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Metal-Free Direct 1,6- and 1,2-Difunctionalization Triggered by Radical Trifluoromethylation of Alkenes

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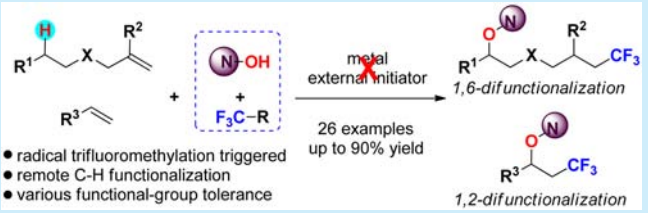
Supporting Information

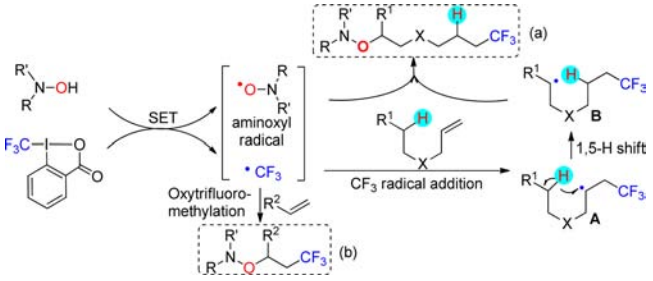
ABSTRACT: A metal-free direct remote C−H functionalization triggered by radical trifluoromethylation of alkenes was explored, realizing highly selective 1,6-difunctionalization of alkenes toward valuable trifluoromethyl α-hydroxycarbonyl compounds. Furthermore, a metal-free direct intermolecular regioselective 1,2-oxytrifluoromethylation of alkenes is also disclosed. With Togni's reagent as both the CF_3 source and oxidant, the reaction exhibits a broad substrate scope with excellent functionality tolerance under mild metal-free conditions, thus showing great potential for synthetic utility.



The increasing importance of trifluoromethyl organic molecules for the synthesis of anticholinergic, antiemetic, and antispastic drugs has spurred vigorous research for the development of new versatile methodologies for the generation of the C−CF_3 bond.[1,2] More recently, significant effort has been devoted to the development of practical and efficient trifluoromethylation of alkenes[3−6] by using nucleophilic, electrophilic, and radical trifluoromethylating reagents with or without transition-metal catalysts. In this field, Togni's reagents[1i,7] have been widely used as a clean source of the CF_3 radical via a single-electron-transfer (SET) process. However, precious and/or toxic transition-metal complexes or organic oxidants were usually required as external radical initiators.[3−6] To address this issue, Studer and co-workers have successfully developed TEMPONa (2,2,6,6-tetramethylpiperidine *N*-oxyl sodium) as a SET reagent for the reduction of Togni's reagent to generate the CF_3 radical and the persistent TEMPO radical for an oxytrifluoromethylation reaction.[4c,8] On the other hand, the reactivity of the short-lived aminoxyl radicals such as the phthalimide-*N*-oxyl radical (PINO) has received continuous attention since the species is a valuable class of intermediates or stoichiometric reactants with interesting synthetic and reactivity properties.[9] These active radicals are commonly formed in situ from *N*-hydroxyphthalimide (NHPI) or related compounds via SET with metal catalysts or nonmetallic mediators as radical initiators.[9] Inspired by these intriguing studies, we hypothesized that NHPI or related compounds in combination with Togni's reagent could concurrently generate the transient CF_3 radical and the short-lived aminoxyl radical via autoxidation without any additional initiators (Scheme 1). To the best of our knowledge, there have been no reported examples concerning such radical reactivity without assistance of additional initiators or transition-metal catalysts.

More recently, the very challenging remote functionalization of sp^3 C−H bonds via transposition of an inherently high-energy radical intermediate has become a research focus in synthetic chemistry,[10,11] as they enable the assembly of functionalized

Scheme 1. Remote C−H Functionalization/ Oxytrifluoromethylation Triggered by Radical Trifluoromethylation of Alkenes



chemical structures with remarkable precision and excellent functional-group tolerance via controlled activation of C−H bonds. In this context and on the basis of our hypothesis described above, we reasoned that the in situ generated CF_3 radical might add to the alkene, producing the transient α-CF_3-alkyl radical intermediate **A**,[3] which could abstract a proximal hydrogen atom[10] to generate a lower energy alkyl radical **B**[11] followed by subsequent trapping by the aminoxyl radical (Scheme 1a). However, such reactions are particularly challenging since such transient α-CF_3-alkyl radicals have been identified as highly reactive intermediates[3−6] but are employed rarely in remote C−H functionalization reactions[12] because of difficulties associated with promiscuous reactivity such as the competitive radical atom-transfer processes and deprotonative trifluoromethylation,[3] hydrotrifluoromethylation,[3i] oxytrifluoromethylation,[4] and carbotrifluoromethylation.[6] In addition, the control of regioselectivity of this process in the presence of two transient adduct radicals would also be a great challenge. In connection with our continuous efforts devoted to develop

