Tetrahedron 66 (2010) 9552–9559

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Cross-coupling reaction on *N*-(3,5-dibromo-2-pyridyl)piperazines: regioselective synthesis of 3,5-disubstituted pyridylpiperazines

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ARTICLE INFO

Article history:
Received 15 September 2010
Received in revised form 28 September 2010
Accepted 28 September 2010
Available online 26 October 2010

Keywords:
Regioselectivity
Cross-coupling
Medicinal chemistry
Palladium
C–C coupling

ABSTRACT

Unsymmetrical 3,5-disubstituted pyridylpiperazines were prepared from tribromopyridine in three coupling reactions. Key to the success of the syntheses is the palladium-catalyzed regioselective cross-coupling reaction in the 3-position of *N*-(3,5-dibromo-2-pyridyl)piperazines.

1. Introduction

Pyridylpiperazines and their analogues are key units in a wide range of relevant pharmacophores with a broad spectrum of activity. For example, selective dopaminergic D4 agonist (ABT-724, **A**),[1] TRPV1 antagonist (**B**),[2] HIV-1 reverse transcriptase inhibitor (**C**),[3] PDE10 inhibitor (**D**),[4] PI3 kinase inhibitor (**E**),[5] histamine H3 receptor modulator (**F**),[6] CXCR antagonist (**G**),[7] capsaicin receptor modulator (**H**),[8] and IMPDH inhibitor (**I**)[9] have been reported (Fig. 1). The number of available substituted pyridylpiperazines remains limited, due to a lack of efficient methodologies for introduction of diversity on the pyridine ring. Palladium-catalyzed cross-coupling provides a powerful methodology for the formation of carbon–carbon and carbon–nitrogen bonds. Regioselective cross-coupling of multiple halogenated pyridines is one of the most important methods for the formation of substituted pyridines.[10] For example, 2,3- or 2,5-dihalopyridines are the prototypical pyridines used to achieve regioselective cross-coupling.

In a recent study, 2,6- or 3,5-dihalopyridines were examined with regard to regioselective Suzuki cross-coupling reactions, which were achieved using a directing group, such as an amide, a pyridinium aminide or a methylamine.[11] However, in the case of *N*-(3,5-dibromo-2-pyridyl)piperazines, the reaction has not yet

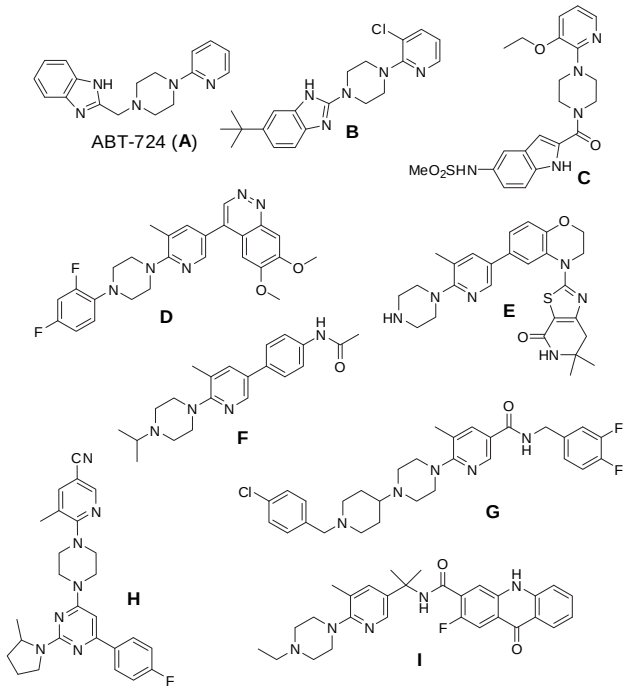

Fig. 1. Pyridylpiperazines with important pharmacological activity.

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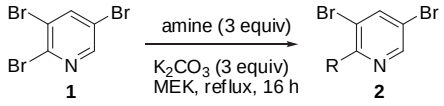
doi:10.1016/j.tet.2010.09.100

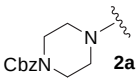
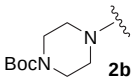
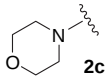
been reported. Herein, we report a methodology for efficient synthesis of unsymmetrical 3,5-disubstituted pyridylpiperazines by three consecutive coupling reactions.

2. Results and discussion

Commercially available 2,3,5-tribromopyridine **1** gave 2-substitution products **2** with complete regiocontrol by S_NAr[12] (Table 1).

Table 1
Preparation of 2-amino-3,5-dibromopyridines **2**

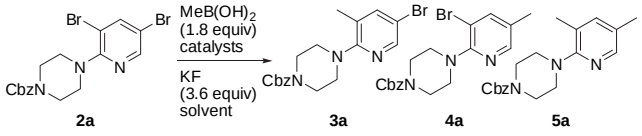


Entry	R	Yield (%)	Entry	R	Yield (%)
1	 **2a**	85	3	 **2b**	90
2	 **2c**	86	4[a]	 **2d**	quant

[a] Amine (1.2 equiv), K_2CO_3 (3 equiv), DMF, 120 °C, 5 h.

We investigated the Suzuki reactions of *N*-(3,5-dibromo-2-pyridyl)piperazine **2a**, because the Suzuki reaction is one of the most efficient methods for the construction of biaryl or substituted aromatic moieties; compounds that contain these substructures constitute numerous biologically active pharmaceuticals. The key advantages of the Suzuki reaction are the mild conditions under, which it is conducted, its high tolerance toward functional groups, and the commercial availability and stability of boronic acids. Table 2 illustrates the effects of the catalyst and solvent on the regioselective reaction of **2a** with methylboronic acid. With regard to the catalyst, the use of bulky electron-rich biaryl ligands[13] or tricyclohexylphosphine resulted in the formation of disubstituted product **5a** (entries 1–3). Using $Pd(PPh_3)_4$ or $Pd(OAc)_2$/BINAP, the reaction proceeded slowly to give the regioselective cross-coupling product **3a** along with **5a** (entries 4 and 5). Switching the catalyst to $PdCl_2$(dppf) afforded the desired product **3a** in 60% yield along with **5a** in 12% yield (entry 6). Furthermore, this reaction proceeded even at room temperature to give the desired product **3a** in 71% yield along with **5a** in 7% yield after 24 h (entry 7). It is very easy to separate the desired product **3a** and disubstituted product **5a** by column chromatography, but it is difficult to separate **3a** and corresponding isomeric product **4a** (R_f value: **3a**=0.52, **4a**=0.45, **5a**=0.35 hexane/AcOEt=4:1). Therefore, the selectivity between desired product and isomer is the most important for the synthesis unsymmetrical 3,5-disubstituted pyridylpiperazines. With regard to the solvent, the use of MeOH or toluene instead of THF afforded the desired product **3a** (entries 8 and 9). However, the use of DMF resulted in no reaction (entry 10). In all cases, the corresponding isomeric product **4a** was not obtained.

