

Copper-catalyzed borylative multi-component synthesis of quaternary α -amino esters

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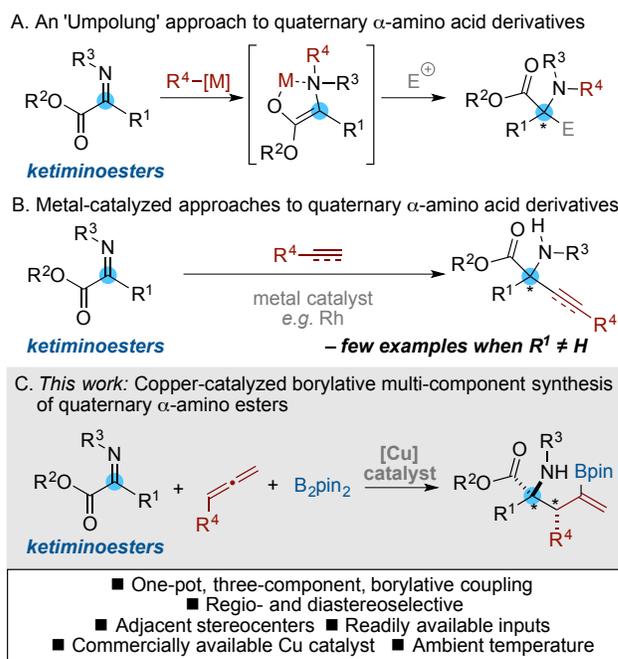
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ABSTRACT: Copper-catalyzed coupling of readily available ketiminoesters, allenes and a diboron affords densely functionalized quaternary α -amino esters bearing adjacent stereocenters and versatile vinyl boronate motifs. The method utilizes a commercially available copper(I) catalyst, operates at ambient temperature and features a catalytic allyl cupration of ketiminoesters.

KEYWORDS: copper catalysis, multicomponent reaction, allenes, borylation, allylation

Due to their enhanced metabolic stability towards hydrolysis and the structural rigidity they lend to peptide backbones, quaternary α -amino acids are vital building blocks in pharmaceutical research and the study of proteins.¹ Although some quaternary α -amino acids arise naturally from post-translational modification,² their synthesis in the laboratory is important and remains a challenge due to the inherent steric congestion encountered during the construction of the fully-substituted stereogenic center at the heart of the motif.

The stereoselective synthesis of quaternary α -amino acids and their derivatives presents a particularly important challenge. Various strategies have been developed including amination at the α -position of carbonyls, introduction of the carboxyl group via nitrile addition, and modification of precursors such as azlactones and ketiminoesters.³ The latter approaches are particularly attractive as a variety of substituents can potentially be introduced at the quaternary center. With particular regard to the use of readily-available ketiminoesters, they have been employed as both nucleophilic and electrophilic partners in approaches to quaternary α -amino acids.^{3a} For example, using an umpolung strategy, nucleophilic attack of an organometallic reagent on nitrogen of ketiminoesters generates enolates that can be quenched using various electrophiles (Scheme 1A).⁴ Ketiminoesters can also be used as electrophiles in additions of stoichiometric organometallic reagents,⁵ organoboranes⁶ and organosilanes.⁷ Crucially, while metal-catalyzed additions to aldiminoesters are widespread,^{3a} there are relatively few examples of metal-catalyzed additions to ketiminoesters and these typically involve alkyne and styrene coupling partners (Scheme 1B).⁸

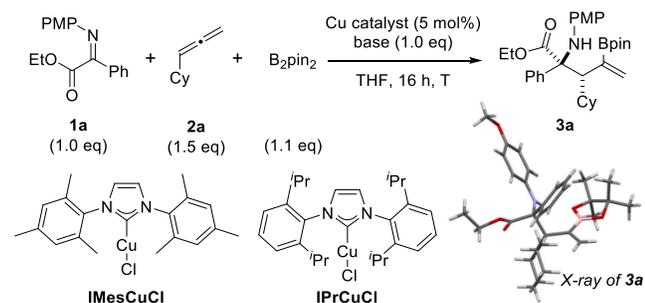


Scheme 1. The use of ketiminoesters provides concise access to quaternary α -amino acids. **A.** Ketiminoesters as pro-nucleophiles. **B.** The use of ketiminoesters as electrophiles in catalytic couplings is rare. **C.** This work: Ketiminoesters in a copper-catalyzed, borylative coupling with allenes.

