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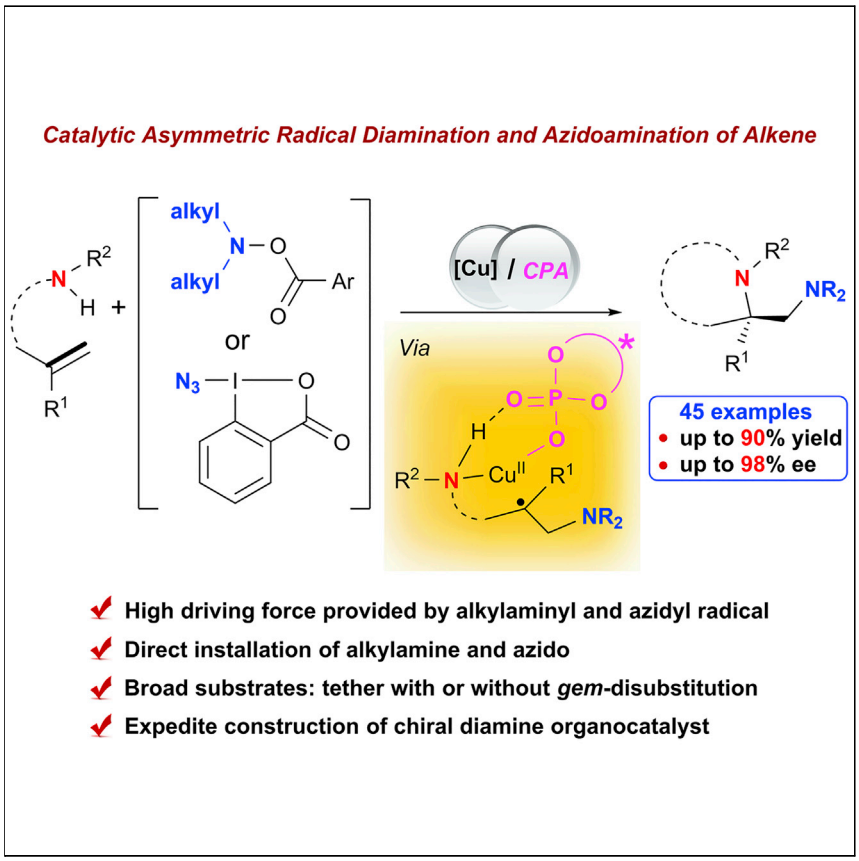
# Catalytic Asymmetric Radical Diamination of Alkenes




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.

Fu-Li Wang, Xiao-Yang Dong, Jin-Shun Lin, ..., Xian-Qi Guo, Can-Liang Ma, Xin-Yuan Liu

liuxy3@sustc.edu.cn

## HIGHLIGHTS

Asymmetric radical diamination under copper/chiral phosphoric acid dual catalysis

Direct incorporation of alkylamine and azido moieties

Efficient synthesis of chiral α-tertiary pyrrolidines

Demonstrated great potential for application of diamine products as organocatalysts

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# Catalytic Asymmetric Radical Diamination of Alkenes

Fu-Li Wang,[1,2,3] Xiao-Yang Dong,[1,3] Jin-Shun Lin,[1,3] Yang Zeng,[1] Guan-Yuan Jiao,[1] Qiang-Shuai Gu,[1] Xian-Qi Guo,[1] Can-Liang Ma,[1] and Xin-Yuan Liu[1,4,*]

## 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 dialkylaminyl 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 azidoiodinane 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).

### The Bigger Picture

Chiral vicinal diamines are characteristic and essential motifs embedded in numerous biologically active molecules. In addition, they are also the core scaffolds for a diverse range of chiral ligands, organocatalysts, and auxiliaries widely used in organic synthesis. For their preparation, asymmetric diamination of readily available alkenes constitutes an expedient and important method for accessing enantio-enriched vicinal diamines. However, none of the known strategies are able to directly introduce a protection-free alkyl amine moiety, mainly because of its strong coordination capability, mostly leading to transition-metal catalyst poisoning and susceptibility to oxidation. As a consequence, both the step economy and amine scope are compromised, thus limiting broad applicability. Here, we report the asymmetric radical diamination of alkenes under Cu(I)/chiral phosphoric acid dual catalysis, enabling direct incorporation of alkyl amine groups.

