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# Metal-Free Oxidative Functionalization of C(sp$^3$)−H Bond Adjacent to Oxygen and Radical Addition to Olefins

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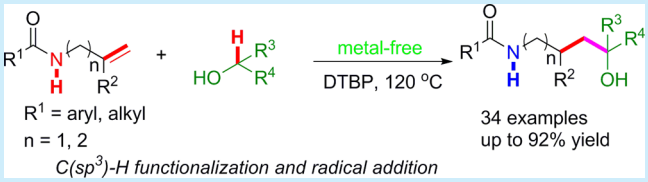
Supporting Information

**ABSTRACT:** A DTBP-promoted oxidative functionalization of a C(sp$^3$)−H bond adjacent to oxygen and intermolecular radical addition to olefins without use of any metal catalyst or photoredox catalysis is reported. The reaction has a wide scope of olefin, alcohol, and cycloether substrates, which provides an easy way for direct preparation of $\alpha,\omega$-amino alcohols.

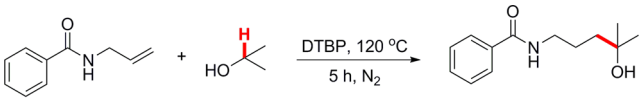



Direct C−C bond formation via selective C−H bond functionalization has been an extremely popular research topic in recent years because it can eliminate synthetic steps, alleviate waste, and improve limitations for the preparation of functionalized substrates.[1] Compared with C(sp$^2$)−H functionalization, the functionalization of C(sp$^3$)−H bonds is more challenging due to the low reactivity of aliphatic C−H bonds and lack of a coordination site for a metal catalyst.[2] Recently, varieties of approaches have been explored on C(sp$^3$)−H bond functionalization adjacent to heteroatoms, which generate new bonds as well as allow introduction of alcohol, ether, amide, or other functional groups.[3] Transition-metal-catalyzed functionalization of C(sp$^3$)−H bonds followed by cross-coupling (cross-dehydrogenative-coupling, CDC) has been well developed by Li and other groups.[4] Further, metal-free cross-dehydrogenative-coupling reactions of C(sp$^3$)−H bonds have been explored very recently.[5] However, the reaction proceeding via functionaliztion of C(sp$^3$)−H bonds and radical addition is a more challenging task and highly appreciated but scarely studied.

The photoredox-catalyzed radical addition reaction, with environmentally friendly conditions and which can be considered as a green tool for the synthetic chemist, has attracted much attention.[6] These reactions usually are performed under visible-light photoredox catalysis with the use of metal catalysts, generating the radicals by homolytic cleavage of C−X (X = O, N, S) bonds and radical addition to electron-deficient olefins.[7] Recently, many examples have been reported on photoredox-catalyzed radical addition with $\alpha$-silyl amines,[8] $\alpha$-bromo carboxylates,[9] amines,[10] $\alpha$-halo amides,[11] aryl diazonium salts,[12] alcohols and ethers[13] as radical precursors. Very recently, the Stephenson group explored a visible light-mediated radical addition of $\alpha$-bromo carboxylates to 3-methylindole in the presence of iridium to gain insight into the kinetic behavior of catalysts.[14] However, all these radical addition reactions usually need light conditions, expensive metal catalysts, and special starting materials, which lower the synthetic efficiency and atom economy.

With our continuous interests in sp$^3$ C−H functionalization, direct sp$^3$ C−H functionalization and subsequent radical addition to simple alkenes under metal-free conditions would be an ideal pathway for the construction of C(sp$^3$)−C(sp$^3$) bonds. Very recently, our group explored a metal-free oxidative C(sp$^3$)−H bond functionalization of alkanes and subsequent conjugate addition to chromones for preparation of 2-alkylchromanones.[15] To the best of our knowledge, the radical addition of hydroxyl alkanes to unactivated olefins under metal-free conditions without the use of photoredox catalysis has never been reported.[16] Herein, we reported a DTBP-promoted oxidative functionalization of the C(sp$^3$)−H bond adjacent to oxygen and intermolecular radical addition to olefins under metal-free conditions, affording the $\alpha,\omega$-amino alcohols as products (Scheme 1). The resulting $\alpha,\omega$-amino alcohols are useful organic intermediates and exist in many medicinal and biological compounds.[17]

