RECENT ADVANCES IN CATALYTIC ASYMMETRIC CYCLOADDITION REACTIONS OF *ortho*-QUINONE METHIDES FOR SYNTHESIS OF *O*-HETEROCYCLES

DOI: http://dx.medra.org/10.17374/targets.2018.21.181

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Abstract. *ortho-Quinone methides (o-QMs) are highly active and versatile class of intermediates which have been widely used for organic synthesis and lignin biosynthesis. However, until 20 years after they were suggested by Fries in 1907, QMs didn't arouse extensive attention. Over the past decades, with ever-increasing recognition of the properties and reactivity of o-QMs, exploration of their applications in asymmetric synthesis has rendered such type of intermediates as powerful precursors to various structurally diverse chrial O-heterocycles. In particular, recent years have witnessed considerable advances in the development of catalytic asymmetric cycloaddition reactions of o-QMs. Employing suitable metals or organocatalyst systems enables controllable generation of structurally diverse o-QMs and highly asymmetric induction in cycloaddition reactions. Thus, this chapter will survey the main recent advances in this field based on different catalytic systems and activation modes.*

Contents

1. Introduction

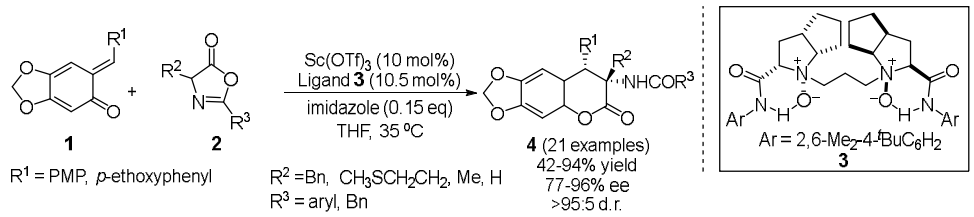
ortho-Quinone methides (*o*-QMs) are a class of highly reactive intermediates with broad applications in organic synthesis and lignin biosynthesis.[1] Compared with the radicals, carbocations, carbenes and other reactive species, *o*-QMs represent a unique family of reagents that contain a cyclohexadiene core and feature an exocyclic alkylidene and a carbonyl moiety. The high reactivity arouses from the thermodynamic drive to undergo rapid rearomatization. Hence, the high reactivity and ephemeral propensity enable these intermediates to be traped by diverese nucleophiles and dipolarphiles upon their generation. In this context, considerable efforts have been devoted to development of a wide range of practical, efficient approaches to construct diversely functionalized *O*-heterocycles via addition of 2π partners or others to capture o-QMs. Despite the rapid development of asymmetric catalysis in the past decades,[2] the asymmetric catalytic transformations of highly reactive *o*-QMs have still been scarce and remain an attractive and challenging task for organic chemists. In 2007, Sigma and coworkers disclosed an enantioselective Pd-catalyzed aerobic dialkoxylation reaction of the *in situ* generated *o*-QMs with alcoholic solvents, which opened an entry to the exploration of these intermediates in catalytic asymmetric synthesis. Since then, a series of organocatalytic and metal-promoted systems have been developed for *in situ* generation of *o*-QMs from various precursors and application in asymmetric reactions for construction of *O*-heterocycles. Thus, the main recent advances in this context and working models will be discussed based on different catalytic systems and activation modes in this chapter.

2. Catalytic asymmetric cycloaddition reactions of *ortho*-quinone methides

2.1. Lewis acid-catalyzed cycloaddition reactions

ortho-Quinone methides are highly reactive intermediates that can be generated under Lewis acidic conditions and then trapped by highly active, electron-rich alkenes.[4] However, such set of conditions for their formation can easily lead to polymerization.[1a] Hence, utilizing of relatively stable and separable *o*-QMs will be an ideal approach to control their reactivity in asymmetric cycloaddition reactions toward *O*-heterocycle synthesis.

In this regard, Feng and coworkers in 2015 reported a highly efficient inverse-electron-demand hetero-Diels–Alder reaction of relatively stable pre-synthesized *o*-QMs **1** and azlactones **2** using a chiral N,N'-dioxide–Sc(III) complex as the catalyst (Scheme 1).[5] Interestingly, in contrast to $Sc(OTf)_3$, other Lewis acids such as $Ni(OTf)_2$ and $Yb(OTf)_3$ showed relatively lower catalytic activity. In addition, it was found that the steric hindrance at the amide moiety of the *N,N'*-dioxide ligand played an important role on the enantioselectivity of the reaction. *N,N'*-dioxide ligand **3** with an additional tertiary butyl substitution on the *para*-position of the phenyl ring can significantly improve the enantioselectivity though with low yield. Further screening of the basic additives and adjusting the metal/ligand ratio, the chiral 3,4-dihydrocoumarin **4** can be obtained in 90% yield with 91% ee. The reaction accommodated a variety of azlactones bearing either electron-withdrawing or electron-donating substituents on the phenyl ring (R^1), providing the corresponding 3,4-dihydrocoumarin **4** in generally good yields with excellent enantioselectivities (up to 94% yield, 96% ee). Mechanistic studies involving Operando IR and control experiments indicated that the reaction proceeded via a concerted [4+2]-cycloaddition pathway. However, the scope of isolated *o*-QMs **1** was quite limited, which restricted potential synthetic applications of this methodology to some extent.



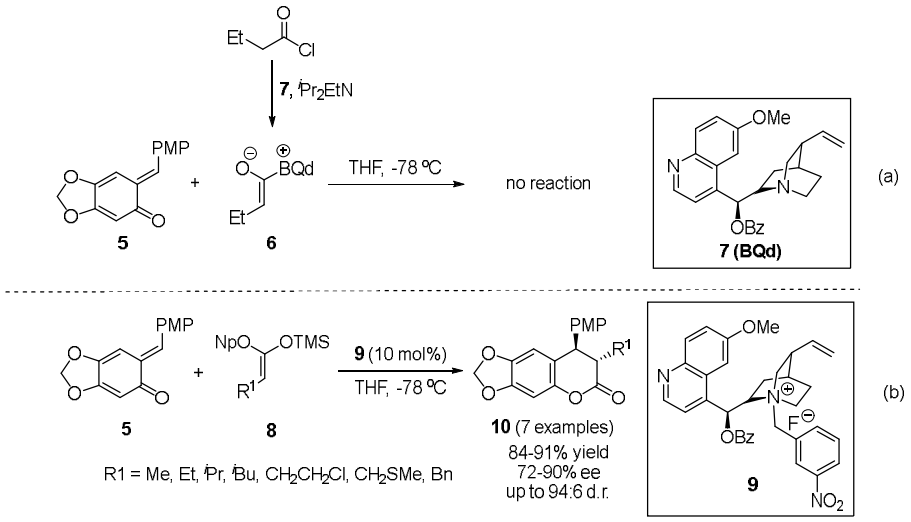
Scheme 1. Sc(III)-complex catalyzed inverse-electron-demand hetero-Diels–Alder reaction.

2.2. Phase-transfer catalytic cycloaddition reactions

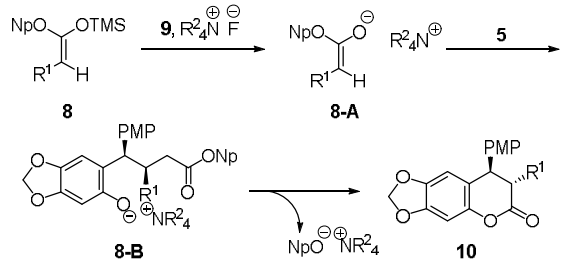
The electron-rich *o*-QMs are ideal candidates for development of new cyclaodditions due to their facile preparation and easy-to-use. As a result, early examples by organocatalysis also mainly focused on the pre-synthesized *o*-QMs. In 2008, the Lectka group disclosed the first example of catalytic asymmetric [4+2] cycloaddition between *o*-QM **5** and silyl ketene acetals **8** by a chiral cinchona alkaloid-derived ammonium fluoride precatalyst complex **9** (Scheme 2b).[6] Notably, when a mixture of *o*-QMs **5** and butyryl chloride **7** derived enolate salt **6** was treated with $^{i}Pr_2EtN$ and chiral catalyst *O*-benzoylquinidine **7**, no reaction occurred (Scheme 2a). The authors rationalized that it may be due to the incompatibility of the high electron density of the *o*-QM with the mild nucleophility of the zwitterionic ketene enolate **6**.

Hence, they turned their attention to the silyl ketene acetal **8**. A wide variety of alkyl-derived silyl ketene acetal were well tolerated to furnish the corresponding 3,4-dihydrocoumarin products **10** in generally excellent yield and with good enantioselectivity (up to 91% yield and 90% ee). Interestingly, it was found that it was the precatalyst's electronic effects rather than steric encumbrance that had great influence on the enantioselectivity of the reaction. In addition, the free hydroxyl group of the cinchona alkaloid moiety was also very important for high enatioselectivity.

The possible mechanism is as shown in Scheme 3, the reactive chiral ion-paired ketene enolate **8-A** is generated after desilylation of the ketene acetal **8** by fluoride ion. Then, the attack of **8-A** to *o*-QM **5** resulted in formation of intermediated **8-B**. An intramolecular lactonization of **8-B** provided the final product **10**.



Scheme 2. Chiral ammonium fluoride-promoted [4+2] cycloaddition reaction of *o*-QMs.

