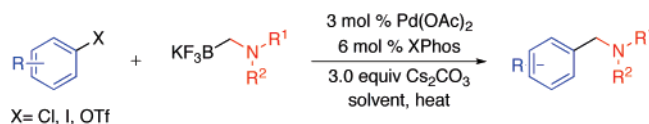# *JOC*Featured Article

Scope of Aminomethylations via Suzuki−Miyaura Cross-Coupling of Organotrifluoroborates

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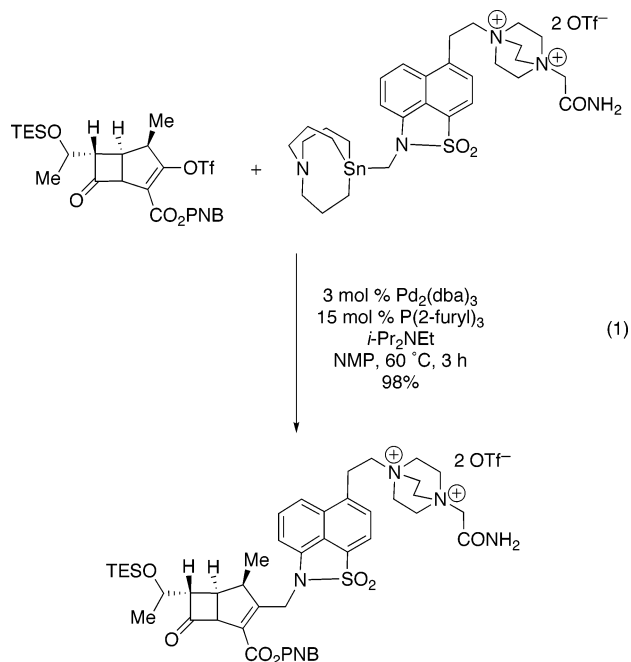
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We previously reported the Suzuki−Miyaura reaction of *N,N*-dialkylaminomethyltrifluoroborates with aryl bromides. Herein, we report a further investigation of the scope and limitations of this palladium-catalyzed aminomethylation reaction. Aryl chlorides, iodides, and triflates coupled in good to excellent yields to give *N,N*-dialkylbenzylic amines. The aminomethylation of alkenyl bromides was also examined.

Introduction

The aminomethyl moiety is found in a wide variety of alkaloid natural products and nitrogen-containing pharmaceuticals.[1] Both the biological activity and structural complexity of these compounds have made them prominent synthetic targets. Several strategies for the construction of the aminomethyl functional group have been developed, including nucleophilic displacement,[2] alkylation of iminium ions, and reductive amination.[3] These methods employ a consonant reactivity pattern, exploiting the inherent nucleophilicity of the amine or electrophilicity of the iminium ion. Despite the successes of these methods in accessing the aminomethyl moiety, a cross-coupling reaction using an aminomethyl coupling partner would provide a complementary route to benzylamines. Furthermore, a cross-coupling reaction, employing dissonant reactivity, could be used synthetically to allow far greater functional group tolerance. Despite the potential of this method, only one cross-coupling of this type had been reported prior to our initial efforts, and this employed a highly specialized aminomethylstannane in conjunction with an enol triflate partner (eq 1).[4]

The inherent toxicity associated with organotin reagents, in addition to the difficulty in purification of the cross-coupled

(1)

products,[5] makes the Stille reaction an undesirable platform for aminomethylation.

The Suzuki−Miyaura reaction[6] provides an attractive alternative. The use of potassium *N,N*-dialkylaminomethyltrifluoro-

