JOC The Journal of Organic Chemistry

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# Suzuki Coupling of Potassium Cyclopropyl- and Alkoxymethyltrifluoroborates with Benzyl Chlorides

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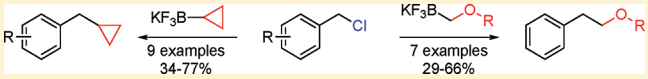
Supporting Information

**ABSTRACT:** Efficient $Csp^3$–$Csp^3$ Suzuki couplings have been developed with both potassium cyclopropyl- and alkoxymethyltrifluoroborates. Moderate to good yields have been achieved in the cross-coupling of potassium cyclopropyltrifluoroborate with benzyl chlorides possessing electron-donating or electron-withdrawing substituents. Benzyl chloride was also successfully cross-coupled to potassium alkoxymethyltrifluoroborates derived from primary, secondary, and tertiary alcohols.




Cyclopropyl groups are of great interest because of their occurrence in many natural products and synthesized drug molecules.[1,2] Phenylethoxy moieties are also important in bioactive compounds because they can enhance molecular properties, in particular the solubility, of drug molecules.[3−5] Both cyclopropyl and ether subunits also present the advantage of preventing the metabolic breakdown of active pharmaceutical ingredients.

Cross-coupling approaches to introduce these subunits into aliphatic core structures can present difficulties because alkyl–alkyl Suzuki–Miyaura coupling reactions remain a challenge.[6,7] Indeed, alkyl halides are less reactive toward oxidative addition than their unsaturated analogues.[8] In the past 15 years, diverse boronic acids and alkylboronates have been tested in their reactions toward numerous alkyl electrophiles.[9,10] Most of these studies were carried out on alkyl bromides,[11−13] but $Csp^3$–$Csp^3$ bond formations have been also reported with iodoalkanes[14] and alkyl tosylates.[15] Fu and co-workers developed a method to couple a range of alkyl chlorides with *B*-alkyl-9-BBN reagents, utilizing $Pd_2(dba)_3$ in conjunction with tricyclohexylphosphine as a ligand.[16]

Benzyl chlorides are activated alkyls that lack beta hydrogens and therefore have been described as good electrophiles in Suzuki–Miyaura cross-couplings with aryl and (hetero)arylboronic acids,[17] but they have rarely been used with alkylboron species. Pertinent to the current work, Deng and co-workers have reported the coupling of benzyl bromides with substituted cyclopropylboronic acids, in which the use of expensive $Ag_2O$ as a base was required to enhance the rate of the reaction.[18] Only a few additional literature accounts describe the use of cyclopropylboron species in Suzuki coupling reactions with $sp^3$-hybridized electrophiles,[19,20] and even cyclopropyl Kumada[21] and Negishi[22] couplings with benzylic halides are exceedingly rare.

Similarly, although Suzuki–Miyaura couplings between potassium alkoxymethyltrifluoroborates and aryl chlorides have been reported,[23] their coupling to $sp^3$-hybridized halides remains unexplored. Having recently demonstrated that good yields are obtained for the Suzuki–Miyaura cross-coupling between substituted benzyl halides and potassium aryltrifluoroborates,[24] we sought to extend this success to two select alkyltrifluoroborate systems. Herein, we describe alkyl–alkyl Suzuki–Miyaura cross-coupling reactions of benzyl chlorides with potassium cyclopropyltrifluoroborate and alkoxymethyltrifluoroborates, neither class of which has ever been cross-coupled to $sp^3$-hybrized electrophiles.

During initial optimization studies of the cyclopropyl system, we investigated several palladium catalysts in combination with a variety of ligands.[25,26] For cyclopropyltrifluoroborate, $Pd(OAc)_2$/RuPhos gave the best conversions when compared to the other biarylphosphines (e.g., SPhos and XantPhos, Figure 1)

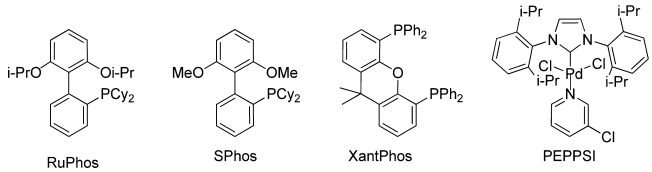



**Figure 1.** Structures of ligands and PEPPSI precatalyst.

and BINAP, resulting in 57% yield of product **1a** (Table 1, entry 1). Interestingly, changing the palladium source from $Pd(OAc)_2$ to $Pd_2(dba)_3$[27,28] resulted in a higher conversion to alkylated product **1a** (Table 1, entry 5). Other palladium catalysts such as tetrakis(triphenylphosphine)palladium(0) (Table 1, entry 6) and bis(triphenylphosphine)palladium(II) chloride (Table 1, entry 7) gave moderate conversions to the desired product.

