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

Kay Yeung,[†] Fabien J. T. Talbot,[†] Gareth P. Howell,[‡] Alexander P. Pulis,[†] and David J. Procter^{*,†}

[†]School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK

[‡]Pharmaceutical Technology and Development, AstraZeneca, Silk Road Business Park, Macclesfield, SK10 2NA, UK

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

A. An 'Umpolung' approach to quaternary α -amino acid derivatives

B. Metal-catalyzed approaches to quaternary α -amino acid derivatives

C. This work: Copper-catalyzed borylative multi-component synthesis of quaternary α -amino esters

- One-pot, three-component, borylative coupling
- Regio- and diastereoselective
- Adjacent stereocenters
- Readily available inputs
- Commercially available Cu catalyst
- Ambient temperature

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 B_2pin_2 . 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 NaOtBu and LiOtBu in place of KOtBu 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 B_2pin_2 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 $B_2(neo)_2$ and $B_2(cat)_2$ (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 B_2pin_2 (1.3 eq) was

used. ^d The reaction was carried out on a 0.25 mmol scale. ^e Isolated yield. PMP = 4- C_6H_4OMe .

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- C_6H_4OMe .

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 medicinally relevant *N*-substituents was also investigated (Scheme 3). Quaternary α -amino acid esters were constructed with bromo (**3j**), fluoro (**3k**), and medicinally-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).

Scheme 3. Varying the *N*-substituent and the *O*-substituent of the ketiminoester in the copper-catalyzed three-component coupling.

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.

Scheme 4. Varying the allene in the copper-catalyzed three-component coupling.

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.

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.

Scheme 5. Proposed catalytic cycle.

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 $\text{H}_2\text{O}_2/\text{NaOH}$ 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 (LiAlH_4), 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.

AUTHOR INFORMATION

Corresponding Author

*E-mail: david.j.procter@manchester.ac.uk

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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REFERENCES

- (1) (a) Brun, K. A.; Linden, A.; Heimgartner, H. *Peptaibiotics: Fungal Peptides Containing α -Dialkyl α -Amino Acids*; Toniolo, C.; Brückner, H., Eds.; Helvetica Chimica Acta: Zürich, 2009; p 261-271. (b) Tanaka, M. Design and Synthesis of Chiral α,α -Disubstituted Amino Acids and Conformational Study of Their Oligopeptides. *Chem. Pharm. Bull.* **2007**, *55*, 349-358. (c) Venkatraman, J.; Shankaramma, S. C.; Balaran, P. Design of Folded Peptides. *Chem. Rev.* **2001**, *101*, 3131-3152. (2) Freeland, S. "Terrestrial" Amino Acids and Their Evolution. In *Amino Acids, Peptides and Proteins in Organic Chemistry: Vol. I. Origins and Synthesis of Amino Acids*; Hughes, A. B., Ed.; Wiley-VCH: Weinheim, 2009; p 43-75. (3) For selected recent reviews on the stereoselective synthesis of quaternary α -amino acids, see: (a) Eftekhari-Sis, B.; Zirak, M. α -Imino Esters in Organic Synthesis: Recent Advances. *Chem. Rev.* **2017**, *117*, 8326-8419. b) Metz, A. E.; Kozłowski, M. C. Recent

Advances in Asymmetric Catalytic Methods for the Formation of Acyclic α,α -Disubstituted α -Amino Acids. *J. Org. Chem.* **2015**, *80*, 1-7. (c) Cativiela, C.; Ordóñez, M. Recent Progress on the Stereoselective Synthesis of Cyclic Quaternary α -Amino Acids. *Tetrahedron: Asymmetry* **2009**, *20*, 1-63. (d) Nájera, C.; Sansano, J. M. Catalytic Asymmetric Synthesis of α -Amino Acids. *Chem. Rev.* **2007**, *107*, 4584-4671. (e) Vogt, H.; Bräse, S. Recent Approaches towards the Asymmetric Synthesis of α,α -Disubstituted α -Amino Acids. *Org. Biomol. Chem.* **2007**, *5*, 406-430. (f) Nájera, C. From α -Amino Acids to Peptides: All You Need for the Journey. *Synlett* **2002**, *9*, 1388-1403.