**Scheme 1. Metal-Free Radical Addition Reaction**




Our initial goal was to optimize the reaction conditions with *N*-allylbenzamide **1a** and isopropanol as model substrates, which is shown in Table 1. According to our previous reports on functionalization of the C(sp$^3$)−H bond,[15] the reaction here between *N*-allylbenzamide **1a** (0.5 mmol) and isopropanol (2.5 mL) was conducted in the presence of 2.0 equiv of TBHP at 120 °C for 5 h. Very surprisingly, the reaction afforded the addition product **2a**, instead of the cross-dehydrogenative-coupling (CDC) product, with a 66% chemical yield (entry 1, Table 1). Next, we decided to screen some oxidants to improve the

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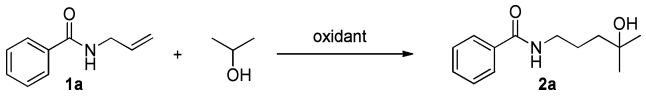
**Table 1. Optimization of Reaction Conditions**[a]




| entry | oxidant (equiv) | temp (°C) | $t$ (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 | TBHP (2.0)[c] | 120 | 5 | 66 |
| 2 | TBPA (2.0)[d] | 120 | 5 | 71 |
| 3 | TBPB (2.0)[e] | 120 | 5 | 57 |
| 4 | DCP (2.0)[f] | 120 | 5 | 33 |
| 5 | DTBP (2.0)[g] | 120 | 5 | 83 |
| 6 | DTBP (2.0) | 100 | 24 | 40 |
| 7 | DTBP (2.0) | 80 | 24 | trace |
| 8 | DTBP (4.0) | 120 | 5 | 81 |
| 9 | DTBP (1.5) | 120 | 24 | 72 |
| 10 | DTBP (1.0) | 120 | 24 | 20 |
| 11 | DTBP (2.0) | 120 | 5 | 63[h] |
| 12 | DTBP (2.0) | 120 | 5 | 31[i] |

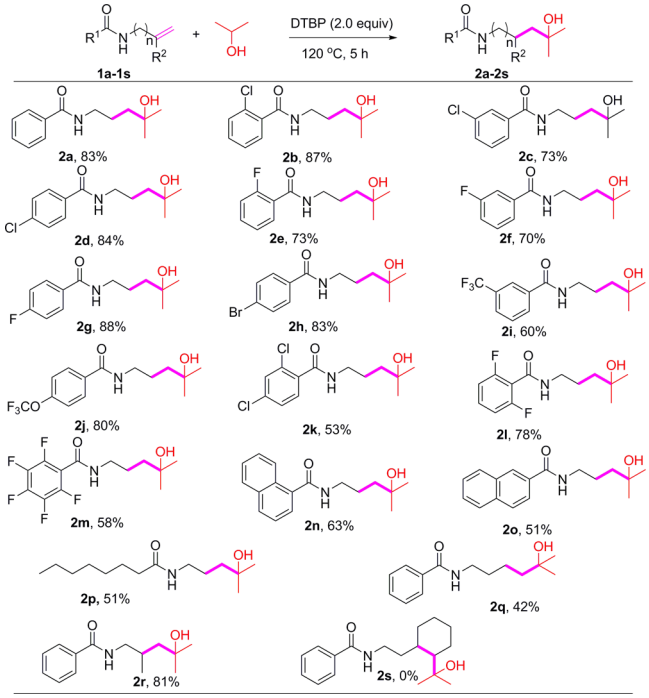
[a]Standard conditions: *N*-allylbenzamide (0.5 mmol), isopropanol 2.5 mL, oxidant 2.0 equiv, 120 °C, 5 h, under $N_2$. [b]Isolated yield based on *N*-allylbenzamide. [c]TBHP = *tert*-Butyl hydroperoxide, 5.0−6.0 M in decane. [d]TBPA = *tert*-Butyl peroxyacetate. [e]TBPB = *tert*-Butyl peroxybenzoate. [f]DCP = Dicumyl peroxide. [g]DTBP = di-*tert*-Butyl peroxide. [h]5.0 mL of isopropanol was used. [i]0.5 mL of isopropanol was used.

