JOC The Journal of Organic Chemistry

Article

Copper-Catalyzed Aminotrifluoromethylation of Unactivated Alkenes with TMSCF3: Construction of Trifluoromethylated Azaheterocycles

Jin-Shun Lin, Xiang-Geng Liu, Xiao-Long Zhu, Bin Tan, and Xin-Yuan Liu

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo5012619 • Publication Date (Web): 08 Jul 2014

Just Accepted

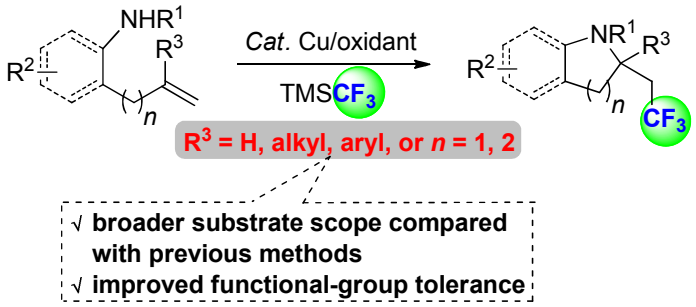
The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Copper-Catalyzed Aminotrifluoromethylation of Unactivated Alkenes with $TMSCF_3$: Construction of Trifluoromethylated Azaheterocycles

Jin-Shun Lin, Xiang-Geng Liu, Xiao-Long Zhu, Bin Tan,* and Xin-Yuan Liu*

Department of Chemistry, South University of Science and Technology of China, Shenzhen, 518055, P. R. China

*E-mail: liuxy3@sustc.edu.cn; tanb@sustc.edu.cn



ABSTRACT: The first example of a copper(I)-catalyzed intramolecular aminotrifluoromethylation of unactivated alkenes using $TMSCF_3$ as the CF_3 source is described. A broad range of electronically and structurally varied substrates undergo convenient and step-economical transformations for the concurrent construction of five or six-membered ring and a C-CF_3 bond toward different types of trifluoromethyl azaheterocycles. The methodology not only circumvents use of expensive electrophilic CF_3 reagents or the photoredox strategy but also expands the substrate scope that is difficult to access by the existed methods. Mechanistic studies are

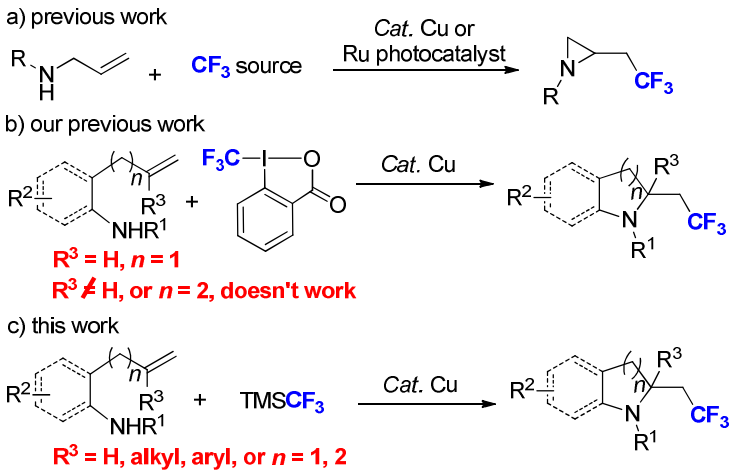
conducted and a plausible mechanism is proposed.

INTRODUCTION

Trifluoromethyl(CF_3)-containing azaheterocycles have been recognized as important building blocks in many bioactive compounds because the presence of a CF_3 group in such biologically active compounds enhances the lipophilicity, metabolic stability, and bioavailability.[1] Toward this end, much attention has been recently paid to the development of new methods for the synthesis of trifluoromethyl azaheterocycles.[2] From the point of high-atom and step economy, intramolecular difunctionalization-type trifluoromethylation of unactivated alkenes with nitrogen-based nucleophiles (i.e. aminotrifluoromethylation) has been proven as an attractive but under-exploited strategy for providing easy access to structurally diverse three or five-membered CF_3-containing compounds.[3,4] In this context, Cho and co-workers have developed elegant visible-light-induced intramolecular trifluoromethylation of terminal allylic amines in the presence of Ru complex as a photocatalyst to produce CF_3-containing aziridines (Scheme 1a).[3a] Very recently, Sodeoka[3b] and our group[4a] have independently reported intramolecular aminotrifluoromethylation of alkenes with diverse nitrogen-based nucleophiles in the presence of copper catalyst with electrophilic Togni's reagent as the CF_3 source to give trifluoromethylated aziridines, pyrrolidines or indolines (Scheme 1a and 1b). Although significant progresses have been made, these reactions have encountered several major restrictions. For example, the aminotrifluoromethylation of alkenes is

almost limited to not only monosubstituted terminal alkenes but also the only formation of three or five-membered azaheterocycles, thus limiting their synthetic value and less applicable to large-scale synthesis. It is noteworthy that recent work from our laboratory has demonstrated that the development of catalytic method that led to the six-membered CF_3-containing azaheterocycles with Togni's reagent remains a formidable challenge[4a] and while the overall transformation can be achieved in a stepwise fashion.[5] Therefore, the development of a convenient and step-economical strategy for expanding aminotrifluoromethylation of unactivated alkenes associated with the aforementioned challenges is still highly desirable.

Scheme 1. Transition-Metal-Catalyzed Aminotrifluoromethylation of Unactivated Alkenes.



Recently, Ruppert-Prakash reagent ($TMSCF_3$), which is commercially available compound, has been widely used as CF_3 source in organic synthesis to construct CF_3-containing diverse molecules.[6-8] In this area, we have also developed a mild and general $PhI(OAc)_2$-mediated direct carbotrifluoromethylation of activated alkenes

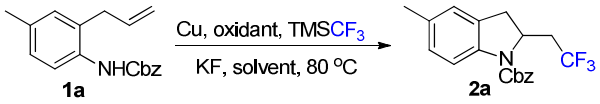
using $TMSCF_3$ under metal-free conditions, thus offering a complementary method to transition-metal-catalyzed methods.[4b] However, to our knowledge, there has been no report on the direct difunctionalization of unactivated alkenes, such as aminotrifluoromethylation, with nucleophilic $TMSCF_3$ as the CF_3 source. In the light of all of those findings[6-8] and as a part of our continued interest in the area of trifluoromethylation, herein, we further report the Cu(I)-catalyzed oxidative aminotrifluoromethylation of unactivated alkenes using nucleophilic $TMSCF_3$ as the CF_3 source (Scheme 1c), which expands the scope and efficiency of aminotrifluoromethylation and avoids the use of the expensive electrophilic CF_3 reagent or photocatalysts. Significantly, this efficient approach would provide a useful alternative to the known aminotrifluoromethylation methods, and would prove especially valuable for the simultaneous formation of five or six-membered ring and a C-CF_3 bond, which should facilitate the development of late-stage introduction of versatile CF_3-containing azaheterocycle moieties into complex scaffolds for diversity-oriented synthetic strategies.

RESULTS AND DISCCUSION

Our prior observation[4a] that substrates bearing *gem*-disubstituted alkenes or longer chain groups have displayed less or no efficiency in the presence of electrophilic CF_3 reagent as shown in Scheme 1b, and the possibility that nucleophilic $TMSCF_3$ could be used as CF_3 source in the presence of appropriate oxidant for the aminotrifluoromethylation of simple alkenes inspired by the high reactivity of such

reagent toward unactivated alkenes[8] and other transformations,[7] led us to further expand the substrate scope of such reaction. To do so and further improve the product yield in our previous report,[4a] we initiated these investigations by examining the reaction of *N*-benzyloxycarbonyl-2-allyl aniline **1a** by using $TMSCF_3$ as the CF_3 source in the present of CuI (25 mol %), $AgNO_3$ as the oxidant and KF as the base or initiator. We found that CuI could catalyze this reaction in DMF at 80 ^oC for 16 h to form the desired product **2a** in 58% yield (Table 1, entry 1). Encouraged by this result, we turned our attention to screen different copper catalysts, and $Cu(CH_3CN)_4BF_4$ was found to provide **2a** in 62% yield (Table 1, entries 1-7). The product yield could be further improved to 68% by reducing the catalyst loadings of $Cu(CH_3CN)_4BF_4$ from 25 to 15 mol % (Table 1, entry 8). Among different organic solvents examined, it turned out that the reaction with DMF gave the best results (Table 1, entries 8-13). Further investigation revealed that $AgNO_3$ behaved as the most efficient oxidant among the screened oxidants (Table 1, entries 14-16); and the negative result was obtained by lowering the amount of $AgNO_3$ (Table 1, entry 17). In contrast, control experiments demonstrated that the reaction did not occur in the presence of Cu catalyst or $AgNO_3$ alone (Table 1, entries 18 and 19), unambiguously revealing that copper catalyst with the combination of $AgNO_3$ is essential for this reaction. It should be noted that the product yield was remarkably improved under the current system as compared to our previous result.[4a]

Table 1. Screening of the Reaction Conditions[a]



entry	Cu	oxidant	solvent	time (h)	yield (%)[b]
1	CuI	$AgNO_3$	DMF	16	58
2	CuBr	$AgNO_3$	DMF	16	35
3	CuTc[c]	$AgNO_3$	DMF	16	60
4	$CuOTf0.5C_6H_6$	$AgNO_3$	DMF	16	55
5	$Cu(CH_3CN)_4BF_4$	$AgNO_3$	DMF	16	62
6	$Cu(OTf)_2$	$AgNO_3$	DMF	16	--[d]
7	$Cu(CH_3CN)_4PF_6$	$AgNO_3$	DMF	16	61
8	$Cu(CH_3CN)_4BF_4$	$AgNO_3$	DMF	16	68
9	$Cu(CH_3CN)_4BF_4$	$AgNO_3$	DMSO	4	65
10	$Cu(CH_3CN)_4BF_4$	$AgNO_3$	NMP	8	63
11	$Cu(CH_3CN)_4BF_4$	$AgNO_3$	EtOAc	16	--[d]
12	$Cu(CH_3CN)_4BF_4$	$AgNO_3$	CH_3OH	16	--[d]
13	$Cu(CH_3CN)_4BF_4$	$AgNO_3$	dioxane	16	--[d]
14	$Cu(CH_3CN)_4BF_4$	AgF	DMF	16	14
15	$Cu(CH_3CN)_4BF_4$	Ag_2CO_3	DMF	16	--[d]
16	$Cu(CH_3CN)_4BF_4$	$PhI(OAc)_2$	DMF	16	9

