Amination

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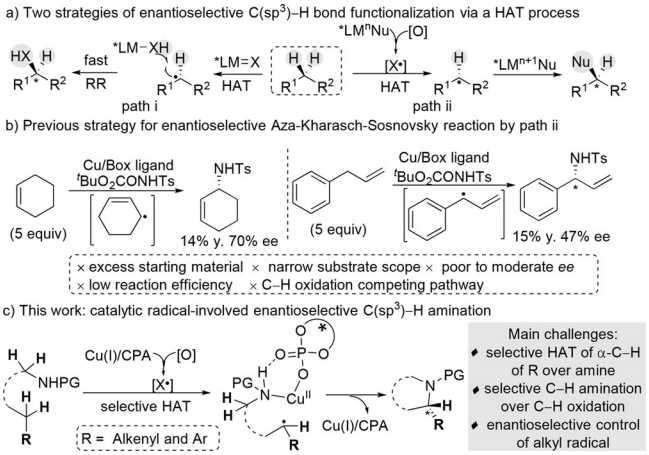
Enantioselective Copper(I)/Chiral Phosphoric Acid Catalyzed Intramolecular Amination of Allylic and Benzylic C–H Bonds

*Liu Ye[+], Yu Tian[+], Xiang Meng, Qiang-Shuai Gu, and Xin-Yuan Liu**

Abstract: *Radical-involved enantioselective oxidative C–H bond functionalization by a hydrogen-atom transfer (HAT) process has emerged as a promising method for accessing functionally diverse enantioenriched products, while asymmetric C(sp^3)–H bond amination remains a formidable challenge. To address this problem, described herein is a dual Cu^I/chiral phosphoric acid (CPA) catalytic system for radical-involved enantioselective intramolecular C(sp^3)–H amination of not only allylic positions but also benzylic positions with broad substrate scope. The use of 4-methoxy-NHPI (NHPI = N-hydroxyphthalimide) as a stable and chemoselective HAT mediator precursor is crucial for the fulfillment of this transformation. Preliminary mechanistic studies indicate that a crucial allylic or benzylic radical intermediate resulting from a HAT process is involved.*

Radical-involved enantioselective C(sp^3)–H bond functionalization by a hydrogen-atom transfer (HAT) process has recently attracted increasing attention to enable the direct transformation of hydrocarbon feedstocks into optically pure products.[1] Two operative catalytic processes are commonly involved: a) Oxygenase-inspired biomimetic approach characterized by an outer-sphere mechanism where a HAT step from a C(sp^3)–H bond to a high-valent metal species takes place to form a carbon-centered radical intermediate, followed by fast radical rebound to the metal-bound ligand to produce the corresponding products as pioneered by the groups of Groves, Katsuki, Che, Zhang, and others (Scheme 1a: path i).[2] b) The other process starts with a single-electron transfer (SET) step between a low-valent metal (M^n) with an oxidant to generate a HAT mediator ($X^{\bullet}$) which abstracts a hydrogen atom from a sp^3-hybridized carbon center to form a key alkyl radical species. Next, this species can directly associate with different chiral metal complex (*$LM^{n+1}Nu$) to realize enantioselective transformation (Scheme 1a: path ii).[3] For the latter process, the Kharasch–Sosnovsky reaction with a Cu/chiral bis(oxazoline) catalyst serves as an early example realizing enantioselective oxidative C–H bond functionalization of cyclic allylic substrates.[4] More recently, Liu, Stahl, and co-workers have made a breakthrough in enantioselective oxidative C(sp^3)–H bond cyanation and arylation of benzylic substrates with a similar catalytic system.[5] Despite these advancements, there is still a need to develop new catalytic systems to broaden the applicability of enantioselective oxidative C(sp^3)–H bond functionalization by widening the substrate scope for construction of various carbon–carbon/carbon–heteroatom bonds.



Scheme 1. Radical-involved enantioselective C(sp^3)–H bond functionalization. PG = protecting group. Ts = 4-toluenesulfonyl.