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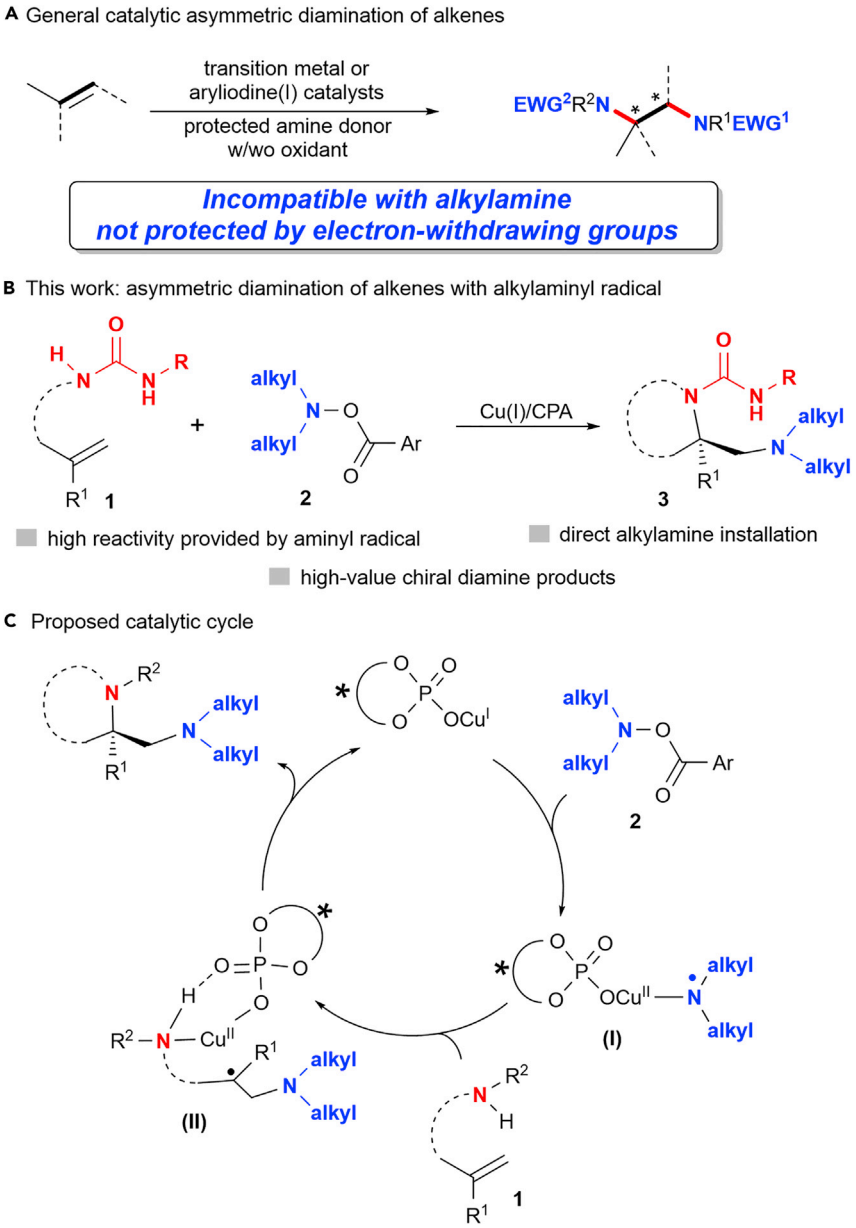


