Applications of chiral spirocyclic phosphoric acid in the synthesis of natural products

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Abstract. With a 10 years development, chiral spirocyclic phosphoric acids (SPAs) have attracted a substantial amount of attention from the synthetic organic chemistry community. This kind of small molecule organic catalysts has some advantages like easy to obtain, no transition metal and wide application range. Because of avoiding the use of toxic substances which are limited in the process of drug synthesis, a large number of studies pay attention to the key structures (such as indole, carbozole.) containing pharmacological active components in natural products. And most of them get a excellent result in yields (more than 80% yield) and enantioselectivities (more than 90% ee). These studies can provide new pathways to nature products.

1 Introduction

Chiral molecules exist widely in natural products and bioactive molecules. Chiral chemistry has been attracted much attention and developed rapidly in chiral medicine, pesticides, special materials and other fields. In 2004, Akiyama group reported the first chiral Brønsted acid catalyzed enantioselective Mannich reaction, which made people pay their attention to BINOL and a series of BINOL-phosphoric acid catalysts with BINOL framework [1]. Because of the significant advantages of BINOL catalyst over other chiral catalysts, it has been developed into a powerful catalyst for asymmetric controlled synthesis of a variety of organic compounds. Compared with metal catalysts, chiral phosphoric acid

catalysts are cheaper, easier to prepare, and avoid transition metals, especially some toxic substances that cannot be used in drugs; compared with other organic catalysts, they are more applicable [2]. In the following 16 years, several chiral phosphoric acid catalysts with different skeletons have been developed, such as BINOL, H8-BINOL, VAPOL, SPA. [3-5](Figure1). Spirodiindene based chiral phosphoric acid catalyst first appeared in F-C reaction, which was catalyzed by SPA, and published by Lin Xufeng in August 2010. [6] Using chiral 1,1'-spirobiindane-7,7'-diol as starting material, the corresponding catalysts were synthesized in four steps (Scheme 1). And Lin patented it in October [7]. In September of the same year, Benjamin list group also published the asymmetric transacetal reaction catalyzed by SPA [8].

Figure 1. Typical chiral phosphoric acid catalysts

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Scheme 1. Route towards the synthesis of SPAs.

In the following 10 years, the application of SPA catalysts has developed rapidly. Through many research and exploration, the intermediate transition states of chiral phosphoric acid catalysts can be roughly divided into two categories, One is bifunctional activation (Figure 2), and the other is Ion-pairing activation (Figure 3)[9-10]. With the development of SPA, many important asymmetric catalytic reactions such as Pictet-Spengler reaction, Fisher indolization, Diels-alder reaction and Ugi reaction have been realized[11-14]. In 2019, Lin Xufeng's group

obtained the first chiral phosphoric acid catalyzed axial chiral N-arylidole by using the second generation SPA catalyst.[15] A series of axially chiral arylindoles (up to 99% ee) were obtained in high yield (up to 93%) (scheme 2). The realization of these reactions not only provides a new idea for the synthesis of a variety of natural products or bioactive chiral molecules, but also expands a new space for the development and application of SPA catalysts.

Figure 2. Bifunctional activation

Figure 3. Ion-pairing activation

Scheme 2. Enantioselective synthesis of axially chiral N-Aryl indoles

2 Common catalytic reaction types

2.1 Cyclization reaction

SPA can catalyze a variety of cyclization reactions, which provide ideas for the chemical synthesis of a variety of bioactive natural products.

Since Diels and alder published the cyclization of dienyl and dienophile in 1928, D-A reaction has been widely used in the synthesis of bioactive cyclic molecules. With the development of asymmetric hetero D-A reactions, many ideas have been provided for the efficient, regioselective and stereoselective construction of various chiral pure heterocycles [16]. In 2013, Zhu Guangyu and

sun Jianwei first discovered the asymmetric catalytic three component aza-Diels- alder reaction (Scheme 3). They realized the rapid assembly of complex polycyclic alkaloids containing indole, tetrahydroquinoline and tetrahydroisoquinoline from simple non chiral materials [17]. The highest yield (85%), ee value (98%) and D.R. > 99:1:0:0 were obtained by the reaction of indole and o-trimethyl ester benzaldehyde in the presence of aniline and catalyzed by 2.5% mol SPA catalyst. A large number of complex molecules containing key subunits such as tetrahydroquinoline and tetrahydroisoquinoline have important biological activities[18-22]. This new catalytic asymmetric multicomponent reaction is of great significance for the synthesis of many alkaloids and drug development.

