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# Recent developments in 1,6-addition reactions of *para*-quinone methides (*p*-QMs)

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In recent years, *para*-quinone methides (*p*-QMs) have emerged as attractive and versatile synthons in organic synthesis owing to their high reactivity. Consequently, *p*-QM chemistry has attracted increasing attention and remarkable advances have been achieved. Among the numerous transformations involving *p*-QMs, catalytic reactions play a pivotal role, and a variety of catalytic systems mediated by Lewis acids, Brønsted acids, bases, transition metals, N-heterocyclic carbenes, and other catalysts have been established for performing 1,6-conjugate addition reactions. Various molecular scaffolds have been constructed using *p*-QMs to obtain the core structures of numerous natural and synthetic substances of chemical and biomedical relevance. In this review, we provide a comprehensive overview of recent progress in this rapidly growing field by summarizing the 1,6-conjugate addition and annulation reactions of *p*-QMs with consideration of their mechanisms and applications.

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## 1. Introduction

*para*-Quinone methides (*p*-QMs; Fig. 1, type A) are ubiquitous structural motifs present in a wide variety of biologically active natural products.[1] *p*-QMs also play numerous roles in biological processes, such as lignin biosynthesis,[2] adrenergic receptors,[3] enzyme inhibition,[4] and DNA alkylation[5] and cross-linking.[6] Owing to their unique structural assembly comprising reactive carbonyl and olefinic moieties, *p*-QMs undergo resonance between neutral and zwitterionic structures (Fig. 1, type B) and display remarkable chemical reactivity as versatile acceptors for 1,6-addition reactions, including Michael addition and radical addition. As Michael acceptors, *p*-QMs have been successfully subjected to 1,6-addition or annulation reactions with carbon-, phosphorus-, and nitrogen-centered

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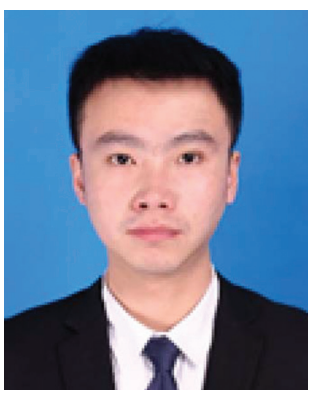

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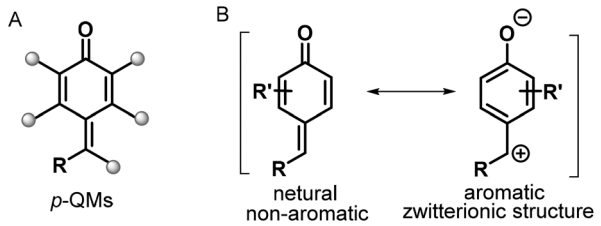


Fig. 1 *p*-QMs and their resonance structures.

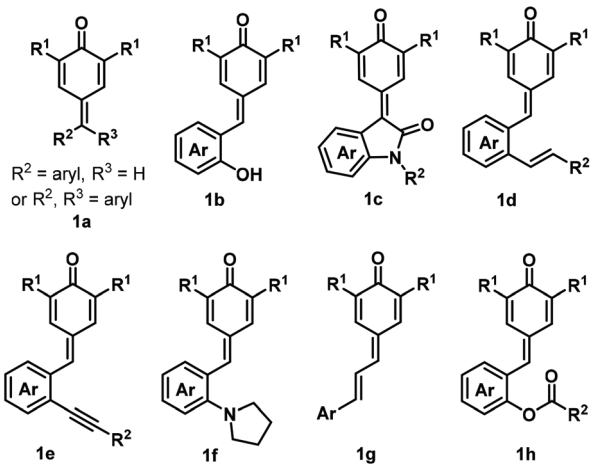


Fig. 2 *p*-QMs and their derivatives.

nucleophiles under various catalytic systems. Interestingly, *p*-QMs have also been exploited as highly reactive radical acceptors for capturing various carbon- and nitrogen-centered radicals *via* radical addition/cyclization or radical cross-coupling. These transformations provide numerous elegant and practical methods for the formation of a variety of carbon–carbon and carbon–heteroatom bonds, permitting the synthesis of important molecules that are difficult to obtain by other approaches. Since two pioneering works describing the synthesis of diarylmethines from *p*-QMs *via* 1,6-conjugate addition were independently reported by Fan[7a] and Jørgensen,[7b] several reaction modes of *p*-QMs have been thoroughly explored,[8] including [2 + 1], [4 + 1], [3 + 2], [4 + 2], [4 + 3], and double annulations involving various *p*-QM substrates containing different functional groups and substitution patterns (Fig. 2, **1a–1h**), resulting in new three-, five-, and six-membered and polycyclic systems. In the past years, Li, Bernardi, Enders, and Tortosa independently highlighted achievements in the asymmetric transformations of *p*-QMs.[9] Undoubtedly, implementing catalytic approaches involving of *p*-QMs is one large research field, which includes both chiral and achiral aspects. Owing to the increasing attention that *p*-QM chemistry has received in recent years, especially with respect to non-asymmetric transformations, there is a strong demand to summarize these recent advances. Therefore, the purpose of this review is to provide our perspective on the strategic design, reaction discovery, and fundamental characteristics of the 1,6-conjugate addition and annulation reactions of *p*-QMs with an emphasis on achiral transformations in consideration with recent asymmetric advances.

## 2. Chemistry of *p*-QMs

### 2.1. 1,6-Addition of nucleophiles to *p*-QMs

**2.1.1. Catalyst-free 1,6-addition.** Environmentally benign and sustainable synthetic approaches to target compounds have attracted increasing attention in recent years, with considerable research effort devoted to the development of reaction conditions for green and sustainable chemistry, such as metal-free catalysis,[10] catalyst-free synthesis, and the utilization of green solvents.[11] In this context, Anand and coworkers reported a straightforward strategy for the 1,6-conjugate addition of dialkylzinc reagents to *p*-QMs **1a** under con-

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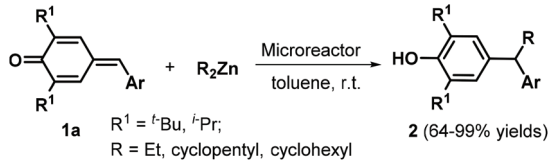
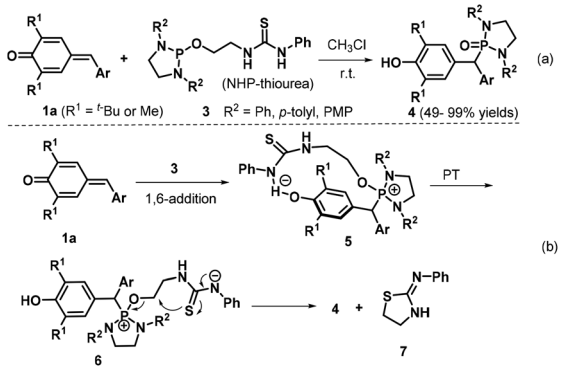
tinuous-flow conditions in a microreactor (Scheme 1).[12] Upon injection of a toluene solution of *p*-QMs **1a** and 2.0 equivalents of dialkylzinc reagent at a flow rate of 5 μL $min^{-1}$ (residence time in the microreactor = 10 min), the reactants were smoothly transformed into unsymmetrical alkyl diarylmethanes **2** at room temperature. This protocol was generally applicable to a wide range of *p*-QMs **1a** and dialkylzinc reagents without any catalyst or promoter.

In 2017, Kang *et al.* synthesized diaryl diazaphosphonates **4** *via* 1,6-hydrophosphonylation of *p*-QMs **1a** with N-heterocyclic phosphine (NHP)-thioureas **3** under catalyst- and additive-free conditions.[13] This transformation proceeded smoothly in $CHCl_3$ at room temperature over 16 h to afford 20 examples of the desired product (Scheme 2a). When the 2,6-diisopropylphenyl-substituted NHP-thiourea **3** was employed under the optimized reaction conditions, the reaction did not proceed. On the basis of control experiments, the authors proposed a plausible reaction pathway (Scheme 2b). The 1,6-conjugate addition between the *p*-QM **1a** and the bifunctional NHP-thiourea **3**, which is activated by hydrogen bond formation with the thiourea Brønsted acid, generates the diazaphosphonium intermediate **5**. Subsequent proton transfer (PT) affords the anionic thiourea intermediate **6**, which undergoes intramolecular nucleophilic substitution to furnish the final product **4** alongside thiazolidine **7**.

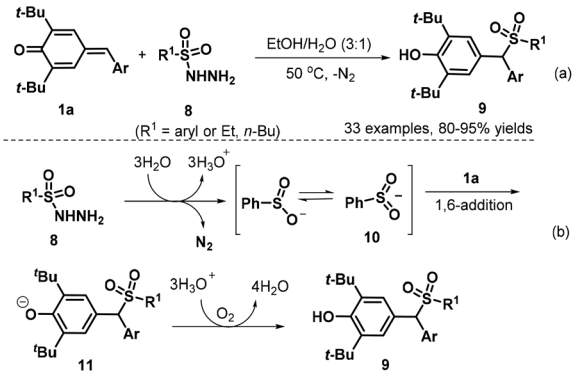
Subsequently, the Liu group developed a 1,6-conjugate addition/sulfonylation reaction of *p*-QMs **1a** with sulfonyl hydrazides **8** to obtain diarylmethyl sulfones **9**. The reaction proceeded efficiently at 50 °C under catalyst-free conditions using EtOH–$H_2O$ (3 : 1 v/v) as the reaction medium, thus providing a highly chemo- and regioselective synthesis of 33 examples of new diarylmethyl sulfones **9** in 80–95% yields




Scheme 1 1,6-Addition of dialkylzinc reagents to *p*-QMs.



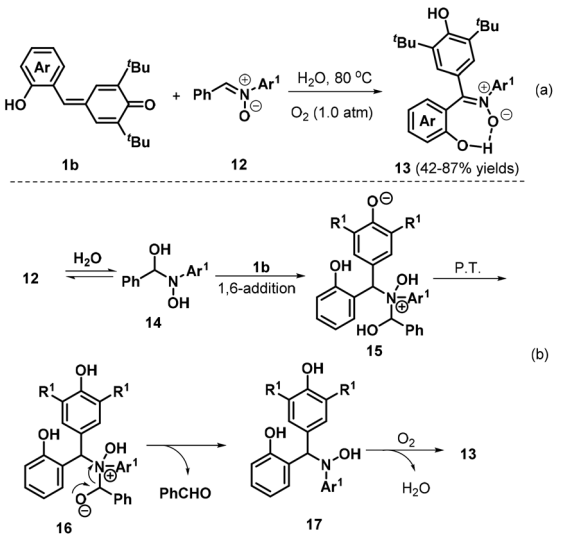

Scheme 2 Catalyst-free synthesis of diaryl diazaphosphonates.




Scheme 3 1,6-Addition of sulfonyl hydrazides to *p*-QMs.

(Scheme 3a). Various types of sulfonyl hydrazides **8** bearing either aryl or alkyl groups were well tolerated in this conjugate addition reaction, and the authors proposed a plausible mechanism for this catalyst-free transformation. In the first step, the sulfinyl anion is formed from sulfonyl hydrazide **8** in the presence of water with the release of $N_2$. The resonance structure of the sulfinyl anion, sulfur-centered anion **10**, undergoes 1,6-conjugate addition to the *p*-QM **1a** to afford intermediate **11**. The desired product **9** is formed upon proton transfer from hydronium ions to the intermediate **11** (Scheme 3b).[14] The similar unsymmetrical *gem*-diarylmethyl sulfones **9** could also be synthesized through HOAc-promoted 1,6-conjugate sulfonylation of *p*-QMs **1a** with arylsulfinate sodium reagents.[15]

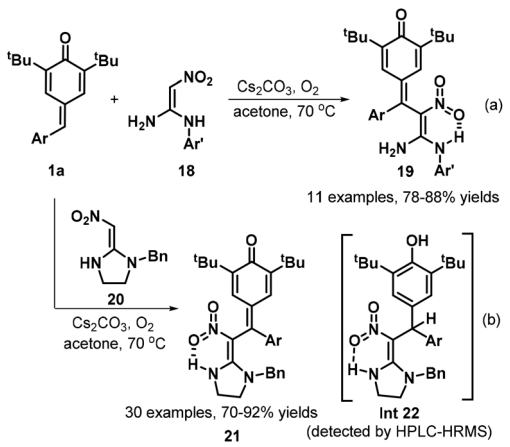
Very recently, Tu, Jiang, and co-workers described a new and environmentally benign protocol for effectively synthesizing triarylated (*Z*)-nitrones **13** with high stereoselectivity and generally excellent yields *via* a metal- and catalyst-free $H_2O$-mediated 1,3-dipolar transfer reaction of *o*-hydroxyphenyl-substituted *p*-QM **1b** and diarylated nitrones **12** (Scheme 4a).[16]



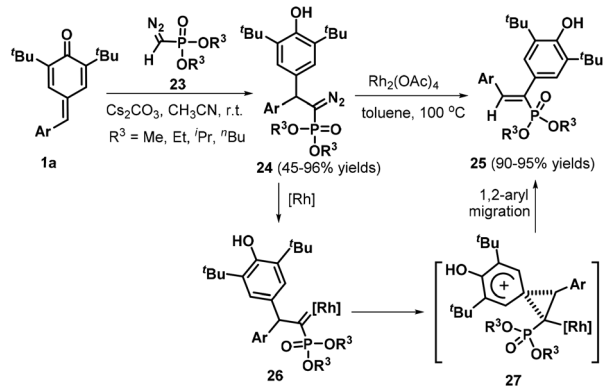

Scheme 4 $H_2O$-Mediated reaction of *p*-QMs with nitrones.

Interestingly, in this reaction, $H_2O$ played a dual role as both a mediator and a green solvent, with oxygen serving as a green oxidant. The reaction was tolerant to both electron-donating and electron-withdrawing substituents at various positions of the nitrone phenyl ring. The authors proposed a reasonable mechanism for this reaction, as depicted in Scheme 4b. In the first step, nucleophilic addition of $H_2O$ to nitrone **12** generates an unstable α-amino alcohol intermediate **14** in a reversible process. Fast 1,6-addition of the nitrogen atom of **14** to *p*-QM **1b** affords intermediate **15**, followed by proton transfer and the release of benzaldehyde to furnish intermediate **17**. Finally, intermediate **17** is converted to product **13** *via* oxidation in the presence of $O_2$.

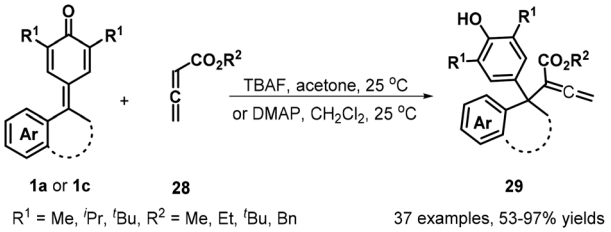
**2.1.2. Base-promoted 1,6-addition.** Owing to the intrinsic electrophilic nature and aromatization driving force of the cyclohexadiene moiety, *p*-QMs act as strongly electrophilic acceptors in 1,6-conjugate addition reactions, especially in the presence of certain bases.[17] Guided by this principle, Yan *et al.* developed a concise and practical strategy for the synthesis of a variety of QM-containing β-nitroenamine derivatives **19** *via* a $Cs_2CO_3$-promoted 1,6-conjugate addition of *N*-benzyl β-nitroenamines **18** with *p*-QMs **1a** in acetone under an air atmosphere (Scheme 5a).[18] Evaluation of the reaction scope using 1,1-enediamine **20** as the enamine component revealed that the reaction worked well, providing the corresponding cyclic β-nitroenamines **21** containing a QM moiety. Control experiments demonstrated that the reaction under the standard conditions afforded intermediate **22**, which was detected by HPLC-HRMS (Scheme 5b). On the basis of the experimental results, the authors proposed a plausible mechanism comprising base-promoted 1,6-addition, imine–enamine tautomerization, and oxidation by atmospheric oxygen. In another impressive work, Mohanan and co-workers documented the 1,6-conjugate addition of Seyferth–Gilbert reagent (SGR) **23** to *p*-QMs **1a** (Scheme 6). In the presence of $Cs_2CO_3$, SGR **23** reacted with *p*-QMs **1a** in $CH_3CN$, furnishing diarylmethylated diazomethylphosphonates **24** in yields ranging from 45% to 96%. This reaction featured a broad substrate scope and high




Scheme 5 Synthesis of β-nitroenamine derivatives.




Scheme 6 1,6-Addition of SGR to *p*-QMs.




Scheme 7 Synthesis of α-diarylmethylated allenic esters.

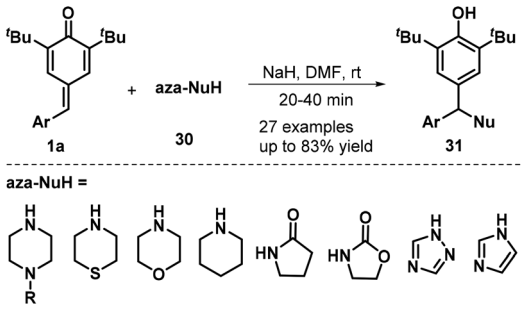
functional group tolerance.[19] To broaden the synthetic utility of these products, the authors also subjected the conjugate adducts **24** to treatment with rhodium acetate, which provided the corresponding 1,2-diaryl alkenylphosphonates **25** in good yields *via* 1,2-aryl migration of the rhodium carbenoid intermediate **27**.

The same group subsequently demonstrated that the use of allenic esters **28** in combination with tetrabutylammonium fluoride (TBAF) activation enabled 1,6-conjugate addition for the synthesis of 37 structurally relevant α-diarylmethylated allenic esters **29** in 53–97% yields (Scheme 7). Furthermore, this transformation could be extended to isatin-derived *p*-QMs **1c**, delivering allenic esters containing 3,3-disubstituted oxindoles **29**.[20a] At the same time, Chandra *et al.* described a Rauhut–Currier reaction between **1a** and **28** for forming similar allenoates **29** in high to excellent yields by using DMAP as a nucleophilic catalyst (Scheme 7).[20b]

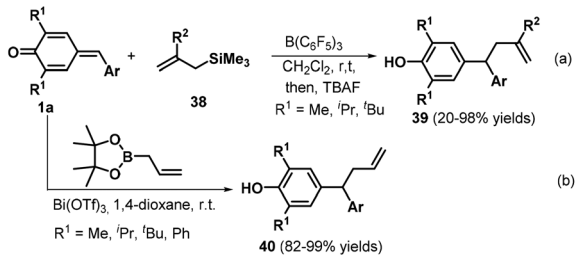
Heterocyclic amines and amides were also found to serve as *N*-nucleophiles **30** for the synthesis of nitrogen-containing trisubstituted methanes **31** in moderate to good yields *via* NaH-mediated 1,6-aza-Michael addition to *p*-QMs **1a** (Scheme 8). A wide range of *N*-nucleophiles **30**, including *N*-substituted piperazines, thiomorpholine, morpholine, piperidine, pyrrolidin-2-one, oxazolidin-2-one, 1*H*-1,2,4-triazole, and 1*H*-imidazole, were compatible with this base-promoted reaction.[21]

**2.1.3. Lewis acid-promoted 1,6-addition.** Lewis acid-promoted 1,6-addition of various nucleophilic and electrophilic reagents to *p*-QMs **1** has become an important research area

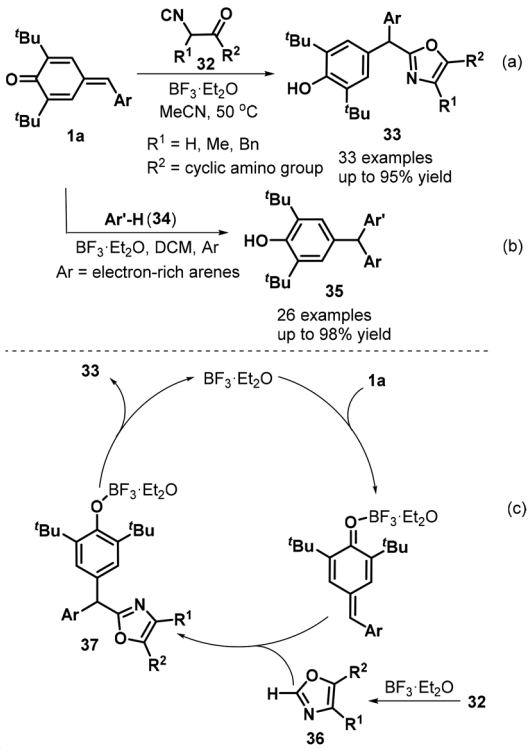



Scheme 8 1,6-Aza-Michael addition to *p*-QMs.