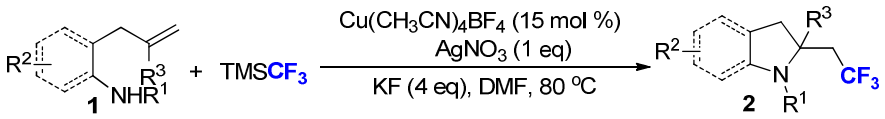
17[e]	$Cu(CH_3CN)_4BF_4$	$AgNO_3$	DMF	16	38
18	$Cu(CH_3CN)_4BF_4$	--	DMF	16	--[d]
19	--	$AgNO_3$	DMF	16	--[d]

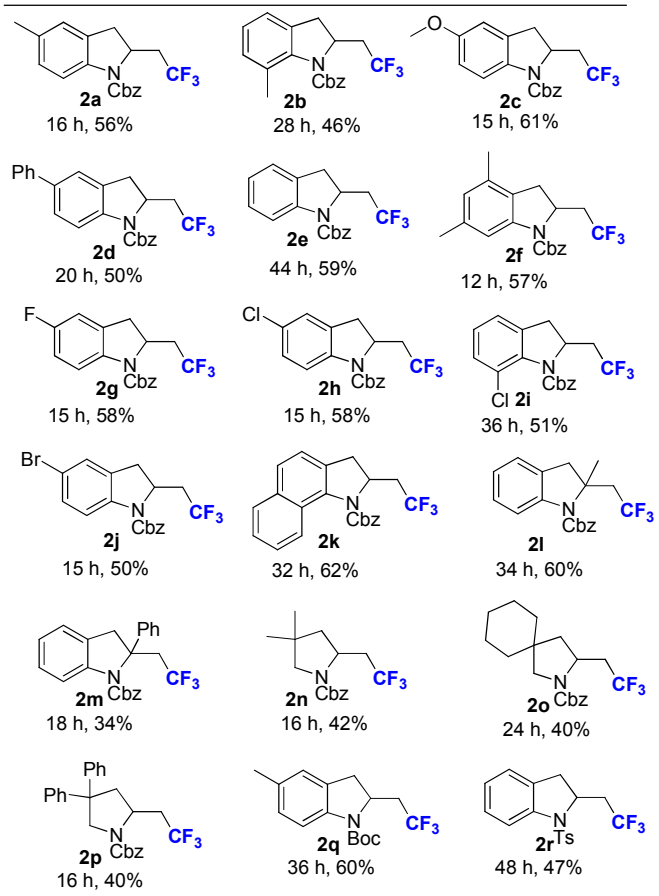
[a] Reaction conditions (unless otherwise mentioned): **1a** (0.05 mmol), solvent (0.3 mL), $TMSCF_3$ (4.0 eq), oxidant (1.0 eq), KF (4.0 eq), Cu catalyst loading (entries 1-7: 25 mol %, entries 8-18: 15 mol %), under argon. [b] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [c] CuTc = copper(I)-thiophene-2-carboxylate. [d] A trace amount of product was observed. [e] 0.5 eq of $AgNO_3$ was used. Cbz = carbobenzyloxy.

With an optimized set of reaction conditions in hand, we next turned our attention to assessing the scope of aminotrifluoromethylation of alkenes. As can be seen in Table 2, regardless of the position and nature of the substituent, various 2-allyl aniline derivatives reacted efficiently with $TMSCF_3$ to afford the desired products in moderate to good yields. Reactions of 2-allyl aniline derivatives **1a-1f** having electron-donating and -neutral substituents on the aryl ring at the different positions worked well, furnishing **2a-2f** in 46-61% yields. Notably, electron-withdrawing substituents including F, Cl and Br at the different aryl positions were proved to be well-tolerated under the standard reaction conditions, giving the corresponding products **2g-2j** in good yields. These results are significant since aryl halides are reactive and, thus, are difficult to be retained in many copper-catalyzed trifluoromethylation reactions,[7d,9] which offer opportunities for further modifications at these positions.[10] Interestingly, a good yield of **2k** containing three-rings was

achieved when exchanging the phenyl moiety for a naphthyl group under similar reaction conditions. It is more encouraging to note that products that are more difficult to prepare via Cu(I)-catalyzed aminotrifluoromethylation with Togni's reagent,[4a] such as **1l** and **1m** that contain *gem*-disubstituted alkenes bearing methyl or phenyl group, can also be accessed by using this method. Furthermore, the protocol could be extended to the reaction of pentenylcarbamate **1n**-**1p** for the synthesis of highly substituted trifluoromethylated pyrrolidine **2n**-**2p**; and the product yields were relatively insensitive to the nature of the substitution on the carbon backbone. Most importantly, a variety of substituents on the nitrogen atom including Boc and Ts are compatible under the reaction conditions, giving the desired products **2q** and **2r** in 60 and 47% yields, respectively.

Table 2. Aminotrifluoromethylation of Alkenes to Form Five-Membered Ring[a,b]



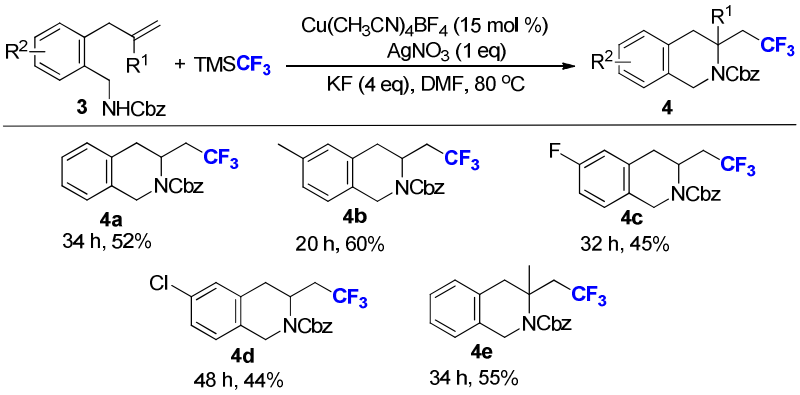


[a] Reaction conditions (Unless otherwise mentioned): **1** (0.5 mmol), $TMSCF_3$ (4.0 eq), KF (4.0 eq), $Cu(CH_3CN)_4BF_4$ (15 mol %), $AgNO_3$ (1.0 eq) in DMF under argon. [b] Yield based on the starting alkene. Boc = *tert*-butyloxycarbonyl. Ts = *p*-toluenesulfonyl.

To further investigate the scope of application, we tested the use of more challenging 2-allyl benzylamine derivatives as substrates, since the expected six-membered products could not also be obtained with the previous Cu-catalyzed aminotrifluoromethylation with Togni's reagent.[4a] We are delighted to find that, when **3a** was employed under the current reaction system in the presence of $TMSCF_3$, the desired trifluoromethylated product **4a** with the formation of six-membered ring was obtained in 52% yield. With regard to the scope of such substrates, monosubstituted and *gem*-disubstituted alkenes bearing electron-donating and electron-withdrawing

groups on the aryl ring also proved to be suitable substrates (**3b-3e**), furnishing the corresponding products **4b-4e** in 44-60% yields. Given the broad substrate scope, this approach is clearly complementary to the previous metal-catalyzed and photoredox trifluoromethylated methods.[3,4a]

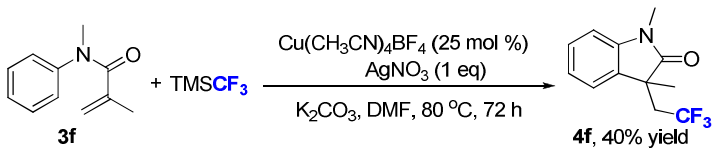
Table 3. Aminotrifluoromethylation of Alkenes to Form Six-Membered Ring[a,b]



[a] Reaction conditions (Unless otherwise mentioned): **1** (0.5 mmol), $TMSCF_3$ (4.0 eq), KF (4.0 eq), $Cu(CH_3CN)_4BF_4$ (15 mol %), $AgNO_3$ (1.0 eq) in DMF under argon. [b] Yield based on the starting alkene.

It is interesting to note that the current protocol in the presence of $TMSCF_3$ could be extended to direct intramolecular carbotrifluoromethylation of alkenes. Thus, our preliminary result showed that, under the similar conditions to those of aminotrifluoromethylation reaction detailed above, the reaction of *N*-methyl-*N*-phenylacrylamide **3f** gave trifluoromethylated product **4f** in 40% yield (Scheme 2).

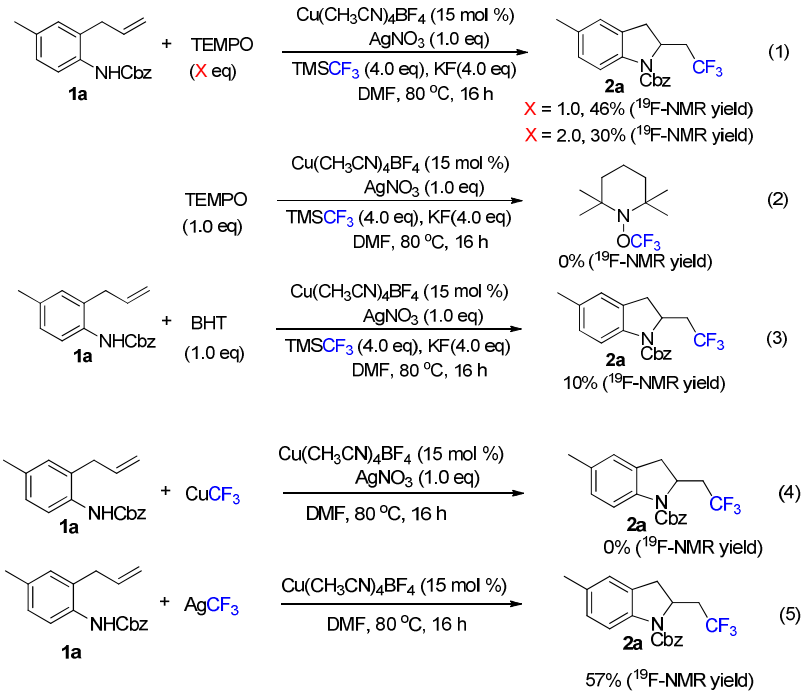
Scheme 2. Direct Intramolecular Carbotrifluoromethylation of Alkenes



