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Letter

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Cobalt-Tertiary Amine Mediated Hydroxytrifluoromethylation of Alkenes with CF_3Br and Atmospheric Oxygen

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KEYWORDS: alkene; hydroxytrifluoromethylation; bromotrifluoromethane; cobalt; tertiary amine.

ABSTRACT: The mild and efficient hydroxytrifluoromethylation of alkenes with bromotrifluoromethane (CF_3Br) and atmospheric oxygen mediated by cobalt-tertiary amine is described. This reaction proceeds with broad substrate scope and with a good functional group compatibility. Mechanistic studies indicate the reaction proceeds through a radical pathway, which is enabled by combination of the previously unexplored highly efficient *N*-isopropyl-*N*,2-dimethylpropan-2-amine with Co(II) for the single electron reduction of CF_3Br to CF_3 radical.

Organofluorine compounds are important substrates in a range of areas, including industrial chemicals, materials, agrochemicals, and pharmaceuticals.[1] In the context of drug discovery, the replacement of a methyl with a trifluoromethyl group (CF_3) dramatically improves the chemical and metabolic stability of the drug, while also increasing the lipophilicity — all of which are key design elements when developing and optimizing bioactive molecules.[2] Over the past few decades, great strides have been made in the development of methods that enable the synthesis of CF_3 containing molecules,[3] with a particular emphasis on the direct trifluoromethylation of alkenes.[4]

The most commonly used intermediate for this process is the trifluoromethyl radical,[5] which itself most commonly generated by one of three major routes:[6] 1) single electron transfer (SET) reduction of electrophilic trifluoromethylating reagents such as CF_3I,[7] *N*-hydroxybenzimidoylchloride trifluoroacetate,[8] Umemoto's reagent or Togni's reagents[9] with photoredox or copper catalysts; 2) SET oxidation of Langlois' reagent (CF_3SO_2Na) in the presence of the oxidants like peroxides or appropriate photoredox catalysts;[10] 3) oxidation of trifluoromethyl metal such as $AgCF_3$ and $CuCF_3$.[11] Despite much progresses, most of the existing trifluoromethylation reagents suffer from drawbacks, such as: multiple step(s) for the preparation, instable, expensive, or some are highly oxidative that would cause compatibility problems. It is therefore highly desirable to explore new methods that could make use of inexpensive and mild trifluoromethylation reagents.

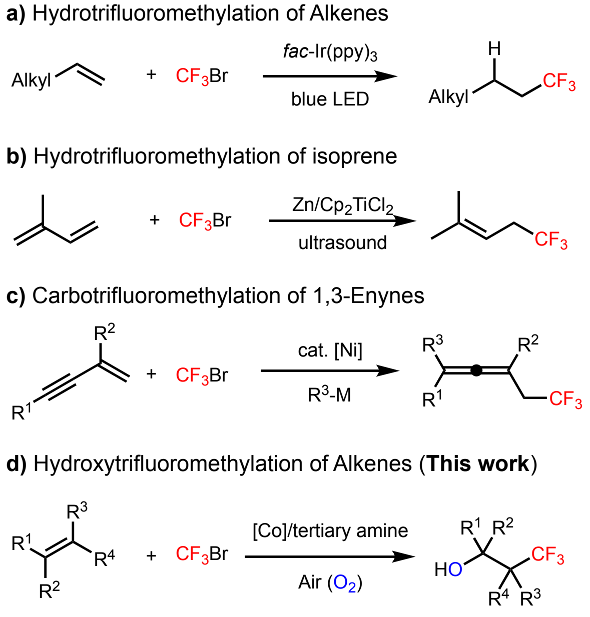
The primary starting material for the preparation of several trifluoromethylation reagents, including $TMSCF_3$, Togni's, Umemoto's, and Langlois' reagent is bromotrifluoromethane (CF_3Br),[12] an inexpensive and abundant material that is used as an effective fire extinguishant.[13]

