Catalytic Asymmetric Radical Diamination of Alkenes

Liu and colleagues describe the asymmetric radical diamination of alkenes triggered by intermolecular addition of dialkylaminyl or azidyl radical to the alkene under Cu(I)/chiral phosphoric acid dual catalysis. This reaction enables direct incorporation of alkylamine moieties and provides convenient and practical access to a wide range of highly enantio-enriched β-alkylamine-containing pyrrolidines. Moreover, the resulting α-tertiary pyrrolidine-derived diamine proves to significantly promote the enantioselectivity of an asymmetric Michael reaction.
Catalytic asymmetric radical diamination of alkenes

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SUMMARY
Catalytic asymmetric diamination of alkenes is a highly attractive method for creating chiral vicinal diamines, which are ubiquitous in biologically active molecules and versatile ligands as well as organocatalysts. We report the use of O-acylhydroxylamines as dialkylaminy l radical precursors to trigger asymmetric diamination of alkene under Cu(I)/chiral phosphoric acid dual catalysis. This reaction allows for direct alkylamine incorporation and features high enantioselectivity, a broad substrate scope, wide functional-group tolerance, and mild reaction conditions, providing convenient and practical access to a wide range of highly enantio-enriched β-alkylamine-containing pyrrolidines. We have also achieved asymmetric azidoamination of alkenes by using azidiodi nane as an azidyl radical precursor, offering a complementary method for preparing diverse chiral β-amino pyrrolidines. The application of the resultant α-tertiary pyrrolidine-derived diamine was showcased to significantly promote the enantioselectivity of an asymmetric Michael reaction.

INTRODUCTION
Chiral vicinal diamines represent key structural elements in a large number of natural products, pharmaceutical agents, and agrochemicals.1–8 They also constitute excellent platforms for the development of chiral ligands, organocatalysts, and auxiliaries with broad utility in asymmetric synthesis.9,10 Consequently, expedited assembly of vicinal diamines from readily available precursors has long been recognized as a preeminent goal in organic synthesis.1–8,11–13 In this regard, catalytic asymmetric diamination of unactivated alkenes with transition-metal or aryliodine(I) catalysts represents a straightforward and highly attractive method for creating such useful vicinal diamine scaffolds, given the facile accessibility of alkene starting materials.14–25 However, the amine introduced by these asymmetric catalytic systems has to be masked by electron-withdrawing protecting groups, and direct incorporation of free alkylamine has so far remained elusive (Scheme 1A).

Two major factors have contributed to the lack of development of asymmetric alkene diamination with protection-free alkylamine.14–25 On the one hand, the high affinity of a strongly Lewis-basic alkylamine for transition metal could lead to the formation of stable amine-metal complexes, thus resulting in poisoning of transition-metal catalysts. On the other hand, protection-free alkylamine is susceptible to oxidation under reported oxidative diamination reaction conditions.14–25 As a result, successful diamination of unactivated alkenes typically requires adequate electron-withdrawing protecting groups to suppress undesired strong ligation and amine oxidation, making these methods indirect for free amine synthesis and inconvenient for subsequent amine transformation (Scheme 1A).
To address these challenges, we became interested in the use of alkylaminyl radical as a key reactive intermediate for direct diamination of unactivated alkenes.\textsuperscript{26–28} We envisioned that the Cu(I)-chiral phosphoric acid-catalyzed\textsuperscript{29–35} asymmetric radical diamination of alkenes with electrophilic aminating reagents such as O-acylhydroxylamines,\textsuperscript{36–55} if successful, would provide a direct, convenient, and powerful approach to enantio-enriched vicinal diamines bearing alkylamine moieties (Scheme 1B).