(4) For examples of the synthesis of acyclic quaternary α -amino acids using ketiminoesters in an umpolung approach, see: (a) Dickstein, J. S.; Fennie, M. W.; Norman, A. L.; Paulose, B. J.; Kozłowski, M. C. Three Component Coupling of α -Iminoesters via Umpolung Addition of Organometals: Synthesis of α,α -Disubstituted Alpha-Amino Acids. *J. Am. Chem. Soc.* **2008**, *130*, 15794-15795. (b) Curto, J. M.; Dickstein, J. S.; Berritt, S.; Kozłowski, M. C. Asymmetric Synthesis of α -Allyl- α -Aryl α -Amino Acids by Tandem Alkylation/ π -Allylation of α -Iminoesters. *Org. Lett.* **2014**, *16*, 1948-1951. (c) Mizota, I.; Matsuda, Y.; Kamimura, S.; Tanaka, H.; Shimizu, M. Regioselective Tandem *N*-Alkylation/ *C*-Acylation of β,γ -Alkynyl α -Imino Esters. *Org. Lett.* **2013**, *15*, 4206-4209. (d) Miyamaru, S.; Umez, K.; Ito, A.; Shimizu, M. Synthesis of Multisubstituted Dihydroquinoxaline Derivatives by Tandem *N*-Alkylation and Addition Reactions of 3-Oxoquinoxaline-2-Carboxylates. *Eur. J. Org. Chem.* **2015**, *2015*, 3327-3337. (e) Chen, P.; Zhang, J. Phosphine-Catalyzed Asymmetric Synthesis of α -Quaternary Amine via Umpolung γ -Addition of Ketimines to Allenates. *Org. Lett.* **2017**, *19*, 6550-6553. For related, recent stereocontrolled approaches to acyclic quaternary α -amino acids involving azomethine ylid formation, see: (f) Huo, X.; Zhang, J.; Fu, J.; He, R.; Zhang, W. Ir/Cu Dual Catalysis: Enantio- and Diastereodivergent Access to α,α -Disubstituted α -Amino Acids Bearing Vicinal Stereocenters. *J. Am. Chem. Soc.* **2018**, *140*, 2080-2084. (g) Huo, X.; He, R.; Fu, J.; Zhang, J.; Yang, G.; Zhang, W. Stereoselective and Site-Specific Allylic Alkylation of Amino Acids and Small Peptides via a Pd/Cu Dual Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 9819-9822. (h) Su, Y.-L.; Li, Y.-H.; Chen, Y.-G.; Han, Z.-Y. Ir/PTC Cooperatively Catalyzed Asymmetric Umpolung Allylation of α -Imino Ester Enabled Synthesis of α -Quaternary Amino Acid Derivatives Bearing Two Vicinal Stereocenters. *Chem. Commun.* **2017**, *53*, 1985-1988. (i) Wei, L.; Zhu, Q.; Xu, S.-M.; Chang, X.; Wang, C.-J. Stereodivergent Synthesis of α,α -Disubstituted α -Amino Acids via Synergistic Cu/Ir Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 1508-1513. (j) Wei, L.; Xu, S.-M.; Zhu, Q.; Che, C.; Wang, C.-J. Synergistic Cu/Pd Catalysis for Enantioselective Allylic Alkylation of Aldimine Esters: Access to α,α -Disubstituted α -Amino Acids. *Angew. Chem. Int. Ed.* **2017**, *56*, 12312-12316. (k) Achgar, A. El; Boumzebra, M.; Roumestant, M.-L.; Viallefont, P. 2-Hydroxy-3-Pinanone as Chiral Auxiliary in the Asymmetric Synthesis of α -Amino Acids. *Tetrahedron* **1988**, *44*, 5319-5332. For additional examples see reference (3b) and (l) Hashimoto, T.; Maruoka, K. Recent Advances of Catalytic Asymmetric 1,3-Dipolar Cycloadditions. *Chem. Rev.* **2015**, *115*, 5366-5412.

