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Note

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Copper-Mediated Cyanotrifluoromethylation of Styrenes Using the Togni Reagent

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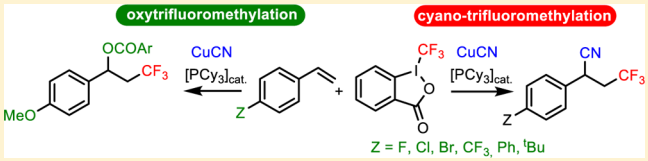
Supporting Information

ABSTRACT: Styrenes with an electron-deficient double bond undergo cyanotrifluoromethylation with a trifluoromethylated hypervalent iodine reagent in the presence of CuCN. The reaction proceeds under mild conditions in the presence of bulky phosphines or B_2pin_2 additives. The process is highly regioselective and involves the consecutive formation of two C−C bonds in a single addition reaction. In the presence of a *p*-methoxy substituent in the styrene, oxytrifluoromethylation occurs instead of the cyanotrifluoromethylation.



Trifluoromethylated compounds represent an important class of bioactive intermediates in the pharmaceutical and agrochemical industries.[1] As a consequence, there is a large demand for new methods for selective synthesis of functionalized trifluoromethylated compounds.[2−5] Recently, new and powerful methodologies have appeared in the literature to introduce the trifluoromethyl functionality using oxidative reagents, such as the Togni reagents **1a** and **1b** and the Umemoto reagent **1c** (Figure 1).[6−22]

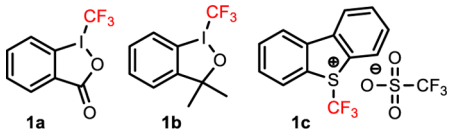
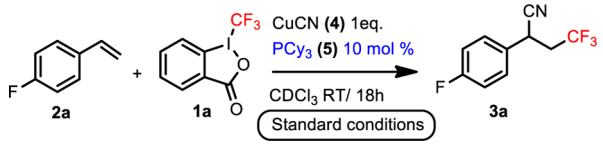


Figure 1. Examples of oxidative CF_3 transfer reagents.

We[8] and others[9−12,17,20] have shown that efficient oxytrifluoromethylation of styrenes and other species lacking *β*-hydrogens can be carried out using **1a**. In a standard reaction with **1a**, the trifluoromethyl group is usually introduced at the terminal position of the styrene,[8,9] while the iodobenzoate (arising from **1a**) is introduced on the other carbon atom of the alkene. However, a few examples in which the second group introduced was a halogenide (instead of iodobenzoate) from the applied CuX mediator of the reaction have been reported.[8,23] In this note, we present our results using CuCN as the mediator for the trifluoromethylation reaction. We have found that under appropriate reaction conditions this copper salt in combination with **1a** is suitable for selective introduction of the CF_3 and CN groups to styrenes, thus creating two C−C bonds in a single addition reaction. Remarkably, in a very recent publication Akita and co-workers[16] reported a similar reaction with a completely different outcome. These authors employed **1c** and organonitriles for bifunctionalization of styrenes under photoredox conditions. This reaction resulted in aminotrifluoromethylation involving C−C and C−N bond formation.

The best results for the presented cyanotrifluoromethylation reaction were achieved using electron-deficient styrenes (e.g., **2a**) with **1a** as the CF_3 source in the presence of catalytic amounts of PCy_3 (**5**)[13] and stoichimetric amounts of CuCN (**4**). Under these conditions, the cyanotrifluoromethylated products (e.g., **3a**) were formed with high regioselectivity in good yields (Table 1, entry 1). Addition of PCy_3 was essential, as in the absence of this bulky/electron-rich phosphine the formation of **3a** was not observed in the crude reaction mixture (entry 2). Replacement of PCy_3 with P^tBu_3 led to the formation of **3a** but in a lower yield (entry 3). Application of PPh_3 was inefficient. The reaction occurred with acceptable yield (52%) using B_2pin_2 instead of PCy_3. We recently reported that B_2pin_2

