

## Asymmetric reactions involving isobenzopyrylium ion intermediates

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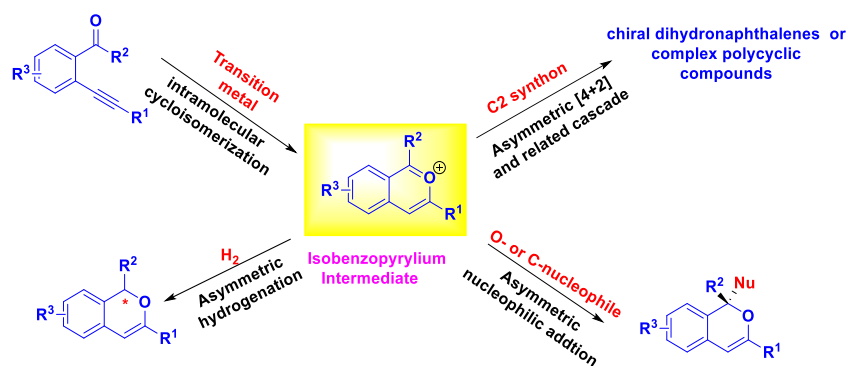
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### Abstract

Isobenzopyrylium ions are highly reactive intermediates which have wide applications in synthetic chemistry. A range of catalytic reactions based on isobenzopyrylium, such as 1,2-nucleophilic addition, [4+2] and [3+2] cycloaddition provide a powerful protocol for constructing complex natural and unnatural products. Their asymmetric variations have been less explored, possibly owing to the lack of coordination sites within their planar structures. This mini-review summarizes the asymmetric transformations developed involving isobenzopyrylium ion intermediates. These works are arranged according to the reaction types. The catalytic systems and reaction mechanisms are described.



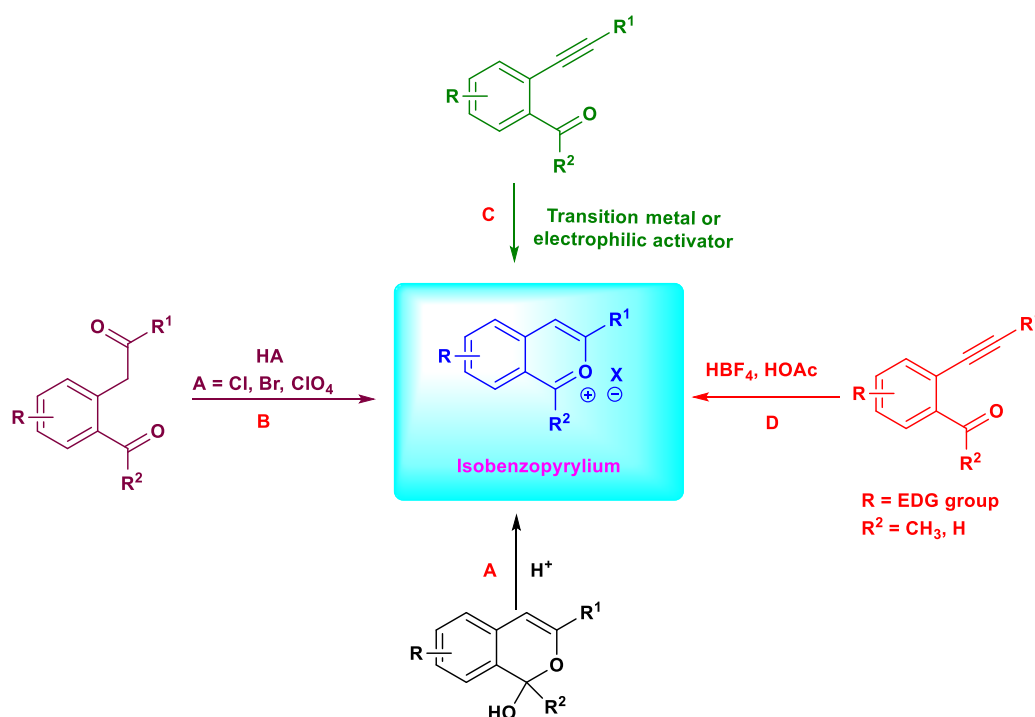
**Keywords:** Isobenzopyrylium, [4+2]-cycloaddition, asymmetric hydrogenation, nucleophilic addition, cascade reactions

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## 1. Introduction

Isobenzopyrylium ion, a unique type of Hückel aromatic oxonium intermediate, attracted great attention in recent years owing to versatile chemical properties and synthetic applications.<sup>1-2</sup> These highly reactive intermediates were originally obtained by dehydration of isocoumarin derivatives or condensation of *ortho*-acylphenylacetones (Scheme 1A and 1B).<sup>3</sup> Both of these methods suffered from the limited availability of the starting materials and unsatisfactory reaction yields. In 2002, Yamamoto's group found that isobenzopyrylium ions could be conveniently produced *in situ* as inseparable intermediates by the treatment of *o*-alkynylbenzaldehydes with AuCl<sub>3</sub>.<sup>4-8</sup> Then other transition metal catalysts (CuX<sub>2</sub>,<sup>9-10</sup> W,<sup>11-14</sup> PdX<sub>2</sub>,<sup>15-17</sup> PtX<sub>2</sub>,<sup>18-22</sup> Rh(I)<sup>23</sup>, InX<sub>3</sub><sup>24-26</sup> etc.) and electrophilic activators (I<sub>2</sub>,<sup>27-29</sup> IPy<sub>2</sub>BF<sub>4</sub>,<sup>30-32</sup> TfOH,<sup>33-35</sup> etc.) proved to be effective in the intramolecular cycloisomerization of *o*-alkynylaryl carbonyl compounds (Scheme 1C). Furthermore, Yao and his co-workers reported in 2009 the isolation of storable and stable isochromenylium tetrafluoroborates (ICTBs) (Scheme 1D).<sup>36</sup>



