JOC The Journal of Organic Chemistry

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Copper-Mediated Radical Trifluoromethylation of Unsaturated Potassium Organotrifluoroborates

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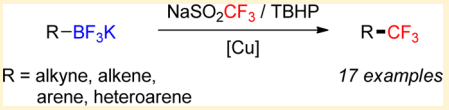
Supporting Information

ABSTRACT: Copper-mediated trifluoromethylation of unsaturated organotrifluoroborates with the Langlois reagent ($NaSO_2CF_3$) and TBHP allows the introduction of trifluoromethyl groups into a variety of organic substructures. The reactions are easy to set up, the conditions are mild and general, and the process provides access to trifluoromethylated alkynes, alkenes, arenes, and heteroarenes in fair to good yields.



The unique properties of the trifluoromethyl group have been appreciated in diverse fields of chemistry.[1] The CF_3 group is notably popular with medicinal chemists as a compact, lipophilic group that slows the metabolic breakdown of aromatics.[2] This has led to the development of many new reagents and methods for its introduction.[3,4] Among the substrates used for these trifluoromethylations, organoboron compounds have emerged as precursors of choice because of their increasing and pivotal role in synthetic organic chemistry.[5] Indeed, the past years have witnessed the emergence of new methods involving different classes of borylated starting materials reacting with nucleophilic, electrophilic, and radical CF_3 species, all of which can be mediated or catalyzed by copper sources (Scheme 1).

Boronic acids were the first class of compounds studied, and in a pioneering study, Qing described the oxidative trifluoromethylation of aryl-, heteroaryl-, and alkenylboronic acids by the nucleophilic Ruppert−Prakash reagent ($TMSCF_3$)[6] in a process similar to Chan−Lam−Evans coupling.[7−9] Shortly thereafter, Buchwald developed a related, but more practical, catalytic version of this reaction,[10] also achieved by Qing 1 year later.[11] Importantly, Grushin developed a protocol using simple fluoroform[12] together with alkylboronic acids that could be used in a strategy similar to that reported by Fu.[13]

The complementary use of electrophilic trifluoromethylation reagents has also been intensively studied in the case of boronic acids. Whereas Liu[14] and Xiao[15] described the use of trifluoromethylsulfonium salts, Shen expanded this reactivity to Togni's reagent.[16] Because protodeborylation of the boronic acid starting material was observed as the main side reaction in all of these examples, the trifluoromethylation of protected boron species was also investigated. Hartwig and Gooßen reported the oxidative nucleophilic trifluoromethylation of aryl pinacol boronates, but these required the use of either [(phen)$CuCF_3$] or $K[CF_3B(OMe)_3]$.[17,18] The use of the electrophilic Togni reagent [3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole] was found to be more general because it could be used for arylboronates,[19] aryltrifluoroborates,[20] or alkenyltrifluoroborates.[21]

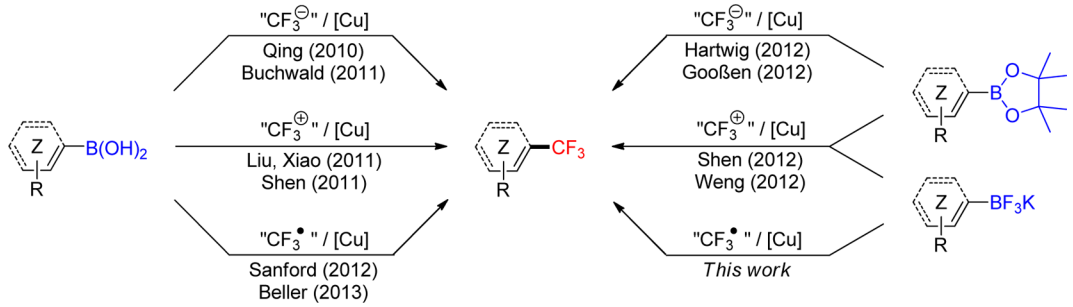
Sanford recently made a very interesting contribution to the field.[22] Her group reported the conversion of aryl- and heteroarylboronic acids by trifluoromethyl radicals generated in situ from the inexpensive Langlois reagent ($NaSO_2CF_3$) and *tert*-butyl hydroperoxide (THBP).[23] This reagent was already used for the C−H trifluoromethylation of heterocycles,[24] and similar copper-mediated conditions were subsequently reported by Beller with an extension to alkenylboronic acids.[25] Importantly, Sanford's protocol is very practical because the reaction proceeds under ambient conditions and isolation of the products is straightforward. Owing to their added value compared to their boronic acid and -ester counterparts,[26−28] an extension of this method to organotrifluoroborates was envisioned because only two examples had been reported in a study published during the course of our investigation.[25] Herein, efforts toward the development of such a general trifluoromethylation method are revealed.

Potassium organotrifluoroborates can be efficiently used in radical reactions,[29] even under aqueous conditions.[30] Therefore, in a quest for a general protocol, investigations were initiated under the previously reported conditions for boronic acids: $NaSO_2CF_3$ (3.0 equiv), TBHP (5.0 equiv), and CuCl (1.0 equiv) in CH_2Cl_2/MeOH/H_2O (1:1:0.8) at rt for electron-rich substrates and $NaSO_2CF_3$ (3.0 equiv), TBHP (4.0 equiv), $(CH_3CN)CuPF_6$ (1.0 equiv), and $NaHCO_3$ (1.0 equiv) in MeOH at rt for electron-poor substrates. Although an excess of the Langlois reagent was required, the overall process remains one of the more cost-effective owing to the lower cost of this reagent compared to other trifluoromethylation reagents.

