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Asymmetric organocatalytic Morita–Baylis–Hillman reaction and asymmetric organocatalytic transformations of Morita–Baylis–Hillman adducts. An update

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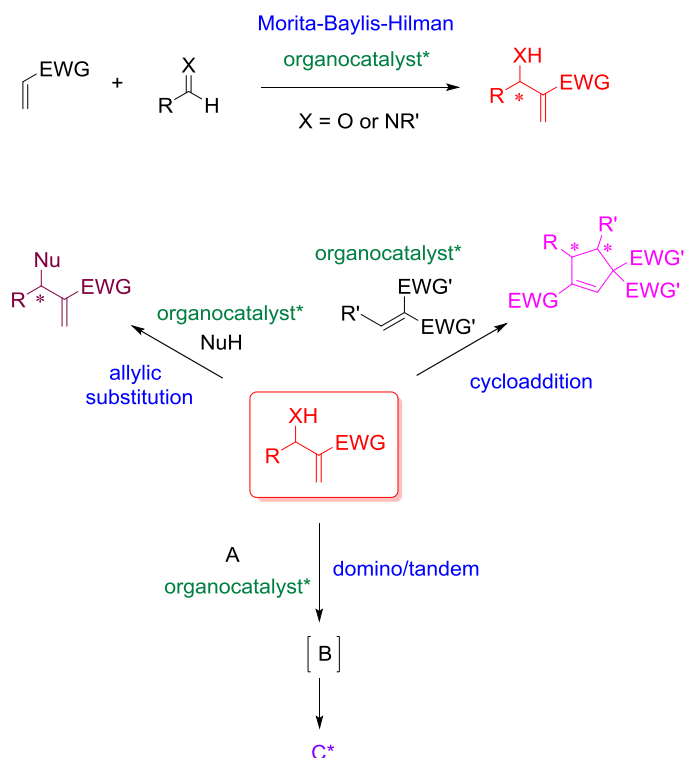
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Graphical Abstract

The goal of this review is to update the field of asymmetric organocatalytic (aza)-Morita–Baylis–Hillman reactions since the beginning of 2017. It also includes the asymmetric organocatalysed transformations of racemic Morita–Baylis–Hillman adducts, allowing the synthesis of useful chiral synthons in organic chemistry. It is divided into two sections, dealing successively with organocatalytic enantioselective (aza)-Morita–Baylis–Hillman reactions, and asymmetric organocatalysed reactions of Morita–Baylis–Hillman adducts and derivatives.



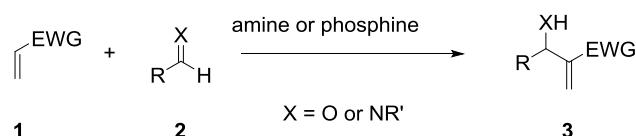
Keywords:

Asymmetric (aza)-Morita–Baylis–Hillman reaction; organocatalysis; asymmetric catalysis; annulations; allylic substitution reactions; domino reactions

1. Introduction

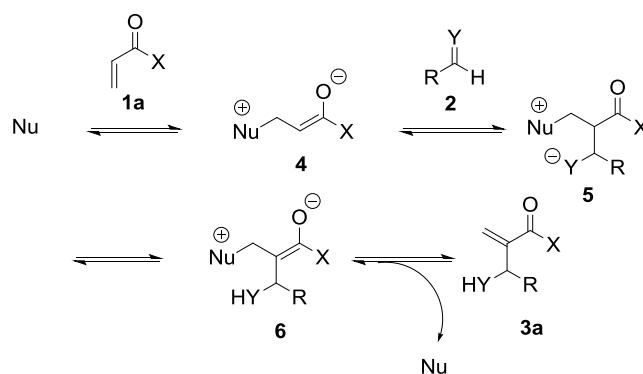
In the Morita–Baylis–Hillman reaction, a phosphine or tertiary amine plays the role of catalyst to promote the carbon–carbon coupling between a carbon electrophile **2** containing an electron-deficient sp^2 carbon atom, such as an aldehyde ($X = O$), with the α -position of an activated alkene **1**, allowing the direct synthesis of α -methylene- β -hydroxycarbonyl compounds **3** (Scheme 1). When an activated imine ($X = NR'$) is employed instead of the aldehyde, the corresponding aza-Morita–Baylis–Hillman reaction leads to α -methylene- β -aminocarbonyl derivatives. Therefore, (aza)-Morita–Baylis–Hillman reactions convert simple and commercially available compounds into multifunctional products under mild reaction conditions by using organocatalysts. Since a stereocentre is formed during the course of the reaction, the use of chiral organocatalysts, such as chiral phosphines [1], *Cinchona* alkaloids

and thioureas among others, allows the generation of chiral products. These types of green catalysts [2] present considerable advantages in comparison with metal complexes [3] since they are non-toxic, inexpensive, robust and often readily available. Their use in the synthesis of drugs is particularly advantageous due to the exclusion of any trace of hazardous metals in the final products.



Scheme 1. The (aza)-Morita-Baylis-Hillman reaction.

The origin of the Morita-Baylis-Hillman reaction dates back to 1968 with the development by Morita et al. of a reaction between acrylates (or acrylonitrile) and aldehydes promoted by tricyclohexylphosphine, leading to the corresponding 2-methylene-3-hydroxy alkanooates (or alkanenitriles) [4]. Later in 1972, Baylis and Hillman reported the use of amines as catalysts in related reactions between activated alkenes and aldehydes [5]. Surprisingly, it was not until a decade later that the Morita-Baylis-Hillman reaction became more popular with developments from Drewes and Emslie [6], Hoffmann and Rabe [7], Perlmutter and Teo [8], and Basavaiah and Gowriswari [9]. Ever since then, this reaction has been extensively developed [10] especially due to the wide synthetic utility of its adducts [11]. On the basis of theoretical and experimental studies [12], the mechanism of the Morita-Baylis-Hillman reaction involves successively a Michael addition, an aldol reaction, a proton transfer and a β -elimination (Scheme 2). Indeed, the first step is a reversible conjugate addition of the organocatalyst (Nu) to an activated alkene **1a** to generate enolate **4**. Subsequently, this enolate intermediate intercepts an aldehyde (or imine) through an aldol condensation to give zwitterionic intermediate **5**. A further proton transfer from the α -carbon atom to the β -alkoxide (amide) followed by a β -elimination finally provide the (aza)-Morita-Baylis-Hillman adduct **3a** along with regenerated organocatalyst.



Scheme 2. Mechanism for the (aza)-Morita–Baylis–Hillman reaction.

The goal of this review is to update the field of organocatalytic asymmetric (aza)-Morita–Baylis–Hillman reactions reported since the beginning of 2017, because this topic was previously reviewed in 2017 [13], covering the literature up to 2016. It must be noted that in 2018, Basavaiah and Naganaboina reported a personal account on the Morita–Baylis–Hillman reaction including only one reference ≥ 2017 dealing with an asymmetric organocatalytic version [14]. Moreover, several reviews focusing on special reactions of Morita–Baylis–Hillman adducts have been published. Among them, one reported in 2018 by Cheng and Liu concerned general annulations of Morita–Baylis–Hillman adducts with only four references ≥ 2017 dealing with enantioselective organocatalytic reactions [15]. In 2020, unconventional transformations of Morita–Baylis–Hillman adducts were the subject of a short review by Companyo with only two references ≥ 2017 concerning organocatalytic enantioselective reactions [16]. Also in 2020, Chen reported a personal account dealing with reactions of special compounds i.e. Morita–Baylis–Hillman adducts derived from isatins including nine references ≥ 2017 on asymmetric reactions [17]. Moreover, the special use of Morita–Baylis–Hillman adducts in modern drug discovery was reviewed in 2018 by Reddy and Rao with only one reference ≥ 2017 concerning asymmetric organocatalysed transformations [18]. A report focusing on applications of the Morita–Baylis–Hillman reaction in the synthesis of heterocyclic systems was published in 2019 by Kaye but included only three references ≥ 2017 dealing with enantioselective organocatalytic reactions [19]. In addition, two reviews focusing on general phosphine organocatalysis were published in 2018, each including only four references ≥ 2017 related to enantioselective phosphine-catalysed transformations of Morita–Baylis–Hillman adducts [1]. In 2023, Coelho et al. published a review on general catalyst systems including metals and enzymes on mechanistically complex

Morita–Baylis–Hillman reactions with no specific emphasis on asymmetric reactions which included only two references of organocatalytic enantioselective reactions ≥ 2017 [20]. In 2023, the special field of synthetic applications of Morita–Baylis–Hillman and Rauhut–Currier adducts of nitroalkenes was updated by Namboothiri et al. with thirteen references dealing with asymmetric organocatalytic works published since 2017 [21]. Finally, Anilkumar et al. published a review in 2024, focusing on general organocatalytic Morita–Baylis–Hillman reactions including only ten references concerning asymmetric reactions along with racemic ones [22]. The present review is divided into two sections, dealing successively with organocatalytic enantioselective (aza)-Morita–Baylis–Hillman reactions, and asymmetric organocatalysed reactions of Morita–Baylis–Hillman adducts and derivatives.

2. Organocatalytic enantioselective (aza)-Morita–Baylis–Hillman reactions

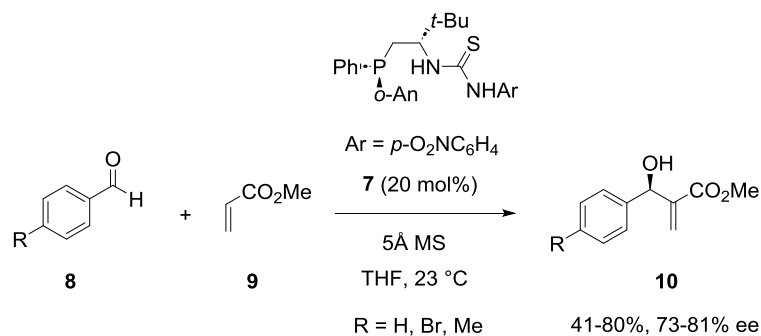
2.1. Morita–Baylis–Hillman reactions

2.1.1. Intermolecular reactions

The first enantioselective organocatalytic versions of Morita–Baylis–Hillman reactions were reported in 1990s by Drewes and Roos [10a], Isaacs et al. [23], and Marko et al. [24], focusing on the use of chiral amine catalysts, such as brucine, *N*-methylprolinol, *N*-methylephedrine and nicotine, albeit providing low enantioselectivities ($\leq 20\%$ ee). In 1992, Hiramama and Oishi reported the use of a chiral DABCO derivative as organocatalyst in the Morita–Baylis–Hillman reaction of aromatic aldehydes with methyl vinyl ketone which allowed enantioselectivities of up to 47% ee to be achieved [25]. Later in 1998, Soai et al. investigated the use of (*S*)-BINAP to promote the Morita–Baylis–Hillman reaction between pyrimidine carboxaldehydes and acrylates, which was also performed in moderate enantioselectivities (9-44% ee) [26]. It was one year later in 1999 that Hatakeyama et al. reported the first highly enantioselective organocatalysed Morita–Baylis–Hillman reaction delivering enantioselectivities of up to 99% ee [27]. It involved aliphatic aldehydes and 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) as substrates and *Cinchona* alkaloid-derived β -isocupreidine as chiral organocatalyst. This key result sparked wide investigation into this field, with very high enantioselectivities described by using different types of organocatalysts including chiral bi/multifunctional phosphines, proline-derived catalysts, *Cinchona* alkaloids, thioureas, and diols among others [10,13].

2.1.1.1. Phosphine catalysts

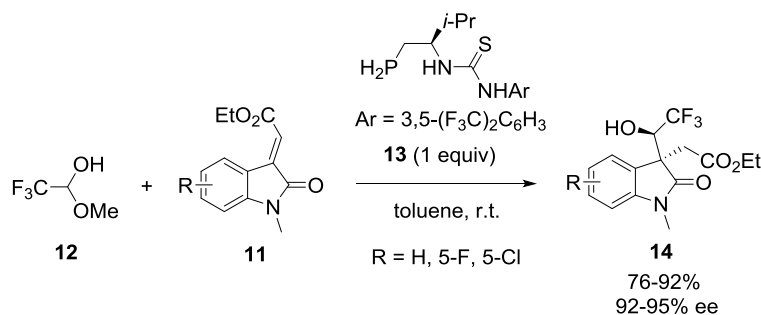
Chiral phosphines have been intensively employed as efficient organocatalysts in (aza)-Morita–Baylis–Hillman reactions [28] with a special mention for bi- or multifunctional chiral phosphines [29]. Indeed, the combination of a hydrogen bonding group with a highly nucleophilic phosphorus centre within one molecule bearing a chiral framework can synergistically and stereoselectively activate the substrates [30]. Moreover, the catalytic activity and enantioselectivity of these catalysts can be tuned by varying the chiral scaffold, the hydrogen bond donors, and the nucleophilicity of phosphorus. In 2017, Taylor and Su reported the synthesis of novel P-stereogenic β -aminophosphines exhibiting both carbon- and phosphorus-based chirality centres [31]. It was based on the resolution of a mixture of β -aminophosphine oxide diastereomers through ring-opening of the corresponding amino alcohol-derived cyclic sulfamidates followed by stereospecific borane-promoted reduction of β -aminophosphine oxides. Diastereomeric P-chiral β -aminophosphine-based thiourea **7** was selected as optimal catalyst to promote the enantioselective Morita–Baylis–Hillman reaction of benzaldehydes **8** with methyl acrylate **9** to give the corresponding chiral products **10** with 41-80% yields and 73-81% ee, as depicted in Scheme 3.