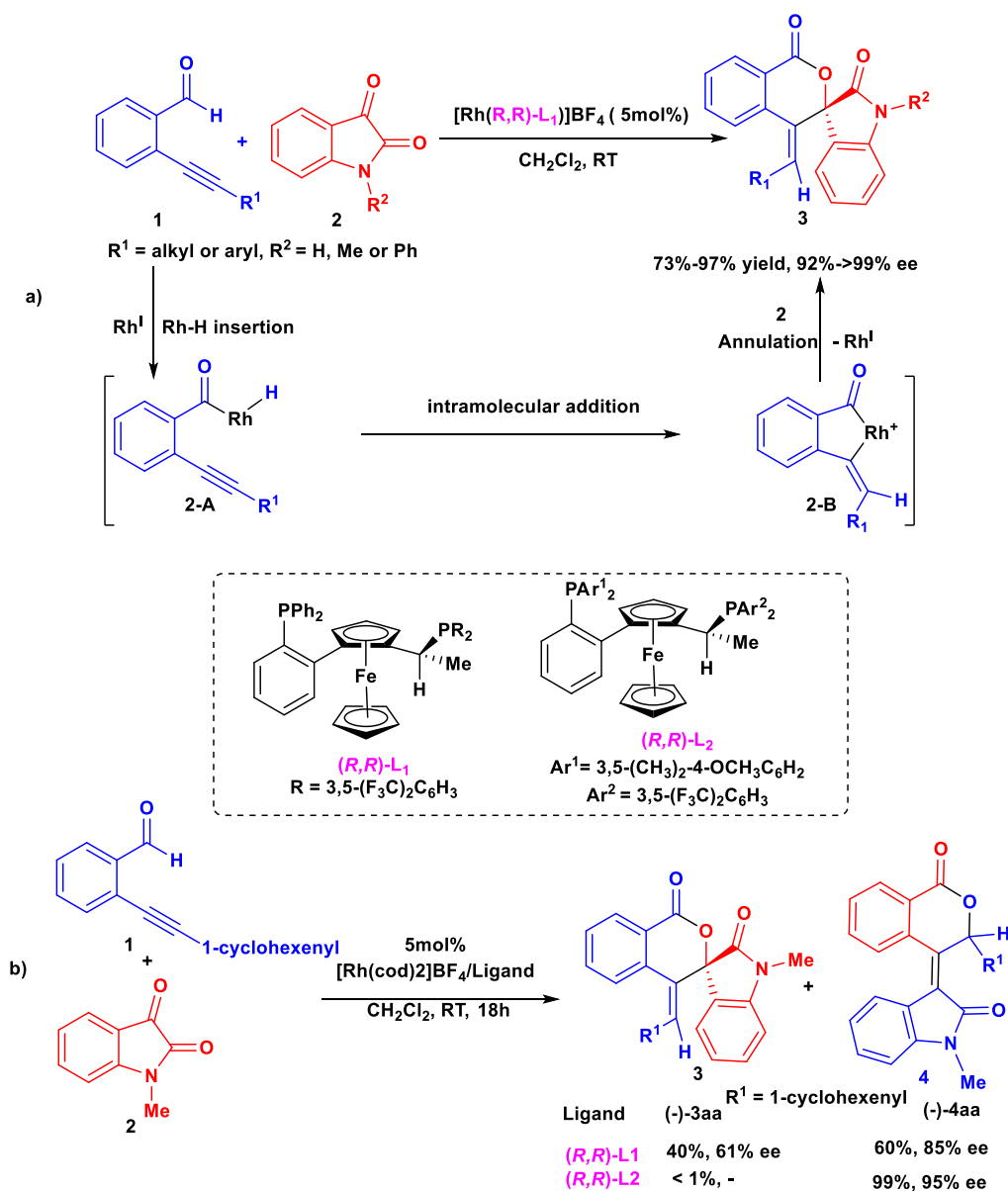
**Scheme 1.** Methods for the generation of isobenzopyryliums.

Since its discovery, the rich chemistry of isobenzopyrylium has been amply demonstrated in the literature, and has provided a powerful protocol for constructing complex natural and unnatural products. The reported reactions included 1,2-nucleophilic addition, [4+2] cycloaddition, [3+2] cycloaddition and various cascade reactions.<sup>37-44</sup> The asymmetric transformations of isobenzopyrylium ions have been less explored.<sup>45</sup> This may be because the planar 10  $\pi$ -electron aromatic structure of the isobenzopyrylium ion lacks an obvious coordination site for a chiral catalyst which is often crucial for achieving high stereoselectivity. Their highly reactive properties also increased the difficulty in obtaining ideal enantioselective results.

