Synthesis of Substituted 3-Amino-6-arylpyridazines via Suzuki Reaction

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Abstract: Starting from the commercially available 3,6-dichloropyridazine, N_3-substituted 3-amino-6-arylpyridazines were prepared in good yields and under mild conditions by means of two simple steps: a nucleophilic substitution and a palladium-catalyzed Suzuki coupling.

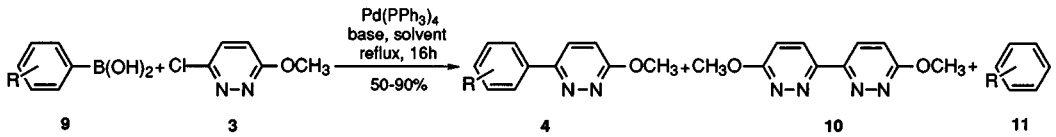
Key words: N_3-substituted 3-amino-6-arylpyridazine, dichloropyridazine, 3-chloro-6-methoxypyridazine, 3-amino-6-chloropyridazine, Suzuki cross-coupling, palladium(0) catalysis.

We have recently reported the synthesis of a series of 3-amino-6-aryl pyridazines derivatives **1** which show acetylcholinesterase inhibiting activities.[1,2] The conventional synthesis of such compounds[3] does not allow a rapid access to various structural analogs, so we became interested in developing a new synthetic pathway involving palladium-catalyzed cross-coupling reactions with organoboranes. The palladium-catalyzed cross-coupling reaction of arylboronic acids with aryl halides is known to give biaryls.[4–7] When using aryl bromides and iodides as electrophiles, high yields have been achieved with substrates bearing various functional groups on either coupling partner.[4,5,7,8] However, much higher energy is required for the oxidative insertion of palladium catalysts into the C–Cl bond of aryl chlorides,[4–9] and transformations of these substrates still remain a significant challenge in synthesis.[10] Therefore the use of aryl chlorides in palladium coupling reactions has been limited to *activated* chloroarenes such as chloropyridines and chlorotriazines[11–14] and chloroarenes bearing an electron-withdrawing group.[6,15] Extension of the palladium-catalyzed coupling to pyridazines has mostly been limited to the coupling of alkynes.[16–18] In general, 3-chloropyridazines have been employed as substrates in these reactions and the harsh working conditions have often resulted in unacceptably low yields. The only example of a cross-coupling reaction of arylboronic acid with 3-chloro-6-methoxypyridazine, using the original conditions described by Suzuki et al.[5] has been reported by Quéguiner et al.[19] In the present article, we report on the synthetic application of the Suzuki reaction to 3-chloro-6-methoxypyridazine and to N_3-substituted 3-amino-6-chloropyridazines examining the scope and the various conditions of the reaction.

In order to study the *feasibility* of the Suzuki reaction in the pyridazine series, we examined the coupling reaction of variously substituted phenylboronic acids with 3-chloro-6-methoxypyridazine **3** (Scheme 1). One example of this reaction was described by Quéguiner et al.[19] Our results are summarized in Table 1. Both the palladium complex and a base are essential for the reaction to proceed. This is in accordance with the observations of Suzuki et al. who report regularly that the addition of a base greatly facilitates the cross-coupling of organoboron reagents with electrophiles by acceleration of the rate of the transmetallation step.[4]

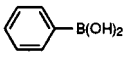
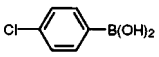
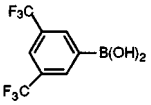
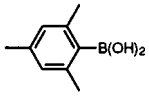
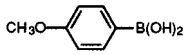
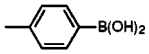
In exploratory experiments we compared the Suzuki coupling using 3-iodo-6-methoxypyridazine to that using 3-chloro-6-methoxypyridazine. As the yields were found to be of the same order of magnitude for both halides, we used subsequently only chloro-substituted pyridazines. For the phenylboronic acids investigated (Table 1), the original procedure of Suzuki[5] using $(Ph_3P)_4Pd$ and 2 M aqueous Na_2CO_3 in toluene at 110 °C, was found to give the expected products **4** in 50–90% yields. Sometimes addition of a small amount of EtOH was effective in facilitating the solubility of pyridazine and phenylboronic acids. Generally some homocoupling occurred, yielding about 5% of **10**, competitive hydrolytic deboronation to form **11** could also take place if the arylboronic acid bears electron-attracting substituents (Scheme 1).