Preliminary mechanistic investigations on this reaction have been carried out (Scheme 3). Firstly, under the standard conditions but with the addition of 1.0 or 2.0 equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the yield of the reaction between **1a** and $TMSCF_3$ was significantly dropped (eq. 1). However, neither an allylic-TEMPO adduct nor a TEMPO-CF_3 adduct were observed, as judged by ^{19}F and ^{1}H NMR analysis of the crude product. It is noteworthy that no TEMPO-CF_3 adduct was also observed in the reaction mixture of $TMSCF_3$, KF, $AgNO_3$, $Cu(CH_3CN)_4BF_4$ (15 mol %) and TEMPO in the absence of **1a** (eq. 2). Collectively, these results reveal that the CF_3 radical or the allylic radical is unlikely involved as the reactive species under the current reaction conditions, which is in agreement with the observation involving oxidative trifluoromethylation of unactivated alkenes with $TMSCF_3$ reported by Qing and co-workers.[8a] Moreover, the reaction was found to be mostly inhibited by 2,6-di-*tert*-butyl-4-methylphenol (BHT) under the standard conditions (eq. 3). These control experiments possibly suggest that the involvement of in situ generated $CuCF_3$ or $AgCF_3$ intermediate followed by a single electron transfer (SET) radical pathway is possible, also based on recent reports involving such reagents for the trifluoromethylation reactions with SET pathway.[7g,7k,11] To further gain some insights about this hypothesis, under the standard reaction conditions we examined the aminotrifluoromethylation reaction of **1a** with $CuCF_3$ or $AgCF_3$ in situ generated from $TMSCF_3$, $Cu(CH_3CN)_4BF_4$ or $AgNO_3$, and KF according to the reported procedures.[7g,7i] Interestingly, no detectable amounts of the product **2a** was observed with $CuCF_3$ as reagent (eq. 4), whereas the product **2a** was observed with

$AgCF_3$ as reagent with 57% yield determined by ^{19}F NMR (eq. 5). These observations clearly indicated that the reaction should proceed with the intermediacy of $AgCF_3$, which is presumably in situ generated from $AgNO_3$ and $TMSCF_3$ assisted with KF.

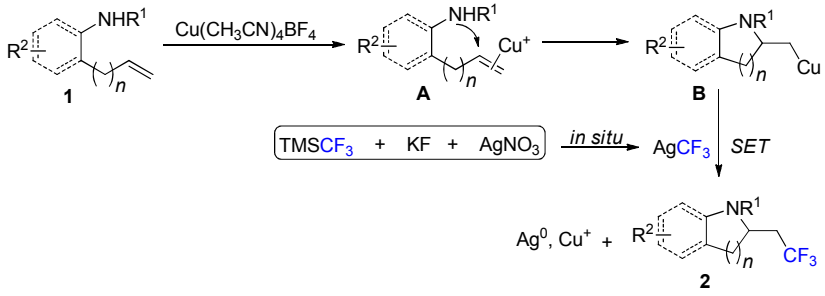
Scheme 3. Mechanistic Studies



On the basis of the above experimental observations and the previous investigation on copper-catalyzed hydroamination or aminotrifluoromethylation of alkenes,[4,8,11] a plausible mechanism for our methodology was proposed (Scheme 4), which first involves outer-sphere attack of the nitrogen atom on the Cu(I)-complexes alkene of **A** to generate the neutral alkyl-copper complex **B**.[12] Second, the reaction of $TMSCF_3$, $AgNO_3$ and KF in situ generates $AgCF_3$, which then reacts with intermediate **B** via single-electron transfer[13] to produce the final product **2** and regenerate the cationic copper catalyst and silver. It is worth noting that a silver mirror was observed at the

end of most of the aminotrifluoromethylation reactions. On the other hand, an alternative catalytic mechanism, which proceeds by the formation of α-CF_3-alkyl radical intermediate initiated from alkene[8] followed by the subsequent coupling of this intermediate and the carbamate nitrogen atom,[4a] cannot be ruled out at the present stage. Therefore, rigorous investigations are necessary to unambiguously elucidate the detailed mechanism.

Scheme 4. Proposed Mechanism for the Aminotrofluoromethylation Reaction of Unactivated Alkenes.



CONCLUSION

In summary, we have demonstrated the first example of a copper(I)-catalyzed aminotrifluoromethylation of unactivated alkenes with nucleophilic $TMSCF_3$ as the CF_3 source. The methodology furnishes a diverse collection of synthetically valuable trifluoromethylated azoheterocyles under mild reaction conditions. Furthermore, it has significant advantages over the conventional aminotrifluoromethylation, because this approach not only circumvents the use of expensive electrophilic CF_3 reagents or the photoredox strategy, but also expands the substrate scope that is difficult to access by known methods, thus reflecting the synthetic utility of this method in medicinal

chemistry and materials science related fields.

Experimental Section

General information. All reactions were carried out under Ar using Schlenk techniques. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. KF was activated by mufflefurnace in high temperature. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 GF254 plates. Flash column chromatography was performed using silica gel (60, particle size 0.040-0.063 mm). Visualization on TLC was achieved by use of UV light (254 nm) or iodine. NMR spectra were recorded on a 400 MHz spectrometer for ^{1}H NMR, 100 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR ($CFCl_3$ as an external reference (0 ppm)) in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in ppm and coupling constants are given in Hz. Data for ^{1}H NMR are recorded as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quarter; m, multiplet; br, broad), coupling constant (Hz), integration. High-resolution mass spectrometry (HRMS) was conducted on a TOF mass spectrometer.

General synthesis of carbamate substrates:

Carbamate substrates **1a**,[4a] **1c**,[14] **1e**,[14] **1g**,[14] **1h**[4a] were synthesized according to the procedures previously reported. The 2-allylaniline substrate[15] was synthesized according to the procedures previously reported.

*Synthesis of substrates **1b**, **1f**, **1i**, **1k** and **1j**.*

To a stirred solution of 2-allylaniline substrates (2.0 mmol) and pyridine (0.3 mL, 4.0 mmol) in CH_2Cl_2 (8 mL) was added CbzCl (0.3 mL, 2.4 mmol) in an ice-water bath, and the solution was left to warm to room temperature and stirred for additional 4-8 hours. After complete conversion (monitored by TLC), the reaction was quenched with H_2O (10 mL), and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were brined, dried (Na_2SO_4), concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 80:1-30:1) to give **1**.

*Benzyl (2-allyl-6-methylphenyl)carbamate (**1b**)*. 450 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.07 (m, 8H), 6.28 (s, 1H), 5.93-5.89 (m, 1H), 5.21 (s, 2H), 5.06 (d, J = 9.6 Hz, 1H), 5.00 (d, J = 17.2 Hz, 1H), 3.37 (d, J = 5.6 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 136.8, 136.6, 136.5, 133.6, 129.1, 128.6, 128.2, 127.7, 127.5, 116.0, 67.1, 36.9, 18.4; HRMS (ESI) m/z calcd. for $C_{18}H_{19}NNaO_2$ $[M+Na]^+$ 304.1313, found 304.1309.

*Benzyl (2-allyl-3,5-dimethylphenyl)carbamate (**1f**)*. 461 mg, 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.37 (m, 6H), 6.87 (s, 1H), 6.63 (br s, 1H), 6.00-5.91 (m, 1H), 5.25 (s, 2H), 5.10 (d, J = 10.4 Hz, 1H), 4.94 (d, J = 17.2 Hz, 1H), 3.38 (d, J = 4.8 Hz, 2H), 2.36 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 136.9, 136.5, 136.3, 135.8, 135.0, 128.5, 128.2, 128.2, 127.6, 125.1, 121.2, 115.6, 66.9, 31.5, 21.1, 19.9; HRMS (ESI) m/z calcd. for $C_{19}H_{22}NO_2$ $[M+H]^+$ 296.1651, found 296.1643.

*Benzyl (2-allyl-6-chlorophenyl)carbamate (**1i**)*. 453 mg, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.17 (m, 8H), 6.41 (br s, 1H), 5.96 -5.87 (m, 1H), 5.28 (m, 4H),

3.41-3.33 (m, 2H); HRMS (ESI) m/z calcd. for $C_{17}H_{16}ClNNaO_2$ $[M+Na]^+$ 324.0767, found 324.0763.

*Benzyl (2-allyl-4-bromophenyl)carbamate (**1j**).* 609 mg, 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.48-7.33 (m, 6H), 7.30 (d, *J* = 2.4 Hz, 1H), 6.66 (br s, 1H), 5.91 (ddt, *J* = 17.2, 10.0, 6.0 Hz, 1H), 5.20-5.17 (m, 3H), 5.06 (dd, *J* = 17.2, 1.6 Hz, 1H), 3.31 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 136.0, 135.2, 134.8, 132.8, 131.2, 130.4, 128.7, 128.5, 128.8, 123.5, 117.5, 117.2, 67.2, 36.1; HRMS (ESI) m/z calcd. for $C_{17}H_{16}BrNNaO_2$ $[M+Na]^+$ 368.0262, found 368.0257.

*Benzyl (2-allylnaphthalen-1-yl)carbamate (**1k**).* 546 mg, 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.55-7.09 (m, 8H), 6.66 (s, 1H), 6.01-5.97 (m, 1H), 5.30-5.05 (m, 4H), 3.56 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 136.3, 136.2, 134.8, 133.1, 131.2, 129.8, 128.6, 128.4, 128.1, 128.0, 127.8, 126.7, 125.6, 122.7, 116.2, 67.3, 36.7; HRMS (ESI) m/z calcd. for $C_{21}H_{20}NO_2$ $[M+H]^+$ 318.1494, found 318.1488.