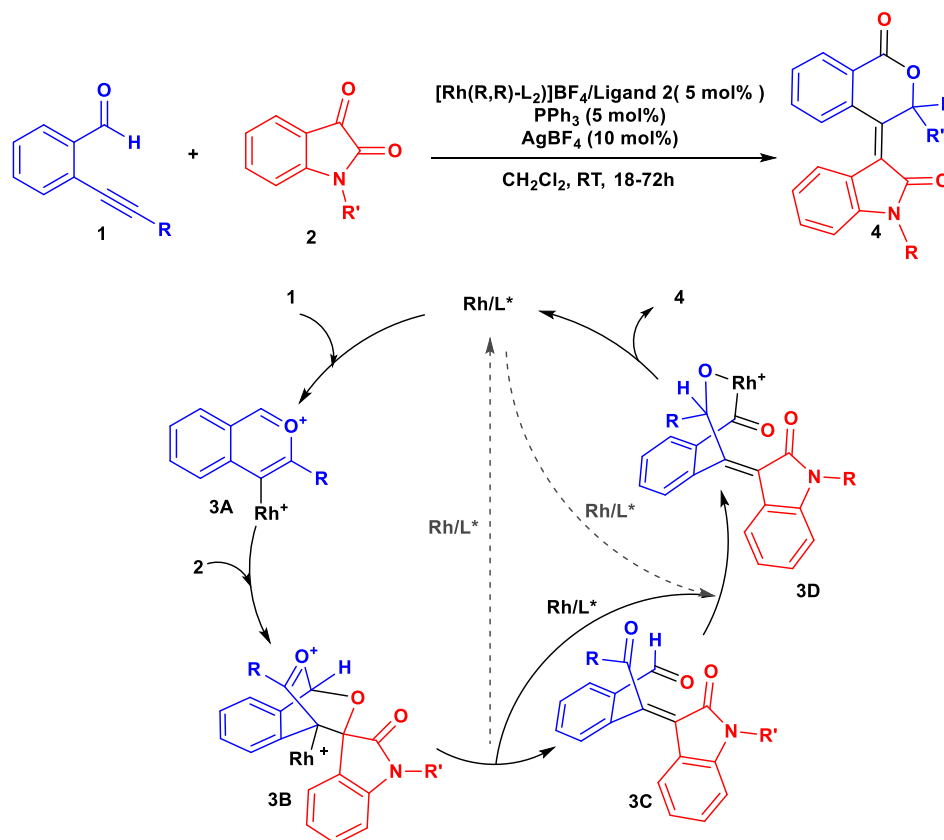
This mini-review summarizes the asymmetric transformations involving isobenzopyrylium intermediates. The works are organised according to the different reaction types, aiming to encourage chemists to think about such cation intermediate from different points of view, thereby identifying new enantioselective transformations with these species.

## 2. Asymmetric [4+2] Cycloaddition and Related Cascade Reactions

The first asymmetric transformation of isobenzopyrylium was achieved by Tanaka's group in 2009.<sup>46</sup> Prior to that, this group had discovered a highly enantioselective annulation of 2-alkynylbenzaldehydes **1** with isatins **2** catalyzed by a cationic rhodium(I)/chiral bisphosphine complex.<sup>47</sup> A variety of spirocyclic isatin derivatives **3** were obtained in good yields with high *ee* values. These spiro-compounds were believed to be formed through the [4+2] cycloaddition of carbonyl compounds **2** with five-membered acylrhodacycle intermediates **2B**, which were formed by the intramolecular addition of a rhodium hydride species **2A** to the pendant alkyne group (Scheme 2a). Both alkyl- and aryl-substituted 2-alkynylbenzaldehydes could react smoothly with *N*-protected or *NH*-free isatin. However, when 2-alkynylbenzaldehyde with a cyclohexenyl group at the alkyne terminus was tested, a moderate yield of tetrasubstituted (helical) alkene **4** was unexpectedly isolated along with a small amount of the expected spirocyclic isatin **3** (Scheme 2b). The reaction selectivity could be greatly improved through a change of chiral ligand (L2 vs L1, 99:1 vs 3:2 ratio). After further optimization, the authors found addition of AgBF<sub>4</sub> and PPh<sub>3</sub> was beneficial for the formation of chiral tetrasubstituted alkenes **4** (Scheme 3). A possible reaction pathway was proposed as follows: the intramolecular cyclization of 2-alkynylbenzaldehydes **1** under the activation of  $\pi$ -electrophilic cationic transition-metal complex generated isobenzopyrylium intermediate **3A**, which reacted with the C=O bond of *N*-methylisatin **2** via [4+2] enantioselective cycloaddition pathway to form ketoaldehyde **3C** through adduct intermediate **3B**. Enantioselective intramolecular ketone hydroacylation of **3C** proceeded through rhodacycle **3D** to furnish the desired tetrasubstituted alkene **4**. Control experiments suggested AgBF<sub>4</sub> was necessary for good yields. It was believed to promote the  $\pi$ -electrophilicity of the cationic rhodium(I) complex, which is essential for the formation of intermediate **3A**. But its precise role is not clear at present. PPh<sub>3</sub> was envisaged to occupy free coordination sites of the rhodium catalyst, with the result of preventing the interaction of rhodium with AgBF<sub>4</sub>. This interaction was believed to lower the catalytic activity towards both  $\pi$ - and  $\sigma$ -bond activation. With the optimal reaction conditions, a variety of tetrasubstituted helical alkenes **4** were obtained in good yields with excellent enantioselectivities, which might be applied to light-driven molecular motors, owing to their fascinating switching properties under UV irradiation.<sup>48</sup>

