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Article

Design of Hemilabile N,N,N-Ligands in Copper-Catalyzed Enantioconvergent Radical Cross-Coupling of Benzyl/Propargyl Halides with Alkenylboronate Esters

Peng-Fei Wang,[⊥] Jiao Yu,[⊥] Kai-Xin Guo,[⊥] Sheng-Peng Jiang, Ji-Jun Chen, Qiang-Shuai Gu, Ji-Ren Liu, Xin Hong, Zhong-Liang Li,* and Xin-Yuan Liu*

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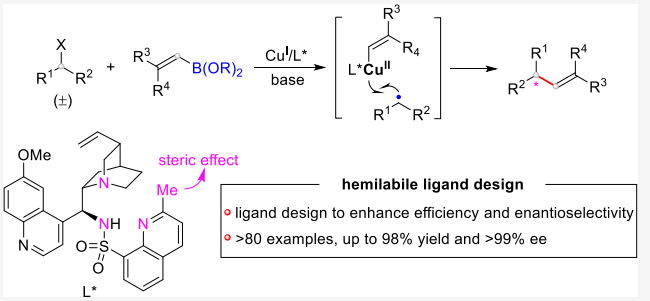
ABSTRACT: The enantioconvergent radical C(sp^3)−C(sp^2) cross-coupling of alkyl halides with alkenylboronate esters is an appealing tool in the assembly of synthetically valuable enantioenriched alkenes owing to the ready availability, low toxicity, and air/moisture stability of alkenylboronate esters. Here, we report a copper/chiral N,N,N-ligand catalytic system for the enantioconvergent cross-coupling of benzyl/propargyl halides with alkenylboronate esters (>80 examples) with good functional group tolerance. The key to the success is the rational design of hemilabile N,N,N-ligands by mounting steric hindrance at the ortho position of one coordinating quinoline ring. Thus, the newly designed ligand could not only promote the radical cross-coupling process in the tridentate form but also deliver enantiocontrol over highly reactive alkyl radicals in the bidentate form. Facile follow-up transformations highlight its potential utility in the synthesis of various enantioenriched building blocks as well as in the late-stage functionalization for drug discovery.



INTRODUCTION

The enantioconvergent C(sp^3)−C cross-coupling of racemic alkyl (pseudo)halides with organometallic reagents represents a powerful tool in the synthesis of enantioenriched molecules.[1−3] Recent progress has led to the development of earth-abundant first-row transition-metal catalysis, which could easily convert racemic alkyl halides to prochiral alkyl radicals and provide a ready mechanism for achieving enantioconvergence, a strategy pioneered by Fu and others.[1] On the other hand, chiral alkenes are valuable synthetic intermediates to allow straightforward access to useful chiral building blocks.[2,4] For example, they easily undergo smooth reduction to alkanes, oxidation to alcohols, aldehydes, and carboxylic acids as well as cross-metathesis and pericyclic reactions to provide complex molecular frameworks.[4a] For the expedient assembly of chiral alkenes, the enantioconvergent radical C(sp^3)−C(sp^2) cross-coupling of alkyl halides with alkenylmetallic reagents represents an appealing strategy. As such, Fu and Zhong have utilized chiral nickel and cobalt catalysis, respectively, to realize the enantioconvergent coupling with alkenyl zinc, silicon, zirconium, and magnesium reagents (Scheme 1A).[5,6] Notably, most of these alkenylation reagents are air- and/or moisture-sensitive and need cautious storage in solution under an inert atmosphere, which may restrict their practical application.[5] Therefore, the development of more practical enantioconvergent C(sp^3)−C coupling with bench-stable alkenyl nucleophiles is highly desirable.

Given that alkenylboronate esters are air/moisture stable, readily accessible, and compatible with many functional groups,[7] the enantioconvergent radical cross-coupling of alkyl halides with alkenylboronate esters would provide a practical approach toward chiral alkenes but remains unexplored.[8] As part of our continuous interest in designing anionic chiral ligands for copper-catalyzed enantioconvergent radical cross-coupling reactions,[9] we wondered whether copper catalysis is applicable to such a transformation. However, several daunting challenges existed (Scheme 1B). First, the transmetalation rate of alkenylboronates is slower compared with other more nucleophilic alkenylmetallic reagents.[5,10] Second, the protodeboronation and oxidative coupling of alkenylboronates are easily occurring side reactions.[10a] In addition, the reducing capability of copper is slightly weaker than those of nickel and cobalt,[5,11] which may retard the initiation of the radical process. Finally, the design of chiral ligands for enantiocontrol over the highly reactive prochiral alkyl radicals is necessary.[9c−f,12] To address these challenges, we surmised that an