Received: October 17, 2013

   dx.doi.org/10.1021/jo4023233 | J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Trifluoromethylations of Organoboron Compounds



The results obtained with aryl- and heteroaryltrifluoroborates are summarized in Table 1. In all of these examples and similar to the case of boronic acids, isolation of the desired products is very easy, as these materials can be obtained with good purity by a simple aqueous workup. As expected, electron-rich substrates such as **1a** and **1c** were efficiently trifluoromethylated, but a decreased yield was observed in the case of ortho-substituted products such as **2c**, which may be attributed to steric hindrance. Additionally, the reaction performed with **1b** led to a poor yield (21%). The case of unactivated substrates was less straightforward. The simple trifluoromethylbenzene **2d** was generated from the corresponding trifluoroborate in 28% yield under the same conditions, and electron-poor arenes such as **1e** and **1f** required the use of modified conditions B. Under these conditions, **2e** and **2f** were obtained in yields of 61 and 27%, respectively. We next turned our attention to the case of heteroaryl substrates. Five- and six-membered heteroaryltrifluoroborates afforded the corresponding trifluoromethylated products in 6−67% yields, and the observed trend was the same as that seen for simple arenes. A broad variety of electron-rich substrates such as indole **1g**, pyrazole **1h**, thiazole **1i**, and benzofuran **1j** afforded the desired products in good yields under generic conditions A. However, the case of electron-poor quinoline was once again problematic, and **2k** was obtained in a poor 6% yield. Even though the yields obtained with electron-poor potassium organotrifluoroborates are, in general, lower than the ones observed with the corresponding boronic acids,[22] the increased stability of the trifluoroborate salts as compared to boronic acids makes the use of the former reagents very attractive.

To investigate the scope of the reaction further, we also evaluated the case of alkynyl- and alkenyltrifluoroborates (Table 2). Owing to the electron-rich nature of these substrates, only conditions A were applied. Alkynyltrifluoroborates **3a** and **3d** afforded the desired products in fair yields, opening a new route to the preparation of trifluoromethyl-substituted alkynes. The case of alkenyltrifluoroborates **4a−d** afforded valuable information. Under exactly the same conditions, simple styrene derivatives **6a** and **6b** were obtained in fair to good yields similar to those reported by other methods,[21,25] and only a small amount (∼5%) of isomerization was detected. Moreover, the substitution pattern of the olefin was found to be crucial. When the trifluoroborate group was placed at the β-position of the aryl ring, the trisubstituted olefin **6c** was obtained in a similarly good yield of 70%, but in the case where CF_3 resides in the α-position, the yield in **6d** decreased to 12%. Ultimately, no product was observed in the case of cyclic olefins such as **4e**, even using specifically designed conditions for alkenyltrifluoroborates.[21]

In conclusion, the copper-mediated radical trifluoromethylation of unsaturated potassium organotrifluoroborates is described. The conditions previously reported were successfully extended to various trifluoroborato-containing arenes and heteroarenes. Additionally, the trifluoromethylation of alkynyltrifluoroborates as well as mono- and disubstituted alkenyltrifluoroborates was achieved. These results, in conjunction with the simplicity of this protocol, demonstrate the usefulness of the radical trifluoromethylation of boronated substrates toward a generic trifluoromethylation protocol.

EXPERIMENTAL SECTION

Preparation of Starting Materials 1, 3, and 4. *General Procedure C from Commercially Available Boronated Derivatives.* In air, the boronated starting material (1.0 mmol, 1.0 equiv) was weighed in a round-bottomed flask and solubilized in MeOH (5 mL, [SM] = 0.2 M). Saturated KHF_2(aq) (0.9 mL, 4.5 M, 4.0 equiv) was added. The flask was closed with a septum, and the resulting mixture was stirred at rt for 1 h. The reaction mixture was evaporated to dryness, and the resulting salt was extracted with hot acetone using a Soxhlet apparatus overnight. The filtrate was concentrated to ca. 5 mL, and precipitation was achieved by dropwise addition of the filtrate to Et_2O (100 mL) at 0 °C. The product was collected by gravity filtration on a fritted funnel and dried to afford the corresponding potassium organotrifluoroborate.

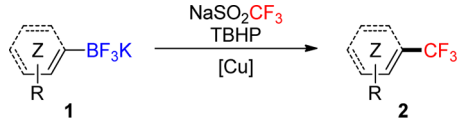
Potassium 3-Benzyloxyphenyltrifluoroborate ***1b***. Following general procedure C, the reaction performed with 3-benzyloxyphenylboronic acid (2.0 g, 8.77 mmol) afforded **1b** (2.24 g, 88%) as a white solid. mp > 200 °C (dec). HRMS (ESI): m/z calcd for $C_{13}H_{11}BF_3O$ $(M - K)^-$, 251.0861; found, 251.0854. ^{1}H NMR (400 MHz/DMSO-d_6): δ 7.46−7.41 (m, 2H), 7.41−7.34 (m, 2H), 7.34−7.27 (m, 1H), 7.03−6.89 (m, 3H), 6.65 (ddd, J = 8, 3, 1 Hz, 1H), 5.02 (s, 2H). ^{13}C NMR (100 MHz/DMSO-d_6): δ 157.2 (C), 138.0 (C), 128.3 (2 CH), 127.5 (CH), 127.4 (2 CH), 127.1 (CH), 124.1 (CH), 117.3 (CH), 111.5 (CH), 68.64 (CH_2). ^{11}B NMR (128 MHz/DMSO-d_6): δ 3.08 (br). ^{19}F NMR (376 MHz/DMSO-d_6): δ −139.2 (br).