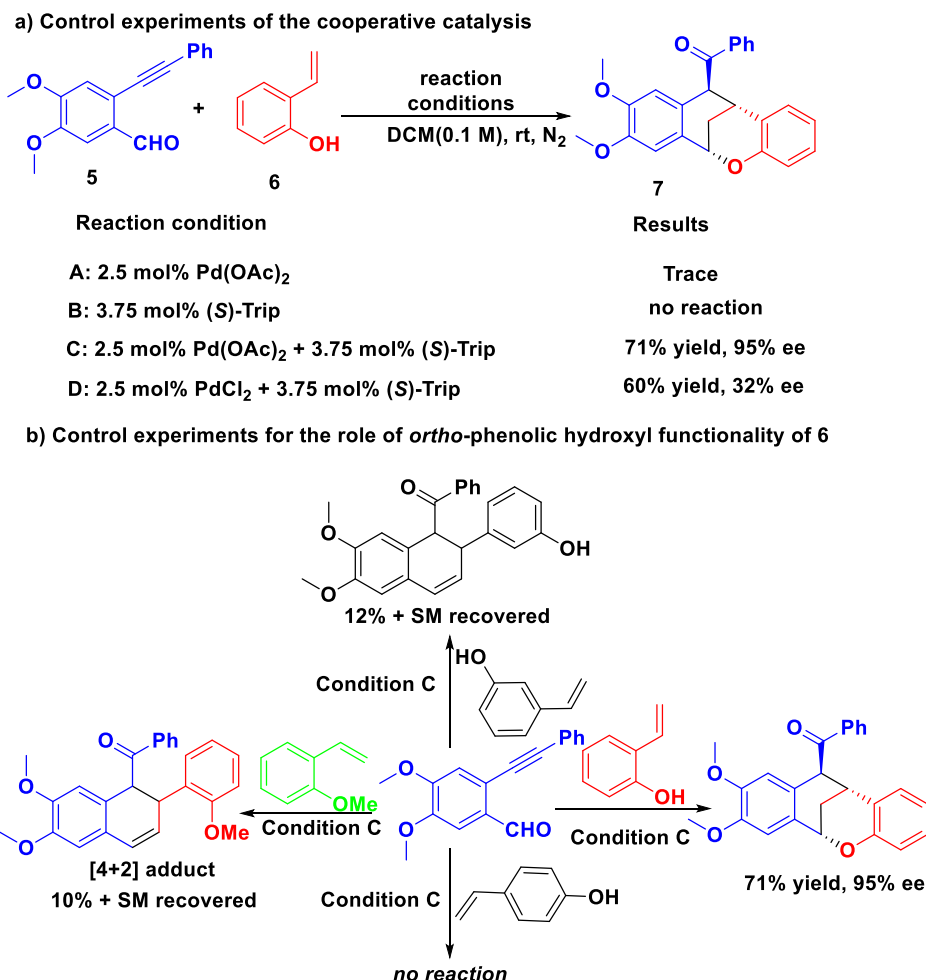


Scheme 2. Different reaction results of 2-alkynylbenzaldehydes with isatins.



**Scheme 3.** Asymmetric [4+2] cycloaddition of isobenzopyrylium with isatins.

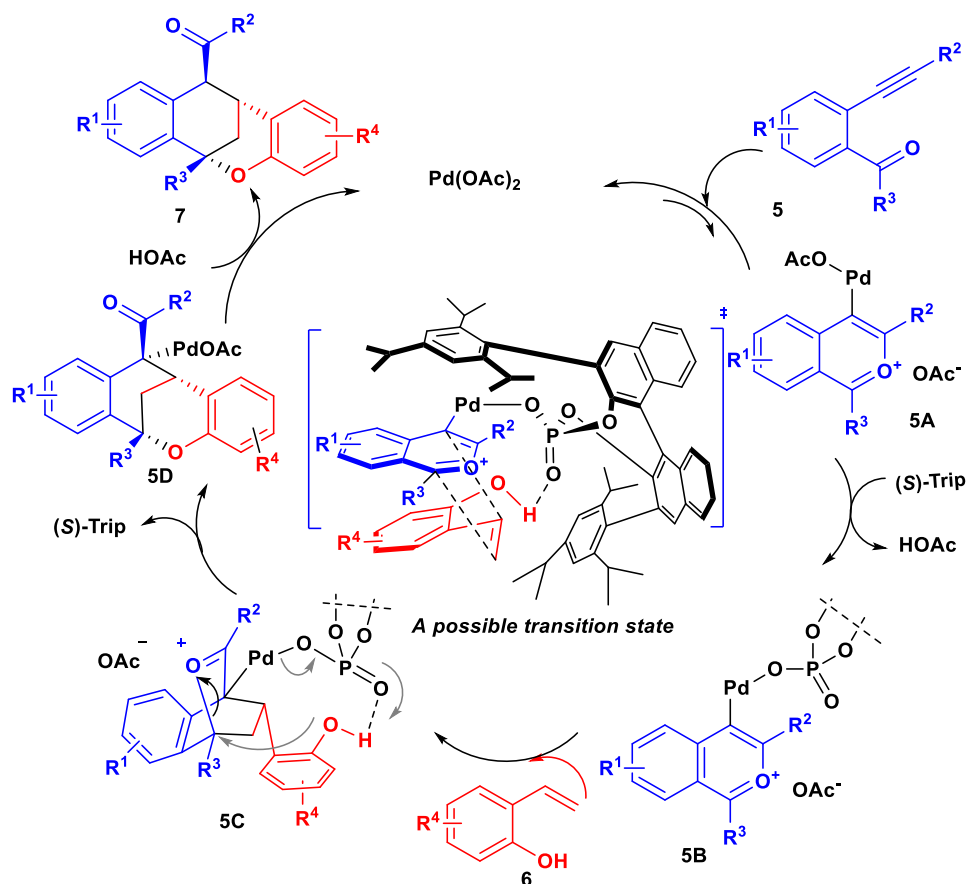
Following the interest in exploring the chemistries of isobenzopyrylium salts, many cascade transformations based on [4+2] cycloadditions were found to show high efficiency in constructing complex multiring structures with multiple stereogenic centers. In 2013, Yao's group reported an asymmetric cascade annulation between 2-hydroxystyrenes and *in situ* generated isobenzopyrylium intermediates based on the enantioselective [4+2] cycloaddition by cooperative binary catalysis of  $\text{Pd}(\text{OAc})_2$  and chiral phosphoric acid (CPA-1, *S*-Trip).<sup>49</sup> The developed method could construct a chiral tetrahydronaphthalene framework in a highly efficient manner. Such a skeleton represents a new type of conformationally constrained analog of podophyllotoxin (PPT), a well-known anticancer natural drug lead.<sup>50,51</sup> Mechanistic investigation suggested that the counter-anion of  $\text{Pd}(\text{II})$  was very important for the reaction ( $\text{AcO}^-$  vs  $\text{Cl}^-$ ) (Scheme 4a), and the *ortho*-phenolic hydroxyl group in the styrene substrate was also essential to achieve this type of highly enantioselective cascade transformations (Scheme 4b). Based on these results, a possible reaction pathway was proposed (Scheme 5). Firstly, the alkyne bond of *o*-alkynylbenzaldehyde **5** was activated by  $\text{Pd}(\text{OAc})_2$  to facilitate the intramolecular cycloisomerization, affording  $\text{Pd}(\text{II})$ -isobenzopyrylium intermediate **5A**. The suitable anion of the isobenzopyrylium salt favored the anionic exchange with (*S*)-Trip. The resulting intermediate **5B** linked with the *o*-hydroxystyrene **6** through hydrogen-bond between the phenolic OH of the styrene and the P=O of Trip to assemble a highly ordered supramolecular assembly transition state. Then "intramolecular" asymmetric [4+2]-cycloaddition generated carbocation **5C**, which was quickly trapped by the internal phenol hydroxyl to provide **5D**. Finally, the protonation of **5D** with HOAc delivered product **7** and regenerated the metal catalyst  $\text{Pd}(\text{OAc})_2$ . The high degree of enantioselectivity was considered to stem from both the steric hindrance of the bulky 1,3,5-triisopropylphenyl group of (*S*)-Trip moiety and the hydrogen-bond interactions between the phenolic hydroxyl group of substrate **6** with the P=O functionality of (*S*)-Trip.



