

Catalytic Enantioconvergent C(sp³)–N Coupling to Access Chiral Amines: A Concept Review

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Nitrogen containing compounds like chiral amines have been widely used in synthetic medicines, biomass, and fine chemical products because of their particularly valuable motifs and exceedingly broad range of functionality. Enantioconvergent synthesis of chiral amines has high atomic economy and enantioselectivity with theoretically 100% yield of enantioenriched products. In this concept article, we hope to provide a

further understanding of chiral amines enantioconvergent synthesis methodology with an introduction of recent progresses in enantioconvergent amination reactions catalyzed by early transition metals and facilitate the development of enantioconvergent C(sp³)–N coupling for benign and efficient preparation of highly valuable chiral nitrogen-containing units.

1. Introduction

Chiral amines play an important role as the structural motifs of variety natural products, biologically active compounds, and industrial chemicals.^[1] Due to the presence of heteroatoms and chiral structures, chiral amines are increasingly used in pharmaceuticals, materials, and agricultural chemicals.^[2] The general methods for synthesizing chiral amines include asymmetric hydrogenation,^[3–5] enzymatic reductive amination,^[6–8] and enantioselective addition.^[9–12] The asymmetric reduction of unsaturated compounds is the most fundamental means to introducing chirality. Other catalytic approaches based on organometallic,^[13–15] biocatalytic,^[16] and organocatalytic^[17–18] strategies have also been widely used in the synthesis of chiral amines. However, most of the above methods have their own different disadvantages, such as chiral resolution difficulty, isomerization side reactions, catalyst poisoning, and low selectivity. The development of highly active and selective methods for atom and step economic synthesis of chiral amines are still challenging.

Asymmetric synthesis from racemate mixtures to single enantiomers is usually achieved through dynamic kinetic resolution, dynamic kinetic transformation, and enantioconvergent synthesis. However, in the process of dynamic kinetic resolution, racemic substrates undergo racemic isomerization more preferentially than selective reactions with catalysts. For

dynamic kinetic asymmetric transformation, only half of the substrates can be converted into chiral products. Enantioconvergent synthesis could effectively avoid substrate racemization equilibrium and consideration of kinetic factors by firstly deracemizing the substrate, as well as convert the racemic substrate to highly enantioenriched products theoretically in up to 100% yield. Compared to traditional chiral synthesis, the enantioconvergent method is easier to achieve higher enantioselectivity and can effectively avoid the kinetic resolution of substrates or products. Over the past decades, enantioconvergent catalysis has been broadly applied in various organic synthesis reactions,^[19] such as cross-coupling reaction for C–C bond formation,^[20–24] substitution reactions of racemic electrophiles,^[25] biotransformations,^[26] and asymmetric addition.^[27]

Metal-catalyzed enantioconvergent cross-coupling for the building of C–C bonds have emerged as a powerful tool. Many advances and methods for constructing C–C bonds through enantioconvergent synthesis, including C–H functionalization of racemic electrophiles or nucleophiles, hydroalkylation of alkenes, allenes, and acetylenes, hydrogen autotransfer, addition of racemic allylic systems, propargylation of alcohols and phenols, and allenylation of carbonyl compounds, have been realized.^[19] However, the corresponding C–heteroatom bond formation reactions are still challenging.^[28–31] Benefitting from the particular advantages of enantioconvergent method, the construction of C–N bond through enantioconvergent amination has recently attracted increasing attentions. The synthesis of chiral amines through enantioconvergent catalysis mainly involves three different mechanisms, including radical-based cross-coupling of racemic alkyl electrophiles with nucleophiles,^[32–42] formation of (σ + π)-allyl-metal intermediate,^[43–44] and redox-neutral amination of alcohols.^[45] In this concept article, we mainly focus on the radical-based C(sp³)–N cross-coupling catalyzed by non-noble metal complex, aiming to promote a further understanding and development of chiral amines enantioconvergent synthesis (Figure 1). All the reactions introduced in this article have been elaborated with general discussion of the reaction conditions,

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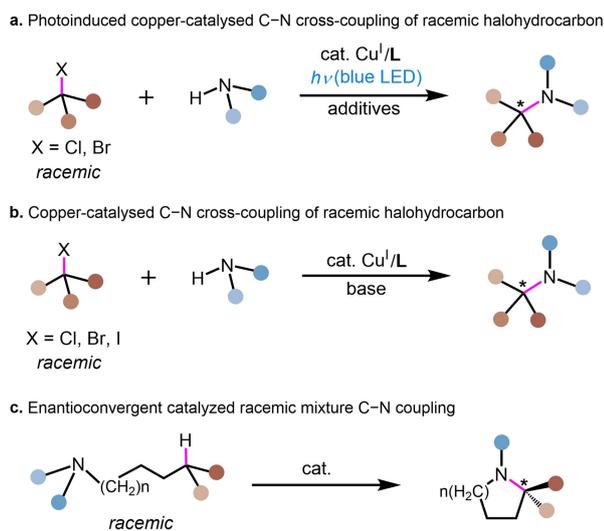


Figure 1. Overview of enantioconvergent formation of C–N bond.

exploration of substrate scope, insight into the catalytic processes and the advantages/shortcomings of the methods.