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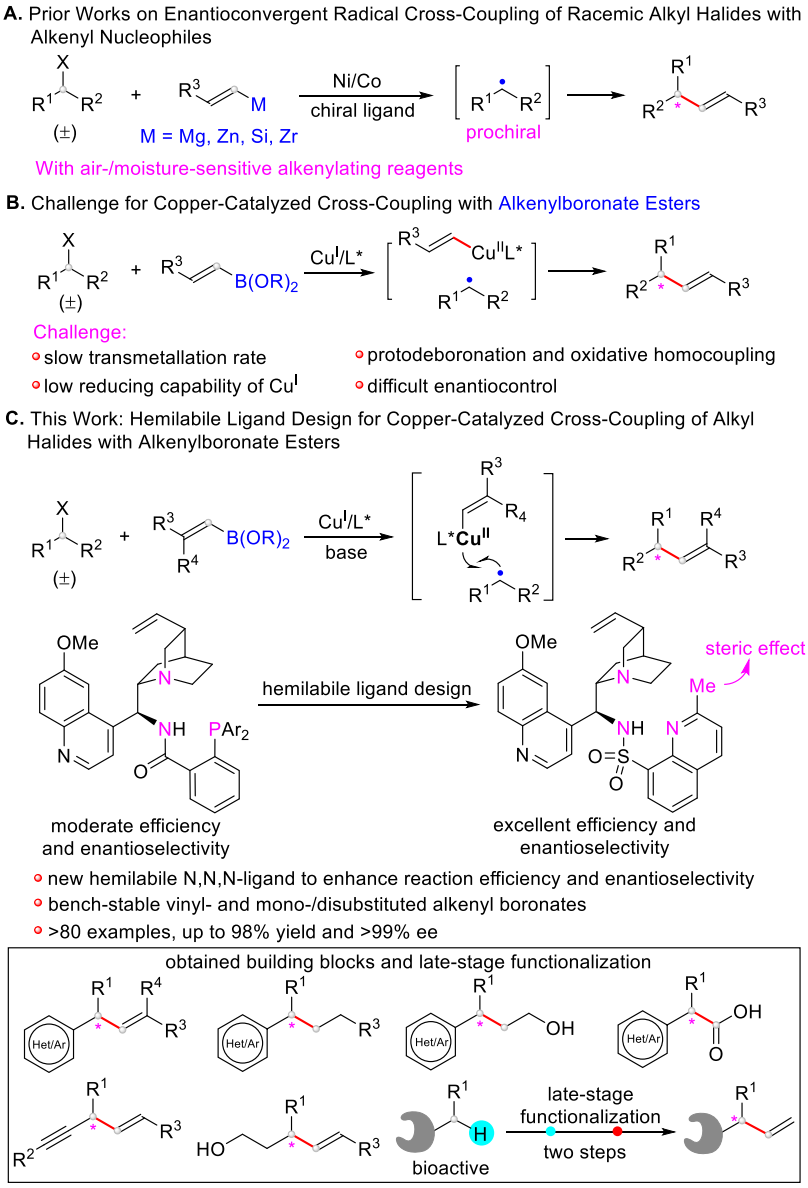
Scheme 1. Copper-Catalyzed Enantioconvergent Radical C(sp^3)−C Cross-Coupling with Alkenylboronate Esters



electron-rich chiral multidentate ligand would not only enhance the reducing capability of copper catalysts to initiate the radical process while suppressing the homocoupling of alkenylboronate esters but also provide a rigid chiral environment for enantiocontrol. Herein, we disclose a copper-catalyzed enantioconvergent radical C(sp^3)−C(sp^2) cross-coupling of alkyl halides with alkenylboronate esters (Scheme 1C). The key to the success is the rational design of a new class of hemilabile chiral N,N,N-ligands to enhance the reaction efficiency in the tridentate form and enantioselectivity in the bidentate form. The reaction tolerates a number of (hetero)benzyl and propargyl bromides and chlorides, as well as vinyl- and mono-/disubstituted alkenyl boronate esters with broad functional group diversity even at 1 mol % catalyst loading. The strategy, when allied with additional one-step manipulation, affords diverse synthetically valuable building blocks (Scheme 1C). Besides, it also provides an alternative approach to formal C(sp^3)−C coupling of purely aliphatic alkyl halides. It further serves as a useful tool in the late-stage functionalization of bioactive molecules.

RESULTS AND DISCUSSION

Reaction Development. At the outset, we investigated the reaction of (1-bromopropyl)benzene **1a** with methylpentanediol (mp)-derived boronate ester **2a**.[13] To promote the transmetalation with the less nucleophilic alkenylboronate ester, we utilized the metal alkoxide LiO^tBu as the base, which would result in a rapid Cu/B exchange driven by the formation of a strong B−O bond.[10,14] Water is also helpful to the transmetalation step by increasing the solubility of the base.[10a] Afterward, we screened a number of chiral ligands with CuI as the catalyst. Chiral bisoxazoline (**L1**) and diamine (**L2**) ligands utilized in nickel and cobalt catalysis[5] afforded trace amounts of the coupling product **3** (Table 1, entries 1 and 2). We then switched to N,N,P-ligands[9c−f,15] and discovered that the reaction with ligand **L3** afforded the desired product **3** in 13% yield with 32% ee, albeit with the formation of **3′** (62%) (Table 1, entry 3). A systematic screening of N,N,P-ligands showed that the ee of **3** could not be significantly enhanced, indicating that the enantiocontrol for the alkenylcopper

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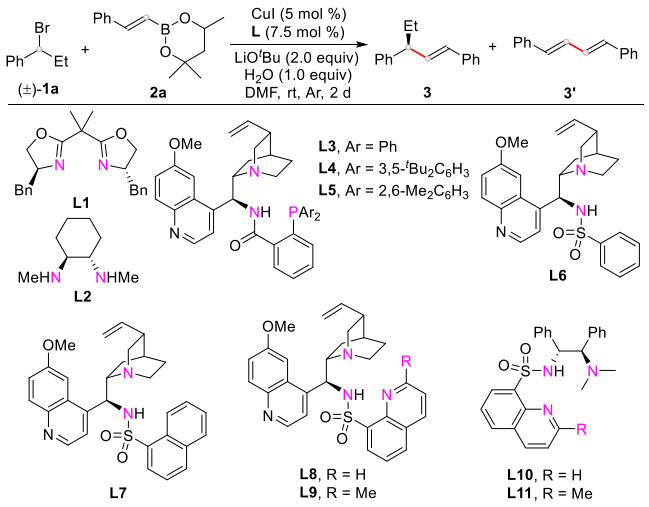
Table 1. Effect of Ligands in the Model Reaction[a]



entry	L	conv. of 2a (%)	y. of 3 (%)	y. of 3′ (%)	Ee (%)
1	L1	>95	trace	29	
2	L2	>95	trace	81	
3	L3	>95	13	62	32
4	L4	90	29	35	43
5	L5	>95	28	32	46
6	L6	>95	4	80	50
7	L7	>95	3	77	31
8	L8	>95	57	15	16
9	L9	>95	57	26	91
10[b]	**L9**	**>95**	**77(80)**	**8**	**95**
11[b]	L10	>95	55	10	−14
12[b]	L11	>95	51	34	−96
13[b,c]	L9	>95	77	17	95