Allenes have acquired privileged status in synthesis and are prized for their utility in mild and atom efficient transformations,⁹ including multi-component reactions.¹⁰ Despite this, allenes have rarely been used in the synthesis of acyclic quaternary α -amino acids.¹¹ Nonetheless, we envisaged that allenes would serve as suitable precursors to allyl metals for catalytic coupling with ketiminoesters and the construction of high-value quaternary α -amino esters.¹² Inexpensive copper catalysts are able to functionalize allenes by selective addition of an *in situ* generated copper-element species, formation of a transient allylcopper species, and subsequent electrophilic

trapping.¹³ However, the use of imines as electrophiles in copper-catalyzed couplings with allenes remains rare¹⁴ and ketimines have not been used in such couplings to prepare α -quaternary amino acid derivatives. Herein, we describe a stereocontrolled, copper-catalyzed coupling of ketiminoesters, allenes, and bis(pinacolato)diboron to afford highly functionalized quaternary α -amino esters (Scheme 1C).

We began by screening various copper catalysts (5 mol%) for the proposed coupling using ketiminoester (**1a**) and cyclohexylallene (**2a**) with B₂pin₂. From the outset, NHC-Cu(I) catalyst systems showed promising results, forging the C–B and C–C bonds in **3a** despite the build-up of significant steric congestion (Table 1; see Supporting Information for details). While the use of commercial IMesCuCl at ambient temperature gave **3a** in moderate yield, albeit with low diastereoselectivity, the use of IPrCuCl gave **3a** in high yield with high diastereoselectivity (Table 1, entries 1 and 2). We tentatively suggest that the increase in selectivity observed with the IPr ligand is due to its increased size. Next, a range of bases were screened (see Supporting Information for details). The use of NaO^tBu and LiO^tBu in place of KO^tBu had a significant detrimental effect on yield (entries 3 and 4). Lowering (0 °C) and raising (50 °C) the reaction temperature decreased the yield and diastereoselectivity (entries 5 and 6). A small increase in the amount of B₂pin₂ used afforded **3a** in 85% isolated yield on a 0.25 mmol scale (entry 7). Low yields were obtained using other diboron reagents such as B₂(neo)₂ and B₂(cat)₂ (see Supporting Information for details). The relative configuration of **3a** was confirmed by X-ray crystallography.



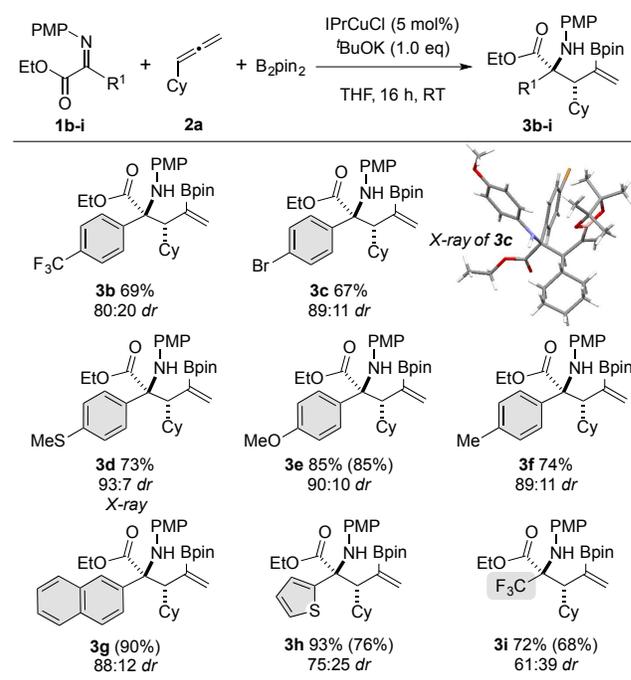
Entry	Cu catalyst	Base	T (°C)	NMR Yield (%) ^a	dr ^b
1	IMesCuCl	^t BuOK	20	53	41:59
2	IPrCuCl	^t BuOK	20	77	92:8
3	IPrCuCl	^t BuONa	20	37	91:9
4	IPrCuCl	^t BuOLi	20	42	92:8
5 ^c	IPrCuCl	^t BuOK	0	29	96:4
6 ^c	IPrCuCl	^t BuOK	50	67	86:14
7 ^{c,d}	IPrCuCl	^t BuOK	20	88 (85) ^e	92:8

Table 1. Optimization of the copper-catalyzed borylative coupling to give quaternary α -amino esters.

