Benzoyl peroxide (BPO)-promoted oxidative trifluoromethylation of tertiary amines with trimethyl(trifluoromethyl)silane†

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The benzoyl peroxide (BPO)-promoted oxidative functionalization of tertiary amines under transition-metal-free reaction conditions was developed. Various 1-trifluoromethylated tetrahydroisoquinoline derivatives were prepared by employing this method. It constitutes the first example of direct trifluoromethylation of tertiary amines.

Amines bearing a trifluoromethyl group located at the α-position are widely applicable in the synthesis of pharmaceuticals and agrochemicals,[1] because the strongly electron withdrawing nature and large hydrophobic domain of the trifluoromethyl group can dramatically influence the basicity and solubility of amines, and thus modify the bioavailability and stability of target drugs. As a result, trifluoromethylated amines have attracted considerable attention as synthetic targets. Among these synthetic methods, one of the most effective methods for synthesizing such compounds is the nucleophilic trifluoromethylation of imines or their equivalents with trimethyl(trifluoromethyl)silane (Ruppert–Prakash reagent, CF_3TMS).[2] Recently, direct functionalization of tertiary amines in the α-position has attracted much interest in organic chemistry and the fine chemical industry, since the starting materials could be used directly without prefunctionalization and thus the reaction had the advantages of atom- and step-economy, high efficiency, low cost and minimal environmental impact.[3–5] Generally, direct oxidative transformation at the α-position of tertiary amines is performed in two steps: α-C–H activation of amine to produce iminium ion intermediates and subsequent reaction with nucleophiles. Transition-metal catalysts[3–5] or metal–oxo species[3a–g] are required for the initial C–H activation. In the light of environmental consciousness and safety concerns, the development of new transition-metal-free functionalization of tertiary amines is desirable. To date, various nucleophiles have been used to capture the iminium ions.[3–5] However, to the best of our knowledge, the reaction of trifluoromethyl-based nucleophilic reagent (CF_3^-) with *in situ* generated iminium ion, which would be a direct route to trifluoromethylated amines, has not been reported. We describe herein the first effective, atom- and step-economical synthesis of trifluoromethylated amines through benzoyl peroxide (BPO)-mediated trifluoromethylation of tertiary amines with trimethyl(trifluoromethyl)silane under transition-metal-free reaction conditions.

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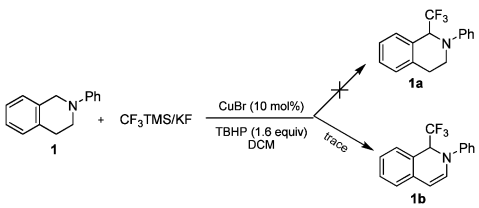
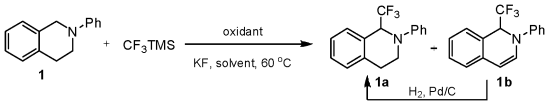
As tetrahydroisoquinoline derivatives are important structural features of pharmaceutical and natural products[6] and synthetic 1-trifluoromethyl analogues of tetrahydroisoquinoline alkaloids are of potential biological interest,[7] we focused on the direct oxidative trifluoromethylation of tetrahydroisoquinoline derivatives. Prior to this work, the only way to construct the 1-trifluoromethyltetrahydroisoquinoline framework was *via* the intramolecular Pictet–Spengler reaction.[7] Recently, an effective CuBr-catalyzed oxidative difluoromethylation of tertiary amine with difluoroenol silyl ethers using *tert*-butyl hydroperoxide (TBHP) as the oxidant was developed by our group.[4q] On the basis of this work, we started the oxidative trifluoromethylation of tertiary amine by treatment of 1,2,3,4-tetrahydroisoquinoline **1** with CF_3TMS/KF in the presence of catalytic CuBr and TBHP. Unfortunately, the desired product **1a** was not observed and only a trace amount of compound **1b** was obtained [eq. (1)]. Compound **1b** may be formed from the further oxidation of **1a**. Altering the relative amounts of reagents, solvents and reaction temperature did not lead to improvement. Since CuBr/TBHP is widely used for α-C–H activation of tertiary amines to produce iminium ion intermediates,[4] we speculated that the failure of oxidative trifluoromethylation under these reaction conditions was because: (1) the rate of formation of nucleophile CF_3^- from CF_3TMS/KF is not consistent with the rate of generation of the iminium ions; (2) the "CF_3Cu",[8] which was *in situ* generated from CF_3TMS/KF/CuBr, does not react with the iminium ion; (3) the Ruppert–Prakash reagent (CF_3TMS) undergoes decomposition under these reaction conditions. Thus, we turned our attention to exploring other transition metal catalysts and oxidants for this oxidative trifluoromethylation.



