Angewandte Chemie International Edition www.angewandte.org

Check for updates

How to cite: *Angew. Chem. Int. Ed.* **2023**, *62*, e202214709
International Edition: doi.org/10.1002/anie.202214709
German Edition: doi.org/10.1002/ange.202214709

Cross-Coupling Hot Paper

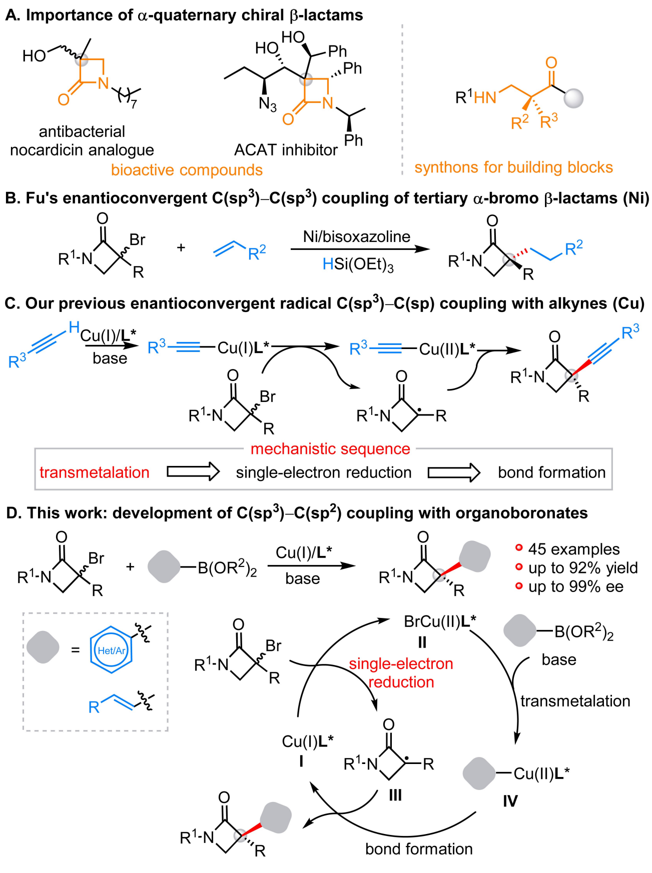
Synthesis of α-Quaternary β-Lactams via Copper-Catalyzed Enantioconvergent Radical C(sp³)–C(sp²) Cross-Coupling with Organoboronate Esters

Fu-Li Wang[+], *Lin Liu*[+], *Chang-Jiang Yang, Cheng Luan, Jing Yang, Ji-Jun Chen, Qiang-Shuai Gu, Zhong-Liang Li,* and Xin-Yuan Liu**

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

Abstract: The copper-catalyzed enantioconvergent radical $C(sp^3)$–$C(sp^2)$ cross-coupling of tertiary α-bromo-β-lactams with organoboronate esters could provide the synthetically valuable α-quaternary β-lactams. The challenge arises mainly from the construction of sterically congested quaternary stereocenters between the tertiary alkyl radicals and chiral copper(II) species. Herein, we describe our success in achieving such transformations through the utilization of a copper/hemilabile N,N,N-ligand catalyst to forge the sterically congested chiral $C(sp^3)$–$C(sp^2)$ bond via a single-electron reduction/transmetalation/bond formation catalytic cycle. The synthetic potential of this approach is shown in the straightforward conversion of the corresponding products into many valuable building blocks. We hope that the developed catalytic cycle would open up new vistas for more enantioconvergent cross-coupling reactions.

Chiral β-lactams are core structures in an array of widely used antibiotics (penicillin, cephalosporins) and many synthetic methods have been developed for their assembly.[1] Due to the antibiotic resistance, the need for new β-lactam skeletons is growing and it has further led to the discovery of β-lactams possessing new potent activities, such as anticancer,[2] antifungal,[3] cholesterol-controlling,[4] etc. Among them, chiral β-lactams bearing an α-quaternary stereocenter are not only an important subunit of this family but also valuable synthons for building blocks in organic synthesis (Scheme 1A).[5] Notably, the catalytic asymmetric methods for the assembly of α-quaternary chiral β-lactams have been less recognized compared with those of β-lactams.[1] In this regard, the catalytic asymmetric cyclo-



Scheme 1. Development of enantioconvergent radical $C(sp^3)$–$C(sp^2)$ coupling.

[*] Dr. F.-L. Wang,[+] Dr. L. Liu,[+] Dr. C.-J. Yang
School of Science and Institute of Scientific Research, Great Bay University
Dongguan 523000 (China)

Dr. F.-L. Wang,[+] Dr. L. Liu,[+] Dr. C.-J. Yang, C. Luan, Dr. J.-J. Chen, 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

C. Luan, 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 (China)
E-mail: lizl@sustech.edu.cn

Dr. J. Yang
College of Health Science and Environmental Engineering, Shenzhen Technology University
Shenzhen 518118 (China)

[+] These authors contributed equally to this work.

