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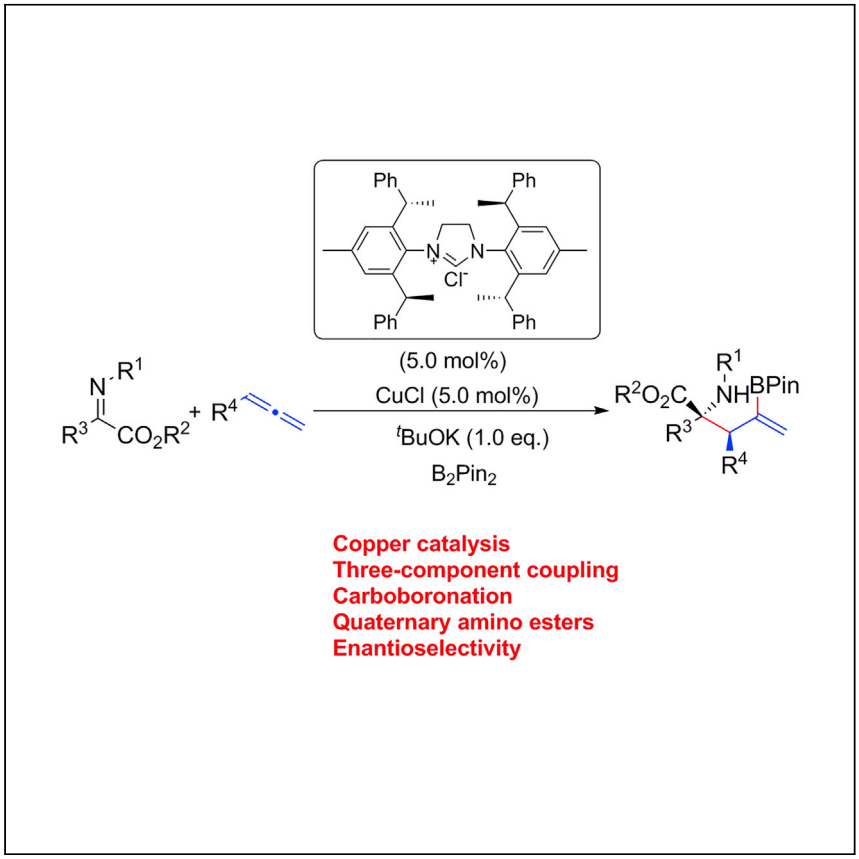
Copper-Catalyzed Asymmetric Carboboronation of Allenes to Access α-Quaternary Amino Esters with Adjacent Stereocenters



Chiral α-quaternary amino acids play an important role in the synthesis of unnatural peptides and proteins with specific biological activities. Here, Zhao et al. develop a copper-catalyzed diastereo- and enantioselective three-component coupling of allenes, boronate, and ketiminoesters to access chiral quaternary amino esters with adjacent stereocenters.

Chao-Yang Zhao, Hao Zheng, Ding-Wei Ji, Xiang-Ting Min, Yan-Cheng Hu, Qing-An Chen

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HIGHLIGHTS

Access α-quaternary amino esters with adjacent stereocenters

Contain boron group for easy derivatization

DFT calculations to elucidate the control of the diastereo- and enantioselectivity

Twenty-eight examples with yields up to 96%, er up to 98:2 and dr up to >20:1

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Copper-Catalyzed Asymmetric Carboboronation of Allenes to Access α-Quaternary Amino Esters with Adjacent Stereocenters

Chao-Yang Zhao,[1,2,3] Hao Zheng,[1,2,3] Ding-Wei Ji,[1,2] Xiang-Ting Min,[1,2] Yan-Cheng Hu,[1] and Qing-An Chen[1,4,*]

SUMMARY

Optically active α-quaternary amino acids have received much attention because of the important biomedical applications implicated for compounds containing this structure. Additionally, asymmetric synthesis of highly functionalized chiral α-quaternary amino esters with vicinal stereocenters by a single catalyst is still a great challenge due to the difficulty in stereocontrol of the configurations. Here, we develop a copper-catalyzed highly diastereo- and enantioselective three-component coupling of allenes, diboron, and ketiminoesters to access chiral quaternary amino esters with adjacent stereocenters. The stereochemical control is enabled by using bulky C_2-symmetric N-heterocyclic carbene (NHC) as a chiral ligand. This protocol also features mild reaction conditions, wide substrate scope, and may subsequently have diverse applications in organic synthesis.