The direct catalytic enantioselective C(sp^3)–H bond amination through either transition metal catalyzed C–H activation[6] or metallonitrene insertion[7] has recently received much attention as a way to access chiral amines, which are widely displayed in natural products and pharmaceuticals, as well as serve as important ligands with broad utility in asymmetric synthesis.[8] Although great endeavors have been devoted to various racemic versions of radical-involved C(sp^3)–H bond amination by a HAT process,[9] the development of catalytic asymmetric methods has proven a formidable challenge. In this regard, the groups of Katsuki and Clark have made initial attempts to try asymmetric oxidative C–H amination of benzylic and cyclic allylic sites with peroxycarbamate as both oxidant and nitrogen source in the presence of a Cu/chiral bis(oxazoline) catalyst (Scheme 1b).[10] However, these reactions have encountered several major restrictions: 1) the low chemical yield due to the inherent instability of alkoxyl radical species, which are prone to decomposition; 2) the poor to moderate enantioselectivity;

[*] Y. Tian,[+] X. Meng, Prof. Dr. X.-Y. Liu
Shenzhen Grubbs Institute and Department of Chemistry, Southern University of Science and Technology
Shenzhen 518055 (China)
E-mail: liuxy3@sustech.edu.cn
Homepage: https://liuxy.chem.sustech.edu.cn
Dr. L. Ye,[+] Dr. Q.-S. Gu
Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of Science and Technology
Shenzhen 518055 (China)
[+] These authors contributed equally to this work.
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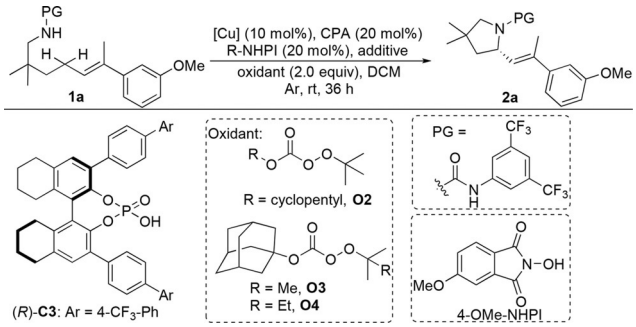
3) the limitation to cyclic olefin substrates and the requirement of a large excess of the alkenes. To address the above-mentioned challenges and inspired by our recent work where chiral Cu^{II} phosphate intimately associates with alkyl radical species to provide a good chiral environment for realizing radical-involved asymmetric alkene difunctionalization,[11] we wondered if the radical-involved asymmetric amination of $C(sp^3)$–H bonds by a HAT process could be realized by the use of a redox Cu^{I}/chiral phosphoric acid (CPA) catalytic system. However, formidable challenges exist: a) identification of a suitable HAT mediator to selectively abstract a hydrogen atom α to an R group over a hydrogen atom α to the amine group;[12] b) identification of a suitable oxidant to selectively initiate this reaction; c) investigation of a suitable chiral catalyst to control the enantioselectivity of the highly reactive alkyl radical intermediate. Herein we describe our efforts toward the development of the first radical-involved intramolecular enantioselective oxidative C–H amination of not only acyclic allylic substrates but also benzylic substrates in a highly site- and stereoselective manner in the presence of a dual Cu^{I}/CPA catalytic system (Scheme 1c).

We initially attempted enantioselective C–H amination of acyclic alkene substrates. The alkenyl urea **1a**, wherein the alkyl amine is protected with a urea group, which is supposed to deactivate C–H bond α to the amine toward HAT,[13] was chosen as a model substrate (Scheme 2). A variety of oxidants