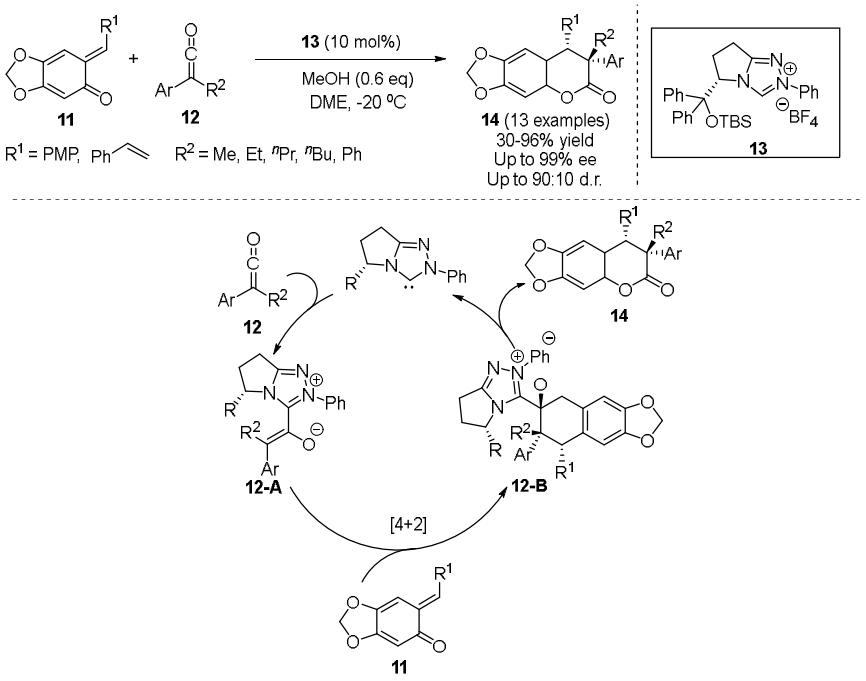


Scheme 3. The possible mechanism for chiral ammonium fluoride-promoted [4+2] cycloaddition reaction.

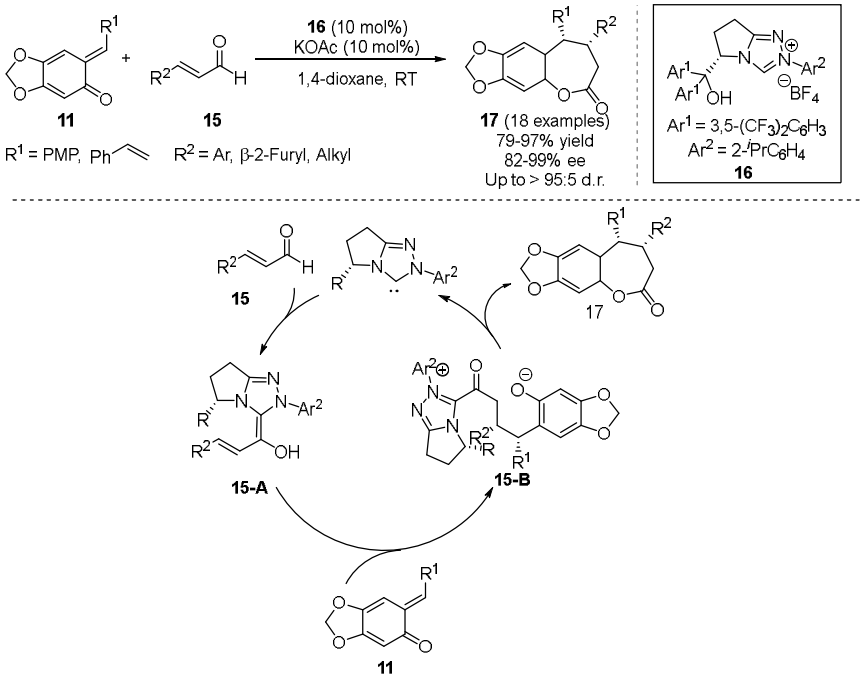
2.3. *N*-Heterocyclic carbene-catalyzed cycloaddition reactions

In the past years, the *N*-heterocyclic carbene (NHC) catalyzed annulation reactions provide powerful methods for various heterocycles.[7] In this context, Ye and coworkers in 2009 developed a NHC **13** catalyzed formal [4+2] cycloaddition of *o*-quinone methides **11** and ketenes **12** (Scheme 4).[8] Generally, the reaction proceeded smoothly to furnish the chiral 3,4-dihydrocoumarins **14** with vicinal tertiary and all-carbon quaternary stereocenters with good yield and excellent enatioselectivity (up to 96% yield, 99% ee and up to 90:10 d.r.). It is worth noting that methanol additive is very significant for the reproducible enantioselectivity. As outlined in Scheme 4, the reaction started with addition of NHC to ketenes **12** to provide the enolate **12-A**. Subsequent inverse electron demand [4+2] cycloaddition of *o*-QMs **11** and enolate **12-A** gave adducts **12-B**, which released the final product by fragmentation with regeneration of NHC.

In 2013, the same group developed an interesting *N*-heterocyclic carbene **16** catalyzed [4+3] annulation of *o*-QMs **11** and cinnamaldehydes **15** (Scheme 5).[9] Remarkably, it was found that a free hydroxy group of NHC catalyst **16** is very crucial for the high reactivity due to the hydrogen bonding interaction between the hydroxy group and *o*-QMs. In addition, addition of Lewis acids such as $Mg(OTf)_2$, $LiClO_4$, and $Cu(OTf)_2$ had no positive effect on the diastereoselectiveties. Under the optimized reaction conditions, an array of benzo-ε-lactones can be obtained in generally good yields with excellent enantioselectivities and diastereoselectiveties (up to 97% yield, 99% ee and >95:5 d.r.). Mechanistically, an initial addition of NHC to cinnamaldehydes **15** generated the Breslow intermediate **15-A**, which can then attack the *o*-QMs **11** to give the Michael adduct **15-B**. Finally, the intramolecular lactonization of **15-B** provided the [4+3] annulation product **17** and regenerated the NHC catalyst **16** (Scheme 5).

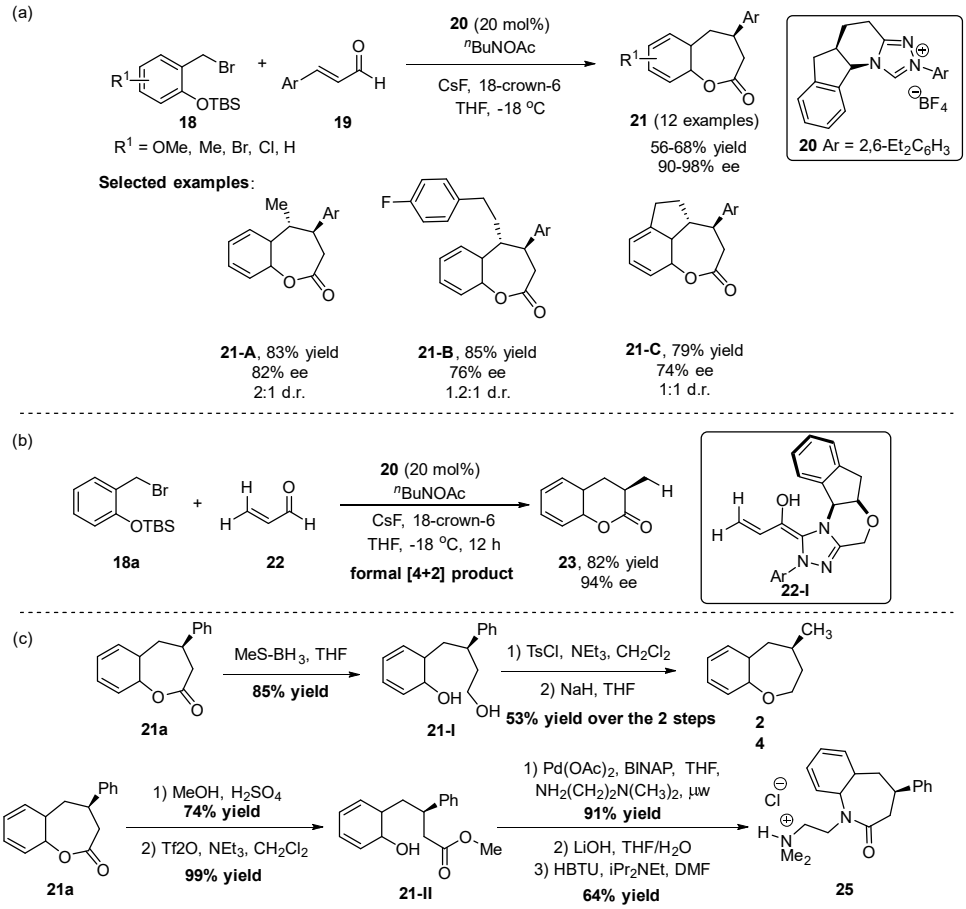


Scheme 4. NHC-Catalyzed formal [4+2] cycloaddition of *o*-QMs and ketenes.



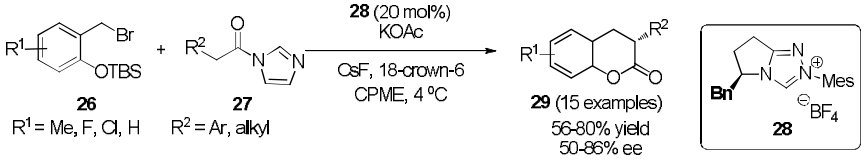
Scheme 5. NHC-Catalyzed [4+3] cycloaddition of *o*-QMs and cinnamaldehydes.

Almost at the same time, the Scheidt group reported a similar catalytic asymmetric formal [4+3] cycloaddition of *in situ*-generated *o*-QMs and cinnamaldehydes by merging *N*-heterocyclic carbene (NHC) catalysis and a second Lewis base, which greatly expanded the substrate scope (Scheme 6).[10] In this reaction, The highly reactive *o*-QMs were formed *in situ* from *tert*-butyldimethylsilyl (TBS)-protected phenol derivatives **18** by using a crown ether/fluoride combination. Interestingly, it was found that the choice of the silyl protected group was very important for the high enantioselectivity because of a controlled generation of the *o*-QMs. In addition, leaving groups such as bromide or chloride had no notable influence on the reaction outcome. The optimal conditions involving CsF/18-crown-6 as fluoride source and tetra-*n*-butylammonium acetate as a mild Brønsted base have demonstrated broad substrate scope and high functional group tolerance. Especially, the incorporation of an additional substituent at the benzylic position was also feasible for this reaction as demonstrated in the synthesis of **21A-C**, which greatly extended the substrate scope though with moderate diastereoselectivity (Scheme 6a). In sharp contrast, the highly reactive aldehyde **22** provided [4+2] product **23** with good yield and enantioselectivity under the standard conditions. The different reactivity was attributed to the fast protonation of NHC−homoenolate intermediate **22-I** that proceeded through a sequential Michael addition/*O*-acylation process to form the six-membered product (Scheme 6b). This protocol can be conveniently applied to the synthesis of biologically relevant benzoxepanes **24** and benzazepinones **25** through several routine steps with good overall yields (Scheme 6c).