INTRODUCTION

Given that the quaternary stereocenter[1–7] can hamper racemization and inhibit conformational flexibility, optically active α-quaternary amino acids (AAs)[8–12] play a pivotal role in the synthesis of unnatural peptides and proteins with specific biological activities.[13,14] Notably, α-quaternary AAs bearing adjacent stereocenters are prevalent in various bioactive natural products, such as sphingofungins E and F,[15] altemicidin,[16,17] and lactacystin.[18,19] Recently, Huo *et al.*[20,21] and Wei et al. [22–24] independently developed facile access to chiral amino esters with contiguous stereocenters through dual iridium (Ir)/copper (Cu) or palladium (Pd)/copper-catalyzed two-component allylation of aldimine esters (Scheme 1A).[25] In these cases, the high stereoselective outcome resulted from a synergistic effect of bimetallic catalysis on controlling both the conformations of electrophiles and nucleophiles. Therefore, asymmetric synthesis of highly functionalized chiral α-quaternary amino esters with vicinal stereocenters by a single catalyst is still a great challenge due to the difficulty in stereocontrol of the configurations.

Catalytic asymmetric multicomponent reactions, featuring rapid formation of multiple new bonds in one step, have received much attention over the past decades.[26–32] For example, copper-catalyzed carboboronation[33,34] of allenes has been demonstrated as a powerful tool to generate novel borylative compounds.[35–58] Recently, Yeung *et al.*[59] have reported a copper-catalyzed borylative allylation of ketiminoesters with allenes and bis(pinacolato)diboron, accessing the desired products with 2:1 to 13:1 *dr* (Scheme 1B). On the basis of these precedents, we sought to develop an asymmetric three-component carboboronation of allenes

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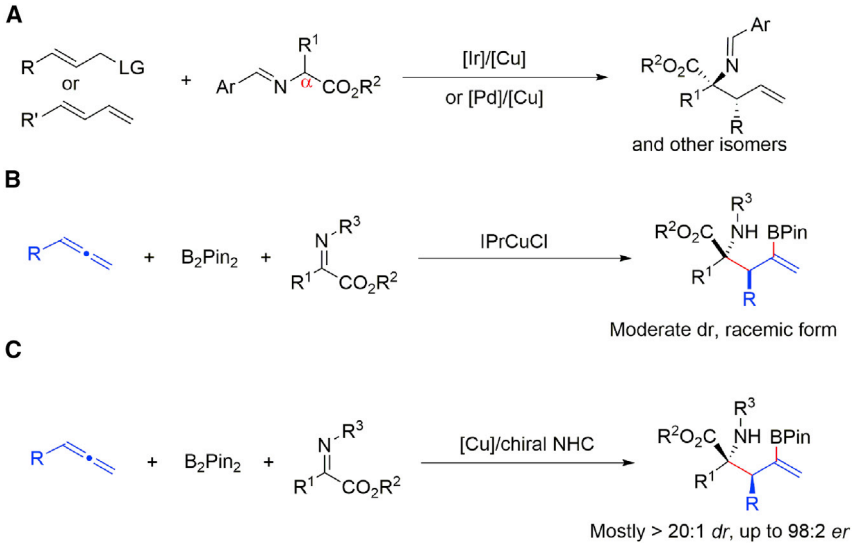

Scheme 1. Access Chiral α-Quaternary Amino Esters with Vicinal Stereocenters

(A) Previous works: two-component allylic substitution via bimetallic catalysis.

(B) Procter's work: copper-catalyzed nonasymmetric carboboronation of allenes.

(C) This work: highly enantioselective carboboronation by a single copper catalysis.

to access chiral α-quaternary amino esters with adjacent stereocenters (Scheme 1C). The major challenge of this proposal is the rigorous requirement in simultaneous control of the chemo-, regio-, diastereo-, and enantioselectivity with a single copper catalyst. To the end, this work shows a Cu-catalyzed highly diastereo- and enantioselective three-component coupling of allenes, diboron, and ketiminoesters to access chiral quaternary amino esters with mild reaction conditions, wide substrate scope, and diverse applications in organic synthesis.

RESULTS AND DISCUSSION

Optimization

Initially, we chose ketiminoester (1a), phenylallene (2a), and $B_2(Pin)_2$ as the model substrates for the copper-catalyzed three-component process. A combination of CuCl and chiral phosphine ligands such as (*R*)-BINAP and (*R*)-Segphos could indeed catalyze the transformation but delivered the desired amino ester 3aa in low diastereomer ratio (*dr*) and enatiomeric ratio (*er*) (Table 1, entries 1 and 2). Varying to chiral N-heterocyclic carbene (NHC) ligands L1–L4 did not give superior results (entries 3–6). To our delight, when using sterically hindered C_2-symmetric NHC ligand L5,[60–67] diastereo- and enantio- selectivity of 3aa were dramatically increased to >20:1 and 96:4, respectively (entry 7). The use of toluene as a solvent resulted in slightly decreased selectivities, whereas 1,2-dichloroethane (DCE) and acetonitrile (MeCN) exerted a significantly detrimental effect on the reactivities and selectivities (entries 8–10). An evaluation of various bases revealed that ^{t}BuOK was the optimal base (entries 11–13). Gratifyingly, the saturated chiral NHC ligand L6 could further increase the yield to 96% with >20:1 *dr* and 95:5 *er* (entry 14).