*Synthesis of carbamate substrate **1d**.* To a solution of **1j** (346.2 mg, 1.0 mmol), phenylboronic acid (183.0 mg, 1.5 mmol), K_2CO_3 (414.0 mg, 3.0 mmol), and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (X-Phos, 9.5 mg, 0.02 mmol) in CH_3CN/H_2O (6 mL/4 mL) was added $Pd(OAc)_2$ (2.3 mg 0.01 mmol). The flask and its contents were put under reduced pressure and then backfilled with argon three times. The mixture was stirred at 60 °C for 12 h under argon atmosphere, then cooled, and extracted with CH_2Cl_2, and the combined organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed *in vacuo* to afford a crude product,

which was purified by flash chromatography (eluent: petroleum ether/EtOAc = 60:1) to **1d** as a white solid.

*Benzyl (3-allyl-[1,1'-biphenyl]-4-yl)carbamate (**1d**).* 268 mg, 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.61-7.34 (m, 12H), 6.75 (br s, 1H), δ 6.01 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.25 (s, 2H), 5.20 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.12 (dd, *J* = 17.2, 1.2 Hz, 1H), 3.44 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 140.6, 137.4, 136.2, 135.7, 135.4, 128.9, 128.8, 128.7, 128.4, 127.2, 127.0, 126.2, 122.2, 117.1, 67.1, 36.7; HRMS (ESI) m/z calcd. for $C_{23}H_{22}NO_2$ $[M+H]^+$ 344.1651, found 344.1645.

*Synthesis of carbamate substrates **1l** and **1m**.* The 2-allylaniline substrate[16] was synthesized according to the procedures previously reported. Benzyl (2-(2-methylallyl)phenyl)carbamate (**1l**) and benzyl (2-(2-phenylallyl)phenyl)carbamate (**1m**) were obtained by the procedure described above.

*Benzyl (2-(2-methylallyl)phenyl)carbamate (**1l**).* 239 mg, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.46-7.36 (m, 5H), 7.32-7.28 (m, 1H), 7.18 (d, *J* = 6.8 Hz, 1H), 7.13-7.09 (m, 1H), 6.87 (br s, 1H), 5.25 (s, 2H), 4.94 (s, 1H), 4.74 (s, 1H), 3.36 (s, 2H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 143.8, 136.5, 136.3, 130.8, 128.6, 128.3, 128.3, 127.6, 124.3, 121.9, 112.5, 66.9, 41.3, 22.4; HRMS (ESI) m/z calcd. for $C_{18}H_{19}NNaO_2$ $[M+Na]^+$ 304.1313, found 304.1309.

*Benzyl (2-(2-phenylallyl)phenyl)carbamate (**1m**).* 282 mg, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (br s, 1H), 7.46-7.28 (m, 12H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.09 (t,

J = 7.2 Hz, 1H), 6.64 (s, 1H), 5.48 (s, 1H), 5.20 (s, 2H), 4.86 (s, 1H), 3.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 145.7, 140.7, 136.2, 136.1, 130.9, 129.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.7, 126.0, 124.7, 114.4, 67.1, 37.9; HRMS (ESI) m/z calcd. for $C_{23}H_{21}NNaO_2$ $[M+Na]^+$ 366.1470, found 366.1463.

*Synthesis of carbamate substrates **1n-1p***. Carbamate substrates **1n-1p** were synthesized according to the procedures previously reported.[17]

*Synthesis of tert-butyl (2-allyl-4-methylphenyl)carbamate (**1q**)*. To a stirred solution of **1a** (441.6 mg, 3.0 mmol) in tetrahydrofuran (10 mL) was added di-*tert*-butyl-dicarbonate (786.0 mg, 3.6 mmol) and triethylamine (TEA, 6.3 ml, 9.0 mmol). The reaction mixture was refluxed for 12 hours, during which time a white precipitate formed. The solvent was removed *in vacuo* and ethyl acetate (10 ml) was added to the residue. The mixture was washed with 1 M citric acid (aq) (3 x 10 ml), brined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 60/1) to give **1q** as a while solid.

*Tert-butyl (2-allyl-4-methylphenyl)carbamate (**1q**).* 608 mg, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.04 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.96 (d, *J* = 1.6 Hz, 1H), 6.35 (s, 1H), 5.95 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.15 (dq, *J* = 10.0, 1.6 Hz, 1H), 5.06 (dq, *J* = 17.2, 1.6 Hz, 1H), 3.33 (d, *J* = 6.0 Hz, 2H), 2.29 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 136.1, 133.8, 133.8, 130.6, 129.5, 127.9, 122.6, 116.4, 80.2, 36.5, 28.4, 20.8; HRMS (ESI) m/z calcd. for $C_{15}H_{21}NNaO_2$ $[M+Na]^+$ 270.1470, found 270.1465.

*Synthesis of carbamate substrates **3a-3e***. Carbamate substrate **3a**[18] was synthesized according to the procedures previously reported. 2-Iodo-4-methylbenzonitrile[19] was prepared according to literature procedure. To a suspension of $Pd_2(dba)_3$ (183.1 mg, 0.2 mmol), triphenylphosphine (419.7 mg, 1.6 mmol) and lithium chloride (1.3 g, 30.0 mmol) in DMF (30 mL) was added 2-iodo-4-methylbenzonitrile (2.4 mg, 10.0 mmol) at room temperature under a argon atmosphere. After 15 minutes, allyl indium reagent which is generated from allyl iodide (2.5 g, 15.0 mmol) and indium (1.1 g, 10.0 mmol) in DMF (5 mL) was added and the mixture was stirred at 100 °C for 8 hours. The reaction mixture was quenched with $NaHCO_3$ (sat. aq.). The aqueous layer was extracted with EtOAc (3 ×50 mL), and the combined organics were washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 80/1) to afford 2-allyl-4-methylbenzonitrile (1.1 g, 68 %).

To a suspension of $LiAlH_4$ (LAH, 425.4 mg, 11.2 mmol) in THF (15 mL) at 0 °C was slowly added a solution of 2-allyl-4-methylbenzonitrile (440.2 mg, 2.8 mmol) in THF (10.0 mL). After being stirred for 3 hours at 0 °C, the reaction mixture was quenched by slow, sequential addition of water (0.5 mL) in Na_2SO_4 (3.0 g). The reaction mixture was warmed to room temperature, stirred for an additional 30 minutes, filtered, and concentrated *in vacuo*. The crude material was directly used in the next reaction. Benzyl 2-allyl-4-methylbenzylcarbamate (**3b**) was obtained by the procedure described above.

*Benzyl 2-allyl-4-methylbenzylcarbamate (**3b**)*. 414 mg, 50% yield, two steps; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.39-732 (m, 5H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 2H), 6.02-5.94 (m, 1H), 5.15-.501 (m, 5H), 4.38 (d, *J* = 5.6 Hz, 2H), 3.42 (d, *J* = 6.0 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 137.7, 137.6, 137.1, 136.6, 133.1, 130.8, 128.9, 128.5, 128.1, 127.4, 115.9, 66.7, 42.4, 36.9, 21.0; HRMS (ESI) m/z calcd. for $C_{19}H_{21}NNaO_2$ $[M+Na]^+$ 318.1470, found 318.1467.

2-Bromo-5-fluorobenzonitrile (400.0 mg, 2.0 mmol) was treated with allyltributyl tin (0.81 mL, 2.6 mmol) and palladium tetrakistriphenylphosphine (462.2 mg 0.4 mmol) in degassed, dry toluene (10 mL) and the mixture was refluxed for 24 hours.[20] Then cooled, the crude mixture was directly filtered through SiO_2 and the solvent was removed *in vacuo*, the residue was purified by a silica gel column chromatography (eluent: petroleum ether/EtOAc = 80/1) to give 2-allyl-5-fluorobenzonitrile (177.3 mg, 55%) as a liquid. Benzyl 2-allyl-4-fluorobenzylcarbamate (**3c**) was obtained by the procedure described above.

*Benzyl 2-allyl-4-fluorobenzylcarbamate (**3c**).* 185 mg, 65% yield, two steps; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.31 (m, 5H), 7.27-7.23 (m, 1H), 6.90 (d, *J* = 9.2 Hz, 2H), 5.93 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.12-4.98 (m, 5H), 4.35 (d, *J* = 5.6 Hz, 2H), 3.40 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (d, *J* = 244.4 Hz), 156.2, 140.3 (d, *J* = 7.1 Hz), 136.4, 136.1, 131.9, 130.5 (d, *J* = 8.4 Hz), 128.6, 128.2, 128.2, 116.8, 116.7 (d, *J* = 21.2 Hz), 113.4 (d, *J* = 21.0 Hz), 66.9, 42.1, 36.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.85 (dd, *J* = 14.9, 8.8 Hz); HRMS (ESI) m/z calcd. for $C_{18}H_{18}FNNaO_2$ $[M+Na]^+$ 322.1219, found 322.1214.

2-Allyl-4-chlorobenzonitrile and 2-(2-methylallyl)benzonitrile was prepared

according to literature procedure.[21] **3d-3e** were obtained by the procedure described above.

*Benzyl 2-allyl-4-chlorobenzylcarbamate (**3d**).* 196 mg, 62% yield, two steps; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 7.26-7.17 (m, 3H), 5.92(ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.12-4.97 (m, 5H), 4.35 (d, *J* = 5.6 Hz, 2H), 3.39 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 139.7, 136.4, 136.0, 134.8, 133.5, 130.0, 129.9, 128.6, 128.2, 128.2, 126.8, 116.9, 67.0, 42.1, 36.7; HRMS (ESI) m/z calcd. for $C_{18}H_{18}ClNNaO_2$ $[M+Na]^+$ 338.0924, found 338.0917.

*Benzyl 2-(2-methylallyl)benzylcarbamate (**3e**).* 171 mg, 58% yield, two steps; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.19 (m, 9H), 5.22 (s, 1H), 5.16 (s, 2H), 4.88 (s, 1H), 4.55 (s, 1H), 4.41 (d, *J* = 6.0 Hz, 2H), 3.40 (s, 2H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 144.8, 137.4, 136.5, 130.6, 128.6, 128.4, 128.0, 127.6, 126.7, 111.9, 66.6, 42.5, 41.0, 22.7; HRMS (ESI) m/z calcd. for $C_{19}H_{21}NNaO_2$ $[M+Na]^+$ 318.1470, found 318.1463.

Experiments to remove Cbz group.

