Rapid Dehydroxytrifluoromethoxylation of Alcohols

Dehydroxytrifluoromethoxylation:

\[ R\text{-}OH + Ag\text{OCF}_3 \xrightarrow{\text{DMF, 15 min}} R\text{-}OCF_3 \]

The formation of the key intermediate:

\[ R'\text{'}_3\text{P} + I \rightarrow R'\text{'}_3\text{P} + Ph_3\text{P}^+I^- \]

Unusual P-I halogen bond

Wide substrate scope: benzyl alcohols, allyl alcohols, propargyl alcohols, alkyl alcohols

Good functional group compatibility

A rapid process: 15 min
Article

Rapid Dehydroxytrifluoromethoxylation of Alcohols

Wei Zhang,1,3 Jia Chen,1,3 Jin-Hong Lin,1,* Ji-Chang Xiao,1,4,* and Yu-Cheng Gu2

SUMMARY

The CF3O functional group is a unique fluorinated group that has received a great deal of attention in medicinal chemistry and agrochemistry. However, trifluoromethoxylation of substrates remains a challenging task. Herein we describe the dehydroxytrifluoromethoxylation of alcohols promoted by a R3P/ICH2CH2I (R3P = Ph3P or Ph2PC=CH2) system in DMF. P-I halogen bonding drives the reaction of R3P with ICH2CH2I in DMF to generate iodophosphonium salt (R3P+II) and a Vilsmeier-Haack-type intermediate, both of which could effectively activate alcohols, thus enabling a fast (15 min) trifluoromethoxylation reaction. A wide substrate scope and a high level of functional group tolerance were observed.

INTRODUCTION

The trifluoromethoxy group (CF3O) has received a great deal of attention in medicinal chemistry and agrochemistry (Jeschke et al., 2007) because of its strong electron-withdrawing nature and high lipophilicity (Hansch et al., 1973). CF3O-containing pharmaceuticals and agrochemicals such as Delamanid, Riluzole, Sonidegib, Metformin, and Indoxacarb have been continuously developed. The high demand for biologically active molecules has stimulated significant efforts to develop efficient methods for the installation of trifluoromethoxy functionality (Landelle et al., 2014; Lin et al., 2015; Tlili et al., 2016). However, the installation of such functionality remains a challenging task. Traditional approaches including chlorine-fluorine exchange (Feiring, 1979; Salomé et al., 2004) and deoxyfluorination (Sheppard, 1964) suffer from harsh reaction conditions and narrow substrate scopes. Trifluoromethylation of alcohols is quite effective and has received increasing attention (Brantley et al., 2016; Koller et al., 2009; Umemoto et al., 2007). Recently, Qing and co-workers realized trifluoromethylation of phenols (Liu et al., 2015a) and alcohols (Liu et al., 2015b) based on the concept of oxidative trifluoromethylation (Chu and Qing, 2014). Wide substrate scopes were observed, but the use of strong oxidants was required. Compared with trifluoromethylation of alcohols, direct trifluoromethoxylation would also be an efficient and straightforward strategy and thus is highly desirable.

Trifluoromethoxylation strategies include transition-metal-promoted, radical, and nucleophilic reactions (Scheme 1, Equation 1). After the pioneering work on Ag-mediated (Chen et al., 2015b; Huang et al., 2011; Zha et al., 2016) and Pd-catalyzed (Chen et al., 2015a) trifluoromethoxylation, a breakthrough in transition-metal-promoted approaches was reported recently by Tang, who described a Ag-catalyzed asymmetric intermolecular bromotrifluoromethoxylation of alkenes with trifluoromethylsulfonate (TFMS) (Guo et al., 2017). The need for a hazardous agent, CF3OX (X=F, Cl, etc.), limits the applicability of conventional radical approaches (Tlili et al., 2016). On the basis of their discovery of intramolecular trifluoromethylation of N-OCF3 substrates (Feng et al., 2016; Hojczyk et al., 2014; Lee et al., 2016a, 2016b), Ngai developed an N-OCF3-type reagent to achieve radical trifluoromethoxylation (Zheng et al., 2018). The nucleophilic reaction is also a widely used strategy (Feng et al., 2016; Hojczyk et al., 2014; Jiang et al., 2018; Lee et al., 2016b; Marrec et al., 2010a, 2010b; Zhou et al., 2018). Hu recently developed a mild nucleophilic trifluoromethoxylation reagent and applied this reagent to trifluoromethylation of arenes to give CF3O arenes (Zhou et al., 2018). Because the trifluromethoxy anion (CF3O−) would readily undergo decomposition to produce carbonyl fluoride (CF2=O), which is an electrophilic species that could react with alcohols to form fluoroformate, Tang used TFMS to generate trifluoromethoxy anions followed by carbonyl fluoride to activate alcohols, allowing for the subsequent dehydroxylative nucleophilic trifluoromethylation (Jiang et al., 2018). Owing to the high instability of the key trifluoromethoxy intermediates, including CF3O− and CF3OM (M = metal), trifluoromethoxylation reactions usually have to be performed at low temperatures (room temperature or even lower), and therefore long reaction times are usually required (>10 hr in most cases) to overcome the free energy barriers.

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Alcohols are readily available starting materials; therefore, trifluoromethylation of alcohols would be an attractive protocol for the installation of CF3O moiety. In continuation of our research interest in the chemistry of RFX (RF = fluoroalkyl group; X = heteroatom) installation (Yu et al., 2017; Zheng et al., 2015, 2017), we have now investigated the trifluoromethylation of alcohols. We found that the Ph3P/ICH2CH2I system could effectively activate the hydroxyl group to achieve dehydroxytrifluoromethylation of alcohols with the CF3O\(^{-}\) anion. In contrast to Tang’s approach for the dehydroxytrifluoromethylation, which required a reaction time of 26 hr (Jiang et al., 2018), the reaction in our protocol proceeded very rapidly, and full conversion was observed within 15 min (Scheme 1, Equation 2).

RESULTS

The Optimization of Reaction Conditions

Our initial attempt at the trifluoromethylation of alcohol 1a was successful with the use of the Ph3P/ICH2CH2I system in slight excess (Table 1, entry 1). A brief survey of the reaction solvent (entries

| Entry | Molar Ratio | Solvent | Temperature (°C) | Time | Yield (%) |
|-------|-------------|---------|------------------|------|-----------|
| 1     | 1:3.0:1.4:1.4 | DMF     | 60               | 5 hr | 36        |
| 2     | 1:3.0:1.4:1.4 | DMSO    | 60               | 5 hr | trace     |
| 3     | 1:3.0:1.4:1.4 | NMP     | 60               | 5 hr | 21        |
| 4     | 1:3.0:1.4:1.4 | Toluene | 60               | 5 hr | 14        |
| 5     | 1:3.0:1.4:1.4 | DMF     | 70               | 5 hr | 45        |
| 6     | 1:3.0:1.4:1.4 | DMF     | 80               | 5 hr | 65        |
| 7     | 1:3.0:1.4:1.4 | DMF     | 90               | 5 hr | 60        |
| 8     | 1:4.0:1.4:1.4 | DMF     | 80               | 5 hr | 80        |
| 9     | 1:4.0:1.2:1.2 | DMF     | 80               | 5 hr | 73        |
| 10    | 1:4.0:1.6:1.6 | DMF     | 80               | 5 hr | 75        |
| 11    | 1:4.0:1.4:1.4 | DMF     | 80               | 1 hr | 76        |
| 12    | 1:4.0:1.4:1.4 | DMF     | 80               | 15 min | 78 |
| 13*   | 1:4.0:1.4:1.4 | DMF     | 80               | 15 min | 63 |
| 14*   | 1:3.5:1.5:1.5 | DMF     | Rt               | 14 hr | 50 |

Table 1. Optimization of Reaction Conditions

NMP, 1-methylpyrrolidin-2-one.

*Reaction conditions: substrate 1a (0.1 mmol), AgOCF3, Ph3P and ICH2CH2I in DMF (1.5 mL) at the indicated temperature under a N2 atmosphere.

*Molar ratio of 1a:AgOCF3:Ph3P:ICH2CH2I.

*The yields were determined by 19F NMR spectroscopy.

*The reaction was performed in an unsealed tube (exposed to air).

