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Copper-Catalyzed Oxidative Trifluoromethylation of Terminal Alkynes and Aryl Boronic Acids Using (Trifluoromethyl)trimethylsilane

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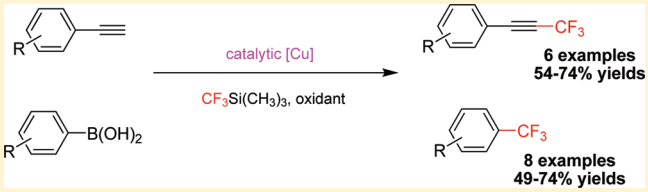
Supporting Information

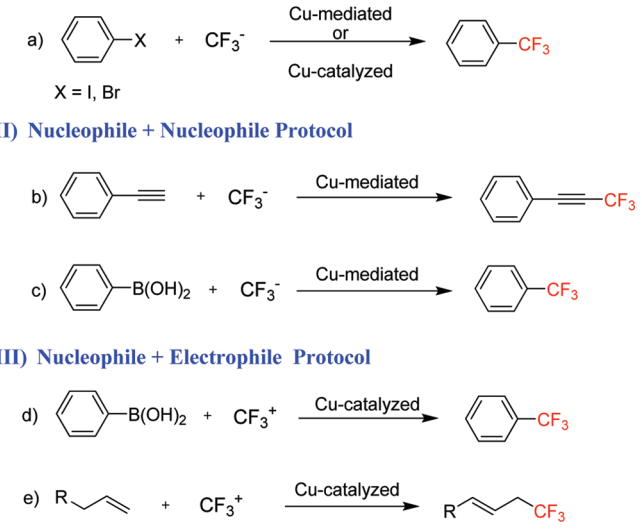
ABSTRACT: Trifluoromethylated acetylenes and arenes are widely applicable in the synthesis of pharmaceuticals and agrochemicals. In 2010, our group has reported the copper-mediated oxidative trifluomethylation of terminal alkynes and aryl boronic acids. This method allows a wide range of functional group tolerant trifluoromethylated acetylenes and arenes to be easily prepared. After the preliminary mechanistic studies of the oxidative trifluoromethylation of terminal alkyne, an efficient copper-catalyzed oxidative trifluoromethylation of terminal alkynes and aryl boronic acids has been developed. The catalytic protocol is successfully achieved by adding both the substrate and a portion of CF_3TMS slowly using a syringe pump to the reaction mixture.



INTRODUCTION

The introduction of trifluoromethyl (CF_3) groups into organic molecules can substantially alter their chemical and metabolic stability, lipophilicity, and binding selectivity because of the strongly electron withdrawing nature and large hydrophobic domain of trifluoromethyl groups.[1] Notably, many biologically active compounds, including the antidepressant Prozac and the herbicide Fusilade, contain the CF_3 groups as the essential motif.[1] As a result, much attention has been paid to the development of new synthetic methods for the introduction of the CF_3 groups into diverse organic compounds.[1,2] In the past few years, promising progress has been made in the area of transition-metal-mediated trifluoromethylation.[3−9] Among these transition-metal-based protocols for the introduction of the CF_3 group to organic molecules, the most utilized protocol should be copper-mediated trifluoromethylation of aromatic substrates.[6−9] Pioneering investigations by Burton identified the $CuCF_3$ complex by NMR.[6a] Further developments by Vicic,[6f] Hartwig,[6i] and Grushin[6j] documented the high reactivity of well-defined $CuCF_3$ complex toward aryl halides. Moreover, the groups of Chen,[7a] Amii,[7b] and Goo*β*en[7c] reported copper-catalyzed trifluoromethylation of aryl iodides with in situ generated $CuCF_3$ species. While substantial progress has been made, current copper-mediated trifluoromethylation methods have been limited almost entirely to the cross-coupling reaction between the nucleophilic trifluoromethylating reagents and the electrophiles such as aryl iodides and bromides (Scheme 1a).[6,7] The development of an alternative coupling manner involving suitable coupling partners for these trifluoromethylations is certainly desirable.

Scheme 1. Copper-Based Trifluoromethylation Protocols



In 2010, our group reported the first copper-mediated oxidative trifluoromethylation of terminal alkynes with

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(trifluoromethyl)trimethylsilane (CF_3TMS) (Scheme 1b).[8a] This is the first report of oxidative cross-coupling between the nucleophilic substrate and the nucleophilic trifluoromethylating reagent in the presence of copper, providing a new viewpoint to construction of C–CF_3 bonds. Soon afterward, we[8b] and Buchwald[8c] independently applied this oxidative trifluoromethylation protocol to aryl boronic acids, allowing access to a variety of trifluoromethylated arenes (Scheme 1c). However, stoichiometric amounts of copper reagents are required to complete the oxidative trifluoromethylation reactions of alkynes and boronic acids. Recently, copper-catalyzed electrophilic trifluoromethylation of aryl boronic acids[9a,b] and terminal olefins[9c−e] have been successively reported, while the use of expensive electrophilic trifluoromethylating reagents is a significant limitation (Scheme 1d,e). Clearly, the development of alternative copper-catalyzed trifluoromethylations with more convenient and more inexpensive trifluoromethylating reagent remains an attractive goal.

