ACES Asian Chemical Editorial Society

doi.org/10.1002/ajoc.202300220

ASIAN JOURNAL OF ORGANIC CHEMISTRY
Research Article

www.asianjoc.org

Special Collection

Copper-Catalyzed Intramolecular Radical Amination of Tertiary C(sp^3)–H Bonds to Access α-Quaternary Pyrrolidines

Ang Gao[+],[a, b] Yang-Qing Ren[+],[b] Cheng Luan,[b] Yu Tian,[b] Lin Liu,[a, b] Qiang-Shuai Gu,[c] Zhong-Liang Li,[c] Chang-Jiang Yang,*[a, b] and Xin-Yuan Liu*[b]

Dedicated to Professor Keiji Maruoka on the occasion of his 70th Birthday

Abstract: Herein, we describe a Cu(I)/phosphoric acid catalyzed intramolecular radical tertiary C(sp^3)–H amination of N-chlorosulfonamide, providing an applicable route to the pyrrolidine structural motifs bearing an α-quaternary stereocenter (>20 examples with up to 94% yield). Mechanistic studies indicate that the reaction involves an intramolecular 1,5-hydrogen atom transfer process to form the key tertiary C-centered radical followed by a C–N bond formation. The corresponding enantioselective amination is accordingly disclosed by Cu(I)/chiral phosphoric acid catalyst to afford the chiral products with up to 81% enantiomeric excess (ee). This strategy is anticipated to facilitate the development of tertiary C(sp^3)–H functionalization.

Introduction

Pyrrolidines are not only key structure elements in a large number of natural products and pharmaceutical agents[1] but also broadly presented in various privileged chiral organocatalysts in organic synthesis.[2] As a specific collection of biologically active pyrrolidines, the α-quaternary containing ones have also aroused considerable interest.[3–6] Shown in Figure 1 are some typical examples of α-quaternary pyrrolidines with attractive pharmacological activities, such as shihunine,[4] veliparib,[5] and rolapitant,[6] etc. Given their promising biological properties and diversified molecular structures, the development of efficient synthetic methods for pyrrolidines has therefore stimulated intensive attention from organic chemists. Traditional approaches have been extensively studied,[1a] such as the 1,3-dipolar cycloadditions of azomethine ylides with alkenyl dipolarophiles.[7] Other alternative synthetic strategies have also been developed for producing pyrrolidines of different structural skeletons.[8] Nonetheless, developing mechanistically distinct methods for the expedient synthesis of α-quaternary containing pyrrolidines under mild conditions still remains desirable.

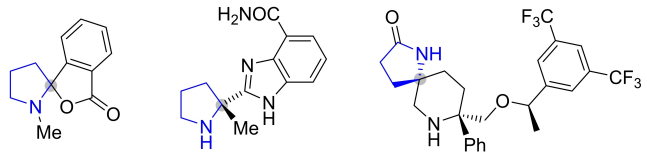


Figure 1. Bioactive molecules containing α-quaternary pyrrolidines.

The classic Hofmann-Löffler-Freytag (HLF) reactions, involving the remote radical C(sp^3)–H amination process,[9] have proven to be a potential platform for accessing functionally diverse cyclic amines from simple hydrocarbon feedstocks (Scheme 1a). Over the past decade, the renewed research interests from Muñiz, Yu, Lei, Nagib, and others have unveiled the attractive versatility of the HLF and related reactions.[10] As such, significant progress in this aspect has already overcome the conventionally required harsh condition limitation,[11] and thus serves as a complementary strategy to transition metal-catalyzed C–H functionalization.[12] Although great endeavors have been devoted to achieving the aminations of various secondary C–H bonds by the HAT process,[13] there are only a few reports aiming at tertiary C(sp^3)–H amination.[10a–d] Moreover, the enantioconvergent[14] amination of racemic tertiary C–H bonds represents a formidable challenge that mainly rests on the intrinsic chirality retention feature of such a process.[13a,15] In 2019, Arnold, Liu, and co-workers pioneered this area by achieving the first intramolecular enantioconvergent tertiary C(sp^3)–H amination of sulfamoyl azide with enzymatic catalysis to afford chiral α-quaternary cyclic sulfamides (Scheme 1b).[15a] In 2020, Zhang and co-workers described this intramolecular

[a] A. Gao,[+] Dr. L. Liu, Dr. C.-J. Yang
Department of Chemistry, School of Sciences
Great Bay University
Dongguan 523000 (P. R. China)
E-mail: yangcj@gbu.edu.cn