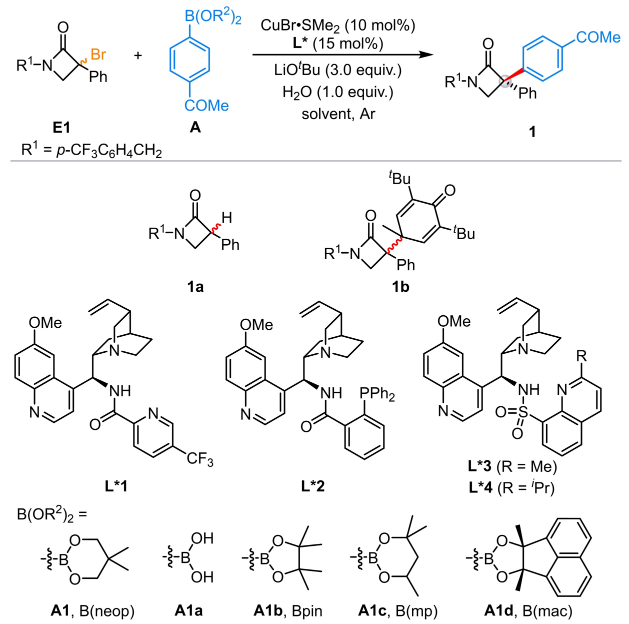
addition strategy represents the most prevailing approach for the construction of the core motif of α-quaternary chiral β-lactams.[6] Given the significance of the structural motifs, the development of a different catalytic system to access new α-quaternary chiral β-lactam skeletons with broad substrate scope is still highly desirable.

The 3d transition metal-catalyzed enantioconvergent radical cross-coupling of alkyl halides represents a powerful tool in asymmetric synthesis owing to the earth abundance of catalysts and the ready availability of coupling partners.[7,8] In contrast to the well-established coupling of secondary alkyl halides, the reaction of tertiary ones is less studied due to the steric congestion and the difficult enantio-differentiation of three distinct carbon substituents.[9,10] In particular, the success of the C(sp^3)–C cross-coupling of tertiary α-bromo-β-lactams would provide α-quaternary chiral β-lactams and have a profound impact on asymmetric synthesis. In an important advance, Fu et al. have accomplished a nickel-catalyzed enantioconvergent radical C(sp^3)–C(sp^3) cross-coupling of tertiary α-bromo-β-lactams with alkenes (Scheme 1B).[9a] We have been focusing on developing the multidentate chiral ligand-copper catalyst for realizing enantioconvergent radical cross-coupling via a transmetalation/single-electron reduction/bond formation sequence.[7d,11] Very recently, we described an enantioconvergent C(sp^3)–C(sp) cross-coupling of the similar tertiary α-bromo-β-lactams with alkynes utilizing the same mechanistic sequence (Scheme 1C).[12] We surmised whether the same copper catalyst could achieve the enantioconvergent C(sp^3)–C(sp^2) coupling with the bench-stable sp^2-hybridized aryl- and alkenylboronate esters to afford a new library of α-quaternary chiral β-lactams with broad scope and functional group tolerance. However, the different configuration of planar aryl-/alkenylcopper(II) and linear alkynylcopper(II) renders the bond formation more sterically crowded in the C(sp^3)–C(sp^2) coupling than that of C(sp^3)–C(sp) coupling.[12]

As part of our ongoing endeavors in the enantioconvergent transformations,[7d,11,12] we herein report an enantioconvergent radical C(sp^3)–C(sp^2) cross-coupling of tertiary α-bromo-β-lactams with aryl- and alkenylboronate esters. The key to the success is the utilization of a hemilabile N,N,N-ligand to enhance the reducing capability of **L***Cu(I) so that it could convert the highly reactive α-bromo-β-lactam to a tertiary alkyl radical **III** via a single-electron reduction process (Scheme 1D).[13] The thus formed BrCu(II)**L*** complex **II** would undergo a fast transmetalation with organoboronate esters to afford complex **IV**.[14] The copper(II) complex **IV** would combine smoothly with the tertiary alkyl radical **III** to forge the sterically congested chiral C(sp^3)–C(sp^2) bond with the designed N,N,N-ligand and regenerate the **L***Cu(I) species (Scheme 1D). Notably, the mechanistic sequence is different from our previously reported enantioconvergent coupling (Scheme 1C).[7d,11,12] The reaction covers a range of tertiary α-bromo-β-lactams as well as aryl-, heteroaryl-, and alkenylboronate esters with broad functional group tolerance. Further elaboration of the corresponding products leads to many valuable chiral building blocks of interest in organic synthesis.

At the outset, we investigated the reaction of tertiary bromide **E1** with neopentyl glycol (neop)-derived arylboronate ester **A1**[15] in the LiO^{t}Bu/*N*,*N*-dimethylformamide (DMF) system, which was proven to promote transmetalation in our previous work.[11e] In the presence of **L*1** that was suitable for the coupling with alkynes,[12] **E1** decomposed completely and the debromination product **1a** was afforded in 60 % yield (Table 1, entry 1). The control experi-

