C–H Activation

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Enantioselective C–H Bond Functionalization Triggered by Radical Trifluoromethylation of Unactivated Alkene**

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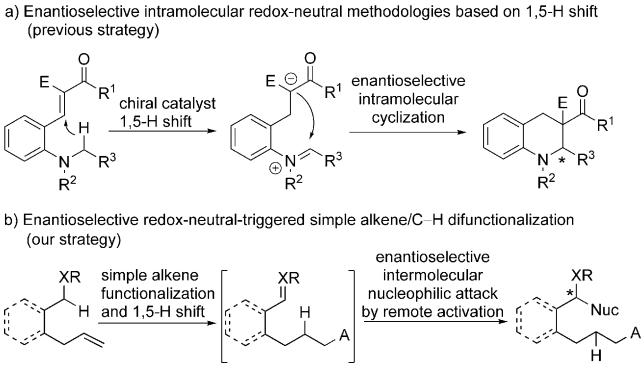
In memory of Carlos F. Barbas III

Abstract: *An asymmetric unactivated alkene/C–H bond difunctionalization reaction for the concomitant construction of C–CF_3 and C–O bonds was realized by using a Cu/Brønsted acid cooperative catalytic system, thus providing facile access to valuable chiral CF_3-containing N,O-aminals with excellent regio-, chemo-, and enantioselectivity. Mechanistic studies revealed that this reaction may proceed by an unprecedented 1,5-hydride shift involving activation of unactivated alkenes and a radical trifluoromethylation to initiate subsequent enantioselective functionalization of C–H bonds. Control experiments also suggested that chiral Brønsted acid plays multiple roles and not only controls the stereoselectivity but also increases the reaction rate through activation of Togni's reagent.*

Enantioselective catalytic carbon–carbon and carbon–heteroatom bond-forming reactions through C–H bond activation without substrate prefunctionalization have rapidly emerged as the forefront of current chemical research.[1] Significant advances have been made in the enantioselective cross-dehydrogenative coupling (CDC) of two C–H bonds in both intra- and intermolecular modes, through the functionalization of C–H bonds adjacent to heteroatoms in the presence of hydrogen acceptors, in recent years.[2] Because of the oxidative nature of these reactions, the use of a stoichiometric external oxidant is generally required. As a means of addressing this problem, redox-neutral processes involving intramolecular hydride shifts and additional functionalization of the position α to the nitrogen atom has attracted considerable attention as it offers an appealing and mechanistically complementary pathway in C–H activation chemistry.[3] However, to date, only a few examples dealing with catalytic and enantioselective processes have been reported.[3] Among these, the hydride acceptor is limited to electron-deficient olefins for the stabilization of the carbanion generated by the hydride shift, a carbanion which undergoes subsequent intramolecular enantioselective cyclization (Scheme 1 a).[3]



Scheme 1. Enantioselective catalytic functionalization of C–H bonds adjacent to heteroatoms based on 1,5-H shift.

In contrast, the incorporation of unactivated alkenes to initiate enantioselective functionalization of C–H bonds, adjacent to heteroatoms, with nucleophiles in an intermolecular mode remains a prominent challenge (Scheme 1 b) as the regio-, chemo-, and enantioselectivity for such transformations are difficult to control using the existing redox-neutral processes because of the presence of two unactivated structures including a simple olefin and C–H bond in the current system. Therefore, the discovery of a broadly applicable and mechanistically distinct protocol to realize such a transformation is highly desired.