Substrate Scope

With the optimized conditions in hand, we subsequently examined the substituent effect by varying protecting groups on nitrogen or oxygen atoms (see Supplemental Experimental Procedures). As demonstrated in Figures 1, S4–S20, and S70–S85, a set of halides, including -F, -Cl, and -Br on the phenyl ring of R^1 were all well

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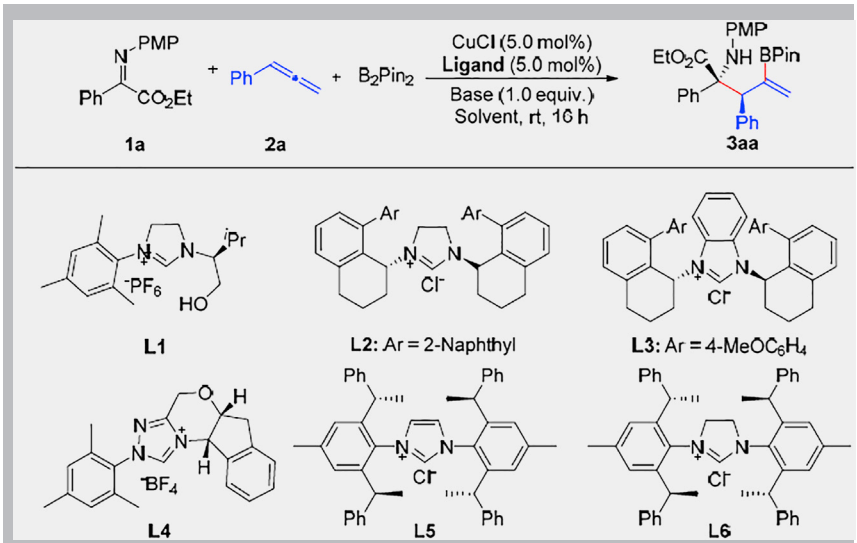
Table 1. Optimization for Copper-Catalyzed Three-Component coupling[a]



Entry	L	Base	Solution	Yield (%)[a]	*Dr*[b]	*Er* (%)[c]
1	(*R*)-BINAP	^{t}BuOK	THF	27	1:1	64:36
2	(*R*)-Segphos	^{t}BuOK	THF	37	1:1	61:39
3	L1	^{t}BuOK	THF	49	4:1	54:46
4	L2	^{t}BuOK	THF	72	5:1	65:35
5	L3	^{t}BuOK	THF	58	7:1	58:42
6	L4	^{t}BuOK	THF	32	3:1	43:57
7	L5	^{t}BuOK	THF	78	>20:1	96:4
8	L5	^{t}BuOK	Tol	80	19:1	95: 5
9	L5	^{t}BuOK	DCE	<5	—	57:43
10	L5	^{t}BuOK	MeCN	37	6:1	56:44
11	L5	^{t}BuOLi	THF	40	>20:1	94:6
12	L5	^{t}BuONa	THF	87	>20:1	95:5
13	L5	MeONa	THF	86	>20:1	95:5
14	L6	^{t}BuOK	THF	96[d]	>20:1	95:5

[a]Conditions: 1a (0.20 mmol), 2a (0.30 mmol), B_2Pin_2 (0.22 mmol), CuCl (5.0 mol%), L (5.0 mol%), base (1.0 equiv.), and solvent (0.6 mL).
[b]Determined by ^{1}H NMR analysis of the crude product mixture using 1,3,5-trimethoxy-benzene as the internal standard.
[c]Determined by chiral HPLC analysis.
[d]Isolated yield.

tolerated, providing the corresponding amino esters in good yields and enantioselectivities (3ba–3da). Other alkyl esters, such as methyl, ^{n}propyl, and benzyl, were compatible with the process (3ea, 3ga, and 3ha). In contrast, submitting bulkier ^{i}propyl ester to the standard conditions furnished 3fa in a moderate enantioselectivity. The absolute configuration of 3aa was unambiguously determined by X-ray analysis (Figure 2; Figure S1; Table S1; Data S2).

