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Aqueous Benzylic C−H Trifluoromethylation for Late-Stage Functionalization

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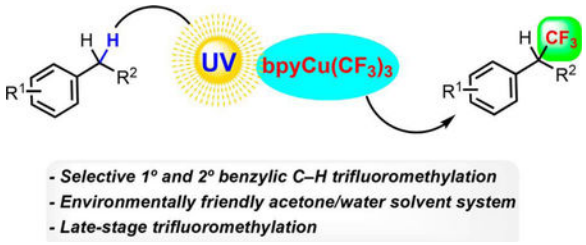
Abstract

The installation of trifluoromethyl groups has become an essential step across a number of industries such as agrochemicals, drug discovery, and materials. Consequently, the rapid introduction of this critical functional group in a predictable fashion would benefit current practitioners in those fields. This communication describes a mild trifluoromethylation of benzylic C−H bonds with high selectivity for the least hindered hydrogen atom. The reaction provides monotrifluoromethylation and proceeds in an environmentally friendly acetone/water solvent system. The method can be used to install benzylic trifluoromethyl groups on highly functionalized drug molecules.

Graphical Abstract



Facile installation of the trifluoromethyl group remains a critical goal for organic synthesis. The unusual and often desirable properties of the trifluoromethyl group (e.g., high electronegativity and Teflon-like stability) have propelled this moiety into the structures of a striking number of drugs, drug-candidates, agrochemicals, and materials.[1] Ever since the McLoughlin−Thrower reaction,[2] chemists have searched for easily implemented couplings to install the trifluoromethyl group.[3] Excitingly, a number of recent reports describe novel trifluoromethylating reagents that offer the potential for new opportunities to trifluoromethylate organic molecules. The wide availability of the Ruppert−Prakash,[4] Togni,[5] Umemoto,[6] Langlois,[7] Grushin,[8] Chen,[9] Shibata,[10] Baran[11] and other reagents[12] have

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Supporting Information

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Experimental details and spectroscopic data (PDF)

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provided chemists with numerous useful trifluoromethyl synthons with unique properties. Evaluating such reagents under traditional reaction conditions should enable rapid access to new chemical matter.

For aromatic trifluoromethylation, methods have primarily focused on metal-mediated couplings related to the McLoughlin−Thrower[2,13] or radical addition to electron-deficient aromatic system to supplant individual Csp^2−H bonds (Figure 1c).[11,14] The introduction of aliphatic trifluoromethyl groups has lagged by comparison.[3b,e, 15] For example, while fluoroform is reasonably acidic (pK_a = 28),[16] the simple S_N2 reaction to install aliphatic trifluoromethyl groups remains troublesome due to the rapid decomposition of the CF_3 anion to fluoride and difluorocarbene.[17] Recent work has demonstrated that the use of radicals generated from aliphatic carboxylic acids,[18] esters,[19] or halides[20] offers a more convenient path to aliphatic trifluoromethylation compared to metal-mediated coupling.[15b] A more direct approach would be to target Csp^3−H bonds for trifluoromethylation without the use of preinstalled functional groups,[21] a variant of which was published by Liu and co-workers during the preparation of this work.[22]

Classic halogenation chemistry uses subtle changes in reaction conditions to select for aromatic or benzylic functionalization (Figure 1a,b). While the halogenation of alkenes and aromatics was known in the 19th century (Figure 1a), it was the Wohl−Ziegler reaction that revolutionized our thinking on how subtle changes in reagents and conditions can have a drastic effect on the outcome of halogenation chemistry (Figure 1b).[23] Mysterious at the time, the divergent selectivity stemmed from the unknown, but critical, mechanistic switch from two-electron to radical chemistry. Based on this classic work, we were curious whether some modern trifluormethylating reagents might be capable of quenching benzylic radicals generated directly from C−H bonds (Figure 1d).