*N*-Heterocyclic carbene ligands (NHC), discovered by Öfele,[29] represent a second class of ligands that are commonly used in C–C bond couplings. These compounds are neutral, electron-rich, excellent $\sigma$-donors, and have a poor capacity to accept $\pi$

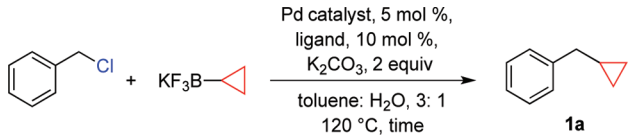
**Received:** December 29, 2011
**Published:** March 6, 2012





dx.doi.org/10.1021/jo202686p | *J. Org. Chem.* 2012, 77, 2966–2970

**Table 1. Optimization**[a]




| entry | catalyst | ligand | yield (%)[b] |
|---|---|---|---|
| 1 | $Pd(OAc)_2$ | RuPhos | 57 |
| 2 | $Pd(OAc)_2$ | SPhos | 41 |
| 3 | $Pd(OAc)_2$ | XantPhos | 23 |
| 4 | $Pd(OAc)_2$ | BINAP | 55 |
| 5 | $Pd_2(dba)_3$ | RuPhos | 62 |
| 6 | $Pd(PPh_3)_4$ | | 29 |
| 7 | $Pd(PPh_3)_2Cl_2$ | $PPh_3$ | 44 |
| 8 | PEPPSI | | 89 |

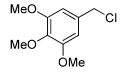
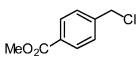
[a]Benzyl chloride (0.2 mmol), potassium cyclopropyltrifluoroborate (0.35 mmol), Pd catalyst (0.01 mmol), ligand (0.02 mmol), $K_2CO_3$ (0.4 mmol), toluene/$H_2O$ 3:1 (0.1 M), 120 °C, 18 h. [b]GC–MS yield determined using dodecane as the internal standard.

back-donation from the metal center.[30] Organ and co-workers recently employed an NHC precatalyst in the formation of $Csp^3$–$Csp^3$ bonds with alkylboronates.[31] Further to this, they reported $Csp^2$–$Csp^3$ Suzuki couplings between potassium organotrifluoroborates and alkyl halides using pyridine enhanced precatalyst preparation stabilization and initiation (PEPPSI) as a catalyst.[32] In the present system, the PEPPSI precatalyst also appeared to be efficient, resulting in a conversion of 89% of **1a** (Table 1, entry 8).

Optimization also involved screening various conventional inorganic bases; in this regard, potassium carbonate gave the best conversion. Additionally, it was important to limit the concentration of the reaction to 0.1 M to suppress dimer formation. Incorporating these parameters, we obtained the highest conversions using two different catalytic systems; $Pd_2(dba)_3$/RuPhos and the PEPPSI precatalyst (Table 1, entries 5 and 8). Subsequently, we also noticed that the mixture of toluene/water in a ratio of 19:1 was important to avoid the formation of benzylic alcohols derived from hydrolysis of solvolytically reactive benzyl chlorides.

Utilizing this reaction protocol, the reactivity of various benzyl chlorides toward potassium cyclopropyltrifluoroborate was evaluated. We initially studied the PEPPSI precatalyst, but its practical application was mostly limited to electron deficient benzyl chlorides (Table 2). The scope of the reaction proved to

**Table 2. Optimization on Substituted Benzyl Chlorides**[a]

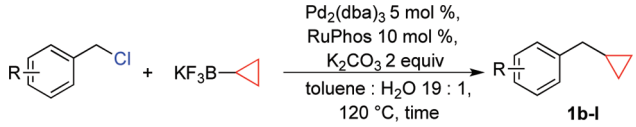
| entry | benzyl chloride | catalytic system | GC/MS yield (%) [b] |
|---|---|---|---|
| 1 |  | $Pd_2(dba)_3$ / RuPhos | 93 |
| 2 | | PEPPSI | 75 |
| 3 |  | $Pd_2(dba)_3$ / RuPhos | 92 |
| 4 | | PEPPSI | 96 |