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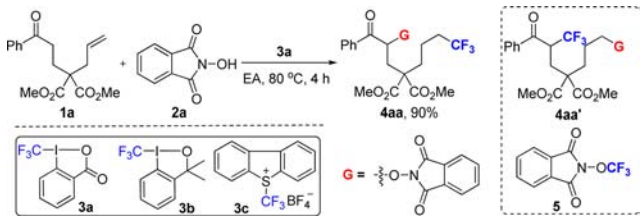
trifluoromethylation of alkenes,[12a,13] herein we describe a novel and convenient radical protocol of 1,6-difunctionalization or 1,2-difunctionalization of alkenes toward valuable trifluoromethyl α-hydroxycarbonyl or α-hydroxytrifluoromethyl compounds by employing Togni's reagent as both the CF_3 source and the oxidant (Scheme 1). Notably, this tandem process offers high levels of regio- and chemoselectivity without any additional reagents under metal-free conditions, and the use of radical trifluoromethylation of alkenes to initiate remote functionalization of C−H bond represents a remarkable new and general approach to hydrocarbon tandem transformations.

We started our investigation by reacting alkenyl α-ketone **1a** with NHPI (**2a**) and Togni's reagent **3a**[7] as the model reaction. On the basis of our hypothesis, the feasibility of this strategy relies on the capability of Togni's reagent to serve as both a CF_3 source and an oxidant to initiate NHPI for such tandem process. The reaction of **1a** with 2.0 equiv of **2a** and **3a** proceeded smoothly in THF at 80 °C for 4 h, giving the desired product **4aa**, albeit with only 25% yield together with a little amount of PINO−CF_3 (**5**), and no regioisomer **4aa′** was detected in the current reaction (Scheme 2 and Table S1, Supporting

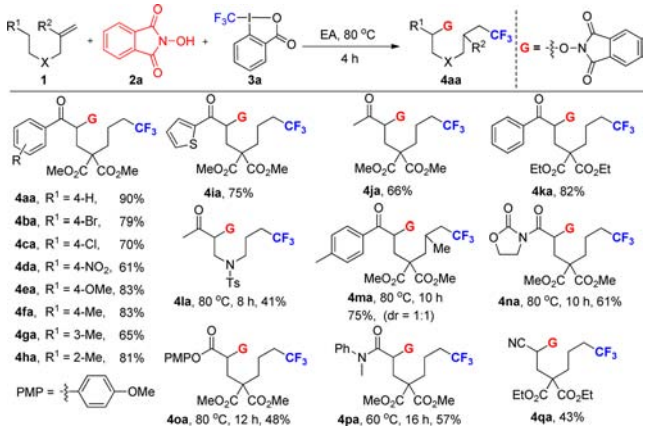
Scheme 2. Initial Investigation



Information). This result indicated that the current reaction can completely control the selectivity after the initial radical addition step. We then screened different solvents for this tandem radical reaction and found that ethyl acetate (EA) gave the best result with 90% yield. Examination of other CF_3 reagents from Togni's reagent **3a** to **3b** or Umemoto's reagent **3c** reveals that **3a** was the best for the reaction. This reaction did not require a large excess of NHPI and Togni's reagent or careful control of reagent addition. Notably, the yield of **4aa** was not significantly affected in the dark under argon, thus strongly supporting Togni's reagent as both a CF_3 source and an oxidant without any additional reagents as our initial assumption.

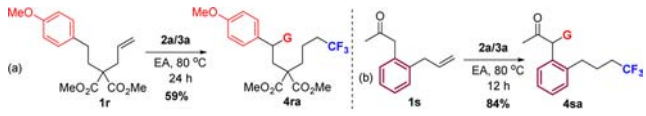
With the optimal conditions in hand, we set out to explore the scope of this protocol with respect to NHPI and other alkenyl α-carbonyl substrates. As shown in Scheme 3, in addition to substrate **1a**, a variety of alkenyl aryl ketones, bearing either electron-donating groups (R^1 = Br, Cl, NO_2) or electron-withdrawing groups (R^1 = OMe, Me) at the *para* position of the phenyl ring, reacted smoothly with **2a** and **3a**, affording the expected products **4ba**−**fa** in good to excellent yields. Notably, the introduction of a methyl group at the *para*-, *meta*-, or *ortho*-position in the phenyl ring did not affect the product yield either. In addition, this reaction shows excellent compatibility with heteroaromatic and alkyl groups at the α position of carbonyl group to give the desired products **4ia** and **4ja** in 75 and 66% yields, respectively. Furthermore, changing the methyl ester (**1a**) to an ethyl ester group (**1k**) in the tether had no influence on the product yield. Most importantly, *N*-tethered α-ketone, as exemplified by *N*-Ts-allyl aryl ketone **1l**, was also a suitable substrate for this reaction with 41% yield (**4la**). It is noteworthy that *gem*-disubstituted alkene **1m** was also an excellent substrate,