**Scheme 1. Asymmetric Diamination of Alkenes for the Construction of Chiral Vicinal Diamines**

To address these challenges, we became interested in the use of alkylaminyl radical as a key reactive intermediate for direct diamination of unactivated alkenes.[26–28] We envisioned that the Cu(I)-chiral phosphoric acid-catalyzed[29–35] asymmetric radical diamination of alkenes with electrophilic aminating reagents such as *O*-acylhydroxylamines,[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

[1]Department of Chemistry, South University of Science and Technology of China, Shenzhen 518055, China

[2]Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

[3]These authors contributed equally

[4]Lead Contact

*Correspondence: liuxy3@sustc.edu.cn

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via a single electron transfer process (Scheme 1C).[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.[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 α-tertiary pyrrolidines bearing a β-alkylamine moiety with excellent yields and enantioselectivity. Such enantio-enriched β-alkylamine-containing pyrrolidines have great potential for applications in asymmetric synthesis and medicinal chemistry.[56–62]

## Optimization Study

We began our investigation by reacting *N*-alkenyl urea **1a** and *O*-benzoyl hydroxylmorpholine **2a** with $Cu(CH_3CN)_4PF_6$ (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[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′-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 $Cu(CH_3CN)_4BF_4$ 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 *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

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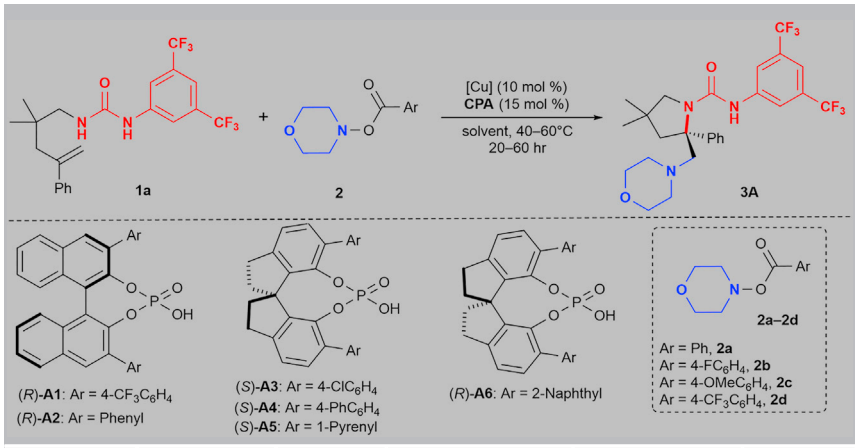
**Table 1. Screening of Reaction Conditions**




| Entry | CPA | 2 | Solvent | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | (*R*)-A1 | 2a | DCE | 85 | 13 |
| 2 | (*R*)-A2 | 2a | DCE | 73 | 8 |
| 3 | (*S*)-A3 | 2a | DCE | 72 | 33 |
| 4 | (*S*)-A4 | 2a | DCE | 82 | 52 |
| 5 | (*S*)-A5 | 2a | DCE | 65 | 26 |
| 6 | (*R*)-A6 | 2a | DCE | 78 | −33 |
| 7 | (*S*)-A4 | 2a | $CHCl_3$ | 88 | 73 |
| 8 | (*S*)-A4 | 2a | toluene | 77 | 76 |
| 9 | (*S*)-A4 | 2a | 1,4-dioxane | 52 | 84 |
| 10[c] | (*S*)-A4 | 2a | 1,4-dioxane | 57 | 86 |
| 11[d] | (*S*)-A4 | 2a | 1,4-dioxane | 32 | 81 |
| 12[e] | (*S*)-A4 | 2a | 1,4-dioxane | 34 | 85 |
| 13[f] | (*S*)-A4 | 2a | 1,4-dioxane | 42 | 80 |
| 14[c] | (*S*)-A4 | 2a | –[g] | 71 | 84 |
| 15[c] | (*S*)-A4 | 2b | –[g] | 68 | 80 |
| 16[c] | (*S*)-A4 | 2c | –[g] | 75 | 84 |
| 17[c] | (*S*)-A4 | 2d | –[g] | 65 | 77 |
| 18[c,h] | (*S*)-A4 | 2c | 1,4-dioxane | 76 | 86 |
| 19[c,i] | (*S*)-A4 | 2c | 1,4-dioxane | 76 | 93 |
| 20[c,j] | (*S*)-A4 | 2c | 1,4-dioxane | 82 | 94 |