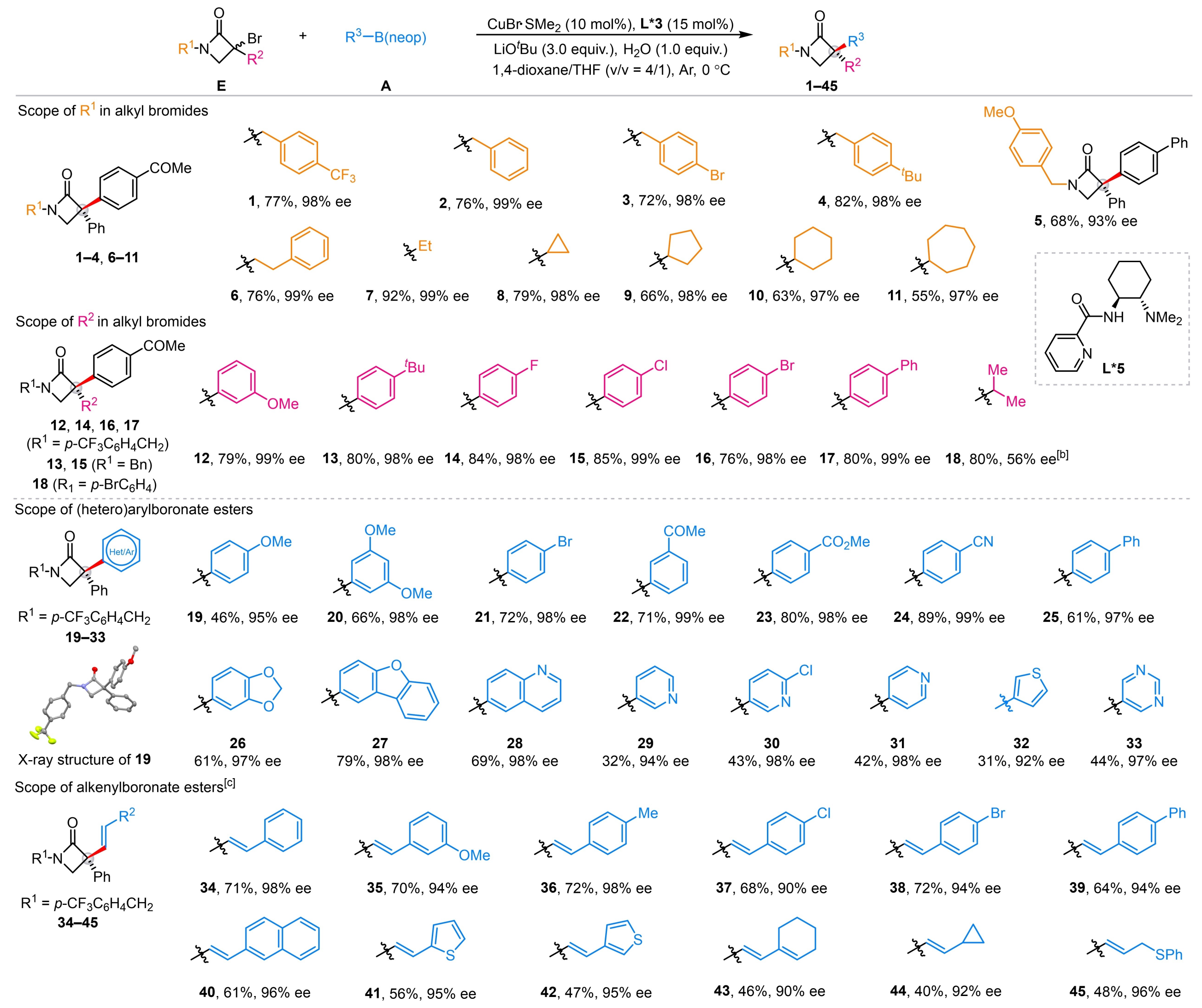
Table 1: Ligand effect for the reaction.[a]



Entry	Solvent	L*	Yield of 1 [%]	Yield of 1a [%]	Yield of 1b [%]	Ee [%]
1	DMF	L*1	0	60	–	–
2[b]	DMF	L*1	0	18	31	–
3	1,4-dioxane	L*1	0	0	–	–
4	1,4-dioxane	L*2	0	45	–	–
5[b]	1,4-dioxane	L*2	0	<5	85	–
6	1,4-dioxane	L*3	60	15	–	97
7[b]	1,4-dioxane	L*3	24	<5	38	97
8[c]	1,4-dioxane/THF	L*3	76	<5	–	98
9[d]	1,4-dioxane/THF	L*3	65	<5	–	98
10[c,e]	1,4-dioxane/THF	L*3	83 (77)	<5	–	98
11[c,e,f]	1,4-dioxane/THF	L*3	18	<5	–	98
12[c,e,g]	1,4-dioxane/THF	L*3	25	<5	–	94
13[c,e,h]	1,4-dioxane/THF	L*3	16	<5	–	96
14[c,e,i]	1,4-dioxane/THF	L*3	50	<5	–	97
15[c,e,j]	1,4-dioxane/THF	L*3	<5	<5	–	–