To start our investigations, we evaluated a variety of mild peroxides for their ability to generate benzylic radicals from toluene (1a). We found ammonium persulfate forms the TEMPO inclusion product and bibenzyl in modest yield (eq 1). Based on a number of recent reports on copper-catalyzed benzylic C−H functionalization,[24] we reasoned that one of the newly introduced $CuCF_3$ complexes 2a−2c might work in synergy with benzylic radical formation.[8,12] To test this hypothesis, ammonium persulfate and Grushin's reagent (2a) were heated to 50 °C in the presence of toluene (Table 1, entry 3). Interestingly, 6% of the desired product 3a formed in the reaction. Since UV light facilitates radical C−H halogenation,[23a] we exposed the reaction to a 365 nm LED bulb (Table 1, entry 4), which dramatically increased the yield to 58%. A variety of strong acids proved beneficial, with trifluoroacetic acid being the most convenient and high yielding (Table 1, entry 5). The presence of acid may facilitate the homolysis of Grushin's reagent (2a) through the protonation of the bipy ligand. No product formed under a variety of reaction conditions with copper complex 2b (Table 1, entry 7), but complex 2c did provide detectable 4% yield (Table 1, entry 8). Based on the observation that aromatic trifluoromethylation was a competing pathway (Figure 1a), we reasoned that the CF_3 radical byproduct from Grushin's reagent (2a) was consuming 1a. Consequently, we sought a mild radical quenching agent that would be degenerate with benzyl radical. After evaluating a series of silanes (see Supporting Information), we found both triisopropylsilane and *t*-butyldimethylsilane dramatically increased the yield (Table 1,

entries 1, 5, 9−10) while suppressing aromatic trifluoromethylation (Figure 1a). Consequently, the direct trifluoromethylation of toluene (1a) could be conducted in near quantitative yield based on 2a with equimolar ammonium persulfate/triisopropylsilane and 8 equiv of TFA[25] in acetone/water solvent system (Table 1, entry 1).

After establishing the optimal reaction conditions for the trifluoromethylation of toluene, we next evaluated a range of benzylic C−H bonds (Table 2). Interestingly, the reaction did not track the reactivity expected of benzylic C−H radical abstraction.[23a] That is to say, the reaction showed a clear dependence on the steric environment of the benzylic C−H bond, whereby primary benzylic C−H bonds reacted faster and in higher yield than secondary benzylic C−H bonds (Table 2a vs 2b). Moreover, tertiary benzylic or tertiary unactivated C−H bonds showed no trifluoromethylation under our standard reaction conditions. This surprising result allows practitioners to reliably and selectively target specific benzylic C−H bonds in more complicated systems. Moreover, the reaction offers a monoselective trifluoromethylation, with excess Grushin's reagent (2a) providing only minimal ditrifluoromethylation. Even in cases with multiple, identical benzylic C−H sites, the monotrifluoromethylation could be achieved in high yield (Table 2a, 3f−3h). The reaction tolerated a range of functional groups, including halides (3c, 3o, 3s, and 3cc), pseudohalides (3b), ketones (3i, 3aa−3cc, and 3ee), esters (3y and 3bb), amides (3j−3r, 3z, and 3dd), aliphatic nitriles (3x), phthalimides (3v and 3w), pyridines (3q and 3t), pyrimidines (3u) and silanes (3e). Moreover, substrates 1 could be used as the limiting reagent with only 10−15% loss in yield (1.5 equiv 2a), if the substrate is of particular value. Interestingly, there were occasions where seemingly valid substrates (simple primary or secondary benzylic C−H bonds with similar structural features) failed to undergo trifluoromethylation (see SI). Consequently, a greater mechanistic understanding was needed to reliably target requisite C−H bonds.