[a]Reaction conditions: (±)-**1a** (0.30 mmol), **2a** (0.20 mmol), CuI (5 mol %), **L** (7.5 mol %), LiO^{t}Bu (2.0 equiv), and H_2O (1.0 equiv) in DMF (2.0 mL) at room temperature for 2 days under argon. Yield (y.) was based on ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard; ee values were based on chiral high-performance liquid chromatography (HPLC) analysis. [b]Conducted at −20 °C for 4 days. The negative ee value represents the opposite configuration (**ent-3**) of **3** as the major enantiomer. [c]CuI (1 mol %) and **L** (1.5 mol %) for 8 days. Isolated yield was shown in parenthesis.

complex is likely different from that of alkynyl- or (hetero)-arylcopper complexes[9] (Table 1, entries 4 and 5; for more N,N,P-ligand screening, see Table S1 in the Supporting Information (SI)).

We then resorted to the cinchona-alkaloid-derived N,N-bidentate ligand,[16] which performed well in our previously disclosed copper-catalyzed asymmetric radical C−O formation.[17] Fortunately, the reactions with **L6** and **L7** generally afforded **3** with higher enantioselectivity than those with N,N,P-ligands, but the yield was very low owing to the formation of a large amount of the homocoupling product **3′** (Table 1, entries 6 and 7). These results implied that the bidentate ligand is beneficial to the enantioselectivity but is ineffective for the desired pathway. We then designed a tridentate N,N,N-ligand **L8** by incorporating additional nitrogen-coordinating site on the basis of **L6**.[18] Using **L8** as the ligand, the yield of the desired product **3** increased significantly to 57%, and the homocoupling product could be greatly inhibited. But the enantioselectivity decreased sharply to 16% (Table 1, entry 8). A direct comparison of **L6** and **L8** revealed that the bidentate N,N-ligand provided good enantiocontrol, while the tridentate N,N,N-ligand promoted the radical cross-coupling. This result prompted us to design a hemilabile N,N,N-ligand by installing a methyl group at the vicinal position of the additional nitrogen-coordinating site (**L9**), hoping that the added steric hindrance might elongate and weaken the coordinating Cu−N bond.[19] As such, the designed ligand would not only promote the desired radical cross-coupling pathway in the tridentate form but also achieve good enantiocontrol in the bidentate form.[19] To our delight, the enantioselectivity of **3** was enhanced to 91% ee with **L9** as the ligand without affecting the yield (Table 1, entry 9). Notably, the moderate yield might arise from the proto-deboronation side reaction of the alkenylboronate ester. A control reaction with naphthyl alkenylboronate ester supported this assumption (Scheme S1 in the SI). After further optimization of reaction parameters, such as the boron sources and bases (Scheme S1 and Table S2 in SI), we found that the yield and ee of **3** could be enhanced to 77 and 95%, respectively, at −20 °C (Table 1, entry 10). Meanwhile, both the homocoupling and protodeboronation side products were greatly suppressed.

The concept of ligand design was also supported by changing the chiral skeleton from quinine to 1,2-diphenyl-ethane-1,2-diamine: the reaction with **L10** and **L11** afforded the enantiomer of **3** (**ent-3**) in similar yields but with totally different enantioselectivities (Table 1, entries 11 and 12). The absolute configuration of **3** was determined to be *S* by comparing its HPLC spectrum and optical rotation with those reported in the literature[9c] and those of other products were assigned in reference to **3**. Reducing the catalyst loading to 1 mol % with an elongated reaction time did not affect the reaction efficiency and enantioselectivity (Table 1, entry 13). Notably, such a low catalyst loading has not been demonstrated in our previously copper/NNP-ligand catalysis,[9c−f] showcasing the potential practicability of the current catalytic system.

Scope of Alkenylboronate Esters and (Hetero)benzyl Halides. With the optimal reaction conditions established, we examined the scope of alkenylboronate esters (Table 2). A series of aryl-/naphthylated alkenylboronate esters with electron-donating or -withdrawing substituents reacted smoothly to form the desired products **4**−**8** in good yields with 89−95% ee. Furthermore, a range of heteroarenes, such as thiophene as well as the coordinating pyridine and quinoline, in alkenylboronate esters were tolerated to afford **9**−**13** in 71−87% yields with 86−95% ee. With respect to alkyl-substituted alkenylboronate esters, barely functionalized aliphatic chains were well tolerated to afford **14**−**16** with excellent ee. A gamut of functional groups, such as conjugating alkene (**17** and **18**) and ester (**19**), ether (**20** and **21**), acetate (**22**), silyl ether (**23**), and coordinating thioether (**24**), remained untouched. Besides, the vinylboronate ester worked well under the standard conditions to provide **25** with 92% ee, of which the facile transformation of the olefin moiety would give rise to many chiral building blocks. The 1,1-disubstituted alkenylboronate ester was also a viable substrate to afford **26**, albeit with moderate enantioselectivity.

