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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Copper-Catalyzed Enantioconvergent Radical Suzuki–Miyaura C(sp^3)–C(sp^2) Cross-Coupling

Sheng-Peng Jiang, Xiao-Yang Dong, Qiang-Shuai Gu, Liu Ye, Zhong-Liang Li,* and Xin-Yuan Liu*

Cite This: https://dx.doi.org/10.1021/jacs.0c09125
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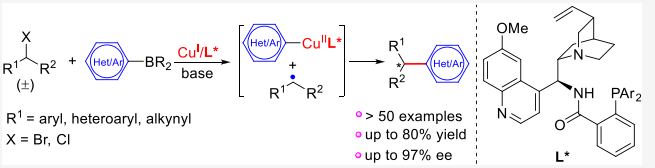
ABSTRACT: A copper-catalyzed enantioconvergent Suzuki–Miyaura C(sp^3)–C(sp^2) cross-coupling of various racemic alkyl halides with organoboronate esters has been established in high enantioselectivity. Critical to the success is the use of a chiral cinchona alkaloid-derived N,N,P-ligand for not only enhancing the reducing capability of copper catalyst to favor a stereoablative radical pathway over a stereospecific S_N2-type process but also providing an ideal chiral environment to achieve the challenging enantiocontrol over the highly reactive radical species. The reaction has a broad scope with respect to both coupling partners, covering aryl- and heteroarylboronate esters, as well as benzyl-, heterobenzyl-, and propargyl bromides and chlorides with good functional group compatibility. Thus, it provides expedient access toward a range of useful enantioenriched skeletons featuring chiral tertiary benzylic stereocenters.



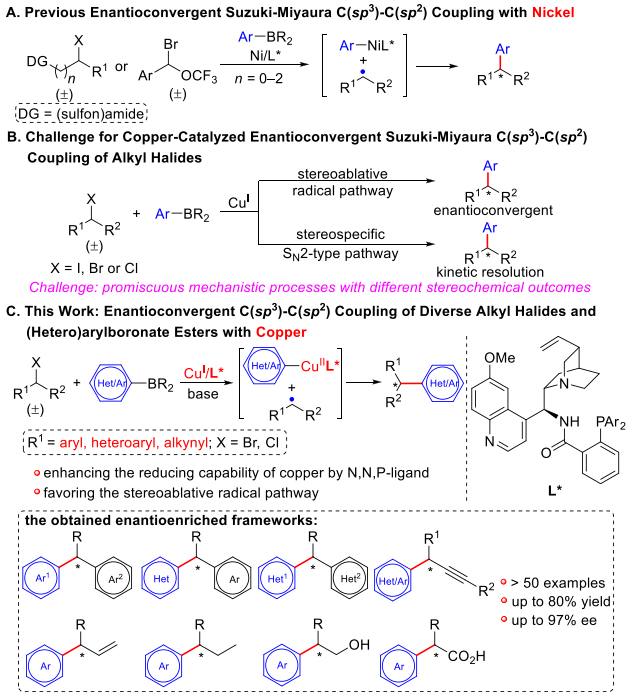
INTRODUCTION

The Suzuki–Miyaura reaction is one of the most widely used cross-coupling reactions for the construction of strategically important C–C bonds owing to its broad reaction scope, as well as the stability, availability, and low toxicity of organoboron reagents.[1] Compared with the classic, powerful Suzuki–Miyaura C(sp^2)–C(sp^2) coupling, the coupling of alkyl (pseudo)halides with organoboron reagents to forge C(sp^3)–C(sp^2) bonds has been less studied due to the relatively difficult oxidative addition and the facile β-H elimination of alkyl metal complexes.[2] Particularly, the development of catalytic asymmetric Suzuki–Miyaura C(sp^3)–C(sp^2) coupling to access enantioenriched three-dimensional molecular frameworks would further expand its exceptional capabilities in organic synthesis.[3] In this scenario, the stereoselective coupling of enantioenriched alkyl electrophiles with organoboron reagents using an achiral catalyst has evolved into a feasible protocol to construct the chiral C(sp^3)–C(sp^2) bonds.[4] In comparison, the utility of chiral transition metal catalysis to accomplish an enantioconvergent coupling of racemic alkyl electrophiles represents a more appealing strategy due to its chirality multiplication nature. In this regard, Fletcher and Tang have independently developed the noble transition metal (Rh, Pd) catalysis for the enantioconvergent coupling of arylboronic acids with racemic cyclic allylic chlorides and α-bromocarboxamides, respectively, through a dynamic kinetic asymmetric transformation or resolution process.[5] Recent increased emphasis on sustainability and economy has shifted the focus of catalysis from noble to first-row transition metals, which could provide a suitable mechanism for stereoconvergence by converting the racemic alkyl halides to prochiral radical intermediates via a single electron reduction process.[6] In this context, the chiral nickel catalysis has been elegantly established to realize the enantioconvergent Suzuki–Miyaura C(sp^3)–C(sp^2) coupling of (sulfon)amide-substituted alkyl halides or trifluoromethoxyl-substituted benzylic halides, a strategy pioneered by Fu (Scheme 1A).[7,8] Recently, Nakamura disclosed a chiral iron/bisphosphine catalyst to realize the coupling of racemic α-bromopropionate, albeit with moderate enantioselectivity.[9] Although these reports have advanced the state of the art, the development of new chiral first-row transition metal catalysts to achieve an enantioconvergent C(sp^3)–C(sp^2) coupling of more alkyl halides in a highly enantioselective fashion is still highly desirable.

