A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Cu(I)/Chiral Phosphoric Acid-Catalyzed Radical-Involved Enantioselective Intramolecular Amination of Allylic and Benzylic C–H Bonds

Authors: Xin-Yuan Liu, Liu Ye, Yu Tian, Xiang Meng, and Qiang-Shuai Gu

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201911742
Angew. Chem. 10.1002/ange.201911742

Link to VoR: http://dx.doi.org/10.1002/anie.201911742
http://dx.doi.org/10.1002/ange.201911742

WILEY-VCH

10.1002/anie.201911742

WILEY-VCH

COMMUNICATION

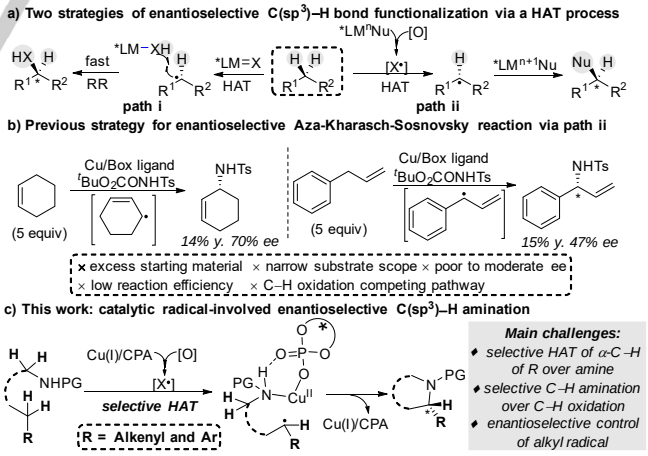
Cu(I)/Chiral Phosphoric Acid-Catalyzed Radical-Involved Enantioselective Intramolecular Amination of Allylic and Benzylic C–H Bonds

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

Abstract: Radical-involved enantioselective oxidative C−H bond functionalization via 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, we herein describe 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-OMe-NHPI 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 via 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) Oxygenases-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 Groves, Katsuki, Che, Zhang and others (Scheme 1a: path i).[2] (b) The other process starts with a single-electron transfer (SET) step between low valent metal (M^n) with oxidant to generate a HAT mediator (X·) which abstracts a hydrogen atom from sp^3-hybridized carbon 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, Kharasch–Sosnovsky reaction with Cu/chiral bis(oxazoline) catalyst is the early example to realize enantioselective oxidative C−H bond functionalization of cyclic allylic substrates.[4] More recently, Liu and Stahl has made a breakthrough in enantioselective oxidative C(sp^3)−H bond cyanation and arylation of benzylic substrates with similar catalytic system.[5] Despite these advancements, it is still eager to develop new catalytic systems to broaden the applicability of enantioselective oxidative C(sp^3)−H bond functionalization with broader substrate scope to construct various carbon-carbon/carbon-heteroatom bonds.

The direct catalytic enantioselective C(sp^3)−H bond amination through transition metal-catalyzed C–H activation[6] or metallonitrene insertion[7] has recently received much attention 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 via a HAT process,[9] the development of catalytic asymmetric methods has proven a formidable challenge. In this regard, Katsuki and Clark have taken 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 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 prone to decomposition; (2) the poor to moderate enantioselectivity; (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 the chiral Cu(II) phosphate intimately associates with alkyl radical species to provide good chiral environment to realize radical-involved asymmetric alkene difunctionalization,[11] we wondered if the radical-involved asymmetric amination of C(sp^3)−H bonds via a HAT process could be realized by the use of redox Cu(I)/CPA catalytic system. However, formidable challenges are encountered due to the following factors: (a) exploration of suitable HAT mediator to selectively abstract hydrogen of α-C−H bond of R group over α-C−H bond of amine group[12]; (b) identification of suitable oxidant to selectively initiate this reaction; (c) investigation of suitable chiral catalyst to control 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).



