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Article

Copper-Catalyzed Enantioconvergent Radical Deborylative Coupling of Racemic Benzylboronic Esters with Alkynes and Alkenylboronic Esters

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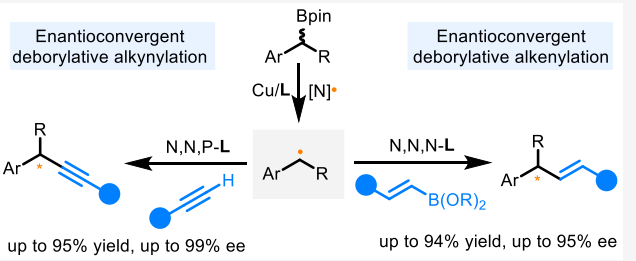
ABSTRACT: Transition metal-catalyzed enantioconvergent deborylative C−C coupling of racemic alkylboronic esters represents a powerful tool to construct chiral C−C bonds given their availability, stability, and functional group tolerance. However, it is challenging, as the classic two-electron transmetalation occurs concertedly with stereoretention, hindering the enantioconvergent deborylative transformations. Herein, we report a radical strategy that enables the copper-catalyzed enantioconvergent deborylative C(sp^3)−C(sp) coupling of benzylboronic esters with alkynes. The success of this strategy relies on two key elements: radical boron abstraction enables the enantioconvergent transformation by generating a prochiral radical; copper/chiral multidentate N,N,P-ligand catalyst promotes the desired pathways, ensuring chemo- and enantioselectivity. The strategy is orthogonal to the halide-based coupling, tolerating electron-rich aromatic rings, proceeding rapidly, and requiring low catalyst loading. We further demonstrate the generality by extending it to an enantioconvergent deborylative C(sp^3)−C(sp^2) coupling with alkenylboronic esters.



INTRODUCTION

Alkylboronic esters are easily accessible and bench-stable building blocks in organic chemistry,[1] capable of undergoing many transformations to form new C−C,[2] C−N,[3] and C−O bonds,[4] *etc.* (Scheme 1A).[5] In asymmetric synthesis, their utility is demonstrated in the enantiospecific homologation,[6] cross-coupling,[7] and other functional group transformations (Scheme 1B).[8] However, these strategies necessitate the use of enantioenriched alkylboronic esters with high optical purity. Compared with the abundant enantiospecific transformations, the enantioconvergent deborylative transformation of racemic alkylboronic esters is more appealing since racemic alkylboronic esters are much easier to obtain. However, the transformation has been less recognized, and this lag may arise from the lack of strategic approaches to achieving enantioconvergence of racemic alkylboronic esters, as the classic C−B bond cleavage typically proceeds via a concerted two-electron process,[8] generally leading to stereoretention (Scheme 1C). Therefore, the development of a general strategy to achieve the enantioconvergent deborylative transformation of racemic alkylboronic esters remains a long-standing goal.

Recent studies demonstrate that alkylboronic esters can undergo smooth radical reactions via photocatalysis, electrocatalysis, or boron-atom abstraction.[2c,9] Accordingly, we envisioned that a radical approach could enable enantioconvergent deborylative transformation of racemic alkylboronic esters, wherein a pair of racemic boronic esters was converted into a prochiral alkyl radical,[10] thereby bypassing the stereoretentive limitation of the two-electron process. Pioneering work by Molander, Reisman, and others has established nickel/bisoxazoline (Box)-catalyzed enantioconvergent arylation/carbonylation of racemic benzyltrifluoroborates (Scheme 1D).[11] More recently, Dong elegantly demonstrated copper/Box-catalyzed highly enantioconvergent cyanation and amination of racemic benzylboronic esters (Scheme 1D).[12] Given the significance of the enantioconvergent deborylative coupling, the development of coupling with more readily available reagents is highly desirable for advancing asymmetric synthesis.