As described previously, we have reported the copper-mediated oxidative trifluoromethylation of terminal alkynes[8a] and aryl boronic acids[8b] using CF_3TMS as a convenient trifluoromethylating agent (Scheme 1b,c). Although various trifluoromethylated alkynes and aromatics were obtained in high yields using this oxidative trifluoromethylation protocol, a significant limitation of the protocol is that a stoichiometric amount of copper was needed to complete the transformation. Herein, we describe that the oxidative trifluoromethylations of terminal alkynes and aryl boronic acids is successfully achieved under the catalysis of copper.

RESULTS AND DISCUSSION

In the hope of developing a catalytic process, we initially turned our attention to the preliminary mechanistic studies to acquire a deeper understanding of copper-mediated oxidative trifluoromethylation. In the case of copper-mediated oxidative trifluoromethylation of 1-*tert*-butyl-4-ethynylbenzene, we noticed that the ^{19}F NMR spectrum of the reaction mixture clearly shows two $CuCF_3$ species: [(phen)$CuCF_3$] (resonates at δ = −23.6 ppm) and [$(phen)_2Cu$][$Cu(CF_3)_2$] (resonates at δ = −34.9 ppm), which is similar to the literature data for the $CuCF_3$ intermediate (Figure 1).[6a,f,i,j] This phenomenon

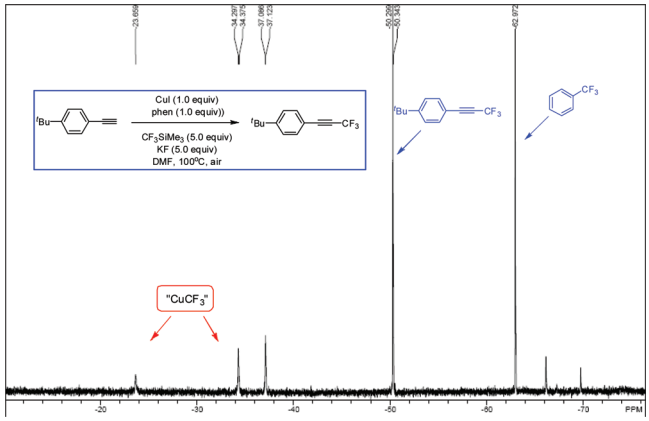
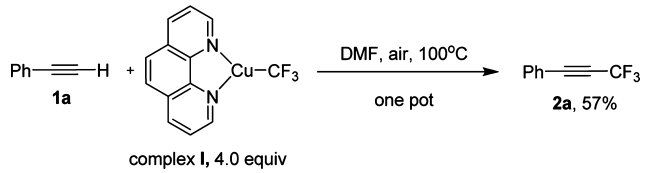


Figure 1. ^{19}F NMR of the reaction mixture of the oxidative trifluoromethylation of 1-*tert*-butyl-4-ethynylbenzene ($PhCF_3$ was added to reaction mixture as an internal standard).

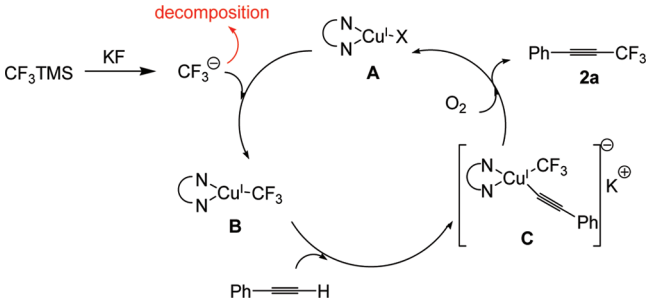
indicated that $CuCF_3$ was generated in situ in the reaction and might be the key intermediate for the Cu-mediated oxidative trifluoromethylation process.[8a] To investigate the intermediates of the present oxidative trifluoromethylation, the complex [(phen)$CuCF_3$] **I** was prepared according to the literature[6i] and then used for oxidative trifluoromethyaltion of terminal alkyne. The reaction of phenylacetylene (**1a**) with complex [(phen)$CuCF_3$] **I** under air gave the desired product **2a** in 57% yield (Scheme 2). This result showed that copper-mediated oxidative trfluoromethylation proceeded through $CuCF_3$ species.