2. Photoinduced Cu Catalyzed Intermolecular Amination

The enantioconvergent cross-couplings of racemic secondary alkyl electrophiles with carbon nucleophiles has been well developed, while highly stereoselective reactions involving tertiary electrophiles are relatively uncharted because the catalyst is required to distinguish the three different substituents on the *pre*-chiral carbon atoms to achieve high enantioselectivity.

In 2016, Fu and co-workers pioneeringly reported a copper catalyzed racemic tertiary alkyl halides enantioconvergent cross-coupling with visible light irradiation (Figure 2).^[32] The reaction occurs at -40°C with the presence of CuCl, chiral phosphine (L^*), and Brønsted bases. The cross-coupling partners are irradiated for 16 hours and provide the desired product



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Zhigang Shuai (born in 1962) received B.S. degree in 1983 from Sun Yat – Sen University and Ph.D. degree in 1989 from Fudan University. He went to work with Prof Jean – Luc Brédas as a postdoc at The University of Mons. In 2000, he received the support of the “Hundred – Talent Program” in the Institute of Chemistry, Chinese Academy of Sciences. He moved to Tsinghua University in 2008 as a Changjiang Scholar Chair Professor. Now he joined The Chinese University of Hong Kong, Shenzhen, as a X.Q. Deng Presidential Chair Professor. He has been working on developing a computational method for modelling and understanding the electronic processes in organic and polymeric materials, focusing on the excited state structure and dynamics. His computational package, MOMAP, has been successfully commercialized. He has published more than 440 papers in scientific peer-reviewed journals, with more than 24,000 citations.



Xinzhen Yang (born in 1978) received B.S. and Ph.D. degree from Nankai University in 1999 and 2004, respectively. He did postdoctoral research with Prof James E. Boggs at The University of Texas at Austin and Prof Michael B. Hall at Texas A&M University from 2004 to 2010. Then he worked as a member of the academic staff in College of Chemistry at the University of California, Berkeley. In 2013, he joined Institute of Chemistry, Chinese Academy of Sciences as a Professor. He moved to University of Washington in 2020 as a visiting professor and research scientist. His research mainly focuses on computational organometallic catalysis and molecular spectroscopy. He has more than 100 authored and co-authored papers published in peer-reviewed scientific journals with over 3,000 citations.

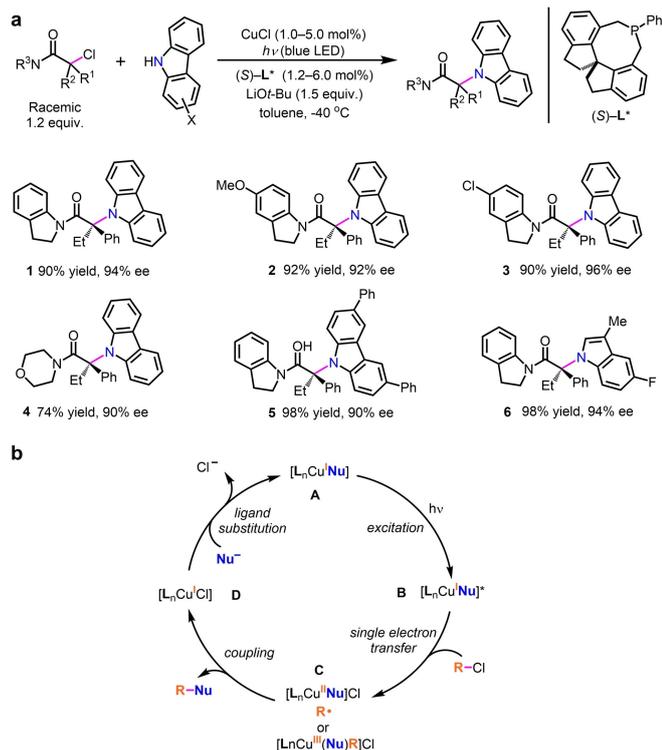


Figure 2. Cu catalyzed enantioconvergent synthesis of chiral amines with visible light irradiation (a) and a possible catalytic pathway (b). L_n is additional ligand(s) coordinated to copper. Reproduced from Ref. [32]. Copyright 2016 American Association for the Advancement of Science.

1 with a 90% yield and 94% enantiomeric excess (ee). Comparing product 2 and 3, the electronegativity of substituents on benzo-tetrahydropyrrole, whether it is electron withdrawing chlorine or electron donating methoxy, does not affect the yield and ee values. The substituent of the carbazole position on the *pre*-chiral carbon atom also has no impact on the productions of 1, 5 and 6. However, the substituents on the carbonyl of products 1 and 4 have a significant influence on the yield. In this reaction, UV-light is required because intermediate A needs to be excited for the formation of B, which undergoes a single electron transfer with the substrate. So light is necessary in the reaction. The above work involved techniques in various fields like asymmetric synthesis, non-precious metal catalysis, photocatalysis, and cross-coupling reactions of alkyl electrophiles, and inspired the development of enantioconvergent C-heteroatom bond formation.

