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

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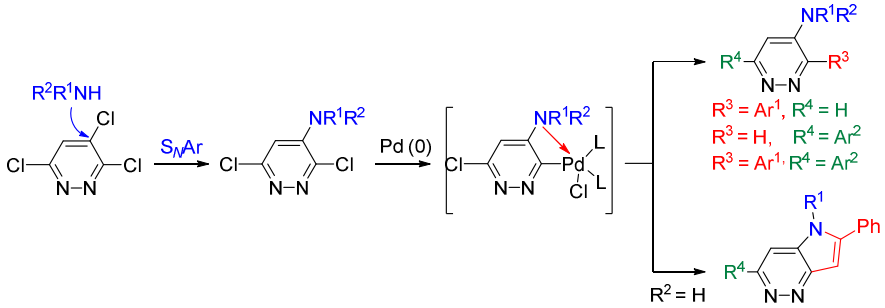
KEYWORDS: 4-alkylaminopyridazine, nitrogen assisted, Pd-catalyzed reaction, regioselective

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 pyrolopyridazines.

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 led to constantly increasing number of reports, especially in the last 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 pre-clinical candidates and several FDA,[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 smaller representation of 4-aminopyridazines compared to 3-aminopyridazines in literature is the absence of high-yielding and reliable methods of their synthesis.[9-12]

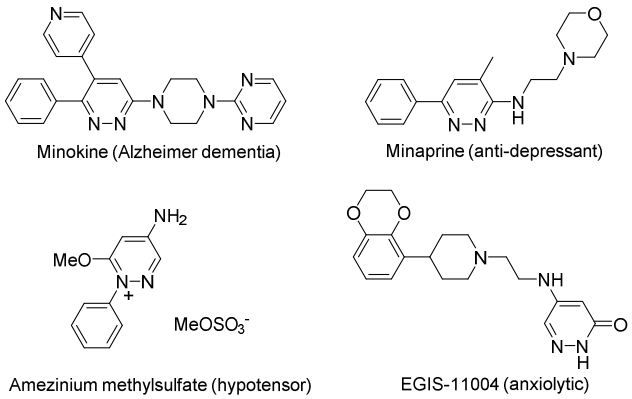


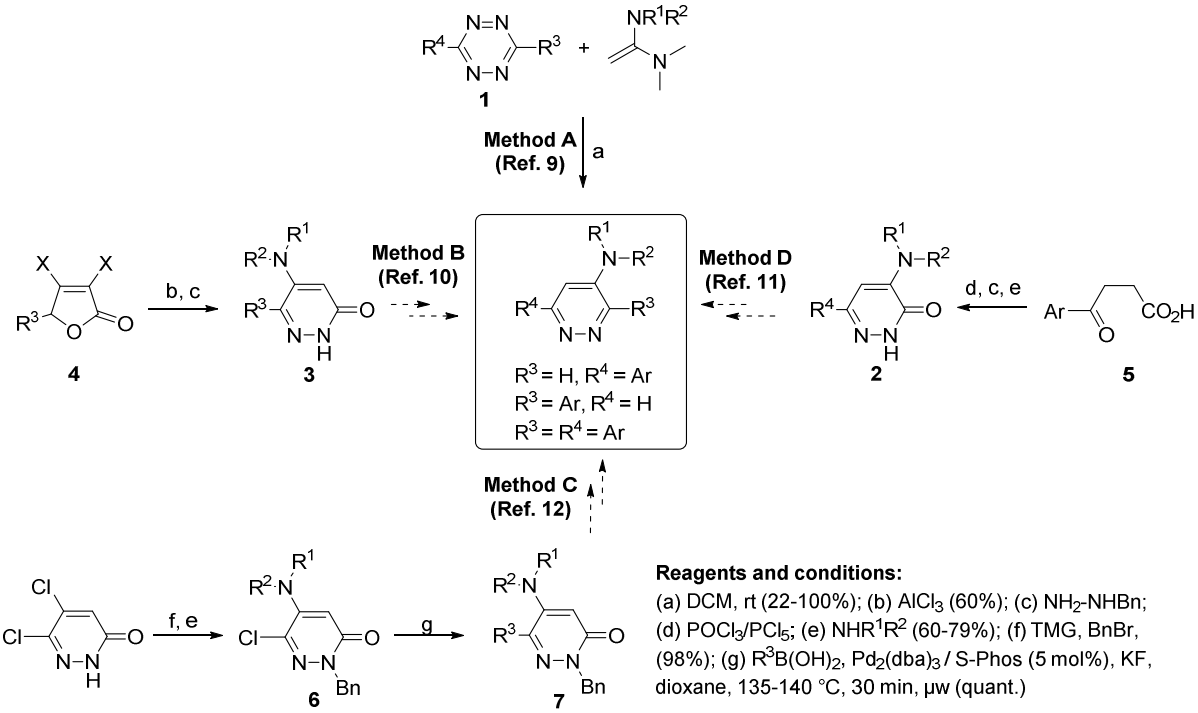
Figure 1. Examples of pharmacologically relevant 3-aminopyridazines: Minokine (Alzheimer dementia), Minaprine (antidepressant). 4-aminopyridazine: Amezinium methylsulfate (antihypotensive)[7] and 5-aminopyridazinone EGIS-11004 (anxiolytic).[8]

