Copper-Catalyzed Asymmetric Hydroamination: A Unified Strategy for the Synthesis of Chiral β-Amino Acid and Its Derivatives

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Introduction

Catalytic asymmetric aza-Michael represents one of the most convenient and atom-economical approaches for the rapid construction of biologically active chiral β-amino acid frameworks. However, the direct enantioselective addition of nitrogen-based nucleophiles to intrinsically low reactivity of α,β-unsaturated carboxylic acid, ester, and amide, as well as simple α,β-unsaturated nitrile, remains a long-standing challenge. Herein, we report a unified Cu-catalyzed asymmetric reversal hydroamination, capable of direct preparation of a series of β-amino acid, ester, amide, and nitrile in a highly regio- and enantioselective manner, without the requirement of traditional preinstallation of stoichiometric quantities of auxiliaries.

Keywords: asymmetric catalysis, reversal hydroamination, chiral β-amino acid and its derivatives, copper catalysis, Michael acceptors

Catalytic asymmetric aza-Michael represents one of the most convenient and atom-economical approaches for the rapid construction of biologically and synthetically important chiral β-amino acid frameworks from readily accessible feedstocks.

![Scheme 1](image)

**Scheme 1**

Reversal hydroamination

More precise enantiocontrol

Suitable for α,β-unsaturated acid and its derivatives

Keywords: asymmetric catalysis, reversal hydroamination, chiral β-amino acid and its derivatives, copper catalysis, Michael acceptors

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deprotection of stoichiometric quantities of activating auxiliaries involves time-consuming multistep sequences and sometimes leads to chiral product racemization and/or incompatibility with delicate molecular architectures during removal of these auxiliaries. To the best of our knowledge, only some sporadic examples described the direct addition to α,β-unsaturated acid and α,β-unsaturated ester as well as enzyme-catalyzed transformations so far. Furthermore, the simple α,β-unsaturated nitriles (β-substituted acrylonitrile), another typical kind of Michael acceptor and versatile building block in synthetic chemistry, the enantioselective addition with nitrogen-based nucleophiles to form a chiral center at the β-position of the nitrile group is only up to 22% enantiomeric excess (ee) value (Scheme 1a, bottom). More importantly, up to now, there remains no unified strategy that is suitable for all of these challenging Michael acceptors. Therefore, exploitation of a general and alternative approach that is capable of rapid preparation of chiral β-amino acid derivatives from unmasked α,β-unsaturated acid, ester, amide, even for simple α,β-unsaturated nitrile, is highly desirable.

Transition-metal-catalyzed asymmetric hydroamination of unsaturated hydrocarbons is a straightforward and powerful approach for rapid assembly of a variety of biologically active chiral amines. In this context, asymmetric hydroamination of various alkenes and alkynes with in situ generated CuH catalysts has attracted much attention since the pioneering reports by Buchwald and Hirano, and Miura in 2013. Besides, an array of electronically matched CuH-catalyzed asymmetric transformations of Michael acceptors, namely undergoing the 1,4-hydrocupration process, have also been disclosed in past decades (Scheme 1b). Given our continuing interest in Cu-catalyzed asymmetric hydrofunctionalization of unsaturated hydrocarbons, herein, we report a Cu-catalyzed asymmetric reversal hydroamination of α,β-unsaturated acid, ester, amide, and nitrile with hydroxylamine derivatives as aminating reagents (Scheme 1c). We provide a unified and straightforward method to synthesize a series of chiral β-amino acid and its derivatives, without the traditional requirement of preinstallation of auxiliaries inaza-Michael addition reaction.

**Results and Discussion**

At the outset of our studies, we selected ethyl cinnamate 1a and O-benzoylhydroxylamine 4a as the model compounds for the state-of-the-art asymmetric aza-Michael addition to α,β-unsaturated acid, ester, amide, and nitrile (Scheme 1a).