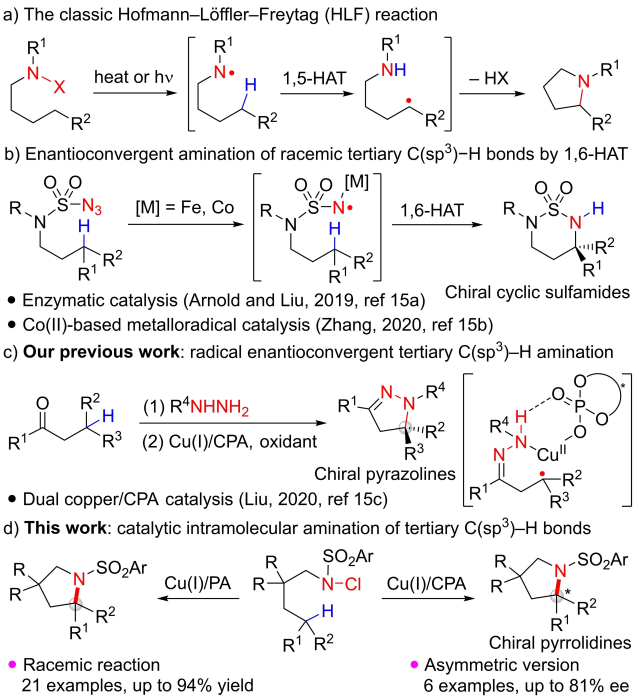
[b] A. Gao,[+] Y.-Q. Ren,[+] C. Luan, Y. Tian, Dr. L. Liu, Dr. C.-J. Yang, Prof. Dr. X.-Y. Liu
Shenzhen Grubbs Institute and Department of Chemistry
Southern University of Science and Technology
Shenzhen 518055 (P. R. China)
E-mail: liuxy3@sustech.edu.cn
yangcj@gbu.edu.cn

[c] Dr. Q.-S. Gu, Dr. Z.-L. Li
Academy for Advanced Interdisciplinary Studies and Department of Chemistry
Southern University of Science and Technology
Shenzhen 518055 (P. R. China)

[+] These authors contributed equally

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ajoc.202300220

Special Collection *This manuscript is part of a special collection on the occasion of Keiji Maruoka's 70th Birthday.*



Scheme 1. Radical intramolecular HAT enabled C–H amination.

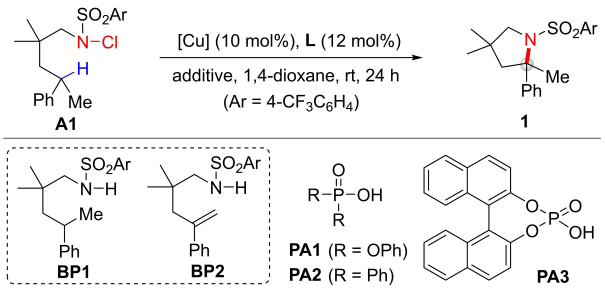
enantioconvergent 1,6-amination of similar substrates with their Co(II)-based metalloradical catalytic system (Scheme 1b).[15b] Meanwhile, our group disclosed a decoupled intramolecular 1,5-HAT strategy for direct radical enantioconvergent tertiary C(sp^3)–H amination of racemic ketones using dual copper/chiral phosphoric acid (CPA) catalysis, providing facile access to a range of chiral α-quaternary pyrazolines (Scheme 1c).[15c] Despite these advances, it is still highly demanded in developing catalytic enantioselective amination of ubiquitous tertiary C–H bonds for accessing diverse amines of different structural skeletons bearing α-quaternary stereocenters.

With our continuous endeavors in copper-catalyzed enantioselective radical reactions,[16] we have discovered that chiral copper catalysis provides a practical avenue for the enantioselective C–H amination and alkynylation.[15c,17] As such, we envisioned that a coupled 1,5-HAT process and intramolecular amination of remote tertiary C(sp^3)–H bonds in N-halogenated amides[18] could provide an applicable approach to forge the synthetic valuable α-quaternary pyrrolidines (Scheme 1d). However, this strategy encountered two considerable challenges: a) potential competing reactions such as the halogen atom transfer pathway[19] and the thus-generated tertiary alkyl radical being quenched or overoxidized to carbocation should be inhibited. b) the enantiocontrol problem of asymmetric tertiary C–H functionalization to access quaternary stereocenters.[15] Herein, we document our efforts toward the development of a Cu(I)/phosphoric acid (PA) catalyzed radical intramolecular amination of tertiary C(sp^3)–H bonds under ambient conditions. This method also provides a general and practical tool to access enantioenriched α-quaternary pyrrolidines enabled by the dual Cu(I)/CPA catalysis.

Results and Discussion

We began our study using N-chlorosulfonamide **A1** as the model substrate to probe the racemic tertiary C(sp^3)–H amination reaction (Table 1). In the presence of Ag_2CO_3 (0.6 equiv) as an additive to quench the in situ generated chloride anion, a mixture of **A1** (0.10 mmol), CuI (10 mol%), and phosphoric acid **PA1** (12 mol%) in 1,4-dioxane (2.0 mL) was stirred at room temperature for 24 h. The reaction afforded the desired product **1** in 65% yield, along with the by-products **BP1** and **BP2** in 7% and 18% yield, respectively (Table 1, entry 1). Control experiments indicated that CuI catalyst was indispensable for initiating the reaction, while the absence of **PA1** or additive leads to a significant decrease in the product yield and an increase in by-product yields (Table 1, entries 2–4). To further improve the reaction efficiency, a survey of reaction parameters was conducted. Other phosphoric acids such as **PA2** and **PA3** both gave comparable results with **PA1** in terms of product **1** yields (60% and 56%, respectively) (Table 1, entries 5 and 6). We next screened different combinations of silver salts and copper catalysts (Table 1, entries 7–14) and the results unveiled that the combination of AgOTf (1.2 equiv) and CuTc (10 mol%) afforded **1** in 95% yield (92% isolated yield) with exclusive reactivity (delivered the by-products in marginal yields). Among

