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Copper(I)-catalyzed coupling reaction of aryl boronic acids with *N*,*O*-acetals and *N*,*N*-aminals under atmosphere leading to α-aryl glycine derivatives and diarylmethylamine derivatives

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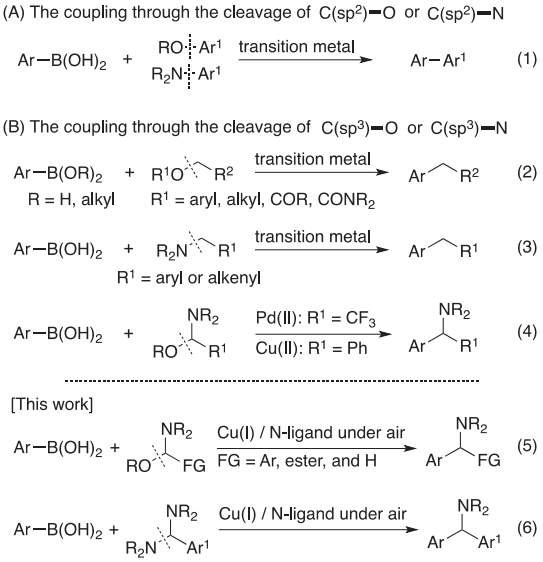
ABSTRACT

We demonstrated a copper(I)-catalyzed coupling reaction of aryl boronic acids with *N*,*O*-acetals and *N*,*N*-aminals leading to the synthesis of α-aryl glycines and diarylmethylamines. Under an ambient atmosphere, this catalytic system could be applied to the activation of a C(sp^3)-O bond of *N*,*O*-acetals with an ester and an aryl group, or without a coordinating substituent, as well as to a C(sp^3)-N bond of *N*,*N*-aminals.

1. Introduction

A transition-metal-catalyzed coupling of organoboron compounds (Suzuki-Miyaura coupling) with a variety of aryl halides/pseudohalides is one of the most important procedures for the formation of a C–C bond, because the method has unique properties that include a high degree of regioselectivity and a functional group tolerance.[1] Although a transition metal-catalyzed coupling with organoboron compounds through the cleavage of either a C(sp^2)-O bond or a C(sp^2)-N bond, instead of a C-X (halide) bond, has recently been widely disclosed (Eq 1 in Scheme 1),[2,3] a similar coupling reaction through the cleavage of either a C(sp^3)-O bond or a C(sp^3)-N bond on electrophiles has not been studied extensively. For the cleavage of a C(sp^3)-O bond (Eq 2 in Scheme 1), thus far, Kuwano et al. have reported the palladium-catalyzed coupling of aryl boronic acids with benzyl methyl carbonates, producing diarylmethane derivatives.[4] As an extension, Shi and co-workers disclosed a nickel-catalyzed coupling with α-pivaloxy ketone in the presence of a base.[5] Also, the coupling of aryl boronic acids with benzyl or allylic pivalates in the presence of a strong base has been reported by Watson's group.[6] Moreover, this Suzuki-Miyaura-type coupling has been expanded to substrates, such as a phenoxy or methoxy groups that have a weaker leaving ability rather than the leaving groups shown above. For example, Lipshutz and Sakamoto independently developed the palladium-catalyzed coupling of aryl boronic acids with allylic ethers.[7] Also, Kakiuchi and Kochi reported the ruthenium-catalyzed coupling of aryl boroxines with aliphatic methyl ethers that have a pyridine ring that functions as a co-



Scheme 1. Diverse couplings of organoboronic acids with carbon sources through a cleavage of a C–N or a C–O bond.

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ordination site.[8] Also, more recently, Chatani et al. demonstrated a nickel-catalyzed coupling of aryl boronic esters with benzyl methyl ethers.[9] However, these coupling partners are generally collected to a structure with a relatively high reactivity site, such as a benzyl, an allylic position or an α-carbon next to a carbonyl moiety.

On the other hand, as examples for the coupling of aryl boronic acid derivatives with the cleavage of a C(sp^3)-N bond (Eq 3 in Scheme 1), the use of several transition metals, such as a nickel, a palladium, or a rhodium with an iridium catalyst, achieved the purpose, although a coupling with an abundant metal, such as a copper catalyst, has not been studied extensively, and the choices of electrophilic substrates that can be employed are limited to either benzylic ammonium salts or benzylamine derivatives.[10]

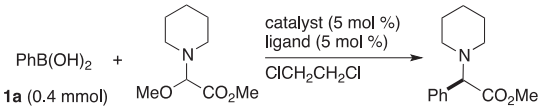
Several metal-catalyzed couplings of aryl boronic acids with *N*,*O*-acetals have recently been reported, in which a selective activation of the C(sp^3)-O bond on the *N*,*O*-acetal occurs, producing the corresponding benzylamine derivatives (Eq 4 in Scheme 1).[11,12] For instance, Lautens and co-workers reported the Pd(II)-catalyzed asymmetric coupling of aryl boroxines with *N*,*O*-acetals to afford α-trifluoromethylbenzylamine derivatives.[13] Quite recently, Rao et al. demonstrated how the use of $Cu(OTf)_2$ undertook the coupling of aryl boronic acids with an isoindolinol that consisted of a *N*,*O*-hemiacetal moiety, and afforded isoindolinone derivatives.[14]

We also reported the Lewis acid-catalyzed coupling of either electron-rich aromatic compounds or various carbon nucleophiles with *N*,*O*-acetals leading to the preparation of derivatives of α-aryl glycine and benzylamine, the structure of which is widely found in a number of natural products and biologically active substances.[15,16] Herein, we report the full details of a Cu(I)-catalyzed coupling of aryl boronic acids with *N*,*O*-acetals and *N*,*N*-aminals, in which the catalytic system was composed of a copper(I) catalyst and a nitrogen-containing bidentate ligand under atmosphere effectively activated both the C(sp^3)-O bond on an *N*,*O*-acetal and the C(sp^3)-N bond on an *N*,*N*-aminal.