*CsOCF3 was used instead of AgOCF3; rt, room temperature.
1–4) revealed that N,N-dimethylformamide (DMF) was a suitable solvent. Elevating the reaction temperature from 60°C to 80°C increased the yield to 65% (entry 6). A higher or lower temperature resulted in lower yields (entry 6 versus entries 1, 5, and 7). A good yield was obtained by increasing the loading of AgOCF₃ (entry 8). Decreasing or increasing the loading of Ph₃P/ICH₂CH₂I led to a slight decrease in the yield (entries 9 and 10). The reaction was monitored using ¹⁹F nuclear magnetic resonance (NMR) spectroscopy; surprisingly, a good yield was obtained within 15 min (entry 12). Because the key trifluoromethoxylation intermediates are so fragile, the trifluoromethoxylation reactions usually have to be performed under an inert gas atmosphere. To our delight, the expected product could be obtained in 63% yield (entry 13) even if the reaction was performed in an unsealed tube (the reaction system was exposed to air). The use of CsOCF₃ instead of AgOCF₃ could give a moderate yield, indicating that the silver ion is not essential for this reaction (entry 14).

**Substrate Scope Investigation**

With the optimized reaction conditions in hand (Table 1, entry 12), we then investigated the substrate scope of the dehydroxytrifluoromethoxylation of alcohols. As shown in Scheme 2, a wide substrate scope and a high level of functional group tolerance were observed. The conversion of various benzyl alcohols occurred smoothly. Electron-rich, electron-neutral, and electron-deficient substrates could be converted into the desired products in moderate to good yields (2a-2p). The transformation was not very sensitive to steric effects, as evidenced by the moderate yields of products 2e, 2g, and 2h. CF₃O-containing heteroarenes could be synthesized by this protocol (2q-2s). Besides benzyl alcohols, allyl alcohols (2t) and propargyl alcohols (2u) also underwent the expected conversion under these conditions. Compared with primary alcohols, lower yields were obtained for secondary alcohols (2v-2x). However, the optimal conditions were not suitable for efficient dehydroxytrifluoromethoxylation of alkyl alcohols (3a).
The low yield of product 3a prompted us to further optimize the reaction conditions for the conversion of alkyl alcohols. After a detailed survey of the reaction conditions (see Supplemental Information, Table S1), we found that the replacement of triphenylphosphine with diphenyl(vinyl)phosphane (Ph$_2$PCH=CH$_2$) at a reaction temperature of 60°C could afford the expected product in 60% yield (3a). A good isolated yield (76%) was obtained by elevating the reaction temperature to 100°C. The substrate scope was then investigated under the optimal conditions (Scheme 3). Like the reaction of benzyl alcohols, the transformation of alkyl alcohols proceeded rapidly, and a 15-min reaction time provided moderate to good yields (3a-3k). Heteroarene-containing alcohols could also be well converted (3g-3i). The conversion of primary alcohols proceeded smoothly, but secondary alcohols could not be effectively transformed (3l).

Although iodide anion could also act as a nucleophile, no iodination product was observed in the above dehydroxytrifluoromethoxylation reactions. This is because iodide anion was excluded from the reaction system by forming AgI precipitate and C-OCF$_3$ bond may be formed in preference to C-I bond due to the higher C-O bond strength.

**Mechanistic Investigations**

Apparently, the R$_3$P/ICH$_2$CH$_2$I (R$_3$P=Ph$_3$P or Ph$_2$PCH=CH$_2$) system in DMF generates key intermediates that could activate alcohols in this dehydroxytrifluoromethoxylation reaction. Both Ph$_3$P and Ph$_2$PCH=CH$_2$ react very quickly with ICH$_2$CH$_2$I in DMF. The mixing of Ph$_3$P and ICH$_2$CH$_2$I in DMF would immediately lead to the full consumption of both Ph$_3$P and ICH$_2$CH$_2$I. ICH$_2$CH$_2$I was converted into ethylene, which was detected by $^1$H NMR spectroscopy, and Ph$_3$P was transformed into Ph$_3$P=O and an unknown species A ($\delta = 11.9$ ppm), as detected by $^{31}$P NMR spectroscopy (Figure 1A). The processes were too quick, which did not allow us to determine and understand how the Ph$_3$P=O and species A were formed. Fortunately, the reaction of Ph$_3$P with ICH$_2$CH$_2$I occurred slowly in chloroform (CHCl$_3$) probably due to its lower polarity. CDCl$_3$ was then used as the reaction solvent to determine what the Ph$_3$P/ICH$_2$CH$_2$I system would be transformed into. After stirring the mixture at room temperature for 15 hr, three phosphorus species were observed, which were determined to be iodophosphonium salt B[Ph$_3$P$^+$I$^-$] (Garegg et al., 1987; Morcillo et al., 2011), triphenylphosphine, and diiodotriphenylphosphane C (Ph$_3$P)$_2$I$_2$ (Garegg et al., 1987) based on

**Scheme 3. Dehydroxytrifluoromethoxylation of Alkyl Alcohols**

Isolated yields. Reaction conditions: alcohol 1 (0.5 mmol), AgOCF$_3$ (2.0 mmol), Ph$_2$PCH=CH$_2$ (1.3 mmol), ICH$_2$CH$_2$I (0.6 mmol), DMF (3 mL), 100°C, 15 min, N$_2$ atmosphere. The yield of product 3i was determined by $^{19}$F NMR spectroscopy. See also Figures S61–S88.
the reported corresponding phosphorus signals (Figure 1B). ICH₂CH₂I was almost completely converted into CH₂=CH₂, as detected by ¹H NMR spectroscopy. The large amount of Ph₃P that remained was because of the reversible equilibrium between Ph₃P and Ph₃PI₂ (Ph₃PI₂ % Ph₃P+I₂) (Morcillo et al., 2011), otherwise Ph₃P would have been almost fully consumed.

The formation of species B and C was due to strong P-I halogen bonding (Gilday et al., 2015). Although triphenylphosphine may easily undergo quaternization with alkyl iodides to give alkylphosphonium salts, 1,2-diiodoethane acted as a halogen bond donor to form a halogen bond with triphenylphosphine (Scheme 4, Equation 1), instead of alkylating triphenylphosphine. The driving force for the halogen bonding was the generation of small ethylene molecules and the good leaving ability of the iodide anion. An equilibrium between B and C explained the observation of C. Clearly, the reaction solvent DMF was involved in the formation of Ph₃P=O and species A from intermediate B (Equation 2). Intermediate A should be a complex formed by the coordination of intermediate B with DMF, because intermediate B can be considered as a Lewis acid. This coordination activated DMF and allowed for the attack of an iodide anion at the amide carbon to produce intermediate D, which could readily undergo C-O bond cleavage to release Ph₃P=O and a Vilsmeier-Haack-type intermediate E.

Because it is known that the Vilsmeier-Haack-type intermediate could well activate hydroxyl groups (Dai et al., 2011; Hepburn and Hudson, 1976), the question arises as to whether species E was the only intermediate that activated the alcohols in the above trifluoromethoxylation reaction. If yes, the only oxygen source for the Ph₃P=O by-product was the reaction solvent DMF. However, the conversion of ¹⁸O-labeled alcohol 1a showed that Ph₃P=¹⁸O was also obtained (Scheme 5), suggesting that another key intermediate was

Figure 1. ³¹P NMR Spectra of the Ph₃P/ICH₂CH₂I Reaction System

Scheme 4. The Formation of Key Intermediates
involved in the activation of the alcohols. The intermediate involved should be species A, because iodo-phosphonium salts have been proved to be powerful intermediates for the activation of alcohols (Appel, 1975; de Andrade and de Mattos, 2015) and this species was also converted into Ph3P=O in the dehydroxytrifluoromethoxylation reaction. No 18O-labeled trifluoromethoxylation product was observed, which indicated that this reaction was a dehydroxylation process.

Based on the above results, we proposed a plausible reaction mechanism, as shown in Scheme 6. The P-I halogen bonding drives the formation of iodo phosphonium salt B, which immediately coordinates with the reaction solvent DMF to form complex A. Ligand exchange of an alcohol with a DMF molecule in complex A furnishes complex G. The alcohol is then activated by coordination and would be easily attacked by a trifluoromethoxy anion generated from AgOCF3 by precipitating AgI, giving the final trifluoromethoxylation product. On the other hand, complex A could also undergo P-O bond formation to release Ph3P=O and the Vilsmeier-Haack-type intermediate E. Intermediate E could activate the alcohols by forming intermediate F, at which the attack of trifluoromethoxy anion also afforded the final product. The generation of the racemic product 2v from enantiopure alcohol indicated that the final attack at G or F may involve an SN1 process (see Supplemental Information, Procedure D. See also Figure S91).