A variety of ketiminoesters were further surveyed (Figure 2; Figures S2, S3, S21–S37 and S86–S101). A bulky 2-naphthyl-derived substrate was readily converted to quaternary α-amino esters 3ia with 91% yield, >20:1 *dr*, and 95:5 *er*. The electronic

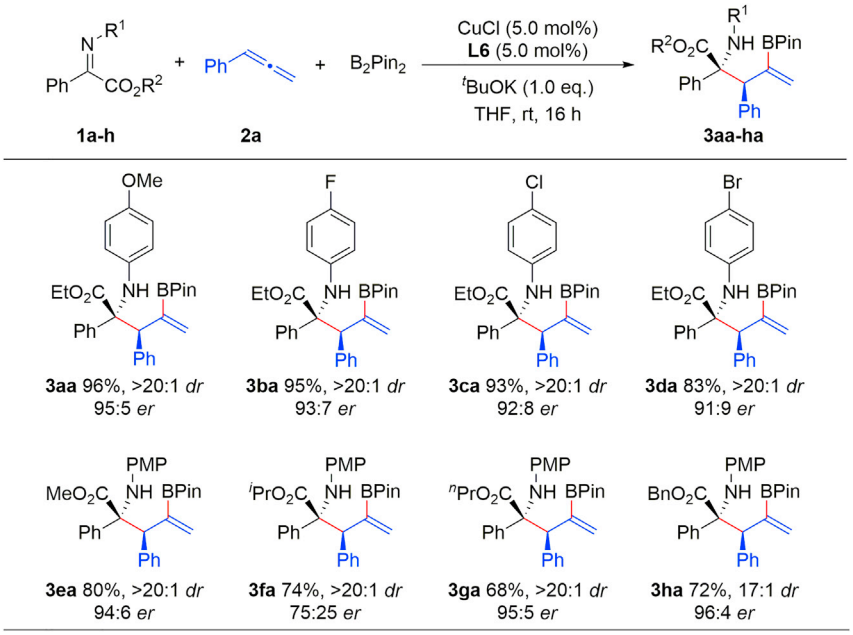


Figure 1. Substituent Effect on Copper-Catalyzed Carboboronation of Allenes

Standard conditions: ketiminoesters 1 (0.20 mmol), allene 2a (0.30 mmol), B_2Pin_2 (0.22 mmol), CuCl (5.0 mol%), L6 (5.0 mol%), ^{t}BuOK (1.0 equiv.), THF (0.6 mL), room temperature (rt), and 16 h; *dr* was determined by ^{1}H NMR analysis of the crude product mixture; *er* was determined by chiral high-performance liquid chromatography (HPLC) analysis.

properties of substituents had negligible influences on the selectivity. Both electron-withdrawing (3ja and 3ka) and electron-donating ketiminoesters (3la–3na) were applicable to the process, leading to the corresponding products in high diastereo- and enantioselectivity. Notably, heteroaryl groups were suitable for the transformation as well. 2-Thienyl-substituted ketiminoester underwent the coupling efficiently to afford 3oa with 76% yield, 13:1 *dr*, and 96:4 *er*. For the 2-pyridyl-derived substrate, the target amino ester 3pa was also obtained in good *dr*. Unfortunately, this protocol is not applicable to cyclic imine 1q.

We next set about to assess the scope with respect to the allenes (Figure 3; Figures S38–S62 and S102–S127). A range of aryl allenes bearing para- and metasubstituents, including -Me, -OMe, -F, and -Br, worked well in this protocol, and the products (3ab–3af) were furnished with exclusive diastereocontrol (>20:1 *dr*) and high enantioselectivities. Remarkably, the couplings of ortho-substituted allenes gave excellent *er* (3ag–3ai), suggesting that steric hindrance is beneficial to the enantiostereocontrol. 2-Naphthyl allene also participated in the reaction, affording 3aj with 75% yield, >20:1 *dr*, and 94:6 *er*. The transformation could be further extended to benzyl- and cyclohexyl-derived allenes to deliver amino esters 3ak and 3al. When phenoxy-substituted allene was used as a coupling partner, the desired product 3am was obtained with a good *dr* (>20:1). The use of disubstituted allene 2n as a substrate delivered the coupling product 3an in 63% yield but with low *er* (55:45).

Scale-Up Synthesis and Transformations

To demonstrate the practical utility of this protocol, scale-up experiments (2.0 mmol) for this three-component coupling were performed and gave 791 mg of chiral amino ester 3aa in 95:5 *er* (Scheme 2). Further synthetic transformations of chiral amino