Two common strategies have been developed in the transformation of CF_3Br:[12a] 1) converting CF_3Br into a nucleophilic CF_3 with strong reducing reagents, including such as Zn,[14] Al[15] or $P(NEt_2)_3$;[12b, 16] 2) converting CF_3Br into a CF_3 radical through electrochemical,[17] sulfinatodehalogenation[18] or transition metal induced SET reduction such as Ir under visible-light,[19] Ni,[20] Pd,[21] or Pt.[22]

Although with similar structure, CF_3Br is less reactive than CF_3I because of their reduction potential difference: CF_3Br −2.07 V, CF_3I −1.52 V (on a glass-carbon cathode).[23] Until now, we find only three reports on the trifluoromethylation of alkenes directly with CF_3Br: i) Zhang group developed a method of Ir catalyzed visible light induced hydrotrifluoromethylation of mono-substituted alkyl alkenes (Scheme 1. a);[19] ii) Kitazume group reported an example of ultrasound-promoted Zn and Cp_2TiCl_2 mediate hydrotrifluoromethylation of isoprene (Scheme 1. b),[24] and iii) Wang group realized a transformation of 1,3-enynes into fluoroalkylated allenes by nickel-catalyzed 1,4-carbofluoroalkylation via a radical relay coupling (Scheme 1. c).[20]

Building upon the foundation of these studies, we envisioned a simultaneous installation of two functional groups onto a carbon–carbon double bond — such difunctionalization of alkenes would be a pathway to increasing molecular complexity and would have wide application. Herein, we report a cobalt/tertiary amine mediated

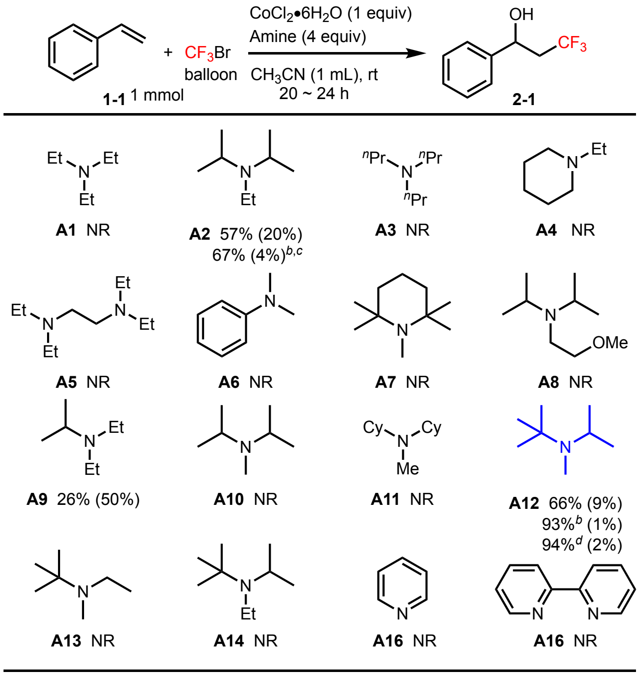
Scheme 1. The reaction of CF_3Br with alkenes.



hydroxytrifluoromethylation of alkenes with CF_3Br under mild conditions (Scheme 1. d).

Tertiary aliphatic amines have long been used as SET reductants.[25] Aiming to develop practical and simple catalytic systems, we proposed that a combination of an appropriate transition metal with a tertiary aliphatic amine would reduce the CF_3Br to CF_3 radical through a SET process. In our initial studies, we investigated the trifluoromethylation of styrene (**1-1**) with CF_3Br in the presence of 1 equiv of $CoCl_2\cdot 6H_2O$ and 4 equiv of NEt_3 (**A1**, Table 1) in CH_3CN, but no product was observed. After screening of several commercially available tertiary amines, we found that when the reaction was performed in the presence of Hünig's base (DIPEA, **A2**), the hydroxytrifluoromethylation product **2-1** was formed in 57% (NMR yield), with 20% of recovered styrene. We next explored different metal salts with DIPEA as the tertiary amine, and confirmed that cobalt was the optimal among those screened [See Table S1 in supporting information (SI)]. These preliminary results led to an empirical reactivity trend of this reaction affected by tertiary amines: The reactivity is very sensitive to the steric hindrance of the tertiary amines. Less hindered (**A1**, **A3**, **A4**) and bidentate (**A5**), aromatic (**A6**) or too bulky amines (**A7**) usually gave no product; proper hindrance in the amine enable the reaction (**A2**, **A9**); bidentate methoxyl-DIPEA (**A8**) would inhibit the reaction totally. With the preliminary data and recognition of the empirical rules at hand, we sought to improve the activity of the system by fine-tuning of the steric hindrance around the amine. When the ethyl group of DIPEA was replaced by a methyl, no product was produced (**A10**). The same result was obtained when two cyclohexyls replaced the two isopropyls (**A11**). Finally, when *N*-isopropyl-*N*-methyl-tert-butylamine (**A12**) was used, the yield improved to 66%. More to our surprise, neither removing a methyl of isopropyl (**A13**), nor changing a methyl to ethyl (**A14**) in **A12** produced any product. No reaction was observed when either pyridine (**A15**) or bipyridine (**A16**) were used.

