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Review

# Recent advances in asymmetric reactions catalyzed by chiral phosphoric acids

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ABSTRACT

This review summarizes the very recent advances in asymmetric reactions catalyzed by chiral phosphoric acids (CPAs), a family of versatile catalysts that catalyze a broad range of reactions to afford diverse chiral molecules. In the past years, different kinds of chiral phosphoric acids have been designed and developed into a privileged class of catalysts in asymmetric synthesis. A number of remarkable achievements have been made by many groups around the world. Due to length limitation, this review only summarizes those works published from January 2016 to November 2017. Meanwhile, catalytic systems which combine metal catalysts and chiral phosphoric acids will not be discussed in this review.


## 1. Introduction

After ground-breaking works devoted by Akiyama [1], Terada and Uraguchi [2], last decade has seen exponential growth in the field of chiral phosphoric acids [3]. This family has become one of the most powerful organic catalysts. New generations of chiral phosphoric acids were continuously developed to catalyze a broad range of reactions with good to perfect enantioselectivities. In a common sense, a chiral phosphoric acid acts as a bifunctional Brønsted acid/base catalyst, in which the nonbonding electron pair of the oxygen atom in the P=O bond is regarded as a basic moiety and the P—OH hydrogen as an acidic moiety. However, in some cases, chiral phosphoric acids just solely act as Brønsted acid catalysts. This review is organized by the type of reactions catalyzed by chiral phosphoric acids.

## 2. Conjugate addition of quinone methides and aza-quinone methides

Quinone methides (*e.g.*, *o*-QMs and *p*-QMs) are highly active organic intermediates which can easily react with nucleophiles to give Michael addition type products. Chiral phosphoric acid catalysts, which bind the QMs (generated *in situ* by CPAs) and the nucleophiles together through hydrogen bonds, can stereoselectively catalyze 1,4 or 1,6-conjugate additions to afford enantio-enriched products from racemic starting materials.

Based on their early exploration works on the asymmetric 1,4 and 1,6-conjugate addition of carbon- [4] and oxygen-centered nucleophiles [5] to quinone methides, Sun and coworkers recently developed a series of conjugate additions employing other kind of nucleophiles. In 2016, they reported the first chiral phosphoric acid catalyzed enantioselective addition of thiols to *in situ* generated *ortho*-quinone methides (*o*-QMs). The reaction condition was mild and moderate to good efficiencies were obtained (Scheme 1) [6].

Soon after that, the same group published a chiral phosphoric acid catalyzed asymmetric 1,6-addition of naphthols to *in situ* generated *para*-quinone methides (*p*-QMs) [7]. In 2016, Li reported an asymmetric 1,6-conjugate addition of *para*-quinone methides using thioacetic acid **5** as nucleophile. Theoretical studies indicated that a water-bridged proton transfer is a potentially favorable reaction pathway (Scheme 2) [8].

In contrast with their oxygen-containing analogous *ortho*-quinone methides, *aza-ortho*-quinone methides are rarely employed in asymmetric reactions. In 2016, Rueping reported an asymmetric 1,4-addition of thiols and alcohols to *aza-ortho*-quinone methides. In this work, the authors provided a reliable method for the synthesis of potent drug candidates which previously are not easily accessible (Scheme 3) [9].

Due to the low nucleophilicity of N—H motif, the conjugate addition of the N—H in indoles and carbazoles to quinone methide

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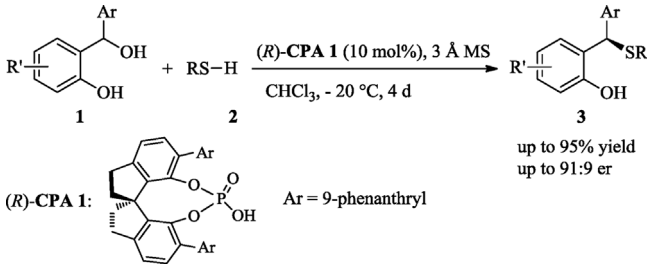
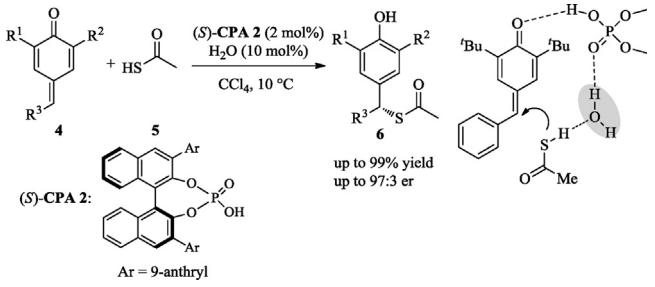
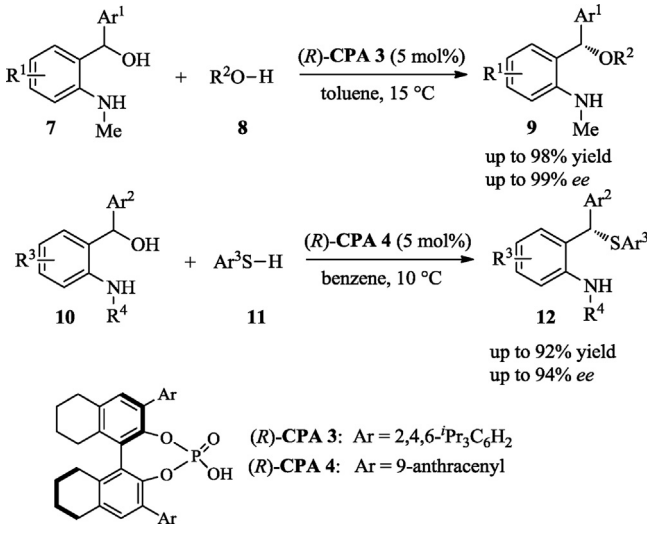