Owing to the low cost and toxicity of copper catalyst, we surmised that it would be a potential first-row transition metal catalyst for such a transformation.[10] However, Liu and Fu have disclosed copper-catalyzed racemic Suzuki–Miyaura coupling of various alkyl halides via promiscuous mechanisms (either a stereoablative radical process or a stereospecific S_N2-type pathway) with different stereochemical consequences (Scheme 1B).[11] Thus, the reaction mechanism has to be to tuned toward the radical process in order to achieve an enantioconvergent transformation.[11] To solve this challenge, we speculated that a rational design of chiral ligands to enhance the reducing capability of copper would be pivotal to drive the reaction toward a radical process by favoring single-electron reduciton of alkyl halides. As part of our continuous

Received: August 25, 2020

Scheme 1. First-Row Transition Metal-Catalyzed Enantioconvergent Suzuki−Miyaura C(sp^3)−C(sp^2) Coupling

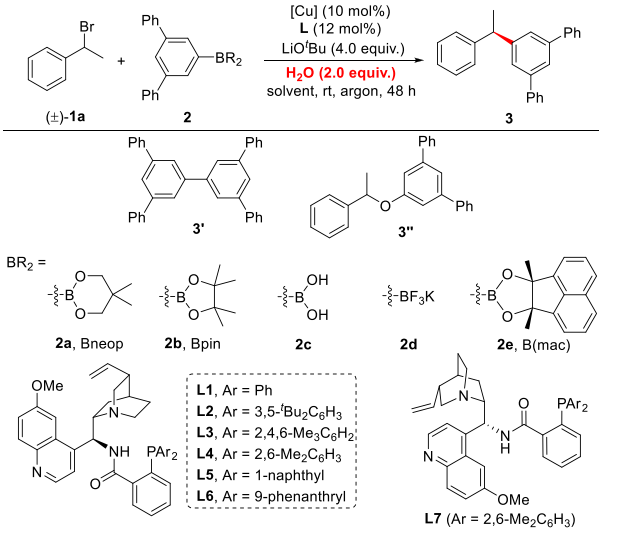


interest in copper-catalyzed asymmetric radical reactions,[12] herein we present a general enantioconvergent C(sp^3)−C(sp^2) coupling of racemic alkyl halides with organoboronate reagents catalyzed by Cu(I)[13] and a chiral electron-rich N,N,P-ligand.[12c,14] Notably, the reaction tolerates a number of aryl- and heteroarylboronate esters as well as benzyl, heterobenzyl, and propargyl bromides and chlorides, and these electrophiles have been underrepresented in previously reported enantioconvergent Suzuki−Miyaura reactions.[5,7−9] Therefore, this strategy (when combined with straightforward follow-up manipulations) delivers a number of pharmaceutically useful chiral 1,1-di(hetero)arylalkane and 1-aryl-1-heteroarylalkane scaffolds[15] as well as highly valuable synthons in organic synthesis, such as chiral alkynes, alkenes, alcohols, and carboxylic acids (Scheme 1C).

RESULTS AND DISCUSSION

Reaction Development. We initiated our study by examining the cross-coupling between (1-bromoethyl)benzene **1a** with arylboronate ester **2** with LiO^{t}Bu as the base, which is beneficial for the transmetalation of organoboron reagents to copper salt.[11a] Unfortunately, the initial attempts with various arylboronate esters **2a**−**2e** in the presence of CuI, ligand **L1**, and LiO^{t}Bu in different solvents indicated very low reaction efficiency at room temperature (Table 1, entry 1 and Table S1 in the Supporting Information). Water is reported to be helpful to the Suzuki−Miyaura reaction due to its vital role in both increasing the solubility of LiO^{t}Bu and promoting the transmetalation step.[16] Indeed, we found that the addition of water greatly promoted the reaction efficiency and the desired product **3** was generated in 39% yield with 31% ee (Table 1, entries 1 and 2). The major side products were the homocoupling product **3′** of boronate ester and ether **3″**. Since the choice of organoboron reagents is also crucial in the

