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Research Highlight

Teaching an old *N*-alkylation new tricks: from S_N1 and S_N2 *N*-alkylation to radical enantioconvergent *N*-alkylation

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Research Highlight

Teaching an old *N*-alkylation new tricks: from S_N1 and S_N2 *N*-alkylation to radical enantioconvergent *N*-alkylation

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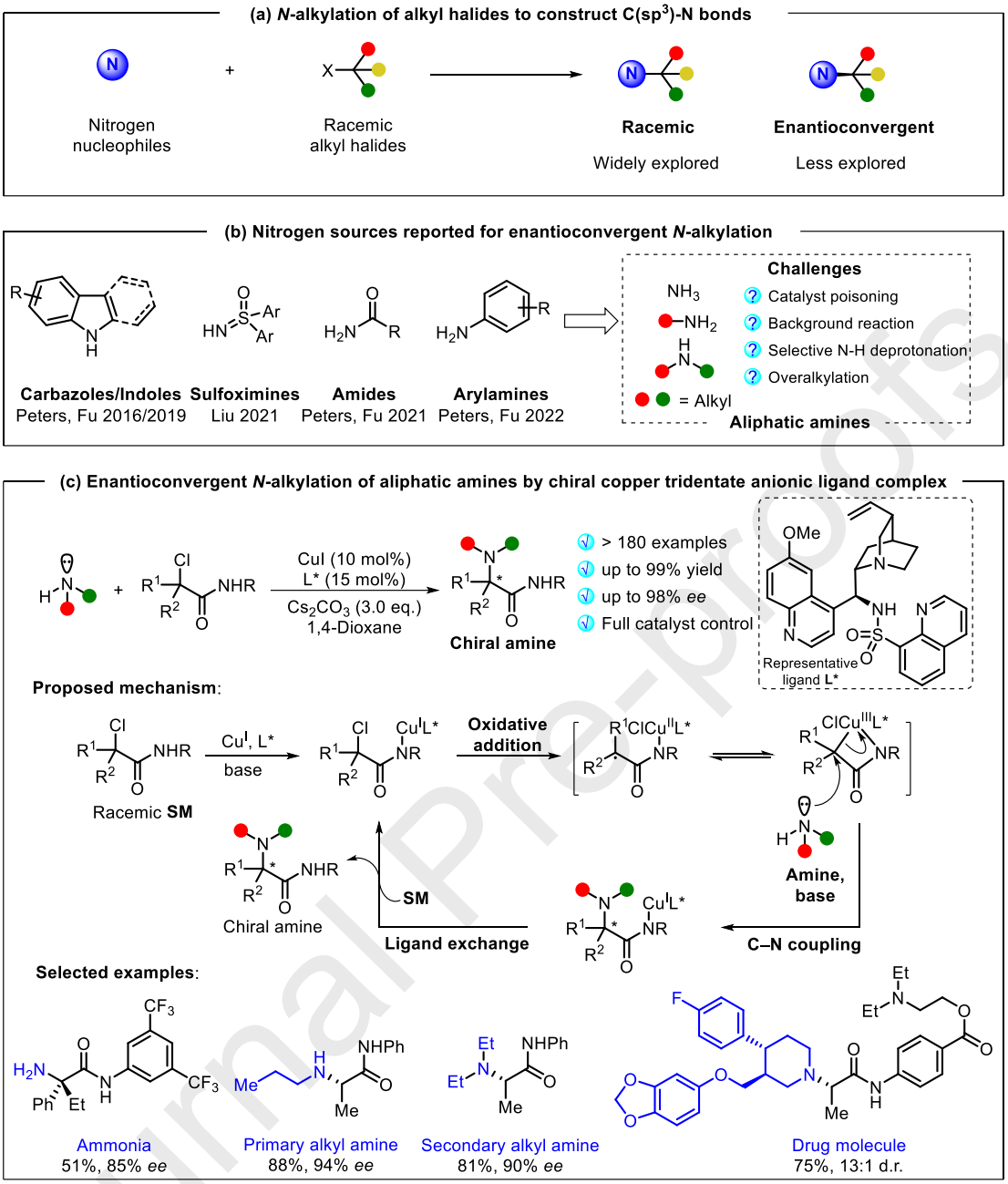
Enantiopure aliphatic amines are common chiral synthons and catalysts for the asymmetric synthesis of natural products, pharmaceutical agents, agrochemicals, and functional materials [1]. Therefore, the development of general, straightforward, and practical methodologies to access enantioenriched aliphatic amines under mild reaction conditions is a long-pursued goal in organic chemistry [2,3]. Among them, the *N*-alkylation of amines with alkyl halides (S_N1 and S_N2), which was discovered by Hofmann in 1850, is the most straightforward and widely applied approach to construct C(sp^3)–N bonds due to the readily available starting materials [4] (Scheme 1a). Although investigated for more than 150 years, its asymmetric version has been early areas of endeavor with only modest success, which largely relied on the use of enantioenriched alkyl halides.



Scheme 1 (Color online) (a) *N*-alkylation of alkyl halides to construct C(sp^3)–N bonds. (b) Nitrogen sources reported for enantioconvergent *N*-alkylation. (c) Enantioconvergent *N*-alkylation of aliphatic amines by using chiral copper tridentate anionic ligand complex.