Potassium 2-Benzyloxyphenyltrifluoroborate ***1c***. Following general procedure C, the reaction performed with 2-benzyloxyphenylboronic acid (0.5 g, 2.19 mmol) afforded **1c** (597 mg, 94%) as a white solid. mp > 200 °C (dec). HRMS (ESI): m/z calcd for $C_{13}H_{11}BF_3O$ $(M - K)^-$, 251.0861; found, 251.0856. ^{1}H NMR (400 MHz/DMSO-d_6): δ 7.54 (d, J = 7 Hz, 2H), 7.40−7.29 (m, 3H), 7.29−7.22 (m, 1H), 6.98 (td, J = 8, 2 Hz, 1H), 6.75−6.65 (m, 2H), 4.99 (s, 2H). ^{13}C NMR (100 MHz/DMSO-d_6): δ 161.5 (C), 138.9 (C), 133.4 (CH), 133.4 (CH), 127.9 (2 CH), 126.8 (2 CH), 126.3 (CH), 119.4 (CH), 111.7 (CH), 68.8 (CH_2). ^{11}B NMR (128 MHz/DMSO-d_6): δ 3.09 (br). ^{19}F NMR (376 MHz/DMSO-d_6): δ −136.8 (br).

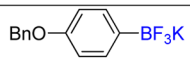
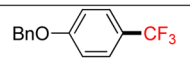
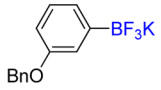
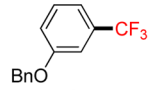
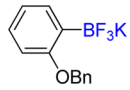
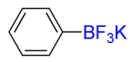
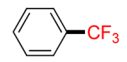
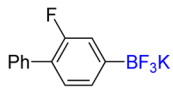
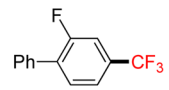
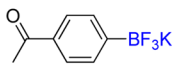
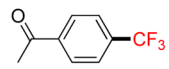
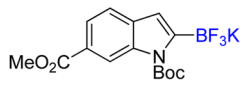
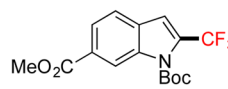
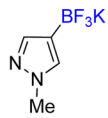
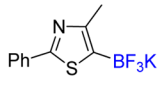
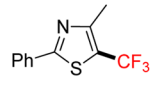
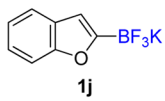
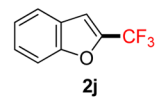
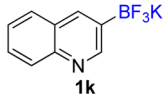
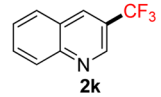
Potassium 1-Boc-6-(methoxycarbonyl)indolyl-2-trifluoroborate ***1g***. Following general procedure C, the reaction performed with 1-Boc-6-(methoxycarbonyl)indole-2-boronic acid (1.0 g, 3.13 mmol) afforded **1g** (903 mg, 76%) as a white solid. mp > 200 °C (dec). HRMS (ESI): m/z calcd for $C_{15}H_{16}BF_3NO_4$ $(M - K)^-$, 342.1130; found, 342.1130. ^{1}H NMR (400 MHz/DMSO-d_6): δ 8.71 (s, 1H), 7.69 (dd, J = 8, 1 Hz, 1H), 7.49 (d, J = 8 Hz, 1H), 6.51 (d, J = 1 Hz,

dx.doi.org/10.1021/jo4023233 | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 1. Scope of the Trifluoromethylation of Aryl- and Heteroaryltrifluoroborates[a]



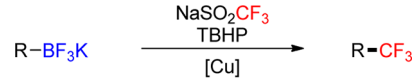
1 2

Entry	Substrate	Method [a]	Product	Yield [b]
1	 **1a**	A	 **2a**	99% (93%)
2	 **1b**	A	 **2b**	21% (14%)
3	 **1c**	A	 **2c**	66% (50%)
4	 **1d**	A	 **2d**	28% (-)
5	 **1e**	B	 **2e**	61% (34%)
6	 **1f**	B	 **2f**	27% (-)
7	 **1g**	A	 **2g**	67% (64%)
8	 **1h**	A	 **2h**	48% (-)
9	 **1i**	A	 **2i**	43% (24%)
10	 **1j**	A	 **2j**	53% (-)
11	 **1k**	B	 **2k**	6% (-)

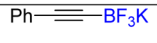
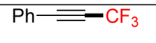
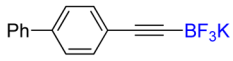
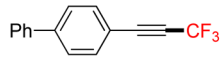
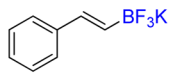
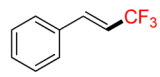
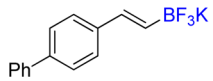
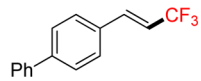
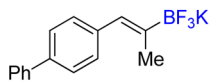
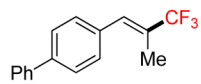
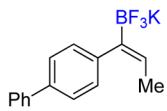
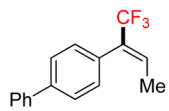
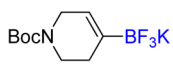
[a]Conditions A: $NaSO_2CF_3$ (3.0 equiv), TBHP (5.0 equiv), CuCl (1.0 equiv), CH_2Cl_2/MeOH/H_2O 1:1:0.8 ([**1**] = 0.1 M), open flask, rt, 12 h; conditions B: $NaSO_2CF_3$ (3.0 equiv), TBHP (4.0 equiv), $(CH_3CN)CuPF_6$ (1.0 equiv), $NaHCO_3$ (1.0 equiv), MeOH ([**1**] = 0.1 M), open flask, rt, 12 h. [b]Yields were determined by ^{19}F analysis; isolated yields are reported in brackets.

dx.doi.org/10.1021/jo4023233 | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Scope of the Trifluoromethylation of Alkynyl- and Alkenyltrifluoroborates



3 or **4** → **5** or **6**

Entry	Substrate	Method [a]	Product	Yield [b]
1	 **3a**	A	 **5a**	50% (-)
2	 **3b**	A	 **5b**	51% (45%)
3	 **4a**	A	 **6a**	54% (-)[c]
4	 **4b**	A	 **6b**	77% (77%)[c]
5	 **4c**	A	 **6c**	70% (59%)
6	 **4d**	A	 **6d**	12% (10%)
7	 **4e**	A	-	-

[a]Conditions A: $NaSO_2CF_3$ (3.0 equiv), TBHP (5.0 equiv), CuCl (1.0 equiv), CH_2Cl_2/MeOH/H_2O 1:1:0.8 ([**3** or **4**] = 0.1 M), open flask, rt, 12 h. [b]Yields were determined by ^{19}F analysis; isolated yields are reported in brackets. [c]With ~5% of the (Z) product.