chemical yields. The use of other oxidants, such as TBPA and TBPB, also provided the expected product with similar yields (71% and 57% respectively, entries 2 and 3). In the presence of DCP, the reaction still happened, but gave a dramatically lower chemical yield (33%, entry 4). DTBP was the best oxidant for this reaction and resulted in obviously an increased yield (83%, entry 5). The temperature showed a significant effect on the yield. Running the same reaction at 100 °C (entry 6) resulted in a dramatically lower yield (40%), and almost no desired product was obtained when the reaction was performed at 80 °C (entry 7); even the reaction time was prolonged to 24 with almost all the starting materials remaining. Finally, we would like to mention here the attempts to use greater (entry 8) and lesser (entries 9 and 10) amounts of the oxidant. Increasing the amount of DTBP to 4 equiv did not lead to any improvement in chemical yield, while decreasing the amount to 1.0 equiv resulted in a low reaction rate and dramatically lower chemistry yields (24 h, 20% yield, entry 10). The loading amount of isopropanol also showed an effect on the reaction, and obvious lower yields were found when 5 or 0.5 mL of isopropanol was used (63% and 31% respectively, entries 11 and 12).

The above optimization study allowed us to carry out the next part of this work for the investigation of the substrate scope. Isopropanol was used as the simple alcohol reactant in the scope study of various olefins with $\alpha$-amido groups (Scheme 2). The process has a broad scope, giving the expected $\alpha,\omega$-amino alcohols with good yields. One may see that, in a series of olefins with substituents on the aromatic ring **1a**−**1m**, neither the nature of the substituent, such as halogen atoms (**2c**−**2h**, **2k**−**2m**), trifluoromethyl (**2i**), or trifluoromethoxy (**2j**), nor the position on the aromatic ring has an apparent effect on the chemical yields of these radical addition reactions, mainly because they are far away from the C−C double bond.

Notably, the substrates with a naphthyl group, instead of a phenyl group, also reacted smoothly with isoproponal to give the desired products in slightly lower yields (63% for **2n** and 51% for **2o** respectively). Interestingly, reactions of an olefin with an

**Scheme 2. Radical Addition of Isopropanol with Substituted *N*-Allylbenzamide**[a]




[a]Standard conditions: olefin **1** (0.5 mmol), isopropanol 2.5 mL, DTBP 2.0 equiv, 120 °C, 5 h, under $N_2$. Isolated yield based on *N*-allylbenzamide.

aliphatic amido group also resulted in the product with moderate yields of 51% (**2p**). In order to further extend the substrate scope, a $\beta$-amido olefin **1q**, was tried in the reaction, which also could work and afford the desired product with a 42% yield (**2q**). Finally, the substrates with substituents on the C−C double bond were tried, and the results indicate that steric hindrance had an effect on the radical addition. For example, the reaction with a terminal substituted olefin did not proceed at all, and no product was found (**2s**), while a 2-methyl substituted olefin could work well affording the product with a good yield of 81% (**2r**).

As the next goal of this study on radical addition reactions, the variation in the substrates with the C($sp^3$)−H bond adjacent to oxygen was studied to investigate the reactivity and regioselectivity of this system (Scheme 3). As shown in Scheme 3, the reaction could work with a range of alcohols, including open chain and cyclo alcohols. It is noticed that the reaction with cyclo alcohols showed higher efficiency, giving the desired product with good chemical yields (**3g**−**3i**, 66−82%), compared with the results of open chain alcohols (**3a**−**3f**, 25−53%). For the cases of open chain alcohols, it is noteworthy that the yield becomes poor if the length of the chain increases, and only a 25% yield was obtained with hexanol as starting material (**3e**).