Table 1. Optimization of the tertiary amines[a]

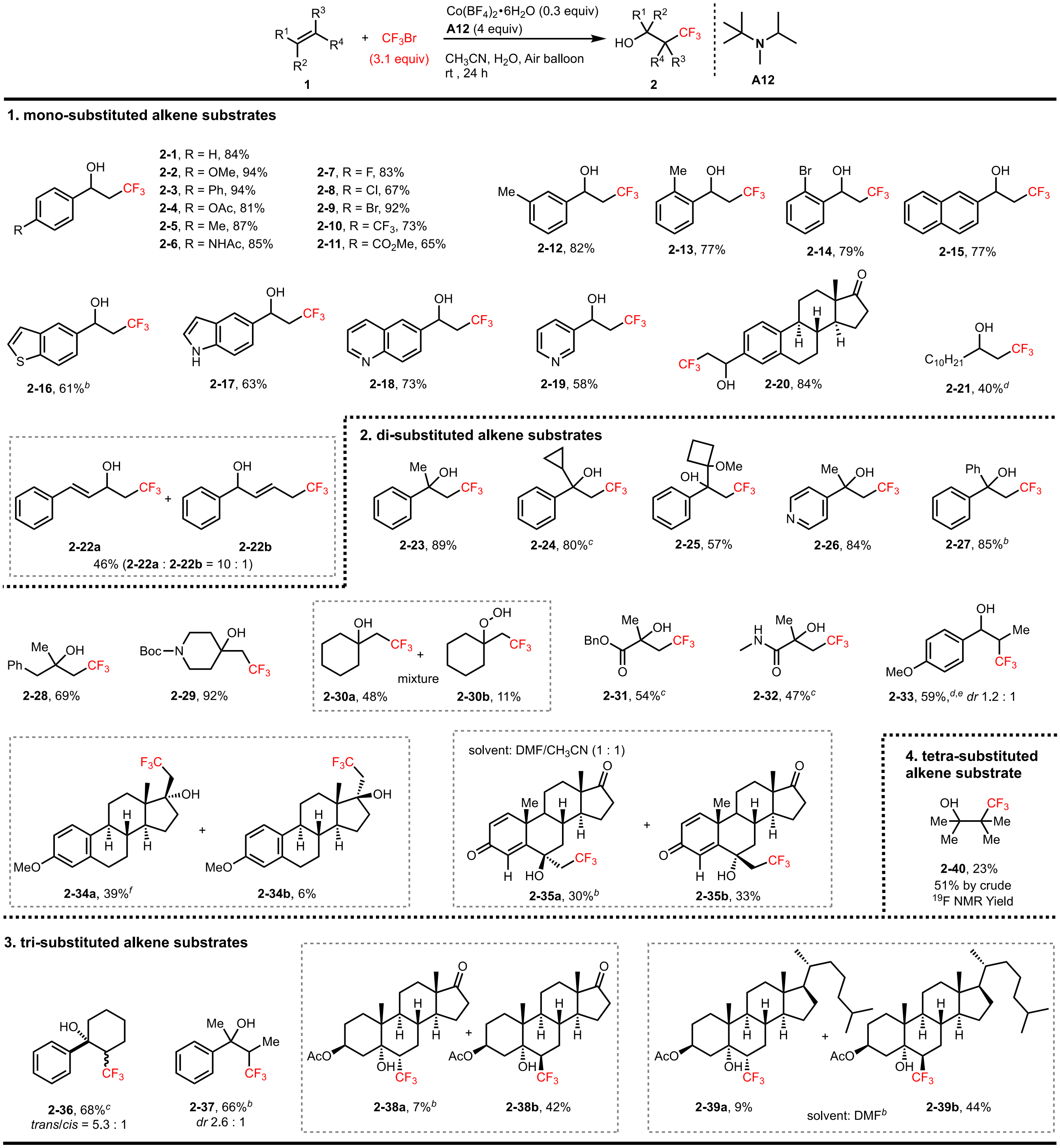


[a] Reaction conditions: **1-1** (1.0 mmol, 1.0 equiv), CF_3Br (1 atm, balloon), $CoCl_2\cdot 6H_2O$ (1.0 equiv), amine (4.0 equiv), CH_3CN (1.0 mL) in 25 mL Schlenk tube, rt. Yields in the brackets are the recovery of starting alkenes based on crude ^{1}H NMR. [b] Reaction conditions: **1-1** (1.0 mmol, 1.0 equiv), CF_3Br (1 atm), $CoCl_2\cdot 6H_2O$ (1.0 equiv), amine (4.0 equiv), CH_3CN (4.0 mL) in 50 mL Schlenk flask equipped with an air balloon, rt. [c] 5% NMR yield of 3,3,3-trifluoro-1-phenylpropan-1-one was obtained. [d] Reaction conditions: **1-1** (1.0 mmol, 1.0 equiv), CF_3Br (3.1 equiv), $Co(BF_4)_2\cdot 6H_2O$ (0.3 equiv), amine (4.0 equiv), CH_3CN (4.0 mL), H_2O (76 μL) in 50 mL schlenk flask equipped with an air balloon, rt.

To minimize the usage of CF_3Br in the reaction, a 50 mL-flask (for 1 mmol scale) was charged with 1 atm CF_3Br (~ 3.1 mmol) and other reaction mixture first, then with an extra air balloon. To our surprise, a 93% yield of the product **2-1** was obtained in 4 mL of CH_3CN solution, but no reaction with O_2 balloon. Under the same conditions, DIPEA is much less efficient under this optimized condition (67% yield vs. 93% yield). Further optimization of the reaction conditions revealed that $Co(BF_4)_2\cdot 6H_2O$ generally performs better than $CoCl_2\cdot 6H_2O$ after compare their reactivity performance in different substrates (See Table S3). Finally, 0.3 equiv of $Co(BF_4)_2\cdot 6H_2O$ gave similar result (94% NMR yield) at room temperature. Control experiments revealed that removing of either the cobalt source or the tertiary amine, gave no product of **2-1**. In addition, there is no noticeable effect of light on this reaction (See Table S4).

With the optimized reaction conditions developed, we explored the scope of the method with a range of alkenes (**1-1** ~ **1-40**, Table 2). The reaction exhibited broad alkene substrate scope: mono-, di, tri-, and even tetra-substituted alkenes worked well, to afford the β-CF_3-alcohols in moderate to excellent yields. The reaction also exhibits good functional group tolerance, proceeding smoothly with fluoride (**1-7**),

Table 2. Hydroxytrifluoromethylation of Alkenes with CF_3Br: Alkene scope[a]



