JOC The Journal of Organic Chemistry

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Trifluoromethylation of Ketones and Aldehydes with Bu_3SnCF_3

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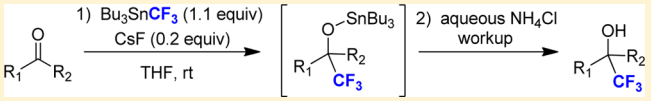
Supporting Information

ABSTRACT: The (trifluoromethyl)stannane reagent, Bu_3SnCF_3, was found to react under CsF activation with ketones and aldehydes to the corresponding trifluoromethylated stannane ether intermediates at room temperature in high yield. Only a mildly acidic extraction (aqueous NH_4Cl) is required to release the corresponding trifluoromethyl alcohol products. The protocol is compatible with acid-sensitive functional groups.



The incorporation of fluorine into molecules results in profoundly different properties and activities of compounds.[1] In this context, a promising and relevant building block is the trifluoromethyl alcohol motif. Figure 1 shows selected examples of biologically and pharmaceutically potent molecules that contain this motif. The activities of these compounds range from sleep induction (**1**),[2] to anti-inflammatory effects in cancer treatment (**2**),[3] and inhibition of the cholesteryl ester transfer protein relevant to heart disease (**3**).[4] A straightforward route to these compounds involves the direct addition of CF_3 to the corresponding ketone or aldehyde precursors.

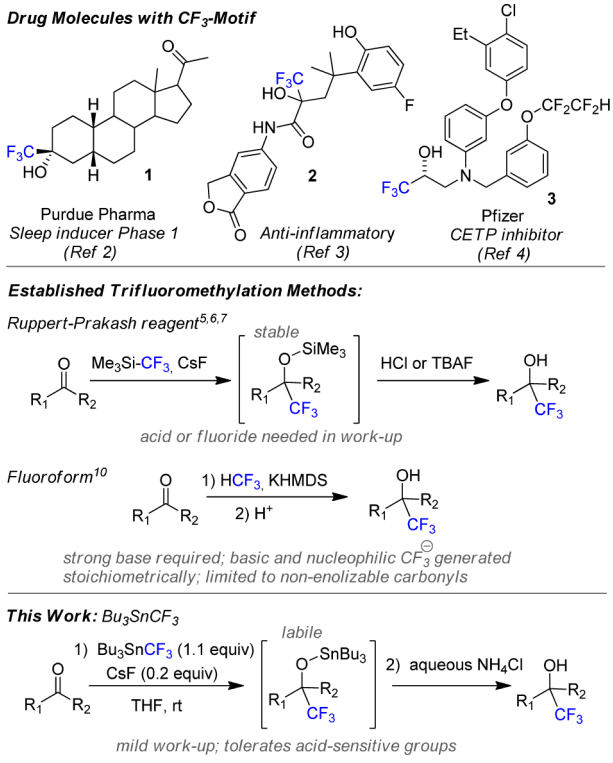


Figure 1. Examples of relevant drugs that bear the trifluoromethyl alcohol motif (top)[2−4] and selected trifluoromethylation methods.[5−7,10,11]

Trifluoromethylation is most commonly accomplished via in situ activation of the *Ruppert−Prakash* reagent, Me_3SiCF_3,[5] with a fluoride source, leading to efficient addition of CF_3 to carbonyl compounds (such as aldehydes,[6,7] ketones,[5b,7] esters[7,8] or Weinreb amides[9]).[10] The Pfizer drug **3** (Figure 1) is synthesized in this way, for example.[4] However, the protocol requires breakdown of the silyl ether intermediate that is formed upon formal addition of Me_3SiCF_3 to the carbonyl group (Figure 1). This is generally accomplished with acid (stirring in HCl) or with fluoride (TBAF).[5b,7] Alternative methods include the use of fluoroform (CF_3H).[11] However, the latter method is limited to nonenolizable carbonyl substrates, as the basic CF_3-anion is generated stoichiometrically in the presence of the substrate via exposure to a strong base, such as KHMDS.[11a] On the other hand, Dolbier and co-workers developed a procedure based on CF_3I that generates the nucleophilic CF_3-anion via reduction by TDAE, but the protocol is inefficient for enolizable aldehydes and ketones.[12]

Given that stannanes are generally softer than silanes,[13,14] we anticipated possibilities for synthetic applications and investigated the potential of stannane reagents in trifluoromethylation reactions. In this context, we recently demonstrated that Bu_3SnCF_3 can be used in Cu-mediated trifluoromethylations of aryl iodides.[15,16]

In this report, we disclose that Bu_3SnCF_3 can also be applied in efficient trifluoromethylation reactions of aldehydes and ketones.