2. Results/discussion

As a model reaction, the coupling of phenylboronic acid (**1a**) with *N*,*O*-acetal **2a** was examined in the presence of various copper catalysts and ligands in degassed 1,2-dichloroethane under an ambient atmosphere (Table 1). The initial combination of CuCl and 2,2′-bipyridine gave α-phenyl glycine derivative **3aa** in a good yield (entry 1). We were able to easily isolate **3aa** via common filtration through a short silica gel pad, and the structure was confirmed by the spectral data we were able to obtain. In a similar manner, CuBr showed a high effect, and the reaction was completed within 2 h to produce **3aa** in a quantitative yield (entry 2). However, combinations of either CuI/bipyridine or CuBr/pyridine were not effective for this reaction (entries 3 and 4). When the reaction was performed with a more rigid ligand, 1,10-phenanthroline in comparison with 2,2′-bipyridine, the corresponding coupling product was obtained in a nearly quantitative yield (entry 5). These results implied that flexibility of coordination site by nitrogen atom did not have an effect to the reactivity. Without a nitrogen-containing ligand, however, the expected coupling would not occur (entry 6). It was interesting that when the coupling was performed with the degassed solvent under a N_2 atmosphere, the expected reaction would not proceed, and resulted only in recovery of the starting boronic acid (entry 7). In contrast, when the solvent was used as it stood without degassing under a N_2 atmosphere, the desired coupling product was formed in a relatively good yield (entry 8). We expected that oxygen had promoted this coupling. Thus, when the reaction was then performed under an O_2 atmosphere (1 atm), however, the yield of **3aa** was decreased to 40% (entry 9). It is noteworthy that copper(II) catalysts, such as $CuBr_2$, $Cu(OAc)_2$ and $Cu(OTf)_2$, were ineffective for the coupling (entries 10–12). Without a copper(I) catalyst, no formation of the product was observed (entry 13).

Table 1
Examinations of the reaction conditions[a]

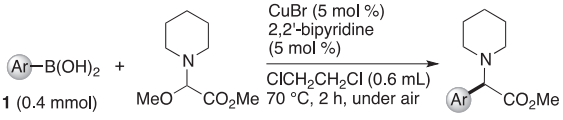


Entry	Catalyst	Ligand	Atmosphere	Yield (%)[c]
1	CuCl	2,2′-Bipyridine	Air	88
2	CuBr	2,2′-Bipyridine	Air	(99)
3	CuI	2,2′-Bipyridine	Air	0
4	CuBr	Pyridine[d]	Air	0
5	CuBr	1,10-Phenanthroline	Air	99
6	CuBr	—	Air	0
7	CuBr	2,2′-Bipyridine	N_2	0
8[e]	CuBr	2,2′-Bipyridine	N_2	69
9	CuBr	2,2′-Bipyridine	O_2	40
10	$CuBr_2$	2,2′-Bipyridine	Air	0
11	$Cu(OAc)_2$	2,2′-Bipyridine	Air	15
12	$Cu(OTf)_2$	2,2′-Bipyridine	Air	25
13	—	2,2′-Bipyridine	Air	0

[b] **3aa** denotes that the first character is derived from the boronic acid and the second character is derived from the acetal.
[a] Conditions: a copper catalyst (5 mol %), a ligand (5 mol %), $ClCH_2CH_2Cl$ (0.6 mL) degassed with a N_2 gas, 70 °C, 2 h.
[c] NMR (Isolated) yield.
[d] 10 mol %.
[e] The solvent used without degassing.

To expand the generality of this coupling reaction, the reaction of a variety of aryl boronic acids **1** with *N*,*O*-acetal **2a** was then examined under the optimal conditions (Table 2). For instance, when boronic acids with a relatively moderate electron-donating group, such as a methyl group, were used, the corresponding amino acid derivatives **3ba** and **3ca** were obtained in nearly quantitative yields (entries 1 and 2). The steric effect of the *o*-substituted methyl group did not have a strong effect on the chemical yield. On the other hand, the substrates that did exert a strong electron-donating group, such as a dimethylamino, a methoxy or a hydroxy group, drastically reduced the product

Table 2
Synthesis of α-aryl glycine derivatives with a variety of aryl boronic acids

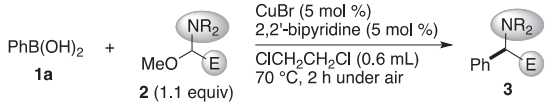


Entry	Boronic acid **1**			Yield of **3** (%)[a]
		Ar		
1	**1b**	*o*-MeC_6H_4	**3ba**	99
2	**1c**	*p*-MeC_6H_4	**3ca**	99
3[b]	**1d**	*p*-$Me_2NC_6H_4$	**3da**	47
4	**1e**	*o*-$MeOC_6H_4$	**3ea**	0
5	**1f**	*p*-$MeOC_6H_4$	**3fa**	0
6[c]	**1g**	*o*-HOC_6H_4	**3ga**	46
7[d,e]	**1h**	*p*-FC_6H_4	**3ha**	98
8[e]	**1i**	*p*-ClC_6H_4	**3ia**	99
9[e]	**1j**	*p*-$CF_3C_6H_4$	**3ja**	83
10	**1k**	*p*-AcC_6H_4	**3ka**	84

[a] Isolated yield.
[b] Reaction time=3 h.
[c] Reaction time=24 h.
[d] Reaction time=1 h.
[e] Bath temperature=80 °C.

yields (entries 3–6). In particular, a boronic acid with a dimethylamino group produced diarylmethane derivative **3da′** through a double substitution by **1a** and the biphenyl derivative through the dimerization of **1a** as by-products in 26 and 2% yields, respectively (entry 3). In particular, when a methoxy group was used, the expected products were not produced (entries 4 and 5). In contrast, with most substrates that possessed an electron-withdrawing substituent, the reaction was completed within 2 h to give the α-aryl glycine derivatives **3ha**–**3ka** in good to excellent yields (entries 7–10) (Table 3).

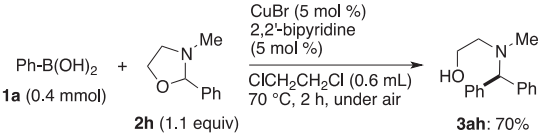
Table 3
Coupling of phenyl boronic acid (**1a**) with a variety of *N*,*O*-acetals **2**



Entry	*N*,*O*-acetal **2**			Yield of **3**	
		NR_2	E		(%)[a]
1[b]	**2b**	NEt_2	CO_2Me	**3ab**	70
2[b]	**2c**	N^iPr_2	CO_2Me	**3ac**	30
3	**2d**	$N(allyl)_2$	CO_2Me	**3ad**	48
4	**2e**	Morpholinyl	CO_2Me	**3ae**	99
5	**2f**	$N(SiMe_3)_2$	CO_2Me	**3af**	0
6	**2g**	Pieperidinyl	Ph	**3ag**	99

[a] Isolated yield.
[b] CuBr (20 mol %), 2,2′-bipyridine (20 mol %).