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 heavily relies on the availability 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 precursors of choice for the synthesis of 4-alkylamino pyridazines, since the activation of the amide function may open a route to additional substitutions on the pyridazine backbone. However, methods for preparation of **2** and **3** intermediates (methods B-D) suffer from limitations such as the

availability of the corresponding butenolides **4**[10] (method B), 1,4-ketoacids **5** (method D), or the need of 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*-benzyl-pyridazine-3-ones **7** (method C).[12] This synthetic route allowed the introduction of chemical diversity at the C-6 position. Unfortunately, it suffers from moderate yields when piperidine was replaced by other secondary amines and scope of the reaction could not be extended to primary alkylamines (R_2 = H).

Scheme 1. Reported synthesis of 4-aminopyridazines and their precursors 2 and 3



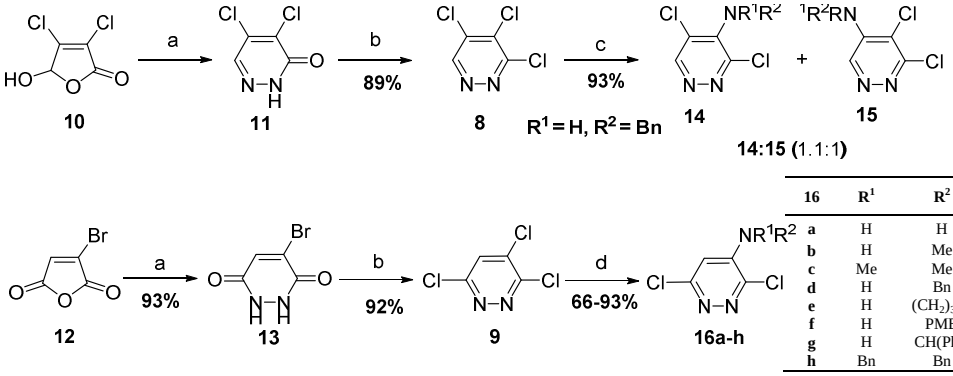
Elaboration of novel versatile approaches leading to 4-aminopyridazines offering the largest structural diversity and thus allowing efficient structural optimization (R^3, R^4 = H, aryl, alkyl, aralkyl, others), around pyridazine core is therefore of importance for drug design. The aim of this work was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

Scheme 2. Reactivity of 8 and 9 towards amination reaction



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

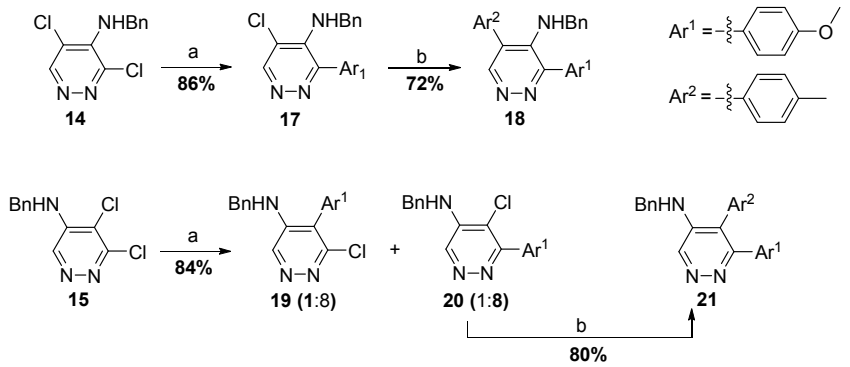
[a] reaction conditions: (a) $N_2H_4.H_2SO_4$, H_2O, 100 °C, 12 h; (b) $POCl_3$, 120 °C, 5 h; (c) $BnNH_2$, *i*-PrOH, 120 °C, 20 min, µw; (d) NHR^1R^2, see experimental part.