Scheme 3. Substrate Scope Involving Remote 1,6-Difunctionalization of Alkene



giving the product **4ma** as a mixture of two diastereomers (1:1 dr) in 75% yield. To further investigate the reaction scope, we tested the use of other α-carbonyl compounds as substrates. The tandem radical process of alkenyl α-carbonyl compound bearing an oxazolidinone substituent proceeded smoothly, giving the product **4na** in 61% yield. Most importantly, a variety of substituents including an ester (**1o**), amide (**1p**), or nitrile (**1q**) group were also found to be compatible with the current reaction system, although exhibiting relatively lower reactivity and giving the expected **4oa**−**qa** in moderate yields. The structure of **4pa** was determined by X-ray crystallographic analysis (see Figure S1, Supporting Information). It is interesting to note that changing the functional carbonyl groups to benzylic carbon **1r** as a substrate did not have a significant influence on the reactivity and efficiency, giving the expected product **4ra** in 59% yield (Scheme 4a). A more challenging substrate 1-(2-allylphenyl)propan-2-one

Scheme 4. Further Investigation of the Substrate Scope



1s without a diester- or tosylamino-tethered group as the substrate was tested and it was found that the corresponding product **4sa** was also obtained in 84% yield (Scheme 4b).

It is notable that the current protocol could be extended to other easily oxidizable substrates to generate short-lived aminoxyl radicals for further transformation. Thus, the reaction of **1a** with benzotriazol-1-ol (HOBT, **2b**) or 3-hydroxybenzotriazin-4-one (NHBO, **2c**) in the presence of **3a** under the standard conditions gave trifluoromethylated α-hydroxylcarbonyl compounds **4ab** and **4ac** in 65 and 67% yields, respectively (Scheme 5). It is encouraging to note that the present tandem radical process is a rather general reaction that can be extended to a wide range of synthetically important functional groups.

To further demonstrate the utility of the current protocol, we surmised that unactivated alkenes may also be suitable substrates for the development of 1,2-difunctionalization to realize the oxytrifluoromethylation of alkenes (Scheme 1b).[4c,i] To our delight, the reaction of aryl alkene (**1t** and **1u**) and aliphatic alkenes (**1t** and **1w**) bearing the functional groups, such as ester and ketone group, were found to be compatible with this reaction system without any additional reagents under metal-free

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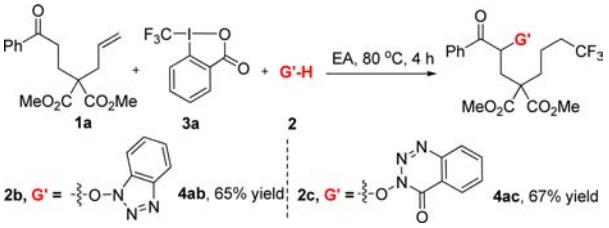
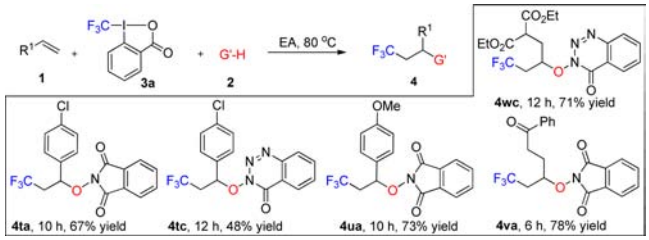
Scheme 5. HOBT and NHBO as Substrate for Aminoxyl Radicals



conditions, giving the desired oxytrifluoromethylated compounds **4ta**–**wc** in 48–78% yields as a single regioisomer, respectively (Scheme 6), which was in sharp contrast to the

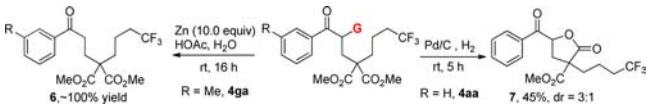
Scheme 6. Scope for Oxytrifluoromethylation of Alkenes



copper-catalyzed oxytrifluoromethylation of alkenes with sodium trifluoromethanesulfinate and hydroxamic acid using *tert*-butyl hydroperoxide (TBHP) as the external oxidant.[4i] Our data indicate that the present metal-free process is a rather general reaction that can realize both 1,2-difunctionalization and remote 1,6-difunctionalization of alkenes under metal-free and very mild conditions.