A couple of years ago, Fu and co-workers reported a photoinduced complementary synthesis of chiral secondary amides with expanded enantioselective N-substitution reactions of unactivated alkyl electrophiles (Figure 3), which not only increased the scope of suitable substrates, but also controlled the stereochemistry of the product through a racemic electrophile.^[33] Moreover, this method makes a clever use of ligands assemble in situ to form two distinct but cooperatively acting catalysts, a copper/bisphosphine/phenoxide complex serving as a photocatalyst for the activation of C–Br bond and a chiral copper/diamine complex catalyzing enantioselective C–N

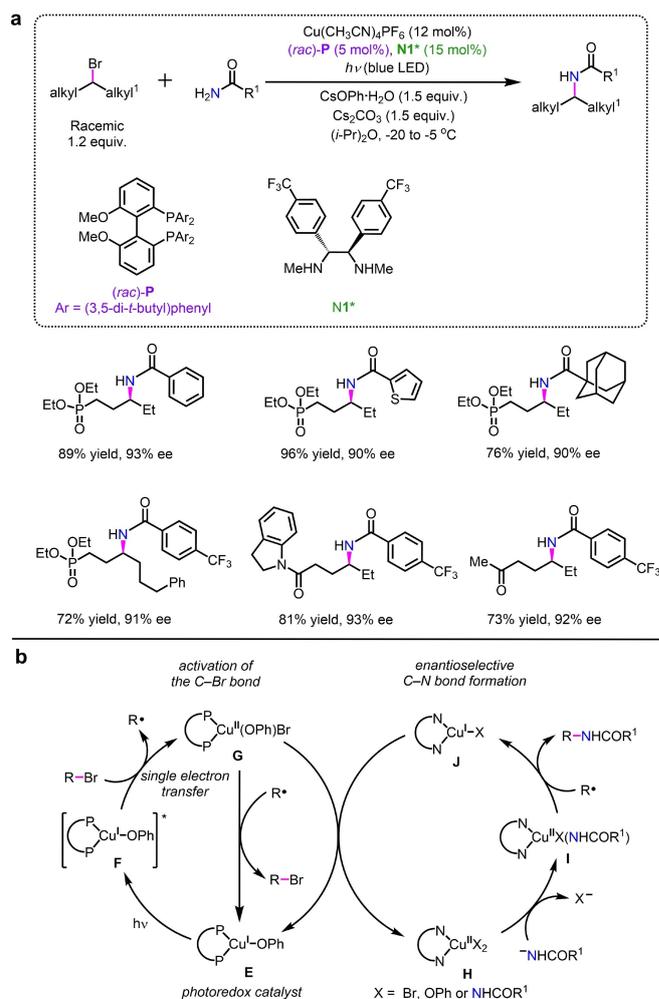


Figure 3. Photoinduced copper-catalyzed asymmetric amination of unactivated racemic alkyl electrophiles via ligand cooperativity (a) and a synergetic catalytic cycle (b). Reproduced from Ref. [33]. Copyright 2021 Springer Nature.

bond formation. Similar to the reaction displayed in Figure 2, photocatalyst E also needs to be excited for the activation of the C–Br bond in the substrate. It effectively addressed the difficulty of distinguishing two different alkyl groups in asymmetric catalysis. However, fussy three classes of ligands in the above reaction resulted in relatively lower yields of some products.

Later on, Fu and co-workers further developed a light-induced and copper-catalyzed enantioconvergent alkylations of anilines by racemic tertiary electrophiles. The reactions could happen at rather low-temperature of -78 °C and form C–N bond with very good enantioselectivities (Figure 4).^[34] Their experimental and computational reaction mechanism studies revealed that Cu_C ((L1)Cu(NHAr)Cl) is a key intermediate in the catalytic cycle. Compared to the secondary electrophiles, this approach distinguished three carbon substituents by using the chiral copper catalyst and overcame the steric hindrance of the tertiary electrophiles.

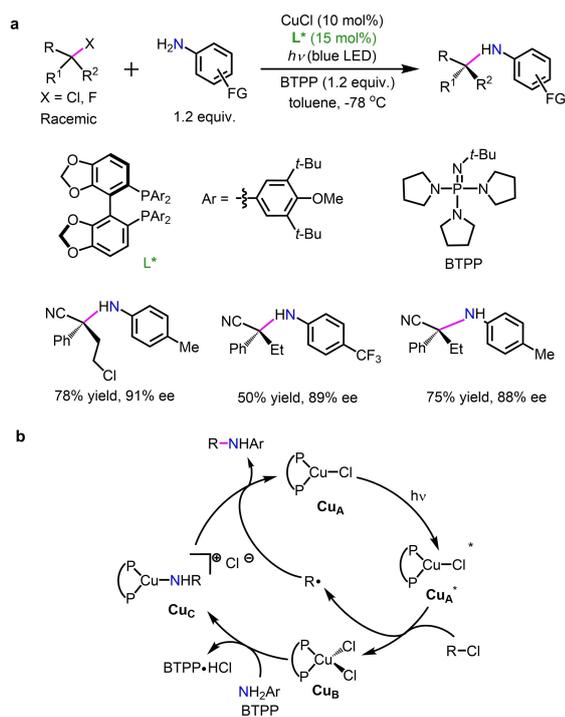


Figure 4. Enantioconvergent alkylations of anilines with racemic tertiary alkyl electrophiles (a) and a possible catalytic cycle (b). Reproduced from Ref. [34]. Copyright 2022 American Chemical Society.