Scheme 3. Morita–Baylis–Hillman reaction of benzaldehydes with methyl acrylate in the presence of a P-stereogenic β -aminophosphine catalyst.

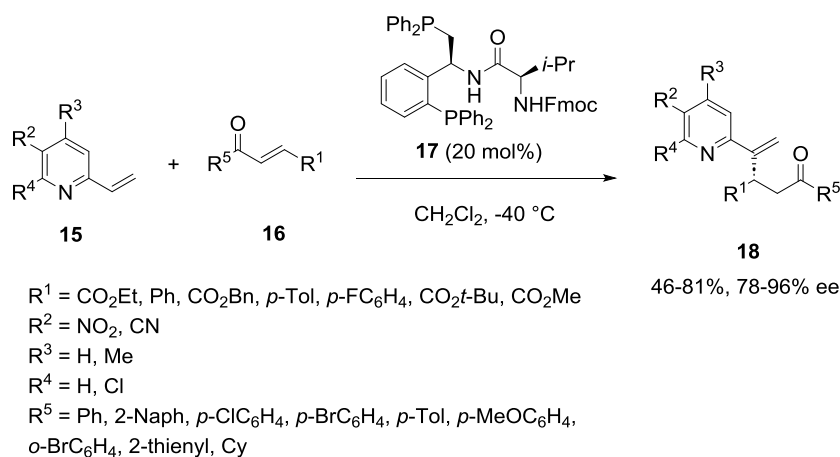
In 2018, Chen and Ouyang described the asymmetric Morita–Baylis–Hillman reaction of α -substituted activated olefins, such as 3-olefinic oxindoles **11** bearing a β -ester group, with trifluoroacetaldehyde methyl hemiacetal **12** promoted by one equivalent of chiral bifunctional phosphine **13** (Scheme 4) [32]. Performed in toluene at room temperature, the reaction

afforded the corresponding chiral products **14** with good yields (76-92%) and excellent enantioselectivities (92-95% ee). The drawback of this methodology was the requirement of a stoichiometric amount of catalyst.



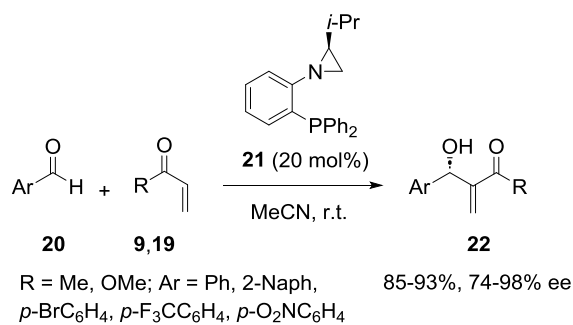
Scheme 4. Morita–Baylis–Hillman reaction of trifluoroacetaldehyde methyl hemiacetal with 3-olefinic oxindoles in the presence of a bifunctional phosphine catalyst.

An enantioselective vinylogous Morita–Baylis–Hillman reaction was developed by Wang and Li, in 2018 [33]. In this process, 2-vinylpyridines **15** were employed as a novel type of activated alkenes to react with 3-aryl acrylates or 2-ene-1,4-diones **16** (Scheme 5). The catalysis was performed by using 20 mol% of novel chiral phosphine **17** exhibiting one amino acid moiety in dichloromethane at $-40\text{ }^\circ\text{C}$. The process delivered a wide range of chiral functionalised pyridine derivatives **18** in moderate to high yields (46-81%) and good to excellent ee values (78-96% ee). Vinylpyridines bearing electron-withdrawing groups reacted smoothly. Concerning 3-aryl acrylates, the presence of either electron-withdrawing or electron-donating substituents on the phenyl ring was well tolerated, leading to the desired products with both good yields (67-71%) and enantioselectivities (85-90% ee). Remarkably, a better ee value (92% ee) was obtained in the reaction of a bulky substrate bearing an *ortho*-substituted aromatic group ($\text{R}^5 = o\text{-BrC}_6\text{H}_4$). Furthermore, fused aromatic naphthyl- and heteroaromatic thienyl substrates ($\text{R}^5 = 2\text{-Naph}, 2\text{-thienyl}$) were tolerated, producing the corresponding products with 71-75% yields and 86-87% ee. Along with aromatic acrylates, an aliphatic substrate ($\text{R}^5 = \text{Cy}$ (cyclohexyl)) was also compatible, thus forming the desired product with 52% yield and 78% ee.

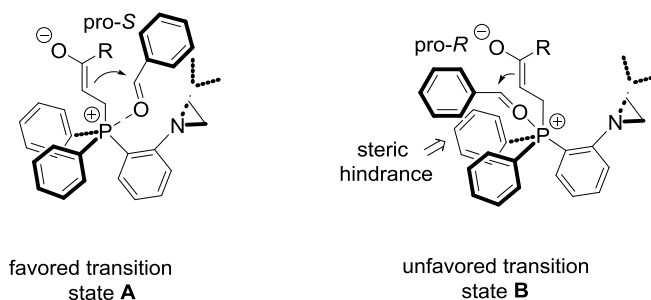


Scheme 5. Vinylogous Morita–Baylis–Hillman reaction of 2-vinylpyridines with 3-aryl acrylates/2-ene-1,4-diones in the presence of a phosphine catalyst.

In 2022, Rachwalski et al. involved for the first time a chiral phosphine catalyst containing an aziridine moiety to promote the asymmetric Morita–Baylis–Hillman reaction of methyl vinyl ketone **19** ($R = \text{Me}$) or methyl acrylate **9** ($R = \text{OMe}$) with aromatic aldehydes **20** (Scheme 6) [34]. The reaction was performed at room temperature in acetonitrile in the presence of 20 mol% of chiral organocatalyst **21** to give the corresponding chiral allylic alcohols **22** with 85-93% yields and 74-98% ee. To explain the stereoselectivity of the reaction, the authors proposed the transition states depicted in Scheme 6. In favored transition state **A**, the complex formed from the coordination of the vinyl ketone to the catalyst presents minimised steric interactions. The bulky aryl substituent on the aziridine nitrogen and the isopropyl group are on either side of the ring. The diphenylphosphine group and the aziridine ring are opposite and the enol complex is situated in the middle. The positive charge of the phosphorus atom interacts with the oxygen atom of the aldehyde, which allows the approach from the side of the unsubstituted methylene group of the ring. However, the approach from the other side of the ring is prevented by the presence of the bulky isopropyl group. The attack to the aldehyde occurs in such a way that the phenyl group is closer to the least hindered side of the ring, delivering the (*S*)-configured product. In contrast, the (*R*)-product would be generated through unfavored transition state **B** in which the phenyl ring approaches through the side of the phenyl group bound to the phosphorus atom, which is sterically impossible.



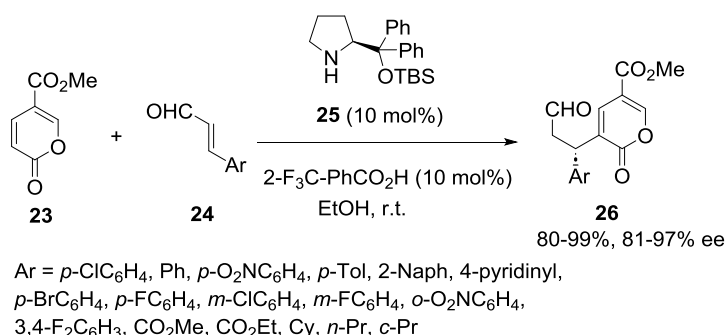
proposed transition states (with Ar = Ph):



Scheme 6. Morita–Baylis–Hillman reaction of aromatic aldehydes with methyl vinyl ketone/methyl acrylate in the presence of a phosphine-aziridine catalyst.

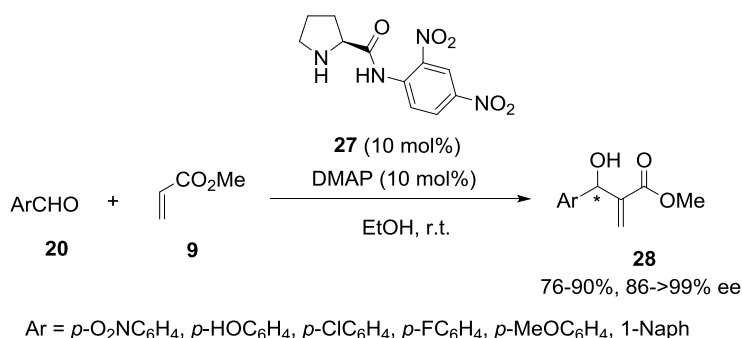
2.1.1.2. Proline-derived catalysts

An asymmetric vinylogous Morita–Baylis–Hillman reaction between methyl coumalate **23** and α,β -unsaturated aldehydes **24** was reported by Zu and Liu, in 2018 (Scheme 7) [35]. The process involved 10 mol% of diphenylprolinol TBS ether **25** as catalyst in ethanol at room temperature and 10 mol% of 2-CF₃-PhCOOH as an additive. The α,β -unsaturated aldehyde was activated through iminium catalysis to serve as Michael acceptor and methyl coumalate was used as an activated diene to generate enolate. The catalyst system tolerated a wide variety of (hetero)aromatic and aliphatic α,β -unsaturated aldehydes which smoothly reacted to give the corresponding products **26** with uniformly high yields (80-99%) and enantioselectivities (81-97% ee).



Scheme 7. Vinylogous Morita–Baylis–Hillman reaction of methyl coumalate with α,β -unsaturated aldehydes in the presence of diphenylprolinol TBS ether as catalyst.

Later in 2020, Bhusare et al. showed that chiral pyrrolidine-based organocatalyst **27** employed at 10 mol% of catalyst loading could efficiently promote the asymmetric Morita–Baylis–Hillman reaction of benzaldehydes **20** with methyl acrylate **9** through hydrogen bonding interaction (Scheme 8) [36]. This methodology performed in ethanol at room temperature in the presence of DMAP as base afforded chiral β -hydroxy acrylates **28** with both high yields (76-90%) and ee values (86->99% ee) regardless of the nature of substituent exhibited on the phenyl ring of the aldehyde.

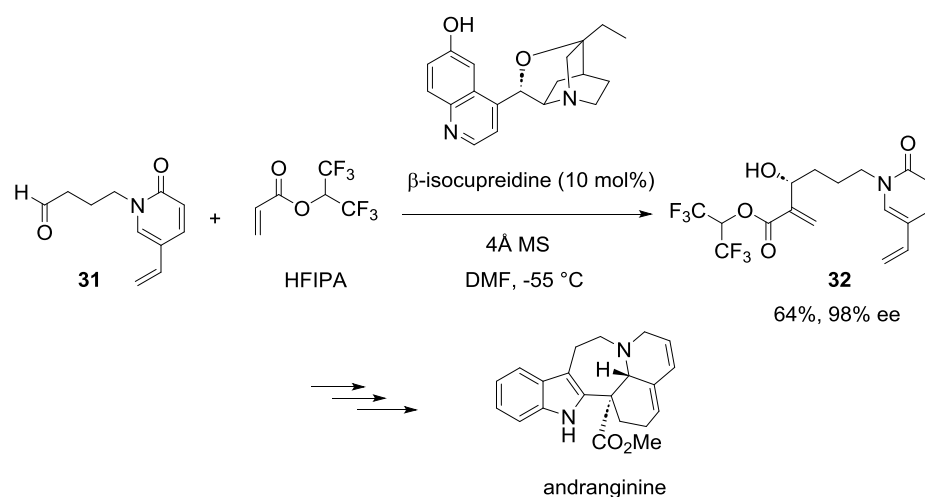


Scheme 8. Morita–Baylis–Hillman reaction of benzaldehydes with methyl acrylate in the presence of an amine catalyst.

Interestingly, Zheng et al. demonstrated in 2022 that simple L-proline used at 12 mol% of catalyst loading in a sodium phosphate buffer was able to promote the asymmetric Morita–Baylis–Hillman reaction of *para*-nitrobenzaldehyde **20b** with 2-cyclohexenone **29**

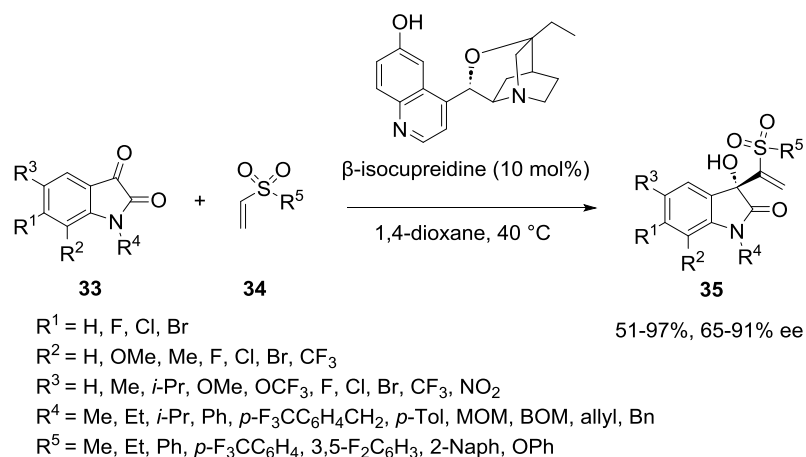
(Scheme 9) [37]. Indeed, without using hazardous solvents, this simple, economic and environmentally benign reaction allowed chiral alcohol (*R*)-**30** to be synthesised in only four hours with 64% ee. Moreover, the enantiomeric product (*S*)-**30** could be produced with 62% ee by using D-proline as catalyst. The authors proposed the mechanism depicted in Scheme 9 to explain the results. D-Proline reacted with 2-cyclohexenone to give iminium ion **C**. Then, the oxygen anion of sodium phosphate added at the β -position of intermediate **C**, resulting in the formation of β -enamine **D**, which subsequently attacked the aldehyde. In this transition state, the intermolecular hydrogen bonding interactions between the oxygen atom of the aldehyde group and the hydroxyl group of D-Proline could control the stereoselectivity, leading to the (*S*)-configured product.