The S_NAr-type amination reactions performed with 3-chloropyridazines needs generally relatively drastic experimental conditions, in particular heating at high temperatures[15] and using acid as catalyst and large excess of amine reagent.[5b,16] The presence of two vicinal nitrogens in the pyridazine ring is clearly associated in the literature with its poor electrophilicity, when compared with other related systems (pyrimidine, pyrazine).[17] However, compare to 3-chloropyridazines, 3,6-dichloropyridazines presented an increased electrophilic character, and thus better reactivity towards S_NAr amination reactions.[18,14b] Interestingly, both the 3,4,5- and 3,4,6-trichloropyridazines **8** and **9** possess an aryl chloride with different electrophilic character towards amination reaction. Finally, when **8** and **9** were submitted to benzylamine : i) 3,4,5-trichloropyridazine **8** yielded a mixture of 3,5-dichloro- (**14**) and 5,6-dichloro- (**15**) 4-benzylaminopyridazines in equal amounts (see Scheme 2). ii) no trace of reaction was observed onto 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 the cases the aryl chloride function was the most reactive towards S_NAr amination reaction.

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

Selectivity of the PCCR of heteroarenes bearing multiple identical halogens is mainly determined by the relative ease of oxidative addition. Based on 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 mono-substitution 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-di-substituted 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.

Scheme 3. SMCC reactions with 14 and 15

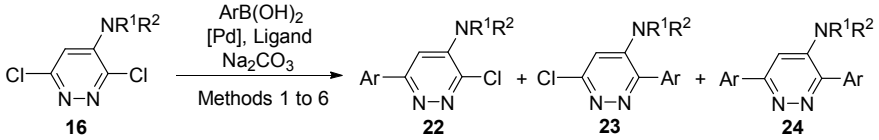


[a]reaction conditions: (a) $Pd(PPh_3)_4$ (5 mol%), 4-MeOPhB$(OH)_2$ (1.05 equiv), Na_2CO_3 (2 equiv), toluene:EtOH:H_2O (3:1:1), 100 °C, 3 h; (b) $Pd(OAc)_2$ (2 mol%), XPhos (2.4 mol%), 4-MePhB$(OH)_2$ (1.5 equiv), CsOH.H_2O (1.7 equiv), *n*-BuOH:H_2O (4:1), 50 °C, 1 h.

For the SMCC reactions of 3,6-dichloro 4-aminopyridazines **16** we envisioned to control regioselectivity of the two nearly-identical iminochlorides. In addition we could hypothesize that steric hindrance induced by the substituted amino group may favour formation of the 6-aryl 4-amino pyridazine **22**, but this effect may be counterbalance by the fact that the position 6 is slightly more electro-enriched by the electrodonor effect of the amino group. Interestingly, with the primary amine **16a**, when using 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 mono-adduct **23a**. Only traces (<5%) of 3,6-diadduct **24a** was 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 2-MeO-phenylboronic acid proceeded efficiently (entry 3). Structure of **23d** was assigned using the 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 *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 equivalent yields than microwave heating (entries 4–6).