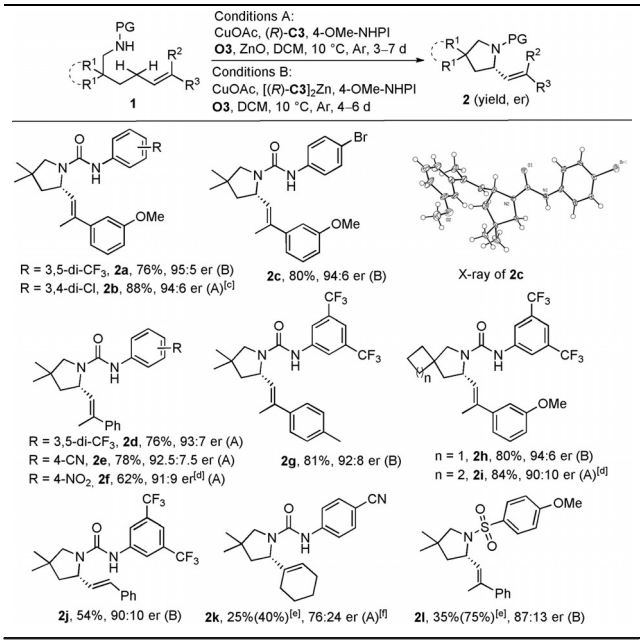


Scheme 2. Enantioselective C–H amination of allylic substrates.

was initially explored, but no desired product was obtained (see Table S1 in the Supporting Information). The failure was probably attributed to the high reactivity of the generated hydrogen abstractors, therefore resulting in low selectivity between different types of C–H bonds in **1a** as well as their inherent instability, making them susceptible to fast fragmentation.[14] It is well-known that the phthalimide *N*-oxyl (PINO) radical derived from *N*-hydroxyphthalimide (NHPI) can abstract a hydrogen atom selectively from a saturated hydrocarbon to form an alkyl radical intermediate.[15] As anticipated, the aminated product **2a** was obtained when a catalytic amount of NHPI was employed (see Table S1).[16] It was disclosed that 4-OMe-NHPI in combination with (*R*)-**C3** and a stoichiometric amount of zinc oxide[17] in the presence of CuTc (Tc = thiophene-2-carboxylate) at 10 °C could achieve a high level of enantioselectivity (see Table S1). Interestingly, the use of zinc phosphate could further improve the enantioselectivity of **2a** with the similar reaction efficiency (see Tables S2 and S3 for details).[18]

With the optimized reaction conditions in hand, the generality of the present enantioselective allylic C–H amination reaction was explored (Table 1). The substrates bearing

Table 1: Scope with respect to the allylic substrates.[a,b]



Reaction conditions A: CuOAc (10 mol%), (*R*)-**C3** (20 mol%), **O3** (2.0 equiv), 4-OMe-NHPI (20 mol%), and ZnO (1.5 equiv) in DCM (0.01 M); Reaction conditions B: CuOAc (10 mol%), $[(R)\text{-}\mathbf{C3}]_2Zn$ (15 mol%), **O3** (2.0 equiv), and 4-OMe-NHPI (20 mol%) in DCM (0.01 M). [a] Reactions were run on 0.1 mmol scale under conditions A or B. [b] Yields of isolated products are shown and the er values were determined by HPLC. [c] **O2** (2.0 equiv) was used. [d] 25 mol% of (*R*)-**C3**. [e] Reaction conversion is shown within parentheses. [f] CuOAc (15 mol%) and (*R*)-**C3** (30 mol%) were used. DCM = dichloromethane.

electron-withdrawing groups (CF_3, NO_2, etc.) on the aromatic rings of urea at the different positions reacted smoothly to afford the α-alkenyl pyrrolidines **2a–f** in 62–88% yields with 91:9–95:5 er. Various aryl substituents (OMe, Me) at the alkenyl group are tolerated and delivered **2a–c** and **2g–i** with high yields (76–88%) and good to high levels of enantioselectivity. The absolute configuration of **2c** was determined to be *S* by X-ray crystal-structure analysis.[19] Changing the dimethyl tether (**1a**) to cyclobutyl (**1h**) or cyclopentanyl (**1i**) variants did not affect the reaction yield, leading to the spirocyclic pyrrolidines **2h** and **2i** in 80% and 84% yields, respectively, with the corressponding 94:6 and 90:10 er values. The disubstituted alkene **1j** was also a suitable substrate, delivering **2j** in moderate yield and good enantioselectivity (90:10 er). The cyclic olefin substrate **1k** was also applicable for the reaction to yield **2k** in acceptable yield and enantioselectivity. A sulfonyl-protected alkenyl amine also worked to afford the cyclized product **2l** in 35% yield and 87:13 er. Notably, allylic C–H amination products were obtained exclusively in all cases and no competitive C–H oxidation