Trifluoromethylated compounds have played a profound role in the realm of medicinal chemistry as it has excellent metabolic stability, lipophilicity, and electrostatic interactions with targets.[4,5] In particular, enantiopure CF_3-containing molecules are at the forefront of innovation in modern organic and medicinal chemistry[4,5a] because the effect of stereochemistry on biological activity is of great importance for medicinal application.[6] More recently, copper-catalyzed trifluoromethylation reactions of unactivated alkenes with trifluoromethylating reagents involving an α-CF_3-alkyl radical intermediate have emerged as important synthetic tools

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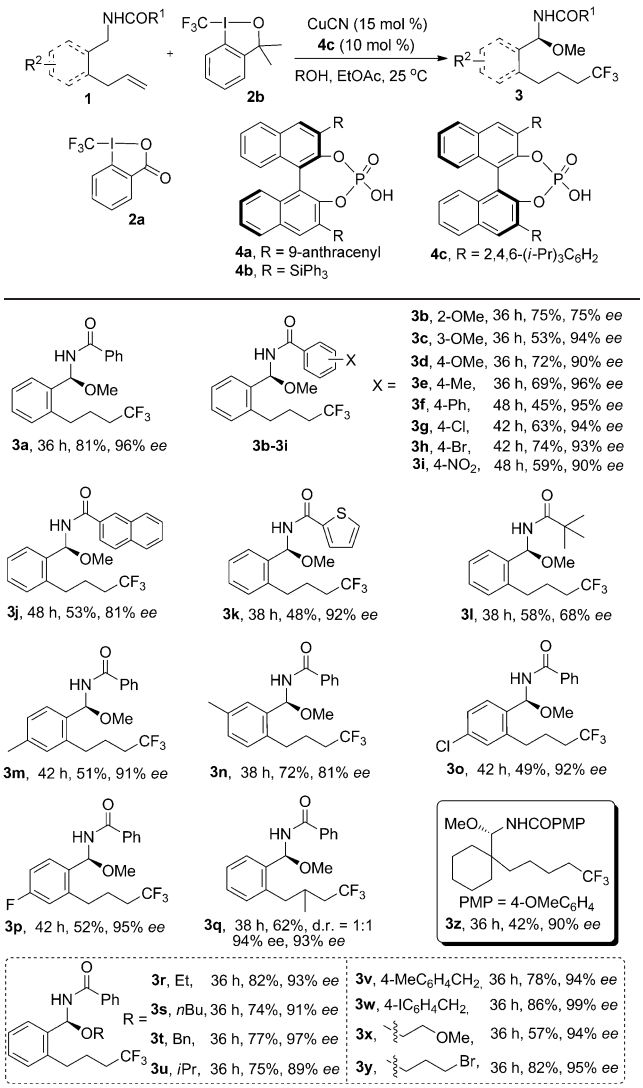
for the synthesis of new potential pharmaceutical candidates.[5,7] In contrast, the challenging functionalization of C–H bonds by transposition of an inherently high-energy radical intermediate has become a research focus in synthetic chemistry,[8,9] as they enable the assembly of functionalized chemical structures with remarkable precision and excellent functional-group tolerance by controlled activation of C–H bonds. However, although the racemic transformations have been well documented, to our knowledge, the development of catalyst-controlled enantioselective C–H bond functionalization by potentially useful radical transposition processes remains an underdeveloped area. Inspired by these racemic discoveries and to address the challenge described above, we envisioned a novel redox-neutral process involving an intramolecular hydride shift and then an enantioselective C–H functionalization of the position α to the nitrogen atom. Such a reaction might be realized by using the inherently high reactivity of an α-CF_3-alkyl radical intermediate, derived from a radical trifluoromethylation of unactivated alkenes,[7] to give valuable enantioenriched CF_3-containing N,O-aminals using the appropriate cooperative catalytic systems (Scheme 1b).[10] Because of their biological and pharmacological activity,[11] asymmetric N,O-aminal synthesis has been proven to be an attractive but underexploited strategy.[12] As part of our continued interest in the area of trifluoromethylation[13] and asymmetric catalysis,[14] herein, we describe the first successful example of a highly enantioselective redox-neutral reaction through a C–CF_3 formation/1,5-H shift/C–H functionalization process in the presence of a copper/Brønsted acid catalytic system and without the need for an external oxidant. Notably, the current process provides a convenient and economical route for facile access to valuable enantioenriched CF_3-containing N,O-aminal motifs with excellent regio-, chemo-, and enantioselectivity under mild reaction conditions.