Scheme 10 1,6-Addition to form allyl diarylmethanes.

that provides an efficient strategy for the construction of polysubstituted arylmethanes. Interestingly, Lin, Yao, and co-workers described an elegant $BF_3{\cdot}Et_2O$-catalyzed 1,6-conjugate addition involving *p*-QMs **1a** and α-isocyanoacetamides **32** that successfully provided access to 33 examples of oxazole-substituted arylmethanes **33** in 46–95% yields. However, α-isocyanoacetates were ineffective reaction partners in this transformation (Scheme 9a). During the reaction process, $BF_3{\cdot}Et_2O$ catalyzed the cyclization of the α-isocyanoacetamide to generate an oxazole **36**, which underwent 1,6-conjugate addition to the *p*-QMs **1a** to give the target products **33** (Scheme 9c). The authors also used electron-rich aromatic compounds **34** to expand the synthetic utility. This reaction proceeded readily under mild conditions to afford diverse unsymmetrical triarylmethanes **35** in 41–98% yields (Scheme 9b).[22]

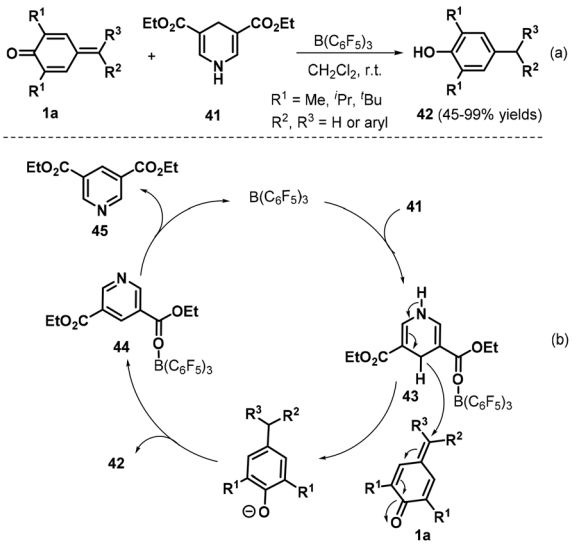



Scheme 9 $BF_3{\cdot}Et_2O$-Catalyzed synthesis of arylmethanes.

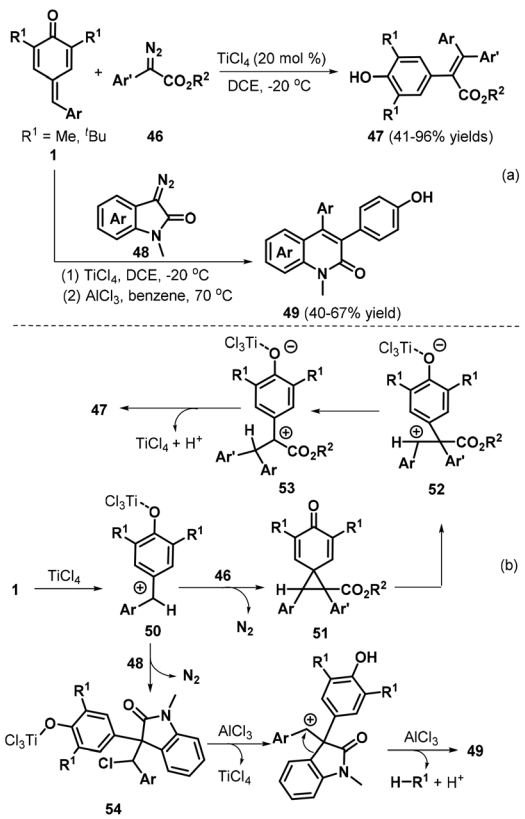
Subsequently, the Anand group reported an interesting transformation of allyltrimethylsilanes. These researchers discovered that the $B(C_6F_5)_3$-catalyzed reaction of *p*-QMs **1a** and allyltrimethylsilanes **38** led to the rapid formation of the expected unsymmetrical allyl diarylmethanes **39** with moderate to excellent yields *via* 1,6-conjugate addition (Scheme 10a).[23] Various aryl-substituted allyltrimethylsilanes worked well in this reaction, whereas a quinoline-based analogue exhibited lower reactivity with a yield of only 20%. Unfortunately, the *p*-QM derived from thiophene-2-carboxaldehyde resulted in the formation of a complex mixture under the reaction conditions. In this protocol, $B(C_6F_5)_3$ is employed as a Lewis acid catalyst to mediate the 1,6-conjugate allylation of *p*-QMs **1a**. Following this study, Li and co-workers reported the bismuth-catalyzed 1,6-allylation addition of *p*-QMs **1a** with 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, affording 25 examples of the allylation product **40**. Optimization of the conditions revealed that the reaction proceeded smoothly in the presence of 0.5–5 mol% $Bi(OTf)_3$ in 1,4-dioxane at room temperature (Scheme 10b).[24]

Exchanging allyltrimethylsilanes for Hantzsch ester **41**, Anand and co-workers presented a $B(C_6F_5)_3$-catalyzed reduction of *p*-QMs **1a**, leading to 31 examples of unsymmetrical diaryl- and triarylmethanes **42** in 45–99% yields (Scheme 11a).[25] Notably, this protocol was applied to the synthesis of beclobrate, a potent cholesterol- and triglyceride-lowering drug that is used for the treatment of hyperlipidemia. Mechanistically, $B(C_6F_5)_3$ activates the Hantzsch ester **41** to afford the corresponding Lewis acid–base complex **43**, which mediates hydride transfer to *p*-QM **1a**, and subsequent protonation yields the desired product **42** along with complex **44**. The complex **44** releases the pyridine byproduct **45** to regenerate the catalyst (Scheme 11b).

Cui and co-workers reported a remarkable insertion reaction between diazo compounds and *p*-QMs **1a** for the formation of C=C double bonds.[26] The $TiCl_4$-catalyzed reaction of *p*-QMs **1a** with α-aryl diazoesters **46** at low temperature enabled aryl group migration to afford a wide array of functionalized tetrasubstituted alkenes **47** (Scheme 12a). Next, the authors reacted *p*-QMs **1a** with diazooxindole **48**. Careful screening of the reaction conditions revealed that the two-step reaction resulted in quinolinone derivatives **49**, in which 1.0




Scheme 11 $B(C_6F_5)_3$-Catalyzed reduction of *p*-QMs.

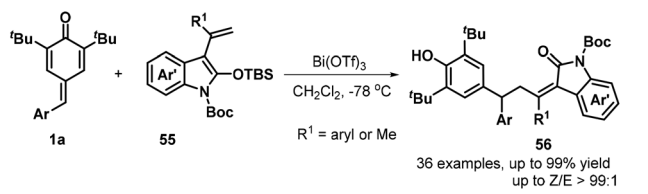



Scheme 12 $TiCl_4$-Catalyzed reaction of *p*-QMs.

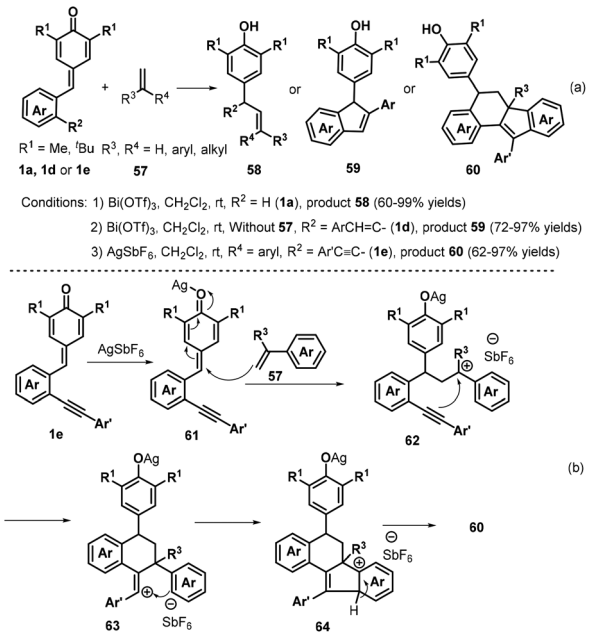
equivalents of $TiCl_4$ were required as the promoter in the first step and $AlCl_3$ promoted the aryl migration and de-*tert*-butylation in the second step. Furthermore, the authors combined these two steps in a one-pot reaction for quinolinone synthesis. Moreover, the authors also presented possible mechanisms for the formation of these products (Scheme 12b). The *p*-QM is first activated by $TiCl_4$ to generate cationic intermediate **50**, which is trapped by α-aryl diazoester **46** to afford cyclopropanation intermediate **51** with the release of nitrogen. Subsequent cyclopropane fragmentation delivers cationic intermediate **52** with a $TiCl_4$-activated quinone moiety, which undergoes rearrangement to form cationic intermediate **53**. Next, intermediate **53** is transformed into tetrasubstituted alkene **47** *via* hydrogen elimination with the regeneration of $TiCl_4$. In contrast, when intermediate **50** is generated *in situ* from the diazooxindole, direct chloride addition to the benzyl cation affords intermediate **54**, which undergoes successive $AlCl_3$-catalyzed dechlorination, ring expansion, and de-*tert*-butylation to yield quinolinone **49**.

In subsequent contributions, a bismuth-catalyzed vinylogous nucleophilic 1,6-conjugate addition reaction of *p*-QMs **1a** and 3-propenyl-2-silyloxyindoles **55** generated substituted α-alkylidene-δ-diaryl-2-oxindoles **56** (Scheme 13).[27] Optimization of the reaction conditions revealed that the use of 10 mol% $Bi(OTf)_3$ in dichloromethane (DCM) at −78 °C for 12 h resulted in the best product yield. A wide range of α-alkylidene-δ-diaryl-2-oxindoles **56** were obtained in 55–99% yields and 94 : 6–98 : 2 *Z*/*E* ratio under the optimized reaction conditions. Subsequently, Anand and co-workers reported a similar bismuth-catalyzed intermolecular 1,6-hydroolefination of *p*-QMs **1a** with olefins, which provided access to 21 examples of vinyl diarylmethanes **58** in up to 99% yield (Scheme 14a). The bismuth-catalyzed reaction also tolerated the intramolecular version to afford six examples of arylated indenes **59** in up to 97% yield. Furthermore, in the presence of $AgSbF_6$ as catalyst, 2-alkenylated *p*-QMs **1e** and 1,1-diphenylethylene **57** underwent 1,6-conjugate electrophilic addition and alkene–alkyne cyclization to furnish a series of substituted dihydrobenzo[*a*]fluorene derivatives **60** in good yields and excellent diastereoselectivity.[28] This transformation was also exploited for the total synthesis of the resveratrol-derived natural product (±)-isopaucifloral F. The authors proposed a plausible mechanism for products **60** (Scheme 14b). The silver salt initially activates the carbonyl group of the *p*-QM **1e** and 1,6-addition of olefin **57** then generates reactive carbocation intermediate **62**, followed by electrophilic cyclization to form **63**, Friedel–Crafts-type cyclization to provide aryl carbocation intermediate **64**, and finally aromatization to generate the final product **60**.

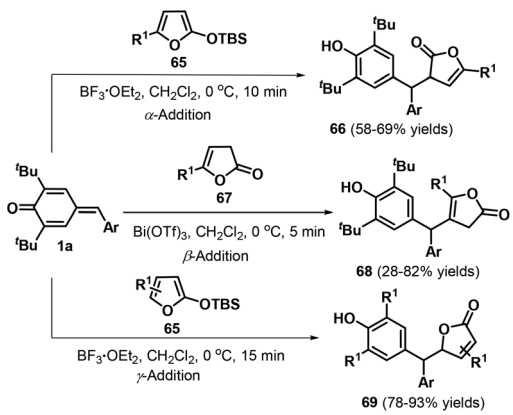
Kumar and co-workers reported another impressive example of the selective 1,6-conjugate addition of *p*-QMs **1a** by switching the nucleophilic reactivity of the α, β, and γ posi-




Scheme 13 Bismuth-catalyzed reaction of *p*-QMs with oxyindoles.



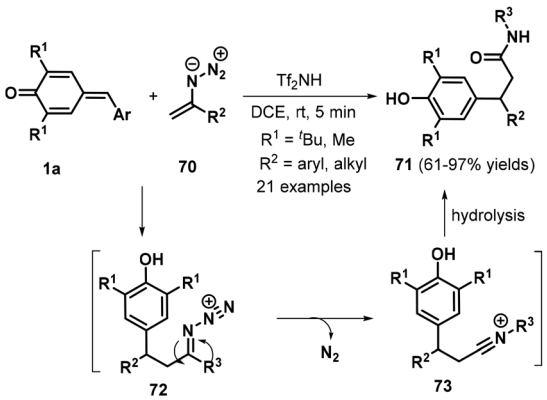

Scheme 14 1,6-Hydroolefination of *p*-QMs with olefins.




Scheme 15 Selective 1,6-addition of *p*-QMs and butenolides.

tions of butenolides **65** and lactone **67** (Scheme 15).[29] For example, α-addition could be achieved by reacting *p*-QMs **1a** and butenolides **65** ($R^1 \neq H$) in the presence of $BF_3{\cdot}Et_2O$, whereas the use of lactone **67** in the presence of $Bi(OTf)_3$ afforded the β-adducts **68**. Butenolides **65** lacking a substituent in the C5 position underwent γ-addition mediated by $BF_3{\cdot}Et_2O$ to yield 5-substituted furan-2(5*H*)-ones **69**. All of these reactions rapidly reached completion in approximately 15 min and featured wide substrate scope and good functional group tolerance under mild conditions.

In 2017, the same researchers reported a $Tf_2NH$-catalyzed 1,6-conjugate addition/Schmidt-type rearrangement of *p*-QMs **1a** with vinyl azides **70**, providing access to 21 examples of β-bisarylated amides **71** in 61–97% yields (Scheme 16).[30] Vinyl azides bearing either variously substituted aryl groups or alkyl functionalities both reacted smoothly to deliver the desired

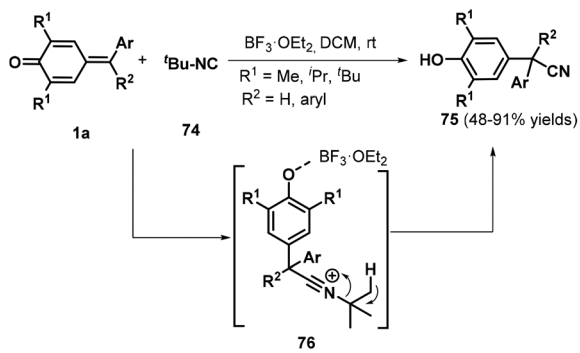



Scheme 16 $Tf_2NH$-Catalyzed rearrangement of *p*-QMs.

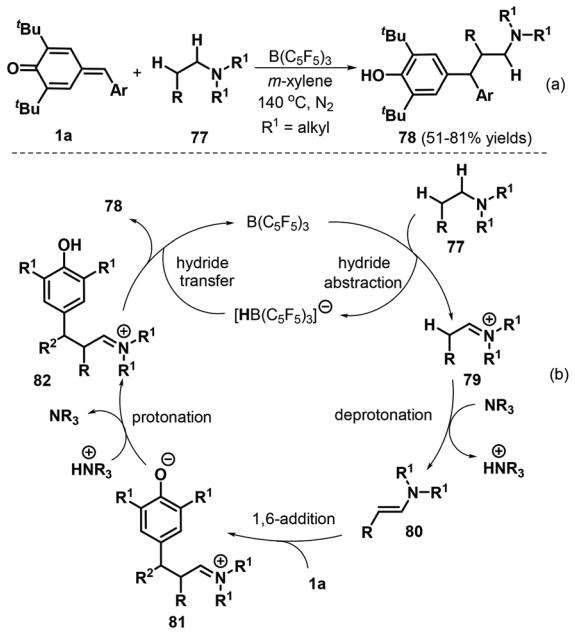
products in generally good yields. The authors also proposed a plausible mechanism for this reaction (Scheme 16). 1,6-Conjugate addition of vinyl azide **70** to proton-activated *p*-QM **1a** generates intermediate **72**, which undergoes Schmidt rearrangement to form the nitrilium ion intermediate **73**. Subsequent hydrolysis affords the target product **71**.

Shortly after this disclosure, Muthukrishnan *et al.* used *tert*-butyl isocyanide **74** as a cyanide source to accomplish the cyanation of *p*-QMs **1a**, permitting the synthesis of α-diaryl and α-triaryl nitriles **75** in good to excellent yields under mild reaction conditions (Scheme 17).[31] Notably, an alkyne-tethered *p*-QM was also compatible with the optimized reaction conditions. However, pyridyl-containing *p*-QMs did not react under the standard conditions. The reaction proceeded *via* the 1,6-addition of *tert*-butyl isocyanide **74** to $BF_3{\cdot}Et_2O$-activated *p*-QM **1a**, subsequent formation of key zwitterionic nitrilium ion intermediate **76**, and the liberation of isobutylene.

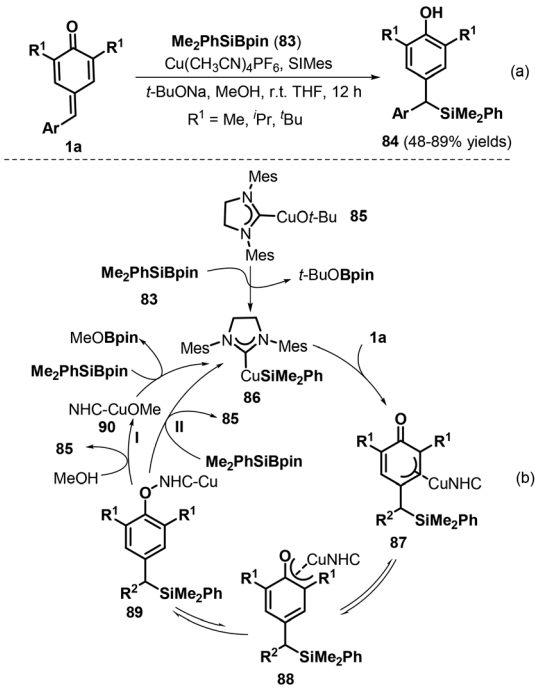
More recently, Ma and co-workers described an elegant intermolecular redox-neutral β-alkylation of acyclic tertiary amines **77** with *p*-QMs **1a** under $B(C_6F_5)_3$ catalysis, which delivered a diverse array of functionalized tertiary amines **78** in good yields of up to 81% (Scheme 18a). This procedure utilized commercially available substrates and catalyst and promoted direct functionalization of the $C(sp^3)$–H bond at the β-position of acyclic tertiary amines **77** *via* 1,6-conjugate addition to




Scheme 17 1,6-Addition of *tert*-butyl isocyanide to *p*-QMs.




Scheme 18 1,6-Addition of acyclic tertiary amines to *p*-QMs.



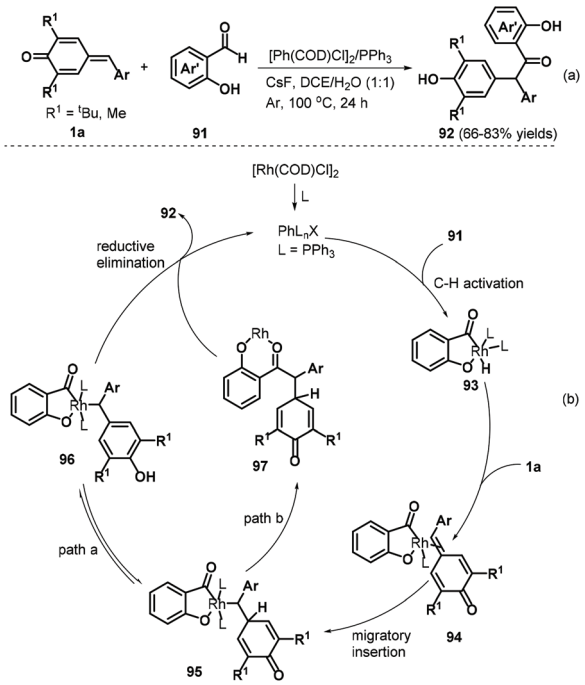

Scheme 19 Copper(I)-catalyzed silylation toward dibenzylic silanes.

*p*-QMs **1a**.[32] Acyclic amines, including triethylamine, *N*,*N*-diethylbutylamine, and tripropylamine, smoothly underwent reaction under these conditions. In contrast, cyclic tertiary amines such as *N*-benzylpiperidine and *N*-mesitylpiperidine displayed lower conversions. This reaction starts with hydride abstraction from tertiary amine **77** by $B(C_6F_5)_3$ to form iminium ion intermediate **79** and $[HB(C_6F_5)_3]^-$ (Scheme 18b). Deprotonation of intermediate **79** then generates enamine intermediate **80**, which reacts with *p*-QM **1a** *via* 1,6-conjugate addition to produce functionalized iminium intermediate **81**. Subsequent protonation of **81** generates strongly electrophilic iminium intermediate **82**, which undergoes hydride transfer from $[HB(C_6F_5)_3]^-$ to generate product **78** and complete the catalytic cycle.