Abbreviations: CPA, chiral phosphoric acid; DCE, 1,2-dichloroethane; and MS, molecular sieves. Reaction conditions: **1a** (0.05 mmol), **2** (2 equiv), $Cu(CH_3CN)_4PF_6$ (10 mol %), CPA (15 mol %), solvent (1.0 mL), 60°C, 20 hr under argon.

[a]Yield based on $^1H$ NMR analysis of the crude product with $CH_2Br_2$ as an internal standard.

[b]Ee value based on high-performance liquid chromatography analysis.

[c]$Cu(CH_3CN)_4BF_4$ (10 mol %).

[d]CuCl (10 mol %).

[e]CuBr (10 mol %).

[f]CuOAc (10 mol %).

[g]1,4-Dioxane/$CHCl_3$ (1:4) was used.

[h]1.2 equiv of **2c** was used with 4 Å MS at 40°C for 40 hr.

[i]1.2 equiv of **2c** was used with 5 Å MS at 40°C for 40 hr.

[j]1.5 equiv of **2c** and 10 mol % of (*S*)-**A4** was used with 5 Å MS at 40°C for 60 hr.

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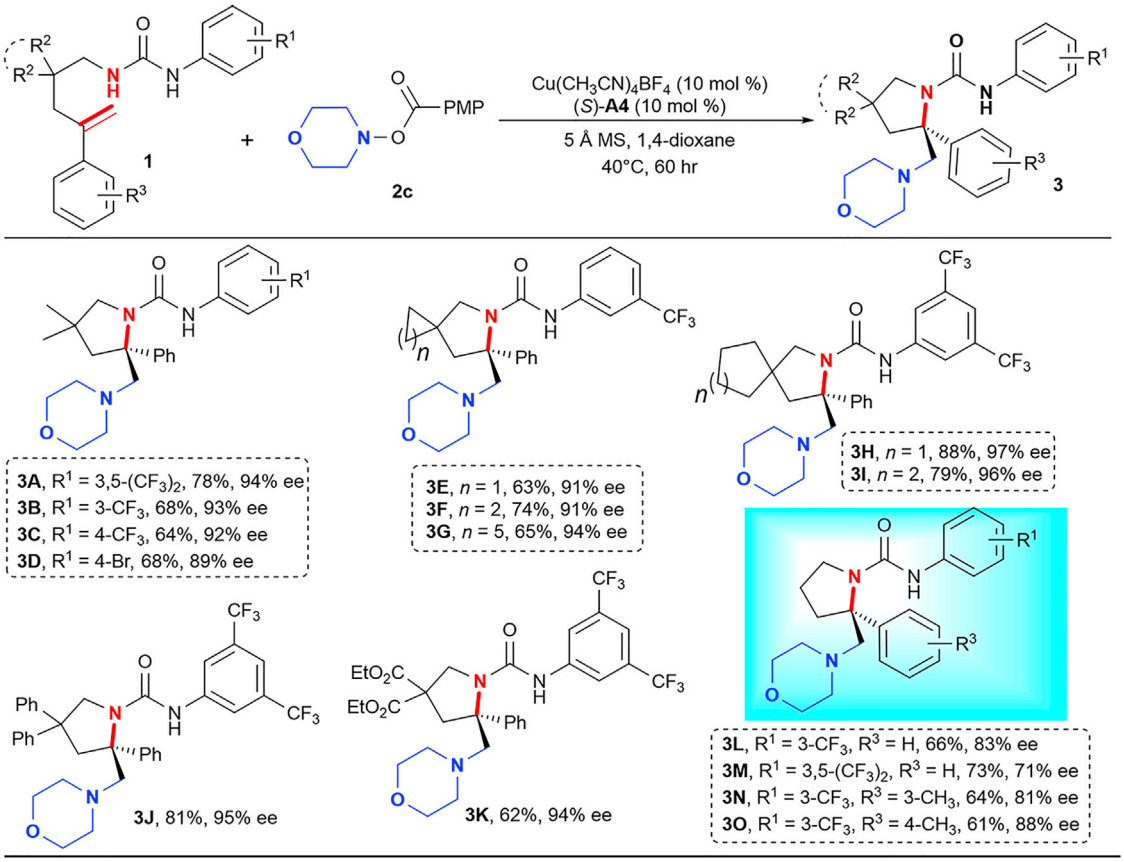