Table 1. SMCC reaction conditions leading to 3-aryl-4-aminopyridazines 23



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

[a]yields refer to isolated, chromatographically, purified materials; [b]Yield determined by NMR using CH_2I_2 as internal standard; [c]Unpublished products **23** were fully characterized by NMR 1D & 2D and HR-MS data; [d]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; [e]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; [f]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; [g]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; [h]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. [i]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. [j]reactions were performed in a mixture of solvent:H_2O except for entry 8

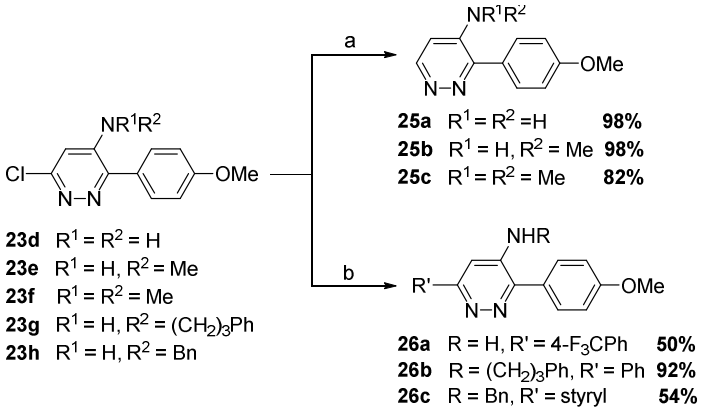
However, when the 4-amino group was substituted by a more sterically hindered phenylpropyl group (**16e**), the resulting steric hindrance led to a less reactive system under our standard conditions (25% recovery of starting material **16e**) and resulted in formation of significant amount of 3,6-disubstituted 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 using $Pd_2(dba)_3.CHCl_3$,[24] no reaction occurred at all (entry 8). With other catalytic systems ($Pd(OAc)_2$/SPhos[25] or $Pd(CH_3CN)_2$/BDPB[26]) we still recovered a significant amount of starting material **16e**, the 6-aryl regioisomer **22g** and the di-substituted pyridazine **24g** (entries 9-10). 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 regioselectively (entry 11).

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

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

Scheme 4. Access to 3-aryl-4-alkylamino pyridazines 25a–c and 3,6-bis-aryl-4-alkylaminopyridazines 26a–c[a]



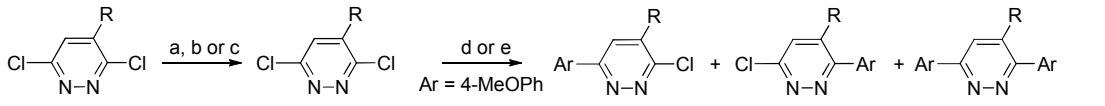
[a]Reagents and conditions: (a) Pd/C or $Pd(OH)_2$/C, MeOH, rt, 60 psi, 6–12 h; (b) $Pd(OAc)_2$ (2 mol%), XPhos (2.4 mol%), $ArB(OH)_2$ (1.5 equiv), $CsOH.H_2O$ (1.7 equiv), *n*-BuOH/H_2O (4:1), 50 °C, 1–12 h.

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-iminochloride 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** and **16f** was easily achieved with $(Boc)_2O$ in 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 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 mixture of DME:H_2O, we isolated the corresponding 6-substituted 4-amino pyridazines **28a** and **28b,** as the major compounds (>60%). Unfortunately, the presence of a significant amount of the di-adducts **30a** and **30b** (between 15 and 20% yield) was not satisfying, even if results are in good agreement with our mechanistic hypothesis.

Table 2. SMCC reactions starting from 4-NRBoc 27 and 4-alkoxy 31 pyridazine derivatives



16b R = NHMe
16f R = NHPMB
2 R = Cl

27a R = N(Me)Boc **97%**
27b R = N(PMB)Boc **98%**
31a R = OMe **94%**
31b R = OBn **70%**

28a R = N(Me)Boc **29a** R = N(Me)Boc **30a** R = N(Me)Boc
28b R= N(PMB)Boc **29b** R = N(PMB)Boc **30b** R = N(PMB)Boc
32a R = OMe **33a** R = OMe **34a** R = OMe
32b R = OBn **33b** R = OBn **34b** R = OBn

(a) Boc_2O, TEA, DMAP, THF, rt, 2 h; (b) NaOMe, dry MeOH, rt, 1 h; (c) BnOH, NaH, dry THF, 0 °C to rt, 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.