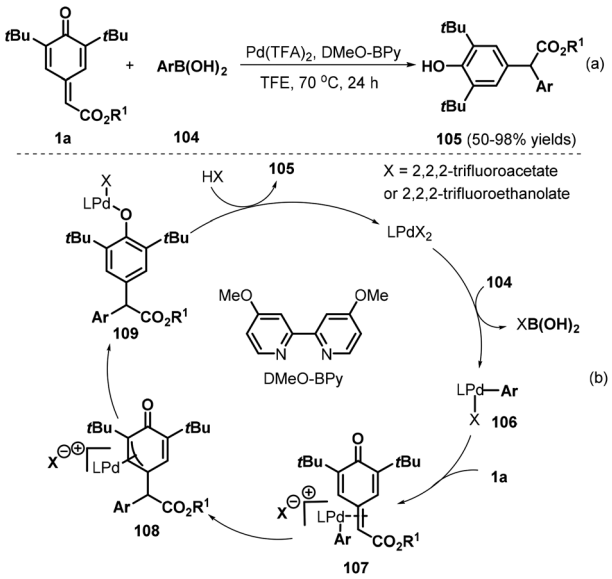
**2.1.4. Metal-catalyzed 1,6-addition.** The construction of carbon–silicon bonds is an important research topic in synthetic organic chemistry owing to the fact that silicon-containing molecules are crucial precursors for producing bioactive natural products *via* various transformations.[33] Specifically, copper(I)-catalyzed silylation reactions have emerged as a powerful strategy for carbon–silicon bond formation. In 2015, Tortosa and co-workers pioneered a copper(I)-catalyzed silylation of *p*-QMs **1a** using silaborane reagent **83** under mild reaction conditions to obtain a series of dibenzylic silanes **84** with high yields (Scheme 19a).[34] This transformation represented the first example of 1,6-conjugate addition to *p*-QMs **1a** for carbon–silicon bond formation. In this process, the silyl–copper(I)-N-heterocyclic carbene (NHC) species **86**, generated by the reaction of copper alkoxide **85** and the silaborane reagent, inserts into the exocyclic double bond of the *p*-QM **1a** through cleavage of the copper–silicon bond to produce π-allylcopper intermediate **87**, which isomerizes to copper phenoxide intermediate **88** (Scheme 19b). Subsequent transformation may occur *via* two reaction pathways. In pathway I, protonolysis provides product **84** in the presence of MeOH with release of NHC–CuOMe **90** to restart the catalytic cycle. In pathway II, intermediate **89** reacts directly with the silaborane to afford product **84** and silyl–copper species **86** with regeneration of the catalyst.

A follow-up work by the Lin group described an interesting rhodium-catalyzed C–H activation for 1,6-addition to *p*-QMs **1a**.[35] The authors reacted salicylaldehydes **91** and *p*-QMs **1a** in a catalytic system comprising $[Rh(COD)Cl]_2$ (2.5 mol%), $PPh_3$ (5 mol%), and the additive CsF (1.0 equivalents) under an argon atmosphere, resulting in a series of α,α-diaryl-2-hydroxyacetophenones **92** (Scheme 20a). A series of salicylaldehydes bearing electron-donating and electron-withdrawing groups at the C5, C4, and C3 positions all afforded the corresponding products in 66–83% yields. However, both C6-methoxy-substituted salicylaldehyde and 3-(methylthio)butanal failed to participate in the reaction. This method displayed good yields, high chemoselectivity, good functional group tolerance, and gram-scale capacity. Mechanistically, this reaction involves hydroxy-assisted C–H activation of the aldehyde group by the rhodium catalyst to form rhodium species **93**, which chelates the exocyclic double bond of *p*-QM **1a** to afford metal–organic intermediate **94** (Scheme 20b). Subsequent migratory hydride insertion into the *exo*-methylene moiety delivers intermediate **95**, which can undergo two reaction pathways. In pathway a, intermediate **96** is formed by isomerization of intermediate **95**, leading to final product **92** *via* reductive elimination with regeneration of the active rhodium complex for the subsequent



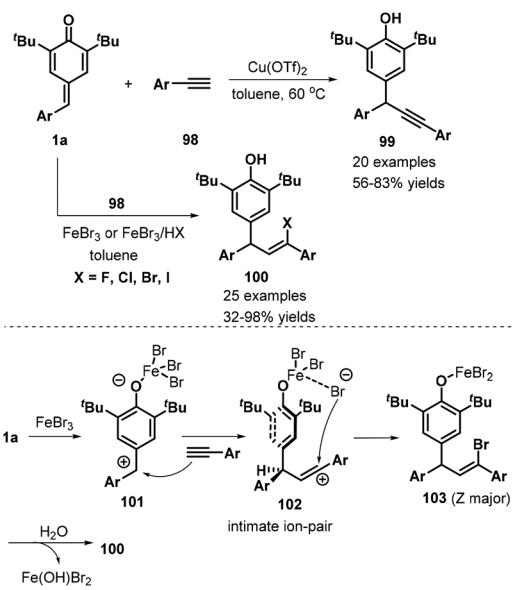

Scheme 20 Rhodium-catalyzed C–H activation for 1,6-addition to *p*-QMs.




Scheme 22 Synthesis of diarylacetates.

catalytic cycle. In pathway b, intermediate **95** undergoes reductive elimination to generate intermediate **97**, which then isomerizes to form product **92** with regeneration of the rhodium catalyst.

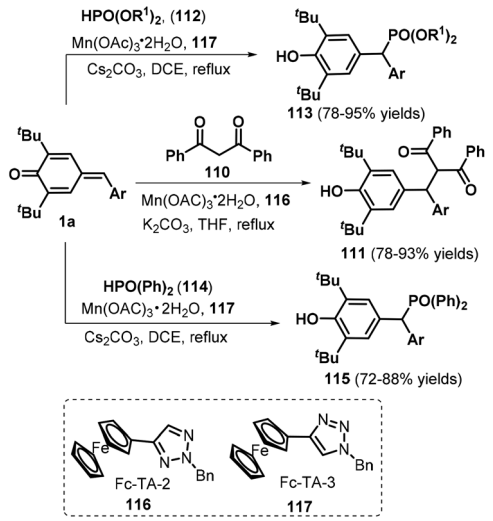
Very recently, Liu, Zhang, and co-workers developed a remarkable catalyst-controlled chemodivergent 1,6-addition of *p*-QMs **1a** and terminal alkynes **98**, which afforded a variety of structurally diverse alkynyl- or vinyl-substituted diarylmethanes **99** or **100** with good yields (Scheme 21).[36] Heteroaryl-, ferrocenyl-, and enyne-derived terminal alkynes all served as suitable substrates in this transformation. The authors also synthesized a TMS-substituted *p*-QM, although the subsequent reaction did not proceed under the standard conditions. In this transformation, direct 1,6-addition of the *p*-QMs and terminal alkynes occurred under copper catalysis, whereas iron catalysis mediated a stereoselective three-component reaction between the *p*-QM, alkyne, and the halogen present in the iron salt or acid HX (fluoride, chloride, bromide, or iodide). Notably, the haloolefin products were obtained with *Z*/*E* ratios ranging from 1 : 1 to >20 : 1 *via* the iron-catalyzed 1,6-electrophilic addition and halogen addition.




Scheme 21 Synthesis of alkynyl- and vinyl-substituted diarylmethanes.

Besides copper and rhodium catalysts, palladium(II) catalysts have also proved suitable for 1,6-addition to *p*-QMs. The Zhang group developed an interesting palladium(II)-catalyzed 1,6-conjugate addition of arylboronic acids **104** to *p*-QMs **1a** for the preparation of diarylacetates **105** by using 4,4′-dimethoxy-2,2′-bipyridine (DMeO-BPy) as the ligand and trifluoroethanol (TFE) as the reaction medium (Scheme 22a).[37] Various ester-substituted *p*-QMs and arylboronic acids reacted smoothly under the optimal reaction conditions. However, arylboronic acids bearing an ester group at the *para* position exhibited lower reactivity. The reaction pathway involves transmetalation, ligand exchange, phenyl insertion into the double bond, tautomerization, and protonation (Scheme 22b).

Recently, Wang and co-workers employed $Mn(OAc)_3^{\bullet}$ as the catalyst to realize 1,6-nucleophilic addition between *p*-QMs **1a** and carbon or phosphorus nucleophiles, such as 1,3-diphenylpropane-1,3-dione **110**, diethylphosphite **112**, and diphenylphosphine oxide **114**, in the presence of ferrocenyl triazole (Fc-TA) ligands **116** and **117** (Scheme 23).[38] This protocol provides an efficient method for obtaining functionalized methines and their analogues in good to high yields. An improved variation



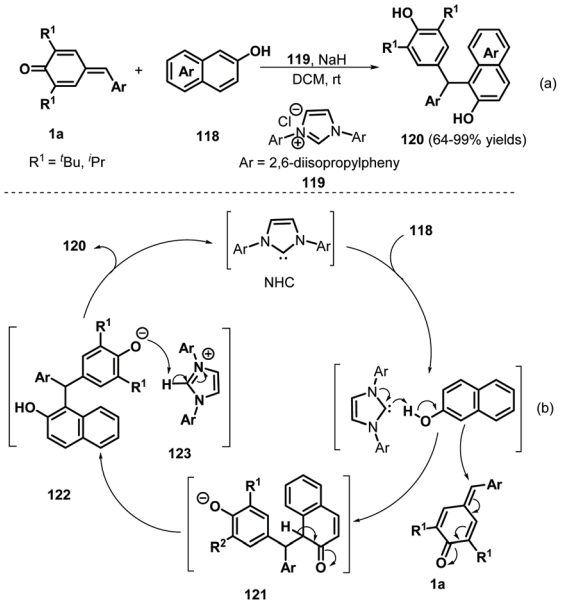

Scheme 23 Manganese-catalyzed 1,6-addition toward functionalized methines.

starting from *p*-QMs **1a** and phosphorus nucleophiles was subsequently documented using different bases including $Cs_2CO_3$ [39] and DBU[40] or aqueous solution.[41] Furthermore, Lu, Jiang, and co-workers presented a one-pot, two-step synthesis of functionalized ketones *via* the 1,6-addition of β-ketoacids to *p*-QMs **1a** and subsequent $Et_3N$-assisted decarboxylation.[42]

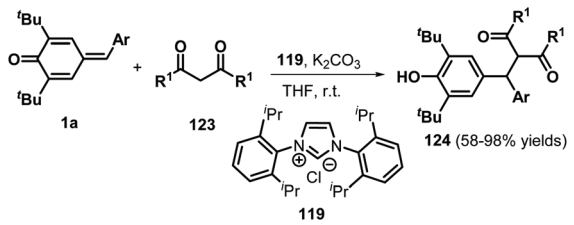
**2.1.5. NHC-catalyzed 1,6-addition.** Over the past decades, NHC catalysis has emerged as a versatile tool for carbon–carbon and carbon–heteroatom bond formation.[43] In 2016, Anand and co-workers reported an NHC-catalyzed 1,6-conjugate addition of 2-naphthols **118** to *p*-QMs **1a** to afford a series of functionalized unsymmetrical triarylmethanes **120** in an atom-economical manner (Scheme 24a).[44] This reaction proceeded readily for various 2-naphthol derivatives to generate the expected triarylmethanes in high yields. However, simple phenol was not converted into the corresponding product under the standard conditions. In this transformation, the NHC **119** acts as a Brønsted base to abstract the phenolic proton of the 2-naphthol to form a 2-naphthoxide anion, which undergoes 1,6-addition of *p*-QM **1a** to generate intermediate **121** (Scheme 24b). Aromatization of **121** followed by proton transfer from **123** to **122** results in the formation of the final product with liberation of the NHC. Guin *et al.* demonstrated a similar catalytic strategy for the synthesis of functionalized trisubstituted methanes **124** in 58–98% yields using **119** as a Brønsted base catalyst (Scheme 25).[45]

Inspired by the extensive studies on NHC-catalyzed 1,6-addition reactions of *p*-QMs, Anand and co-workers described another interesting NHC-catalyzed reaction involving silicon activation for vinylogous conjugate cyanation of *p*-QMs **1a** (Scheme 26). The NHC-catalyzed reaction of **1a** proceeded smoothly using $Me_3SiCN$ **125** as a cyanide source, providing general and straightforward access to a series of α-diaryl- and α-triarylnitriles **127** in good to excellent yields.[46] Notably, this protocol was the first example of NHC-catalyzed 1,6-conjugate addition of $Me_3SiCN$ to a dienone system for cyanation.

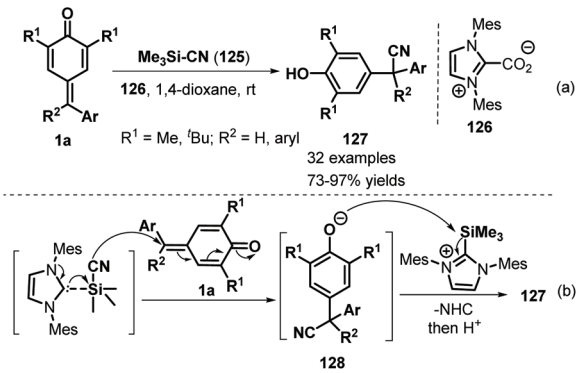
Anand and co-workers employed bis(amino)cyclopropenylidene **130** as an effective NHC catalyst to mediate the 1,6-addition of *p*-QMs **1a** and α,β-unsaturated carbonyls **129**. This reaction proceeded readily to furnish 26 examples of vinyl diarylmethanes **131** in moderate to good yields (Scheme 27a).[47] Various α,β-unsaturated carbonyls, including 2-cyclopentenone, 2-cyclohexen-1-one and 5,6-dihydro-2*H*-



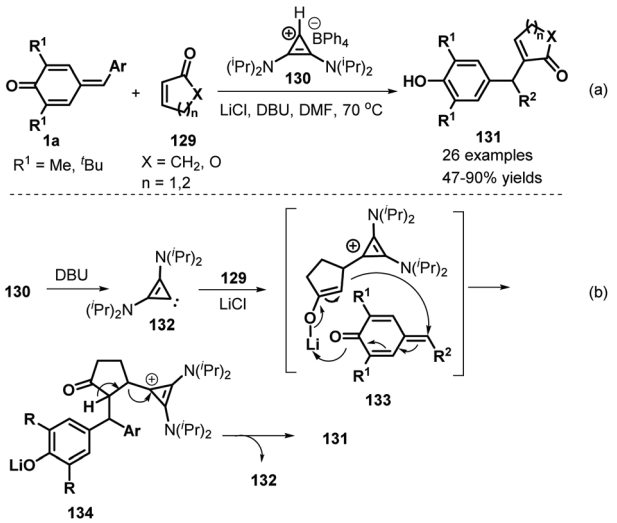

Scheme 24 NHC-Catalyzed 1,6-addition of 2-naphthols to *p*-QMs.




Scheme 25 NHC-Catalyzed synthesis of trisubstituted methanes.



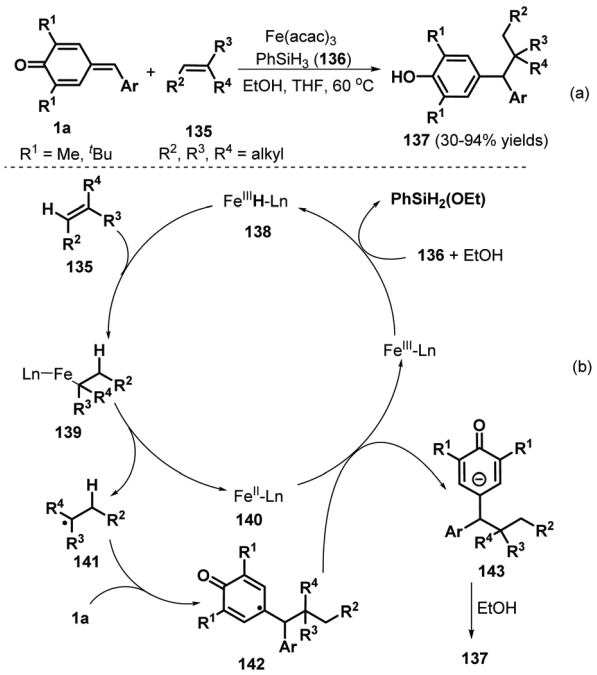

Scheme 26 Synthesis of α-diaryl- and α-triarylnitriles.




Scheme 27 1,6-Addition of *p*-QMs and α,β-unsaturated carbonyls.

pyran-2-one, reacted smoothly. Unfortunately, 2-(5*H*)-furanone, α,β-unsaturated lactams, and acyclic enones such as vinyl ketones, acrylates, and acrylamides were all found to be unreactive. A plausible mechanism for the formation of these products may include *in situ* generation of carbene intermediate **132**, Michael addition in the presence of lithium salts, and 1,6-addition alongside regeneration of the carbene intermediate **133** (Scheme 27b).

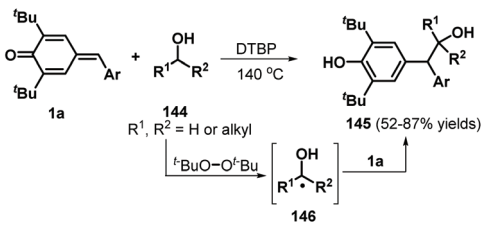
**2.1.6. Radical-enabled 1,6-addition.** Cascade radical reactions permit the formation of multiple carbon–carbon and carbon–heteroatom bonds and have become a valuable synthetic strategy for accessing densely functionalized structures in a highly controlled manner with good functional group tolerance. Undoubtedly, the design and preparation of versatile radical acceptors is the key to developing radical chemistry approaches for the construction of skeletally diverse molecules. Compounds possessing unsaturated structures such as alkene and alkyne moieties have proven to be versatile radical acceptors. *p*-QMs have often been employed to capture various radical species *via* 1,6-radical addition to construct diarylated methanes. In 2016, the Cui group reported a catalytic radical-triggered 1,6-addition involving *p*-QMs **1a** and olefins **135** (Scheme 28a). This radical-induced reaction was conducted in a mixed solvent system containing THF and EtOH at 60 °C using $Fe(acac)_3$ and $PhSiH_3$ **136**, generating the corresponding phenols **137** in 30–94% yields.[48] The hydroalkylation process was readily applicable to terminal olefins bearing hydroxy, amide, ester, and PMP moieties and tolerated not only cyclic olefins such as dihydropyran but also internal alkenes containing ester, ketone, and hydroxy groups and (*S*)-(−)-β-citronellol. On the basis of several control experiments, the authors proposed that the iron(III) catalyst is first converted to iron hydride species **138** in the presence of $PhSiH_3$ and EtOH, followed by the addition of olefin **136** and dissociation of intermediate **139** to generate iron(II) species **140** and alkyl radical **141**



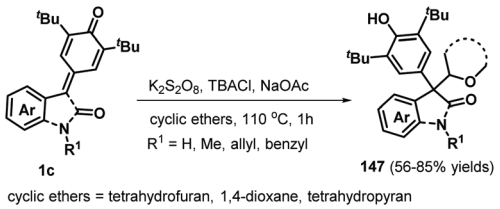

Scheme 28 Radical 1,6-addition of *p*-QMs and olefins.

(Scheme 28b). The latter component then undergoes radical addition of *p*-QM **1a** to form intermediate **142**, which is reduced by the iron(II) species **140** to furnish the phenol product **137** in the presence of EtOH with regeneration of the iron(III) catalyst.

Following this successful work, the same group reported another α-oxy radical-induced 1,6-addition of *p*-QMs **1a** to obtain phenols **145** under metal-free conditions using di-*tert*-butyl peroxide (DTBP) as a radical initiator (Scheme 29).[49] Various primary alcohols, such as methanol, ethanol, and *n*-propanol, reacted well and underwent α-oxy addition to *p*-QMs **1a**. Secondary alcohols such as isobutanol and cyclopentanol also furnished the corresponding functionalized alcohols in moderate yields. In the presence of DTBP, alcohol **144** is transformed to α-oxy radical **146**, which is trapped by the *p*-QM to afford products **145** through hydrogen atom transfer from alcohol **144**. In a subsequent work, cyclic ethers were converted into carbon-centered radicals under oxidative conditions ($K_2S_2O_8$/tetrabutylammonium chloride (TBACl)), which




Scheme 29 Radical 1,6-addition of *p*-QMs toward functionalized alcohols.