Scheme 6. [4+3] Cycloaddition of *o*-QMs and cinnamaldehydes promoted by a dual Lewis base activation.

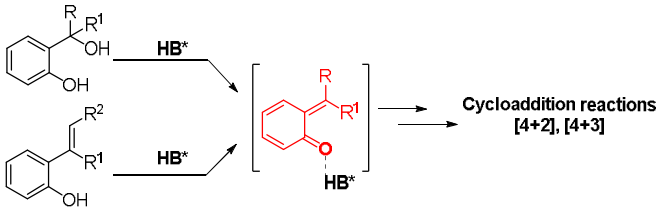
In 2005, Scheidt and coworkers successfully extended the dual activation strategy to the formal [4+2] cycloaddition of *o*-QMs with acyl imidazoles **27** (Scheme 7).[11] Notably, the reaction should be performed at 4 °C due to the decomposition of acyl imidazole at 23 °C. And the choice of base is also very crucial to suppressing racemization of products. Finally, chiral dihydrocoumarins **29** can be obtained with good yield and enatioselectivity using 1.0 equivalent of potassium acetate as the base. Under the optimal conditions, a wide range of differently substituted benzyl bromide derivatives **26** and acyl imidazoles **27** could participate in the reaction well to give the desired products **29** with good yield and enatioselectivity. The transformation can provide a rapid access to valuable chiral α-substituted dihydrocoumarins.



Scheme 7. [4+2] Cycloaddition of *o*-QMs and acyl imidazole promoted by a dual Lewis base activation.

2.4. Brønsted acid-catalyzed cycloaddition reactions

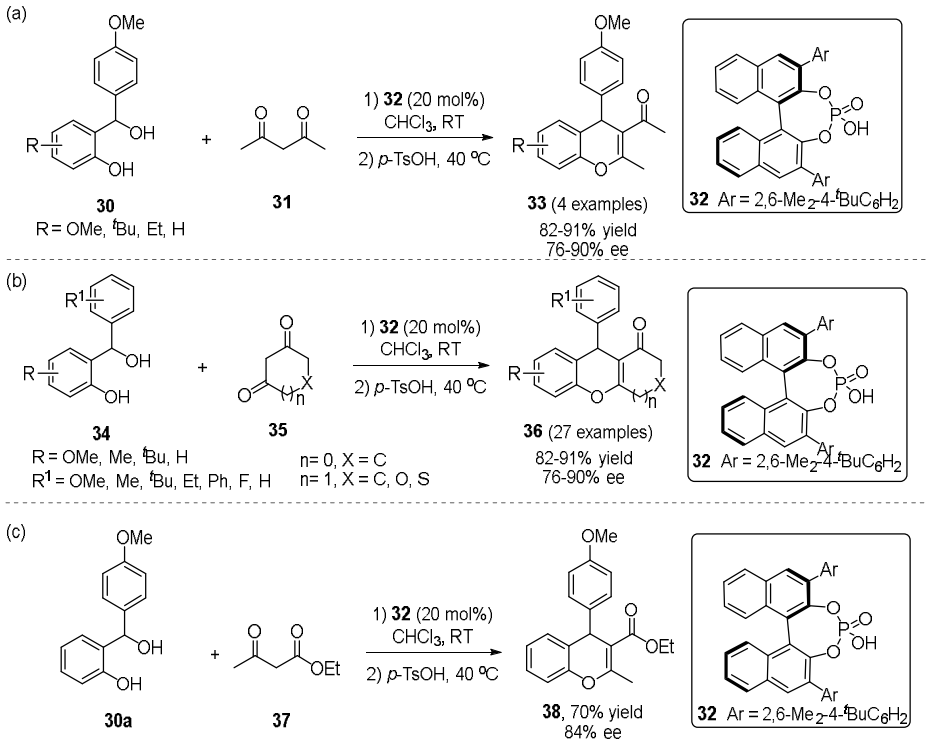
From a practical point of view, it is advantageous to develop generally applicable methods for *in situ* generation of *o*-QMs since the scope of stable and isolable *o*-QM is very limited. Therefore, many chemists focused their attention on *in situ*-formation of *o*-QMs from finely designed precursors by employing Lewis acidic, basic, thermal or photochemical conditions. Among them, acid catalyzed dehydration of *o*-hydroxybenzyl alcohols and the protonation of *o*-hydroxystyrenes are predominant strategies for the generation of *o*-QMs. Importantly, the use of chiral Brønsted acids can not only promote the formation of *o*-QMs, but also enable asymmetric induction (Scheme 8). In this context, the strategy of chiral phosphoric acid catalysis has enjoyed considerable impressive advances.



Scheme 8. Generation of *o*-QMs by chiral Brønsted acids.

In 2013, Schneider and coworkers reported an elegant Brønsted acid catalyzed one-pot subsequential conjugate addition of β-dicarbonyls of type **31** to *o*-QMs generated *in situ* from **30** and cyclodehydration, furnishing chiral 4*H*-chromenes **33** with excellent yields and high enantioselectivities (Scheme 9).[12] Under the optimal conditions, a variety of acyclic and cyclic 1,3-dicarbonyl compounds and *ortho*-hydroxybenzylic alcohols were well tolerated to give the corresponding products **36** with high efficiency and good enantioselectivity (Scheme 9a). In addition, the substrate scope can also be readily extended to oxa- and thiaxanthenones (Scheme 9b). Ethyl acetoacetate **37** reacted well with **30a** to provide 4-*para*-methoxyphenyl-4H-chromene **38** in 70% yield and with 84% ee (Scheme 9c). Notably, the addition of *para*-toluenesulfonic acid was not necessary for some substrates, wherein the initially formed adduct can cyclize directly to generate the final formal [4+2] cycloaddition product. In these cases, the chiral phosphoric acid can not only promote the dehydration of *ortho*-hydroxy benzyl alcohols toward *o*-QM formation, but also interact with the enol tautomers of the β-dicarbonyl compounds through hydrogen bonding to induce good stereoselectivity in their reaction with *o*-QMs.

At the same time, the Rueping group inpendently reported a similar asymmetric addition/cyclization cascade of 1,3-dicarbonyl compounds to *o*-QM (Scheme 10).[13]

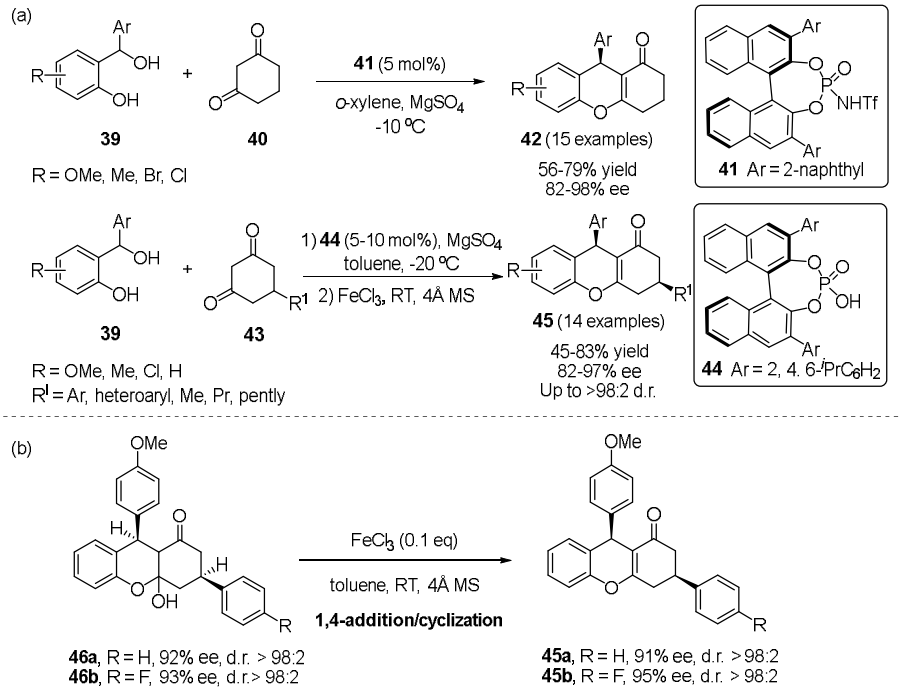


Scheme 9. Asymmetric addition of 1,3-dicarbonyl compounds to *in situ*-formed *o*-QMs.

The optimal conditions involving *o*-xylene as solvent, $MgSO_4$ as an additive and chiral *N*-triflylphosphoramide **41** as a chiral organocatalyst show broad substrate scope and good functional group tolerance. The reaction provides a practical and efficient access 9-substituted tetrahydroxanthenes **42** with generally good yields and excellent enantioselectivities (Scheme 10a). Notably, when chiral *N*-triflylphosphoramides was used to catalyze the reaction, any external acid is not necessary presumably due to its strong acidity. Moreover, the scope of 1,3-diketones can be further extended to *meso*-5-monosubstituted-1,2-cyclohexanediones for synthesis of valuable tetrahydroxanthenes derivatives bearing stereocenters at the 3- and 9-positions. The reaction was well suit to kinds of 5-alky or 5-aryl substituted 1,3-cyclohexanediones, which gave the desired products **45** in moderate to high yields with excellent enantioselectivities and diastereoselectivity. Importantly, the isolated hemiacetal intermediates **46** could afford tetrahydroxanthene products **45a** and **45b** catalyzed by $FeCl_3$ (Scheme 10c), which suggested that the reaction proceed through 1,4-addition/cyclization pathway.