A solution of **2o** (35.5 mg, 0.1 mmol) in CH_3OH (5.0 mL) was stirred in the presence of 10% $Pd(OH)_2/C$ (60.0 mg) under H_2 (H_2 balloon) at room temperature for 24 h. The catalyst was filtered through celite and washed with EtOAc, the filtrate was concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (eluent: CH_2Cl_2/CH_3OH = 100/1-30/1) to give **5** (18 mg, 81%) as a liquid. The present spectrum is consistent with our previous reported.[4a]

*3-(2,2,2-trifluoroethyl)-2-azaspiro[4.5]decane (**5**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ

3.43 (s, 1H), 2.75-2.85 (m, 2H), 2.38-2.17 (m, 4H), 1.89 (s, 1H), 1.44-1.41 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.6 (q, *J* = 275.3 Hz), 58.2, 52.1, 45.3, 43.0, 40.5 (q, *J* = 26.6 Hz), 38.4, 37.0, 26.1, 24.0, 23.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.31 (s, 3F); HRMS (ESI) m/z calcd. for $C_{11}H_{19}F_3N$ $[M+H]^+$ 222.1470, found 222.1461.

General procedure: copper-catalyzed intramolecular aminotrifluoromethylation of unactivated alkenes with $TMSCF_3$

Under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with activated KF (116.0 mg, 2.0 mmol, 4.0 equiv), $Cu(CH_3CN)_4BF_4$ (26.0 mg, 0.075 mmol, 15 mol %), carbamate substrates (0.5 mmol, 1.0 equiv), $AgNO_3$ (85.0 mg, 0.5 mmol, 1.0 equiv), DMF (super dry, 3.0 mL), trimethyl(trifluoromethyl)silane ($TMSCF_3$, 0.3 mL, 2.0 mmol, 4.0 equiv). The sealed tube was then stirred at 80 °C. Upon completion (monitored by TLC), solvent was removed *in vacuo*, and the residue was purified by a silica gel column chromatography (eluent: petroleum ether/EtOAc = 80/1-15/1) to give the desired products. (NOTE: the reaction was water-sensitive, the reagents and Schlenk tube must be dried prior to use).

*Benzyl 5-methyl-2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2a**).*[4a] 98 mg, 56% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (br s, 1H), 7.48-7.36 (m, 5H), 7.02 (s, 2H), 5.34 (s, 2H), 4.80-4.78 (m, 1H), 3.40 (dd, *J* = 16.4, 9.6 Hz, 1H), 2.97 (d, *J* = 16.4 Hz, 1H), 2.66 (br s, 1H), 2.40-2.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3 (br s), 138.7 (br s), 136.1, 133.0, 129.2, 128.7, 128.5, 128.4, 128.2, 126.0 (q, *J* = 275.9 Hz), 125.8, 115.3, 67.5, 54.3, 38.2 (br s), 33.7 (br s), 20.8; ^{19}F NMR (376 MHz, $CDCl_3$,

observed as a mixture of rotamers, major and minor) δ -62.86 (br s, 3F, minor), -63.24 (br s, 3F, major); HRMS (ESI) m/z calcd. for $C_{19}H_{18}F_3NNaO_2$ $[M+Na]^+$ 372.1187, found 372.1182.

*Benzyl 7-methyl-2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2b**).* 80 mg, 46% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.34 (m, 5H), 7.08-7.02 (m, 3H), 5.27 (q, *J* = 12.4 Hz, 2H), 5.02 (dd, *J* = 14.8, 7.2 Hz, 1H), 3.47 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.66 (d, *J* = 16.0 Hz, 1H), 2.50-2.39 (m, 1H), 2.31-2.19 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 139.6, 136.0, 131.9, 130.3, 128.9, 128.6, 128.3, 128.2, 125.8 (q, *J* = 275.7 Hz), 125.2, 122.3, 67.8, 56.6, 38.4 (q, *J* = 27.0 Hz), 35.1, 20.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.44 (t, *J* = 10.6 Hz, 3F); HRMS (ESI) m/z calcd. for $C_{19}H_{19}F_3NO_2$ $[M+H]^+$ 350.1368, found 350.1362

*Benzyl 5-methoxy-2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2c**).* 111 mg, 61% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.78 (br s, 1H), 7.46-7.33 (m, 5H), 6.76 (s, 2H), 5.31 (s, 2H), 4.79 (s, 1H), 3.77 (s, 3H), 3.40 (dd, *J* = 16.4, 9.6 Hz, 1H), 2.95 (d, *J* = 16.4 Hz, 1H), 2.62 (br s, 1H), 2.39-2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 152.1 (br s), 136.0, 134.8 (br s), 130.3 (br s), 128.7, 128.4, 128.2, 125.9 (q, *J* = 275.8 Hz), 116.0, 112.5, 111.3, 67.4 (br s), 55.6, 54.2 (br s), 38.4 (br s), 34.2 (br s); ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ -62.87 (br s, 3F, minor), -63.27 (br s, 3F, major); HRMS (ESI) m/z calcd. for $C_{19}H_{18}F_3NNaO_3$ $[M+Na]^+$ 388.1136, found 388.1128.

*Benzyl 5-phenyl-2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2d**).* 103 mg, 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.66-7.27 (m, 12H), 5.36 (s, 2H),

4.89-4.84 (m, 1H), 3.51 (dd, *J* = 16.4, 9.6 Hz, 1H), 3.08 (d, *J* = 16.4 Hz, 1H), 2.88-2.64 (m, 1H), 2.46-2.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4 (br s), 140.7, 136.8, 135.8, 128.9, 128.8, 128.5, 128.3, 127.1, 126.9, 126.9, 125.9 (q, *J* = 273.7 Hz), 123.9, 115.7, 67.8 (br s), 54.6 (br s), 38.5 (br s), 34.0 (br s); ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ -62.88 (br s, 3F, minor), -63.28 (br s, 3F, major); HRMS (ESI) m/z calcd. for $C_{24}H_{20}F_3NNaO_2$ $[M+Na]^+$ 434.1344, found 434.1337.

*Benzyl 2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2e**).* 99 mg, 59% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (br s, 1H), 7.47-7.35 (m, 5H), 7.20 (d, *J* = 7.2 Hz, 2H), 7.02 (t, *J* = 7.6 Hz, 1H), 5.33 (s, 2H), 4.83-4.78 (m, 1H), 3.43 (dd, *J* = 16.8, 9.6 Hz, 1H), 3.00 (d, *J* = 16.4 Hz, 1H), 2.64 (br s, 1H), 2.40-2.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1 (br s), 140.9 (br s), 135.9, 128.7, 128.4, 128.3, 127.9, 125.9 (q, *J* = 275.7 Hz), 125.1, 123.4, 115.5, 67.6 (br s), 54.2 (br s), 38.3 (br s), 33.9 (br s); ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ -62.92 (br s, 3F, minor), -63.28 (br s, 3F, major); HRMS (ESI) m/z calcd. for $C_{18}H_{16}F_3NNaO_2$ $[M+Na]^+$ 358.1031, found 358.1026.

*Benzyl 4,6-dimethyl-2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2f**).* 103 mg, 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.25 (m, 6H), 6.70 (s, 1H), 5.33 (s, 2H), 4.85-4.79 (m, 1H), 3.26 (dd, *J* = 16.4, 9.6 Hz, 1H), 2.88 (d, *J* = 16.4 Hz, 1H), 2.65 (br s, 1H), 2.39-2.27 (m, 4H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3 (br s), 141.0 (br s), 138.0, 136.0, 134.2, 128.7, 128.4, 128.2, 125.9 (q, *J* = 275.8 Hz), 125.3, 124.7, 113.7, 67.5 (br s), 54.4 (br s), 38.7 (br s), 32.6 (br s), 21.6, 18.6, 18.5; ^{19}F NMR

(376 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ -62.91 (br s, 3F, minor), -63.27 (br s, 3F, major); HRMS (ESI) m/z calcd. for $C_{20}H_{20}F_3NNaO_2$ $[M+Na]^+$ 386.1344, found 386.1337.

*Benzyl 5-fluoro-2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2g**).* 102 mg, 58% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.45-7.34 (m, 5H), 6.90 (s, 1H), 6.88 (s, 1H), 5.31 (s, 2H), 4.81 (s, 1H), 3.41 (dd, *J* = 16.8, 9.6 Hz, 1H), 2.97 (d, *J* = 16.8 Hz, 1H), 2.63 (br s, 1H), 2.40-2.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (d, *J* = 241.8 Hz), 152.2 (br s), 137.3 (br s), 135.7, 130.8 (br s), 128.7, 128.5, 128.3, 125.6 (q, *J* = 275.9 Hz), 116.2 (d, *J* = 8.3 Hz), 114.2 (d, *J* = 23.1 Hz), 112.4 (d, *J* = 23.9 Hz), 67.7 (br s), 54.5 (br s), 38.4 (br s), 33.9 (br s); ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ -62.91 (br s, 3F, minor), -63.29 (br s, 3F, major); -119.91 (br s, 1F, major), -120.29 (br s, 1F, minor); HRMS (ESI) m/z calcd. for $C_{18}H_{15}F_4NNaO_2$ $[M+Na]^+$ 376.0937, found 376.0931.

*Benzyl 5-chloro-2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2h**).*[4a] 107 mg, 58% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 7.42-7.35 (m, 5H), 7.14 (br s, 2H), 5.29 (s, 2H), 4.81-4.76 (m, 1H), 3.39 (dd, *J* = 16.8, 9.6 Hz, 1H), 2.96 (d, *J* = 16.8 Hz, 1H), 2.64 (br s, 1H), 2.38-2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 139.8, 135.8, 131.1, 128.8, 128.6, 128.4, 128.3, 127.9, 125.8 (q, *J* = 275.8 Hz), 125.3, 116.5, 67.9, 54.6, 38.1, 33.6; ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ -62.93 (br s, 3F, minor), -63.27 (br s, 3F, major); HRMS (APCI) m/z calcd. for $C_{17}H_{16}ClF_3N$ $[M-CO_2+H]^+$ 326.0923, found 326.0856.

*Benzyl 7-chloro-2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2i**).* 94 mg, 51% yield;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.33 (m, 5H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 5.31 (s, 2H), 4.99 (td, *J* = 8.4, 5.2 Hz, 1H), 3.51 (dd, *J* = 16.0, 8.4 Hz, 1H), 2.78 (d, *J* = 16.0 Hz, 1H), 2.59-2.48 (m, 1H), 2.37-2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 138.4, 135.6, 134.6, 129.7, 128.6, 128.4, 126.2, 125.7 (q, *J* = 275.7 Hz), 124.7, 123.4, 68.2, 57.4 (q, *J* = 2.6 Hz), 38.5 (q, *J* = 27.0 Hz), 35.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.38 (t, *J* = 10.6 Hz, 3F); HRMS (ESI) m/z calcd. for $C_{18}H_{15}ClF_3NNaO_2$ $[M+Na]^+$ 392.0641, found 392.0633.