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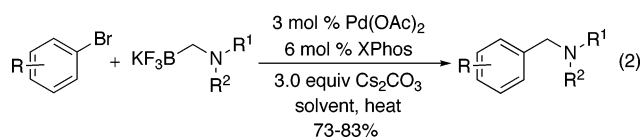
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borates circumvents many of the drawbacks associated with the Stille reaction. Potassium trifluoroborate salts are air- and moisture-stable crystalline solids that are easy to handle and indefinitely bench-stable.[7] Unlike boronic acids, which can form dimeric and trimeric species, organotrifluoroborates exist as monomers. Additionally, they are less prone to protodeboronation during cross-coupling,[8] allowing the use of stoichiometric quantities of reagents as compared to boronic acids, which generally require a considerable (20−50%) excess. Furthermore, aminomethyltrifluoroborates can be rapidly and economically synthesized from easily prepared potassium bromomethyltrifluoroborate and a wide variety of secondary amines under mild conditions.[9] This synthesis has proved to be extremely robust and scalable. Potassium bromomethyltrifluoroborate has been prepared in our laboratory on a 100 g scale, and various aminomethyltrifluoroborates are routinely prepared on 5 g scale. Using these easily accessed starting materials, we previously demonstrated that aryl bromides couple readily in moderate to excellent yields (eq 2).[9b]

$$R \overset{\parallel}{\bigcirc}\!\!-\!\!Br + KF_3B\!\!-\!\!\underset{R^2}{\overset{R^1}{N}} \xrightarrow[\substack{\text{solvent, heat} \\ 73\text{-}83\%}]{\substack{3 \text{ mol } \% \text{ Pd(OAc)}_2 \\ 6 \text{ mol } \% \text{ XPhos} \\ 3.0 \text{ equiv Cs}_2\text{CO}_3}} R \overset{\parallel}{\bigcirc}\!\!-\!\!\underset{R^2}{\overset{R^1}{N}} \quad (2)$$

Recently, we discovered that the reaction conditions for aryl bromide cross-coupling can be equally applied to the aminomethylation of aryl chlorides. This result represents an important extension of the method, allowing the use of more stable and less expensive electrophilic partners in the cross-coupling reactions. Furthermore, relatively few examples of alkylboron cross-coupling to aryl chlorides exist in the literature, and these appear to be limited in scope.[10] Herein, we disclose a thorough investigation of the scope and limitations of the aminomethylation reaction via Suzuki-Miyaura cross-coupling of potassium organotrifluoroborates with aryl and heteroaryl chlorides. Additionally, we have confirmed the generality of these reactions with aryl iodides and triflates.

Results and Discussion

The current study began with an examination of various aryl electrophiles in the cross-coupling reaction with potassium *N*-(trifluoroboratomethyl)piperidine. We first examined the reaction of chlorobenzene **1a** with the piperidine-derived trifluoroborate using our previously optimized conditions for the reaction: 3 mol % of Pd(OAc)$_2$ and 6 mol % of 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos)[11] as the catalyst system, Cs$_2$CO$_3$ (3.0 equiv) as the base, and a 10:1 THF/H$_2$O mixture at 80 °C for 22 h.[9b] The heterogeneous reaction mixture gave the desired cross-coupled product **2a** in 85% yield. This promis-

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TABLE 1. Cross-Coupling of Potassium *N*-(Trifluoroboratomethyl)-piperidine with Various Aryl Chlorides[a]

entry	aryl chloride	product	% isolated yield
1	**1a**	**2a**	85[b]
2	**1b**	**2b**	63[b]
3	**1c**	**2c**	66[b]
4	**1d**	**2d**	92[c] (64)[d]
5	**1e**	**2e**	94[b]
6	**1f**	**2f**	92[c]
7	**1g**	**2g**	83[c]
8	**1h**	**2h**	99[b]
9	**1i**	**2i**	91[b]
10	**1j**	**2j**	92[b]

[a] All reactions were carried out using 1.0 mmol of the aryl chloride and 1.01 mmol of potassium *N*-(trifluoroboratomethyl)piperidine. [b] 10:1 THF/H$_2$O (0.25 M) was used as the solvent, 80 °C. [c] 10:1 CPME/H$_2$O (0.25 M) was used as the solvent, 95 °C. [d] The reaction was carried out on a 5 mmol scale.

ing result led us to examine the generality of the method using various aryl chlorides. The results are summarized in Table 1.