			Yields (%)[a, b]			
entry	R	Method	Starting material N° (%)	6-adduct N° (%)	3-adduct N° (%)	3,6-di adduct N° (%)
1	NMeBoc	2	**27a** (-)	**28a** (63)	**29a** (-)	**30a**(19)
2	NPMBBoc	2	**27b** (-)	**28b** (67)	**29b** (-)	**30b** (15)
3[c]	OMe	2	**31a** (30)	**32a** (45)	**33a** (15)	**34a** (10)
4[c]	OMe	6	**31a** (-)	**32a** (60)	**33a** (20)	**34a** (14)
5[c]	OBn	6	**31b** (-)	**32b** (50)	**33b** (11)	**34b** (15)

[a]yields refer to isolated, chromatographically, purified materials; [b]Unpublished products were fully characterized by NMR 1D & 2D and HR-MS data; [c]yields were determined by NMR using CH_2I_2 as internal standard

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 electronic effects of the amino function. The 4-OMe and 4-OBn pyridazine derivatives (**31a** and **31b** respectively) were synthesized following a previously reported method.[27] However, starting from **31a,** the SMCC reaction appeared to be favoured at position 6. Besides the 6-adduct **32a**, we observed a significant amount of the second regioisomeric pyridazine **33a** along with 14% of the bis-arylated product **34a** (entry 4). Even if 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 observed regioselectivity can be explained with 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]

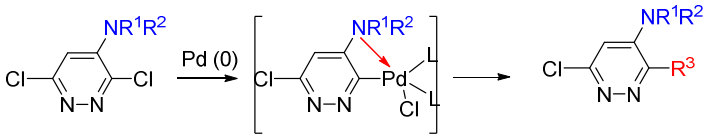
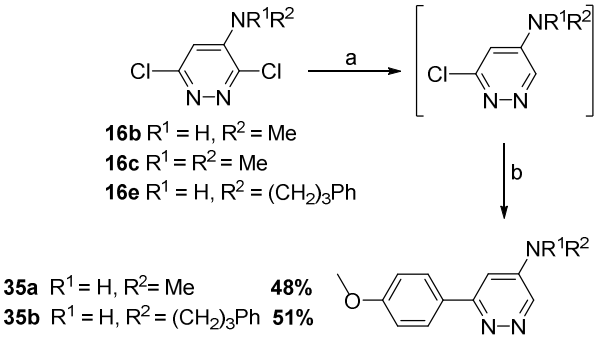


Figure 2: Suggested palladacycle for regioselective C-C bond formation.

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 presence of $Pd(OAc)_2$ and S-Phos. These conditions allowed access to the awaited 6-aryl 4-alkylaminopyridazines **35a–c** with a two steps cumulative yield ranging from 48% to 51%.

Scheme 5. Regioselective palladium-catalyzed hydrogenation: access to 6-arylpyridazin-4-amines 35a-c

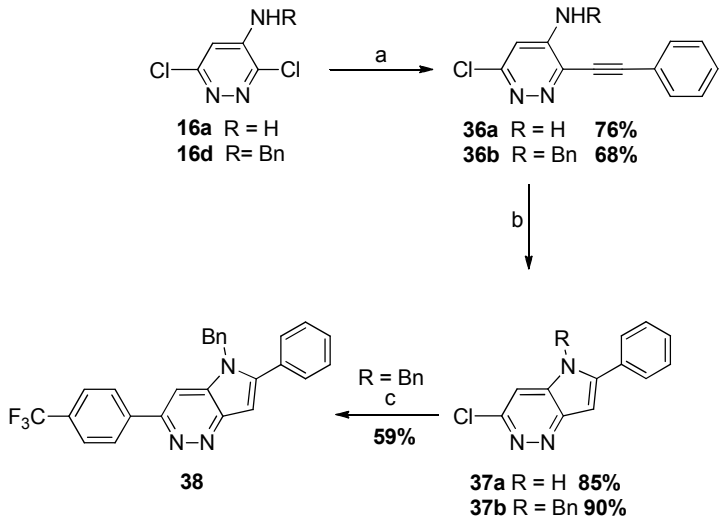


[a]reaction conditions: (a) $Pd(PPh_3)_4$ (4 mol%), HCO_2H (1 equiv), TEA (12 equiv), DMF, 100 °C, 45 min, µw; (b) $Pd(OAc)_2$ (2 mol%), SPhos (4 mol%), 4-MeOPhB$(OH)_2$ (1.5 equiv), K_2CO_3 (2.5 equiv), MeCN/H_2O (5:1), 115 °C, 12 h

We next paid attention to extend this regioselectivity to the Sonogashira reaction in order to access 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** and **16d** to afford the corresponding expected monosubstituted adducts **36a** and **36b**, respectively. Cyclisation of **36a** and **36b** was carried out in the presence of CuI to give the fused pyrrolo[3,2-*c*]pyridazines **37a** in 85% and **37b** in 90% yield.