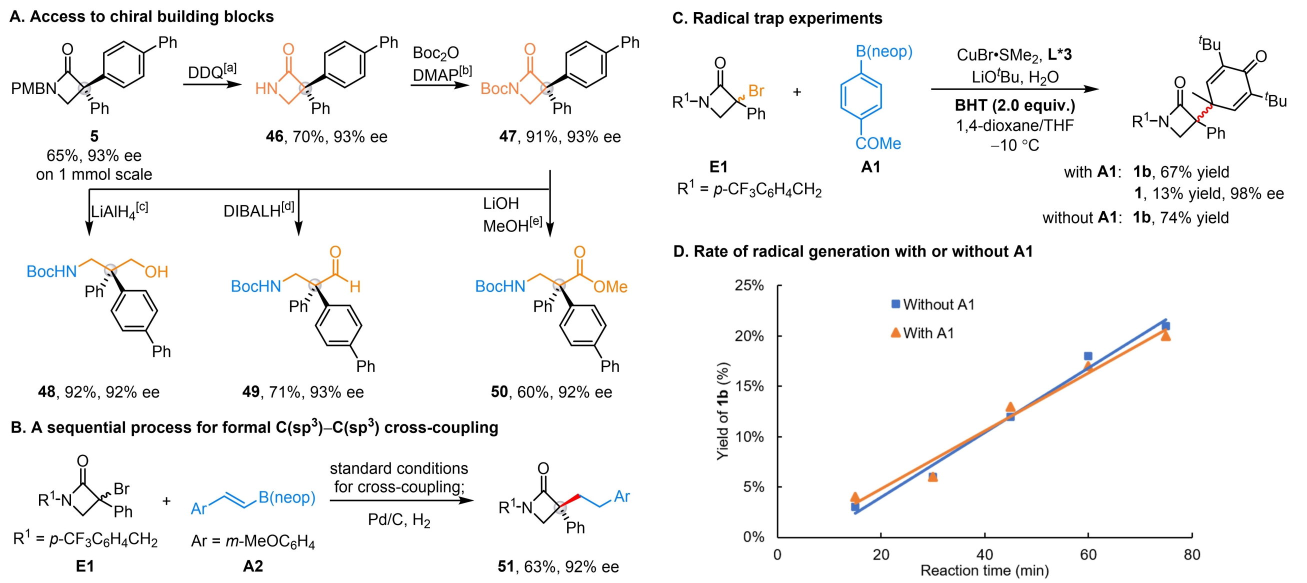
[a] Reaction conditions: **E1** (0.15 mmol), **A1** (0.10 mmol), CuBr·SMe_2 (10 mol %), **L*** (15 mol %), LiO^{t}Bu (3.0 equiv) and H_2O (1.0 equiv) in solvent (2.0 mL) at room temperature (rt) for 30 h under argon (Ar). Yields were based on ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. **1** was based on **A1**. **1a** and **1b** were based on **E1**. Isolated yield in parenthesis. Ee values were based on chiral HPLC analysis. [b] BHT (2.0 equiv) was added. [c] Conducted at 0 °C in 1,4-dioxane/THF (v/v = 4/1) for 45 h. [d] Conducted at −10 °C in 1,4-dioxane/THF (v/v = 3/1) for 45 h. [e] **E1** (0.12 mmol) was used. [f] **A1a** was used. [g] **A1b** was used. [h] **A1c** was used. [i] **A1d** was used. [j] Without H_2O. neop, neopentyl glycol; pin, pinacol; mp, methyl pentanediol; mac, methylated acenaphthoquinone; DMF, *N*,*N*-dimethylformamide; BHT, butylated hydroxytoluene; THF, tetrahydrofuran.

Table 2: Scope of alkyl bromides and organoboronate esters.[a]



[a] Reaction conditions: **E** (0.12 mmol), **A** (0.10 mmol), $CuBr\cdot SMe_2$ (10 mol%), **L*3** (15 mol%), LiO*t*Bu (3.0 equiv) and H_2O (1.0 equiv) in 1,4-dioxane (1.6 mL) and THF (0.4 mL) at 0°C for 45 h; isolated yields; ee values were based on chiral HPLC analysis. [b] **E** (0.1 mmol), **A** (0.12 mmol), $CuBr\cdot SMe_2$ (10 mol%), **L*5** (15 mol%), LiO*t*Bu (3.0 equiv) and H_2O (1.0 equiv) in DMF (2.0 mL) at rt for 24 h; the absolute configuration of **18** was not determined. [c] **E** (0.15 mmol), **A** (0.10 mmol), $CuBr\cdot SMe_2$ (10 mol%), **L*4** (15 mol%) in THF (2.0 mL) at −40°C for 5 d.

ment with the radical scavenger butylated hydroxytoluene (BHT) gave rise to the BHT-trapped product **1b** in 31% yield, indicating the generation of an alkyl radical (Table 1, entry 2). We reasoned that nucleophile-sequestered **L*1**Cu(I)Ar could reduce **E1** to the tertiary alkyl radical **III** (Scheme 1D), but the ligand architecture for forging the C(sp^3)–C(sp) bond[12] was not applicable to the C(sp^3)–C(sp^2) formation due to the large steric congestion of the latter. Meanwhile, we found that **E1** decomposed easily in the absence of the catalyst under the LiO*t*Bu/DMF conditions (Figure S1 in the Supporting Information). We had to switch to a less polar solvent where **E1** was stable enough. We then carried out the reaction in 1,4-dioxane, but observed almost no conversion of **E1** and **A1** (Table 1, entry 3). We theorized that the transmetalation of **A1** with **L*1**Cu(I) might be slow in the less polar 1,4-dioxane, and the **L*1**Cu(I) complex could not reduce **E1**. As such, we envisioned that a more electron-donating ligand might enhance the reducing capability of the Cu(I) catalyst to reduce **E1** to the alkyl radical. The radical would further react with **L***Cu(II)Ar, in situ generated via transmetalation of **A1** with **L***Cu(II), to provide the coupling product **1** via a catalytic cycle different from our previous system (Scheme 1D).[7d,11,12] Thus, we investigated Dixon's N,N,P-ligand (**L*2**)[11,16] but observed the formation of **1a** and the protodeboronation product acetophenone, which were also suppressed in the presence of BHT (Table 1, entries 4 and 5). We theorized that the failure of the reaction lies in the difficult bond formation due to the steric bulkiness of the tridentate ligand **L*2**. We then resorted to our recently