Scheme 1. Radical-involved enantioselective C(sp^3)−H bond functionalization.

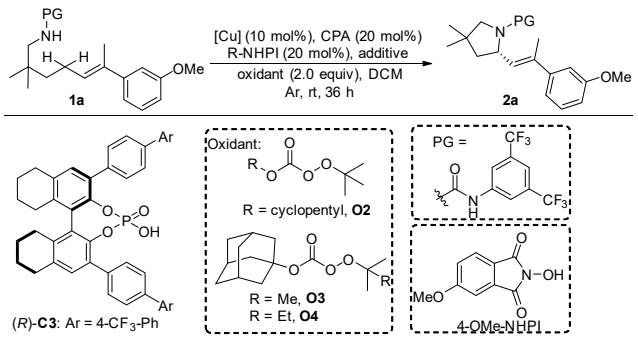
We initially attempted to test the possibility of enantioselective C−H amination for acyclic alkene substrates. Alkenyl urea **1a** where alkyl amine was protected with urea group which was supposed to deactivate α-C−H bond of amine toward HAT,[13] was chosen as model substrate (Scheme 2). A variety of oxidants was initially explored, while no desired product was obtained (Table S1 in SI). The failure was probably attributed to the high reactivity

[*] 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.

Supporting information for this article is given via a link at the end of the document.

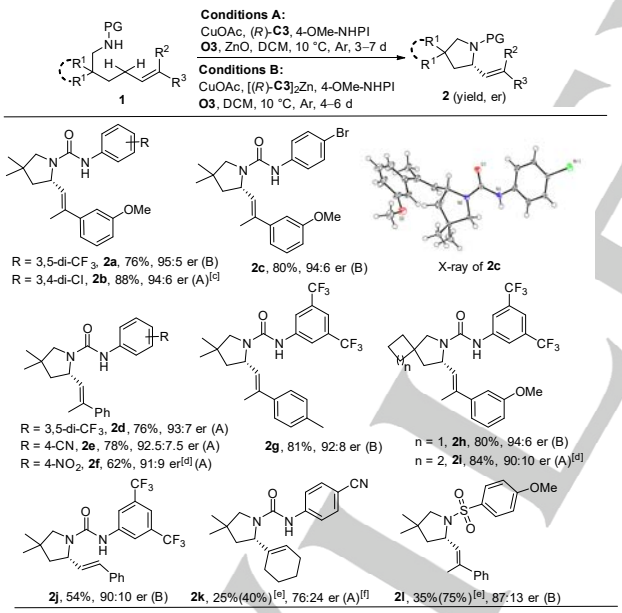
10.1002/anie.201911742

of the generated hydrogen abstractors, therefore resulting in low selectivity between different types of C−H bonds in the substrate **1a** as well as their inherent instability susceptible to fast fragmentation.[14] It is well-known that phthalimide N-oxyl (PINO) radical derived from N-hydroxyphthalimide (NHPI) can abstract hydrogen atom selectively from the saturated hydrocarbon to form alkyl radical intermediate.[15] As anticipated, the aminated product **2a** was obtained when a catalytic amount of NHPI was employed (Table S1).[16] It was disclosed that 4-OMe-NHPI in combination with (*R*)-**C3** and stoichiometric amount of zinc oxide[17] in the presence of CuTc (Tc = thiophene-2-carboxylate) at 10 °C could achieve high level of enantioselectivity (Table S1). Interestingly, the use of zinc phosphate could further improve the enantioselectivity of **2a** with the similar reaction efficiency (see Table S2 and Table S3 in SI for details).[18]



Scheme 2. Enantioselective C−H amination of allylic substrates

Table 1. Scope of allylic substrates[a,b]



Conditions A: CuOAc (10 mol%), (*R*)-**C3** (20 mol%), **O3** (2.0 equiv), 4-OMe-NHPI (20 mol%), ZnO (1.5 equiv), DCM (0.01 M); Conditions B: CuOAc (10 mol%), [(*R*)-**C3**]$_2$Zn (15 mol%), **O3** (2.0 equiv), 4-OMe-NHPI (20 mol%), DCM (0.01 M). [a] Reactions were run on 0.1 mmol scale under conditions A or B. [b] Isolated yields were shown and er value was determined by HPLC. [c] **O2** (2.0 equiv) was used. [d] 25 mol% of (*R*)-**C3**. [e] Reaction conversion was shown in parentheses. [f] CuOAc (15 mol%) and (*R*)-**C3** (30 mol%) were used.