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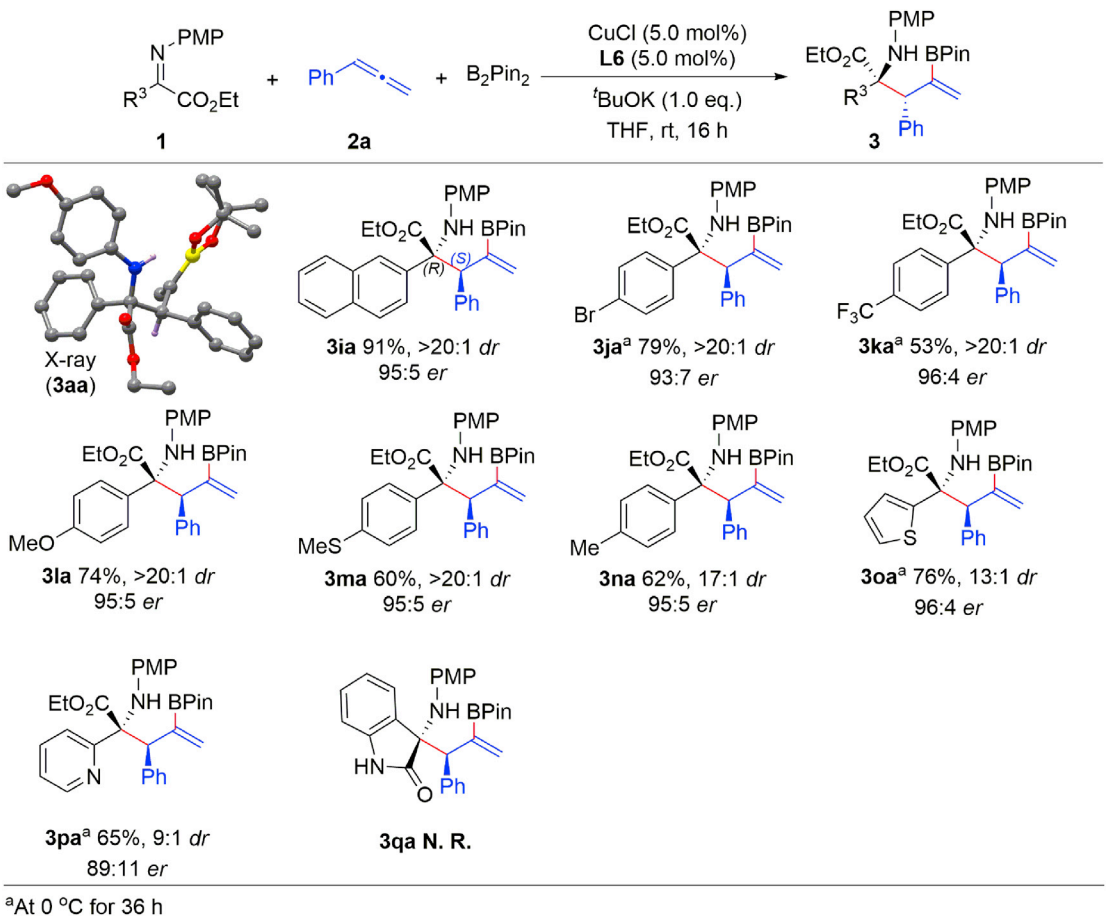


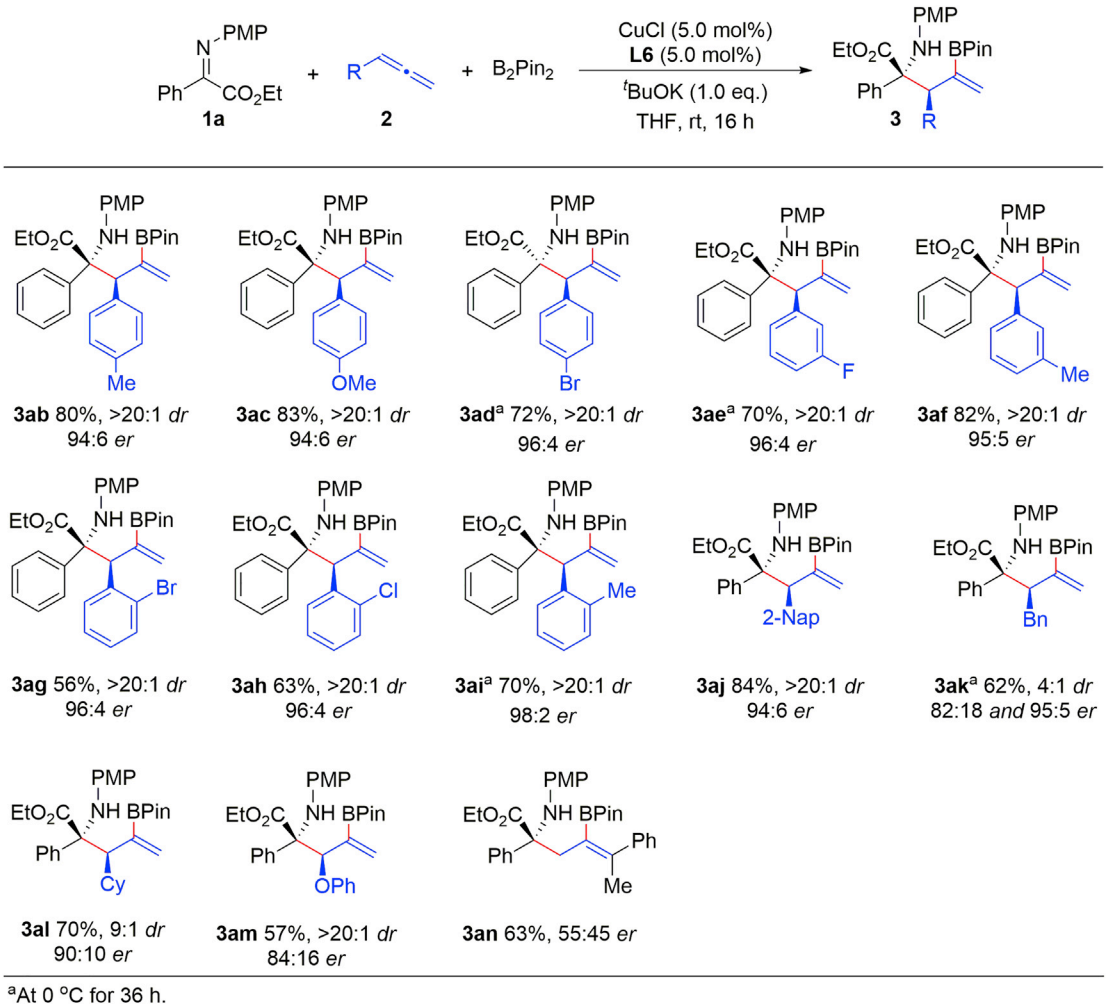
Figure 2. Ketiminoester Scope for Copper-Catalyzed Carboboronation of Allenes