*Benzyl 5-bromo-2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2j**).* 104 mg, 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.46-7.28 (m, 7H), 5.33 (s, 2H), 4.84-4.79 (m, 1H), 3.43 (dd, *J* = 16.8, 9.6 Hz, 1H), 3.00 (d, *J* = 16.8 Hz, 1H), 2.63 (br s, 1H), 2.41-2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2 (br s), 140.3 (br s), 135.6, 131.3, 130.8, 128.7, 128.6, 128.3, 128.2, 125.7 (q, *J* = 275.7 Hz), 116.9, 115.8, 67.9 (br s), 54.5 (br s), 38.2 (br s), 33.6 (br s); ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ -62.86 (br s, 3F, minor), -63.26 (br s, 3F, major); HRMS (ESI) m/z calcd. for $C_{18}H_{15}BrF_3NNaO_2$ $[M+Na]^+$ 436.0136, found 436.0130.

*Benzyl 2-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-benzo-[g]indole-1-carboxylate (**2k**).* 119 mg, 62% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.92 (m, 1H), 7.87-7.82 (m, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.52-7.33 (m, 8H), 5.39 (d, *J* = 12.4 Hz, 1H), 5.25 (d, *J* = 12.4 Hz, 1H), 5.19 (q, *J* = 7.2 Hz, 1H), 3.67 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.82 (d, *J* = 16.0 Hz, 1H), 2.62-2.48 (m, 1H), 2.36-2.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 136.6, 135.9, 134.0, 128.6, 128.3, 128.2, 126.6, 125.9 (q, *J* = 275.8 Hz), 125.5,

125.2, 124.8, 122.5, 68.0, 57.4 (q, J = 3.8 Hz), 38.7 (q, J = 26.9 Hz), 35.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.28 (t, J = 10.5 Hz, 3F); HRMS (ESI) m/z calcd. for $C_{22}H_{19}F_3NO_2$ $[M+H]^+$ 386.1368, found 386.1364.

*Benzyl 2-methyl-2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2l**).* 105 mg, 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.34 (m, 6H), 7.13 (d, J = 7.6 Hz, 2H), 6.98 (t, J = 7.6 Hz, 1H), 5.31 (dd, J = 18.4, 12.0 Hz, 2H),3.46 (d, J = 16.4 Hz, 1H), 3.05 (d, J = 16.4 Hz, 1H), 2.89 (br s, 2H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 141.6 (br s), 135.8, 128.8, 128.5, 128.4, 127.9, 126.0 (q, J = 275.8 Hz), 124.7, 123.2, 115.8, 67.6, 63.9, 42.7, 41.1 (br s), 26.5 (br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.83 (s, 3F); HRMS (ESI) m/z calcd. for $C_{19}H_{19}F_3NO_2$ $[M+H]^+$ 350.1368, found 350.1361.

*Benzyl 2-phenyl-2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2m**).* 70 mg, 34% yield; ^{1}H NMR (400 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ 8.16 (d, J = 6.4 Hz, 1H, major), 7.67 (s, 1H, minor), 7.56-6.98 (m, 13H, major + minor), 6.74 (d, J = 14.4 Hz, 1H, major + minor), 5.32-4.93 (m, 2H, major + minor), 3.95 (br s, 1H, minor), 3.76 (d, J = 17.2 Hz, 1H, major + minor), 3.56-3.45 (m, 1H, major), 3.39 (d, J = 16.8 Hz, 1H, major + minor), 3.05-2.94 (m, 1H, major + minor); ^{13}C NMR (100 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ 152.7, 147.4, 143.2, 135.3, 129.1, 128.6, 128.5 (major), 128.5 (minor), 128.3, 128.0, 127.8, 127.3, 127.1 (overlap), 126.0, 124.2 (overlap), 123.4 (major), 123.1 (minor), 115.3, 67.2 (major), 66.2 (minor), 46.5, 45.1, 41.6 (q, J = 26.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ -60.54 (br s, 3F, minor), -60.93 (br s, 3F, major); HRMS (ESI) m/z calcd. for $C_{24}H_{21}F_3NO_2$

$[M+H]^+$ 412.1524, found 412.1518.

Benzyl 4,4-dimethyl-2-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxyl-ate (***2n***). 66 mg, 42% yield; ^{1}H NMR (400 MHz, DMSO, observed as a mixture of rotamers, major and minor) δ 7.40-7.31 (m, 5H, major + minor), 5.11-5.09 (m, 2H, major + minor), 4.03-3.95 (m, 1H, major + minor), 3.35-3.33 (m, 1H, major + minor), 3.06-2.96 (m, 2H, major + minor), 2.84-2.75 (m, 1H, minor), 2.48-2.36 (m, 1H, major + minor), 1.96-1.91 (m, 1H, major + minor), 1.64-1.59 (m, 1H, major + minor), 1.06 (s, 3H, major + minor), 0.93 (s, 3H, major + minor); ^{13}C NMR (100 MHz, DMSO, observed as a mixture of rotamers, major and minor) δ 154.8 (major), 154.7 (minor), 137.4 (major), 137.4 (minor), 128.9, 128.3, 127.9, 127.0 (q, J = 275.3 Hz), 66.8 (minor), 66.4 (major), 58.9 (minor), 58.7 (major), 52.4 (major), 51.8 (minor), 46.1 (minor), 45.1 (major), 38.6 (q, J = 25.6 Hz, minor), 37.2 (q, J = 25.6 Hz, major), 37.8 (major), 37.5 (minor), 26.1, 25.7; ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ -63.26 (t, J = 11.6 Hz, 3F, major), -63.50 (t, J = 11.6 Hz, 3F, minor).

^{1}H NMR (500 MHz, DMSO, 60 ^{o}C) δ 7.51-7.43 (m, 5H), 5.28-5.19 (dd, J = 18.5, 10.5, Hz, 2H), 4.18-4.12 (m, 1H), 3.49 (d, J = 10.5 Hz, 1H), 3.15 (d, J = 10.5 Hz, H), 3.07 (br s, 1H), 2.63-2.45 (m, 1H), 2.09 (dd, J = 12.5, 7.5 Hz, 1H), 1.76 (dd, J = 12.5, 8.5 Hz, 1H), 1.21 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (126 MHz, DMSO, 60 ^{o}C) δ 154.9, 137.4, 128.8, 128.3, 127.9, 127.0 (q, J = 278.1 Hz), 66.7, 59.1, 52.3, 45.6, 37.6, 26.2, 25.9; HRMS (ESI) m/z calcd. for $C_{16}H_{20}F_3NNaO_2$ $[M+Na]^+$ 338.1344, found 338.1339.

*Benzyl 3-(2,2,2-trifluoroethyl)-2-azaspiro[4.5]decane-2-carboxylate (**2o**).* 71 mg, 40% yield; ^{1}H NMR (400 MHz, $CDCl_3$ observed as a mixture of rotamers, major and minor) δ 7.37-7.32 (m, 5H, major + minor), 5.21-5.09 (m, 2H, major + minor), 4.09-4.02 (m, 1H, major + minor), 3.69 (d, *J* = 10.8 Hz, 1H, major), 3.58 (d, *J* = 10.8 Hz, 1H, minor), 3.25-3.13 (m, 1H, minor), 2.96 (d, *J* = 11.2 Hz, 1H, major + minor), 2.92-2.80 (m, 1H, major), 2.18-2.00 (m, 2H, major + minor), 1.49-1.38 (m, 11H, major + minor); ^{13}C NMR (100 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ 155.3 (major), 155.1 (minor), 136.8 (major), 136.4 (minor), 128.6, 128.2 (minor), 128.1 (major), 127.8, 126.3 (q, *J* = 275.3 Hz), 67.3 (minor), 66.9 (major), 56.7 (minor), 56.5 (major), 51.8 (major), 51.2 (minor), 44.5 (minor), 43.3 (major), 41.6 (major), 41.4 (minor), 39.6 (q, *J* = 25.1 Hz, minor), 38.1 (q, *J* = 26.4 Hz, major), 36.3, 34.4 (minor), 34.3 (major), 26.1, 23.8, 22.9 (minor), 22.8 (major); ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ -63.24 (t, *J* = 10.9 Hz, 3F, major), -63.62 (t, *J* = 10.9 Hz, 3F, minor); HRMS (ESI) m/z calcd. for $C_{19}H_{24}F_3NNaO_2$ $[M+Na]^+$ 378.1657, found 378.1653.

*Benzyl 4,4-diphenyl-2-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxylate (**2p**).* 88 mg, 40% yield; ^{1}H NMR (400 MHz, $CDCl_3$ observed as a mixture of rotamers, major and minor) δ 7.44-7.16 (m, 15H, major + minor), 5.35-5.11(m, 2H, major + minor), 4.73 (dd, *J* = 11.6, 2.0 Hz, 1H, major), 4.59 (dd, *J* = 11.6, 1.6 Hz, 1H, minor), 4.01-3.91 (m, 1H, major + minor), 3.73 (d, *J* = 11.6 Hz, 1H, major + minor), 3.28-3.15 (m, 1H, minor), 3.08-3.00 (m, 1H, major + minor), 2.97-2.84 (m, 1H, major), 2.59-2.49 (m, 1H, major + minor), 2.18-2.01 (m, 1H, major + minor); ^{13}C NMR (100 MHz, $CDCl_3$,

observed as a mixture of rotamers, major and minor) δ 155.0 (minor), 154.8 (major), 145.0 (major), 144.9 (minor), 144.2 (major), 144.2 (minor), 136.7 (major), 136.4 (minor), 128.8 (minor), 128.8 (major), 128.7 (minor), 128.7 (major), 128.6, 128.3 (minor), 128.2 (major), 128.1, 127.7, 126.8, 126.7, 126.3 (minor), 126.2 (major), 126.1 (q, *J* = 275.6 Hz), 67.3 (major), 67.2 (minor), 55.6 (minor), 55.6 (major), 53.0 (major), 52.9 (minor), 52.0 (q, *J* = 3.2 Hz, major), 51.5 (q, *J* = 3.0 Hz, minor), 44.7 (minor), 43.5 (major), 39.0 (q, *J* = 26.3 Hz, minor), 37.6 (q, *J* = 26.7 Hz, major); ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ -63.08 (t, *J* = 11.3 Hz, 3F, major), -63.41 (t, *J* = 11.3 Hz, 3F, minor); HRMS (ESI) m/z calcd. for $C_{26}H_{25}F_3NO_2$ $[M+H]^+$ 440.1837, found 440.1835.