With the optimized conditions in hand, the generality of the present enantioselective allylic C−H amination reaction was explored (Table 1). The substrates bearing electron-withdrawing groups (CF_3, NO_2 *etc.*) on the aromatic rings of urea at the different positions reacted smoothly to afford α-alkenyl pyrrolidines **2a**–**2f** in 62–88% yields with 91:9–95:5 er. Various aryl substituents (OMe, Me) at the alkenyl group are accepted to deliver **2a**–**2c** and **2g**–**2i** with high yields (76–88%) and good to high level 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, attaining the spirocyclic pyrrolidines **2h** and **2i** in 80% and 84% yields with 94:6 and 90:10 er, respectively. Di-substituted alkene **1j** was also suitable substrate to give **2j** in moderate yields and good enantioselectivity (90:10 er). Cyclic olefin substrate **1k** was also applicable for the reaction to yield **2k** in acceptable yield and enantioselectivity. The sulfonyl-protected alkenyl amines also worked to afford the cyclized products **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 aziridines products were observed, further featuring the excellent chemoselectivity of this method.

We then turned our attention to benzylic substrates due to the similar BDE between 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** between benzylic radical and PINO were obtained in some cases[21] (see Scheme 4a and Table S4 for details). After systematical screening of reaction parameters (Table S4), the optimal 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 (0.01 M) 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 products **4a**–**4c** in 69–84% yields with up to 95:5 er. Various functional groups (OMe, F, *etc.*) on aryl rings are tolerated, affording **4d**–**4g** with 61−80% yields and excellent enantioselectivity (94:6 to 95:5 er). Notably, *para*-alkenyl and alkynyl-substituted aromatic substrates were amenable to C–H amination, yielding **4h**–**4o** with excellent enantiocontrol up to 97:3 er, and the unsaturated carbon-carbon bonds are kept intact. Noteworthy is that chiral α-aryl pyrrolidines with olefin or alkyne functional groups at *para* position are core components of drug candidates (see Figure S1 in SI).[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 well compatible with the transformation, and **4p** and **4q** were formed in 91:9 and 94:6 er, respectively. Furthermore, substrates with different cycle-ring tether (**3r** and **3s**) also worked to yield spirocyclic pyrrolidines **4r** and **4s** with 95:5 to 92:8 er, respectively. Notably, 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 *para* position of phenyl ring (**3u**) is also well tolerated and no competing byproduct arising from benzylic position of *n*-Pr group was detected. This excellent regioselectivity might originate from the interaction between 4-OMe-PINO and urea moiety. Amination of α-C–H bond of thiophenyl ring was also achieved, furnishing **4v** in good yield and moderate er.