Other working conditions, such as the use of aqueous $Ba(OH)_2$ in DME, which were claimed to accelerate the coupling rate,[20] were less favorable when applied to phenylboronic acid itself, leading only to 50% yield of the desired product, besides the unreacted 3-chloro-6-methoxypyridazine **3** (26%) and the homocoupling product **10** (24%). On the other hand, the coupling of phenylboronic acid with 3-chloro-6-methoxypyridazine (**3**) under phase



Scheme 1

Table 1 Reaction Conditions for the Pd(0)-Catalyzed Cross-Coupling of 3-Chloro-6-methoxypyridazine (**3**) with Phenylboronic Acids

Product	$ArB(OH)_2$	Reaction Conditions[a]		Yield[b] (%)
		Base	Solvent	
4a		Na_2CO_3	toluene/ EtOH	80
		Na_2CO_3	toluene	86
		$Ba(OH)_2$	DME	50
		–[c]	–[c]	55
4b		Na_2CO_3	toluene/ EtOH	60
		Na_2CO_3	toluene	60
4c		Na_2CO_3	toluene/ EtOH	55
4d		Na_2CO_3	toluene/ EtOH	60
4e		Na_2CO_3	toluene/ EtOH	81
4f		Na_2CO_3	toluene	90

[a] Catalyst: $(Ph_3P)_4Pd$.
[b] Yield of isolated pure product.
[c] Under phase transfer catalysis conditions (see text).

transfer catalysis conditions yielded only 55% of the corresponding 3-methoxy-6-phenylpyridazine accompanied by traces of the pyridazine dimer. The synthesis of the arylpyridazines **4b**, **4c**, and **4d** implies the use of arylboronic acids either substituted with electron-withdrawing groups or bearing sterically hindering substituents in ortho or ortho'-position, both factors limiting the yields owing to competitive hydrolytic deboration or to steric hindrance. Here again the use of a stronger base [$Ba(OH)_2$] did not improve the yields.

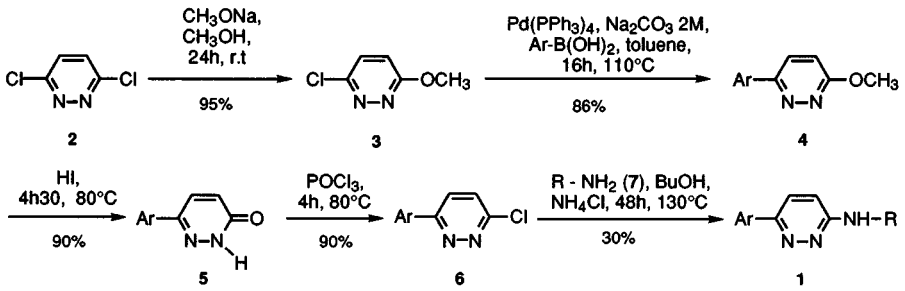
When the reaction was applied to *m*-*N*-acetylamidophenylboronic acid (**9**, R = NHAc) the conventional coupling conditions produced an appreciable amount of the deboronated acetanilide **11** (R = NHAc). Surprisingly, conducting the same cross-coupling reaction in the presence of anhydrous K_3PO_4 in DMF at 100 °C leads to the pyridazinic dimer **10** in 80% yield.