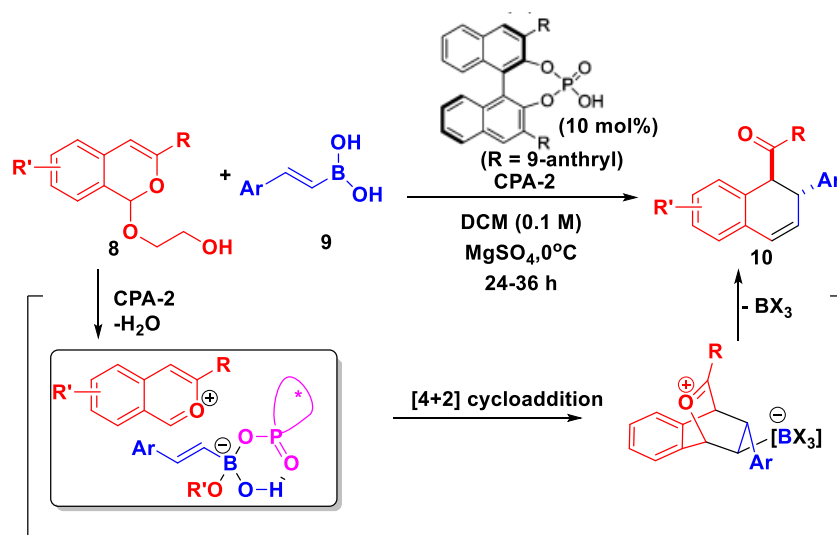
**Scheme 4.** Control experiments for the investigation of mechanism.

1,2-Dihydronaphthalenes represent an important structural motif in many natural products and biologically active molecules.<sup>52,53</sup> They are also important synthetic intermediates toward various tetrahydronaphthalene molecules. Consequently, many strategies have been developed for their synthesis (achiral or racemic).<sup>54-56</sup> However, regarding their asymmetric synthesis, for a long time the traditional dearomatization of electron-deficient naphthalene has been the major approach. It not only suffers from limited substrate scope (electron-deficient) but also requires the use of either chiral auxiliary or stoichiometric chiral ligands.<sup>57,58</sup> Indeed, truly catalytic asymmetric approaches remain few. In 2015, the Sun group disclosed an organocatalytic enantio- and diastereoselective synthetic method for 1,2-dihydronaphthalenes based on the [4+2] cycloaddition of isobenzopyrylium intermediate with boronic acid (Scheme 6).<sup>59</sup> In this work, acetal **8** was chosen as isobenzopyrylium precursor. Obviously different from other asymmetric transformation of isobenzopyrylium, this excellent asymmetric induction is achieved for the first time without an anchoring group or a metal catalyst in the 4-position of isobenzopyrylium. Only by treatment with chiral phosphoric acid (CPA-2), did the elimination of the alkoxy group from acetal **8** afford an isobenzopyrylium intermediate and generate a well-organized cyclic counteranion in the process, which was formed *in situ* by the combination of the leaving alkoxy group, the boronic acid **9** and the chiral phosphate. Such an unusual chiral counteranion served as a reactive nucleophile with chiral moiety in close proximity to react with isobenzopyrylium intermediate in sufficient chiral induction manner. Then the resulting bicyclic zwitterion underwent intramolecular elimination to give the desired dihydronaphthalene product **10** with satisfactory selectivity.

The authors believed that excellent enantioselectivity was attributed to the well-organized cyclic counteranion.