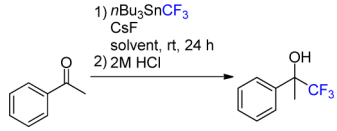
We began our studies by adding 1 equiv of Bu_3SnCF_3 and a catalytic amount of CsF (0.1 equiv) to an excess of neat acetophenone at room temperature. We observed that the stannane reagent was fully consumed within 5 h reaction time at room temperature, and the corresponding trifluoromethylated derivative had formed (as judged by ^{19}F-NMR), indicating that trifluoromethylation of ketones using the stannane reagent

Received: June 4, 2013
Published: July 8, 2013

   dx.doi.org/10.1021/jo401099e | J. Org. Chem. 2013, 78, 7749−7753

is indeed possible. Thus, we subsequently set out to identify a general and more practical reaction protocol. A solvent screen (Table 1) revealed that the use of a minimal amount of THF

Table 1. Optimization of Conditions for the Trifluoromethylation of Acetophenone[a]



entry	equiv of CsF	solvent	yield (%)[b]
1	0.1	ethylene glycol diethyl ether	31
2	0.1	CH_2Cl_2	9
3	0.1	*n*-hexane	0
4	0.1	THF	76
5	0.2	THF	>95
6	0.5	THF	>95
7	1.0	THF	>95

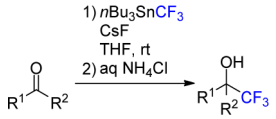
[a]Conditions: 0.2 mmol acetophenone used in 0.3 mL of solvent, with 1.1 equiv of nBu_3SnCF_3. [b]Yield quantified after workup, by integration of the ^{19}F NMR spectrum against a known amount of the internal standard, 4,4′-difluorobiphenyl.

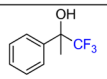
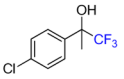
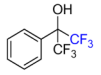
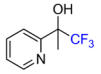
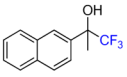
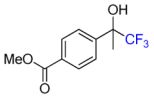
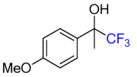
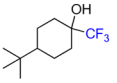
allowed the efficient transformation of 1.0 equiv of acetophenone to the corresponding trifluoromethylated derivative in 24 h at room temperature, employing a slight excess of Bu_3SnCF_3 (1.1 equiv) and a catalytic amount of CsF (see Table 1). The superior reactivity observed in THF over CH_2Cl_2, hexane or alternative ether solvents appeared to primarily be a consequence of the better solubility of CsF in THF.

With the optimized reaction conditions in hand, we subsequently employed a variety of ketones under these conditions. Table 2 gives a summary of the results. Aromatic (entries 1–7) as well as an example of aliphatic (entry 8) ketones reacted efficiently at room temperature. The overall reaction time decreased with greater electron deficiency of the ketone. The trifluoromethylations can conveniently be carried out at ambient temperature and do not require cooling. Moreover, as manifested in entry 6 (Table 2), selective trifluoromethylation of the ketone functional group was observed, even in the presence of excess stannane reagent. Additional experiments on aromatic ester compounds (e.g., methyl benzoate) confirmed that the stannane reagent is not capable of trifluoromethylating the ester functional group under these conditions. In contrast, under analogous conditions involving Me_3SiCF_3, trifluoromethylations of esters do occur. (Selective trifluoromethylation of a ketone over ester can be achieved with Me_3SiCF_3, if the reagent is employed in ≤1.0 equiv).[7,8] The slightly lower reactivity of the stannane therefore bears potential for selective and mild trifluoromethylations in the presence of alternative functional groups.