*Tert-butyl 5-methyl-2-(2,2,2-trifluoroethyl)indoline-1-carboxylate (**2q**).* 95 mg, 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (br s, 1H), 7.01-6.96 (m, 2H), 4.69 (br s, 1H), 3.38 (dd, *J* = 16.4, 9.6 Hz, 1H), 2.90 (d, *J* = 16.4 Hz, 1H), 2.64 (br s, 1H), 2.33-2.25 (m, 4H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8 (br s), 139.1 (br s), 132.6, 129.0 (br s), 128.2, 126.0 (q, *J* = 275.7 Hz), 125.6, 115.1, 81.5 (br s), 55.3, 54.2, 38.6 (br s), 34.1 (br s), 28.4, 20.9; ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ -62.98 (br s, 3F, minor), -63.63 (br s, 3F, major); HRMS (ESI) m/z calcd. for $C_{16}H_{20}F_3NNaO_2$ $[M+Na]^+$ 338.1344, found 338.1335.

*Tosyl-2-(2,2,2-trifluoroethyl)indoline (**2r**).*[4a] 84 mg, 47% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.26-7.21 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.07-7.03 (m, 2H), 4.47-4.40 (m, 1H), 2.97-2.87 (m, 2H), 2.77

(dd, J = 16.4, 2.8 Hz, 1H), 2.51-2.40 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 140.9, 134.4, 130.8, 129.9, 128.3, 127.3, 125.8 (q, J = 275.9 Hz), 125.4, 125.3, 117.4, 57.0 (q, J = 3.3 Hz), 40.8 (q, J = 26.6 Hz), 34.39, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.08 (s, 3F); HRMS (ESI) m/z calcd. for $C_{17}H_{17}F_3NO_2S$ $[M+H]^+$ 356.0932, found 356.0922.

*Benzyl 3-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (**4a**).* 91 mg, 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.33 (m, 5H), 7.25-7.12 (m, 4H), 5.22 (s, 2H), 5.05-4.85 (m, 2H), 4.39 (dd, J = 17.6, 11.2 Hz, 1H), 3.17 (d, J = 16.0 Hz, 1H), 2.78 (dd, J = 24.0, 16.0 Hz, 1H), 2.40-2.28 (m, 1H), 2.12-2.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ 155.2 (minor), 155.0 (major), 136.5 (major), 136.3 (minor), 132.0 (major), 131.8 (minor), 131.7 (minor), 131.3 (major), 129.4 (minor), 129.2 (major), 128.6, 128.2, 128.1, 127.2 (major), 127.1 (minor), 126.9 (major), 126.9 (minor), 126.4 (minor), 126.2 (major), 126.0 (q, J = 275.5 Hz), 67.7 (major), 67.6 (minor), 45.0 (major), 44.8 (minor), 43.0, 35.7 (q, J = 26.8 Hz), 33.6 (minor), 33.1 (major); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.83 (t, J = 10.5 Hz, 3F); HRMS (ESI) m/z calcd. for $C_{19}H_{18}F_3KNO_2$ $[M+K]^+$ 388.0927, found 388.0937.

*Benzyl 6-methyl-3-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (**4b**).* 109 mg, 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.32 (m, 5H), 7.08-6.96 (m, 3H), 5.21 (s, 2H), 5.04-4.88 (m, 1H), 4.84(t, J = 18.0, 1H), 4.34 (dd, J = 16.8, 9.2 Hz, 1H), 3.12 (d, J = 15.6 Hz, 1H), 2.73 (dd, J = 24.0, 16.0 Hz, 1H), 2.39-2.26 (m, 4H), 2.11- 2.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, observed as a mixture of

rotamers, major and minor) δ 155.3 (major), 155.0 (minor), 136.9 (minor), 136.8 (major), 136.5 (major), 136.4 (minor), 131.6 (minor), 131.2 (major), 130.0 (major), 129.8 (minor), 129.0 (major), 128.8 (minor), 128.6, 128.2, 128.1, 127.8 (major), 127.7 (minor), 126.3 (minor), 126.1 (major), 126.1 (q, J = 275.6 Hz), 67.7 (major), 67.5 (minor), 45.0 (minor), 44.9 (major), 42.9, 35.8 (q, J = 26.8 Hz), 33.6 (major), 33.1 (minor), 21.1; ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, A and B) δ -63.92 (t, J = 10.9 Hz, 3F, A), -64.14 (t, J = 10.9 Hz, 3F, B); HRMS (ESI) m/z calcd. for $C_{20}H_{20}F_3NNaO_2$ $[M+Na]^+$ 386.1344, found 386.1337.

Benzyl 6-fluoro-3-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate ***(4c)***. 83 mg, 45% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.32 (m, 5H), 7.15-706 (m, 1H), 6.94 (t, J = 8.0 Hz, 1H), 6.87 (t, J = 10.0 Hz, 1H), 5.20 (s, 2H), 5.04-4.79 (m, 2H), 4.34 (dd, J = 16.8, 11.6 Hz, 1H), 3.14 (dd, J = 16.0, 3.6 Hz, 1H), 2.75 (dd, J = 25.6, 16.0 Hz, 1H), 2.39-2.26 (m, 1H), 2.10-1.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ 161.7 (d, J = 244.5 Hz), 155.2 (major), 155.0 (minor), 136.4 (major), 136.3 (minor), 128.6, 128.3, 128.2, 128.1 (minor), 128.0 (major), 127.9 (minor), 127.8 (major), 125.9 (q, J = 275.3 Hz), 115.9 (t, J = 20.8 Hz), 114.3 (d, J = 7.9 Hz), 114.1 (d, J = 5.4 Hz), 67.8 (major), 67.7 (minor), 44.7 (major), 44.6 (minor), 42.6 (major), 42.5 (minor), 35.7 (q, J = 27.2 Hz), 33.7 (major), 33.2 (minor); ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, A and B) δ -63.91 (t, J = 11.7 Hz, 3F, A), -64.14 (t, J = 12.0 Hz, 3F, B), -115.18--115.24 (m, 1F, A), -115.32--115.36 (m, 1F, B); HRMS (ESI) m/z calcd. for $C_{19}H_{17}F_4NNaO_2$ $[M+Na]^+$ 390.1093, found 390.1087.

Benzyl 6-chloro-3-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate ***(4d)***. 84 mg, 44% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.03 (m, 8H), 5.20 (s, 2H), 5.03-4.80 (m, 2H), 4.32 (dd, *J* = 17.2, 12.8 Hz, 1H), 3.15-3.10 (m, 1H), 2.74 (dd, *J* = 26.0, 16.0 Hz, 1H), 2.34-2.26 (m, 1H), 2.07-2.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, observed as a mixture of rotamers, major and minor) δ 155.1 (major), 154.9 (minor), 136.4 (minor), 136.2 (major), 133.7 (minor), 133.2 (major), 132.8 (minor), 132.8 (major), 130.5 (major), 130.3 (minor), 129.3 (major), 129.1 (minor), 128.6, 128.3, 128.2, 127.8 (major), 127.6 (minor), 127.3 (major), 127.2 (minor), 125.9 (q, *J* = 275.9 Hz), 67.9 (minor), 67.7 (major), 44.7 (major), 44.5 (minor), 42.6 (minor), 42.5 (major), 35.7 (q, *J* = 26.4 Hz), 33.5 (major), 33.0 (minor); ^{19}F NMR (376 MHz, $CDCl_3$, observed as a mixture of rotamers, A and B) δ -63.93 (t, *J* = 10.8 Hz, 3F, A), -64.16 (t, *J* = 10.8 Hz, 3F, B); HRMS (ESI) m/z calcd. for $C_{19}H_{17}ClF_3NNaO_2$ $[M+Na]^+$ 406.0798, found 406.0792.

Benzyl 3-methyl-3-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate ***(4e)***. 100 mg, 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.21 (m, 9H), 5.21 (dd, *J* = 20.4, 12.4 Hz, 2H), 4.79 (d, *J* = 14.8 Hz, 1H), 4.47 (d, *J* = 14.8 Hz, 1H), 3.33 (d, *J* = 14.8 Hz, 1H), 2.92-2.67 (m, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 136.5, 135.2, 135.2, 128.6, 128.1, 128.0, 127.9, 127.6, 127.0, 126.2 (q, *J* = 276.3 Hz), 125.6, 67.2, 56.1, 46.0, 41.4, 40.1 (br s), 26.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.78 (t, *J* = 11.6 Hz, 3F); HRMS (ESI) m/z calcd. for $C_{20}H_{20}F_3NNaO_2$ $[M+Na]^+$ 386.1344, found 386.1337.

Direct Intramolecular Carbotrifluoromethylation of Alkenes

An oven-dried vessel equipped with a magnetic stir bar was charged with activated KF (138.0 mg, 1.0 mmol, 10.0 equiv), $Cu(CH_3CN)_4BF_4$ (8.5 mg, 0.025 mmol, 25 mol %), **3f** (17.5 mg, 0.1 mmol, 1.0 equiv), $AgNO_3$ (17.0 mg, 0.1 mmol, 1.0 equiv), DMF (super dry, 1.0 mL), trimethyl(trifluoromethyl)silane ($TMSCF_3$, 0.15 mL, 1.0 mmol, 10.0 equiv). The sealed vessel was then stirred at 80 °C for 72 h. DMF was removed *in vacuo*, and the residue was purified by a silica gel column chromatography (eluent: petroleum ether/EtOAc = 90/1-40/1) to give the desired products. The present spectrum is consistent with our previous reported.[4b]

Experiments for mechanism study

(NOTE: The reaction was water-sensitive, the reagents and Schlenk tube must be dried prior to use).