As part of our ongoing efforts to develop copper-catalyzed asymmetric radical reactions,[13] we have achieved the enantioconvergent C−C cross-coupling of racemic benzyl halides with alkynes and alkenylboronic esters.[14] However, the approach cannot generate enantioenriched benzyl alkynes and alkenes bearing electron-rich aromatic rings due to the

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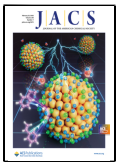


Scheme 1. Enantioconvergent Deborylative Coupling

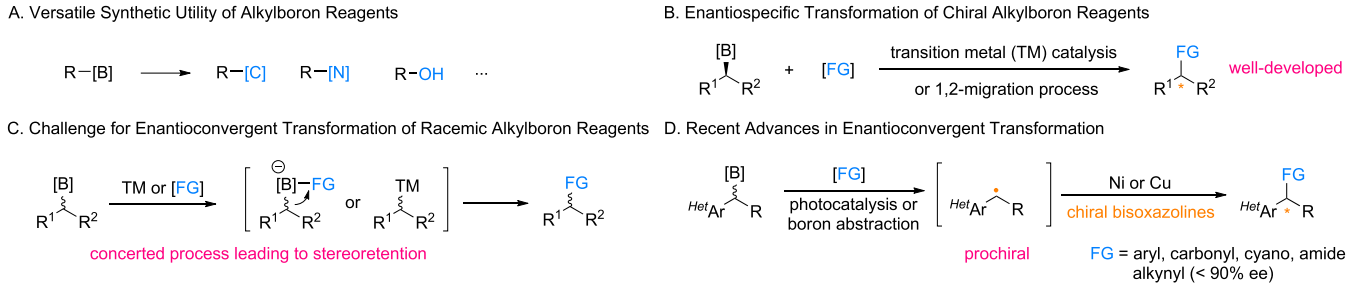
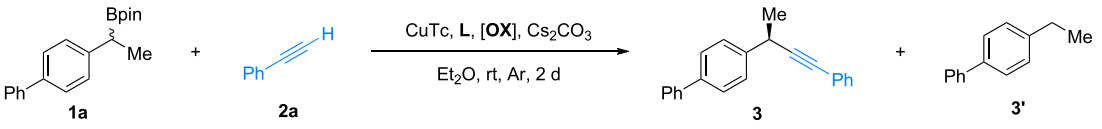
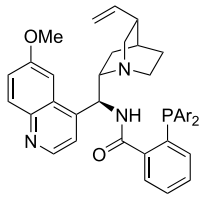
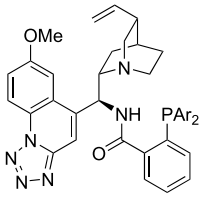


Table 1. Screening of Reaction Conditions[a]

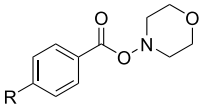




L1, Ar = Ph
L2, Ar = 4-^{t}BuC$_6$H$_4$
L3, Ar = 3,5-^{t}Bu$_2$C$_6$H$_3$
L4, Ar = 3,5-^{i}Pr$_2$C$_6$H$_3$
L5, Ar = 2-^{i}PrC$_6$H$_4$



L6, Ar = 2-^{i}PrC$_6$H$_4$



OX1, R = H
OX2, R = OMe
OX3, R = CF$_3$

Entry	L	OX	Conv. (%)	Yield of 3 (%)	ee of 3 (%)	Yield of 3′ (%)
1	L1	OX1	55	15	70	31
2	L2	OX1	57	13	72	35
3	L3	OX1	60	45	93	10
4	L4	OX1	65	25	86	30
5	L5	OX1	67	48	98	11
6	L6	OX1	95	84	98	8
7	L6	OX2	>95	90	98	<5
8	L6	OX3	73	65	98	6
9[b]	L6	OX2	>95	>95	98	<5
10[c]	L6	OX2	>95	>95	98	<5
11[cd]	L6	OX2	>95	>95	98	<5
12[ce]	L6	OX2	**>95**	**>95**	**97**	< **5**
13[f]	L6	OX2	>95	80	98	13

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.06 mmol), **OX** (0.06 mmol), CuTc (10 mol %), **L** (15 mol %), and Cs_2CO_3 (3.0 equiv) in Et_2O (1.0 mL) at rt for 2 d under argon; yield of **3** is based on ^{1}H NMR analysis of the crude product using 1,3,5-trimethylbenzene as an internal standard; ee values were based on chiral HPLC analysis. [b]$PhCF_3$ was used. [c]CuTc (5.0 mol %) and **L** (7.5 mol %) in $PhCF_3$. [d]Conducted at 40 °C for 12 h. [e]Conducted at 60 °C for 4 h. [f]CuTc (1.0 mol %) and **L** (1.5 mol %) in $PhCF_3$ conducted at 40 °C for 3 d.