Scheme 2. Synthetic utility and mechanistic investigation. [a] DDQ (3.0 equiv) in CH_2Cl_2/H_2O at rt for 24 h. [b] DMAP (2.0 equiv) and Boc_2O (5.0 equiv) in CH_2Cl_2 at rt for 1 h. [c] $LiAlH_4$ (3.0 equiv) in THF at 0 °C for 4 h. [d] DIBALH (2.0 equiv) in CH_2Cl_2 at −78 °C for 2 h. [e] LiOH (5.0 equiv) in MeOH at rt for 2 h. DDQ, 2,3-dichloro-5,6-dicyano-*para*-benzoquinone; Boc, *tert*-butyloxy carbonyl; DMAP, 4-(dimethylamino)pyridine; DIBALH, diisobutylaluminium hydride.

developed hemilabile N,N,N-ligand/copper catalyst,[11e,17] which resembles an electron-rich tridentate form in the reaction initiation and a bidentate form in the bond formation process.[11e] We found that **L*3** delivered the desired product **1** in 60 % yield with 97 % ee, along with the formation of **1a** in 15 % yield (Table 1, entry 6). A control experiment with BHT revealed that the yield of **1** greatly decreased (Table 1, entry 7). Further screening of the reaction parameters (Table 1, entries 8–10) led us to identify the optimal conditions as follows: **E1** (1.2 equiv), **A1** (1.0 equiv), $CuBr\cdot SMe_2$ (10 mol %), **L*3** (15 mol %), LiO^{t}Bu (3.0 equiv), and H_2O (1.0 equiv) in 1,4-dioxane/tetrahedrofuran (THF) (v/v = 4/1) at 0 °C for 45 h, providing **1** in 77 % isolated yield with 98 % ee (Table 1, entry 10). The investigation of other boron sources revealed that boronic acid **A1a**, pinacol (pin)-, and methyl pentanediol (mp)-derived boronate esters (**A1b**, **A1c**) gave **1** in much lower yields (Table 1, entries 11–13), while the methylated acenaphthoquinone (mac)-derived one **A1d** provided **1** in a moderate yield (50 %, Table 1, entry 14). However, the ee value was less influenced (Table 1, entries 11–14). Almost no reaction was observed in the absence of water, which is supposed to play a vital role in both increasing the solubility of LiO^{t}Bu and promoting the transmetalation step (Table 1, entry 15).[18]

We next investigated the scope of alkyl bromides for the reaction (Table 2). A range of substituents, such as the functionalized benzyl ring (**1–5**), homobenzyl ring (**6**), purely aliphatic chain (**7**), and cyclic ring (**8–11**) on the nitrogen of α-bromo-β-lactams was tolerated to afford the coupling products in good yields with 93–99 % ee. Phenyl rings possessing electron-donating or -withdrawing substituents at the *meta* and *para* positions of α-bromo-β-lactams were well compatible with the reaction conditions to deliver **12–17** in up to 85 % yield with excellent ee. In addition, we tested the reaction of tertiary α-bromo α-isopropyl β-lactam with **A1** and found that **L*3** was not suitable for the reaction. Instead, the cyclohexyl diamine-derived N,N,N-ligand **L*5** provided **18** with the best result (80 % yield, 56 % ee, Table S1 in the Supporting Information). The reactions are currently undergoing further optimization in our laboratory. The subsequent investigation on the scope of arylboronate esters showed excellent tolerance of many labile functional groups toward nucleophiles, such as bromide (**21**), carbonyl (**22**), ester (**23**), nitrile (**24**), and acetal (**26**). The absolute configuration of **19** was determined to be *S* by X-ray structural analysis and those of other products were assigned by analogy (Table 2 and Figure S2 in the Supporting Information).[19] In addition, a gamut of heteroarylboronate esters featuring medicinally relevant heterocycles including dibenzo[*b*,*d*]furan (**27**), quinoline (**28**), pyridine (**29–31**), thiophene (**32**), and pyrimidine (**33**) were viable partners to generate the desired products with excellent ee, albeit with low yields in some case. The easy transformation of the alkene moiety in organic synthesis prompted us to develop the corresponding coupling with alkenylboronate esters. We were pleased to find that the utilization of the more hindered ligand **L*4** (Tables 1 and 2) provided chiral alkene **34** in 71 % yield with 98 % ee under reoptimized reaction conditions (Table S2 in the Supporting Information). An array of (hetero)aryl-/naphthylated alkenylboronate esters proceeded smoothly to provide **35–42** with 90–98 % ee. In addition, the alkenyl- and alkyl-substituted alkenylboronate esters were also amenable to the standard conditions, delivering **43–45** in moderate yields with excellent ee.

To demonstrate the synthetic utility of this methodology, we firstly synthesized **5** on a one-mmol scale under standard conditions and observed comparable yield and enantioselectivity (Scheme 2A). The importance of α-quaternary chiral β-lactams as synthetic intermediates was shown by straightforward transformations of **5** to a series of chiral building blocks. First, the oxidative deprotection of **5** gave rise to free β-lactam **46**. Second, the subsequent ring-opening of **47** under different reaction conditions delivered β-quaternary γ-amino alcohol **48**, α-quaternary β-amino aldehyde **49**, as well as α-quaternary β-amino acid ester **50**, respectively. Moreover, a sequential cross-coupling and hydrogenation were performed to afford β-lactam **51**, thus offering a complementary approach to the direct enantioconvergent $C(sp^3)$–$C(sp^3)$ cross-coupling of α-bromo-β-lactams (Scheme 2B). Notably, no obvious loss of enantiopurity was observed during all these transformations.