The transformation of the obtained 6-aryl-3-methoxypyridazines **4** into the corresponding 6-aryl-3-aminated analogues **1** is possible but somewhat lengthy. This involves the cleavage of the methoxy ether by means of hydroiodic acid in order to return to the pyridazones **5**, the action of phosphorus oxychloride to yield the iminochlorides **6** and their nucleophilic substitution with the appropriate amino side chain, thus furnishing the expected N_3-substituted 3-amino-6-arylpyridazines **1** (Scheme 2).

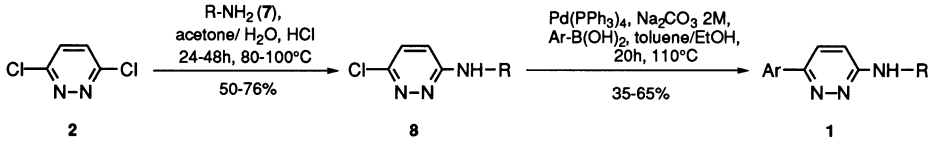
For this reason, in second part of our study, we examined the applicability of the Suzuki reaction directly to the already amino-substituted chloropyridazines **8** (Scheme 3). This alternative approach would allow a faster and simple two-step access to the unsymmetrical 3,6-disubstituted pyridazines **1**. The synthesis begins with a nucleophilic monosubstitution of 3,6-dichloropyridazine **2** by an aminoalkyl chain affording the 3-amino-6-chloropyridazine **8** in 50–76% yield. Then the palladium-catalyzed cross-coupling reaction was performed with various phenylboronic acid using tetrakis(triphenylphosphine)palladium(0) and an aqueous base such as aqueous 2 M Na_2CO_3 in toluene at 110 °C for 20h (Method A) as described by Suzuki.[5] The expected 3-amino-6-arylpyridazines **1** were obtained in 35–65% yields (Table 2). The above coupling conditions were unsuccessful in the case of sterically hindered reactants such as mesitylboronic acid and necessitated the use of aqueous $Ba(OH)_2$ in DME (Method B).

In conclusion, a variety of 3-amino-6-arylpyridazines **1** have been efficiently prepared by palladium-catalyzed cross-coupling reactions. The advantages of this methodology reside in increased chemical yields, easy operating conditions, the commercial availability of the arylboronic acids and 3,6-dichloropyridazine and in shorter synthetic sequence.

All experiments were carried out under an argon atmosphere. Toluene, DME, THF were distilled from benzophenone ketyl. $(Ph_3P)_4Pd$, 3,6-dichloropyridazine and arylboronic acids were purchased from Lancaster. Melting points were determined with a Mettler FP62 apparatus and are uncorrected. All ^1H NMR spectra were recorded on a Bruker AC 200 (200 MHz) or on a Bruker AC 300



Scheme 2



Scheme 3

(300MHz) instruments, and chemical shifts are reported in parts per million (δ) relative to TMS for $CDCl_3$ and DMS*O*-d_6 solutions. Flash chromatography was carried out on silica gel (70–230 mesh ASTM). Elemental analyses were performed by CNRS (Vernaison) and are indicated only by the symbols of the elements; analytical results were within 0.4% of the theoretical values. Organic extracts were dried over Na_2SO_4.

3-Chloro-6-methoxypyridazine (**3**) was prepared by the literature procedure;[21]

mp 92 °C (Lit.[22] mp 91–92 °C).

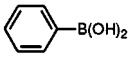
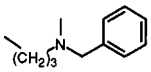
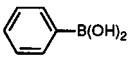
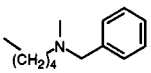
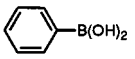
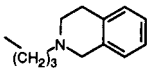
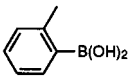
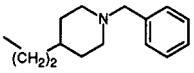
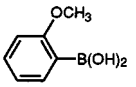
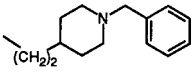
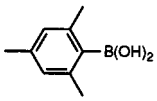
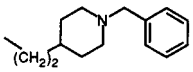
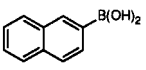
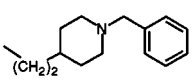
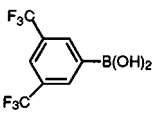
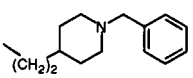
The amines **7** were prepared by literature procedures.

