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Preview

Removing the Mask in Catalytic Asymmetric Diamination of Alkenes

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In this issue of *Chem*, Liu and co-workers report an extremely general and mild radical diamination protocol that permits the asymmetric synthesis of vicinal diamines in a highly enantioselective manner under a copper(I)/chiral phosphate dual-catalytic system. Notably, this work represents the first asymmetric radical alkene diamination that allows for direct alkylamine incorporation.

Chiral vicinal diamines have been identified as one of the most important structural motifs. Not only are they abundant in natural products and biologically active molecules, but they are also privileged scaffolds for various auxiliaries, ligands, and organocatalysts because they enable a broad range of stereoselective transformations, including reductions, oxidations, additions, and many other types of bond-formation reactions.^{1,2} Because of their extreme importance, continuing efforts have been devoted to accessing these scaffolds. For example, classical resolution, chiral pool strategy, and multi-step asymmetric trans-

formations based on different starting materials have been developed. Nevertheless, given the ready availability of structurally diverse starting material, time efficiency, and practicality, the diamination of alkenes represents one of the most convenient and straightforward approaches to forging two nitrogen-based functional groups at the same time. In contrast to well-established dihydroxylation and amino-hydroxylation processes, the conceptually similar, catalytic enantioselective alkene diamination is still a long-standing challenge and remains largely underdeveloped. The inherent capability of diamines to coordinate almost

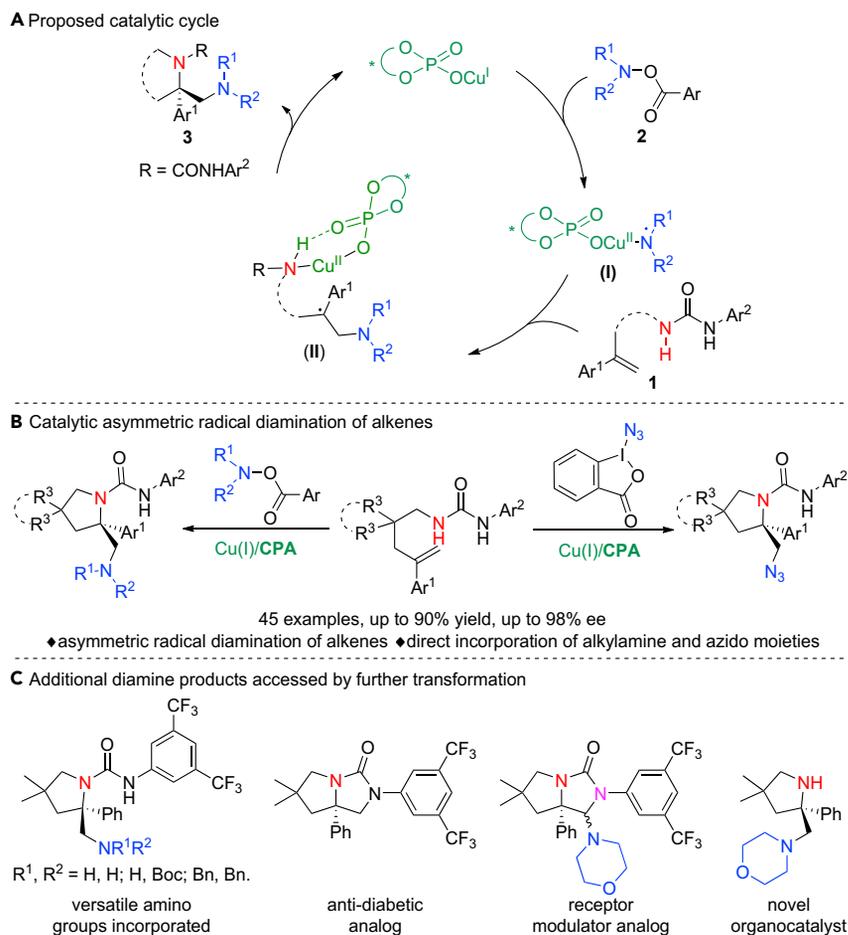
every transition metal renders catalytic enantioselective variants particularly unfavorable because of the poisoning of the potential metal catalyst, thus leading this field to lag far behind.

In this regard, the so-far-reported examples involving the catalytic enantioselective diamination of alkenes with metals, although still scarce, are of great significance.³ For instance, Shi and co-workers achieved a Pd(0)-catalyzed intermolecular diamination of dienes and trienes by using diaziridine reagent as both a diamine source and an oxidant in a highly regio- and enantioselective fashion.⁴ The novel asymmetric diamination of unactivated alkenes enabled by Pd(TFA)₂ combined with a chiral oxazoline ligand was revealed by Michael and co-workers, who used *N*-fluorobenzene-sulfonamide as one source of nitrogen as well as the oxidant.⁵ In addition to establishing the palladium catalytic system, Chemler and co-workers have

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<https://doi.org/10.1016/j.chempr.2017.11.012>





Scheme 1. Catalytic Asymmetric Radical Diamination of Alkenes Enabled by Copper(I)/Chiral Phosphate Dual Catalysts

developed a highly efficient copper-catalyzed asymmetric intra- or intermolecular alkene diamination with a broader substrate scope in the presence of a stoichiometric amount of MnO_2 and catalytic amounts of KMnO_4 .⁶ Aside from conventional metal promoters, it is worth highlighting that an alternative and attractive intermolecular diamination of styrenes based on homogeneous iodine catalysis was achieved by Muñiz and co-workers very recently, which represents an intriguing concept.⁷ In this case, inexpensive and commercially available 3-chloroperbenzoic acid was used as the terminal oxidant.