Scheme 2. Mechanistic Study



On the basis of these experimental results, we proposed that the oxidative trifluoromethylation of terminal alkynes proceeds by the formation of trifluoromethyl anion, which undergoes generation of $CuCF_3$ **B**. The subsequent transmetalation with phenylacetylene to afford Cu(alkynyl)(trifluoromethyl) complex **C**. Oxidation of complex **C** to a Cu(III) intermediate[10] and followed by reductive elimination delivered the desired product and regenerated copper catalyst (Scheme 3).

Scheme 3. Proposed Mechanism of Oxidative Trifluoromethylation of Terminal Alkyne



In view of the inherent instability of the trifluoromethyl anion,[2a] the decomposition rate of the trifluoromethyl anion under the oxidative reaction condition would be much higher than the reductive elimination rate for regeneration copper catalyst. As a result, there was no sufficient amount of the regenerated copper **A** to combine with trifluoromethyl anion before its decomposition, directly impeding the formation of the key $CuCF_3$ intermediate **B**. This is why a stoichiometric amount of copper is needed for the oxidative trifluoromethylation of terminal alkynes (Scheme 1b). Actually, by simply reducing the loading of copper to 20 mol % under the optimized reaction conditions of oxidative trifluoromethylation of terminal alkyne,[8a] the yield of the desired product **2a** was dramatically decreased to 13% yield (Scheme 4a). To obviate the problem of quick decomposition of trifluoromethyl anion under the oxidative reaction conditions, we reasoned that CF_3TMS should be added slowly to the reaction mixture other than in one portion. On the other hand, phenylacetylene (**1a**) should be also added slowly to a pregenerated $CuCF_3$ to inhibit the homocoupling of phenylacetylene.[8a] Combined with the above considerations, the following addition method was

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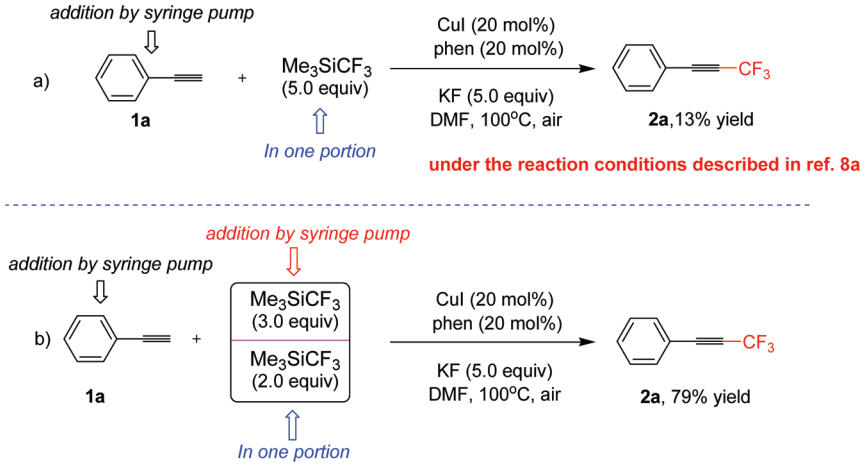
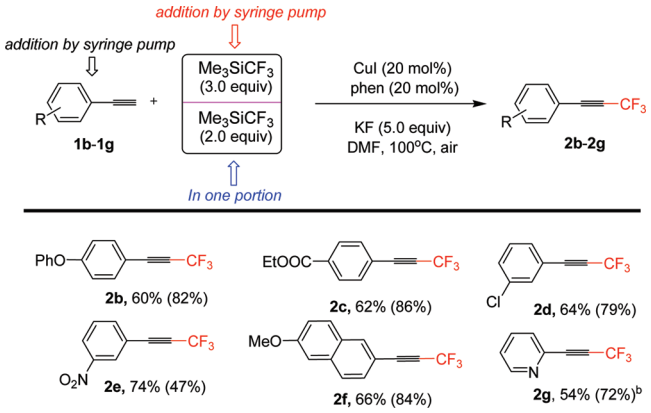
Scheme 4. Catalytic Process of Oxidative Trifluoromethylation



conducted: a portion of CF_3TMS was added to the mixture of CuI, phenanthroline, and KF in DMF to ensure the pregeneration of $CuCF_3$, and the rest of CF_3TMS was added slowly to the reaction mixture to avoid the quick decomposition of CF_3TMS, accompanying with the slow addition of phenylacetylene to inhibit the homocoupling side product. Indeed, when phenylacetylene (1.0 equiv) and CF_3TMS (3.0 equiv) were added slowly by using a syringe pump over a period of 4 h to the mixture of CF_3TMS (2.0 equiv), KF (5.0 equiv), CuI (20 mol %), and phenanthroline (20 mol %), the copper-catalyzed oxidative trifluoromethylation of terminal alkyne proceeded smoothly to give the desired product **2a** in 79% yield (Scheme 4b).