Table 1. Variation of the Reaction Conditions for Cyanotrifluoromethylation



entry	variation from the "standard conditions"	yield (%)
1	none	73
2	without **5**	<5
3	P^tBu_3 instead of **5**	28
4	B_2pin_2 (5 mol %) instead of **5**	52
5	**1b** or **1c** instead of **1a**	<5
6	CuCN (10 mol %) and 1 equiv of Bu_4NCN	47
7	CuCN (10 mol %) and 1 equiv of KCN	32
8	MeOH instead of $CDCl_3$	22
9	DMF instead of $CDCl_3$	12
10	DMSO instead of $CDCl_3$	7
11	THF instead of $CDCl_3$	<5

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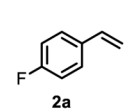
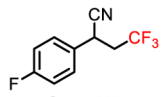
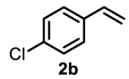
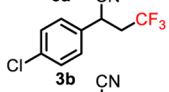
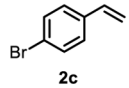
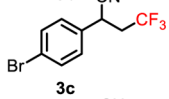
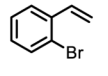
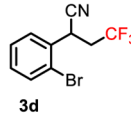
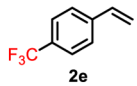
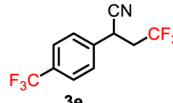
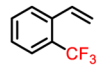
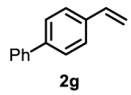
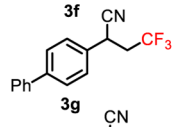
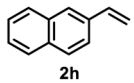
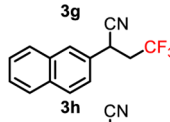
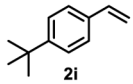
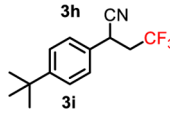
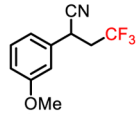
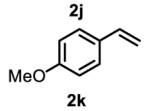
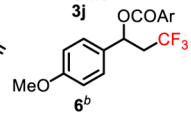
has an activating effect in Cu-mediated trifluoromethylation of quinones.[14] A similar effect was observed for the above cyanotrifluoromethylation reaction. Other CF_3 sources such as **1b** or **1c** could not be used instead of **1a** (entry 5). The reaction obviously requires stoichimetric amounts of cyanide. However, the cyanide component does not necessarily have to come from **4**. A catalytic amount of CuCN (10 mol %) is sufficient in the presence of a stoichimetric amount of Bu_4NCN or another cyanide source (entries 6 and 7). However, the yield is lower with Bu_4NCN (47%) than with a stoichimetric amount of CuCN (cf. entries 1 and 6). Application of a catalytic amount of CuCN with a stoichimetric amount of KCN (entry 7) gave an even lower yield than the reaction with Bu_4NCN (entry 6), possibly because of the poor solubility of KCN in the reaction medium. Considering this and the fact that CuCN is less expensive than Bu_4NCN, we employed stoichimetric amounts of CuCN in the further studies. Using only Bu_4NCN in the absence of CuCN, we did not observe any reaction of 2**a**. We also briefly screened other solvents for the process. However, the yield was substantially decreased when the reaction was conducted in MeOH, DMF, DMSO, or THF instead of $CDCl_3$ (the reactions were conducted in deuterated solvents to directly study the crude reaction mixture with ^1H and ^{19}F NMR spectroscopy).

We also attempted the reaction using CuOAc in place of CuCN. In this process, most of the starting material (**2a**) remained intact, and according to ^{19}F NMR analysis, only traces of trifluoromethylated product were formed (i.e., the oxytrifluoromethylated product did not form either). This is in line with our previous studies,[8] which showed that styrenes with electron-withdrawing groups are reluctant to undergo oxytrifluoromethylation at room temperature.