On the basis of our hypothesis, our investigation commenced with the reaction of *N*-(2-allylbenzyl)benzamide (**1a**) with MeOH and Togni's reagent[15] (**2a**) in the presence of a cooperative catalyst system comprising a copper catalyst and chiral phosphoric acid (CPA).[16] As such, in the presence of different copper salts [CuI, CuBr, or CuCl (20 mol%)] and known CPAs, the reaction gave **3a** in good yields with almost complete regio- and chemoselectivity, albeit with only minimal levels of enantioselectivity (not shown). This finding can be attributed to the fact that 2-iodobenzoic acid, generated by the reaction system, prevents enantioselective reaction catalyzed by CPAs. Therefore, we surmised that Togni's reagent (**2b**) may be a suitable CF_3 source for the development of an enantioselective redox-neutral reaction. As expected, we were delighted to find that the desired product **3a** was obtained with 77% *ee*, albeit in only 22% yield, when **1a** was treated with **2b** in the presence of 15 mol% of the 9-anthracenyl-derived CPA **4a** and 15 mol% of CuI (see Table S1 in the Supporting Information). To improve the product yield and enantioselectivity, various reaction conditions were examined. Upon optimizing the reaction conditions through variation of the copper salt, phosphoric acid, catalyst loadings, solvent, and the molar ratio of the reactants (Table S1), we identified the following protocol as optimal: the reaction of **1a**, **2b**, and methanol with the molar ratio of 1.0: 1.7: 1.5 in the presence of 15 mol% of CuCN and 10 mol% of the 2,4,6-triisopropylphenyl-derived CPA **4c** [(*S*)-TRIP] in EtOAc at room temperature (25°C); **3a** was obtained in 81% yield with 96% *ee* (Table 1).

Given the optimal reaction conditions, we next investigated the scope with respect to *N*-(2-allylbenzyl)amides, having various substituents, for the synthesis of enantioenriched trifluoromethyl-containing N,O-aminals. As shown in Table 1, the tandem reaction proceeded smoothly, irrespective of the electronic nature and position of substituents, to afford the desired products in moderate to good yields with excellent enantioselectivities. For example, various *N*-(2-allylbenzyl)amides, bearing either electron-donating groups (X = OMe, Me, Ph) or electron-withdrawing groups (X = Cl, Br, NO_2) on the aryl ring α to the amide group, reacted

Table 1: Asymmetric reaction scope for *N*-(2-allylbenzyl)amides and alcohols.[a,b,c]



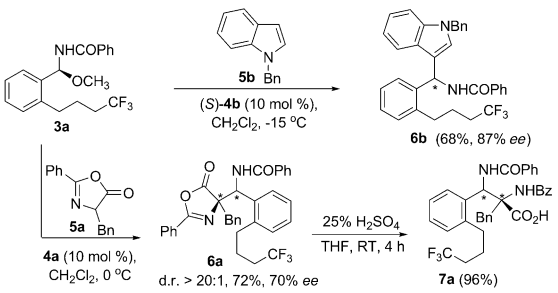
[a] Reaction conditions: **1** (0.2 mmol), **2b** (1.7 equiv), ROH (1.5 equiv), CuCN (15 mol%), **4c** (10 mol%), EtOAc (1.0 mL), 25°C, Ar. [b] Yield of isolated product. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase.