SCHEME 1
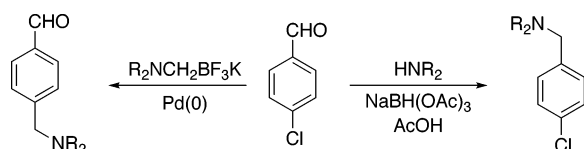
The reaction conditions proved to be general across a wide variety of electron-rich, electron-neutral, electron-poor, and hindered aryl chlorides, affording the cross-coupled products in good to excellent yields. Essentially stoichiometric amounts of the trifluoroborate (1% excess) were used as opposed to 1.5−2 equiv of boronic acid typically required for cross-coupling reactions.[12] Furthermore, the reaction tolerated a wide variety of functional groups including ketones, nitriles, esters and aldehydes. The latter observation underscores the complementarity of cross-coupling technologies in introducing the aminomethyl moiety as compared to other methods. A cross-coupling reaction allows the aminomethylation of an aryl chloride in the presence of an aldehyde, whereas reductive amination at the aldehyde would retain the halide functional group (Scheme 1).

Only hindered arenes **1b** and **1c** showed a marked decrease in reactivity, yet still coupled in synthetically useful yields. Surprisingly, electron-rich arenes such as 4-chloroanisole (**1e**) and 5-chloro-1,3-dimethoxybenzene (**1h**), typically challenging substrates owing to the difficulty of activating the C−Cl bond in oxidative addition,[13] coupled in higher yields compared to electron-poor aryl chlorides. In fact, to obtain satisfactory yields using some electron-poor arenes, the use of a 10:1 cyclopentyl methyl ether (CPME)/H_2O solvent system was required. The increase in yield is presumably a result of the increased reaction temperature (95 °C) allowed by the CPME solvent, compared to 80 °C using THF in a sealed vessel.

Furthermore, aryl chlorides gave higher yields as compared to bromides in many cases. Fu has reported unexpected relative reactivities using different catalyst systems, even allowing the selective coupling of a chloride in the presence of a triflate.[14] The improved yields we observed using aryl chlorides relative to aryl bromides led us to investigate the possibility that our catalyst system reacted preferentially with chlorides, potentially explaining our results. We conducted a competition study between 4-chloroanisole and 4-bromoanisole as depicted in eq 3. Upon GC/MS analysis, only the cross-coupled product and 4-chloroanisole were observed, indicating a preference of the catalyst to react with the bromide. While this result supports the accepted order of reactivity in the Suzuki−Miyaura reaction, it does not explain the improved yields when using aryl chlorides.
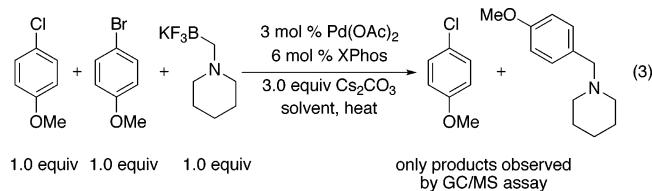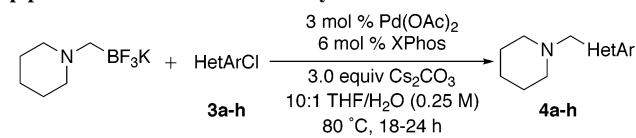

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(14) (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (b) Espino, G.; Kurbangalieva, A.; Brown, J. M. *Chem. Commun.* **2007**, 1742−1744.

TABLE 2. Cross-Coupling of Potassium *N*-(Trifluoroboratomethyl)-piperidine with Various Heteroaryl Chlorides[a]
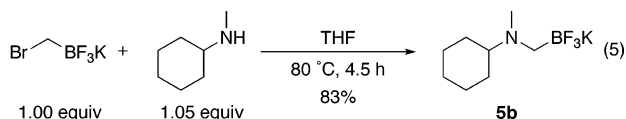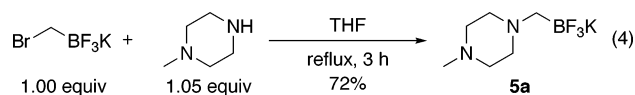

entry	heteroaryl chloride	product	% isolated yield
1	**3a**	**4a**	77
2	**3b**	**4b**	97
3	**3c**	**4c**	87
4	**3d**	**4d**	60
5	**3e**	**4e**	65
6	**3f**	**4f**	78
7	**3g**	**4g**	93
8	**3h**	**4h**	82

[a] All reactions were carried out using 1.0 mmol of the heteroaryl chloride and 1.01 mmol of potassium *N*-(trifluoroboratomethyl)piperidine.