Besides 1,3-diketone, enamides bearing an electron-withdrawing group on the nitrogen atom are also highly reactive nucleophiles that can also be applied to various carbon–carbon bond-forming reactions. In 2015, Schneider and coworkers reported the first highly enantioselective conjugate addition of enamides and enecarbamates of type of **47** to the *in situ*-generated *ortho*-quinone methides from **39** under the condition of chiral Brønsted acid catalysis (Scheme 11).[14] Under the optimal condition, a variety of ortho-hydroxy benzyl alcohols **39** and enamides were well tolerated, furnishing the corresponding products **49** with generally good yields and excellent stereoselectivities (Scheme 11a). Interestingly, the cyclic enamide-containing products can be subjected to acid treatment to generate 4*H*-chromenes **50a–50f** with retained enantiopurity (Scheme 11b). The same group also extended this methodology to various 1-(*o*-hydroxyphenyl)propargylic alcohols, which furnished the useful 7-alkynyl-12a-acetamido-substituted benzo[c]xanthenes and related heterocycles with excellent diastereo- and enantioselectivity.[15] In order to demonstrate the synthetic potential of this

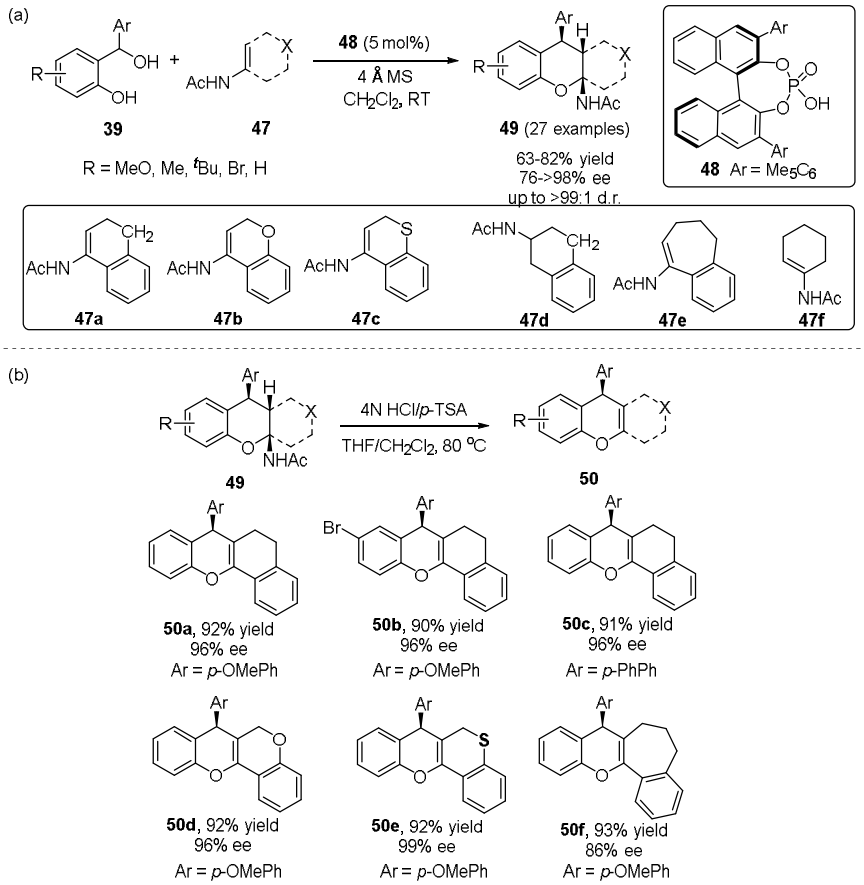
process, several products were converted to the corresponding saturated analogues under the condition of 10% Pd/C. This work greatly extended the scope of this methodology.



Scheme 10. Asymmetric addition of 1,3-dicarbonyl compounds to *o*-QMs.

Shortly afterwards, Shi and coworkers reported a highly enantioselective inverse-electron-demand oxa-Diels–Alder reaction of the *in situ*-generated *ortho*-quinone methides and 2-vinylindoles of type **52** (Scheme 12).[16] Unlike Schneider's work, the authors chose olefins of relatively low reactivity that had not been previously used in asymmetric reactions of *o*-QMs. In Shi's reaction, introduction of a methyl group at the C3-position of 2-vinylindoles can avoid the simple addition of indoles to the *o*-QM intermediate. Under the optimal conditions, a range of substituted *ortho*-hydroxybenzyl alcohols **51** with an alkyl substituent at the benzylic position participated in the reaction smoothly to give the desired products **54** bearing multiple stereogenic centers in good yields and excellent stereoselectivities. In addition, a range of 3-methyl-2-vinylindoles **52** bearing various terminal aromatic or aliphatic substituents are all suitable for this reaction (Scheme 12a). Interestingly, when using the *N*-methyl-protected 3-methyl-2-vinylindole **52**, no reaction occurred and this result demonstrated that the N-H group of 2-vinylindoles is of significant importance for the reaction efficiency (Scheme 12b). Hence, the high stereoselectivity can be attributed to a dual hydrogen-bonding activation mode. Notably, the use of a *E/Z* mixture of vinylindoles had no influence on the stereoselectivity of the reaction. This methodology provides a rapid access to enantioenriched chroman frameworks with three adjacent stereogenic centers.

Almost at the same time, Rueping and coworkers reported another example of oxa-Diels–Alder reaction of *o*-QMs with unactivated alkenes of type **56** to give chiral chromanes **58** bearing multiple stereogenic centers with general good yields and high steroselectivities (Scheme 13).[17] They exploited the styrenes as dienophiles, so more acidic chiral BINOL-based *N*-triflylphosphoramide (NTPA) **57** is necessary. Moreover, it was postulated that the high enantioselectivity was attributed to the H-bond interaction between *o*-QMs and NTPAs and stabilizing effect of the methylene group by the lone pair of the phosphoryl oxygen atom. In contrast, there was no obvious interaction between styrene partners and catalyst.

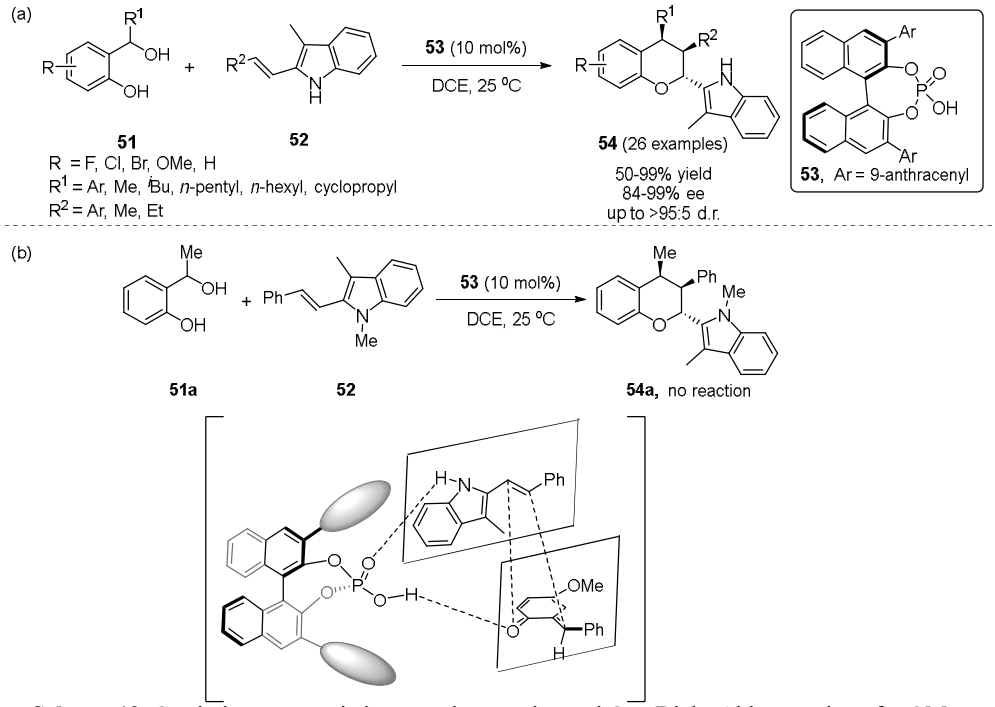


Scheme 11. Asymmetric sequential conjugate addition/cyclization of enamides and enecarbamates with *o*-QMs.

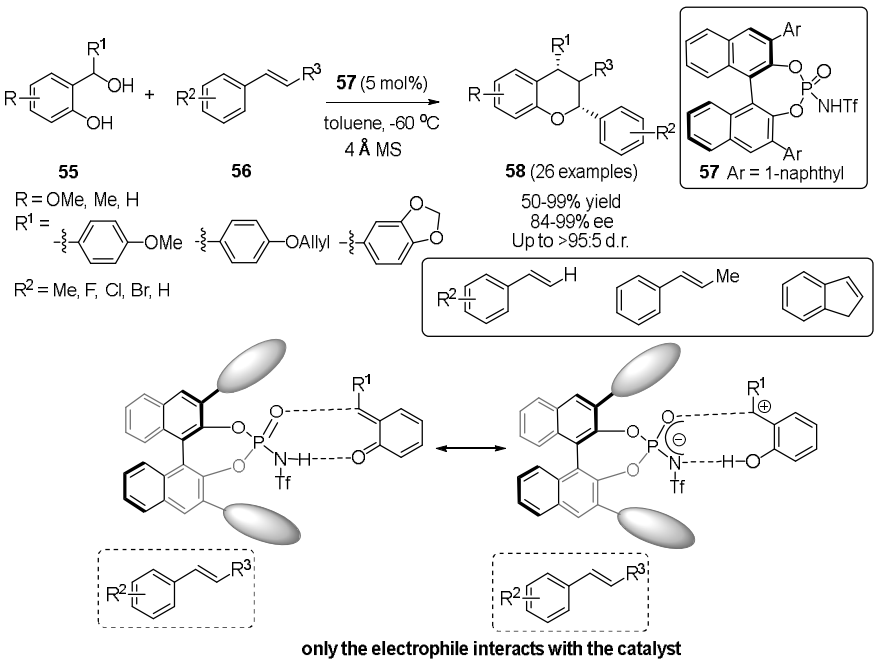
In 2016, Shi and coworkers reported a similar chiral phosphoric acid-catalyzed asymmetric [4＋2] cycloaddition of *o*-hydroxyl styrenes with *in situ* generated *o*-QMs.[18] In this reaction, the incorporating of a hydroxyl group at the ortho position of styrenes eliminated strong acid catalyst. This methodology showed quite broad substrate scope with respect to both components. A wide range of *o*-hydroxyl styrenes and *o*-hydroxybenzyl alcohols were well tolerated under the standard reaction conditions, furnishing the corresponding chroman derivatives with generally good yields and excellent stereoselectivities.