Subsequently, we explored the synthetic scope of the reaction (Table 2). Styrenes with an electron-withdrawing group proved to be particularly useful substrates for cyanotrifluoromethylation (entries 1−7). Inspection of the crude reaction mixtures by ^{19}F NMR indicated the formation of the desired cyanotrifluoromethylated products together with other CF_3 species. For example, in some of the reactions small traces of oxytrifluoromethylation products were probably also formed. We did not attempt to isolate these trace amounts of oxytrifluoromethylation products. The relatively low yield in some reactions (e.g., entries 4, 5, and 9) is a consequence of the formation of oxotrifluoromethylated and other byproducts, which could easily be removed by column chromatography. *p*-Chloro- and -bromo-substituted styrenes (entries 2 and 3) all gave good yields similarly to the fluoro-substituted analogue (entry 1). *Ortho*-substituted substrates (entries 4 and 6) also reacted smoothly, indicating that the reaction is not sensitive to steric hindrance. Even styrenes with weakly electron-withdrawing phenyl and aryl substituents could be applied in the cyanotrifluoromethylation. *p*-Phenyl-substituted styrene **2g** and 2-vinylnaphthalene (**2h**) gave the corresponding bifunctionalized products **3g** and **3h** in relatively good yields (71 and 58%, respectively). When ^{t}Bu-substituted styrene **2i** was reacted (entry 9), mainly **3i** was formed together with a substantial amount of another trifluoromethylated product, probably the oxytrifluoromethylated analogue. Therefore, the yield was lowered to 51% and could not be improved by further optimization, for example by increasing the amount of cyanide salt in the reaction mixture. Even 3-methoxystyrene (**2j**) gave the corresponding cyanotrifluoromethylated product **3j** in 59% yield. However, the reaction of the *p*-methoxy analogue **2k** under the standard reaction conditions afforded oxytrifluoromethylated product **6** in high yield. In this reaction, only a trace, if any, of the cyanotrifluoromethylated product was formed. Thus, the cyanotrifluoromethylation reaction with CuCN and **1a** as the CF_3 source seems to be limited to styrenes with electron-withdrawing *para* and *ortho* substituents, such as F, Cl, Br, CF_3, Ph, and aryl groups, or in the case of methoxy groups, *meta* substition. In the presence of the *p*-^{t}Bu substituent (entry 9), the cyanotrifluoromethylation still dominates, but in this reaction a substantial amount of another product was also formed. In the presence of a strong π-electron donor group, such as *p*-methoxy, the chemoselectivity is shifted from cyanotrifluoromethylation to oxytrifluoromethylation. The synthetic scope of the process under the applied reaction conditions is probably limited to the above or related styrene

Table 2. Cyanotrifluoromethylation of Various Styrene Derivatives[a]

Entry	Substrate	Product	Yield (%)
1	 **2a**	 **3a**	73
2	 **2b**	 **3b**	56
3	 **2c**	 **3c**	72
4	 **2d**	 **3d**	50
5	 **2e**	 **3e**	50
6	 **2f**	 **3f**	68
7	 **2g**	 **3g**	71
8	 **2h**	 **3h**	58
9	 **2i**	 **3i**	51
10	 **2j**	 **3j**	59
11	 **2k**	 **6**[b]	87

[a]A mixture of styrene **2** (0.1 mmol), **1a** (0.15 mmol), CuCN (0.1 mmol), and PCy_3 (0.01 mmol, 10 mol %) was dissolved in $CDCl_3$ under Ar. The reaction mixture was stirred at room temperature for 18 h. [b]Ar = 2-iodophenyl.

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derivatives. Other types of substrates with an electron-poor double bond, such as methyl acrylate or methyl vinyl ketone, do not undergo the trifluoromethylation reaction under the above conditions.