Table 1. Survey on the model reaction conditions.[a]



Entry	[Cu]	L	Additive (equiv)	Yield (%)[b] 1	BP1	BP2
1	CuI	**PA1**	Ag_2CO_3 (0.6)	65	7	18
2	–	**PA1**	Ag_2CO_3 (0.6)	–	–	–
3	CuI	–	Ag_2CO_3 (0.6)	40	8	35
4	CuI	**PA1**	–	51	32	6
5	CuI	**PA2**	Ag_2CO_3 (0.6)	60	<5	26
6	CuI	**PA3**	Ag_2CO_3 (0.6)	56	<5	32
7	CuI	**PA1**	Ag_3PO_4 (0.4)	66	5	25
8	CuI	**PA1**	AgOAc (1.2)	11	10	64
9	CuI	**PA1**	$AgNO_3$ (1.2)	22	8	31
10	CuI	**PA1**	$AgBF_4$ (1.2)	78	5	6
11	CuI	**PA1**	AgOTf (1.2)	85	8	<5
12	CuBr	**PA1**	AgOTf (1.2)	64	17	<5
13	CuOAc	**PA1**	AgOTf (1.2)	50	13	<5
14	CuTc	**PA1**	AgOTf (1.2)	95 (92)	<5	trace
15[c]	CuTc	**PA1**	AgOTf (1.2)	72	14	trace
16[d]	CuTc	**PA1**	AgOTf (1.2)	19	21	trace
17[e]	CuTc	**PA1**	AgOTf (1.2)	84	9	<5
18[f]	CuTc	**PA1**	AgOTf (1.2)	21	27	9

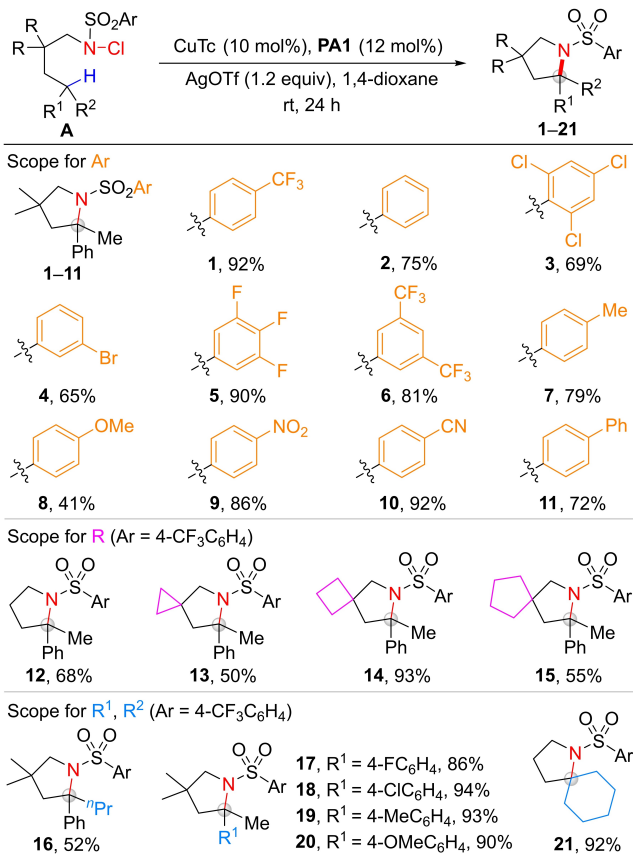
[a] Reaction conditions: **A1** (0.10 mmol), [Cu] (10 mol%), **L** (12 mol%), and additive in 1,4-dioxane (2.0 mL) at room temperature (rt) for 24 h under argon. [b] Yields were based on ^{19}F NMR analysis of the crude product using (trifluoromethyl)benzene as an internal standard. Isolated yield in parenthesis. [c] THF was used. [d] CH_2Cl_2 was used. [e] EtOAc was used. [f] Chlorobenzene was used. Tc, 2-thiophenecarboxylato.

the solvents tested, 1,4-dioxane remained the best one (entries 15–18). As such, the optimal reaction conditions were established as those listed in entry 14 of Table 1.