(5) For examples of nucleophilic, stoichiometric addition of organomagnesium and organozinc reagents to ketiminoesters using, see: (a) Hatano, M.; Yamashita, K.; Mizuno, M.; Ito, O.; Ishihara, K. Synthetic Methods C-Selective and Diastereoselective Alkyl Addition to β,γ -Alkynyl- α -Imino Esters with Zinc(II)ate Complexes. *Angew. Chem. Int. Ed.* **2015**, *54*, 2707-2711. (b) Almansa, R.; Collados, J. F.; Guisjarro, D.; Yus, M. Asymmetric Synthesis of α - and β -Amino Acids by Diastereoselective Addition of Triorganozincates to *N*-(Tert-Butanesulfinyl)imines. *Tetrahedron: Asymmetry* **2010**, *21*, 1421-1431. (c) Fustero, S.; Mateu, N.; Albert, L.; Aceña, J. L. Straightforward Stereoselective Access to Cyclic Peptidomimetics. *J. Org. Chem.* **2009**, *74*, 4429-4432. (d) Hata, S.; Koyama, H.; Shimizu, M. Synthesis of α,α -Disubstituted α -Amino Esters: Nucleophilic Addition to Iminium Salts Generated from Amino Ketene Silyl Acetals. *J. Org. Chem.* **2011**, *76*, 9670-9677. (e) Shimizu, M.; Yato, A.; Kawamura, T. Nucleophilic Addition Reaction to the Iminium Salts

Generated from Pipecolic Acid Derivatives and Application to the Synthesis of Bicyclic Compounds. *Asian J. Org. Chem.* **2015**, *4*, 128–131. (f) Fu, P.; Snapper, M. L.; Hoveyda, A. H. Catalytic Asymmetric Alkylations of Ketoimines. Enantioselective Synthesis of *N*-Substituted Quaternary Carbon Stereogenic Centers by Zr-Catalyzed Additions of Dialkylzinc Reagents to Aryl-, Alkyl-, and Trifluoroalkyl-Substituted Ketoimines. *J. Am. Chem. Soc.* **2008**, *130*, 5530–5541. (g) Aslam, N. A.; Babu, S. A.; Sudha, A. J.; Yasuda, M.; Baba, A. Chelation-Controlled Diastereoselective Construction of *N*-Aryl-, *N*-Acyl/tosylhydrazono β -Substituted Aspartate Derivatives via Barbier-Type Reaction. *Tetrahedron* **2013**, *69*, 6598–6611. (h) Min, Q.-Q.; He, C.-Y.; Zhou, H.; Zhang, X. Highly Diastereoselective Synthesis of Quaternary α -Trifluoromethyl α -Amino Acids from Chiral Imines of Trifluoropyruvate. *Chem. Commun.* **2010**, *46*, 8029–8031.

(6) For recent examples of nucleophilic, stoichiometric addition of organoboranes to ketiminoesters, see: (a) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. Reactive Ketimino Radical Acceptors: Intermolecular Alkyl Radical Addition to Imines with a Phenolic Hydroxyl Group. *J. Org. Chem.* **2006**, *71*, 2099–2106. (b) Wang, H.; Jiang, T.; Xu, M.-H. Simple Branched Sulfur–Olefins as Chiral Ligands for Rh-Catalyzed Asymmetric Arylation of Cyclic Ketoimines: Highly Enantioselective Construction of Tetrasubstituted Carbon Stereocenters. *J. Am. Chem. Soc.* **2013**, *135*, 971–974. (c) Takechi, R.; Nishimura, T. Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to Cyclic *N*-Sulfonyl Ketoimines towards the Synthesis of α,α -Diaryl- α -Amino Acid Derivatives. *Org. Biomol. Chem.* **2015**, *13*, 4918–4924.