As it has been reported that iodophosphonium salt B (Ph3P+-I-) could also be formed by the reaction of Ph3P with I2 (Morcillo et al., 2011; Pathak and Rokhum, 2015), I2 was then used instead of ICH2CH2I in the dehydroxytrifluoromethoxylation reaction (Scheme 7). Desired products were obtained for the conversion of both benzyl alcohol 1a (Equation 1) and alkyl alcohol 1a’ (Equation 2), further supporting the proposed mechanism. Compared with the R3P/I2 system, which is not quite effective for the conversion of alkyl alcohols (Equation 2) and suffers from the toxicity of I2, the R3P/ICH2CH2I system is more attractive due to the high efficiency for dehydroxytrifluoromethoxylation. In addition, the P-I halogen bond between a trivalent phosphine and an alkyl iodide is quite unusual, and this unexpected observation may offer new opportunities for other chemistry.

DISCUSSION

In summary, we have described the dehydroxytrifluoromethoxylation of alcohols promoted by a R3P/ICH2CH2I system in DMF. The combination of R3P and ICH2CH2I in DMF could rapidly activate alcohols, resulting in the successful development of an efficient protocol for fast trifluoromethoxylation. A moderate yield was obtained even if the reaction was performed under an air atmosphere. The convenient Ph3P/ICH2CH2I system in DMF for highly effective dehydroxylation may find synthetic utility in other research areas.
METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Transparent Methods, 91 figures, and 1 table and can be found with this article online at https://doi.org/10.1016/j.isci.2018.07.004.

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AUTHOR CONTRIBUTIONS

W.Z. and J.C. performed the experiments. J.-H.L. analyzed the data and wrote the manuscript. J.-C.X. designed the experiments and wrote the manuscript. Y.-C.G. designed some experiments.

DECLARATION OF INTERESTS

There are no conflicts to declare.

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Supplemental Information

Rapid Dehydroxytrifluoromethoxylation of Alcohols

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Supplemental Figures for $^1$H NMR, $^{13}$C NMR, and $^{19}$F NMR Spectra

Figure S1. $^1$H NMR spectrum of 2a, Related to Scheme 2
Figure S2. $^{19}$F NMR spectrum of 2a, Related to Scheme 2
**Figure S3.** $^1$H NMR spectrum of 2b, Related to Scheme 2
Figure S4. $^{19}$F NMR spectrum of 2b, Related to Scheme 2
Figure S5. $^1$H NMR spectrum of 2c, Related to Scheme 2
Figure S6. $^{19}$F NMR spectrum of 2c, Related to Scheme 2
Figure S7. $^{13}$C NMR spectrum of 2c, Related to Scheme 2
Figure S8. $^1$H NMR spectrum of 2d, Related to Scheme 2
Figure S9. $^{19}$F NMR spectrum of 2d, Related to Scheme 2
Figure S10. $^{13}$C NMR spectrum of 2d, Related to Scheme 2
Figure S11. $^1$H NMR spectrum of 2e, Related to Scheme 2
Figure S12. $^{19}$F NMR spectrum of 2e, Related to Scheme 2
Figure S13. $^1$H NMR spectrum of 2f, Related to Scheme 2
Figure S14. $^{19}$F NMR spectrum of 2f, Related to Scheme 2
Figure S15. $^1$H NMR spectrum of 2g, Related to Scheme 2
Figure S16. $^{19}$F NMR spectrum of 2g, Related to Scheme 2
Figure S17. $^{13}$C NMR spectrum of 2g, Related to Scheme 2
Figure S18. $^1$H NMR spectrum of 2h. Related to Scheme 2
Figure S19. $^{19}$F NMR spectrum of 2h, Related to Scheme 2
Figure S20 $^1$H NMR spectrum of 2i, Related to Scheme 2
Figure S21. $^{19}$F NMR spectrum of 2i, Related to Scheme 2
Figure S22. $^1$H NMR spectrum of 2i, Related to Scheme 2
Figure S23. $\textsuperscript{19}$F NMR spectrum of 2j, Related to Scheme 2
Figure S24. $^{13}$C NMR spectrum of 2j, Related to Scheme 2
Figure S25. $^1$H NMR spectrum of 2k, Related to Scheme 2
Figure S26. $^{19}$F NMR spectrum of 2k, Related to Scheme 2
Figure S27. $^1$H NMR spectrum of 2l, Related to Scheme 2
Figure S28. $^{19}$F NMR spectrum of 2l, Related to Scheme 2
Figure S29. $^1$H NMR spectrum of 2m, Related to Scheme 2
Figure S30. $^{19}$F NMR spectrum of 2m, Related to Scheme 2
Figure S31. $^{13}$C NMR spectrum of 2m. Related to Scheme 2
Figure S32. $^1$H NMR spectrum of 2n, Related to Scheme 2
**Figure S33.** $^{19}$F NMR spectrum of 2n, Related to Scheme 2
Figure S34. $^1$H NMR spectrum of 2o, Related to Scheme 2
Figure S35. $^{19}$F NMR spectrum of 2o, Related to Scheme 2
Figure S36. $^1$H NMR spectrum of 2p. Related to Scheme 2.
Figure S37. $^{19}$F NMR spectrum of 2p, Related to Scheme 2
Figure S38. \(^1\)H NMR spectrum of 2q, Related to Scheme 2
Figure S39. $^{19}$F NMR spectrum of 2q, Related to Scheme 2
Figure S40. $^{13}$C NMR spectrum of 2q, Related to Scheme 2
Figure S41. $^1$H NMR spectrum of 2r, Related to Scheme 2
Figure S42. $^{19}$F NMR spectrum of 2r, Related to Scheme 2
Figure S43. $^{13}$C NMR spectrum of 2r, Related to Scheme 2
Figure S44. $^1$H NMR spectrum of 2s, Related to Scheme 2
Figure S45. $^{19}\text{F}$ NMR spectrum of 2s, Related to Scheme 2.
Figure S46. $^{13}$C NMR spectrum of 2s, Related to Scheme 2
Figure S47. $^1$H NMR spectrum of 2t, Related to Scheme 2
Figure S48. $^{19}$F NMR spectrum of 2t, Related to Scheme 2
Figure S49. $^1$H NMR spectrum of 2u, Related to Scheme 2
Figure S50. $^{19}$F NMR spectrum of 2u, Related to Scheme 2
Figure S51. $^{13}$C NMR spectrum of 2u, Related to Scheme 2
Figure S52. $^1$H NMR spectrum of 2v, Related to Scheme 2
**Figure S53.** $^{19}$F NMR spectrum of 2v, Related to **Scheme 2**
Figure S54. $^{13}$C NMR spectrum of 2v, Related to Scheme 2
Figure S55. $^1$H NMR spectrum of 2w, Related to Scheme 2
Figure S56. $^{19}$F NMR spectrum of 2w, Related to Scheme 2
Figure S57. $^{13}$C NMR spectrum of 2w, Related to Scheme 2
Figure S58. $^1$H NMR spectrum of 2x, Related to Scheme 2
Figure S59. $^{19}$F NMR spectrum of 2x, Related to Scheme 2
Figure S60. $^{13}$C NMR spectrum of 2x, Related to Scheme 2
Figure S61. $^1$H NMR spectrum of 3a, Related to Scheme 3
Figure 62. $^{19}$F NMR spectrum of 3a, Related to Scheme 3
Figure S63. $^{13}$C NMR spectrum of 3a, Related to Scheme 3
Figure S64. $^1$H NMR spectrum of 3b. Related to Scheme 3
Figure S65. $^{19}$F NMR spectrum of 3b, Related to Scheme 3
Figure S66. $^1$H NMR spectrum of 3c, Related to Scheme 3
$^{19}$F NMR spectrum of 3c, Related to Scheme 3