Table 2
Effects of catalyst and solvent on regioselective reaction of **2a**



Entry	Catalysts	Solvent	Temp (°C)	Time (h)	Yield (%)		
					3a	**5a**	Recov. of **2a**
1[a]	$Pd(OAc)_2$ S-Phos	THF	Reflux	2		28	54
2[a]	$Pd(OAc)_2$ X-Phos	THF	Reflux	2		24	45
3	$PdCl_2(PCy_3)_2$[b]	THF	Reflux	2		18	72
4	$Pd(PPh_3)_4$[b]	THF	Reflux	2	37	11	20
5[a]	$Pd(OAc)_2$ BINAP	THF	Reflux	2	27		34
6	$PdCl_2$(dppf)[b]	THF	Reflux	2	60	12	9
7[c]	$PdCl_2$(dppf)[b]	THF	rt	24	71	7	9
8	$PdCl_2$(dppf)[b]	MeOH	Reflux	2	59	12	10
9	$PdCl_2$(dppf)[b]	Toluene	100	2	44		35
10	$PdCl_2$(dppf)[b]	DMF	100	2	No reaction		

[a] $Pd(OAc)_2$ (5 mol %) and ligand (10 mol %) were used.
[b] 5 mol %.
[c] $MeB(OH)_2$ (2 equiv) and KF (4 equiv) were used.

As shown in Table 3, the use of (hetero)aryl or cyclopropylboronic acid instead of methylboronic acid was tested in the regioselective Suzuki reaction. *N*-(3,5-Dibromo-2-pyridyl) piperazine **2** was reacted with phenylboronic acid (1.1 equiv) by method A (KF in THF under reflux for 3 h) or method B (Na_2CO_3 in THF/H_2O under reflux for 3 h) to give the desired product **3b** (entries 1 and 2). The highest yield was obtained, when the same reaction proceeded at room temperature for 1 day to give the product **3b** in 82% yield along with **5b** in 15% yield (entry 3). The reaction also proceeded to give **3b** in 77% yield along with **5b** in 14% yield in the presence of water (entry 4). The use of several boronic acids, such as 3-pyridyl, 4-methoxyphenyl, 4-cyanophenyl or cyclopropylboronic acid, also afforded regioselectivity at the 3-position (entries 5–8). In addition to the Suzuki reaction, the Heck reaction also occurred to give the desired product **3g** along with the disubstituted product **5e** (entry 9).

As shown in Table 4, our catalytic system was applied to other substrates. In addition to Cbz-piperazine, other amines, such as Boc-piperazine, morphorine, and pyrroridine also worked well to produce regioselective cross-coupling products **3** (entries 1–3). However, in the cases of benzylamine and *n*-butylamine, regioselectivity was decreased (entries 4 and 5). This observation suggested that cyclic or secondary amines might play a role in providing regioselectivity in the cross-coupling reaction.

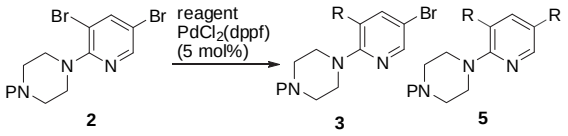
Once 3-substituted 5-bromopyridylpiperazine **3** had been prepared (Table 3 or 4), a second coupling on the remaining bromine in the 5-position was achieved to give unsymmetrical 3,5-disubstituted pyridylpiperazine **6** in good yields (Table 5, entries 1–4).

Furthermore, we investigated one-pot syntheses of 3,5-disubstituted pyridylpiperazine. As shown in Scheme 1, 3,5-dibromopyridine **2b** was treated with methylboronic acid, then phenylboronic acid to give the desired product **6a** in 60% yield along with **5b** in 18% yield. Compound **6c** was also afforded in 65% yield along with **5b** in 5% yield using this methodology.

As shown in Scheme 2, cross-coupling of 5-bromo-3-methyl-2-(pyrrolidin-1-yl)pyridine **3j** with Cbz-piperazine gave 5-methyl-6-(pyrrolidin-1-yl)pyridin-3-ylpiperazine **7** in quantitative yield. This procedure will be applicable to synthesis of 5,6-disubstituted pyridin-3-ylpiperazine.

Regioselective cross-coupling products **3a**, **3i**–**l**, isomer **4a**–**d**, and 3,5-disubstituted pyridylpiperazines **6a**,**b** were identical with alternative synthesis products (Scheme 3). Commercially available 2,5-dibromo-3-methylpyridine and 2,3-dibromo-5-methylpyridine were used.

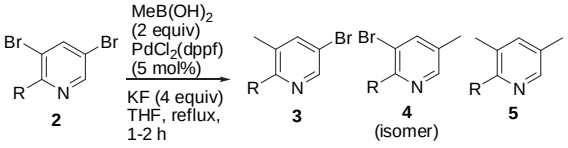
Table 3
Regioselective cross-coupling of **2** with boronic acids or olefin

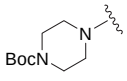
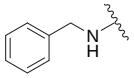
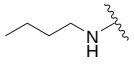


Entry	P (substrate)	Reagent (equiv)	Method	R	Yield (%)		
					3	**5**	Recov. of **2**
1		Phenylboronic acid (1.1)	A		57 (**3b**)	13 (**5b**)	24
2	Boc (**2b**)		B		63	26	8
3		(1.3)	C		82	15	
4		(1.5)	D		77	14	
5	Cbz (**2a**)	3-Pyridyl boronic acid (1.2)	B		60 (**3c**)	23 (**5c**)	
6	Cbz (**2a**)	4-Methoxyphenyl boronic acid (1.2)	B		58 (**3d**)	25 (**5d**)	
7	Cbz (**2a**)	4-Cyanophenylboronic acid (1.2)	B		52 (**3e**)		4
8	Boc (**2b**)	Cyclopropylboronic acid (2.5)	B		47 (**3f**)		23
9	Boc (**2b**)	2-Methyl-3-buten-2-ol (3)	E		55 (**3g**)	22 (**5e**)	

Method A: KF (4 equiv), THF, reflux, 3 h; method B: 2 M Na_2CO_3 aq, reflux, THF, 3 h; method C: KF (2.6 equiv), THF, rt, 1 day; method D: 2 M Na_2CO_3 aq, THF, rt, 1 day; method E: Et_3N (5 equiv), toluene, 120 °C, 5 h.

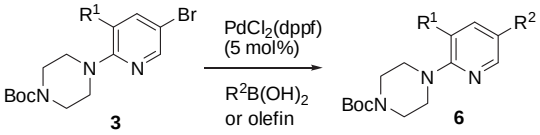
Table 4
Effects of amines on regioselective cross-coupling of **2**

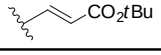


Entry	R	Substrate	Yield (%)			
			3	**4**	**5**	Recov. of **2**
1		**2b**	56 (**3h**)		22 (**5f**)	
2[a]		**2c**	50 (**3i**)			22
3		**2d**	62 (**3j**)		9 (**5g**)	
4		**2e**	37 (**3k**)	7 (**4b**)	19 (**5h**)	10
5		**2f**	35 (**3l**)	8 (**4c**)		10

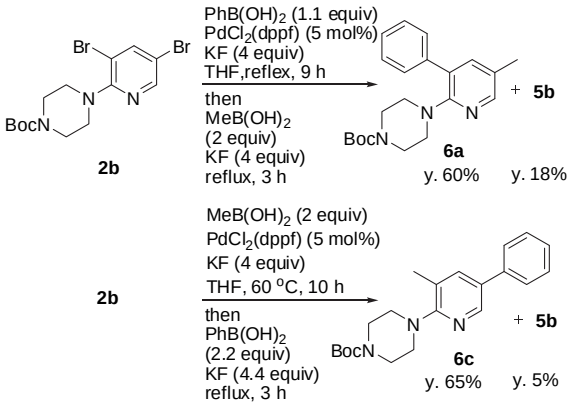
[a] $MeB(OH)_2$ (1.8 equiv) and KF (3.6 equiv) were used.