Regarding the mechanism, we carried out the radical trap experiment with BHT for the model reaction at −10 °C and observed the formation of BHT-trapped product **1b** in 67 % yield (Scheme 2C). More significantly, we found that **1b** was also obtained in 74 % yield without **A1**, indicating that **L*3**Cu(I) (intermediate **I** in Scheme 1D) could undergo a single-electron reduction with the alkyl bromide **E1** to generate the tertiary radical **III**. A further kinetic experiment revealed that the rate for the formation of **1b** is similar with or without **A1**, suggesting that the reaction is probably initiated via the single-electron reduction of **E1** with **L*3**Cu (I) without transmetalation. The transmetalation of organoboronate esters with **L*3**Cu(II)[14] and subsequent interaction with **III** furnished the desired coupling products as depicted in Scheme 1D.

In summary, we have developed a copper-catalyzed enantioconvergent radical $C(sp^3)$–$C(sp^2)$ cross-coupling of tertiary α-bromo-β-lactams with organoboronate esters with high efficiency and enantioselectivity. The utilization of a hemilabile N,N,N-ligand is crucial for forging the sterically congested chiral $C(sp^3)$–$C(sp^2)$ bond. The reaction covers both (hetero)aryl- and alkenylboronate esters and provides a highly flexible and practical platform for the rapid assembly of a library of α-quaternary chiral β-lactams. The strategy offers many chiral building blocks and provides a complementary approach to enantioconvergent $C(sp^3)$–$C(sp^3)$ cross-coupling when allied with follow-up transformations. We anticipate that the mechanistic sequence of this strategy will inspire the discovery of more enantioconvergent radical cross-coupling reactions in the future.

Acknowledgements

Financial support from the National Key R&D Program of China (Nos. 2021YFF0701604 and 2021YFF0701704), the National Natural Science Foundation of China (Nos. 22025103, 21831002, 21901106, 22001109, 22201127, 22271133, 22101186 and 22101122), Guangdong Innovative Program (No. 2019BT02Y335), Guangdong Provincial Key Laboratory of Catalysis (No. 2020B121201002), Shenzhen Special Funds (No. JCYJ20200109141001789), Shenzhen Science and Technology Program (KQTD20210811090112004), and Great Bay University is gratefully acknowledged. The authors appreciate the assistance of SUSTech Core Research Facilities.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Cambridge Crystallographic Data Centre at https://www.ccdc.cam.ac.uk/structures/, reference number 2210247.

Keywords: Asymmetric Catalysis · Copper · Cross-Coupling · Radical Chemistry · β-Lactam

[1] For selected reviews, see: a) C. R. Pitts, T. Lectka, *Chem. Rev.* **2014**, *114*, 7930–7953; b) S. France, A. Weatherwax, A. E. Taggi, T. Lectka, *Acc. Chem. Res.* **2004**, *37*, 592–600; c) P. A. Magriotis, *Eur. J. Org. Chem.* **2014**, 2647–2657; d) *β-Lactams: Unique Structures of Distinction for Novel Molecules* (Ed.: B. K. Banik), Springer, Heidelberg, **2013**; e) *Beta-Lactams: Novel Synthetic Pathways and Applications* (Ed.: B. K. Banik,), Springer International Publishing AG, **2017**; f) *Synthesis of β-Lactam Antibiotics* (Ed.: A. Bruggink), Springer-Science + Business Media, B.V., **2001**.

[2] X. Zhang, Y. Jia, *Curr. Top. Med. Chem.* **2020**, *20*, 1468–1480.

[3] M. O′Driscoll, K. Greenhalgh, A. Young, E. Turos, S. Dickey, D. V. Lim, *Bioorg. Med. Chem.* **2008**, *16*, 7832–7837.

[4] T. Kosoglou, P. Statkevich, A. Johnson-Levonas, J. F. Paolini, A. J. Bergman, K. B. Alton, *Clin. Pharmacokinet.* **2005**, *44*, 467–494.

[5] For selected reviews, see: a) P. Imbach, M. Lang, C. García-Echeverría, V. Guagnano, M. Noorani, J. Roesel, F. Bitsch, G. Rihs, P. Furet, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 358–362; b) C. Gerardin-Charbonnier, S. Auberger, L. Molina, S. Achilefu, M. A. Manresa, P. Vinardell, M. R. Infante, C. Selve, *Prep. Biochem. Biotechnol.* **1999**, *29*, 257–272; c) F. Benfatti, G. Cardillo, L. Gentilucci, A. Tolomelli, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1946–1950.