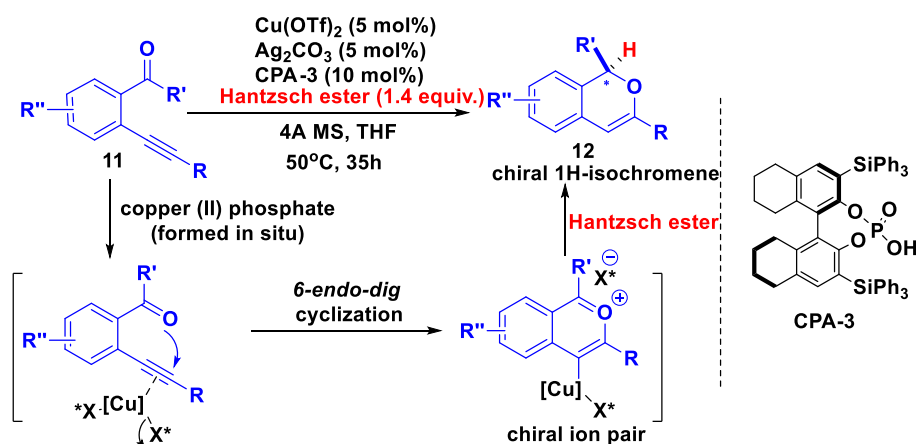
**Scheme 5.** Possible mechanism of cascade reaction based on [4+2] cycloaddition.



**Scheme 6.** Asymmetric [4+2] cycloaddition of isobenzopyrylium with boronic acid.

### 3. Asymmetric Hydrogenation

1-Substituted-1*H*-isochromenes are an important class of heterocyclic compounds because of their fascinating biological and pharmacological activities.<sup>60-62</sup> Among the methods for constructing such types of oxygen-containing heterocycles, the cycloisomerization of *o*-alkynylaryl alcohols is one of the most reliable and atom-economic.<sup>63-64</sup> Nevertheless, the enantioselective version of this reaction has rarely been reported. In 2013, Akiyama and co-workers developed an alternative method for chiral 1-substituted-1*H*-isochromenes through the copper(II) phosphate-catalyzed intramolecular cyclization/asymmetric transfer hydrogenation sequence of *o*-alkynylacetophenone by asymmetric counterion-directed catalysis (ACDC).<sup>65</sup> Since the term was coined in 2006, the use of enantiomerically pure counteranions for the induction of asymmetry in reactions proceeding through cationic intermediates has emerged as a powerful tool for a range of asymmetric transformations and greatly promoted by the incorporation of chiral binaphthyl phosphoric acids.<sup>66,67</sup> Inspired by these great success, the Akiyama group surmised that intramolecular *6-endo-dig* cycloisomerization of *o*-alkynylacetophenone **11** activated by transition metal could afford a cationic metallic isobenzopyrylium intermediate, which could form a tight ion pair with the chiral phosphate counteranion to subsequently induce the desired asymmetric hydrogenation (Scheme 7). After careful screening of reaction conditions, this asymmetric sequence was achieved by the catalysis of copper(II)/chiral phosphate which formed *in situ* from Cu(OTf)<sub>2</sub>, Ag<sub>2</sub>CO<sub>3</sub> and chiral chiral phosphoric acid (CPA-3). With the stereocontrol of chiral counteranion, chiral 1-substituted-1*H*-isochromenes containing various substituents were obtained in high yields with good to excellent enantioselectivities with Hantzsch esters as hydrogen source.



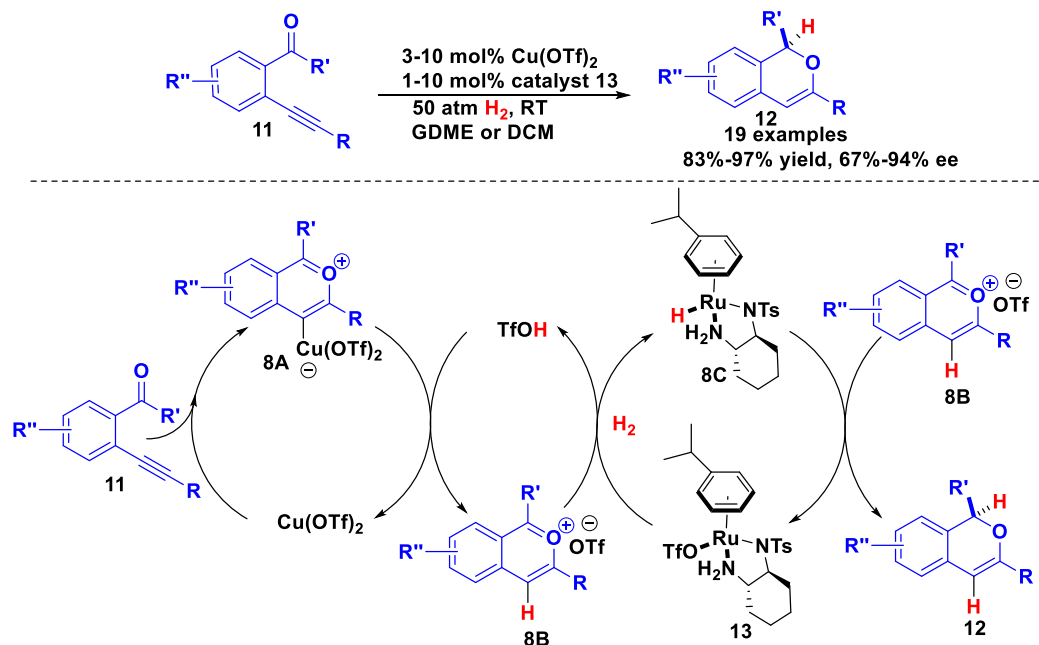
**Scheme 7.** Asymmetric hydrogenation of isobenzopyrylium by the catalysis of ACDC.