To understand the observed C−H selectivity, we probed the underlying mechanism for trifluoromethylation of primary, secondary, and tertiary benzylic C−H bonds (Figure 2). Experimentally, we observed that tertiary benzylic substrates react to produce benzylic hydroxylation and styrene (see SI), providing evidence for the formation of a tertiary benzylic radical that is slow to recombine with Cu(II). To better understand this observation, we calculated the relative energies for the reaction coordinate of primary (1_p), secondary (1_s), and tertiary (1_t) radicals. While the recombination with bipyCu(CF_3)$_2$ (4) is thermodynamically favorable for primary (1_p) and secondary (1_s) by −4.2 and −4.0 kcal/mol, respectively, the lowest energy cumenyl-copper(III) species (5_t) was +5.6 kcal/mol less stable than 1_t. This thermodynamically uphill radical Cu−C recombination is surprising, but reflects the unfavorable steric hindrance in 5_t. Moreover, the rate-determining reductive elimination is definitively higher for tertiary 5_t-TS but not so unfavorable as to subvert the overall reaction at 23 °C. Consequently, the energetically uphill recombination of the tertiary radicals with Cu(II) (4) allows unfavorable side reactions (e.g., oxidation/elimination to form styrene) before productive reductive elimination can occur.

While we constructed this reaction through analogy to the Wohl−Ziegler reaction, a detailed picture for our current mechanistic understanding arose through key mechanistic experiments (Figure 3). The UV light serves multiple roles, facilitating persulfate cleavage and homolysis of 2a to form the active Cu(II) species (4) and CF_3 radical (Figure 3).[20] While both sulfate radical anion and silyl radical could form the benzylic radical (1-rad), H-atom abstraction with sulfate is −12.9 kcal/mol more favorable thermodynamically than with silyl radical (see SI). We were intrigued by the production of significant quantities of fluoroform in the reaction. Examination of deuterated toluene (*d*8−1a), silane, and water revealed $CDCF_3$ forms from the reaction of CF_3 radical with silane (see SI). These experiments explain the underlying mechanism for the ability of silane to suppress aromatic trifluoromethylation (Figure 1c), through the quenching of CF_3 radical (see SI). Subsequent steps remain favorable whether the Cu(II) species is unligated, complexed with bpy, or the aqua complex 5 (see SI). Since the Cu(II) forms in acidic water, aqua complex 5 represents the most relevant intermediate along the reaction coordinate. Since 1-rad recombination with the $Cu(CF_3)_2$ (4) is only ~4 kcal/mol, we ruled out the outersphere mechanism (i.e., where 1-rad abstractsa CF_3 directly), which would requirea >61 kcal/mol transition state (see SI). Finally, the reductive elimination continues through a low 10.5−21.8 kcal/mol barrier (depending on ligation state, see SI) to form desired product 3 and unreactive 6 (cf. 2c in Table 1).

The primary kinetic isotope effect (KIE) of k_H/k_D = 2.8 observed for the intermolecular, same-flask competition of toluene (1a) and toluene-d_8 (d_8-1a) suggests that the C−H bond-cleavage step or a prior step is rate determining (see SI).[26] In combination with the k_H/k_D = 4.2 for the intramolecular KIE of mono-CD_3 *p*-xylene (d3−1f), the homolysis of persulfate at 23 °C under 365 nm light offers the most likely rate-determining step for the overall reaction. While similar to radical halogenation,[27] the facility with which the benzylic radical is quenched with trifluoromethylcopper reagent 4 is remarkable.

The clear advantage of this reaction is the ability to predictably incorporate the trifluoromethyl group at benzylic sites of elaborated molecules. To test this methodology, we subjected several biologically relevant small molecules trifluoromethylation (Scheme 1). Trifluoromethylation of protected 4-methylphenylglycine, meclizine, or celecoxib provided novel, undisclosed CF_3 analogs in all cases. Clearly, the method should find immediate use for the facile trifluoromethylation of important molecules.