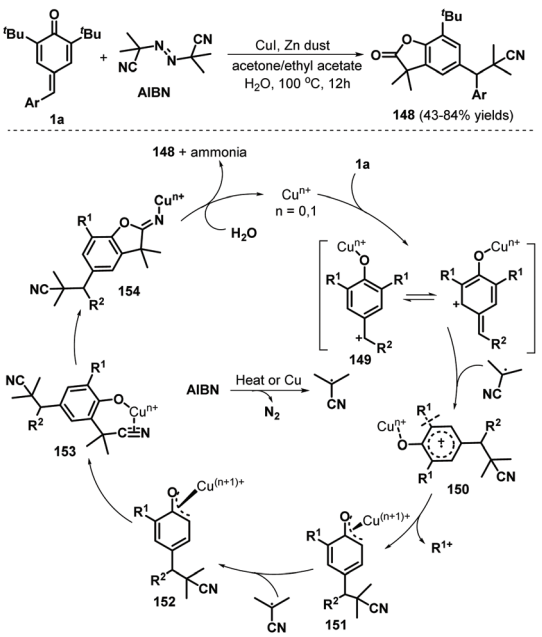



**Scheme 30** Radical 1,6-addition of cyclic ethers to *p*-QMs.

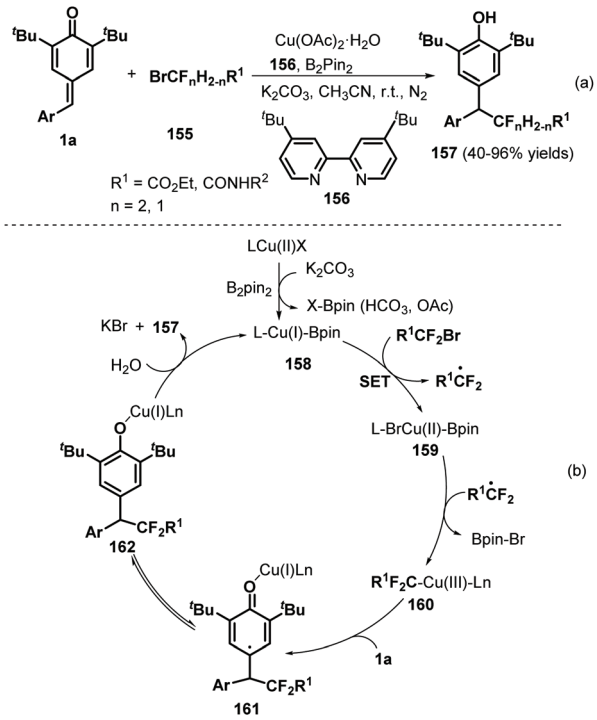
were then captured by *p*-QMs **1c** to afford cyclic ether-substituted diarylmethanes and triarylmethanes **147** with good yields (Scheme 30). Tetrahydrofuran, 1,4-dioxane, and tetrahydropyran as representative cyclic ethers also reacted well. However, 1,3,5-trioxane and 1,2-dimethoxyethane were incompatible.[50]

Tang, Chen, and co-workers reported the use of a radical cascade reaction of *p*-QMs **1a** in the presence of azodiisobutyronitrile (AIBN) and water to access benzofuran-2(3*H*)-ones in 43–84% yields (Scheme 31). Various *p*-QMs bearing electron-rich, electron-neutral, or electron-deficient aromatic moieties, some of which contained relatively bulky substituents, reacted well with AIBN in the presence of CuI (20 mol%) to afford cyano-containing benzofuran-2(3*H*)-ones **148**. Unfortunately, the desired products were not obtained after replacement of the *t*-Bu substituents with methyl or isopropyl groups. This cascade reaction is believed to proceed *via* 1,6-conjugate addition/aromatization, α-cyanoalkylation with cleavage of the unstrained and non-polar C(aryl)–C(*t*-Bu) bond, and downstream cyano-insertion/cyclization/hydrolysis.[51]

Using $Cu/B_2Pin_2$ as a catalytic system, Song and co-workers documented an elegant 1,6-hydrodifluoroacetylation of *p*-QMs




**Scheme 31** Radical reaction of *p*-QMs with AIBN.

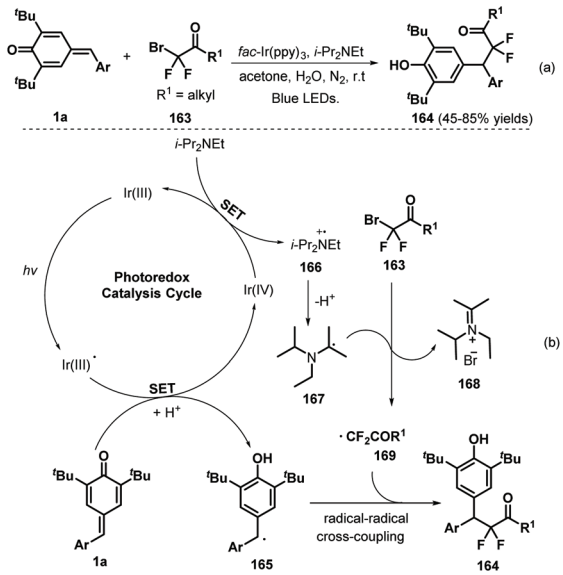



**Scheme 32** 1,6-Hydrodifluoroacetylation of *p*-QMs.

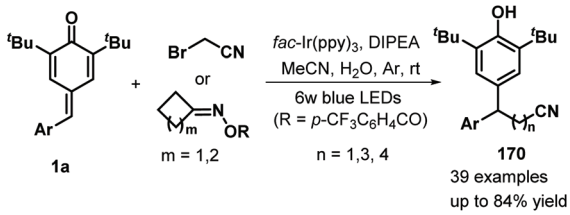
**1a** with difluoroalkyl bromides **155** (Scheme 32a).[52] This reaction featured a broad substrate scope and $B_2Pin_2$ as the reductant, resulting in the formation of a $C(sp^3)$–$CF_2$ bond. Both difluoromethylated and monofluoromethylated bromides and a variety of *p*-QMs were compatible with this reaction. During the reaction, the copper salt is considered to be reduced by $B_2Pin_2$ to afford Cu(I)–BPin species **158** (Scheme 32b). Then, oxidative addition of **158** into the difluoroalkyl bromide *via* single-electron transfer (SET) generates Cu(II)–BPin species **159** and a difluoroalkyl radical, which react to form Cu(III) species **160** with the elimination of Br–BPin. Subsequently, intermediate **160** is further trapped by *p*-QM **1a** to generate carbon-centered radical **161**, which yields the desired product **157** after isomerization and proton transfer with regeneration of the Cu(I) species for the next catalytic cycle.

Later, Xu and co-workers applied visible-light photocatalysis to achieve 1,6-hydrodifluoroacetylation between *p*-QMs **1a** and difluoroalkyl bromides **163**, leading to 22 examples of difluoroalkylated diarylmethanes **164** in 45–85% yields *via* radical cross-coupling (Scheme 33a).[53] Difluoroalkylating reagents containing various functional groups, including carbonyl, ester, acylamino, and heteroaryl moieties, reacted well to afford the expected products in moderate to good yields. The reaction pathway consists of SET, deprotonation, and radical–radical cross-coupling (Scheme 33b). In another example of visible-light photocatalysis, Li and co-workers exploited bromoacetonitrile as an α-cyanomethyl radical precursor for the cyanomethylation of *p*-QMs **1a** (Scheme 34). The use of cyclobutanone oximes as γ-cyanoalkyl radical donors permitted the successful synthesis of 3-cyanopropyl diarylmethanes **170** with



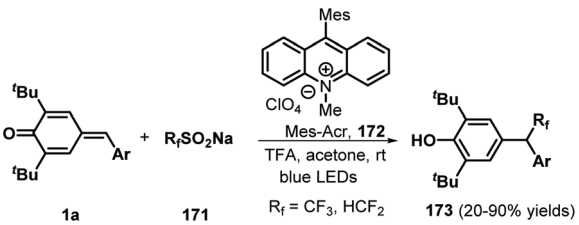

Scheme 33 Photocatalytic 1,6-hydrodifluoroacetylation of *p*-QMs.



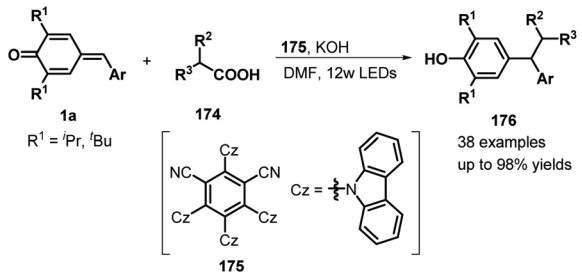

Scheme 34 Synthesis of cyanated diarylmethanes.

good yields. Unfortunately, a *p*-QM with a methyl moiety did not react, which may be attributable to the stability of the radical intermediate. The catalytic process is similar to that described for the above transformation.[54]

Similarly, difluoromethylated diarylmethanes **173** were obtained in high yields *via* visible-light-initiated photoredox catalysis of *p*-QMs **1a** and $CF_3SO_2Na$/$HCF_2SO_2Na$ **171** (Scheme 35).[55] It should be noted that the strong inductive effect of fluorine atoms may have played a critical role in the reactivity of the sodium sulfinates. A similar photocatalytic reaction for the trifluoromethylation of *p*-QMs **1a** was described by Sureshkumar and co-workers using 2,4,6-tri-*p*-tolylpyrylium tetrafluoroborate (T(*p*-$CH_3$)PPT) as the photo-




Scheme 35 Synthesis of difluoromethylated diarylmethanes.

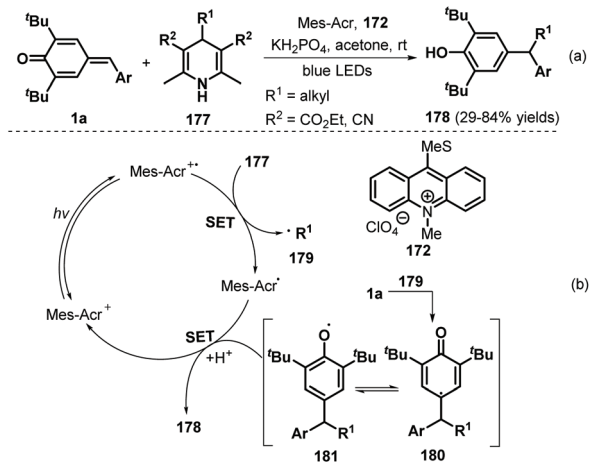



Scheme 36 Photocatalytic decarboxylation of carboxylic acids.

catalyst.[56] As a continuation of the above study, Lu, Weng, and co-workers developed a new photocatalytic decarboxylative 1,6-conjugate addition between carboxylic acids **174** and *p*-QMs **1a** to obtain 1,1,2-triarylethanes and 2,2-diarylethylamines **176** in good to excellent yields under metal-free conditions (Scheme 36). A range of structurally diverse (hetero)arylacetic, secondary fatty, and amino acids were suitable for this addition reaction. During this reaction, 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN) **175** served as a photocatalyst, accelerating decarboxylation of the carboxylic acid *via* SET.[57]

In 2018, the Liu group demonstrated the visible-light-initiated alkylation of *p*-QMs **1a** using 4-substituted Hantzsch esters/nitriles **177** as the alkyl radical precursor and $KH_2PO_4$ as an additive, which afforded a wide range of functionalized phenols **178** in reasonable yields (Scheme 37a).[58] Hantzsch esters/nitriles bearing various alkyl groups were compatible with this reaction, and the mechanism is very similar to that described in previous works,[56,57] consisting of SET and radical addition (Scheme 37b).

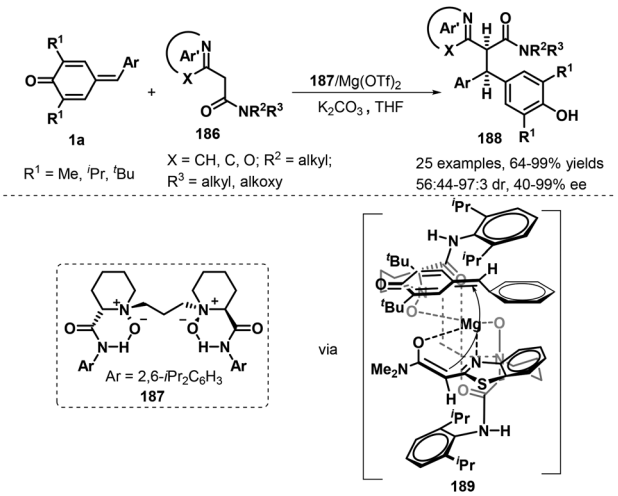
**2.1.7. Catalytic asymmetric 1,6-addition.** Catalytic asymmetric 1,6-addition reactions in recent years have proven to be a powerful tool for the generation of chiral molecules with important biological and medical interests in modern synthetic chemistry. As a versatile and readily available class of synthetic intermediates, *p*-QMs have been extensively used to construct chiral diarylmethane or triarylmethane frameworks




Scheme 37 Visible-light-initiated alkylation of *p*-QMs.

*via* asymmetric 1,6-conjugate addition. Consequently, efforts have been devoted to developing organocatalytic asymmetric nucleophilic addition between *p*-QMs and different nucleophiles. After recent comprehensive review highlighted by Li and co-workers,[9a] many elegant asymmetric transformations of *p*-QMs have been documented. Guin and co-worked developed a novel highly diastereo- and enantioselective 1,6-addition of 1,3-ketoamides **182** to *p*-QMs **1a** using chiral N-heterocyclic carbenes **183** as Brønsted base catalysts, furnishing the desired products **184** with 48–98% yields and high stereoselectivity (54 : 46–99 : 1 dr and 70–99% ee). A series of *p*-QMs **1a** with different substituents at both aromatic ring and quinone moiety were easily transformed into the corresponding products. Notably, this reaction could be extended to the alkylated *p*-QM as well, providing the expected product with 66% yield and 96% ee, albeit with an approximate 1 : 1 dr. Similarly, α-aroylacetamides with a methyl or an aryl group relative to carbonyl moiety and an aryl or a quinolin-8-yl functionality linked by amide unit were found to be applicable to this asymmetric reaction, furnishing the desired products in good yields and enantioselectivity. Some of these products could be applied to synthesize highly enantioenriched β and γ-lactam derivatives. On the basis of $^1$H NMR spectroscopy studies, it is believed that the reaction proceeds through a chiral ion-pair intermediate consisting of the enolate and the azolium ion (Scheme 38).[59]

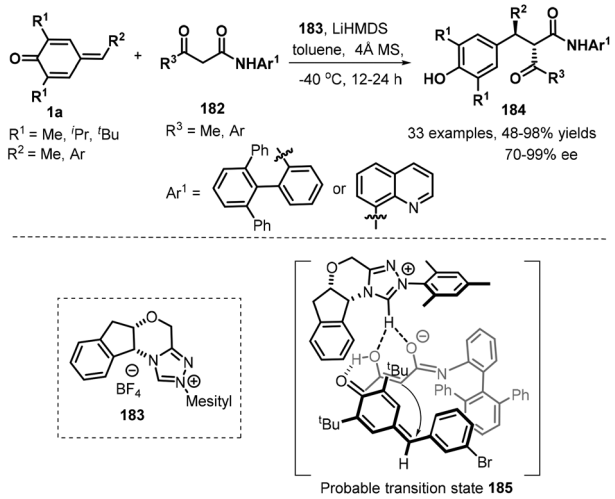
Another interesting catalytic asymmetric approach involving 1,6-addition to *p*-QMs **1a** was demonstrated by Feng's group. During the reaction process, chiral Mg(II)/*N*,*N*′-dioxide **187** complex could effectively promote the diastereo- and enantioselective 1,6-addition of azaarylacetamides **177** to *p*-QMs **1a**, and a series of chiral azaarene derivatives **186** were provided in 64–99% yields, 56 : 44→19 : 1 dr, and 87–99% ee. Various azaarylacetamides including benzothiazole, benzoxazole, pyridine, and pyrazine all reacted with *p*-QMs **1a** smoothly under the mild conditions. In addition, it is proposed that tetradentate *N*,*N*′-dioxide ligand and azaarylacetamides coordinates with the central metal Mg(II) to form a slightly distorted octahedral structural transition state. Because of the steric hinderance, the *Si*-face of the enolate of azaarylacetamides prefers to attack the *Si*-face of **1a** to afford chiral product **188** (Scheme 39).[60] This inference would be consistent with the experimental observations that decreasing the steric hindrance of *p*-QMs by replacing the *tert*-butyl group with an isopropyl or methyl resulted in reduced diastereoselectivity.




Scheme 39 1,6-Addition of 2-azaarylacetamides to *p*-QMs.

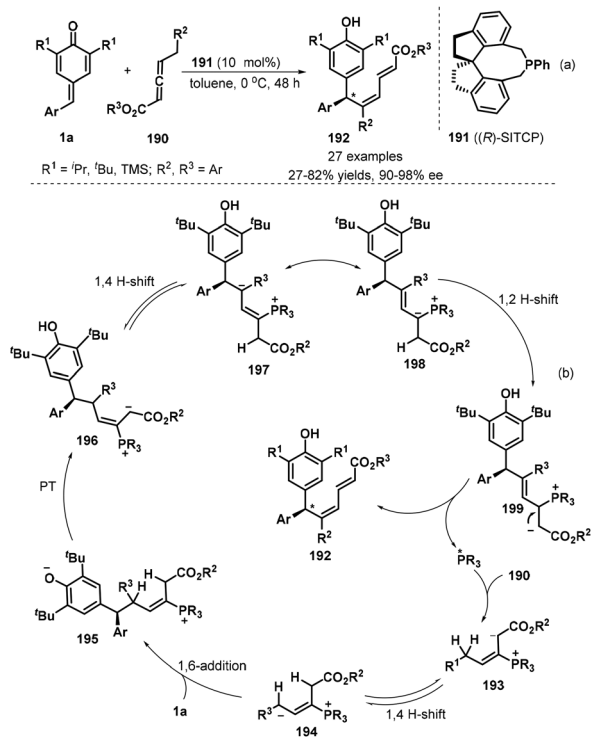
Xu and co-workers developed the first chiral phosphine-catalyzed isomerization/1,6-conjugate addition of substituted allenoates **190** to *p*-QMs **1a**. The reaction worked well in toluene in the presence of 10 mol% of (*R*)-SITCP **191** as a chiral phosphine catalyst at 0 °C without any additives in a one-pot, generating 27 chiral dienylated bisarylmethides **192** in 27–82% yields and 90–98% ee (Scheme 40a).[61] Various substituents such as *t*-butyl, i-propyl and TMS on the *p*-QM **1a** unit were compatible. However, the introduction of methyl group into *p*-QM framework led to severe decomposition with no desired product isolated. Besides aryl-substituted *p*-QMs, pyridine- and indole-containing counterparts also displayed good tolerance by obtaining in both good yield and high enantioselectivity. The proposed mechanism starts with nucleophilic addition of chiral phosphine *$PR_3$ to allenoates, which undergoes 1,4-H shift, 1,6-addition, proton transfer (PT) and 1,2-H shift to achieve the asymmetric dienylation reaction *p*-QMs (Scheme 40b).

Binaphthyl-based spiro ammonium salt proved to be a high-effieicent chiral phase-transfer catalyst (Maruoka PTC **201**), which could promote asymmetric 1,6-conjugate addition of isoxazolidin-5-ones **200** to *p*-QMs **1a**. A variety of differently substituted isoxazolidin-5-ones **200** and *p*-QMs **1a** were performed similarly in the reaction, giving access to 25 examples of functionalized isoxazolidin-5-one derivatives **202** in good yields (70–99% yields) and with excellent enantioselectivities (96.5→99.5% ee) and good diastereoselectivities (4 : 1 to 20 : 1 dr, Scheme 41).[62] *N*-Cbz-protected isoxazolidin-5-one enabled

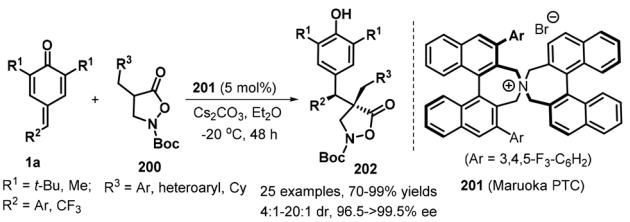



Scheme 38 NHC-Catalyzed asymmetric 1,6-addition of *p*-QMs.



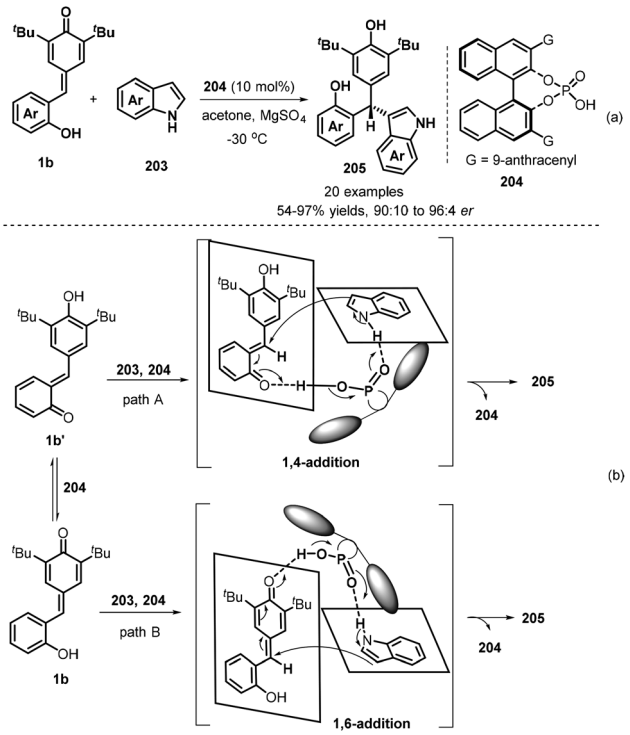

Scheme 40 Enantioselective dienylation of *p*-QMs.




Scheme 41 Asymmetric 1,6-addition of isoxazolidin-5-ones to *p*-QMs.

a similarly highly enantioselective direction to access the corrosponding product, despite with lower yield of 35%. The authors also demnstarted late-stage appliation of these products for the preapration of *N*-protected β-amino acid and dipeptide.