**RESULTS AND DISCUSSION**

**Research Design**

We expected a catalytic cycle wherein the copper-stabilized dialkylaminyl radical I would be first generated from the reaction of O-acylhydroxylamine 2 with Cu(I)/CPA.
via a single electron transfer process (Scheme 1C).\textsuperscript{26–28,47,48,52} Subsequently, the electrophilic dialkylaminyl radical I would undergo intermolecular addition to an olefin acceptor to deliver two new C–N bonds, hopefully with a superior level of enantiocontrol in the presence of Cu/CPA catalyst. Noteworthy is the dual role of O-acylhydroxylamine 2 as both an alkylamine source and an oxidant in this process, which would not only circumvent the catalyst poisoning associated with the use of a free alkylamine but also dispense with excess external oxidants required in oxidative diamination reactions, thus overcoming challenges in previous asymmetric diamination of alkenes.\textsuperscript{14–25} Here, we describe our efforts toward the development of asymmetric radical diamination of alkenes with dialkylaminyl or azidyl radical species in the presence of a dual Cu(I)/CPA catalytic system, affording \( \alpha \)-tertiary pyrrolidines bearing a \( \beta \)-alkylamine moiety with excellent yields and enantioselectivity. Such enantio-enriched \( \beta \)-alkylamine-containing pyrrolidines have great potential for applications in asymmetric synthesis and medicinal chemistry.\textsuperscript{56–62}

**Optimization Study**

We began our investigation by reacting \( \text{N-alkenyl urea} \) 1a and O-benzoyl hydroxylmorpholine 2a with Cu(CH\(_3\)CN)\(_4\)PF\(_6\) (10 mol %) and CPA (\(R\))-A1 (15 mol %). To our delight, the desired 1,2-diamination product 3A was obtained in 85% yield, albeit with low enantioselectivity (13% ee) (Table 1, entry 1). Under these reaction conditions, a variety of BINOL- and SPINOL-based CPAs\textsuperscript{63–71} were initially evaluated (entries 1–6) and good results (52% ee, entry 4) were obtained with SPINOL-based (S)-A4 with 4-Ph-phenyl groups at the 3,3\textsuperscript{0} positions of the backbone. We next screened a series of Cu(I) catalysts and organic solvents (entries 7–13) and found that the use of Cu(CH\(_3\)CN)\(_4\)BF\(_4\) as catalyst in 1,4-dioxane was the best (57% yield and 86% ee; entry 10). Fine-tuning of the electronic nature of the benzoyl group of 2a–2d (entries 14–17) led to the identification of 2c bearing an OMe group at the para position of the benzene ring as the optimal aminyl radical precursor, because the use of 2c gave the best result with 3A in 75% yield and 84% ee with a mixed solvent system of 1,4-dioxane/CHCl\(_3\) (1:4) (entry 16). In addition, the use of 5 Å molecular sieves improved the reaction efficiency remarkably (76% yield and 93% ee; entry 19). Furthermore, elongating the reaction time and increasing the amount of 2c together with a lowered catalyst loading of CPA slightly boosted both the reaction efficiency and enantioselectivity (entry 20).

**Scope of the Investigation**

With the optimal reaction conditions in hand, we first investigated the substrate scope of the asymmetric radical alkene 1,2-diamination for urea aryl and tethering groups (Figure 1; see also Figures S3–S46 and S152–S181). Typically, ureas 3A–3D bearing electro-deficient aryl rings were viable substrates. Substrates containing three- to seven-membered rings within the backbone were well tolerated to produce spiro products 3E–3I in good yields with excellent ee. Interestingly, geminal di-phenyl (1j) and di-ester (1k) groups in the tether had no significant influence on the reaction to give 3J and 3K in 81% and 62% yields with 95% and 94% ee, respectively. It is more encouraging to note that the unbranched substrates 1l–1o underwent the current reaction smoothly to give the corresponding products 3L–3O in good enantioselectivities with an increased catalyst loading.

Next, a wide range of substrates with different alkenyl aryl rings were surveyed (Figure 2; see also Figures S47–S92 and S182–S213). It was found that \( \text{meta or para} \) substitutions on the benzene ring generally did not significantly affect the enantioselectivity, whatever the electronic nature (91%–94% ee, 3P–3V). A bicyclic naphthalene ring in 1t was also suitable for this reaction to provide comparable
Table 1. Screening of Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>CPA</th>
<th>2</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>(R)-A1</td>
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<td>DCE</td>
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<td>2a</td>
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<td>77</td>
<td>76</td>
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<td>9</td>
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<td>2a</td>
<td>1,4-dioxane</td>
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<td>2c</td>
<td>1,4-dioxane</td>
<td>82</td>
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Abbreviations: CPA, chiral phosphoric acid; DCE, 1,2-dichloroethane; and MS, molecular sieves. Reaction conditions: 1a (0.05 mmol), 2 (2 equiv), Cu(CH3CN)4PF6 (10 mol %), CPA (15 mol %), solvent (1.0 mL), 60 °C, 20 hr under argon.