1H), 3.85 (s, 3H), 1.58 (s, 9H). ^{13}C NMR (100 MHz/DMSO-d_6): δ 167.2 (C), 151.1 (C), 136.9 (C), 134.6 (C), 122.6 (C), 122.3 (CH), 119.0 (CH), 115.9 (CH), 111.4 (CH), 82.0 (C), 51.7 (CH_3), 27.5 (3 CH_3). ^{11}B NMR (128 MHz/DMSO-d_6): δ 1.29 (br). ^{19}F NMR (376 MHz/DMSO-d_6): δ −136.7 (br).

Potassium 4-Methyl-2-phenyl-5-(trifluoroborato)-1,3-thiazole ***1i.*** Following general procedure C, the reaction performed with 4-methyl-2-phenyl-5-boronic-1,3-thiazole acid pinacol ester (0.5 g, 1.66 mmol) afforded **1i** (386 mg, 83%) as a white solid. mp > 200 °C (dec). HRMS (ESI): m/z calcd for $C_{10}H_8BF_3NS$ $(M - K)^-$, 242.0428; found, 242.0421. ^1H NMR (400 MHz/DMSO-d_6): δ 7.86−7.79 (m, 2H), 7.45−7.37 (m, 2H), 7.37−7.31 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz/DMSO-d_6): δ 163.4 (C), 152.5 (C), 134.5 (C), 128.8 (2 CH), 128.5 (CH), 125.5 (2 CH), 16.8 (CH_3). ^{11}B NMR (128 MHz/DMSO-d_6): δ 2.25 (br). ^{19}F NMR (376 MHz/DMSO-d_6): δ −132.3 (br).

Potassium (E)-4-Phenylstyryltrifluoroborate ***4b.*** Following general procedure C, the reaction performed with (*E*)-4-phenylstyrylboronic acid (535 mg, 2.39 mmol) afforded **4b** (292 mg, 43%) as a white solid. mp > 200 °C (dec). HRMS (ESI): m/z calcd for $C_{14}H_{11}BF_3$ $(M - K)^-$, 247.0911; found, 247.0904. ^1H NMR (400 MHz/DMSO-d_6): δ 7.67−7.62 (m, 2H), 7.56 (d, J = 8 Hz, 2H), 7.48−7.37 (m, 4H), 7.36−7.29 (m, 1H), 6.52 (d, J = 18 Hz, 1H), 6.30−6.20 (m, 1H). ^{13}C NMR (100 MHz/DMSO-d_6): δ 140.1 (C), 139.5 (C), 137.5 (C), 132.5 (CH), 128.9 (2 CH), 127.0 (CH), 126.5 (2 CH), 126.3 (2 CH), 125.9 (2 CH). ^{11}B NMR (128 MHz/DMSO-d_6): δ 2.67 (br). ^{19}F NMR (376 MHz/DMSO-d_6): δ −137.8 (br).

Potassium N-Boc-1,2,5,6-tetrahydropyridinyl-4-trifluoroborate ***4e.*** Following general procedure C, the reaction performed with *N*-Boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (0.5 g, 1.62 mmol) afforded **4e** (396 mg, 85%) as a white solid. mp > 200 °C (dec). HRMS (ESI): m/z calcd for $C_{10}H_{16}BF_3NO_2$ $(M - K)^-$, 250.1232; found, 250.1237. ^1H NMR (400 MHz/acetone-d_6): δ 5.56 (br, 1H), 3.72 (br, 2H), 3.33 (t, J = 6 Hz, 2H), 2.07 (br, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz/acetone-d_6): δ 155.4 (C), 121.3 (CH), 78.7 (C), 44.7 (CH_2), 42.3 (CH_2), 28.8 (3 CH_3), 27.6 (CH_2). ^{11}B NMR (128 MHz/acetone-d_6): δ 2.91 (br). ^{19}F NMR (376 MHz/acetone-d_6): δ −146.7 (br).

Preparation of ***3b:***[31] In air, 4-ethynylbiphenyl (1.0 g, 5.61 mmol, 1.0 equiv) was weighed in a 50 mL round-bottomed flask equipped with a stir bar. The flask was closed with a septum, evacuated, and backfilled with N_2. THF (10 mL, [SM] = 0.5 M) was added, and the mixture was cooled to −78 °C. *n*-BuLi (2.2 mL, 2.5 M in hexanes, 5.61 mmol, 1.0 equiv) was added slowly, and the reaction was stirred 1 h at −78 °C. Triisopropyl borate (1.9 mL, 8.42 mmol, 1.5 equiv) was added, and the reaction was stirred 1 h at −78 °C and then warmed to