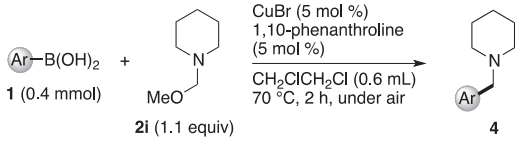
To clarify the substituent effect of an amino group on *N*,*O*-acetals **2**, a coupling reaction of phenylboronic acid (**1a**) with several *N*,*O*-acetals was carried out under our optimal conditions (Table 2). Using a typical acyclic amine, such as an ethyl group, the yield of the corresponding amino acid derivative **3ab** was obtained in a good yield (entry 1). However, the coupling reaction with either *N*,*O*-acetal **2e** bearing a relatively bulky substituent or *N*,*O*-acetal **2d** with a diallylamino group gave the desired products **3ac** and **3ad** in low yields (entries 2 and 3). In contrast, *N*,*O*-acetal **2e** with a morpholine ring produced the α-aryl glycine derivative **3ae** in an excellent yield (entry 4). Unfortunately, when the reaction was conducted in the hope of producing an *N*-unsubstituted α-phenyl glycine derivative by using *N*,*O*-acetal **2f** with a bis(trimethylsilyl) amino group, the desired coupling reaction did not occur (entry 5). On the other hand, the use of an *N*,*O*-acetal with a phenyl group instead of an ester, produced the diphenylmethylamine derivative **3ag** in an excellent yield (entry 6). Also, when the reaction of phenylboronic acid (**1a**) with cyclic acetal **2h**, which possessed a phenyl group, was treated with the present catalytic system, the expected coupling occurred smoothly to produce the ring-opening product **3ah** in a 70% yield (Scheme 2).



Scheme 2. The coupling of phenylboronic acid (**1a**) with cyclic *N*,*O*-acetal **2h**.

We also investigated the coupling of several aryl boronic acids with *N*,*O*-acetal **2i** using no substituent at the α-carbon (Table 4). Our procedure was unlike the conventional example reported by Bergin and co-workers, in which a coordinate substituent, such as an ester, on the substrate required a Petasis-type coupling.[17] With our procedure, a combination of copper(I) bromide and 1,10-phenanthroline effectively undertook the expected coupling, even when the *N*,*O*-acetal had no substituent, to produce the

Table 4
The coupling of aryl boronic acids **1** with *N*,*O*-acetal **2i** without a substituent at the α-position



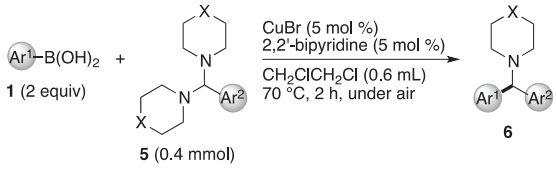
Entry	Aryl boronic acid **1**		Yield of **4** (%)[a]	
1	**1a**	Ph	**4ai**	94
2	**1c**	*p*-MeC_6H_4	**4ci**	87
3[b]	**1g**	*o*-HOC_6H_4	**4gi**	80
4	**1i**	*p*-ClC_6H_4	**4ii**	84

[a] Isolated yield.
[b] 2,2′-Bipyridine.

corresponding benzylamine derivatives **4** in relatively good yields (entries 1–4).

In further applications, the coupling of several aryl boronic acids **1** and a variety of *N*,*N*-aminals **5** with piperidine or morpholine rings was examined in the hope that a C(sp^3)-N bond could be cleaved (Table 5). In most cases, the electric effect of a substituent on the benzene ring of both boronic acids and *N*,*N*-aminals did not influence the yield of the coupling product **6**. With the exception of entry 8, when the reaction was performed with 2 equiv of boronic acids, most cases smoothly undertook the expected C–N coupling, producing the corresponding diarylmethylamine derivatives in moderate to good yields (entries 1–10). An *N*,*N*-aminal effectively functioned as a coupling partner of boronic acids. It is noteworthy that, unlike the results with *N*,*O*-acetals, in all couplings with *N*,*N*-aminals the formation of a small amount of the biphenyl derivative that was derived from the homo-coupling of **1** as a by-product was observed.

Table 5
Synthesis of diarylmethylamine derivatives **6** with a variety of *N*,*N*-aminals **5**



Entry	Aryl boronic acid **1**		*N*,*N*-aminal **5**			Yield of **6**	
		Ar^1		Ar^2	X		(%)[a]
1	**1a**	Ph	**5a**	*o*-MeC_6H_4	CH_2	**6aa**	60
2	**1a**	Ph	**5b**	*p*-MeC_6H_4	CH_2	**6ab**	70
3	**1a**	Ph	**5c**	*p*-FC_6H_4	CH_2	**6ac**	91
4	**1a**	Ph	**5d**	*p*-ClC_6H_4	CH_2	**6ad**	64
5	**1a**	Ph	**5e**	*p*-$CF_3C_6H_4$	CH_2	**6ae**	60
6	**1c**	*p*-MeC_6H_4	**5b**	*p*-MeC_6H_4	CH_2	**6cb**	80
7	**1c**	*p*-MeC_6H_4	**5c**	*p*-FC_6H_4	CH_2	**6cc**	90
8	**1h**	*p*-FC_6H_4	**5b**	*p*-MeC_6H_4	CH_2	**6cc**	42
9	**1h**	*p*-FC_6H_4	**5c**	*p*-FC_6H_4	CH_2	**6hc**	87
10	**1a**	Ph	**5f**	Ph	O	**6af**	99

[a] Isolated yield.

To clarify the reaction path for this coupling, several control experiments were then conducted. First, when the coupling reaction was conducted with the iminium compound, 1-methylenepiperidinium chloride, which was isolated from 1-(methoxymethyl)piperidine and methyltrichlorosilane,[18] under the optimal conditions, the expected coupling did not occur to recover the starting boronic acid. This result suggested that the coupling series would proceed through the nucleophilic substitution of either the *N*,*O*-acetal or the *N*,*N*-aminal activated by a copper catalyst rather than the nucleophilic addition of the phenyl boronic acid to

the in situ-formed iminium intermediate. Also, when the reaction mixture involving CuBr (2 equiv for **1a**), bipyridine (2 equiv for **1a**), phenyl boronic acid (**1a**: 2.5×10^{-3} M), and 1,2-dichloroethane was monitored by UV spectrophotometer, a strong absorption of the aryl copper species composed of the phenyl anion, which would be generated from **1a**, and a counter anion was gradually observed at 445 nm during the specified time course (see Fig. 1 in SD).[19] Also, we observed that during the coupling the solution color of the reaction mixture turned from brown to pale blue.

On the basis of these results and the fact that a copper(II) catalyst, such as $CuBr_2$, $Cu(OAc)_2$, or $Cu(OTf)_2$, was ineffective for the coupling, we anticipate that a copper(I) catalyst would function as the main catalyst as well as the mechanism proposed by Bergin et al.[11,17a] However, we can not propose the reasonable reaction mechanism with the copper(I) catalyst under atmosphere at this stage.[20] On the other hand, in the case of an *N*,*N*-aminal, a double transmetalation of two aryl boronic acids to a copper(II) complex occurs to produce the homo-coupling product as a by-product with the formation of a copper(0) catalyst. The copper(0) is reoxidized with oxygen to form a copper(II) catalyst.