^aYield based on ^1H NMR analysis of the crude product with CH2Br2 as an internal standard.

^bEe value based on high-performance liquid chromatography analysis.

^cCu(CH3CN)4BF4 (10 mol %).

^dCuCl (10 mol %).

^eCuBr (10 mol %).

^fCuOAc (10 mol %).

^g1,4-Dioxane/CHCl3 (1:4) was used.

^h1.2 equiv of 2c was used with 4 Å MS at 40 °C for 40 hr.

^i1.2 equiv of 2c was used with 5 Å MS at 40 °C for 40 hr.

^j1.5 equiv of 2c and 10 mol % of (S)-A4 was used with 5 Å MS at 40 °C for 60 hr.
enantioselectivity with those obtained with other monocyclic aryl rings. Importantly, many common functional groups, such as acid-sensitive acetal, oxidant-labile free aldehyde, and potentially amine-reactive ester, were all well tolerated to give the desired products $3W$–$3Y$ in 64%–70% yield and 86%–93% ee. In addition, extra double and triple bonds in the substrates remained intact during the reaction to afford corresponding highly enantio-enriched products $3Z$ and $3Za$, respectively. To further investigate the reaction scope, we tested the use of alkenyl-substituted alkenes (dienes) as the substrate under the standard reaction conditions. To our delight, the reaction gave the desired products $3Zb$ and $3Zc$ in 72% and 98% ee, respectively. Heteroarene-substituted alkenes could also be used in the reaction to give the desired products $3Zd$ and $3Ze$ in moderate yields with good to excellent enantioselectivity. Such broad functional-group tolerance ensures great potential for further versatile transformations. The absolute configuration of the chiral carbon center in $3T$ has been determined to be $S$ by X-ray crystallographic analysis (Figure 2; see also Figure S1 and the Supplemental Information for details).

We then evaluated the scope for dialkylaminyl radical by using various O-benzoylhydroxylamines $2$ (Figure 3; see also Figures S93–S110 and S214–S225). A wide range of six-membered cyclic dialkylaminyl radicals, including piperidyl, 4-methoxy-piperidyl, 4-ethoxycarbonyl-piperidyl, 4-methylsulfonyl-piperazyl, and 4-tosyl-piperazyl ones, were all applicable to afford desired products $3Zf$–$3Zj$ in 44%–88% yields.
with 90%–97% ee. In addition, a seven-membered dialkylaminyl radical derived from 1,4-diazepane was also viable, giving rise to the formation of 3Zk in 67% yield with 93% ee. Asymmetric diamination of alkenes with an acyclic amine reagent such as...
N-fluorobenzenesulfonimide (NFSI) as the nitrogen source in the presence of the Cu(I)/CPA catalytic system has been achieved in moderate yield with moderate enantioselectivity, and is currently under further optimization in our laboratory (Scheme S1 and Figures S111–S113, S226, and S227).

To expand the scope of other radical precursors of this methodology, we next focused our attention on the azidyl radical generated from iodine(III) reagent azidoiodinane (4a). As expected, the reaction of substrate 1a with 4a in the presence of CuI (10 mol%) and (S)-A5 (10 mol%) with 1.2 equiv. of NaHCO₃ and 4 Å molecular sieves in 1,4-dioxane at 25°C for 24 hr delivered the desired azidoamination product 5A in 83% yield with 92% ee (Figure 4; see also Figures S114–S116, S228, and S229), after systematic optimization of different reaction parameters (Table S1). Similar results were obtained in the reaction of a series of N-alkenyl ureas to afford the expected products 5B–5E (Figures S117–S127) in 75%–90% yields with 85–94% ee (Figures S230–S237).

