A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Copper-Catalyzed Enantioconvergent Cross-Coupling of Racemic Alkyl Bromides with Azole C(sp2)–H Bonds

Authors: Xiao-Long Su, Liu Ye, Ji-Jun Chen, Xiao-Dong Liu, Sheng-Peng Jiang, Fu-Li Wang, Lin Liu, Chang-Jiang Yang, Xiao-Yong Chang, Zhong-Liang Li, Qiang-Shuai Gu, and Xin-Yuan Liu

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202009527

Link to VoR: https://doi.org/10.1002/anie.202009527

WILEY-VCH

10.1002/anie.202009527

WILEY-VCH

RESEARCH ARTICLE

Copper-Catalyzed Enantioconvergent Cross-Coupling of Racemic Alkyl Bromides with Azole C(sp^2)–H Bonds

Xiao-Long Su[+], Liu Ye[+], Ji-Jun Chen[+], Xiao-Dong Liu[+], Sheng-Peng Jiang, Fu-Li Wang, Lin Liu, Chang-Jiang Yang, Xiao-Yong Chang, Zhong-Liang Li, Qiang-Shuai Gu, and Xin-Yuan Liu*

Dedicated to Professor Ilhyong Ryu on the occasion of his 70th birthday

[*] Dr. X.-L. Su[+]
Shaanxi Key Laboratory of Phytochemistry, College of Chemistry and Chemical Engineering
Baoji University of Arts and Sciences, Baoji, Shaanxi 721013 (China)

Dr. X.-L. Su,[+] Dr. J.-J. Chen,[+] Dr. X.-D. Liu,[+] Dr. S.-P. Jiang, Dr. F.-L. Wang, Dr. L. Liu, Dr. C.-J. Yang, Dr. X.-Y. Chang, Prof. Dr. X.-Y. Liu
Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis
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. Z.-L. Li, Dr. Q.-S. Gu
Academy for Advanced Interdisciplinary Studies and Department of Chemistry
Southern University of Science and Technology, Shenzhen 518055 (China)

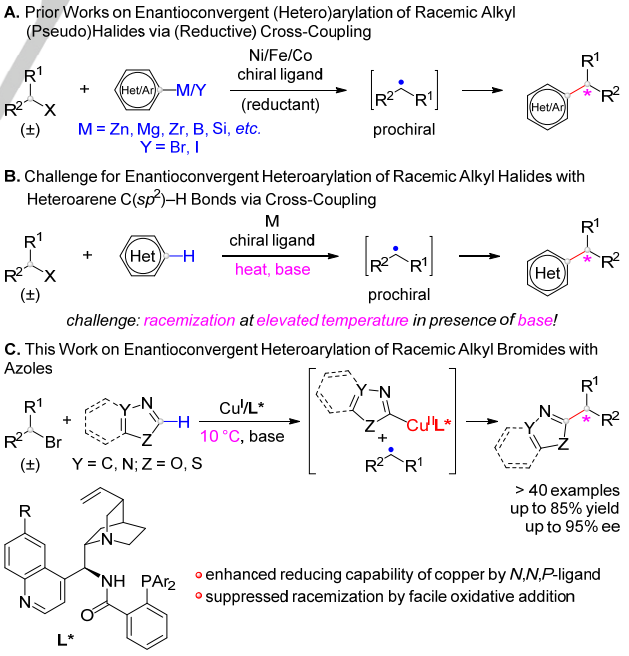
[+] These authors contributed equally to this work.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.2020XXXX.

Abstract: The development of enantioconvergent cross-coupling of racemic alkyl halides directly with heteroarene C(sp^2)–H bonds has been impeded by the commonly necessary use of base at elevated temperature that leads to racemization. We herein report a copper(I)/cinchona-alkaloid-derived *N*,*N*,*P*-ligand catalytic system that enables oxidative addition with racemic alkyl bromides under mild conditions. Thus, the coupling with azole C(sp^2)–H bonds has been achieved in high enantioselectivity, affording a number of potentially useful α-chiral alkylated azoles, such as 1,3,4-oxadiazoles, oxazoles, and benzo[*d*]oxazoles as well as 1,3,4-triazoles, for drug discovery. Mechanistic experiments indicated facile deprotonation of an azole C(sp^2)–H bond and the involvement of alkyl radical species under the reaction conditions.