We next evaluated the scope of (hetero)benzyl halides. As for the aryl ring of alkyl bromides, a gamut of electron-donating and -withdrawing substituents at different positions (*ortho*, *meta*, or *para*) of the phenyl rings as well as the naphthyl rings were compatible with the reaction to provide

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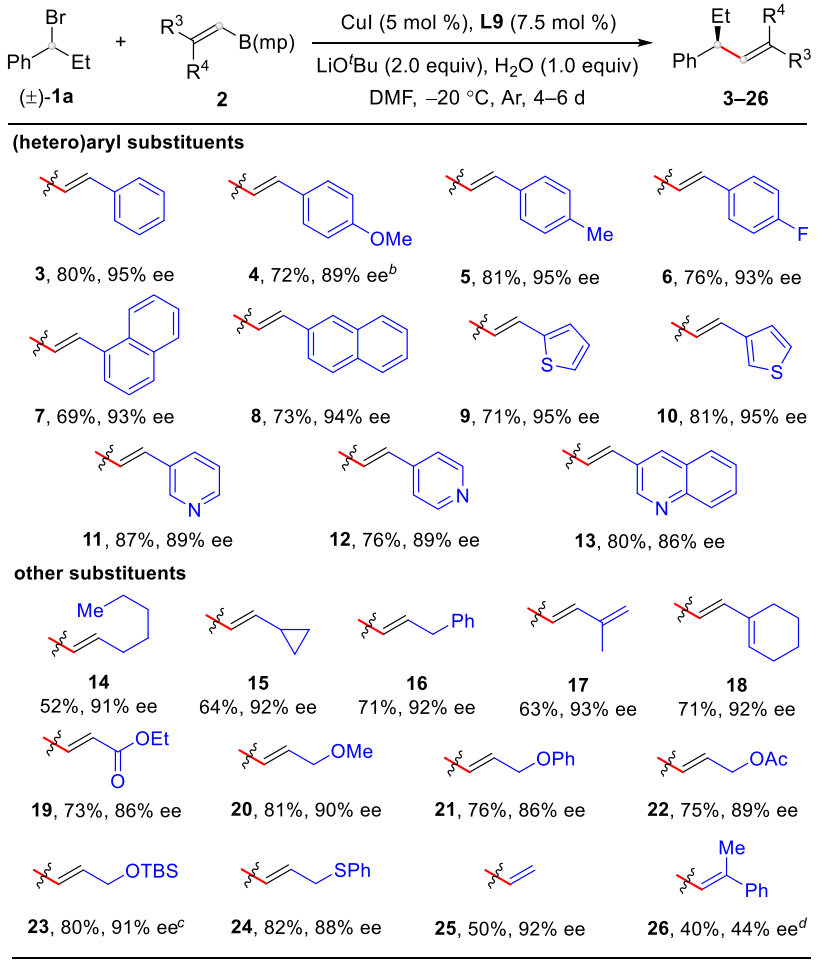
Table 2. Substrate Scope of Alkenylboronate Esters[a,b,c,d]



[a]Reaction conditions: (±)-**1** (0.30 mmol), **2** (0.20 mmol), CuI (5 mol %), **L9** (7.5 mol %), LiO^{t}Bu (2.0 equiv) and H_2O (1.0 equiv) in DMF (2.0 mL) at −20 °C for 4−6 days under argon. [b](±)-(1-bromoethyl)benzene was used. [c]The ee value was obtained by conversion to alcohol. [d]CuI (10 mol %) and **L9** (15 mol %).

27−**37** in 61−93% yields with 88−99% ee (Table 3). Alkyl bromides possessing medicinally relevant heterocycles, such as thiophene (**38**), benzo[*b*]thiophene (**39**), and quinoline (**40**), were also accommodated in the process. With respect to the alkyl side chain of benzyl bromides, simple unfunctionalized aliphatic groups and (hetero)aryl groups were suitable for this reaction to afford chiral alkenes **41**−**46** in good yields with 90−98% ee. A variety of potentially reactive functional groups, such as terminal alkene (**47**), primary chloride (**48**) and bromide (**49**), silyl ether (**50**), ether (**51**), sulfone (**52**) ketone (**53**), ester (**54**), and cyano (**55**), on the side chains of benzyl bromides were tolerated. Notably, a good chemoselectivity was observed for secondary benzyl bromides over primary chloride (**48**) and bromide (**49**). In addition, the cyclic benzyl bromides also reacted well, delivering **56**−**59** with up to 93% ee.

Scope of Propargyl Halides. Chiral 1,4-enynes are another important class of versatile synthons since both the alkenyl and alkynyl groups near the chiral center are readily converted to many functional groups.[20] To further demonstrate the generality of the methods, we studied the coupling of propargyl halides with alkenylboronate esters.[21] Again, we investigated the ligand effect on the reaction of propargyl bromides **1b** and **2a**. The reaction followed the same trend with that of benzyl bromide: while the reaction with the bidentate ligand **L6** afforded the coupling product **60** with a low yield and high ee, the reaction with the tridentate ligand **L8** provided **60** with a higher yield and lower ee; the hemilabile ligand **L9** performed best in both the efficiency and enantioselectivity (Table 4, entries 1−3). These results further supported the concept of ligand design in the cross-coupling. Further lowering the temperature and adding water provided the optimal conditions for the enantioconvergent coupling with propargyl bromides: the reaction of **1b** and **2a** in a molar ratio of 1.25:1.0 in the presence of 5 mol % CuI, 5 mol % **L9**, 1.5 equiv of LiO^{t}Bu, and 3.0 equiv of H_2O in DMF afforded **60** in 86% yield with 97% ee at −30 °C (Table 4, entries 4 and 5).