We next investigated the use of diverse heteroaryl chlorides in the cross-coupling. In general, these substrates coupled in moderate to excellent yields (Table 2). Pyridine, thiophene, quinoline, and furan derivatives were all coupled using the same conditions as those employed for aryl chlorides. Unfortunately, 2-chloropyridine and 2-chloropyrimidine, heterocycles chlorinated adjacent to the nitrogen, were found to be unsuitable coupling partners. 2-Chloropyridine gave rise almost exclusively to the homocoupled bipyridyl product, whereas the direct amination product was observed using 2-chloropyrimidine.
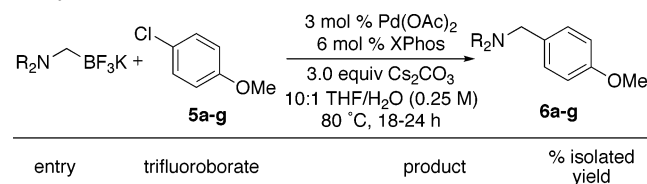
Studies concerning the scope of the aminomethyl component of the reaction were subsequently undertaken. In addition to aminomethyltrifluoroborates previously prepared in our laboratory,[9] we synthesized two additional examples (eqs 4 and 5). As was the case in our preliminary studies, simply using a slight

excess of the amine nucleophile in the presence of the bromomethyltrifluoroborate in THF at reflux afforded excellent isolated yields of the corresponding aminomethyltrifluoroborates as crystalline solids.

(4)

$Br\text{-}BF_3K$ + (N-methylpiperazine) 1.00 equiv / 1.05 equiv → THF reflux, 3 h 72% → **5a**

(5)

$Br\text{-}BF_3K$ + 1.00 equiv / 1.05 equiv → THF 80 °C, 4.5 h 83% → **5b**

The reaction conditions developed for cross-coupling tolerated many different aminomethyltrifluoroborates (Table 3). As it transpires, the process appears general for a variety of aminomethylating agents, including those derived from acyclic

TABLE 3. Cross-Coupling of Various Potassium *N,N*-Dialkylamino-methyltrifluoroborates with 4-Chloroanisole[a]

$R_2N\text{-}BF_3K$ + 4-chloroanisole → 3 mol % Pd(OAc)$_2$ / 6 mol % XPhos / 3.0 equiv Cs$_2$CO$_3$ / 10:1 THF/H$_2$O (0.25 M) / 80 °C, 18-24 h → **6a-g**

5a-g

entry	trifluoroborate	product	% isolated yield
1	5a	6a	68
2	5b	6b	75
3	5c	6c	75
4	5d	6d	84
5	5e	6e	95
6	5f	6f	74
7	5g	6g	82

[a] All reactions were carried out using 1.0 mmol of 4-chloroanisole and 1.01 mmol of the potassium *N,N*-dialkylaminomethyltrifluoroborate.

TABLE 4. Electrophile Compatibility in the Suzuki−Miyaura Cross-Coupling with Potassium *N*-(Trifluoroboratomethyl)-piperidine[a]

piperidine-BF$_3$K + E-Ar-R → 3 mol % Pd(OAc)$_2$ / 6 mol % XPhos / 3.0 equiv Cs$_2$CO$_3$ / 10:1 THF/H$_2$O (0.25 M) / 80 °C, 18-24 h → **2a, d**

7a-d

entry	aryl electrophile	product	% isolated yield
1	7a	2a	83
2	7b	2d	82
3	7c	2a	65
4	7d	2a	0

[a] All reactions were carried out using 1.0 mmol of the aryl electrophile and 1.01 mmol of potassium *N*-(trifluoroboratomethyl)piperidine.
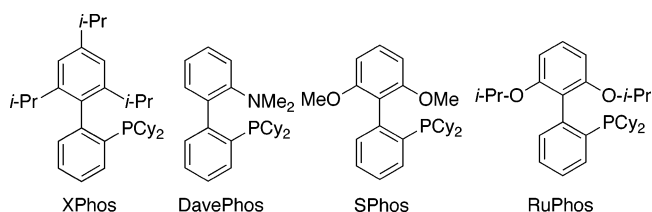

FIGURE 1. Buchwald ligands.

amines, cyclic amines, and heterocycles. Of particular interest are the Boc-protected piperazine and Bn-protected methylamine (entries 5 and 6), both of which would allow a secondary amine to be revealed and further elaborated as needed subsequent to deprotection.