Figure S67. $^{19}$F NMR spectrum of 3c, Related to Scheme 3
$^{13}$C NMR spectrum of 3c, Related to Scheme 3
Figure S69. $^1$H NMR spectrum of 3d, Related to Scheme 3
Figure S70. $^{19}$F NMR spectrum of 3d, Related to Scheme 3
**Figure S71.** $^{13}$C NMR spectrum of 3d, Related to Scheme 3
Figure S72. $^1$H NMR spectrum of 3e, Related to Scheme 3
$\text{CH}_2=\text{CH}(\text{CH}_2)_9\text{OCF}_3$

$3e$

**Figure S73.** $^{19}\text{F}$ NMR spectrum of $3e$, Related to **Scheme 3**
Figure S74. $^{13}$C NMR spectrum of 3e, Related to Scheme 3
Figure S75. $^1$H NMR spectrum of 3f, Related to Scheme 3
Figure S76. $^{19}$F NMR spectrum of 3f, Related to Scheme 3
Figure S77. $^1$H NMR spectrum of 3g, Related to Scheme 3
Figure S78. $^{19}\text{F}$ NMR spectrum of 3g, Related to Scheme 3
Figure S79. $^1$H NMR spectrum of 3h. Related to Scheme 3
Figure S80. $^{19}$F NMR spectrum of 3h, Related to Scheme 3
Figure S81. $^1$H NMR spectrum of 3i, Related to Scheme 3
Figure S82. $^{19}$F NMR spectrum of 3i, Related to Scheme 3
Figure S83. $^{13}$C NMR spectrum of 3i, Related to Scheme 3
**Figure S84.** $^1$H NMR spectrum of 3j, Related to Scheme 3
Figure S85. $^{19}$F NMR spectrum of 3j, Related to Scheme 3
Figure S86. $^{13}$C NMR spectrum of 3j, Related to Scheme 3
Figure S87. $^1$H NMR spectrum of 3k, Related to Scheme 3
Figure S88. $^{19}$F NMR spectrum of 3k, Related to Scheme 3
### Table

| m/z  | RA% | m/z  | RA% | m/z  | RA% |
|------|-----|------|-----|------|-----|
| 77.10 | 21.0 | 154.20 | 15.0 | 167.10 | 27.0 |
| 152.05 | 38.0 | 155.20 | 78.0 | 184.20 | 20.0 |
| 153.05 | 25.0 | 166.10 | 18.0 | 186.20 | 100.0 |

$^{18}$O: $^{16}$O = 100:20 = 83:17

### Figure S89

$^{18}$O-labeled-alcohol, Related to Scheme 5 and Procedure C.
| m/z  | RA% | m/z  | RA% | m/z  | RA% |
|------|-----|------|-----|------|-----|
| 51.10| 8.0 | 183.10| 19.0| 278.15| 37.0 |
| 77.10| 14.0| 199.10| 27.0| 279.10| 54.0 |
| 152.20| 10.0| 277.10| 100.0| 280.15| 20.0 |

\[ ^{18}\text{O}:^{16}\text{O} = 20:37 = 35.65 \]

**Figure S90.** $^{18}$O-labeled triphenylphosphine oxide, Related to Scheme 5 and Procedure C.
Figure S91. HPLC spectrum of racemic product 2v, Related to Scheme 6 and Procedure D.
Supplemental Table

Table S1. Screening conditions for trifluoromethoxylation of alkyl alcohols, Related to Scheme 3

| Entry | Molar ratio<br> | [P] | Temp (°C) | Time (h) | Yield [%]<br> |
|-------|----------------|-----|-----------|----------|----------------|
| 1     | 1:4.0:1.4:1.4  | Ph$_3$P | 80       | 6        | 16             |
| 2     | 1:4.0:1.4:1.4  | Ph$_3$P | 60       | 6        | 16             |
| 3     | 1:4.0:1.6:1.6  | Ph$_3$P | 100      | 6        | 29             |
| 4     | 1:4.0:1.8:1.8  | Ph$_3$P | 120      | 6        | 29             |
| 5     | 1:4.0:1.2:1.2  | Ph$_3$P | 100      | 6        | 33             |
| 6     | 1:4.0:1.6:1.6  | Ph$_3$P | 100      | 6        | 28             |
| 7     | 1:4.0:1.4:1.4  | (p-OMePh)$_3$P | 100 | 6   | 6             |
| 8     | 1:4.0:1.4:1.4  | (p-CF$_3$Ph)$_3$P | 100 | 6   | 5             |
| 9     | 1:4.0:1.4:1.4  | (p-MePh)$_3$P | 100 | 6   | 8             |
| 10    | 1:4.0:1.4:1.4  | (C$_6$F$_5$)$_3$P | 100 | 6 | 17     |
| 11    | 1:4.0:1.4:1.4  | (EtO)$_3$P | 100 | 6 | 23     |
| 12    | 1:4.0:1.4:1.4  | Cy$_3$P | 100      | 6        | 0             |
| 13    | 1:4.0:1.4:1.4  | t-Bu$_3$P | 100 | 6 | 4             |
| 14    | 1:4.0:1.4:1.4  | (Me$_2$N)$_3$P | 100 | 6 | 8             |
| 15    | 1:4.0:1.4:1.4  | Ph$_3$P(C$_2$H$_3$) | 100 | 6 | 40            |
| 16    | 1:4.0:1.4:1.8  | Ph$_3$P(C$_2$H$_3$) | 100 | 6 | 54            |
| 17    | 1:4.0:1.2:1.8  | Ph$_3$P(C$_2$H$_3$) | 100 | 6 | 70            |
| 18    | 1:4.0:1.2:2.0  | Ph$_3$P(C$_2$H$_3$) | 100 | 6 | 73            |
| 19    | 1:4.0:1.2:2.4  | Ph$_3$P(C$_2$H$_3$) | 100 | 6 | 75            |
| 20    | 1:4.0:1.2:2.6  | Ph$_3$P(C$_2$H$_3$) | 100 | 6 | 78            |
| 21    | 1:4.0:1.2:2.8  | Ph$_3$P(C$_2$H$_3$) | 100 | 6 | 68            |
| 22    | 1:4.0:1.2:3.0  | Ph$_3$P(C$_2$H$_3$) | 100 | 6 | 66            |
23  1:4.0:1.2:2.6  Ph3P(C2H3)  100  0.25  79
24  1:4.0:1.2:2.6  Ph3P  100  0.25  41
25  1:4.0:1.2:2.6  Ph3P(C2H3)  60  12  60

"Reaction conditions: 1a (0.1 mmol), AgOCF3, [P] and ICH2CH2I in DMF (1.5 mL) under a N2 atmosphere; "Molar ratio of 1a:AgOCF3:[P]:ICH2CH2I; "The yields were determined by 19F NMR spectroscopy.

**Transparent Methods**

1H, 13C and 19F NMR spectra were detected on a 500 MHz, 400 MHz or 300 MHz NMR spectrometer. Data for 1H NMR, 13C NMR and 19F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, coupling constant (s) in Hz). Mass spectra were obtained on GC-MS or LC-MS (ESI). High resolution mass data were recorded on a high resolution mass spectrometer in the EI or ESI mode. The CH3CN-solvated AgOCF3 (Chen et al., 2015) and 18O-labeled alcohol 1a (Jiang et al., 2018) were prepared according to the literature procedures.

**Procedure A for the dehydroxytrifluoromethoxylation of benzyl alcohols, Related to Scheme 2**

![Chemical reaction diagram]

Into the solution of alcohol 1 (0.5 mmol, 1.0 equiv.) and Ph3P (0.7 mmol, 183.6 mg, 1.4 equiv.) in DMF (3 mL) was added 1,2-diiodoethane (0.7 mmol, 197.3 mg, 1.4 equiv) in a 10 mL sealed tube under N2 atmosphere. After the reagents were completely dissolved, CH3CN-solvated AgOCF3 (2.0 mmol, 2 mL, 1.0 M, 4.0 equiv) was added. The tube was sealed and the resulting mixture was stirred at 80 °C for 15 min. The reaction mixture was cooled to room temperature and filtered through a plug of silica gel. The solid was washed with EtOAc. The filtrate was concentrated, and the residue was subjected to flash column chromatography to give product 2.