Table 5
Cross-coupling of bromopyridines

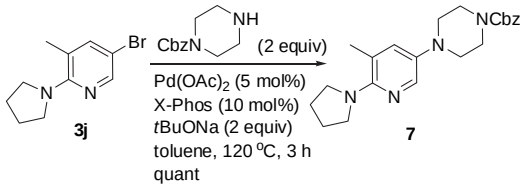


Entry	Substrate	R^1	Method	R^2	Product	Yield (%)
1	**3b**	Ph	A	Me	**6a**	70
2	**3f**	Cyclopropyl	A	Me	**6b**	79
3	**3h**	Me	B	Ph	**6c**	90
4	**3h**	Me	C		**6d**	81

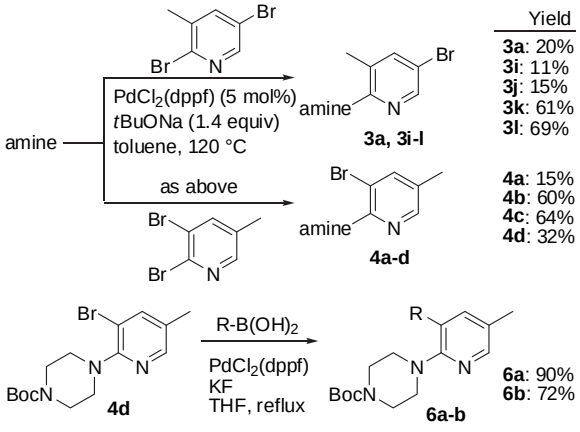
Method A: $MeB(OH)_2$ (3 equiv), KF (6 equiv), THF, reflux, 2 h; method B: $PhB(OH)_2$ (1.2 equiv), Na_2CO_3 (3 equiv), THF/H_2O, reflux, 2 h; method C: *tert*-butyl acrylate (3 equiv), Et_3N (5 equiv), toluene, 120 °C, 3 h.



Scheme 1. One-pot synthesis of 3,5-disubstituted pyridylpiperazines **6a** and **6c**.



Scheme 2. Preparation of 5,6-disubstituted pyridin-3-ylpiperazine **7**.



Scheme 3. Alternative syntheses of **3a**, **3i**–**l**, **4a**–**d**, and **6a**–**b**.

3. Conclusion

In summary, we have developed a methodology for achieving regioselective cross-coupling of *N*-(3,5-dibromo-2-pyridyl)piperazine **2**. This methodology offers a short (three steps) and convergent synthesis of unsymmetrical 3,5-disubstituted pyridylpiperazine **6** from commercially available 2,3,5-tribromopyridine **1**. The directing effect may be attributed to chelation of the piperazine nitrogen atom to the Pd species, which undergoes the oxidative addition step (Fig. 2). We believe this represents a new efficient methodology for the preparation of pyridylpiperazine derivatives having biological activity.

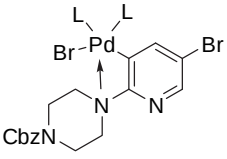


Fig. 2. Chelation of the piperazine nitrogen atom to the Pd species.

4. Experimental section

4.1. General

All the reagents and anhydrous solvents were purchased from commercial suppliers and used without further purification. Melting points were determined on a Yanagimoto micro-melting hot stage apparatus and were uncorrected. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. NMR spectra were recorded on a JEOL GX-400 (400 MHz) spectrometer. For ^{1}H NMR, tetramethylsilane (TMS) (δ=0) served as an internal standard. For ^{13}C NMR, $CDCl_3$ (δ=77.00) served as an internal standard. Mass spectra were recorded on a JEOL GCmate spectrometer. Separations were performed using PSQ60B (Fuji Silysia Chemical Ltd.) for silica gel column chromatography. Thin layer chromatography (TLC) was performed on precoated plates of silica gel 60F_{254} (Merck).

*4.1.1. Benzyl 4-(3,5-dibromopyridin-2-yl)piperazine-1-carboxylate (**2a**) (Table 1, entry 1).* A mixture of 2,3,5-tribromopyridine **1** (316 mg, 1 mmol), K_2CO_3 (415 mg, 3 mmol), and benzyl piperazine-1-carboxylate (580 μL, 3 mmol) in 2-butanone (3 mL) was reflux for 16 h under argon atmosphere. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to give **2a** (387 mg, 85%) as a white solid. Mp 98–100 °C; IR (KBr) (cm^{-1}) 1701 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.20–3.30 (m, 4H), 3.50–3.70 (m, 4H), 5.16 (s, 2H), 7.26–7.50 (m, 5H), 7.91 (d, *J*=2.2 Hz, 1H), 8.24 (d, *J*=2.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 43.6, 49.3, 67.2, 112.6, 112.9, 127.9, 128.0, 128.5, 136.6, 144.0, 147.1, 155.3, 158.0; MS-EI: *m*/*z* 453 (M^+, 8%), 455 (M^++2, 15%), 457 (M^++4, 8%), 91 (BP); HRMS-EI: *m*/*z* (M^+) calcd for $C_{17}H_{17}Br_2N_3O_2$ 452.9688, found 452.9687.

*4.1.2. tert-Butyl 4-(3,5-dibromopyridin-2-yl)piperazine-1-carboxylate (**2b**) (Table 1, entry 2).* A mixture of 2,3,5-tribromopyridine **1** (3.2 g, 10 mmol), K_2CO_3 (4.1 g, 30 mmol), and *tert*-butyl piperazine-1-carboxylate (5.6 g, 30 mmol) in 2-butanone (30 mL) was reflux for 16 h under argon atmosphere. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to give **2b** (3.6 g, 86%) as a white solid. Mp 82–84 °C; IR (KBr) (cm^{-1}) 1692 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H), 3.20–3.30 (m, 4H), 3.50–3.70 (m, 4H), 7.91 (d, *J*=2.2 Hz, 1H), 8.25 (d, *J*=2.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 28.4, 49.4, 79.8, 112.4, 112.9, 143.9, 147.1, 154.8, 158.1; MS-EI: *m*/*z* 419 (M^+, 8%), 421 (M^++2, 12%), 423 (M^++4, 5%), 57 (BP).