With regard to the scope, both (hetero)arylated and alkylated alkenylboronate esters are suitable for the reaction to afford **60**−**63** in good yields with excellent ee (Table 5). As for the substituents at the aliphatic chain of propargyl halides, simple unfunctionalized linear and steric hindered propargyl bromides worked well to give **64**−**67** with 96−98% ee. A variety of functional groups, such as phenyl ring (**68** and **69**), furan (**70**), terminal alkene (**71**), internal alkene (**72**), ester (**73** and **77**), nitrile (**74**), acetal (**75**), ether (**76**) as well as primary chloride (**78**), at different distances away from the reactive site were well tolerated, affording the products with

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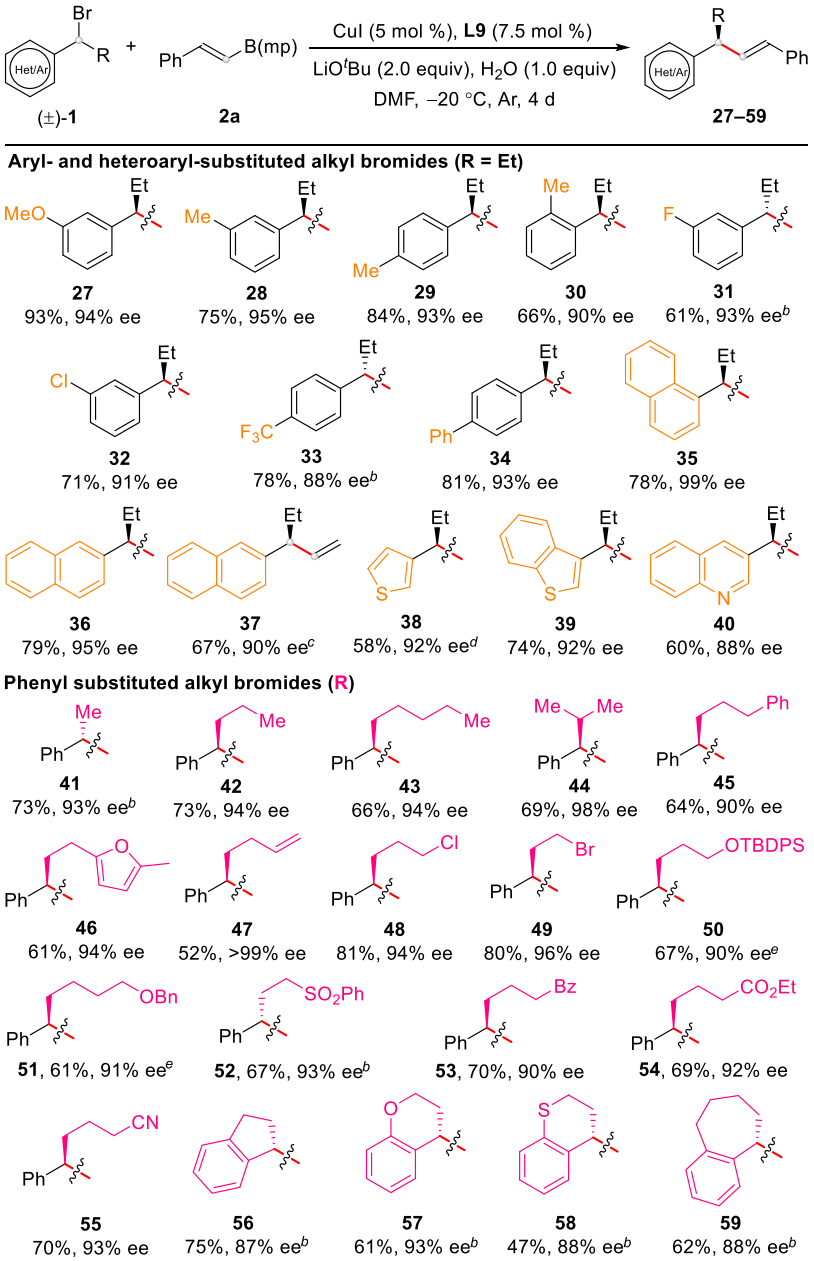
Table 3. Substrate Scope of (Hetero)benzyl Halides[a,b,c,d,e]



[a]Reaction conditions: (±)-**1** (0.30 mmol), **2a** (0.20 mmol), CuI (5 mol %), **L9** (7.5 mol %), LiO^{t}Bu (2.0 equiv), and H_2O (1.0 equiv) in DMF (2.0 mL) at −20 °C for 4 days under argon. [b]**L11** was used. [c]Reaction was performed on a 1.0 mmol scale using vinylboronate ester as the coupling partner. [d]CuI (10 mol %) and **L9** (15 mol %). [e]Ee was obtained by conversion to the alcohol analogues.

good yields and 97−99% ee. More importantly, the propargyl chloride was also a suitable substrate for the cross-coupling to provide **69** in 90% ee, albeit with a moderate yield. Most significantly, the substituents on the alkynyl moiety were diverse, ranging from sterically crowded TIPS (**60**), TES (**79**), TBDMS (**80**), and *t*-butyl (**81**) groups to less sterically hindered cyclohexyl (**82**) and linear *n*-butyl (**83**) groups. In addition, the phenyl-substituted propargyl bromide reacted as well to give **84** with excellent ee. These results demonstrate the broad substrate scope of the current Cu/hemilabile N,N,N-ligand-catalyzed reactions.

Synthetic Utility. To evaluate the practicability of the strategy, we carried out a gram-scale reaction at a low catalyst loading, and the coupling product **3** was obtained without an apparent loss of yield or enantioselectivity (Scheme 2A). To demonstrate the synthetic utility of enantioenriched alkenes, facile transformations were performed to convert them to other enantioenriched building blocks, such as alcohol **85**, carboxylic acid **86**, and ester **87** (Scheme 2B). A sequential cross-coupling and hydrogenation process afforded **88** with a chiral C(sp^3)−C(sp^3) bond, thus providing a complementary strategy to the direct enantioconvergent C(sp^3)−C(sp^3) cross-coupling. To get structurally diverse enantioenriched alkenes, product **69** was hydrated to alkenyl aldehyde **89** and further converted to alcohol **90**. Thus, the strategy affords an alternative approach for the C(sp^3)−C coupling of unfunctionalized alkyl halides. No obvious loss of enantiopurity was observed during all of these transformations. The expedient