Further SMCC on the iminochloride at position 6 provided pyrrolo[3,2-*c*]pyridazine **38** in 59% yield. These new 3-substituted bicyclic pyridazine scaffolds were not previously described in the literature.

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

CONCLUSION

In summary, we described here a general method to aminopyridazines starting from 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 (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, that could be extended to Sonogashira reaction with 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 scaffolds, as illustrated with 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 0.040-0.063mm). 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 MHz or 400 MHz and 101 MHz respectively, using deuterated chloroform ($CDCl_3$), methanol (MeOH-d_4) or dimethylsulfoxide (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 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, compounds **11** or **12**) in $POCl_3$ (2.5 mL) was heated at 110 °C for 5 h. After cooling at room temperature, the yellow solution was evaporated to dryness. The crude residue was diluted with DCM and washed twice with iced 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 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**, **16d**, **16e**, and **16f**).

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), 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 expected products **14**, **15**, **16d**, **16e** and **16f**.

Method C: General procedure for the S_NAr reaction using hindered amines (preparation of compounds **16g** and **16h**).

A microwave vial was charged with a solution of trichloropyridazine derivatives (1 equiv, 1 mmol, compound **9**) in *i*-PrOH (3.5 mL). The corresponding amine was added (3 equiv, 3 mmol), then the reaction mixture was capped properly and heated at 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 expected products **16g** and **16h**.

General Procedures for Pd(0) catalyzed Suzuki-Miyaura reaction:

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 4-alkylaminopyridazine derivatives (1 equiv, 1 mmol, compounds **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 mixture of DME:H_2O 3:1 (6.5 mL). The vial was capped properly, nitrogen flushed and heated under microwaves irradiation (110°C, 10 min) or conventional heating (110°C, 3 h). After cooling, the suspension was concentrated and the crude residue extracted with EtOAc twice. 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 expected products **23a**, **23b**, **23c**, **23d**, **23e**, **23f**, **28a** and **28b**.

Method E: General Suzuki-Miyaura procedure using $Pd(PPh_3)_4$ in toluene:EtOH:H_2O (preparation of compounds **17**, **19**, **20**, **23g-j**)[21d]

A microwave vial (oven-dried and under nitrogen) was charged with the corresponding 4-alkylaminopyridazine derivatives (1 equiv, 1 mmol, compounds **14**, **15**, **16d-e**, **16g-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 mixture of toluene:EtOH:H_2O 3:1:1 (12 mL). The vial was capped properly,

nitrogen flushed and heated at 100 °C for 3 h. After cooling, the suspension was concentrated and the crude residue extracted with EtOAc twice. 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 expected products **17**, **19**, **20**, **23g**, **23h**, **23i**, **23j**.

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 derivatives (1 equiv, 1 mmol, compounds **17**, **20**, **23d**, **23g** or **23h**), 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, nitrogen flushed and heated at 50 °C until complete conversion of the starting material. After cooling, the reaction mixture was concentrated and the crude residue was purified by chromatography on silica gel using EtOAc/heptane 50/50 to afford 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 to the Paar at pressure P = 60 psi for 12 h. The medium was then filtered over celite and the filtrate was evaporated to dryness to afford expected products **25a-c**.

Method H: Pd-catalyzed reductive dehalogenation with HCOOH (preparation of compound **35a-b**)

To a solution of corresponding 4-alkylaminopyridazine derivative (1 equiv, 1 mmol, compounds **16b** or **16e**) in dry DMF (7 mL), was added TEA (12 equiv, 12 mmol) and $Pd(PPh_3)_4$ (4 mol%). The vial was capped properly, degassed and 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 microwaves irradiation at 100 °C for 45 min. After cooling, 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 derivatives (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 mixture of CH_3CN:H_2O 5:1 (3.8 mL). The vial was capped properly, nitrogen flushed and heated at 115 °C for 12 h. After cooling, the reaction mixture was concentrated and the crude residue was purified by chromatography on silica gel using EtOAc/MeOH 80/20 to afford expected products **35a** and **35b**.