Recently, the group of Sun selected commercially available vinyl sulfides that can be easily converted or removed as key 2π partners to accomplish a highly enantioselective catalytic [4+2] cycloaddition of *ortho*-quinone methides.[19] The reaction also showed broad substrate scope and furnished corresponding chiral chromanes with good to excellent efficiency and enantioselectivity. This efficient protocol resulted in indirect entrance to generally substituted chromanes framework lacking easy access before.

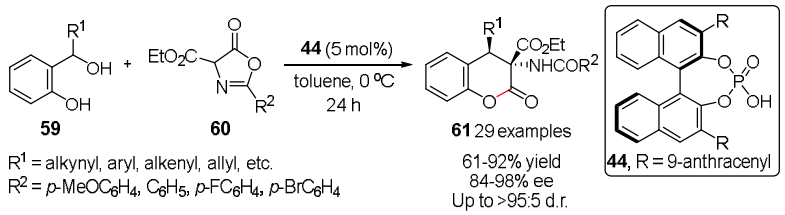
In 2016, our group developed a convergent and highly stereoselective [4+2] cycloaddition reaction between *ortho*-hydroxybenzyl alcohols **59** derived *o*-QMs and azlactones **60** by a triple Brønsted acid catalysis strategy (Scheme 14).[20] The optimal conditions involving (*R*)-BINOL-derived chiralphosphoric acid **44** as a catalyst and toluene as the solvent at 0 °C have demonstrated broad substrate scope with both reaction components. The corresponding highly functionalized 3,4-dihydrocoumarins **61** can be obtained in good yields with excellent stereoselectivities.



Scheme 12. Catalytic asymmetric inverse-electron-demand Oxa-Diels–Alder reaction of *o*-QMs with 2-vinylindoles.



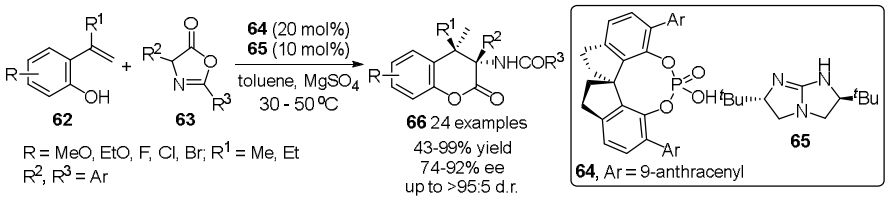
Scheme 13. Oxa-Diels–Alder reaction of *o*-QMs with styrenes.



Scheme 14. Triple Brønsted acid activation-promoted asymmetric cycloaddition reaction of *in situ*-formed *o*-QMs with azlactones.

Interestingly, this strategy can be extended to *ortho*-hydroxybenzyl alcohols with alkenyl, allyl or aliphatic groups at the benzylic position. In this reaction, it was hypothesized that the chiral phosphoric acid not only promoted the *in situ* generation of both reactive *o*-QMs and azlactone enols, but also subsequently controlled the stereochemistry of the cycloaddition step through a bifunctional catalysis mode. The operational simplicity and high functional group tolerance of this protocol make this reaction an attractive approach to diversely functionalized 3,4-dihydrocoumarins bearing adjacent tertiary and quaternary stereogenic centers.

Notably, *o*-hydroxylstyrenes can also be employed as *ortho*-quinone methide precursors to react with azlactones. For instance, the Shi group reported an enantioselective [4+2] cycloaddition of *o*-hydroxylstyrenes **62** with azlactones **63** synergistically catalyzed by chiral phosphoric acid **64** and chiral guanidine base **65** in the presence of $MgSO_4$ in toluene at 30 °C. The protocol enables construction of a wide range of dihydrocoumarin scaffolds **66** moderate to good yields with high enantioselectivities (Scheme 15).[21] However, those azlactones with aliphatic R^2/R^3 groups failed to participate in the expected [4+2] cycloaddition reaction; and the *o*-hydroxylstyrenes with R^1 as a hydrogen atom proved to be ineffective for the reaction. Further derivation of these dihydrocoumarin products by routine aminolysis could provide a convenient access to the biologically interesting chiral dipeptide.[22]

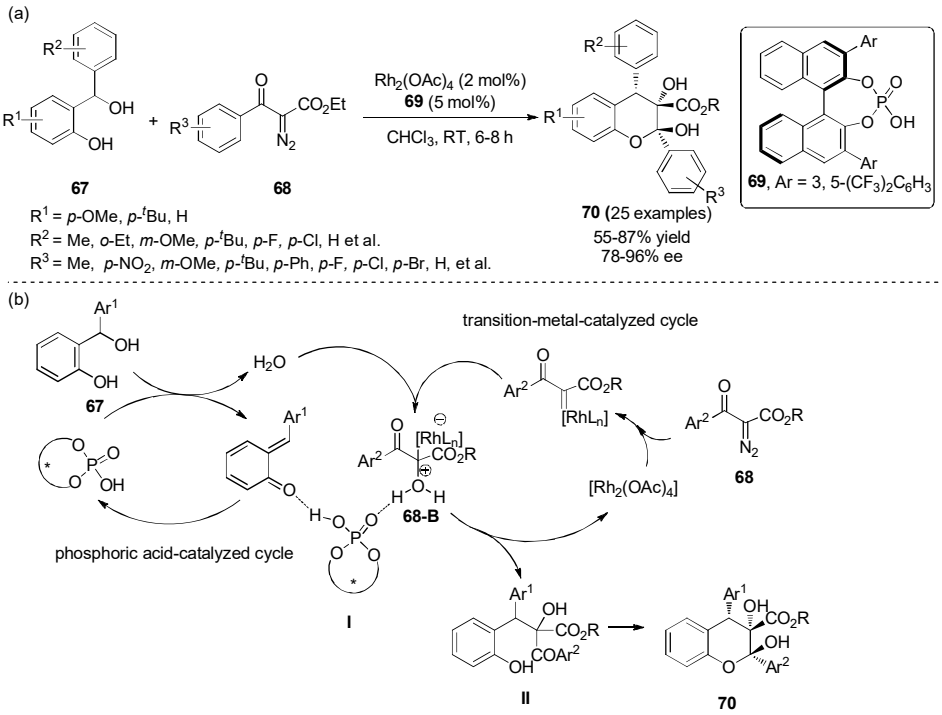


Scheme 15. Catalytic asymmetric cycloaddition reaction of *o*-hydroxylstyrenes with azlactones.

Synergistic catalysis has emerged as a powerful catalytic strategy to engineer otherwise inaccessible chemical transformations. In this context, a combination of a transition metal and an organocatalyst has provided a potentially powerful platform to discover new reactivity patterns of *o*-QMs.

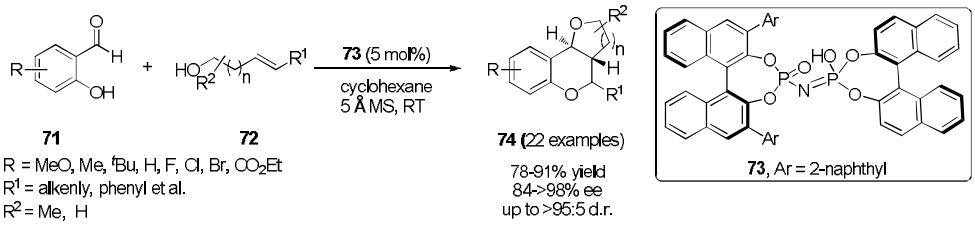
For instance, in 2016, Schneider and coworkers disclosed a pioneering synergistic rhodium/Brønsted acid catalyzed domino-type reaction of oxonium ylides to *o*-QMs, both of which were formed *in situ* from *ortho*-hydroxybenzyl alcohols **67** and α-diazo-β-ketoesters **68** (Scheme 16a).[23] The optimal conditions consisting of phosphoric acid catalyst **69** and $[Rh_2(OAc)_4]$ in toluene at room temperature exhibited wide substrate scope, resulting in formation of densely functionalized chromans **70** with three contiguous stereogenic centers in one step with good yields and excellent steroselectivities. Remarkably, a solution of diazoester **68** should be added to the reaction system via a syringe pump over a period of 1 h. It was also found that various electron-withdrawing and electron-donating groups at the *meta*- or *para*-position of β-aryl group of α-diazo-β-ketoesters can be tolerated to give the desired products as single diastereomers with good yields and high enantioselectivities. However, *ortho*-substituted β-aryl diazoesters proved to be inefficient for this reaction. As for the mechanism, it was postulated that the water that was generated as a by-product during the acid-catalyzed dehydration of *ortho*-hydroxy benzyl alcohol was of significant importance to the formation of oxonium ylide **68-B**. Subsequently, intermediate **68-B** underwent a sequential conjugate

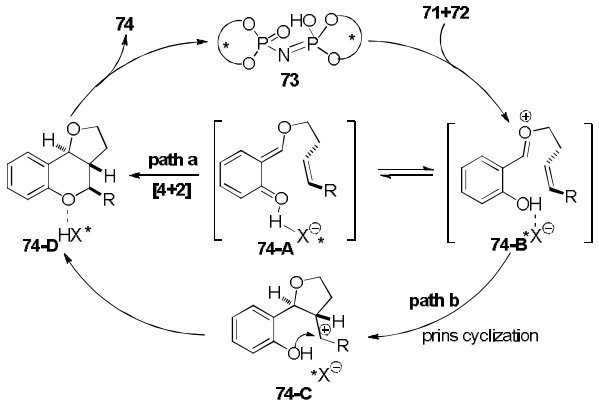
addition to the *o*-QM through a high ordered transition state enabled a bifunctional phosphoric acid and intramolecular cyclization to afford the final product (Scheme 16b). Thus, this strategy of merging a transition-metal and a Brønsted acid catalyst opened a new way to the design of new enantioselective reactions *o*-QMs.