*4.1.3. 4-(3,5-Dibromopyridin-2-yl)morpholine (**2c**) (Table 1, entry 3).* A mixture of 2,3,5-tribromopyridine **1** (948 mg, 3 mmol), K_2CO_3 (1.24 g, 9 mmol), and morpholine (784 mL, 9 mmol) in 2-butanone (9 mL) was reflux for 16 h under argon atmosphere. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to give **2c** (869 mg, 90%) as a white solid. Mp 90–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.20–3.40 (m, 4H), 3.70–3.90 (m, 4H), 7.92 (d, *J*=2.2 Hz, 1H), 8.26 (d, *J*=2.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 49.9, 66.8, 112.4, 112.7, 144.0, 147.2, 158.0; MS-EI: *m*/*z* 320 (M^+, 33%), 322 (M^++2, 63%), 324 (M^++4, 31%), 237 (BP); HRMS-EI: *m*/*z* (M^+) calcd for $C_9H_{10}Br_2N_2O$ 319.9160, found 319.9163.

*4.1.4. 3,5-Dibromo-2-(pyrrolidin-1-yl)pyridine (**2d**) (Table 1, entry 4).* A mixture of 2,3,5-tribromopyridine **1** (3.2 g, 10 mmol), K_2CO_3 (4.2 g, 30 mmol), and pyrrolidine (1.0 mL, 12 mmol) in DMF (30 mL) was heated at 120 °C for 5 h under argon atmosphere. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine and, concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to give **2d** (3.1 g, quant) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80–2.00 (m, 4H), 3.50–3.70 (m, 4H), 7.77 (d, *J*=2.2 Hz, 1H), 8.08 (d, *J*=2.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 25.8, 50.3, 104.7, 106.6, 143.9, 146.2, 154.9; MS-EI: *m*/*z* 304 (M^+, 40%), 306 (M^++2, 62%), 308 (M^++4, 29%), 277 (BP); HRMS-EI: *m*/*z* (M^+) calcd for $C_9H_{10}Br_2N_2$ 303.9211, found 303.9208.

4.2. Procedure for the synthesis of 3a and 5a (Table 2, entry 7)

A mixture of **2a** (114 mg, 0.25 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex

(10 mg, 0.0125 mmol), methylboronic acid (30 mg, 0.5 mmol), and KF (58 mg, 1.0 mmol) in THF (1 mL) was stirred at room temperature for 1 day. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **3a** (69 mg, 71%) as an off-white solid and **5a** (6 mg, 7%) as a colorless oil.

*4.2.1. Benzyl 4-(5-bromo-3-methylpyridin-2-yl)piperazine-1-carboxylate (**3a**).* Mp 64–65 °C; IR (KBr) (cm^{-1}) 1703 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H), 3.00–3.20 (m, 4H), 3.50–3.70 (m, 4H), 5.17 (s, 2H), 7.27–7.40 (m, 5H), 7.53 (d, J=2.2 Hz, 1H), 8.17 (d, J=2.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 18.0, 43.7, 49.1, 67.0, 113.5, 126.6, 127.7, 127.8, 128.3, 136.5, 141.3, 145.7, 155.1, 159.8; MS-EI: m/z 389 (M^+, 20%), 391 (M^++2, 20%), 91 (BP); HRMS-EI: m/z (M^+) calcd for $C_{18}H_{20}BrN_3O_2$ 389.0739, found 389.0739.

*4.2.2. Benzyl 4-(3,5-dimethylpyridin-2-yl)piperazine-1-carboxylate (**5a**).* IR (neat) (cm^{-1}) 1697 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 2.22 (s, 3H), 2.25 (s, 3H), 3.00–3.10 (m, 4H), 3.60–3.70 (m, 4H), 5.17 (s, 2H), 7.25 (d, J=1.4 Hz, 1H), 7.30–7.40 (m, 5H), 7.97 (d, J=2.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 17.5, 17.8, 44.1, 49.7, 67.1, 124.6, 127.6, 127.8, 128.0, 128.5, 136.8, 140.3, 145.3, 155.4, 159.4; MS-EI: m/z 325 (M^+, 28%), 135 (BP); HRMS-EI: m/z (M^+) calcd for $C_{19}H_{23}N_3O_2$ 325.1790, found 325.1792.

4.3. Procedure for the synthesis of 3b and 5b (Table 3, entry 3)

A mixture of **2b** (105 mg, 0.25 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (10 mg, 0.0125 mmol), phenylboronic acid (40 mg, 0.325 mmol), and KF (38 mg, 0.65 mmol) in THF (1 mL) was stirred for 1 day. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to give **3b** (86 mg, 82%) as a white solid and **5b** (16 mg, 15%) as a white solid.

*4.3.1. tert-Butyl 4-(5-bromo-3-phenylpyridin-2-yl)piperazine-1-carboxylate (**3b**).* Mp 98–100 °C; IR (KBr) (cm^{-1}) 1692 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 3.00–3.20 (m, 4H), 3.30–3.50 (m, 4H), 7.32–7.38 (m, 1H), 7.40–7.46 (m, 2H), 7.52–7.57 (m, 2H), 7.57 (d, J=2.2 Hz, 1H), 8.23 (d, J=2.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 28.3, 48.5, 79.6, 112.3, 127.6, 127.9, 128.5, 128.9, 138.4, 141.4, 146.8, 154.7, 158.0; MS-EI: m/z 417 (M^+, 51%), 419 (M^++2, 51%), 261 (BP); HRMS-EI: m/z (M^+) calcd for $C_{20}H_{24}BrN_3O_2$ 417.1052, found 417.1045.

*4.3.2. tert-Butyl 4-(3,5-diphenylpyridin-2-yl)piperazine-1-carboxylate (**5b**).* Mp 190–192 °C; IR (KBr) (cm^{-1}) 1686 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 9H), 3.00–3.20 (m, 4H), 3.30–3.40 (m, 4H), 7.30–7.40 (m, 2H), 7.40–7.50 (m, 4H), 7.56 (d, J=7.8 Hz, 2H), 7.63 (d, J=7.8 Hz, 2H), 7.71 (s, 1H), 8.46 (d, J=2.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 28.3, 48.7, 79.5, 126.4, 126.8, 127.2, 127.5, 127.9, 128.8, 128.9, 130.2, 137.7, 138.1, 139.7, 144.4, 154.8, 158.5; MS-EI: m/z 415 (M^+, 39%), 259 (BP); HRMS-EI: m/z (M^+) calcd for $C_{26}H_{29}N_3O_2$ 415.2260, found 415.2261.

4.4. Procedure for the synthesis of 3c and 5c (Table 3, entry 3)

A mixture of **2a** (228 mg, 0.5 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (20 mg, 0.025 mmol), pyridin-3-ylboronic acid (74 mg, 0.6 mmol), and Na_2CO_3 (159 mg, 1.5 mmol) in THF (1.5 mL) and H_2O (0.75 mL) was reflux for 3 h. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **3c** (137 mg, 60%) as a white solid and **5c** (52 mg, 23%) as an off-white solid.