**Figure 1. Substrate Scope for Urea Aryl and Tethering Groups**

All the reactions were conducted on 0.1 mmol scale. All yields are isolated yields based on **1**. Ee was determined by high-performance liquid chromatography (HPLC) analysis. For **3B**, the reaction was run for 80 hr. For **3L-O**, 15 mol % $Cu(CH_3CN)_4BF_4$ and 20 mol % (*S*)-**A4** were used.

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-ethoxylcarbonyl-piperidyl, 4-methylsulfonyl-piperazyl, and 4-tosyl-piperazyl ones, were all applicable to afford desired products **3Zf–3Zj** in 44%–88% yields

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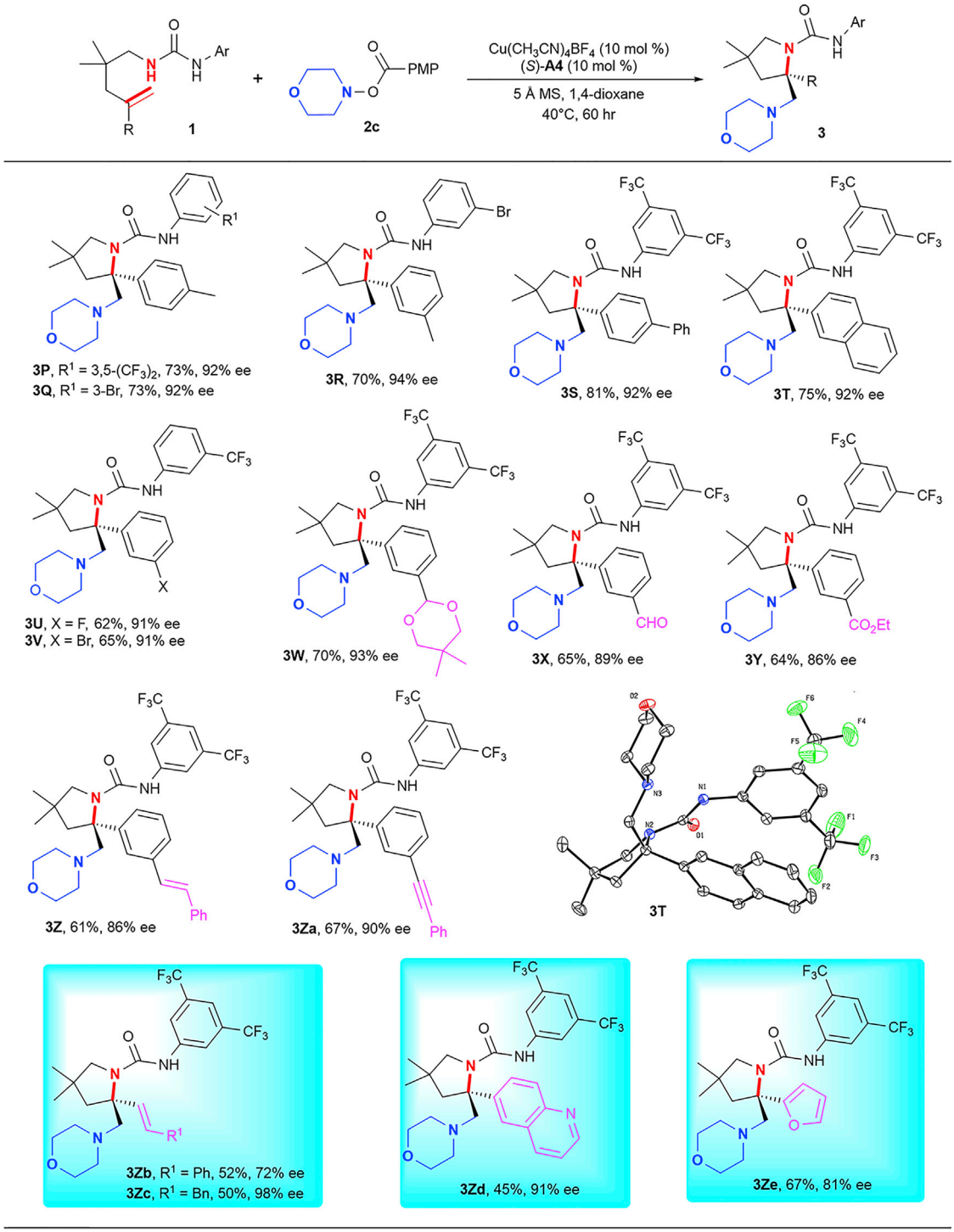