10 mol% of β -isocupreidine. Performed at $-55\text{ }^{\circ}\text{C}$ in DMF, the reaction delivered enantiopure alcohol **32** (98% ee) in 64% yield. This key intermediate was further converted into expected andranginine through three additional steps.

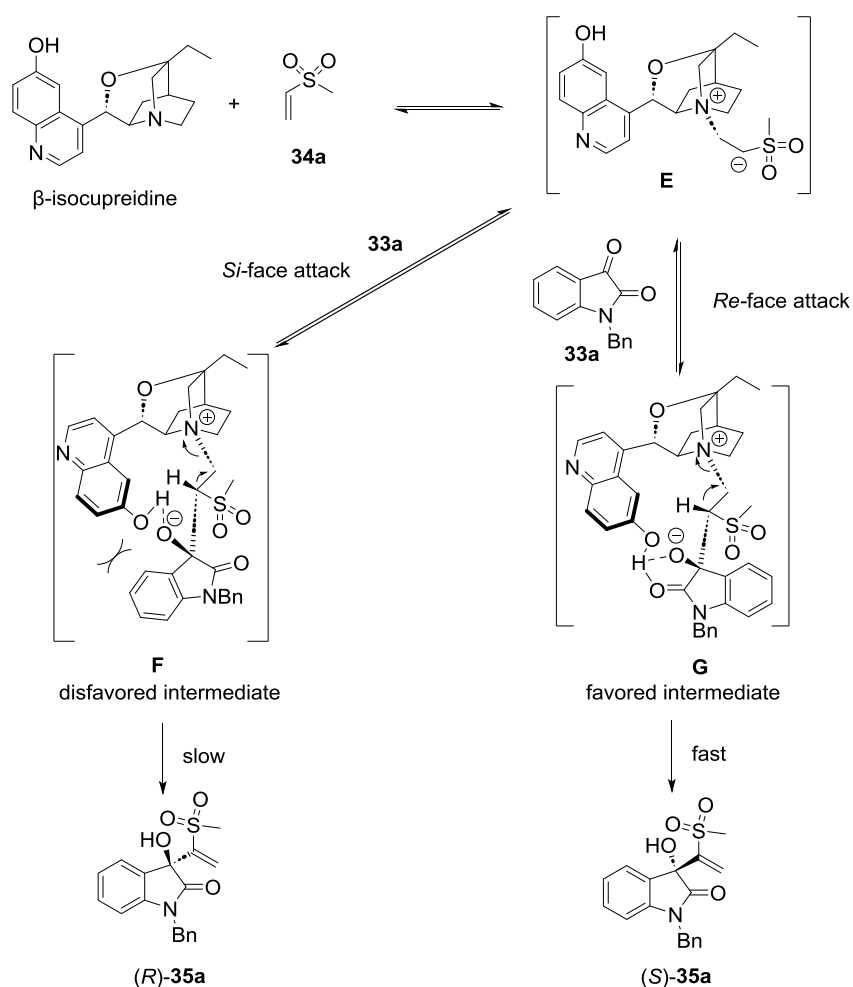


Scheme 10. Morita–Baylis–Hillman reaction of an aldehyde with HFIPA and synthesis of andranginine in the presence of β -isocupreidine as catalyst.

In 2023, Chen and Xiao described the first asymmetric Morita–Baylis–Hillman reaction using vinyl sulfones as nucleophiles (Scheme 11) [40]. Isatin derivatives **33** reacted at $40\text{ }^{\circ}\text{C}$ in the presence of 10 mol% of β -isocupreidine with various vinyl sulfones **34** to give the corresponding chiral 3-hydroxyoxindoles **35** with 51–97% yields and 65–91% ee. The authors proposed the mechanism depicted in Scheme 11, beginning with the nucleophilic addition of the catalyst to vinyl sulfone **34a** to give intermediate **E**. Then, aldol-type addition of **E** to isatin derivative **33a** delivered intermediates **F** or **G**. The latter was stabilised through hydrogen bonding between the oxyanion and the carbonyl group of **33a** with the aromatic hydroxyl group of β -isocupreidine, while intermediate **F** was unstable due to steric interactions between the aromatic rings of the catalyst and substrate **33a**. Finally, the desired product (*S*)-**35a** was generated from intermediate **G** through subsequent proton transfer and elimination. This novel methodology presented the advantage to extend the substrate scope of the Morita–Baylis–Hillman reaction to novel activated alkenes such as vinyl sulfones.



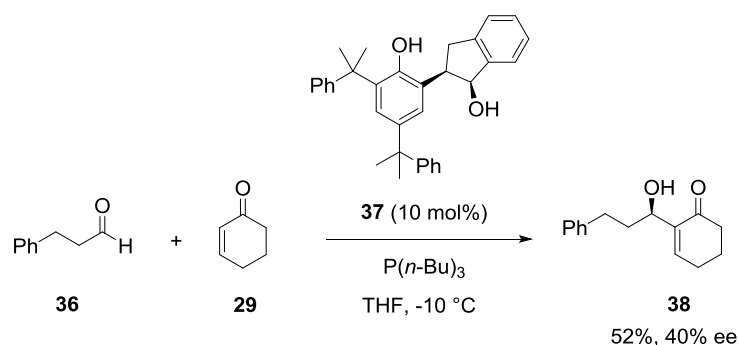
proposed transition state (with $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$, $\text{R}^4 = \text{Bn}$, $\text{R}^5 = \text{Me}$):



Scheme 11. Morita–Baylis–Hillman reaction of isatin derivatives with vinyl sulfones in the presence of β -isocupreidine as catalyst.

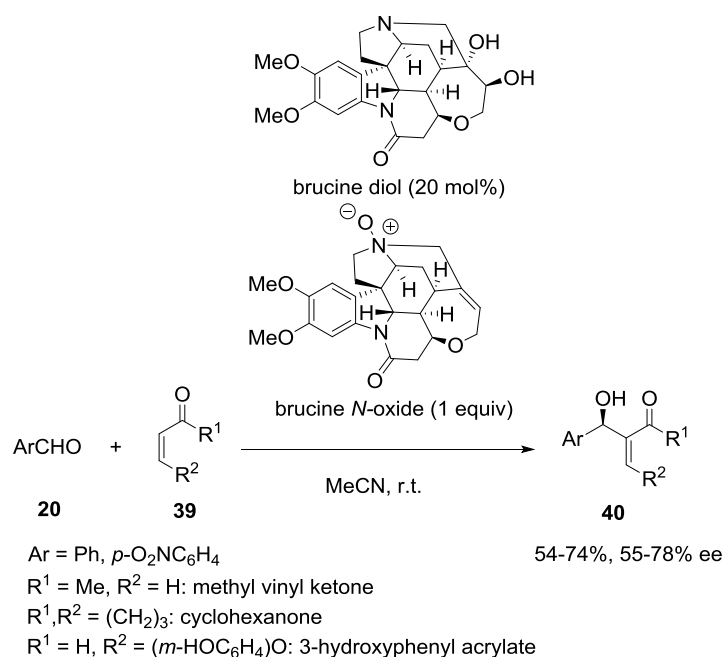
2.1.1.4. Diol catalysts

In 2018, Ertürk et al. developed the synthesis of a novel type of 1,4-diol organocatalysts [41]. Due to their ability to form hydrogen bonds with carbonyl compounds, these new chiral 1,4-diols were investigated as promoters in the Morita–Baylis–Hillman reaction between 3-phenylpropanal **36** and 2-cyclohexenone **29** (Scheme 12). Performed at -10 °C in the presence of 10 mol% of optimal catalyst **37** in THF, the reaction afforded in the presence of two equivalents of P(*n*-Bu)₃ the desired product **38** in 52% yield and 40% ee.



Scheme 12. Morita–Baylis–Hillman reaction of 3-phenylpropanal with 2-cyclohexenone in the presence of a 1,4-diol catalyst.

In 2021, Angamuthu et al. disclosed the use of 20 mol% of a brucine-derived diol combined with one equivalent of brucine *N*-oxide as cocatalyst to promote the enantioselective Morita–Baylis–Hillman reaction between benzaldehydes **20** and cyclic/acyclic α,β -unsaturated ketones/esters **39** (Scheme 13) [42]. The reaction occurred at room temperature in acetonitrile, leading to chiral products **40** with 54-74% yields and 55-78% ee. In spite of a limited scope, the highest enantioselectivity (78% ee) was obtained when cyclohexanone ($R^1, R^2 = (\text{CH}_2)_3$) was used as the nucleophilic partner, whereas the lowest ee value (55% ee) was observed in the reaction of methyl vinyl ketone ($R^1 = \text{Me}, R^2 = \text{H}$) with benzaldehyde ($\text{Ar} = \text{Ph}$). Although the enantioselectivity of the reaction was not excellent, this work demonstrated the possibility of using a novel type of chiral organocatalysts in asymmetric Morita–Baylis–Hillman reactions.

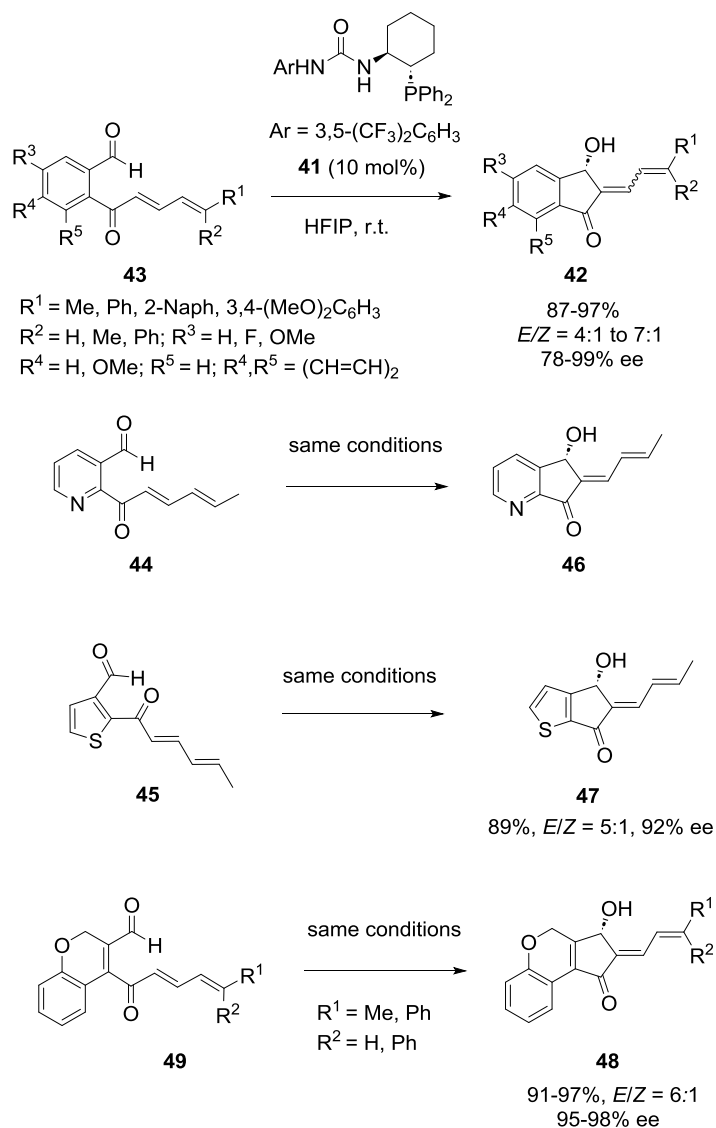


Scheme 13. Morita–Baylis–Hillman reaction of benzaldehydes with cyclic/acyclic α,β -unsaturated ketones/esters in the presence of brucine diol catalyst.