The above examples represent important advances in the catalytic

asymmetric diamination reactions and generally require the utilization of amines bearing electron-withdrawing groups under oxidative conditions. The direct incorporation of free alkyl amines for diaminations has not been available, yet. This is always problematic and can be traced back to two major difficulties: first, strong binding affinity of the alkylamine to metals could lead to catalyst poisoning, thus rendering the process inhibited or noncatalytic; and second, alkylamines, which are prone to oxidation, are not compatible with previously reported oxidative conditions. Accordingly, developing a diamination that has excellent asymmetric induction while involving the incorporation of alkylamines is highly challenging.

In this issue of *Chem*, Liu and co-workers have stood up to the challenge and disclose a radical process for the catalytic asymmetric diamination of alkenes.⁸ For the first time, they directly enantioselectively incorporated alkylamine and azido moieties in such a process. It is worth mentioning that steering the reaction course of highly reactive odd-number electron species in a stereocontrolled and catalytic fashion is always problematic. However, Liu and co-workers recently championed the development of a copper(I)/chiral phosphate system as a robust single-electron-transfer catalyst, which enables several successful transformations involving the catalytic asymmetric radical difunctionalization of alkenes.^{9–11} On this basis, Liu and co-workers started to initiate a program to determine whether they could achieve a straightforward entry to enantioenriched vicinal diamines bearing alkylamine moieties by exploiting the radical process promoted by copper(I)/chiral phosphate catalysis.

The entry point was the investigation of electrophilic aminating reagents *O*-acylhydroxylamines **2**. Liu and co-workers proposed that a single-electron transfer between the copper(I)/chiral phosphate and *O*-acylhydroxylamines would generate the copper-stabilized dialkylaminyl radical **I**, which could undergo a rapid addition to the terminal alkene (**1**) to form the corresponding alkyl radical **II**. At this stage, the key to the superior enantiocontrol rests with the critical step involving second C–N bond formation promoted by the copper(I)/chiral phosphate (Scheme 1A).

Because of the rational and smart design, *O*-acylhydroxylamines **2** have been successfully exploited as the dialkylaminyl radical precursor and a mild oxidant to facilitate the diamination process smoothly. Under the optimized reaction conditions, Liu and co-workers revealed a remarkably broad substrate scope for

this transformation. The variation of the urea aryl tethering group as well as alkenyl aryl rings in the substrates was well accommodated, and in all cases, good yields and excellent enantioselectivities were achieved for the desired vicinal diamines. Gratifyingly, the reaction conditions were so mild that various additional functionalities, including double and triple bonds, aldehyde, and heterocycles, remained intact during the course of the reaction. On the other hand, different six- and seven-membered cyclic dialkylaminy groups were efficiently installed, further highlighting the versatility of this protocol. In addition, Liu and co-workers developed diamination reactions by employing iodine(III) reagent azidoiodinane as the nitrogen source, thus providing straightforward access to diverse enantioenriched β -azido pyrrolidines (Scheme 1B).

Liu and co-workers also conducted various transformations to demonstrate the utility of the current methodology (Scheme 1C). For example, they easily converted the azido moiety into various nitrogen-containing scaffolds without any loss in enantiopurity in any case. Particularly, a notable transformation included the removal of the urea group to afford the α -tertiary pyrrolidine-derived diamine, which served as a promising organocatalyst for the asymmetric Michael reaction of β -nitrostyrene with propionaldehyde.

In conclusion, Liu and co-workers have introduced a previously elusive asymmetric radical diamination reaction where the dialkyl amine and diazo moieties can be incorporated in a straightforward fashion under copper(I)/chiral phosphate catalysis. Based on a simple operation with mild reaction conditions, diverse enantioenriched β -alkylamine-containing pyrrolidines or β -azido pyrrolidines bearing various functional groups can be accessed with high enantioselectivities. More importantly, the resultant chiral diamines exhibit a significant performance in promoting the asymmetric Michael addition reaction, further showcasing the potential of this newly developed methodology. Given that amines masked with electron-withdrawing groups are no longer essential, this work represents a big breakthrough in the development of catalytic asymmetric diamination reactions. As an illustrative example, this work also highlights that radical processes involving highly reactive odd species can be realized in a controllable catalytic and asymmetric fashion with a rational design, which opens the door for other previously inaccessible transformations.

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