Table 1. Screening of Reaction Conditions[a]



entry	2	[Cu]	L	solvent	yield (%)	ee (%)
1[b]	**2a**	CuI	**L1**	DMSO	0	
2	**2a**	CuI	**L1**	DMSO	39	31
3	**2b**	CuI	**L1**	DMSO	51	31
4	**2c**	CuI	**L1**	DMSO	0	
5	**2d**	CuI	**L1**	DMSO	0	
6	**2e**	CuI	**L1**	DMSO	55	31
7	**2e**	CuI	**L2**	DMSO	86	28
8	**2e**	CuI	**L3**	DMSO	41	87
9	**2e**	CuI	**L4**	DMSO	51	89
10	**2e**	CuI	**L5**	DMSO	56	85
11	**2e**	CuI	**L6**	DMSO	47	60
12	**2e**	CuTc	**L4**	DMSO	36	87
13	**2e**	CuSCN	**L4**	DMSO	19	89
14	**2e**	CuOAc	**L4**	DMSO	17	87
15[c]	**2e**	CuI	**L4**	DMSO/CH_2Cl_2	80	94
16[c]	**2e**	CuI	**L4**	DMSO/DCE	58	91
17[c]	**2e**	CuI	**L4**	DMSO/CH_3CN	18	91
18[c]	**2b**	CuI	**L4**	DMSO/CH_2Cl_2	16	87

[a]Reaction conditions: (±)-**1a** (0.075 mmol), **2** (0.05 mmol), [Cu] (10 mol %), **L** (12 mol %), LiO^{t}Bu (4.0 equiv), and H_2O (2.0 equiv) in solvent (0.60 mL) at room temperature for 24 h under argon. Yield was based on ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard. The ee values are based on HPLC analysis. [b]Without H_2O. [c]Solvent ratio (2:1), conducted at −5 °C for 48 h.

transmetalation step and may ultimately influence the reaction efficiency,[1d] we screened several organoboron reagents **2b**−**2e** and identified that the methylated acenaphthoquinone-derived boronate (B(mac)) ester **2e**[17] gave the best yield (55%), without affecting the ee value (Table 1, entry 6). The subsequent ligand test revealed that our previously reported 3,5-di-*tert*-butyl-substituted N,N,P-ligand **L2**[13] for C(sp^3)−C(sp) coupling provided a slightly lower ee value, indicating that further modification of ligands with different steric properties at different positions was necessary (Table 1, entry 7). We surmised that the *ortho*-substituted N,N,P-ligands might increase the steric hindrance and be beneficial to the enantioselectivity. Then, we synthesized a series of *ortho*-substituted N,N,P-ligands **L3**−**L6** (see Supporting Information for their synthesis). The 2,4,6-trimethyl-substituted N,N,P-ligand **L3** indeed significantly enhanced the ee value to 87%,