2.1.2. Intramolecular reactions

In 2017, Ramasastry et al. developed the first enantioselective organocatalytic intramolecular Morita–Baylis–Hillman reaction of dienones (Scheme 14) [43]. Indeed, performed at room temperature in the presence of 10 mol% of bifunctional chiral urea catalyst **41** in hexafluoroisopropanol (HFIP) as solvent, a range of dienones **43** underwent intramolecular Morita–Baylis–Hillman reaction to afford the corresponding chiral indanones **42** in both uniformly high yields (87-97%) and enantioselectivities (78-99% ee) albeit combined in moderate diastereoselectivities (*E/Z* ratios = 4:1 to 7:1). Actually, in all cases of substrates, the enantioselectivity of the reaction was found $\geq 92\%$ ee excepted in the Morita–Baylis–Hillman reaction of a substrate exhibiting a strong electron-donating group ($R^1 = 3,4\text{-(MeO)}_2\text{C}_6\text{H}_3$) which led to the product with only 78% ee. The scope of this methodology was extended to heteroaromatic dienones **44** and **45**, which afforded chiral cyclopentannulated heteroarenes **46** and **47** with 88-89% yields, moderate *E/Z* ratios (4:1 to 5:1) and 92-96% ee. Moreover, the versatility of the process was demonstrated with the synthesis of chiral cyclopentafused chromenes **48** with 91-97% yields and 95-98% ee combined with a higher *E/Z* ratio (6:1) from the corresponding dienones **49**. This result

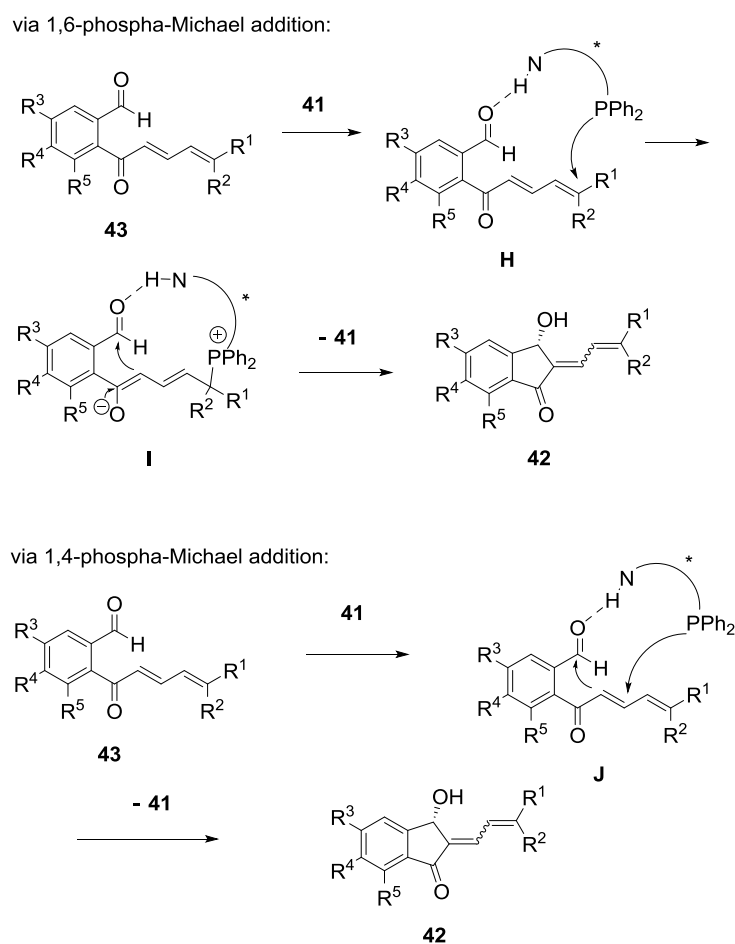
suggested that the reaction could also be performed on substrates with non-aromatic backbones.



Scheme 14. Intramolecular Morita–Baylis–Hillman reactions of dienones in the presence of a bifunctional phosphine catalyst.

The catalytic system **41** exhibited both Lewis acid and Lewis base functionalities which was supposed to activate the substrate as depicted in **H** (Scheme 15) via a 1,6-phospha-Michael addition of the Lewis base to the dienone, generating intermediate **I**. Then, an intramolecular aldol reaction followed by elimination of the regenerated catalyst resulted in the formation of product **42**. Alternatively, product **42** could also be generated through a 1,4-

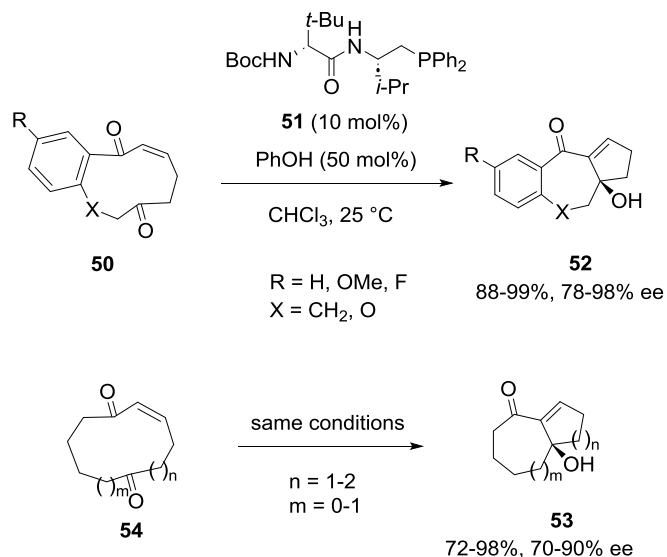
phospha-Michael addition followed by intramolecular aldol reaction depicted in **J**. The synthetic utility of the formed chiral Morita–Baylis–Hillman adducts was demonstrated by their conversion into 3,4-disubstituted chiral fluorenones which represent potent bioactive products.



Scheme 15. Mechanisms for intramolecular Morita–Baylis–Hillman reaction of dienones.

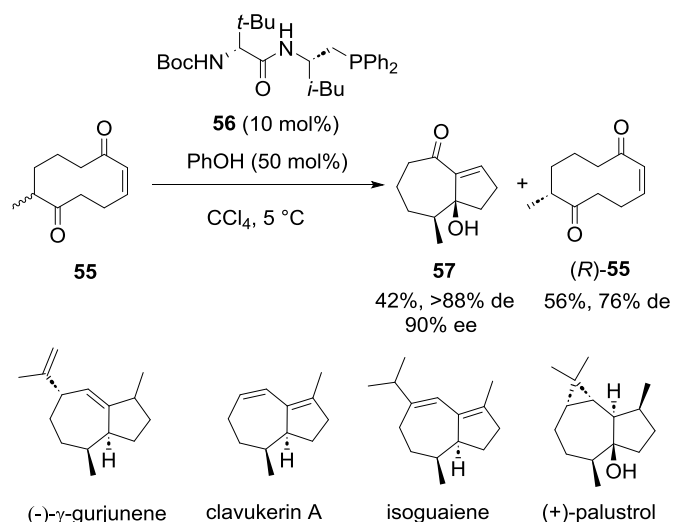
With the aim of synthesising guaiene-derived sesquiterpenes, Vicario and Reyes developed in 2019 a novel methodology to access bicyclic chiral carbo- and heterocyclic systems with different ring sizes (Scheme 16) [44]. It evolved through enantioselective transannular Morita–Baylis–Hillman reaction of medium size ketoenone substrates **50** catalysed by 10 mol% of chiral bifunctional phosphine **51** in chloroform at 25 °C. The reaction allowed a variety of chiral bicyclo[5.3.0]decane systems **52** ($n = m = 1$) to be synthesised with both high

yields (88-99%) and enantioselectivities (78-98% ee) as well as bicyclo [5.4.0]undecane products **53** with 72-98% yields and 70-90% ee from the corresponding ketoenones **54**.



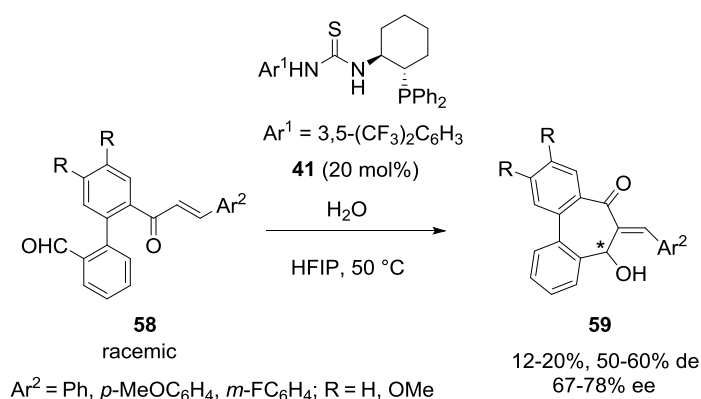
Scheme 16. Transannular Morita–Baylis–Hillman reactions of medium size ketoenones in the presence of a bifunctional phosphine catalyst.

Later in 2022, the same authors employed related chiral phosphine catalyst **56** in the enantioselective transannular Morita-Baylis-Hillman reaction of racemic medium-sized cyclic ketoenone **55** [45]. Using 10 mol% of this organocatalyst in CCl_4 as solvent allowed the reaction to occur at $5\text{ }^\circ\text{C}$, yielding under kinetic resolution chiral decahydroazulene derivative **57** along with recovered (*R*)-**55** (Scheme 17). The former was obtained in 42% yield, >88% de, and 90% ee while the unreacted (*R*)-configured cyclic ketoenone was recovered with 56% yield and 76% ee. This product was further employed in the total synthesis of several sesquiterpene-related compounds, including (-)- γ -gurjunene, clavukerin A, unnatural isomer of isoguaiene, and an intermediate for the synthesis of (+)-palustrol.



Scheme 17. Transannular Morita-Baylis-Hillman reaction of a medium-sized cyclic ketoenone in the presence of a bifunctional phosphine catalyst.

Earlier in 2021, Rachwalsky et al. described the first organocatalytic synthetic methodology to prepare chiral functionalised dibenzocycloheptanes [46]. As illustrated in Scheme 18, it dealt with an intramolecular asymmetric Morita–Baylis–Hillman reaction of racemic axially chiral enone-aldehydes **58** performed at 50 °C in HFIP as the solvent in the presence of 20 mol% of phosphine catalyst **41**. Under these conditions, several seven-membered chiral products **59** were formed as mixture of diastereomers in low yields (12–20%), moderate diastereoselectivities (50–60% de) combined with moderate to good enantioselectivities (67–78% ee).

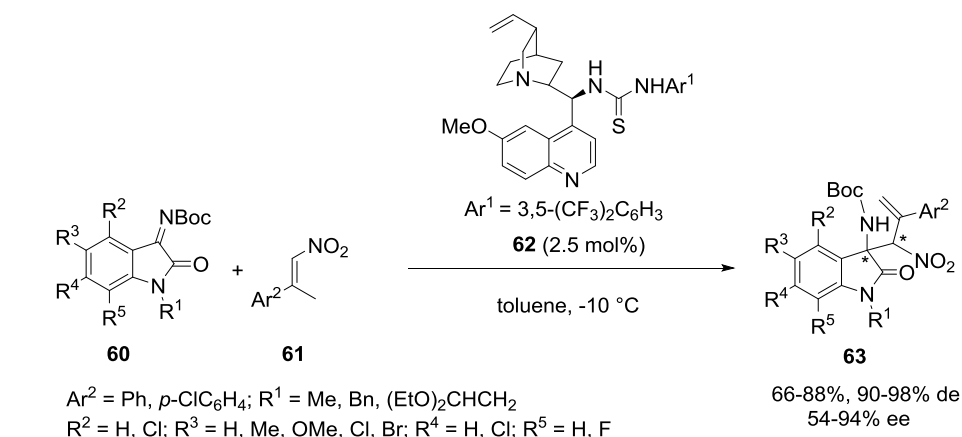


Scheme 18. Intramolecular Morita–Baylis–Hillman reaction of enone-aldehydes in the presence of a bifunctional phosphine catalyst.

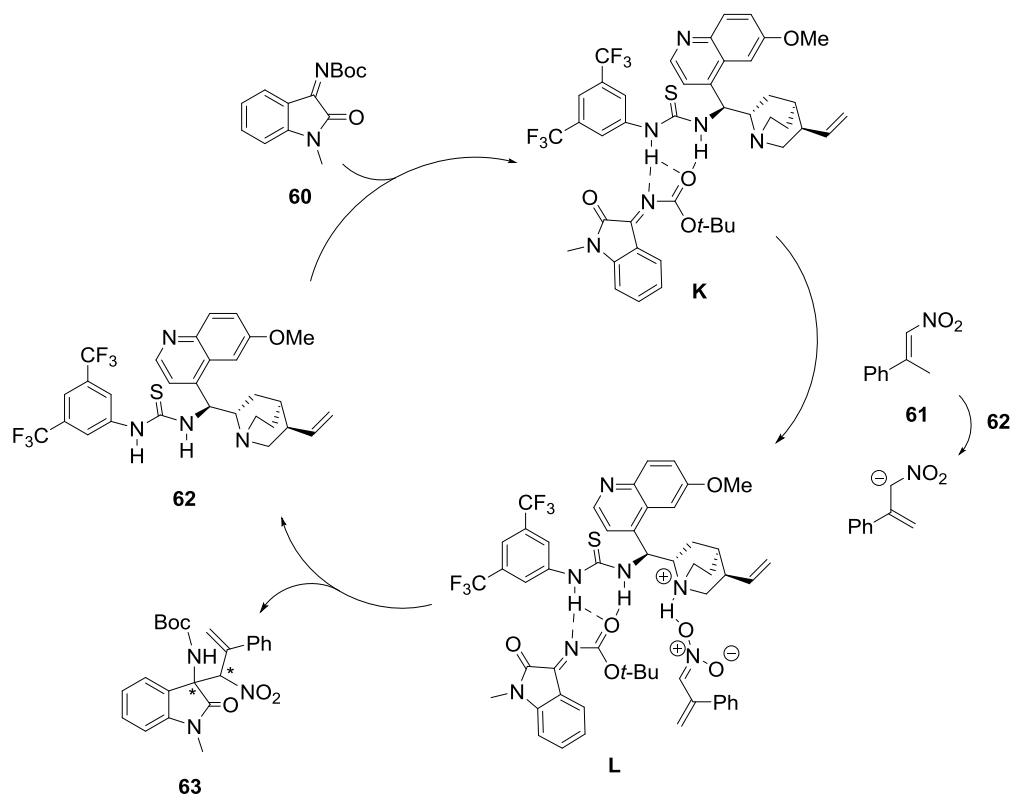
2.2. Aza-Morita-Baylis-Hillman reactions