(7) For recent examples of nucleophilic, stoichiometric addition of organosilanes to ketiminoesters, see: (a) Chaume, G.; Van Severen, M.-C.; Marinkovic, S.; Brigaud, T. Straightforward Synthesis of (*S*)- and (*R*)- α -Trifluoromethyl Proline from Chiral Oxazolidines Derived from Ethyl Trifluoropyruvate. *Org. Lett.* **2006**, *8*, 6123–6126. (b) Fustero, S.; Mateu, N.; Simón-Fuentes, A.; Aceña, J. L. Diastereoselective Intramolecular Additions of Allyl- and Propargylsilanes to Iminium Ions: Synthesis of Cyclic and Bicyclic Quaternary Amino Acids. *Org. Lett.* **2010**, *12*, 3014–3017.

(8) For the few examples of the metal-catalyzed synthesis of acyclic quaternary α -amino acids using ketiminoesters, see: (a) Huang, G.; Yin, Z.; Zhang, X. Construction of Optically Active Quaternary Propargyl Amines by Highly Enantioselective Zinc/BINOL-Catalyzed Alkynylation of Ketoimines. *Chem. - A Eur. J.* **2013**, *19*, 11992–11998. (b) Huang, G.; Yang, J.; Zhang, X. Highly Enantioselective zinc/BINOL-Catalyzed Alkynylation of α -Ketoimine Ester: A New Entry to Optically Active Quaternary α -CF₃ α -Amino Acids. *Chem. Commun.* **2011**, *47*, 5587–5589. (c) Zhang, F.-G.; Ma, H.; Zheng, Y.; Ma, J.-A. Zinc-Mediated Enantioselective Addition of Terminal 1,3-Diynes to *N*-Arylimines of Trifluoropyruvates. *Tetrahedron* **2012**, *68*, 7663–7669. (d) Morisaki, K.; Sawa, M.; Nomaguchi, J.-Y.; Morimoto, H.; Takeuchi, Y.; Mashima, K.; Ohshima, T. Rh-Catalyzed Direct Enantioselective Alkynylation of α -Ketiminoesters. *Chem. - A Eur. J.* **2013**, *19*, 8417–8420. (e) Morisaki, K.; Sawa, M.; Yonesaki, R.; Morimoto, H.; Mashima, K.; Ohshima, T. Mechanistic Studies and Expansion of the Substrate Scope of Direct Enantioselective Alkynylation of α -Ketiminoesters Catalyzed by Adaptable (Phebox)Rhodium(III) Complexes. *J. Am. Chem. Soc.* **2016**, *138*, 6194–6203. (f) Liu, R.-R.; Wang, D.-J.; Wu, L.; Xiang, B.; Zhang, G.-Q.; Gao, J.-R.; Jia, Y.-X. Nickel-Catalyzed Enantioselective Addition of Styrenes to Cyclic *N*-Sulfonyl α -Ketiminoesters. *ACS Catal.* **2015**, *5*, 6524–6528.

(9) For selected recent reviews on allenes in organic synthesis, see: (a) *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; p 1–1143. (b) Ma, S. Transition-Metal-Catalyzed Reactions of Allenes. *Pure Appl. Chem.* **2006**, *78*, 197–208. (c) Yu, S.; Ma, S. Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses. *Angew. Chem. Int. Ed.* **2012**, *51*, 3074–3112. (d) Ma, S. Some Typical Advances in the Synthetic Applications of Allenes. *Chem. Rev.* **2005**, *105*, 2829–2871.

(10) For selected recent reviews on allenes in multi-component reactions, see: (a) Reissig, H.-U.; Zimmer, R. Allenes in Multicomponent Synthesis of Heterocycles. In *Multicomponent Reactions in Organic Synthesis*; Zhu, J., Wang, Q., Wang, M.-X., Eds.; Wiley-VCH: Weinheim, 2015; p 301–332. (b) Pulis, A. P.; Yeung, K.; Procter, D.

J. Enantioselective Copper Catalyzed, Direct Functionalisation of Allenes via Allyl Copper Intermediates. *Chem. Sci.* **2017**, *8*, 5240–5247. (c) Fujihara, T.; Tsuji, Y. Cu-Catalyzed Borylative and Silylative Transformations of Allenes: Use of β -Functionalized Allyl Copper Intermediates in Organic Synthesis. *Synthesis* **2018**, *50*, 1737–1749. (d) Ma, S. Palladium-Catalyzed Two- or Three-Component Cyclization of Functionalized Allenes. In *Palladium in Organic Synthesis. Topics in Organometallic Chemistry*; Tsuji, J., Ed.; Springer: Berlin, Heidelberg, 2005; p 183–210.

