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Advances in Asymmetric N Construction of Metal and Organic Small Molecules

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Abstract: *Lot of natural products, pharmaceuticals and functional materials with chiral amines do many useful job, and this group also a valuable constituents of versatile building blocks and important chiral catalysts as well as chiral auxiliaries in organic synthesis. Therefore, to develop efficient methods for the synthesis of structurally diverse chiral amines and chiral amine scaffolds has great importance and huge application vaule. symmetric catalysis is the most efficient method to synthesize chiral organic molecules. Cooperatively catalyzed by transition metal and small organic molecules can be used to simultaneously or continuously activates the bonds and rebuild, it can help some reaction which can not happen with only one catalyst to move on. This article reviews some cases of chiral nitrogen formation through metal catalysis, organic small molecule catalysis and their synergistic catalysis, and briefly discusses the challenges and future development directions in this area.*

Keywords: *Organic small molecule. Metal catalysis. Construction of chiral C-N bond. Asymmetric catalysis*

1. Introduction

The Nobel Prize in Chemistry 2021 was for the development of asymmetric organocatalysis, this has a great impact on medicine research. It simplifies the links in synthesis, reduces energy consumption and makes synthesis more simple, environmentally friendly and economical, which will be one of the direction of development in the fields of organic chemistry and medicine in this century.

Chiral amines are important chiral auxiliaries and main group in lot of medicine and natural products. Efficient and convenient synthesis of chiral amine compounds is an important direction for the research of organic synthetic chemistry [1]. The Petasis reaction is one of the synthetic methods [2]. Nowadays in the chemical synthesis of chiral amine compounds, catalysis is the main direction of integrating high efficiency and green environmental protection. At present, the catalysts used in various laboratories mainly include enzymes, metal catalysts and organic small molecule catalysts. Each of the three catalysts has its own advantages and complement, jointly promoting the development of chiral amine synthesis [3].

2. Metal Catalysts

Metal catalysis also won the Nobel Prize in Chemistry in 2001, because of its small amount and high catalytic efficiency, scientists have the most depth research on the asymmetric synthesis of transition metal catalysis, and the most widely used. In recent years, with the development of transition metal catalysis more and more mature, scientists continue to try to apply monovalent copper, palladium, rhodium and other metal catalysts in the synthesis process of chiral amine compounds.

In the synthesis of metal-catalyzed chiral amines, the research on the synthesis method using tert-butyl sulfenamide as a chiral auxiliary group has been continuously developed, and it has become a widely used method for asymmetric synthesis of amines. Direct condensation of tert-butanesulfinamide with aldehydes and ketones provides tert-butanesulfinyl imines in uniformly high yields. The tert-butanesulfinyl group activates the imines for the addition of many different classes of nucleophiles, serves as a powerful chiral directing group, and after nucleophilic addition is readily cleaved by treatment with acid. A wide range of highly enantioenriched amines are efficiently synthesized using this methodology. In the process of hydrogenation deoxidation imine, different chirality deoxidation products can be obtained by selecting different hydrogenation reagents [4-6].

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2017, Suna syntheticed Pseudotabersonine alkaloids under the catalysis of $TiCl_2(Oi\text{-}Pr)_2$, tert-butylsulfinamide was used to condense with ketone to form imine to introduce chiral source, and different chiral products could be obtained by using $LiBEt_3$ and BH_3-THF deoxidation respectively [7]. 2019, Zhou used a similar method to syntheticed maraviroc. The difference is that in the hydrogenation they used boron reagents such as $NaBH_4$, $LiBH_4$ and BH_3 and DIBAl-H [8].

Except this, transition metal-catalyzed asymmetric carbene insertion reactions also one of the method to get Chiral amine [9].

3. Organic small molecule catalysis

The chiral organic small molecule catalysis developed in recent years has unique advantages such as inexpensive, easy to prepare and environmentally friendly in asymmetric catalysis.

2017, Zhu developed a method for the synthesis of chiral vicinal diamines via nucleophilic addition of hydrazones to imines. The chemo-, diastereo-, and enantioselectivity were all excellent and the adducts can be easily transformed into monoprotected or free diamines (*Figure 1*) [10].