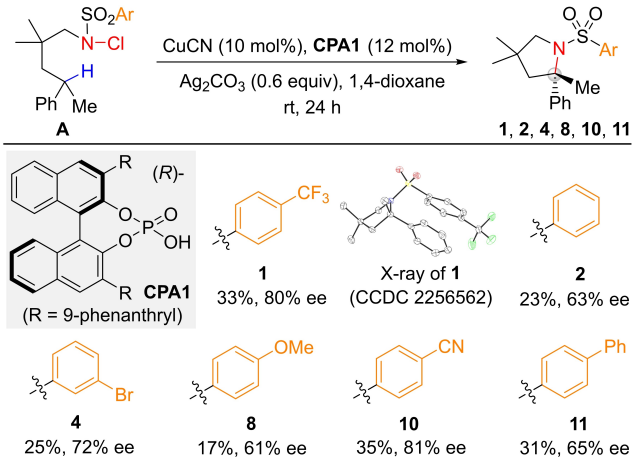
With the optimal reaction conditions being established, we next investigated the generality of the reaction, and the results are summarized in Scheme 2. In regard to the aryl-substituted sulfonyl scope, a variable range of differently unsubstituted and substituted phenyls having different electronic and steric properties were compatible with this reaction, affording the corresponding products **1**–**11** in moderate to excellent yields. Notably, 2,4,6-trichloro-substitution (**3**) was well tolerated, and the substrate with strong electron-donating methoxyl group (**8**) gave lower yield in comparison to those bearing electron-withdrawing functionalities, such as trifluoromethyl (**1** and **6**), halo (**3**–**5**), nitro (**9**) and cyano (**10**), which provided their products in good to excellent yields. By changing the dimethyl tether group to a linear chain, the substrate proceeded well under the standard conditions to give the corresponding product **12** in 68% yield. In addition, replacing the tether with cycloalkyl groups, such as cyclopropyl and cyclopentyl tethers delivered the amination products **13** and **15** in moderate yields. However, a cyclobutyl variant had no significant influence compared with the model substrate and the spirocyclic α-quaternary pyrrolidine **14** was efficiently obtained in 93% yield. To further investigate the reaction scope, we tested the generality of the tertiary C(sp^3)–H moieties and found the simple unfunctionalized linear alkyl group was viable in the reaction, giving the product **16** in moderate yield. Furthermore, the substrates bearing electron-withdrawing or -donating groups on the aromatic rings (R^1) all reacted smoothly to afford the α-quaternary pyrrolidines **17**–**20** in excellent yields (86–94%). Noteworthy is that the substrate containing a tertiary C(sp^3)–H bond on a cyclohexane ring also underwent the reaction to afford the spirocyclic product **21** in 92% yield. These results suggested the intramolecular amination of tertiary C(sp^3)–H bonds has a broad substrate scope and accordingly provides facile access to many α-quaternary pyrrolidines.

Given the importance of chiral α-quaternary pyrrolidines, we further investigated the corresponding enantioselective intramolecular amination of tertiary C(sp^3)–H bonds to access enantioenriched α-quaternary pyrrolidines.[16] After systematic screening of reaction parameters (see Table S1 in the Supporting Information), the preferred reaction conditions were identified as follows: N-chlorosulfonamide **A1** (0.10 mmol), CuCN (10 mol%), (*R*)-**CPA1** (12 mol%) and Ag_2CO_3 (0.6 equiv) in 1,4-dioxane (2.0 mL) at room temperature for 24 h, providing **1** with 80% ee albeit in relatively low isolated yield (33%) for the time being (Scheme 3). The absolute configuration of **1** was determined to be *S* by X-ray crystallographic analysis[20] (Scheme 3 and Figure S1 in the Supporting Information), and those of other products were assigned by analogy. The preliminary result on asymmetric tertiary C(sp^3)–H amination encouraged us to expand the scope of this methodology. As shown in Scheme 3, N-chlorosulfonamide **A** bearing different aryl-substituted sulfonyl groups all underwent this asymmetric intramolecular amination smoothly to give the enantioenriched products **2**, **4**, **8**, **10**, and **11** with 61–81% ee, however, the yields are still poor (17–35%) with alkene as the major by-product (see Table S1 in the Supporting Information), and further optimization is currently ongoing in our laboratory.

To illustrate the practicality and utility of this method, we then performed a gram-scale synthesis of pyrrolidine **1** from N-

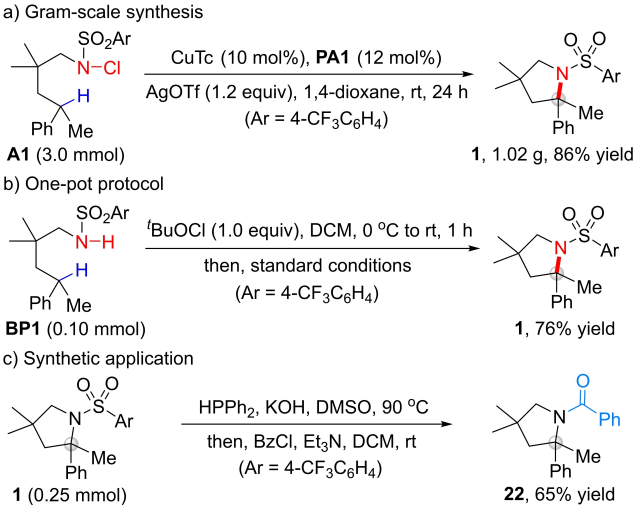


Scheme 2. Scope for intramolecular amination of tertiary C(sp^3)–H bonds.[a,b] [a] Standard conditions: **A** (0.10 mmol), CuTc (10 mol%), **PA1** (12 mol%), and AgOTf (1.2 equiv) in 1,4-dioxane (2.0 mL) at rt for 24 h under argon. [b] Yields were isolated.