*4.4.1. Benzyl 4-(5-bromo-3,3′-bipyridin-2-yl)piperazine-1-carboxylate (**3c**).* Mp 138–140 °C; IR (KBr) (cm^{-1}) 1707 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 2.90–3.20 (m, 4H), 3.30–3.50 (m, 4H), 5.11 (s, 2H), 7.27–7.40 (m, 6H), 7.59 (d, J=2.2 Hz, 1H), 7.88–7.94 (m, 1H), 8.30 (d, J=2.2 Hz, 1H), 8.59–8.62 (m, 1H), 8.80–8.82 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 43.1, 48.7, 67.0, 112.8, 123.4, 125.3, 127.7, 127.9, 128.3, 134.0, 134.9, 136.4, 141.4, 147.8, 148.7, 149.2, 155.1, 158.2; MS-EI: m/z 452 (M^+, 30%), 454 (M^++2, 30%), 91 (BP); HRMS-EI: m/z (M^+) calcd for $C_{22}H_{21}BrN_4O_2$ 452.0848, found 452.0848.

*4.4.2. Benzyl 4-(3,5-bis(3-pyridyl)pyridin-2-yl)piperazine-1-carboxylate (**5c**).* Mp 131–133 °C; IR (KBr) (cm^{-1}) 1700 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 3.00–3.30 (m, 4H), 3.30–3.50 (m, 4H), 5.12 (s, 2H), 7.27–7.50 (m, 7H), 7.68 (d, J=2.2 Hz, 1H), 7.86 (d, J=7.8 Hz, 1H), 7.98 (d, J=7.8 Hz, 1H), 8.50 (d, J=2.2 Hz, 1H), 8.62 (s, 2H), 8.84 (s, 1H), 8.88 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 43.3, 48.8, 67.1, 123.5, 123.7, 123.8, 127.4, 127.8, 128.0, 128.4, 133.0, 133.7, 135.1, 136.4, 138.0, 145.4, 147.6, 148.7, 148.9, 149.0, 155.2, 159.2; MS-EI: m/z 451 (M^+, 28%), 261 (BP); HRMS-EI: m/z (M^+) calcd for $C_{27}H_{25}N_5O_2$ 451.2008, found 451.2010.

4.5. Procedure for the synthesis of 3d and 5d (Table 3, entry 4)

A mixture of **2a** (228 mg, 0.5 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (20 mg, 0.025 mmol), 4-methoxyphenylboronic acid (91 mg, 0.6 mmol), and Na_2CO_3 (159 mg, 1.5 mmol) in THF (1.5 mL) and H_2O (0.75 mL) was reflux for 3 h. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **3d** (140 mg, 58%) as a white solid and **5d** (63 mg, 25%) as a pale yellow oil.

*4.5.1. Benzyl 4-(5-bromo-3-(4-methoxyphenyl)pyridin-2-yl)piperazine-1-carboxylate (**3d**).* Mp 119–120 °C; ^1H NMR (400 MHz, $CDCl_3$): IR (KBr) (cm^{-1}) 1702 (CO); δ 3.00–3.10 (m, 4H), 3.30–3.50 (m, 4H), 3.85 (s, 3H), 5.11 (s, 2H), 6.95 (d, J=9.0 Hz, 2H), 7.28–7.40 (m, 5H), 7.48 (d, J=9.0 Hz, 2H), 7.55 (d, J=2.4 Hz, 1H), 8.21 (d, J=2.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 43.4, 48.4, 55.2, 67.0, 112.5, 114.2, 127.8, 127.9, 128.4, 128.8, 130.4, 136.5, 141.1, 146.3, 155.2, 157.9, 159.2; MS-EI: m/z 481 (M^+, 47%), 483 (M^++2, 48%), 291 (BP); HRMS-EI: m/z (M^+) calcd for $C_{24}H_{24}BrN_3O_3$ 481.1001, found 481.0996.

*4.5.2. Benzyl 4-[3,5-bis(4-methoxyphenyl)pyridin-2-yl]piperazine-1-carboxylate (**5d**).* IR (neat) (cm^{-1}) 1701 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 3.00–3.20 (m, 4H), 3.40–3.60 (m, 4H), 3.85 (s, 3H), 3.86 (s, 3H), 5.12 (s, 2H), 6.90–7.00 (m, 4H), 7.26–7.34 (m, 5H), 7.48 (d, J=8.8 Hz, 2H), 7.55 (d, J=8.8 Hz, 2H), 7.63 (d, J=2.4 Hz, 1H), 8.39 (d, J=2.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 43.6, 48.6, 55.2, 67.0, 114.1, 114.4, 126.8, 127.5, 127.8, 127.9, 128.4, 129.1, 130.2, 131.8, 136.6, 137.6, 143.6, 155.3, 158.1, 159.0, 159.1; MS-EI: m/z 509 (M^+, 50%), 319 (BP); HRMS-EI: m/z (M^+) calcd for $C_{31}H_{31}N_3O_4$ 509.2315, found 509.2312.

*4.5.3. Benzyl 4-[5-bromo-3-(4-cyanophenyl)pyridin-2-yl]piperazine-1-carboxylate (**3e**) (Table 3, entry 5).* A mixture of **2a** (228 mg, 0.5 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (20 mg, 0.025 mmol), 4-cyanophenylboronic acid (88 mg, 0.6 mmol), and Na_2CO_3 (159 mg, 1.5 mmol) in THF (1.5 mL) and H_2O (0.75 mL) was reflux for 3 h. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and

concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **3e** (125 mg, 52%) as a pale yellow oil. IR (neat) (cm^{-1}) 2227 (CN), 1699 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 2.90–3.10 (m, 4H), 3.30–3.50 (m, 4H), 5.11 (s, 2H), 7.28–7.35 (m, 4H), 7.58 (d, J=2.4 Hz, 1H), 7.70–7.75 (m, 5H), 8.30 (d, J=2.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 43.1, 48.7, 67.1, 111.6, 112.5, 118.2, 126.3, 127.7, 127.9, 128.3, 132.6, 136.3, 141.3, 143.0, 148.0, 155.0, 157.6; MS-EI: m/z 476 (M^+, 18%), 478 (M^++2, 19%), 91 (BP); HRMS-EI: m/z (M^+) calcd for $C_{24}H_{21}BrN_4O_2$ 476.0848, found 476.0845.

*4.5.4. tert-Butyl 4-(5-bromo-3-cyclopropylpyridin-2-yl)piperazine-1-carboxylate (**3f**) (Table 3, entry 6).* A mixture of **2b** (210 mg, 0.5 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (20 mg, 0.025 mmol), cyclopropylboronic acid monohydrate (67 mg, 0.55 mmol), and Na_2CO_3 (318 mg, 3 mmol) in THF (1.5 mL) and H_2O (1.5 mL) was reflux for 2 h. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **3f** (91 mg, 47%) as a white solid. Mp 111–113 °C; IR (KBr) (cm^{-1}) 1691 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 0.68–0.78 (m, 2H), 1.00–1.10 (m, 2H), 1.48 (s, 9H), 1.95–2.02 (m, 1H), 3.10–3.30 (m, 4H), 3.50–3.70 (m, 4H), 7.18 (d, J=2.4 Hz, 1H), 8.12 (d, J=2.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 9.4, 11.6, 28.4, 29.6, 49.6, 79.7, 113.7, 132.0, 135.4, 145.1, 154.9, 160.3; MS-EI: m/z 381 (M^+, 8%), 383 (M^++2, 9%), 57 (BP).