https://dx.doi.org/10.1021/jacs.0c09125
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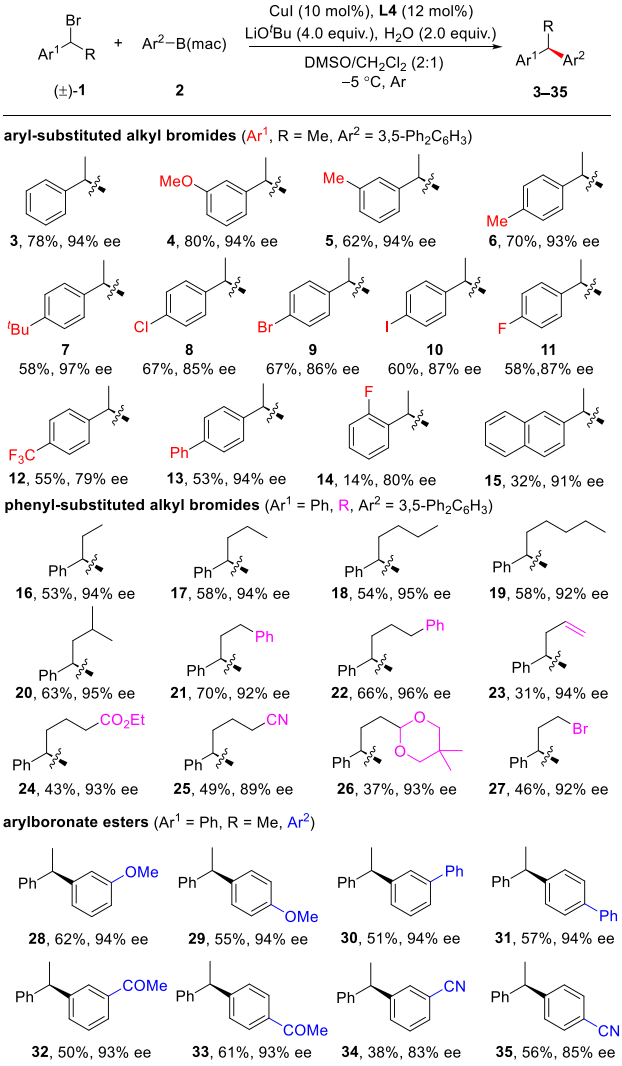
albeit in a lower yield (Table 1, entry 8). Ligand **L4** with 2,6-dimethyl substituents further enhanced the reaction efficiency and enantioselectivity (Table 1, entry 9). The 1-naphthyl- and 9-phenanthryl-subsituted N,N,P-ligands (**L5** and **L6**) did not give better results than **L4** (Table 1, entries 10 and 11). At last, we identified that **L4** was the best one, affording product **3** with 89% ee at ambient conditions. Further varying the copper salts resulted in a decreasing yield of product **3** with almost a similar ee (Table 1, entries 12−14). Lowering the temperature to −5 °C by adding a cosolvent further increased the enantioselectivity, and the mixed solvent of DMSO/CH_2Cl_2 significantly enhanced the reaction efficiency (Table 1, entries 15−17). A trial with the more readily available boronate ester **2b** under the optimized conditions indicated a very low conversion of **2b** (Table 1, entry 18). We finally identified the optimal conditions as follows: the reaction of **1a** and **2e** in a molar ratio of 1.5:1.0 in the presence of 10 mol % of CuI, 12 mol % of **L4**, 4.0 equiv of LiO^tBu, and 2.0 equiv of H_2O in DMSO/CH_2Cl_2 (v/v = 2:1) generated **3** in 80% yield with 94% ee (Table 1, entry 15). Replacing **L4** with its pseudoenantiomer **L7** gave rise to the enantiomer of **3** (**ent-3**) in 72% yield with 95% ee under otherwise identical conditions.

With the optimal reaction conditions in hand, we then investigated the scope of benzyl bromides (Table 2). Substrates with either electron-donating or electron-withdrawing functional groups at the *para* or *meta* positions of the phenyl rings reacted smoothly in comparable yields with up to 97% ee (**4**−**13**). The substituents at the *ortho* positions of the phenyl rings significantly affected the reaction efficiency: the 2-fluoro-substituted product **14** was obtained in very low yield, while other substrates with methyl or methoxyl groups at the *ortho* positions did not give rise to the desired products. Notably, the aryl−X (X = Cl, Br, I, F) bonds did not interfere with the reaction and the desired products **8**−**11** were efficiently generated. The naphthyl bromide was also a suitable substrate for the coupling reaction to deliver the desired product **15** with 91% ee, albeit with a low yield. In addition, the simple linear benzyl bromides also worked well to provide **16**−**27** in moderate to good yields with 89−96% ee. A myriad of functional groups, such as terminal olefin (**23**), ester (**24**), nitrile (**25**), and acetal (**26**) at different distances away from the reaction site were all compatible with the reaction conditions. Furthermore, good chemoselectivity was observed for the reaction of secondary benzylic bromide in preference to the primary bromide (**27**). We next turned our attention to examining the scope of arylboronate esters. The electron-donating methoxyl group at the *meta*/*para* position was tolerated to give rise to **28** and **29** in 55−62% yields with 94% ee. The absolute configuration of **29** was determined to be *R* by comparing its HPLC spectrum and optical rotation with those reported in literature,[18] and those of other products were determined in reference to **29**. Besides, the phenyl-substituted arylboronates were also amenable to the coupling reaction to afford **30** and **31** in excellent enantioselectivity. More importantly, the electron-withdrawing functional groups (carbonyl, cyano) at the *meta*/*para* position of arylboronates were also suitable for the reaction to furnish the coupling products **32**−**35** with 83−93% ee. Overall, by variation of functional groups at either benzylic halides or B(mac)-derived arylboronate esters, this strategy provided a wide range of enantioenriched 1,1-diarylalkanes.[15]

Table 2. Scope for Synthesis of Enantioenriched 1,1-Diarylalkanes[a]



[a]Reaction conditions: (±)-**1** (1.5 equiv), **2** (0.20 mmol), CuI (10 mol %), **L4** (12 mol %), LiO^tBu (4.0 equiv), and H_2O (2.0 equiv) in DMSO/DCM (2:1, 2.4 mL) at −5 °C for 48 h under argon.