Reaction carried out on a 0.1 mmol scale. ^a NMR yields were determined by ¹H NMR analysis of the crude product mixture using an internal standard. ^b dr values were determined by ¹H NMR analysis of the crude product mixture. ^c B₂pin₂ (1.3 eq) was

used. ^d The reaction was carried out on a 0.25 mmol scale. ^e Isolated yield. PMP = 4-C₆H₄OMe.

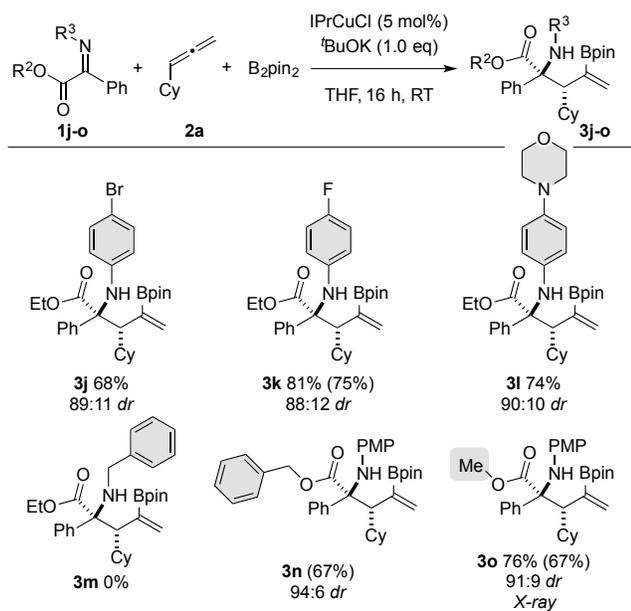
We next set about assessing the reach of the three-component approach to quaternary α -amino esters. The scope with regard to the C-substituent of the ketiminoester input was first explored (Scheme 2). Aryl substituents bearing trifluoromethyl (**3b**), bromo (**3c**), thiomethyl (**3d**) and methoxy (**3e**) functionality proved to be compatible with the process. Furthermore, the use of ketiminoesters bearing naphth-2-yl and 2-thienyl units delivered quaternary α -amino esters **3g** and **3h**, respectively, in high isolated yields and with good diastereocontrol. Finally, a trifluoromethyl substituted ketiminoester underwent efficient coupling to give **3i** in good yield and with moderate diastereocontrol.



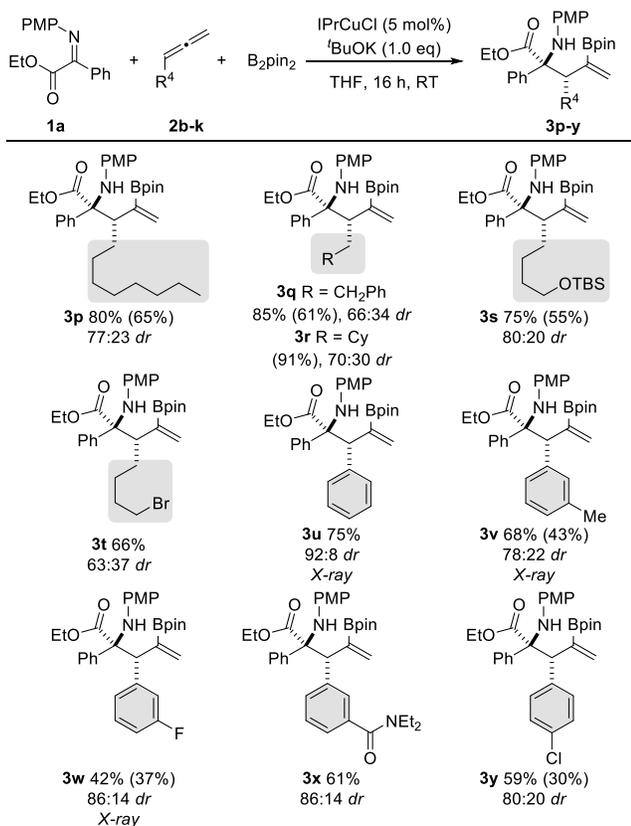
Scheme 2. Varying the C-substituent of the ketiminoester in the copper-catalyzed three-component coupling.