instability of the halide substrates. We envisioned that an enantioconvergent deborylative coupling of bench-stable racemic benzylboronic esters could access diverse enantioenriched benzyl alkynes and alkenes, particularly those incorporating electron-rich aromatic rings, thus providing a complementary platform to the halide-coupling strategy.[14] Several challenges may impede its success: (i) benzylboronic esters are less stable toward the basic conditions required for nucleophilic transmetalation,[15] often resulting in protodeboronation as a competing pathway; (ii) racemic benzylboronic

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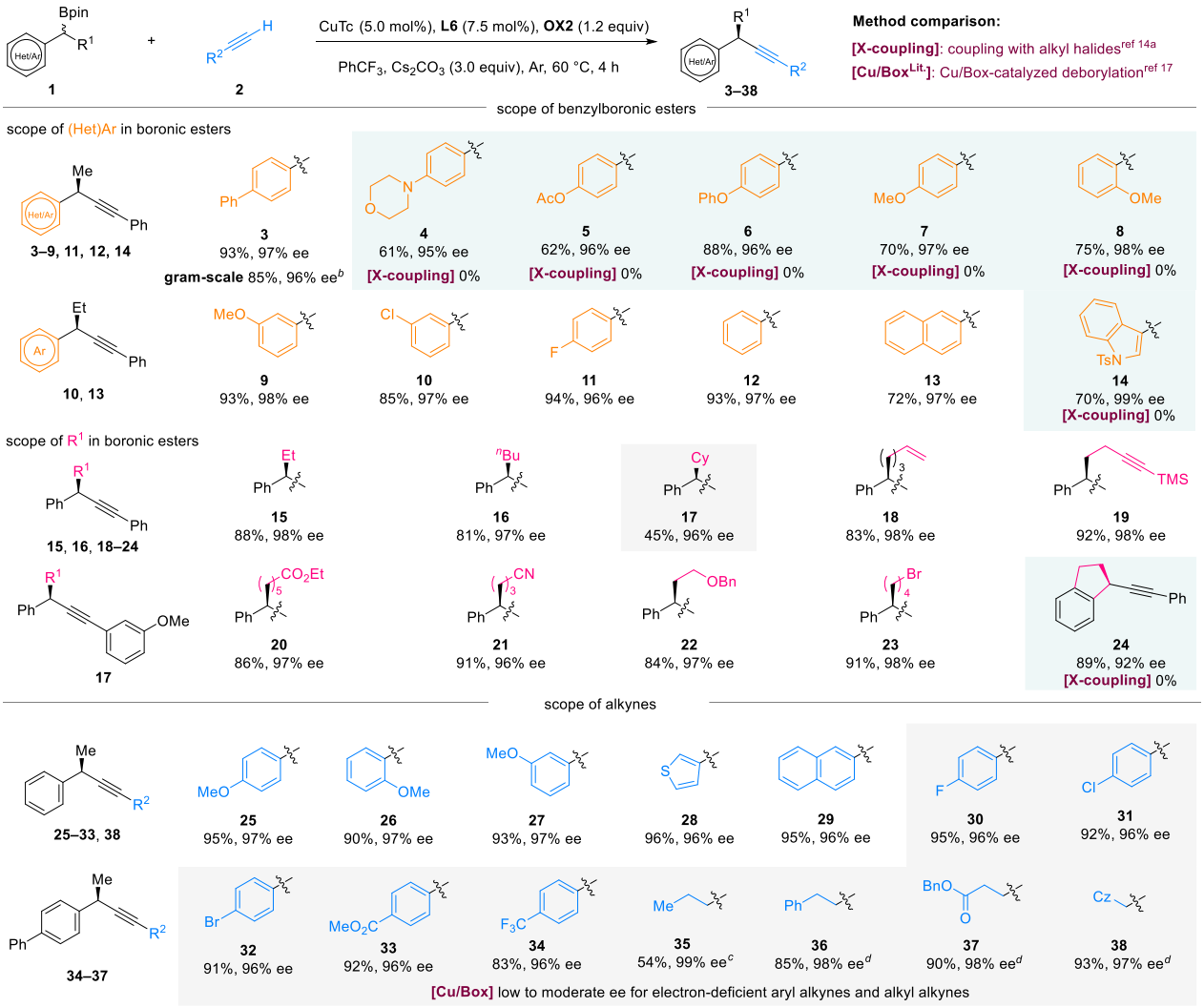
Table 2. Scope of Deborylative Coupling with Alkynes[a]