With the copper-catalyzed oxidative trifluoromethylation reaction conditions, the substrate scope was then investigated, and the results are shown in Table 1. Similar to the previous examples of oxidative trifluoromethylation of terminal alkynes using stoichiometric amount of copper,[8a] the catalytic reaction could be carried out with a series of electron-rich and electron-poor aryl alkynes, as well as terminal alkyne containing a pyridine skeleton. Notably, the copper-catalyzed oxidative trifluoromethylation of **1e** containing a nitro group on the aromatic ring gave the trifluoromethylated product **2e** in 74% yield. In contrast, the reaction of **1e** under the stoichiometric copper reaction afforded compound **1e** in only 47% yield, together with some unidentified side products.

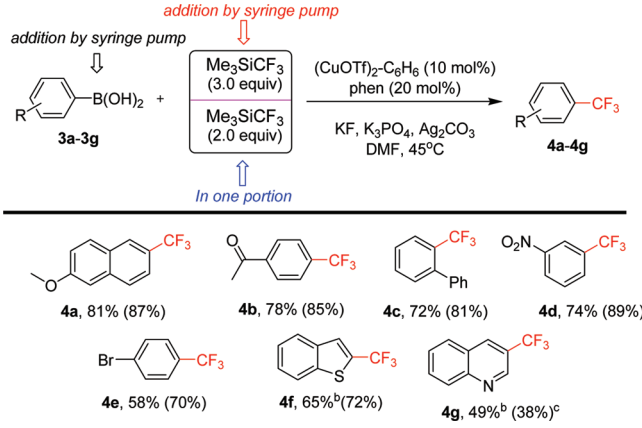
Table 1. Catalytic Oxidative Trifluoromethylation of Terminal Alkynes[a]



[a]Reaction was conducted in 0.2 mmol of terminal alkynes. Yield in parentheses is the yield under the stoichiometric reaction described in ref 8a. [b]Reaction was conducted on a 0.4 mmol scale.

The modified methodology was further found to be successfully applied to copper catalyze the oxidative trifluoromethylation of a range of aryl boronic acids with CF_3TMS. The yields of the desired trifluoromethylated aromatics were comparable to those of the reaction of these boronic acids under the stoichiometric copper reaction conditions (Table 2).[8b] Both electron-rich and electron-poor aryl boronic acids were suitable substrates. Functional groups such as carbonyl, nitro, and bromo could be compatible (**4b**, **4d**, **4e**). Different from the stoichiometric copper reaction reported by us[8b] and Buchwald,[8c] heteroaryl boronic acids under the catalytic copper condition did not proceed well at room temperature or 45 °C. To our delight, the corresponding trifluoromethylated heteroarenes could be obtained in moderate yields when the reaction temperature was elevated to 70 °C (**4f**, **4g**).

Table 2. Catalytic Oxidative Trifluoromethylation of Aryl Boronic Acids[a]



[a]On a 0.2 mmol scale. Yield in parentheses is the yield under the stoichiometric reaction described in ref 8b. [b]Reaction temperature is 70 °C. [c]Yield in parentheses reported in ref 8c.

Notably, copper-catalyzed oxidative trifluoromethylation of compound **12**, prepared from commercially available 3-chlorocinnamic acid **5** by multisteps, proceeded smoothly under the optimized reaction conditions, affording the desired

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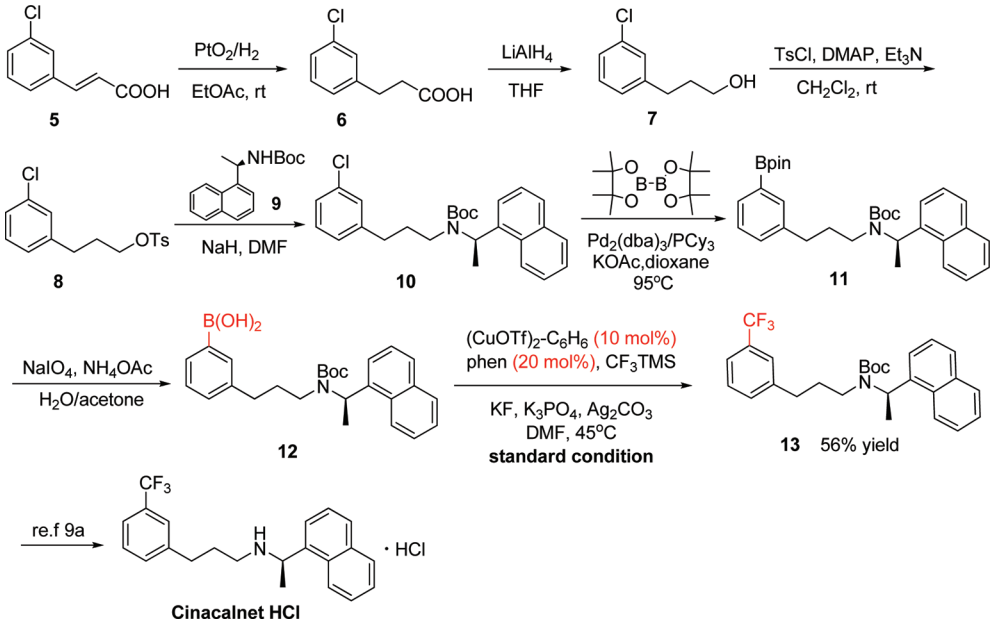
Scheme 5. Synthesis of the Precursor of Cinacalcet



product **13** in 56% yield (Scheme 5). Compound **13** is the important precursor for the synthesis of the calcimimetic agent, Cinacalcet.[11]