The exact mechanism of the cyanotrifluoromethylation reaction is not known. However, the electronic control of the chemoselectivity to obtain the cyanotrifluoromethylated (**3a–j**) versus oxytrifluoromethylated (**6**) product under the same reaction conditions is interesting. A plausible explanation for this chemoselectivity control is given in Figure 2. As mentioned

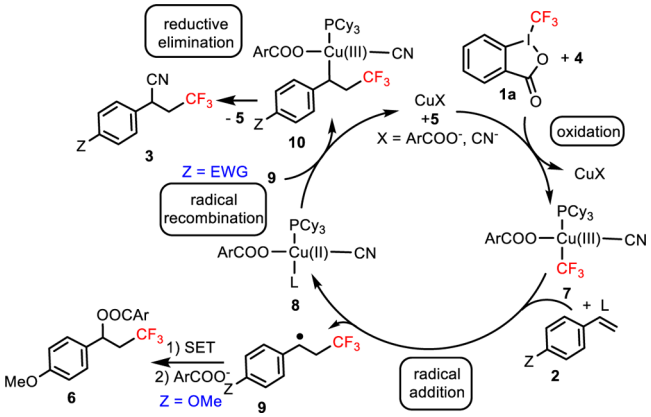

Figure 2. Plausible reaction mechanism.

previously, the reaction can also be carried out using catalytic amounts of CuCN in the presence of other cyanide sources (Table 1, entries 6 and 7). However, because of the low price of CuCN and the good yield of the reaction, we employed stoichiometric amounts of it.

The initial steps of the reaction are probably identical to those of the previously reported Cu-catalyzed oxytrifluoromethylation reaction[8−11] and the closely related allylic/vinylic C−H activation reactions[14,24−26] using **1** as the CF_3 source. Thus, we suggest that **1a** undergoes oxidative addition with CuCN to form complex **7**. In this complex, the Cu−CF_3 bond may undergo homolytic cleavage to give a CF_3 radical and Cu(II) complex **8** in a doublet electronic state. The applied PCy_3 ligand probably facilitates this process by increasing the electron density on Cu. A Bpin ligand formed by transmetalation[27] of CuCN by B_2pin_2 (Table 1, entry 4) may have a similar effect. The CF_3 radical may add to the double bond of the styrene substrate to give **9**. We suggest that recombination of radical **9** with Cu(II) complex **8** gives complex **10**. The styrene substrate (η^1-benzyl moiety) in which Z is an electron-withdrawing group (EWG) is supposed to occupy the position *trans* to the electron-rich and bulky PCy_3. Both ligands are sterically demanding, rendering them to a *trans* geometry. This geometry is probably also stabilized by the *trans* influence involving an electron-donating PCy_3 ligand and an electron-deficient η^1-benzyl moiety. The sterically nondemanding cyano group may occupy a position *cis* to the η^1-benzyl moiety and thus may undergo facile reductive elimination to afford product **3**. Coordination of the relatively bulky 2-iodobenzoyl ligand is less favorable, and its reductive elimination is probably slower than that for the CN ligand. In case of a styrene with an electron-donating OMe group at the *para* position (Z = OMe), the recombination of **8** and **9** is probably not favored. The *trans* coordination of the bulky PCy_3 and η^1-benzyl (Z = OMe) moieties is supposed to be destabilizing because of the "transphobia"[28,29] that would occur between the two electron-rich ligands. Instead, radical **9** probably undergoes a single-electron oxidation by copper, forming a stabilized carbocation, followed by nucleophilic attack of the iodobenzoate anion. An alternative mechanism could be that the cyano radical recombines with **9**. However, this would be less probable with styrenes bearing electron-withdrawing substituents, which is in contrast with the above findings.

We postulate that similar types of trifluoromethylation reactions can be developed using other appropriate Cu salts. For example, when the process was attempted using CuI instead of CuCN with **2a** as the substrate, we isolated an unstable compound that according to NMR and MS analysis was identified as iodo derivative **11** (Figure 3). Compound **11**

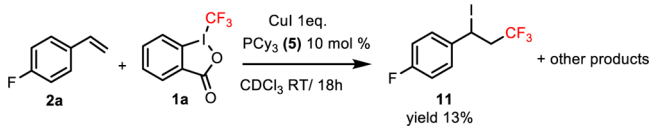

Figure 3. Iodotrifluoromethylation using CuI.

can be regarded as a product of a Cu-mediated iodotrifluoromethylation reaction. This process has a much lower yield than the cyanotrifluoromethylation, which is probably due to the fact that the C−I bond in **11** is much weaker than the C−CN bond in **2a**.