**Figure 2. Substrate Scope for Alkenyl Aryl Rings**

All the reactions were conducted on 0.1 mmol scale. All yields are isolated yields based on **1**. Ee was determined by HPLC analysis. For **3Q**, **3R**, **3U**, and **3V**, the reaction was run for 80 hr.

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 alkene with an acyclic amine reagent such as

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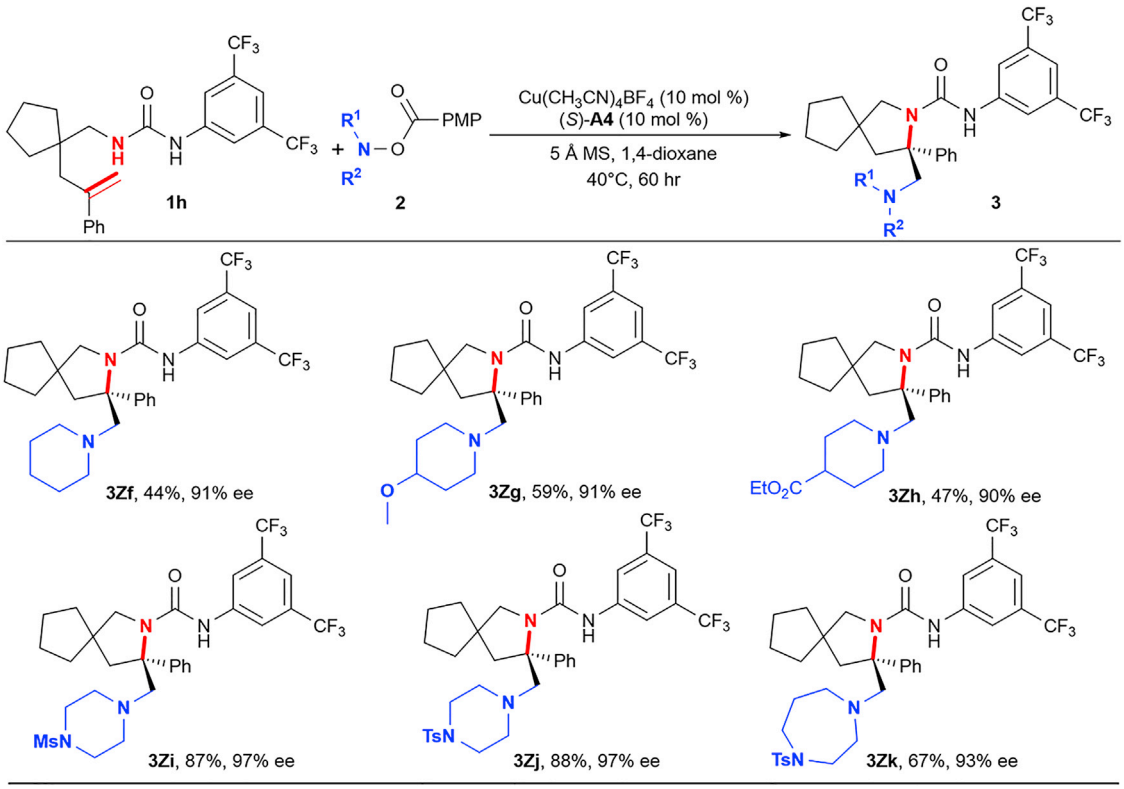