CONCLUSION

In summary, the preliminary mechanistic studies on the copper-mediated oxidative trifluoromethylation of terminal alkynes had been successfully used to design the copper-catalyzed oxidative trifluoromethylation of aryl and heteroaryl terminal alkynes protocol. An efficient catalytic oxidative trifluoromethylation process was developed by adding both terminal alkynes and a portion of CF_3TMS slowly using a syringe pump to the reaction mixture. The catalytic trifluoromethylation protocol could also be applied to the oxidative trifluoromethylation of aryl boronic acids.

EXPERIMENTAL SECTION

General Experimental Methods. ^1H NMR (TMS as the internal standard) and ^{19}F NMR spectra ($CFCl_3$ as the outside standard and low field is positive) were recorded on a 300 or 400 MHz spectrometer. ^{13}C NMR was recorded on 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Substrates **1d**, **1f**, **1g**, and **4a**–**g** and compound **5** were purchased from commercial sources and used as received. Substrates **1b**,[12] **1c**,[13] and **1e**[14] were prepared according to literature procedures. Compounds **2b**,[8a] **2c**,[8a] **2d**,[8a] **2e**,[8a] **2f**,[8a] **2g**,[8a] **4a**,[8b] **4b**,[8b] **4c**,[8b] **4d**,[8b] **4e**,[8b] **4f**,[8b] and **4g**[8c] are all known compounds.

General Procedure for the Copper-Catalyzed Oxidative Trifluoromethylation of Terminal Alkynes with Me_3SiCF_3. In a glovebox, CuI (0.04 mmol), phen (0.04 mmol), and KF(1.0 mmol) were added to a reaction tube that was equipped with a stirring bar. The tube was capped with a septum and taken out. The vial was evacuated and then refilled with air for three times. DMF (1.0 mL) was added, and the mixture was stirred for 15 min at room temperature. Next, Me_3SiCF_3 (2.0 equiv) was added in one portion, and then the resulting mixture was heated to 100 °C. A solution of terminal alkyne (0.2 mmol) and Me_3SiCF_3 (2.0 equiv) in 1.0 mL DMF was added to the tube over 4 h by using a syringe pump under air atmosphere (1 atom). After addition of the solution, the reaction mixture was kept for another 2 h at 100 °C. At the conclusion of the reaction, the mixture was allowed to cool to room temperature, and water was added to the mixture at 0 °C. The resulting mixture was extracted by ethyl ether, and the combined organic phase was washed with a large amount of water threee times and with brine once and then dried with sodium sulfate. The solvent was removed by rotary evaporation in ice bath and purified by column chromatography on silica gel with pentane to give the product.

1-Phenoxy-4-(3,3,3-trifluoroprop-1-ynyl)benzene (2b): ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.50 (d, J = 8.7 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 7.05 (d, J = 8.1 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −49.3 (s, 3F).

Ethyl 4-(3,3,3-trifluoroprop-1-ynyl)benzoate (2c): ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.07 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H), 4.40 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −49.9 (s, 3F).

1-Chloro-3-(3,3,3-trifluoroprop-1-ynyl)benzene (2d): ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.51 (s, 1H), 7.25–7.42 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −49.9 (s, 3F).

1-Nitro-3-(3,3,3-trifluoroprop-1-ynyl)benzene (2e): ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.43 (s, 1H), 8.35 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.64 (t, J = 8.1 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −50.2 (s, 3F).

2-Methoxy-6-(3,3,3-trifluoroprop-1-ynyl)naphthalene (2f): ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.01 (s, 1H), 7.70 (d, J = 9.3 Hz, 2H), 7.48 (d, J = 8.1 Hz, 1H), 7.19 (d, J = 9.1 Hz, 1H), 7.11 (s, 1H), 3.92 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −49.0 (s, 3F).

2-(3,3,3-Trifluoroprop-1-ynyl)pyridine (2g): ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.68 (d, J = 3.9 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.41 (t, J = 6.0 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −51.0 (s, 3F).