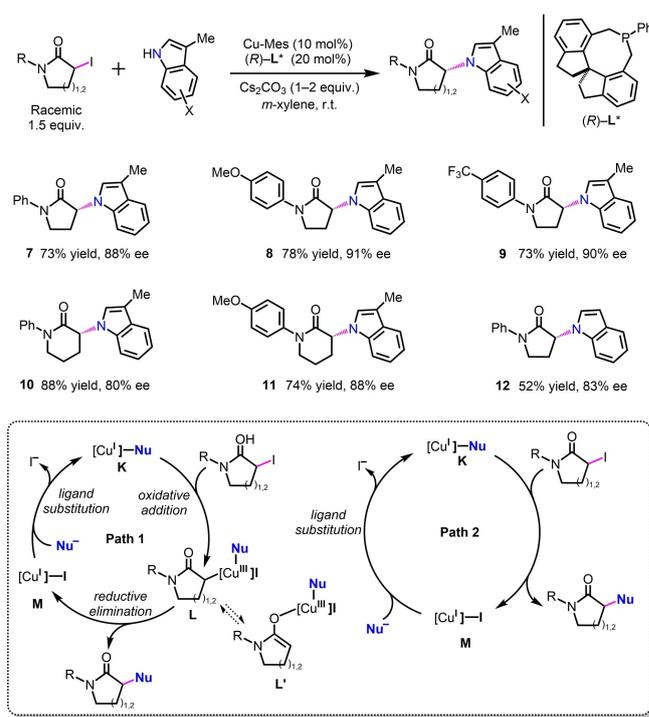


Figure 5. Chiral amines synthesis via copper-catalyzed enantioconvergent alkylation and two possible catalytic paths. Reproduced from Ref. [35]. Copyright 2019 American Chemical Society.

3. Cu Catalyzed Intermolecular Amination

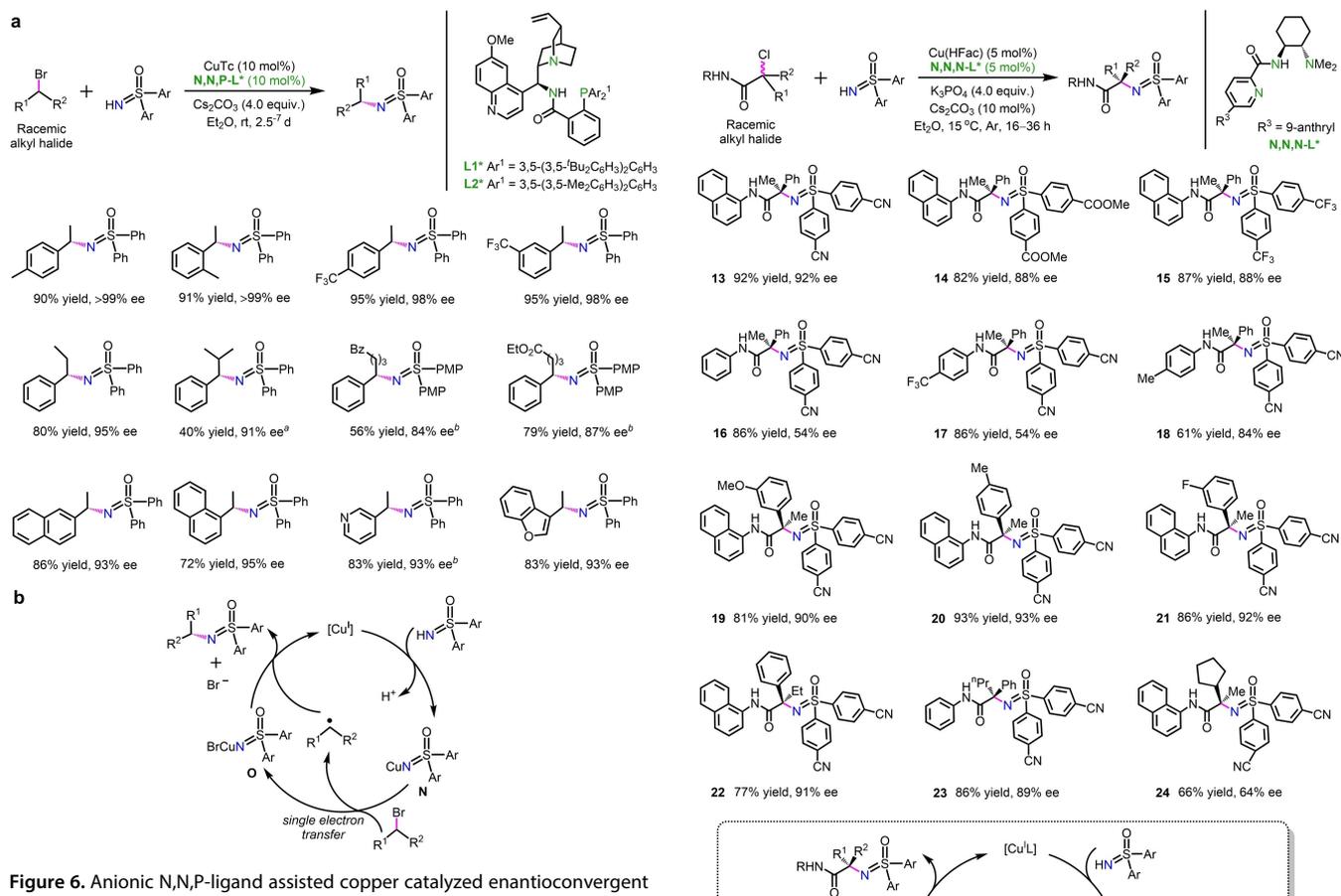
In 2019, Fu and co-workers^[35] reported another copper catalyzed complementary reaction for the synthesis of chiral amines with a different chiral monodentate phosphine and Cs_2CO_3 base at room temperature (Figure 5). The electronegativity of substituents attached to the phenyl (**7**, **8** and **9**) and the size of the heterocyclic ring (**7** and **10**) in the racemic mixture has mild influence on the yield and enantioselectivity. Substrate indole with electron donating substituents (**7** and **12**) is more beneficial for higher yield. Both possible reaction pathways indicate that the C–I bond in the substrate can directly react with catalyst **K**. However, the substrate for this reaction is relatively limited and worth to be further expanded to a wider range while maintaining mild reaction conditions.