Introduction

α-Chiral alkyl heteroarenes are common structural motifs in many drugs, bioactive small molecules, and natural products.[1] Synthetically, transition metal-catalyzed enantioconvergent radical C(sp^3)–C cross-coupling of racemic alkyl (pseudo)halides has received much attention over the past two decades.[2] In this context, enantioconvergent (hetero)arylation of alkyl (pseudo)halides via coupling with a diverse array of prefunctionalized (hetero)aryl reagents has emerged as a powerful method for the efficient construction of α-chiral alkyl (hetero)arene scaffolds with high levels of stereocontrol (Scheme 1A).[3–6] Thus, a variety of chiral catalysts based on first-row transition metals such as Ni, Co, and Fe have been utilized to convert racemic alkyl electrophiles to prochiral alkyl radicals, a strategy pioneered by Fu, Reisman and others.[2–5] Although impressive results have been achieved with this approach, the direct use of heteroarenes in place of these prefunctionalized heteroaryl reagents would be more desirable considering the ready material availability, operational simplicity, and high atom economy of C−H functionalization.[7,8] Nonetheless, the usually inevitable use of base at elevated temperature (typically 80–160 °C)[8–10] in racemic coupling of alkyl electrophiles with heteroarene C(sp^2)–H bonds poses a remarkable challenge for enantioconvergent synthesis: racemization might readily occur (Scheme 1B), particularly with electron-deficient heteroarenes.



Scheme 1. Enantioconvergent heteroarylation of racemic alkyl electrophiles.

As a part of our research program on asymmetric chemistry involving alkyl radical species,[11] we recently discovered that

10.1002/anie.202009527

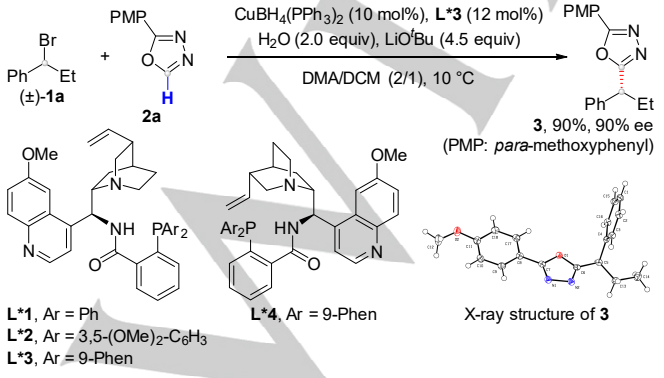
WILEY-VCH

RESEARCH ARTICLE

chiral alkaloid-derived multidentate *N*,*N*,*P*-ligand greatly enhanced the reducing capability of copper catalyst.[12] Thus, the resulting chiral copper catalyst readily reduced alkyl halides to alkyl radicals under ambient conditions. In view of the aforementioned racemization issue as well as the importance of azole in drug discovery (Scheme S1 in the Supporting Information),[1] we envisioned that our Cu(I)/*N*,*N*,*P*-ligand catalyst might promote the desired enantioconvergent coupling of alkyl halides with azole C(sp^2)–H bonds under mild conditions. As such, the remaining challenges would be: i. efficient inhibition of homocoupling of heterocycles[13] and/or alkyl halides;[14] ii. enantiocontrol over the heteroarylation of alkyl radicals. If successful, this method would provide not only an excellent complementary approach to the previous reported enantioselective heteroarene C(sp^2)–H alkylation,[15] but also an immediate access to enantioenriched α-chiral alkylated azoles for potential drug discovery (Scheme S1).[1] Herein, we describe the development of a mild copper(I)/cinchona alkaloid-derived *N*,*N*,*P*-ligand catalytic system for an asymmetric radical C(sp^3)–C(sp^2) cross-coupling of racemic alkyl bromides with azole C(sp^2)–H bonds (Scheme 1C).