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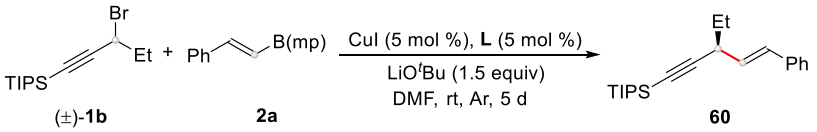
Table 4. Effect of Ligands in the Reaction of Propargyl Halides[a]

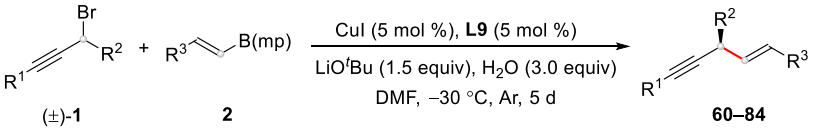


(±)-**1b** **2a** **60**

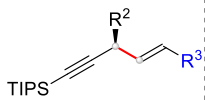
entry	L	conv. of **2a** (%)	y. of **60** (%)	Ee (%)
1	**L6**	>95	22	65
2	**L8**	>95	55	4
3	**L9**	>95	68	87
4[b]	**L9**	60	33	92
5[b,c]	**L9**	**>95**	**86(86)**	**97**

[a]Reaction conditions: (±)-**1b** (0.25 mmol), **2a** (0.20 mmol), CuI (5 mol %), **L** (5 mol %), and LiO^{t}Bu (1.5 equiv) in DMF (1.0 mL) at room temperature for 5 days under argon. Yield (y.) was based on ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard. Ee values were based on chiral (HPLC) analysis. [b]Conducted at −30 °C. [c]H_2O (3.0 equiv) was added. Isolated yield was shown in parenthesis.

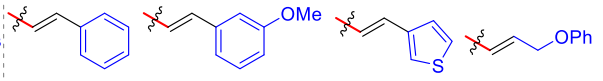
Table 5. Substrate Scope of Propargyl Halides[a,b]



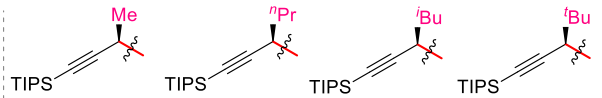
(±)-**1** **2** **60–84**



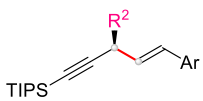
60, **61**, **63** (R^2 = Et)
62 (R^2 = CH_2Bn)



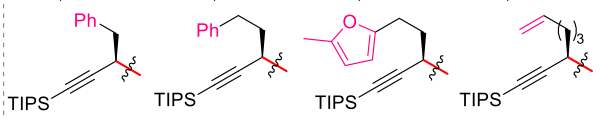
60 86%, 97% ee
61 90%, 99% ee
62 86%, 99% ee
63 82%, 98% ee



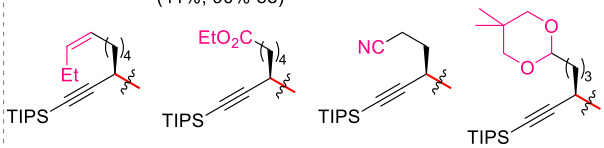
64 53%, 97% ee
65 76%, 96% ee
66 82%, 96% ee
67 72%, 98% ee



64, **66**, **68–78** (Ar = Ph)
65, **67** (Ar = 3-MeOC$_6$H$_4$)

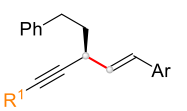


68 88%, 98% ee
69 98%, 98% ee (41%, 90% ee)[b]
70 87%, 98% ee
71 78%, 97% ee

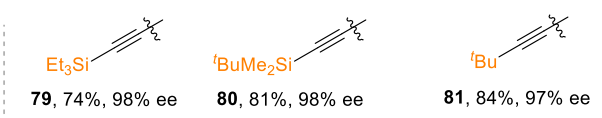


72 89%, 98% ee
73 79%, 98% ee
74 81%, 97% ee
75 92%, 98% ee

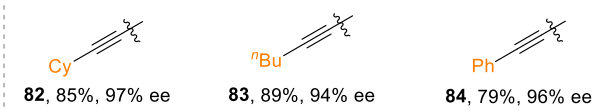
76, 72%, 98% ee
77, 78%, 98% ee
78, 88%, 99% ee



79–81 (Ar = 3-MeOC$_6$H$_4$)
82–84 (Ar = Ph)



79, 74%, 98% ee
80, 81%, 98% ee
81, 84%, 97% ee



82, 85%, 97% ee
83, 89%, 94% ee
84, 79%, 96% ee

[a]Reaction conditions: (±)-**1** (0.25 mmol), **2** (0.20 mmol), CuI (5 mol %), **L9** (5 mol %), LiO^{t}Bu (1.5 equiv), and H_2O (3.0 equiv) in DMF (1.0 mL) at −30 °C for 5 days under argon. [b]The corresponding propargyl chloride (0.25 mmol) was used at 0 °C.