Reported for the first time in 1984 by Perlmutter and Teo [8], the enantioselective aza-Morita-Baylis-Hillman reaction constitutes one of the most employed routes to chiral α -methylene- β -amino carbonyl compounds [10f,i,n]. It can be organocatalysed by chiral phosphines or amines. Actually, it was only in 2002 that high enantioselectivities were reported in this field by Shi and Xu, who developed the enantioselective aza-Morita-Baylis-Hillman reaction of methyl vinyl ketone with aromatic aldimines promoted by β -isocupreidine [47]. Indeed, this process afforded chiral aza-Morita-Baylis-Hillman adducts with excellent enantioselectivities of up to 99% ee. Later, these authors extended the scope of this methodology to various other activated alkenes, spanning from acrolein, methyl acrylate, acrylonitrile, and ethyl vinyl ketone to more hindered substrates, such as α -naphthyl and phenyl acrylates, that provided the corresponding products with enantioselectivities of up to 99% ee [48]. Ever since, a variety of chiral bifunctional phosphines, tertiary amines derived from *Cinchona* alkaloids, or thioureas have been successfully applied to promote these reactions. Despite the fact that they allow the synthesis of key structures in medicinal chemistry that are chiral 3-amino-2-oxindoles, enantioselective aza-Morita-Baylis-Hillman-type reaction of isatin-derived ketimines have been rarely investigated [49]. In 2014, Wu and Sha reported the first example of enantioselective aza-Morita-Baylis-Hillman-type reaction of these substrates with acrylates catalysed by a chiral squaramide-derived phosphine, providing enantioselectivities of up to 91% ee [50]. Later in 2017, Khan et al. reported the first asymmetric aza-Morita-Baylis-Hillman-type reaction of isatin-derived *N*-Boc ketimines **60** with activated nitroolefins **61** [51]. As illustrated in Scheme 19, chiral *Cinchona* alkaloid-derived thiourea **62** was selected as optimal catalyst to promote at only 2.5 mol% of catalyst loading the process in toluene as the solvent. The reaction carried out at -10 °C resulted in the formation of a range of chiral functionalised 3-aminooxindoles **63** with 66-88% yields, 90-98% de, and 54-94% ee. The catalyst system tolerated the presence of various substituents on the phenyl ring of the isatin substrates, but the reaction of a 5-brominated substrate ($R^3 = \text{Br}$) provided the lowest ee value (54% ee). In addition to 1-methyl-*N*-Boc ketimines ($R^1 = \text{Me}$), 1-benzyl- and 1-(1-(2,2-diethoxyethyl))-*N*-Boc ketimines were compatible ($R^1 = \text{Me}$ or $(\text{EtO})_2\text{CHCH}_2$). Concerning the nitroolefin scope, an activated nitroolefin having a *para*-chloro substituent ($\text{Ar} = p\text{-ClC}_6\text{H}_4$) provided comparable results (72-82% ee) to phenyl-substituted nitroolefins ($\text{Ar} = \text{Ph}$). To explain the stereoselectivity of the process, a mechanism is proposed in Scheme 19, beginning with the formation of intermediate **K** from hydrogen bonding

between the two N-H protons of the catalyst and the isatin substrate. Then, the nitroolefin activated by the tertiary amine group of the catalyst led to the generation of intermediate **L**. The latter finally provided the product along with the regenerated catalyst.

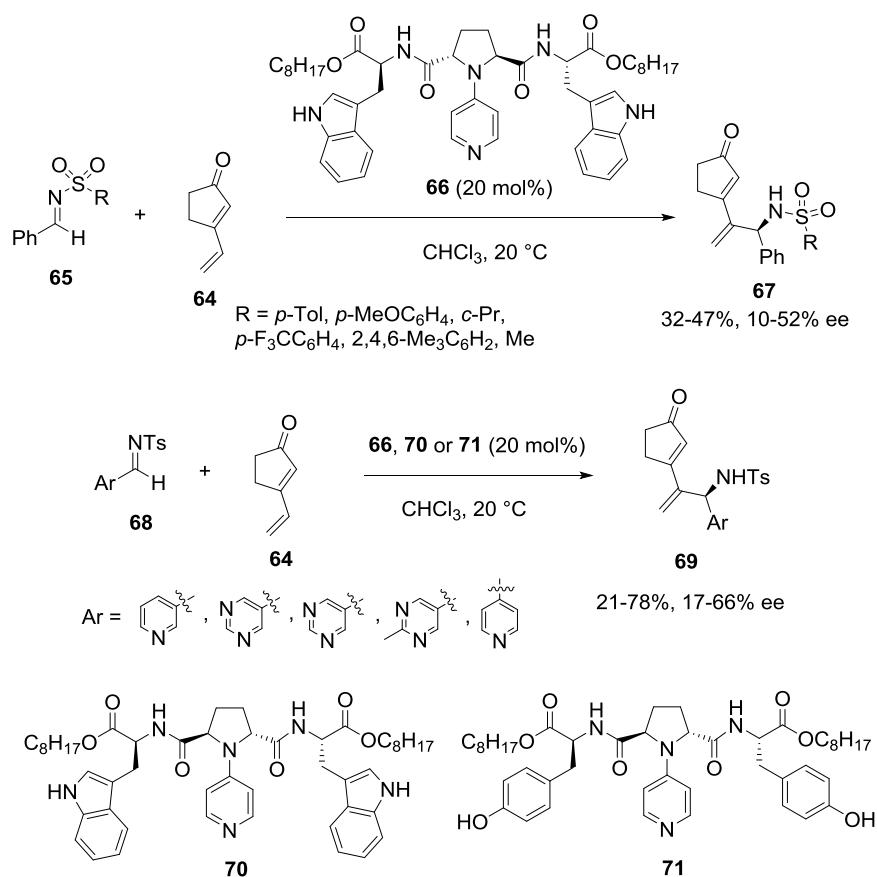


proposed mechanism (with $\text{Ar}^2 = \text{Ph}$, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{R}^5 = \text{H}$):



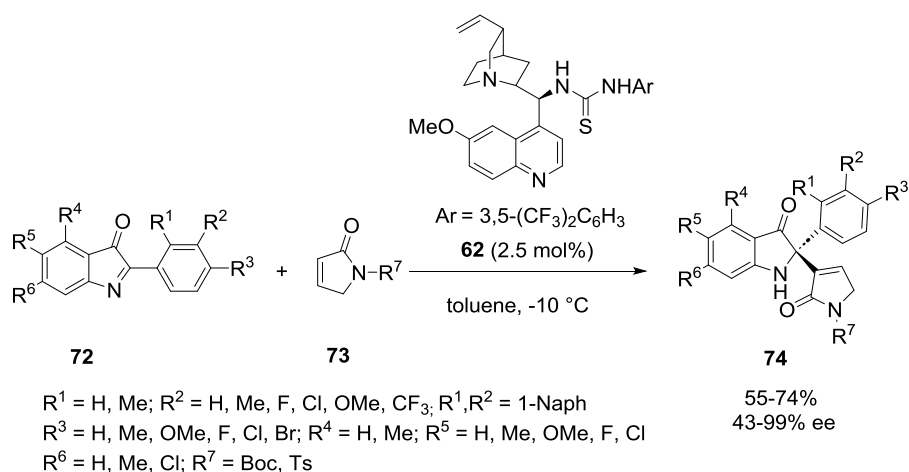
Scheme 19. Aza-Morita-Baylis-Hillman-type reaction of isatin-derived *N*-Boc ketimines with activated nitroolefins in the presence of a *Cinchona* alkaloid-derived thiourea catalyst.

In 2020, Browne and Morrill applied the technique of ball-milling to aza-Morita–Baylis–Hillman reactions of aldimines with acrylates catalysed by tertiary amines [52]. This methodology presented the advantage to be performed in the absence of solvent and required shorter reaction times. However, in the enantioselective version based on the use of 20 mol% of β -isocupreidine as catalyst, the process between *N*-tosyl benzaldimine and ethyl acrylate afforded the corresponding aza-Morita–Baylis–Hillman adduct in only low yield (20%) and moderate ee value (64% ee). More recently in 2023, Ueda and Kawabata described the first example of catalytic asymmetric γ -selective vinylogous aza-Morita–Baylis–Hillman reactions (Scheme 20) [53]. This occurred between 3-vinylcyclopentenone **64** and aromatic *N*-tosyl imines **65** under catalysis with 20 mol% of chiral 4-pyrrolidinopyridine catalyst **66** at 20 °C in chloroform. The regioselective process led exclusively to the corresponding chiral γ -adducts **67**. When phenyl *N*-tosyl imines **65** were used as substrates, products **67** were obtained with 32-47% yields and 10-52% ee. The scope was extended to heteroaromatic aldimines **68** which provided by reaction with 3-vinylcyclopentenone **64** catalysed by 4-pyrrolidinopyridine catalysts **66**, **70** or **71**, chiral γ -adducts **69** with comparable moderate yields (21-78%) and enantioselectivities (17-66% ee). In spite of the moderate enantioselectivity and yield, this work represented the first example of enantioselective γ -selective vinylogous aza-Morita–Baylis–Hillman reactions of conjugated dienes with aldimines, allowing an attractive challenge to provide densely functionalised chiral allylic amines.



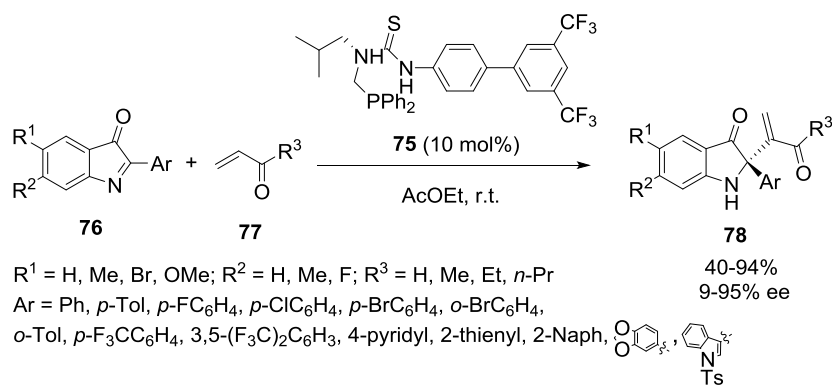
Scheme 20. Vinylogous aza-Morita–Baylis–Hillman reactions of aromatic aldimines with 3-vinylcyclopentenone in the presence of 4-pyrrolidinopyridine catalysts.

In 2023, Zhao and Li developed the first enantioselective aza-Morita–Baylis–Hillman reaction of unactivated cyclic ketimines such as **72** (Scheme 21) [54]. The latter smoothly reacted at 30 °C in DCE with α,β -unsaturated γ -butyrolactams **73** in the presence of 20 mol% of chiral *Cinchona* alkaloid-derived thiourea **62** to give the corresponding chiral indolin-3-one derivatives **74** bearing a quaternary stereocentre. These highly functionalised products were achieved with 55-74% yields and generally high enantioselectivities (43-99% ee). Indeed, a range of variously substituted cyclic ketimines **72** reacted with homogeneously high enantioselectivities ($\geq 83\%$ ee) while a substrate bearing a methyl group at the *ortho*-position of the phenyl ring ($R^1 = \text{Me}$) yielded the desired product with only 43% ee. Moreover, the presence of an electron-deficient substituent at the C5-position ($R^5 = \text{F}, \text{Cl}$) was also found to decrease the enantioselectivities (52-68% ee). An even lower ee value (47% ee) was observed in the reaction of a substrate exhibiting a naphthyl substituent ($R^1, R^2 = 1\text{-Naph}$). In addition to use cyclic ketimines for the first time, this novel process presented the originality to involve α,β -unsaturated γ -butyrolactams as rare nucleophilic alkenes.

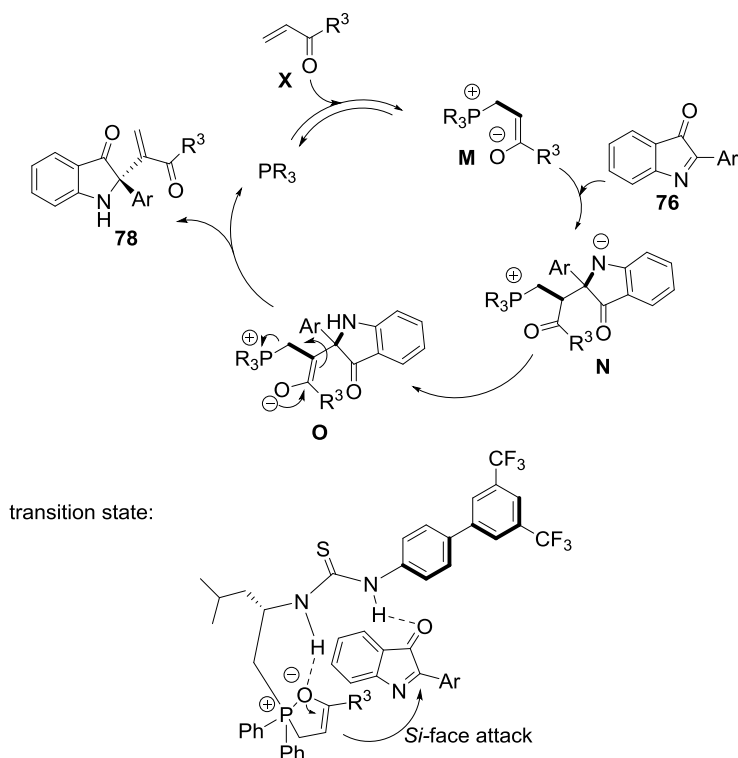


Scheme 21. Aza-Morita–Baylis–Hillman-type reaction of α,β -unsaturated γ -butyrolactams with cyclic ketimines in the presence of a *Cinchona* alkaloid-derived thiourea catalyst.