Fortunately, ethers (Scheme 4), such as tetrahydrofuran, 2,2-dimethyl-1,3-dioxolane, tetrahydropyran, 1,4-dioxane, benzo[*d*]-[1,3]dioxole, 2-methyltetrahydrofuran, and 1,3-dioxane, could also work well in this system resulting in good to excellent yields (**3j**−**3p**, 58−92%). It was noted that the reactions showed almost no evident regioselectivity, and ratios of 1.8:1 (**3o-1**:**3o-2**) and 1:1.2 (**3p-1**:**3p-2**) were found.

To understand the mechanism of this reaction, an intermolecular competing kinetic isotope effect (KIE) experiment was conducted with isoproponal and [D]-isoproponal as



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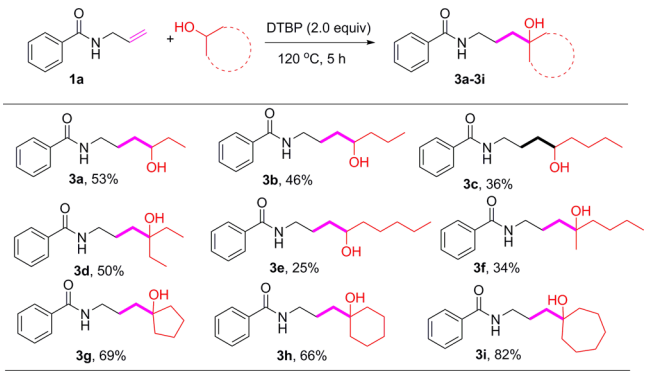
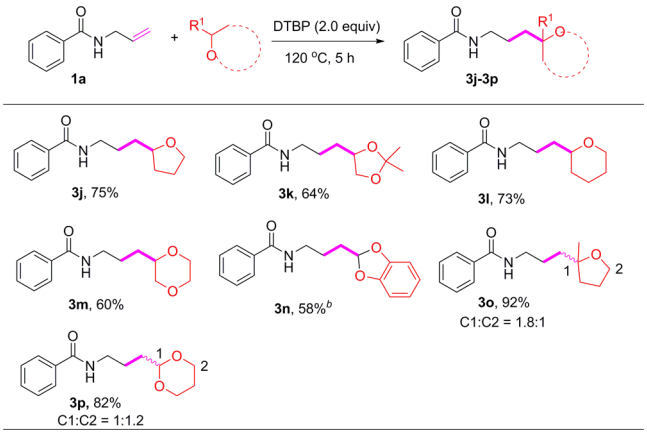
**Scheme 3. Radical Addition of Primary and Secondary Alcohol with *N*-Allylbenzamide[a]**




[a]Standard conditions: *N*-allylbenzamide **1a** (0.5 mmol), isopropanol 2.5 mL, DTBP 2.0 equiv, 120 °C, 5 h, under $N_2$. Isolated yield based on **1a**.

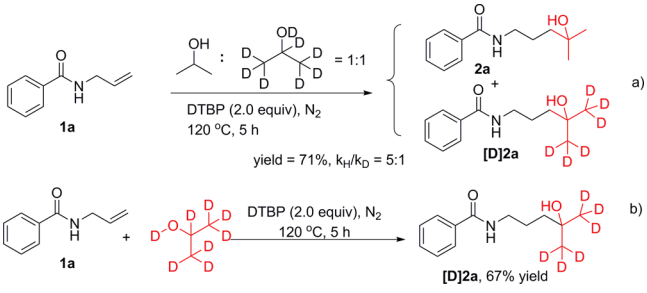
**Scheme 4. Radical Addition of Ether with *N*-Allylbenzamide[a]**




[a]Standard conditions: *N*-allylbenzamide **1a** (0.5 mmol), ether 2.5 mL, DTBP 2.0 equiv, 120 °C, 5 h, under $N_2$. Isolated yield based on **1a**. [b]Using 5 equiv of 1,3-benzodioxole with 2.5 mL of EtOAc as solvent.

starting material. As shown in Scheme 5a, an obvious KIE was found with the ratio of 5:1 ($k_H$:$k_D$), which was determined by $^1$H