To demonstrate the synthetic applicability of the compounds derived from this current protocol, we have also performed additional experiments as shown in Scheme 7. For example, *N*-

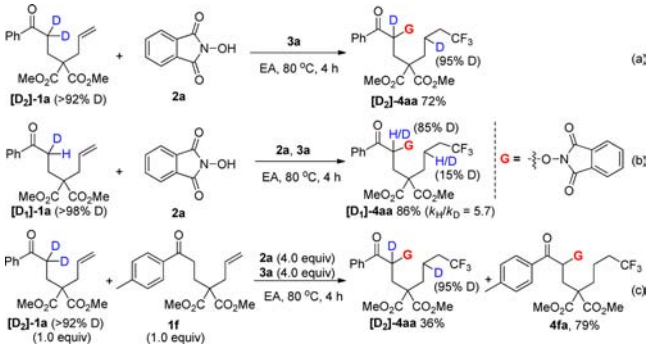
Scheme 7. Transformations of Compounds 4ga and 4aa



hydroxyphthalimide group could be readily removed to produce trifluoromethyl compound **6** in quantitative yield through selective mild reduction using Zn in a 10:1 AcOH/H_2O solvent mixture. Reduction using H_2/Pd/C resulted in tandem N–O bond cleavage and lactonization process, producing CF_3-containing lactone **7** in 45% yield as a 3:1 mixture of diastereomers.

We also tested the model reaction in the presence of radical scavengers such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) under the standard conditions and found that the reactions were almost completely inhibited by BHT (Scheme S1a, Supporting Information). On the other hand, the reaction of NHPI with Togni's reagent **3a** gave PINO-CF_3 (**5**) (Scheme 2) in 45% yield (Scheme S1b, Supporting Information), and even a small amount of PINO-CF_3 was always formed during the course of the current reaction in almost all cases.[8] All of these results revealed that CF_3 radical and short-lived aminoxyl radicals are likely involved as the reactive species under the current reaction conditions.[3] Furthermore, no reaction of PINO-CF_3 (**5**) with **2a** under the standard conditions was observed (Scheme S1c, Supporting Information), revealing that a mechanism involving PINO–CF_3-initiated radical reaction through homolysis to generate the CF_3 radical and the aminoxyl radical to give final product is unlikely. To further investigate the mechanism, the reactions of deuterated substrates [D_2]-**1a** and [D_1]-**1a** were carried out under the optimized conditions (Scheme 8). The

Scheme 8. Control Experiments with Deuterated Substrates



substrate [D_2]-**1a** afforded the corresponding product [D_2]-**4aa** in 72% yield, with complete transfer of the deuterium label to the β-position of alkene (Scheme 8a). The kinetic isotope effect was also examined through the reaction of deuterated [D_1]-**1a** under the standard conditions, and k_H/k_D = 5.7 was observed (Scheme 8b), which suggested that the activation of the C–H bond adjacent to the carbonyl group should be a kinetically relevant process in this tandem reaction.[14] In addition, a cross experiment was performed under the standard conditions using a 1:1 mixture of [D_2]-**1a** and **1f**, and it was found that H/D scrambling between [D_2]-**1a** and **1f** was not observed (Scheme 8c). The results indicated that the current redox-neutral reaction proceeds with an intramolecular 1,5-H shift process. All these experimental results are in support of our initial proposal as shown in Scheme 1. The highly regioselectivity of the current process in the presence of two transient adduct radicals would be possibly attributed to the intrinsic nature of the more active CF_3 radical for faster formation of α-CF_3-alkyl radical intermediate as compared to the relatively stable aminoxyl radical.[4c,i,8,9] Thus, hydroxyl groups are regioselectively substituted at the sp^3 carbon adjacent to the carbonyl groups, with concomitant generation of a C–CF_3 bond from unactivated alkene.

In summary, we have developed the novel and convenient metal-free radical tandem protocol for highly selective 1,6-difunctionalization of alkenes, providing valuable trifluoromethyl α-hydroxycarbonyl compounds via a C–CF_3 formation/1,5-H shift/remote sp^3 C–H bond functionalization tandem process. Furthermore, a new approach for the metal-free direct intermolecular regioselective oxytrifluoromethylation of unactivated alkenes has also been disclosed. Notably, this new radical reaction is operationally simple and can be conducted under metal-free and very mild conditions. A wide range of synthetically important functional groups are well-tolerated. Preliminary mechanistic study revealed that a tandem radical process is involved, and Togni's reagent not only acts as the CF_3 source, but also plays a vital role in generating aminoxyl radicals. Efforts toward expanding the applications to a series of novel organic reactions and an asymmetric variant of this transformation are currently underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of all new compounds, Table S1, Figure S1, Scheme S1, and X-ray data (CIF) of **4pa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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