3. Conclusions

A catalytic system combined of either CuBr and 2,2′-bipyridine or 1,10-phenanthroline under an ambient atmosphere effectively catalyzed the coupling of a variety of aryl boronic acids with either *N*,*O*-acetals or *N*,*N*-aminals, which led to α-aryl glycine derivatives and diarylmethylamine derivatives. The important finding is that this catalytic system successfully activated both the $C(sp^3)$-O bond of *N*,*O*-acetals as well as the $C(sp^3)$-N bond of *N*,*N*-aminals. In particular, we found that this catalytic system successfully activated the $C(sp^3)$-O bond of the *N*,*O*-acetal having no activating substituent. Also, this method could be extended to the coupling of aromatic compounds having an electron-withdrawing group that would not undertake the desired coupling with *N*,*O*-acetals in our previous work. For the catalytic cycle of the copper catalyst in this coupling series, we have no reasonable explanation at this stage. We continue to examine the catalytic cycle mechanism, and the results will be reported in due course.

4. Experimental section

4.1. General

All reactions were carried out under air, unless otherwise noted. Copper salts, acid catalysts, amines, aldehydes, and methyl 2-methoxyacetate were commercially available, and were used without further purification. Boronic acids were commercially available and were purified with a common purification procedure. 1,2-Dichloroethane (DCE) was first distilled from P_2O_5, and the distillate was then re-distilled from K_2CO_3, and was finally kept dry on molecular sieves (4 Å). THF and benzene were distilled from sodium–benzophenone, and were kept dry on molecular sieves (4 Å). Methanol was distilled from Mg–I_2, and was kept dry on molecular sieves (3 Å). Piperidine and triethylamine were distilled over CaH_2. Reactions were monitored via the TLC analysis of reaction aliquots. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254}, and the components were located via observation under UV light. Column chromatography was also performed using silica gel. ^{1}H NMR spectra were measured at 500 (or 300) MHz using tetramethylsilane as an internal standard (0.00 ppm). ^{13}C NMR spectra were measured at 125 (or 75) MHz using the center peak of chloroform (77.0 ppm). High-resolution mass spectra (FAB) were measured using a *p*-nitrobenzyl alcohol (NBA) matrix.

*4.1.1. Preparation of N,O-acetal **2a**–**e**.* To a distilled benzene solution (50 mL) of methyl 2-methoxyacetate (5.2 g, 50 mmol) were added a magnetic stirring bar and *N*-bromosuccinimide (8.9 g, 50 mmol), and the mixture was stirred at room temperature for 1 h under irradiation of a sunlight lamp. The reaction mixture was filtered, and then evaporated under reduced pressure. The residue was dissolved in THF (50 mL) containing *sec*-amine (60 mmol) and triethylamine (6.1 g, 60 mmol), and the mixture was stirred for 2 h at room temperature. The mixture was directly filtered without a common workup and was evaporated under reduced pressure. The filtrate was distilled (a Kugelrohr distillation) to give the *N*,*O*-acetal **2**.

*4.1.1.1. Methyl 2-methoxy-2-(piperidin-1-yl)acetate[16d] (**2a**).* 75% yield (7.02 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (m, 2H), 1.57 (m, 4H), 2.56 (m, 2H), 2.69 (m, 2H), 3.39 (s, 3H), 3.78 (s, 3H), 4.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4, 26.0, 48.7, 51.7, 55.8, 94.3, 169.0; MS (ESI): *m*/*z* 210 $[M+Na]^+$; HRMS (ESI): Calcd for $C_9H_{17}NNaO_3$: 210.1106, Found: 210.1126.

*4.1.1.2. Methyl 2-(diethylamino)-2-methoxyacetate (**2b**).* 72% yield (6.31 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (t, 6H, *J*=7.0 Hz), 2.70–2.78 (m, 4H), 3.37 (s, 3H), 3.77 (s, 3H), 4.42 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 43.3, 51.8, 55.2, 91.1, 170.0; MS (ESI): *m*/*z* 198 $[M+Na]^+$; HRMS (ESI): Calcd for $C_8H_{17}NNaO_3$: 198.1106, Found: 198.1109.

*4.1.1.3. Methyl 2-(diisopropylamino)-2-methoxyacetate (**2c**).* 60% yield (6.10 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (d, 6H, *J*=7.0 Hz), 1.11 (d, 6H, *J*=7.0 Hz), 3.28 (s, 3H), 3.36 (m, 2H), 3.74 (s, 3H), 4.48 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 22.8, 45.0, 51.8, 54.0, 86.4, 171.4; MS (ESI): *m*/*z* 226 $[M+Na]^+$; HRMS (ESI): Calcd for $C_{10}H_{21}NNaO_3$: 226.1419, Found: 226.1415.

*4.1.1.4. Methyl 2-(diallylamino)-2-methoxyacetate[16d] (**2d**).* 75% yield (7.47 g); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26–3.36 (m, 7H), 3.77 (s, 3H), 4.46 (s, 1H), 5.13–5.24 (m, 4H), 5.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8, 52.1, 55.5, 89.7, 117.5, 135.7, 169.8; MS (ESI): *m*/*z* 222 $[M+Na]^+$; HRMS (ESI): Calcd for $C_{10}H_{17}NNaO_3$: 222.1106, found: 222.1095.

*4.1.1.5. Methyl 2-methoxy-2-morpholinoacetate[16d] (**2e**).* 88% yield (8.33 g); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (m, 2H), 2.78 (m, 2H), 3.43 (s, 3H), 3.70 (m, 4H), 3.80 (s, 3H), 4.24 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.7, 51.7, 55.8, 66.9, 93.4, 168.2; MS (ESI): *m*/*z* 212 $[M+Na]^+$.

*4.1.2. Preparation of N,O-acetal **2f**.* To a distilled benzene solution (50 mL) of methyl 2-methoxyacetate (5.2 g, 50 mmol) were added a magnetic stirring bar and *N*-bromosuccinimide (8.9 g, 50 mmol). The resultant mixture was stirred at room temperature for 1 h under sunlight. The reaction mixture was filtered, and then evaporated under reduced pressure to give a crude methyl 2-bromo-2-methoxyacetate. To a freshly distilled THF solution (50 mL) of hexamethyldisilazane (9.7 g, 60 mmol) in a glass flask that contained a magnetic stirring bar, *n*-BuLi (15 mL, 1.6 M in hexane) was dropwise added under a N_2 atmosphere at 0 °C. The unpurified methyl 2-bromo-2-methoxyacetate was dropwise added to the solution at 0 °C, and the mixture was stirred for 2 h at room temperature. The mixture was directly filtered without a common work-up and was evaporated under reduced pressure. The filtrate was distilled (a Kugelrohr distillation) to give *N*,*O*-acetal **2f**.