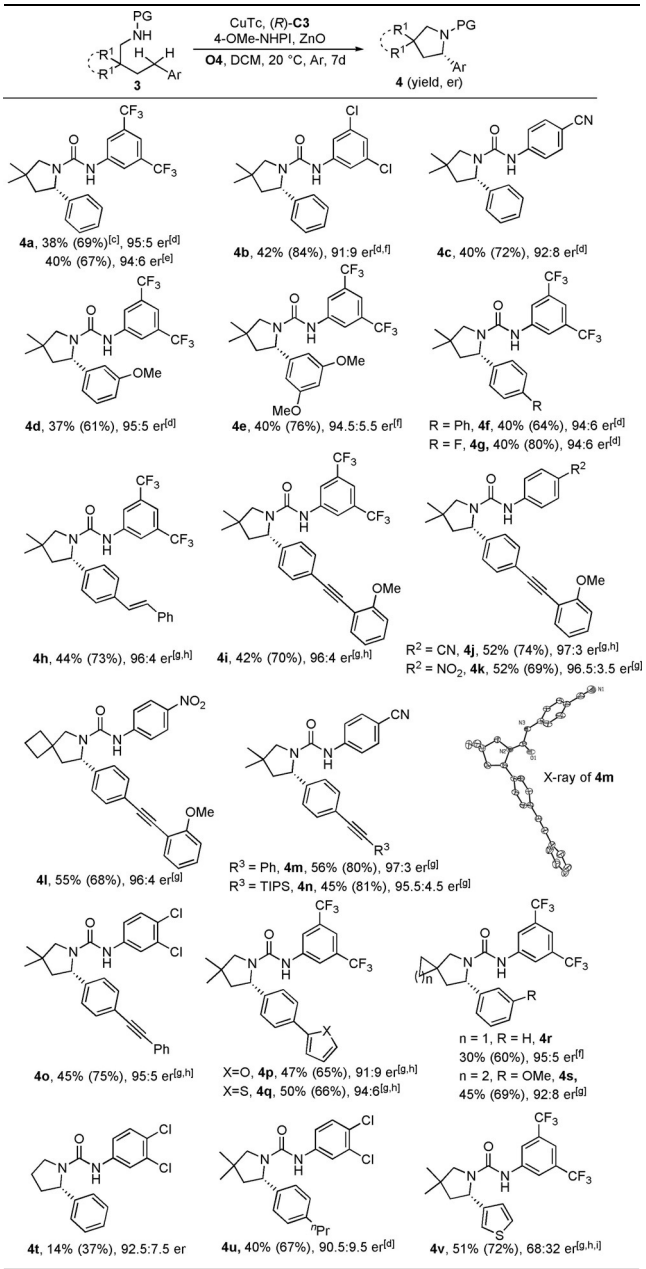
or aziridine products were observed, further demonstrating the excellent chemoselectivity of this method.