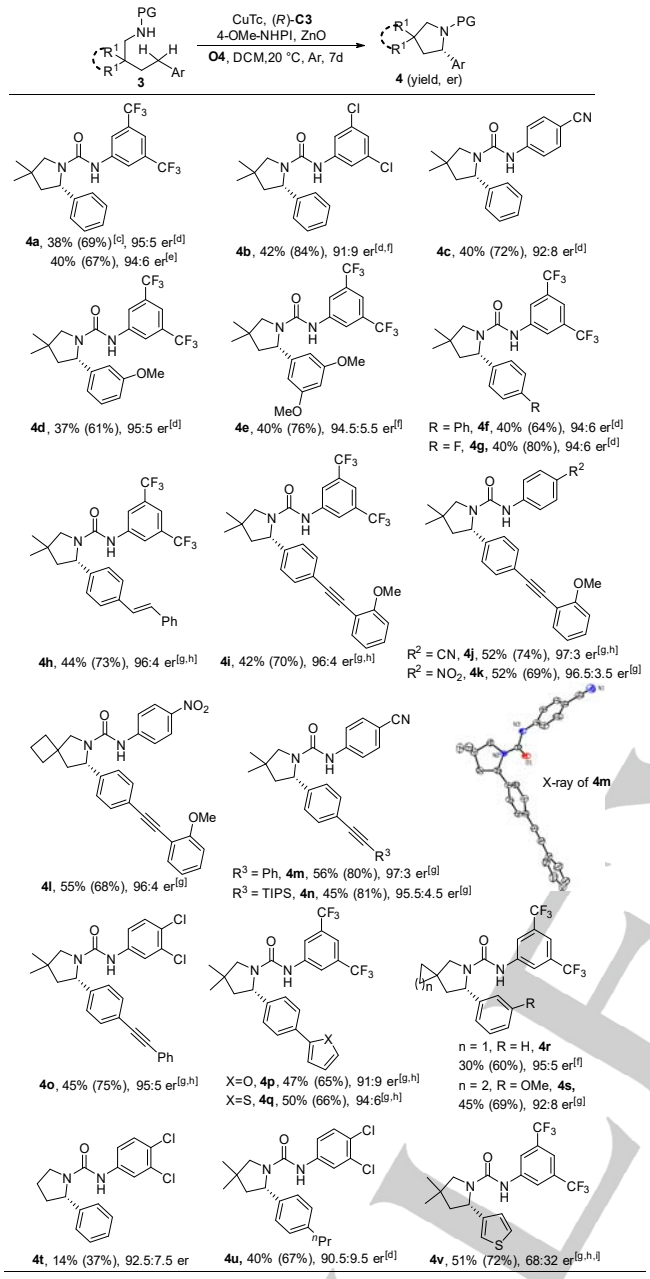
To illustrate the synthetic applicability of this protocol, a preparative scale of **2a** was conducted and there was only negligible erosion in the enantioselectivity, indicating this method should be potential for large-scale chemical production (Scheme 3a). Interestingly, the product **2a** was readily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

10.1002/anie.201911742

WILEY-VCH

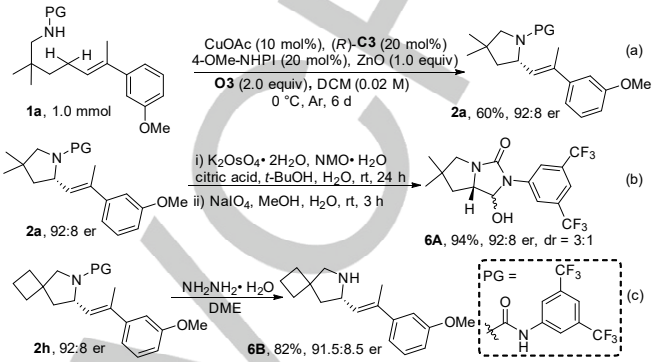
COMMUNICATION

Table 2. Scope of benzylic substrates[a,b]

