Direct nucleophilic trifluoromethylation of carbonyl compounds by potent greenhouse gas, fluoroform: Improving the reactivity of anionoid trifluoromethyl species in glymes

Takuya Saito¹, Jiandong Wang¹, Etsuko Tokunaga¹, Seiji Tsuzuki² & Norio Shibata¹,3

A simple protocol to overcome the problematic trifluoromethylation of carbonyl compounds by the potent greenhouse gas "HFC-23, fluoroform" with a potassium base is described. Simply the use of glymes as a solvent or an additive dramatically improves the yields of this transformation. Experimental results and DFT calculations suggest that the beneficial effect deals with glyme coordination to the K⁺ to produce [K(polyether)ₙ]⁺ whose diminished Lewis acidity renders the reactive anionoid CF₃ counterion species more 'naked', thereby slowing down its undesirable decomposition to CF₂ and F⁻ and simultaneously increasing its reactivity towards the organic substrate.

There has been remarkable progress recently in the synthetic incorporation of a trifluoromethyl (CF₃) moiety into potential bioactive molecules, prompting the discovery of new pharmaceuticals and agrochemicals¹⁻⁵. Fluoroform (HFC-23, HCF₃, trifluoromethane) is a potent greenhouse gas that is formed as a by-product in huge amounts during the synthesis of poly-tetrafluoroethylene (PTFE) and polyvinylidene difluoride (PVDF) from chlorodifluoromethane (ClCHF₂). Fluoroform has a 11,700-fold higher GWP than carbon dioxide with an atmospheric lifetime of 264 years and is used to a very limited extent as a refrigerant or as a raw material⁶⁻¹⁰. At present, fluoroform abatement techniques involve thermal oxidation, catalytic hydrolysis and plasma destruction, so there are operation and economical limits to transform fluoroform to useful refrigerants or fire extinguishers¹¹⁻¹⁷. HFC-23 is an easily handled, stable and non-toxic trifluoromethyl (CF₃) source¹⁸⁻²⁴. Thus the synthetic use of HCF₃ serving as feedstock for various trifluoromethylations is highly desirable. However, chemoselective and efficient activation of HCF₃ for nucleophilic trifluoromethylation processes, is a long-standing, challenging and intriguing issue in organic chemistry. One of the primary problems in the extensive usage of HCF₃ for trifluoromethylations is the facile decomposition of the CF₃⁻ anion to difluorocarbene (:CF₂) and fluoride (F⁻)¹⁸. This decomposition is probably induced by the strong repulsion between the lone electron pairs on the carbon and fluorine atoms of CF₃⁻ (Fig. 1a). In the presence of alkali (M⁺) and other metal cations, the decomposition to difluorocarbene is particularly favored due to the formation of highly stable fluoride salts, such as MF.

Several strategies have emerged to use HCF₃ for trifluoromethylation via deprotonation with strong organic or inorganic bases¹⁸⁻²⁴. In 1991, Shono and co-workers for the first time reported the trifluoromethylation of carbonyl compounds with fluoroform by electrogenerated bases as well as common bases such as NaH and 'BuOK in DMF¹⁹. Subsequently, Barhdadi, Troupel and Perichon reported the trifluoromethylation of aldehydes with fluoroform by a strong base generated via cathodic reduction of iodobenzene²⁰. Then Nomant and Roques demonstrated use of MeSOCH₂K²¹ and KHMDS²³ in DMF for trifluoromethylation of carbonyl compounds. It

¹Department of Nanopharmaceutical Sciences, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya, 466-5888, Japan. ²Research Center for Computational Design of Advanced Functional Materials, AIST, Tsukuba, Ibaraki, 305-8568, Japan. ³Institute of Advanced Fluorine-Containing Materials, Zhejiang Normal University, 688 Yingbin Avenue, 321004, Jinhua, China. Correspondence and requests for materials should be addressed to N.S. (email: nozshiba@nitech.ac.jp)
should be pointed out that, in all of these original developments, N,N-dimethylformamide (DMF, Me₂NCHO) was used as the solvent. The crucial role of DMF was to stabilize the CF₃⁻ generated on deprotonation of HCF₃ in the form of the hemiaminalate [Me₂NCH(O)CF₃]⁻, which served as a CF₃⁻ “reservoir” in the reaction (Fig. 1b). In 2011, Grushin and co-workers reported the direct cupration of fluoroform with the dialkoxycuprate produced from CuCl and ‘BuOK in a 1:2 ratio to prepare CuCF₃, which since then has been successfully applied to a wide variety of trifluoromethylations. The cupration of fluoroform is governed by a concerted ambiphilic metal-ligand activation (AMLA) mechanism rather than simple deprotonation to give CF₃⁻ and/or difluorocarbene intermediates. The important dual effect of the alkali-metal counterion, which would slowly decompose CuCF₃ via α-fluoride elimination but also provides electrophilic assistance for the CF₃H cupration, was demonstrated by adding stoichiometric amounts of 18-crown-6 or [2.2.2]crypt and (crypt-222) before and after the cupration, in order to diminish the electrophilicity of alkali-metal cation. While the CuCF₃ is stable, its direct synthesis from HCF₃ requires an amide solvent, such as DMF, DMA, and NMP.