3-Benzyl-3-methylaminopropylamine (7a)[2,24,25]
Yellow oil; yield:75%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63 (quint., 2 H, *J* = 10.4 Hz), 2.18 (s, 3 H), 2.28 (br s, 2 H), 2.43 (t, 2 H, *J* = 10.4 Hz), 2.72 (m, 2 H), 3.46 (s, 2 H), 7.29 (m, 5 H).

4-Benzyl-4-methylaminobutylamine (7b)[2,26]
Yellow oil; yield:75%.

Table 2 Pd(0)-Catalyzed Cross-Coupling of 3-Alkyl-6-chloroaminopyridazines **8** with Phenylboronic Acids

Product	$ArB(OH)_2$[a]	R	Reaction Conditions[b]	Yield[c] (%)	Mp[d] (°C)
1a			A	66	159
1b			A	45	45
1c			A	40	195
1d			A	35	95
1e			A	45	128
1f			A B	0 65	dec.
1g			A	60	205
1h			A	50	220

[a] Catalyst: $(Ph_3P)_4Pd$.
[b] A: $(Ph_3P)_4Pd$, Na_2CO_3 2M, $ArB(OH)_2$, toluene, 20h, 110 °C; B:$(Ph_3P)_4Pd$, $Ba(OH)_2$, $8H_2O$, $ArB(OH)_2$, DME, 20h, 110 °C.
[c] Yield of isolated pure product.
[d] All melting points refer to hydrochlorides.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63 (quint, 2 H, *J* = 10.4 Hz), 2.18 (s, 3 H), 2.28 (br s, 2 H), 2.43 (t, 2 H, *J* = 10.4 Hz), 2.72 (m, 2 H), 3.46 (s, 2 H), 7.29 (m, 5 H).

3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propylamine (7c)[2,27]
Colourless oil; yield:85%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60–1.79 (m, 4 H), 2.57 (m, 2 H), 2.70–2.82 (m, 4 H), 2.90 (t, 2 H, *J* = 5.3 Hz), 3.63 (s, 2 H), 6.98–7.10 (m, 4 H).

2-(1-Benzylpiperidin-4-yl)ethylamine (7d)[2,28–32]
Yield: 53%; mp (dihydrochloride) 137 °C (Lit.[2,28–32] mp 175–178 °C).

^{1}H NMR (200 MHz, $CDCl_3$) : δ = 1.18–1.45 (m, 5 H), 1.59-1.64 (m, 2 H), 1.85–1.96 (m, 2 H), 2.18 (br s, 2 H), 2.63–2.71 (m, 2 H), 2.80–2.86 (m, 2 H), 3.44 (s, 2 H), 7.18–7.29 (m, 5 H).

3-Methoxy-6-phenylpyridazines 4; General Procedure
Argon was passed for 30 mn through a suspension of **3** (500 mg, 3.46 mmol, 1 equiv), arylboronic acid (1.15 equiv), aq 2 M Na_2CO_3 solution (3.7mL, 7.33mmol, 2.12 equiv), toluene (20mL) and a small amount of EtOH in order to ensure an homogenous reaction medium. $(Ph_3P)_4Pd$ (123 mg, 0.11 mmol, 0.031 equiv) was added and the mixture was heated at 110 °C for at least 16 h. The toluene was removed in vacuo and the residue was diluted with H_2O and extracted with EtOAc (3x5 mL). The organic layer was washed with H_2O (3x5 mL) and concentrated in vacuo to give a residue which was purified by column chromatography (silica gel, CH_2Cl_2 / EtOAc, 95:5).