(a) The state-of-the-art asymmetric aza-Michael addition to α,β-unsaturated acid, ester, amide, and nitrile

![Scheme 1](image)

**Scheme 1** (a–c) Approaches for asymmetric aza-Michael addition reaction to α,β-unsaturated carboxylic acid and its derivatives and CuH-catalyzed transformations of Michael acceptors.
substrates in the presence of 5 mol % of Cu(OAc)$_2$ and (S)-DTBM-SEGPHOS L1, the extremely powerful catalytic system of CuH-catalyzed asymmetric hydroamination pioneeredly developed by the Buchwald’s group, with an excess of TMDS (1,1,3,3-tetramethyldisiloxane) at room temperature under N$_2$ atmosphere in tetrahydrofuran (THF) for 48 h (Table 1). In line with the regioselectivity of previous CuH-catalyzed transformations of α,β-unsaturated ester, the α-alkylaminyl-substituted product 5a’ was obtained in 39% yield but without enantioinduction. Moreover, 5a’ was also observed in 46% and 63% yields with (R)-Tol-BINAP and (R,R)-DIPAMP as chiral ligands, respectively (see Supporting Information for details). During a thorough evaluation of various chiral ligands, we were surprised to discover that the regioisomer 5a with L2 as the ligand. Examination of other commercially available hydrosilanes and solvents was also performed, and slightly inferior yield or enantiocontrol under available hydrosilanes and solvents was also performed. An array of electronic-withdrawing groups, including alkyl, methoxy, phenyl, and methylthioiyl, halogens, trifluoromethoxy and trifluoro- methyl, and (E)-3-(quinolin-3-yl)acrylic acid (20), were suitable coupling partners for this amination. They provided corresponding β-alkylaminyl-substituted acid 6a–6o with high efficiency and generally excellent level of enantiocontrol. In addition, some representative hydroxylamine esters were also examined and could be readily converted into chiral β-aminyl acids 6p–6r with over 90% ee. α,β-Unsaturated amides 3a–3f could also be converted into corresponding β-aminyl amides 7a–7f under this catalytic system with high efficiency, despite showing relatively low enantiocontrol in some cases compared with that of α,β-unsaturated ester and acid.

Encouraged by these promising results, we were next particularly interested in whether this reversal hydroamination strategy could be applicable to α,β-unsaturated nitriles to form synthetically challenging chiral β-amino nitriles. We then began our investigation using (E)-cinnamionitrile 8 as the Michael acceptor. To our delight, the expected β-amino-substituted nitrile 9a was indeed generated in 91% yield and 92% ee without any further optimization reaction conditions. Encouraged by this result, we then commenced assessment of substrate scope and the functional group compatibility (Table 2). In general, this reaction also showed good functional group tolerance. For example, either electron-donating functional groups (–CH$_3$, –OCH$_3$, –SCH$_3$, –C$_6$H$_5$, –OAc, and –OC$_6$H$_5$) or electron-withdrawing functional groups (–F, –Cl, –Br, –OCF$_3$, –CF$_3$, –C(O)OMe, and some privileged heteroaromatic ring motifs widespread in bioactive molecules and pharmaceuticals, such as pyridine and thiophene, were also readily accommodated. They provided expected hydroamination products 5l–5u in good yields with excellent enantioselectivities. In addition to examining the scope of α,β-unsaturated esters, we also surveyed the substrate scope with respect to the hydroxylamine ester component. We found that electron-rich or electron-deficient hydroxylamine esters, nitrogen-containing heterocyclic hydroxylamine esters, as well as the enantiomeric hydroxylamine esters were all applicable to this hydroamination. They provided β-aminalyl esters 5v–5z with high efficiency and good-to-excellent enantiocontrol. Structurally more complicated diaceton-d-glucose and cholesterol-derivated α,β-unsaturated esters could also be transferred smoothly into corresponding β-amino ester 5aa and 5 ab in good yield with excellent diastereo- and enantiocontrol. The relatively low yields in some cases, such as 5e, 5t, and 5u, ascribed to the competitive reduction reaction of C–C double bond, and corresponding reduction products were obtained in 43%, 41%, and 38% yields. In addition, the β-alkyl-substituted α,β-unsaturated ester, such as ethyl (E)-but-2-enoate, was also assessed under the present conditions, whereas α-alkylaminyl-substituted product was obtained in 68% yield (see Supporting Information). The success of this asymmetric hydroamination strategy for α,β-unsaturated ester encouraged us to continue examining whether this approach could also be applied to synthesize chiral β-aminyl acids and amides. To our delight, by slightly improving the temperature and increasing the amount of silane, a diverse range of α,β-unsaturated acids with various electronic-withdrawing or donating functional groups on the aromatic rings (2a–2n), including methyl, ethoxyl, ester, phenyl, methylthioiyl, halogens, trifluoromethoxy and trifluoro- methyl, and (E)-3-(quinolin-3-yl)acrylic acid (20), were suitable coupling partners for this amination. They provided corresponding β-alkylaminyl-substituted acid 6a–6o with high efficiency and generally excellent level of enantiocontrol. In addition, some representative hydroxyamine esters were also examined and could be readily converted into chiral β-aminyl acids 6p–6r with over 90% ee. α,β-Unsaturated amides 3a–3f could also be converted into corresponding β-aminyl amides 7a–7f under this catalytic system with high efficiency, despite showing relatively low enantiocontrol in some cases compared with that of α,β-unsaturated ester and acid.
### Table 1. Scope of Hydroamination of α,β-Unsaturated Ester, Acid, and Amide$^a$$^b$