General Procedure for the Copper-Catalyzed Oxidative Trifluoromethylation of Boronic Acids with Me_3SiCF_3. In a glovebox, $[Cu(OTf)]_2{\cdot}C_6H_6$ (0.02 mmol), phen (0.04 mmol), K_3PO_4 (0.6 mmol), and KF (1.0 mmol) were added to a reaction tube that was equipped with a stirring bar. The tube was capped with a septum and taken out. Ag_2CO_3 (0.2 mmol) and DMF (2.0 mL) were added. Next, Me_3SiCF_3 (2.0 equiv) was added in one portion, and then the resulting mixture was heated to 45 °C (70 °C for substrates **4f** and **4g**). Both the solution of boronic acid (0.2 mmol) in 1.0 mL of DMF and the solution of Me_3SiCF_3 (2.0 equiv) in 1.0 mL of DMF were added to the tube together over 2 h by using a syringe pump under N_2

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atmosphere (1 atom). After addition of the solution, the reaction mixture was kept for another 2 h at 45 °C (70 °C for substrates **4f** and **4g**). At the conclusion of the reaction, the mixture was allowed to cool to room temperature, and water was added to the mixture at 0 °C. The resulting mixture was extracted by ethyl ether, and the combined organic phase was washed with a large amount of water three times and with brine once and then dried over magnesium sulfate. The solvent was removed by rotary evaporation and purified by column chromatography on silica gel with pentane to give the product.

2-Methoxy-6-(trifluoromethyl)naphthalene (4a): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.05 (s, 1H), 7.80 (d, J = 12.0 Hz, 2H), 7.59 (d, J = 11.6 Hz, 1H), 7.22 (d, J = 9.0 Hz, 1H), 7.16 (s, 1H), 3.94 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −61.8 (s, 3F).

1-(4-(Trifluoromethyl)phenyl)ethanone (4b): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.08 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H), 2.67 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −62.8 (s, 3F).

2-(Trifluoromethyl)biphenyl (4c): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.74 (d, J = 7.5 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.45−7.40 (m, 3H), 7.36−7.35 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −56.6 (s, 3F).

1-Nitro-3-(trifluoromethyl)benzene (4d): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.52 (s, 1H), 8.45 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.74 (t, J = 8.1 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −62.7 (s, 3F).

1-Bromo-4-(trifluoromethyl)benzene (4e): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.65 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −62.1 (s, 3F).

2-(Trifluoromethyl)benzo[*b*]thiophene (4f): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.85−7.89 (m, 2H), 7.69 (s, 1H), 7.41−7.49 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −56.0 (s, 3F).

3-(trifluoromethyl)quinoline (4g): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.11 (s, 1H), 8.47 (s, 1H), 8.21 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.1 Hz, 1H), 7.88 (t, J = 8.4 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −61.5 (s, 3F).

3-(3-Chlorophenyl)propanoic Acid (6). A suspension of 3-chlorocinnamic acid (1.092 g, 6.00 mmol) and Pt(IV) oxide (0.027 g, 0.12 mmol) was stirred in ethyl acetate (50 mL) under H_2 (1 atm) at room temperature for 48 h. The catalyst was removed by filtration, and solvent from the filtrate was removed by rotary evaporation. The residue was dried further in vacuo to give the compound **6** (1.030 g, 93% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.08−7.26 (m, 4H), 2.94 (t, J = 7.6 Hz, 2H), 2.68(t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.3, 142.2, 134.4, 129.9, 128.6, 126.7, 126.6, 35.3, 30.2; IR (neat) ν 3035, 2922, 1709 cm^{-1}; MS (ESI) m/z 182.9 (M^- − H), 367.0 ($2M^-$ − H); HRMS calcd for $C_9H_8ClO_2$ (M^- − H) 183.0218, found 183.0223.

3-(3-Chlorophenyl)propan-1-ol (7). To a suspension of $LiAlH_4$ (0.912, 24.00 mmol) in THF (20 mL) at 0 °C was added compound **6** (1.900 g, 10.30 mmol) slowly. The resulting mixture was allowed to warm to room temperature and stirred for 45 min, and it was then refluxed until the reaction was complete. The reaction mixture was cooled to 0 °C, and H_2O (0.9 mL), 15% NaOH solution (0.9 mL), and H_2O (7 mL) were added slowly to quench the reaction. The resulting solid was removed by filtration through Celite. The obtained filtrate was washed with water three times and with brine once and then dried with sodium sulfate. The solvent was removed by rotary evaporation and purified by column chromatography on silica gel with a mixture of petroleum ether and ethyl acetate (3:1) as the eluent to give the compound **7** (1.622 g, 93% yield) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.06−7.23 (m, 5H), 3.66 (t, J = 6.3 Hz, 2H), 2.68(t, J = 7.6 Hz, 2H), 1.82−1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 144.0, 134.1, 129.7, 128.6, 126.7, 126.0, 61.8, 33.9, 31.7; IR (thin film) ν 3345, 3066, 2939, 1080 cm^{-1}; MS (EI) m/z 170 (M^+); HRMS Calculated for $C_9H_{11}ClO$ (M^+) 170.0499, Found: 170.0498.

