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Copper-catalyzed oxidative trifluoromethylation of benzylic sp^3 C–H bond adjacent to nitrogen in amines

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ABSTRACT

Copper-catalyzed trifluoromethylation via oxidative sp^3 C–H activation at the α-position of nitrogen in tetrahydroisoquinoline derivatives using DDQ and Ruppert–Prakash reagent has been successfully achieved. The reaction of various amines gave the corresponding trifluoromethylated products in 15–90% yields under mild conditions.

Fluorinated moieties such as the trifluoromethyl group can dramatically influence the polarity, solubility, chemical reactivity, and intermolecular interactions of an entire molecule.[1a–c] Amines trifluoromethylated at the α-position of nitrogen are important intermediates for pharmaceuticals, agrochemicals, and organic materials.[1d–g] One of the general methods to obtain trifluoromethyl containing amines is based on the addition of a CF_3 group on to imine double bonds by using, for example, the Ruppert–Prakash reagent (trifluoromethyltrimethylsilane, CF_3TMS).[2] Although these methods have provided α-trifluoro-methylated amine derivatives effectively,[3] a more direct and simpler synthetic method such as the direct trifluoro-methylation of the α-position of nitrogen via sp^3 C–H activation is still highly attractive.

In our own studies, we recently reported various cross-dehydrogenative-coupling reactions between various nucleophiles and sp^3 C–H bonds via the in situ generation of iminium intermediates by using an oxidizing reagent.[4] Highly efficient arylation[5] and phosphinylation[6] of sp^3 C–H bonds are also possible. We speculated the possibility of a direct catalytic conversion of the sp^3 C–H bond at the α-position of amines into trifluoromethylated products by using CF_3TMS, amenable for potential asymmetric synthesis to generate optically active trifluoromethylated derivatives. Herein, we wish to report a highly efficient copper-catalyzed trifluoromethylation via oxidative sp^3 C–H activation at the α-position of nitrogen in tetrahydroisoquinoline derivatives using DDQ and CF_3TMS under very mild conditions (Fig. 1).

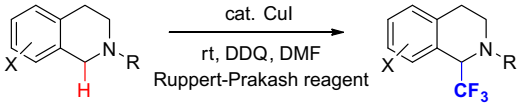

Figure 1. Copper-catalyzed trifluoromethylation of C–H bond.

To begin our study, the substrate and oxidant reported by our group earlier[4] were selected as the initial trial (Table 1, entry 1). Unfortunately, the desired product was not observed and most of the starting materials were recovered without change. We contemplated that CF_3TMS was most likely decomposed by the reaction with oxidants under these reaction conditions. It is important to note that during the process of our investigations, Qing and co-workers reported a direct trifluoromethylation of tertiary amines with benzoyl peroxide using CF_3TMS in methylene chloride under refluxing conditions.[7] However, the reaction conditions provided over-oxidized byproducts and required an additional reduction step to obtain the desired products. Furthermore, it cannot be modified for asymmetric synthesis readily. In addition, transition metal catalyzed trifluoromethylation of imine and iminium (proposed intermediates in our investigation) has not been reported to the best of our knowledge.

In order to find conditions that will selectively oxidize the amine while at the same time will not destroy CF_3TMS, different oxidants were further tested and we found that the reaction with DDQ[8] as an oxidant gave the desired compound in moderate yield (Table 1, entry 2).

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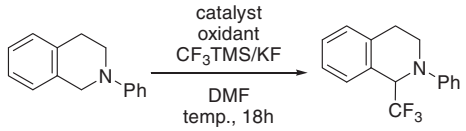
Table 1
Optimization of reaction conditions[a]