*4.1.2.1. Methyl 2-(1,1,1,3,3,3-hexamethyldisilazan-2-yl)-2-methoxyacetate[16d] (**2f**).* 47% yield (6.19 g); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.18 (s, 18H), 3.37 (s, 3H), 3.75 (s, 3H), 4.69 (s,

1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 2.4, 52.2, 55.1, 87.8, 172.3; MS (ESI): *m*/*z* 286 $[M+Na]^+$; HRMS (ESI): Calcd for $C_{10}H_{25}NNaO_3Si_2$: 286.1270, Found: 286.1248.

*4.1.3. Preparation of N,O-acetal **2g** and **2i**.* To a glass flask under a N_2 atmosphere were successively added a magnetic stirring bar, piperidine (852 mg, 10.0 mmol), methanol (417 mg, 13.0 mmol), aldehyde (10.0 mmol), K_2CO_3 (2.76 g, 20.0 mmol), and Na_2SO_4 (2.84 g, 20.0 mmol). The reaction mixture was stirred at room temperature for 16 h. The mixture was directly filtered without a common workup and was evaporated under reduced pressure. The filtrate was distilled (a Kugelrohr distillation) to give *N,O*-acetal **2**.

*4.1.3.1. 1-(Methoxy(phenyl)methyl)piperidine[21] (**2g**).* 88% yield (1.81 g); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37–1.42 (m, 2H), 1.48–1.52 (m, 4H), 2.54 (t, 4H, *J*=5.4 Hz), 3.37 (s, 3H), 4.72 (s, 1H), 7.25–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 26.1, 485, 56.4, 98.4, 127.3, 127.5, 127.8, 138.3; MS (FAB): *m*/*z* 174 $[M-OMe]^+$.

*4.1.3.2. 1-(Methoxymethyl)piperidine[22] (**2i**).* 75% yield (969 mg); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (m, 2H),1.56–1.58 (m, 4H), 2.67 (m, 4H), 3.31 (s, 3H), 4.03 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.9, 25.9, 50.7, 53.1, 82.8; MS (FAB): *m*/*z* 98 $[M-OMe]^+$.

*4.1.4. Preparation of **2h**.* To a distilled benzene solution (5 mL) of *N*-methyl-2-aminoethanol (2.25 g, 30.0 mmol) in glass flask under air atmosphere were added a magnetic stirring bar and benzaldehyde (1.06 g, 10.0 mmol). The reaction mixture was stirred at room temperature for 2 h. The mixture was directly filtered without a common workup and was evaporated under reduced pressure. The filtrate was distilled (a Kugelrohr distillation) to give *N,O*-acetal **2h**.

*4.1.4.1. 3-Methyl-2-phenyloxazolidine[23] (**2h**).* 95% yield (1.55 g); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.70 (dd, 1H, *J*=9.0 and 17.1 Hz), 3.32 (sext, 1H, *J*=3.8 Hz), 4.07 (m, 2H), 4.65 (s, 1H), 7.34–7.48 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.2, 54.6, 65.3, 98.3, 127.5, 128.2, 128.8, 139.0; MS (FAB): *m*/*z* 164 $[M+H]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{10}H_{13}N_1O_1$: 164.1075, Found: 164.1078.

*4.1.5. Preparation of N,N-aminal **5a**–**e**.* To a distilled benzene solution (5 mL) of *sec*-amine (15.0 mmol) in a glass flask under a N_2 atmosphere were successively added a magnetic stirring bar and aldehyde (10.0 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with $NaHCO_3$ aq (60 mL), and the organic layer was separated, washed with $NaHCO_3$ aqueous solution (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give *N,N*-aminal **5**. The *N,N*-aminal prepared was used without further purification.[24]

*4.1.5.1. 1,1′-(o-Tolylmethylene)dipiperidine (**5a**).* 98% yield (2.67 g); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (m, 4H), 1.49 (m, 8H), 2.32–2.42 (m, 11H), 4.01 (s, 1H), 7.11–7.17 (m, 3H), 7.38 (d, 1H, *J*=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 25.3, 26.3, 50.1, 83.8, 124.6, 126.3, 128.7, 130.2, 135.3, 136.9; MS (FAB): *m*/*z* 188 $[M-N(C_5H_{10})]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{13}H_{18}N$: 188.1439, Found: 188.1418.

*4.1.5.2. 1,1′-(p-Tolylmethylene)dipiperidine[25] (**5b**).* 99% yield (2.70 g); white solid; mp 42–44 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (m, 4H), 1.50 (m, 8H), 2.34 (m. 11H), 3.52 (s, 1H), 7.10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 25.3, 26.2, 50.2, 89.5, 128.0, 128.6, 133.2, 136.4; MS (FAB): *m*/*z* 188 $[M-N(C_5H_{10})]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{13}H_{18}N$: 188.1439, Found: 188.1441.

*4.1.5.3. 1,1′-((4-Fluorophenyl)methylene)dipiperidine (**5c**).* 96% yield (2.65 g); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (m, 4H), 1.50 (m, 8H), 2.29 (m, 8H), 3.55 (s, 1H), 6.99 (m, 2H), 7.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 26.2, 50.1, 88.9, 114.0 (d, J_{C-F}=21 Hz), 129.8 (d, J_{C-F}=7 Hz), 131.9, 161.8 (d, J_{C-F}=245 Hz); MS (FAB): *m*/*z* 192 $[M-N(C_5H_{10})]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{12}H_{15}NF$: 192.1189, Found: 192.1191.

*4.1.5.4. 1,1′-((4-Chlorophenyl)methylene)dipiperidine[25] (**5d**).* 97% yield (2.84 g); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (m, 4H), 1.50 (m, 8H), 2.29 (m, 8H), 3.54 (s, 1H), 7.13 (d, 2H, *J*=8.4 Hz), 7.28 (d, 2H, *J*=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 26.2, 50.0, 88.9, 127.5, 129.8, 132.5, 134.7; MS (FAB): *m*/*z* 208 $[M-N(C_5H_{10})]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{12}H_{15}NCl$: 208.0893, Found: 208.0883.