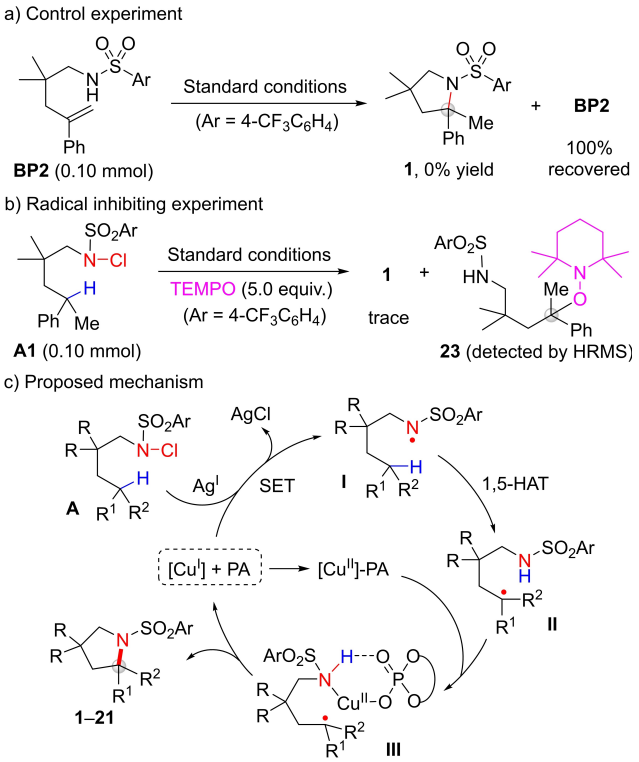


Scheme 3. Scope for enantioselective tertiary C(sp^3)–H amination.[a,b] [a] Standard conditions: **A** (0.10 mmol), CuCN (10 mol%), **CPA1** (12 mol%), and Ag_2CO_3 (0.6 equiv) in 1,4-dioxane (2.0 mL) at rt for 24 h under argon. [b] Yields were isolated. Ee values were determined by chiral HPLC analysis.

chlorosulfonamide **A1** (3.0 mmol) under standard conditions, which delivered 1.02 g of product **1** in 86% yield (Scheme 4a). Notably, the current methodology is compatible with a sequential one-pot protocol for the direct use of readily available sulfonamide **BP1** in the reaction without the need for isolating the N-chlorosulfonamide intermediate. Thus, the sulfonamide **BP1** sequentially underwent N–H chlorination in the presence of *tert*-butyl hypochlorite and further intramolecular tertiary C(sp^3)–H amination under the standard conditions to generate **1** in 76% yield (Scheme 4b). In addition, the sulfonyl protecting group in pyrrolidine **1** is readily convertible to the common acyl group through a tandem two steps one-pot procedure, and thus affording the corresponding N-benzoyl pyrrolidine **22** in 65% yield (Scheme 4c). These transformations further strengthen the applicability of this intramolecular amination in the synthesis of structurally diverse α-quaternary pyrrolidines.



Scheme 4. Scalability and synthetic utility.



Scheme 5. Mechanistic investigation.

Regarding the mechanism of this reaction, we initially conducted a control experiment using terminal alkene by-product **BP2** (from Table 1) as the substrate under otherwise standard reaction conditions and failed to afford product **1** (Scheme 5a). This experiment excluded the formation of the amination products directly from intramolecular hydroamination of alkenes.[8a,b] In addition, a completely inhibition effect was observed when TEMPO was added into the model reaction and the formation of TEMPO-trapped product **23** was detected by high-resolution mass spectrometry (HRMS) analysis (Scheme 5b). This result supported the involvement of a tertiary C-centered radical specie under the current reaction conditions, which is likely yielded from the in situ generated N-centered radical via a fast intramolecular 1,5-HAT process.[15]

Based on our mechanistic studies and previous reports,[18] we tentatively proposed a plausible mechanism for the reaction as depicted in Scheme 5c. The reaction sequence should be initiated with the generation of the N-centered radical specie **I** and Cu(II) phosphate by a single-electron transfer process of the corresponding Cu(I) and PA catalyst with N-chlorosulfonamide **A**. The thus formed chloride anion is scavenged by Ag(I) salt along with the concurrent liberation of insoluble AgCl in organic solution. The subsequent intramolecular 1,5-HAT process of radical **I** produces the crucial tertiary C-centered radical intermediate **II**, which associates with the Cu(II) phosphate via the in situ generated intermediate **III** and promotes the intramolecular C–N bond formation to give the amination product and regenerate the Cu(I)/PA catalyst. During this course, the chiral Cu(II) phosphate from a Cu(I)/CPA catalytic system could control the enantioselectivity of the amination reaction.

Conclusion

In summary, we have developed a Cu/PA catalyzed intramolecular radical amination of tertiary C(sp^3)–H bonds in N-chlorosulfonamide, giving facile access to structurally diverse α-quaternary pyrrolidines with moderate to excellent yields. This strategy features a sequential radical intramolecular 1,5-HAT and C–N bond formation that enables the challenging tertiary C–H functionalization. In addition, the preliminary success of enantioselective tertiary C(sp^3)–H amination with a dual Cu/CPA catalysis showcases the potential of this method for rapidly achieving enantioenriched pyrrolidines bearing α-quaternary stereocenters. Further investigations on the improvement of the asymmetric transformations are currently underway in our laboratory.