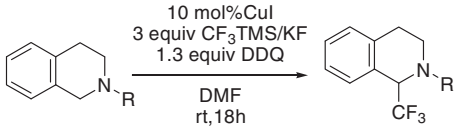


1a 2a

Entry	Oxidant (equiv)	Catalyst (mol%)	KF[c] (equiv)	Temp	Yield[b] (%)
1	TBHP(2.0)	CuI (10)	2	70 °C	nd (73)
2	DDQ (2.0)	CuI (10)	2	70 °C	52
3	DDQ (1.0)	CuI (10)	2	70 °C	72 (4)
4	DDQ (2.0)	CuI (10)	3	70 °C	77
5	DDQ (1.3)	CuI (5)	3	70 °C	90
6	DDQ (1.3)	CuI (10)	3	70 °C	87
7	DDQ (1.3)	CuI (20)	3	70 °C	84
8	DDQ (1.3)	CuBr (10)	3	70 °C	72
9	DDQ (1.3)	CuCl (10)	3	70 °C	68
10	DDQ (1.3)	CuOTf (10)	3	70 °C	68
11	DDQ (1.3)	CuI (10)	4	70 °C	86
12	DDQ (1.3)	CuI (10)	3	rt	85
13	DDQ (1.3)	CuI (10)	0[d]	rt	46
14	DDQ (1.3)	None	3	rt	0

[a] Reactions were carried out on a 0.15 mmol scale in DMF (0.5 mL) under argon with oxidant, CF_3TMS/KF and catalyst.
[b] Reported yields were based on **1a** and determined by NMR methods using an internal standard. Recoveries are given in parentheses.
[c] Same amount of CF_3TMS was added in the reaction.
[d] 3 equiv of CF_3TMS was added in the reaction.

Table 2
Copper-catalyzed trifluoromethylation of amines[a]



1 2

Entry	R	Product	Yield[b] (%)
1	Ph-	**2a**	85 (81)
2	2-$MeOC_6H_4$–	**2b**	67 (65)
3	3-$MeOC_6H_4$–	**2c**	62 (57)
4	4-$MeOC_6H_4$–	**2d**	73 (73)
5	4-BrC_6H_4–	**2e**	76 (69)
6	4-ClC_6H_4–	**2f**	63(58)
7	4-$CF_3C_6H_4$–	**2g**	49 (41)
8	1-Naphthyl-	**2h**	60 (46)
9	2-Pyridyl-	**2i**	15 (11)
10	Bn-	**2j**	52 (40)
11	2-Pyridylmethyl-	**2k**	55 (48)
12	Allyl-	**2l**	32(––)
13	Piv-	––	ND[c]
14	Boc-	––	ND[c]
15	H-	––	ND

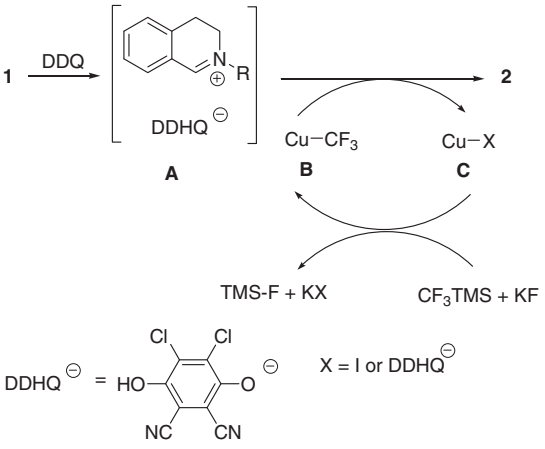
[a] Reactions were carried out on a 0.15 mmol scale in DMF (0.5 mL) under argon with CF_3TMS/KF as oxidant and catalyst.
[b] Reported yields were based on **1** and determined by ^1H NMR methods using an internal standard. Isolated yields are given in parentheses.
[c] Starting materials were recovered.

In order to improve the yield, the reaction was conducted by changing the reaction parameters, such as catalyst, solvent, and reactant ratio. The reaction with 3.0 equiv of CF_3TMS/KF, 1.3 equiv of DDQ, together with 5–10 mol% of CuI as the catalyst stirred in DMF under an argon atmosphere at 70 °C overnight gave the desired product **2a** in high yield (Table 1, entries 5 and 6). It is important to note that, in these cases, the over oxidized byproduct as reported by Qing and co-workers was not detected by ^1H NMR. We then carried out further examinations to know more details about the reaction: in the absence of KF, product **1a** was observed in moderate yield under the above conditions (Table 1, entry 13); and no product was detected in the absence of CuI (Table 1, entry 14). The reaction proceeded equally well at room temperature (Table 1, entry 12), which is very important for potential asymmetric synthesis.