The proposed mechanism for trifluoromethylation involving the stannane reagent is illustrated in Figure 2. The reaction proceeds via the intermediacy of stannane ether **5**, as we demonstrated separately through isolation and characterization of adduct **6** that resulted from Bu_3SnCF_3 addition to anthracene-9-carbaldehyde. We fully characterized adduct **6** with ^1H and ^{13}C NMR spectroscopic analyses and high resolution mass spectrometry (that gave the expected molecular

Table 2. Trifluoromethylation of Ketones[a]



entry	product	time (h)	yield – ^{19}F NMR / isolated (%)[b]
1		24	>95 / 53
2		24	>95 / 69
3		96	66 / --[c]
4		15	77 / 41
5		30	>95 / 78
6		15	>95 / 71
7		24	78 / 72
8		15	70 / 51[d]

[a]Conditions: 0.4 mmol ketone in 0.3 mL of THF, 0.2 equiv of CsF and 1.1 (entries 1, 3–6 and 8) or 1.3 equiv (entries 2 and 7) of nBu_3SnCF_3. [b]^{19}F NMR yield quantified by integration against a known amount of the internal standard, 4,4′-difluorobiphenyl. [c]An isolated yield cannot be reported because of the volatility of the compound. [d]Two diastereomers were produced in the reaction in a ratio of 5.5/1.0, the isolated yield being for the major diastereomer.

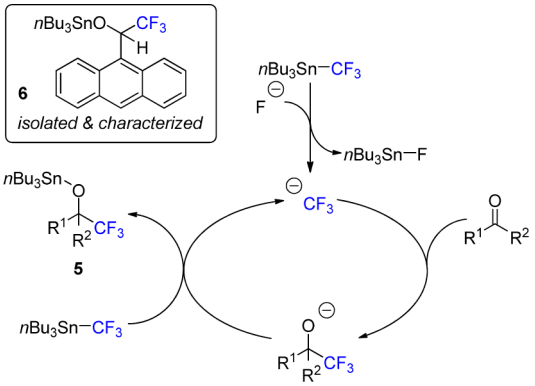


Figure 2. Proposed mechanism for trifluoromethylation.

dx.doi.org/10.1021/jo401099e | J. Org. Chem. 2013, 78, 7749–7753

ion at $[M]^+$= 566.1811; see Supporting Information for further information).

We previously demonstrated that the formation of $[CuCF_3]$ intermediates from Bu_3SnCF_3 in the presence of CuI and CsF is only marginally less efficient than that from Me_3SiCF_3,[15] which suggests that the stannane can just as readily release its CF_3 group upon activation. We therefore hypothesize that the origin of slower reactivity of the stannane observed in the trifluoromethylation of ketones stems primarily from the lower driving force to form stannane ether intermediate **5** as compared to a silyl ether analogue (see Figure 2). The O−Sn bond is much more labile than the corresponding O−Si bond (reported bond dissociation energies are ΔH(O−Sn) = 548 kJ/mol and ΔH(O−Si) = 798 kJ/mol).[17] Greater electron deficiency around the O−Sn moiety in turn would be expected to strengthen the bond and increase the thermodynamic driving force to form **5**, in line with the reactivity trend observed in Table 2.

The weakness of the O−Sn bond in the formed stannane ether intermediate **5** (Figure 2) gives the advantage that **5** also readily breaks down to release the final alcohol product. In hydrolysis studies of the reaction given in entry 1 of Table 2, we observed that upon addition of water to the corresponding stannane ether intermediate **5**, hydrolysis had already taken place to about 60%. In subsequent studies, we identified that complete conversion to the trifluoromethyl alcohol can be achieved through a simple, aqueous NH_4Cl extraction. The corresponding silyl ether intermediates (analogous to **5**) tend to be more stable and may require stirring in acid (up to 6 N HCl) over hours (≥3 h) or addition of TBAF to release the final product.[5b,7] Thus, the stannane protocol may be advantageous to the synthesis of molecules with functional groups that are sensitive to stronger acids, nucleophiles or show high lipophilicity.

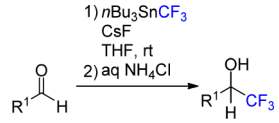
We subsequently expanded our studies to aldehydes (see Table 3). In accord with the reactivities observed for the ketones above, the electron deficient carbonyl moiety of the aldehydes showed excellent reactivity toward trifluoromethylation with Bu_3SnCF_3. High conversions and good isolated yields were obtained after 8−22 h reaction time at room temperature (see Table 3). Noteworthy are the successful isolations of the trifluoromethylated alcohols in entries 7−9, in which acid-sensitive protecting groups (THP, trityl and MEM) were tolerated in the trifluoromethylation and workup procedure. This highlights the mildness of the stannane protocol.