[6] For selected representative examples, see: a) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831–7832; b) B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 1578–1579; c) R. Shintani, G. C. Fu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4082–4085; *Angew. Chem.* **2003**, *115*, 4216–4219; d) Y.-R. Zhang, L. He, X. Wu, P.-L. Shao, S. Ye, *Org. Lett.* **2008**, *10*, 277–280; e) S. Chen, E. C. Salo, K. A. Wheeler, N. J. Kerrigan, *Org. Lett.* **2012**, *14*, 1784–1787; f) T. Shu, L. Zhao, S. Li, X.-Y. Chen, C. von Essen, K. Rissanen, D. Enders, *Angew. Chem. Int. Ed.* **2018**, *57*, 10985–10988; *Angew. Chem.* **2018**, *130*, 11151–11154; g) J. Qi, F. Wei, S. Huang, C.-H. Tung, Z. Xu, *Angew. Chem. Int. Ed.* **2021**, *60*, 4561–4565; *Angew. Chem.* **2021**, *133*, 4611–4615; h) J. Qi, F. Wei, C.-H. Tung, Z. Xu, *Angew. Chem. Int. Ed.* **2021**, *60*, 13814–13818; *Angew. Chem.* **2021**, *133*, 13933–13937; i) X. Zhong, M. Huang, H. Xiong, Y. Liang, W. Zhou, Q. Cai, *Angew. Chem. Int. Ed.* **2022**, *61*, e202208323; *Angew. Chem.* **2022**, *134*, e202208323; for the intramolecular cyclization strategy, see: j) L.-Z. Huang, Z. Xuan, H. J. Jeon, Z.-T. Du, J. H. Kim, S.-g. Lee, *ACS Catal.* **2018**, *8*, 7340–7345.

[7] a) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *Chem. Rev.* **2015**, *115*, 9587–9652; b) J. Choi, G. C. Fu, *Science* **2017**, *356*, eaaf7230; c) G. C. Fu, *ACS Cent. Sci.* **2017**, *3*, 692–700; d) X.-Y. Dong, Z.-L. Li, Q.-S. Gu, X.-Y. Liu, *J. Am. Chem. Soc.* **2022**, *144*, 17319–17329.

[8] For selected reviews and examples of asymmetric radical transformations, see: a) M. P. Sibi, S. Manyem, J. Zimmerman, *Chem. Rev.* **2003**, *103*, 3263–3296; b) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77–80; c) J. Du, K. L. Skubi, D. M. Schultz, T. P. Yoon, *Science* **2014**, *344*, 392–396; d) T. Hashimoto, Y. Kawamata, K. Maruoka, *Nat. Chem.* **2014**, *6*, 702–705; e) H. Huo, X. Shen, C. Wang, L. Zhang, P. Röse, L.-A. Chen, K. Harms, M. Marsch, G. Hilt, E. Meggers, *Nature* **2014**, *515*, 100–103; f) R. Brimioulle, D. Lenhart, M. M. Maturi, T. Bach, *Angew. Chem. Int. Ed.* **2015**, *54*, 3872–3890; *Angew. Chem.* **2015**, *127*, 3944–3963; g) J. J. Murphy, D. Bastida, S. Paria, M. Fagnoni, P. Melchiorre, *Nature* **2016**, *532*, 218–222; h) W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014–1018; i) N. Kern, M. P. Plesniak, J. J. W. McDouall, D. J. Procter, *Nat. Chem.* **2017**, *9*, 1198–1204; j) Y. Wang, X. Wen, X. Cui, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 1049–1052; k) C. Li, K. Lang, H. Lu, Y. Hu, X. Cui, L. Wojtas, X. P. Zhang, *Angew. Chem. Int. Ed.* **2018**, *57*, 16837–16841; *Angew. Chem.* **2018**, *130*, 17079–17083; l) R. S. J. Proctor, H. J. Davis, R. J. Phipps, *Science* **2018**, *360*, 419–422; m) K. F. Biegasiewicz, S. J. Cooper, X. Gao, D. G. Oblinsky, J. H. Kim, S. E. Garfinkle, L. A. Joyce, B. A. Sandoval, G. D. Scholes, T. K. Hyster, *Science* **2019**, *364*, 1166–1169; n) Y. Yang, I. Cho, X. Qi, P. Liu, F. H. Arnold, *Nat. Chem.* **2019**, *11*, 987–993; o) K. Lang, C. Li, I. Kim, X. P. Zhang, *J. Am. Chem. Soc.* **2020**, *142*, 20902–20911; p) K. M. Nakafuku, Z. Zhang, E. A. Wappes, L. M. Stateman, A. D. Chen, D. A. Nagib, *Nat. Chem.* **2020**, *12*, 697–704; q) J. Xie, P. Xu, Y. Zhu, J. Wang, W.-C. C. Lee, X. P. Zhang, *J. Am. Chem. Soc.* **2021**, *143*, 11670–11678; r) Q. Zhou, M. Chin, Y. Fu, P. Liu, Y. Yang, *Science* **2021**, *374*, 1612–1616; s) H. Iwamoto, K. Endo, Y. Ozawa, Y. Watanabe, K. Kubota, T. Imamoto, H. Ito, *Angew. Chem. Int. Ed.* **2019**, *58*, 11112–11117; *Angew. Chem.* **2019**, *131*, 11229–11234; t) L. Wu, G. Yang, W. Zhang, *CCS Chem.* **2020**, *2*, 623–631.

[9] a) Z. Wang, H. Yin, G. C. Fu, *Nature* **2018**, *563*, 379–383; b) Z. Wang, Z.-P. Yang, G. C. Fu, *Nat. Chem.* **2021**, *13*, 236–242.