In 2021, Liu and co-workers reported a copper catalyzed enantioconvergent radical C–N coupling of sulfoximines with diverse racemic secondary alkyl halides under mild conditions (Figure 6).^[36] By using electron-rich multidentate anionic N,N,P-ligands, which can significantly enhance the reducing capability of Cu(I) catalysts for facile converting alkyl halides into alkyl radicals, the efficiency and yields of reducing racemic alkyl halides to prochiral alkyl radicals were drastically improved without light induction. The mechanism observations also support the direct formation of alkyl radical species from alkyl halides through a single electron transfer process. Furthermore, the substrate compatibility of this catalytic enantioconvergent reaction is well expanded. Sulfonamide with different aryl

substituents and a series substituted alkyl halogen substrates have very high yields and ee values.

In their recent study, Liu and co-workers further developed a chiral anionic N,N,N-ligand assisted copper-catalyzed enantioconvergent $\text{C}(\text{sp}^3)\text{--N}$ cross-coupling of racemic tertiary alkyl halides with sulfoximines to afford a collection of enantioenriched α,α -disubstituted amines (Figure 7).^[37] The small-sized coordinating atoms and a long spreading side arms of N,N,N-ligands play an important role for the formation of highly crowded carbon stereocenter with excellent efficiency and enantioselectivity under mild conditions. Sulfoximines with diverse substituted aryl rings display a better performance in both yield and enantioselectivity (**13–16**). The N-aryl substituent on the alkyl halides revealed that the electron-rich substituents are likely to provide higher ee (**18**) than those with electron-deficient/neutral ones (**16** and **17**). Various α -aryl α -chain alkyl chloro amides are suitable substrates for the reaction with yields ranging from 77 to 93% and ee values from 89 to >93% (**19–23**). The α -aryl α -cycloalkyl chloro amide (**24**) have relatively lower yield of 66% and enantioselectivity of 64%. The mechanism investigation in the experiment indicates that the single electron transfer of the substrate to form the intermediate **Q** is important.

Almost at the same time, Liu and co-workers also reported the enantioconvergent N-alkylation of aliphatic amines with α -carbonyl alkyl chlorides catalyzed by copper and chiral tridentate anionic ligands with rather highly chemoselective and enantioselectivity (Figure 8).^[38] This reaction enables direct conversion of feedstock chemicals, such as ammonia and



pharmaceutically relevant amines, into unnatural chiral α -amino amides under mild and robust conditions. The reported synthesis method also avoids potential poisoning of transition metal catalysts caused by the high Lewis basicity of aliphatic amines and ammonia. Particularly, the catalytic reaction has an excellent substrate compatibility (>180 substrates) for the synthesis of a large variety of compounds, including aliphatic amines (25–28), secondary alkyl amines (29–32), and tertiary amines (33–35). In the proposed outer-sphere amine attacking mechanism (Figure 8), the reaction starts with the coordination of the nitrogen atom in amide to the catalyst C^*L^* . The C–Cl bond undergoes oxidative addition with the assistance of copper to form intermediate 37. Racemic substrate amine catches the *pre*-chiral carbon radical from 38 resulting in the C–N bond coupling. The intermediate 39 then releases the product and regenerates the catalyst Cu^*L^* . Although the proposed catalytic cycle provides a conceptual understanding of the observed reaction, detailed microscopic kinetic processes like energy barriers of each elementary steps, the rate-determining states, the important role of chiral anionic ligands, the paths of different configurations of racemic substrates, and the origin of selectivity need to be further elucidated.

Figure 7. Chiral anionic N,N,N-ligand assisted copper catalyzed enantioconvergent synthesis of chiral amines from tertiary alkyl halides. Reproduced from Ref. [37]. Copyright 2023 John Wiley & Sons.

4. Enzyme and Transition Metal Catalyzed Intramolecular Amination

Bioinspired catalyst design is primarily a mimic of enzyme features by using the active site center of enzymes and well-defined ligands and functional groups, which could significantly simplify the complexity of the enzyme structures and reduce the cost of catalysts, but still maintain the high reaction rates and selectivities of enzymes as much as possible.