Results and Discussion

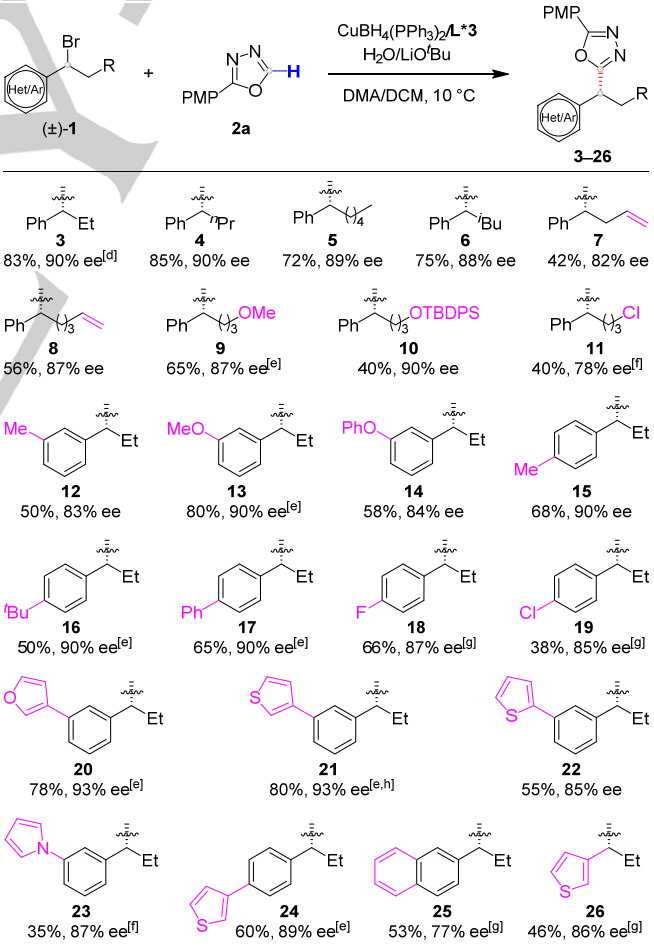
Initially we found that the desired coupling product **3** was formed in 24% yield with 49% ee from racemic **1a** and 1,3,4-oxadiazole **2a** under the catalysis of $CuBH_4(PPh_3)_2$ and **L*1** in presence of LiO^{t}Bu in DMA (*N*,*N*-dimethylacetamide) at room temperature (Scheme 2 and Table S1, entry 1 in the Supporting Information). The addition of two equivalents of H_2O greatly increased the yield of **3** to 58% without affecting the enantioselectivity (49% ee) (Table S1, entry 4), possibly due to enhanced transmetalation for the formation of a C–Cu bond (Scheme S2).[16] Besides, the presence of H_2O also rendered the reaction results readily repeatable. Further screening of solvents, ligands **L*1**–**L*3**, base additives, copper salts, and reaction temperatures identified the optimal conditions as follows (Scheme 2 and Table S1, entry 19): (±)-**1a** (2 equiv), **2a** (1 equiv), $CuBH_4(PPh_3)_2$ (10 mol%), **L*3** (12 mol%), H_2O (2 equiv), and LiO^{t}Bu (4.5 equiv) in DMA/DCM (2/1, 0.60 mL) at 10 °C under argon, affording **3** in 90% NMR yield and 90% ee. The absolute configuration of **3** was determined to be *R* by X-ray[17] structural analysis (Scheme 2 and Figure S1 in the Supporting Information) and those of other products in this work were assigned by analogy.



Scheme 2. Reaction development.

Next, we examined the scope of alkyl bromides in this reaction (Table 1). Thus, benzyl bromides featuring linear and branched purely aliphatic side chains were all suitable substrates for this reaction (**3**–**6**). In addition, substituents such as terminal alkene (**7** and **8**), ether (**9**), silyl-protected alcohol (**10**), and primary chloride (**11**) on the alkyl side chains were tolerated. On the other hand, various functional groups of either electron-donating or -withdrawing properties on the phenyl rings of benzyl bromides were compatible with the reaction conditions, delivering product **12**–**19** in moderate to good yield with good enantioselectivity. Interestingly, medicinally relevant heteroaryl substituents such as furanyl (**20**), thiophenyl (**21**, **22**, and **24**), and pyrrolyl (**23**) appended on the phenyl rings were also applicable to the reaction. In addition, bicyclic 2-naphthalenyl- and heterocyclic 3-thiophenyl-substituted alkyl bromides were viable substrates, leading to products **25** and **26**, respectively, in moderate yield and good enantioselectivity. Interestingly, a mixture of regioisomeric allylic bromides also gave rise to the coupling product as a single regioisomer in good yield with promising enantioselectivity (Scheme S3), of which the result is currently under further

Table 1: Substrate scope of alkyl bromides.[a,b,c]