(1)

After screening of a number of reaction conditions, we were delighted to find that the desired product **1a** and the corresponding oxidative product **1b** were generated in 18% yield (determined by ^{19}F NMR) by using diethyl azodicarboxylate (DEAD) as an oxidant in the absence of transition metal catalyst. To improve this transformation, different oxidants were further tested. Benzoyl peroxide (BPO) was found as the best oxidant (Table 1, entries 1–5). Switching the solvent to dichloromethane (DCM), the yield of the desired product **1a** and **1b** was increased to 84%. Other solvents such as CH_3CN, 1,2-dimethoxyethane (DME), 1,2-dichloroethane (DCE), tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF)

Table 1 Oxidative trifluoromethylation of tetrahydroisoquinoline **1**[a]



Entry	Oxidant	Solvent	Yield (%)[b] (**1a** : **1b**)
1	DEAD	CH_3CN	18 (3.5 : 1)
2	NBS	CH_3CN	35 (8.2 : 1)
3	AIBN	CH_3CN	8 (2.1 : 1)
4	DDQ	CH_3CN	—
5	BPO	CH_3CN	72 (3.7 : 1)
6	BPO	DME	44 (3.0 : 1)
7	BPO	DCE	64 (4.2 : 1)
8	BPO	THF (reflux)	68 (1.5 : 1)
9	BPO	DMF	52 (3.5 : 1)
10	BPO	DCM (reflux)	84 (3.4 : 1) (82[c])

[a] The reaction was carried out with 0.2 mmol of **1**, 0.6 mmol of CF_3TMS, 0.6 mmol of KF, 0.3 mmol of BPO in DCM (0.25 M). [b] The ratio of **1a/1b** and yield were determined by ^{19}F NMR using benzotrifluoride as an internal standard. [c] Isolated yield.

were also suitable for this oxidative trifluoromethylation albeit giving moderate yields (entries 5–9). It should be noted that **1a** and **1b** were not easily separated by flash chromatography. To simplify the purification, hydrogenation of a mixture of **1a** and **1b** in the presence of Pd/C gave a single product **1a**.

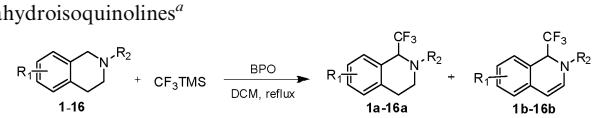
Next, the scope of this BPO-promoted oxidative trifluoromethylation was investigated by treatment of different tetrahydroisoquinoline derivatives under the aforementioned optimized reaction conditions. As shown in Table 2, the oxidative trifluoromethylation of all the substrates proceeded smoothly to give the corresponding products in 35–89% yields. In general, both *N*-aryl-substituted and *N*-alkyl substituted tetrahydroisoquinolines underwent the reaction. However, *N*-alkyl-substituted tetrahydroisoquinolines proved less reactive (**13–15**). The presence of Cl, Br and allyl groups in the products is very useful for further synthetic transformation (**5a**, **11a**, **14a**). It is apparent that the increasing electron density on the *N*-aromatic ring resulted in high selectivities (high ratio of products **a/b**) while it had a slight impact on the yields (**3**, **7**). Furthermore, 2-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole underwent the oxidative trifluoromethylation and the somewhat lower yield might be imputable to the presence of unprotected amine (**16**).