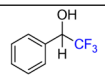
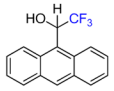
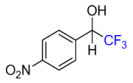
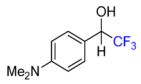
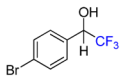
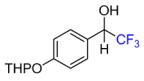
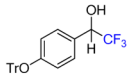
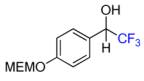
In conclusion, we have demonstrated the feasibility of stannanes, such as Bu_3SnCF_3, to trifluoromethylate aldehydes and ketones at room temperature in high yield. The reactions proceed via the intermediacy of stannane ethers that in turn are readily hydrolyzed through mildly acidic extraction (aqueous NH_4Cl). The protocol was shown to tolerate acid-sensitive functional groups.

EXPERIMENTAL SECTION

General Procedure for the Screening of Solvents. Solvent (0.3 mL, see Table 1) and tributyl(trifluoromethyl)stannane (79 mg, 0.22 mmol, 1.1 equiv) were added to a mixture of acetophenone (24 mg, 0.20 mmol, 1.0 equiv), cesium fluoride (0.1−1.0 equiv, see Table 1) and internal standard 4,4′-difluorobiphenyl (19 mg, 0.10 mmol, 0.5 equiv) in a vial. The reaction mixture was stirred at room temperature for 24 h, after which the reaction mixture was diluted with diethyl ether (2 mL) and quenched with 2 M hydrochloric acid (1 mL). The layers were separated, and the organic phase was used for ^{19}F NMR studies.

Table 3. Trifluoromethylation of Aldehydes[a]



entry	product	time (h)	yield – ^{19}F NMR / isolated (%)[b]
1		8	>95 / --[c]
2		8	>95 / 83
3		9	73 / 49
4		22	88 / 70
5		9	>95 / 70
6		9	>95 / --[c]
7		8	>95 / 64
8		8	>95 / 68[d]
9		8	>95 / 67

[a]Conditions: 0.4 mmol ketone in 0.3 mL of THF (0.6 mL of THF for entry 2), 0.2 equiv of CsF and 1.1 (entries 1−5) or 1.3 equiv (entries 6−9) of nBu_3SnCF_3. [b]^{19}F NMR yield quantified by integration against a known amount of the internal standard, 4,4′-difluorobiphenyl. [c]An isolated yield cannot be reported because of the volatility of the compound. [d]This compound was found to decompose upon standing

General Procedure for the Trifluoromethylation of Aldehydes and Ketones. THF (0.3 mL, if not stated otherwise) and tributyl(trifluoromethyl)stannane (1.1−1.3 equiv; see Tables 2 and 3) were added to a mixture of aldehyde or ketone (0.40 mmol, 1.0 equiv), internal standard 4,4′-difluorobiphenyl (19 mg, 0.10 mmol, 0.25 equiv) and cesium fluoride (12 mg, 0.08 mmol, 0.2 equiv) in a vial. The reaction mixture was stirred at room temperature for the requisite time (see Tables 2 and 3). The reaction mixture was then diluted with diethyl ether (20 mL) and washed with a saturated aqueous ammonium chloride solution (4 × 5 mL). The combined aqueous layers were extracted with diethyl ether (20 mL), the combined organics were then dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography using silica gel impregnated with potassium fluoride (20% w/w), eluting with 9:1 *n*-hexane:diethyl ether.

dx.doi.org/10.1021/jo401099e | J. Org. Chem. 2013, 78, 7749−7753

1,1,1-Trifluoro-2-phenylpropan-2-ol (Table 2, Entry 1). 40 mg, 53%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61−7.56 (m, 2H, Ar*H*), 7.44−7.36 (m, 3H, Ar*H*), 2.28 (br s, 1H, Ar*H*), 1.79 (br s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 128.7, 128.4, 126.1, 125.7 (q, J = 285), 75.0 (q, J = 29), 24.1; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −81.5 (s, CF_3). This data is consistent with that reported in the literature.[11e]

2-(4-Chlorophenyl)-1,1,1-trifluoropropan-2-ol (Table 2, Entry 2). 62 mg, 69%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54−7.50 (m, 2H, Ar*H*), 7.40−7.35 (m, 2H, Ar*H*), 2.39 (s, 1H, O*H*), 1.77 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.9, 134.9, 128.7, 127.8, 125.5 (q, J = 286), 74.7 (q, J = 30), 24.1; ^{19}F NMR ($CDCl_3$, 282 MHz,) δ −81.7 (s, CF_3). This data is consistent with that reported in the literature.[18]