Scheme 3. Asymmetric multicomponent Aza-Diels-Alder reaction

Chiral 2,3-disubstituted-2,3-dihydrobenzofurans are common fragments of many bioactive molecules and natural products [23-28]. In 2016, Géraldine Masson's group developed the [3 + 2] cycloaddition of quinones with olefins and sulfoxide carbamates under the catalysis of SPA, and obtained 3-amino-2,3-dihydrobenzofuran, which achieved good diastereoselectivity and excellent

enantioselectivity [29] (Scheme 4). They obtained a template reaction with 99% yield, 99% ee and 6:1 Dr. In addition, the Géraldine Masson's group also realized the asymmetric tandem oxidative [3 + 2] cycloaddition. Hydroquinone was used as the starting material, phenyliodo (III) diacetate (PIDA) and chiral phosphoric acid were carried out in the same reactor (Scheme 5).

Scheme 4. Asymmetric [3 + 2] cycloaddition of quinones with ene- and thioene-carbamates

Scheme 5. Asymmetric tandem oxidative cycloaddition

Paeoveitol is one of the main antipsychotic components of *Radix Paeoniae Rubra*. [30-31] In 2017, Chen Jijun's group reported for the first time the enantioselective 6-step total synthesis of Paeoveitol with an overall yield of 42% [32], and the best result was the 7-

step total synthesis published by Xie Zhixiang's group with an overall yield of 26% [33]. SPA catalyzed hetero Diels alter reaction, as a key step, provides high yield (up to 95%) and good corresponding selectivity (up to 90% ee). (Scheme 6)

Scheme 6. [4 + 2] Hetero-Diels-Alder reaction

Cyclic ethers are ubiquitous in natural products and are commonly used in organic synthesis [34-36]. In 2018, Terada Masaharu's group published a report on the synthesis of chiral seven membered cyclic ethers via the

intrinsic homology of Nicholas reaction. Under the catalysis of SPA, the racemic diols were cyclized to obtain good yield and good enantioselectivity [37]. (Scheme 7)

Scheme 7. Synthesis of seven-membered cyclic ethers

Trisubstituted chromone frameworks have three adjacent chiral centers, which are ubiquitous in many natural products and bioactive molecules [38-40]. In 2020, Yuan Weicheng group (scheme 8) and Shao Zhihui group (scheme 9) published papers on the use of chiral phosphoric acid catalyst to obtain chiral 2,3,4-trisubstituted chromones with high stereoselectivity through [4 + 2] cycloaddition [41-42]. These methods have good yield and enantioselectivity, and have a wide range of applications. Two of the groups used 1 - ((2-aryl) vinyl) naphthalene-2-phenol as raw material for asymmetric synthesis of trisubstituted chromones, however, different catalysts were selected through

different specific conditions, and good catalytic effect was achieved. At the same time, the two groups have also carried out experiments and discussions on the catalytic mechanism. (scheme 10) by protecting the hydroxyl group and not reacting, it is proved that the free hydroxyl group of the two substrates is necessary for the reaction. In addition, the chiral phosphoric acid catalyst was activated to dehydrate O-hydroxybenzyl alcohol to o-quinolone formamide. At the same time, 1 - ((2-aryl) vinyl) naphthalene-2-phenol was activated to increase the nucleophilicity. SPA was used as a bifunctional catalyst to combine the two intermediates into a transition state by hydrogen bonding.

Scheme 8. The research of Wei-Cheng Yuan's group

Scheme 9. The research of Zhihui Shao's group

Scheme 10. Exploring experiments and plausible transition states

2.2 Friedel-Crafts reaction

Friedel Crafts (F-C) reaction is a common reaction to construct C-C bond on aryl group in organic synthesis. In

F-C reaction, hydrogen atoms in aromatic compounds and directional heterocyclic compounds are replaced by active olefins, halogenated hydrocarbons, carbonyl compounds and imines [43-47].

Indoles are widely distributed in bioactive molecules as skeletons or functional groups (Figure. 4). Alkaloids

containing indole structure showed antifungal, anticancer, antimalarial and antibacterial activities [48-51].