[a]Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), CuTc (5.0 mol %), **L6** (7.5 mol %), **OX2** (1.2 equiv), and Cs_2CO_3 (3.0 equiv) in $PhCF_3$ (4.0 mL), 60 °C, 4 h. Yields were isolated ones; ee values were determined by HPLC. [b]Gram-scale synthesis with CuTc (1.0 mol %) and **L6** (1.5 mol %) at 40 °C. [c]CuTc (10 mol %), **L6** (15 mol %), rt, 3 d. [d]CuTc (10 mol %), **L6** (15 mol %), 40 °C, 12 h. Cz, 9-carbazolyl.

esters may undergo concerted two-electron transmetalation under strongly basic conditions, potentially leading to undesired racemic background reactions.[16] Addressing these challenges requires the development of efficient boron-abstraction reagents and chiral catalysts to accelerate the desired enantioconvergent pathway. Herein, we report a general paradigm for the enantioconvergent deborylative $C(sp^3)-C(sp)$ coupling of racemic benzylboronic esters with alkynes. The key to success lies in the synergistic combination of hydroxylamine derivatives as boron-abstraction reagents with chiral N,N,P-ligand/copper catalysts, which together accelerate the desired process, achieving high chemo- and enantioselectivity. During this course, Dong concurrently reported a copper/Box ligand-catalyzed deborylative alkynylation, which was limited to aryl alkynes with electron-rich/neutral substituents and achieved unsatisfactory enantioselectivity (~80% ee on average).[17] In contrast, our strategy accommodates both aryl alkynes with diverse electronic properties and alkyl alkynes, delivering excellent enantioselectivity (~95% ee on average). The deborylative coupling process is also orthogonal to our previous halide-based coupling[14a] in several key aspects: (i) it tolerates electron-rich aromatic rings; (ii) it proceeds rapidly, often within a few hours; and (iii) it operates efficiently with a low catalyst loading of 1.0 mol % without compromising enantioselectivity. The generality of our method is further underscored by its application to an enantioconvergent deborylative $C(sp^3)-C(sp^2)$ coupling of benzylboronic esters with alkenylboronic esters, a transformation that has not previously been disclosed in the literature.

RESULTS AND DISCUSSION

Reaction Development

At the outset, we investigated the reaction of benzylboronic ester **1a** with alkyne **2a** in the presence of CuTc, morpholino benzoate **OX1**,[9e] and Cs_2CO_3 in anhydrous Et_2O. The quinine-derived N,N,P-ligand[14a,18] **L1** furnished the desired product **3** only in 15% yield with 70% ee after 2 d at room temperature (rt), along with the formation of the proto-deboronation product **3′** in 31% yield (Table 1, entry 1). A control experiment revealed that **1a** could undergo partial

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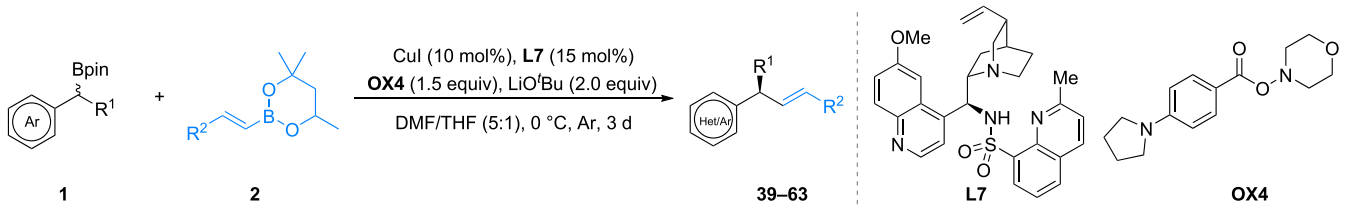
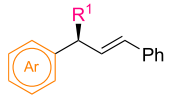
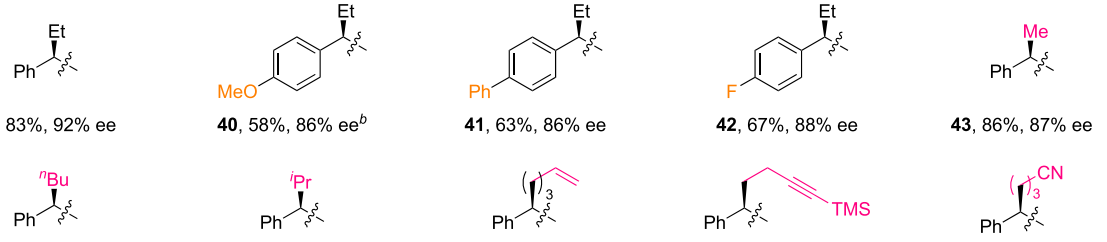
Table 3. Deborylative Coupling with Alkenylboronic Esters and Scope[a]