Acknowledgements

Financial support from the National Natural Science Foundation of China (Nos. 22025103, 92256301, 21831002, 22101122, and 22201127), National Key R&D Program of China (Nos. 2021YFF0701604 and 2021YFF0701704), Guangdong Innovative Program (No. 2019BT02Y335), Shenzhen Science and Technology Program (Nos. KQTD20210811090112004, JCYJ20200109141001789, and JCYJ20220530115409020), and Great Bay University is gratefully acknowledged. The authors appreciate the assistance of SUSTech Core Research Facilities.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: amination · C–H functionalization · copper catalysis · pyrrolidine · radical reaction

[1] a) T. Aniszewski, in *Alkaloids (Second Edition), Chapter 2* (Ed.: T. Aniszewski), Elsevier, Boston, **2015**, pp. 99–193; b) G. Li Petri, M. V. Raimondi, V. Spanò, R. Holl, P. Barraja, A. Montalbano, *Top. Curr. Chem.* **2021**, *379*, 34.

[2] a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; b) P. Kumar, S. Satbhaiya, in *Green Synthetic Approaches for Biologically Relevant Heterocycles (Second Edition), Chapter 6* (Ed.: G. Brahmachari), Elsevier, **2021**, pp. 215–251.

[3] For a recent review, see: a) N. Jeelan Basha, S. M. Basavarajaiah, K. Shyamsunder, *Mol. Diversity* **2022**, *26*, 2915–2937; For selected examples, see: b) W. J. Thompson, P. S. Anderson, S. F. Britcher, T. A. Lyle, J. E. Thies, C. A. Magill, S. L. Varga, J. E. Schwering, P. A. Lyle, *J. Med. Chem.* **1990**, *33*, 789–808; c) R. Sakai, C. Oiwa, K. Takaishi, H. Kamiya, M. Tagawa, *Tetrahedron Lett.* **1999**, *40*, 6941–6944; d) C. G. Thomson, E. Carlson, G. G. Chicchi, J. J. Kulagowski, M. M. Kurtz, C. J. Swain, K.-L. C. Tsao, A. Wheeldon, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 811–814; e) R. F. George, N. S. M. Ismail, J. Stawinski, A. S. Girgis, *Eur. J. Med. Chem.* **2013**, *68*, 339–351; f) G. Li, Q. Wang, J. Zhu, *Nat. Commun.* **2021**, *12*, 36.

[4] a) Y. Inubushi, Y. Tsuda, T. Konita, S. Matsumoto, *Chem. Pharm. Bull.* **1964**, *12*, 749–750; b) E. Leete, G. B. Bodem, *J. Am. Chem. Soc.* **1976**, *98*, 6321–6325.

[5] a) J. M. Albert, C. Cao, K. W. Kim, C. D. Willey, L. Geng, D. Xiao, H. Wang, A. Sandler, D. H. Johnson, A. D. Colevas, J. Low, M. L. Rothenberg, B. Lu, *Clin. Cancer Res.* **2007**, *13*, 3033–3042; b) T. D. Penning, G.-D. Zhu, V. B. Gandhi, J. Gong, X. Liu, Y. Shi, V. Klinghofer, E. F. Johnson, C. K. Donawho, D. J. Frost, V. Bontcheva-Diaz, J. J. Bouska, D. J. Osterling, A. M. Olson, K. C. Marsh, Y. Luo, V. L. Giranda, *J. Med. Chem.* **2009**, *52*, 514–523.

[6] a) R. A. Duffy, C. Morgan, R. Naylor, G. A. Higgins, G. B. Varty, J. E. Lachowicz, E. M. Parker, *Pharmacol. Biochem. Behav.* **2012**, *102*, 95–100; b) Y. Y. Syed, *Drugs* **2015**, *75*, 1941–1945.

[7] For leading reviews, see: a) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765–2810; b) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484–4517; c) R. Narayan, M. Potowski, Z.-J. Jia, A. P. Antonchick, H. Waldmann, *Acc. Chem. Res.* **2014**, *47*, 1296–1310; d) I. Arrastia, A. Arrieta, F. P. Cossío, *Eur. J. Org. Chem.* **2018**, *2018*, 5889–5904; e) L. Wei, X. Chang, C.-J. Wang, *Acc. Chem. Res.* **2020**, *53*, 1084–1100.

[8] For selected examples, see: a) C. F. Bender, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2005**, *127*, 1070–1071; b) J.-S. Lin, P. Yu, L. Huang, P. Zhang, B. Tan, X.-Y. Liu, *Angew. Chem. Int. Ed.* **2015**, *54*, 7847–7851; *Angew. Chem.* **2015**, *127*, 7958–7962; c) N. S. Sheikh, D. Leonori, G. Barker, J. D. Firth, K. R. Campos, A. J. H. M. Meijer, P. O'Brien, I. Coldham, *J. Am. Chem. Soc.* **2012**, *134*, 5300–5308; d) J.-S. Lin, X.-Y. Dong, T.-T. Li, N.-C. Jiang, B. Tan, X.-Y. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 9357–9360; e) C.-L. Ma, X.-H. Li, X.-L. Yu, X.-L. Zhu, Y.-Z. Hu, X.-W. Dong, B. Tan, X.-Y. Liu, *Org. Chem. Front.* **2016**, *3*, 324–329; f) C. Che, Y.-N. Lu, C.-J. Wang, *J. Am. Chem. Soc.* **2023**, *145*, 2779–2786; g) Y. Liu, H. Diao, G. Hong, J. Edward, T. Zhang, G. Yang, B.-M. Yang, Y. Zhao, *J. Am. Chem. Soc.* **2023**, *145*, 5007–5016.