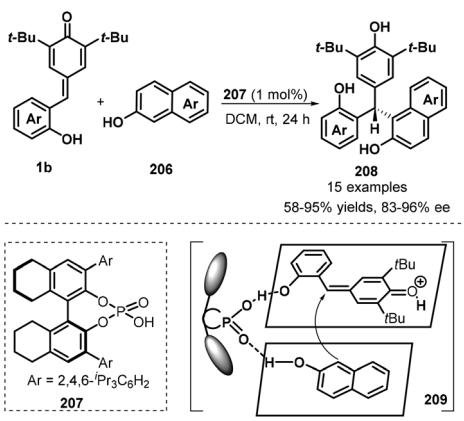
Hydrogen bonding activation of chiral phosphoric acids has applied in asymmetric 1,6-conjugate addition of *p*-QMs, which also exhibits high enantioselectivity. Since the pioneering work of chiral phosphoric acids-catalysed 1,6-addition of *p*-QMs reported by Sun's group,[63] many asymmetric versions were developed by using different nucleophilies. In 2019, Shi and co-workers established a catalytic asymmetric conjugate 1,6-addition of indoles **203** to *p*-QMs **1b** in the presence of chiral phosphoric acid **204** and using acetone as solvent in −30 °C for 12 hours, which afforded chiral indole-containing triarylmethanes **205** in generally high yields (54–98%) and good enantioselectivities (90 : 10–96 : 4 er, Scheme 42a). By conducting control experiments, the authors believed that the



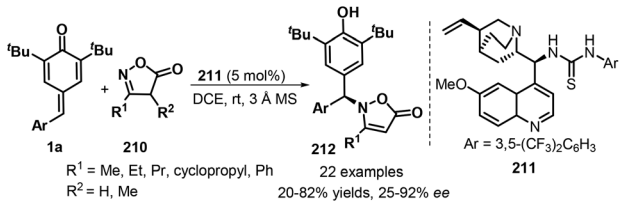

Scheme 42 Asymmetric addition of indoles to *p*-QMs.

reaction had a great possibility to undergo 1,4-conjugate addition of indoles to *in situ*-generated *o*-QMs **1b′** from **1b** in the presence of chiral phosphoric acid, although its 1,6-conjugate addition pathway may occur (Scheme 42b).[64]

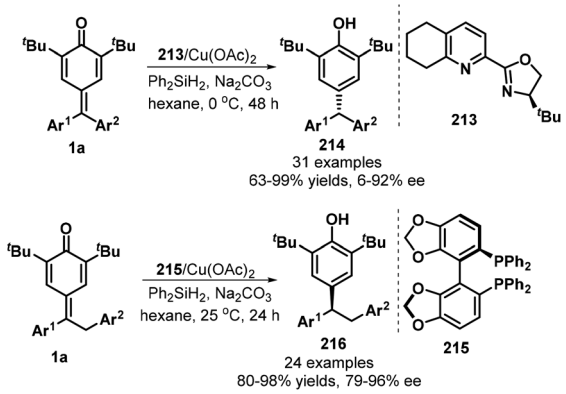
Another example of the application of chiral phosphoric acid **207** as a Brønsted catalyst in asymmetric 1,6-conjugate addition of *p*-QMs **1b** was reported by Li and co-workers (Scheme 43).[65] In this work, 2-naphthols **206** were selected as *C*-nucleophiles, enabling the enantioselective addition to *p*-QMs **1b** to construct chiral naphthol-containing triarylmethane skeleton **208**. This strategy not only was applicable to various *p*-QMs **1b** bearing different types of substituents but




Scheme 43 Enantioselective addition of 2-naphthols to *p*-QMs.




Scheme 44 Asymmetric 1,6-aza-Michael addition to *p*-QMs **1a**.




Scheme 45 Asymmetric 1,6-conjugate reduction of *p*-QMs.

also could carry out with various substituents including electron-withdrawing (Br, CN, $CO_2Me$, $CO_2Et$) and electron-donating groups (MeO, EtO) at different positions of the aromatic ring of the 2-naphthols **206**, giving generally good yields (58–95%) and high enantioselectivities (83–96%). The proposed mechanism is analogue to Shi's protocol, in which 1,4-conjugate addition of 2-naphthols **206** to *in situ*-generated *o*-QMs **1b′** from **1b** proceeds in the presence of chiral phosphoric acid.

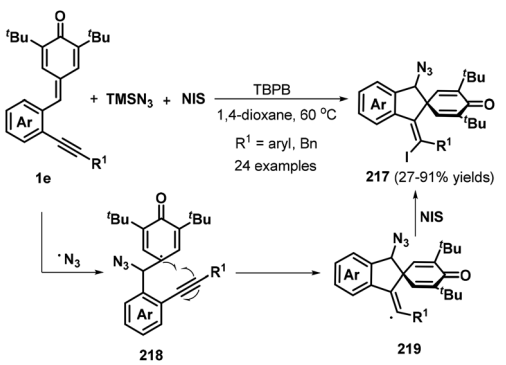
An impressive protocol involving the asymmetric 1,6-aza-Michael addition to *p*-QMs **1a** was described by Blay and co-workers in 2020. Here, quinine-derived thiourea **211** as a bifunctional catalyst was adopted in the presence of 3 Å molecular sieve (MS) to promote the enantioselective 1,6-aza-addition reaction between *p*-QMs **1a** and isoxazolinones **210** as *N*-nucleophiles, leading to chiral isoxazolinone-containing diarylmethanes **212** with moderate to good yields (20–82%) and enantioselectivity (25–92% ee). Notably, for a same substituent in *p*-QMs **1a**, *ortho*- or *para*-substituted rings showed higher reactivity profiles than *meta*-substituted ones (Scheme 44).[66]

Chiral copper complexes could be applied in the asymmetric 1,6-conjugate reduction of *p*-QMs, as demonstrated by Fan's group in 2019 (Scheme 45).[67] By using tetrahydroQuinox **213** as ligand and $Ph_2SiH_2$ as hydrogen source, CuH-catalyzed reaction of diarylated *p*-QMs **1a** in the presence of $Na_2CO_3$ in hexane at 0 °C provided chiral triarylmethanes **214** in good yields (63–99%) with high enantioselectivities (up to 96% ee). When benzyl-substituted *p*-QMs were exploited as 1,6-addition acceptors, the combination of $Cu(OAc)_2$ with 4,4′-bi-1,3-benzodioxole-5,5′-diylbis(diphenylphosphane) (SEGPHOS, **215**) ligand drove this transformation into 24 examples of 1,1,2-triarylethanes **216** in 80–98% yields with 79–96% ee. Generally, *meta*- and *para*-substituted *p*-QMs were reduced to the triarylmethanes with low enantioselectivities.

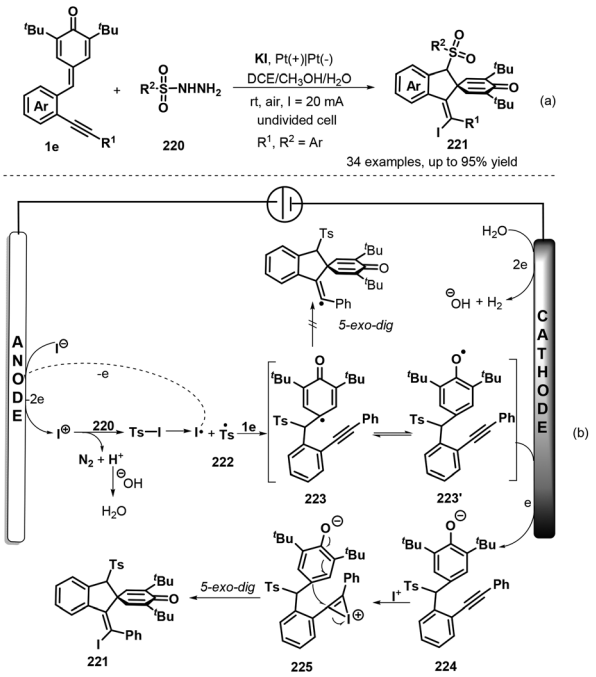
## 2.2. 1,6-Addition/annulation reactions of *p*-QMs

**2.2.1. 1,6-Addition/intramolecular annulation of *p*-QMs.** *o*-Alkynylphenyl-substituted *p*-QMs containing both alkene and alkyne moieties have emerged as versatile 1,5-enyne equivalents with high reactivity toward 1,6-addition/intramolecular annulation reactions. Owing to the differences in the electronic properties of the alkene and alkyne moieties and the aromatization driving force of the cyclohexadiene ring, radical species and nucleophiles preferentially attack the alkene unit *via* 1,6-addition followed by intramolecular cyclization across the alkyne moiety to form useful spiro-cyclohexadiene targets with excellent regioselectivity. In a seminal report, Yao, Lin, and co-workers documented an elegant 1,6-addition/intramolecular annulation for the direct conversion of *o*-alkynylphenyl-substituted *p*-QMs **1e** to functionalized spiro[4.5]deca-6,9-dien-8-ones **217** (Scheme 46). In this process, $TMSN_3$ first reacts with *tert*-butyl peroxybenzoate (TBPB) to generate the $N_3$ radical, which then undergoes radical addition to the *o*-alkynylphenyl-substituted *p*-QM. Subsequent 5-*exo*-*dig* cyclization yields vinyl radical **219**, which is trapped by *N*-iodosuccinimide (NIS) to furnish the corresponding product **217** in good to excellent yields.[68] This three-component protocol permits the direct construction of three new σ bonds (C–N, C–C, and C–I) in a one-pot process with complete chemo- and regioselectivity.

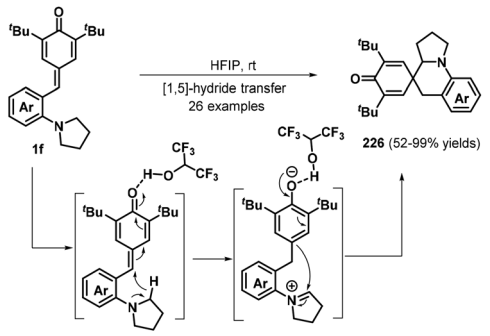
To develop practical and green methods to construct these skeletons, recently, Jiang, Tu and co-workers established an electrochemical three-component annulation-iodosulfonylation of *p*-QMs **1e** by using available arylsulfonyl hydrazides **220** and potassium iodide under environmentally benign conditions, offering a sustainable and efficient access to construct 34 examples of spirocyclohexadienone-containing (*E*)-indenes **221** in 30%–95% yields (Scheme 47a).[69] However, substrate with a *n*-butyl or a cyclopropyl group on the alkynyl moiety of *p*-QMs was not adaptable for this reaction Notably, potassium



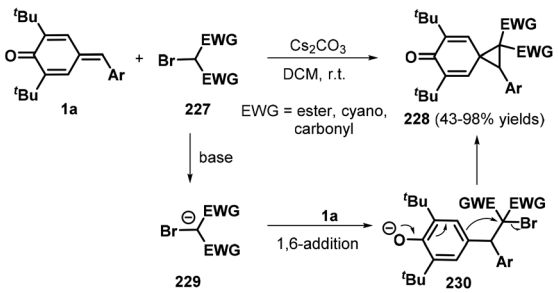

Scheme 46 Three-component reaction of *p*-QMs with $TMSN_3$ and NIS.




Scheme 47 Electrochemical three-component annulation-iodosulfonylation of *p*-QMs.




Scheme 48 Intramolecular annulation of *p*-QMs.

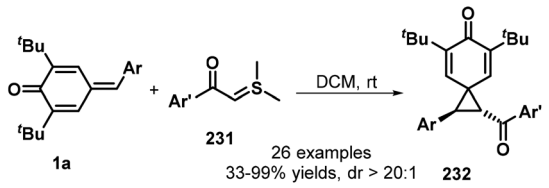



Scheme 49 [2 + 1] annulation of *p*-QMs with α-bromomalonates.

iodide plays triple roles of an electrolyte and a redox catalyst as well as an iodination reagent. Based on the control experiments, the authors proposed a plausible mechanism depicted in Scheme 47b. Initially, the anodic oxidation of iodide ion generates iodonium $I^+$ with losing two electrons, which reacts with *p*-tolylsulfonyl hydrazide **220** to give arylsulfonyl iodide intermediate, followed by homolysis to yield arylsulfonyl radical **222** and iodine radical. The latter was converted into $I^+$ species by electric current whereas sulfonyl radical **222** adds to activated carbon–carbon double bond of *p*-QM **1e** through 1,6-addition, generating cyclohexadienone radical **223**, which undergoes aromatic zwitterionic resonances to access phenol radical **223′**. Then, the cathodic reduction of intermediate **223′** occurs to produce phenol anion **224**. Subsequently, iodonium $I^+$ is intercepted by carbon–carbon triple bond of **224** to yield highly reactive intermediate **225**, which is converted into the final product **221** through intramolecular *ipso*-cyclization. The concomitant cathodic half-reaction involves the reduction of two protons to $H_2$.

As a different approach for realizing the 1,6-addition/intramolecular annulation of *p*-QMs, the Xiao group prepared *o*-pyrrolidin-1-ylphenyl-substituted *p*-QMs **1f** and transformed these compounds into 2-azaspiro[5.5]undeca-7,10-dien-9-ones **226** *via* hydrogen-bonding-activated [1,5]-hydride transfer[70] and 1,2-addition in hexafluoroisopropanol (HFIP) (Schemes 48). Furthermore, an *o*-dimethylaminophenyl analogue also proved suitable for this transformation. Nevertheless, substrates containing electron-donating substituents such as methyl and methoxy groups afforded complex mixtures that were difficult to purify.[70a]

**2.2.2. 1,6-Addition/[2 + 1] annulation of *p*-QMs.** Annulation reactions remain a hot topic in modern organic synthesis as they provide a facile method for synthesizing large functionalized cyclic molecular libraries with precisely defined stereochemical arrangements from simple precursors with high step economy, efficiency, and scalability. Specifically, [2 + 1] annulation has been recognized as an important and step-economical synthetic strategy for the assembly of three-membered rings with an extreme convergence. Owing to their ring tension, such targets could exhibit unique reactivity profiles that enable their direct ring-opening/expansion to construct valuable molecular architectures that are not accessible *via* other methods. Thus, the development of [2 + 1] annulation for small-ring synthesis is of substantial interest.[71] To this end, the Lin and Yao group explored a 1,6-conjugate addition/[2 + 1] annulation strategy for the formation of spiro[2.5]octa-4,7-dien-6-ones **228** from *p*-QMs **1a** and α-bromomalonates **227** under $Cs_2CO_3$-promoted conditions (Scheme 49). All of the desired products contained two consecutive quaternary centers and were obtained in high yields of up to 98%. Various electron-withdrawing groups, such as allyl ester, cyano, and carbonyl moieties, were well tolerated in this reaction, affording the desired products in good yields. The authors proposed a mechanism involving 1,6-conjugate addition and intramolecular nucleophilic substitution.[72] Exchanging the α-bromomalonates for benzyl chlorides successfully afforded spiro[2.5]octa-4,7-dien-6-ones **228** *via* $Cs_2CO_3$-mediated tandem 1,6-addition/[2 + 1] annulation.[73]

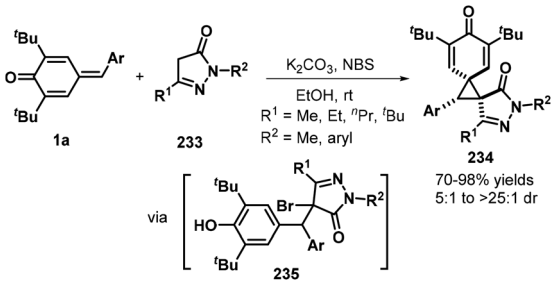



Scheme 50 [2 + 1] annulation of *p*-QMs with sulfur ylides.

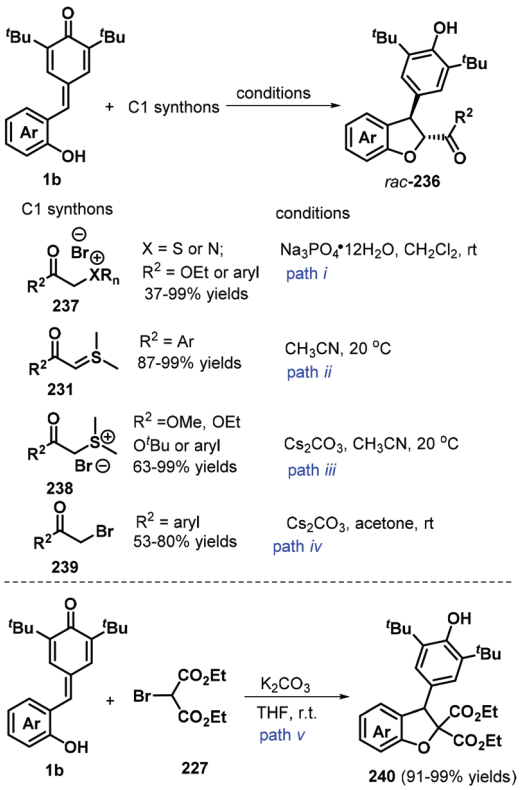
In a similar manner, the same group then exploited sulfur ylides **231** as the C1 synthon in this 1,6-conjugate addition/[2 + 1] annulation (Scheme 50). This reaction proceeded smoothly in DCM at ambient temperature without any catalyst or base, affording the functionalized spiro[2.5]octa-4,7-dien-6-ones **232** in 33–99% yields with >20 : 1 dr. This transformation also exhibited good functional group tolerance and scalability.[74] A similar reaction between *p*-QMs **1a** and sulfonium salts in the presence of DBU was reported by Fan and co-workers.[75]

Das and co-workers reported an *N*-bromosuccinimide (NBS)-mediated reaction between *p*-QMs **1a** and pyrazolones **233**, which afforded a series of new bis-spiro[cyclohexadienone–cyclopropane–pyrazolone] compounds **234** in good yields and diastereoselectivity. Pyrazolones **233** containing various aryl and alkyl nitrogen-protecting groups and C5 substituents were well tolerated, furnishing the corresponding bis-pirocyclic products in 70–98% yields and dr values of 5 : 1 to >25 : 1. However, substrates containing either phenyl or trifluoromethyl groups at the pyrazolone C5 position did not undergo spirocyclization. A plausible mechanism consists of 1,6-conjugate addition, bromination, and de-aromatic nucleophilic substitution (Scheme 51).[76]

**2.2.3. 1,6-Addition/[4 + 1] annulation of *p*-QMs.** 2,3-Dihydrobenzofurans are among the most important and versatile oxygen-containing heterocycles and frequently occur in many natural and synthetic bioactive compounds, such as those exhibiting remarkable anticancer or antibacterial activities.[77] The 1,6-addition/[4 + 1] annulation of *o*-hydroxyphenyl-substituted *p*-QMs using one-carbon synthons offers a convenient and mild strategy for the preparation of 2,3-dihydrobenzofuran derivatives. For instance, the Huang and Yao group reported an impressive method for synthesizing *trans*-2,3-dihydrobenzofurans **236** *via* the 1,6-addition/[4 + 1] annulation of *o*-hydroxyphenyl-substituted *p*-QM **1b** using sulfonium




Scheme 51 NBS-Mediated reaction of *p*-QMs and pyrazolones.

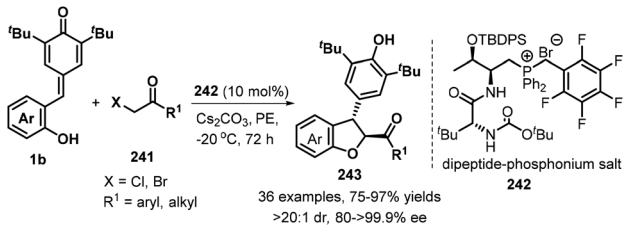



Scheme 52 [4 + 1] annulation toward 2,3-dihydrobenzofurans.

or ammonium bromides **238** (Scheme 52, path i).[78] This transformation afforded a series of products in 34–99% yields with high diastereoselectivity (>20 : 1 dr). This domino-type process featured good functional group tolerance and scalability, mild reaction conditions, high yields of up to 99%, and high stereoselectivity. However, in this report, a sulfonium salt containing an alkyl ester group provided the corresponding product in only low yield (37%).[78] The reaction proceeds *via* 1,6-conjugate addition, proton transfer, and intramolecular $S_N2$ nucleophilic substitution. In subsequent works, sulfur ylides **231** (Scheme 52, path ii),[79] sulfonium salts **238** (Scheme 52, path iii),[80] α-haloketones **239** (Scheme 52, path iv),[81] and α-bromomalonates **227** (Scheme 52, path v)[82] were applied as $C_1$ synthons and independently reacted with *o*-hydroxyphenyl-substituted *p*-QM **1b** in similar 1,6-addition/[4 + 1] annulation processes, affording 2,3-dihydrobenzofurans **236** and **240**.