dx.doi.org/10.1021/jo4023233 | J. Org. Chem. XXXX, XXX, XXX−XXX

−20 °C in 1 h. Saturated KHF_2(aq) (7.5 mL, 4.5 M, 6.0 equiv) was added, and the reaction was stirred at rt for 2 h. The reaction mixture was evaporated to dryness, and the resulting salt was extracted with hot acetone using a Soxhlet apparatus overnight. The filtrate was concentrated to ca. 5 mL, and precipitation was achieved by dropwise addition of the filtrate to Et_2O (100 mL) at 0 °C. The resulting product was collected by gravity filtration on a fritted funnel and dried to afford **3b** (280 mg, purity = 95%, 17%) as a white solid. mp > 200 °C (dec). HRMS (ESI): *m/z* calcd for $C_{14}H_9BF_3$ $(M - K)^-$, 245.0755; found, 245.0750. ^{1}H NMR (400 MHz/DMSO-d_6): δ 7.66 (d, J = 7 Hz, 2H), 7.59 (d, J = 8 Hz, 2H), 7.46 (dd, J = 8, 8 Hz, 2H), 7.40−7.33 (m, 3H). ^{13}C NMR (100 MHz/DMSO-d_6): δ 139.5 (C), 138.2 (C), 131.5 (2 CH), 128.9 (2 CH), 127.4 (CH), 126.4 (2 CH), 126.4 (2 CH), 124.7 (C), 89.0 (C). ^{11}B NMR (128 MHz/DMSO-d_6): δ −1.56 (br). ^{19}F NMR (376 MHz/DMSO-d_6): δ −131.7 (br).

*Preparation of **4c** and **4d**. 4-(Propyn-1-yl)-biphenyl.* In air, 4-ethynylbiphenyl (1.0 g, 5.61 mmol, 1.0 equiv) was weighed in a round-bottomed flask equipped with a stir bar. The flask was closed with a septum, evacuated, and backfilled with N_2. THF (20 mL, [SM] = 0.25 M) was added, and the mixture was cooled to −78 °C. *n*-BuLi (2.5 mL, 2.5 M in hexanes, 6.17 mmol, 1.1 equiv) was slowly added (by syringe), and the reaction was stirred 15 min at −78 °C. MeI (0.4 mL, 6.17 mmol, 1.1 equiv) was added, and the reaction was allowed to warm to rt over 2 h and then stirred at rt for 4 h. Subsequently, the reaction mixture was poured into saturated NH_4Cl(aq) (20 mL), and the resulting solution was extracted twice with EtOAc (20 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and evaporated to afford the crude product. Purification by flash column chromatography (80 g SiO_2, heptane to EtOAc/heptane 1:9) afforded the title compound (654 mg, 60%) as a white solid. mp 69−70 °C. ^{1}H NMR (400 MHz/$CDCl_3$): δ 7.63−7.58 (m, 2H), 7.57−7.53 (m, 2H), 7.51−7.43 (m, 4H), 7.40−7.34 (m, 1H), 2.10 (s, 3H). Spectral data were consistent with that previously reported.[32]

*Compound **4c**.* [33] In air, CuCl (5 mg, 0.05 mmol, 5 mol %), Ph_3P (27 mg, 0.10 mmol, 10 mol %), and NaO*t*-Bu (20 mg, 0.21 mmol, 20 mol %) were weighed in a 2−5 mL MW vial equipped with a stir bar. The vial was sealed, evacuated, and backfilled with N_2 (×3). THF (0.5 mL) was added, and the resulting mixture stirred at rt for 30 min. A solution of bis(pinacolato)diboron (290 mg, 1.14 mmol, 1.1 equiv) in THF (1 mL) was added, and the mixture was stirred at rt for 5 min. A solution of 4-(propyn-1-yl)-biphenyl (200 mg, 1.04 mmol, 1.0 equiv) in THF (0.5 mL) and MeOH (84 μL, 2.08 mmol, 2.0 equiv) were successively added, and the reaction stirred at rt for 14 h. Then, the reaction mixture was diluted with Et_2O (10 mL) and filtered through a pad of Celite. The filtrate was evaporated and purified by flash column chromatography (24 g SiO_2, heptane to EtOAc/heptane 1:4). In air, this boronate was charged in a round-bottomed flask and solubilized in THF (10 mL). Saturated KHF_2(aq) (0.9 mL, 4.5 M, 4.2 mmol, 4.0 equiv) was added. The flask was closed with a septum, and the resulting mixture stirred at rt for 2 h. The reaction mixture was evaporated to dryness, and the resulting salt was extracted with hot acetone using a Soxhlet apparatus overnight. The filtrate was concentrated to ca. 5 mL, and precipitation was achieved by dropwise addition of the filtrate to Et_2O (100 mL) at 0 °C. The product was collected by gravity filtration on a fritted funnel and dried to afford **4c** (208 mg, 67%) as a white solid. mp > 200 °C (dec). HRMS (ESI): *m/z* calcd for $C_{15}H_{13}BF_3$ $(M - K)^-$, 261.1068; found, 261.1065. ^{1}H NMR (400 MHz/DMSO-d_6): δ 7.65 (d, J = 8 Hz, 2H), 7.57 (d, J = 8 Hz, 2H), 7.44 (dd, J = 8, 8 Hz, 2H), 7.36−7.30 (m, 1H), 7.27 (d, J = 8 Hz, 2H), 6.41 (s, 1H), 1.76 (s, 3H). ^{13}C NMR (100 MHz/DMSO-d_6): δ 140.2 (C), 139.9 (C), 136.1 (C), 129.0 (2 CH), 128.8 (2 CH), 126.9 (CH), 126.3 (2 CH), 126.0 (2 CH), 125.6 (CH), 16.7 (CH_3). ^{11}B NMR (128 MHz/DMSO-d_6): δ 3.08 (br). ^{19}F NMR (376 MHz/DMSO-d_6): δ −143.6 (br).