1) Reaction of TEMPO with $TMSCF_3$.[8a] Under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with activated KF (23.2 mg, 0.4 mmol), $Cu(CH_3CN)_4BF_4$ (5.1 mg, 0.015 mmol), $AgNO_3$ (17.0 mg, 0.1 mmol), 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 15.6 mg, 0.1 mmol), DMF (super dry, 0.6 mL), trimethyl(trifluoromethyl)silane ($TMSCF_3$, 59 μL, 0.4 mmol). The sealed tube was then stirred at 80 °C for 16 hours, then cooled to room temperature, α,α,α-trifluorotoluene (internal standard, 14.6 mg, 0.1 mmol) was added. ^{19}F NMR analysis of this reaction mixture showed that TEMPO-CF_3 was formed in 0% yield.

*2) Reaction of TEMPO and $TMSCF_3$ with **1a**.*[8a] Under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with activated KF (11.6 mg, 0.2 mmol), **1a** (14.0 mg, 0.05 mmol), $Cu(CH_3CN)_4BF_4$ (2.6 mg, 0.0075 mmol),

$AgNO_3$ (8.5 mg, 0.05 mmol), 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 7.8 mg, 0.05 mmol or 15.6 mg, 0.1 mmol), DMF (super dry, 0.3 mL), trimethyl(trifluoromethyl)silane ($TMSCF_3$, 29.5 μL, 0.2 mmol). The sealed tube was then stirred at 80 °C for 16 hours, then cooled to room temperature, α,α,α-trifluorotoluene (internal standard, 7.3 mg, 0.05 mmol) was added. ^{19}F NMR analysis of this reaction mixture showed that **2a** was formed in 46% yield (TEMPO, 1.0 eq.), ^{19}F NMR analysis of this reaction mixture showed that **2a** was formed in 30% yield (TEMPO, 2.0 eq.).

*3) Reaction of BHT and $TMSCF_3$ with **1a**.* Under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with activated KF (11.6 mg, 0.2 mmol), **1a** (14.0 mg, 0.05 mmol), $Cu(CH_3CN)_4BF_4$ (2.6 mg, 0.0075 mmol), $AgNO_3$ (8.5 mg, 0.05 mmol), 2,6-di-*tert*-butyl-4-methylphenol (BHT, 11.0 mg, 0.05 mmol), DMF (super dry, 0.3 mL), trimethyl(trifluoromethyl)silane ($TMSCF_3$, 29.5 μL, 0.2 mmol). The sealed tube was then stirred at 80 °C for 16 hours, then cooled to room temperature, α,α,α-trifluorotoluene (internal standard, 7.3 mg, 0.05 mmol) was added. ^{19}F NMR analysis of this reaction mixture showed that **2a** was formed in 10% yield.

*4) Reaction of $CuCF_3$[7i] with **1a**.* Under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with activated KF (2.9 mg, 0.05 mmol), trimethyl(trifluoromethyl)silane ($TMSCF_3$, 7.4 μL, 0.05 mmol), $Cu(CH_3CN)_4BF_4$ (17.1 mg, 0.05 mmol), DMF (super dry, 0.3 mL). The sealed tube was then stirred at 25 °C for 30 minutes, then **1a** (14.0 mg, 0.05 mmol), $AgNO_3$ (8.5 mg, 0.05 mmol),

$Cu(CH_3CN)_4BF_4$ (2.6 mg, 0.0075 mmol) were added under argon. The sealed tube was then stirred at 80 °C for additional 16 hours, then cooled to room temperature, α,α,α-trifluorotoluene (internal standard, 7.3 mg, 0.05 mmol) was added. ^{19}F NMR analysis of this reaction mixture showed that **2a** was formed in 0% yield.

*5) Reaction of $AgCF_3$[7g] with **1a**.* Under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with activated KF (11.6 mg, 0.2 mmol), trimethyl(trifluoromethyl)silane ($TMSCF_3$, 29.5 μL, 0.2 mmol), $AgNO_3$ (34.0 mg, 0.2 mmol), DMF (super dry, 0.3 mL). The sealed tube was then stirred at 25 °C for 30 minutes, then **1a** (14.0 mg, 0.05 mmol), $Cu(CH_3CN)_4BF_4$ (2.6 mg, 0.0075 mmol) were added under argon. The sealed tube was then stirred at 80 °C for additional 16 hours, then cooled to room temperature, α,α,α-trifluorotoluene (internal standard, 7.3 mg, 0.05 mmol) was added. ^{19}F NMR analysis of this reaction mixture showed that **2a** was formed in 57% yield.

ACKNOWLEDGMENT

We are thankful for the financial support from the National Natural Science Foundation of China (Nos. 21302088, 21302087), Shenzhen special funds for the development of biomedicine, internet, new energy, and new material industries (JCYJ20130401144532131, JCYJ20130401144532137), and South University of Science and Technology of China (Talent Development Starting Fund from Shenzhen Government).

ASSOCIATED CONTENT

Supporting Information Available

Characterization for compounds, including copies of ^{1}H, ^{13}C and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) For selected reviews: (a) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.,* **2008**, *37*, 320. (c) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(2) For selected reviews on trifluoromethylation of organic compounds, see: (a) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (b) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111,* 455. (c) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (d) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Asian J.* **2012**, *7*, 1744. (e) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950. (f) Ye, Y.; Sanford, M. S. *Synlett* **2012**, *23*, 2005. (g) Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013**, *355*, 617. (h) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214.

(3) (a) Kim, E.; Choi, S.; Kim, H.; Cho, E. J. *Chem. Eur. J.* **2013**, *19*, 6209. (b) Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7841.

(4) (a) Lin, J.-S.; Xiong, Y.-P.; Ma, C.-L.; Zhao, L.-J.; Tan, B.; Liu, X.-Y. *Chem. Eur. J.* **2014**, *20*, 1332. (b) Li, L.; Deng, M.; Zheng, S.-C.; Xiong, Y.-P.; Tan, B.; Liu, X.-Y.

Org. Lett. **2014**, *16*, 504. (c) Xiong, Y.-P.; Wu, M.-Y.; Zhang, X.-Y.; Ma, C.-L.; Huang, L.; Zhao, L.-J.; Tan, B.; Liu, X.-Y. *Org. Lett.* **2014**, *16*, 1000. (d) Zhu, X.-L.; Xu, J.-H.; Cheng, D.-J.; Zhao, L.-J.; Liu, X.-Y.; Tan, B. *Org. Lett.* **2014**, *16*, 2192.

(5) (a) Böhm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (b) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013. (c) De Matteis, V.; Van, D. F. L.; Jakobi, H.; Lindell, S.; Tiebes, J.; Rutjes, F. P. J. T. *J. Org. Chem.* **2006**, *71*, 7527. (d) Dolfen, J.; Kenis, S.; Hecke, K. V.; Kimpe, N. D.; D'hooghe, M. *Chem. Eur. J.* **2014**, *20*, DOI: 10.1002/chem.201304759.

(6) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.

(7) For selected representative examples on trifluoromethylation with Ruppert-Prakash reagent, see: (a) Cho, E. J. ; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679. (b) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2010**, *132*, 7262. (c) Chu, L.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 5060. (d) Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3793. (e) Tomashenko, O. A.; Escudero-Adan, E. C.; Belmonte, M. M.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 7655; (f) Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. *J. Org. Chem.* **2011**, *76*, 1174. (g) Ye, Y.; Lee, S. H.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 5464. (h) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298; (i) Hu, M.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2012**, *134*, 15257. (j) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51,* 536; (k) Hafner, A.; Bräse, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3713. (l) Chen, C.; Chu, L.; Qing, F.-L. *J.*

Am. Chem. Soc. **2012**, *134*, 12454. (m) Hu, M.; He, Z.; Gao, B.; Li, L.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 17302.

(8) For examples on trifluoromethylation of alkenes with Ruppert-Prakash reagent, see: (a) Chu, L.; Qing, F.-L. *Org. Lett.,* **2012**, *14*, 2106. (b) Wu, X.; Chu, L.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 2198.

(9) (a) Kitazume, T.; Nakajima, S. *J. Fluorine Chem.* **2004**, *125*, 1447. (b) Kremlev, M. M.; Mushta, A. I.; Tyrra, W.; Yagupolskii, Y. L.; Naumann, D.; Möller, A. *J. Fluorine Chem.* **2012**, *133*, 67. (c) Lishchynskyi, A.; Novikov, M. A.; Martin, E.; Escudero-Adan, E. C.; Novak, P.; Grushin, V. V. *J. Org. Chem.* **2013**, *78*, 11126. (d) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev*. **2008**, *108*, 3054. (e) Correa, A.; Bolm, C. *Adv. Synth. Catal*. **2007**, *349*, 2673.

(10) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270.

(11) (a) Dai, J.-J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z. J.; Lu, X.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8436. (b) Wang, X.; Xu, Y.; Mo, F.; Ji, G.; Qiu, D.; Feng, J.; Ye, Y.; Zhang, S.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2013**, *135*, 10330. (c) Danoun, G.; Bayarmagnai, B.; Grunberg, M. F.; Goossen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 7972. (d) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 20901.

(12) For selected examples on copper-catalyzed hydroamination of unactivated alkenes, see: (a) Zabawa, T. P. Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250. (b) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*,

2938.

(13) Mao, Z.; Huang, F.; Yu, H.; Chen, J.; Yu, Z.; Xu, Z. *Chem. Eur. J.* **2014**, *20*, 3439.

(14) Miyaji, R.; Asano, K.; Matsubara, S. *Org. lett.* **2013**, *15*, 3658.

(15) Majumdar, K.; Samanta, S.; Chattopadhyay, B.; Nandi, R. *Synthesis* **2009**, *2010*, 863.

(16) Miyazaki, Y.; Ohta, N.; Semba, K.; Nakao, Y. *J. Am. Chem. Soc*. **2014**, *136*, 3732.

(17) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc*. **2009**, *131*, 9488.

(18) Fustero, S.; Moscardo, J.; Jimenez, D.; Perez-Carrion, M. D.; Sanchez-Rosello, M.; Del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868.

(19) Du, B.; Jiang, X.; Sun, P. *J. Org. Chem*. **2013**, *78*, 2786.

(20) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc*. **2005**, *127*, 11250.

(21) Julian, L. D.; Hartwig, J. F. *J. Am. Chem. Soc*. **2010**, *132*, 13813.