*4.1.5.5. 1,1′-((4-(Trifluoromethyl)phenyl)methylene)dipiperidine[25] (**5e**).* 92% yield (3.00 g); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (m, 4H), 1.51 (m, 8H), 2.29 (m, 8H), 3.62 (s, 1H), 7.31 (d, 2H, *J*=8.1 Hz), 7.57 (d, 2H, *J*=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 26.2, 50.1, 89.1, 124.3 (q, J_{C-F}=4 Hz), 128.2 (q, J_{C-F}=283 Hz), 128.7, 129.1 (q, J_{C-F}=32 Hz), 140.3; MS (FAB): *m*/*z* 242 $[M-N(C_5H_{10})]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{13}H_{18}NF_3$: 242.1157, Found: 242.1166.

*4.1.5.6. 4,4′-(Phenylmethylene)dimorpholine[25] (**5f**).* 99% yield (2.60 g); white solid; mp 100–102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (m, 8H), 3.64–3.69 (m, 9H), 7.19 (d, 2H, *J*=6.6 Hz), 7.30–7.34 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.5, 67.2, 89.0, 127.7, 127.8, 128.8, 134.0; MS (FAB): *m*/*z* 176 $[M-N(C_2H_4OC_2H_4)]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{11}H_{14}N_1O_1$: 176.1075, Found: 176.1088.

4.1.6. General procedure for the coupling reaction of boronic acid 1 with N,O-acetal 2. In a glove box, CuBr (2.87 mg, 0.0200 mmol) and 2,2′-bipyridyl (3.12 mg, 0.0200 mmol) was weighed directly into a screw glass vial. The vial was sealed with a PTFE sealed screw cap under a N_2 atmosphere and was removed from the glove box. To the vial was added a distilled DCE (0.6 mL). The solution was stirred at room temperature for 1 min. To the mixture were added an *N,O*-acetal (0.440 mmol) and a boronic acid (0.400 mmol). The solution was stirred at 70 °C under air until TLC analysis indicated the disappearance of the starting material. After the reaction, the mixture was directly subjected to silica gel without the usual work-up, and was purified via silica gel chromatography (hexane: AcOEt=9: 1) to give the corresponding coupling compound.

*4.1.6.1. Methyl 2-phenyl-2-(piperidin-1-yl)acetate[16f] (**3aa**).* 99% yield (92.4 mg); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (m, 2H), 1.59 (m, 4H), 2.39 (m, 4H), 3.68 (s, 3H), 3.98 (s, 1H), 7.31 (m, 3H), 7.43 (d, 2H, *J*=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3, 25.8, 51.8, 52.4, 75.0, 128.1, 128.4, 128.8, 136.2, 172.3; MS (EI): *m*/*z* 233 $[M]^+$.

*4.1.6.2. Methyl 2-(piperidin-1-yl)-2-o-tolylacetate[26] (**3ba**).* 99% yield (97.9 mg); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (m, 2H), 1.56 (m, 4H), 2.42 (m, 7H), 3.66 (s, 3H), 4.25 (s, 1H), 7.18 (m, 3H), 7.54 (t, 1H, *J*=4.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 24.4, 25.8, 51.7, 52.0, 70.3, 126.1, 127.7, 128.3, 130.5, 134.6, 137.3, 172.4; MS (EI): *m*/*z* 247 $[M]^+$.

*4.1.6.3. Methyl 2-(piperidin-1-yl)-2-p-tolylacetate[16f] (**3ca**).* 99% yield (97.9 mg); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (m, 2H), 1.59 (m, 4H), 2.36 (m, 7H), 3.67 (s, 3H), 3.93 (s, 1H), 7.14 (d, 2H, *J*=8.1 Hz), 7.32 (d, 2H, *J*=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 24.3, 25.7, 51.9, 52.4, 74.8, 128.7, 129.1, 133.1, 137.9, 172.5; (EI): *m*/*z* 247 $[M]^+$.

4.1.6.4. Methyl 2-(4-(dimethylamino)phenyl)-2-(piperidin-1-yl) acetate[16d] (***3da***). 47% yield (52.0 mg); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (m, 2H), 1.59 (m, 4H), 2.37 (m, 4H), 2.95 (s, 6H), 3.67 (s, 3H), 3.83 (s, 1H), 6.68 (d, 2H, *J*=9.0 Hz), 7.28 (d, 2H, *J*=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4, 25.7, 40.4, 51.8, 52.5, 74.6, 112.1, 123.5, 129.6, 150.3, 173.0; MS (FAB): *m*/*z* 277 $[M+H]^+$.

*4.1.6.5. Methyl 2,2-bis(4-(dimethylamino)phenyl)acetate (**3da**′).* 26% yield (16.2 mg); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (s, 12H), 3.71 (s, 3H), 4.86 (s, 1H), 6.68 (d, 4H, *J*=8.5 Hz), 7.16 (d, 4H, *J*=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.3, 50.7, 53.9, 111.3, 117.9, 127.8, 148.3, 172.8; MS (FAB): *m*/*z* 312 $[M]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{19}H_{24}N_2O_2$: 312.1838, Found: 312.1824.

*4.1.6.6. Methyl 2-(2-hydroxyphenyl)-2-(piperidin-1-yl)acetate (**3ga**).* 46% yield (45.9 mg); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (m, 2H), 1.66 (m, 4H), 2.57 (m, 4H), 3.71 (s, 3H), 4.15 (s, 1H), 6.75–6.85 (m, 2H), 7.00 (d, 1H, *J*=7.8 Hz), 7.22 (t, 1H, *J*=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 25.8, 51.7, 52.1, 73.8, 116.8, 119.2, 128.9, 129.7, 157.6, 170.4; MS (FAB): *m*/*z* 250 $[M+H]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{14}H_{19}NO_3$: 249.1365, Found: 249.1335.

4.1.6.7. Methyl 2-(4-fluorophenyl)-2-(piperidin-1-yl)acetate[16f] (***3ha***). 98% yield (98.5 mg); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (m, 2H), 1.59 (m, 4H), 2.36 (m, 4H), 3.69 (s, 3H), 3.95 (s, 1H), 7.02 (m, 2H), 7.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 25.7, 52.0, 52.3, 74.2, 115.3 (d, J_{C-F}=21 Hz), 130.4 (d, J_{C-F}=8 Hz), 132.0, 162.6 (d, J_{C-F}=247 Hz), 172.2; MS (EI): *m*/*z* 251 $[M]^+$.

4.1.6.8. Methyl 2-(4-chlorophenyl)-2-(piperidin-1-yl)acetate[16f] (***3ia***). 99% yield (106.0 mg); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (m, 2H), 1.59 (m, 4H), 2.36 (m, 4H), 3.68 (s, 3H), 3.95 (s, 1H), 7.31 (d, 2H, *J*=8.5 Hz), 7.38 (d, 2H, *J*=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 25.7, 52.0, 52.3, 74.2, 128.6, 130.1, 134.0, 134.8, 171.9; MS (FAB): *m*/*z* 267 $[M+H]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{14}H_{19}NO_2Cl$: 268.1104, Found: 268.1133.