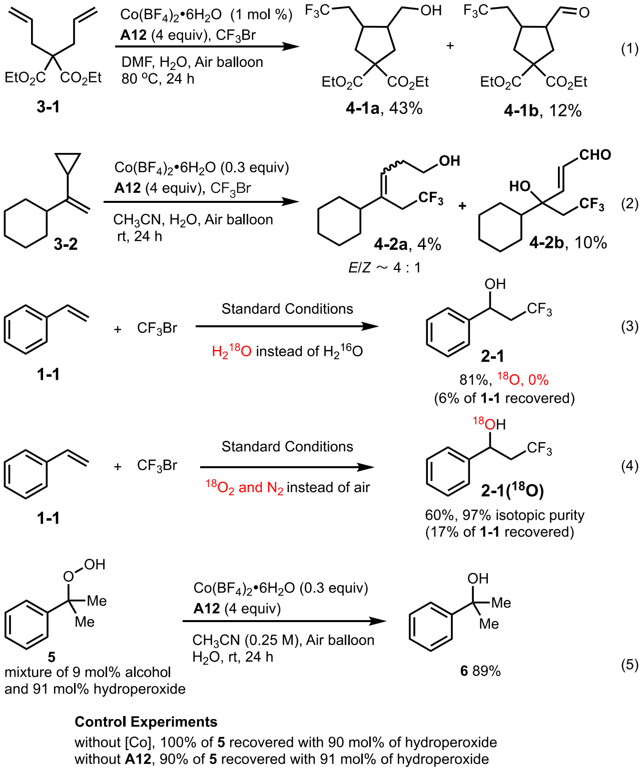
[a]Reaction conditions: **1** (1.0 mmol), CF_3Br (3.1 equiv), $Co(BF_4)_2{\bullet}6H_2O$ (0.3 mmol, 30 mol %), **A12** (4.0 mmol), H_2O (76 µL), CH_3CN (4.0 mL), rt, 24 h; Some starting alkenes were recovered based on the crude ^1H NMR in some examples, see SI for details. [b]65 °C. [c]45 °C. [d]Reaction conditions: **1** (1.0 mmol), CF_3Br (3.1 equiv), $Co(BF_4)_2{\bullet}6H_2O$ (0.01 mmol, 1 mol %), **A12** (4.0 equiv), H_2O (106 µL), DMF (4.0 mL), 80 °C, 24 h; [e]followed by reduction with $NaBH_4$ (1.0 equiv) in methanol. [f]50 °C.

chloride (**1-8**), bromide (**1-9**), CF_3 (**1-10**), ester (**1-4**, **1-11**, **1-31**, **1-38**, **1-39**), amide (**1-6**, **1-32**) and ketone (**1-20**, **1-35**, **1-38**) functionality. Alkenes bearing heteroaryl, such as thianaphthene (**1-16**), indole (**1-17**), quinoline (**1-18**), and pyridine (**1-19**, **1-26**), were also applicable to the reaction and produced the corresponding products in good to high yields.

The alkene **1-24**, comprising a cyclopropyl group, rendered the product in good yield without opening of the three-membered ring. Similarly, the cyclobutyl (**1-25**) also tolerates the reaction conditions. Electron deficient acrylate (**1-31**) and acrylamide (**1-32**) gave moderate yields of α-hydroxy-β-CF_3-ester (**2-31**) or amide (**2-32**) with slight increase of temperature. It is noteworthy that good regio-selectivity could be reached in this reaction from a conjugated diene (**1-22**). Complex molecules with biology activities are also compatible with this transformation: the modified estrone (**1-20**, **1-34**), dehydroepiandrosterone acetate (**1-38**), cholesteryl acetate (**1-39**), and exemestane (**1-35**) each afforded the corresponding products in moderate to good yields.

In order to glean mechanistic insights of the reaction, several control experiments were performed. The cyclic compound **4-1a** (43% yield) and an aldehyde **4-1b** (12% yield), the ring-opening product **4-2a** (4%) and unexpected **4-2b** (10%) were formed through radical clock substrate **3-1** and **3-2** under the standard conditions demonstrating that a radical pathway is involved in the reaction. We reason that the cyclopropyl of **1-24** survived in the reaction due to the double stabilization of benzyl and tertiary radical. Isotope labelling studies with $H_2^{18}O$ and $^{18}O_2$ confirmed that the installed oxygen atom was derived totally from the oxygen gas, which is also supports a radical mechanism [Scheme 2, (3) and (4)]. In order to clarify whether cobalt and tertiary amine participate the final reduction, hydroperoxide **5** was selected as a simplified model, which was efficiently transferred into alcohol in standard conditions without CF_3Br [Scheme 2, (5)]. Control experiments show that when either cobalt or **A12** is removed, the reduction is dramatically suppressed, revealing that both cobalt and **A12** play a synergist role in the reduction.