As demonstrated in the above examples, the synthesis of achiral 2,3-dihydrobenzofurans from *p*-QMs has been well-developed. In contrast, catalytic asymmetric [4 + 1] annulation reaction of *p*-QMs toward optically pure 2,3-dihydrobenzofurans still constitutes a daunting challenge. Until 2019, Wang's group reported the first catalytic enantioselective 1,6-addition/[4 + 1] annulation of *p*-QMs **1b** and α-halogenated ketones **241** by employing O-TBDPS-protected L-Thr-D-*tert*-Leu-derived phosphonium salt **242** as a bifunctional catalyst. They discovered that the bifunctional catalyst promotes this transformation in petroleum ether (PE) in the presence of $Cs_2CO_3$, fur-

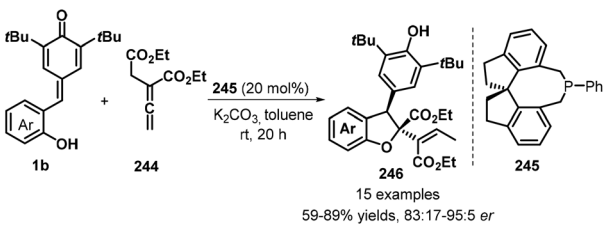



**Scheme 53** [4 + 1] annulation reaction between *p*-QMs and α-halogenated ketones.

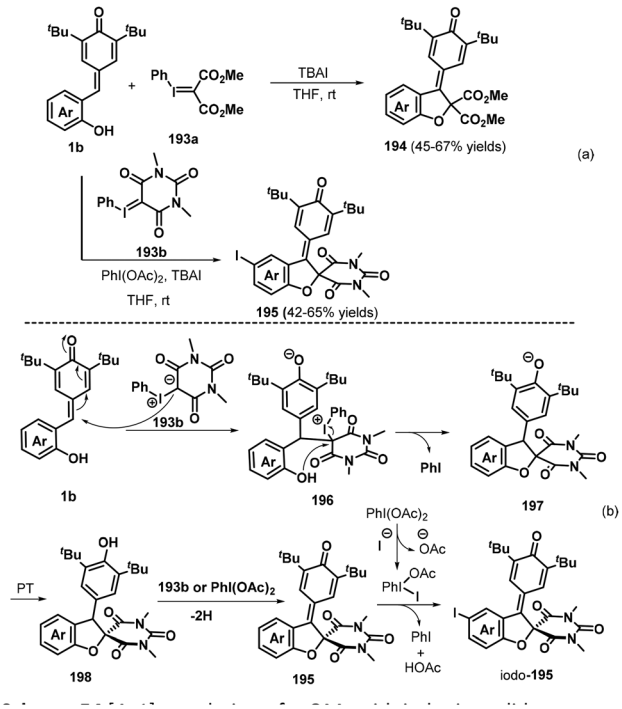
nishing functionalized *trans*-2,3-dihydrobenzofurans **243** exclusively with high enantioselectivities. α-Halogenated ketones **241** having electron-withdrawing and -donating aromatic groups were tolerated, as well as cyclic ketones such as 3,4-dihydronaphthalen-1(2*H*)-one and benzofuran-3(2*H*)-one and bulky alkyl group such as *t*-butyl group. Mechanistic studies supported the annulation cascade consisting of intermolecular nucleophilic substitution and subsequent intramolecular 1,6-addition. Furthermore, the authors also elaborated a triad of hydrogen-bonding interactions in the L-Thr-derived dipeptide system for the key to the high enantioselectivity of this catalytic reaction by conducting DFT calculations (Scheme 53).[83]

A relatively new development in this area is the use of allenoates as C1 synthons for [4 + 1] annulation. Waser group's research revealed the use of commercially available (*R*)-SITCP **245** as a chiral spiro phosphine catalyst promotes the reaction of **1b** with allenoates **244** to give enantioenriched dihydrobenzofurans 246 as single diastereomers in yields up to 90% and with up to 95 : 5 er (Scheme 54).[84] This methodology could tolerate benzyl and ethyl esters. The extension of this procedure to *tert*-butyl ester was found to be suitable, but with somewhat lower enantiomeric ratios.

By using acyclic and cyclic phenyl iodonium ylides **247a** and **247b** as the $C_1$ component, Tu, Jiang, and co-workers recently presented a new dehydrogenative [4 + 1] annulation of *o*-hydroxyphenyl-substituted *p*-QM **1b** without any base or acid promoter (Scheme 55a).[85] This method provided facile and direct access to a wide range of 2,3-dihydrobenzofurans **248** and **249** with retention of the *p*-QM moiety. Notably, when C4-unsubstituted *p*-QM **1b** was reacted with **247b** in the presence of 1.0 equivalents of iodobenzene diacetate ($PhI(OAc)_2$), all of the reactions proceeded readily to afford the corresponding




**Scheme 54** Enantioselective catalytic [4 + 1]-cyclization of *p*-QMs with allenoates.

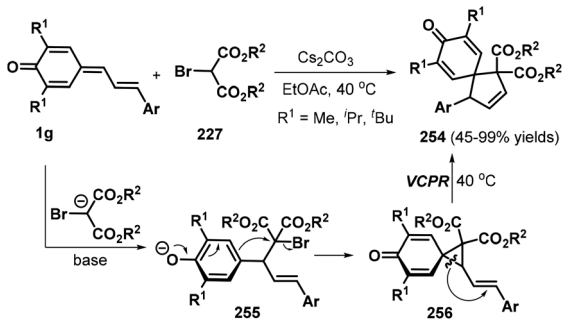



**Scheme 55** [4 + 1] annulation of *p*-QMs with iodonium ylides.

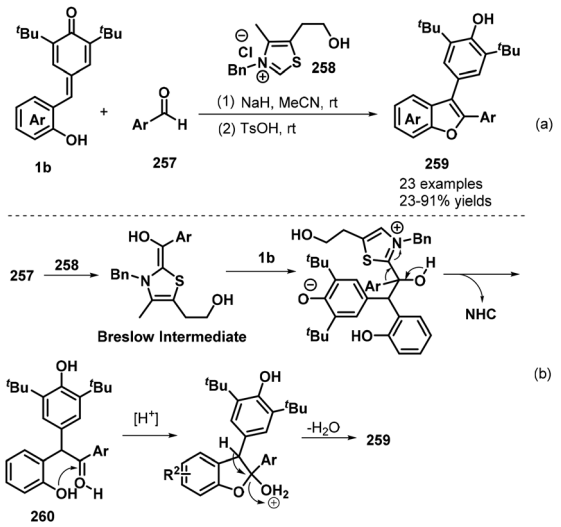
spiro products with C4 iodination of the phenol ring. The phenyl iodonium ylides **247** played a dual role as both a reaction component and an oxidant in this transformation. The reaction pathway involves successive 1,6-nucleophilic addition, proton transfer, nucleophilic substitution, and oxidation (Scheme 55b).

An interesting tandem [4 + 1] annulation between vinylogous *p*-QMs **1g** and 2-bromomalonates **227** was disclosed by Yao, Lin, and co-workers. In the presence of $Cs_2CO_3$, the reaction proceeded *via* sequential 1,6-conjugate addition, cyclization, and vinylcyclopropane rearrangement (VCPR) to provide access to 26 examples of spiro[4.5]cyclohexadienones **254** in 45–99% yields.[86] The authors also proposed a plausible mechanism for this transformation. Under basic conditions, 2-bromomalonate **227** is converted to a 2-bromomalonate carbanion, which engages in nucleophilic 1,6-conjugate addition to the vinylogous *p*-QM **1g** to generate intermediate **255**. This intermediate then undergoes an intramolecular ring closure reaction to form the key three-membered spiro intermediate **256**, which smoothly undergoes VCPR to furnish the product **254** upon increasing the temperature to 40 °C (Scheme 56).

In subsequent work, the Anand group prepared 2,3-diarylbenzo[*b*]furans **259** *via* an NHC-catalyzed 1,6-conjugate addition of aromatic aldehydes **257** to *o*-hydroxyphenyl-substituted *p*-QMs **1b** followed by a TsOH-promoted dehydrative annulation reaction (Scheme 57a).[87] This one-pot protocol proceeded well for various aldehydes bearing electron-poor, sterically hindered, and heteroaromatic substituents, although ali-



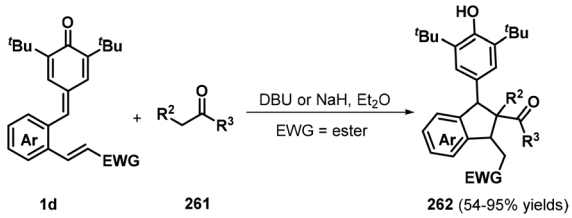

Scheme 56 [4 + 1] annulation of *p*-QMs with 2-bromomalonates.




Scheme 57 NHC-Catalyzed synthesis of 2,3-diarylbenzo[*b*]furans.

phatic aldehydes were very sluggish to react and resulted in only poor product yields. The one-pot [4 + 1] annulation involved two steps. The proposed mechanism involves generation of the Breslow intermediate from the aromatic aldehyde **257** and the NHC, 1,6-conjugate addition, regeneration of the NHC catalyst, oxo-cyclization, and dehydration (Scheme 57b).

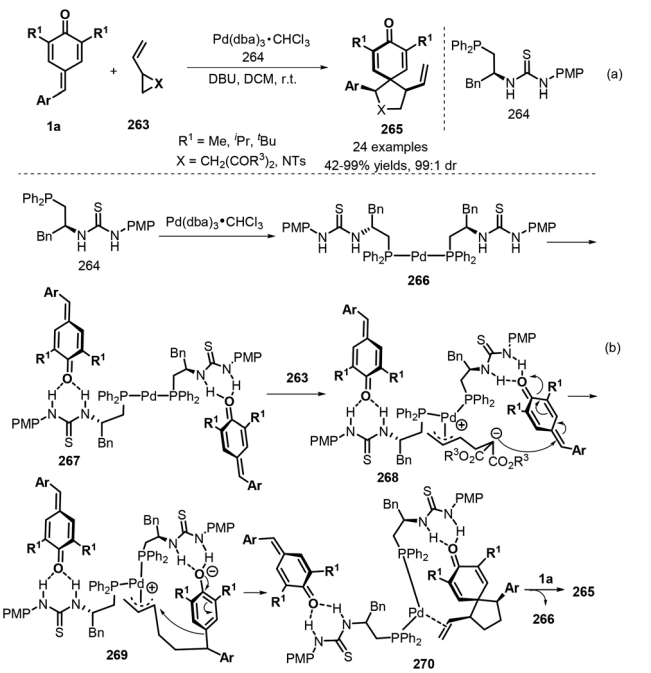
To further expand the variety and applicability of *p*-QMs, Yao, Huang, and a co-worker introduced a vinyl ester or vinyl sulfone into the phenyl ring of *p*-QMs to prepare *o*-vinyl ester or *o*-vinyl sulfone substituted *p*-QMs **1d** and reacted these compounds with various carbon nucleophiles **261** in the presence



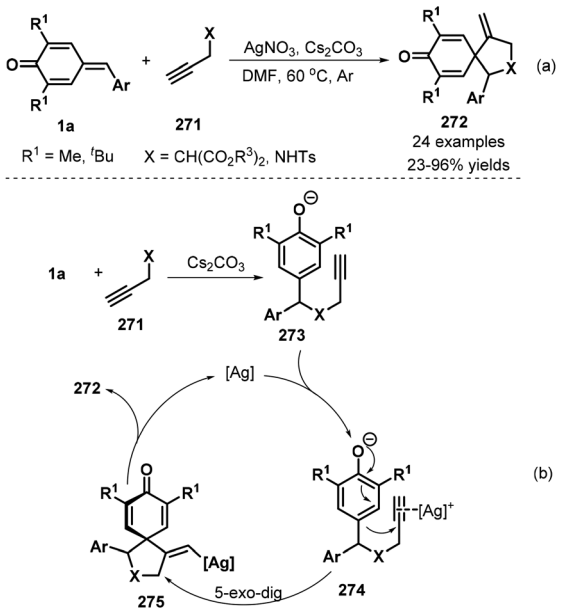

Scheme 58 Base-mediated synthesis of indanes.

of DBU or NaH, which furnished a wide range of functionalized indanes 262 with good yields (Scheme 58). Various carbon nucleophiles such as malonate esters, pentane-2,4-dione, indene-1,3-dione, 1,3-dimethylbarbituric acid, and acetophenone successfully participated in this reaction. In addition, isoindolines were obtained by reacting the *p*-QMs with *p*-toluenesulfonamide as a nitrogen nucleophile in the presence of a base, which proceeded *via* tandem 1,6-conjugate addition/1,4-Michael addition. The authors also attempted to use aniline and benzylamine as nitrogen nucleophiles to further extend the utility of this reaction, although these reactions were unsuccessful.[88]

**2.2.4. 1,6-Addition/[3 + 2] annulation of *p*-QMs.** Spirocyclohexadienones are important structures that constitute the core unit of a myriad of natural products with a broad spectrum of biological activities, such as spirobacillene A, stepharine, and annosqualine.[89] Furthermore, spirocyclohexadienones are versatile intermediates in the synthesis of important alkaloids and related products.[90] In this context, [3 + 2] annulation reactions involving *p*-QMs have emerged as a useful strategy for the preparation of these compounds. Yao, Lin, and co-workers pioneered a new 1,6-addition/[3 + 2] annulation reaction using *p*-QMs **1a** and vinylcyclopropanes **263**, in which the reactivity and diastereoselectivity could be adequately controlled *via* a palladium/phosphine-thiourea co-catalytic system (Scheme 59a).[91] A wide variety of vinylcyclopropanes and 1-tosyl-2-vinylaziridine underwent this reaction to afford spirocyclohexadienones **265** in high yields and diastereoselectivities. Mechanistically, phosphine–Pd(II) complex **266** is first formed from the palladium source and phosphine–thiourea, which then activates *p*-QM **1a** through intermolecular




Scheme 59 [3 + 2] annulation of *p*-QMs with vinylcyclopropanes.

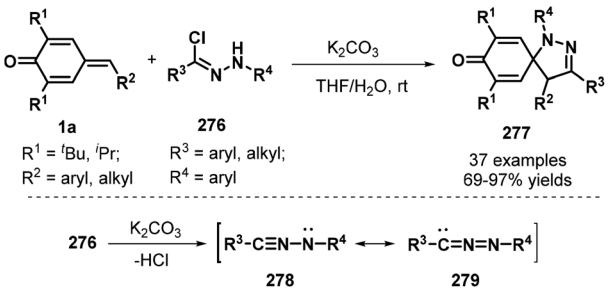



Scheme 60 [3 + 2] annulation toward spirocyclohexadienones.

hydrogen-bond interactions to generate complex **267** (Scheme 59b). Then, activated zwitterionic π-allylpalladium species **268** is produced *via* ring opening of vinylcyclopropane **263**. Subsequent 1,6-conjugate addition of the carbanion moiety to *p*-QM **1a** affords intermediate **269**, followed by ring closure and de-aromatization to generate complex **270**. Disassociation of this complex yields the product **265** and regenerates the catalyst **266** for the next catalytic cycle.

Following the above success, the same group also synthesized spirocyclohexadienones **272** using propargyl malonates **271** as the nucleophiles *via* silver-catalyzed cascade 1,6-addition/5-*exo-dig* cyclization (Scheme 60a).[92] Various ester substituents, namely, dimethyl, diethyl, diisopropyl, di-*tert*-butyl, and dibenzyl, were compatible with this reaction. The procedure also tolerated propargyl *p*-toluenesulfonamide, albeit with low yield. However, internal alkynes did not undergo the reaction. The first step of this reaction is 1,6-addition of *p*-QM **1a** to propargyl malonate **271** in the presence of $Cs_2CO_3$ to generate intermediate **273** (Scheme 60b). This intermediate coordinates with the silver catalyst to form intermediate **274**, followed by 5-*exo-dig* cyclization to afford vinyl-silver intermediate **275**, which is converted to spirocyclic product **272** *via* protodemetalation with regeneration of the silver catalyst for the next catalytic cycle.

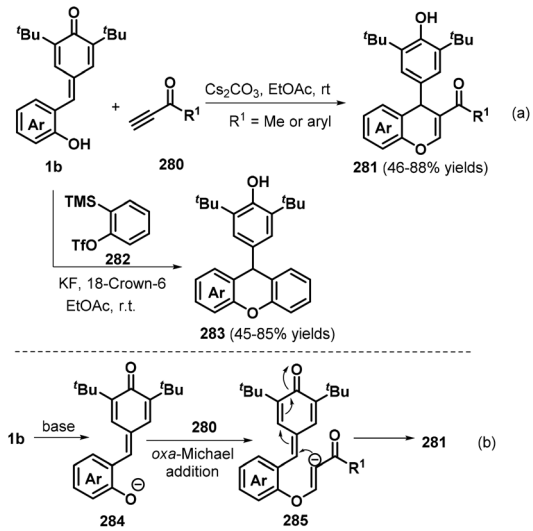
To further broaden the diversity of spirocyclohexadienones, Su and co-workers developed an impressive [3 + 2] cycloaddition between *p*-QMs **1a** and hydrazonyl chlorides**276** in the presence of $K_2CO_3$, which proceeded with complete regioselectivity to afford spiro-pyrazoline-cyclohexadienone products **277** in 69–97% yields (Scheme 61). The mechanistic pathway involves *in situ* generation of a nitrile imine with two resonance structures, namely, propargylic 278 and allenic 279,



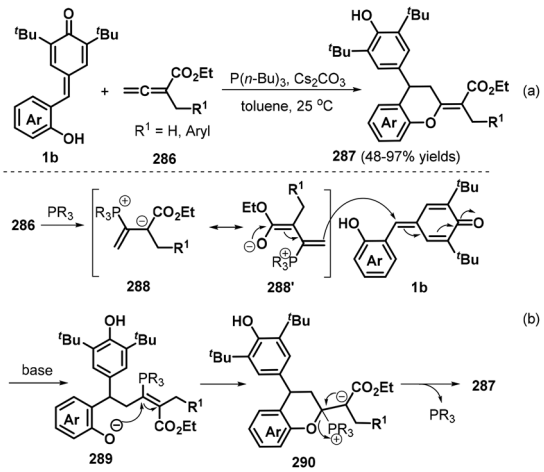

Scheme 61 [3 + 2] annulation of *p*-QMs with hydrazonyl chlorides.

*via* the base-mediated dehydrochlorination of **276**, followed by [3 + 2] cycloaddition.[93]

**2.2.5. 1,6-Addition/[4 + 2] annulation of *p*-QMs.** Chromanes and their derivatives constitute a privileged and fascinating class of oxygen-containing frameworks that are commonly found in numerous natural products, synthetic substances, and medicinally relevant compounds.[94] To construct these versatile molecules, the Shi group pioneered a new $Cs_2CO_3$-promoted [4 + 2] cyclization between *o*-hydroxyphenyl-substituted *p*-QMs **1b** and ynones **280**, which efficiently delivered a range of functionalized chromenes **281** with generally good yields (Scheme 62a). The reaction also worked well upon replacing the ynone component with benzyne precursor **282** in the presence of KF and 18-crown-6 at room temperature, furnishing the corresponding functionalized xanthene **283** in good yields.[95] Investigation of the reaction mechanism indicated that the [4 + 2] cyclization is initiated by the deprotonation of *p*-QM **1b** under basic conditions to generate the strongly nucleophilic intermediate **284**, which attacks ynone **280** *via* nucleophilic addition to afford intermediate **285**, followed by intramolecular 1,6-conjugate addition to yield the desired product **281** (Scheme 62b). Product **283** was formed *via* a similar pathway. Shortly after, He *et al.* reported a similar




Scheme 62 [4 + 2] annulation of *p*-QMs with alkynes.



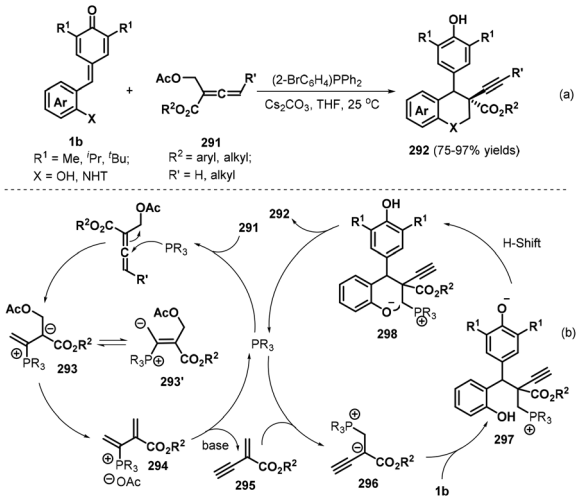
Scheme 63 Phosphine-catalyzed [4 + 2] annulation of *p*-QMs.

1,6-addition/[4 + 2] annulation reaction between *p*-QMs **1b** and benzyne precursor **282**.[96]

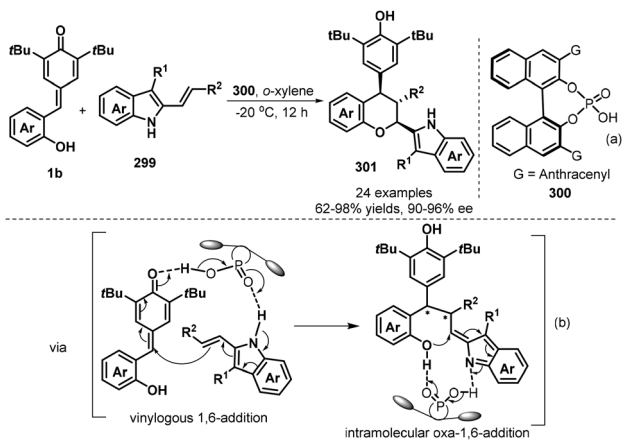
In a subsequent publication, the Shi group also documented an elegant phosphine-catalyzed [4 + 2] annulation between *o*-hydroxyphenyl-substituted *p*-QMs **1b** and α-substituted allenoates **286** to afford a series of functionalized chroman derivatives **287** in 48–97% yields with complete (*E*) selectivity (Scheme 63a).[97] When the $R^1$ group of the allene component was ethyl or isopropyl, the reaction afforded a complex mixture of products. The proposed reaction mechanism involves activation of allene ester **286** by the phosphine catalyst to generate intermediate **288** and its isomer **288′**, followed by 1,6-conjugate addition of the *p*-QM **1b** to afford transient intermediate **289**, which undergoes intramolecular nucleophilic addition and elimination of the phosphine catalyst to yield the final product **287** (Scheme 63b).