1,1,1,3,3,3-Hexafluoro-2-phenylpropan-2-ol (Table 2, Entry 3). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74−7.71 (m, 2H, Ar*H*), 7.49−7.45 (m, 3H, Ar*H*), 3.55 (s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.4, 129.5, 128.8, 126.7, 122.8 (q, J = 288), 77.1 (septet, J = 30); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −76.1 (s, CF_3). An isolated yield cannot be reported because of the volatility of the compound. This data is consistent with that reported in the literature.[19]

1,1,1-Trifluoro-2-(pyridin-2-yl)propan-2-ol (Table 2, Entry 4). 31 mg, 41%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.62−8.57 (m, 1H, Ar*H*), 7.85−7.78 (m, 1H, Ar*H*), 7.55−7.50 (m, 1H, Ar*H*), 7.40−7.34 (m, 1H, Ar*H*), 6.33 (s, 1H, O*H*), 1.73 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 147.4, 137.6, 126.8, 123.9, 121.2, 73.6, 21.9; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −81.4 (s, CF_3). This data is consistent with that reported in the literature.[20]

1,1,1-Trifluoro-2-(naphthalen-2-yl)propan-2-ol (Table 2, Entry 5). 75 mg, 78%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (s, 1H, Ar*H*), 7.92−7.83 (m, 3H, Ar*H*), 7.67 (d, J = 8.7, 1H, Ar*H*), 7.55−7.48 (m, 2H, Ar*H*), 2.51 (s, 1H, O*H*), 1.89 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.8, 133.1, 132.9, 128.5, 128.1, 127.5, 126.7, 126.4, 125.8 (q, J = 285), 125.6, 123.6, 75.1 (q, J = 29), 24.0; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −81.1 (s, CF_3). This data is consistent with that reported in the literature.[18]

Methyl 4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoate (Table 2, Entry 6). 70 mg, 71%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10−8.04 (m, 2H, Ar*H*), 7.70−7.64 (m, 2H, Ar*H*), 3.93 (s, 3H, OCH_3), 2.46 (s, 1H, O*H*), 1.81 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 143.3, 130.3, 129.5, 126.2, 125.4 (q, J = 285), 74.8 (q, J = 29), 52.3, 23.9; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −81.3 (s, CF_3). This data is consistent with that reported in the literature.[21]

1,1,1-Trifluoro-2-(4-methoxyphenyl)propan-2-ol (Table 2, Entry 7). 63 mg, 72%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, J = 9.0, 2H, Ar*H*), 6.91 (app d, J = 9.0, 2H, Ar*H*), 3.82 (s, 3H, OCH_3), 2.56 (br s, 1H, O*H*), 1.77 (s, 3H, CCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.9, 130.8, 127.6, 125.8 (q, J = 285), 113.8, 74.7 (q, J = 29), 55.4, 24.0; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −81.8 (s, CF_3). This data is consistent with that reported in the literature.[18]

4-*tert*-Butyl-1-(trifluoromethyl)cyclohexanol (Table 2, Entry 8). 46 mg, 51%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.26−2.19 (m, 2H, CH_2), 1.96 (br s, 1H, O*H*), 1.76−1.68 (m, 2H, CH_2), 1.52−1.45 (m, 2H, CH_2), 1.38−1.25 (m, 2H, CH_2), 1.15−1.05 (m, 1H, $CHC(CH_3)_3$), 0.86 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 127.0 (q, J = 286), 72.0 (q, J = 27), 46.3, 33.3, 32.3, 27.5, 23.0; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −78.3 (s, CF_3). This data is consistent with that reported in the literature.[22]