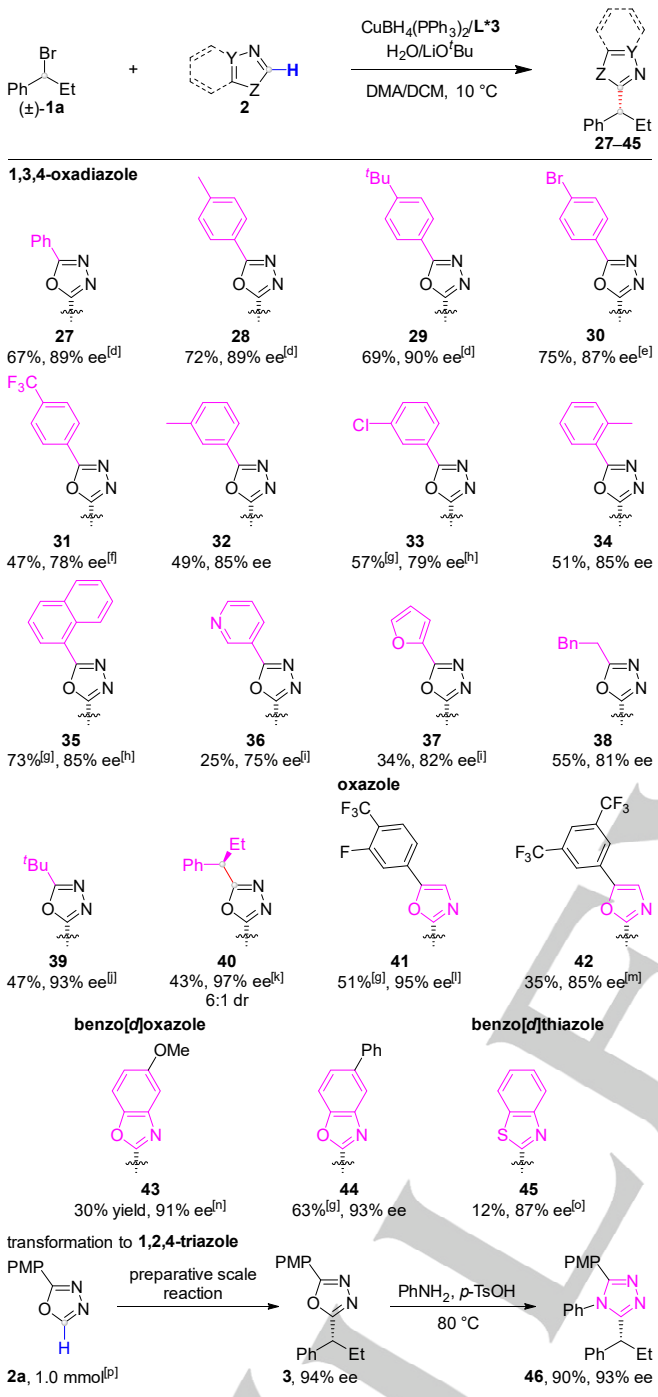
[a] Reaction conditions: **1** (2.0 equiv), **2a** (0.10 mmol), $CuBH_4(PPh_3)_2$ (10 mol%), **L*3** (12 mol%), H_2O (2.0 equiv) and LiO^{t}Bu (4.5 equiv) in DMA/DCM (2/1, 1.05 mL) at 10 °C. [b] Isolated yield. [c] The ee value was determined by HPLC. [d] The enantiomer of **3**, i.e., **ent-3**, was obtained using **L*4** (see Scheme 2 for structure) in 78% with 89% ee. [e] **1** (2.5 equiv). [f] **1** (3.0 equiv), H_2O (3.0 equiv), and LiO^{t}Bu (3.5 equiv). [g] **1** (3.0 equiv). [h] **2a** (0.20 mmol) and LiO^{t}Bu (3.8 equiv) were used. TBDPS: *tert*-butyldiphenylsilyl.

10.1002/anie.202009527

WILEY-VCH

RESEARCH ARTICLE

Table 2: Scope of azoles and transformation.[a,b,c]



[a] Reaction conditions: **1a** (2.0 equiv), **2** (0.10 mmol), $CuBH_4(PPh_3)_2$ (10 mol%), **L*3** (12 mol%), H_2O (2 equiv) and LiO^{t}Bu (4.5 equiv) in DMA/DCM (2/1, 1.05 mL) at 10 °C. [b] Isolated yield. [c] The ee value was determined by HPLC. [d] **1a** (3.0 equiv) and LiO^{t}Bu (2.5 equiv). [e] **1a** (3.0 equiv) and **2** (0.20 mmol). [f] **1a** (3.0 equiv) at rt. [g] Yield based on recovered starting material. [h] **1a** (3.0 equiv) and H_2O (3 equiv) in DMA/$PhCF_3$ (1/2, 1.05 mL) at rt. [i] **1a** (3.0 equiv) and LiO^{t}Bu (2.5 equiv) in DMA/$PhCF_3$ (1/2, 1.05 mL) at rt. [j] **1a** (3.0 equiv) and LiO^{t}Bu (3.0 equiv). [k] **1a** (10 equiv). Mono-alkylated product **40′** was obtained in 34% with 77% ee. [l] **1a** (3.0 equiv) and Cu(O^{i}PrCO$_2$)$_2$ (10 mol%). [m] **1a** (3.0 equiv) and CuI (10 mol%) at rt. [n] **1a** (2.5 equiv) and Cu(acac)$_2$ (10 mol%). [o] **1a** (2.5 equiv) and CuI (10 mol%) at rt. [p] **1a** (2.5 equiv), **2a** (1.0 mmol), $CuBH_4(PPh_3)_2$ (10 mol%), **L*3** (12 mol%), H_2O (2.0 equiv), and LiO^{t}Bu (2.5 equiv) in DMA/DCM (2/1, 10 mL) at 10 °C. Acac: acetylacetonate.