4.6. Procedure for the synthesis of 3g and 5e (Table 3, entry 7)

A mixture of **2b** (105 mg, 0.25 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (10 mg, 0.0125 mmol), 2-methyl-3-buten-2-ol (80 μL, 0.75 mmol), and Et_3N (175 μL, 1.25 mmol) in toluene (1 mL) was heated at 120 °C for 5 h under argon atmosphere in sealed tube. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **3g** (59 mg, 55%) as a white solid and **5e** (24 mg, 22%) as a pale yellow solid.

*4.6.1. (E)-tert-Butyl 4-[5-bromo-3-(3-hydroxy-3-methylbut-1-enyl) pyridin-2-yl]piperazine-1-carboxylate (**3g**).* Mp 119–121 °C; IR (KBr) (cm^{-1}) 3493 (OH), 1674 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 6H), 1.48 (s, 9H), 3.10–3.20 (m, 4H), 3.50–3.60 (m, 4H), 6.32 (d, J=16.1 Hz, 1H), 6.58 (d, J=16.1 Hz, 1H), 7.72 (d, J=2.2 Hz, 1H), 8.18 (d, J=2.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 28.4, 29.9, 49.7, 70.9, 79.9, 113.3, 122.2, 125.8, 137.5, 140.0, 146.8, 154.8, 158.6; MS-EI: m/z 425 (M^+, 33%), 427 (M^++2, 33%), 252 (BP); HRMS-EI: m/z (M^+) calcd for $C_{19}H_{28}BrN_3O_3$ 425.1314, found 425.1319.

*4.6.2. tert-Butyl 4-[3,5-bis((E)-3-hydroxy-3-methylbut-1-enyl)pyridin-2-yl]piperazine-1-carboxylate (**5e**).* Mp 159–161 °C; IR (KBr) (cm^{-1}) 3447 (OH), 1671 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 6H), 1.45 (s, 6H), 1.48 (s, 9H), 3.10–3.20 (m, 4H), 3.50–3.60 (m, 4H), 6.31 (d, J=16.1 Hz, 1H), 6.36 (d, J=16.1 Hz, 1H), 6.52 (d, J=16.1 Hz, 1H), 6.64 (d, J=16.1 Hz, 1H), 7.68 (d, J=2.2 Hz, 1H), 8.11 (d, J=2.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 28.4, 29.9, 49.8, 71.0, 79.8, 122.7, 123.3, 123.8, 127.0, 132.1, 137.4, 138.9, 145.2, 154.9, 159.4; MS-EI: m/z 431 (M^+, 61%), 316 (BP); HRMS-EI: m/z (M^+) calcd for $C_{24}H_{37}N_3O_4$ 431.2784, found 431.2784.

4.7. Procedure for the synthesis of 3h and 5f (Table 4, entry 1)

A mixture of **2b** (210 mg, 0.5 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (20 mg, 0.025 mmol), methylboronic acid (60 mg, 1.0 mmol), and KF (116 mg, 2 mmol) in THF (2 mL) was reflux for 2 h under argon atmosphere. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **3h** (100 mg, 56%) as a white solid and **5f** (33 mg, 22%) as a colorless oil.

*4.7.1. tert-Butyl 4-(5-bromo-3-methylpyridin-2-yl)piperazine-1-carboxylate (**3h**).* Mp 82–84 °C; IR (KBr) (cm^{-1}) 1697 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H), 2.26 (s, 3H), 3.00–3.10 (m, 4H), 3.50–3.60 (m, 4H), 7.53 (d, J=2.4 Hz, 1H), 8.18 (d, J=2.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 18.1, 28.4, 49.4, 79.8, 113.6, 126.8, 141.4, 145.9, 154.8, 160.2; MS-EI: m/z 355 (M^+, 4%), 357 (M^++2, 4%), 199 (BP).

*4.7.2. tert-Butyl 4-(3,5-dimethylpyridin-2-yl)piperazine-1-carboxylate (**5f**).* IR (neat) (cm^{-1}) 1694 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H), 2.23 (s, 3H), 2.25 (s, 3H), 3.00–3.10 (m, 4H), 3.50–3.60 (m, 4H), 7.26 (s, 1H), 7.98 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 17.4, 17.8, 28.4, 49.7, 79.5, 124.6, 127.4, 140.2, 145.2, 154.9, 159.4; MS-EI: m/z 291 (M^+, 25%), 135 (BP).

*4.7.3. 4-(5-Bromo-3-methylpyridin-2-yl)morpholine (**3i**) (Table 4, entry 2).* A mixture of **2c** (81 mg, 0.25 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (10 mg, 0.0125 mmol), methylboronic acid (27 mg, 0.45 mmol), and KF (52 mg, 0.9 mmol) in THF (1 mL) was reflux for 1 h under argon atmosphere. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **3i** (32 mg, 50%) as an off-white solid. Mp 51–53 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.00–3.20 (m, 4H), 3.70–3.90 (m, 4H), 7.53 (d, J=2.4 Hz, 1H), 8.19 (d, J=2.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 18.2, 49.9, 66.9, 113.4, 126.6, 141.4, 145.9, 160.0; MS-EI: m/z 256 (M^+, 7%), 258 (M^++2, 6%), 171 (BP).

4.8. Procedure for the synthesis of 3j and 5g (Table 4, entry 3)

A mixture of **2d** (153 mg, 0.5 mmol), [1,1′-bis(diphenylphosphino) ferrocene]palladium(II) dichloride dichloromethane complex (20 mg, 0.025 mmol), methylboronic acid (60 mg, 1.0 mmol), and KF (116 mg, 2.0 mmol) in THF (2 mL) was reflux for 1 h under argon atmosphere in sealed tube. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **3j** (75 mg, 62%) as a pale yellow oil and **5g** (8 mg, 9%) as a pale yellow oil.

*4.8.1. 5-Bromo-3-methyl-2-(pyrrolidin-1-yl)pyridine (**3j**).* ^1H NMR (400 MHz, $CDCl_3$): δ 1.80–2.00 (m, 4H), 2.28 (s, 3H), 3.40–3.60 (m, 4H), 7.32 (d, J=2.4 Hz, 1H), 8.02 (d, J=2.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.4, 25.6, 49.7, 108.1, 121.3, 141.1, 145.1, 158.0; MS-EI: m/z 240 (M^+, 61%), 242 (M^++2, 56%), 70 (BP).

*4.8.2. 3,5-Dimethyl-2-(pyrrolidin-1-yl)pyridine (**5g**).* ^1H NMR (400 MHz, $CDCl_3$): δ 1.80–2.00 (m, 4H), 2.16 (s, 3H), 2.27 (s, 3H), 3.40–3.47 (m, 4H), 7.10 (s, 1H), 7.85 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 17.1, 20.1, 25.4, 49.7, 119.7, 123.0, 140.3, 144.2, 157.9; MS-EI: m/z 176 (M^+, 77%), 147 (BP); HRMS-EI: m/z (M^+) calcd for $C_{11}H_{16}N_2$ 176.1314, found 176.1318.