(11) For examples of allenes in the synthesis of acyclic quaternary α -amino acids, see: (a) Paik, Y. H.; Dowd, P. β -Methyleneglutamic Acid and β -Methyleneglutamine. *J. Org. Chem.* **1986**, *51*, 2910–2913. (b) Imada, Y.; Ueno, K.; Kutsuwa, K.; Murahashi, S.-I. Palladium-Catalyzed Asymmetric Alkylation of 2,3-Alkadienyl Phosphates. Synthesis of Optically Active 2-(2,3-Alkadienyl)malonates. *Chem. Lett.* **2002**, *31*, 140–141. (c) Maity, P.; Lepore, S. D. Catalytic Synthesis of Nonracemic Azaproline Derivatives by Cyclization of β -Alkynyl Hydrazines under Kinetic Resolution Conditions. *Angew. Chem. Int. Ed.* **2011**, *50*, 8338–8341. (d) Fujiwara, Y.; Fu, G. C. Application of a New Chiral Phosphine to the Catalytic Asymmetric Synthesis of Highly Functionalized Cyclopentenones That Bear an Array of Heteroatom-Substituted Quaternary Stereocenters. *J. Am. Chem. Soc.* **2011**, *133*, 12293–12297. The use of allenes in the synthesis of cyclic quaternary α -amino acids has been reported. This generally involves a [3+2] cycloaddition approach or a phosphine-catalyzed coupling of oxazolones with electron-deficient allenes. For related reviews, see: (e) Wei, Y.; Shi, M. Lu's [3 + 2] Cycloaddition of Allenes with Electrophiles: Discovery, Development and Synthetic Application. *Org. Chem. Front.* **2017**, *4*, 1876–1890. (f) Ni, H.; Chan, W.-L.; Lu, Y. Phosphine-Catalyzed Asymmetric Organic Reactions. *Chem. Rev.* **2018**, *118*, 9344–9411.

(12) There are only few reports of the synthesis of acyclic quaternary α -amino acids using allenes with imines. For a phosphine-catalyzed umpolung addition of ketiminoesters to allenates, see Ref (4e). For the deprotonation of *N*-CH₂CO₂R substituted ketimines and umpolung addition to allenates, see Ref. (4k).

(13) For selected recent reviews on the generation of nucleophilic organocopper intermediates by Cu-H, Cu-B and Cu-Si functionalisation of allenes, see: (10b); (10c); Tsuji, Y.; Fujihara, T. Copper-Catalyzed Transformations Using Cu-H, Cu-B, and Cu-Si as Active Catalyst Species. *Chem. Rev.* **2016**, *16*, 2294–2313.

(14) For examples of copper-catalyzed couplings of allenes and imines, see: (a) Rae, J.; Yeung, K.; McDouall, J. J. W.; Procter, D. J. Copper-Catalyzed Borylative Cross-Coupling of Allenes and Imines: Selective Three-Component Assembly of Branched Homoallyl Amines. *Angew. Chem. Int. Ed.* **2016**, *55*, 1102–1107. (b) Yeung, K.; Ruscoe, R. E.; Rae, J.; Pulis, A. P.; Procter, D. J. Enantioselective Generation of Adjacent Stereocenters in a Copper-Catalyzed Three-Component Coupling of Imines, Allenes, and Diboranes. *Angew. Chem. Int. Ed.* **2016**, *55*, 11912–11916. (c) Liu, R. Y.; Yang, Y.; Buchwald, S. L. Regiodivergent and Diastereoselective CuH-Catalyzed Allylation of Imines with Terminal Allenes. *Angew. Chem. Int. Ed.* **2016**, *55*, 14077–14080. (d) Jang, H.; Romiti, F.; Torker, S.; Hoveyda, A. H. Catalytic Diastereo- and Enantioselective Additions of Versatile Allyl Groups to *N*-H Ketoimines. *Nat. Chem.* **2017**, *9*, 1269–1275.