*Compound **4d**.* [34] In air, CuCl (4 mg, 0.04 mmol, 5 mol %), xantphos (51 mg, 0.09 mmol, 10 mol %), and NaO*t*-Bu (17 mg, 0.18 mmol, 20 mol %) were weighed in a 2−5 mL MW vial equipped with a stir bar. The vessel was sealed, evacuated, and backfilled with N_2 (×3). Toluene (1 mL) was added, and the mixture stirred at rt for 15 min. Pinacolborane (0.2 mL, 1.33 mol, 1.5 equiv) was added, and the mixture stirred at rt for 5 min. A solution of 4-(propyn-1-yl)-biphenyl (171 mg, 0.89 mmol, 1.0 equiv) in toluene (1 mL) was added, and the reaction was stirred at rt for 3 days. The reaction mixture was diluted with EtOAc (10 mL) and filtered through a pad of Celite. The filtrate was evaporated to afford the crude boronate intermediate. In air, this boronate was charged in a round-bottomed flask and solubilized in THF (10 mL). Saturated KHF_2(aq) (0.8 mL, 4.5 M, 3.6 mmol, 4.0 equiv) was added. The flask was closed with a septum, and the resulting mixture was stirred at rt for 2 h. The reaction mixture was evaporated to dryness, and the resulting salt was extracted with hot acetone using a Soxhlet apparatus overnight. The filtrate was concentrated to ca. 5 mL, and precipitation was achieved by dropwise addition of the filtrate to Et_2O (100 mL) at 0 °C. The product was collected by gravity filtration on a fritted funnel and dried to afford **4d** (69 mg, 26%) as a white solid. mp > 200 °C (dec). HRMS (ESI): *m/z* calcd for $C_{15}H_{13}BF_3$ $(M - K)^-$, 261.1068; found, 261.1058. ^{1}H NMR (400 MHz/DMSO-d_6): δ 7.63 (dd, J = 8, 1 Hz, 2H), 7.50−7.40 (m, 4H), 7.33−7.27 (m, 1H), 7.12 (d, J = 8 Hz, 2H), 5.69 (q, J = 7 Hz, 1H), 1.48 (t, J = 7 Hz, 3H). ^{13}C NMR (100 MHz/DMSO-d_6): δ 145.2 (C), 140.8 (C), 135.4 (C), 128.9 (2 CH), 128.7 (2 CH), 126.6 (CH), 126.2 (2 CH), 125.2 (2 CH), 122.6 (CH), 15.0 (CH_3). ^{11}B NMR (128 MHz/DMSO-d_6): δ 2.73 (br). ^{19}F NMR (376 MHz/DMSO-d_6): δ −139.4 (br).

Radical Trifluoromethylation of Unsaturated Potassium Organotrifluoroborates. *General Procedure A for the Preparation of Trifluoromethylated Compounds **2**, **5**, and **6**.* In air, potassium organotrifluoroborates **1**, **3**, or **4** (0.5 mmol, 1.0 equiv), $NaSO_2CF_3$ (234 mg, 1.5 mmol, 3.0 equiv), and CuCl (50 mg, 0.5 mmol, 1.0 equiv) were weighed in a 2−5 mL MW vial equipped with a stir bar. MeOH (1 mL), CH_2Cl_2 (1 mL), and distilled H_2O (0.8 mL) were successively added, and the tube was sealed with a tap open to air by a needle. This solution was cooled to 0 °C, and TBHP (0.35 mL, 70% in H_2O, 2.5 mmol, 5.0 equiv) was slowly added. The reaction was allowed to warm to rt and stirred at rt for 12 h. The reaction mixture was diluted with Et_2O (10 mL), and this solution was washed successively with saturated $NaHCO_3$(aq) (5 mL) and 5% $Na_2S_2O_3$(aq) (5 mL). The organic layer was dried ($MgSO_4$), and 1,3,5-trifluorobenzene (51.7 μL, 0.5 mmol, 1.0 equiv) was added as an internal standard. The solution was analyzed by ^{19}F NMR and GCMS. Additionally, this solution can be evaporated and purified by flash column chromatography (SiO_2, mixtures of EtOAc and heptane) to afford the pure compounds **2**, **5**, or **6**.

*General Procedure B for the Preparation of Trifluoromethylated Compounds **2**.* In air, potassium organotrifluoroborates **1** (0.5 mmol, 1.0 equiv), $NaSO_2CF_3$ (234 mg, 1.5 mmol, 3.0 equiv), and $(MeCN)_4CuPF_6$ (157 mg, 0.5 mmol, 1.0 equiv) were weighed in a 2−5 mL MW vial equipped with a stir bar. MeOH (3 mL) was added, and the tube was sealed with a tap open to air by a needle. This solution was cooled to 0 °C, and TBHP (0.28 mL, 70% in H_2O, 2.0 mmol, 4.0 equiv) was slowly added. The reaction was allowed to warm to rt and stirred at rt for 12 h. The reaction mixture was diluted with Et_2O (10 mL), and this solution was washed successively with saturated $NaHCO_3$(aq) (5 mL) and 5% $Na_2S_2O_3$(aq) (5 mL). The organic layer was dried ($MgSO_4$), and 1,3,5-trifluorobenzene (51.7 μL, 0.5 mmol, 1.0 equiv) was added as an internal standard. The solution was analyzed by ^{19}F NMR and GCMS. Additionally, this solution can be evaporated and purified by flash column chromatography (SiO_2, mixtures of EtOAc and heptane) to afford the pure compound **2**.