efficiently with methanol to afford the corresponding products **3c–i** in 45–74% yield with *ee* values of 90–96%. The sterically hindered *ortho*-methoxy-substituted *N*-(2-allylbenzyl)amide (**1b**) gave the expected product **3b** in 75% yield and 75% *ee*. Moreover, the reaction of a naphthalene and thiophene substrate (**1j** or **1k**) was facile under the catalytic system, thus leading to the corresponding products **3j** and **3k** in moderate yields with 81 and 92% *ee*, respectively. In addition, an aliphatic amide, as a case study of *N*-(2-allylbenzyl)pivalamide (**1l**) was also a suitable substrate for this reaction, thus resulting in a product yield of 58% with good enantioselectivity (68%). Most importantly, substituents including methyl, chloro, and fluoro groups on the phenyl ring of the substrates at the different positions were well-tolerated under the standard reaction conditions, thus giving the desired products **3m–p** in 51–72% yields with excellent enantioselectivities. It is noteworthy that the geminal-disubstituted alkene **1q** was also an excellent substrate and gave the product **3q** as a mixture of two diastereomers (1:1 d.r.) in 62% yield with 94 and 93% *ee*. The absolute configuration of **3k** was determined to be *S* by X-ray crystallographic analysis[17] (see Figure S1), and those of other trifluoromethyl-containing N,O-aminals were determined in reference to **3k**.

Next, we explored the scope with respect to the functionalized alcohols (see box in Table 1). A range of substrates, including primary and secondary alcohols, were viable in this transformation. For instance, the present cooperative catalysis could be applied to primary alcohols, thus giving the corresponding chiral trifluoromethyl-containing N,O-aminals **3r–y** in good yields (57–86%) with excellent enantioselectivites (91–99% *ee*). Notably, reactive groups, such as benzyl or methoxy groups, or halo substituents including Cl (**3o**) and Br (**3h** and **3y**), were well tolerated. The aryl iodide group remained intact throughout the reaction and the product **3w** was obtained in 86% yield with 99% *ee*. These results are significant as halides, Br and I in particular, are reactive in many transition-metal-catalyzed reactions and offer opportunities for further modifications at these positions.[18] Moreover, even the isopropyl group is also applicable without loss in reaction efficiency and enantiocontrol (**3u**). This promising result marks the first example of an enantioselective method to generate chiral N,O-aminals by redox-neutral-triggered C–H functionalization of the position α to the nitrogen atom.

It is interesting to note that the asymmetric redox-neutral protocol could be extended to other aliphatic compounds as viable substrates for this reaction. Thus, our preliminary result shows that under the standard reaction conditions the reaction of *N*-{[1-(but-3-en-1-yl)cyclohexyl]methyl}-4-methoxybenzamide gave the chiral product **3z** in 42% yield with 90% *ee* (Table 1). This result indicates that the α-functionalization of the amide was not severely affected by switching the nature of the benzylic carbon to the inactive methylene group.

To demonstrate the synthetic applicability of the compounds derived from this current protocol, we have also performed additional experiments [Eq. (1)]. For example, treatment of **3a** with 4-benzyl-2-phenyloxazol-5(4*H*)-one (**5a**) in the presence of **4a** provided the desired CF_3-



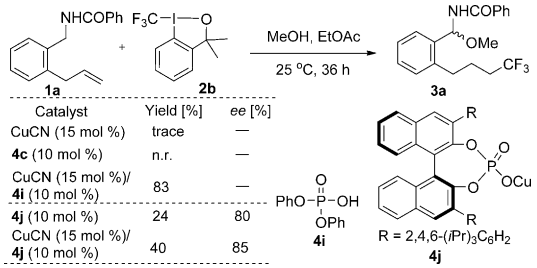
(1)

oxazolone **6a** with 72% yield with excellent diastereoselectivity and good enantioselectivity. Final hydrolysis of the easily obtained **6a** successfully afforded the optically active quaternary α,β-diamino acid **7a** in 96% yield.[19] Reaction of **3a** with 1-benzyl-1*H*-indole (**5b**) in the presence of (*S*)-**4b** produced the chiral CF_3-containing indole derivative **6b** in 68% yield with 87% *ee*.