At almost the same time, the Terada group reported the chiral silver phosphate catalysed enantioselective transformation of *ortho*-alkynylaryl ketones into 1*H*-isochromene derivatives by ACDC. Different from Akiyama's work, this intramolecular-cyclization/enantioselective-reduction sequence was conducted with the chiral silver phosphate prepared in advance from Ag<sub>2</sub>CO<sub>3</sub> and the corresponding binol-derived phosphoric acid.<sup>68</sup>

Recently, the Fan group's work has shown that cationic ruthenium complexes of chiral monosulfonated diamines are very efficient catalysts for the asymmetric hydrogenation of various *N*-heteroaromatic compounds.<sup>69-71</sup> Encouraged by these findings, the authors attempted to use these catalysts for the asymmetric hydrogenation of the highly reactive isobenzopyryliums. Because isobenzopyryliums were often



generated *in situ* by treatment of *ortho*-alkynylaryl ketones with various metal catalysts, it was thus important to find two compatible catalysts for the overall reaction that also controlled the chemoselectivity and enantioselectivity. After optimization of reaction conditions, they successfully developed tandem catalysis with a binary system consisting of  $\text{Cu}(\text{OTf})_2$  and chiral cationic ruthenium-diamine complex **13** (Scheme 8).<sup>72</sup>



**Scheme 8.** Asymmetric hydrogenation of isobenzopyrylium by tandem catalysis.

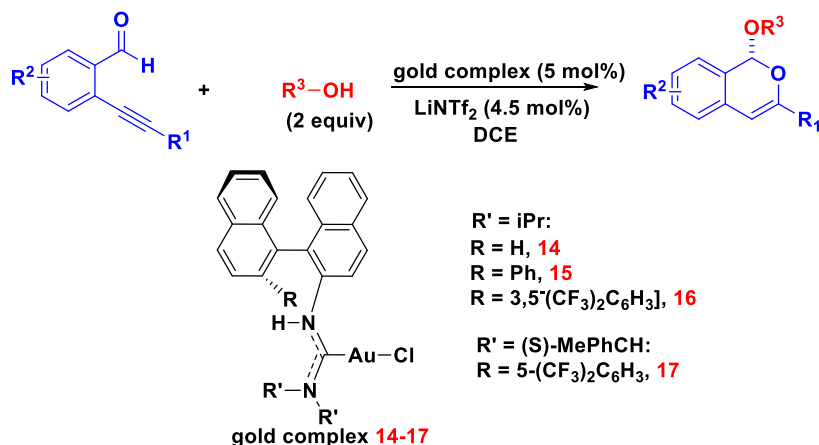
Activated by  $\text{Cu}(\text{OTf})_2$ , the intramolecular cyclization of *ortho*-alkynylaryl ketone **11** generated isobenzopyrylium **8A**. Meanwhile, the ruthenium-diamine catalyst **13** reacted with dihydrogen to produce Ru-H complex **8C** and  $\text{TfOH}$ . Then protonolysis of the C-Cu bond of **8A** by  $\text{TfOH}$  regenerated  $\text{Cu}(\text{OTf})_2$  and gave another isobenzopyrylium intermediate **8B**. Finally, hydride transfer from the Ru-H complex **8C** to isobenzopyrylium intermediate **8B** afforded the desired product **12** and regenerated the ruthenium-diamine catalyst **13**.

#### 4. Asymmetric Nucleophilic Addition

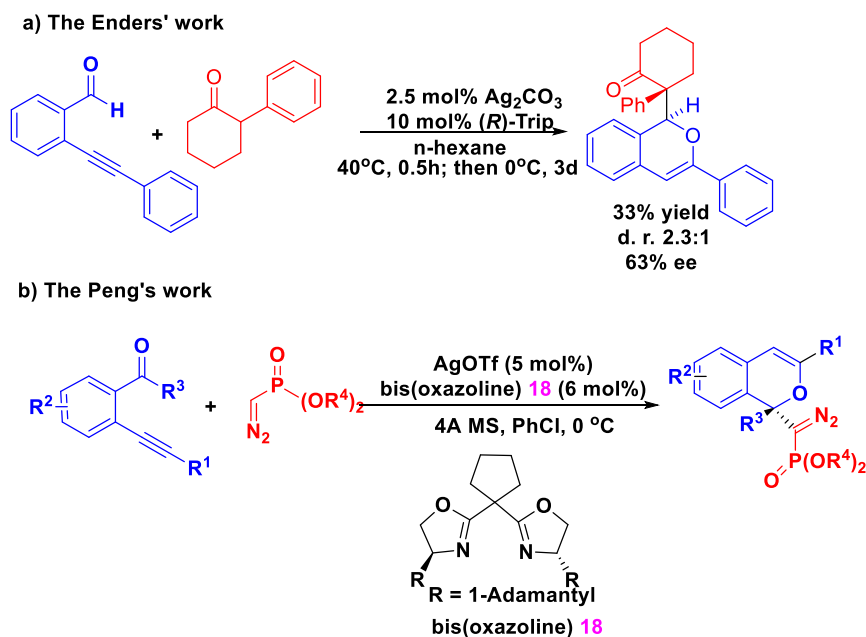
Following the electrophilic cyclization of *o*-alkynylaryl carbonyl compounds, nucleophilic addition reactions at the 1-position of isobenzopyrylium ions have been demonstrated as another efficient method for the construction of 1-substituted 1*H*-isochromene derivatives. A wide variety of nucleophiles involving oxygen,<sup>73-76</sup> nitrogen,<sup>77</sup> phosphites,<sup>78</sup> terminal alkynes,<sup>79</sup> allyl trialkylsilanes<sup>80,81</sup> and activated methylenes<sup>82-86</sup> proved to be applicable substrates. And recently, (hetero)aromatics also can be used as good external nucleophiles.<sup>87-90</sup> Nevertheless, their asymmetric version remains underdeveloped. Thus far, the reported asymmetric nucleophilic addition of isobenzopyrylium has been limited only to the addition of alcohols and activated methylene compounds.