**Procedure B for the dehydroxytrifluoromethoxylation of alkyl alcohols, Related to Scheme 3**

![Chemical reaction diagram]

Into the solution of alcohol 1 (0.5 mmol, 1.0 equiv.) and Ph3P(C2H3) (1.3 mmol, 0.25 mL, 2.6 equiv.) in DMF (3 mL) was added 1,2-diiodoethane (0.6 mmol, 169.2 mg, 1.2 equiv) in a 10 mL sealed tube under N2 atmosphere. After the reagents were completely dissolved, CH3CN-solvated AgOCF3 (2.0 mmol, 2 mL, 1.0 M, 4.0 equiv) was added. The tube was sealed and the reaction mixture was stirred at 80 °C for 15 min. The reaction mixture was cooled to room temperature and filtered through a plug of silica gel. The solid was washed with EtOAc. The filtrate was concentrated, and the residue was subjected to flash column chromatography to give product 3.

**Procedure C for the generation of Ph3P=18O from 18O-labeled alcohol, Related to**
Scheme 5

\[
\begin{align*}
\text{Ph} & \quad \text{+ Ph}_{3}\text{P(1.4 equiv)} \\
\text{Ph} & \quad \text{+ ICH}_{2}\text{CH}_{2}(1.4 \text{ equiv}) \\
\text{Ph} & \quad \text{OCF}_{3} \\
\text{Ph} & \quad \text{+ Ph}_{3}\text{P=^{18}O}
\end{align*}
\]

Into the solution of \(^{18}\text{O}-1\text{a} \quad (^{18}\text{O}:^{16}\text{O} = 84:16\text{, }0.186 \text{ mmol}, 34.6 \text{ mg, 1.0 equiv.}) and \text{Ph}_{3}\text{P} (0.26 \text{ mmol, 68.5 mg, 1.4 equiv.}) in DMF (2.8 ml) was added 1,2-diiodoethane (0.26 mmol, 73.4 mg, 1.4 equiv) in a 5 mL sealed tube under N\(_2\) atmosphere. After the reagents were completely dissolved, CH\(_3\)CN-solvated AgOCF\(_3\) (0.74 mmol, 0.75 mL, 1.0 M, 4.0 equiv) was added. The tube was sealed and the resulting mixture was stirred at 80 °C for 15 min. The reaction mixture was cooled to room temperature and filtered through a plug of silica gel. The solid was washed with EtOAc. The filtrate was concentrated, and the residue was subjected to flash column chromatography to give 35.5 mg 4-((trifluoromethoxy)methyl)-1,1'-biphenyl (2\text{a}) (75% yield) and 70.9 mg triphenylphosphine oxide (98%).

The \(^{18}\text{O}:^{16}\text{O}\) ratios for alcohol and triphenylphosphine oxide were determined by EI spectroscopy shown in Figures 89 and 90.

**Procedure D for the conversion of an enantiopure alcohol, Related to Scheme 6**

\[
\begin{align*}
\text{Ph} & \quad \text{+ AgOCF}_{3} \\
\text{Ph} & \quad \text{Me} \\
\text{Ph} & \quad \text{Me} \\
\text{Ph} & \quad \text{Me}
\end{align*}
\]

Into the solution of enantiopure alcohol 1\text{v} (0.5 mmol, 99 mg, 1.0 equiv.) and \text{Ph}_{3}\text{P} (0.7 mmol, 183.6 mg, 1.4 equiv.) in DMF (3 mL) was added 1,2-diiodoethane (0.7 mmol 197.3 mg, 1.4 equiv) in a 10 mL sealed tube under N\(_2\) atmosphere. After the reagents were completely dissolved, CH\(_3\)CN-solvated AgOCF\(_3\) (2.0 mmol, 2 mL, 1.0 M 4.0 equiv) was added. The tube was sealed and the reaction mixture was stirred at 80 °C for 15 min. The reaction mixture was cooled to room temperature and filtered through a plug of silica gel. The solid was washed with EtOAc. The filtrate was concentrated, and the residue was subjected to flash column chromatography to give product 2\text{v}. Enantiomeric excess was determined by HPLC with a Chiralpak adh (0.46 x 25 cm, 5μm) (CO\(_2\):MeOH = 98:2, 21 nm, 2 mL/min); enantiomer rt = 2.695 min and 2.909 min. HPLC spectrum is shown in Figure S91.

**Procedure E for R\(_3\)P/I\(_2\)-Promoted Dehydroxytrifluoromethoxylation of Alcohols, Related to Scheme 7**

\[
\begin{align*}
\text{Ph} & \quad \text{+ AgOCF}_{3} \\
\text{Ph} & \quad \text{Me} \\
\text{Ph} & \quad \text{Me}
\end{align*}
\]

Into the solution of alcohol (0.1 mmol, 1.0 equiv.) and \text{Ph}_{3}\text{P} (0.14 mmol, 36.8 mg, 1.4 equiv.) in DMF (1.5 mL) was added molecular iodine (0.14 mmol, 35.5 mg, 1.4 equiv) in a 5 mL sealed tube under N\(_2\) atmosphere. After the reagents were completely dissolved, CH\(_3\)CN-solvated AgOCF\(_3\) (0.4 mmol, 0.4 mL, 1.0 M, 4.0 equiv) was added. The tube was sealed and the resulting mixture was stirred at 80 °C for 15 min.
The reaction mixture was cooled to room temperature. The yield of product 2a was determined by $^{19}$F NMR spectroscopy.

\[
\begin{array}{c}
\text{Ph} \quad \text{OH} \\
1a' \quad (0.1 \text{ mmol}) \\
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{Ph} \quad \text{OF} \\
\text{P} \quad \text{C} \\
\end{array}
\begin{array}{c}
\text{Ph} \quad \text{P} \quad \text{CH} = \text{CH}_2 \quad (0.26 \text{ mmol}) \\
\text{DMF} \quad 100 \degree \text{C}, \ 15 \text{ min} \\
\end{array}
\text{AgOCF}_3 \\
(0.4 \text{ mmol}) \\
\end{array}
\begin{array}{c}
\text{Ph} \quad \text{OF} \\
3a \quad (41\%) \\
\end{array}
\]

Into the solution of alcohol (0.1 mmol, 1.0 equiv.) and Ph$_3$P(C$_2$H$_3$) (0.26 mmol, 51 µL, 2.6 equiv.) in DMF (1.5 mL) was added molecular iodine (0.12 mmol, 30.5 mg, 1.2 equiv) in a 5 mL sealed tube under N$_2$ atmosphere. After the reagents were completely dissolved, CH$_3$CN-solvated AgOCF$_3$ (0.4 mmol, 0.4 mL, 1.0 M, 4.0 equiv) was added. The tube was sealed and the reaction mixture was stirred at 80 °C for 15 min. The reaction mixture was cooled to room temperature. The yield of product 3a was determined by $^{19}$F NMR spectroscopy.

**Characterization of all compounds**

\[
\begin{array}{c}
\text{Ph} \quad \text{OF} \\
2a \\
\end{array}
\]

Following procedure A, 4-((trifluoromethoxy)methyl)-1,1′-biphenyl (Liu et al., 2015) was obtained as white solid (related to Scheme 2). (95.4 mg, 76%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.67 – 7.59 (m, $J = 4$H), 7.51 – 7.43 (m, 4H), 7.39 (t, $J = 7.3$ Hz, 1H), 5.05 (s, 2H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -60.3 (s, 3F).

\[
\begin{array}{c}
\text{MeO} \quad \text{OF} \\
2b \\
\end{array}
\]

Following procedure A, 1-methoxy-4-((trifluoromethoxy)methyl)benzene (Liu et al., 2015) was obtained as yellow oil (related to Scheme 2). (67.8 mg, 66%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.5$ Hz, 2H), 4.92 (s, 2H), 3.82 (s, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -60.0 (s, 3F).

\[
\begin{array}{c}
\text{Ph} \quad \text{OF} \\
2c \\
\end{array}
\]