Scheme 16. Synergistically catalyzed sequential conjugate addition/cyclization of oxonium ylides and *o*-QMs.

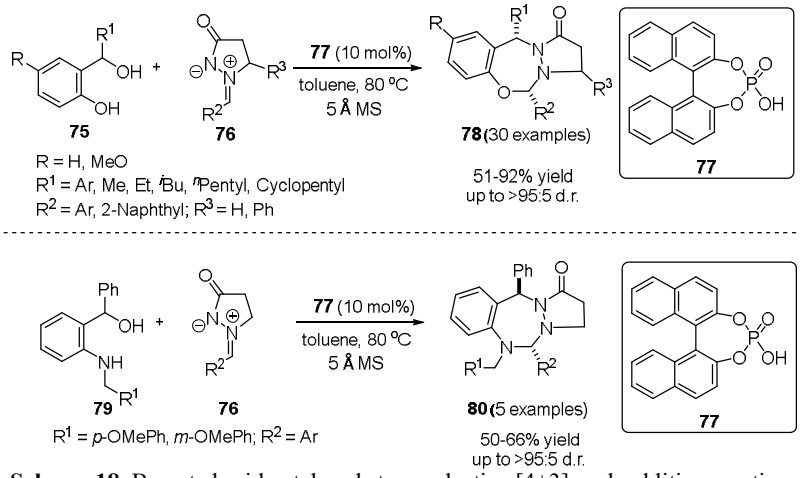
Despite many precedents about the use of *ortho*-quinone methides as key intermediates in catalytic asymmetric intermolecular cycloaddition reactions, but their intramolecular variants are still scarce. As a matter of fact, the development of such a transformation would provide an efficient and direct access to construct polycyclic frameworks. Quite recently, the List group disclosed the first example of intramolecular [4+2] cycloaddition of *in situ* generated *ortho*-quinone methides bearing an *in situ*-tethered alkene moiety in the presence of imidodiphosphoric acid as catalyst (Scheme 17).[24] Under the optimal conditions, a variety of furanochromane and pyranochromane derivatives **74** could be synthesized in good yields with high enantioselectivities. Remarkably, this methodology can be extended to less substituted, longer alkyl chain substituted or aryl substituted dienyl alcohols **72**. Interestingly, in this reaction, diastereoselective and enantioselective synthesis of furanochromanes starting from racemic chiral dienyl alcohols by kinetic resolution also proved to be feasible. A possible mechanism is as follows: an initial acid-catalyzed dehydrative condensation of **71** and **72** generated oxocarbenium ion **74-B**, which could isomerize to *ortho*-quinone methide **74-C**, followed by [4+2] cycloaddition to provide corresponding product **74-A**. An alternative pathway involves an intramolecular Prins cyclization of **74-B** and subsequent trapping of the resultant cationic intermediate **74-C** by the phenol hydroxy group. The author preferred the concerted path a as a favoured pathway, but could not entirely rule out the path b. There is no doubt that this strategy will found broad application in the synthesis of natural products that contain the tricyclic chromane core. Inspired by this work of List, other types of intramolecular cycloadditions of *o*-QMs can be anticipated.





Scheme 17. Intramolecular [4+2] cycloaddition of *in situ* generated *ortho*-quinone methides.

Besides the chiral acid-catalyzed [4+2] cycloaddition reaction, [4+3] cycloaddition of *ortho*-quinone methides have been also been established under the condition of phosphoric acid catalysis. In 2017, Shi and coworkers reported the first example of racemic phosphoric acid **77** catalyzed [4+3] cycloaddition of *in situ* formed *o*-QMs **75** or aza-*o*-QMs **79** with azomethine imines of type **76** to construct biologically relevant benzo-oxadiazepines **78** and benzo-triazepines **80** with generally good yields and excellent diastereoselectivities (Scheme 18).[25]



Scheme 18. Brønsted acid-catalyzed stereoselective [4+3] cycloaddition reactions between ortho-hydroxybenzyl alcohols and azomethine imines.

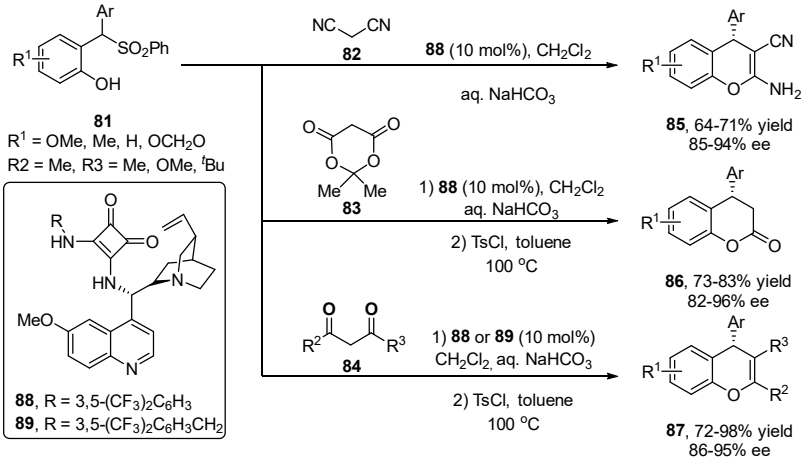
However, the asymmetric variants haven not been achieved so far. Hence, in this context, the catalytic asymmetric synthesis of pyrazoline and pyrazolidine products remains a challenging and attractive task for organic chemists.

2.5. Bifunctional chiral Brønsted base catalysis

Bifunctional Brønsted base catalysis is another important catalytic strategy, which had also exhibited powerful potential in promoting enantioselective cycloaddition reactions of *o*-QMs. It has been well documented that *ortho*-hydroxybenzylsulfones **81** with a leaving group at the benzyl position can easily undergo elimination to form transient *o*-QMs in the presence of base.[26] As a result, in principle, an enantioselective nucleophilic addition to *o*-QMs can be achieved by the dual activating nature of the bifunctional chiral Brønsted base catalysts such as **88** and **89**, which would not only interacts with the *o*-QM by hydrogen bonding, but also enables deprotonating of the nucleophiles through its tertiary amine fragment.

For example, in 2015, the Bernardi group reported a series of highly enantioselective additions of 1,3-dicarbonyl compounds such as Meldrum's acid, malononitrile, 1,3-diketones, and β-ketoesters to the *o*-QMs *in situ* generated from 2-(arylsulfonyl)alkyl phenols **81** using cinchona-derived bifunctional organocatalysts **88** and **89** (Scheme 19).[27] Subsequently, acid treatment resulted in the cyclized products **85-87** with good yields and high enantioselectivities (Scheme 19).[27] It was worth noting that subtle change at the aryl group of the sulfone played an important role on the reaction efficiency. This methodology allows an efficient access to a wide range of valuable 3,4-dihydrocoumarin and 4*H*-chromene scaffolds. The independent similar work from the Han group extended this catalytic method to isolable *o*-QMs by reacting them with malononitriles.[28] The optimal conditions involving quinine-based chiral bifunctional-urea as the catalyst, toluene as solvent at -40 °C furnished the [4+2] cyclization product in generally good yields with excellent enantioselectivities. This strategy has also been successfully applied to the synthesis of potential antitumor agents, 2-amino-3-cyano-4*H*-chromenes. Of significance, this reaction could also be scaled up with no loss of optical purity.

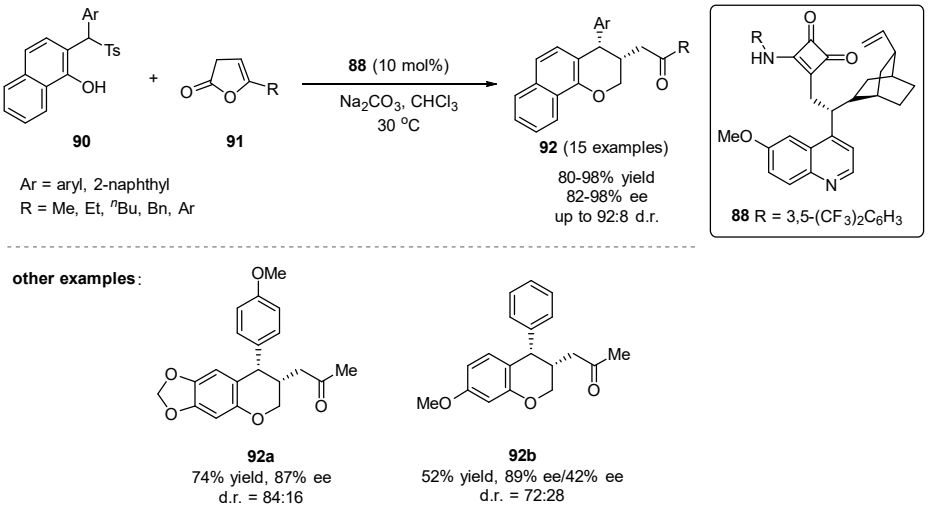
At the same time, Zhou and coworkers developed a novel C−H oxidation/Michael addition/cyclization cascade of 2-alkyl-substituted phenols and cyano-containing methylene compounds for enantioselective synthesis of 2-amino-4*H*-chromenes from readily available 2-alkyl-substituted phenols using bifunctional squaramide **89** as the catalyst.[29] This protocol features *in situ* generation of *o*-QM intermediates by use of stoichiometric MnO_2 as the oxidant.



Scheme 19. Catalytic enantioselective additions of 1,3-dicarbonyl compounds to *in situ*-formed *o*-QMs.