The same year, Wang et al. designed novel chiral phosphine **75** derived from L-leucine, which allowed highly enantioselective aza-Morita–Baylis–Hillman-type reactions between 3-oxindole ketimines **76** and vinyl ketones or acrolein **77** to be achieved (Scheme 22) [55]. When 10 mol% of this catalyst was employed at room temperature in ethyl acetate, the reaction of alkyl vinyl ketones ($R^3 = \text{alkyl}$) with 2-phenyl-3H-indol-3-one ($\text{Ar} = \text{Ph}, R^1 = R^2 = \text{H}$) led to chiral indolinones **78** with 90-94% yields and 90-91% ee. In addition, acrolein ($R^3 = \text{H}$) was also tolerated, reacting with variously substituted endocyclic ketimines. When the latter exhibited substituents at the *meta*- or *para*-position of the phenyl ring (Ar), they provided products with uniformly excellent enantioselectivities ($\geq 87\%$ ee) while sterically hindered *ortho*-substituted substrates ($\text{Ar} = o\text{-BrC}_6\text{H}_4, o\text{-Tol}$) reacted with dramatically lower ee values (9-11% ee). The authors proposed the mechanism depicted in Scheme 22 which begins with the reversible conjugate addition of the phosphine catalyst to the α,β -unsaturated carbonyl compound producing intermediate **M**. Then, the latter adds to the ketimine to give intermediate **N**, which subsequently undergoes a 1,3-proton shift to form enolate **O**. Subsequently, a β -elimination yields the final product along with regenerated organocatalyst. The stereoselectivity of the reaction can be explained by the transition state shown in Scheme 22, in which the nucleophilic addition of intermediate **A** to the ketimine occurs through the less hindered *Si*-face.



proposed mechanism (with $R^1 = R^2 = \text{H, X} = \text{PR}_3$):



Scheme 22. Aza-Morita-Baylis-Hillman-type reaction of 3-oxindole ketimines with vinyl ketones/acrolein in the presence of a bifunctional phosphine catalyst.

3. Asymmetric organocatalysed reactions of Morita-Baylis-Hillman adducts

Morita-Baylis-Hillman adducts have been extensively employed in different types of reactions, such as annulations, allylic alkylations, domino and tandem processes, Friedel-Crafts reactions, hydrogenations, rearrangement reactions, etc.

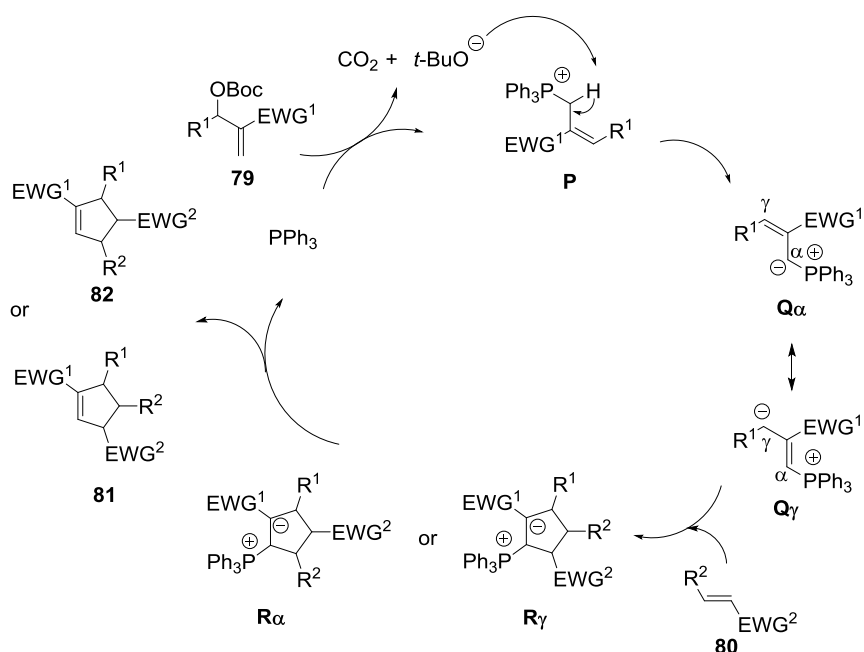
3.1. Annulations of Morita-Baylis-Hillman carbonates, acetates, naphthoates and alcohols

Asymmetric organocatalytic cycloadditions have been extensively developed to reach in one step chiral cyclic complex molecules [20,x-y,56]. Different types of (formal) cycloadditions of Morita–Baylis–Hillman adducts, such as [3+2], [4+1], [4+2], [3+3], [5+3], [4+3], [3+6], [2+1], etc have been demonstrated to be efficient approaches for the preparation of a diversity of cyclic functionalised products [15,19]. However, it must be recognised that enantioselective versions of these processes still remain rare, with the most employed methodology being the [3+2] cycloaddition to prepare chiral five-membered rings. Many examples cited in this Section could be considered as domino reactions and, consequently, could also appear in Section 3.3 dealing with domino reactions.

3.1.1. [3+2] Annulations

3.1.1.1. Phosphine catalysts

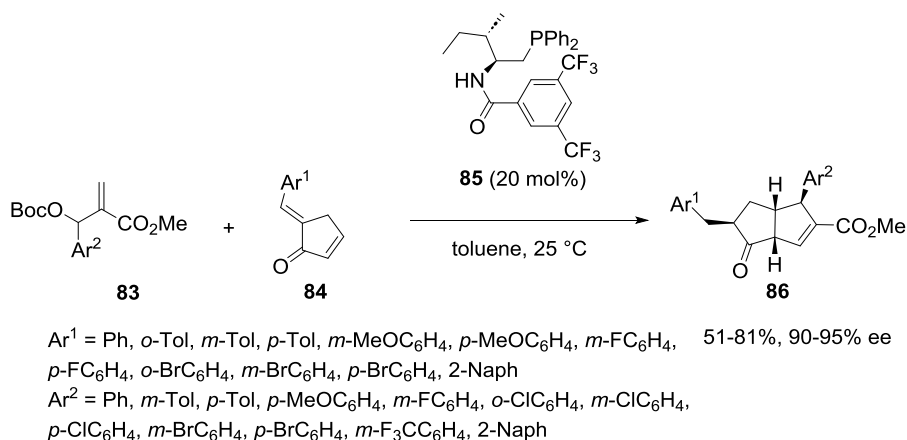
The [3+2] cycloaddition occurs between a dipolarophile and a 1,3-dipolar compound to produce a five-membered cyclic product [57]. In 2003, Lu et al. reported the first [3+2] annulation between Morita–Baylis–Hillman adducts **79** and electron-deficient alkenes **80** catalysed by achiral phosphine PPh₃ [58]. The mechanism depicted in Scheme 23 begins with the addition of the phosphine catalyst to the Morita–Baylis–Hillman adduct **79**, delivering intermediate **P**. Subsequently, the latter releases CO₂ and *t*-BuO[−], which deprotonates the α-hydrogen atom in **P** to afford ylide intermediates **Q**. Then, [3+2] cycloaddition between **Q** and dipolarophile **80** occurs, resulting in the formation of phosphonium anions **R**, which undergo elimination of PPh₃ and delivers the final product **81** or **82**.



Scheme 23. Mechanism of PPh₃-catalysed [3+2] annulation of Morita–Baylis–Hillman adducts with electron-deficient alkenes.

In 2010, Tang and Zhou disclosed the first asymmetric version by using spirobiindane-based chiral phosphines as catalysts in intramolecular [3+2] cycloadditions of modified Morita–Baylis–Hillman adducts, allowing enantioselectivities of up to 92% ee to be achieved [59]. In 2011, Barbas et al. described the first asymmetric intermolecular [3+2] annulation between Morita–Baylis–Hillman carbonates and methyleneindolinones promoted by chiral trialkyl bisphosphines to access chiral spirooxindoles with enantioselectivities of 46-99% ee [60]. Inspired by these pioneering works, a wide array of asymmetric annulations between Morita–Baylis–Hillman adducts and a diversity of dipolarophiles have been successfully developed, relying on the catalytic formation of chiral allylic N- or P-ylides used as reactive 1,3-dipoles. For example, isatin-derived Morita–Baylis–Hillman carbonates have demonstrated their great potential in the construction of chiral spirocyclic cyclopentene/pyrrolidine/dihydrothiophene oxindole derivatives by reacting with electron-deficient C=C [61], C=N, or C=S double bonds [62]. In these reactions and according to the more general mechanism shown in Scheme 23, the isatin-derived Morita–Baylis–Hillman carbonate undergoes a nucleophilic addition with the chiral Lewis base catalyst to give a zwitterionic intermediate. Then, an asymmetric [3+2] cycloaddition of the latter with the electron-deficient double bond of a dipolarophile occurs through α/γ -regioselectivity to

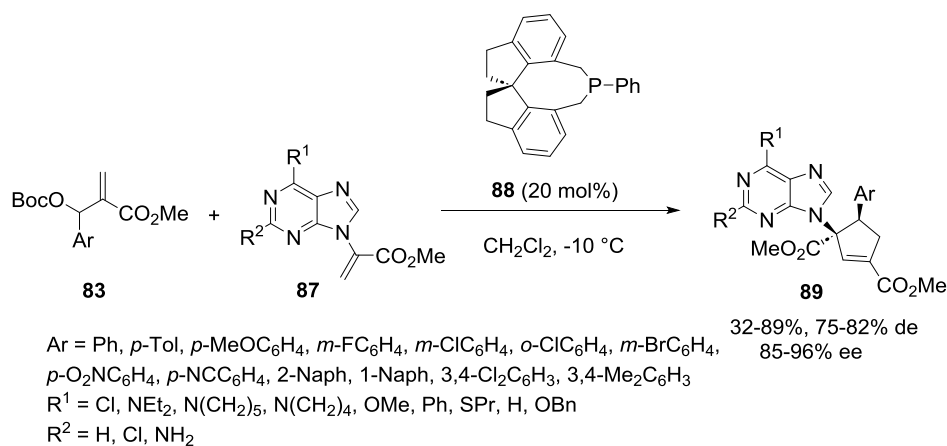
generate the corresponding functionalised spirooxindoles. Along with isatin-derived Morita–Baylis–Hillman carbonates, more simple Morita–Baylis–Hillman carbonates have been widely involved with many types of activated alkenes [59,63], such as maleimides, isatylidenemalononitriles, 2-arylideneindane-1,3-diones, methyleneindolinones, methylene-benzofuranones, barbiturate-derived alkenes and cyclic 1-aza-dienes. Meanwhile, asymmetric [3+2] cycloadditions of Morita–Baylis–Hillman carbonates with less activated alkenes still remain rare. To fill this gap, Guo et al. investigated in 2018 cyclopentenones as dipolarophiles in these reactions [64]. As depicted in Scheme 24, Morita–Baylis–Hillman carbonates **83** reacted with 5-arylmethylenecyclopent-2-enones **84** in the presence of 20 mol% of chiral bifunctional phosphine catalyst **85** to give at 25 °C in toluene chiral bicyclic products **86**. These biologically interesting products were achieved in moderate to good yields (51-81%) and uniformly excellent ee values (90-95% ee). It was found that alkyl-substituted Morita–Baylis–Hillman carbonate (*i*-Pr instead of Ar²) did not undergo the reaction as well as alkyl-substituted cyclopentenones (Et instead of Ar¹).



Scheme 24. [3+2] Annulation of Morita–Baylis–Hillman carbonates with 5-arylmethylenecyclopent-2-enones.

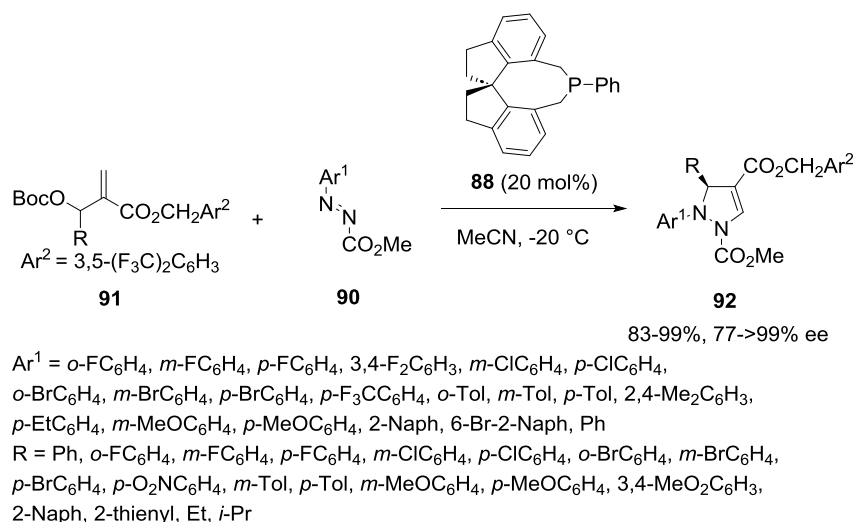
Chiral cyclic nucleosides and their derivatives are known to display antiviral and antitumor activities and, consequently, their synthesis is challenging [65]. In this context, Guo and Xie investigated in 2018 the enantioselective [3+2] cycloaddition of Morita–Baylis–Hillman carbonates **83** with α -purine-substituted acrylates **87** [66]. As illustrated in Scheme 25, when this annulation was performed at -10 °C in dichloromethane as the solvent in the presence of 20 mol% of spirocyclic chiral phosphine **88**, it led to chiral

carbocyclic nucleosides **89** bearing a quaternary stereocentre and a C=C double bond in the cyclopentyl moiety. These chiral cyclopentyl purine nucleosides were produced in 32-89% yields, 75-82% de, and 85-96% ee. Actually, all the substrates reacted with good yields ($\geq 73\%$) except a guanine-derived acrylate ($R^2 = \text{NH}_2$) which afforded the corresponding product with only 32% yield.