| Entry | Product Structure | Yield (%) | ee (%) |
|-------|-------------------|-----------|--------|
| 5a    | ![Product Structure 5a](image) | 77% | 97% ee |
| 5b    | ![Product Structure 5b](image) | 80% | 90% ee |
| 5c    | ![Product Structure 5c](image) | 88% | 86% ee |
| 5d    | ![Product Structure 5d](image) | 63% | 96% ee |
| 5e    | ![Product Structure 5e](image) | 52% | 95% ee |
| 5f    | ![Product Structure 5f](image) | 57% | 86% ee |
| 5g    | ![Product Structure 5g](image) | 75% | 98% ee |
| 5h    | ![Product Structure 5h](image) | 61% | 92% ee |
| 5i    | ![Product Structure 5i](image) | 67% | 91% ee |
| 5j    | ![Product Structure 5j](image) | 69% | 97% ee |
| 5k    | ![Product Structure 5k](image) | 60% | 99% ee |
| 5l    | ![Product Structure 5l](image) | 60% | 97% ee |
| 5m    | ![Product Structure 5m](image) | 74% | 90% ee |
| 5n    | ![Product Structure 5n](image) | 60% | 97% ee |
| 5o    | ![Product Structure 5o](image) | 69% | 97% ee |
| 5p    | ![Product Structure 5p](image) | 43% | 73% ee |
| 5q    | ![Product Structure 5q](image) | 68% | 79% ee |
| 5r    | ![Product Structure 5r](image) | 76% | 87% ee |
| 5s    | ![Product Structure 5s](image) | 69% | 84% ee |
| 5t    | ![Product Structure 5t](image) | 51% | 97% ee |
| 5u    | ![Product Structure 5u](image) | 85% | −90% ee<sup>**</sup> |
| 5v    | ![Product Structure 5v](image) | 84% | 90% ee<sup>**</sup> |
| 5w    | ![Product Structure 5w](image) | 72% | 86% ee |
| 5x    | ![Product Structure 5x](image) | 68% | 97% ee |
| 5y    | ![Product Structure 5y](image) | 89% | 90% ee |
| 5z    | ![Product Structure 5z](image) | 85% | −90% ee<sup>**</sup> |
| 6a    | ![Product Structure 6a](image) | 91% | 95% ee<sup>**</sup> |
| 6b    | ![Product Structure 6b](image) | 92% | 90% ee<sup>**</sup> |
| 6c    | ![Product Structure 6c](image) | 78% | 85% ee<sup>**</sup> |
| 6d    | ![Product Structure 6d](image) | 85% | 89% ee<sup>**</sup> |
| 6e    | ![Product Structure 6e](image) | 70% | 97% ee<sup>**</sup> |
| 6f    | ![Product Structure 6f](image) | 69% | 88% ee<sup>**</sup> |
| 6g    | ![Product Structure 6g](image) | 72% | 98% ee<sup>**</sup> |
| 6h    | ![Product Structure 6h](image) | 78% | 83% ee<sup>**</sup> |
| 6i    | ![Product Structure 6i](image) | 75% | 85% ee<sup>**</sup> |
| 6j    | ![Product Structure 6j](image) | 79% | 80% ee<sup>**</sup> |
| 6k    | ![Product Structure 6k](image) | 55% | 93% ee<sup>**</sup> |
| 6l    | ![Product Structure 6l](image) | 90% | 83% ee<sup>**</sup> |
| 6m    | ![Product Structure 6m](image) | 69% | 87% ee<sup>**</sup> |
| 6n    | ![Product Structure 6n](image) | 69% | 90% ee<sup>**</sup> |
| 6o    | ![Product Structure 6o](image) | 51% | 90% ee<sup>**</sup> |
| 6p    | ![Product Structure 6p](image) | 68% | 96% ee<sup>**</sup> |
| 6q    | ![Product Structure 6q](image) | 74% | 94% ee<sup>**</sup> |
| 6r    | ![Product Structure 6r](image) | 48% | 78% ee<sup>**</sup> |
| 6s    | ![Product Structure 6s](image) | 51% | 81% ee<sup>**</sup> |