Following procedure A, 1-phenoxy-4-((trifluoromethoxy)methyl)benzene was obtained as colourless oil (related to Scheme 2). (103.9 mg, 74%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36 – 7.25 (m, 4H), 7.11 (t, $J = 7.4$ Hz, 1H), 7.04 – 6.95 (m, 4H), 4.91 (s, 2H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -60.2 (s, 3F). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 158.2 (s), 156.7 (s), 130.1 (s), 129.9 (s), 128.4 (s), 123.8 (s), 121.7 (q, $J = 255.4$ Hz), 119.3 (s), 118.7 (s), 68.8 (q, $J = 3.5$ Hz). IR (neat) ν 3041, 2966, 1615, 1591, 1489, 1241, 1204, 1142, 1071, 1013, 871, 692 cm$^{-1}$. HRMS (El) Calculated for C$_{14}$H$_{11}$F$_3$O$_2$ 268.0711, Found [M]$^+$ 268.0713.
Following procedure A, 5-((trifluoromethoxy)methyl)benzo[d][1,3]dioxole was obtained as colourless oil (related to Scheme 2). (82.3 mg, 75%). $^1$H NMR (400 MHz, CDCl$_3$) δ 6.91 – 6.75 (m, 3H), 5.99 (s, 2H), 4.88 (s, 2H). $^{19}$F NMR (376 MHz, CDCl$_3$) δ -60.2 (s, 3F). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 148.2 (s), 148.0 (s), 127.5 (s), 122.3 (s), 121.6 (q, $J = 255.5$ Hz), 108.8 (s), 108.3 (s), 101.3 (s), 69.2 (q, $J = 3.5$ Hz). IR (neat) ν 2958, 2917, 2849, 1609, 1949, 1449, 1253, 1142, 1041, 931, 807, 668 cm$^{-1}$. HRMS (EI) Calculated for C$_9$H$_7$F$_3$O 220.0347, Found [M]$^+$ 220.0346.

Following procedure A, N-(4'-fluoro-5-isopropyl-6-((trifluoromethoxy)methyl)-1,1'-biphenyl-3-yl)-N-methylmethanesulfonamide (Liu et al., 2015) was obtained as colourless oil (related to Scheme 2). (141.2 mg, 66%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.66 – 7.61 (m, 2H), 7.18 (t, $J = 8.6$ Hz, 2H), 4.94 (s, 2H), 3.56 (s, 3H), 3.50 (s, 3H), 3.40 – 3.27 (m, 1H), 1.33 (d, $J = 6.6$ Hz, 6H). $^{19}$F NMR (376 MHz, CDCl$_3$) δ -60.9 (s, 3F).

Following procedure A, 1-(tert-butyl)-4-((trifluoromethoxy)methyl)benzene (Liu et al., 2015) was obtained as colourless oil (related to Scheme 2). (88.1 mg, 76%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.42 (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.2$ Hz, 2H), 4.95 (s, 2H), 1.32 (s, 9H). $^{19}$F NMR (376 MHz, CDCl$_3$) δ -60.3 (s, 3F).

Following procedure A, 1,3,5-trimethyl-2-((trifluoromethoxy)methyl)benzene was obtained as colourless oil (related to Scheme 2). (74.2 mg, 68%). $^1$H NMR (400 MHz, CDCl$_3$) δ 6.93 (s, 2H), 5.09 (s, 2H), 2.41 (s, 6H), 2.32 (s, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) δ -60.7 (s, 3F). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 139.3 (s), 138.4 (s), 129.3 (s), 127.0 (s), 121.7 (q, $J = 255.4$ Hz), 63.7 (q, $J = 3.5$ Hz), 21.04 (s), 19.16 (s). IR (neat) ν 2957, 2925, 2854, 1733, 1669, 1616, 1583, 1506, 1457, 1396, 1264, 1244, 849, 793 cm$^{-1}$. HRMS (EI) Calculated for C$_{11}$H$_{13}$F$_3$O 218.0918, Found [M]$^+$ 218.0922.
Following procedure A, 1-((trifluoromethoxy)methyl)naphthalene (Liu et al., 2015) was obtained as colourless oil (related to Scheme 2). (84.9 mg, 75%). 1H NMR (400 MHz, CDCl3) δ 8.07 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 7.4 Hz, 2H), 7.69 – 7.46 (m, 4H), 5.48 (s, 2H). 19F NMR (376 MHz, CDCl3) δ -60.3 (s, 3F).

Following procedure A, 2-((trifluoromethoxy)methyl)naphthalene (Liu et al., 2015) was obtained as white solid (related to Scheme 2). (80.5 mg, 71%). 1H NMR (400 MHz, CDCl3) δ 7.95 – 7.79 (m, 4H), 7.58 – 7.43 (m, 3H), 5.16 (s, 2H). 19F NMR (376 MHz, CDCl3) δ -60.2 (s, 3F).

Following procedure A, 1-bromo-3-((trifluoromethoxy)methyl)benzene was obtained as colourless oil (related to Scheme 2). (86.5 mg, 68%). 1H NMR (400 MHz, CDCl3) δ 7.54 – 7.48 (m, 2H), 7.32 – 7.26 (m, 2H), 4.95 (s, 2H). 19F NMR (376 MHz, CDCl3) δ -60.6 (s, 3F). 13C NMR (101 MHz, CDCl3) δ 136.0 (s), 132.0 (s), 130.9 (s), 130.3 (s), 126.4 (s), 122.7 (s), 121.6 (q, J = 255.9 Hz), 68.0 (q, J = 3.6 Hz). IR (neat) ν 2955, 2919, 2850, 1734, 1653, 1559, 1458, 1377, 1124, 1083, 1025, 668 cm⁻¹. HRMS (EI) Calculated for C9H6F3BrO 253.9554, Found [M]+ 253.9557.

Following procedure A, 1-bromo-4-((trifluoromethoxy)methyl)benzene (Liu et al., 2015) was obtained as colourless oil (related to Scheme 2). (96.5 mg, 76%). 1H NMR (400 MHz, CDCl3) δ 7.52 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 4.93 (s, 2H). 19F NMR (376 MHz, CDCl3) δ -60.9 (s, 3F).

Following procedure A, 1-iodo-4-((trifluoromethoxy)methyl)benzene (Liu et al., 2015) was obtained as colourless oil (related to Scheme 2). (112.8 mg, 75%). 1H NMR (400 MHz, CDCl3) δ 7.74 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 4.93 (s, 2H). 19F NMR (376 MHz, CDCl3) δ -60.5 (s, 3F).
Following procedure A, 1-iodo-2-((trifluoromethoxy)methyl)benzene was obtained as colourless oil (related to Scheme 2). (94.7 mg, 63%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.87 (d, $J = 7.9$ Hz, 1H), 7.47 – 7.37 (m, 2H), 7.07 (t, $J = 7.5$ Hz, 1H), 5.02 (s, 2H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -60.6 (s, 3F). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 139.5 (s), 136.4 (s), 130.3 (s), 128.9 (s), 128.5 (s), 121.6 (q, $J = 256.0$ Hz), 97.2 (s), 72.6 (q, $J = 3.5$ Hz). IR (neat) $\nu$ 2955, 2919, 2850, 1734, 1653, 1559, 1458, 1377, 1124, 1083, 1025, 668 cm$^{-1}$. HRMS (EI) Calculated for C$_8$H$_6$F$_3$I_2O$_3$ 301.9415, Found [M]$^+$ 301.9418.

Following procedure A, methyl 4-((trifluoromethoxy)methyl)benzoate (Liu et al., 2015) was obtained as colourless oil (related to Scheme 2). (78.2 mg, 67%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J = 8.2$ Hz, 2H), 7.43 (d, $J = 8.1$ Hz, 2H), 5.03 (s, 2H), 3.92 (s, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -60.7 (s, 3F).

Following procedure A, 3-((trifluoromethoxy)methyl)benzonitrile (Liu et al., 2015) was obtained as colourless oil (related to Scheme 2). (61.4 mg, 61%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 – 7.64 (m, 2H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.56 – 7.50 (m, 1H), 5.02 (s, 2H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -60.7 (s, 3F).

Following procedure A, 1-nitro-4-((trifluoromethoxy)methyl)benzene (Liu et al., 2015) was obtained as yellow oil (related to Scheme 2). (54.3 mg, 49%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.24 (d, $J = 8.7$ Hz, 2H), 7.53 (d, $J = 8.3$ Hz, 2H), 5.08 (s, 2H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -60.8 (s, 3F).

