*The Journal of Organic Chemistry*



Note

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*J. Org. Chem.*, **Just Accepted Manuscript** • DOI: 10.1021/jo401099e • Publication Date (Web): 08 Jul 2013



The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

# Trifluoromethylation of Ketones and Aldehydes with $Bu_3SnCF_3$

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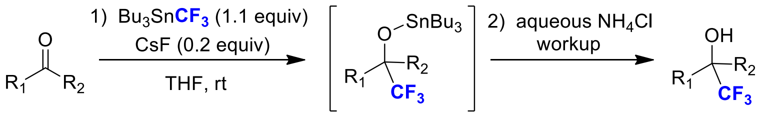



**Abstract:** The (trifluoromethyl)stannane reagent, $Bu_3SnCF_3$, was found to react under CsF activation with ketones and aldehydes to the corresponding trifluoromethylated stannane ether intermediates at room temperature in high yield. Only a mildly acidic extraction (aqueous $NH_4Cl$) is required 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.

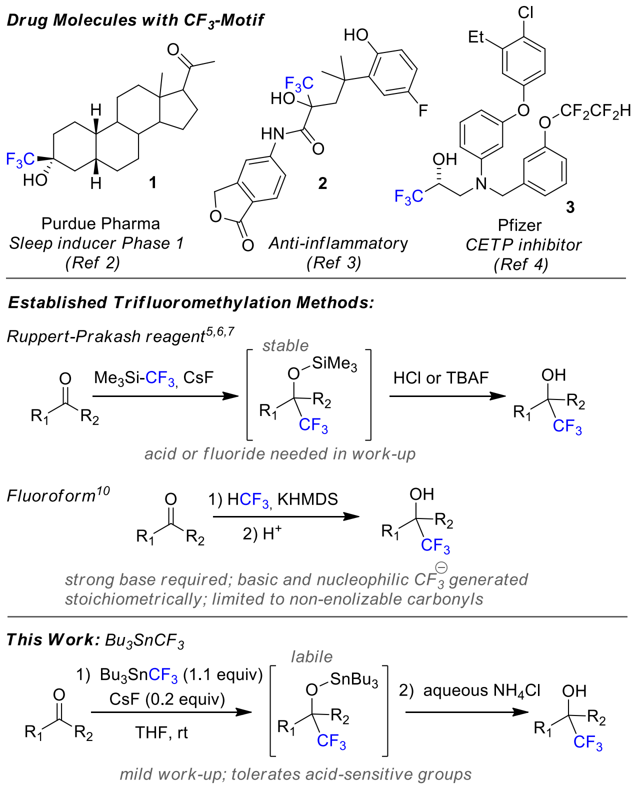


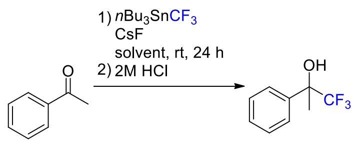

**Figure 1.** Examples of relevant drugs that bear the trifluoromethyl alcohol motif (top)[2-4] and selected trifluoromethylation methods.[5-7,10,11]

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 non-enolizable 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 enolisable 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 one equivalent 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 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 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.

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



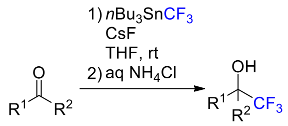
| entry | equiv CsF | solvent | yield (%)[b] |
|---|---|---|---|
| 1 | 0.1 | ethylene glycol diethyl ether | 31 |
| 2 | 0.1 | $CH_2Cl_2$ | 9 |
| 3 | 0.1 | *n*-hexane | 0 |
| 4 | 0.1 | THF | 76 |
| 5 | 0.2 | THF | >95 |
| 6 | 0.5 | THF | >95 |
| 7 | 1.0 | THF | >95 |

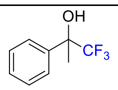
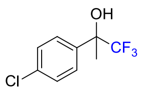
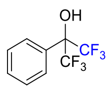
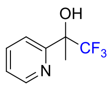
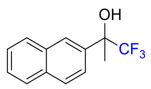
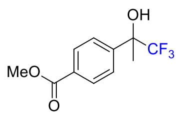
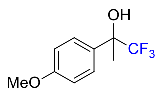
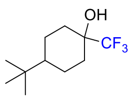
[a] conditions: 0.2 mmol acetophenone used in 0.3 mL solvent, with 1.1 equiv of $n$Bu$_3$SnCF$_3$; [b] yield quantified after work-up, by integration of the $^{19}$F NMR spectrum against a known amount of the internal standard, 4,4'-difluorobiphenyl.

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 $\leq$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.

**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 THF, 0.2 equiv CsF and 1.1 (entries 1, 3–6 and 8) or 1.3 equiv (entries 2 and 7) $n\mathrm{Bu_3SnCF_3}$; [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 due to 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.

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 $^1$H- and $^{13}$C-NMR spectroscopic analyses and high resolution mass spectrometry (that gave the expected molecular ion at $[M]^+$= 566.1811, see supporting information for further information).