*1-(Benzyloxy)-4-(trifluoromethyl)benzene **2a**.* Following general procedure A, the reaction performed with **1a** (145 mg, 0.5 mmol) afforded **2a** in ^{19}F yield = 99% and, after purification, 117 mg (93%) as a white solid. mp 79−80 °C. GC−MS: 5.438 min (*m/z* 252 $(M)^+$). ^{19}F NMR (376 MHz/$CDCl_3$): δ −61.4 (s). Spectral data were consistent with that previously reported.[16]

*1-(Benzyloxy)-3-(trifluoromethyl)benzene **2b**.* Following general procedure A, the reaction performed with **1b** (145 mg, 0.5 mmol) afforded **2b** in ^{19}F yield = 21% and, after purification, 18 mg (14%) as a colorless oil. GC−MS: 5.241 min (*m/z* 252 $(M)^+$). ^{19}F NMR (376 MHz/$CDCl_3$): δ −62.9 (s). Spectral data were consistent with that previously reported.[35]

dx.doi.org/10.1021/jo4023233 | *J. Org. Chem.* XXXX, XXX, XXX−XXX

1-(Benzyloxy)-2-(trifluoromethyl)benzene **2c**. Following general procedure A, the reaction performed with **1c** (145 mg, 0.5 mmol) afforded **2c** in ^{19}F yield = 66% and, after purification, 63 mg (50%) as a colorless oil. GC−MS: 5.462 min (m/z 252 $(M)^+$). HRMS (ESI): m/z calcd for $C_{14}H_{11}F_3O$ $(M)^+$, 252.0762; found, 252.0748. ^{1}H NMR (400 MHz/$CDCl_3$): δ 7.64 (dd, J = 8, 1 Hz, 1H), 7.52−7.46 (m, 3H), 7.46−7.40 (m, 2H), 7.39 - 7.33 (m, 1H), 7.11−7.00 (m, 2H), 5.22 (s, 2H). ^{13}C NMR (100 MHz/$CDCl_3$): δ 156.4 (C), 136.3 (C), 133.2 (CH), 128.6 (2 CH), 127.9 (CH), 127.1 (q, J = 5 Hz, CH), 126.8 (2 CH), 123.8 (q, J = 272 Hz, C), 120.2 (CH), 119.2 (q, J = 31 Hz, C), 113.2 (CH), 70.2 (CH_2). ^{19}F NMR (376 MHz/$CDCl_3$): δ −62.3 (s).

Trifluoromethylbenzene **2d**. Following general procedure A, the reaction performed with **1d** (92 mg, 0.5 mmol) afforded **2d** in ^{19}F yield = 28%. GC−MS: 0.624 min (m/z 146 $(M)^+$). ^{19}F NMR (376 MHz/$CDCl_3$): δ −62.9 (s). Spectral data were consistent with that previously reported.[22]

1-Fluoro-2-phenyl-5-trifluoromethylbenzene **2e**. Following general procedure B, the reaction performed with **1e** (139 mg, 0.5 mmol) afforded **2e** in ^{19}F yield = 61% and, after purification, 41 mg (34%) as a colorless oil. GC−MS: 4.151 min (m/z 240 $(M)^+$). ^{19}F NMR (376 MHz/$CDCl_3$): δ −62.8 (s, 3F), 115.7 (s, 1F). Spectral data were consistent with that previously reported.[16]

4-Acetyl-trifluoromethylbenzene **2f**. Following general procedure B, the reaction performed with **1f** (113 mg, 0.5 mmol) afforded **2f** in ^{19}F yield = 27%. GC−MS: 2.437 min (m/z 188 $(M)^+$). ^{19}F NMR (376 MHz/$CDCl_3$): δ −63.2 (s). Spectral data were consistent with that previously reported.[22]

1-Boc-2-trifluoromethyl-6-(methoxycarbonyl)indole **2g**. Following general procedure A, the reaction performed with **1g** (191 mg, 0.5 mmol) afforded **2g** in ^{19}F yield = 67% and, after purification, 110 mg (64%) as a white solid. mp 83−84 °C. GC−MS: 7.321 min (m/z 343 $(M)^+$). HRMS (ESI): m/z calcd for $C_{11}H_8F_3NO_2$ $(M\text{-Boc+H})^+$, 243.0507; found, 243.0533. ^{1}H NMR (400 MHz/$CDCl_3$): δ 8.99 (s, 1H), 7.99 (d, J = 8 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 7.16 (s, 1H), 3.97 (s, 3H), 1.70 (s, 9H). ^{13}C NMR (100 MHz/$CDCl_3$): δ 167.1 (C), 148.0 (C), 137.1 (C), 129.9 (C), 129.5 (q, J = 40 Hz, C), 128.6 (C), 124.5 (CH), 121.8 (CH), 120.4 (q, J = 268 Hz, C), 118.1 (CH), 112.8 (q, J = 5 Hz, CH), 86.1 (C), 52.2 (CH_3), 27.8 (3 CH_3). ^{19}F NMR (376 MHz/$CDCl_3$): δ −58.4 (s).

1-Methyl-4-trifluoromethyl-1H-pyrazole **2h**. Following general procedure A, the reaction performed with **1h** (47 mg, 0.25 mmol) afforded **2f** in ^{19}F yield = 48% (in this case, 2.0 equiv of internal standard was used). GC−MS: 0.882 min (m/z 150 $(M)^+$). ^{19}F NMR (376 MHz/$CDCl_3$): δ −56.4 (s). Spectral data were consistent with that previously reported.[36]

4-Methyl-2-phenyl-5-trifluoromethyl-1,3-thiazole **2i**. Following general procedure A, the reaction performed with **1i** (140 mg, 0.5 mmol) afforded **2i** in ^{19}F yield = 43% and, after purification, 37 mg (24%) as a colorless oil (contaminated by 5% of the bis-trifluoromethylated product). GC−MS: 4.642 min (m/z 243 $(M)^+$). HRMS (ESI): m/z calcd for $C_{11}H_8F_3NS$ $(M)^+$, 243.0330; found, 243.0331. ^{1}H NMR (400 MHz/$CDCl_3$): δ 7.95−7.89 (m, 2H), 7.50−7.43 (m, 3H), 2.62 (q, J = 2 Hz, 3H). ^{13}C NMR (100 MHz/$CDCl_3$): δ 168.4 (C), 155.2 (C), 132.5 (C), 131.0 (CH), 129.1 (2 CH), 126.7 (2 CH), 122.7 (q, J = 269 Hz, C), 119.7 (q, J = 37 Hz, C), 16.1 (CH_3). ^{19}F NMR (376 MHz/$CDCl_3$): δ −53.0 (s).