In summary, we developed a mild method for the trifluoromethylation of unhindered benzylic C−H bonds. The method tolerates a wide range of functional groups and basic heterocycles and can be used in the late-stage trifluoromethylation of bioactive molecules. Moreover, the reaction proceeds in an environmentally friendly 1:1 acetone/water mixture. Detailed mechanistic analysis offers a framework to understand selectivity of Grushin's reagent 2a toward trifluoromethylation of primary and secondary benzylic hydrogens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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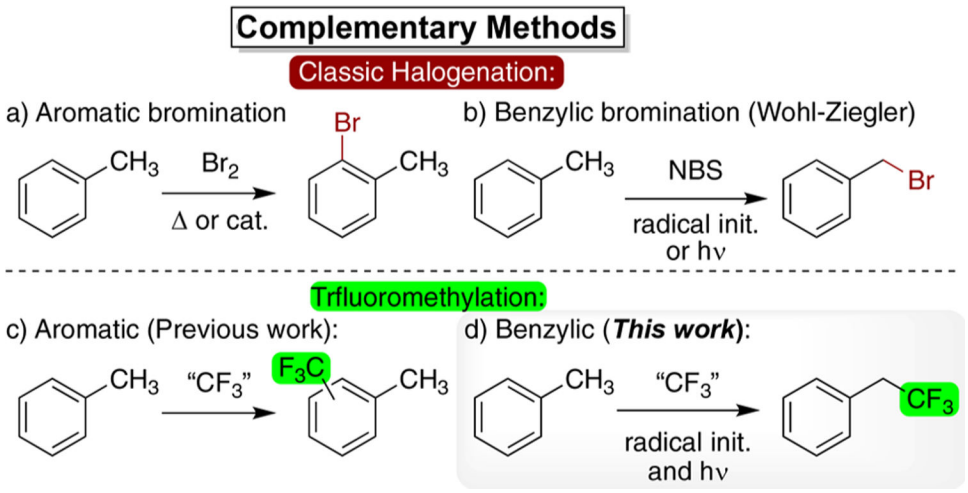


Figure 1.

The switch from aromatic bromination (a) to benzylic bromination (b) requires relatively minor changes to the reaction conditions. The modern switch from aromatic trifluoromethylation (c) to benzylic trifluoromethylation (d) has yet to be realized.

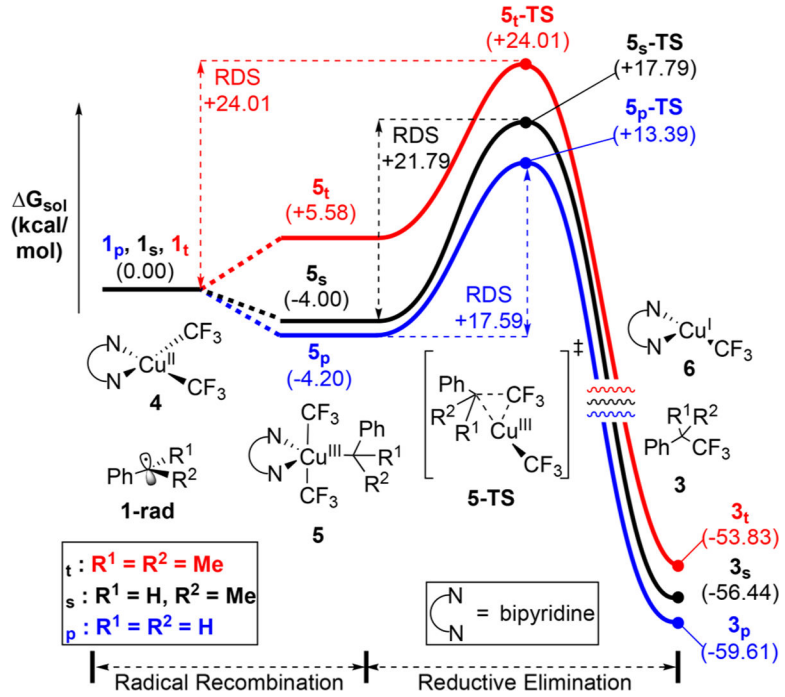


Figure 2.

Computed energy profile of C−H selectivity. Bipyridineligated Cu illustrated here possessed the highest energy barriers relative to water- or unligated Cu.