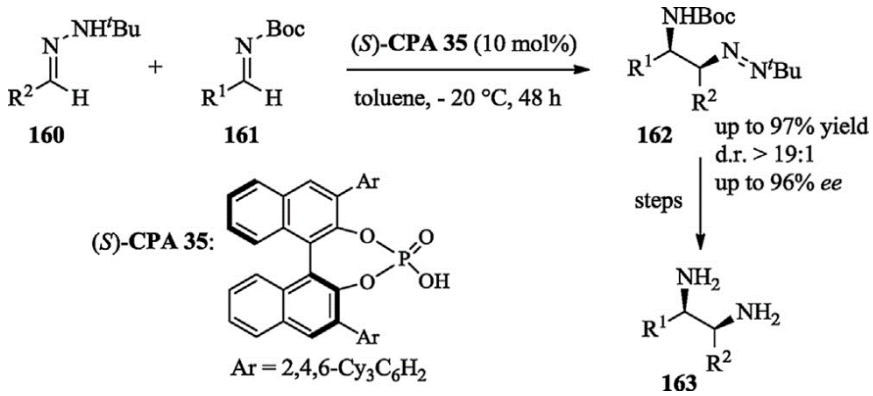

Figure 1: Asymmetric nucleophilic addition of hydrazones to imines.

At the same year, Shi reported a catalyst-controlled chemoselective and enantioselective reactions. As part of this work, a diastereoselective and enantioselective dearomative cyclization reaction was developed in the presence of a chiral phosphoric acid (*Figure 2*) [11].

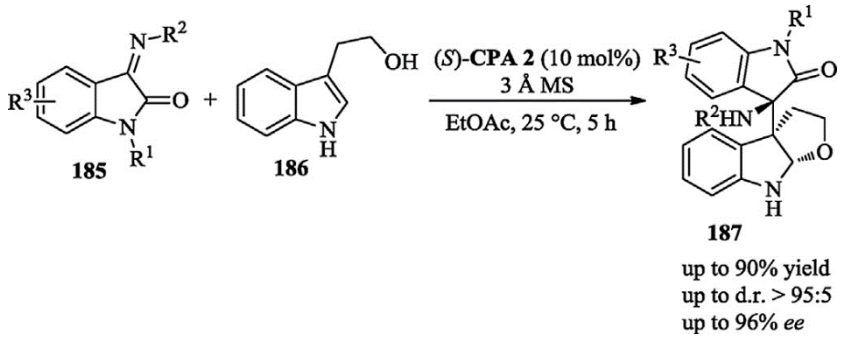

Figure 2: Diastereoselective and enantioselective dearomative cyclization reactions.

In the synthesis of chiral amines, the organic small molecule catalysts used are mainly chiral phosphoric acid. Chiral phosphates are strongly acidic and Lewis basic, enabling them to activate a variety of reaction substrates, it is commonly used in Mannich-type reactions to build chiral amines.

4. Metal and Organic small molecule co-catalysis

The main drawback of organic molecular catalysis is the difficulty in realizing the activation of inert chemical bonds and inert molecular systems. The organic small molecule and metal joint catalyst system can simultaneously or continuously activate multiple chemical bonds and make them reorganize in an orderly manner, so it is possible to develop reactions that are difficult to achieve with a single catalyst system, thereby making up for the shortcomings of both sides [12]. In this problem, many disciplines have made attempts to combine the two catalysts, and have achieved good results.

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2011, Hu developed a method with $Rh_2(OAc)_4$ and chiral Brønsted acid to cocatalyzed three-component Mannich-type reaction of a diazo compound, a carbamate, and an imine provides rapid and efficient access to both syn- and anti-α-substituted α, β-diamino acid derivatives with a high level control of chemo-, diastereo-, and enantioselectivity (*Figure 3*). The methyl phenyldiazoacetate (1a)/benzyl carbamate (2a)/ phenylbenzylimine (3a) combination was chosen as the starting point for the three-component reaction. The yields obtained by the reaction are all above 60%, and some can reach above 80%; in some conditions, as high as 99% ee is obtained [13].