3-(3-Chlorophenyl)propyl 4-methylbenzenesulfonate (8). To a solution of compound **7** (1.603 g, 9.40 mmol), DMAP (0.132 g, 1.10 mmol), and Et_3N (1.8 mL, 13.20 mmol) in CH_2Cl_2 (10 mL) was added TsCl (2.324 g, 12.2 mmol) at room temperature. After the mixture was stirred overnight at 40 °C, water was added to quench the reaction. Products were exacted with ethyl ether. The combined organic layers were washed with water and brine, dried over sodium sulfate, and concentrated to give a crude mixture, which was purified by column chromatography on silica gel with a mixture of petroleum ether and ethyl acetate (10:1) as the eluent to give the compound **8** (2.321 g, 76% yield) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.79 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 6.96−7.17 (m, 4H), 4.02 (t, J = 6.0 Hz, 2H), 2.63(t, J = 7.4 Hz, 2H), 2.46 (s, 3H), 1.92−1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 144.9, 142.5, 134.2, 133.0, 130.0, 129.8, 128.5, 127.9, 126.7, 126.4, 69.3, 31.1, 30.2, 21.7; IR (thin film) ν 3066, 2959, 1360, 1176, 1080 cm^{-1}; MS (ESI): m/z 324.8 (M^+ + H), 346.3 (M^+ + Na); HRMS calcd for $C_{16}H_{17}ClO_3SNa$ (M^+ + Na) 347.0479, found 347.0485.

(*R*)-*tert*-Butyl 1-(Naphthalen-1-yl)ethylcarbamate (9). Compound **9** was prepared following the procedure in the literature:[15] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.40−7.54 (m, 4H), 5.61 (s,1H), 4.93 (d, J = 6.8 Hz, 1H), 1.60 (d, J = 6.4 Hz, 3H), 1.43 (s, 9H).

(R)-*tert*-Butyl-3-(3-chlorophenyl)propyl(1-(naphthalen-1-yl)-ethyl)carbamate (10). To a suspension of NaH (0.180 g, 2.5 mmol) in DMF (8 mL) was added compound **9** (0.813 g, 3.00 mmol) at room temperature. After stirring 15 min, compound **8** (0.990 g, 3.10 mmol) was added dropwise. The reaction was stirred for 24 h at 35 °C, quenched with water (8 mL) and extracted with ethyl ether (3 × 15 mL). The ether layers were washed with water and brine, dried over sodium sulfate, and concentrated to give a crude mixture, which was purified by column chromatography on silica gel with a mixture of petroleum ether and ethyl acetate (12:1) as the eluent to give the compound **10** (1.101 g, 79% yield) as a colorless liquid: $[\alpha]_D$ 26 = +56.4 (*c* 3.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (d, J = 7.6 Hz, 1H), 7.85 (d, 8.0 Hz, 1H), 7.79 (t, J = 4.8 Hz, 1H), 7.46−7.53 (m, 2H), 7.39 (d, J = 5.2 Hz, 2H), 6.99−7.06 (m, 2H), 6.63 (s, 1H), 6.55 (d, J = 6.8, 1H), 6.16−6.19 (m, 1H), 2.72−2.96 (m, 2H), 2.07 (t, J = 7.2 Hz, 2H), 1.58 (d, J = 6.8 Hz, 3H), 1.52(s, 9H), 1.21−1.26 (m, 1H), 0.71−0.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.4, 143.8, 136.7, 134.0, 133.8, 132.4, 129.4, 128.8, 128.6, 128.3, 126.5, 126.4, 125.9, 125.8, 125.1, 124.3, 79.7, 49.4, 42.0, 33.0, 30.7, 28.6, 17.1; IR (thin film) ν 3048, 2974, 1682, 1407, 1154 cm^{-1}; MS (ESI) m/z 446.3 (M^+ + Na); HRMS calcd for $C_{26}H_{30}ClNO_2Na$ (M^+ + Na) 446.1857, found 446.1860.