scope of benzylboronic esters



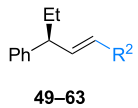
39–48



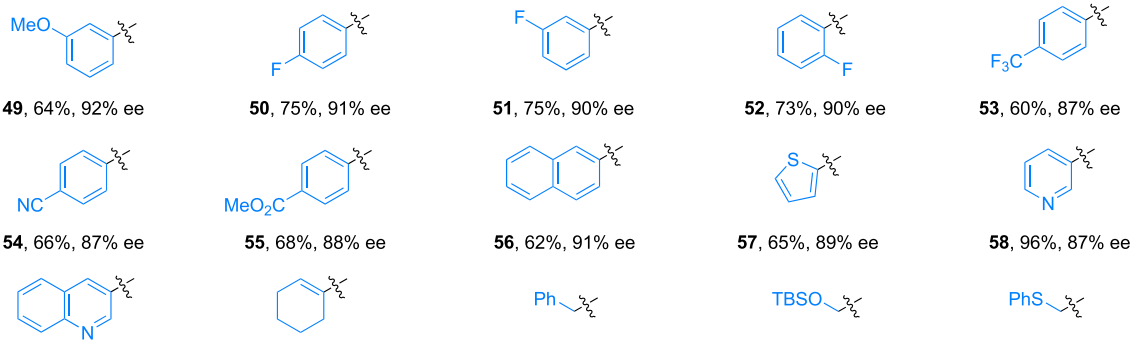
39, 83%, 92% ee; **40**, 58%, 86% ee[b]; **41**, 63%, 86% ee; **42**, 67%, 88% ee; **43**, 86%, 87% ee

44, 80%, 91% ee; **45**, 60%, 95% ee; **46**, 94%, 89% ee; **47**, 54%, 91% ee[c]; **48**, 84%, 90% ee

scope of alkenylboronic esters



49–63



49, 64%, 92% ee; **50**, 75%, 91% ee; **51**, 75%, 90% ee; **52**, 73%, 90% ee; **53**, 60%, 87% ee

54, 66%, 87% ee; **55**, 68%, 88% ee; **56**, 62%, 91% ee; **57**, 65%, 89% ee; **58**, 96%, 87% ee

59, 79%, 85% ee; **60**, 63%, 87% ee; **61**, 65%, 89% ee; **62**, 60%, 90% ee[c]; **63**, 94%, 87% ee

[a]Reaction conditions: **1** (0.30 mmol), **2** (0.20 mmol), CuI (10 mol %), **L7** (15 mol %), **OX4** (1.5 equiv), and LiOtBu (2.0 equiv) in DMF/THF (2 mL, 5:1), 0 °C, 3 d. Yields were isolated ones; ee values were determined by HPLC. [b]CuI (20 mol %), **L7** (30 mol %). [c]The ee was determined after desilylation.