(1-(Anthracen-9-yl)-2,2,2-trifluoroethoxy)tributylstannane (6). To a mixture of anthracene-9-carbaldehyde (41.2 mg, 0.20 mmol) and cesium fluoride (30.5 mg, 0.20 mmol) in THF (0.4 mL) was added tributyl(trifluoromethyl)stannane (79.0 mg, 0.22 mmol). The mixture was stirred at rt for 3 h, diluted with Et_2O (3 mL) and filtered through Celite. The filtrate was concentrated in vacuo, and to the resulting crude mixture was added hexane (5 mL). The suspension was filtered, and the filtrate was concentrated to provide the title compound as a yellow oil: 109 mg, 96%; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.35 (d, J = 9.2, 1H, Ar*H*), 8.51 (s, 1H, Ar*H*), 8.23 (d, J = 9.2, 1H, Ar*H*), 8.05 (d, J = 9.2, 1H, Ar*H*), 8.01−7.99 (m, 1H, Ar*H*), 7.59−7.55 (m, 1H, Ar*H*), 7.50−7.44 (m, 3H, Ar*H*), 6.61−6.53 (m, 1H, $CHCF_3$), 1.33−1.24 (m, 6H, CH_2), 1.14−1.04 (m, 6H, CH_2), 0.92−0.84 (m, 6H, CH_2), 0.73 (t, J = 11.2, 9H, CH_3); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 132.6, 131.9, 131.5, 130.9, 129.9 (2C), 129.4, 129.3 (q, J = 3.1), 128.9, 127.0, 126.0, 125.4, 125.2, 124.9, 123.2, 73.5 (q, J = 33), 28.0, 27.4, 15.5, 13.7; ^{19}F NMR (CD_2Cl_2, 282 MHz,) δ −74.3 (d, J = 8.2); ESI HRMS calculated for $C_{28}H_{37}F_3OSn^+$ 566.1818, found 566.1811.

2,2,2-Trifluoro-1-phenylethanol (Table 3, Entry 1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44−7.37 (m, 2H, Ar*H*), 7.38−7.33 (m, 3H, Ar*H*), 5.01−4.92 (m, 1H, $CHCF_3$), 2.46 (d, J = 4.6, 1H, O*H*); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −78.9 (d, J = 6.7, CF_3). An isolated yield cannot be reported, and it was not possible to record a ^{13}C NMR spectrum because of the volatility of the compound. This data is consistent with that reported in the literature.[23]

1-(Anthracen-9-yl)-2,2,2-trifluoroethanol (Table 3, Entry 2). 92 mg, 83%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.96 (br s, 1H, Ar*H*), 8.52 (s, 1H, Ar*H*), 8.11 (br s, 1H, Ar*H*), 8.02 (d, J = 8.3, 2H, Ar*H*), 7.60−7.45 (m, 4H, Ar*H*), 6.62 (m, 1H, $CHOH$), 2.98 (d, J = 4.4, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 131.9, 130.9, 129.5, 127.2, 126.4, 125.6 (q, J = 284), 125.1, 123.9, 122.6, 70.3 (q, J = 34); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −74.5 (d, J = 7.9, CF_3). This data is consistent with that reported in the literature.[24]

2,2,2-Trifluoro-1-(4-nitrophenyl)ethanol (Table 3, Entry 3). 43 mg, 49%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34−8.23 (m, 2H, Ar*H*), 7.74−7.65 (m, 2H, Ar*H*), 5.18 (q, J = 6.3, 1H, $CHCF_3$), 2.86 (s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 140.4, 128.5, 123.7, 123.7 (q, J = 282), 71.9 (q, J = 32); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −78.7 (dd, J = 6.1, 3.7, CF_3). This data is consistent with that reported in the literature.[25]

1-[4-(Dimethylamino)phenyl]-2,2,2-trifluoroethanol (Table 3, Entry 4). 61 mg, 70%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.30 (m, 2H, Ar*H*), 6.74−6.70 (m, 2H, Ar*H*), 4.91 (qd, J = 6.8, 4.4, 1H, $CHOH$), 2.98 (s, 6H, NCH_3), 2.32 (d, J = 4.5, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.3, 128.4, 124.6 (q, J = 282), 121.7, 112.3, 72.7 (q, J = 32), 40.4; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −79.0 (d, J = 6.7, CF_3). This data is consistent with that reported in the literature.[26]

1-(4-Bromophenyl)-2,2,2-trifluoroethanol (Table 3, Entry 5). 75 mg, 70%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58−7.53 (m, 2H, Ar*H*), 7.36 (d, J = 8.7, 2H, Ar*H*), 5.01 (q, J = 6.6, 1H, $CHCF_3$), 2.60 (br s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.8, 131.8, 129.1, 123.9 (q, J = 282), 123.8, 72.2 (q, J = 32); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −79.0 (dd, J = 6.7, 2.1, CF_3). This data is consistent with that reported in the literature.[27]