To the best of our knowledge, Arnold and co-workers reported the first bio-mimic catalyst, which was based on the active center of cytochrome P450 enzyme, for intramolecular enantioconvergent amination of tertiary C(sp³)–H bonds in 2019 (Figure 9).^[39] The P450 derived catalysts can aminate a variety of aliphatic C–H bonds in excellent enantioselectivity ($\geq 98\%$). Their density functional theory (DFT) calculations

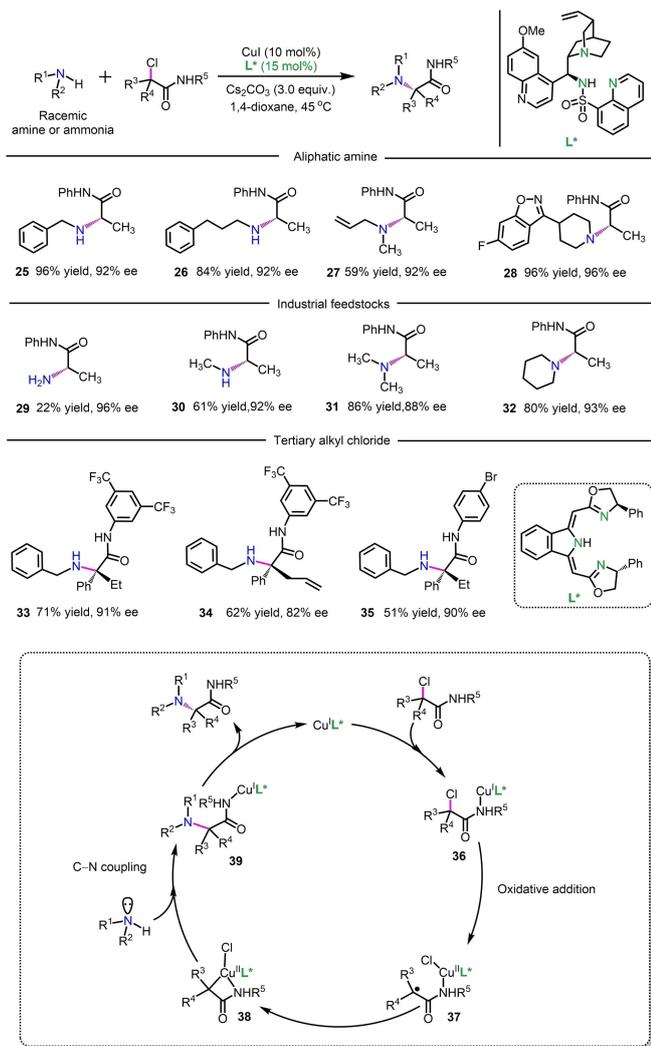


Figure 8. Chiral anionic N,N,N'-ligand assisted copper catalyzed enantioconvergent synthesis of chiral amines from tertiary alkyl halides. The inset shows the corresponding mechanism. Reproduced from Ref. [38]. Copyright 2023 Springer Nature.

revealed an outer-sphere mechanism with the formation of high-spin triplet intermediates **46** and **47** and spin-crossover processes. However, the substrate compatibility of this method is very limited with only the six products shown in Figure 9a. Although the reactions with different substrates have rather high selectivities, their reaction efficiencies are not very stable. For example, the yield of product **42** is 98%, but only 30% for **41**. This pioneering work in intramolecular enantioconvergent amination enlightened subsequent development of enantioconvergent intramolecular C–N coupling.

In 2020, Liu and co-workers developed a dual Cu(I)/chiral phosphoric acid (CPA) catalytic protocol for the radical enantioconvergent transformation of racemic ketones into chiral cyclic amines with excellent substrate compatibility (Figure 10a).^[40] An extensive range of different substituents bearing the electron-donating or electron-withdrawing groups for Ar-, R¹-, R²-, and R³- are all compatible with this reaction. However, the yield and enantioselectivity are also not stable