[9] For early examples, see: a) A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 558–560; b) K. Löffler, C. Freytag, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3427–3431; c) E. J. Corey, W. R. Hertler, *J. Am. Chem. Soc.* **1960**, *82*, 1657–1668; d) P. de Armas, R. Carrau, J. I. Concepción, C. G. Francisco, R. Hernández, E. Suárez, *Tetrahedron Lett.* **1985**, *26*, 2493–2496; For early reviews, see: e) M. E. Wolff, *Chem. Rev.* **1963**, *63*, 55–64; f) G. Majetich, K. Wheless, *Tetrahedron* **1995**, *51*, 7095–7129.

[10] For leading examples, see: a) C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed.* **2015**, *54*, 8287–8291; *Angew. Chem.* **2015**, *127*, 8405–8409; b) T. Liu, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 5871–5874; c) X. Hu, G. Zhang, F. Bu, L. Nie, A. Lei, *ACS Catal.* **2018**, *8*, 9370–9375; d) 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*, 8912–8916; *Angew. Chem.* **2019**, *131*, 9004–9009; e) Q. Qin, S. Yu, *Org. Lett.* **2015**, *17*, 1894–1897; f) E. A. Wappes, S. C. Fosu, T. C. Chopko, D. A. Nagib, *Angew. Chem. Int. Ed.* **2016**, *55*, 9974–9978; *Angew. Chem.* **2016**, *128*, 10128–10132; g) Q.-Q. Min, J.-W. Yang, M.-J. Pang, G.-Z. Ao, F. Liu, *Org. Lett.* **2020**, *22*, 2828–2832; h) G.-L. Chen, S.-H. He, L. Cheng, F. Liu, *Org. Lett.* **2021**, *23*, 8338–8342; i) Q.-Q. Min, J.-W. Yang, M.-J. Pang, G.-Z. Ao, F. Liu, *Org. Chem. Front.* **2021**, *8*, 249–253; j) J.-W. Yang, G.-Q. Tan, K.-C. Liang, K.-D. Xu, M. Su, F. Liu, *Org. Lett.* **2022**, *24*, 7796–7800.

[11] For selected reviews, see: a) X.-Q. Hu, J.-R. Chen, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2017**, *56*, 1960–1962; *Angew. Chem.* **2017**, *129*, 1988–1990; b) H. Chen, S. Yu, *Org. Biomol. Chem.* **2020**, *18*, 4519–4532; c) W. Guo, Q. Wang, J. Zhu, *Chem. Soc. Rev.* **2021**, *50*, 7359–7377.

[12] a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; b) J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed.* **2018**, *57*, 62–101; *Angew. Chem.* **2018**, *130*, 64–105.

[13] For selected reviews, see: a) C. Zhang, Z.-L. Li, Q.-S. Gu, X.-Y. Liu, *Nat. Commun.* **2021**, *12*, 475; b) Q. Lu, F. Glorius, *Angew. Chem. Int. Ed.* **2017**, *56*, 49–51; *Angew. Chem.* **2017**, *129*, 49–51; c) M. Milan, M. Bietti, M. Costas, *Chem. Commun.* **2018**, *54*, 9559–9570; d) J. Loup, U. Dhawa, F. Pesciaioli, J. Wencel-Delord, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 12803–12818; *Angew. Chem.* **2019**, *131*, 12934–12949; e) Z. Zhang, P. Chen, G. Liu, *Chem. Soc. Rev.* **2022**, *51*, 1640–1658.

[14] V. Bhat, E. R. Welin, X. Guo, B. M. Stoltz, *Chem. Rev.* **2017**, *117*, 4528–4561.

[15] For enantioconvergent tertiary C(sp^3)–H amination, see: a) Y. Yang, I. Cho, X. Qi, P. Liu, F. H. Arnold, *Nat. Chem.* **2019**, *11*, 987–993; b) K. Lang, C. Li, I. Kim, X. P. Zhang, *J. Am. Chem. Soc.* **2020**, *142*, 20902–20911; c) C.-J. Yang, C. Zhang, Q.-S. Gu, J.-H. Fang, X.-L. Su, L. Ye, Y. Sun, Y. Tian, Z.-L. Li, X.-Y. Liu, *Nat. Catal.* **2020**, *3*, 539–546; d) Y. Dong, C. J. Lund, G. J. Porter, R. M. Clarke, S.-L. Zheng, T. R. Cundari, T. A. Betley, *J. Am. Chem. Soc.* **2021**, *143*, 817–829.