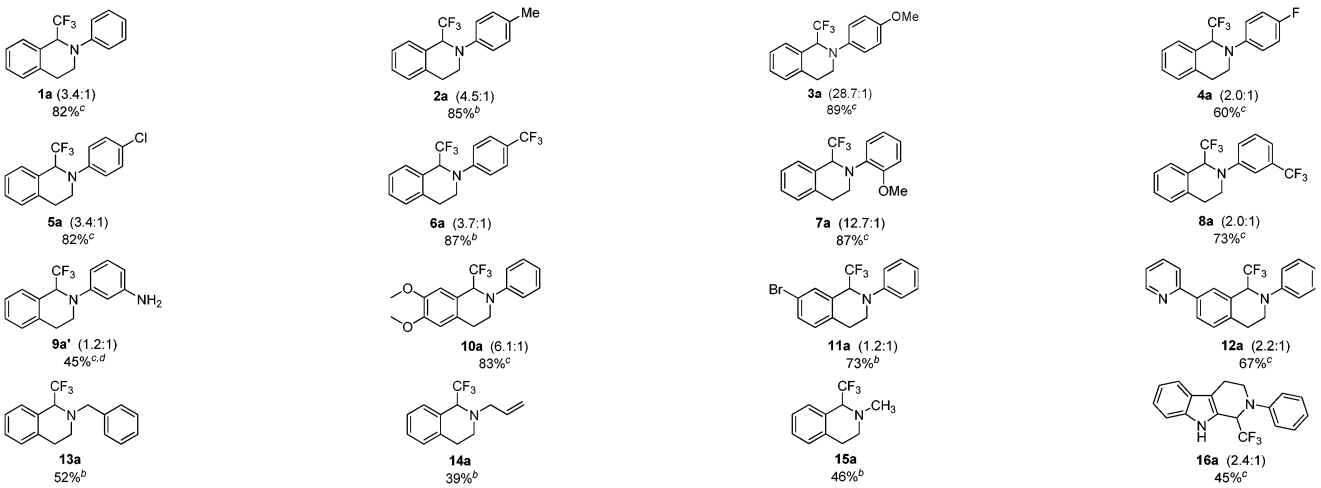
Considering that the presence of trace transition metal impurities may play a catalytic role in this transformation, all reagents were purified extensively before use. Furthermore, quantitative elemental analysis of BPO by ICP-AES (inductively coupled plasma-atomic emission spectrometry) showed that the concentration of all transition metals in the BPO employed in our experiments is less than 0.50 ppm, and thus the possibility of transition metal catalysis of this oxidative trifluoromethylation could be excluded.

The detailed mechanism remains to be elucidated. However, it is reasonable to assume that the reaction proceeds through a radical intermediate on the basis of the previous literature.[9,10] The radical intermediate **A** was probably formed by hydrogen transfer *via* either of two different pathways. Electron transfer from intermediate **A** gave iminium intermediate **B**. The subsequent nucleophilic capture of intermediate **B** by CF_3^- afforded the desired product (Scheme 1).

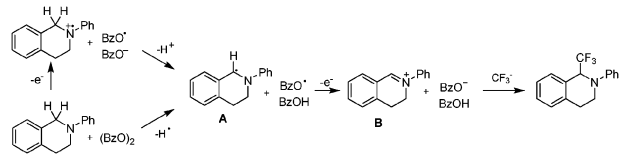
We also examined the BPO-promoted direct functionalization of tetrahydroisoquinoline **1** with other nucelophiles. The results are depicted in Fig. 1. Indole, nitromethane, and TMSCN all afforded the desired oxidative products **1c–1e** in moderate and high yields respectively, while a catalytic amount of CuBr was needed in the reaction of **1** with phenylacetylene, in which the participation of CuBr in the generation of iminium ion could not be excluded. It was

Table 2 Trifluoromethylation of tetrahydroisoquinolines[a]





[a] Reaction conditions: amine (0.5 mmol), CF_3TMS (1.5 mmol), KF (1.5 mmol), BPO (0.75 mmol), DCM (2 mL), reflux, 5–10 h. The data in parentheses are the ratio of two products **a/b**, which determined by ^{19}F NMR. [b] Isolated yield after chromatography. [c] Isolated yield of product **a** after hydrogenation. [d] The NO_2 group was transformed to the NH_2 group in the course of reduction by Pd/C.



Scheme 1 The proposed mechanism of oxidative trifluoromethylation.

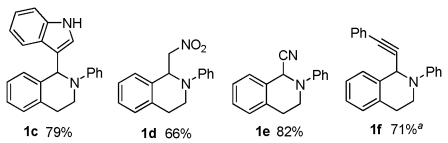


Fig. 1 Oxidative functionalization of **1** with various nucleophiles. Reaction conditions: **1** (0.5 mmol), BPO (0.75 mmol), nucleophile (1.5 mmol), DCM (2 mL), reflux, 5–10 h. 20 mmol% CuBr was added in the reaction of **1** with phenylacetylene.

noteworthy that only the desired products were produced in the oxidative functionalization of tetrahydroisoquinolines with these nucleophiles and no corresponding further oxidative products generated compared to the reactions of oxidative trifluoromethylation, indicating the unique characteristics of the trifluoromethyl group.

In summary, the first oxidative transformation of tertiary amines promoted by benzoyl peroxide (BPO) without transition metal was developed.[11] Various 1-trifluoromethylated tetrahydroisoquinoline derivatives were prepared by employing this method. It constituted the first example of direct trifluoromethylation of tertiary amines.

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