3-Methoxy-6-(4-chlorophenyl)pyridazine (4b)
Mp 151 °C.

^{1}H NMR (DMS*O*-d_6, 200 MHz): δ = 4.07 (s, 3 H), 7.33 (d, 1 H, *J* = 9.5 Hz), 7.59 (m, 2 H), 8.09 (m, 2 H), 8.19 (d, 1 H, *J* = 9 Hz).

Anal. calc. for $C_{11}H_9ClN_2O$: C, 59.87; H, 4.11; N, 12.69. Found: C, 59.76; H, 4.28; N, 12.43.

3-Methoxy-6-(3,5-ditrifluoromethylphenyl)pyridazine (4c)
Mp 97 °C.

^{1}H NMR (DMS*O*-d_6, 200 MHz): δ = 4.10 (s, 3 H), 7.43 (d, 1 H, *J* = 9.5 Hz), 8.24 (s, 1 H), 8.50 (d, 1 H, *J* = 9.5 Hz), 8.74 (s, 2 H).

Anal. calc. for $C_{13}H_8F_6N_2O$: C, 48.46; H, 2.50; N, 8.69. Found: C, 48.69; H, 2.72; N, 8.50.

3-Methoxy-6-(2,4,6-trimethylphenyl)pyridazine (4d)
Mp 201 °C.

^{1}H NMR (DMS*O*-d_6, 200 MHz): δ = 1.93 (s, 6 H), 2.28 (s, 3 H), 4.06 (s, 3 H), 6.96 (s, 2 H), 7.28 (d, 1 H, *J* = 9 Hz), 7.54 (d, 1 H, *J* = 9 Hz).

Anal. calc. for $C_{14}H_{16}N_2O$•HCl•0.25H_2O: C, 62.45; H, 6.55; N, 10.40. Found: C, 62.28; H, 6.59; N, 10.13.

3-Methoxy-6-(4-methoxyphenyl)pyridazine (4e)
Mp 134 °C.

^{1}H NMR (DMS*O*-d_6, 200 MHz): δ = 3.81 (s, 3 H), 4.04 (s, 3 H), 7.06 (m, 2 H), 7.25 (d, 1 H, *J* = 9.5 Hz), 8.01 (m, 2 H), 8.09 (d, 1 H, *J* = 9.5 Hz).

Anal. calc. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.59; H, 5.64; N, 12.90.

3-Methoxy-6-(4-methylphenyl)pyridazine (4f)
Mp 109.5 °C.

^{1}H NMR (DMS*O*-d_6, 200 MHz): δ = 2.36 (s, 3 H), 4.06 (s, 3 H), 7.30 (m, 3 H), 7.95 (m, 2 H), 8.12 (d, 1 H, *J* = 6 Hz).

Anal. calc. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.07; H, 6.17; N, 13.64.

3-Methoxy-6-(3-*N*-acetylphenyl)pyridazine (4g)
^{1}H NMR (DMS*O*-d_6, 200 MHz): δ = 2.06 (s, 3 H), 4.07 (s, 3 H), 7.31 (d, 1 H, *J* = 9.5 Hz), 7.60 (m, 4 H), 8.06 (d, 1 H, *J* = 9 Hz).

3,6-di-(4-methoxyphenyl)pyridazine (10)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.19 (s, 6 H), 7.11 (d, 2 H, *J* = 9.42 Hz), 8.60 (d, 2 H, *J* = 9.42 Hz).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 55.17, 118.28, 127.48, 152.65, 165.59.

Anal. calc. for $C_{10}H_{10}N_2O_4$: C, 55.03; H, 4.62; N, 25.67. Found: C, 54.98; H, 4.78; N, 25.46.