Scheme 25. [3+2] Annulation of Morita–Baylis–Hillman carbonates with α -purine-substituted acrylates.

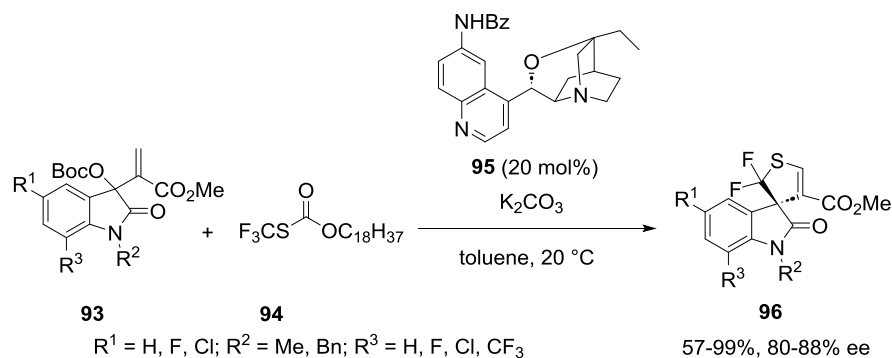
While C=C, C=N, and C=O double bonds have been widely applied as dipolarophiles in enantioselective [3+2] cycloadditions, a N=N double bond was investigated for the first time by Guo et al., in 2019 [67]. The reaction occurred at -20 °C between diazenes **90** and Morita–Baylis–Hillman carbonates **91** in acetonitrile as the solvent (Scheme 26). It required the use of 20 mol% of spirocyclic chiral phosphine **88** to allow the synthesis of chiral pharmaceutically interesting functionalised dihydropyrazoles **92** in 83-99% yields and 77->99% ee. Actually, in all cases of aryl-substituted Morita–Baylis–Hillman carbonates (R = aryl), the reaction provided excellent enantioselectivities (90->99% ee) while lower ee values (77-80% ee) were obtained for alkyl-substituted substrates (R = Et, *i*-Pr).



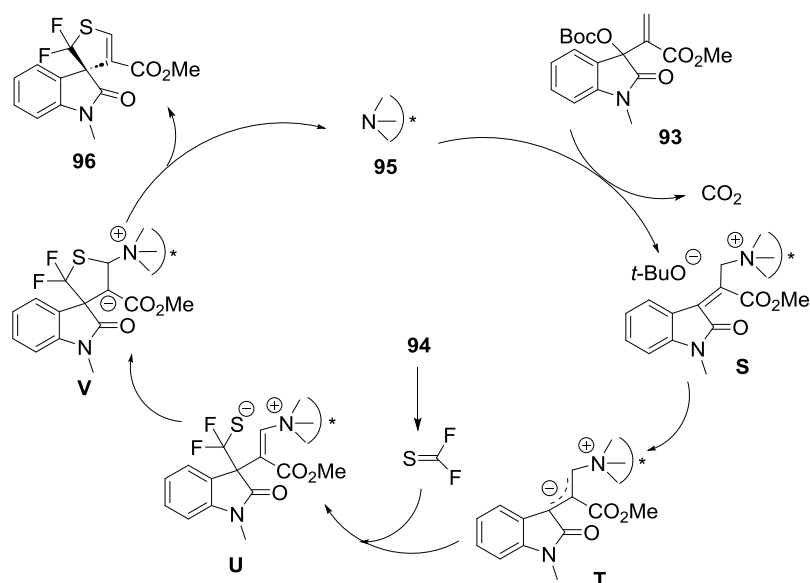
Scheme 26. [3+2] Annulation of Morita–Baylis–Hillman carbonates with diazenes.

3.1.1.2. *Cinchona* alkaloid catalysts

Along with chiral phosphines, *Cinchona* alkaloids, such as α - or β -isocupreine, have been successfully used as catalysts in enantioselective [3+2] cycloadditions of isatin-derived Morita–Baylis–Hillman carbonates with different dipolarophiles including aromatic nitroolefins [68]. In 2017, Shi et al. described the first asymmetric [3+2] cycloaddition of isatin-derived Morita–Baylis–Hillman carbonates **93** with Zard's reagent **94** catalysed by a chiral tertiary amine [69]. The reaction was promoted at 20 °C by 20 mol% of *Cinchona* alkaloid **95** in toluene to produce chiral difluoromethylthiolated spirocyclic oxindoles **96** which represent highly interesting fluorinated complex molecules for medicinal chemistry (Scheme 27). A range of these functionalised tricyclic products were produced in 57-99% yields and 80-88% ee. The catalyst both activated the Morita–Baylis–Hillman carbonate and Zard's reagent. In the proposed mechanism depicted in Scheme 27, the reaction began with the formation of intermediate **S** from the addition of the amine catalyst to the isatin. Then, the latter was deprotonated in the presence of strong Brønsted base *t*-BuO⁻ to give allylic ylide **T** which underwent a nucleophilic addition to CF₂=S species *in situ* generated from Zard's reagent **94**, leading to intermediates **U**. Then, the latter cyclised into intermediate **V**, which was subsequently submitted to elimination of the catalyst to afford the final product.



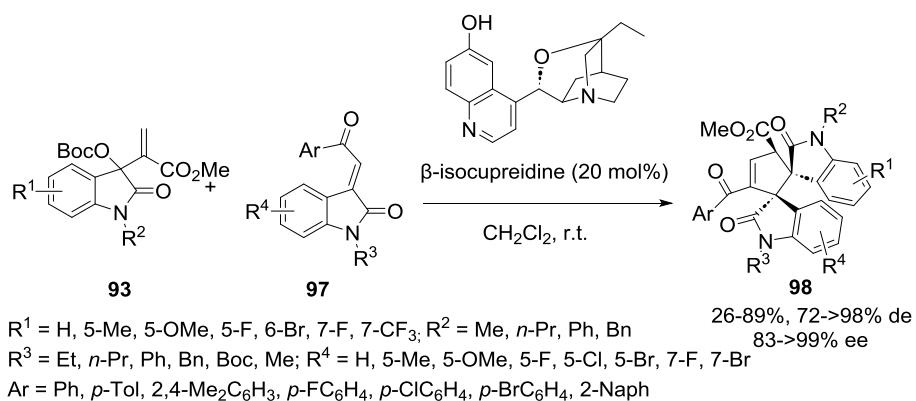
proposed mechanism (with $\text{R}^1 = \text{R}^3 = \text{H}, \text{R}^2 = \text{Me}$):



Scheme 27. [3+2] Annulation of isatin-derived Morita–Baylis–Hillman carbonates with Zard’s reagent.

In 2018, chiral dispirooxindoles including two adjacent quaternary spirostereocentres were synthesised by Chen and Cui [70]. The synthetic methodology was based on a [3+2] cycloaddition between isatin-derived Morita–Baylis–Hillman carbonates **93** and 3-methyleneoxindoles **97** promoted by β -isocupreidine (Scheme 28). The highly regio- and stereoselective [3+2] cycloaddition led at room temperature to a series of densely functionalised chiral 3,3'-cyclopentenyl-dispirooxindoles **98** often obtained with both high diastereo- (72->98% de) and enantioselectivities (83->99% ee) in generally high yields (26-89%) by employing 20 mol% of the catalyst loading in dichloromethane as solvent. Uniformly excellent results were obtained regardless of the electronic nature and position of substituents on the phenyl ring of the Morita–Baylis–Hillman carbonates. Moreover, 3-methyleneoxindoles could bear different substituents on the aromatic ring of the oxindole

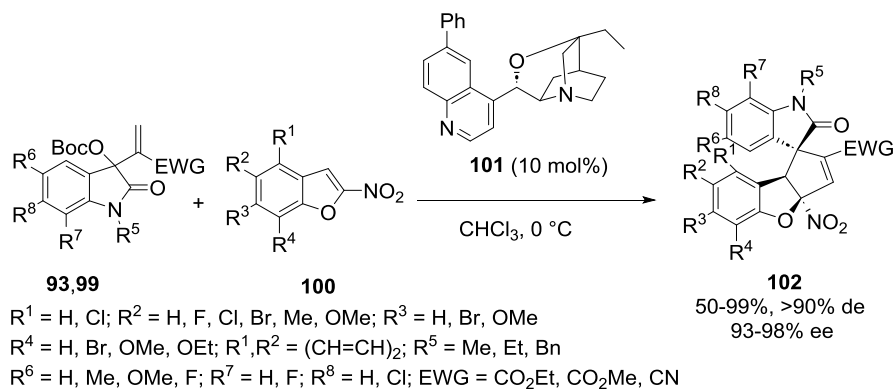
moiety (R^4) and on the N1 position (R^3). The lowest diastereoselectivity (72% de vs >92% de in all other cases of 3-methyleneoxindoles) was found in the reaction of a *N*-ethyl-substituted 3-methyleneoxindole ($R^3 = \text{Et}$) albeit combined with 90% yield and 99% ee. The ee values were always $\geq 87\%$ ee except in the reaction of a 3-methyleneoxindole bearing an electron-withdrawing group at the N1 position ($R^3 = \text{Boc}$, 83% ee) which also gave the lowest yield (26%). Furthermore, a bulky 2-naphthyl-substituted substrate ($\text{Ar} = 2\text{-Naph}$) also provided a slightly lower ee value (85% ee).



Scheme 28. [3+2] Annulation of isatin-derived Morita–Baylis–Hillman carbonates with 3-methyleneoxindoles.

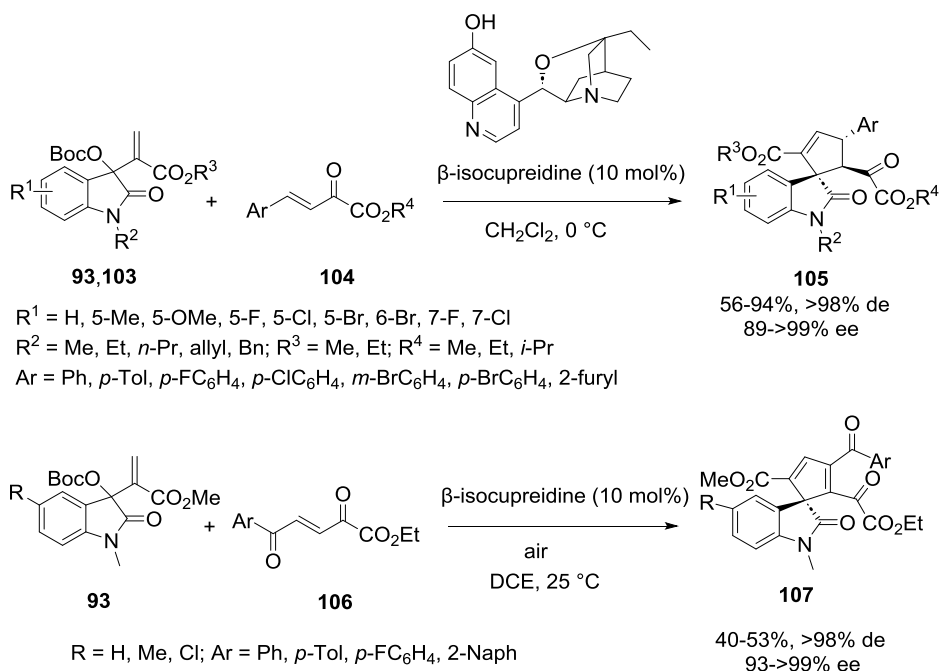
The cyclopenta[*b*]benzofuran moiety constitutes the skeleton of many biologically active products. With the aim of developing a novel route to these important products, Yuan et al. developed in 2019 the first organocatalysed enantioselective dearomative [3+2] cycloaddition of isatin-derived Morita–Baylis–Hillman carbonates **93,99** with 2-nitrobenzofurans **100** (Scheme 29) [71]. This process carried out at 0 °C by 10 mol% of *Cinchona* alkaloid **101** in chloroform delivered very complex chiral cyclopenta[*b*]benzofuran derivatives **102** exhibiting three contiguous stereocentres, including a spiro-quaternary chiral centre. Remarkably, these highly elaborated polycyclic skeletons were achieved as almost single diastereomers (>90% de) in moderate to quantitative yields (50-99%) and uniformly excellent enantioselectivities (93-98% ee) whatever the nature and electronic properties of substituents exhibited on the phenyl rings of both the two substrates. In addition to isatin-derived Morita–Baylis–Hillman carbonates derived from acrylates (EWG = CO_2Et , CO_2Me), the scope of the reaction was extended to an isatin derived from acrylonitrile (EWG = CN) which afforded the corresponding chiral polycyclic product albeit with both the lowest ee value (93% ee) and

yield (50%) probably due to its easy decomposition. It must be noted that this novel methodology represents the first example of enantioselective organocatalysed reaction involving 2-nitrobenzofurans.