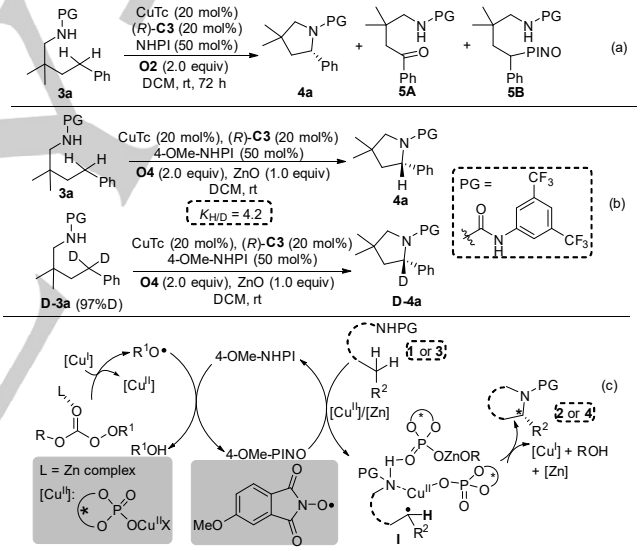


Conditions: CuTc (10 mol%), (*R*)-**C3** (20 mol%), 4-OMe-NHPI (0.5–1.0 equiv), ZnO (1.5 equiv), **O4** (3.0 equiv), DCM (0.01 M). [a] Reactions were run on 0.1 mmol scale and (*R*)-**C3** (5 mol%) was added at 12 h and 36 h, respectively. [b] Isolated yields were shown and er value was determined by HPLC. [c] Yields in parentheses were 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.

To gain some insights into the reaction mechanism, a set of control experiments were conducted. First, the significant inhibition effect was observed in allylic C–H amination of substrate **1a** when TEMPO or BHT was added (Scheme S1). Second, the direct C–H oxidation byproduct **5A** and cross coupling adducts **5B** and **5C** were detected in the benzylic C–H amination of **3a** and **3b** (Scheme 4a and Scheme S2). Collectively, these results support the involvement of proposed allylic or benzylic radical intermediate in this C–H amination process. Third, the measured intermolecular KIE data (4.2) of substrates **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 non-linear effect[23] on the ee value of **2c** was observed, which indicates that more than one CPA molecule is involved in the enantioselective transformation (see Figures S2 and S3 for details).



Scheme 3. Preparative-scale reaction and versatile transformations



Scheme 4. Mechanistic studies and proposed catalytic cycle

Based on the above mechanistic studies and previous studies,[11] we proposed a tentative mechanism for this C–H amination (Scheme 4c). Initially, Cu(I) reacts with peroxide which was activated by 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 highly reactive alkoxyl radical species to 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 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 carbon-centered radical intermediate **I** with 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.

10.1002/anie.201911742

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/α-aryl pyrrolidines with excellent levels of enantioselectivity, moderate to high efficiency, broad substrate scope and good functional group tolerance. This is the first example to construct 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 H atom of 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.

Acknowledgements

Financial support from the National Natural Science Foundation of China (nos 21722203, 21831002, and 21702093), Shenzhen special funds for the development of biomedicine, Internet, new energy, and new material industries (JCYJ20180302174416591) and Shenzhen Nobel Prize Scientists Laboratory Project (C17783101).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: copper • chiral phosphoric acid • radical asymmetric amination • pyrrolidine • allylic and benzylic C−H bonds

[1] a) Q. Lu, F. Glorius, *Angew. Chem. Int. Ed.* **2017**, *56*, 49; *Angew. Chem.* **2017**, *129*, 49; b) M. Milan, M. Bietti, M. Costas, *Chem. Commun.* **2018**, *54*, 9559; c) F. Wang, P. Chen, G. Liu, *Acc. Chem. Res.* **2018**, 51, 2036; d) J. Loup, U. Dhawa, F. Pesciaioli, J. Wencel-Delord, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 12803; *Angew. Chem.* **2019**, *131*, 12934; e) J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed.* **2018**, *57*, 62; *Angew. Chem.* **2018**, *130*, 64.