NMR yield and dr values were determined by ¹H NMR analysis of the crude product mixture. Isolated yields are given in parentheses. PMP = 4-C₆H₄OMe.

In addition to employing *p*-methoxyphenyl as the protecting group on the nitrogen of the ketiminoesters and of our products, the use of other synthetically and medically relevant *N*-substituents was also investigated (Scheme 3). Quaternary α -amino acid esters were constructed with bromo (**3j**), fluoro (**3k**), and medically-relevant morpholino (**3l**) groups on the *N*-aryl substituent. No product was observed using an *N*-benzyl ketiminoester (**1m**). This is likely due to the presence of acidic benzylic protons in the ketiminoester. Finally, we varied the ester group of the ketiminoester: The use of benzyl and methyl ester substrates gave the expected products **3n** and **3o**, respectively, in good yield and with high diastereocontrol (Scheme 3).



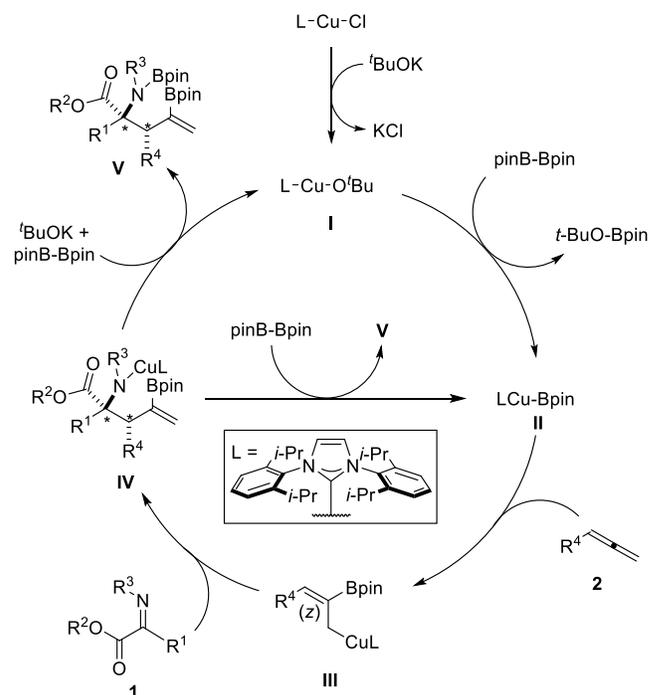
NMR yields and *dr* values were determined by ¹H NMR analysis of the crude product mixture. Isolated yields are given in parentheses. PMP = 4-*C*₆H₄OMe.



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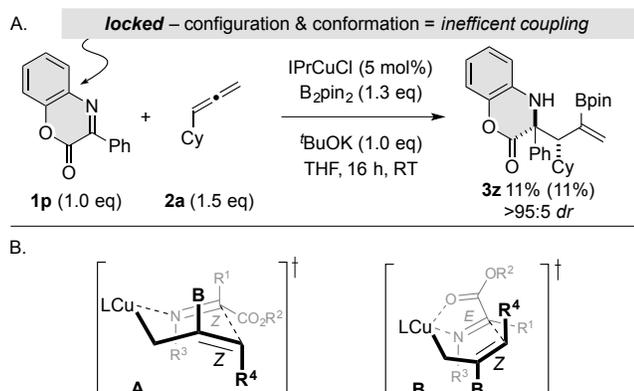
The scope with regard to the allene input was also assessed (Scheme 4). Gratifyingly, a range of primary alkyl allenes bearing various substituents, including linear and branched alkyl groups (**3p**, **3q**, **3r**), silyl ether (**3s**) and alkyl bromide (**3t**) functionality, afforded the desired products in good yield (up to 91%) and moderate to good diastereoselectivity (up to 80:20 *dr*). The chemoselectivity observed in the presence of an electrophilic primary alkyl bromide group is particularly noteworthy (formation of **3t**).¹⁵ Aryl allenes were also compatible with the copper-catalyzed process. For example, phenylallene afforded **3u** in 75% yield and 92:8 *dr*. Aryl allenes bearing fluoro (**3w**), amidyl (**3x**), and chloro (**3y**) substituents also delivered the corresponding products with good to high diastereocontrol (up to 86:14 *dr*) albeit in moderate yield (42-61%).