In summary, we have shown that with **1a** as the CF_3 source and CuCN as the cyanide source, various styrene derivatives undergo cyanotrifluoromethylation reactions. The addition is highly regio- and chemoselective, involving the formation of two C−C bonds in a single addition reaction. Thus, the above cyanotrifluoromethylation is suitable for bifunctionalization of styrenes by late introduction of the CF_3 functionality.[4] Both *para*- and *ortho*-substituted electron-deficient styrenes react readily and selectively. Under the same reaction conditions, when the *para* substituent is changed to a methoxy group, an oxytrifluoromethylation reaction occurs instead of the cyanotrifluoromethylation. The switch of the chemoselectivity was explained by the effects of the styrene substituent on the stability of the reaction intermediate formed prior to the product-forming step.

EXPERIMENTAL SECTION

General Information. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ (internal standard at 7.26 ppm for ^1H and 77.16 ppm for ^{13}C; α,α,α-trifluorotoluene external standard at −63.73 ppm for ^{19}F) using a 400 MHz spectrometer. HRMS data were recorded on a micrOTOF instrument using the ESI technique. The reported melting points are not corrected. For column chromatography, silica gel (35−70 μm) was used.

3-Vinylanisole (2j). This compound was synthesized from 3-anisaldehyde according to a known literature procedure[30] and isolated as a colorless oil (77%) by column chromatography using pentane:diethyl ether 9:1. The NMR data obtained for **2j** are in agreement with literature values.[31] ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (at, 1H), 7.06−7.02 (m, 1H), 6.99−6.97 (m, 1H), 6.84 (ddd, J_{HH} = 8.2, 2.6, 0.9 Hz, 1H), 6.72 (dd, J_{HH} = 17.6, 10.9 Hz, 1H), 5.77 (dd, J_{HH} = 17.6, 0.9 Hz, 1H), 5.28 (dd, J_{HH} = 10.9, 0.9 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 139.2, 136.9, 129.6, 119.0, 114.2, 113.6, 111.7, 55.3. HRMS (ESI) m/z: calcd for $[C_9H_{10}O + Na]^+$ 157.0624, found 157.0618.

General Procedure for Cyanotrifluoromethylation of Styrenes. To a 3 mL screwtop vial were added copper cyanide (**4**) (9.0 mg, 0.1 mmol, 1 equiv) and trifluoromethylating agent **1a** (47 mg, 0.15

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mmol, 1.5 equiv). The vial was subsequentially brought into a glovebox, and tricyclohexylphosphine (**5**) (3 mg, 0.01 mmol, 10 mol %), the corresponding styrene **2** (0.1 mmol, 1 equiv), and $CDCl_3$ (0.5 mL) were added. The vial was equipped with a stirring bar, screwed shut, and stirred at room temperature for 18 h. The products were isolated by column chromatography.

*4,4,4-Trifluoro-2-(4-fluorophenyl)butanenitrile (**3a**).* The product was isolated as a transparent oil (16.5 mg, 73%) using pentane:dichloromethane 1:1 as the eluent system. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.33 (m, 2H), 7.16−7.09 (m, 2H), 4.10 (dd, J_{HH} = 9.0, 5.5 Hz, 1H), 2.90−2.75 (m, 1H), 2.66−2.51 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.96 (t, J_{HF} = 9.6 Hz), −111.91 to −112.00 (m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0 (d, J_{CF} = 249.1 Hz), 129.4 (d, J_{CF} = 3.4 Hz), 129.2 (d, J_{CF} = 8.4 Hz), 124.9 (q, J_{CF} = 277.7 Hz), 118.5, 116.8 (d, J_{CF} = 22.1 Hz), 39.9 (q, J_{CF} = 29.4 Hz), 30.8 (q, J_{CF} = 3.1 Hz). HRMS (ESI) *m*/*z*: calcd for $[C_{10}H_7F_4N + Na]^+$ 240.0412, found 240.0401.