*4.1.6.9. Methyl 2-(piperidin-1-yl)-2-(2-(trifluoromethyl)phenyl) acetate (**3ja**).* 83% yield (100.0 mg); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (m, 2H), 1.57 (m, 4H), 2.35 (m, 4H), 3.67 (s, 3H), 4.35 (s, 1H), 7.42 (t, 1H, *J*=7.8 Hz), 7.57 (t, 1H, *J*=7.8 Hz), 7.64 (d, 1H, *J*=7.8 Hz), 8.08 (d, 1H, *J*=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 25.8, 52.1, 52.5, 69.4, 124.1 (q, J_{C-F}=275 Hz), 125.5 (q, J_{C-F}=6 Hz), 128.0, 129.3 (q, J_{C-F}=30 Hz), 130.7, 132.1, 135.8, 171.9; MS (FAB): *m*/*z* 302 $[M+H]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{15}H_{19}NO_2F_3$: 302.1368, Found: 302.1389.

*4.1.6.10. Methyl 2-(4-acetylphenyl)-2-(piperidin-1-yl)acetate (**3ka**).* 84% yield (92.5 mg); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (m, 2H), 1.60 (m, 4H), 2.38 (m, 4H), 2.60 (s, 3H), 3.70 (s, 3H), 4.06 (s, 1H), 7.55 (d, 2H, *J*=8.5 Hz), 7.94 (d, 2H, *J*=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 25.7, 26.6, 52.1, 52.3, 74.6, 128.4, 128.9, 136.8, 141.6, 171.6, 197.7; MS (FAB): *m*/*z* 276 $[M+H]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{16}H_{22}NO_3$: 276.1600, Found: 276.1576.

4.1.6.11. Methyl 2-(diethylamino)-2-phenylacetate[27] (***3ab***). 70% yield (62.0 mg); yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (m, 6H), 2.62 (m, 4H), 3.70 (s, 3H), 4.49 (s, 1H), 7.31 (m, 3H), 7.43 (d, 2H, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 43.6, 51.7, 69.3, 127.9, 128.3, 128.7, 137.0, 172.9; MS (FAB): *m*/*z* 222 $[M+H]^+$.

*4.1.6.12. Methyl 2-(diisopropylamino)-2-phenylacetate (**3ac**).* 30% yield (29.9 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, 6H, *J*=6.6 Hz), 1.11 (d, 6H, *J*=6.6 Hz), 3.30 (m, 2H), 3.74 (s, 3H), 3.79 (s, 1H), 7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 23.1, 45.8, 51.5, 61.5, 127.1, 128.1, 128.3, 129.3, 176.1; MS (FAB): *m*/*z* 250 $[M+H]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{15}H_{24}NO_2$: 250.1807, Found: 250.1797.

4.1.6.13. Methyl 2-(diallylamino)-2-phenylacetate[28] (***3ad***). 48% yield (47.1 mg); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.21 (d, 4H, *J*=6.6 Hz), 3.71 (s, 3H), 4.61 (s, 1H), 5.14 (m, 4H), 5.82 (m, 2H), 7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.6, 53.2, 67.6, 117.6, 127.9, 128.4, 128.6, 135.6, 136.5, 172.6; MS (FAB): *m*/*z* 246 $[M+H]^+$.

4.1.6.14. Methyl 2-morpholino-2-phenylacetate[29] (***3ae***). 99% yield (93.2 mg); yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (m, 4H), 3.68 (m, 7H), 3.98 (s, 1H), 7.33 (m, 3H), 7.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.5, 52.0, 66.7, 74.4, 128.5, 128.6, 128.8, 135.2, 171.6; MS (FAB): *m*/*z* 236 $[M+H]^+$.

4.1.6.15. 1-Benzhydrylpiperidine[30] (***3ag***). 99% yield (99.5 mg); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (m, 2H), 1.55 (m, 4H), 2.31 (m, 4H), 4.21 (s, 1H), 7.15 (t, 2H, *J*=7.5 Hz), 7.25 (t, 4H, *J*=7.5 Hz), 7.39 (d, 4H, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 26.2, 53.1, 76.7, 126.6, 128.0, 128.3, 143.2; MS (FAB): *m*/*z* 251 $[M]^+$.

4.1.6.16. 2-(Benzhydryl(methyl)amino)ethanol[31] (***3ah***). 70% yield (67.6 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.54 (t, 2H, *J*=5.4 Hz), 2.76 (br s, 1H), 3.62 (t, 2H, *J*=5.4 Hz), 4.48 (s, 1H), 7.18–7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.5, 56.0, 58.7, 75.6, 127.0, 128.0, 128.5, 142.2; MS (FAB): *m*/*z* 241 $[M]^+$.

4.1.6.17. 1-Benzylpiperidine[32] (***4ai***). 95% yield (66.6 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (m, 2H), 1.56 (m, 4H), 2.37 (m, 4H), 3.47 (s, 2H), 7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 25.9, 54.5, 63.9, 126.8, 128.1, 129.2, 138.6; MS (EI): *m*/*z* 175 $[M]^+$.

4.1.6.18. 1-(4-Methylbenzyl)piperidine[32] (***4ci***). 87% yield (65.9 mg); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61–2.90 (m, 10H), 3.78 (s, 3H), 3.88 (s, 2H), 6.80–7.27 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 24.5, 26.0, 54.5, 63.7, 128.9, 129.4, 135.3, 136.6; MS (FAB): *m*/*z* 190 $[M+H]^+$.

4.1.6.19. 2-(Piperidin-1-ylmethyl)phenol[33] (***4gi***). 80% yield (61.2 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–1.65 (m, 6H), 2.49 (m, 4H), 3.66 (s, 2H), 6.77 (m, 2H), 6.95 (d, 1H, *J*=6.6 Hz), 7.15 (m, 1H), 10.7 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 25.8, 53.8, 62.1, 115.9, 118.8, 121.6, 128.4128.5, 158.0; MS (FAB): *m*/*z* 192 $[M+H]^+$.

4.1.6.20. N-(4-Chlorobenzyl)piperidine[32] (***4ii***). 84% yield (70.5 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (m, 2H), 1.56 (m, 4H), 2.34 (m, 4H), 3.41 (s, 2H), 7.22–7.28 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 25.9, 54.4, 63.0, 128.2, 130.4, 132.4, 137.1; MS (FAB): *m*/*z* 210 $[M+H]^+$.