The proposed catalytic cycle for the multi-component coupling (Scheme 5) is thought to involve initial formation of the ligated copper-alkoxide complex **I** and subsequent transmetalation with B₂pin₂ to afford borylcopper species **II**. Complex **II** reacts with allene **2** through a chemo- and regioselective borocupration to generate an allylcopper intermediate. Due to the bulkiness of the NHC ligand, copper coordinates to the terminal double bond of the allene, avoiding unfavourable steric interactions with the R⁴ group, and adds to the least hindered terminal carbon to give *Z*-allylcopper **III**. Allylcopper **III** then undergoes γ -addition to the ketiminoester **1**, generating two stereocenters. Copper-alkoxide **I** or borylcopper species **II** is then regenerated from copper amide **IV**. The desired quaternary α -amino esters are obtained by hydrolysis of **V** upon work up.



X-ray crystallographic analysis reveals that ketiminoesters **1** possess *Z*-geometry.¹⁶ However, ketimines are prone to *E/Z* isomerization¹⁷ and this could take place under the conditions of the reaction. Thus, to probe the importance of ketiminoester configuration and conformation, we prepared a substrate in

which both are locked and explored its reactivity: Cyclic ketiminoester **1z**, locked in a *Z*-configuration and with a mandatory *s*-trans conformation gave product **3aa** in only 11% yield albeit with high diastereocontrol. This suggests that the reaction can proceed with *Z*-ketiminoesters, however, the ability to access the *s*-cis conformation and/or *E*-imine geometry could be important for optimal cross-coupling.



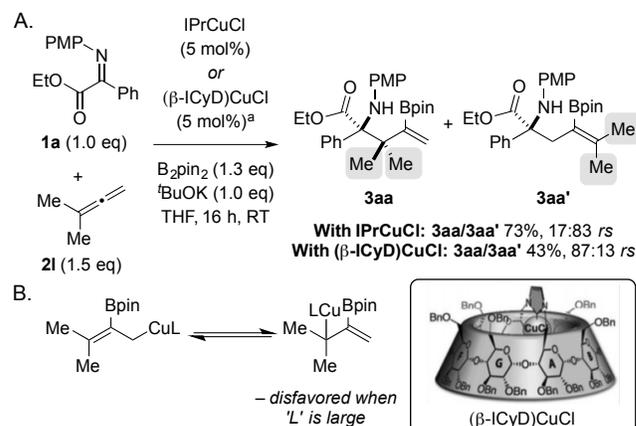
Scheme 6. A. Using a configurationally and conformationally locked ketiminoester.

NMR yield and *dr* value was determined by ^1H NMR analysis of the crude product mixture. Isolated yield is given in parentheses. B. Possible transition states for the coupling of the *Z*-allylcopper and ketiminoester.

Based on this and previous observations,^{14a,14b} we propose two possible transition states for the addition of the allylcopper intermediate to the ketiminoester that are consistent with the relative stereochemistry observed in the products (Scheme 6B). It has previously been suggested that *Z*-allylcopper species undergo 1,2-addition to imines through a chair-like transition state involving coordination of copper to the nitrogen of the imine.¹⁸ Thus transition structure A, featuring a *Z*-configured imine may be relevant. However, the control experiment using locked substrate **1p** may implicate a boat-like transition structure B in which both the imine nitrogen and ester coordinate to copper. Crucially, in transition structure B, isomerization to the *E*-ketiminoester and adoption of an *s*-cis conformation is necessary thus explaining why **1p** performs poorly in the coupling (Scheme 6B).

The use of 1,1-disubstituted allenes in couplings to form quaternary α -amino acid esters bearing two new, vicinal fully-substituted centers was investigated: ketiminoester **1a** underwent smooth coupling with 1,1-dimethylallene **2l** to give a mixture of regioisomers in 73% yield. Interestingly, tetrasubstituted vinylboronate **3aa'** was the major product although the highly-congested, terminal vinyl boronate **3aa** was also formed (**3aa/3aa'**, 17:83 *rs*) (Scheme 7A). Such a switch in regioselectivity with 1,1-disubstituted allenes has not previously been observed in catalytic allylcopper addition to imines.¹⁴ Suspecting that the initially formed primary allylcopper may isomerize to the tertiary allyl copper prior to γ -addition to the ketiminoester (Scheme 7B), and thus leading to **3aa'** as the major regioisomeric product, we proposed that a larger ligand on copper might prevent isomerization on steric grounds. Thus, we employed Sollogoub's large cyclodextrin NHC-Cu catalyst ((β -ICyD)CuCl)¹⁹ and observed a dramatic switch in