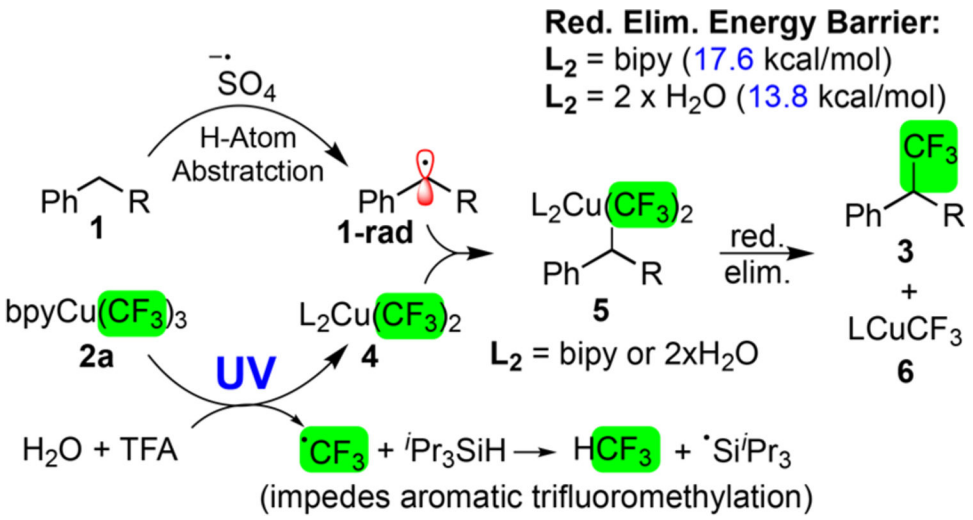
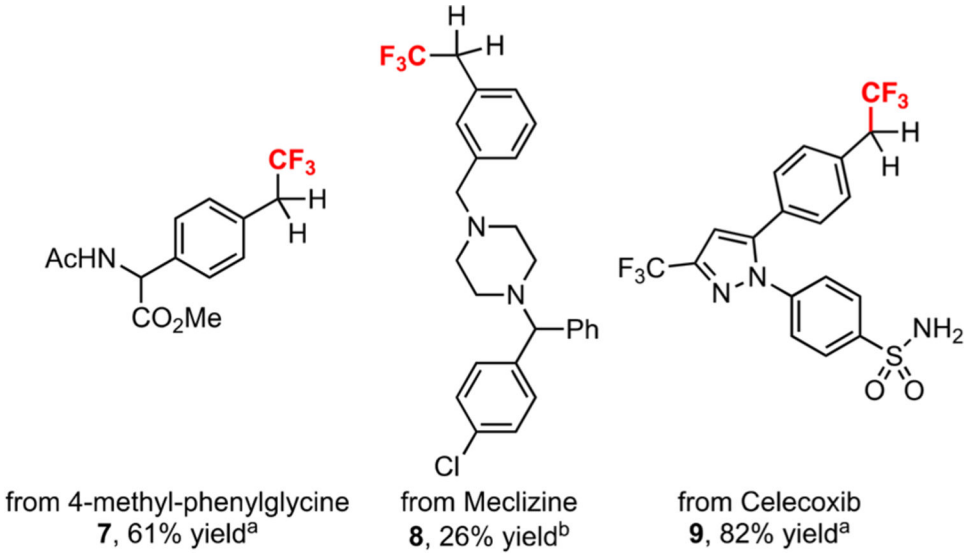


Figure 3.
Mechanistic details.

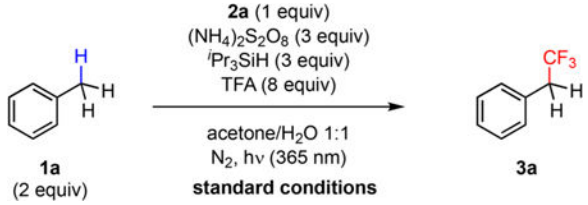


Scheme 1. Late-Stage C−H Trifluoromethylation of Bioactive Molecules

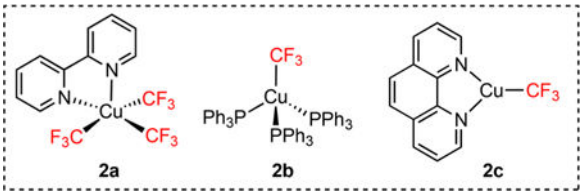
[a]The reactions were run on 0.3 mmol scale with substrate (0.6 mmol) and 2a (0.3 mmol) in 3.0 mL of solvent for 18 h unless otherwise noted. Isolated yield.[b]10 equiv of TFA was used.