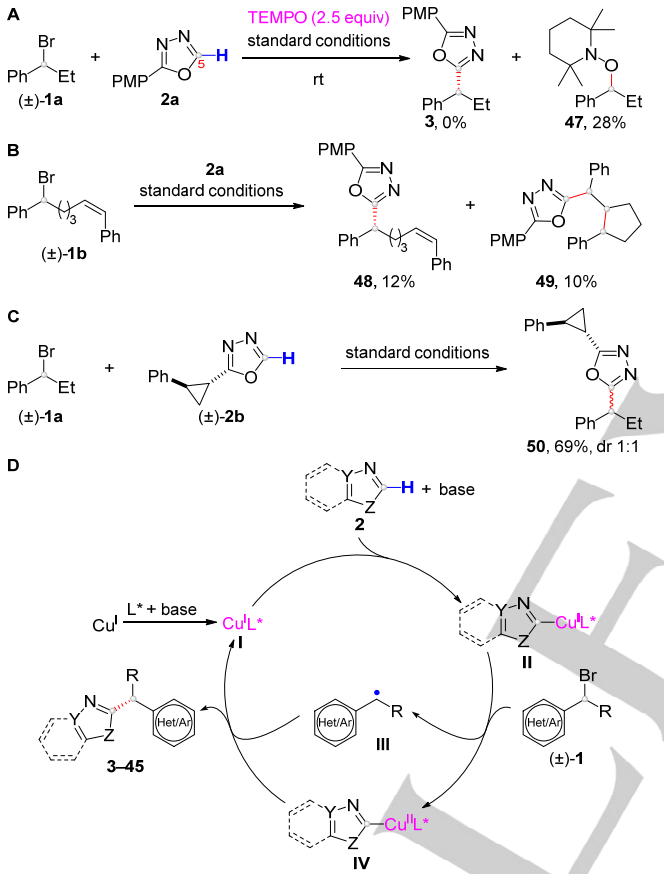
optimization. Nonetheless, alkyl bromides α to carbonyl groups have so far failed to provide the desired products in spite of high conversions.

As for the scope of azoles (Table 2), a variety of 2-phenyl-substituted 1,3,4-oxadiazoles smoothly underwent the desired alkylation reaction (**27**–**34**). Further, 1,3,4-oxadiazoles bearing naphthalenyl, pyridinyl, and furanyl substituents also delivered the desired coupling products **35**, **36**, and **37**, respectively, in good enantioselectivity. Notably, replacing the (hetero)aryl substituents with alkyl groups did not obviously affect the reaction efficiency or stereoselectivity and the products **38** and **39** were forged in moderate yield with good to excellent ee. Interestingly, unsubstituted 1,3,4-oxadiazoles delivered bis-alkylated product **40** in high enantioselectivity and moderate diastereoselectivity. The reaction is not limited to 1,3,4-oxadiazoles and structurally similar and medicinally important oxazoles and benzo[*d*]oxazoles were suitable heteroarylation reagents,[1] too, providing products **41**–**44** in moderate yield and excellent enantioselectivity. In addition, benzo[*d*]thiazole was also applicable to the reaction and the corresponding product **45** was obtained in 87% ee albeit of low yield. However, many other azoles and cyanothiophenes either remained intact or underwent decomposition under the reaction conditions (see Scheme S4 for structures). Importantly, the enantioenriched 1,3,4-oxadiazole product **3**, obtained in the preparative scale reaction of **2a**, was readily converted to 1,2,4-triazole **46** without obvious loss of enantiopurity, thus indicating the synthetic potential of the current method towards this kind of pharmaceutically useful heterocycles.[1] Additionally, the good chemoselectivity observed in substrates containing additional potentially reactive halides (**11**, **19**, **30**, and **33**), which are amenable to follow-up manipulations, further strengthens the synthetic potential.

Control experiments at higher reaction temperatures indicated drastically diminished enantioselectivity starting at around 50 °C (Table S1, entries 20 and 21). In addition, obvious racemization of an enantioenriched alkylation product was observed at 60 °C while only marginal racemization occurred at 40 °C under the otherwise standard conditions (Tables S2 and S3). Besides, other common bidentate or tridentate ligands only provided less than 15% yield and poor enantioselectivity under the otherwise identical conditions (Table S1, entries 22–24). All these results strongly support the indispensable role of our ligand in enabling facile oxidative addition at around ambient temperature for suppressing product racemization. In regard to the overall reaction mechanism, control experiments indicated that copper, ligand, and base are all indispensable for the reaction to provide the desirable product **3** (Table S4). Further, we observed facile D/H exchange of the C5–H in substrate **2a** with an excessive amount of D_2O at room temperature in the presence or absence of copper (Scheme S2). Thus, the C5–H should be acidic enough for direct deprotonation without the need for copper. The subsequent radical trap experiment with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) led to the formation of TEMPO-trapped product **47** while providing no desired product **3** (Scheme 3A). In addition, benzyl bromide (±)-**1b** tethered with an alkene moiety underwent tandem *5-exo-trig* cyclization and C(sp^3)–C(sp^2) coupling, delivering **49** in addition to **48** (Scheme 3B; no corresponding cyclization side products were observed for products **7** and **8**). Collectively, these results strongly support the involvement of alkyl radical species in the reaction. Further radical clock experiment with **2b** provided only alkylation product **50** with