The reaction with other aryl electrophiles was also examined. Not surprisingly, aryl iodides and triflates coupled cleanly using our standard conditions (Table 4). Only phenyl tosylate showed no reactivity.

Encouraged by the generality and success of our method using aryl electrophiles, we sought to apply the method to alkenyl bromides, allowing access to the allylamine subunit. We first explored a variety of reaction conditions employing several catalyst/ligand systems. The reaction of *N*-(trifluoroborato-methyl)piperidine with β-bromostyrene was chosen as the model system owing to the ready availability of these reagents. After screening several palladium sources [Pd(OAc)$_2$, PdCl$_2$, PdCl$_2$(dppf)•CH$_2$Cl$_2$] only Pd(OAc)$_2$ showed reasonable reactivity. We then examined numerous ligands (Figure 1), catalyst/ligand loadings and solvents (Table 5). The reaction proceeded satisfactorily using 0.6 mol % of Pd(OAc)$_2$ and 1.2 mol % of XPhos as the catalyst system in 10:1 THF/H$_2$O (0.25 M) in the presence of Cs$_2$CO$_3$ as the base. A low catalyst loading was

TABLE 5. Optimization of Conditions for the Cross-Coupling of Alkenyl Bromides
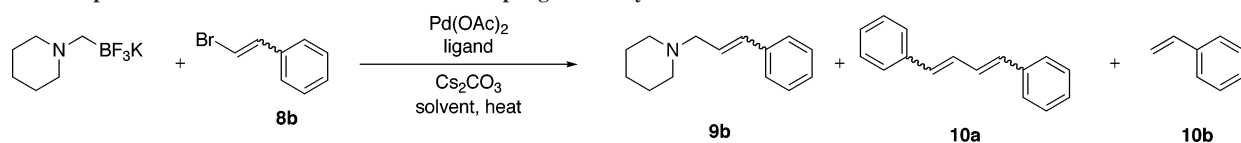
entry	ligand	catalyst/ligand loading (mol %)	solvent	T (°C)	reaction time (h)	ratio of **8a/9a/10a/10b**[a]
1	PPh$_3$	3/6	THF/H$_2$O	80	24	0/2/85/13
2	PPh$_3$	1/2	THF/H$_2$O	80	48	68/4/22/6
3	SPhos	3/6	THF/H$_2$O	80	24	0/15/78/7
4	DavePhos	3/6	THF/H$_2$O	80	24	0/7/88/5
5	RuPhos	3/6	THF/H$_2$O	80	24	0/10/75/15
6	XPhos	3/6	THF/H$_2$O	80	24	0/27/68/4
7	XPhos	2/4	THF/H$_2$O	80	24	0/58/38/4
8	XPhos	1/2	THF/H$_2$O	80	24	4/64/32/0
9	XPhos	1/2	CPME/H$_2$O	95	24	0/53/47/0
10	XPhos	1/2	toluene/ H$_2$O	105	24	0/43/57/0
11	**XPhos**	**0.5/1**	**THF/H$_2$O**	**80**	**48**	**6/94/0/0**
12	XPhos	0.5/1	dioxane/H$_2$O	110	48	0/67/33/0
13	**XPhos**	**0.6/1.2**	**THF/H$_2$O**	**80**	**48**	**0/96/4/0**

[a] Ratio of **8b/9b/10a/10b** in the crude reaction mixture by GC assay.