The first DMF-free trifluoromethylation with HCF₃ was reported by Langlois and co-workers in 2000. Although a catalytic amount of DMF was still needed for trifluoromethylation of carbonyl compounds with HCF₃/N(TMS)₃/[‘Bu₄N][Ph₃SiF₂] or Me₄NF/DMF, the trifluoromethylation of dioctyl disulfide was successfully carried out in pure THF (66% yield). In 2012, Prakash et al. also reported nucleophilic trifluoromethylations of Si, B, S, and C centers by HCF₃ using potassium hexamethyldisilazide (KHMDS) in the absence of DMF. The formation of a KCF₃ intermediate followed by CF₃ transfer to the organic substrate was proposed in a DFT study. Simultaneously, we reported that a sterically demanding Schwesinger base, phosphazene P₄-Bu, is effective for pushing inert HCF₃ to nucleophilic trifluoromethylation of carbonyl compounds, disulfides, and arylsulfonyl fluorides in the absence of DMF and any metals. Being metal-free, our HCF₃/P₄-Bu system efficiently suppresses the decomposition of CF₃⁻ to difluorocarbene and fluoride, as explained above (Fig. 1c). Very recently, Szymczak and co-workers reported a new type of Lewis acid-CF₃ adducts formed from an alkali metal hydride, HCF₃, and boron-based Lewis acids. Although these are important developments, simple, cost-efficient, and environmentally benign methods are needed to perform trifluoromethylation reactions with HCF₃ on a large scale. We now report a simple protocol for one-step trifluoromethylation of carbonyl compounds with HCF₃ in the presence of ‘BuOK or KHMDS. While being fundamentally similar to the previously reported methods based on deprotonation of HCF₃, our new protocol features a dramatic improvement from performing the reaction in the presence of a suitable amount of polyethers such as glymes (Fig. 1d). A wide variety of ketones, chalcones and aldehydes are nicely converted to the trifluoromethylated carbinols by HCF₃ under the optimized glyme conditions. Cyclic polyethers such as 18-crown-6 and crypt-222 are even more effective. The encapsulation of the K⁺ by acyclic or cyclic polyethers is the key for this transformation, which makes the reactive anionoid CF₃⁻ species more “naked”.