We then turned our attention to benzylic substrates given the similar BDEs between the allylic C–H bond and benzylic C–H bond. However, the reaction efficiency of benzylic C–H amination is lower than that observed in allylic C–H amination and the side-product **5A**, arising from C–H oxidation,[20] and the direct cross-coupling adduct **5B** of the benzylic radical and PINO were obtained in some cases[21] (see Scheme 4a and Table S4 for details). After systematic screening of reaction parameters (see Table S4), the optimal reaction conditions were established as follows: CuTc (10 mol%), (*R*)-**C3** (20 mol%), 4-OMe-NHPI (50–100 mol%), **O4** (3.0 equiv), and ZnO (1.5 equiv) in DCM (0.01M) at 20°C for 7 days (Table 2). As shown in Table 2, benzylic substrates with different ureas bearing electron-withdrawing groups underwent C–H amination smoothly to yield the products **4a–c** in 69–84% yields with up to 95:5 er. Various functional groups (OMe, F, etc.) on the aryl rings are tolerated, affording **4d–g** with 61–80% yields and excellent enantioselectivities (94:6 to 95:5 er). Notably, *para*-alkenyl and alkynyl-substituted aromatic substrates were amenable to C–H amination, yielding **4h–o** with excellent enantiocontrol of up to 97:3 er, and the unsaturated carbon–carbon bonds remain intact. Noteworthy is that chiral α-aryl pyrrolidines with either olefin or alkyne functional groups at the *para* position are core components of drug candidates (see Figure S1).[22] The absolute configuration of **4m** was determined to be *S* by X-ray crystal-structure analysis.[19] Importantly, heterocycles such as furan and thiophene are compatible with the transformation, and **4p** and **4q** were formed in 91:9 and 94:6 er, respectively. Furthermore, substrates with different cycle tethers (**3r** and **3s**) also worked to yield the spirocyclic pyrrolidines **4r** and **4s** with 95:5 and 92:8 er, respectively. Notably, the linear substrate **3t** cyclized successfully to give the desired product **4t** with 92.5:7.5 er, albeit with lower conversion. Interestingly, ^{n}Pr at the *para* position of the phenyl ring (**3u**) is also well tolerated and no competing byproduct arising from benzylic position of the ^{n}Pr group was detected. This excellent regioselectivity might originate from the interaction between 4-OMe-PINO and the urea moiety. Amination of the α-C–H bond of a thiophenyl ring was also achieved, furnishing **4v** in good yield and with a moderate er value.

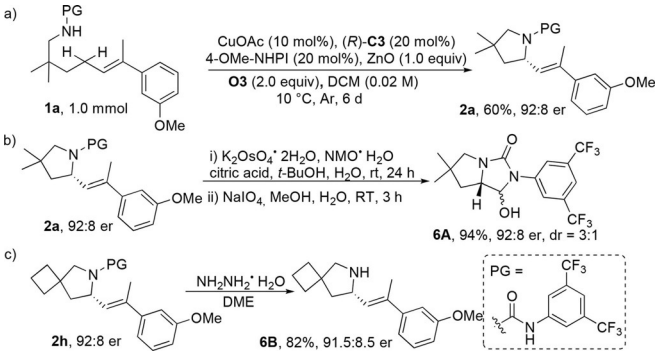
To illustrate the synthetic applicability of this protocol, a preparative scale reaction for **2a** was conducted and there was only negligible erosion in the enantioselectivity, indicating this method has potential for large-scale chemical production (Scheme 3a). Interestingly, **2a** was readily cyclized under oxidative cleavage conditions to give the bicyclic compound **6A** in 94% yield without erosion of the optical purity (Scheme 3b). Furthermore, the removal of urea group of **2h** proceeded smoothly to give the pyrrolidine **6B** in 82% yield and the *ee* value was almost retained (Scheme 3c).

To gain some insight into the reaction mechanism, a set of control experiments were conducted. First, a significant inhibition effect was observed in allylic C–H amination of **1a** when either TEMPO or BHT was added (see Scheme S1 in the Supporting Information). Second, the direct C–H oxidation byproduct **5A** and cross-coupling adduct **5B** were detected in the benzylic C–H amination of **3a** (a similar cross-coupling adduct with 4-OMe-PINO was also observed in the benzylic C–H amination of **3b**; Scheme 4a; see Scheme S2). Collectively, these results support the involvement of the proposed allylic or benzylic radical intermediates in this C–H amination process. Third, the measured inter-