TABLE 6. Cross-Coupling of Potassium *N*-(Trifluoroboratomethyl)-piperidine with Some Alkenyl Bromides
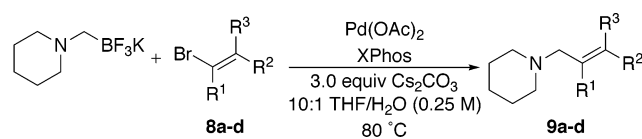
entry	alkenyl bromide	product	% isolated yield
1	**8a**	**9a**	80[a]
2	**8b**	**9b**	78[a]
3	**8c**	**9c**	67[a]
4	**8d**	**9d**	63[b]

[a] 2.0 mmol of the alkenyl bromide, 2.1 mmol of potassium *N*-(trifluoroboratomethyl)piperidine, Pd(OAc)$_2$ (0.6 mol %), XPhos (1.2 mol %), 48 h. [b] 1.0 mmol of the alkenyl bromide, 1.05 mmol of potassium *N*-(trifluoroboratomethyl)piperidine, Pd(OAc)$_2$ (1 mol %), XPhos (2 mol %), 24 h.

found to be essential to discourage homocoupling of the halide. The desired product **9b** was obtained in 78% yield.

The generality of this reaction was demonstrated by subjecting numerous alkenyl bromides to the optimized reaction conditions with *N*-(trifluoroboratomethyl)piperidine. Unfortunately, the reaction proved to be substrate dependent; however, we were able to obtain synthetically useful yields for a few substrates (Table 6). While styrenyl (**8a−c**) and largely unfunctionalized alkenyl bromides, such as **8d**, proved amenable to the reaction,

the attempted coupling of several others (e.g., α-bromocyclo-pentenone, bromotriphenylethylene, 2-bromo-3-methyl-2-butene and bromomethylenecyclohexane) resulted in a complex mixture of products or unacceptably low yields, despite variation of the reaction conditions.

Conclusion

In conclusion, we have extended the palladium catalyzed aminomethylation previously developed for aryl bromides to allow the use of various aryl electrophiles, most notably aryl chlorides. The method consists of Suzuki−Miyaura cross-coupling of these aryl electrophiles with potassium amino-methyltrifluoroborates prepared via S$_N$2 displacement of potas-sium bromomethyltrifluoroborate with various secondary amines. The cross-coupling reaction tolerates various electron rich and electron poor aryl and heteroaryl electrophiles containing varied functional groups (esters, nitriles, aldehydes, etc.). We have also demonstrated that the reaction of alkenyl bromides, although not amenable to general coupling conditions, can be effected using substrate dependent conditions. The novel coupling methods described herein will allow the facile incorporation of the aminomethyl moiety into a wide variety of molecules in a manner that is complementary to existing procedures.

Experimental Section

General Procedure for the Preparation of Potassium Ami-nomethyltrifluoroborates. Preparation of Potassium 1-Methyl-4-trifluoroboratomethylpiperazine (5a). Potassium bromometh-yltrifluoroborate (1.0 g, 5.00 mmol) was added to a solution of 1-methylpiperazine (0.59 g, 5.25 mmol) in THF (7 mL) at rt, and the mixture was heated at 80 °C until the reaction was complete as indicated by ^{19}F NMR. The resulting reaction mixture was concentrated in vacuo. The product was dissolved in a solution of dry acetone (150 mL) and K$_2$CO$_3$ (691 mg, 5.0 mmol) and stirred for 30 min. The solution was filtered through a pad of Celite to remove the insoluble salts, and the filtrate was concentrated. The crude solid was dissolved in a minimal amount of hot acetone, (∼25 mL) and Et$_2$O (∼75 mL) was added dropwise, leading to precipita-tion of the product. The product was then filtered, collected, and dried overnight in vacuo to afford the desired pure compound in 72% yield (785 mg, 3.56 mmol) as a yellow crystalline solid: mp 119−121 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ: 3.27 (br s, 4H), 2.68 (br s, 4H), 2.29 (s, 3H), 2.08 (s, 2H); ^{13}C NMR (125.8 MHz,

acetone-d_6) δ: 55.6, 52.9, 45.7; ^{19}F-NMR (471 MHz, acetone-d_6) δ −142.68; ^{11}B-NMR (128.37 MHz, acetone-d_6) δ 1.13; IR (KBr) = 3197, 2950, 2805, 1454, 1286, 1150, 1046 cm^{-1}; HRMS (ESI) calcd for $C_6H_{13}BF_3N_2$ (M − K) 181.1124, found 181.1120.