In 2017, Zhou and Lan extended the scope of C2 synthon to deconjugated butenolides, and accomplished an unprecedented asymmetric α-addition/transesterification of deconjugated butenolides **91** with *in situ* generated *o*-QMs (Scheme 20).[30] Under the standard conditions, a wide range of 2-(1-

tosylalkyl)-naphthols **90** could react well with deconjugated butenolides to give the corresponding formal [4+2] annulations products, highly functionalized 3,4-dihydrocoumarins **92** containing two contiguous stereogenic centers in good yields with good diastereoselectivity and excellent enantioselectivity. It was found that when 2-(phenyl(tosyl)methyl)phenol was used as the substrate, no desired product was obtained. So, electron-donating group on the phenolic ring was crucial to the success of the desired reaction. DFT calculations showed that both of the regioselectivity and enantioselectivity greatly depended on distortion energy that resulted from the interaction between dienolate and *ortho*-quinone methide. Shortly thereafter, this group also successfully realized a bifunctional squaramide-catalyzed Michael addition/cyclization between 2-(1-tosylalkyl)-phenols-derived *o*-QMs and azlactones, providing an efficient and highly enantioselective access to various chiral dihydrocoumarins containing adjacent tertiary and quaternary stereogenic centers.[31] The mild reaction conditions and wide substrate scope makes this protocol particularly useful.

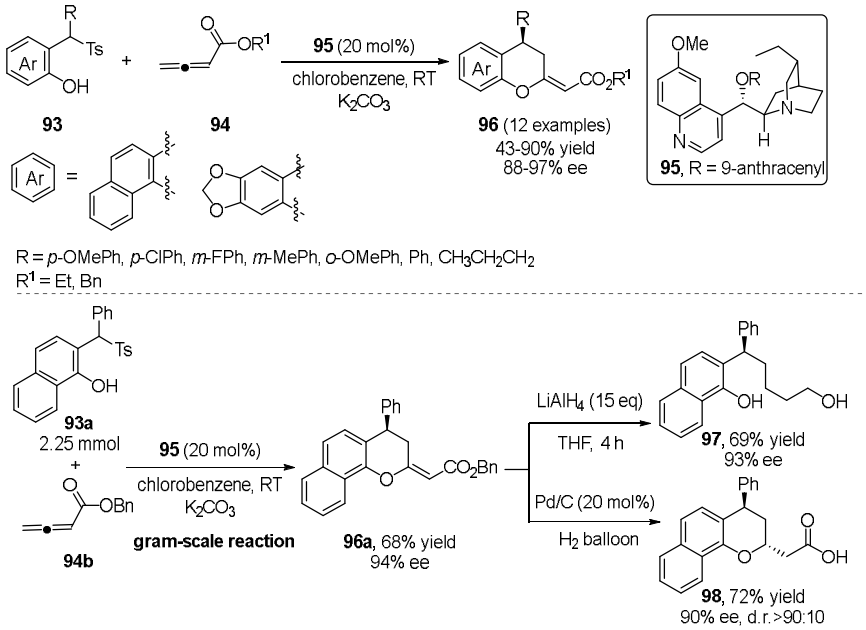


Scheme 20. Regio- and enantioselective α–addition/transesterification reaction of deconjugated butenolides with *o*-QMs.

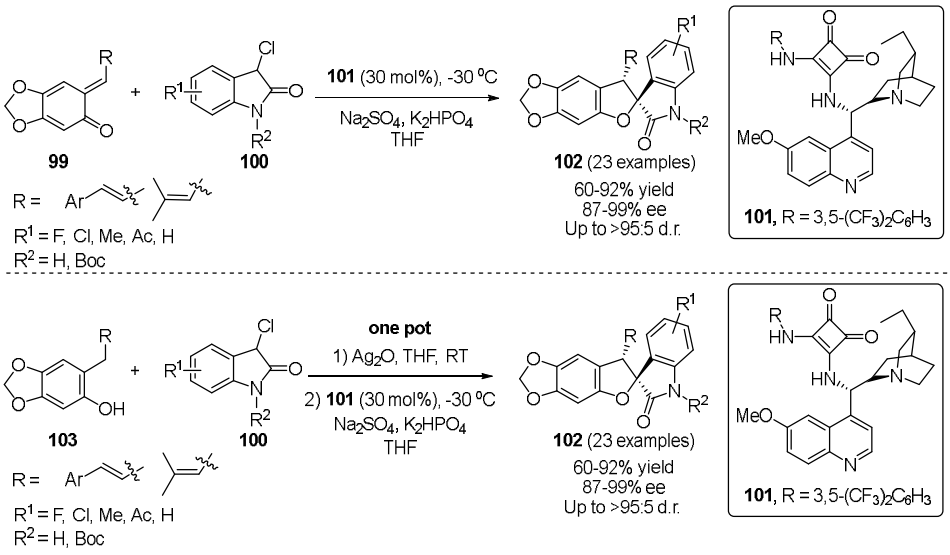
During the course of the study on dynamic kinetic resolution (DKR) of *ortho*-quinone methides, Li, Liu and co-workers in 2017 revealed that the reaction preferentially underwent [4+2] cycloaddition in the case of substrates that could generate more stable *o*-QMs (Scheme 21).[32] On the basis of this observation, they screened a series of conditions and finally identified cinchona alkaloid derivative **95** as the suitable Lewis base catalyst in the presence of K_2CO_3. The reaction accommodated a broad range of functional groups on the phenyl ring (R) of 2-(tosylmethyl)naphthols **93**, generating the corresponding biologically interesting 4-substituted chromans **96** in generally good yields with high enantioselectivities. In addition, gram-scale reaction and straightforward transformation of the functional group in **96a** demonstrated the practical synthetic utility of this methodology.

Except for the [4+2] cycloaddition reactions of *o*-QMs, organocatalytic enantioselective [4+1] cyclization of *o*-QMs **99** with 3-chlorooxindoles **100** has recently been developed by the Shi group with chiral squaramide-tertiary amine as the catalyst (Scheme 22).[33,34] Under the optimal reaction conditions, the protocol showed broad substrate scope and high functional group tolerance, producing the expected spirooxindole-based 2,3-dihydrobenzofuran scaffolds **102** in generally good yields with excellent enantioselectivity. Remarkably, they also developed a more practical two-step one-pot domino reaction starting from readily accessible and stable 2-alkyl phenols **103**. This method provides a step-economic and straightforward approach for construction of enantioenriched spirooxindole-containing 2,3-dihydrobenzofuran derivatives. At the same time, the group of Han also reported an organocatalytic [4+1]

cycloaddition of *o*-QMs and bromomalonates utilizing a chiral quinine and BINOL-derived phase-transfer catalyst, providing a highly enantioselective approach to optically active dihydrobenzofurans.[35]



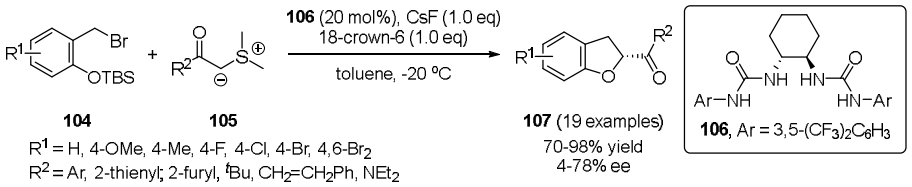
Scheme 21. Catalytic asymmetric [4+2] cycloaddition of 2-sulfonylalkyl phenols with allenic esters.



Scheme 22. Catalytic asymmetric [4+1] cyclization of *o*-QMs with 3-chlorooxindoles.

It has been well established that sulfur ylides are a versatile type of 1,1-dipoles and have found wide application in cycloaddtition reaction.[36] A recent work of Yang also revealed that the use of C2-symmetric chiral urea enabled an enantioselective [4+1] cyclization between *o*-QMs and sulfur ylides **105** under basic

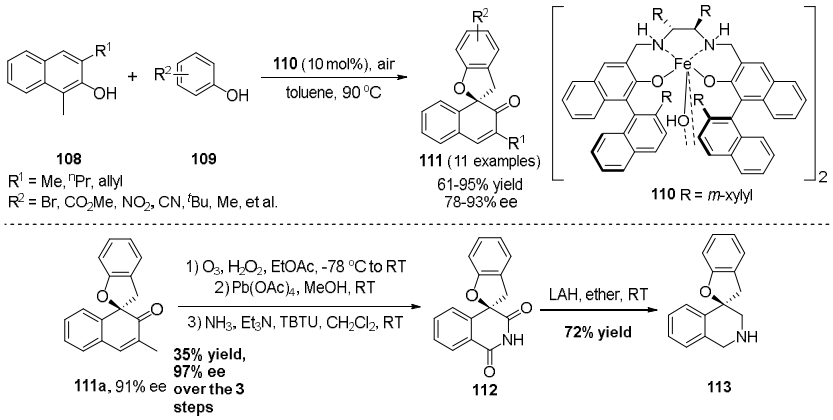
conditions (Scheme 23).[37] Notably, the *o*-QMs were conveniently generated *in situ* from TBS-protected phenols **104** in the presence of stoichiometric CsF and 18-crown-6. This protocol provides a complementary access to chiral 2,3-dihydrobenzofurans **107** though with moderate enantioselectivities.



Scheme 23. Catalytic asymmetric [4+1] cyclization between *in situ*-formed *o*-QMs and sulfur ylides.