Next, the scope of our reaction was investigated by the treatment of various amines under the aforementioned optimized reaction conditions (Table 2).

Both 2-aryl-substituted and 2-alkyl-substituted tetrahydroisoquinolines were effective substrates for the oxidative trifluoromethylation reaction. The reaction with 2-benzyl, 2-pyridylmethyl, and 2-allyl tetrahydroisoquinolines gave 1-trifluoromethylated tetrahydroisoquinolines regioselectively (Table 2, entries 10–12). In the case of the 4-trifluoromethylphenyl group, the yield decreased possibly due to the increased oxidative potential of the corresponding amine derivative caused by the electron-withdrawing trifluoromethyl group. Consistent with this hypothesis, substrates bearing even stronger electron-withdrawing groups, such as 2-acyl and alkoxycarbonyl group did not react at all with DDQ at room temperature (Table 2, entries 13 and 14).

The detailed mechanism for the reaction remains to be elucidated. On the basis of the previous literature of the copper catalyzed trifluoromethylation[9] and the oxidation of tetrahydroisoquinolines with DDQ,[8] oxidation of *N*-substituted tetrahydroisoquinoline with DDQ generates dihydroquinoline salt **A** as the first step. Next, trifluoromethylcopper **B**, generated by the reaction of CuI and CF_3TMS/KF, undergoes nucleophilic addition to give the desired products and copper salt **C**. The generated **C** would be reused to form CF_3Cu **B** in the nucleophilic step again (Scheme 1.)



Scheme 1. Plausible mechanism for the trifluoromethylation.

In summary, a copper-catalyzed trifluoromethylation of sp^3 C–H bonds adjacent to a nitrogen atom was developed. The reaction of various tetrahydroisoquinoline derivatives gave the corresponding trifluoromethylated products in 15–90% yields under very mild conditions. The scope, applications, mechanism, and asymmetric version of this reaction are under investigation.

Experimental procedure: Compounds **2a**, **2b**, **2d**, **2f**, **2g**, **2j,** and **2l** are known compounds and their ^1H NMR, ^{19}F NMR, and ^{13}C NMR spectra are consistent with the literature.[7]

To a mixture of CuI (3.0 mg, 0.015 mmol), 2-phenyl-1,2,3,4-tetrahydroisoquinoline (36.4 mg, 0.15 mmol), potassium fluoride (26.1 mg, 0.45 mmol), and 0.3 mL DMF were added. Then trifluoromethyltrimethylsilane (66 μL, 0.45 mmol) was dropped into the mixture under argon at room temperature. The resulting mixture was stirred for 15 min. Then DDQ (0.2 mL, 1.0 M in DMF,

0.2 mmol) was dropped into the mixture over 5 min under argon at room temperature. The resulting mixture was stirred at the same temperature for 15 min. The resulting suspension was diluted with hexane/ethyl acetate (3/1) solution and then saturated sodium hydrogen carbonate aqueous solution was dropped into the reaction mixture. After the organic layer was separated, the water layer was extracted twice with hexane/ethyl acetate (3/1) solution. The combined organic layer was washed twice with water and dried with sodium sulfate. The resulting solution was filtered through a short silica gel in a pipette eluting with hexane/ethyl acetate (3/1). Solvent was evaporated and the residue was purified by flash column chromatography on silica gel with hexane as eluent to give the desired product.[10]