Heterocycles are prevalent in many pharmacologically important core structures, and we envisioned that the installation of various heterocycles into the enantioenriched 1,1-driarylalkane skeletons might be potentially useful for drug discovery. Thus, we investigated the scope toward the synthesis of enantioenriched 1-aryl-1-heteroarylalkanes and 1,1-diheteroarylalkanes from heterobenzyl bromides and heteroarylboronate esters (Table 3). As such, alkyl bromides bearing heteroarenes such as pyridine (**36** and **37**) and quinoline (**38**) worked well to yield the enantioenriched 1-aryl-1-heteroarylalkanes, and the quinoline-substituted product was generated in a higher yield and enantioselectivity. Similarly, the boronate esters containing different types of electron-rich heteroarenes, such as the furan and thiophene, coupled smoothly to provide **39** and **40** in good yields and excellent enantioselectivity. The electron-withdrawing 2-chloropyridylboronate ester was also suitable for the reaction to provide **41** in good yield and enantioselectivity. Unfortunately, no product was observed for the Bpin-derived pyridyl boronate ester without substituents *ortho* to the nitrogen.

https://dx.doi.org/10.1021/jacs.0c09125
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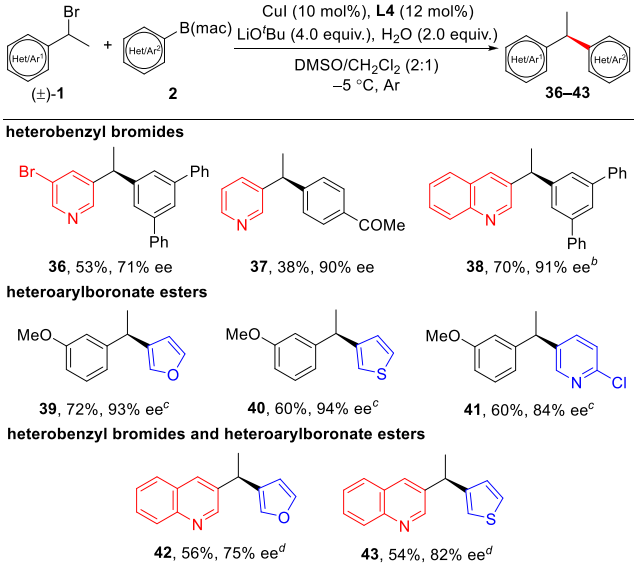
Table 3. Scope for Synthesis of Enantioenriched 1-Aryl-1-heteroarylalkanes and 1,1-Diheteroarylalkanes[a]

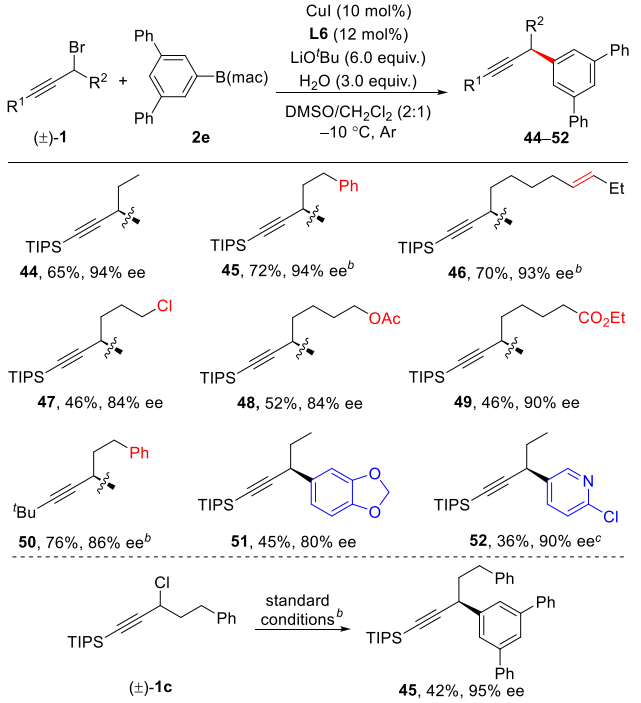


[a]Reaction conditions: (±)-**1** (1.5 equiv), **2** (0.20 mmol), CuI (10 mol %), **L4** (12 mol %), LiO^{t}Bu (4.0 equiv), and H_2O (2.0 equiv) in DMSO/DCM (2:1, 2.4 mL) at −5 °C for 48 h under argon. [b]At room temperature for 24 h under argon. [c](±)-**1** (1.0 equiv) for 72 h. [d]At −10 °C for 72 h.

Noteworthy is that the coupling reaction between heterobenzyl bromides and heteroarylboronate esters proceeded smoothly as well to afford the enantioenriched 1,1-diheteroarylalkanes **42** and **43** with good enantioselectivity.