3. Miscellaneous

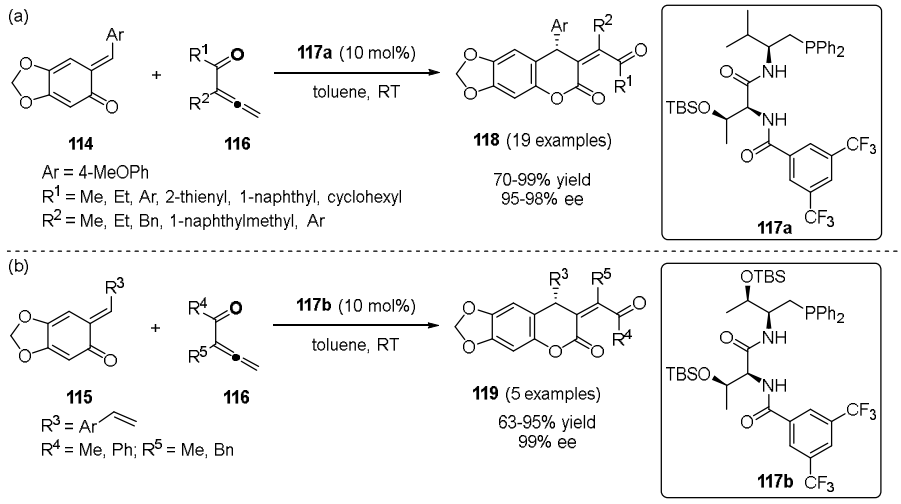
Oxidative dearomatization of *o*-substituted arenols also provides an efficient access to generate *ortho*-quinone methide intermediates. In 2014, the Katsuki group disclosed that the combination of chiral iron–salan complex **110** as catalyst and dioxygen in air as oxidant allowed oxidative *in situ*-generation of *o*-QMs from 1-methyl-2-naphthols **108** and their subsequent Michael addition/asymmetric dearomatization with phenols **109** (Scheme 24).[38] In this reaction, a variety of functional groups such as halo, ester, nitro, acetal and cyano can be well tolerated under the optimal condition to furnish the corresponding valuable spirocyclic-(2*H*)-dihydrobenzofurans **111** in generally good yields with high enantioselectivities except formyl group. However, as for the 1-ethyl-3-methyl-2-naphthol, no product was detected. This methodology was also successfully applied for the synthesis of spiro[benzofuranisoquinoline], which is a family member of spiro(benzofuranazaalkane)s of unique biologically activity.



Scheme 24. Synthesis of spirocyclic (2*H*)-dihydrobenzofuran by Fe-catalyzed tandem aerobic oxidative cycloaddition of *o*-QMs and phenols.

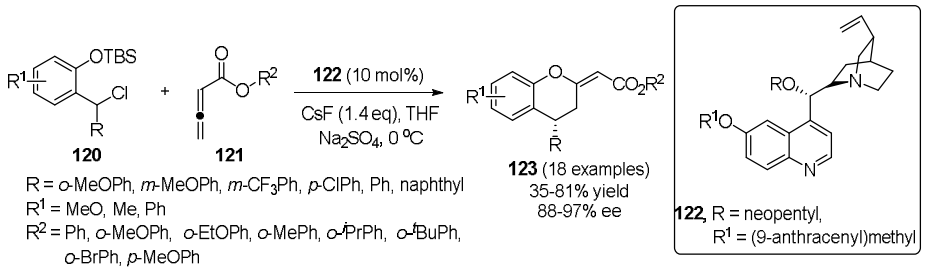
Quite recently, Wang and Lu revealed that their previously developed amino acid-derived bifunctional phosphine catalysts **117a-b** could efficiently catalyze the enantioselective [4+2] annulation between pre-prepared *o*-QMs **114-115** and allene ketones **116** (Scheme 25).[39] Due to the different reactivities of allene esters and allene ketones, the authors finally focused on the [4+2] annulation between isolable *o*-QMs **114** and allene ketones **116**. It was found that the matched configurations of dipeptide phosphines and the hydrogen bond donating group of the second amino acid residue were critical to the stereoselectivity of the reaction. A range of differently substituted allene ketones could participate in the reaction smoothly to give the desired products **118** or **119** with good yields and excellent enantioselectivities. Also, the substrate scope of *o*-QMs can be successfully extended to vinyl-substituted ones **115** by employing dipeptide phosphine

117b as the catalyst. There is no doubt that this methodology provides an efficient and mild approach to access diverse highly functionalized and biologically interesting chiral chromane derivatives.



Scheme 25. Catalytic asymmetric [4+2] annulation of allene ketones with pre-prepared *o*-QMs.

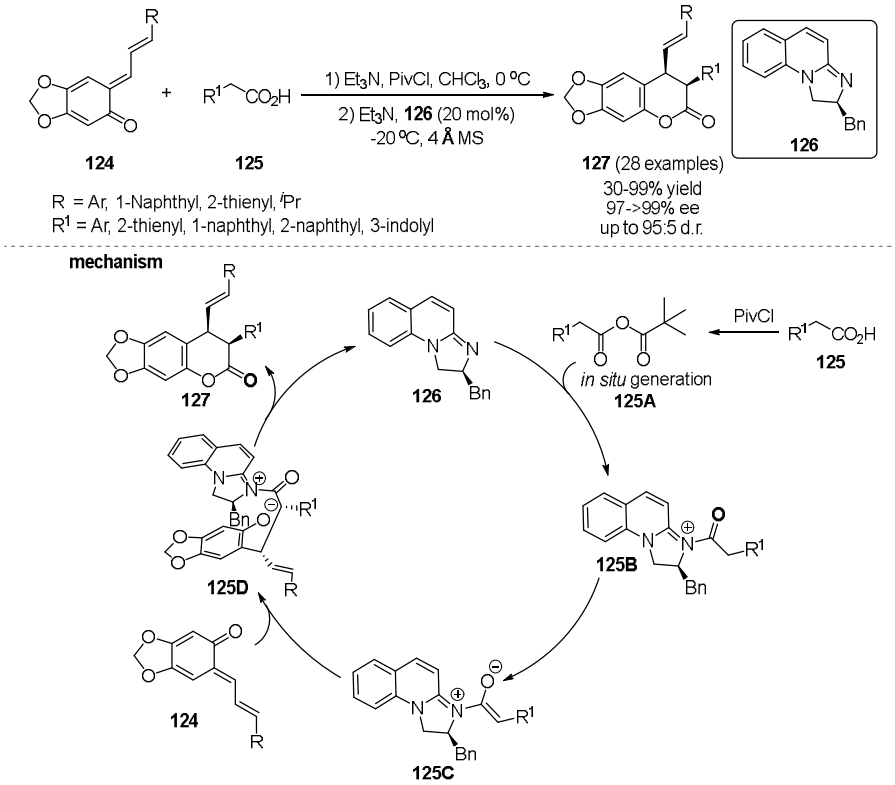
At the same time, the group of Fan independently reported a highly enantioselective [4+2] annulation of allenoates **121** and *o*-QMs *in situ* generated from TBS-protected precursors **120** using *Cinchona* alkaloid-derived amine **122** as the catalyst and CsF as the base (Scheme 26).[40] The catalytic system proved to be suitable for a series of aryl 2,3-butadienoates bearing substituents on the *ortho*-position of benzene ring, affording the biologically and synthetically important chiral chromans derivatives **123** with good to excellent enantioselectivities. However, *meta*- or *para*-substituted 2, 3-butadienoate showed lower reaction activity. As for the *o*-QM precursors, substrates bearing the electron-donating groups typically gave better results compared with those bearing electron-withdrawing groups. Undoubtedly, this methodology provided an efficient and complementary access to the catalytic asymmetric construction of highly functionalized chiral chromans. Moreover, this work also highlighted the potential of fluoride-promoted *in situ*-formation of *o*-QMs in asymmetric synthesis.



Scheme 26. Asymmetric catalytic [4+2] annulation *o*-QMs with allenoates.

Recently, carboxylic acids have been widely utilized as C1-ammonium/azolium enolate precursors in many cycloaddition reactions for carbocycle and heterocycle synthesis using chiral Lewis base as organocatalyst.[41] Employing such type of activation mode, the Deng group reported that carboxylic acids of type **125** could serve as a C2 synthon to undergo tandem Michael addition/lactonization reaction with stable pre-formed *o*-QMs **124** in the presence of chiral amidine derivative **126** as a catalyst (Scheme 27).[42] The two-step one-pot procedure tolerated a significant wide range of aryl and heteroaromatic-containing acetic

acids **125** and *o*-QMs **124**, allowing for rapid synthesis of diversely functionalized *cis*-3,4-dihydrocoumarins **127** in high yields with good stereoselectivities. As for the mechanism, it was postulated that carboxylic acid **125** was initially transformed into a mixed anhydride **125-A** by reaction with pivaloyl chloride, which then react with catalyst **126** to form reactive acyl ammonium intermediate **125-B**. A deprotonation of **125B** produced enolate **125C**. Then, an asymmetric Michael addition/intramolecular lactonization cascade occurred to afford the formal [4+2] cycloaddition product **127**. In analogy to carboxylic acids, carboxylic esters and anhydrides might also undergo similar cycloadditions with *o*-QMs when using chiral Lewis base activation.



Scheme 27. Catalytic asymmetric [4+2] annulation between *o*-QMs and carboxylic acids.

4. Conclusions

In conclusion, during the past few decades, catalytic asymmetric cycloaddition reactions of *o*-QMs have enjoyed many impressive advances toward synthesis of diversely functionalized *O*-heterocycles. In addition to the use of the isolable and preformed *o*-QMs, many efficient methods and precursors have been developed for *in situ* generation of structurally diverse *o*-QMs that are otherwise inaccessible. Exploration of their applications in asymmetric synthesis has rendered such type of intermediates as powerful precursors to various structurally diverse chrial *O*-heterocycles. Representative catalytic activation tactics are based on chiral Lewis acids, phase-transfer catalyst, NHC, Brønsted acids and Brønsted bases. Moreover, appropriate combination of these catalytic modes also enabled development of some novel catalytic systems for enantioselective cycloadditions of *o*-QMs, providing new entry to structurally complex *O*-heteorcycles.

Despite these considerable advances described above, much more endeavors should be further devoted to this field, particularly regarding to the development of more structurally diverse *o*-QM precursors. The discovery of more new catalytic systems and combination of two or more catalytic activation modes will

also provide a powerful platform for synthesis of natural product-like heterocycles or complex molecules. Besides, it is anticipated that the development of catalytic asymmetric reactions should also be of great potential for synthesis of *O*-containing spirocycles. Thus, we hope that this chapter will prompt more research endeavors in this emerging field.

Acknowledgements

We sincerely thank our collaborators and coworkers, whose names appear in the related references, for their contributions to our own work described herein. The authors' works in this area have been sponsored by the National Science Foundation of China (NO. 21472058, 21472057, and 21622201), the Distinguished Youth Foundation of Hubei Province (2016CFA050), and the Program of Introducing Talents of Discipline to Universities of China (111 Program, B17019).

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