3-Alkylamino-6-chloropyridazines 8; General Procedure
To 3,6-dichloropyridazine (**2**; 500 mg, 3.36 mmol, 1 equiv) in a 50 mL two-necked flask equipped with a magnetic stirrer were added amine **7** (3 equiv), H_2O (1.7 mL) and then 37% HCl (0.07 mL) through the neck of the flask. The mixture was stirred between 80 and 100 °C for 24 to 48 h. The reaction was allowed to cool to r.t. and the solvent was removed in vacuo. The residue was diluted with H_2O, brought to pH 11 with alkali and extracted with EtOAc (3x15 mL). The organic phase was concentrated and the crude product was purified by chromatography on silica gel eluting with a 9:1:2 (v/v) mixture of EtOAc/MeOH/Et_3N.

3-[(3-Benzyl-3-methylamino)propylamino]-6-chloropyridazine (8a)
Reaction conditions:95–100 °C, 24 h; yield:50%.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.82 (m, 2 H), 2.25 (s, 3 H), 2.54 (t, 2 H, *J* = 6.2 Hz), 3.50 (m, 4 H), 6.07 (s, 1 H), 6.47 (d, 1 H, *J* = 9.5 Hz), 7.09 (d, 1 H, *J* = 9 Hz), 7.29 (m, 5 H).

3-[(4-Bbenzyl-4-methylamino)butylamino]-6-chloropyridazine (8b)
Reaction conditions:95–100 °C, 72 h; yield:76%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.67 (m, 4 H), 2.21 (s, 3 H), 2.45 (t, 2 H, *J* = 36 Hz), 3.45 (m, 4 H), 6.08 (s, 1 H), 6.48 (d, 1 H, *J* = 14 Hz), 7.10 (d, 1 H, *J* = 14 Hz), 7.31 (m, 5 H).

6-Chloro-3-[3-(1,2,3,4-tetrahydroisoquinolin-2-yl)propylamino]pyridazine (8c)
Reaction conditions:95–100 °C, 48 h; yield:50%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.93 (m, 2 H), 2.72 (t, 2 H, *J* = 6.99 Hz), 2.80 (t, 2 H, *J* = 6.33 Hz), 2.95 (t, 2 H, *J* = 7.26 Hz), 3.57 (m, 2 H), 3.67 (s, 2 H), 6.28 (s, 1 H), 6.44 (d, 1 H, *J* = 9.4 Hz), 7.04 (m, 2 H), 7.15 (m, 3 H).

3-[(2-Benzylpiperidin-4-yl)ethylamino]-6-chloropyridazine (8d)
Reaction conditions:95–100 °C, 24 h; yield:72%.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.32 (m, 3 H), 1.65 (m, 4 H), 1.96 (t, 2 H, *J* = 7.5 Hz), 2.89 (d, 2 H, *J* = 12 Hz), 3.42 (m, 4 H), 4.73 (s, 1 H), 6.61 (d, 1 H, *J* = 9.5 Hz), 7.16 (d, 1 H, *J* = 9.5 Hz), 7.29 (m, 5 H).

3-Alkylamino-6-phenylpyridazines 1a–e,g,h; General Procedure
Method A: Argon was passed through a suspension of **8** (3.46 mmol, 1 equiv), arylboronic acid (3.98 mmol, 1.15 equiv), aq 2 M Na_2CO_3 solution (3.7 mL, 7.34 mmol, 2.12 equiv), toluene (20 mL) and if necessary EtOH (to facilitate the solubility of pyridazine and the phenylboronic acid used) for 30 min. $(Ph_3P)_4Pd$ (0.10 mmol, 0.031 equiv) was added and the mixture was heated at 110 °C for 24 h. The toluene was removed in vacuo, the residue diluted with H_2O and extracted with EtOAc (3x5 mL). The organic layer was washed with H_2O (3x5 mL) and concentrated in vacuo. The crude product was purified by chromatography on silica gel using a 9:1:2 (v/v) mixture of EtOAc/MeOH/Et_3N. The corresponding hydrochlorides were prepared by treating the free base dissolved in Et_2O and/or

EtOAc with gaseous HCl or with 2.1 equiv of 37% HCl. The collected solids were recrystallized from *i*-PrOH/Et_2O.