Almost simultaneously, Huang and co-workers reported another interesting phosphine-catalyzed [4 + 2] cycloaddition between *p*-QMs **1b** and α-substituted allenoates **291**, which provided 29 examples of chroman and tetrahydroquinoline derivatives **292** bearing an alkynyl-substituted quaternary carbon in up to 97% yield and 20 : 1 dr (Scheme 64a).[98] Both internal and terminal alkynes could be constructed at the quaternary carbon center of the chroman products by using $(2\text{-}BrC_6H_4)PPh_2$ (20 mol%) as the catalyst and $Cs_2CO_3$ (2.4 equivalents) as the base. Allenes containing an alkyl substituent and various aromatic rings in the ester moiety, including benzyl, *o*-fluorobenzyl, 3,5-bis-trifluoromethylbenzyl, and heteroaryl, were found to be well tolerated, with the desired products obtained in high yields with moderate dr values. Importantly, this domino process provided internal alkynes without loss of reactivity when γ-substituted allenes were used. According to the proposed mechanism, this reaction is initiated by nucleophilic attack of the phosphine catalyst on the α-substituted allenoate **291** to form intermediates **293** and **293′**, followed by elimination of an acetate group and the phosphine catalyst under basic conditions to generate 1,3-enyne intermediate **295** (Scheme 64b). Subsequent nucleophilic addition of the phosphine catalyst to **295** produces intermediate **296**, which undergoes 1,6-conjugate addition to *p*-QM **1b** to afford intermediate **297**. Finally, intermediate **297** is transformed into the target compound through proton transfer and nucleophilic cyclization with release of the phosphine catalyst.

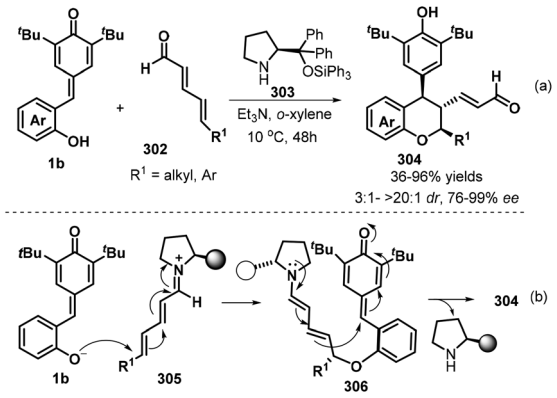
The emergence of organocatalysis opened a new opportunity in catalytic asymmetric [4 + 2] annulation of *p*-QMs for the synthesis of enantioenriched chromanes. In 2018, Shi and co-workers succeeded in realizing the first catalytic asymmetric [4 + 2] cyclization of *p*-QMs **1b** with electron-rich alkenes **299** by using chiral phosphoric acid **300** (Scheme 65a).[99] They discovered that a catalytic amount of chiral phosphoric acid facilitates the reaction of **1b** with 3-alkyl-2-vinylindoles bearing various substituents efficiently, affording chiral chromanes products **301** in good yields (63–98%) with high diastereoselectivities (78 : 22→95 : 5 dr) and excellent enantioselectivities (90–96% ee). The mechanism is considered to undergo



Scheme 64 [4 + 2] annulation of *p*-QMs with allenoates.



Scheme 65 Asymmetric [4 + 2] cyclization of *p*-QMs with 3-alkyl-2-vinylindoles.

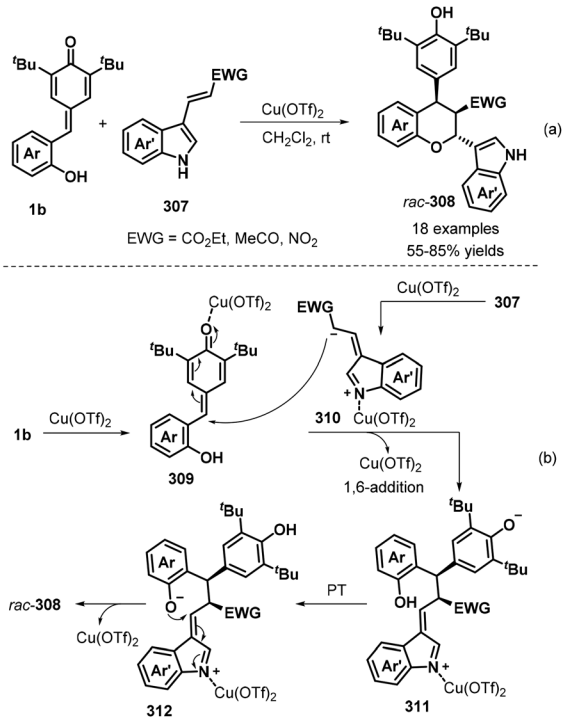



Scheme 66 Double 1,6-addition for the synthesis of chiral chromans.

vinylogous 1,6-addition and oxa-1,6-addition. High diastereo- and enantioselectivities were controlled by the hydrogen-bonding network between chiral phosphoric acid **300** and substrates (Scheme 65b).

To enrich the library of chiral chromanes, Chatterjee and co-workers elegantly described a secondary amine catalyzed vinylogous double 1,6-addition strategy for the synthesis of enantioenriched poly-substituted chroman derivatives.[100] Starting from *p*-QMs **1b** and 2,4-dienal derivatives **302**, use of chiral diphenylprolinol silyl ether **303** as a secondary amine catalyst facilitates their transformations in *o*-xylene in the presence of $Et_3N$ to generate chroman derivatives **304** with generally excellent yields (up to 96%) and excellent stereocontrol (up to >20 : 1 dr, >99% ee, Scheme 66a). A variety of δ-substituted unbiased 2,4-dienals, such as alkyl (ethyl, methyl, *n*-pentyl, phenylethyl, cyclohexyl) and aryl group, were successfully engaged in this protocol, in which δ-aryl substituted one seemed to be more reluctant to undergo this process as the low yield (36%) and enantioselectivity (76% ee) was obtained. The authors also conducted the late-stage application of some chromans with α,β-unsaturated enal functionality to introduce molecular complexity without loss of enantioselectivity. It is proposed that this reaction triggers by the intermolecular vinylogous iminium-ion based 1,6-addition (oxa-Michael) of the deprotonated oxygen anion of *p*-QMs **1b** to the linear unbiased 2,4-dienal, producing intermediate **305**, which is transformed into the targets *via* an intramolecular vinylogous dienamine-based another 1,6-addition (Scheme 66b).

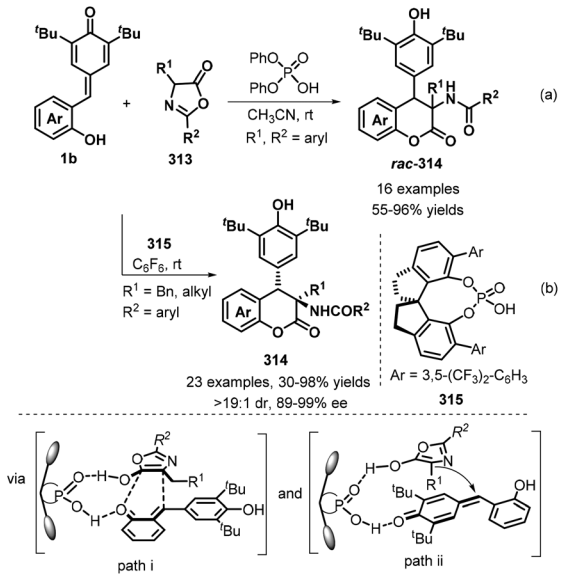
Furthermore, a novel [4 + 2] cycloaddition reaction between *p*-QMs **1b** and electron-poor 3-vinylindoles **307** was investigated by Wang, Jiang, and co-workers (Scheme 67a).[101] In the presence of 10 mol% $Cu(OTf)_2$ in DCM at room temperature, the desired polysubstituted chromans **308** were obtained in moderate to good yields and poor diastereoselectivity. The reaction tolerated various substituents, including fluoro, chloro, bromo, cyano, methyl, and methoxy, in the C4 to C6 positions of the indole ring of the electron-poor 3-vinylindole component **307**, furnishing the corresponding indole-chroman derivatives **308** in 55–85% yields. It is also worth noting that indoles containing α,β-unsaturated ketone and α,β-unsaturated




Scheme 67 [4 + 2] annulation toward chromans.

nitroalkene moieties were well tolerated under these conditions, affording the corresponding products in 59% and 27% yields, respectively. Mechanistic studies revealed that $Cu(OTf)_2$ activates 3-vinylindole **307** to form 1,5-dipolar intermediate **310**, followed by sequential 1,6-addition of *p*-QM **1b** in the presence of $Cu(OTf)_2$, proton transfer, and intramolecular 1,4-addition to diastereoselectively afford the final chroman product (Scheme 67b).

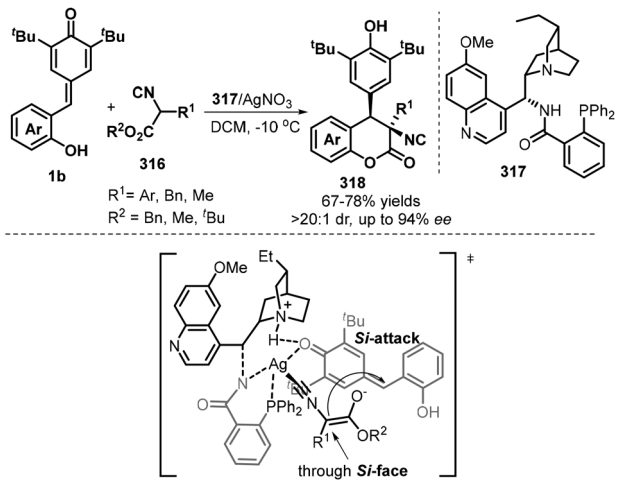
Given the importance of 4-arylchromanones in natural products and pharmaceuticals,[102] in 2018, Mei and co-workers employed *o*-hydroxyphenyl-substituted *p*-QMs **1b** and azlactones **313** as starting materials in a [4 + 2] annulation catalyzed by diphenyl phosphate as a Brønsted acid catalyst to construct highly functionalized 4-arylchromanones **314** in excellent yields and high diastereoselectivity (Scheme 68a).[103] In this process, the Brønsted acid plays a dual role, both activating the two substrates and controlling the diastereoselectivity of the reaction *via* hydrogen-bonding interactions. In the same year, its asymmetric version was achieved by Li's group.[104] An employment of chiral phosphoric acid catalyst **315** oriented the complete diastereoselectivity and high enantioselectivity to give enantioenriched 4-arylchromanones **314** in moderate to excellent yields under mild condition. A broad range of *p*-QMs **1b** and azlactones **313** were well-tolerate. Two possible pathways were proposed by the author to explain the stereoselectivity, including (i) [4 + 2] cycloaddition between the enol tautomer of the azlactones and *o*-QM from **1b** (path i) and (ii) 1,6-addition of the enol tautomer of the azlactones to *p*-QMs **1b**. Also, the hydrogen-bonding interaction controls the dia-



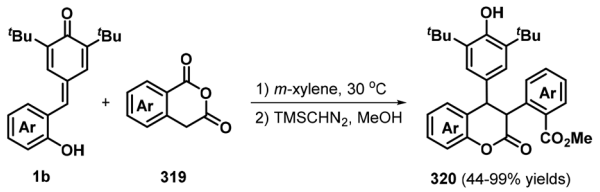

Scheme 68 [4 + 2] annulation toward 4-arylchromanones.

stereo- and enantio-selectivity of this asymmetric reaction (Scheme 68b).

As an expansion of asymmetric synthesis of 4-arylchromanones, very recently, Zhao *et al.* investigated the asymmetric [4 + 2] annulation reaction between *p*-QMs **1b** and α-isocyanoacetates **316** by using Ag(I)/dihydroquinidine-derived aminophosphine **317** catalyst (Scheme 69).[105] The reaction tolerated a wide range of isocyanoacetates and *p*-QMs, giving rise to the desired 4-arylchromanones **318** in 67–78% yields with excellent diastereoselectivities (>20 : 1 dr) and good to excellent enantioselectivities (up to 94% ee). However, some less reactive α-substituted isocyanoacetates ($R^1$ = 2-methylphenyl, benzyl and methyl) proved to be unsuited. The authors proposed a plausible transition-state model, which includes the coordination of **317**/Ag catalytic system to isocyanides and hydrogen




Scheme 69 Asymmetric synthesis of dihydrocoumarins.



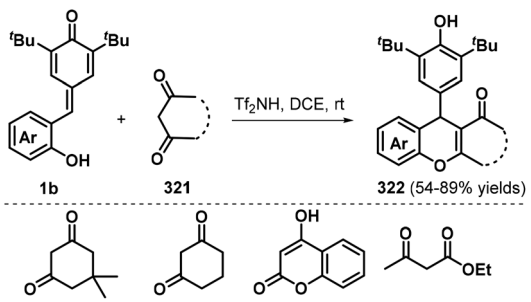

Scheme 70 [4 + 2] annulation of *p*-QMs with homophthalic anhydrides.

bonding of the protonated quinuclidine with the coordinated ketone oxygen atom.

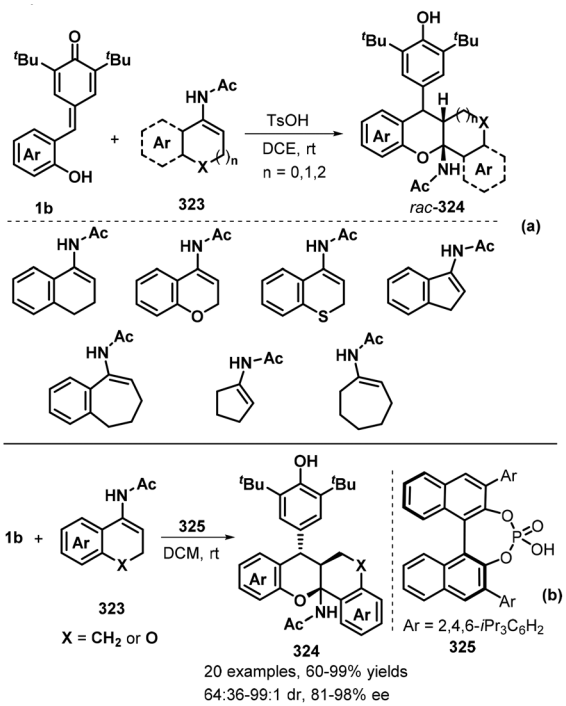
Besides the above examples, an achiral [4 + 2] annulation between *p*-QMs **1b** and homophthalic anhydrides **319** followed by esterification with $TMSCHN_2$ in MeOH was found to deliver a wide range of 4-arylchromanones **320** in 44–99% yields and 77 : 23 to >95 : 5 dr (Scheme 70).[106] The authors examined the substrate scope for the homophthalic anhydride component and demonstrated good tolerance to fluoro and methyl substituents at the C6 and C7 positions of the phenyl ring. The proposed reaction mechanism involves 1,6-addition, ring-opening of the cyclic anhydride, and esterification with $TMSCHN_2$.

An efficient method for the synthesis of xanthenones and chromenes **322** using *p*-QMs **1b** and β-functionalized ketones **321** as the starting materials was reported by the Kumar group in 2019 (Scheme 71).[107] A series of xanthenones and chromenes **322** were obtained in good yields using 10 mol% $Tf_2NH$ as a Brønsted acid catalyst in 1,2-dichloroethane (DCE). A number of β-functionalized ketones **321** such as dimedone, cyclohexane-1,3-dione, 4-hydroxy-2*H*-chromen-2-one, and ethyl 3-oxobutanoate were suitable for this [4 + 2] annulation transformation.

Yuan, Yu, and co-workers elegantly orchestrated a stereoselective TsOH-catalyzed [4 + 2] annulation between *p*-QMs **1b** and cyclic enamides **323** under mild conditions to obtain a variety of skeletally diverse chroman-containing heterocyclic compounds **324** in 75% to >99% yields and 2 : 1 to >20 : 1 dr (Scheme 72a).[108] This protocol tolerated a wide range of cyclic enamides **323**, such as 3,4-dihydronaphthalen-1-yl, chromen-4-yl, thiochromen-4-yl, inden-3-yl, 6,7-dihydro-5*H*-benzo[7]annulen-9-yl, cyclopentenyl, and cycloheptenyl derivatives. The proposed mechanistic pathway involves sequential 1,6-



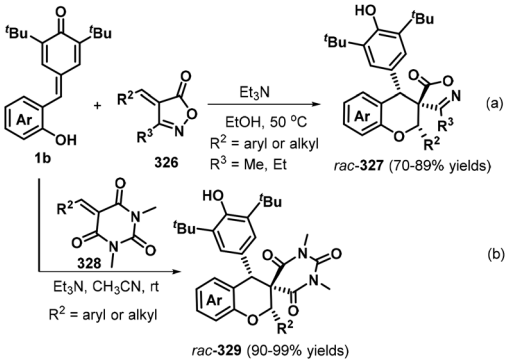

Scheme 71 [4 + 2] annulation of *p*-QMs with ketones.




Scheme 72 [4 + 2] annulation of *p*-QMs with cyclic enamides.

addition and oxa-Mannich reaction. Impressively, the chiral phosphoric acid-catalysed [4 + 2] annulation of these substrates enantioselectively provided a series of acetamido-substituted tetrahydroxanthenes **324** bearing three adjacent stereogenic centers as revealed by Li's group (Scheme 72b).[109] Use of BINOL-based chiral phosphoric acid **325** as an efficient catalyst facilitates the generation of tetrahydroxanthenes in 60–99% yields with high diastereo- and enantioselectivities (up to >99 : 1 dr and 98% ee). Both electron-donating and electron-withdrawing substituents of *p*-QMs **1b** on the phenyl ring and substituents on the aryl moiety of enamides were well tolerated in this asymmetric reaction.

The spirochroman skeleton is a core structural motif present in a range of biologically active molecules and natural products.[110] The [4 + 2] annulation between *o*-hydroxyphenyl-substituted *p*-QMs and exocylic electron-deficient olefins is one of the most efficient and direct processes for synthesizing functionalized spirochromans. Zhou, Yu, and co-workers reported a mild $Et_3N$-catalyzed [4 + 2] annulation between *o*-hydroxyphenyl-substituted *p*-QMs **1b** and isoxazolone-derived olefins **326** (Scheme 73a). This reaction proceeded smoothly to generate new *syn*-spiroisoxazolonechromans **327** in 70–89% yield.[111] Notably, aryl- and heteroaryl-substituted unsaturated isoxazolones reacted with complete diastereoselectivity to afford the target products (>99 : 1 dr), while a cyclohexyl-substituted isoxazolone exhibited a lower yield and diastereoselectivity (2.1 : 1 dr). Cyclic barbiturate-based olefins **328** also successfully participated in this [4 + 2] annulation reaction to provide a series of new chroman-spirobarbiturates **329** in 90–99% yields and >99 : 1 dr (Scheme 73b).[112] This

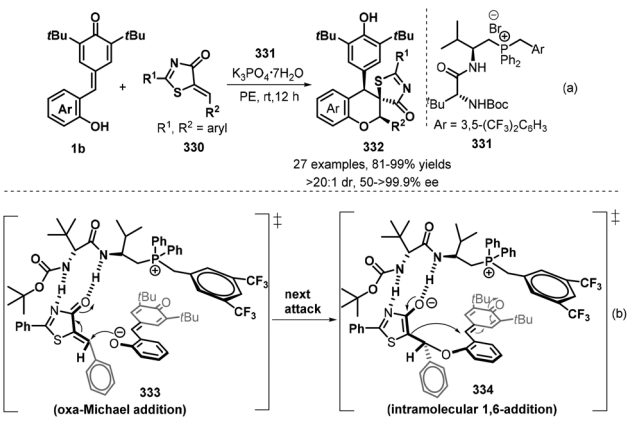



Scheme 73 Synthesis of spirochromans.

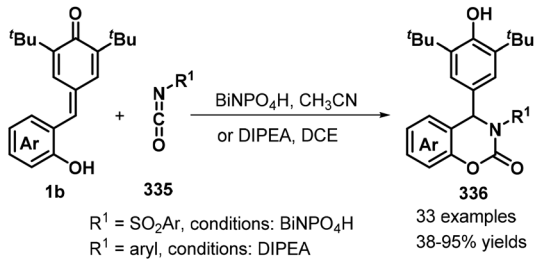
transformation tolerated a variety of functionalities to provide access to highly functionalized products. The mechanisms of both reactions are expected to involve oxa-Michael reaction and 1,6-addition.