Figure 4. The clinically used indole-containing drugs

In 2010, Lin Xufeng's group developed the F-C reaction of indole and imine catalyzed by spirodiindene skeleton chiral phosphoric acid [6], which has a high degree of corresponding selection, and can obtain the highest yield of 97% and the highest ee value of 99%. (scheme 11) β - carbazoline compounds are important pharmacological active components in indole alkaloids,

which widely exist in natural products and drugs [44, 52-57]. In 2017, Lin Xufeng's group further explored the aza Friedel Crafts reaction of indole and 1-trifluoromethyl-3,4-dihydro- β - carboline catalyzed by SPA [58], and obtained high yield (81%) and corresponding selectivity (86% ee), and proposed intermediate transition state. (Scheme 12)

Scheme 11. First SPA catalyzed F-C reaction of indole and imine

In 2017, the Gredicak Matija's group provided an aza Friedel Crafts reaction for the preparation of chiral α -tetrasubstituted (3-indolyl) - (diaryl) methylamines [59]. Before that, there was no synthesis method with high corresponding selectivity [60-61]. By using N-protected

isindolinol and N-protected indole to catalyze the reaction respectively, the group of Gredicak Matija pointed out that the chiral phosphoric acid catalyst connects the H atoms on the N of two substrates to form a transition state for catalytic reaction. (Scheme 13)

Scheme 12. Enantioselective aza-Friedel-Crafts reaction

Scheme 13. The research of Gredicak Matija's Group

N-substituted indoles and carbazole are the main components of some natural products and bioactive molecules, which are widely used in pharmaceutical chemistry and material chemistry [62-63]. In 2017, sun Jianwei's group used SPA to catalyze N-alkylation of

indoles and carbazole compounds [64], and obtained high yield and high enantioselectivity under mild conditions. It provides a new idea for asymmetric N-alkylation of indole and carbazole. (Scheme 14)

Scheme 14. Asymmetric N-Alkylation of Indoles and Carbazoles through SPAs

Chiral disubstituted carbonyl indoles are important bioactive molecules [65]. In 2018, Lin Xufeng's team reported the first case of using chiral SPA to catalyze the 1,6-conjugate addition of indole to the unprotected

indirubin derivative structure on N [66], and obtained good yield and corresponding selectivity (up to 97% ee). (Scheme 15)

Scheme 15. Asymmetric organocatalytic synthesis of chiral 3,3-disubstituted oxindoles

In 2019, Zhao Junling and his colleagues used SPA as catalyst and trifluoromethyl ketone as electrophilic reagent to realize the F-C reaction on the 7th position of indole [67]. Good results have been obtained, and the possible mechanism has been discussed in connection with the experimental results and the previous report [68]. In this reaction, SPA catalyst, as a bifunctional catalyst,

activates the substrate through hydrogen bonding. In addition to the traditional nucleophilic C3 site, the C7 site of indole is also activated by the para activation of the amino part. Moreover, due to the steric hindrance caused by the substituted amino part at the C4 position, the alkylation at the C7 position prevails, which makes the product have good regioselectivity. (Scheme 16)

Scheme 16. C7-Friedel-Crafts alkylation of indoles

2.3 Other catalytic reactions

Fischer indolization is a simple synthesis of indole by cyclization of aromatic hydrazones of aldehydes or

ketones under acidic conditions. In 2011, the list team reported the first case of asymmetric Fischer indole reaction catalyzed by SPA, in which phenylhydrazones derived from 4-substituted cyclohexanones had high corresponding selectivity [69]. (Scheme 17)

Scheme 17. Fischer indolization

Pictet Spengler reaction is a common method to synthesize β - carbazoline compounds. In 2012, Lin Xufeng's team reported the Pictet Spengler reaction for the

synthesis of tetrahydro - β - carbazoline with high enantioselectivity using SPA catalyst[70]. (Scheme18)

Scheme 18. Pictet-Spengler reaction

SPA is also suitable for a variety of dual catalytic systems [71-73]. In 2019, Jiang Zhiyong's group published Povarov reaction without transition metal catalysis [74]. Under the catalysis of SPA and DPZ, a series of chiral isoindoline-1-ones were synthesized under

the influence of visible light, and the highest yield of 97% and ee value of 98% were obtained. (scheme 19) These dual catalytic systems also provide more ideas for the application and development of SPA catalysts.

Scheme 19. Povarov reaction

3 Conclusion

Although SPA catalyst has only been developed for ten years, it has attracted wide attention as a new chiral phosphoric acid catalyst. Because of the safety and environmental protection, it is very suitable for the synthesis of drug molecules, and provides a new synthetic idea for a variety of compounds with pharmacological activities. As a young chiral phosphoric acid catalyst, SPA catalyst has developed a second-generation catalyst based on the original framework, with the development of applied chemistry, more efficient, mild and green SPA catalysts will be developed and more applications will emerge. However, it should also be noted that the limitations of the current catalytic reaction, most of the reports have not reached the gram level reaction, there are still many limitations to achieve industrial production.

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