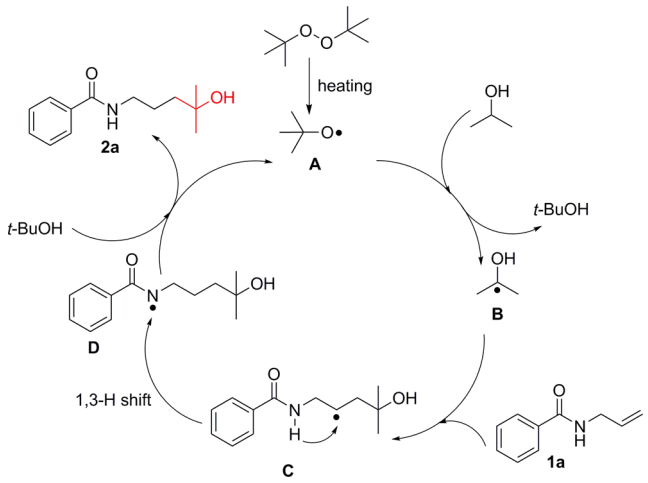
**Scheme 5. Investigation of Mechanism**




NMR spectroscopy by analyzing the ratio of **2a** and [**D**]**2a**. This discloses that cleavage of the C($sp^3$)−H bond adjacent to oxygen to form the radical may be involved in the rate-determining steps of this procedure. In addition, one radical-trapping reagent 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction, which was found to completely inhibit the reaction. The reaction gave almost no desired product, and this supports radical intermediates during the transformation. Finally, [D]-isoproponal was used as starting material for this reaction and still the same product [**D**]**2a** was obtained, which indicates that the H introduced into the product should be from the original *N*-allylamide part.

Based on the above results and previous studies,[15] we proposed a mechanism for the current metal-free oxidative radical addition reaction (Scheme 6). The reaction is initiated by

**Scheme 6. Possible Mechanism**

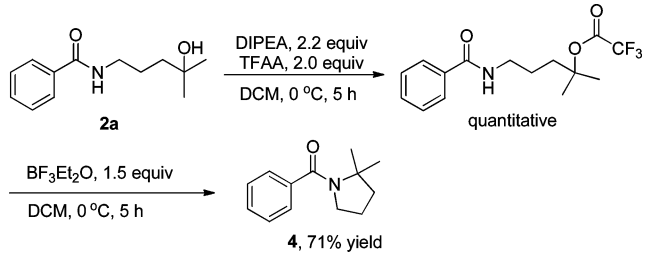



homolysis of DTBP, affording *tert*-butoxy radical intermediate **A** under heating. Then, cleavage of the C($sp^3$)−H bond gives the $\alpha$-hydroxyisopropyl radical **B** through oxidation of isopropanol by intermediate **A**. A subsequent radical addition of **B** to olefin **1a** generates intermediate **C**, which undergoes a 1,3-H shift from the N−H group to give intermediate **D**. Then, intermediate **D** reacts with *t*-BuOH, affording the final product **2a** and a *tert*-butoxy radical intermediate **A**. The *tert*-butoxy radical intermediate **A** goes into the next radical cycle.

As an integral part of this study, we sought preliminary results on the chemistry of the radical addition product **2a**, which is a useful chemical transformation. Of particular interest is the intramolecular cyclization of the compound **2a** into the compound **4**, which proceeds through the intramolecular substitution resulting in the amide bearing a cycloamino group (Scheme 7). First, **2a** was transferred into ester, which underwent cyclization in the presence of $BF_3$−$Et_2O$ with a total 71% chemical yield.

In summary, we explored an unexpected DTBP-promoted radical addition reaction of olefins with alcohols and ethers without use of any metal catalyst and any light initiation. This reaction involves new C($sp^3$)−C($sp^3$) bond formations via C($sp^3$)−H bond functionalization and an unexpected radical

**Scheme 7. Transformation of 2a**



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addition cascade process, which affords $\alpha,\omega$-amino alcohols directly from readily available olefins. The system shows a wide ranging scope of alcohol and ether substrates with good chemical yields. This process enriches the content of radical addition under metal-free conditions.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, full spectroscopic data for compounds **2**, **3**, and **4** and copies of $^{1}H$ and $^{13}C$ NMR spectra. 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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