4.9. Procedure for the synthesis of 3k, 4b, and 5h (Table 4, entry 4)

A mixture of **2e** (171 mg, 0.5 mmol), [1,1′-bis(diphenylphosphino) ferrocene]palladium(II) dichloride dichloromethane complex (20 mg,

0.025 mmol), methylboronic acid (60 mg, 1.0 mmol), and KF (116 mg, 2.0 mmol) in THF (2 mL) was reflux for 2 h under argon atmosphere. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **3k** (51 mg, 37%) as a pale yellow oil, **4b** (10 mg, 7%) as a pale yellow oil and **5h** (20 mg, 19%) as a pale yellow oil.

*4.9.1. N-Benzyl-5-bromo-3-methylpyridin-2-amine (**3k**).* IR (neat) (cm^{-1}) 3448 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 4.41 (br s, 1H), 4.63 (d, J=5.2 Hz, 2H), 7.20–7.24 (m, 6H), 8.05 (d, J=2.3 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 16.7, 45.8, 107.0, 118.4, 127.3127.8, 128.6, 138.9, 139.5, 145.8, 155.2; MS-EI: m/z 276 (M^+, 85%), 278 (M^++2, 79%), 106 (BP).

*4.9.2. N-Benzyl-3-bromo-5-methylpyridin-2-amine (**4b**).* IR (neat) (cm^{-1}) 3427 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H), 4.65 (d, J=5.5 Hz, 2H), 5.15 (br s, 1H), 7.27–7.40 (m, 5H), 7.48–7.51 (m, 1H), 7.89–7.91 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 17.0, 45.8, 105.2, 122.9, 127.1, 127.6, 128.6, 139.6, 140.5, 146.3, 152.7; MS-EI: m/z 276 (M^+, 76%), 278 (M^++2, 61%), 106 (BP); HRMS-EI: m/z (M^+) calcd for $C_{13}H_{13}BrN_2$ 276.0262, found 276.0261.

*4.9.3. N-Benzyl-3,5-dimethylpyridin-2-amine (**5h**).* IR (neat) (cm^{-1}) 3444 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H), 2.17 (s, 3H), 4.22 (br s, 1H), 4.65 (s, 2H), 7.09 (s, 1H), 7.20–7.50 (m, 5H), 7.86 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 16.9, 17.4, 46.0, 116.2, 121.7, 127.1, 127.9, 128.6, 138.3, 140.2, 144.8, 154.9; MS-EI: m/z 212 (M^+, 100%); HRMS-EI: m/z (M^+) calcd for $C_{14}H_{16}N_2$ 212.1314, found 212.1312.

4.10. Procedure for the synthesis of 3l and 4c (Table 4, entry 5)

A mixture of **2f** (154 mg, 0.5 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (20 mg, 0.025 mmol), methylboronic acid (60 mg, 1.0 mmol), and KF (116 mg, 2.0 mmol) in THF (2 mL) was reflux for 2 h under argon atmosphere. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **3l** (42 mg, 35%) as a pale yellow oil and **4c** (10 mg, 8%) as a pale yellow oil.

*4.10.1. 5-Bromo-N-butyl-3-methylpyridin-2-amine (**3l**).* IR (neat) (cm^{-1}) 3451 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J=7.4 Hz, 3H), 1.30–1.50 (m, 2H), 1.50–1.70 (m, 2H), 2.05 (s, 3H), 3.30–3.50 (m, 2H), 4.10 (br s, 1H), 7.25–7.35 (m, 1H), 8.02 (d, J=2.3 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 13.9, 16.7, 20.2, 31.8, 41.5, 106.3, 118.3, 138.6145.8, 155.6; MS-EI: m/z 242 (M^+, 37%), 244 (M^++2, 34%), 199 (BP).

*4.10.2. 3-Bromo-N-butyl-5-methylpyridin-2-amine (**4c**).* IR (neat) (cm^{-1}) 3432 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J=7.4 Hz, 3H), 1.30–1.50 (m, 2H), 1.50–1.70 (m, 2H), 2.16 (s, 3H), 3.30–3.50 (m, 2H), 4.80 (br s, 1H), 7.45 (d, J=1.9 Hz, 1H), 7.86–7.89 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 13.9, 16.9, 20.2, 31.8, 41.7, 105.3, 122.1, 140.3, 146.3, 153.0; MS-EI: m/z 242 (M^+, 29%), 244 (M^++2, 29%), 199 (BP); HRMS-EI: m/z (M^+) calcd for $C_{10}H_{15}BrN_2$ 242.0419, found 242.0417.

*4.10.3. tert-Butyl 4-(5-methyl-3-phenylpyridin-2-yl)piperazine-1-carboxylate (**6a**) (Table 5, entry 1).* A mixture of **3b** (154 mg, 0.37 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (15 mg, 0.019 mmol), methylboronic acid (66 mg, 1.1 mmol), and KF (128 mg, 2.2 mmol) in THF (1.5 mL) was reflux for 2 h under argon atmosphere. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to give **6a** (91 mg, 70%) as a white solid. Mp 113–114 °C; IR (KBr) (cm^{-1}) 1702 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.28 (s, 3H), 2.90–3.10 (m, 4H), 3.25–3.38 (m, 4H), 7.28–7.35 (m, 2H), 7.38–7.43 (m, 2H), 7.58 (s, 1H), 7.59–7.60 (m, 1H), 8.05 (d, J=1.6 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 17.4, 28.4, 48.9, 79.5, 126.5, 127.0, 127.3, 128.0, 128.6, 139.8, 140.4, 146.2, 154.9, 157.7; MS-EI: m/z 353 (M^+, 36%), 197 (BP); HRMS-EI: m/z (M^+) calcd for $C_{21}H_{27}N_3O_2$ 353.2103, found 353.2106.

*4.10.4. tert-Butyl 4-(3-cyclopropyl-5-methylpyridin-2-yl)piperazine-1-carboxylate (**6b**) (Table 5, entry 2).* A mixture of **3f** (91 mg, 0.24 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (20 mg, 0.025 mmol), methylboronic acid (43 mg, 0.72 mmol), and KF (81 mg, 1.4 mmol) in THF (1.0 mL) was reflux for 2 h under argon atmosphere. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to give **6b** (60 mg, 79%) as a white solid. Mp 106–108 °C; IR (KBr) (cm^{-1}) 1693 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 0.64–0.78 (m, 2H), 0.96–1.60 (m, 2H), 2.00–2.10 (m, 1H), 2.21 (s, 3H), 3.10–3.30 (m, 4H), 3.50–3.70 (m, 4H), 6.89 (d, J=2.2 Hz, 1H), 7.92 (d, J=2.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 9.1, 11.1, 17.7, 28.4, 50.0, 79.6, 127.3, 129.7, 133.4, 144.5, 155.0, 159.7; MS-EI: m/z 317 (M^+, 24%), 161 (BP); HRMS-EI: m/z (M^+) calcd for $C_{18}H_{27}N_3O_2$ 317.2103, found 317.2100.