*2-(4-Chlorophenyl)-4,4,4-trifluorobutanenitrile (**3b**).* The product was isolated as a transparent oil (13.0 mg, 56%) using pentane:dichloromethane 3:1 as the eluent system. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.41 (m, 2H), 7.37−7.31 (m, 2H), 4.11 (dd, J_{HH} = 9.1, 5.4 Hz, 1H), 2.93−2.78 (m, 1H), 2.68−2.54 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.93 (t, J_{HF} = 9.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.3, 131.9, 129.8, 128.6, 124.6 (q, J_{CF} = 277.5 Hz), 118.1, 39.6 (q, J_{CF} = 29.7 Hz), 30.8 (q, J_{CF} = 3.2 Hz). HRMS (ESI) *m*/*z*: calcd for $[C_{10}H_7ClF_3N + Na]^+$ 256.0111, found 256.0105.

*2-(4-Bromophenyl)-4,4,4-trifluorobutanenitrile (**3c**).* The product was isolated as a transparent oil (19.9 mg, 72%) using pentane:dichloromethane 1:1 as the eluent system. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59−7.55 (m, 2H), 7.28−7.24 (m, 2H), 4.07 (dd, J_{HH} = 9.1, 5.5 Hz, 1H), 2.90−2.75 (m, 1H), 2.65−2.51 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.93 (t, J_{HF} = 9.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.0, 132.6, 129.1, 124.4 (q, J_{CF} = 277.7 Hz), 123.5, 118.2, 39.7 (q, J_{CF} = 29.7 Hz), 31.0 (q, J_{CF} = 3.2 Hz). HRMS (ESI) *m*/*z*: calcd for $[C_{10}H_7BrF_3N + Na]^+$ 299.9606, found 299.9595.

*2-(2-Bromophenyl)-4,4,4-trifluorobutanenitrile (**3d**).* The product was isolated as a transparent oil (14.0 mg, 50%) using pentane:dichloromethane 2:1 as the eluent system. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66−7.61 (m, 2H), 7.46−7.40 (m, 1H), 7.30−7.24 (m, 1H), 4.61 (dd, J_{HH} = 9.9, 4.3 Hz, 1H), 2.81−2.58 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.12 (t, J_{HF} = 9.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.0, 132.9, 130.9, 129.3, 128.9, 124.7 (q, J_{CF} = 278.4 Hz), 122.8, 118.1, 38.2 (q, J_{CF} = 29.9 Hz), 31.5 (q, J_{CF} = 3.1 Hz). HRMS (ESI) *m*/*z*: calcd for $[C_{10}H_7BrF_3N + Na]^+$ 299.9606, found 299.9618.

*4,4,4-Trifluoro-2-(4-(trifluoromethyl)phenyl)butanenitrile (**3e**).* The product was isolated as a transparent oil (13.4 mg, 50%) using pentane:dichloromethane 1:1 as the eluent system. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76−7.71 (m, 2H), 7.56−7.53 (m, 2H), 4.21 (dd, J_{HH} = 9.0, 5.5 Hz, 1H), 2.97−2.82 (m, 1H), 2.72−2.58 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.93 (s), −64.89 (t, J_{HF} = 9.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4 (q, J_{CF} = 1.2 Hz), 131.7 (q, J_{CF} = 32.9 Hz), 128.0, 126.8 (q, J_{CF} = 3.7 Hz), 124.5 (q, J_{CF} = 277.7 Hz), 123.8 (q, J_{CF} = 272.5 Hz), 117.9, 39.7 (q, J_{CF} = 29.9 Hz), 31.3 (q, J_{CF} = 3.2 Hz). HRMS (ESI) *m*/*z*: calcd for $[C_{11}H_7F_6N + Na]^+$ 290.0375, found 290.0363.