In 2012, Slaughter and co-workers achieved asymmetric formation of chiral 1-alkoxyisochromenes through the enantioselective addition of alcohols to isobenzopyryliums in the presence of a gold(I) acyclic diaminocarbene complex (Scheme 9).<sup>74</sup> Owing to the ability of gold(I) to activate a variety of unsaturated bonds toward nucleophilic attack, catalysis with gold has emerged as a powerful tool for the synthesis of complex organic structures in the last decades.<sup>91-96</sup> But its linear coordination geometry resulted in the remoteness of chiral ligand substituents and the inability of substrates to adopt a chelate binding mode that favoured asymmetric induction, which represented challenges to developing enantioselective catalysis.<sup>97-100</sup> However, in some intriguing reports, the secondary interactions of ligands-Au were found to be helpful to overcome the inherent difficulty of achieving chiral environment, and thus high enantioselective results have been achieved with gold catalysts in some asymmetric reactions.<sup>101</sup> Encouraged by these findings, Slaughter's group firstly created three gold acyclic diaminocarbene complexes **14-16**, and then investigated their solid-state structural differences through their X-ray crystal structures. Compared with **14** and **15**, a significantly more pronounced chiral environment at the metal center was observed in **16** owing to the presence of the aryl group adjacent to Au. This difference was directly reflected on the ability of chiral induction. Only with gold complex **16** were good yields and high enantioselectivities attained. However, for alcohols containing shorter *n*-alkyl chains or alkynes containing *n*-propyl instead of an aryl group, a new Au(I)/ADC complex **17** must be employed for ideal results. The chiral amine substituent in this modified catalyst **17** was believed to augment the chiral environment at the metal through steric interactions with the binaphthyl moiety.

The asymmetric addition reactions of C-nucleophiles to isobenzopyrylium ions at the 1-position provided a straight route to structurally diverse chiral 1-substituted 1*H*-isochromene derivatives.<sup>102-104</sup> In 2016, the Enders group demonstrated the type of asymmetric addition could be realized under a combination of Ag<sub>2</sub>CO<sub>3</sub> and chiral phosphoric acid, but only with moderate success (Scheme 10a).<sup>105</sup> Just recently, Peng and his co-workers disclosed an efficient asymmetric addition of isobenzopyrylium with diazomethylphosphonate as C-nucleophile (Scheme 10b).<sup>106</sup> Considering that transition-metal catalyst was still attached to the isobenzopyrylium ion at the 4-position after it activated the alkyne bond to conduct the intramolecular cyclization, the authors surmised that it could be exploited to create a chiral environment. The central metal coordinated with a chiral ligand possessing a sufficiently long arm, which might pass on chiral environment proximity to the 1-position, and thus, asymmetric nucleophile addition could be achieved at this position. Under the guidance of this assumption, chiral BOXes were chosen as promising ligands, because the chiral BOXes with different long arms could be easily prepared by using different chiral starting materials.<sup>107-110</sup> The results of ligand screening showed that the BOXes with a cyclic ring at the bridging carbon gave better stereoselectivity than these with simple substituents, and the substituents at the 4,4'-position of the ligand also had a great effect on the catalytic performance. Ultimately, bis(oxazoline) ligand **18** combining with AgOTf was established as the optimal catalytic system. A variety of functional phosphine-containing isochromenes derivatives bearing tetrasubstituted stereocenters at the 1-position were easily prepared with up to 94% enantiomeric excess. The deuterium labeling experiment and DFT calculation were further performed to get more insight into the reaction mechanism. The steric hindrance between the isobenzopyrylium and attacking diazomethylphosphonate affected the facial coordination of Ag (I) and chiral ligand, which was considered to be the main reason for the satisfactory stereoselectivity.



**Scheme 9.** Asymmetric nucleophilic addition of alcohols to isobenzopyrylium.



**Scheme 10.** Asymmetric C-nucleophilic addition to isobenzopyryliums.

## 5. Conclusions

Although the planar aromatic structure of isobenzopyrylium intermediates posed great challenges to their asymmetric transformations, many asymmetric reactions have been achieved with good to excellent diastereoselectivities by asymmetric counterion-directed catalysis, cooperative catalysis or unusual chiral ligands in recent years. And thus, a series of optically pure 1H-isochromene derivatives, 1,2-dihydronaphthalenes or complex polycyclic compounds could be obtained in efficient and straightforward manners through asymmetric hydrogenation, asymmetric nucleophilic addition and asymmetric [4+2] cycloaddition and related cascade reactions. Inspired by these works, we believe that more interesting asymmetric reactions will be disclosed, such as asymmetric [3+2] cycloaddition reactions which remain unexplored in this stage.

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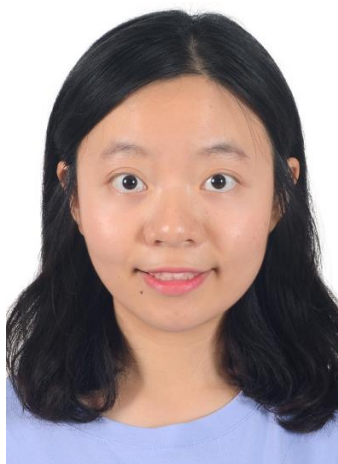
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