Enantioenriched alkynes are found in not only natural products and therapeutics, such as efavirenz and AMG 837, but also highly valuable synthons in organic synthesis.[19] Having this in mind, we next switched our attention to the synthesis of enantioenriched alkynes from the Suzuki−Miyaura coupling of racemic propargyl bromides. However, the optimal conditions for cross-coupling of benzyl halides were not suitable for the reaction of propargyl bromides and only moderate reaction efficiency and enantioselectivity were observed (Table S2 in the Supporting Information). Upon systematic screening of reaction parameters (Table S2), we found that the reaction of the triisopropylsilyl (TIPS)-substituted propargyl bromide **1b** provided **44** with the best result in the presence of **L6**, with 6.0 equiv of LiO^{t}Bu and 3.0 equiv of water at −10 °C (Table S2, entry 8). Under the optimal conditions, a number of racemic propargyl bromides were amenable to the reaction to afford enantioenriched alkynes **44**−**50** in moderate to good yields with 84−94% ee (Table 4). Noteworthy is that many functional groups at different positions away from the reaction site of propargyl bromides were well tolerated, such as internal alkene (**46**), chloride (**47**), and esters (**48** and **49**). The scope was not limited to TIPS-substituted propargyl bromides, as can be seen by the formation of **50**. Other B(mac)-derived boronate esters, containing different types of heterocycles such as the 1,3-benzodioxole and pyridine, were also applicable to the coupling reaction to deliver the desired products **51** and **52** with 80% and 90% ee, respectively. Notably, the substrates were not limited to alkyl bromides and the less reactive propargyl chloride **1c** also underwent the desired reaction to afford **45** in 42% yield with 95% ee.

Table 4. Scope for Synthesis of Enantioenriched (Hetero)Benzyl Alkynes[a]



[a]Reaction conditions: (±)-**1** (1.5 equiv), **2** (0.20 mmol), CuI (10 mol %), **L6** (12 mol %), LiO^{t}Bu (6.0 equiv), and H_2O (3.0 equiv) in DMSO/DCM (2:1, 2.4 mL) at −10 °C for 120 h under argon. [b]For 72 h. [c]For 96 h.

Synthetic Utility. The translation from small-scale to preparative scale synthesis is a key step to transform the reaction methodology to the industrial realm. To demonstrate the preparative utility of our protocol, the enantioconvergent Suzuki−Miyaura reaction was conducted on a gram scale, providing the desired product **4** without a decrease in reaction efficiency (Scheme 2A). Alkynes are one of the most important and versatile synthetic intermediates in organic synthesis, and to showcase the synthetic value of enantioenriched benzyl alkynes, we carried out a myriad of transformations of our coupled products to furnish other synthetically valuable synthons (Scheme 2B). As such, alkyne **45** underwent the oxidative cleavage of the triple bond smoothly to give rise to the chiral benzyl carboxylic acid **53** in 89% yield, which was smoothly converted to alcohol **54** via a sequential esterification and $LiAlH_4$ reduction in 93% yield with 94% ee. Upon exposure to tetrabutylammonium fluoride (TBAF), the TIPS group was easily removed to afford the terminal alkynes **55a** and **55b** in high efficiency with 94% ee. Further, a partial hydrogenation of chiral alkyne **55b** afforded chiral terminal alkene **56** in 92% yield with 95% ee. In addition, the complete hydrogenation of **55b** provided **57** with 90% ee, featuring a saturated aliphatic chain. Most importantly, the structural variations in the alkynyl moiety were also feasible. As shown in Scheme 2B, the Sonogashira coupling between terminal alkyne **55a** and different types of organohalides, such as aryl, heteroaryl, and aliphatic halides, was successfully achieved to generate diverse enantioenriched alkynes **58a**−**58c**. Specifically, the coupling of 5-chloropyrazolo[1,5-*a*]pyrimidine with **55a** afforded the product **58b**, an analog of a patented mGluR modulator,[13] indicating its potential application in drug