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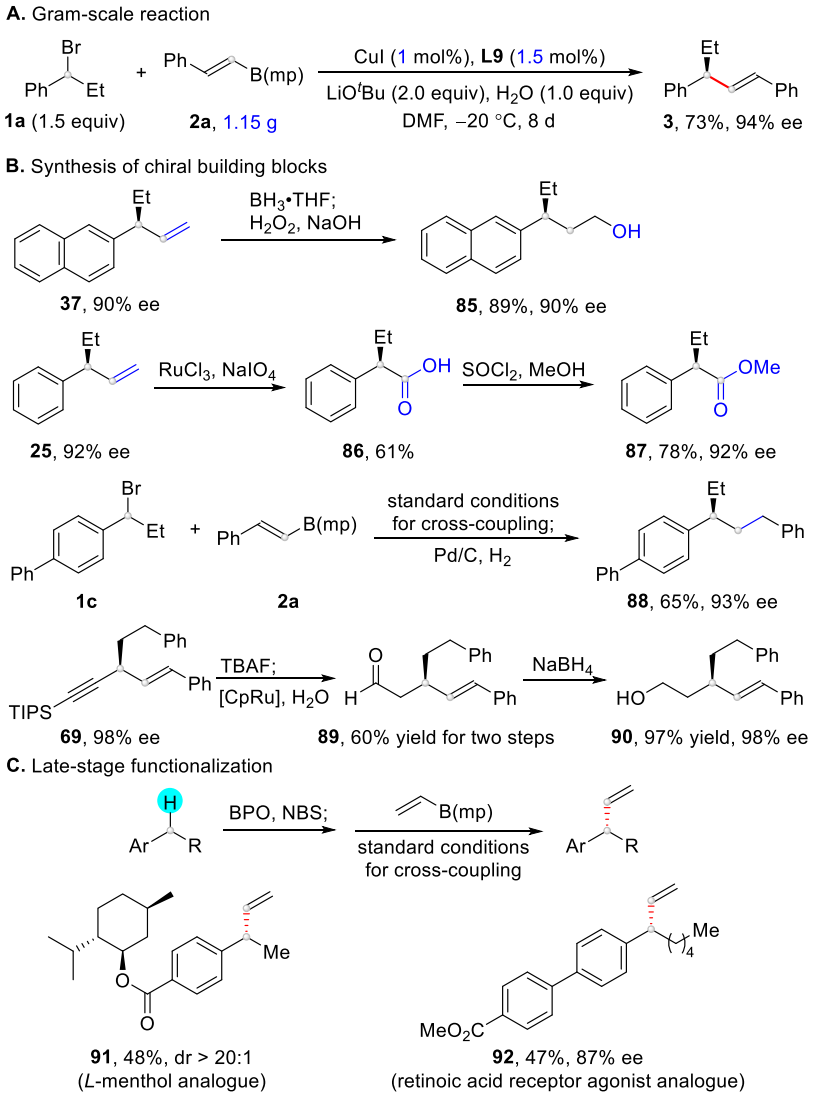
Scheme 2. Synthetic Utility



access to analogues of drug lead is an important goal in drug discovery. As such, a sequential benzylic C−H bromination and enantioconvergent cross-coupling protocol was implemented to showcase the significance of the current method in the late-stage functionalization of bioactive compounds. For example, the substrate containing an *L*-menthol moiety underwent the sequence smoothly to generate **91** in high stereoselectivity (Scheme 2C). A retinoic acid receptor agonist analogue[22] reacted well and delivered **92** with 87% ee. Notably, the combination of the late-stage functionalization and facile transformations of the vinyl moiety would provide more analogues for drug discovery.

Mechanistic Studies. To gain insights into the reaction mechanism, a series of control experiments were conducted. A radical trap experiment with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) revealed that the coupling was completely inhibited and the TEMPO-trapped product **93** was isolated instead, indicating the involvement of a benzyl radical (Scheme 3A). The reaction of an alkene-tethered substrate **94** gave rise to 5-*exo-trig* radical cyclization/cross-coupling product **95**, further supporting the generation of the radical intermediate (Scheme 3B). Although we failed to synthesize the alkenylcopper complex, a control experiment without **2a** showed that no conversion of **1a** was observed (Scheme 3C). Thus, it is the transmetalation of Cu^I with the alkenylboronate ester that possibly occurs first rather than the single-electron transfer[23] between Cu^I and benzyl bromide. The reaction of (±)-**1d** or (*S*)-**1d** with *p*-methoxyphenyl (PMP)-derived alkenylboronate ester **2b** provided the coupling product **4** in a similar yield, and no enantioenrichment or enantioerosion of **1d** was observed (Scheme 3D). This result excluded kinetic resolution or dynamic kinetic resolution via fast racemization of alkyl bromides.

Based on the above-mentioned control experiments and previous reports,[9] we proposed a possible mechanism (Scheme 4A). First, the reaction of Cu^I, chiral ligand, and LiO^{t}Bu afforded a catalytically active copper complex **I**, where the ligand behaved as a tridentate form.[14] Complex **I** underwent transmetallation with alkenylboronate esters **2** to generate the alkenyl Cu^I complex **II**, along with the formation of borate **III**. The protodeboration of **2** can be greatly inhibited by lowering the reaction temperature. Intermediate **II** then reacted with alkyl halides **1** through either an inner- or an outer-sphere single-electron-transfer process,[23] giving rise to π-system-stabilized prochiral alkyl radical **IV** and the alkenyl Cu^{II} complex **V**. The easily occuring homocoupling of complex **V**