<sup>a</sup> Reaction conditions: α,β-unsaturated esters (0.2 mmol), 4 (0.3 mmol, 1.5 equiv), 1,1,3,3-tetramethyldisiloxane (TMDS) (3.0 equiv), Cu(OAc)<sub>2</sub> (5 mol %), and chiral ligand L2 (5 mol %) in 2.0 mL dry THF at room temperature for 48 h.<br><sup>b</sup> Yields were determined by 1H NMR spectroscopy using CH<sub>2</sub>Br<sub>2</sub> as an internal standard and ee value determined by HPLC.<br><sup>c</sup> (R,R)-Ph-BPE was used.<br><sup>d</sup> α,β-Unsaturated acids (0.3 mmol, 1.5 equiv), 4 (0.2 mmol), 6.0 equiv TMDS were used and the reactions were performed at 50 °C.<br><sup>e</sup> α,β-Unsaturated amides (0.3 mmol, 1.5 equiv), 4 (0.2 mmol) were used and the reactions were performed at 50 °C.
was unequivocally determined by single-crystal X-ray diffraction. In addition, the success of the reversal hydroamination of α,β-unsaturated nitrile also suggested that the regioselectivity of this method was not dominated by the chelation effect of the carbonyls in Michael acceptors because the linear configuration of nitrile group was not favorable as a directing group in this transformation. In addition, other α,β-unsaturated carbonyls, such as α,β-unsaturated ketone and imine, were also evaluated, and the complex mixture of α,β-unsaturated ketone and almost completely recovered α,β-unsaturated nitrile also suggested that these types of chiral compounds might have unusual regio- and enantioselectivity.