**Mechanistic Study**

To probe the reaction mechanism, a radical trapping experiment with 2,2,6,6-tetramethylpiperidinylhydroxylamine (TEMPO) was conducted to reveal significant inhibition of the desired reaction (Scheme S2, equation 1). This observation suggests that alkylaminyl radical I is likely generated in situ, which upon further addition to alkene gives rise to alkyl radical II (Scheme 1C). Next, no reaction of 1a occurred in the absence of O-benzoylhydroxylamine 2c under the otherwise standard conditions (Scheme S2, equation 2). Thus, a mechanism involving an initial aminocupration followed by...
homolysis of the resultant C–Cu bond and subsequent coupling with an alkylaminyl radical is unlikely. Overall, all these experimental observations as well as previous studies favor our initial mechanistic proposal involving a process initiated by the intermolecular addition of aminyl radical to alkene, as shown in Scheme 1C.

**Transformation and Application**

To demonstrate the synthetic utilities of the current protocol, the urea group of 3A was readily removed to give α-tertiary pyrrolidine-derived diamine 6 in 68% yield and the enantiopurity was completely retained (Scheme 2, equation 1; see also Figures S128, S129, S238, and S239). In addition, product 3A was also smoothly cyclized under oxidative conditions to give bicyclic amine 7 in 96% yield as a 1:1 mixture of diastereomers without obvious loss in enantiopurity (Scheme 2, equation 2; see also Figures S130–S135, S240–S243, and S255–S258). The structure of 7 is the core component of many biologically active compounds (Figure S2). Pyrrolidine tethered with a tertiary amine moiety has been widely used as powerful organocatalysts. To further demonstrate the potential of the resulting α-tertiary pyrrolidine-derived diamine as organocatalyst, the asymmetric Michael reaction of β-nitrostyrene with propionaldehyde was investigated as a model reaction. To our delight, 6 as the catalyst showed better enantioselectivity and diastereoselectivity (Figures S136–S139 and S252–S254) than the commonly used (S)-(+) 1-(2-pyrrolidinylmethyl)pyrrolidine catalyst 8 under otherwise identical reaction conditions (Scheme 2, equation 3). Most importantly, the azido group in the resultant pyrrolidine-derived product can be easily converted to a number of useful nitrogen-containing functional groups, such as β-primary, secondary, or tertiary amine-containing pyrrolidines 10–12 in moderate to good yields through simple and versatile transformations (Scheme 2, equation 4; see also Figures S140–S148 and S244–S249). In addition, anti-diabetic analog 13 was obtained from 5A in 90% yield (Scheme 2, equation 5; see also Figures S2, S149–S151, S250, and S251). No erosion of enantiomeric excess was observed in any of these cases. These results clearly indicated great potential application in asymmetric synthesis for these chiral diamine compounds.

**Conclusion**

We have developed an asymmetric radical diamination and azidoamination of alkenes for the direct incorporation of alkylamine under Cu(I)/phosphoric acid dual catalysis. This transformation enables facile access to enantio-enriched α-tertiary
pyrrolidines bearing a β-alkylamine moiety with high efficiency, remarkable enantioselectivity, excellent functional-group compatibility, and wide substrate scope. Furthermore, the resultant α-tertiary pyrrolidine-derived diamine was showcased to significantly promote the enantioselectivity of an asymmetric Michael reaction, bringing about a different direction for the development of such organocatalysts. Further studies including the expansion toward other substrate classes, product application, and the development of a more challenging intermolecular asymmetric version are ongoing in our laboratory.1–8

**EXPERIMENTAL PROCEDURES**

Full experimental procedures are provided in the Supplemental Information.
AUTHOR CONTRIBUTIONS

F.-L.W., X.-Y.D., and J.-S.L. discovered the reaction. F.-L.W. and X.-Y.D. performed the optimization. F.-L.W., X.-Y.D., Y.Z., G.-Y.J., X.-Q.G., and C.-L.M. investigated the scope of the substrate, and G.-Y.J. and Q.-S.G. performed the application. X.-Y.L. directed the project. X.-Y.L. wrote the manuscript with input from all authors. All authors analyzed the results and commented on the manuscript.

ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (nos. 21722203, 21572096, and 21602098) and Shenzhen special funds for the development of biomedicine, Internet, new energy, and new material industries (JCYJ20170412152435366 and JCYJ20170307105638498) is greatly appreciated.

Received: June 29, 2017
Revised: September 4, 2017
Accepted: October 17, 2017
Published: November 9, 2017

REFERENCES AND NOTES