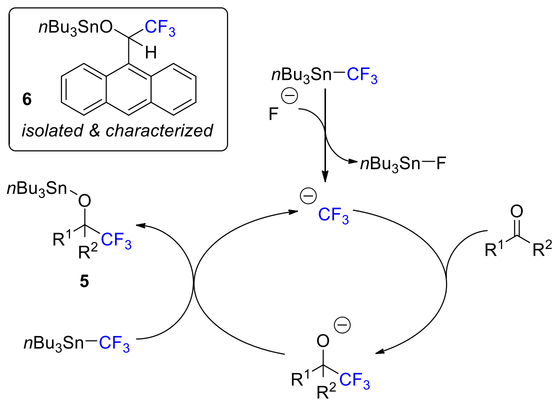


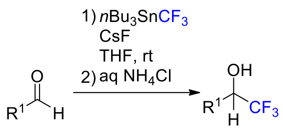

**Figure 2.** Proposed mechanism for trifluoromethylation.

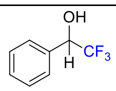
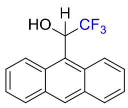
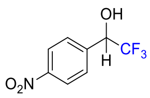
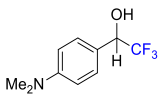
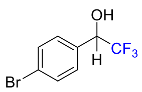
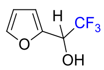
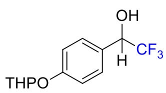
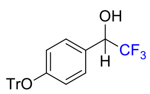
We previously demonstrated that the formation of $[CuCF_3]$ intermediates from $Bu_3SnCF_3$ in the presence of CuI and CsF is only marginally less efficient than that from $Me_3SiCF_3$,[15] which suggests that the stannane can just as readily release its $CF_3$ group upon activation. We therefore hypothesize 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.

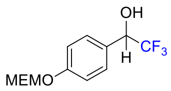
The weakness of the O-Sn bond in the formed stannane ether intermediate **5** (Figure 2) gives the advantage that **5** also readily breaks down to release the final alcohol product. In hydrolysis studies of the reaction given in entry 1 of Table 2, we observed that upon addition of water to the corresponding 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 work-up procedure. This highlights the mildness of the stannane protocol.

**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 THF (0.6 mL THF for entry 2), 0.2 equiv CsF and 1.1 (entries 1–5) or 1.3 equiv (entries 6–9) $n$$Bu_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 due to volatility of the compound; [d] this compound was found to decompose upon standing

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 2M hydrochloric acid (1 mL). The layers were separated and the organic phase was used for $^{19}$F NMR studies.

**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 (30 mg, 0.20 mmol, 0.5 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 x 5 mL). The combined aqueous layers were extracted with diethyl ether (20 mL) and the combined organics were then dried over magnesium sulfate, 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.

**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, C$H_3$); $^{13}$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, C$F_3$). 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, C$H_3$); $^{13}$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, C$F_3$). 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 due to 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, C*F*$_3$). 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, OC*H*$_3$), 2.56 (br s, 1H, O*H*), 1.77 (s, 3H, CC*H*$_3$); $^{13}$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, C*F*$_3$). 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, C*H*$_2$), 1.96 (br s, 1H, O*H*), 1.76-1.68 (m, 2H, C*H*$_2$), 1.52-1.45 (m, 2H, C*H*$_2$), 1.38-1.25 (m, 2H, C*H*$_2$), 1.15-1.05 (m, 1H, C*H*C($CH_3$)$_3$), 0.86 (s, 9H, C*H*$_3$); $^{13}$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, C*F*$_3$). 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 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, C*H*$CF_3$), 1.33-1.24 (m, 6H, C$H_2$), 1.14-1.04 (m, 6H, C$H_2$), 0.92-0.84 (m, 6H, C$H_2$), 0.73 (t, *J* = 11.2, 9H, C$H_3$); $^{13}$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, C*H*$CF_3$), 2.46 (d, *J* = 4.6, 1H, O*H*); $^{19}$F NMR ($CDCl_3$, 282 MHz) δ -78.9 (d, *J* = 6.7, C$F_3$). An isolated yield cannot be reported and it was not possible to record a $^{13}$C NMR spectrum due to 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, C*H*OH), 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, C$F_3$). 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, C*H*$CF_3$), 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, C$F_3$). 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, C*H*OH), 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, C$F_3$). 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, C*H*$CF_3$), 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, C$F_3$). 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, C*H*OH); $^{19}$F NMR ($CDCl_3$, 282 MHz) δ -78.5 (d, *J* = 6.7, C$F_3$). An isolated yield cannot be reported and it was not possible to record a $^{13}$C

NMR spectrum due to volatility of the compound. This data is consistent with that reported in the literature.[28]

**2,2,2-Trifluoro-1-[4-(tetrahydro-2H-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 x m, 2H, Ar*H*), 7.08-7.03 (2 x m, 2H, Ar*H*), 5.45-5.40 (2 x m, 1H, OC*H*O), 4.97-4.89 (2 x m, 1H, C*H*$CF_3$), 3.92-3.84 (2 x m, 1H, OCHC$H_2$), 3.64-3.56 (2 x m, 1H, OC$H_2$), 2.90 (1 x d, *J* = 4.6, 1H O*H*), 2.88 (1 x d, *J* = 4.7, 1H, O*H*), 2.05-1.95 (2 x m, 1H, C$H_2$), 1.88-1.83 (2 x m, 2H, C$H_2$), 1.75-1.55 (2 x m, 3H, C$H_2$); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 157.9 (2 x C), 128.7 (4 x C), 127.1 (2 x C), 124.3 (2 x C, q, *J* = 283), 116.5 (2 x C), 116.4 (2 x C), 96.3 (2 x C), 72.5 (1 x C, q, *J* = 32), 72.4 (1 x C, q, *J* = 32), 62.1 (2 x C), 30.3 (2 x C), 25.1 (2 x C), 18.7 (2 x C); $^{19}$F NMR ($CDCl_3$, 282 MHz) δ -79.0 (d, *J* = 7.1, C$F_3$); m.p. 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 colourless 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, C*H*$CF_3$), 2.31 (br d, *J* = 4.5, 1H, O*H*); $^{13}$C NMR ($CDCl_3$, 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, C$F_3$). 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 colourless 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.

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

**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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