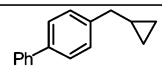
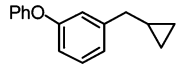
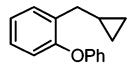
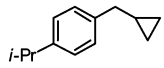
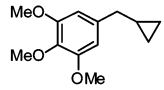
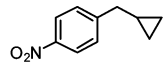
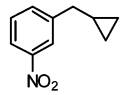
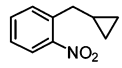
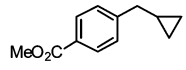
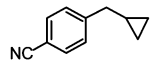
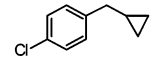
[a]Benzyl chloride (0.2 mmol), potassium cyclopropyltrifluoroborate (0.35 mmol), Pd catalyst (0.01 mmol), ligand (0.02 mmol), $K_2CO_3$

be much broader using $Pd_2(dba)_3$ and RuPhos as the catalytic system, as both electron-rich and electron-poor substrates were successfully cross-coupled with moderate to good yields.

Using the RuPhos system, benzyl chlorides decorated with electron-donating groups in the *ortho*, *meta*, and *para* positions proved to be suitable substrates for the reactions, resulting in yields of the desired products as high as 80% (Table 3). The

**Table 3. Scope of Substituted Benzyl Chlorides**[a]




| entry | product | | time | yield (%) |
|---|---|---|---|---|
| 1 |  | **1b** | 5 h | 58 |
| 2 |  | **1c** | 3 h | 77 |
| 3 |  | **1d** | 3 h | 76 |
| 4 |  | **1e** | 7 h | 62 |
| 5 |  | **1f** | 5 h | 56 (72)[b] |
| 6 |  | **1g** | 3 h | 49 |
| 7 |  | **1h** | 7 h | 80 |
| 8 |  | **1i** | 6 h | 0 |
| 9 |  | **1j** | 4 h | 73 |
| 10 |  | **1k** | 2.5 h | 59 |
| 11 |  | **1l** | 24 h | 34 |

[a]Benzyl chloride (2.0 mmol), potassium cyclopropyltrifluoroborate (3.5 mmol), $Pd_2(dba)_3$ (0.1 mmol), RuPhos (0.2 mmol), $K_2CO_3$ (4.0 mmol), toluene/$H_2O$ 19:1 (0.1 M), 120 °C. [b]Reaction performed on 1 g scale.

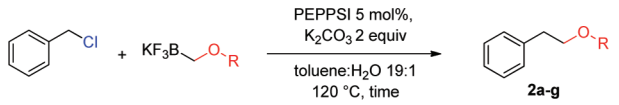
coupling between 3,4,5-trimethoxybenzyl chloride and potassium cyclopropyltrifluoroborate could be performed on one gram scale, demonstrating the scalability of these couplings. The desired compound **1f** was isolated in a yield of 72% (Table 3, entry 5). Electron-deficient substituents such as carbonyl-, cyano-, and nitro- groups were tolerated when they were placed *para* (Table 3, entries 6, 9, 10) or *meta* to the chloromethyl group (Table 3, entry 7). However, no coupling was observed

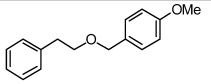
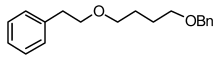
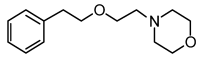
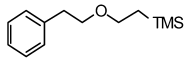
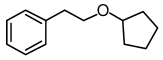
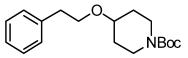
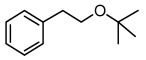

dx.doi.org/10.1021/jo202686p | J. Org. Chem. 2012, 77, 2966–2970

when 2-nitrobenzyl chloride was tested (Table 3, entry 8). Using optimized conditions, we obtained modest chemoselectivity in the cross-coupling of 4-chlorobenzyl chloride (Table 3, entry 11), giving the desired $Csp^3$-alkylated compound **1l** in 34% yield, with 1-chloro-4-methylbenzene as well as dialkylated materials being observed among the byproducts.