To gain some insights into the mechanism of the current reaction, a series of control experiments were conducted. First, the model racemic and chiral reactions were performed in the presence of radical scavengers such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the standard reaction conditions, and a significant drop in yield was observed. Notably, for the reaction in the presence of TEMPO, the TEMPO-CF_3 adduct was formed in 95% (racemic) and 88% (chiral) yield (see Scheme S1). The results reveal that the CF_3 radical is likely involved as the reactive species under the current reaction conditions.[7]

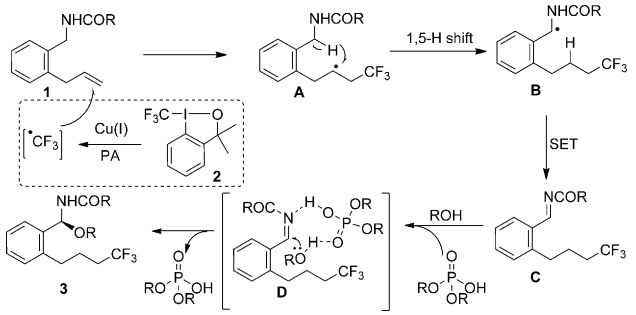
With regard to the 1,5-hydride shift, a series of deuterium-labelling experiments in the racemic version[20] were carried out (see Scheme S2). The deuterium-substituted [D_2]-**1a** afforded the corresponding aminal [D_2]-(±)-**3a** in 68% yield, with complete transfer of the deuterium label to the β-position of the alkene [see Eq. (1) in Scheme S2]. In addition, a crossover experiment was performed under the standard reaction conditions using a 1:1 mixture of [D_2]-**1a** and **1d**, and it was found that H/D scrambling between [D_2]-**1a** and **1d** was not observed [see Eq. (2) in Scheme S2]. The results indicate that the current reaction proceeds with the intramolecular 1,5-H shift process. The kinetic isotope effect was also examined through the reaction of [D_1]-*N*-(2-allylbenzyl)benzamide ([D_1]-**1a**) under the standard reaction conditions, and a k_H/k_D of 4.0 was observed [see Eq. (3) in Scheme S2]. This result indicated that the activation of the C–H bond adjacent to the nitrogen atom should be a kinetically relevant process in this tandem reaction.[21] In addition, the copper(I)-catalyzed reaction of **1a** in the absence of MeOH under the standard reaction conditions furnished the imine intermediate *N*-[2-(4,4,4-trifluorobutyl)benzylidene]benzamide **8** [see Eq. (4) in Scheme S2], thus revealing the formation of an imine intermediate in the current system, which was easily hydrolyzed to the corresponding aldehyde 2-(4,4,4-trifluorobutyl)benzaldehyde **9** with 47% yield in the presence of water.

Additionally, to acquire a further understanding of the roles of the phosphoric acid in this enantioselective reaction,



Catalyst	Yield [%]	*ee* [%]
CuCN (15 mol %)	trace	—
4c (10 mol %)	n.r.	—
CuCN (15 mol %)/ **4i** (10 mol %)	83	—
4j (10 mol %)	24	80
CuCN (15 mol %)/ **4j** (10 mol %)	40	85

Scheme 2. Control experiments with phosphoric acid catalyst. n.r. = no reaction.



Scheme 3. Proposed mechanism for the current reaction system.