**Results**

Towards an economical and practical method, we intended to use glymes for tuning the Lewis acidity, hardness and steric bulk of the potassium-based counter-cation to CF₃⁻. Glymes, saturated non-cyclic polyethers, are usually less volatile, miscible with water, and less toxic than many other organic solvents. We initiated our investigation with the reaction of benzophenone (1a) and HCF₃ (excess) with ‘BuOK (2.0 equiv) in THF or 1,2-dimethoxyethane (DME) at room temperature (rt) for 6 h (runs 1 and 2, Table 1 and Fig. 2). While a desired 2,2,2-trifluoro-1,1-diphenylethanol-1-ol (2a) was obtained in 52% yield in THF (run 1), a much higher yield of 88% was observed in monoglyme (run 2). This yield (88%) in monoglyme is noticeably higher than in the reported DMF-free reaction employing much more costly KHMDS (71%) and comparable with our ‘Bu-P₄ method (92%). Encouraged by the initial result, we explored the possibility of using diglyme, triglyme and tetraglyme in this reaction. The yields of 2a appeared to increase with the size of the glyme (runs...
Subsequently, several chalcones were transformed to the corresponding products under modified reaction conditions employing KHMDS (2.0 equiv) as the base at −40 °C for 12 hours. (77–91%) under modified reaction conditions using triglyme and potassium to the NO2 group and to the heteroatoms of the substrate. After further brief screenings of the reaction conditions, better yields were also detected for bulky aliphatic-substituted ketones 1q, a noticeable increase in the yield was observed in triglyme. Slightly and 1o at rt. For cyclic diaryl ketones 1p–2a and trifluoromethyl groups, were smoothly converted to corresponding trifluoromethyl carbinols than additives (runs 2 and 4). The 2:1 coordination was also confirmed for tetraglyme/K+ was obtained in toluene 2a (runs 11–16; see Table S1 for more details). In the absence of triglyme, a 32% yield of 2a was obtained. A series of similar experiments. The comparison of the amount of HCF3 was finally examined (runs 4, 17–20). In triglyme and tetraglyme, the desired product was produced quantitatively (99%, runs 4 and 5). By using 1.0 equiv of BuOK in triglyme or tetraglyme, the yields were lower, 64% and 74%, respectively (runs 6 and 7). HMDS bases were also examined in triglyme, and only potassium base was effective (runs 8–10). In order to gain more insight into the importance of coordination of triglyme to the K+, control experiments were conducted (runs 11–16; see Table S1 for more details). In the absence of triglyme, a 32% yield of 2a was obtained in toluene with ‘BuOK. Interestingly, a steady increase in the yield (from 54% to >99%) was observed as the amount of trifluoromethyl carbinols was increased from 1.0 to 4.0 equiv. These results suggested 2:1 coordination of triglyme to K+, furnishing the complex cation [K(triglyme)2]+. While the use of trifluoromethyl (4.0 equiv) in toluene was clearly a good choice for the conditions (run 15), for simplicity we selected monoglyme and triglyme as solvents rather than additives (runs 2 and 4). The 2:1 coordination was also confirmed for tetraglyme/K+, [K(tetraglyme)2]+, in a series of similar experiments. The comparison of the amount of HCF3 was finally examined (runs 4, 17–20). In principle, one equiv of HCF3 was enough for nearly quantitative transformation (runs 4 vs 17), and the slightly lower yield (99% vs 90%) was probably due to the technical issues. Thus, we concluded that one equiv of HCF3 is suitable for this transformation. More details of the optimization of the reaction conditions are shown in Table S1.

The substrate generality of this process in monoglyme or triglyme was next investigated using a variety of ketones, chalcones and aldehydes (Fig. 3). While one equiv of HCF3 is enough for the almost quantitative transformation (run 17, Table 1), we carried out the reaction mainly by using HCF3 in excess for simplicity. A series of diaryl ketones 1a–h with a variety of substituents on the aromatic rings, such as methyl, methoxyl, chloro, bromo and trifluoromethyl groups, were smoothly converted to corresponding trifluoromethyl carbinols 2a–h in good to excellent yield (72–93%) in monoglyme (0.4 M) and in nearly quantitative yield (up to 99%) in triglyme (0.4 M) at rt. For cyclic diaryl ketones 1o and 1p, a noticeable increase in the yield was observed in triglyme. Slightly better yields were also detected for bulky aliphatic-substituted ketones 1q and 1r. As for the nitro-substituted ketone 1i and heteroaryl substrates 1j–n, the transformation was less efficient, possibly due to coordination with potassium to the NO2 group and to the heteroatoms of the substrate. After further brief screenings of the reaction conditions (see Tables S2 and S3), the desired trifluoromethylated products 2i–n were obtained in high yields (77–91%) under modified reaction conditions employing KHMD (2.0 equiv) as the base at −40 °C for 12 hours. Subsequently, several chalcones 1s–w with electron-donating and electron-withdrawing substituents on the aryl ring were also converted to the corresponding products 2s–w in 54–88% yields under such conditions. Aromatic aldehydes were found to be compatible with the reaction conditions using trifluoromethyl ‘BuOK to produce the corresponding products 2x–2ee in 44–80% yields. The diminished yield in some cases might be due to side processes, such as the Cannizaro reaction. Unfortunately, only 6% of product 2f was obtained in the reaction of 1f bearing an enolizable α-proton. To demonstrate the scalability of the method, trifluoromethyl carbinol 2a was synthesized from benzophenone 1a (1.822 g, 10.0 mmol) in 93% isolated yield under the standard triglyme reaction conditions.