[2] a) J. T. Groves, P. Viski, *J. Am. Chem. Soc.* **1989**, *111*, 8537; b) K. Hamachi, R. Irie, T. Katsuki, *Tetrahedron Lett.* **1996**, *37*, 4979; c) V. Dantignana, M. Milan, O. Cussó, A. Company, M. Bietti, M. Costas, *ACS Cent. Sci.* **2017**, *3*, 1350; d) R. Zhang, W.-Y. Yu, T.-S. Lai, C.-M. Che, *Chem. Commun.* **1999**, 1791; e) Y. Wang, X. Wen, X. Cui, X. P. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 4792; f) C. Li, K. Lang, H. Lu, Y. Hu, X. Cui, L. Wojtas, X. P. Zhang, *Angew. Chem. Int. Ed.* **2018**, *57*, 16837; *Angew. Chem.* **2018**, *130*, 17079; g) K. Lang, S. Torker, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2019**, *141*, 12388; h) F. Burg, M. Gicquel, S. Breitenlechner, A. Pöthig, T. Bach, *Angew. Chem. Int. Ed.* **2018**, *57*, 2953; *Angew. Chem.* **2018**, *130*, 3003. i) E. T. Hennessy, T. A. Betley, *Science* **2013**, *340*, 591; j) V. Lyaskovskyy, A. I. O. Suarez, H. Lu, H. Jiang, X. P. Zhang, B. de Bruin, *J. Am. Chem. Soc.* **2011**, *133*, 12264.

[3] For examples of enantioselective cross-coupling of alkyl radical with different chiral metal complex, see: a) C. Fischer, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 4594; b) J. Mao, F. Liu, M. Wang, L. Wu, B. Zheng, S. Liu, J. Zhong, Q. Bian, P. J. Walsh, *J. Am. Chem. Soc.* **2014**, *136*, 17662; c) M. Jin, L. Adak, M. Nakamura, *J. Am. Chem. Soc.* **2015**, *137*, 7128; d) Q. M. Kainz, C. D. Matier, A. Bartoszewicz, S. L. Zultanski, J. C. Peters, G. C. Fu, *Science* **2016**, *351*, 681.

[4] a) M. S. Kharasch, G. Sosnovsky, *J. Am. Chem. Soc.* **1958**, *80*, 756; b) J. Eames, M. Watkinson, *Angew. Chem. Int. Ed.* **2001**, *40*, 3567; *Angew. Chem.* **2001**, *113*, 4725; c) M. B. Andrus, Z. Zhou, *J. Am. Chem. Soc.* **2002**, *124*, 8806; d) B. Zhang, S.-F. Zhu, Q.-L. Zhou, *Tetrahedron Lett.* **2013**, *54*, 2665.

[5] a) W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014; b) W. Zhang, L. Wu, P. Chen, G. Liu, *Angew. Chem. Int. Ed.* **2019**, *58*, 6425; *Angew. Chem.* **2019**, *131*, 6491.

[6] P.-S. Wang, M.-L. Shen, T.-C. Wang, H.-C. Lin, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2017**, *56*, 16032; *Angew. Chem.* **2017**, *129*, 16248.

[7] For selected reviews, see: a) F. Collet, C. Lescot, P. Dauban, *Chem. Soc. Rev.* **2011**, *40*, 1926; b) J. L. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res.* **2012**, *45*, 911; c) J. M. Alderson, J. R. Corbin, J. M. Schomaker, *Acc. Chem. Res.* **2017**, *50*, 2147; For representative examples, see: d) J.-L. Liang, S.-X. Yuan, J.-S. Huang, W.-Y. Yu, C.-M. Che, *Angew. Chem. Int. Ed.* **2002**, *41*, 3465; *Angew. Chem.* **2002**, *114*, 3615; e) C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois, *J. Am. Chem. Soc.* **2004**, *126*, 15378; f) R. P. Reddy, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 5013; g) E. Milczek, N. Boudet, S. Blakey, *Angew. Chem. Int. Ed.* **2008**, *47*, 6825; *Angew. Chem.* **2008**, *120*, 6931; h) A. Nasrallah, V. Boquet, A. Hecker, P. Retailleau, B. Darses, P. Dauban, *Angew. Chem. Int. Ed.* **2019**, *58*, 8192. *Angew. Chem.* **2019**, *131*, 8276; i) Q. Xing, C.-M. Chan, Y.-W. Yeung, W.-Y. Yu, *J. Am. Chem. Soc.* **2019**, *141*, 3849; j) Y. Park, S. Chang, *Nat. Catal.* **2019**, *2*, 219; k) H. Wang, Y. Park, Z. Bai, S. Chang, G. He, G. Chen, *J. Am. Chem. Soc.* **2019**, *141*, 7194.