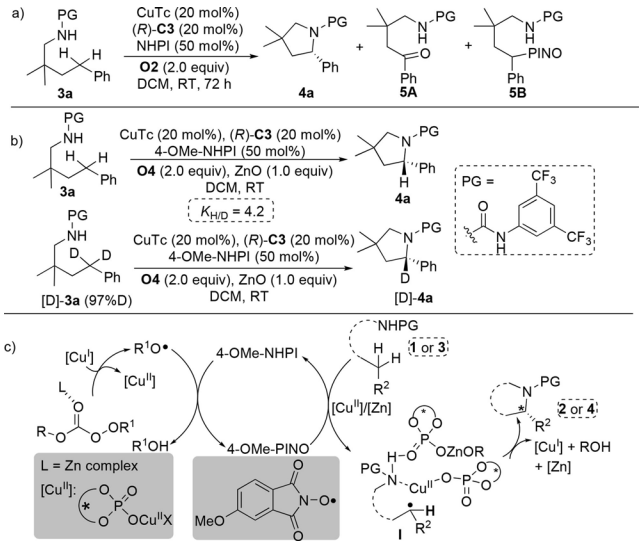
Table 2: Scope with respect to the benzylic substrates.[a,b]



Reaction conditions: CuTc (10 mol%), (*R*)-**C3** (20 mol%), 4-OMe-NHPI (0.5–1.0 equiv), ZnO (1.5 equiv), **O4** (3.0 equiv), DCM (0.01 M).
[a] Reactions were run on 0.1 mmol scale and (*R*)-**C3** (5 mol%) was added at 12 h and 36 h. [b] Yields of isolated products are shown and er values were determined by HPLC. [c] Yields within parentheses are based on recovered starting material. [d] $NaSbF_6$ (0.5 equiv) was added. [e] 0.5 mmol scale. [f] 75 mol% of 4-OMe-NHPI. [g] 50 mol% of 4-OMe-NHPI. [h] At 10°C. [i] CuOAc (10 mol%) and **O3** (2.0 equiv) were used.



Scheme 3. Preparative-scale reaction and versatile transformations. DME = 1,2-dimethoxyethane.



Scheme 4. Mechanistic studies and proposed catalytic cycle.

molecular KIE data (4.2) of **3a** and [D]-**3a** suggests that the HAT process is likely involved in the rate-determining step in the catalytic cycle (Scheme 4b). Finally, a nonlinear effect[23] on the *ee* value of **2c** was observed, and indicates that more than one CPA molecule is involved in the enantioselective transformation (see Figures S2 and S3 for details).

Based on the above mechanistic studies and previous studies,[11] we propose a tentative mechanism for this C–H amination (Scheme 4c). Initially, Cu^{I} reacts with peroxide, which was activated by a zinc complex to afford the reactive alkoxyl radical species and the chiral Cu^{II} phosphate complex. In the presence of 4-OMe-NHPI, conversion of the highly reactive alkoxyl radical species into a relatively stable 4-OMe-PINO then occurs,[24] and it could selectively abstract a hydrogen atom from allylic/benzylic positions (**1** or **3**) in the presence of a chiral Cu^{II} phosphate complex and zinc phosphate complex[25] to produce the key alkyl radical intermediate **I**,[26] accompanied by the regeneration of 4-OMe-NHPI. The subsequent combination of **I** with the tethered nitrogen nucleophile finally gives rise to pyrrolidine products (**2** or **4**), with the concurrent liberation of ROH, which was detected after the reaction, and Cu^{I} to finish the catalytic cycle.

In conclusion, we have developed a Cu^{I}/CPA-catalyzed asymmetric intramolecular radical-involved C–H amination of allylic and benzylic substrates, giving facile access to chiral α-alkenyl and α-aryl pyrrolidines, respectively, with excellent levels of enantioselectivity, moderate to high efficiency, broad substrate scope, and good functional-group tolerance. This reaction is the first example of the construction of a C–N bond with excellent enantiocontrol through asymmetric radical oxidative C–H bond amination. Critical to the success of this protocol is the application of 4-OMe-PINO as a stable and chemoselective HAT mediator to selectively abstract the hydrogen atom at the allylic and benzylic positions. The fulfillment of this asymmetric radical-involved C–H amination might provide useful insight for radical-involved enantioselective oxidative $C(sp^3)$–H bond functionalization.

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Conflict of interest

The authors declare no conflict of interest.

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