Our previously optimized conditions using PEPPSI precatalyst proved best for the coupling of potassium alkoxymethyltrifluoroborates with benzyl chloride. The desired coupling products were isolated in yields between 29 and 66% (Table 4). The cross coupling was adversely affected by

**Table 4. Scope of Potassium Alkoxymethyltrifluoroborates**[a]




| entry | product | | time | yield (%) |
|---|---|---|---|---|
| 1 |  | **2a** | 24 h | 66 |
| 2 |  | **2b** | 16 h | 62 |
| 3 |  | **2c** | 3 h | 45 |
| 4 |  | **2d** | 5 d | 45 |
| 5 |  | **2e** | 3 d | 40 |
| 6 |  | **2f** | 4 d | 42 |
| 7 |  | **2g** | 20 h | 29 |

[a]Benzyl chloride (2.0 mmol), potassium alkoxymethyltrifluoroborate (3.5 mmol), PEPPSI (0.1 mmol), $K_2CO_3$ (4.0 mmol), toluene/$H_2O$ 19:1 (0.1 M), 120 °C.

steric hindrance. Potassium alkoxymethyltrifluoroborates derived from primary alcohols gave moderate to good yields (Table 4, entries 1−4). Potassium alkoxymethyltrifluoroborates bearing secondary substituents afforded products **2e−f** with yields up to 42% yield (Table 4, entries 5−6). Finally, the cross-coupling of potassium (*tert*-butoxymethyl)trifluoroborate led to the alkylated compound **2g** with only 29% yield (Table 4, entry 7).

In summary, we have developed Suzuki−Miyaura conditions that allow the formation of $Csp^3$−$Csp^3$ bonds between potassium cyclopropyl- or alkoxymethyltrifluoroborates and benzyl chlorides with yields up to 77%. Electron-rich and electron-poor substituents on the benzyl chlorides are allowed, and potassium alkoxymethyltrifluoroborates derived from primary, secondary, and tertiary alcohol precursors are all suitable reagents for the process. This method broadens the application of potassium organotrifluoroborates in $Csp^3$−$Csp^3$ bond formation.

## EXPERIMENTAL SECTION

**Procedure A.** *1-Cyclopropylmethyl-4-phenylbenzene (**1b**).* A Biotage microwave vial was charged with 4-phenylbenzyl chloride (413.6 mg, 2.0 mmol), potassium cyclopropyltrifluoroborate (443.9 mg, 3.0 mmol), $Pd_2(dba)_3$ (91.6 mg, 0.1 mmol), RuPhos (98.2 mg, 0.2 mmol), and $K_2CO_3$ (552.8 mg, 4.0 mmol). The tube was sealed and purged with nitrogen. A degassed mixture of toluene/water, 19:1 (mL/mL), was added under a nitrogen atmosphere. The reaction was stirred at 120 °C for 7 h. After cooling to room temperature, the reaction mixture was filtered through Celite and $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by preparative plate chromatography (silica gel, heptanes/EtOAc 95:5) to obtain **1b** as a colorless oil (240.8 mg, 58%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.62−7.59 (m, 2H), 7.57−7.53 (m, 2H), 7.47−7.42 (m, 2H), 7.37−7.32 (m, 3H), 2.61 (d, $J$ = 7.0 Hz, 2H), 1.10−0.99 (m, 1H), 0.58−0.58 (m, 2H), 0.26−0.22 (m, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 141.4, 141.3, 138.9, 128.9 (2C), 128.8 (2C), 127.1 (3C), 127.0 (2C), 40.1, 12.0, 4.9 (2C); HRMS (EI) calcd for $C_{16}H_{16}$ [($M^{+\cdot}$)] 208.1252, found 208.1247; IR (neat) $\nu$ 3001, 2913, 1487, 1016, 825, 697 cm$^{-1}$.

*1-Cyclopropylmethyl-3-phenoxybenzene (**1c**).* Following standard procedure A, the reaction was performed starting from 3-phenoxybenzyl chloride (446.3 mg, 2.0 mmol). After 3 h, the resulting crude was purified by preparative plate chromatography (heptane/EtOAc 98:2); **1c** was obtained as a colorless oil (343.5 mg, 77%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.38 (td, $J$ = 8.1, 1.8 Hz, 2H), 7.30 (td, $J$ = 3.7, 1.8 Hz, 1H), 7.14 (t, $J$ = 7.0 Hz, 1H), 7.08−7.04 (m, 3H), 7.00 (br s, 1H), 6.88 (dd, $J$ = 7.9, 2.4 Hz, 1H), 2.57 (d, $J$ = 7.0 Hz, 2H), 1.07−0.96 (m, 1H), 0.59−0.54 (m, 2H), 0.25−0.21 (m, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 157.5, 157.2, 144.4, 129.8 (2C), 129.5, 123.4, 123.2, 119.1, 118.9 (2C), 116.4, 40.3, 11.8, 4.8 (2C); HRMS (EI) calcd for $C_{16}H_{16}O$ [($M^{+\cdot}$)] 224.1201, found 224.1185; IR (neat) $\nu$ 3075, 3000, 1582, 1485, 1250 cm$^{-1}$.