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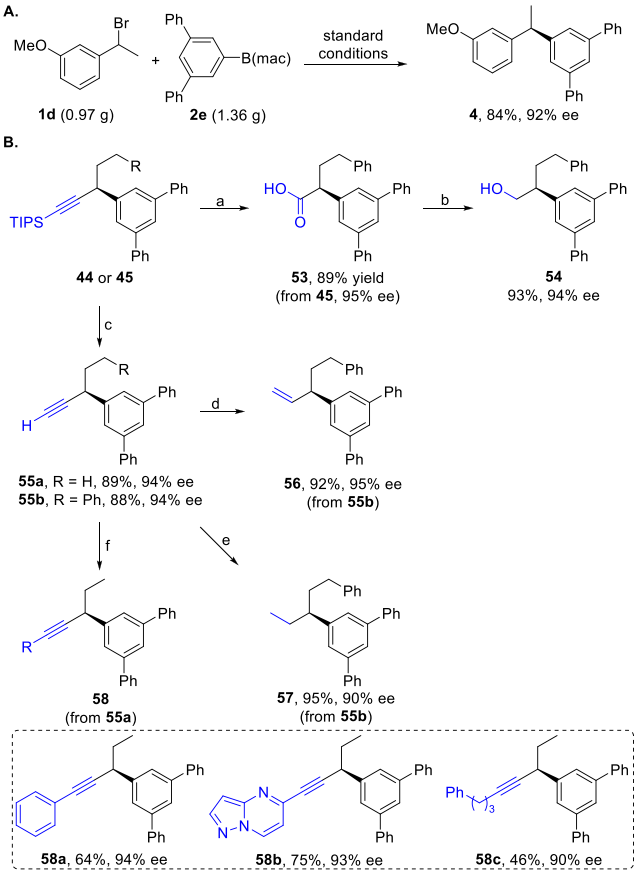
Scheme 2. Synthetic Applications[a]

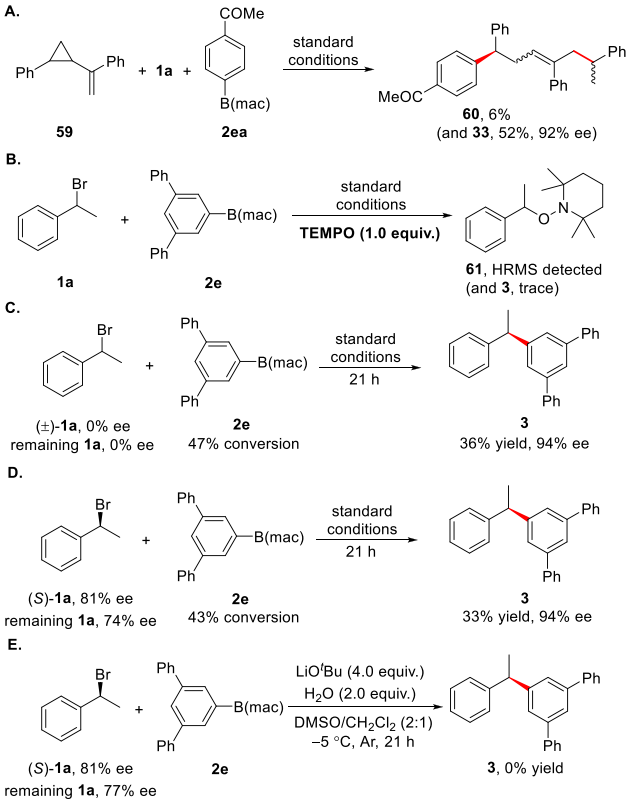


[a]Reaction conditions: (a) $RuCl_3$ (5 mol %) and $NaIO_4$ in a mixed solvent of $CCl_4/CH_3CN/H_2O$ (v/v/v = 2:2:3), rt, 4 h. (b) $SOCl_2$, MeOH, 0 °C to rt, 3 h; $LiAlH_4$, THF, rt, 3 h. (c) TBAF in THF, rt, 1 h. (d) Pd/C (10 wt %) and H_2 (1.0 atm) in THF, rt, 0.5 h. (e) Pd/C (10 wt %) and H_2 (1.0 atm) in THF, rt, 12 h. (f) For synthesis of **58a**: PhI, $Pd(PPh_3)_4$ (5 mol %), CuI (5 mol %) and Et_3N in THF, 80 °C, 18 h. For synthesis of **58b**: 5-chloropyrazolo[1,5-*a*]pyrimidine, $Pd(PPh_3)_4$ (5 mol %), CuI (5 mol %) and KOAc in THF, rt, 18 h. For synthesis of **58c**: (3-bromopropyl)benzene, $[(\pi\text{-allyl})PdCl]_2$ (2.5 mol %), CuI (7.5 mol %), IPr·HCl (5 mol %) and Cs_2CO_3 in a mixed solvent of DMF/Et_2O (v/v = 1:2), 45 °C, 24 h. IPr·HCl = 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride.

discovery. Therefore, this strategy (when combined with straightforward manipulations) delivers a number of highly valuable synthons in organic synthesis.