(15) For a recent report of allylcopper intermediates reacting with primary alkyl bromides, see: Ozawa, Y.; Iwamoto, H.; Ito, H. Copper(I)-Catalyzed Regio- and Diastereoselective Intramolecular Alkylboration of Terminal Allenes via Allylcopper(I) Isomerization. *Chem. Commun.* **2018**, *54*, 4991–4994.

(16) See the Supporting Information for the X-ray crystal structures and CCDC numbers of ketiminoesters **1c**, **1d**, **1e**, **1f**, **1g**, and **1h**.

(17) (a) Jennings, W. B.; Boyd, D. R. The Mechanism of Interconversion of (*Z*)- and (*E*)-Ketoimines. *J. Am. Chem. Soc.* **1972**, *94*, 7187–7188. (b) Bjørge, J.; Boyd, D. R.; Watson, C. G.; Jennings, W. B. Equilibrium Distribution of *E*-*Z*-Ketoimine Isomers. *J. Chem. Soc., Perkin Trans. 2* **1974**, *0*, 757–762.

(18) For reports of the 1,2-addition of allylcopper species to imines proceeding through a chair-like transition state, see: (14); (a) Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. Enantioselective Syn-

thesis of Homoallylic Amines through Reactions of (Pinacolato)allylborons with Aryl-, Heteroaryl-, Alkyl-, or Alkene-Substituted Aldimines Catalyzed by Chiral C1-Symmetric NHC-Cu Complexes. *J. Am. Chem. Soc.* **2011**, *133*, 3332–3335. (b) Jiang, L.; Cao, P.; Wang, M.; Chen, B.; Wang, B.; Liao, J. Highly Diastereo- and Enantioselective Cu-Catalyzed Borylative Coupling of 1,3-Dienes and Aldimines. *Angew. Chem. Int. Ed.* **2016**, *55*, 13854–13858. (c) Kanai, M.; Wada, R.; Shibuguchi, T.; Shibasaki, M. Cu(I)-Catalyzed Asymmetric Allylation of Ketones and Ketimines. *Pure Appl. Chem.* **2008**, *80*, 1055–1062.

(19) (a) Zhang, P.; Suárez, J. M.; Driant, T.; Derat, E.; Zhang, Y.; Ménand, M.; Roland, S.; Sollogoub, M. Cyclodextrin Cavity-Induced Mechanistic Switch in Copper-Catalyzed Hydroboration. *Angew. Chem. Int. Ed.* **2017**, *129*, 10961–10965. (b) Guitet, M.; Zhang, P.; Marcelo, F.; Tugny, C.; Jiménez-Barbero, J.; Buriez, O.; Amatore, C.; Mouriès-Mansuy, V.; Goddard, J.-P.; Fensterbank, L.; Zhang, Y.; Roland, S.; Ménand, M.; Sollogoub, M. NHC-Capped Cyclodextrins (ICyDs): Insulated Metal Complexes, Commutable Multicoordination Sphere, and Cavity-Dependent Catalysis. *Angew. Chem. Int. Ed.* **2013**, *52*, 7213–7218. (c) Zhang, P.; Tugny, C.; Mejjide Suárez, J.; Guitet, M.; Derat, E.; Vanthuyne, N.; Zhang, Y.; Bistri, O.; Mouriès-Mansuy, V.; Ménand, M.; Roland, S.; Fensterbank, L.; Sollogoub, M. Artificial Chiral Metallo-pockets Including a Single Metal Serving as Structural Probe and Catalytic Center. *Chem* **2017**, *3*, 174–191. For the full chemical structure of ((β -ICyD)CuCl), see Supporting Information.

(20) (a) Nishiyabu, R.; Kubo, Y.; James, T. D.; Fossey, J. S. Boronic Acid Building Blocks: Tools for Sensing and Separation. *Chem. Commun.* **2011**, *47*, 1106–1123. (b) Bélanger-Chabot, G.; Braunschweig, H.; Kumar Roy, D. Recent Developments in Azaborinine Chemistry. *Eur. J. Inorg. Chem.* **2017**, *2017*, 4353–4368.