A gram-scale synthesis was conducted to demonstrate the practicability of this method, the target chiral β-amino ester 5a was obtained in good yield without any erosion in enantioselectivity with 1 mol % Cu(OAc)2 and 1 mol % chiral ligand L2 (Scheme 2a). We also examined further applications of this chiral compound (Scheme 2b). For instance, chiral β-amino ester 5a underwent a selective monodebenzylation or reduction process, offering chiral β-amino ester 10 and important chiral γ-amino alcohol 11 in excellent yield with 95% and 92% ee, respectively. In addition, ester 5a also converted into the chiral cyclic β-amino ketone 12 smoothly in 68% yield with slight erosion of enantioselectivity. The chiral β-amino ester 5a was further functionalized at the α-position of the ester group and deliver more complex molecules. For example, 5a was efficiently allylated with allyl bromide in the presence of potassium bis(trimethylsilyl)amide (KHMDS), providing synthetically versatile compound 13 with 2:1 diastereoselectivity. Moreover, without any racemization, the chiral center in 5a was observed under harsh conditions [e.g., in the presence of NaOH or trifluoroacetic acid (TFA)], indicating that these types of chiral compounds might have the capacity to transfer into more complicated chiral compounds while maintaining the enantioselectivity. According to previous reports, a mechanism involving a regio- and enantioselective insertion of CuH into C–C double bond in a Michael acceptor to form benzylcopper intermediate, followed by an amination process with hydroxylamine 4 to provide expected chiral β-amino carboxyls, might be possible. Other mechanisms cannot be excluded, and further studies need to be carried out to illuminate the origin of this unusual regio- and enantioselectivity.

### Table 2 | Scope of Hydroamination of α,β-Unsaturated Nitrile

| α,β-Unsaturated Nitrile | Reaction Conditions | Yields | Enantiomeric Excess (%) |
|-------------------------|--------------------|--------|-------------------------|
| 9a, 91%, 92% ee         | 8 (0.2 mmol), 4 (0.3 mmol, 1.5 equiv), TMDS (3.0 equiv), Cu(OAc)2 (5 mol %), and chiral ligand L2 (5 mol %) in 2.0 mL dry THF at room temperature for 48 h | 9b, 9c, 9d, 9e, 9f, 9g, 9h, 9i, 9j, 9k, 9l, 9m, 9n, 9o, 9p, 9q, 9r, 9s, 9t, 9u, 9v, 9w, 9x, 9y, 9z | 72%, 93%, 82%, 96%, 99%, 95%, 98%, 96%, 97%, 99%, 78%, 90%, 99%, 84%, 83%, 84%, 82%, 96%, 90%, 92%, 96%, 90%, 93% |
| Ar-CN                  | R1R2N-OBz          | Cu(OAc)2 (5 mol %) | L2 (5 mol %) |
| THF, rt, 48 h          | TMDS (3.0 equiv)   |

* Reaction conditions: α,β-ununsaturated nitrile 8 (0.2 mmol), 4 (0.3 mmol, 1.5 equiv), TMDS (3.0 equiv), Cu(OAc)2 (5 mol %), and chiral ligand L2 (5 mol %) in 2.0 mL dry THF at room temperature for 48 h.
* Yields were determined by 'H NMR spectroscopy using CH2Br2 as an internal standard and ee value determined by HPLC.
Conclusion

We have developed an efficient reversal hydroamination strategy of α,β-unsaturated carboxylic acid, ester, amide, and nitrile through precise choice of chiral ligand, providing a unified approach for the convenient and rapid synthesis of an array of important chiral β-amino acids and their derivatives with a high level of regio- and enantiocontrol. This approach not only provides an alternative route to traditional aza-Michael addition but also opens a new door to the challenging asymmetric addition of other nucleophiles to low reactivity of Michael acceptors. Mechanism studies are currently underway in our lab.

Footnote

*a* We note that during the preparation of this manuscript (the preprint version was submitted on July 3, 2020), with 1,2-benzisoxazole as the aminating reagent, Guo, Buchwald, and co-worker reported a reversal asymmetric hydroamination of mainly focusing on β-aryl-substituted acrylates.

Supporting Information

Supporting Information is available.

Conflict of Interest

There is no conflict of interest to report.

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