10.1002/anie.202009527

an intact cyclopropane ring (Scheme 3C). Accordingly, the direct addition of alkyl radical to the azole ring is unlikely under our conditions.[18] On the basis of the experimental results as well as our previous works,[11,12a,12b] a working mechanism was proposed, shown in Scheme 3D. In the presence of base, the $Cu^{I}L^{*}$ complex **I** first forms and further reacts with azole **2**, giving Cu^{I} intermediate **II**. This intermediate next reduces alkyl bromide (±)-**1** to alkyl radical **III** and itself transforms to Cu^{II} complex **IV**. Finally, C(sp^3)–C(sp^2) coupling occurs possibly via formation of a Cu^{III} intermediate[19] and its subsequent reductive elimination (see Figure S2 for a tentative stereodiscrimination proposal via the copper(III) intermediate). Nonetheless, we currently have no solid experimental or theoretical evidence supporting this Cu^{III} intermediate and thus, are carrying out further studies on this step.



Scheme 3. Mechanistic experiments and proposal.

Conclusion

In summary, the use of *N*,*N*,*P*-ligand has enabled the realization of direct enantioconvergent coupling of racemic alkyl bromides with azole C(sp^2)–H bonds. And the enhanced reducing power of copper by the *N*,*N*,*P*-ligand is key to lower the reaction temperature close to room temperature, thus effectively suppressing undesired racemization of the newly formed chiral stereocenters. This method provides a convenient access to a range of enantioenriched α-chiral alkylated azoles, such as 1,3,4-oxadiazoles, oxazoles, and benzo[*d*]oxazoles as well as 1,3,4-triazoles, all of which are common structural motifs in many bioactive molecules and drugs. Further studies on expanding the scope to other heteroarenes as well as arenes and on investigating the reaction mechanism in details are currently undergoing in this lab.

Acknowledgements

Financial support from the National Natural Science Foundation of China (Nos. 21722203, 21831002, 21702093, and 21801116), Guangdong Provincial Key Laboratory of Catalysis (No. 2020B121201002), Guangdong Innovative Program (No. 2019BT02Y335), Shenzhen Special Funds (No. JCYJ20180302174416591), Shenzhen Nobel Prize Scientists Laboratory Project (No. C17783101), SUSTech Special Fund for the Construction of High-Level Universities (No. G02216303), the Shaanxi Provincial Key Laboratory Project (No. 19JS007), the Project of Science and Technology Department of Shaanxi Province (No. 2020JQ-894), Baoji University of Arts and Sciences (No. 209040030), and the China Postdoctoral Science Foundation (No. 2019M662155) is greatly appreciated. The authors acknowledge the assistance of the SUSTech Core Research Facilities for technical support.

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkylation • asymmetric radical reaction • azole • copper • racemic alkyl bromides

[1] a) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257; b) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451; c) A. Kleemann, J. Engel, B. Kutscher, D. Reichert, *Pharmaceutical Substances: Syntheses, Patents and Applications of the most relevant APIs*, 5th ed., Thieme Chemistry, **2009**.

[2] a) J. Choi, G. C. Fu, *Science* **2017**, *356*, eaaf7230; b) G. C. Fu, *ACS Cent. Sci.* **2017**, *3*, 692; c) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *Chem. Rev.* **2015**, *115*, 9587.

[3] For selected recent examples using Ni catalysis: a) H. Yin, G. C. Fu, *J. Am. Chem. Soc.* **2019**, *141*, 15433; b) A. Varenikov, M. Gandelman, *Nat. Commun.* **2018**, *9*, 3566; for a selected example using Co catalysis: c) 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; for a selected example using Fe catalysis: d) M. Jin, L. Adak, M. Nakamura, *J. Am. Chem. Soc.* **2015**, *137*, 7128.

[4] For selected representative enantioconvergent reductive cross-coupling examples: a) H. Guan, Q. Zhang, P. J. Walsh, J. Mao, *Angew. Chem. Int. Ed.* **2020**, *59*, 5172; *Angew. Chem.* **2020**, *132*, 5210; b) K. E. Poremba, N. T. Kadunce, N. Suzuki, A. H. Cherney, S. E. Reisman, *J. Am. Chem. Soc.* **2017**, *139*, 5684; c) N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc.* **2015**, *137*, 10480.

[5] For selected representative enantioconvergent cross-coupling examples using alkyl radical precursors other than alkyl halides: a) Z. Zuo, H. Cong, W. Li, J. Choi, G. C. Fu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, *138*, 1832; b) O. Gutierrez, J. C. Tellis, D. N. Primer, G. A. Molander, M. C. Kozlowski, *J. Am. Chem. Soc.* **2015**, *137*, 4896.