**Scheme 1.** Enantioselective addition of thiols to *ortho*-quinone methides (*o*-QMs).



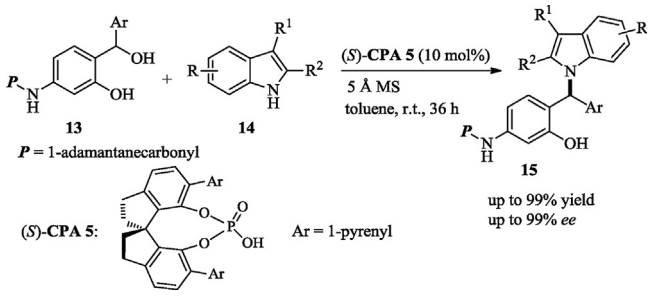

**Scheme 2.** Enantioselective addition of thioacetic acids to *para*-quinone methides (*p*-QMs).




**Scheme 3.** Enantioselective addition of thiols and alcohols to *aza-ortho*-quinone methides.

analogues is more difficult than other hetero-atom-centered nucleophiles. After screening of a series of different protecting groups, Sun found that by employing a chiral phosphoric acid as catalyst, bulky 1-adamantanecarbonyl protected 4-amino-benzyl alcohols **13** reacted with 2,3-disubstituted indoles or carbazoles smoothly to afford desired products with excellent enantioselectivities (up to 99% *ee*, Scheme 4) [10].

Hantzsch esters are regarded as hydride surrogate which reduce a series of organic compounds. Sun and coworkers recently realized the asymmetric reduction of 4-hydroyl benzyl tertiary alcohols to corresponding methine derivatives using chiral phosphoric acid as catalyst and Hantzsch ester as reductant. It should be noted that, after mechanism studies, they fully disclosed the actual role of the additive boronic acid through the whole reaction process (Scheme 5) [11].




**Scheme 4.** Enantioselective addition of indole and carbazoles to *aza-para-*quinone methides.

In addition to the widely reported 1,4 and 1,6-conjugate addition, Sun and coworkers recently demonstrated a synthesis of chiral tetrasubstituted allenes *via* a rarely reported 1,8-conjugate addition of *para*-quinone methides. This process characterized by the construction of axial chirality from quinone methides (Scheme 6) [12].

Studies on the conjugate addition of carbon-centered nucleophiles to quinone methides and *aza*-quinone methides were also reported by other groups [13].

## 3. Conjugate addition of other Michael acceptors

In 2016, Terada reported a highly enantioselective *aza* Michael-type addition reactions between *N*-protected alkenyl benzimidazoles and either pyrazoles or indazoles. Structural analysis of the transition states revealed that both the catalyst substituent and the N-protective group of benzimidazole are essential to obtain high enantioselectivity (Scheme 7) [14].

List and Coelho recently reported a catalytic asymmetric conjugate addition of indolizines to $\alpha,\beta$-unsaturated ketones (Scheme 8) [15]. Mechanistically, the reaction proceeded *via* a monofunctional activation mode, because indolizines lack an available NH moiety to bond with the basic moiety of chiral phosphoric acid catalyst *via* hydrogen-bonding.

You recently reported a chiral phosphoric acid catalyzed intramolecular dearomative Michael addition of indoles to enones. This method provided spiro-indolenines bearing a quaternary stereogenic center with good yields and enantioselectivities (Scheme 9) [16].

Chiral phosphoric acid catalyzed intramolecular Michael addition was successfully applied in the total synthesis of lycoposerramine-Z. The enantioselective construction of the multifuctionalized cyclohexanone was the initial step of the whole process (Scheme 10) [17].

## 4. Cycloaddition reaction

In addition to Michael addition, *o*-QMs have a high propensity to undergo [4 + 2] hetero-Diels–Alder reaction with dienophiles. In 2017, List reported an asymmetric intramolecular [4 + 2] cycloaddition of *in situ* generated *ortho*-quinone methides catalyzed by a confined chiral imidodiphosphoric acid catalyst. Through the reaction pathway, salicylaldehydes first react with dienyl alcohols to give transient *ortho*-quinone methide intermediates, which then undergo an intramolecular [4 + 2] cycloaddition to afford the highly functionalized final products with perfect diastereoselectivity and enantioselectivity (Scheme 11) [18].

Sun recently reported a catalytic asymmetric [4 + 2] cycloaddition of *ortho*-quinone methides and vinyl sulfides (Scheme 12) [19]. Mechanistically, the reaction is a new example of the rarely achieved sole activation of *o*-QM for asymmetric control.

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