to 130 °C for 12 h. After it was cooled, the reaction mixture was diluted in ice−water and filtered under reduced pressure to afford **37b** as an orange solid (135 mg, 0.59 mmol, 90%): mp 167−169 °C; IR (neat; cm^{-1}) 3060, 2924, 1600, 1421, 934, 695; ^1H NMR (400 MHz, DMSO-d_6; δ (ppm)) 8.11 (d, J = 1.0 Hz, 1H), 7.60−7.58 (m, 2H), 7.53−7.51 (m, 3H), 7.25−7.19 (m, 3H), 7.16 (d, J = 0.9 Hz, 1H), 6.84 (dd, J = 7.9 Hz, J = 2.1 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6; δ (ppm)) 151.2, 149.5, 147.9, 137.0, 133.8, 130.5, 130.2, 129.7, 129.4, 129.2, 128.0, 126.6, 108.3, 102.2, 47.4; HRMS (ESI-TOF) m/z calcd for $C_{19}H_{15}ClN_3$ [M + H^+] 320.0949, found 320.0950.

5-Benzyl-6-phenyl-3-(4-(trifluoromethyl)phenyl)-5*H*-pyrrolo[3,2-*c*]pyridazine (38). Following general method E and starting from **37b** (32 mg, 0.10 mmol) and 4-trifluoromethylphenylboronic acid (1.5 equiv, 283.5 mg, 0.15 mmol), **38** was obtained as an orange oil (25 mg, 0.06 mmol, 59%): IR (neat; cm^{-1}) 2925, 2854, 1617, 1323, 1121, 1068, 729, 697; ^1H NMR (500 MHz, $CDCl_3$; δ (ppm)) 8.15 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.53 (s, 1H), 7.49−7.47 (m, 5H), 7.33−7.27 (m, 3H), 7.13 (s, 1H), 7.00 (d, J = 8.1 Hz, 2H), 5.43 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$; δ (ppm)) 151.2, 150.6, 148.8, 141.7, 136.1, 132.4, 130.5, 129.7, 129.3, 129.2, 129.0, 128.1, 127.5, 125.9, 125.7, 123.1, 104.2, 102.6, 47.8; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{19}F_3N_3$ [M + H^+] 430.1526, found 430.1531.

■ ASSOCIATED CONTENT

Supporting Information

Figures and a table giving optimization data, NMR spectra, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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