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10. Characterization of unknown compounds. *2-(3-Methoxyphenyl)-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline* **2c**: ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ ppm 7.34–7.19 (m, 5H), 6.59 (dd, J = 2.4 Hz, J = 8.1 Hz, 1H), 6.53 (t, J = 2.4 Hz, 1H), 6.42 (dd, J = 2.4 Hz, J = 8.1 Hz, 1H), 5.14 (q, J = 7.8 Hz, 1H), 3.82 (s, 3H), 3.83–3.75 (m, 1H), 3.55–3.47 (m, 1H), 3.07–3.02 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ ppm −71.5 (d, J = 7.9 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ ppm 160.7, 150.7, 136.8, 130.0, 128.8 (t, J = 1.7 Hz), 128.7, 128.5, 127.9, 107.3 (d, J = 1.1 Hz), 103.5, 101.4, 60.7 (q, J = 26.5 Hz), 55.3, 43.6, 27.4 (d, J = 1.1 Hz). HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{17}H_{17}ONF_3$, 308.12568; found, 308.12536. *2-(4-Bromophenyl)-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline* **2e**: ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ ppm 7.38–7.23 (m, 6H), 6.83 (d, J = 9.0 Hz, 2H), 5.06 (q, J = 8.1 Hz, 1H), 3.80–3.73 (m, 1H), 3.48–3.40 (m, 1H), 3.09–3.01 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ ppm −71.6 (d, J = 7.6 Hz, 3F). ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): δ ppm 148.3, 136.6, 132.0, 128.8 (d, J = 4.4 Hz), 128.5, 126.5, 116.0, 111.2, 60.4 (q, J = 30.4 Hz), 43.7, 27.4. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{16}H_{14}BrNF_3$, 356.02567; found, 356.02592. *2-(1-Naphthyl)-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline* **2h**: ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ ppm 8.35–8.31 (m, 1H), 7.89–7.86 (m, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.57–7.46 (m, 3H), 7.40–7.24 (m, 4H), 7.02 (br s, 1H), 4.99 (q, J = 8.4 Hz, 1H), 3.87 (br s, 1H), 3.44–3.40 (m, 1H), 2.82 (br s, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ ppm −72.5 (br s, 3F). ^{13}C NMR (75.4 MHz, $CDCl_3$, 293 K, TMS): δ ppm 148.3, 137.3, 134.9, 129.3, 128.7 (q, J = 2.2 Hz), 128.4, 126.3, 126.2, 126.1, 125.7, 125.0, 123.8, 119.8, 113.1, 62.3(q, J = 28.7 Hz), 47.2, 26.2. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{20}H_{17}NF_3$, 328.13076; found, 328.13126. *2-(2-Pyridyl)-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline* **2i**: ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ ppm 8.23 (d, J = 3.6 Hz, 1H), 7.52 (t, J = 6.6 Hz, 1H), 7.40 (d, J = 7.2 Hz, 1H), 7.33–7.22 (m, 3H), 6.71 (d, J = 7.8 Hz, 1H), 6.67 (t, J = 5.1 Hz, 1H), 6.46 (q, J = 8.4 Hz, 1H), 3.87–3.81 (m, 1H), 3.78–3.70 (m, 1H), 3.18–3.09 (m, 1H), 5.05–2.56 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ ppm −71.6 (d, J = 8.8 Hz, 3F). ^{13}C NMR (75.4 MHz, $CDCl_3$, 293 K, TMS): δ ppm 157.7, 147.6, 137.8, 136.6, 129.2, 129.1, 129.0, 128.6, 128.5, 127.8, 126.4, 124.0, 113.8, 106.5, 54.6 (q, J = 30.4 Hz), 41.5, 27.5 (d, J = 1.1 Hz). HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{15}H_{14}N_2F_3$, 279.11036; found, 279.10998. *2-(2-Pyridylmethyl)-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline* **2k**: ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): δ ppm 8.52 (d, J = 4.5 Hz, 1H), 7.74–7.68 (m, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.31–7.16 (m, 5H), 4.36 (q, J = 8.1 Hz, 1H), 4.14 (s, 2H), 3.31–3.23 (m, 1H), 2.87–2.85 (m, 2H), 2.79–2.73 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ ppm −73.2 (s, 3F). ^{13}C NMR (75.4 MHz, $CDCl_3$, 293 K, TMS): δ ppm 159.1, 148.9, 137.3, 136.9, 129.5 (d, J = 2.2 Hz), 128.6, 128.3, 128.2, 126.1, 122.6, 122.3, 62.8(d, J = 27.6 Hz), 62.5, 46.3, 27.3. HRMS ESI (m/z): $[M+H]^+$ calcd for $C_{16}H_{16}N_2F_3$, 293.12601; found, 293.12555.