[8] a) W. Li, X. Zhang, *Stereoselective Formation of Amines*, *Topics in Current Chemistry*, Springer, Berlin, **2014**, Vol. *343*; b) T. C. Nugent, *Chiral amine synthesis: methods, developments and applications*, Wiley-VCH, Weinheim, **2010**; c) A. Ricci, *Modern Amination Methods*, Wiley-VCH, Weinheim, **2008**.

[9] a) G. Pelletier, D. A. Powell, *Org. Lett.* **2006**, *8*, 6031; b) Z. Ni, Q. Zhang, T. Xiong, Y. Zheng, Y. Li, H. Zhang, J. Zhang, Q. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 1244; *Angew. Chem.* **2012**, *124*, 1270; c) E. S. Jang, C. L. McMullin, M. Käß, K. Meyer, T. R. Cundari, T. H. Warren, *J. Am. Chem. Soc.* **2014**, *136*, 10930; d) B. L. Tran, B. Li, M. Driess, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, 136, 2555; e) S. Herold, D. Bafaluy, K. Muñiz, *Green Chem.* **2018**, *20*, 3191.

[10] a) Y. Kohmura, K. Kawasaki, T. Katsuki, *Synlett* **1997**, 1456; b) J. S. Clark, C. Roche, *Chem. Commun.* **2005**, 5175.

[11] a) P. Yu, J.-S. Lin, L. Li, S.-C. Zheng, Y.-P. Xiong, L.-J. Zhao, B. Tan, X.-Y. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 11890; *Angew. Chem.* **2014**, *126*, 12084; b) J.-S. Lin, X.-Y. Dong, T.-T. Li, N.-C. Jiang, B. Tan, X.-Y. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 9357; c) Y.-F. Cheng, X.-Y. Dong, Q.-S. Gu, Z.-L. Yu, X.-Y Liu, *Angew. Chem. Int. Ed.* **2017**, *56*, 8883; *Angew. Chem.* **2017**, *129*, 9009; d) J.-S. Lin, F.-L. Wang, X.-Y. Dong, W.-W. He, Y. Yuan, S. Chen, X.-Y. Liu, *Nat. Commun.* **2017**, *8*, 14841; e) F.-L. Wang, X.-Y. Dong, J.-S. Lin, Y. Zeng, G.-Y. Jiao, Q.-S. Gu, X.-Q. Guo, C.-L. Ma, X.-Y. Liu, *Chem* **2017**, *3*, 979; f) X.-F. Li, J.-S. Lin, J. Wang, Z.-L. Li, Q.-S. Gu, X.-Y. Liu, *Acta Chim. Sinica* **2018**, *76*, 878; g) J.-S. Lin, T.-T. Li, J.-R. Liu, G.-Y. Jiao, Q.-S. Gu, J.-T. Cheng, Y.-L. Guo, X. Hong, X.-Y. Liu, *J. Am. Chem. Soc.* **2019**, *141*, 1074.

[12] BDE of different C–H bonds, see: Y.-R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Boca Raton, **2007**.

[13] Y. Amaoka, S. Kamijo, T. Hoshikawa, M. Inoue, *J. Org. Chem.* **2012**, *77*, 9959.

[14] K. Jia, Y. Chen, *Chem. Commun.* **2018**, *54*, 6105.