Standard conditions: ketiminoesters 1 (0.20 mmol), allene 2a (0.30 mmol), B_2Pin_2 (0.22 mmol), CuCl (5.0 mol%), L6 (5.0 mol%), ^tBuOK (1.0 equiv.), THF (0.6 mL), rt, and 16 h; *dr* was determined by ^1H NMR analysis of the crude product mixture; *er* was determined by chiral HPLC analysis.

ester 3aa were carried out to construct highly functionalized five-membered cyclic compounds.[68,69] A 5-exo-trig cyclization of 3aa occurred in the presence of the reducing reagent $LiAlH_4$, giving azaborolidinol 4 in 40% yield, with maintained enantioselectivity (Scheme 2; Figures S63, S64, and S128–S139). Next, An oxidation of 3aa by H_2O_2/NaOH resulted in the formation of γ-carbonyl amino ester 5 in 86% yield without affecting stereochemical integrity (Scheme 2; Figures S65, S66, S130, and S131). A highly substituted lactone 6 was obtained through reducing the carbonyl group on 5 in 64% yield (Scheme 2; Figures S67 and S68). The absolute configuration of the newly generated chiral center on lactone 6 was determined by two-dimensional nuclear overhauser effect spectroscopy (2D-NOESY) (Figure S69). The Suzuki coupling product 7 could not be obtained mainly because 3aa is easy to decompose into 1a under heating. Besides, the attempted fluorination of 3aa just delivered ethyl benzoylformate other than compound 8.

Computational Results

To better understand why chiral C_2-symmetric NHC L6 is so superior in the control of the diastereo- and enantioselectivity of the reaction, we evaluated the relative energy difference for the formation of allylcopperisomers (Scheme 3A)[59] and transition states in the coupling between allylcopper and ketiminoesters (Scheme 3B) by



3ab 80%, >20:1 *dr*
94:6 *er*

3ac 83%, >20:1 *dr*
94:6 *er*

3ad[a] 72%, >20:1 *dr*
96:4 *er*

3ae[a] 70%, >20:1 *dr*
96:4 *er*

3af 82%, >20:1 *dr*
95:5 *er*

3ag 56%, >20:1 *dr*
96:4 *er*

3ah 63%, >20:1 *dr*
96:4 *er*

3ai[a] 70%, >20:1 *dr*
98:2 *er*

3aj 84%, >20:1 *dr*
94:6 *er*

3ak[a] 62%, 4:1 *dr*
82:18 *and* 95:5 *er*

3al 70%, 9:1 *dr*
90:10 *er*

3am 57%, >20:1 *dr*
84:16 *er*

3an 63%, 55:45 *er*

[a]At 0 °C for 36 h.