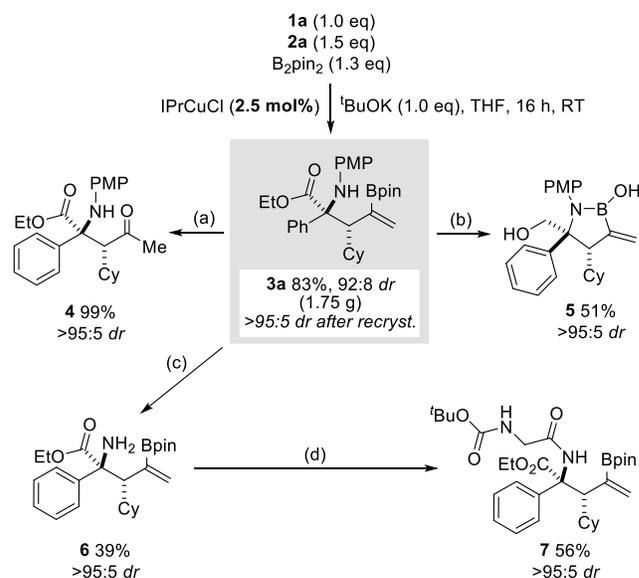
regioselectivity and the major regioisomeric product was now **3aa** (**3aa/3aa'**, 87:13 *rs*).



Scheme 7. The use of a 1,1-disubstituted allene in the copper-catalyzed three-component coupling.

The NMR yield and *rs* value were determined by ^1H NMR analysis of the crude product mixture. ^a The reaction was carried out at 60 °C. PMP = 4- $\text{C}_6\text{H}_4\text{OMe}$.

The three-component coupling was successfully performed on a gram scale (3.5 mmol) using only 2.5 mol% of the copper catalyst and affording **3a** in 83% yield and 92:8 *dr* (1.75 g). After recrystallization, **3a** was obtained with >95:5 *dr*. The synthetic utility of the quaternary α -amino ester products, bearing multiple functional groups, was investigated using **3a**.



Scheme 8. Gram scale three-component coupling and manipulation of **3a.**

Dr values were determined by ^1H NMR analysis of the crude product mixture. Isolated yields are given. (a) H_2O_2 (5.0 eq), aq. NaOH (5.0 eq), THF, 0 °C, 0.5 h; (b) LiAlH_4 (1.0 eq), THF, 0 °C, 4 h; (c) $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ (3.0 eq), MeCN, H_2O , -10 °C, 1.5 h then HCl (1 M aq. soln, 2.6 eq), 20 °C, 0.25 h; (d) (*tert*-butoxycarbonyl)glycine (1.0 eq), *N*-methylmorpholine (1.0 eq), isobutyl chloroformate (1.0 eq), THF, -15 °C to RT, 17 h. PMP = 4- $\text{C}_6\text{H}_4\text{OMe}$.

The versatile vinyl boronate motif was successfully oxidized using H₂O₂/NaOH to afford methyl ketone **4** with no erosion of relative stereochemical integrity (Scheme 8). Thus, our method allows facile access to 1,4-dicarbonyl compounds bearing α - and β -stereocenters. Under reducing conditions (LiAlH₄), ester **3a** was converted to the corresponding primary alcohol **5**, with spontaneous formation of aminoborane. B-N heterocycles have found application as isosteres in biomedical research and materials science.²⁰ Finally, the PMP protecting group on nitrogen was removed using ceric ammonium nitrate (CAN) to afford the primary amine **6**, and can be coupled with a glycine derivative to afford dipeptide **7**.

In summary, we have developed a copper-catalyzed borylative allylation of ketiminoesters using allenes and bis(pinacolato)diboron. The process involves selective borocupration of allenes and the diastereoselective allylcupration of ketiminoesters, operates at ambient temperature, overcomes significant steric congestion, and delivers quaternary α -amino esters bearing adjacent stereocenters and versatile vinylboronate motifs.

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Author Contributions

All authors have given approval to the final version of the manuscript.

ASSOCIATED CONTENT

Supporting Information.

This following files are available free of charge via the Internet at <http://pubs.acs.org>.

Detailed experimental procedures and characterizations.

Crystallographic information for **1c**, **1d**, **1e**, **1f**, **1g**, **1h**, **3a**, **3c**, **3d**, **3o**, **3u**, **3v**, **3w**.

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