[10] For enantioconvergent transformation of tertiary alkyl halides other than radical strategies, see: a) S. Ma, X. Han, S. Krishnan, S. C. Virgil, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2009**, *48*, 8037–8041; *Angew. Chem.* **2009**, *121*, 8181–8185; b) J. Li, M. Kong, B. Qiao, R. Lee, X. Zhao, Z. Jiang, *Nat. Commun.* **2018**, *9*, 2445; c) X. Zhang, J. Ren, S. M. Tan, D. Tan, R. Lee, C.-H. Tan, *Science* **2019**, *363*, 400–404.

[11] 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*, 1158–1166; b) S.-P. Jiang, X.-Y. Dong, Q.-S. Gu, L. Ye, Z.-L. Li, X.-Y. Liu, *J. Am. Chem. Soc.* **2020**, *142*, 19652–19659; c) X.-L. Su, L. Ye, J.-J. Chen, X.-D. Liu, S.-P. Jiang, F.-L. Wang, L. Liu, C.-J. Yang, X.-Y. Chang, Z.-L. Li, Q.-S. Gu, X.-Y. Liu, *Angew. Chem. Int. Ed.* **2021**, *60*, 380–384; *Angew. Chem.* **2021**, *133*, 384–388; d) Y.-F. Zhang, X.-Y. Dong, J.-T. Cheng, N.-Y. Yang, L.-L. Wang, F.-L. Wang, C. Luan, J. Liu, Z.-L. Li, Q.-S. Gu, X.-Y. Liu, *J. Am. Chem. Soc.* **2021**, *143*, 15413–15419; e) P.-F. Wang, J. Yu, K.-X. Guo, S.-P. Jiang, J.-J. Chen, Q.-S. Gu, J.-R. Liu, X. Hong, Z.-L. Li, X.-Y. Liu, *J. Am. Chem. Soc.* **2022**, *144*, 6442–6452.

[12] F.-L. Wang, C.-J. Yang, J.-R. Liu, N.-Y. Yang, X.-Y. Dong, R.-Q. Jiang, X.-Y. Chang, Z.-L. Li, G.-X. Xu, D.-L. Yuan, Y.-S. Zhang, Q.-S. Gu, X. Hong, X.-Y. Liu, *Nat. Chem.* **2022**, *14*, 949–957.

[13] a) Q. Liang, P. J. Walsh, T. Jia, *ACS Catal.* **2020**, *10*, 2633–2639; b) T. Iwamoto, C. Okuzono, L. Adak, M. Jin, M. Nakamura, *Chem. Commun.* **2019**, *55*, 1128–1131.

[14] a) D. T. Richens, *Chem. Rev.* **2005**, *105*, 1961–2002; b) A. E. King, B. L. Ryland, T. C. Brunold, S. S. Stahl, *Organometallics* **2012**, *31*, 7948–7957; c) A. Vasilopoulos, S. L. Zultanski, S. S. Stahl, *J. Am. Chem. Soc.* **2017**, *139*, 7705–7708; d) W. Zhang, L. Wu, P. Chen, G. Liu, *Angew. Chem. Int. Ed.* **2019**, *58*, 6425–6429; *Angew. Chem.* **2019**, *131*, 6491–6495; e) L. Wu, F. Wang, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2019**, *141*, 1887–1892; f) L. Wu, F. Wang, X. Wan, D. Wang, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2017**, *139*, 2904–2907.

[15] a) M. Lauer, G. Wulff, *J. Organomet. Chem.* **1983**, *256*, 1–9; b) F. Dallacker, E. M. Both-Pollmann, W. Muellners, *Chem.-Ztg.* **1984**, *108*, 287–288; for copper-catalyzed racemic cross-coupling of organoboron esters, see: c) Y.-Y. Sun, J. Yi, X. Lu, Z.-Q. Zhang, B. Xiao, Y. Fu, *Chem. Commun.* **2014**, *50*, 11060–11062; d) G.-Z. Wang, J. Jiang, X.-S. Bu, J.-J. Dai, J. Xu, Y. Fu, H.-J. Xu, *Org. Lett.* **2015**, *17*, 3682–3685; e) C.-T. Yang, Z.-Q. Zhang, Y.-C. Liu, L. Liu, *Angew. Chem. Int. Ed.* **2011**, *50*, 3904–3907; *Angew. Chem.* **2011**, *123*, 3990–3993.

[16] F. Sladojevich, A. Trabocchi, A. Guarna, D. J. Dixon, *J. Am. Chem. Soc.* **2011**, *133*, 1710–1713.

[17] a) N. Hara, S. Nakamura, Y. Funahashi, N. Shibata, *Adv. Synth. Catal.* **2011**, *353*, 2976–2980; b) N. Hara, S. Nakamura, M. Sano, R. Tamura, Y. Funahashi, N. Shibata, *Chem. Eur. J.* **2012**, *18*, 9276–9280; c) K. Fujita, M. Miura, Y. Funahashi, T. Hatanaka, S. Nakamura, *Org. Lett.* **2021**, *23*, 2104–2108; d) S. Nakamura, N. Matsumoto, M. Kibe, K. Abe, T. Takehara, T. Suzuki, *Adv. Synth. Catal.* **2022**, *364*, 781–786.

[18] a) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3166; b) D. V. Partyka, *Chem. Rev.* **2011**, *111*, 1529–1595; c) I. Hoffmann, B. Blumenröder, S. Onodi neé Thumann, S. Dommer, J. Schatz, *Green Chem.* **2015**, *17*, 3844–3857.

[19] Deposition number 2210247 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: October 6, 2022
Accepted manuscript online: November 10, 2022
Version of record online: December 2, 2022