Mechanistic Studies. To gain some insight into the possible radical mechanism, we carried out some control experiments. The reaction of radical clock substrate **59** with **1a** and **2ea** led to the radical addition/ring-opening/arylation product **60** in 6% yield along with the coupling product **33** under the standard reaction conditions (Scheme 3A). When TEMPO was added under the otherwise standard conditions, the reaction of **1a** with **2e** was completely inhibited and the TEMPO-trapped product **61** could be detected by high resolution mass spectroscopy (HRMS) (Scheme 3B). Similar results were also observed for the corresponding control experiments with propargyl bromide **1b** (Scheme S1 in the Supporting Information). These experiments implied the involvement of a radical process in the reaction. In addition, the reactions with either racemic or enantioenriched (1-bromoethyl)benzene **1a** afforded the desired products **3** in

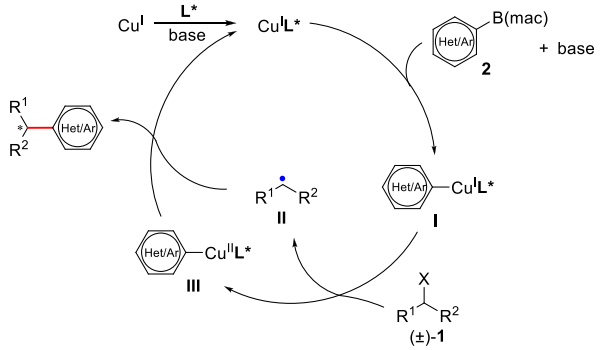
Scheme 3. Mechanistic Study



comparable yields (Scheme 3C and Scheme 3D), indicating roughly the same reaction rates. Further, the enantiopurities of the recovered **1a** did not significantly change compared with that of the starting materials in both of the two reactions (slight racemization of **1a** occurred under the reaction conditions devoid of copper/chiral ligand, Scheme 3E). Collectively, these results excluded a (dynamic) kinetic resolution or dynamic kinetic asymmetric transformation process.[20]

On the basis of these experiments and previous reports,[11−13] we proposed a plausible mechanism as shown in Scheme 4. In

Scheme 4. Proposed Mechanism



the presence of base, Cu^I salt reacts with ligand **L*** to afford the Cu^I**L*** complex, which further undergoes a transmetalation process with B(mac)-derived arylboronate ester **2** and gives the intermediate **I**. Afterward, this intermediate undergoes a single electron reduction with alkyl bromide (±)-**1** to concomitantly deliver a prochiral alkyl radical **II** and the Cu^{II} complex **III**.

https://dx.doi.org/10.1021/jacs.0c09125
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The alkyl radical **II** might react efficiently with the complex **III** to forge the chiral $C(sp^3)-C(sp^2)$ bond and regenerate the $Cu^{I}L^*$ complex for the next catalytic cycle.

CONCLUSION

We have established a general copper-catalyzed enantioconvergent radical Suzuki–Miyaura $C(sp^3)-C(sp^2)$ cross-coupling of racemic alkyl halides with B(mac)-derived boronate esters in high enantioselectivity. A multidentate cinchona alkaloid-derived N,N,P-ligand is strategically utilized to enhance the reducing capability of copper, thus providing a ready mechanism for stereoconvergence by reducing the racemic alkyl halides to the prochiral radical intermediate. The copper/chiral N,N,P-ligand catalytic system is also crucial in the enantiocontrol over the highly reactive radical species to forge a chiral $C(sp^3)-C(sp^2)$ bond. In addition, the reaction features a broad substrate scope with high functional group tolerance, covering aryl- and heteroarylboronate esters, as well as benzyl, heterobenzyl, and propargyl halides. Therefore, this method provides a valuable approach to a variety of potentially useful chiral building blocks for organic synthesis and drug discovery when allied with follow-up transformations. Further expansion of the reaction scope and detailed mechanistic studies are still in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09125.

Experimental procedures, characterization of compounds, Tables S1 and S2, and Scheme S1 (PDF)

AUTHOR INFORMATION

Corresponding Authors

Zhong-Liang Li − *Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China*; Email: lizl@sustech.edu.cn

Xin-Yuan Liu − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, China*; orcid.org/0000-0002-6978-6465; Email: liuxy3@sustech.edu.cn

Authors

Sheng-Peng Jiang − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, China*

Xiao-Yang Dong − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, China*; orcid.org/0000-0002-0663-1482

Qiang-Shuai Gu − *Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China*; orcid.org/0000-0002-3840-425X

Liu Ye − *Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c09125

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support is from the National Natural Science Foundation of China (Grants 21722203, 21831002, and 21801116), Guangdong Provincial Key Laboratory of Catalysis (Grant 2020B121201002), Guangdong Innovative Program (Grant 2019BT02Y335), Natural Science Foundation of Guangdong Province (Grant 2018A030310083), Shenzhen Special Funds (Grant JCYJ20180302180235837), and SUSTech Special Fund for the Construction of High-Level Universities (Grant G02216303). The authors acknowledge the assistance of SUSTech Core Research Facilities. This paper is dedicated to the 10th anniversary of Department of Chemistry, SUSTech.

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