Interestingly, Wang's group succeeded in developing an enantioselective formal [4 + 2] annulation of 5-alkenyl thiazolones **330** with *p*-QMs **1b** by employing a dipeptide-based phosphonium salt **331** as phase transfer catalyst, leading to 27 examples of chiral functionalized spiro-chroman-thiazolone compounds **332** bearing three contiguous stereocenters with good yields, excellent diastereo- and enantioselectivities (>20 : 1 dr and up to >99.9% ee, Scheme 74a).[113] Of note, thienyl-substituted thiazolone could work smoothly to access the spirocyclic product in 81% yield but with moderate ee value. The authors proposed the plausible transition state models for the formation of major isomers, which includes oxa-Michael addition and subsequent 1,6-addition. The high enantioselectivity mainly relies on the hydrogen-bonding and ion–pair interactions between the catalyst **331** and generated phenolate anion (Scheme 74b).

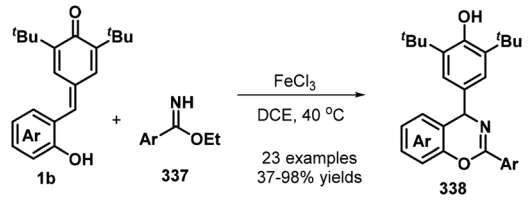
As an important class of O,N-heterocycles, the 1,3-benzoxazine framework is found in a wide range of synthetic compounds exhibiting broad-spectrum biological activities. To obtain these targets, the Shi group synthesized a series of ben-




Scheme 74 Enantioselective construction of chroman-thiazolones.




Scheme 75 [4 + 2] annulation of *p*-QMs with isocyanates.

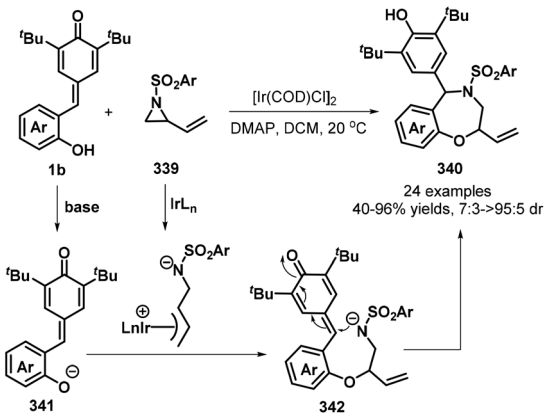



Scheme 76 Synthesis of 2,4-diaryl-1,3-benzoxazines.

zoxazin-2-ones **336** with varying degrees of substitution in 38–95% yields through the acid- and base-tunable [4 + 2] annulation between *p*-QMs **1b** and isocyanates **335**.[114] The choice of Brønsted acid or Brønsted base catalysis was dependent on the isocyanate substituent. 1,1′-Binaphthyl-2,2′-diyl phosphate ($BiNPO_4H$) was found to be an effective Brønsted acid catalyst for the [4 + 2] annulation using isocyanates bearing arylsulfonyl groups, whereas DIPEA was more suitable for isocyanates containing aryl groups, resulting in benzoxazin-2-ones **336** with good to excellent yields. This catalytic [4 + 2] annulation tolerated a variety of electronically distinct substituents at various positions of the phenyl rings of both *p*-QMs **1b** and isocyanates **335** (Scheme 75).

Subsequent work by Zhao and co-workers revealed that readily available ethyl arylimidates **337** can serve as effective [4 + 2] annulation substrates for the direct synthesis of 2,4-diaryl-1,3-benzoxazines **338** in 37–98% yields (Scheme 76).[115] Using 30 mol% $FeCl_3$ as the catalyst, a diverse range of *p*-QMs and ethyl arylimidates possessing various substituents, including hydrogen, methoxy, methyl, fluoro, chloro, bromo, nitro, and chloromethyl moieties, cyclized smoothly to form the desired 1,3-benzoxazine products. Ethyl arylimidates with electron-donating groups on the phenyl ring generally afforded higher yields than those bearing electron-withdrawing groups.

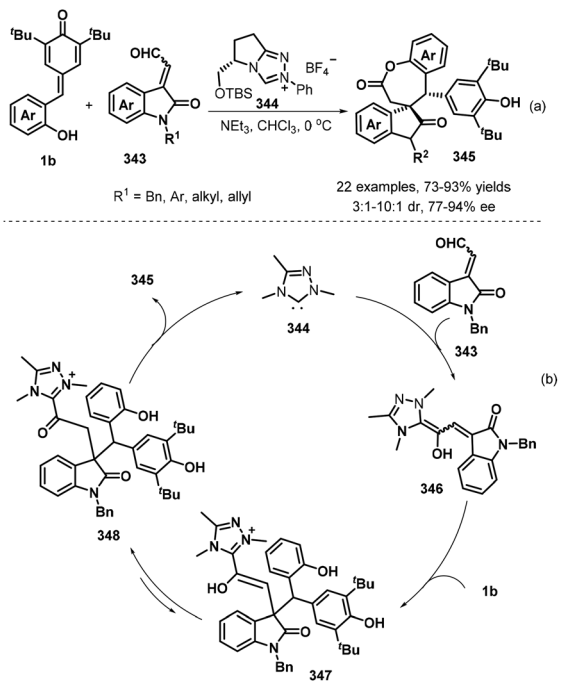
**2.2.6. 1,6-Addition/[4 + 3] annulation of *p*-QMs.** As a class of versatile nitrogen–carbon–carbon synthetic building blocks, vinyl aziridines are broadly applied in numerous annulation reactions to construct aza-heterocycles *via* zwitterionic π-allyl metal intermediates under metal catalysis.[116] Very recently, the Shi group accomplished the first iridium-catalyzed [4 + 3] annulation between vinyl aziridines **339** and *o*-hydroxyphenyl-substituted *p*-QMs **1b**, providing a diastereoselective protocol for the synthesis of seven-membered benzoxazepines **340** in 40–96% yields and 7 : 3 to >95 : 5 dr (Scheme 77).[117] This trans-




Scheme 77 [4 + 3] annulation of vinyl aziridines with *p*-QMs.

formation tolerated electron-rich, neutral, and electron-poor substituents on the benzenesulfonyl group of the vinyl aziridine component **339** to smoothly furnish products **340** with high diastereoselectivities and generally reasonable yields. Various substituents linked to the olefin moiety, such as cyclic, methyl, phenyl, and ester groups, favored this cyclization. The reaction process is believed to involve *in situ* generation of a zwitterionic π-allyl iridium species, oxa-allylic addition, and aza-1,6-nucleophilic addition.

As an extension of the NHC-catalysis, Enders's group revealed that use of a chiral NHC precursor **344** in the presence of $Et_3N$ accelerates enantioselective [4 + 3] cycloaddition of *p*-QMs **1b** with isatin-derived enals **343**, leading to spirocyclic oxindole-ε-lactones **345** in high yields (73–93%) and high

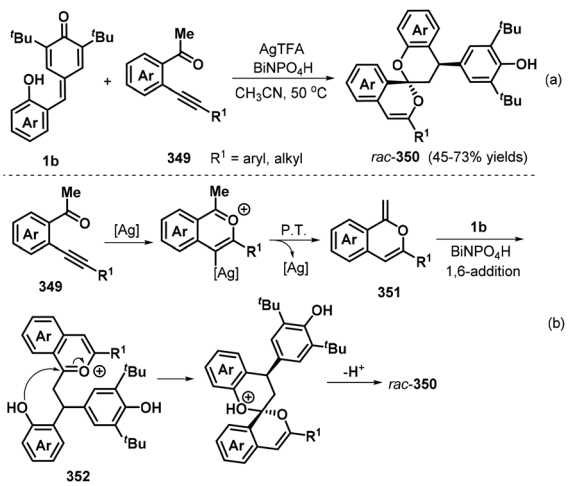



Scheme 78 Asymmetric synthesis of spiro-oxindole-ε-lactones.

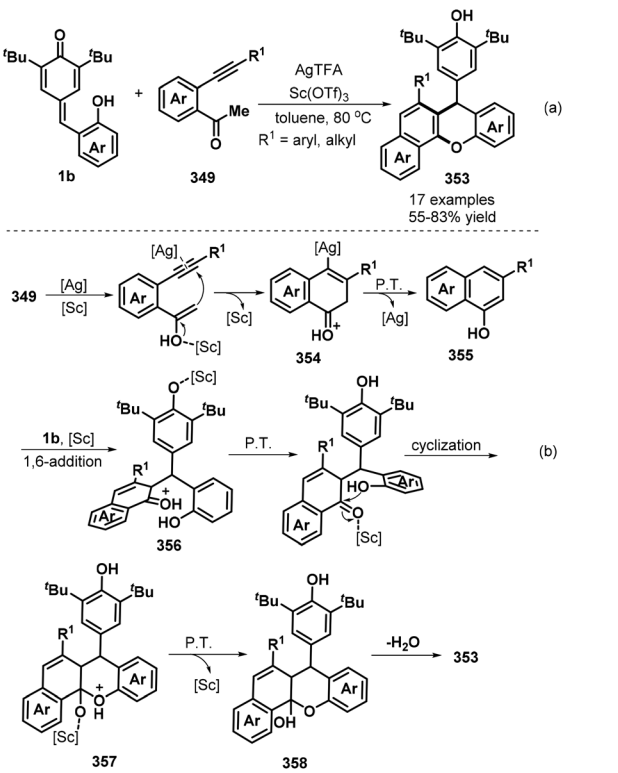
stereoselectivities (up to 97 : 3 er, Scheme 78a).[118] This new protocol involves a 1,6-addition of the homoenolate equivalent intermediates to the hydroxy donor-1,6-Michael acceptors. Gratifyingly, the isatin-derived enals **343** with varying nitrogen protecting groups (*N*-methyl, *N*-ethyl, *N*-benzyl, *N*-allyl and *N*-aryl) all proceeded smoothly and gave products in good yields with high diastereoselectivities and enantiomeric ratios. At the beginning, the addition of the NHC catalyst to the isatin-derived enal gives the Breslow intermediate **346**, which reacts with the *p*-QMs **1b** by 1,6-Michael addition to give the adduct **347**. Tautomerization of **347** leads to the acyl azolium intermediate **348**. The final intramolecular lactonization of **348** furnishes the product **345** and regenerates the NHC catalyst (Scheme 78b). At the same time, Li's group have also developed a similar NHC-catalysis for the synthesis of the same products by adopting NaOAc as a base and DCE as a solvent at room temperature.[119]

**2.2.7. 1,6-Addition/bicyclization of *p*-QMs.** Bicyclization reactions have emerged as an efficient and reliable synthetic tool for the construction of polycyclic ring systems of chemical and biomedical interest, enabling the synergistic utilization of several reactive sites in starting materials to directly establish two new rings in a single step.[120] Such transformations possess good bond-forming/annulation efficiency and afford high levels of structural complexity. In recent years, the widespread utilization of bicyclization reactions has paved the way to assembling various fused carbocyclic and heterocyclic molecules that are not accessible *via* conventional methods.[121] By exploiting a bicyclization strategy, Tu, Jiang, and co-workers recently established a new and selective silver/Brønsted acid dual synergistic catalytic system involving β-alkynyl ketones **349** and *o*-hydroxyphenyl-substituted *p*-QMs **1b**, which permitted the preparation of 25 examples of spiro[chromane-2,1′-isochromene] derivatives **350** in generally good yields and excellent diastereoselectivity (Scheme 79a).[122] Notably, the β-alkynyl ketone **349** bearing an *n*-butyl group on the alkynyl moiety was a suitable substrate, providing the corresponding product as a sole diastereoisomer in 50% yield. However, the β-alkynyl ketone bearing a 1-naphthyl group did not react. The authors found that the key step in the formation of these products is the *in situ* generation of methyleneisochromenes **351** with a nucleophilic site. A reasonable mechanism for this spiroketalization was proposed (Scheme 79b). Initially, silver-catalyzed 6-*endo-dig* oxo-cyclization of β-alkynyl ketone **349** generates an isobenzopyrylium intermediate, followed by proton transfer to afford isochromene **351**. Next, $BiNPO_4H$-catalyzed 1,6-addition between **351** and **1b** yields intermediate **352**, which undergoes intramolecular oxa-nucleophilic addition and subsequent proton transfer to afford the final product.

Interestingly, the above reaction was also conducted under silver/scandium bimetallic synergistic catalysis, which proceeded in a completely different direction to afford 17 examples of unexpected benzo[*c*]xanthenes **353** in 55–83% yields (Scheme 80a).[123] A wide variety of β-alkynyl ketones possessing a diverse set of substituents at various positions of the arylalkynyl ($R^1$) moiety were perfectly tolerated, providing good product yields in all cases. On the basis of control experiments, the authors postulated that the corresponding 3-arylnaphthalen-1-ol **355** behaves as a key intermediate in this transformation. Mechanistically, silver/scandium-*co*-catalyzed 6-*endo-dig* cyclization of the β-alkynyl ketone could generate intermediate **354**, followed by proton transfer and tautomerization to afford 1-naphthol **355** (Scheme 80b). Next, scandium-catalyzed 1,6-addition of **355** to **1b** yields the adduct intermediate **356**, which undergoes proton transfer and intramolecular



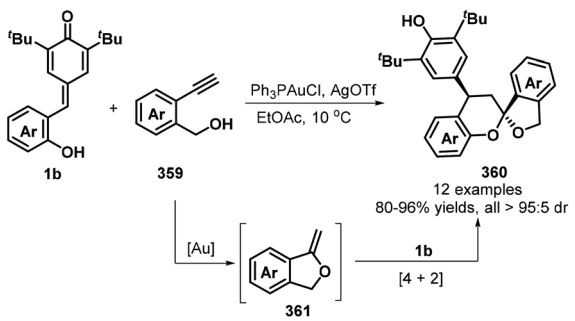

Scheme 79 Bicyclization of *p*-QMs with β-alkynyl ketones.



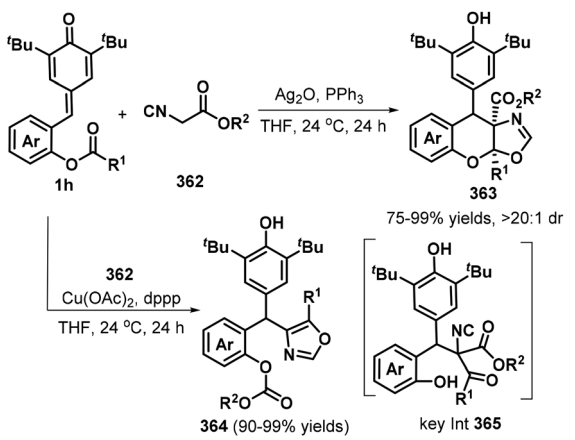

Scheme 80 Silver/scandium-co-catalyzed bicyclization of *p*-QMs.

oxa-nucleophilic addition to furnish intermediate **357**. Finally, intermediate **358** is transformed into product **353** *via* deprotonation and dehydration. Subsequently, the Shi group developed a similar protocol for the synthesis of spiroacetal derivatives **360** in excellent yields and good diastereoselectivities from alkynyl benzyl alcohols **359** with $Ph_3PAuCl$ as the catalyst (Scheme 81).[124] Au-Catalyzed *in situ* generation of electron-rich vinyl ether intermediate **361** is vital for this transformation, which then undergoes [4 + 2] annulation to yield the spiroacetal product.

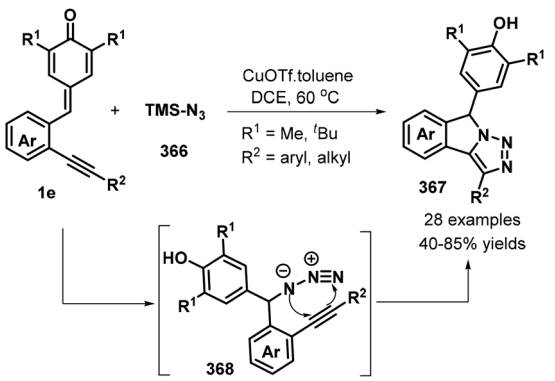
In 2017, Zhao and co-workers established an impressive catalyst-controlled reaction between *p*-QM aryl esters **1h** and activated isocyanides **362** to afford two new types of skeletally diverse heterocycles with high chemo- and stereoselectivity (Scheme 82).[125] The combination of $Ag_2O$ (5 mol%) and $PPh_3$ (10 mol%) as a catalytic system led to tricyclic ketals **363**, whereas oxazole-containing triarylmethanes **364** were produced in good to excellent yields *via* an unexpected carbon–carbon bond cleavage when the catalytic system was switched to $Cu(OAc)_2$ (10 mol%)/dppp (20 mol%). Variation of the ester moiety in both substrates was well tolerated, and both alkyl and aryl substituents resulted in excellent selectivities. The authors postulated that the key species is intermediate **365**,




Scheme 81 Oxa-[4 + 2] cyclization toward spiroacetals.




Scheme 82 Catalyst-controlled reaction of *p*-QMs with isocyanides.



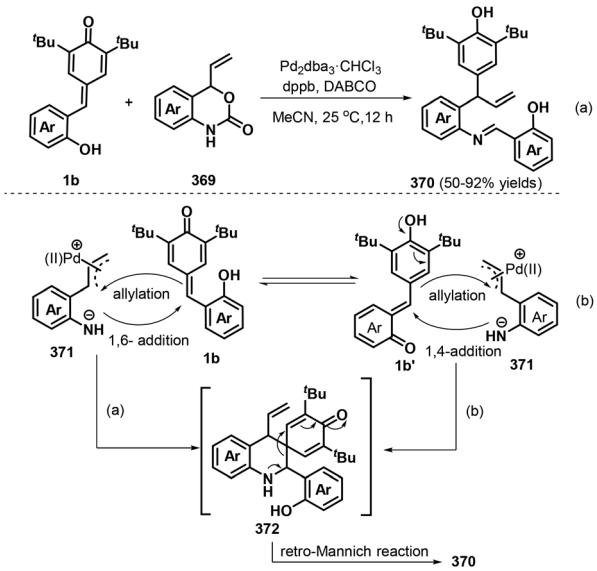

Scheme 83 Copper-catalyzed bicyclization of *p*-QMs with $TMSN_3$.

which is highly reactive and spontaneously undergoes subsequent reaction, although this intermediate was not directly observed.

Anand and co-workers exploited 2-alkenylated *p*-QMs **1e** with $Me_3SiN_3$ **366** as substrates to establish a copper-catalyzed 1,6-conjugate addition reaction followed by intramolecular click cycloaddition, which provided access to a wide range of functionalized 1,2,3-triazole-fused isoindolines **367** in moderate to good yields (Scheme 83).[126] Azide **368** was confirmed to be a key intermediate by NMR and IR spectroscopy.

### 2.3. Other reaction types of *p*-QMs

Recently, Shi and co-workers established the first [4 + 2] cyclization/retro-Mannich reaction cascade between *o*-hydroxyphenyl-substituted *p*-QMs **1b** and vinyl benzoxazinanones **288** to realize carbon–carbon double bond cleavage (Scheme 84a).[127] A series of vinyl benzoxazinanones **369** bearing various substituents, such as fluoro, chloro, bromo, methyl, and methoxy groups, at different positions (C5, C6, C7, and C8) were all




Scheme 84 Catalytic C=C bond cleavage of *p*-QMs.

applicable in this reaction, providing the products **370** in good to excellent yields. Two plausible reaction pathways were proposed (Scheme 84b). First, palladium-containing 1,4-dipolar compound **371** could be generated *via* decarboxylation of vinyl benzoxazinanone **369**. In pathway a, the [4 + 2] cyclization occurs *via* a domino 1,6-addition/allylation dearomatization sequence. In pathway b, owing to the small isomerization energy of 6.7 kcal $mol^{-1}$, *p*-QM **1b** is transformed into *o*-QM **1b′**, followed by [4 + 2] cyclization *via* a domino 1,4-addition/allylation dearomatization sequence. Both pathways would afford the same [4 + 2] annulation product as transient intermediate **372**, which rapidly undergoes a retro-Mannich reaction to yield final product **370**.

## 3. Conclusions

In summary, various categories of reactions involving *p*-QMs, such as 1,6-addition, annulation, radical-induced cyclization, and radical–radical cross-coupling, have been explored in this review. The numerous examples of successful transformations expounded herein clearly demonstrate that *p*-QMs can serve as highly reactive and versatile synthons for the direct formation of multiple carbon–carbon and carbon–heteroatom bonds by acting as Michael acceptors or radical acceptors. The reactions highlighted in this review are expected to find great application in the fields of organic chemistry and pharmaceutical chemistry to provide more efficient access to important building blocks in organic synthesis, drug discovery, and materials science. Despite the tremendous advances and achievements made so far, there remain many opportunities and challenges for further exploration in this field. For example, 1,6-nucleophilic addition and annulation reactions of *p*-QMs using reactive oxygen-containing nucleophiles or *S*-, *P*-, or *N*-centered compounds as radical donors, especially with enantioselective control, have yet to be comprehensively investigated. Furthermore, the introduction of highly reactive substituents to prepare new types of *p*-QMs and further exploration of their reactivity profiles *via* 1,6-nucleophilic addition and/or annulation reactions would be of considerable interest. The substrate dependence also remains an important issue for some of the presented reactions.

## Conflicts of interest

There is no conflicts of interest.

## Acknowledgements

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