*4.10.5. tert-Butyl 4-(3-methyl-5-phenylpyridin-2-yl)piperazine-1-carboxylate (**6c**) (Table 5, entry 3).* A mixture of **3h** (178 mg, 0.5 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (20 mg, 0.025 mmol), phenylboronic acid (73 mg, 0.6 mmol), and Na_2CO_3 (318 mg, 3.0 mmol) in THF (1.5 mL) and H_2O (1.5 mL) was reflux for 2 h. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to give **6c** (159 mg, 90%) as a white solid. Mp 125–127 °C; IR (KBr) (cm^{-1}) 1700 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 9H), 2.36 (s, 3H), 3.11–3.18 (m, 4H), 3.56–3.63 (m, 4H), 7.31–7.38 (m, 1H), 7.41–7.47 (m, 2H), 7.51–7.56 (m, 2H), 7.63 (d, J=2.1 Hz, 1H), 8.39 (d, J=2.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 18.2, 28.3, 49.4, 79.5, 124.5, 126.5, 127.2, 128.8, 131.0, 137.8, 143.3, 154.8, 160.5; MS-EI: m/z 353 (M^+, 28%), 197 (BP); HRMS-EI: m/z (M^+) calcd for $C_{21}H_{27}N_3O_2$ 353.2103, found 353.2103.

*4.10.6. (E)-tert-Butyl 4-[5-(3-tert-butoxy-3-oxoprop-1-enyl)-3-methylpyridin-2-yl]piperazine-1-carboxylate (**6d**) (Table 5, entry 4).* A mixture of **3h** (89 mg, 0.25 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (10 mg, 0.0125 mmol), *tert*-butyl acrylate (110 μL, 0.75 mmol), and Et_3N (175 μL, 1.25 mmol) in toluene (1 mL) was heated at 120 °C for 3 h under argon atmosphere in sealed tube. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **6d** (82 mg, 81%) as a pale yellow solid. Mp 113–114 °C; IR (KBr) (cm^{-1}) 1700 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.53 (s, 9H), 2.29 (s, 3H), 3.14–3.21 (m, 4H), 3.52–3.62 (m, 4H), 6.27 (d, J=16.0 Hz, 1H), 7.50 (d, J=16.0 Hz, 1H), 7.57 (s, 1H), 8.22 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 18.6, 28.0, 28.1, 28.4, 49.1, 79.7, 80.4, 119.0, 124.1, 124.5, 137.1, 140.0, 146.0, 154.8, 162.2, 166.1;

MS-EI: m/z 403 (M^+, 43%); HRMS-EI: m/z (M^+) calcd for $C_{22}H_{33}N_3O_4$ 403.2471, found 403.2472.

*4.10.7. Benzyl 4-[5-methyl-6-(pyrrolidin-1-yl)pyridin-3-yl]piperazine-1-carboxylate (**7**) (Scheme 2).* A mixture of **3j** (30 mg, 0.124 mmol), palladium acetate (II) (3 mg, 0.0124 mmol), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (12 mg, 0.025 mmol), *t*-BuONa (24 mg, 0.248 mmol), benzyl piperazine-1-carboxylate (55 mg, 0.248 mmol) in toluene (1 mL) was heated at 120 °C for 3 h under argon atmosphere in sealed tube. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **7** (29 mg, quant) as a brown oil. IR (neat) (cm^{-1}) 1703 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.85–1.95 (m, 4H), 2.29 (s, 3H), 2.90–3.10 (m, 4H), 3.35–3.48 (m, 4H), 3.60–3.70 (m, 4H), 5.16 (s, 2H), 7.03 (d, J=2.7 Hz, 1H), 7.27–7.45 (m, 5H), 7.74 (d, J=2.7 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.2, 25.4, 43.9, 49.8, 50.8, 67.2, 121.2, 127.9, 128.0, 128.5, 131.1, 133.6, 136.6, 140.5, 155.1; MS-EI: m/z 380 (M^+, 100%); HRMS-EI: m/z (M^+) calcd for $C_{22}H_{28}N_4O_2$ 380.2338, found 380.2336.

*4.10.8. Benzyl 4-(3-bromo-5-methylpyridin-2-yl)piperazine-1-carboxylate (**4a**) (Scheme 3).* A mixture of 2,3-dibromo-5-methylpyridine (251 mg, 1.0 mmol), [1,1′-bis(diphenylphosphino)ferrocene] palladium(II) dichloride dichloromethane complex (41 mg, 0.05 mmol), *t*-BuONa (136 mg, 1.4 mmol), and benzyl piperazine-1-carboxylate (330 mg, 1.5 mmol) in toluene (2 mL) was heated at 120 °C for 3 h under argon atmosphere in sealed tube. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **4a** (60 mg, 15%) as a pale yellow solid. Mp 56–58 °C; IR (KBr) (cm^{-1}) 1698 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H), 3.10–3.30 (m, 4H), 3.60–3.80 (m, 4H), 5.17 (s, 2H), 7.27–7.50 (m, 5H), 7.65 (d, J=2.1 Hz, 1H), 8.05 (d, J=2.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 17.0, 43.7, 49.5, 67.0, 113.0, 127.8, 127.9, 128.4, 128.8, 136.7, 142.7, 146.4, 155.3, 157.2; MS-EI: m/z 389 (M^+, 21%), 391 (M^++2, 21%), 91 (BP); HRMS-EI: m/z (M^+) calcd for $C_{18}H_{20}BrN_3O_2$ 389.0739, found 389.0738.

*4.10.9. tert-Butyl 4-(3-bromo-5-methylpyridin-2-yl)piperazine-1-carboxylate (**4d**) (Scheme 3).* A mixture of 2,3-dibromo-5-methylpyridine (251 mg, 1.0 mmol), [1,1′-bis(diphenylphosphino) ferrocene]palladium(II) dichloride dichloromethane complex (41 mg, 0.05 mmol), *t*-BuONa (136 mg, 1.4 mmol), and *tert*-butyl piperazine-1-carboxylate (245 mg, 1.3 mmol) in toluene (2 mL) was heated at 120 °C for 8 h under argon atmosphere in sealed tube. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, hexanes/EtOAc) to give **4d** (115 mg, 32%) as a pale yellow oil. IR (neat) (cm^{-1}) 1701 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H), 2.25 (s, 3H), 3.10–3.30 (m, 4H), 3.60–3.70 (m, 4H), 7.65 (s, 1H), 8.05 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 17.0, 28.3, 79.6, 113.0, 128.7, 142.7, 146.4, 154.8, 157.3; MS-EI: m/z 355 (M^+, 36%), 357 (M^++2, 34%), 199 (BP).

Acknowledgements

We are grateful to the ‘Open Research Center Project’ for private universities, a matching fund subsidy from the Ministry of Education, Sports, Culture, Science, and Technology, Japan (MEXT).

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