**Figure 3. Substrate Scope for Dialkylaminyl Radical**

All the reactions were conducted on 0.1 mmol scale. All yields are isolated yields based on **1h**. Ee was determined by HPLC analysis. For **3Zg**, 15 mol % (*S*)-**A4** was used.

*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 $NaHCO_3$ 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-tetramethyl-1-piperidinyloxy (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

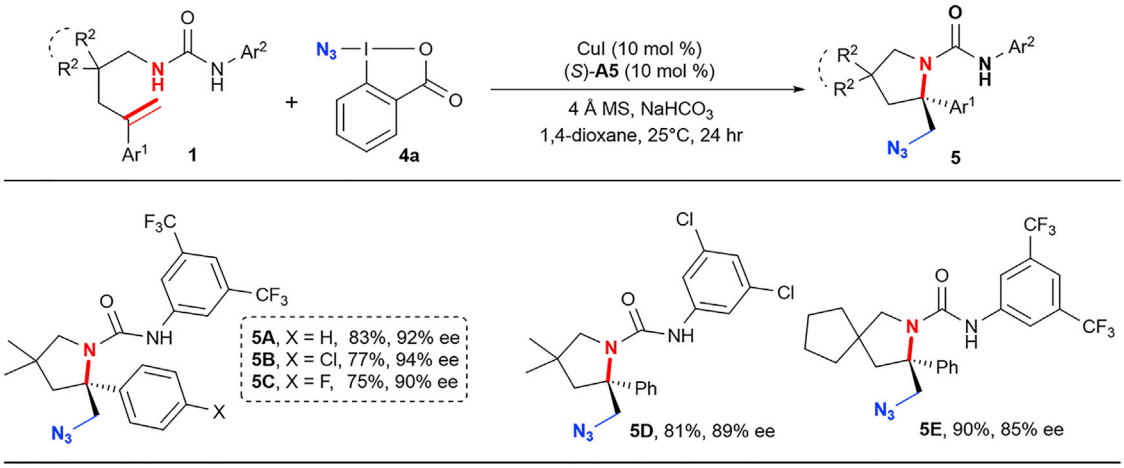



**Figure 4. Substrate Scope for Azidyl Radical**

All the reactions were conducted on 0.1 mmol scale. All yields are isolated yields based on **1**. Ee was determined by HPLC analysis.