conversion to **3′** (50%) in the presence of Cs_2CO_3 alone (Scheme S1 in the Supporting Information). These results suggested that the coupling process must be fast enough to compete with the protodeboronation process. Our previous study showed that the steric bulkiness of *P*-substituents of the ligand could affect the reaction efficiency and enantioselectivity.[14a] As such, we screened N,N,P-ligands **L2**−**L5** with bulky groups at different positions of the *P*-aryl ring (Table 1, entries 2−5). To our delight, increasing steric effect at the *meta*- and *ortho*-positions of the *P*-aryl ring could not only accelerate the desired pathway but also enhance the enantioselectivity, with ligand **L5** providing **3** with 48% yield and 98% ee (Table 1, entry 5). To suppress the possible *N*-coordination, the quinoline moiety of ligand **L5** was replaced with a tetrazole unit to afford ligand **L6**,[13a,19] which led to a remarkable improvement in the conversion of **1a** and the yield of **3** without any loss of ee (Table 1, entry 6). The subsequent evaluation of boron-abstraction reagents revealed that the electron-donating benzoate derivative **OX2** afforded product **3** in higher yield (90%), whereas the electron-deficient analogue **OX3** gave a slightly lower yield (65%) (Table 1, entries 7 and 8). Nevertheless, both reagents provided the same ee as **OX1**. Variation of copper salts did not lead to improved results, while solvent screening revealed that the yield could be slightly enhanced to 95% in $PhCF_3$ (Table 1, entry 9 and Tables S1 and S2 in the Supporting Information). Notably, reducing the catalyst loading to 5.0 mol % had no adverse effect (Table 1, entry 10). Encouragingly, raising the temperature dramatically accelerated the reaction and shortened the reaction time, achieving completion in 12 h at 40 °C and just 4 h at 60 °C (Table 1, entries 11 and 12; and Table S3 of Supporting Information). Consequently, the optimal conditions were established as follows: the reaction of **1a** and **2a** in the presence of CuTc (5.0 mol %), **L6** (7.5 mol %), **OX2** (1.2 equiv), and Cs_2CO_3 (3.0 equiv) in $PhCF_3$ proceeded at 60 °C for 4 h to afford **3** with 95% yield and 97% ee (Table 1, entry 12). Interestingly, an even lower catalyst loading (1.0 mol %) could be employed at 40 °C, resulting in the formation of **3** in good yield without any loss in ee at elongated reaction time (Table 1, entry 13). Under the optimal conditions, quinine-derived N,N-ligands failed to produce **3** and instead afforded the side product **3′**, highlighting the essential role of the tridentate N,N,P-ligand in this transformation (Table S4 in the Supporting Information).

Scope of Deborylative Coupling with Alkynes

With the optimal conditions established, we examined the scope of benzylboronic esters (Table 2). A gram-scale reaction

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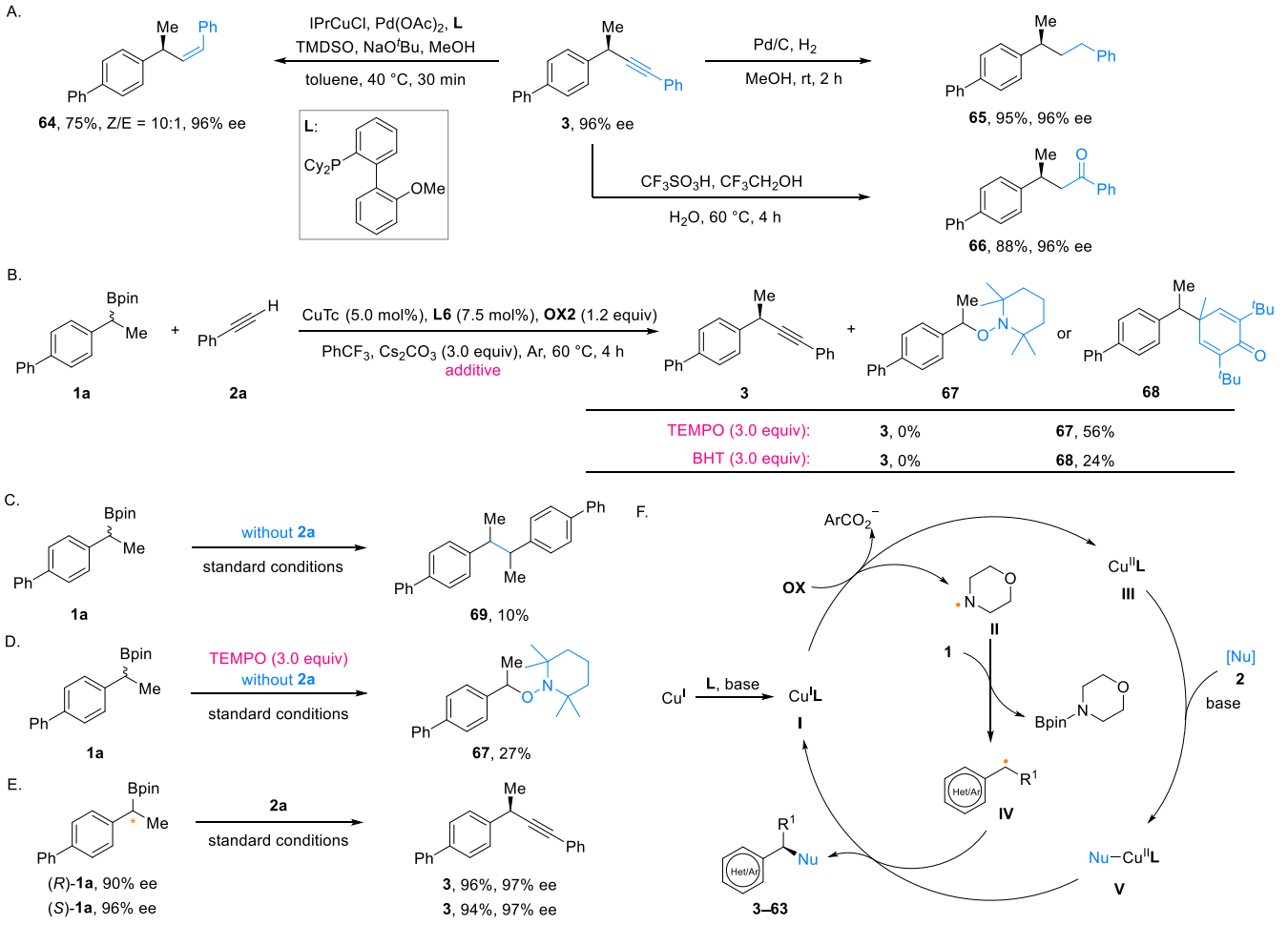
Scheme 2. Synthetic Utility and Mechanistic Investigation