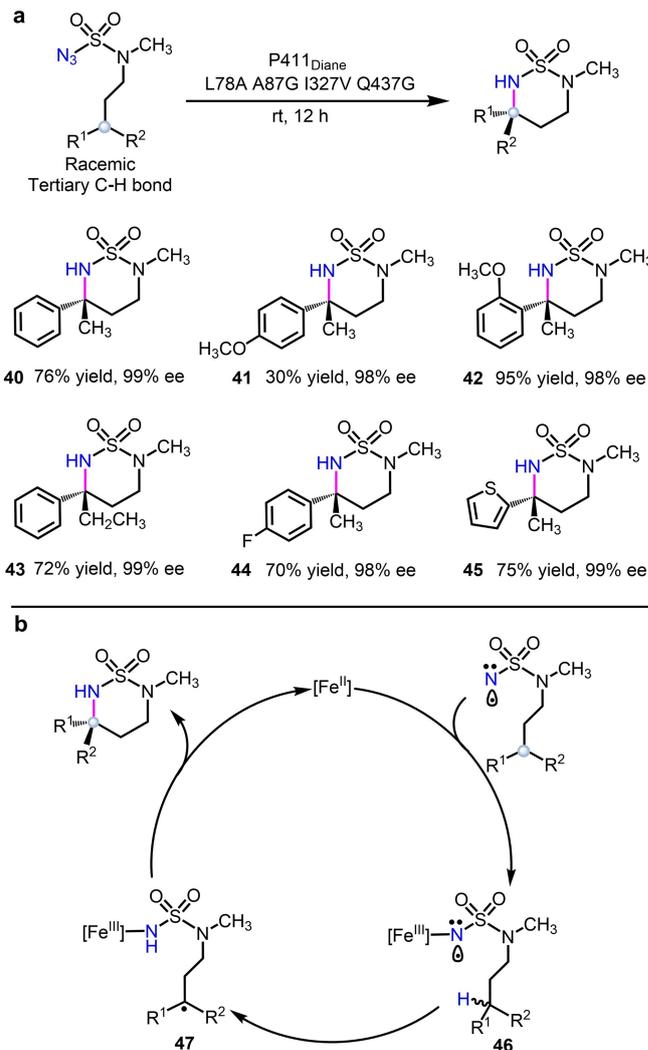


Figure 9. Biocatalytic enantioconvergent synthesis of chiral cyclic amines (a) and the catalytic cycle of iron porphyrin-catalyzed C(sp³)–H amination (b). Reproduced from Ref. [39]. Copyright 2019 Springer Nature.

with ranges of 39–85% and 52–94%, respectively. The physical insights into the above C(sp³)–H enantioconvergent amination reactions were computationally investigated by Li and Yang by using the DFT method (Figure 10b).^[41] They found that the turnover-limiting step is O–O bond homolysis of *tert*-butyl 4-phenylbutaneperoxoate with a total free energy barrier of 19.1 kcal/mol (**48**→**TS1**), while **TS2S** and **TS2R** are the enantio-determining steps with a 1.7 kcal/mol difference in free energy. The enantioconvergent amination was realized to obtain the same intermediate **50** through prochiral carbon atom. Based on the computationally predicted mechanisms and key element steps in the reactions, Li and Yang also proposed two new phosphoric acids, diphenyl hydrogen phosphate and 2-biphenyl hydrogen phosphate as potentially more efficient auxiliary catalysts near 4.0 kcal/mol lower in free energy barriers for the O–O bond cleavage.

It is worth to note that the formations of intramolecular and free radicals are usually involved in enantioconvergent reactions while racemization has an intrinsic stereochemical feature of

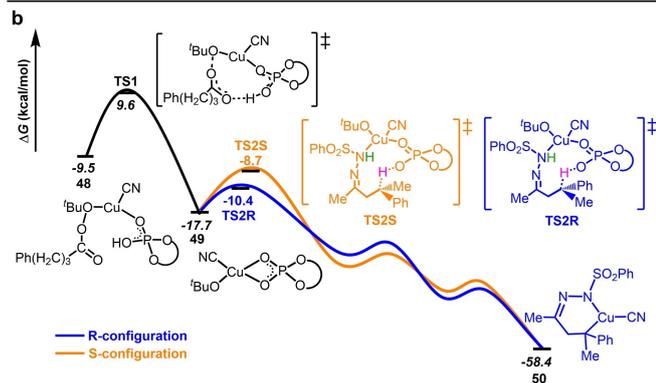
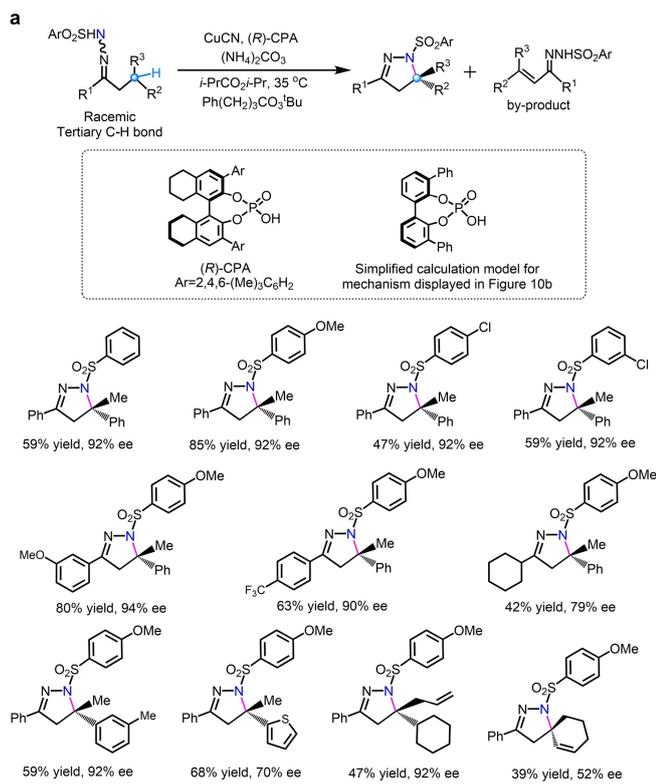