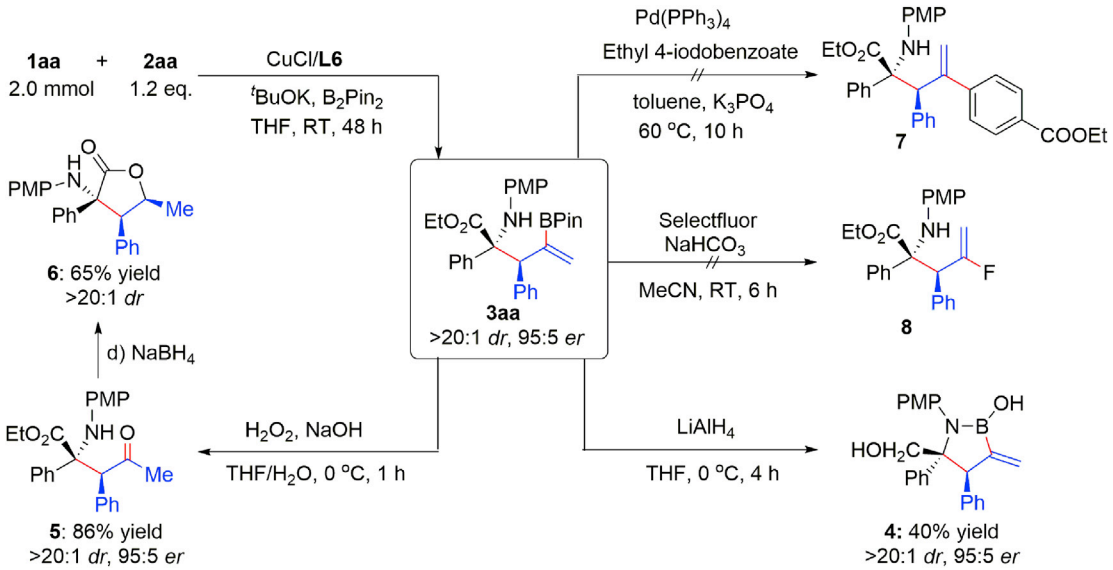
Figure 3. Allene Scope in Copper-Catalyzed Carboboronation

Standard conditions: ketiminoester 1a (0.20 mmol), allenes 2 (0.30 mmol), B_2Pin_2 (0.22 mmol), CuCl (5.0 mol%), L6 (5.0 mol%), ^tBuOK (1.0 equiv.), THF (0.6 mL), rt, and 16 h; *dr* was determined by ^1H NMR analysis of the crude product mixture; *er* was determined by chiral HPLC analysis.

density functional theory (DFT) calculations (Data S1; Note S1). Considering the computational cost, we used below model molecules 1b as reactants.

The migratory insertion of allene 2 into borylcopper will produce allylcopper intermediate in two stereoisomers, namely, A1 and A2 (Scheme 3a). To know more about this step, we calculated the relative energy of the key transition state (Ln-A1 versus Ln-A2). For both two NHC ligands (L6 and L7), *Z*-configured (A1) allylcopper is relative thermodynamic favorable to form. By comparing the relative energy difference, we determined that the use of bulkier L6 instead of L7 will lead to better selectivity (the ratio of A1/A2), which is important for controlling the diastereoselectivity during coupling with ketiminoester.

Based on speculation by Yeung et al. [59] and our observation, we proposed four different transition states for the coupling of allylcopper with ketiminoester (Scheme 3B). Comparing the relative energy difference between chair conformation Ln-B1 and boat conformation Ln-B2, -B3 and -B4, we find that the DFT calculation suggests



Scheme 2. Scale-Up Synthesis and Transformations of Chiral Amino Ester 3aa

Scale-up synthesis, oxidation, and reduction of 3aa were conducted to demonstrate the practical utility of this method, but the suzuki coupling and fluorination of 3aa did not give desired products.

this coupling proceeds through boat conformation Ln-B3. Also, this result is consistent with the absolute stereochemistry observed in the products (*2R*, *3S*)-3ba in the presence of L6. The calculated results from the use of achiral NHC ligand L7 also support that the boat conformation L7-B3 is more favorable than chair conformation L7-B1 during the coupling of allylcopper with ketiminoester 1.

In conclusion, we have developed an asymmetric three-component assembly of quaternary amino esters with adjacent stereocenters by copper-catalyzed coupling of allenes, $B_2(Pin)_2$, and ketiminoesters. The use of bulky C_2-symmetric NHC as a chiral ligand enables the copper catalysis to tackle the challenge in simultaneous control of the chemo-, regio-, diastereo-, and enantioselectivity in this protocol. The salient features of this protocol also include mild reaction conditions, broad functional group tolerance, and diverse applications in organic synthesis.