*4,4,4-Trifluoro-2-(2-(trifluoromethyl)phenyl)butanenitrile (**3f**).* The product was isolated as a white solid (18.3 mg, 68%) using pentane:dichloromethane 1:1 as the eluent system. Melting point 43.9−46.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78−7.73 (m, 2H), 7.72−7.66 (m, 1H), 7.57−7.50 (m, 1H), 4.52 (dd, J_{HH} = 10.4, 3.9 Hz, 1H), 2.88−2.73 (m, 1H), 2.66−2.53 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −59.16 (s), −65.52 (t, J_{HF} = 9.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.4 (q, J_{CF} = 1.0 Hz), 132.4 (q, J_{CF} = 1.4 Hz), 129.7, 129.6, 127.9 (q, J_{CF} = 30.7 Hz), 127.1 (q, J_{CF} = 5.6 Hz), 124.4 (q, J_{CF} = 277.8 Hz), 123.9 (q, J_{CF} = 273.7 Hz), 118.3, 39.8 (q, J_{CF} = 30.1 Hz), 27.91−27.70 (m). HRMS (ESI) *m*/*z*: calcd for $[C_{11}H_7F_6N + Na]^+$ 290.0375, found 290.0375.

*2-([1,1′-Biphenyl]-4-yl)-4,4,4-trifluorobutanenitrile (**3g**).* The product was isolated as a white solid (19.7 mg, 71%) using pentane:dichloromethane 1:1 as the eluent system. Melting point 87.2−90.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67−7.63 (m, 2H), 7.60−7.56 (m, 2H), 7.49−7.43 (m, 4H), 7.41−7.36 (m, 1H), 4.17 (dd, J_{HH} = 9.4, 5.1 Hz, 1H), 2.95−2.80 (m, 1H), 2.71−2.58 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.03 (t, J_{HF} = 9.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 140.0, 132.5, 129.1, 128.4, 128.0, 127.8, 127.3, 124.8 (q, J_{CF} = 282.8 Hz), 118.7, 39.9 (q, J_{CF} = 29.6 Hz), 31.1 (q, J_{CF} = 3.2 Hz). HRMS (ESI) *m*/*z*: calcd for $[C_{16}H_{12}F_3N + Na]^+$ 298.0814, found 298.0815.

*4,4,4-Trifluoro-2-(naphthalen-2-yl)butanenitrile (**3h**).* The product was isolated as a transparent oil (14.4 mg, 58%) using pentane:dichloromethane 1:1 as the eluent system. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J_{HH} = 8.5 Hz, 1H), 7.89−7.84 (m, 3H), 7.59−7.52 (m, 2H), 7.42 (dd, J_{HH} = 8.5, 1.9 Hz, 1H), 4.27 (dd, J_{HH} = 9.5, 5.1 Hz, 1H), 2.99−2.85 (m, 1H), 2.77−2.63 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.02 (t, J_{HF} = 9.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.4, 133.3, 130.8, 129.9, 128.1, 128.0, 127.3, 127.3, 126.8, 124.9 (q, J_{CF} = 277.6 Hz), 124.2, 118.7, 39.9 (q, J_{CF} = 29.6 Hz), 31.6 (q, J_{CF} = 3.2 Hz). HRMS (ESI) *m*/*z*: calcd for $[C_{14}H_{10}F_3N + Na]^+$ 272.0658, found 272.0662.