2,2,2-Trifluoro-1-(furan-2-yl)ethanol (Table 3, Entry 6). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (dd, J = 1.9, 0.8, 1H, Ar*H*), 6.54 (d, J = 3.4, 1H, Ar*H*), 6.43 (d, J = 3.4, 1.9 Hz, 1H, Ar*H*), 5.06 (m, 1H, $CHOH$); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −78.5 (d, J = 6.7, CF_3). An isolated yield cannot be reported, and it was not possible to record a ^{13}C NMR spectrum because of the volatility of the compound. This data is consistent with that reported in the literature.[28]

2,2,2-Trifluoro-1-[4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl]-ethanol (Table 3, Entry 7). Compound was isolated as a white solid, as a 1: 1 mixture of two diastereomers: 71 mg, 64%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.36 (2× m, 2H, Ar*H*), 7.08−7.03 (2× m, 2H, Ar*H*), 5.45−5.40 (2× m, 1H, $OCHO$), 4.97−4.89 (2× m, 1H, $CHCF_3$), 3.92−3.84 (2× m, 1H, $OCHCH_2$), 3.64−3.56 (2× m, 1H, OCH_2), 2.90 (1× d, J = 4.6, 1H O*H*), 2.88 (1× d, J = 4.7, 1H, O*H*), 2.05−1.95 (2× m, 1H, CH_2), 1.88−1.83 (2× m, 2H, CH_2), 1.75−1.55 (2× m, 3H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.9 (2× C), 128.7 (4× C), 127.1 (2× C), 124.3 (2× C, q, J = 283), 116.5 (2× C), 116.4 (2× C), 96.3 (2× C), 72.5 (1 × C, q, J = 32), 72.4 (1 × C, q, J = 32), 62.1 (2× C), 30.3 (2× C), 25.1 (2× C), 18.7 (2× C); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −79.0 (d, J = 7.1, CF_3); mp 68.1−69.9; MALDI/ESI HRMS calculated for $C_{13}H_{15}F_3NaO_3^+$ 299.0866, found 299.0867.

2,2,2-Trifluoro-1-(4-(trityloxy)phenyl)ethanol (Table 3, Entry 8). Compound was isolated as a colorless oil: 118 mg, 68%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46−7.43 (m, 6H, Ar*H*), 7.31−7.21 (m, 9H, Ar*H*), 7.08 (d, J = 8.8, 2H, Ar*H*), 6.74−6.66 (m, 2H, Ar*H*), 4.82−4.80 (m, 1H, $CHCF_3$), 2.31 (br d, J = 4.5, 1H, O*H*); ^{13}C NMR ($CDCl_3$,

dx.doi.org/10.1021/jo401099e | J. Org. Chem. 2013, 78, 7749−7753

100 MHz) δ 157.5, 144.0, 129.0, 128.0, 127.9, 127.8, 127.4, 126.7, 124.4 (q, J = 282), 90.8, 72.6 (q, J = 33); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −79.0 (d, J = 6.6, CF_3). It was not possible to acquire mass spectrometry data for this compound using EI, ESI or MALDI ionization techniques.

2,2,2-Trifluoro-1-(4-((2-methoxyethoxy)methoxy)phenyl)-ethanol (Table 3, Entry 9). Compound was isolated as a colorless oil; 75 mg, 67%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.37 (m, 2H, Ar*H*), 7.10−7.06 (m, 2H, Ar*H*), 5.28 (s, 2H, OCH_2O), 4.97 (q, J = 6.8, 1H, $CHCF_3$), 3.84−3.80 (m, 2H, OCH_2), 3.57−3.53 (m, 2H, OCH_2), 3.37 (s, 3H, OCH_3), 2.61 (br s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.3, 130.3, 128.9, 124.4 (q, J = 283), 116.4, 93.5, 72.6 (q, J = 33), 71.7, 67.9, 59.2; ^{19}F NMR ($CDCl_3$, 282 MHz,) δ −79.0 (d, J = 6.8); ESI HRMS calculated for $C_{12}H_{15}F_3NaO_4^+$ 303.0815, found 303.0817.

■ ASSOCIATED CONTENT

Supporting Information

General experimental details, ^{1}H NMR spectra of previously reported compounds, 1D and 2D NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by ETH Zürich, an ETH Independent Investigator's Research Award, and the Carlsberg Foundation (postdoctoral fellowship to M.C.N.).

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