Scheme 2. Mechanism studies



Based upon both previous reports[10c, 19] and the above described results, a plausible mechanism for the new hydroxytrifluoromethylation reaction is proposed (Figure 1). First, the CF_3Br accepts one electron from cobalt-tertiary amine complex **Int 1** *via* SET, forming a cobalt-amine radical cation **Int 2**, a CF_3 radical and a bromide, followed by a radical addition with styrene producing a trifluoropropyl radical intermediate **Int 5**. Meanwhile, **Int 1** is reformed *via* ligand exchange of **Int 2** with a tertiary amine. The intermediate **Int 5** was then captured by the atmospheric O_2 from air to form peroxide radical **Int 6**, which abstract a hydrogen atom to form the hydroperoxide **Int 7**, followed by the cobalt-tertiary amine complex **Int 1** mediated reduction to β-CF_3-alchols. While the precise SET process between **Int 1** and CF_3Br is not fully understood at this stage, we posit that the distance between cobalt center to the nitrogen in tertiary amine, which is predominantly determined by the steric hindrance of that amine, is crucial to the SET process in this reaction based on the results in Table 1 and this mechanism.[26]

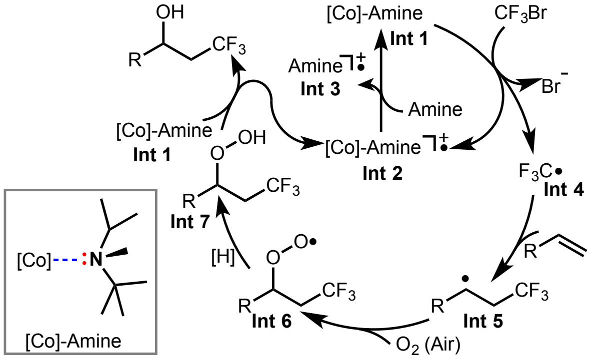


Figure 1. Proposed Mechanism for the hydroxytrifluoromethylation of alkene

In conclusion, we have described an efficient cobalt/tertiaryamine mediated the hydroxytrifluoromethylation of alkenes with a broad substrate scope and functional group tolerance. The straightforward reaction employs CF_3Br as the trifluoromethyl source and atmospheric dioxygen as the source of the hydroxyl oxygen. The reaction conditions are very mild, and each reagent is readily available and inexpensive. Mechanistic studies demonstrate that a radical reaction mechanism is involved, and that the oxygen atom in hydroxy group is derived from the atmospheric dioxygen. The compatibility of this reaction with complex drug molecules pave the way to its application in the late-stage drug modification, which would greatly accelerate the drug discovery process. In addition, we examined the reactivity of various tertiary amines, and proposed that the efficiency of cobalt-amine mediated SET process is largely determined by the distance between cobalt center to the nitrogen in tertiary amine. This understanding led to the discovery of a previously unexplored highly efficient SET reductant *N*-isopropyl-*N*,2-dimethylpropan-2-amine (**A12**).

ASSOCIATED CONTENT

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Notes

The authors declare the following competing financial interest(s):

S. Li, Q. Li, A method for preparation of trifluoropropanol derivatives from alkenes, CF_3Br and Atmospheric Oxygen, Provisional patent application Serial Number 201910884188.3, filed on Sep/19/2019.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, additional figures and tables, compound characterization data, NMR spectra (PDF)

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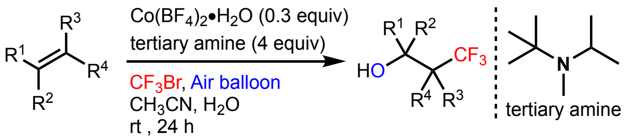
Co(BF$_4$)$_2$•H$_2$O (0.3 equiv)
tertiary amine (4 equiv)
CF$_3$Br, Air balloon
CH$_3$CN, H$_2$O
rt , 24 h
R^1
R^2
R^3
R^4
HO
CF$_3$
N
tertiary amine