*1-Cyclopropylmethyl-2-phenoxybenzene (**1d**).* Following standard procedure A, the reaction was performed starting from 2-phenoxybenzyl chloride (437.4 mg, 2.0 mmol). After 3 h, the resulting crude was purified by preparative plate chromatography (heptane/EtOAc 98:2); **1d** was obtained as a colorless oil (341.9 mg, 76%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.40−7.29 (m, 3H), 7.08−7.05 (m, 5H), 6.88 (dd $J$ = 7.9, 2.0 Hz, 1H), 2.57 (d, $J$ = 7.0 Hz, 2H), 1.02−0.91 (m, 1H), 0.58−0.45 (m, 2H), 0.25−0.21 (m, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 157.5, 157.2, 144.3, 129.8 (2C), 129.5, 123.4, 123.1, 116.1, 118.8 (2C), 116.4, 40.2, 11.8, 4.8 (2C); HRMS (EI) calcd for $C_{16}H_{16}O$ [($M^{+\cdot}$)] 224.1201, found 224.1223; IR (neat) $\nu$ 3074, 3001, 1582, 1486, 1250 cm$^{-1}$.

*1-Cyclopropylmethyl-4-(propan-2-yl)benzene (**1e**).* Following standard procedure A, the reaction was performed starting from 4-*iso*-propylbenzyl chloride (347.8 mg, 2.0 mmol). After 7 h, the resulting crude was purified by preparative plate chromatography (heptane/EtOAc 85:15); **1e** was obtained as a colorless oil (217.1 mg, 62%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.20 (d, $J$ = 8.4 Hz, 2H), 7.16 (d, $J$ = 8.1 Hz, 2H), 2.89 (sept, $J$ = 6.9 Hz, 1H), 2.52 (d, $J$ = 7.0 Hz, 2H), 1.25 (d, $J$ = 7.0 Hz, 6H), 1.03−0.94 (m, 1H), 0.54−0.49 (m, 2H), 0.22−0.18 (m, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 146.4, 139.6, 128.4 (2C), 126.4 (2C), 40.1, 33.9, 24.2 (2C), 12.0, 4.8 (2C); HRMS (EI) calcd for $C_{13}H_{18}$ [($M^{+\cdot}$)] 174.1409, found 174.1424; IR (neat) $\nu$ 2959, 1731, 1514, 1460, 825 cm$^{-1}$.

*5-Cyclopropylmethyl-1,2,3-trimethoxybenzene (**1f**).* Following standard procedure A, the reaction was performed starting from methyl 3,4,5-trimethoxybenzyl chloride (433.3 mg, 2.0 mmol). After 4 h, the resulting crude was purified by preparative plate chromatography (heptanes/EtOAc 95:5); **1f** was obtained as a yellow oil (248.4 mg, 56%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 6.50 (s, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 2.51 (d, $J$ = 6.6 Hz, 2H), 1.05−0.94 (m, 1H), 0.58−0.53 (m, 2H), 0.20−0.24 (m, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 153.0 (2C), 137.9, 136.1, 105.2 (2C), 60.7, 56.0 (2C), 40.6, 11.7, 4.6 (2C); HRMS (EI) calcd for $C_{13}H_{18}O_3$ [($M^{+\cdot}$)] 222.1256, found 222.1249; IR (neat) $\nu$ 2997, 2936, 1588, 1237, 1127 cm$^{-1}$.

*1-Cyclopropylmethyl-4-nitrobenzene (**1g**).* Following standard procedure A, the reaction was performed starting from 4-nitrobenzyl chloride (343.2 mg, 2.0 mmol). After 3 h, the resulting crude was purified by preparative plate chromatography (heptane/EtOAc 85:15);


dx.doi.org/10.1021/jo202686p | J. Org. Chem. 2012, 77, 2966−2970

**1g** was obtained as a colorless oil (175.2 mg, 49%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 8.16 (dt, $J$ = 8.8, 2.2 Hz, 2H), 7.42 (dt, $J$ = 8.1, 2.6 Hz, 2H), 2.65 (d, $J$ = 7.0 Hz, 2H), 1.06−0.95 (m, 1H), 0.62−0.57 (m, 2H), 0.27−0.23 (m, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 150.2, 146.6, 129.2 (2C), 123.7 (2C), 40.3, 11.5, 5.0 (2C); HRMS (EI) calcd for $C_{10}H_{11}NO_2$ [($M^{+\cdot}$)] 177.0790, found 177.0803; IR (neat) $\nu$ 3079, 2933, 1599, 1516, 1344 cm$^{-1}$.