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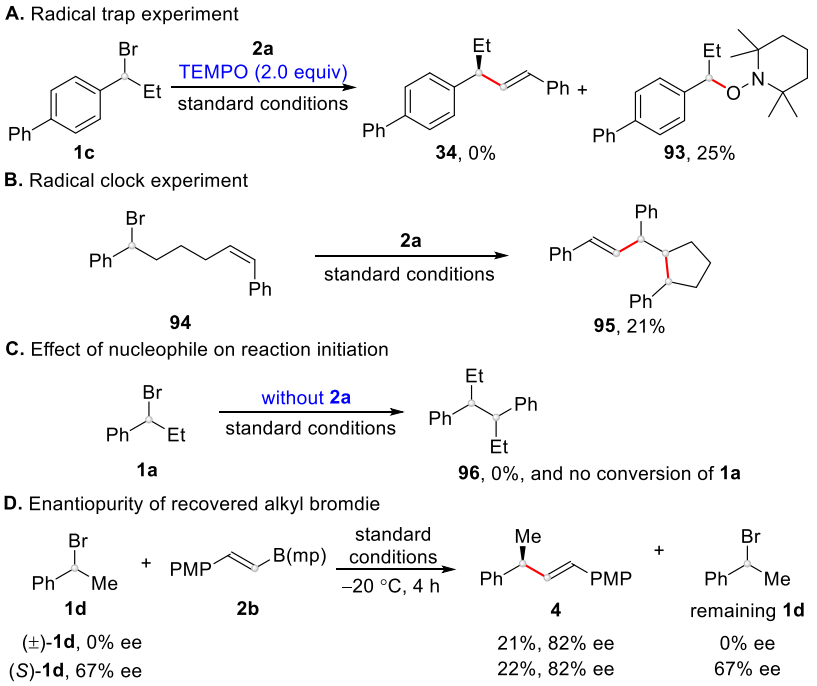
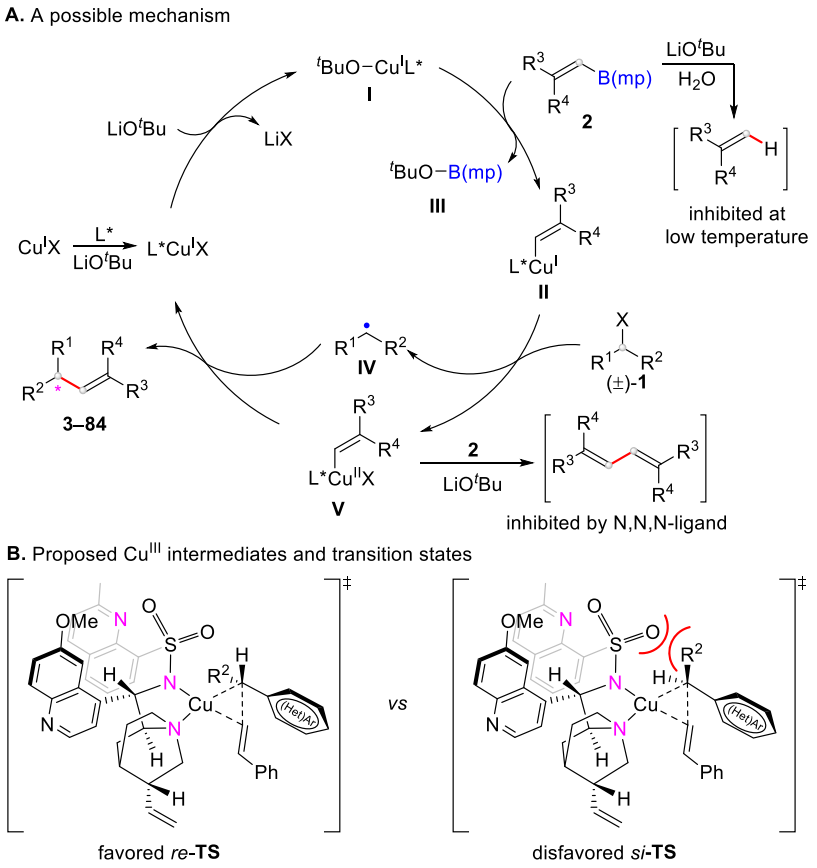
Scheme 3. Mechanistic Investigations



Scheme 4. Mechanistic Proposal



was significantly suppressed via the utilization of the designed hemilabile N,N,N-ligand. Next, radical **IV** reacted efficiently with complex **V** to provide the cross-coupling product and regenerate L*Cu^I for the next catalytic cycle.

With regard to the key bond formation step between **IV** and **V**, we tentatively assume that a Cu^{III} complex is first generated (Scheme 4B).[12b,24] The subsequent reductive elimination would afford the coupling products. As such, the ligand would coordinate with copper in the bidentate form at this

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bond formation step, and two enantiodiscrimination transition states of distorted square planar Cu^{III} complexes were deduced. The steric collision between the alkyl group in the substrate and the sulfonyl group in the ligand makes the *si*-**TS** unfavorable. The favorable *re*-**TS** delivers the desired coupling products of an *S* configuration, which is consistent with the experimental results. However, we do not have enough evidence to support the proposed enantiodiscrimination process and are currently performing more experimental and theoretical studies to disclose the detailed mechanism.

CONCLUSIONS

In summary, we have described a copper/chiral N,N,N-ligand catalytic system for enantioconvergent radical $C(sp^3)-C$ cross-coupling of benzyl/propargyl halides with alkenylboronate esters for expedient synthesis of synthetically valuable enantioenriched alkenes. The installation of steric hindrance at the vicinal position of one coordinating quinoline nitrogen atom led us to strategically design a new class of hemilabile N,N,N-ligands to enhance the reaction efficiency as well as the enantioselectivity. We envision that the concept of ligand design will open up new vistas for enantioconvergent radical cross-coupling reactions. Further efforts to disclose the detailed role of the bulky N,N,N-ligands played on the reaction are currently undergoing in this lab.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c00957.

Experimental procedures; characterization of compounds; investigation of protodeboronation side products; and determination of absolute stereochemistry (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 Key Laboratory of Small Molecule Drug Discovery and Synthesis, Southern University of Science and Technology, Shenzhen 518055, China; 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

Peng-Fei Wang − *Shenzhen Key Laboratory of Small Molecule Drug Discovery and Synthesis, Southern University of Science and Technology, Shenzhen 518055, China; Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, China*

Jiao Yu − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, China*

Kai-Xin Guo − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis and Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China*

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*

Ji-Jun Chen − *Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, China*

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

Ji-Ren Liu − *Department of Chemistry, Zhejiang University, Hangzhou 310027, China*

Xin Hong − *Department of Chemistry, Zhejiang University, Hangzhou 310027, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.2c00957

Author Contributions

[⊥]P.-F.W., J.Y., K.-X.G. contributed equally to this work. This manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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