[16] a) Q.-S. Gu, Z.-L. Li, X.-Y. Liu, *Acc. Chem. Res.* **2020**, *53*, 170–181; b) Z.-L. Li, G.-C. Fang, Q.-S. Gu, X.-Y. Liu, *Chem. Soc. Rev.* **2020**, *49*, 32–48; c) X.-Y. Dong, Z.-L. Li, Q.-S. Gu, X.-Y. Liu, *J. Am. Chem. Soc.* **2022**, *144*, 17319–17329.

[17] a) L. Ye, Y. Tian, X. Meng, Q.-S. Gu, X.-Y. Liu, *Angew. Chem. Int. Ed.* **2020**, *59*, 1129–1133; *Angew. Chem.* **2020**, *132*, 1145–1149; b) Z.-H. Zhang, X.-Y. Dong, X.-Y. Du, Q.-S. Gu, Z.-L. Li, X.-Y. Liu, *Nat. Commun.* **2019**, *10*, 5689.

[18] For selected reviews, see: a) T. Xiong, Q. Zhang, *Chem. Soc. Rev.* **2016**, *45*, 3069–3087; b) J. M. Muñoz-Molina, T. R. Belderrain, P. J. Pérez, *Synthesis* **2021**, *53*, 51–64; For selected examples, see: c) Z. Li, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2018**, *57*, 13288–13292; *Angew. Chem.* **2018**, *130*, 13472–13476; d) Z. Liu, H. Xiao, B. Zhang, H. Shen, L. Zhu, C. Li, *Angew. Chem. Int. Ed.* **2019**, *58*, 2510–2513; *Angew. Chem.* **2019**, *131*, 2532–2535; e) A. Modak, E. N. Pinter, S. P. Cook, *J. Am. Chem. Soc.* **2019**, *141*, 18405–18410; f) X. Zeng, W. Yan, M. Paeth, S. B. Zacate, P.-H. Hong, Y. Wang, D. Yang, K. Yang, T. Yan, C. Song, Z. Cao, M.-J. Cheng, W. Liu, *J. Am. Chem. Soc.* **2019**, *141*, 19941–19949; g) Z. Zhang, L. M. Stateman, D. A. Nagib, *Chem. Sci.* **2019**, *10*, 1207–1211; h) C.-Y. Wang, Z.-Y. Qin, Y.-

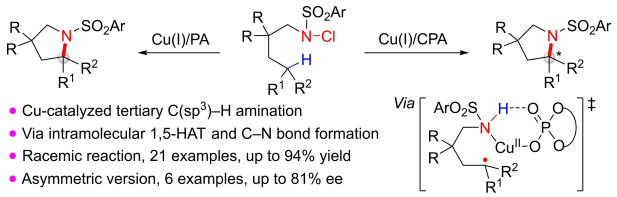
L. Huang, Y.-M. Hou, R.-X. Jin, C. Li, X.-S. Wang, *Org. Lett.* **2020**, *22*, 4006–4009.
[19] For selected examples, see: a) T. Liu, M. C. Myers, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 306–309; *Angew. Chem.* **2017**, *129*, 312–315; b) S. P. Morcillo, E. M. Dauncey, J. H. Kim, J. J. Douglas, N. S. Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* **2018**, *57*, 12945–12949; *Angew. Chem.* **2018**, *130*, 13127–13131; c) Y. Xia, L. Wang, A. Studer, *Angew. Chem. Int. Ed.* **2018**, *57*, 12940–12944; *Angew. Chem.* **2018**, *130*, 13122–13126; d) R.-Z. Liu, J. Li, J. Sun, X.-G. Liu, S. Qu, P. Li, B. Zhang, *Angew. Chem. Int. Ed.* **2020**, *59*, 4428–4433; *Angew. Chem.* **2020**, *132*, 4458–4463.
[20] Deposition number 2256562 (for **1**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Manuscript received: April 26, 2023
Revised manuscript received: June 1, 2023
Accepted manuscript online: June 3, 2023
Version of record online: ■■, ■■

ACES Asian Chemical Editorial Society

ASIAN JOURNAL OF ORGANIC CHEMISTRY
Research Article

RESEARCH ARTICLE



- Cu-catalyzed tertiary C(sp^3)–H amination
- Via intramolecular 1,5-HAT and C–N bond formation
- Racemic reaction, 21 examples, up to 94% yield
- Asymmetric version, 6 examples, up to 81% ee

A. Gao, Y.-Q. Ren, C. Luan, Y. Tian, Dr. L. Liu, Dr. Q.-S. Gu, Dr. Z.-L. Li, Dr. C.-J. Yang, Prof. Dr. X.-Y. Liu**

1 – 7

Copper-Catalyzed Intramolecular Radical Amination of Tertiary C(sp^3)–H Bonds to Access α-Quaternary Pyrrolidines

The direct functionalization of tertiary C–H bonds is a challenging task in organic synthesis. We disclose a Cu/phosphoric acid-catalyzed intramolecular radical amination of tertiary C(sp^3)–H bonds in N-chlorosulfonamides via a sequential radical intramolecular 1,5-HAT process/C–N formation. The asymmetric version is also enabled by dual Cu/chiral phosphoric acid catalysis to afford enantioenriched α-quaternary pyrrolidines.