*1-Cyclopropylmethyl-3-nitrobenzene (**1h**).* Following standard procedure A, the reaction was performed starting from 3-nitrobenzyl chloride (353.8 mg, 2.0 mmol). After 7 h, the resulting crude was purified by preparative plate chromatography (heptane/EtOAc 85:15); **1h** was obtained as a colorless oil (281.9 mg, 80%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 8.14 (s, 1H), 8.07 (br d, $J$ = 8.4 Hz, 1H), 7.60 (d, $J$ = 7.3 Hz, 1H), 7.46 (t, $J$ = 7.9 Hz, 1H), 2.65 (d, $J$ = 7.0 Hz, 2H), 1.07−0.96 (m, 1H), 0.61−0.58 (m, 2H), 0.27−0.23 (m, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 148.4, 144.3, 134.7, 129.2, 123.2, 121.2, 34.0, 11.5, 4.9 (2C); HRMS (EI) calcd for $C_{10}H_{11}NO_2$ [($M^{+\cdot}$)] 177.0790, found 177.0767; IR (neat) $\nu$ 3078, 3002, 1524, 1349, 806 cm$^{-1}$.

*Methyl 4-Cyclopropylmethylbenzoate (**1j**).* Following standard procedure A, the reaction was performed starting from methyl 4-(chloromethyl)benzoate (380.7 mg, 2.0 mmol). After 4 h, the resulting crude was purified by preparative plate chromatography (heptane/EtOAc 70:30); **1j** was obtained as a colorless oil (278.2 mg, 73%).$^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.97 (d, $J$ = 8.4 Hz, 2H), 7.33 (d, $J$ = 8.4 Hz, 2H), 3.90 (s, 3H), 2.6 (d, $J$ = 7.0 Hz, 2H), 1.05−0.94 (m, 1H), 0.57−0.52 (m, 2H), 0.24−0.20 (m, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 167.2, 147.7, 129.7 (2C), 128.4 (2C), 127.9, 52.0, 40.3, 11.6, 4.8 (2C); HRMS (EI) calcd for $C_{12}H_{14}O_2$ [($M^{+\cdot}$)] 190.0994, found 190.0981; IR (neat) $\nu$ 3001, 1719, 1434, 1277, 1108 cm$^{-1}$.

*4-Cyclopropylmethyl-benzonitrile (**1k**).* Following standard procedure A, the reaction was performed starting from 4-chloromethylbenzonitrile (309.4 mg, 2.0 mmol). After 3 h, the resulting crude was purified by preparative plate chromatography (heptane/EtOAc 80:20); **1k** was obtained as a colorless oil (186.8 mg, 59%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.59 (dt, $J$ = 8.1, 1.8 Hz, 2H), 7.37 (d, $J$ = 8.1 Hz, 2H), 2.61 (d, $J$ = 7.0 Hz, 2H), 1.03−0.93 (m, 1H), 0.61−0.56 (m, 2H), 0.24−0.20 (m, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 148.0, 132.2 (2C), 129.2 (2C), 119.3, 109.9, 40.5, 11.4, 4.9 (2C); HRMS (EI) calcd for $C_{11}H_{11}N$ [($M^{+\cdot}$)] 157.0897, found 157.0918; IR (neat) $\nu$ 3079, 3003, 2227, 1608, 1020, 826 cm$^{-1}$.

*1-Chloro-4-cyclopropylmethylbenzene (**1l**).* Following standard procedure A, the reaction was performed starting from 4-chloro-benzyl chloride (332.1 mg, 2.0 mmol). After 10 h, the resulting crude was purified by preparative plate chromatography (heptanes/EtOAc 95:5); **1l** was obtained as a colorless oil (112.9 mg, 34%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.07 (dt, $J$ = 8.4, 1.8 Hz, 2H), 7.00 (dt, $J$ = 8.1, 1.8 Hz, 2H), 2.51 (d, $J$ = 7.0 Hz, 2H), 1.00−0.89 (m, 1H), 0.55−0.50 (m, 2H), 0.21−0.17 (m, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 140.7, 131.6, 129.8 (2C), 128.4 (2C), 39.8, 11.9, 4.8 (2C); HRMS (EI) calcd for $C_{10}H_{11}Cl$ [($M^{+\cdot}$)] 166.0549, found 166.0524; IR (neat) $\nu$ 3002, 2918, 1491, 1088, 1016 cm$^{-1}$.