Following procedure A, 6-((trifluoromethoxy)methyl)quinoline was obtained as colourless oil (related to Scheme 2). (79.3 mg, 70%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.94 (d, $J = 3.9$ Hz, 1H), 8.15 (d, $J = 8.5$ Hz, 1H), 8.13 (d, $J = 8.6$ Hz, 1H), 7.81 (s, 1H), 7.68 (d, $J = 8.7$ Hz, 1H), 7.42 (dd, $J = 8.2$, 4.2 Hz, 1H), 5.16 (s, 2H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -60.4 (s, 3F). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 151.1 (s), 148.2 (s), 136.2 (s), 132.2 (s), 130.2 (s), 128.7 (s), 128.0 (s), 126.9 (s), 121.7 (q, $J = 255.9$ Hz), 121.7 (s), 68.6 (q, $J = 3.5$ Hz).
IR (neat) ν 3040, 2966, 1597, 1505, 1467, 1403, 1266, 1143, 831, 734, 670 cm⁻¹, HRMS (EI) Calculated for C₁₁H₇F₃NO 227.0558, Found [M]+ 227.0559.

Following procedure A, 3-((trifluoromethoxy)methyl)pyridine was obtained as pale yellow oil (related to Scheme 2). (39.9 mg, 45%). ¹H NMR (400 MHz, CDCl₃) δ 8.63 (s, 2H), 7.72 (d, J = 7.4 Hz, 1H), 7.39 – 7.31 (m, 1H), 5.01 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 150.4 (s), 149.3 (s), 135.8 (s), 129.6 (s), 123.6 (s), 121.6 (q, J = 256.1 Hz), 66.5 (q, J = 3.6 Hz). IR (neat) ν 3058, 2960, 2925, 2853, 1721, 1459, 1373, 1261, 1020, 800, 696 cm⁻¹, HRMS (EI) Calculated for C₁₁H₈F₃N₂O 227.0558, Found [M]+ 227.0559.

Following procedure A, 2-((trifluoromethoxy)methyl)benzo[b]thiophene was obtained as white solid (related to Scheme 2). (86.1 mg, 74%). mp 58.0°C. ¹H NMR (400 MHz, CDCl₃) δ 7.87 – 7.81 (m, 1H), 7.81 – 7.75 (m, 1H), 7.42 – 7.36 (m, 2H), 7.35 (s, 1H), 5.24 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 140.6 (s), 139.0 (s), 136.4 (s), 125.1 (s), 125.0 (d, J = 5.2 Hz), 124.6 (s), 124.1 (s), 122.5 (s), 121.6 (q, J = 258.3 Hz), 64.4 (q, J = 3.8 Hz). IR (neat) ν 3032, 2989, 2930, 1488, 1452, 1368, 1277, 1224, 1140, 1062, 765, 697 cm⁻¹, HRMS (EI) Calculated for C₁₀H₇F₃S 232.0170, Found [M]+ 232.0176.

Following procedure A, (E)-(3-(trifluoromethoxy)prop-1-en-1-yl)benzene (Liu et al., 2015) was obtained as colourless oil (related to Scheme 2). (57.3 mg, 57%). ¹H NMR (400 MHz, CDCl₃) δ 7.41 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.30 (d, J = 7.4 Hz, 1H), 6.70 (d, J = 15.9 Hz, 1H), 6.26 (dt, J = 15.8, 6.4 Hz, 1H), 4.63 (d, J = 6.4 Hz, 2H). ¹⁹F NMR (376 MHz, CDCl₃) δ -60.1 (s, 3F).

Following procedure A, (3-(trifluoromethoxy)prop-1-yn-1-yl)benzene was obtained as colourless oil (related to Scheme 2). (40.2 mg, 42%). ¹H NMR (400 MHz, CDCl₃) δ 7.50 – 7.44 (m, 2H), 7.30 (d, J = 7.4 Hz, 1H), 6.70 (d, J = 15.9 Hz, 1H), 6.26 (dt, J = 15.8, 6.4 Hz, 1H), 4.63 (d, J = 6.4 Hz, 2H). ¹⁹F NMR (376 MHz, CDCl₃) δ -60.7 (s, 3F). ¹³C NMR (101 MHz, CDCl₃) δ 131.90 (s), 129.17 (s), 128.40 (s), 121.63 (q, J = 257.3 Hz), 121.60 (s), 88.17 (s), 80.75 (s), 55.98 (q, J = 4.4 Hz). IR (neat) ν 2926, 2855, 1457, 1379, 1261, 1151, 1023, 800, 688 cm⁻¹, HRMS (EI) Calculated for C₁₁H₁₃F₃O 200.0449, Found [M]+ 200.0455.
Following procedure A, 4-(1-(trifluoromethoxy)ethyl)-1,1'-biphenyl was obtained as white solid (related to Scheme 2). (77.2 mg, 58%). Mp 38 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.67 - 7.58\) (m, 4H), 7.51 - 7.42 (m, 4H), 7.39 (t, \(J = 7.3\) Hz, 1H), 5.38 (q, \(J = 6.6\) Hz, 1H), 1.70 (d, \(J = 6.6\) Hz, 3H). \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta -58.0\) (s, 3F). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 141.5\) (s), 140.6 (s), 139.4 (s), 128.9 (s), 127.5 (s), 127.4 (s), 127.2 (s), 126.3 (s), 121.8 (q, \(J = 255.2\) Hz), 77.00 (q, \(J = 2.6\) Hz), 23.32 (s). IR (neat) \(\nu 3445, 3058, 1957, 1622, 1458, 1399, 1261, 1211, 1188, 1135, 841, 756, 729\) cm\(^{-1}\), HRMS (EI) Calculated for C\(_{15}\)H\(_{13}\)F\(_{3}\)O \(266.0918\), Found [M]+ 226.0923.

Following procedure A, 1-bromo-4-(1-(trifluoromethoxy)ethyl)benzene was obtained as colourless oil (related to Scheme 2). (80.7 mg, 60%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.51\) (d, \(J = 8.5\) Hz, 2H), 7.23 (d, \(J = 8.6\) Hz, 2H), 5.26 (q, \(J = 6.6\) Hz, 1H), 1.61 (d, \(J = 6.6\) Hz, 3H). \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta -58.2\) (s, 3F). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 139.5\) (s), 131.8 (s), 127.4 (s), 122.4 (s), 121.6 (q, \(J = 255.5\) Hz), 76.4 (q, \(J = 2.7\) Hz), 23.3 (s). IR (neat) \(\nu 2990, 2928, 2855, 1492, 1410, 1275, 1225, 1143, 1073, 1012, 822, 536\) cm\(^{-1}\), HRMS (EI) Calculated for C\(_9\)H\(_8\)F\(_3\)OBr \(267.9711\), Found [M]+ 267.9722.

Following procedure A, 1-chloro-3-(1-(trifluoromethoxy)ethyl)benzene was obtained as colourless oil (related to Scheme 2). (42.1 mg, 38%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.35\) (s, 1H), 7.32 - 7.30 (m, 2H), 7.25 - 7.19 (m, 1H), 5.26 (q, \(J = 6.6\) Hz, 1H), 1.62 (d, \(J = 6.6\) Hz, 3H). \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta -58.3\) (s, 3F). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 142.5\) (s), 134.6 (s), 130.0 (s), 128.6 (s), 125.9 (s), 123.9 (s), 121.6 (q, \(J = 255.6\) Hz), 76.2 (q, \(J = 2.7\) Hz), 23.4 (s). IR (neat) \(\nu 2954, 2922, 2845, 1653, 1616, 1559, 1426, 1393, 1261, 1084, 766, 668\) cm\(^{-1}\), HRMS (EI) Calculated for C\(_9\)H\(_7\)F\(_3\)ClO \(224.0216\), Found [M]+ 224.0224.

Following procedure B, (4-(trifluoromethoxy)butyl)benzene was obtained as colourless oil (related to Scheme 3). (83.2 mg, 76%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.36 - 7.12\) (m, 5H), 3.96 (t, \(J = 5.5\) Hz, 2H), 2.65 (t, \(J = 6.5\) Hz, 2H), 1.76 - 1.68 (m, 4H). \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta -60.7\) (s, 3F). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 141.7\) (s), 128.41 (s), 128.39 (s), 126.0 (s), 121.7 (q, \(J = 253.6\) Hz), 67.3 (q, \(J = 3.1\) Hz),
Following procedure B, 1-bromo-4-(3-(trifluoromethoxy)propyl)benzene (Kanie et al., 2000) was obtained as colourless oil (related to Scheme 3). (116.9 mg, 83%). ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 3.95 (t, J = 6.2 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 2.04 – 1.92 (m, 2H). ¹⁹F NMR (376 MHz, CDCl₃) δ -60.7 (s, 3F).