with only 1.0 mol % catalyst afforded product **3** without apparent loss in ee. Benzylboronic esters with electron-donating groups, such as morpholine (**4**), AcO (**5**), PhO (**6**), and MeO (**7**, **8**) on the *para* and *ortho* positions of the aryl ring, as well as an indole-derived benzylboronic ester (**14**), delivered the desired products with good yields and excellent ee (95−99%). In comparison, these products cannot be generated via our previously reported halide-coupling strategy.[14a] Substrates bearing other aryl rings and a naphthyl ring underwent the reaction smoothly as well to afford **9**−**13** with 72−94% yield and 96−98% ee. The investigation of the alkyl chain of benzylboronic esters showed good tolerance of functionalities and moderate tolerance of steric hindrance. For example, linear alkyl group (**15**, **16**), alkenyl (**18**), alkynyl (**19**), ester (**20**), cyano (**21**), ether (**22**), and halide (**23**) are all compatible with the reaction conditions, resulting in the desired products with >80% yield and 96−98% ee. Benzylboronic ester with a bulky cyclohexyl group gave the desired product **17** with excellent ee but in moderate yield. Cyclic benzyl bromides are also unstable, and thus the halide-coupling failed to afford **24**, whereas the deborylative alkynylation successfully generated **24** in 89% yield with 92% ee. Investigation of the scope of alkynes demonstrated that electron-rich, neutral, and -deficient aryl alkynes all worked well to afford the desired products **25**−**34** with excellent yield and ee. Moreover, alkyl alkynes with different functionalities, such as aliphatic chain (**35**), phenyl (**36**), ester (**37**), and carbazolyl (**38**), proceeded smoothly to furnish the desired products with excellent ee. Notably, according to Dong's report, steric bulky benzylboronic ester, electron-deficient aryl alkynes, and alkyl alkynes cannot be tolerated with their catalyst,[17] while our catalyst is suitable for these substrates (**17**, **30**−**38**).

Scope of Deborylative Coupling with Alkenylboronic Esters

To further validate the reaction generality, we next explored more nucleophiles. Notably, the enantioconvergent deborylative alkenylation has not been previously disclosed. Given the importance of chiral alkenes as valuable synthons in organic synthesis, we employed bench-stable alkenylboronic esters as coupling partners to synthesize chiral alkenes. Based on our experience in the halide-coupling strategy, we found that the reaction of benzylboronic ester **1b** and alkenylboronic ester **2b** in the presence of CuI, N,N,N-ligand **L7**,[14b] **OX1**, and LiOtBu afforded the desired chiral alkene **39** with 85% yield and 88% ee in DMF at 0 °C after 3 d (see Table S5 in the Supporting Information). After further screening of oxidant and solvent, we identified the optimal conditions as follows: the reaction of **1b** and **2b** in the presence of CuI (10 mol %), **L7** (15 mol %), **OX4** (1.5 equiv), and LiOtBu (2.0 equiv) in a mixed solvent of DMF/THF (5:1) afforded **39** with 83% isolated yield and 92% ee at 0 °C after 3 d (Table S5). Control experiment showed that quinine-derived N,N-ligands only