**Procedure B.** *1-Methoxy-4-phenethyloxymethylbenzene (**2a**).* A Biotage microwave vial was charged with benzyl chloride (255.7 mg, 2.0 mmol), potassium (4-methoxy)benzyltrifluoroborate (900.5 mg, 3.0 mmol), PEPPSI (69.5 mg, 0.1 mmol), and $K_2CO_3$ (552.8 mg, 4.0 mmol). The tube was sealed and purged with nitrogen. A degassed mixture of toluene/$H_2O$ 19:1 (mL/mL) was added under a nitrogen atmosphere. The reaction was stirred at 120 °C for 24 h. After cooling to room temperature, the reaction mixture was filtered through Celite and $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by preparative plate chromatography (silica gel, heptanes/EtOAc 70:30) to obtain **2a** as a colorless oil (377.1 mg, 66%): The spectral data match those reported in the literature;[33] $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.31−7.18 (m, 7H), 6.86 (dt, $J$ = 8.4, 2.6 Hz, 2H), 4.46 (s, 2H), 3.80 (s, 3H), 3.66 (t, $J$ = 7.3 Hz, 2H), 2.92 (t, $J$ = 7.1 Hz, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 159.2, 139.1, 130.6, 129.2 (2C), 129.0 (2C), 128.4 (2C), 126.2, 113.8 (2C), 72.6, 71.0, 55.2, 36.4; HRMS (EI) calcd for $C_{16}H_{18}O_2$ [($M^{+\cdot}$)] 242.1307, found 242.1288; IR (neat) $\nu$ 2958, 2906, 1612, 1513, 1247, 1096 cm$^{-1}$.

*{[4-(2-Phenylethoxy)butoxy]methyl}benzene (**2b**).* Following standard procedure B, the reaction was performed starting from potassium (4-methoxy)benzyloxymethyltrifluoroborate (900.5 mg, 3.0 mmol). After 24 h, the resulting crude was purified by preparative plate chromatography (heptanes/EtOAc 70:30); **2b** was obtained as a colorless oil (302.4 mg, 62%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.37−7.18 (m, 10H), 4.49 (s, 2H), 3.62 (t, $J$ = 7.1 Hz, 2H), 3.49−3.44 (m, 4H), 2.88 (t, $J$ = 7.3 Hz, 2H), 1.68−1.65 (m, 4H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 139.1, 138.7, 128.9 (2C), 128.3 (2C), 128.3 (2C), 127.6 (2C), 127.5, 126.1, 72.8, 71.8, 70.7, 70.1, 36.4, 28.5; HRMS (EI) calcd for $C_{19}H_{25}O_2$ [($M^{+\cdot}$)] 285.1855, found 285.1839; IR (neat) $\nu$ 2932, 2858, 1454, 1363, 1102 cm$^{-1}$.

*4-(2-Phenethyloxyethyl)-morpholine (**2c**).* Following standard procedure B, the reaction was performed starting from potassium [2-(morpholin-4-yl)ethoxy]methyltrifluoroborate (792.9 mg, 3.0 mmol). After 24 h, the resulting crude was purified by preparative plate chromatography [$CH_2Cl_2$/ammonia (7 M in MeOH)/heptanes 60:2:38]; **2c** was obtained as a colorless oil (211.5 mg, 45%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.28 (t, $J$ = 7.3 Hz, 2H), 7.22−7.18 (m, 3H), 3.70−3.64 (m, 6H), 3.59 (t, $J$ = 5.7 Hz, 2H), 2.88 (t, $J$ = 7.1 Hz, 2H), 2.57 (t, $J$ = 5.5 Hz, 2H), 2.46−2.45 (m, 4H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 139.0, 129.0 (2C), 128.4 (2C), 126.3, 72.2, 68.5, 66.9 (2C), 58.3, 54.1 (2C), 36.3; HRMS (EI) calcd for $C_{14}H_{21}NO_2$ [($M^{+\cdot}$)] 235.1572, found 235.1577; IR (neat) $\nu$ 2854, 1453, 1115, 699 cm$^{-1}$.

*Trimethyl-(2-phenethyloxyethyl)silane (**2d**).* Following standard procedure B, the reaction was performed starting from (2-trimethylsilyl)-ethoxymethyl trifluoroborate (752.1 mg, 3.0 mmol). After 5 days, the resulting crude was purified by preparative plate chromatography (heptanes/EtOAc 70:30); **2d** was obtained as a yellow oil (198.6 mg, 45%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.32−7.19 (m, 5H), 3.64 (t, $J$ = 7.3 Hz, 2H), 3.55−3.51 (m, 2H), 2.94−2.88 (m, 2H), 0.98−0.93 (m, 2H), 0.01 (s, 9H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 139.3, 129.0 (2C), 128.5 (2C), 126.3, 71.4, 68.2, 36.6, 18.3, −1.2 (3C); HRMS (CI) calcd for $C_{13}H_{26}NOSi$ [($MNH_4^+$)] 240.1784, found 240.1765; IR (neat) $\nu$ 2951, 2855, 1248, 1102, 835 cm$^{-1}$.