[6] For selected non-radical enantioconvergent C(sp^3)–C(sp^2) coupling examples: a) M. Sidera, S. P. Fletcher, *Nat. Chem.* **2015**, *7*, 935; b) P. Schäfer, T. Palacin, M. Sidera, S. P. Fletcher, *Nat. Commun.* **2017**, *8*, 15762; c) F. W. Goetzke, M. Mortimore, S. P. Fletcher, *Angew. Chem. Int. Ed.* **2019**, *58*, 12128; *Angew. Chem.* **2019**, *131*, 12256; d) J. González, P. Schäfer, S. P. Fletcher, *Organometallics* **2019**, *38*, 3991.

[7] For selected reviews on asymmetric (hetero)arene C(sp^2)–H functionalization: a) J. Loup, U. Dhawa, F. Pesciaioli, J. Wencel-Delord, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 12803; *Angew. Chem.* **2019**, *131*, 12934; b) C. G. Newton, S.-G. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.* **2017**, *117*, 8908; c) C. Zheng, S.-L. You, *RSC Adv.* **2014**, *4*, 6173; d) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242.

[8] For selected reviews on racemic (hetero)arene C(sp^2)–H functionalization: a) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192; b) G. Evano, C. Theunissen, *Angew. Chem. Int. Ed.* **2019**, *58*, 7558; *Angew. Chem.* **2019**, *131*, 7638; c) Y. Yang, J. Lan, J. You, *Chem. Rev.* **2017**, *117*, 8787; d) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei, *Chem. Rev.* **2015**, *115*, 12138; e) X.-X. Guo, D.-W. Gu, Z. Wu, W. Zhang, *Chem. Rev.* **2015**, *115*, 1622.

[9] For selected examples of racemic cross-coupling of alkyl halides with azole C(sp^2)–H: a) W. Li, A. Varenikov, M. Gandelman, *Eur. J. Org. Chem.* **2020**, *2020*, 3138; b) X. Wu, C. Lei, G. Yue, J. Zhou, *Angew. Chem. Int. Ed.* **2015**, *54*, 9601; *Angew. Chem.* **2015**, *127*, 9737; c) X. Wu, J. W. T. See, K. Xu, H. Hirao, J. Roger, J.-C. Hierso, J. Zhou, *Angew. Chem. Int. Ed.* **2014**, *53*, 13573; *Angew. Chem.* **2014**, *126*, 13791; d) P. Ren, I. Salihu, R. Scopelliti, X. Hu, *Org. Lett.* **2012**, *14*, 1748; e) L. Ackermann, S. Barfüsser, C. Kornhaass, A. R. Kapdi, *Org. Lett.* **2011**, *13*, 3082; f) L. Ackermann, B. Punji, W. Song, *Adv. Synth. Catal.* **2011**, *353*, 3325; g) O. Vechorkin, V. Proust, X. Hu, *Angew. Chem. Int. Ed.* **2010**, *49*, 3061; *Angew. Chem.* **2010**, *122*, 3125; h) T. Yao, K. Hirano, T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 12307; i) D. Lapointe, K. Fagnou, *Org. Lett.* **2009**, *11*, 4160.

[10] For a selected example of racemic azole alkylation with *N*-tosylhydrazones: X. Zhao, G. Wu, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 3296.

[11] For selected summaries: a) Q.-S. Gu, Z.-L. Li, X.-Y. Liu, *Acc. Chem. Res.* **2020**, *53*, 170; b) Z.-L. Li, G.-C. Fang, Q.-S. Gu, X.-Y. Liu, *Chem. Soc. Rev.* **2020**, *49*, 32; for selected examples: 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; d) X.-T. Li, L. Lv, T. Wang, Q.-S. Gu, G.-X. Xu, Z.-L. Li, L. Ye, X. Zhang, G.-J. Cheng, X.-Y. Liu, *Chem* **2020**, *6*, 1692; e) Y.-F. Cheng, J.-R. Liu, Q.-S. Gu, Z.-L. Yu, J. Wang, Z.-L. Li, J.-Q. Bian, H.-T. Wen, X.-J. Wang, X. Hong, X.-Y. Liu, *Nat. Catal.* **2020**, *3*, 401; f) L. Ye, Y. Tian, X. Meng, Q.-S. Gu, X.-Y. Liu, *Angew. Chem. Int. Ed.* **2020**, *59*, 1129; *Angew. Chem.* **2020**, *132*, 1145; g) J.-S. Lin, X.-Y. Dong, T.-T. Li, N.-C. Jiang, B. Tan, X.-Y. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 9357.