several control experiments with the phosphoric acid catalyst were conducted (Scheme 2). Treatment of **1a** with **2b** and MeOH at 25 °C for 36 hours in the presence of either CuCN alone or **4c** alone gave the corresponding product **3a** in only low yield, thus revealing that both the metal catalyst and phosphoric acid are needed for the reaction, and activation of Togni's reagent could be facilitated by the phosphoric acid in this catalytic system. Notably, the relationship between the nature of a Brønsted acid and its ability for the activation of the Togni's reagent has recently been investigated by Togni and co-workers.[22] This hypothesis is further supported by the finding that **3a** was obtained in 83% yield when **1a** was treated with **2b** and MeOH under the same reaction conditions using the CuCN /achiral **4i** combination. Considering the possibility that a chiral copper phosphate complex could be generated in situ in the presence of a copper(I) compound and a chiral phosphoric acid to catalyze the current reaction,[22] we conducted the same reactions with a catalytic amount of the isolated **4j** alone and the combination of CuCN and **4j**, respectively. The use of such catalytic systems resulted in the formation of **3a** with corresponding *ee* values of 80 and 85% and yields of only 24 and 40%, and clearly shows that the present reaction can be catalyzed by the chiral copper phosphate complex. However, we found that the conversions in the presence of such catalytic systems were lower than that in the presence of the CuCN/**4c** catalyst system. These control experiments indicate that the use of a chiral phosphoric acid not only plays a vital role in controlling the stereoselectivity for the last stage of the asymmetric nucleophilic attack process, but also acts as an acid to successfully activate Togni's reagent together with copper catalyst.

On the basis of the above observations and literature precedence,[7] a mechanism was proposed for the current system (Scheme 3). First, a CF_3 radical is generated from the reaction of **2** with copper(I) and the phosphoric acid (PA), and then it adds to the alkene to afford the nascent α-CF_3-alkyl radical intermediate **A**.[7] Once formed, this inherently high-energy **A** abstracts a proximal hydrogen atom[9a,g] adjacent to the nitrogen atom of the amide to generate a lower-energy alkyl radical (**B**),[8] followed by single-electron oxidation[7] to afford the imine intermediate **C**. Finally, the attack of an alcohol nucleophile on the imine via the zwitterionic transition-state **D**, which features a two-point hydrogen-bonding interaction in the presence of a chiral phosphoric acid, furnishes the final product **3**, with excellent enantioselectivity resulting from the proximity effect, and is most consistent with a mechanism involving nucleophilic attack of nucleophiles to imines catalyzed by chiral Brønsted acids.[23,24]

In summary, we have presented here the first example of a highly enantioselective redox-neutral tandem process to realize concomitant formation of two new C–CF_3 and C–O bonds by functionalization of a C–H bond adjacent to an amide, and it is triggered by radical trifluoromethylation of alkenes. The sustainable protocol provides a highly efficient method for the rapid synthesis of valuable enantioenriched trifluoromethylated N,O-aminals in good to excellent yields and with excellent regio-, chemo-, and enantioselectivity as well as a broad substrate scope using a copper(I)/Brønsted acid cooperative system. This study led us to discover a 1,5-hydride transfer which involves activation of unactivated alkenes triggered by radical trifluoromethylation to initiate subsequent enantioselective functionalization of C–H bonds adjacent to nitrogen atoms by a radical process.

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[22] For examples of the activation of Togni's reagent by Brønsted acids, see: a) R. Koller, Q. Huchet, P. Battaglia, J. M. Welch, A. Togni, *Chem. Commun.* **2009**, 5993; b) K. Niedermann, N. Früh, E. Vinogradova, M. S. Wiehn, A. Moreno, A. Togni, *Angew. Chem. Int. Ed.* **2011**, *50*, 1059; *Angew. Chem.* **2011**, *123*, 1091.
[23] For selected examples of the reactions using chiral copper(I)/phosphate complex, see: a) K. Saito, Y. Kajiwara, T. Akiyama, *Angew. Chem. Int. Ed.* **2013**, *52*, 13284; *Angew. Chem.* **2013**, *125*, 13526; b) M. Terada, F. Li, Y. Toda, *Angew. Chem. Int. Ed.* **2014**, *53*, 235; *Angew. Chem.* **2014**, *126*, 239.
[24] For the representative excellent theoretical studies on a related mechanism, see: a) M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2007**, *129*, 6756; b) L. Simón, J. M. Goodman, *J. Am. Chem. Soc.* **2008**, *130*, 8741.