2-Trifluoromethylbenzofuran **2j**. Following general procedure A, the reaction performed with **1j** (124 mg, 0.5 mmol) afforded **2j** in ^{19}F yield = 53%. GC−MS: 1.902 min (m/z 186 $(M)^+$). ^{19}F NMR (376 MHz/$CDCl_3$): δ −65.0 (s). Spectral data were consistent with that previously reported.[22]

3-Trifluoromethylquinoline **2k**. Following general procedure B, the reaction performed with **1k** (117 mg, 0.5 mmol) afforded **2k** in ^{19}F yield = 6%. GC−MS: 3.277 min (m/z 197 $(M)^+$). ^{19}F NMR (376 MHz/$CDCl_3$): δ −62.0 (s). Spectral data were consistent with that previously reported.[16]

1′-Trifluoromethylphenylacetylene **5a**. Following general procedure A, the reaction performed with **1j** (104 mg, 0.5 mmol) afforded **5a** in ^{19}F yield = 50%. GC−MS: 1.344 min (m/z 170 $(M)^+$). ^{19}F NMR (376 MHz/$CDCl_3$): δ −49.9 (s). Spectral data were consistent with that previously reported.[37]

1′-Trifluoromethyl-1-biphenylacetylene **5b**. Following general procedure A, the reaction performed with **3b** (149 mg, 0.5 mmol) afforded **5b** in ^{19}F yield = 51% and, after purification, 56 mg (45%) as a white solid. mp 82−83 °C. GC−MS: 5.471 min (m/z 246 $(M)^+$). ^{19}F NMR (376 MHz/$CDCl_3$): δ −49.9 (s). Spectral data were consistent with that previously reported.[37]

Compound **6a**. Following general procedure A, the reaction performed with **4a** (105 mg, 0.5 mmol) afforded **6a** in ^{19}F yield = 54% (contaminated by 5% of the isomerized (Z)-product). GC−MS: 1.806 min (m/z 172 $(M)^+$). ^{19}F NMR (376 MHz/$CDCl_3$): δ −63.4 (s). Spectral data were consistent with that previously reported.[38]

Compound **6b**. Following general procedure A, the reaction performed with **4b** (143 mg, 0.5 mmol) afforded **6b** in ^{19}F yield = 77% and, after purification, 101 mg (77%) as a white solid (contaminated by 5% of the isomerized (Z)-product). GC−MS: 5.890 min (m/z 248 $(M)^+$). ^{19}F NMR (376 MHz/$CDCl_3$): δ −63.4 (s). Spectral data were consistent with that previously reported.[16]

Compound **6c**. Following general procedure A, the reaction performed with **4c** (75 mg, 0.25 mmol) afforded **6c** in ^{19}F yield = 70% (in this case, 2.0 equiv of internal standard was used) and, after purification, 39 mg (59%) as a white solid. mp 82−83 °C. GC−MS: 6.183 min (m/z 262 $(M)^+$). HRMS (ESI): m/z calcd for $C_{16}H_{13}F_3$ $(M)^+$, 262.0969; found, 262.0970. ^{1}H NMR (400 MHz/$CDCl_3$): δ 7.73−7.60 (m, 4H), 7.54−7.35 (m, 5H), 7.12 (s, 1H), 2.10 (s, 3H). ^{13}C NMR (100 MHz/$CDCl_3$): δ 141.0 (C), 140.3 (C), 133.5 (C), 130.9 (q, J = 6 Hz, CH), 129.7 (2 CH), 128.9 (2 CH), 127.6 (CH), 127.1 (2 CH), 127.0 (2 CH), 126.2 (q, J = 29 Hz, C), 124.6 (q, J = 272 Hz, C), 12.3 (CH_3). ^{19}F NMR (376 MHz/$CDCl_3$): δ −69.5 (s).

Compound **6d**. Following general procedure A, the reaction performed with **4d** (62 mg, 0.21 mmol) afforded **6d** in ^{19}F yield = 12% (in this case, 2.0 equiv of internal standard was used) and, after purification, 6 mg (10%) as a white solid. mp 64−65 °C. GC−MS: 5.862 min (m/z 262 $(M)^+$). HRMS (ESI): m/z calcd for $C_{16}H_{13}F_3$ $(M)^+$, 262.0969; found, 262.0963. ^{1}H NMR (400 MHz/$CDCl_3$): δ 7.68−7.57 (m, 5H), 7.54−7.42 (m, 2H), 7.42−7.30 (m, 2H) 6.58 (m, 1H), 1.74 (m, 3H). ^{13}C NMR (100 MHz/$CDCl_3$): δ 141.2 (C), 140.5 (C), 131.9 (C), 131.6 (q, J = 5 Hz, CH), 131.3 (q, J = 45 Hz, C), 130.1 (2 CH), 128.8 (2 CH), 128.6 (q, J = 275 Hz, C), 127.5 (CH), 127.1 (4 CH), 14.3 (CH_3). ^{19}F NMR (376 MHz/$CDCl_3$): δ −65.7 (s).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental considerations and copies of GCMS monitoring and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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■ ACKNOWLEDGMENTS

This research was supported by the NIH (NIGMS R01 GM081376) and by the Neuroscience Medicinal Chemistry Department of Janssen. Michel Carpentier and Guy Winderickx (Janssen) are acknowledged for obtaining HRMS data.

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dx.doi.org/10.1021/jo4023233 | *J. Org. Chem.* XXXX, XXX, XXX−XXX