*(2-Cyclopentyloxyethyl)benzene (**2e**).* Following standard procedure B, the reaction was performed starting from potassium cyclopentoxymethyltrifluoroborate (650.7 mg, 3.0 mmol). After 24 h, the resulting crude was purified by preparative plate chromatography (heptanes/EtOAc 70:30); **2e** was obtained as a colorless oil (153.0 mg, 40%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.31−7.18 (m, 5H), 3.93−3.88 (m, 1H), 3.58 (t, $J$ = 7.3 Hz, 2H), 2.87 (t, $J$ = 7.5 Hz, 2H), 1.73−1.48 (m, 8H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 139.4, 129.1 (2C), 128.4 (2C), 126.2, 81.6, 70.0, 36.9, 32.4 (2C), 23.6 (2C); HRMS (EI) calcd for $C_{13}H_{16}$ [($M^{+\cdot}$ − $H_2O$)] 172.1252, found 172.1274; IR (neat) $\nu$ 2954, 2777, 1736, 1349, 1093 cm$^{-1}$.

*tert-Butyl 4-(2-Phenylethoxy)piperidine-1-carboxylate (**2f**).* Following standard procedure B, the reaction was performed starting from potassium (1-Boc-4-piperidinylmethoxyoxy)methyltrifluoroborate (1.01 g, 3.0 mmol). After 24 h, the resulting crude was purified by preparative plate chromatography ($CH_2Cl_2$/heptane/ammonia 60:37:3); **2f** was obtained as a yellow oil (253.9 mg, 42%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.31−7.19 (m, 5H), 3.71−3.64 (m, 4H), 3.10 (sept, $J$ = 3.7 Hz, 1H), 3.07 (ddd, $J$ = 13.1, 9.2, 3.3 Hz, 2H), 2.88 (t, $J$ = 7.3 Hz, 2H), 1.81−1.53 (br m, 2H), 1.54−1.46 (m, 2H), 1.45 (s, 9H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 155.0, 139.2, 129.1 (2C), 128.4 (2C), 126.3, 79.5, 77.4, 74.7, 69.2, 41.2, 36.9, 31.0, 28.6 (3C); HRMS (EI) calcd for $C_{14}H_{18}NO_3$ [($M^{+\cdot}$ − $C_4H_9$)] 248.1287, found 248.1290; IR (neat) $\nu$ 2929, 2861, 1690, 1420, 1169, 1028 cm$^{-1}$.

*(2-tert-Butoxy-ethyl)-benzene (**2g**).* Following standard procedure B, the reaction was performed starting from potassium *tert*-butoxymethyltrifluoroborate (612.8 mg, 3.0 mmol). After 24 h, the resulting crude was purified by preparative plate chromatography (heptanes/EtOAc 95:5); **2g** was obtained as a colorless oil (104.0 mg, 29%): $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.31−7.19 (m, 5H), 3.54 (t, $J$ = 7.7 Hz, 2H), 2.83 (t, $J$ = 7.7 Hz, 2H), 1.18 (s, 9H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 139.5, 129.1 (2C), 128.4 (2C), 126.2, 73.0, 63.2, 37.6, 27.7


dx.doi.org/10.1021/jo202686p | J. Org. Chem. 2012, 77, 2966−2970

(3C); HRMS (EI) calcd for $C_{12}H_{18}O$ [$(M^{+\cdot})$] 178.1358, found 178.1361; IR (neat) $\nu$ 2973, 1735, 1362, 1197, 1080 $cm^{-1}$.

## ■ ASSOCIATED CONTENT

### Supporting Information

$^{1}H$ and $^{13}C$ NMR spectra of compounds **1b**−**1l** and **2a**−**2g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We acknowledge the National Institutes of Health (R01 GM035249) and the Neuroscience Medicinal Chemistry Department of Janssen Pharmaceutica for their generous support of this work. Additionally, we thank Dr. Andrés Trabanco (Janssen Pharmaceutica) and Dr. Marc Presset (University of Pennsylvania) for their helpful advice and suggestions.

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