EXPERIMENTAL PROCEDURES

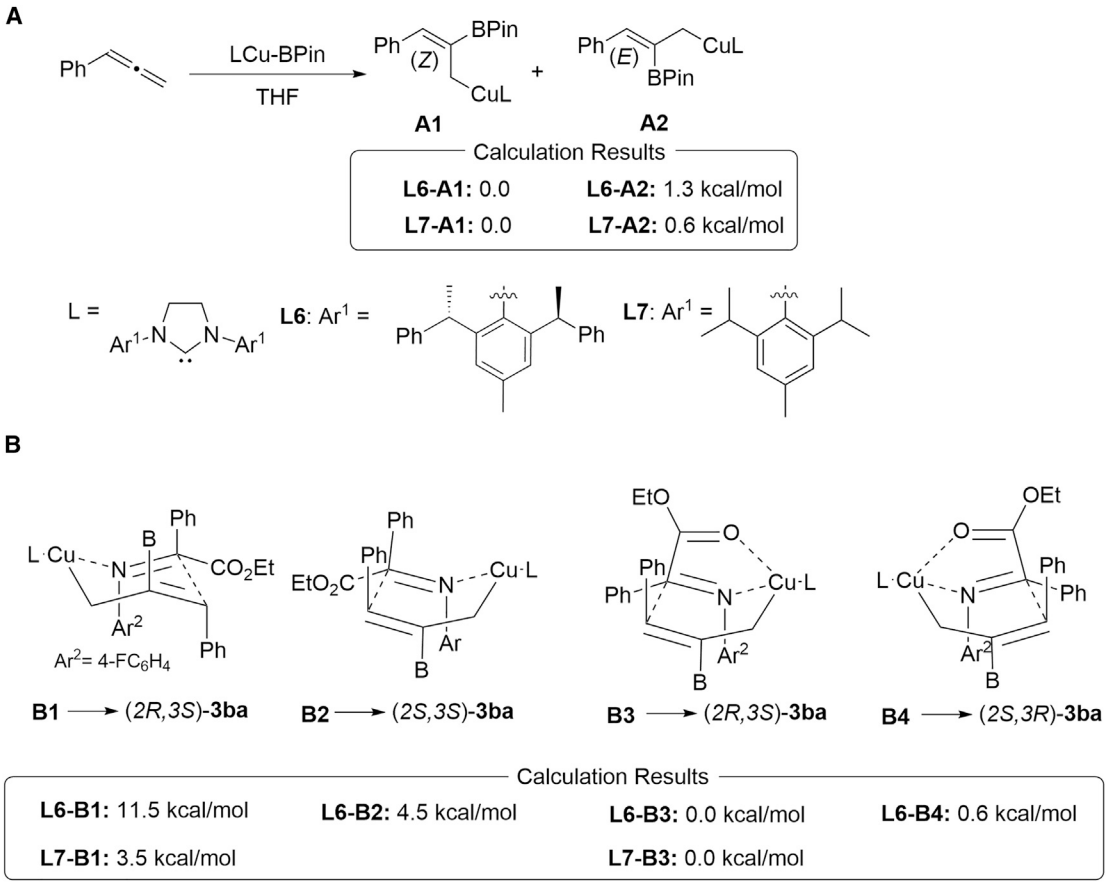
Resource Availability

Lead Contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Qing-An Chen (qachen@dicp.ac.cn).

Materials Availability

Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. Unless otherwise stated, all reactions were conducted under inert atmosphere using standard Schlenk techniques or in an nitrogen-filled glove-box. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ on an 400-MHz instrument with tetramethylsilane (TMS) as an internal standard. Flash column chromatography was performed on silica gel (200–300 mesh). All reactions were monitored by TLC or NMR analysis. High-resolution mass spectrometry (HRMS) data were obtained with a Micromass HPLC-Q-TOF mass spectrometer



Scheme 3. DFT Calculation Results for Transition States

(A) Formation of allylcopper species.

(B) Proposed transition states for the coupling of the (*Z*)-allylcopper and imines.

(electrospray ionization, ESI) or Agilent 6540 Accurate-MS spectrometer (quadrupole time-of-flight, Q-TOF).

Data and Software Availability

The authors declare that data supporting the findings of this study are available within the article and the Supplemental Information. Crystallographic data for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under accession numbers CCDC 1963956 (3aa). Copies of the data can be obtained free of charge from https://www.ccdc.cam.ac.uk/structures/. All other data are available from the Lead Contact upon reasonable request.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.xcrp.2020.100067.

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AUTHOR CONTRIBUTIONS

Q.-A.C. conceived and supervised the project. Q.-A.C., C.-Y.Z., and H.Z. designed the experiments. C.-Y.Z., H.Z., D.-W.J., X.-T.M., and Y.-C.H. performed the experiments and analyzed the data.

DECLARATION OF INTERESTS

The authors declare no conflict of interest.

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