*2-(4-tert-Butylphenyl)-4,4,4-trifluorobutanenitrile (**3i**).* The product was isolated as a transparent oil (13.1 mg, 51%) using pentane:diethyl ether 9:1 as the eluent system. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.41 (m, 2H), 7.31−7.27 (m, 2H), 4.07 (dd, J_{HH} = 9.7, 4.9 Hz, 1H), 2.89−2.75 (m, 1H), 2.65−2.51 (m, 1H), 1.32 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.18 (t, J_{HF} = 9.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 130.4, 126.9, 126.5, 124.9 (q, J_{CF} = 277.7 Hz), 118.7, 39.9 (q, J_{CF} = 29.5 Hz), 34.7, 31.2, 30.8 (q, J_{CF} = 3.2 Hz). HRMS (ESI) *m*/*z*: calcd for $[C_{14}H_{16}F_3N + Na]^+$ 278.1127, found 278.1139.

*4,4,4-Trifluoro-2-(3-methoxyphenyl)butanenitrile (**3j**).* The product was isolated as a colorless oil (13.5 mg, 59%) using pentane:dichloromethane 1:1 as the eluent system. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.31 (m, 1H), 6.96−6.88 (m, 3H), 4.06 (dd, J_{HH} = 9.6, 4.9 Hz, 1H), 3.83 (s, 3H), 2.90−2.76 (m, 1H), 2.66−2.53 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.14 (t, J_{HF} = 9.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 135.0, 130.8, 124.8 (q, J_{CF} = 276.8 Hz), 119.5, 118.6, 114.5, 113.2, 55.6, 39.9 (q, J_{CF} = 29.6 Hz), 31.4 (q, J_{CF} = 3.2 Hz). HRMS (ESI) *m*/*z*: calcd for $[C_{11}H_{10}F_3NO + Na]^+$ 252.0607, found 252.0615.

*3,3,3-Trifluoro-1-(4-methoxyphenyl)propyl 2-Iodobenzoate (**6**).* The product was isolated as a colorless oil (39.1 mg, 87%) using pentane:diethyl ether 19:1 as the eluent system. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (dd, J_{HH} = 7.9, 1.1 Hz, 1H), 7.81 (dd, J_{HH} = 7.8, 1.7 Hz, 1H), 7.47−7.40 (m, 3H), 7.20−7.14 (m, 1H), 6.99−6.89 (m, 2H), 6.31 (dd, J_{HH} = 8.9, 4.4 Hz, 1H), 3.80 (s, 3H), 3.09−2.95 (m, 1H), 2.75−2.59 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.75 (t, J_{HF} = 10.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 160.0, 141.5, 134.4, 132.9, 131.0, 130.2, 128.2, 128.0, 125.3 (q, J_{CF} = 277.5 Hz), 114.2, 94.2, 70.7 (q, J_{CF} = 3.2 Hz), 55.3, 40.2 (q, J_{CF} = 28.2 Hz). HRMS (ESI) *m*/*z*: calcd for $[C_{17}H_{14}F_3IO_3 + Na]^+$ 472.9832, found 472.9814.

*3,3,3-Trifluoro-1-(4-fluorophenyl)-1-iodopropane (**11**).* The product was synthesized according to the general procedure except that copper iodide (19 mg, 0.1 mmol, 1 equiv) was used instead of copper cyanide. The compound was isolated as a colorless oil (4.1 mg, 13%) using pentane:dichloromethane 20:1 as the eluent system. This product was unstable and decomposed within a couple of hours, turning into a pink oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.36 (m, 2H), 7.05−6.97 (m, 2H), 5.30 (dd, J_{HH} = 9.4, 6.1 Hz, 1H), 3.30−3.09 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.45 (t, J_{HF} = 9.5 Hz), −112.30 to −112.39 (m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5 (d, J_{CF} =248.9 Hz), 138.3 (d, J_{CF} =3.5 Hz), 128.7 (d, J_{CF} = 8.4 Hz), 124.9 (q, J_{CF} = 278.9 Hz), 115.9 (d, J_{CF} = 21.9 Hz), 46.0 (q, J_{CF} = 28.3 Hz), 16.4 (q, J_{CF} = 3.1 Hz). (EI) *m*/*z* (rel. intensity): 191 (M^+ − I, 83), 127 (100). Because of the instability of **11**, we were not able to perform HRMS analysis.

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■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of the products. 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.

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