Figure 10. Cu/CPA catalyzed enantioconvergent β -C(sp^3)-H amination (a). Reproduced from Ref. [40]. Copyright 2020 Springer Nature. And the corresponding free energy profile with a simplified structure model of CPA (b). Reproduced from Ref. [41]. Copyright 2023 John Wiley & Sons.

free radical chemistry. In 2020, Zhang and co-workers successfully applied the concept of metalloradical catalysis to the design of a Co(II)-based catalytic system for enantioconvergent radical amination of racemic tertiary C(sp^3)-H bond (Figure 11).^[42] The Co(II) metalloradical catalyst and D_2 -symmetric chiral ligand amidoporphyrin with suitable steric, chiral and electronic effect, are the key factors give rise to this reaction. The enantioselectivity in the reported catalytic reactions has an optimal temperature of 50 °C and begins to decrease when the temperature is further elevated up to 70 °C. This new metalloradical approach expanded the door and offer great potentials for enantioconvergent asymmetric synthesis despite the high reactivity and diverse competing pathways in the catalytic

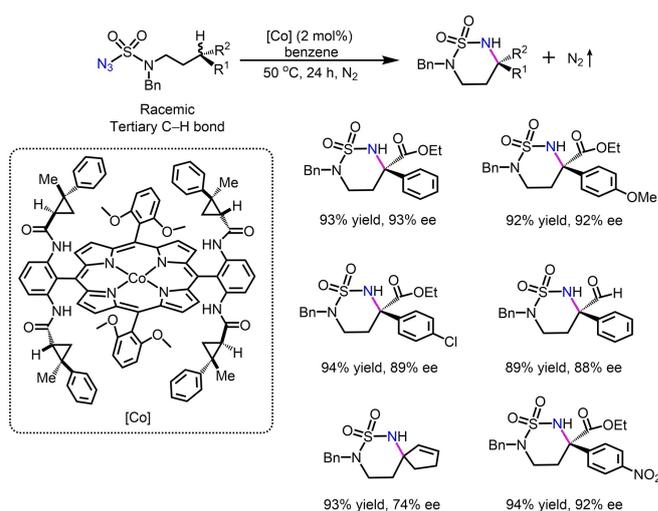


Figure 11. Co(II)-metalloradical catalyzed enantioconvergent racemic tertiary C-H bond amination. Reproduced from Ref. [42]. Copyright 2020 American Chemical Society.

reactions, which could be challenging to achieve high chemoselectivity, stereoselectivity, and enantioselectivity.

5. Summary and Outlook

In summary, enantioconvergent synthesis of chiral amines has emerged as an efficient and powerful asymmetric synthesis strategy in recent years. Compared with traditional asymmetric synthesis, enantioconvergent conversion effectively avoids complicated reaction processes and has high efficiency and selectivity. Significant progresses have been achieved in enantioconvergent amination of racemic mixtures, including photoinduced intermolecular amination, Cu catalyzed intermolecular amination, and intramolecular amination. Photoinduced intermolecular amination catalyzed by transition metal complexes generally requires the assistance of various chiral ligands. Recent developed copper catalyzed intermolecular amination reactions without light induction only requires one chiral ligand at room temperature and has high substrate compatibility. Although enantioconvergent intramolecular amination still exists numerous limits and difficulties, such as unstable enantioselectivity, poor chemoselectivity, and low yield, it has shed light on the synthesis of chiral cyclic amines. At present, the enantioconvergent C-N bond coupling of racemic mixtures is still in the early stage, and faces many challenges and problems, such as a single kind of catalyst, unstable catalytic activity, and particularly unclear reaction mechanism. We hope that this review could provide some basic concepts of catalytic enantioconvergent C-N coupling reactions and accelerate future development of atom economic enantioconvergent asymmetry strategies with high efficiency, selectivity, and yield, as well as wide substrate compatibility under mild conditions.

Acknowledgements

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Conflict of Interests

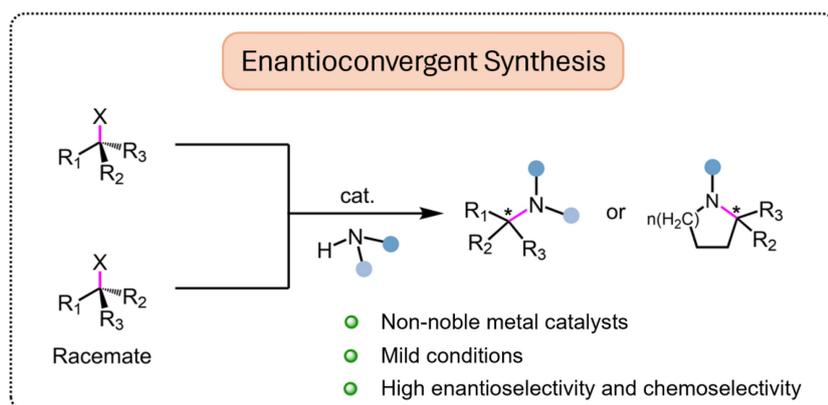
There are no conflicts to declare.

Keywords: Enantioconvergent synthesis · C(sp³)-N coupling · Chiral amines · Transition metal catalysts

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CONCEPT



The enantioconvergent synthesis method not only has high efficiency and selectivity, but also a simple and

mild reaction processes, opening up a new path for the efficient synthesis of chiral amines.

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