3-[(3-Benzyl-3-methylamino)propylamino]-6-phenylpyridazine (1a)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.87 (m, 2 H), 2.26 (s, 3 H), 2.55 (t, 2 H, *J* = 15.8 Hz), 3.53 (m, 4 H), 5.89 (s, 1 H), 6.59 (d, 1 H, *J* = 14 Hz), 7.42 (m, 9 H), 7.99 (d, 2 H, *J* = 13.5 Hz).

1a•2HCl; mp 159 °C (*i*-PrOH).

Anal. calc. for $C_{21}H_{24}N_4$•2 HCl•0.5 H_2O: C, 60.87; H, 6.57; N, 13.52. Found: C, 60.96; H, 6.61; N, 13.46.

3-[(4-Benzyl-4-methylamino)butylamino]-6-phenylpyridazine (1b)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.70 (m, 4 H), 2.21 (s, 3 H), 2.44 (t, 2 H, *J* = 10.5 Hz), 3.47 (m, 4 H), 5.40 (s, 1 H), 6.60 (d, 1 H, *J* = 14 Hz), 7.47 (m, 9 H), 7.98 (d, 2 H, *J* = 9.8 Hz).

1b•2 HCl; mp 45 °C (*i*-PrOH).

Anal. calc. for $C_{22}H_{26}N_4$•2 HCl•H_2O): C, 60.41; H, 6.91; N, 12.81. Found: C, 60.10; H, 6.63; N, 12.54.

3-[3-(1,2,3,4-tetrahydroisoquinolin-2-yl)propylamino]-6-phenylpyridazine (1c)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.95 (m, 2 H), 2.75 (m, 4 H), 2.93 (m, 2 H), 3.54 (m, 1 H), 3.65 (m, 3 H), 6.22 (s, 1 H), 6.51 (m, 1 H), 6.61 (d, 1 H, *J* = 9 Hz), 7.09 (m, 4 H), 7.46 (m, 3 H), 7.97 (d, 2 H, *J* = 12 Hz).

1c•2 HCl; mp 195 °C (*i*-PrOH).

Anal. calc. for $C_{22}H_{24}N_4$•2 HCl•2 H_2O: C, 58.27; H, 6.27; N, 12.36. Found: C, 58.12; H, 6.27; N, 13.23.

3-[2-(1-Benzylpiperidin-4-yl)ethylamino]-6-(2-methylphenyl)pyridazine (1d)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.30 (m, 3 H), 1.69 (m, 4 H), 1.98 (t, 2 H, *J* = 9 Hz), 2.41 (s, 3 H), 2.91 (d, 2 H, *J* = 11 Hz), 3.50 (m, 4 H), 4.73 (s, 1 H), 6.69 (d, 1 H, *J* = 9 Hz), 7.40 (m, 9 H).

1d•2 HCl; mp 95 °C (*i*-PrOH).

Anal. calc for $C_{25}H_{30}N_4$•2 HCl•H_2O: C, 62.88; H, 7.18; N, 11.74. Found: C, 62.44; H, 7.58; N, 11.18.

3-[2-(1-Benzylpiperidin-4-yl)ethylamino]-6-(2-methoxyphenyl)pyridazine (1e)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.30 (m, 3 H), 1.67 (m, 4 H), 1.97 (t, 2 H, *J* = 8 Hz), 2.91 (d, 2 H, *J* = 12 Hz), 3.45 (m, 4 H), 3.86 (s, 3 H), 4.72 (s, 1 H), 6.64 (d, 1 H, *J* = 9 Hz), 7.00 (d, 1 H, *J* = 6 Hz), 7.09 (t, 1 H, *J* = 10 Hz), 7.31 (m, 6 H), 7.8 (d, 1 H, *J* = 9 Hz), 7.89 (d, 1 H, *J* = 6 Hz).