Following procedure B, 1-(trifluoromethoxy)tetradecane was obtained as colourless oil (related to Scheme 3). (114.3 mg, 81%). ¹H NMR (400 MHz, CDCl₃) δ 3.95 (t, J = 6.6 Hz, 2H), 1.73 – 1.63 (m, 2H), 1.41 – 1.22 (m, 22H), 0.88 (t, J = 6.8 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -60.7 (s, 3F). ¹³C NMR (101 MHz, CDCl₃) δ 121.7 (q, J = 253.6 Hz), 67.5 (q, J = 3.1 Hz), 31.9 (s), 29.7 (s), 29.65 (s), 29.62 (s), 29.5 (s), 29.44 (s), 29.36 (s), 29.1 (s), 28.7 (s), 25.4 (s), 22.7 (s), 14.1 (s). IR (neat) ν 2926, 2845, 1652, 1635, 1616, 1582, 1428, 1393, 1262, 1083, 855, 766, 668 cm⁻¹. HRMS (EI) Calculated for C₁₄H₂₆F₃O 282.2171, Found [M⁺] 282.2178.

Following procedure B, 9-(trifluoromethoxy)nonyl 4-methylbenzenesulfonate was obtained as colourless oil (related to Scheme 3). (132.1 mg, 69%). ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 4.01 (t, J = 6.5 Hz, 2H), 3.93 (t, J = 6.5 Hz, 2H), 2.44 (s, 3H), 1.69 – 1.58 (m, 4H), 1.39 – 1.18 (m, 10H). ¹⁹F NMR (376 MHz, CDCl₃) δ -60.7 (s, 3F). ¹³C NMR (101 MHz, CDCl₃) δ 144.6 (s), 133.2 (s), 129.8 (s), 127.9 (s), 121.7 (q, J = 253.6 Hz), 70.6 (s), 67.4 (q, J = 3.1 Hz), 29.1 (s), 28.9 (s), 28.77 (s), 28.76 (s), 28.6 (s), 25.34 (s), 25.26 (s), 21.6 (s). IR (neat) ν 2932, 2859, 1599, 1466, 1362, 1274, 1177, 1139, 1098, 1038, 959, 815, 766, 664, 555 cm⁻¹. HRMS (ESI) Calcd for C₁₈H₂₉F₃NO₂S [M+NH₄]⁺: 400.1757, Found: 400.1759.

Following procedure B, 11-(trifluoromethoxy)undec-1-ene as colourless oil (related to Scheme 3). (96.6 mg, 81%). ¹H NMR (400 MHz, CDCl₃) δ 5.81 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (d, J = 17.2 Hz, 1H), 4.93 (d, J = 10.2 Hz, 1H), 3.95 (t, J = 6.6 Hz, 2H), 2.04 (q, J = 6.9 Hz, 2H), 1.77 – 1.56 (m, 2H), 1.43 – 1.33 (m, 4H), 1.33 – 1.23 (m, 8H). ¹⁹F NMR (376 MHz, CDCl₃) δ -60.7 (s, 3F). ¹³C NMR (101 MHz, CDCl₃) δ 139.2 (s), 121.7 (q, J = 253.6 Hz), 114.1 (s), 67.5 (q, J = 3.0 Hz), 33.8 (s), 29.38 (s), 29.35 (s), 29.1 (s), 29.0 (s), 28.9 (s), 28.7 (s), 25.4 (s). IR (neat) ν 3077, 2927, 2856, 1641, 1466, 1408, 1262, 1142, 1023, 910, 804, 724, 699 cm⁻¹. HRMS (EI) Calculated for C₁₂H₂₁F₃O 238.1544, Found [M⁺] 238.1545.
Following procedure B, 2,6-dimethyl-8-(trifluoromethoxy)oct-2-ene (Marrec et al., 2010) was obtained as colourless oil (related to Scheme 3). (60.6 mg, 54%). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.13 – 5.05 (m, 1H), 4.07 – 3.92 (m, 2H), 2.13 – 1.88 (m, 2H), 1.79 – 1.71 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.56 – 1.11 (m, 4H), 0.92 (d, $J = 6.6$ Hz, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) δ -60.8 (s, 3F).

![3g](image)

Following procedure B, 4-(4-(trifluoromethoxy)butyl)pyridine (Liu et al., 2015) was obtained as yellow oil (related to Scheme 3). (60.3 mg, 55%). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.50 (d, $J = 6.0$ Hz, 2H), 7.12 (d, $J = 5.9$ Hz, 2H), 3.97 (t, $J = 5.8$ Hz, 2H), 2.65 (t, $J = 7.2$ Hz, 2H), 1.81 – 1.69 (m, 4H). $^{19}$F NMR (376 MHz, CDCl$_3$) δ -60.8 (s, 3F).

![3h](image)

Following procedure B, 2-(4-(trifluoromethoxy)butyl)thiophene (Jiang et al., 2018) was obtained as colourless oil (related to Scheme 3). (68.3 mg, 61%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.14 (d, $J = 4.7$ Hz, 1H), 6.97 – 6.91 (m, 1H), 6.83 – 6.78 (m, 1H), 3.99 (t, $J = 5.2$ Hz, 2H), 2.89 (t, $J = 6.6$ Hz, 2H), 1.86 – 1.71 (m, 4H). $^{19}$F NMR (376 MHz, CDCl$_3$) δ -60.8 (s, 3F).

![3i](image)

Following procedure B, 1-phenyl-5-((3-(trifluoromethoxy)propyl)thio)-1H-tetrazole was obtained as light yellow oil (related to Scheme 3). (92.7 mg, 58%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.56 – 7.50 (m, 5H), 3.97 (t, $J = 6.1$ Hz, 2H), 3.39 (t, $J = 7.1$ Hz, 2H), 2.02 – 1.88 (m, 2H), 1.88 – 1.73 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 154.1 (s), 133.6 (s), 130.2 (s), 129.8 (s), 121.6 (q, $J = 254.2$ Hz), 66.6 (q, $J = 3.1$ Hz), 32.6 (s), 27.6 (s), 25.5 (s). IR (neat) ν 3067, 2922, 2857, 1597, 1499, 1410, 1273, 1089, 1074, 1051, 761, 712, 695, cm$^{-1}$, HRMS (ESI) Calcd for C$_{12}$H$_{14}$F$_{3}$N$_{4}$O$_{5}$ [M+H]$^+$: 319.0835, Found: 319.0834.

![3j](image)

Following procedure B, 1-(2-(trifluoromethoxy)ethyl)naphthalene was obtained as colourless oil (related to Scheme 3). (51.4 mg, 43%). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, $J = 8.4$ Hz, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.81 (d, $J = 8.1$ Hz, 1H), 7.58 (t, $J = 7.6$ Hz, 1H), 7.53 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 1H), 7.40 (d, $J = 6.9$ Hz, 1H), 4.31 (t, $J = 7.5$ Hz, 2H), 3.51 (t, $J = 7.5$ Hz, 2H). $^{19}$F NMR (376 MHz, CDCl$_3$) δ -60.7 (s, 3F). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 133.9 (s), 132.3 (s), 131.8 (s), 129.0 (s), 127.9 (s), 127.3 (s),
126.5 (s), 125.8 (s), 125.5 (s), 123.0 (s), 121.7 (q, \( J = 254.5 \) Hz), 67.1 (q, \( J = 3.1 \) Hz), 32.4 (s). IR (neat) ν 3065, 2973, 2915, 1511, 1405, 1270, 1139, 1053, 1025, 798, 789, 776, cm\(^{-1}\), HRMS (EI) Calculated for C\(_{13}\)H\(_{11}\)F\(_3\)O 240.0762, Found [M]\(^+\) 240.0770.

Following procedure B, 2,3-dimethoxy-5-methyl-6-(10-(trifluoromethoxy)decyl)cyclohexa-2,5-diene-1,4-dione (Liu et al., 2015) was obtained as red oil (related to Scheme 3). (166.3 mg, 81%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.02 – 3.92 (m, 8H), 2.45 (t, \( J = 7.2 \) Hz, 2H), 2.01 (s, 3H), 1.74 – 1.61 (m, 2H), \( \delta \) 1.45-1.20 (m, 14H). \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \( \delta \) -60.7 (s, 3F).
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