The trifluoromethylation of enolizable ketones such as 1f could be improved by reducing the Lewis acidity of the counter cation K+ with more powerful ligands. Tetraglyme and cyclic ethers were further considered. After additional optimization of the reaction conditions (Table S4), 1ff was converted to the desired trifluoromethylated

| run | solvent | base | additive (equiv) | yield (%) | run | solvent | base | additive (equiv) | yield (%) |
|-----|---------|------|-----------------|----------|-----|---------|------|-----------------|----------|
| 1   | THF     | ‘BuOK|                 | 52       | 11  | toluene | ‘BuOK|                | 32       |
| 2   | monoglyme | ‘BuOK|                 | 88       | 12  | toluene | ‘BuOK| triflyme (1.0) | 54       |
| 3   | diglyme | ‘BuOK|                 | 94       | 13  | toluene | ‘BuOK| triflyme (2.0) | 74       |
| 4   | triglyme | ‘BuOK| >99              | 14       | toluene | ‘BuOK| triflyme (3.0) | 86       |
| 5   | tetraglyme | ‘BuOK| >99              | 15       | toluene | ‘BuOK| triflyme (4.0) | >99      |
| 6   | triglyme | ‘BuOK| (1.0 equiv)     | 64       | 16  | toluene | ‘BuOK| triflyme (5.0) | >99      |
| 7   | triglyme | ‘BuOK| (1.0 equiv)     | 74       | 17† | triglyme | ‘BuOK|                | 90       |
| 8   | triglyme | KHMDS |                 | 90       | 18† | triglyme | ‘BuOK|                | 92       |
| 9   | triglyme | LiHMDS |                 | 0        | 19‡ | triglyme | ‘BuOK|                | >99      |
| 10  | triglyme | NaHMDS |                 | 0        | 20³ | triglyme | ‘BuOK|                | >99      |

Table 1: Optimization of reaction conditions of 1a to 2a by HCF3. *1H NMR yield with PhCF3 as internal standard. †HCF3 (1.0 equiv) was used. ‡HCF3 (2.0 equiv) was used. §HCF3 (3.0 equiv) was used. ||HCF3 (6.0 equiv) was used.

Figure 2: Optimization of reaction conditions of 1a to 2a by HCF3.
product 2ff in moderate to good yields, up to 96% depending on ligand used (triglyme, tetraglyme, 18-crown-6, crypt-222; Fig. 4). The yield of 2ff clearly increased with stronger ligation of the K\(^+\) prompting a weakening in its Lewis acidity in the order: [K(triglyme)]\(^+\) > [K(tetraglyme)]\(^+\) > [K(18-crown-6)]\(^+\) > [K(crypt-222)]\(^+\). Substrate generality of enolizable ketones 1 is shown in Fig. 4. These reactions were performed using 18-crown-6/K\(_4\)BuO\(_4\)) in THF at rt. Using THF as the solvent is important (see Table S3) and is discussed below. The strategy of tuning the Lewis acidity of the potassium-based counter-cations enabled the effective trifluoromethylation of enolizable ketones with fluoroform, although the need to use stoichiometric amounts of rather costly 18-crown-6 may limit the applicability of the method on a larger scale.
Discussion

The reactive anionoid CF$_3$ species in the mismatched Lewis acid-base adducts [K(polyethers)$_n$][CF$_3$] with diminished Lewis acidity of the K$^+$ is rather stable, which is good agreement with the experimental observation in our previous report. Namely, the sterically demanding and poorly electrophilic protonated tBuP$_4$ base, [H$_t$BuP$_4$]$^+$, improves the reactivity and stability of the CF$_3^-$ for nucleophilic trifluoromethylation. This observation is in good agreement with the report by Prakash and co-workers that the anionoid CF$_3$ species derived from iPr$_3$SiCF$_3$ in the presence of [K(18-crown-6)]$^+$ is stable enough to be observed by NMR at $-78^\circ$C. In spite of the apparent high degree of iconicity, the bonding between the coordinatively unsaturated and Lewis acidic K$^+$ in [K(18-crown-6)]$^+$ and the CF$_3$ moiety certainly has a covalent component. Grushin and co-workers have reported the existence of the free or naked (uncoordinated) CF$_3^-$ anion with the [K(crypt-222)]$^+$ cation, in which the K$^+$ is caged inside the 3-dimensional host. This ionic complex has been characterized by a combination of methods, including X-ray diffraction, solution NMR, and reactivity toward electrophiles data, as well as labeling, acid-base, and DFT studies.