General Procedure for Suzuki−Miyaura Cross-Coupling Reactions of Aryl Electrophiles. Preparation of (Piperidin-1-ylmethyl)benzene (2a). A Biotage microwave vial was charged with Pd(OAc)$_2$ (7 mg, 0.03 mmol), XPhos (29 mg, 0.06 mmol), potassium N-(trifluoroboratomethyl)piperidine (207 mg, 1.01 mmol), and Cs$_2$CO$_3$ (978 mg, 3.0 mmol). The tube was sealed with a cap lined with a disposable Teflon septum and evacuated under vacuum and filled with N$_2$ three times. Chlorobenzene (113 mg, 1.0 mmol), and THF/H$_2$O (10:1) (0.25 M, 4 mL) were added by syringe and the reaction was stirred at 80 °C for 24 h, then cooled to rt and diluted with H$_2$O (2 mL). The reaction mixture was extracted with CH$_2$Cl$_2$ (3 × 5 mL) or alternatively with EtOAc (3 × 5 mL). The organic layer was dried (Na$_2$SO$_4$). The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (elution with hexane/EtOAc/Et$_3$N 4:1:0.05: R_f 0.18) to yield the product as a clear yellow oil in an 85% yield (150 mg, 0.85 mmol): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.27−7.31 (m, 3H), 7.22−7.24 (m, 2H), 3.46 (s, 2H), 2.36 (br s, 4H), 1.54−1.58 (m, 4H), 1.41−1.44 (m, 2H); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 138.9, 129.4, 128.3, 127.0, 64.1, 54.7, 26.2, 24.6; IR (neat) = 2932, 2792 cm^{-1}; HRMS (CI) calcd for $C_{12}H_{18}N$ (MH$^+$) 176.1439, found 176.1431.

General Procedure for Suzuki−Miyaura Cross-Coupling Reactions of Alkenyl Bromides. Preparation of 1-Phenyl-1-(piperidin-1-ylmethyl)ethylene (9a). A 50 mL round-bottom flask was charged with Pd(OAc)$_2$ (2.7 mg, 0.012 mmol), XPhos (11.4 mg, 0.024 mmol), potassium N-(trifluoroboratomethyl)piperidine (430 mg, 2.1 mmol), and Cs$_2$CO$_3$ (1.95 g, 6.0 mmol). The flask was fitted with a reflux condenser and a rubber septum, evacuated under vacuum, and purged with N$_2$ three times. α-Bromostyrene (366 mg, 2.0 mmol) and THF/H$_2$O (10:1) (0.25 M, 8 mL) were

added by syringe, and the reaction was stirred at 80 °C for 48 h, then cooled to rt and diluted with H$_2$O (4 mL). The reaction mixture was extracted with CH$_2$Cl$_2$ (3 × 5 mL). The organic layer was dried (Na$_2$SO$_4$). The solvent was removed in vacuo, and the crude product was purified by basic aluminum oxide column chromatography (elution with hexane/EtOAc/Et$_3$N 36:1:0.2: R_f 0.28) to yield the product as a clear yellow oil in an 80% yield (342 mg, 1.70 mmol): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.52 (d, J = 8.5 Hz, 2H), 7.28−7.31 (m, 2H), 7.24−7.26 (m, 1H), 5.44 (d, J = 1.7 Hz, 1H), 5.23 (d, J = 1.6 Hz, 1H), 3.28 (s, 2H), 2.40 (br s, 4H), 1.52−1.56 (m, 4H), 1.39−1.43 (m, 2H); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 144.8, 141.0, 128.2, 127.5, 126.5, 114.9, 63.9, 54.7, 26.3, 24.7. The spectral data were in agreement with those reported in the literature.[15]

Supporting Information Available: Experimental procedures, spectral characterization, and copies of ^{1}H, ^{13}C, ^{11}B, and ^{19}F spectra for all compounds prepared by the method described. This material is available free of charge via the Internet at http://pubs.acs.org.

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