(R)-*tert*-Butyl-1-(naphthalen-1-yl)ethyl (3-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)carbamate (11). In a glovebox, bis(pinacolato)diboron (0.852 g, 3.40 mmol), $Pd_2(dba)_3$ (0.078 g, 0.09 mmol), PCy_3 (0.057 g, 0.2 mmol), and KOAc (0.430 g, 4.25 mmol) were added to a reaction tube that was equipped with a stirring bar. The tube was capped with a septum and taken out. Compound **10** (0.710 g, 1.70 mmol) and 1,4-dioxane (8 mL) were added via syringe, and the resulting mixture was stirred for 12 h at 95 °C. After removal of solvent, water (10 mL) was added, and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate, and concentrated to give a crude mixture, which was purified by column chromatography on silica gel with a mixture of petroleum ether and ethyl acetate (9:1) as the eluent to give the compound **11** (0.700 g, 80% yield) as a colorless liquid: $[\alpha]^{26}_D$ = +38.2 (*c* 6.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.16 (d, J = 6.9 Hz, 1H), 7.84(d, J = 7.6, 1H), 7.78(t, J = 4.8 Hz, 1H), 7.38−7.58(m, 5H), 7.32 (s, 1H), 7.16 (t, J = 7.2 Hz, 1H), 6.78 (d, J = 7.2 Hz, 1H), 6.16−6.18 (m, 1H), 2.74−2.87 (m, 2H), 2.16 (t, J = 7.5 Hz, 2H), 1.58 (d, J = 6.4 Hz, 3H), 1.50(s, 9H), 1.26−1.34 (m, 13H), 0.86−0.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.5, 141.0, 136.9, 134.7, 133.8, 132.4, 132.2, 131.2, 128.7, 128.6, 127.7, 126.5, 125.9, 125.1, 124.3, 83.8, 79.6, 49.5, 42.3, 33.3, 31.0, 28.7, 25.0, 25.0, 17.4; IR (thin film) ν 2976, 1741, 1682, 1364, 1151 cm^{-1}; MS (ESI): m/z 537.8 (M^+ + Na); HRMS calcd for $C_{32}H_{42}BNO_4Na$ (M^+ + Na) 537.3135, found 537.3147.

(*R*)-3-(3-(*tert*-Butoxycarbonyl(1-(naphthalen-1-yl)ethyl)-amino)propyl)phenylboronic Acid (12). To a solution of compound **11** (0.381 g, 0.74 mmol) in acetone (8 mL) and water (4 mmol) were added NH_4OAc (0.231 g, 3.00 mmol) and $NaIO_4$

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(0.642 g, 3.00 mmol), and the mixture was stirred overnight at room temperature. The solution was concentrated, water was added to the residue, and the resulting mixture was extracted with ethyl acetate (3 × 8 mL). The combined organic extracts were washed with water and brine, dried over sodium sulfate, and concentrated to give a crude mixture, which was purified by column chromatography on silica gel with a mixture of petroleum ether and ethyl acetate (3:1) as the eluent to give the compound **12** (0.291 g, 91% yield) as a white, foam-like solid: $[\alpha]^{26}_{D}$ = +48.0 (*c* 3.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.17 (d, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 7.2 Hz, 1H), 7.75−7.82 (m, 2H), 7.25−7.54 (m, 6H), 6.93 (s, 1H), 6.16−6.20 (m, 1H), 2.81−2.98 (m, 2H), 2.29 (t, *J* = 7.2 Hz, 2H), 1.52−1.61 (m, 13H), 0.91−0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.5, 141.2, 136.8, 135.5, 133.7, 133.2, 132.6, 132.4, 130.1, 128.7, 128.6, 127.9, 127.7, 126.5, 125.9, 125.0, 124.3, 79.6, 49.5, 42.4, 33.4, 31.2, 28.7, 17.3; IR (thin film) ν 3441, 3054, 2977, 1681, 1366, 1349, 1154 cm^{-1}; MS (ESI) *m*/*z* 455.9 $(M + Na)^+$; HRMS calcd for $C_{26}H_{32}BNO_4Na$ $(M^+ + Na)$ 455.2353, found 455.2364.

(*R*)-*tert*-Butyl 1-(naphthalen-1-yl)ethyl(3-(3-(trifluoromethyl)phenyl)propyl)carbamate (13): $[\alpha]^{26}_{D}$ = +42.9 (*c* 2.58, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.17 (d, *J* = 6.9 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.20−7.55 (m, 6H), 6.82−6.90 (m, 2H), 6.12−6.20 (m, 1H), 2.74−3.00 (m, 2H), 2.14 (t, *J* = 7.5 Hz, 2H), 1.60 (d, *J* = 6.9 Hz, 3H), 1.50(s, 9H), 1.23−1.25 (m, 1H), 0.71−0.73 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −62.2 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.4, 142.7, 136.8, 133.8, 132.5,131.6, 130.6 (q, *J* = 31.4 Hz), 128.8, 128.7, 128.6, 126.1, 126.0, 125.7, 125.1, 124.9 (q, *J* = 3.6 Hz), 124.3 (q, *J* = 270.5 Hz), 124.3, 122.6, 79.8, 49.6, 42.1, 33.2, 30.9, 28.7, 17.2; IR (thin film) ν 3051, 2975, 1683, 1408, 1329, 1160, 1124 cm^{-1}; MS (ESI) *m*/*z* 479.8 $(M^+ + Na)$; HRMS calcd for $C_{27}H_{30}F_3NO_2Na$ $(M^+ + Na)$ 480.2121, found 480.2130.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{19}F NMR spectra for the compounds **2b−g** and **4a−g**. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. These material are available free of charge via the Internet at http://pubs.acs.org.

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