As [K(polyethers)$_n$][CF$_3$] intermediates are expected to be much more stable than KCF$_3$ (see above), a reaction mechanism in glymes (triglyme or tetraglyme) is proposed as shown in Fig. 5a. First, two molecules of glymes coordinate to tBuOK to form, reversibly, a 2:1 complex of [K(glyme)$_2$][tBuO], followed by deprotonation of HCF$_3$ with the tBuO$^-$ to furnish [K(glyme)$_2$][CF$_3$]. In this complex, the K$^+$ is ligated by the glyme molecules, which reduces its Lewis acidity and, consequently, ability to decompose the CF$_3^-$.

The structures of [K(triglyme)$_2$][CF$_3$] and [K(tetraglyme)$_2$][CF$_3$] were studied by DFT calculations using reported X-ray structural data for [K(triglyme)$_2$][CF$_3$] and [K(tetraglyme)$_2$][CF$_3$]. The four selected minima identified (Fig. 5; see also the Supplementary Information) display coordination of the CF$_3$ to the glyme-ligated K$^+$ through the C or F atoms. This is also the case with the computed structures of KCF$_3$ and [K(18-crown-6)(CF$_3$)], in which K-F contacts were found. A deviation from the tetrahedral geometry is observed in all of the computed structures, featuring longer C-F bonds and distorted F-C-F angles. Without glyme ligands, optimized KCF$_3$ displayed coordination via two of the three F atoms and an overall tighter bonding, as follows from the bond distances.

Figure 5. (a) Reaction mechanism for trifluoromethylation of 1 with HCF$_3$/tBuOK in triglyme and tetraglyme. The optimized structures of (b) [t$_1$-K(triglyme)$_2$][CF$_3$], (c) [t$_1$-K(triglyme)$_2$][CF$_3$] disordered isomer, (d) [t$_1$-K(tetraglyme)$_2$][CF$_3$], (e) [t$_1$-K(tetraglyme)$_2$][CF$_3$] disordered isomer, (f) [K(18-crown-6)]([CF$_3$]), (g) [K(18-crown-6)/THF][CF$_3$] and [K][CF$_3$] complexes obtained by B3LYP/6-311G** level DFT calculations.
presented in Fig. 5. Naturally, the less Lewis acidic K\(^+\) interacts with CF\(_3\)\(^-\) more weakly, which not only inhibits the undesired formation ofKF andCF\(_3\), but also enhances the nucleophilicity of the anionoid CF\(_3\) species toward the organic substrate.

With regard to the beneficial effect ofTHF in the trifluoromethylation of enolizable ketones with HCF\(_3\) in the presence of 18-crown-6 (Fig. 4), we optimized the structure of [K(18-crown-6)(CF\(_3\))] in THF, using the X-data for [K(18-crown-6)(BuO)]\(^{49,52,53}\). This structure \([\eta^2-(K(18-crown-6))(CF_3)]\) (Fig. 5f) also showed the coordination of the CF\(_3\) to the K center via two of the three fluoride atoms. Also, using the X-ray data for [K(18-crown-6)(THF)]\(^{44,54}\), the structure of [K(18-crown-6)(THF)(CF\(_3\))] was computed (Fig. 5g)\(^{45,53}\). The binding energies (\(E_{\text{bind}}\)) for [K(18-crown-6)(BuO)] and [K(18-crown-6)(CF\(_3\))] in THF were computed at \(-26.7\) and \(-24.1\) kJ/mol, respectively\(^{49,53}\). For [K(18-crown-6)(THF)(BuO)] and [K(18-crown-6)(THF)(CF\(_3\))], also in THF, the K-O and K-F interactions were weaker, according to the computed \(E_{\text{bind}}\) values of \(-19.3\) and \(-20.1\) kJ/mol, respectively\(^{49,53}\). We therefore conclude that THF is also capable of serving as a ligand to the potassium in the reaction, thereby additionally diminishing the Lewis acidity of the cation and consequently enhancing both the reactivity of the anionoid CF\(_3\) intermediate and its stability toward fluoride elimination.