*4.1.7. General procedure for the coupling reaction of boronic acid 1 with N,N-aminal **5**.* In a glove box, CuBr (2.87 mg, 0.0200 mmol) and 2,2′-bipyridyl (3.12 mg, 0.0200 mmol) was weighed directly into a screw glass vial. The vial was sealed with a PTFE sealed screw cap under a N_2 atmosphere and was removed from the glove box. To the vial was added a distilled DCE (0.6 mL). The solution was stirred at room temperature for 1 min. To the mixture was successively added an *N,N*-aminal (0.400 mol) and a boronic acid (0.800 mol). The solution was stirred at 70 °C under air until TLC analysis indicated the disappearance of the starting material. After the reaction, the mixture was directly subjected to silica gel without the usual work-up, and was purified via silica gel

chromatography (hexane: AcOEt=9: 1) to give the corresponding coupling compound.

4.1.7.1. 1-(Phenyl(o-tolyl)methyl)piperidine[30] (***6aa***). 60% yield (63.7 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42–1.56 (m, 6H), 2.10–2.45 (m, 7H), 4.38 (s, 1H), 7.05–7.26 (m, 6H), 7.37 (d, 2H, *J*=8.2 Hz), 7.78 (d, 1H, *J*=8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 24.8, 26.2, 53.4, 71.8, 126.1, 126.2, 126.6, 127.3, 128.7, 130.4, 135.7, 141.6, 142.3; MS (FAB): *m*/*z* 266 $[M+H]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{19}H_{24}N$: 266.1909, Found: 266.1900.

4.1.7.2. 1-(Phenyl(p-tolyl)methyl)piperidine[34] (***6ab***). 70% yield (74.3 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (m, 2H), 1.47 (m, 4H), 2.19 (m, 7H), 4.10 (s, 1H), 6.99–7.30 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 24.7, 26.2, 53.1, 76.4, 126.5, 127.9, 128.3, 129.0, 136.1, 140.2, 143.5; MS (FAB): *m*/*z* 266 $[M+H]^+$.

4.1.7.3. 1-((4-Fluorophenyl)(phenyl)methyl)piperidine (***6ac***). 91% yield (98.1 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (m, 2H), 1.55 (m, 4H), 2.29 (m, 4H), 4.21 (s, 1H), 6.93 (m, 2H), 7.16 (t, 1H, *J*=7.5 Hz), 7.13–7.37 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 26.2, 53.0, 75.8, 115.1 (d, J_{C-F}=21 Hz), 126.8, 127.8, 128.4, 129.3 (d, J_{C-F}=8 Hz), 139.0, 143.0, 161.6 (d, J_{C-F}=244 Hz); MS (FAB): *m*/*z* 269 $[M+H]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{18}H_{20}NF$: 269.1580, Found: 269.1573.

4.1.7.4. 1-((4-Chlorophenyl)(phenyl)methyl)piperidine (***6ad***). 64% yield (73.2 mg); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (m, 2H), 1.55 (m, 4H), 2.29 (m, 4H), 4.20 (s, 1H), 7.16–7.36 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 26.2, 53.0, 75.9, 126.9, 127.9, 128.4, 128.5, 129.2, 132.2, 141.9, 142.6; MS (FAB): *m*/*z* 285 $[M]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{18}H_{20}NCl$: 285.1284, Found: 285.1278.

4.1.7.5. 1-(Phenyl(4-(trifluoromethyl)phenyl)methyl)piperidine (***6ae***). 60% yield (76.7 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (m, 2H), 1.56 (m, 4H), 2.30 (m, 4H), 4.27 (s, 1H), 7.17–7.38 (m, 5H), 7.52 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 26.2, 53.1, 76.3, 124.2 (q, J_{C-F}=271 Hz), 125.3 (q, J_{C-F}=4 Hz), 127.1, 128.0, 128.1, 128.5, 128.8 (q, J_{C-F}=32.7 Hz), 142.2, 147.6; MS (FAB): *m*/*z* 319 $[M]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{19}H_{20}NF_3$: 319.1548, Found: 319.1554.

4.1.7.6. 1-(Di-p-tolylmethyl)piperidine[35] (***6cb***). 80% yield (89.4 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (m, 2H), 1.55 (m, 4H), 2.27 (m, 10H), 4.15 (s, 1H), 7.06 (d, 4H, *J*=8.1 Hz), 7.27 (d, 4H, *J*=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 24.7, 26.2, 53.1, 76.2, 127.8, 129.0, 136.1, 140.5; MS (FAB): *m*/*z* 279 $[M]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{20}H_{25}N$: 279.1987, Found: 279.2004.

4.1.7.7. 1-((4-Fluorophenyl)(p-tolyl)methyl)piperidine (***6cc***). 90% yield (102.0 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (m, 2H), 1.55 (m, 4H), 2.28 (m, 7H), 4.17 (s, 1H), 6.93 (m, 2H), 7.08 (d, 2H, *J*=8.1 Hz), 7.24 (d, 2H, *J*=8.1 Hz), 7.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 24.7, 26.2, 53.0, 75.6, 115.0 (d, J_{C-F}=21 Hz), 127.8, 129.1, 129.2 (d, J_{C-F}=7 Hz), 136.4, 139.2, 140.0, 161.6 (d, J_{C-F}=245 Hz); MS (FAB): *m*/*z* 283 $[M]^+$; HRMS (FAB): Calcd for $C_{19}H_{22}NF$: 283.1736, Found: 283.1742.

4.1.7.8. 1-(Bis(4-fluorophenyl)methyl)piperidine[35] (***6hc***). 87% yield (100.0 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (m, 2H), 1.55 (m, 4H), 2.27 (m, 4H), 4.21 (s, 1H), 6.95 (m, 4H), 7.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 25.5, 52.1, 73.5, 114.9 (d, J_{C-F}=21 Hz), 129.1 (d, J_{C-F}=8 Hz), 138.7, 160.8 (d, J_{C-F}=244 Hz); MS (FAB): *m*/*z* 287 $[M]^+$; HRMS (FAB-Magnetic Sector): Calcd for $C_{18}H_{19}NF_2$: 287.1486, Found: 287.1487.

4.1.7.9. 4-Benzhydrylmorpholine[35] (***6af***). 99% yield (100.3 mg); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (m, 4H), 3.71 (m, 4H), 4.19 (s, 1H), 7.17 (t, 2H, 7.2 Hz), 7.26 (t, 4H, *J*=7.2 Hz), 7.17 (d, 4H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.6, 61.2, 76.7, 127.0, 127.9, 128.5, 142.3; MS (FAB): *m*/*z* 253 $[M]^+$.

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Supplementary data

Supplementary data (Copies of the ^{1}H and ^{13}C NMR spectra of the products produced by this procedure.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2015.05.068.

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