[12] a) X.-Y. Dong, Y.-F. Zhang, C.-L. Ma, Q.-S. Gu, F.-L. Wang, Z.-L. Li, S.-P. Jiang, X.-Y. Liu, *Nat. Chem.* **2019**, *11*, 1158; b) X.-Y. Dong, J.-T. Cheng, Y.-F. Zhang, Z.-L. Li, T.-Y. Zhan, J.-J. Chen, F.-L. Wang, N.-Y. Yang, L. Ye, Q.-S. Gu, X.-Y. Liu, *J. Am. Chem. Soc.* **2020**, *142*, 9501; for an elegant work of ligand design for copper-catalyzed radical enantioconvergent reaction: c) H. Iwamoto, K. Endo, Y. Ozawa, Y. Watanabe, K. Kubota, T. Imamoto, H. Ito, *Angew. Chem. Int. Ed.* **2019**, *58*, 11112; *Angew. Chem.* **2019**, *131*, 11229.

[13] X. Qin, B. Feng, J. Dong, X. Li, Y. Xue, J. Lan, J. You, *J. Org. Chem.* **2012**, *77*, 7677.

[14] A. C. P. F. d. Sá, G. M. A. Pontes, J. A. L. d. Anjos, S. R. Santana, L. W. Bieber, I. Malvestiti, *J. Braz. Chem. Soc.* **2003**, *14*, 429.

[15] For selected reviews on enantioselective Friedel-Crafts alkylation of heteroarenes, see: a) M. M. Heravi, V. Zadsirjan, B. Masoumi, M. Heydari, *J. Organomet. Chem.* **2019**, *879*, 78; b) Y. Zhang, X. Liu, L. Lin, X. Feng, *Prog. Chem.* **2018**, *30*, 491; c) V. Terrasson, R. Marcia de Figueiredo, J. M. Campagne, *Eur. J. Org. Chem.* **2010**, *2010*, 2635; for selected enantioselective alkylation of heteroarenes using other strategies: d) R. S. J. Proctor, H. J. Davis, R. J. Phipps, *Science* **2018**, *360*, 419; e) X. Liu, Y. Liu, G. Chai, B. Qiao, X. Zhao, Z. Jiang, *Org. Lett.* **2018**, *20*, 6298; f) X. Bao, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 9577; *Angew. Chem.* **2017**, *129*, 9705; g) J. Loup, D. Zell, J. C. A. Oliveira, H. Keil, D. Stalke, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 14197; *Angew. Chem.* **2017**, *129*, 14385; h) M. Odachowski, A. Bonet, S. Essafi, P. Conti-Ramsden, J. N. Harvey, D. Leonori, V. K. Aggarwal, *J. Am. Chem. Soc.* **2016**, *138*, 9521; i) B. M. Trost, L. Debien, *Chem. Sci.* **2016**, *7*, 4985; j) H. Ohmiya, H. Zhang, S. Shibata, A. Harada, M. Sawamura, *Angew. Chem. Int. Ed.* **2016**, *55*, 4777; *Angew. Chem.* **2016**, *128*, 4855; k) C. M. Filloux, T. Rovis, *J. Am. Chem. Soc.* **2015**, *137*, 508; l) P.-S. Lee, N. Yoshikai, *Org. Lett.* **2015**, *17*, 22; m) J. Llaveria, D. Leonori, V. K. Aggarwal, *J. Am. Chem. Soc.* **2015**, *137*, 10958; n) G. Song, W. W. N. O, Z. Hou, *J. Am. Chem. Soc.* **2014**, *136*, 12209; o) C. S. Sevov, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, *135*, 2116.

[16] T. Xiong, Y. Li, X. Bi, Y. Lv, Q. Zhang, *Angew. Chem. Int. Ed.* **2011**, *50*, 7140; *Angew. Chem.* **2011**, *123*, 7278.

[17] CCDC 1999436 (**3**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[18] a) D. Li, W.-C. Yang, *Tetrahedron Lett.* **2019**, *60*, 1792; b) C. Theunissen, J. Wang, G. Evano, *Chem. Sci.* **2017**, *8*, 3465.

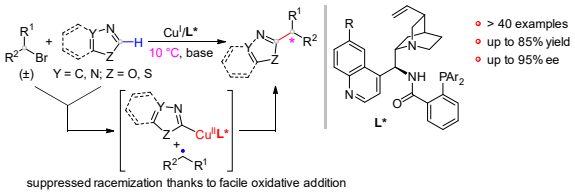
[19] For C–C bond formation via copper(III) intermediates, see: S. Liu, H. Liu, S. Liu, Z. Lu, C. Lu, X. Leng, Y. Lan, Q. Shen, *J. Am. Chem. Soc.* **2020**, *142*, 9785 and references cited therein.

10.1002/anie.202009527

WILEY-VCH

RESEARCH ARTICLE

Entry for the Table of Contents



Racemization-free: The use of cinchona-alkaloid-derived *N*,*N*,*P*-ligand leads to the realization of direct enantioconvergent coupling of racemic alkyl bromides with azole C(sp^2)–H bonds by copper catalysis. The key to success is the ligand-enabled facile oxidative addition at around room temperature that suppresses the otherwise product racemization at elevated temperature. This method provides a range of enantioenriched α-chiral alkylated azoles.