In summary, we have developed an advantageous, simple and high-yielding method to trifluoromethylation of ketones, chalcones and aldehydes to the corresponding trifluoromethyl carbinals with HCF\(_3\), and a potassium base in the presence of glymes and/or 18-crown-6. The beneficial event of the polyethers deals with their coordination to the K\(^+\), rendering it less prone to fluoride abstraction from the reactive anionoid CF\(_3\) intermediate. Our data provide complementary evidence for enhanced stability of CF\(_3\)\(^-\) toward fluoride elimination and formation of difluorocarbene (:CF\(_2\)), which is strongly induced by metal-fluorine interactions.

**Methods**

**Trifluoromethylation of acyclic diaryl ketones 1a–1h, cyclic diaryl ketones 1o, 1p and bulky aliphatic-substituted ketones 1q, 1r by using monoglyme or triglyme as solvent in Table 1b (see Supplementary Information, the general synthetic procedure A and B).** The solution of BuOK (45 mg, 0.4 mmol) in dry monoglyme or triglyme (0.5 mL), was cooled in liquid nitrogen followed by adding carbonyl compounds (diaryl ketones 1a–1h, cyclic diaryl ketones 1o, 1p and bulky aliphatic-substituted ketones 1q, 1r, 0.2 mmol) under argon atmosphere. After being charged with HCF\(_3\) (1.0 equiv or excess) by cooling at the same temperature under vacuum, the resulting mixture was allowed to warm to room temperature. Then the reaction mixture was stirred at rt for 6 h monitored by TLC, quenched by addition of sat. NH\(_4\)Cl aq., extracted with Et\(_2\)O, dried over with Na\(_2\)SO\(_4\) and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (n-hexane/ethyl acetate) to give corresponding α-trifluoromethyl alcohols 2a–2h, 2o–2r in good to high yields.

**Trifluoromethylation of nitro group substituted diaryl ketones 1i, heteroaryl groups substituted ketones 1j–1n and chalcones 1s–w, aryl aldehydes 1x–1z and 1aa-1ee by using triglyme as solvent in Table 1b (see Supplementary Information, the general synthetic procedure C and D).** The solution of BuOK (45 mg, 0.4 mmol) or KHMDMS (80 mg, 0.4 mmol) in dry triglyme (0.5 mL), was cooled in liquid nitrogen followed by adding carbonyl compounds (enolizable ketones 1j–1n and chalcones 1s–w, aryl aldehydes 1x–1z and 1aa-1ee by using triglyme as solvent in Table 1b (see Supplementary Information, the general synthetic procedure C and D). The solution of BuOK (45 mg, 0.4 mmol) or KHMDMS (80 mg, 0.4 mmol) in dry triglyme (0.5 mL) was charged with HCF\(_3\) by cooling at the same temperature under vacuum. Then the solution was allowed to warm to room temperature. After being stirred for 6–12 h monitoring by TLC upon the completion of the reaction, the resulting mixture was quenched with sat. NH\(_4\)Cl aq., extracted with Et\(_2\)O, dried over with Na\(_2\)SO\(_4\) and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (n-hexane/ethyl acetate) to give corresponding α-trifluoromethyl alcohols 2i–n and 2s–2z and 2aa-2ee in good yields.

**Trifluoromethylation of enolizable ketones 1ff–1kk in the presence of 18-crown-6 in Fig. 4 (see Supplementary Information, the general synthetic procedure E).** The solution of BuOK (67 mg, 0.6 mmol), 18-crown-6 (159 mg, 0.6 mmol) in THF (2.0 mL), was cooled in liquid nitrogen followed by adding carbonyl compounds (enolizable ketones 1ff–1kk, 0.2 mmol) under argon atmosphere. Then the resulting mixture was charged with HCF\(_3\) by cooling at the same temperature under vacuum. Then the solution was allowed to warm to room temperature. After being stirred for 6–12 h monitoring by TLC upon the completion of the reaction, the resulting mixture was quenched with sat. NH\(_4\)Cl aq., extracted with Et\(_2\)O, dried over with Na\(_2\)SO\(_4\) and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (n-hexane/ethyl acetate) to give corresponding α-trifluoromethyl alcohols 2ff–2kk in good yields.

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Author Contributions
T.S. and J.W. contributed equally. T.S., J.W., E.T. conducted and analysed the experiments and compounds. S.T. conducted the DFT calculations. N.S. designed, directed the project, and wrote the manuscript with contributions from T.S., J.W., E.T. and S.T. All authors contributed to discussions.

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