A pioneering work of Peters, Fu, and co-workers [5,6] in 2016 demonstrated the catalytic enantioconvergent coupling of secondary and tertiary alkyl halides with carbazoles or indoles using photoinduced copper catalysis, providing a novel strategy for enantioconvergent C(sp^3)–N coupling. Shortly after, Liu group [7] utilized ureas as nucleophiles to construct

C(sp^3)–N bonds with alkenes by the introduction of a Cu(I)/chiral phosphoric acid dual-catalytic system. These two conceptual works paved the way for a shift toward radical-based *N*-alkylation, providing an attractive approach to traditional S_N1 and S_N2 process. Following these elegant works, other nitrogen nucleophiles, such as amides [8], aryl amines [9] could also undergo the corresponding enantioconvergent *N*-alkylations with alkyl halides (Scheme 1b). In the meantime, Liu and co-workers [10] have also reported copper(I)/*N,N,P*-ligand catalysts for the similar amination using sulfoximines as ammonia surrogates, thus providing expedited access to α-chiral primary amines after simple manipulation [10] (Scheme 1b). Despite these advances achieved, all these methods suffer from multistep deprotection and alkylation to synthesize α-chiral aliphatic amines, which limit the real-world applications in medicinal chemistry. As such, the development of a practical one-step enantioconvergent *N*-alkylation that directly uses feedstock chemicals, such as aliphatic amines and ammonia, would fit the strong synthetic demand for chiral aliphatic amines in both academic and industrial research. However, several daunting challenges exist in this aspect: (i) high Lewis basicity of aliphatic amines and ammonia results in poisoning metal catalysts due to strong coordination ability, (ii) the selectivity to the desired amines is generally low due to the overalkylation.

Very recently, Liu and co-workers [11] from Southern University of Science and Technology have reported a breakthrough in the catalytic asymmetric *N*-alkylation of aliphatic amines in *Nature* (Scheme 1c). In this report, divergent chiral aliphatic amines are obtained via Cu-catalyzed enantioconvergent coupling of racemic α-carbonyl alkyl halides with aliphatic amines. Building on their previous success of the copper catalyst with the cinchona alkaloid-derived bidentate anionic sulfonamide ligand in the radical cross couplings of alkyl halides, the installation of an additional coordination site such as an 8-quinolinyl group in the bidentate ligand to form a tridentate ligand, which further tighten the ligand binding, is crucial for achieving high reaction efficiency and ideal stereoselectivity for this *N*-alkylation of aliphatic amines. With the chiral tridentate anionic ligands-coordinated copper catalyst, the catalyst-poisoning problem is overcome and the undesired achiral background reaction is well suppressed. Due to the low N–H acidity of aliphatic amines, an inner-sphere process is difficult, and thus a primary or secondary amide electrophile with a free N–H group

to bind the chiral Cu catalyst to form cuprate intermediate is indispensable to enable the high chemo- and enantioselectivities.

This novel methodology shows an extremely broad substrate scope with more than 180 examples reported. Under the optimized conditions, various primary and secondary aliphatic amines including α-secondary or tertiary carbon centers could be alkylated with high chemo- and enantioselectivities. Moreover, an array of drug-related heterocycles and function groups could be well tolerated. Gratifyingly, bulk industrial feedstock amines, such as methylamine, dimethylamine, and especially the challenging ammonia of note, could transform into chiral amines with acceptable to high efficiency regardless of their well-known catalyst-poisoning effect. More importantly, 12 amine-contained pharmaceuticals with complex structures could be quickly modified and the preexisting stereocenters do not affect the catalyst-controlled stereoselectivity. Except for the secondary electrophile, tertiary racemic α-aminocarbonyl chlorides are also suitable for this reaction and the amide motifs allow the drug orthogonality. This reaction is highlighted by the expedited synthesis of useful chiral amines and drugs which presents a huge application prospect.

To shed light on the mechanism of this powerful catalytic enantioconvergent *N*-alkylation of racemic electrophiles with aliphatic amines, mechanistic studies are conducted. The radical trapping experiment and the radical clock experiment in combination with the electron paramagnetic resonance (EPR) test indicate a radical process involved in this reaction attributed to the single-electron transfer between the polyanionic coordinated copper intermediate and racemic α-aminocarbonyl chlorides. A cross-over experiment with dual nucleophilic substrate bearing aliphatic amine and sulfoximine undergoes highly chemoselective C–N cross-coupling under the present and previous conditions, which showcases a different mechanism and an out-sphere amine nucleophilic attack of Cu(III) intermediate generated from intramolecular single-electron oxidative addition is proposed.

In summary, this report features the development of a new family of chiral copper tridentate anionic ligands for the chemoselective and enantioconvergent Cu-catalyzed *N*-alkylation of aliphatic amines with α-carbonyl alkyl chlorides. This protocol provides a straightforward and efficient approach to unnatural chiral α-amino amides from feedstock chemicals including ammonia and pharmaceutically-relevant amines. The power of this

method is also demonstrated in the expedited synthesis of diversely complex amine drug molecules. Mechanistic studies show that multidentate anionic ligands are crucial for overcoming transition metal catalyst poisoning, and we believe these findings will certainly inspire future studies on the enantioconvergent construction of other C(sp^3)-heteroatom bonds.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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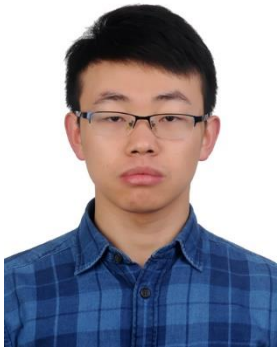

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