[15] The BDE of allylic/benzylic C–H bond typically ranges from 88 to 90 kcal/mol, and the BDE of NHPI is 88 kcal/mol, which account for the high chemoselectivity of the present C–H amination. For reviews, see: a) Y. Ishii, S. Sakaguchi, T. Iwahama, *Adv. Synth. Catal.* **2001**, *343*, 393; For leading references, see: b) Y. Ishii, T. Iwahama, S. Sakaguchi, K. Nakayama, Y. Nishiyama, *J. Org. Chem.* **1996**, *61*, 4520; c) N. Koshino, Y. Cai, J. H. Espenson, *J. Phys. Chem. A* **2003**, *107*, 4262; d) M. Rafiee, F. Wang, D. P. Hruszkewycz, S. S. Stahl, *J. Am. Chem. Soc.* **2018**, *140*, 22.

[16] E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate, P. S. Baran, *Nature* **2016**, *533*, 77.

[17] L. Hong, W. Sun, D. Yang, G. Li, R. Wang, *Chem. Rev.* **2016**, *116*, 4006.

[18] The role of ZnO is likely to form zinc phosphate in situ with (*R*)-**C3**.

[19] CCDC 1959977 (**2c**) and CCDC 1953405 (**4m**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[20] D. P. Hruszkewycz, K. C. Miles, O. R. Thiel, S. S. Stahl, *Chem. Sci.* **2017**, *8*, 1282.

[21] J. M. Lee, E. J. Park, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 7824.

[22] a) Z.-Y. Xue, L.-X. Liu, Y. Jiang, W.-C. Yuan, X.-M. Zhang, *Eur. J. Org. Chem.* **2012**, *2012*, 251.

[23] A linear effect on the ee value of **2c** was observed without ZnO, which indicates $Cu(CPA)_2$ is less likely as catalyst state, see: C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.* **1998**, *37*, 2922; *Angew. Chem.* **1998**, *110*, 3088.

[24] F. Minisci, F. Recupero, A. Cecchetto, C. Gambarotti, C. Punta, R. Paganelli, G. F. Pedulli, F. Fontana, *Org. Proc. Res. Devel.* **2004**, *8*, 163.

[25] Substrate might coordinate with Cu(II) phosphate complex in advance before hydrogen abstraction by 4-OMe-PINO. HRMS results indicate that Cu(II) phosphate complex might be generated from $(CPA)_2Zn$ via transmetallation between Cu(II) and $(CPA)_2Zn$, see Scheme S3 for details.

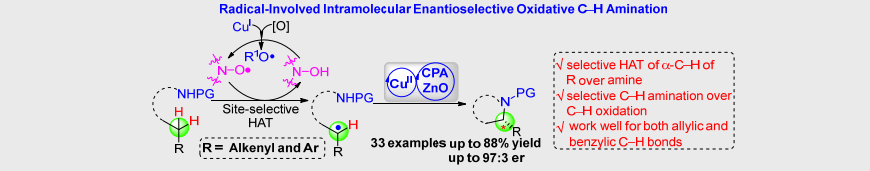
[26] D. Bafaluy, J. M. Muñoz-Molina, I. Funes-Ardoiz, S. Herold, A. J. de Aguirre, H. Zhang, F. Maseras, T. R. Belderrain, P. J. Pérez, K. Muñiz, *Angew. Chem. Int. Ed.* **2019**, *58*, 8912; *Angew. Chem.* **2019**, *131*, 9004.

10.1002/anie.201911742

WILEY-VCH

Entry for the Table of Contents

COMMUNICATION



Asymmetric radical control: The first radical-involved intramolecular enantioselective oxidative C−H amination of not only allylic substrates but also benzylic substrates via a HAT process with Cu(I)/chiral phosphoric acid catalytic system was reported. Critical to the success of this protocol is the use of 4-OMe-PINO as a stable and chemoselective hydrogen abstractor to selectively abstract H atom of allylic and benzylic positions.

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

Page No. – Page No.

Cu(I)/Chiral Phosphoric Acid-Catalyzed Radical-Involved Enantioselective Intramolecular Amination of Allylic and Benzylic C–H Bonds