Table 1.

Optimization of Pertinent Reaction Parameters[a]



Entry	conditions	Yield of 3a (%)[b]
1	standard conditions	99%
2	without $(NH_4)_2S_20_8$	0%
3	50°C intead of UV	6%
4	without TFA and $^{i}Pr_3SiH$	58%
5	without $^{i}Pr_3SiH$	78%
6	without TFA	62%
7	**2b** instead of **2a**	0%
8	**2c** instead of **2a**	*4%*
9	Et_3SiH instead of $^{i}Pr_3SiH$	60%
10	$^{t}BuMe_2SiH$ instead of' $^{i}Pr_3SiH$	81%

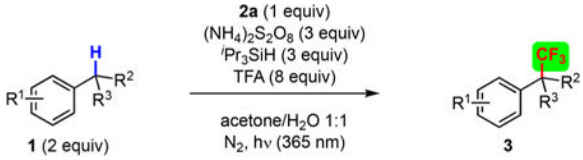


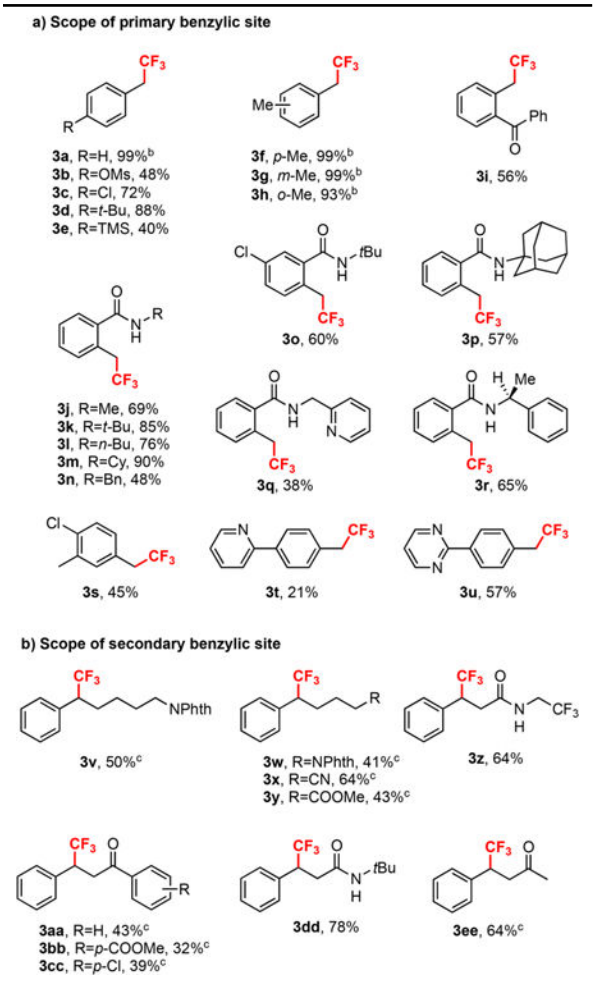
[a]Unless otherwise noted, all the reactions were run with 1a (0.6 mmol) and 2a (0.3 mmol) in 3.0 mL of solvent for 18 h.

[b]Yields were determined by ^{19}F NMR spectroscopy with 1-chloro-4-fluorobenzene as the internal standard.

Table 2.

Substrate Scope for Trifluoromethylation[a]





[a]All reactions were run on 0.3 mmol scale with 1a (0.6 mmol) and 2a(0.3 mmol) in 3.0 mL of solvent for 18 h unless otherwise noted. Isolated yield.

[b]Yield determined by ^{19}F NMR spectroscopy with 1-bromo-4-fluorobenzene as the internal standard.

[c]2.0 equiv of *t*BuMe$_2$SiH instead of 3.0 equiv of *i*Pr$_3$SiH, and 4.0 equiv of (NH$_4$)$_2$S$_2$O$_8$ were used. Cy = cyclohexyl, Phth = phthalimido.