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afforded a trace amount of the desired product with moderate ee (Table S5). Evaluation of the substrate scope showed that a variety of benzylboronic esters underwent the reaction smoothly to generate the desired products **39**−**48** with good yields and 86−95% ee. In particular, chiral benzyl alkene with an electron-rich aryl ring (**40**) was successfully formed, which is inaccessible in our previously reported halide-coupling strategy.[14b] Notably, no 5-*exo*-*trig* cyclized product was observed in the reaction to afford **46**. A wide array of alkenylboronic esters, including arylated and alkylated ones, are also suitable for the reaction, leading to the formation of chiral alkenes **49**−**63** with good yield and ee. The absolute configurations of **21** and **61** are determined by comparing their HPLC spectra with those reported in literature (see the Supporting Information),[14] and other products in Tables 2 and 3 were assigned by analogy thereafter.

Synthetic Utility

To demonstrate the synthetic utility, we performed further transformations of the synthesized alkynes (Scheme 2A). We could easily convert the alkynyl moiety in alkyne **3** to a *Z*-alkenyl group in **64** in a reduction step. Furthermore, the complete hydrogenation of alkyne **3** afforded **65** bearing an alkyl group. Thus, the combination of the current deborylative strategy with the following manipulations could provide a complementary approach for the coupling with *Z*-alkenyl and alkyl nucleophiles. In addition, the hydration of alkyne **3** efficiently furnished chiral ketone **66**. Notably, no loss of ee was observed during all transformations.

Mechanistic Studies

Preliminary mechanistic investigations using radical scavengers were conducted. The model reaction was significantly inhibited by 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) or (butylated hydroxytoluene) BHT, leading to the isolation of the trapped adducts **67** and **68** instead of the desired product **3**. These observations clearly indicated the participation of a benzylic radical intermediate (Scheme 2B). Furthermore, a control experiment showed that **69** could be generated in the absence of alkyne **2a**, and its formation was suppressed by TEMPO. This indicated that the benzyl radical generation is independent of transmetalation (Scheme 2C and D). Replacing the racemic **1a** with the enantiopure (*R*)-**1a** or (*S*)-**1a** provided the same enantiomer **3** with similar yield and ee, which implies the stereochemical information at the benzylic center of the boronic ester is lost during the reaction (Scheme 2E). Based on these control experiments and previous reports,[12,14,17] we proposed a plausible mechanism as depicted in Scheme 2F. First, the Cu^{I} salt coordinates with ligand **L** in the presence of a base to afford the Cu^{I}**L** complex **I**. Complex **I** then undergoes a single-electron transfer process with oxidant **OX**, furnishing an amino radical **II** and a Cu^{II}**L** complex **III**. The amino radical **II** subsequently abstracts a Bpin group from a pair of racemic benzylboronic esters **1**, forming a prochiral benzyl radical intermediate **IV**. Meanwhile, the in situ generated Cu^{II} complex **III** undergoes transmetalation with the alkyne or alkenylboronic ester **2**, yielding the nucleophile-sequestered Cu^{II} complex **V**. Finally, radical coupling between intermediates **IV** and **V** furnishes the desired products **3**−**63** while regenerating complex **I** for the next catalytic cycle. Based on our previous reports,[14,20] the enantiodetermining step likely involves the formation of the Cu(III) intermediate and its subsequent reductive elimination.

CONCLUSIONS

In summary, we have developed a copper-catalyzed enantioconvergent deborylative $C(sp^3)-C(sp)$ coupling of racemic benzylboronic esters with alkynes. The success of this reaction arises from two key design elements: radical-mediated boron abstraction, which smoothly converts racemic benzylboronic esters into prochiral benzyl radicals to achieve enantioconvergence; chiral anionic N,N,P-ligand/copper catalyst, which ensures high yields and enantioselectivities. This approach tolerates electron-rich aromatic rings, proceeds rapidly, and operates under low catalyst loading, thus constituting an orthogonal method to existing benzyl halide-based coupling. As further proof of this concept, it has been extended to the enantioconvergent deborylative $C(sp^3)-C(sp^2)$ coupling of racemic benzylboronic esters with alkenylboronic esters. We anticipate that this strategy could be extended to other alkylboronic esters and coupling partners, further expanding the scope of enantioconvergent deborylative coupling.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c21668.

Experimental procedures, characterization of compounds, Tables S1−S5, Schemes S1 (PDF)

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Notes

The authors declare no competing financial interest.

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