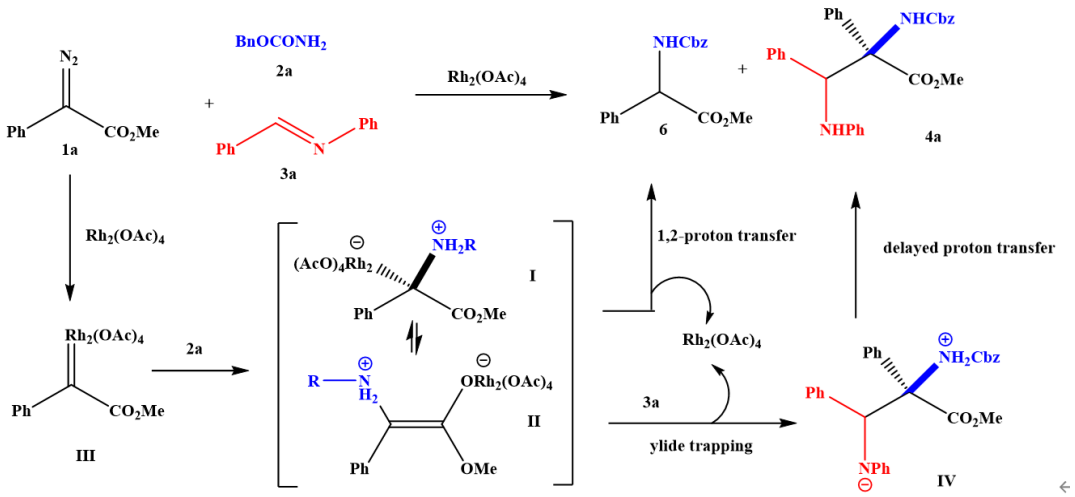

Figure 3: Proposed mechanism for the three component reaction of 1a, 2a, and 3a catalyzed by $Rh_2(OAc)_4$.

2013, they used the same condition, $Rh_2(OAc)_4$ and chiral Brønsted acid to cocatalyzed three-component Mannich-type reaction of tert-butyl diazoacetate with arylamines and imines afford α, β-bis(arylamino) acid derivatives in good yields (56–90%) with high diastereoselectivities (up to >95:5 dr) and excellent enantioselectivities (up to 96% ee) [14]. At the same year, Gong used $Rh_2(OAc)_4$ and chiral Brønsted acid to make a research. The reaction basically proceeds via a rhodium-catalyzed generation of ammonium ylides from 3-diazooxindoles (1) and anilines (2) followed by a chiral Brønsted acid-catalyzed enantioselective aldol-type reaction with glyoxylates to give optically active products 4 (*Figure 4*). They can achieve 95% yield and 99% ee [15]. These two groups both got a good result when R=2,4,6-$(i\text{-}Pr)_3C_6H_2$ on chiral phosphoric acid. In other groups, some show the phenomenon of non-reaction.

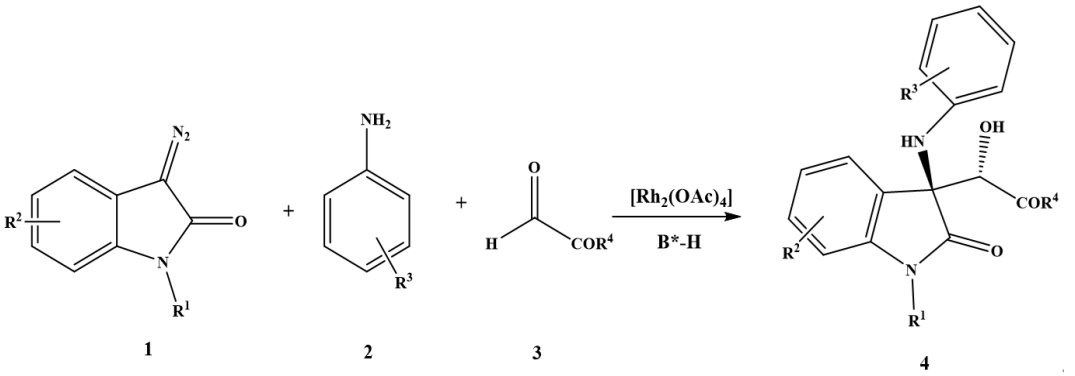

Figure 4: Brønsted acid/rhodium acetate cooperative catalytic asymmetric three-component aldol-type reaction for the synthesis of 3-amino oxindoles.

5. Conclusion and outlook

The co-catalysis of chiral amines by small organic molecules and metals has received increasing attention. The importance of this strategy in the discovery of new reactions and the control of stereoselectivity has been widely recognized. These three methods of asymmetric synthesis have won the Nobel Prize in Chemistry three times since the 21st century, which is precisely the affirmation of the

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emerging academic achievements and potential application value in the field of asymmetric catalysis, and also an encouragement to basic chemical researchers. In addition, the use of enzymes and metals for synergistic catalysis or the simultaneous action of more catalysis to achieve better results have also received attention. A variety of catalysts can complement each other's defects while maintaining the original function, and it is expected to achieve a better catalytic effect. This may be one of the future directions.

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