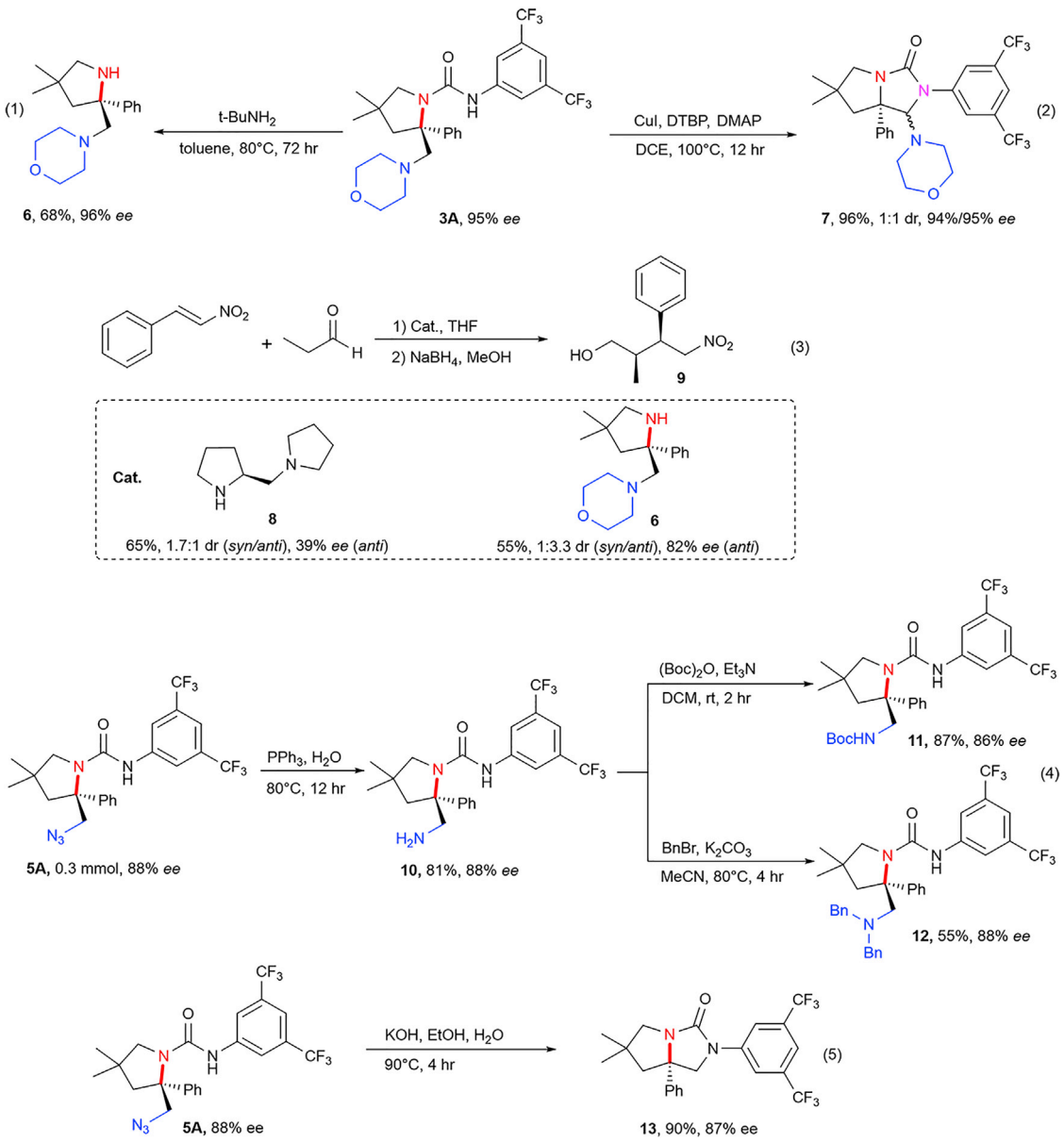
homolysis of the resultant C–Cu bond and subsequent coupling with an alkylaminyl radical is unlikely.[47,72] Overall, all these experimental observations as well as previous studies[26–33,47,48,52] favor our initial mechanistic proposal involving a process initiated by the intermolecular addition of 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).[56–60,73] Pyrrolidine tethered with a tertiary amine moiety has been widely used as powerful organocatalysts.[61,62,74–78] 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).[74] 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).[73] 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




**Scheme 2. Representative Product Transformation and Application**

Abbreviations: DCE, 1,2-dichloroethane; DMAP, 4-dimethylaminepyridine; DTBP, di-*tert*-butyl peroxide; and THF, tetrahydrofuran.

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.

## DATA AND SOFTWARE AVAILABILITY

The data for the X-ray crystallographic structure of **3T** have been deposited in the Cambridge Crystallographic Data Center under accession number CCDC: 1542541.

## SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, X-Ray Crystallographic Data, 258 figures, 1 table, 2 schemes, and 1 data file and can be found with this article online at https://doi.org/10.1016/j.chempr.2017.10.008.

## 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.

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