General Procedure for the protection of amines with *tert*-butyloxycarbonyl (Boc) group.

Method I: (preparation of compounds **27a** and **27b**).

To a solution of corresponding 4-alkylaminopyridazine derivative (1 equiv, 1 mmol, compounds **16b** or **16f**) 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, then, a solution of di-*tert*-butyldicarbonate (2.1 equi, 2.1 mmol) in dry THF (3 mL) was added dropwise. After additional 15 min of stirring, DMAP (4 mol%) was added and the reaction mixture was stirred 1 h at room temperature. The solvent was evaporated to dryness, the crude residue was diluted in water and extracted with EtOAc twice. 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 afford expected products **27a** and **27b**.

General Procedures for Pd(0) catalyzed Sonogashira reaction:

Method J: General Sonogashira procedure using $PdCl_2(PPh_3)_2$/CuI (preparation of compounds **37a** and **37b**)

A microwave vial (oven-dried and under nitrogen) was charged with the corresponding 4-alkylaminopyridazine derivatives (1 equiv, 1 mmol, compounds **16a** or **16d**), TEA (5 equiv, 5 mmol), $PdCl_2(PPh_3)_2$ (3 mol%) and CuI (6 mol%). After adding CH_3CN (6.3 mL), the vial was capped properly and the reaction mixture degassed. Phenylacetylene (1.05 equiv, 1.05 mmol) was added after 10 min stirring at room temperature. The reaction mixture was heated at 60 °C for 5 h. After cooling, the suspension was concentrated and the crude residue extracted with EtOAc twice. 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 afford 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; ^{1}H 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%): ^{1}H 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 (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 then cooled at 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; ^{1}H 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 microwaves 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; ^{1}H 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 microwaves 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; ^{1}H 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 ammonia 30% water (27 equiv, 11.6 mL) in dioxane (10 mL) was heated at 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; ^{1}H 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 methylamine solution 40% water (36 equiv, 3.4 mL) in dioxane (3 mL) was stirred at rt 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; ^{1}H 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 dimethylamine solution 40% 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; ^{1}H 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 microwaves 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) microwaves 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 microwaves 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; ^1H 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; ^1H 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; ^1H 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; ^1H 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; ^1H 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; ^1H 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; ^1H 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; ^1H 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 microwaves irradiation, **23a** was obtained as a yellow oil (58 mg, 0.28 mmol, 78%): IR (neat cm^{-1}) 3060, 2918, 1641, 1563, 752; ^1H 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; ^1H 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 microwaves 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 microwaves 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; ^1H 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; ^1H 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; ^1H 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; ^1H 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 %w), **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; ^1H 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 %w), **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; ^1H 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 %w), **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; ^1H 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, 0.91 mmol, 98%): IR (neat cm^{-1}) 2979, 2934, 1717, 1560, 1513, 1395, 1369, 1248, 1157, 1070, 847; ^{1}H 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; ^{1}H 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; ^{1}H 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, then, evaporated to dryness. The crude residue was diluted in water and extracted with

EtOAc twice. 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 flamed-dried two-neck round bottom flask containing Na_2SO_4, was dissolved benzylic alcohol (60 µL, 0.60 mmol) in dry THF (5 mL). When the solution reach 0 °C, NaH (16 mg, 0.65 mmol) was added by portion 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 with EtOAc twice. 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; ^{1}H 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 colorless oil (68 mg, 0.21 mmol, 68%): IR (neat cm^{-1}) 3239, 3062, 2207, 1565, 1490, 1275, 1132, 689; ^{1}H 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 at 130 °C 12 h. After cooling, the reaction mixture was diluted in water-iced and filtered under reduce 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; ^{1}H 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 at 130 °C 12 h. After cooling, the reaction mixture was diluted in water-iced and filtered under reduce 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; ^{1}H 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; ^{1}H 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.

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

We declare no competing financial interest.

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