1e•2 HCl; mp 128 °C (*i*-PrOH).

Anal. calc. for $C_{25}H_{30}N_4O$•2 HCl•3 H_2O: C, 56.70; H, 7.23; N, 10.58. Found: C, 57.36; H, 7.04; N, 10.59.

3-[2-(1-Benzylpiperidin-4-yl)ethylamino]-6-(2-naphthyl)pyridazine (1g)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.27 (m, 3 H), 1.67 (m, 4 H), 2.01 (t, 2 H, *J* = 11.3 Hz), 2.92 (d, 2 H, *J* = 11.3 Hz), 3.53 (m, 4 H), 4.72 (s, 1 H), 6.74 (d, 1 H, *J* = 9.5 Hz), 7.31 (m, 5 H), 7.51 (m, 2 H), 7.77 (d, 1 H, *J* = 9.5 Hz), 7.92 (m, 3 H), 8.23 (d, 1 H, *J* = 8.6 Hz), 8.39 (s,1 H).

1g•2 HCl; mp 205 °C (*i*-PrOH).

Anal. calc. for $C_{25}H_{26}N_4$•2 HCl•1.25 H_2O: C, 62.24; H, 6.48; N, 11.60. Found: C, 62.43; H, 6.51; N, 11.15.

3-[2-(1-Benzylpiperidin-4-yl)ethylamino]-6-(3,5-ditrifluoromethylphenyl)pyridazine (1h)
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.30 (m, 3 H), 1.67 (m, 4 H), 1.70 (t, 2 H, *J* = 7.9 Hz), 2.89 (d, 2 H, *J* = 11 Hz), 3.48 (m, 4 H), 5.45 (s, 1 H), 6.77 (d, 1 H, *J* = 9.5 Hz), 7.30 (m, 5 H), 7.62 (d, 1 H, *J* = 9.5 Hz), 7.88 (s, 1 H), 8.46 (s, 2 H).

1h•2 HCl; mp 220 °C (*i*-PrOH).

Anal. calc. for $C_{26}H_{26}N_4F_6$•2 HCl: C, 53.71; H, 4.85; N, 9.64. Found: C, 53.83; H, 5.04; N, 9.43.

3-[2-(1-Benzylpiperidin-4-yl)ethylamino]-6-(2,4,6-trimethylphenyl)pyridazine (1f)
Method B: The procedure is almost same as Method A except for the solvent and base used. To a degassed and repeatedly flushed with Ar mixture of **8** (3.46 mmol, 1 equiv), arylboronic acid (3.98 mmol, 1.15 equiv) in DME (20 mL), was added $Ba(OH)_2$•8 H_2O(1.15 equiv) and the system was degassed again. Then $(Ph_3P)_4Pd$ (0.10 mmol, 0.031 equiv) was added and after heating at 110 °C for 24 h, the resulting mixture and the corresponding hydrochloride were worked up as described in Method A.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.40 (m, 3 H), 1.70 (m, 4 H), 2.01 (m, 8 H), 2.34 (s, 3 H), 2.92 (d, 2 H, *J* = 11 Hz), 3.47 (m, 4 H), 4.75 (s, 1 H), 6.69 (d, 1 H, *J* = 9 Hz), 6.95 (s, 2 H), 7.09 (d, 1 H, *J* = 9 Hz), 7.33 (m, 7 H).

1f•2 HCl (*i*-PrOH); mp could not be determined due to decomposition.

Anal. calc. for $C_{27}H_{34}N_4$•2 HCl•1.5 H_2O: C, 63.02; H, 7.64; N, 10.89. Found: C, 62.77; H, 7.59; N, 10.71.

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