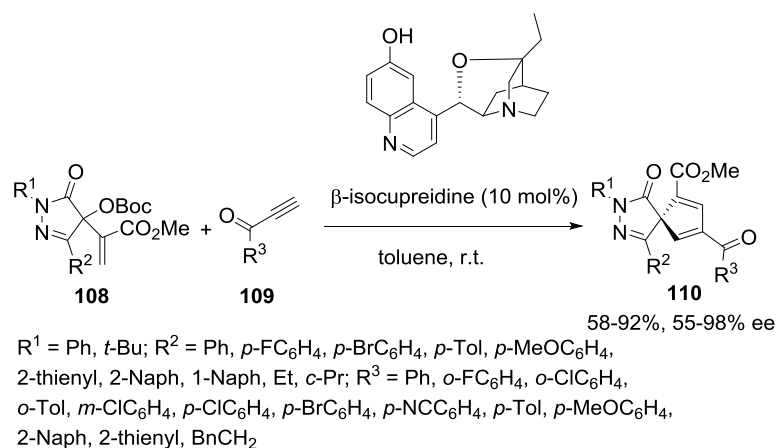
Scheme 29. [3+2] Annulation of isatin-derived Morita–Baylis–Hillman carbonates with 2-nitrobenzofurans.

The same year, Chen and Cui developed enantioselective [3+2] cycloadditions of isatin-derived Morita–Baylis–Hillman carbonates with β,γ -unsaturated α -ketoesters (Scheme 30) [72]. Under catalysis with 10 mol% of β -isocupreidine in dichloromethane as solvent, the reaction of a range of isatin-derived Morita–Baylis–Hillman carbonates **93,103** with β,γ -unsaturated α -ketoesters **104** resulted in the regioselective formation of chiral spirooxindoles **105** bearing a cyclopentene ring with good to excellent yields (56-94%) and as almost single diastereo- (>98% de) and enantiomers (89->99% ee). These remarkable results were obtained regardless of the electronic nature and position of substituents on the phenyl rings of both the two substrates. The scope of the methodology was also extended to another type of β,γ -unsaturated α -ketoesters **106**. In this case, the reaction with isatin-derived Morita–Baylis–Hillman carbonates **93** performed at 25 °C in chloroform as solvent afforded chiral spirooxindoles **107** exhibiting a cyclopentadiene moiety in moderate yields (40-53%) albeit combined with excellent enantioselectivities (93->99% ee), as illustrated in Scheme 30.



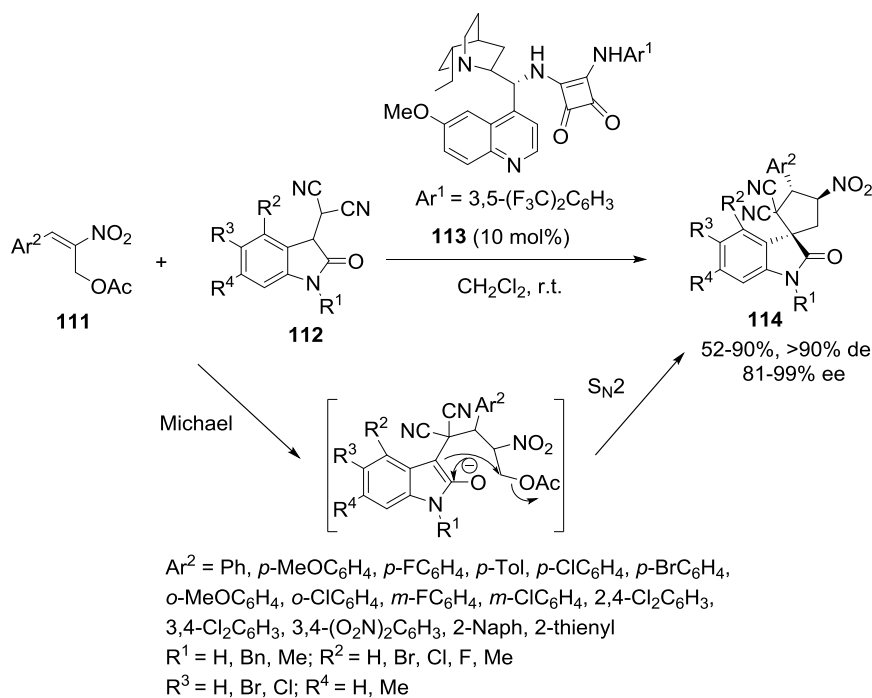
Scheme 30. [3+2] Annulations of isatin-derived Morita–Baylis–Hillman carbonates with β,γ -unsaturated α -ketoesters.

In 2022, Wang et al. developed enantioselective [3+2] annulations of pyrazolone-derived Morita–Baylis–Hillman carbonates **108** with alkynyl ketones **109** (Scheme 31) [73]. Among a series of *Cinchona* alkaloids investigated, β -isocupreidine was selected as optimal catalyst to promote at 10 mol% of catalyst loading in toluene at room temperature the reaction of a wide variety of both Morita–Baylis–Hillman carbonates and alkynyl ketones to afford the corresponding chiral spiro[cyclopentadiene-pyrazolone] derivatives **110** with 58-92% yields and 55-98% ee. The poorest results (58% yield, 55% ee) were obtained in the reaction of an alkyl alkynyl ketone ($R^3 = \text{BnCH}_2$).



Scheme 31. [3+2] Annulation of pyrazolone-derived Morita–Baylis–Hillman carbonates with alkynyl ketones.

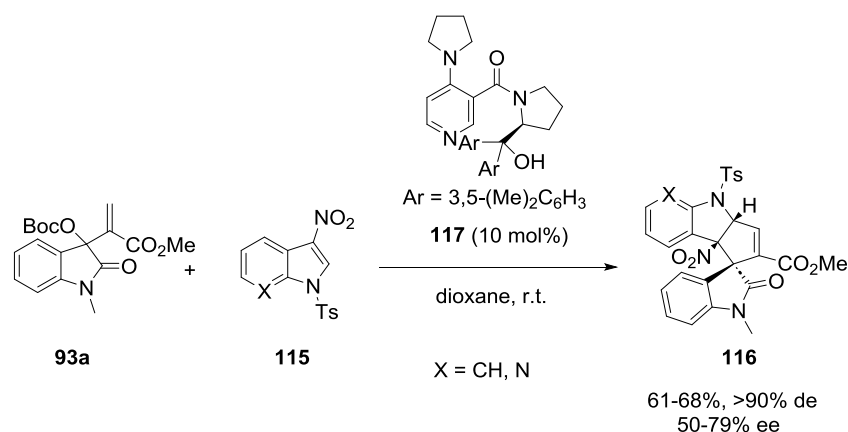
Earlier in 2021, another type of enantioselective [3+2] annulations was developed by Han et al., involving Morita–Baylis–Hillman-type acetates **111** and 2-(2-oxindolin-3-yl)malononitriles **112** as substrates (Scheme 32) [74]. Under catalysis with 10 mol% of chiral quinine-derived squaramide catalyst **113** in dichloromethane as solvent, the process evolved at room temperature through successive Michael addition of Morita–Baylis–Hillman acetates **111** to oxindolin-3-yl-malononitriles **112** followed by an intramolecular S_N2 reaction to give highly functionalised chiral spirocyclopentane oxindoles **114** as single regio- as well as diastereomers (>90% de) with 52-90% yields and uniformly high enantioselectivities (81-99% ee). This constituted the first use of 2-(2-oxindolin-3-yl) malononitriles as 1,2-carbon bisnucleophiles.



Scheme 32. [3+2] Annulation of Morita–Baylis–Hillman-type acetates with 2-(2-oxoindolin-3-yl)malononitriles.

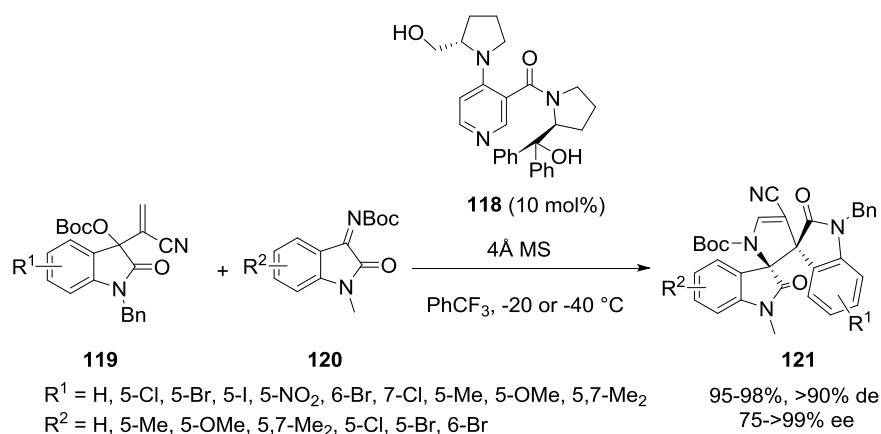
3.1.1.3. DMAP-type catalysts

In 2017, Chen et al. developed regio- and diastereoselective [3+2] cycloaddition of isatin-derived Morita–Baylis–Hillman carbonate **93a** with 3-nitro-7-azaindoles **115** (X = N) to give the corresponding complex polycyclic spirooxindoles **116** containing fused azaindoline skeletons and vicinal quaternary centres [75]. The racemic reactions were performed in the presence of a DMAP as catalyst. An enantioselective version was achieved at room temperature by employing 10 mol% of chiral DMAP derivative **117** in dioxane as solvent, resulting in the synthesis of enantioenriched products **116** with high diastereoselectivities (>90% de) albeit combined with both moderate yields (61-68%) and enantioselectivities (50-79% ee), as illustrated in Scheme 33.

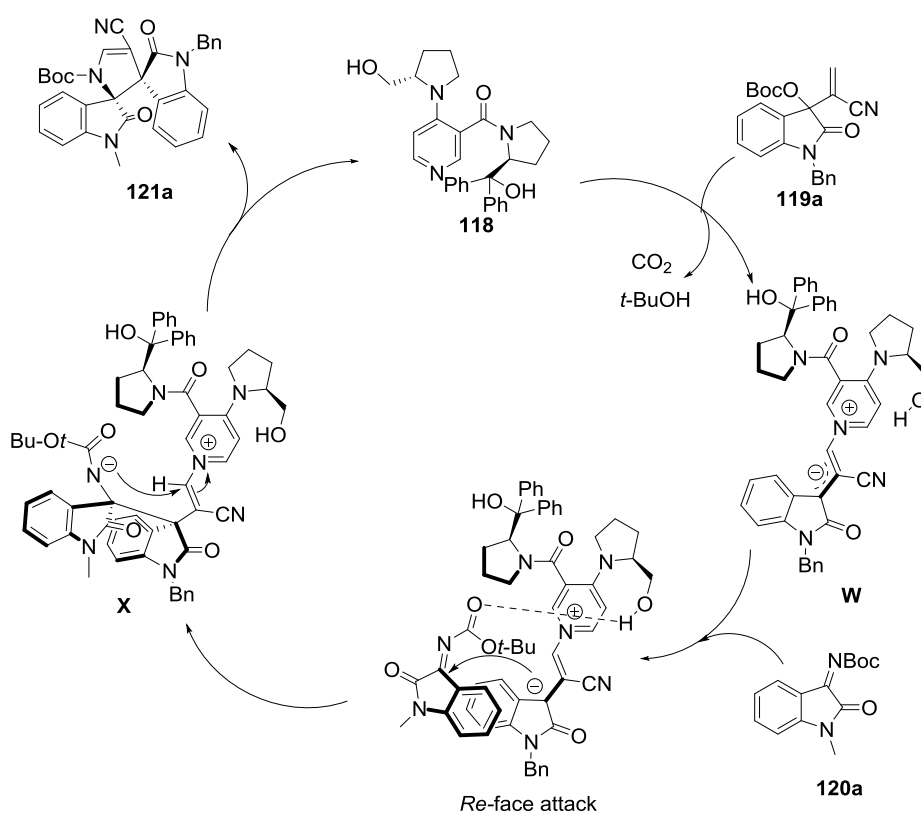


Scheme 33. [3+2] Annulation of an isatin-derived Morita–Baylis–Hillman carbonate with 3-nitro-(7-aza)indoles.

With the aim of synthesizing other highly attractive molecules for medicinal chemistry, such as chiral bispirooxindoles, the same authors designed novel multifunctional DMAP catalyst **118** to be investigated in enantioselective [3+2] cycloaddition of isatin-derived Morita–Baylis–Hillman carbonates **119** with isatin-derived *N*-Boc-ketimines **120** [76]. Using 10 mol% of this organocatalyst in PhCF₃ as the solvent, the reaction occurred at -20 or -40 °C through high γ -regioselectivity, producing highly complex chiral 1,2-bispirooxindoles **121** including a dihydropyrrolidine motif in uniformly excellent yields (95-98%) and high to remarkable enantioselectivities (75->99% ee). Moreover, the products were produced as almost single diastereomers (>90% de), as presented in Scheme 34. In general, Morita–Baylis–Hillman carbonates exhibiting electron-withdrawing groups on the phenyl ring reacted with outstanding enantioselectivity while the reaction of carbonates with electron-donating groups provided lower enantiocontrol (75-79% ee with R¹ = 5-Me, 5-OMe, 5,7-Me₂). On the other hand, isatin-derived *N*-Boc-ketimines bearing electron-donating substituents on the phenyl ring led to the desired products with better ee values than ketimines with electron-withdrawing groups (78-88% ee with R² = 5-Cl, 5-Br, 5-I, 6-Br). A mechanism is proposed in Scheme 34 in which the catalyst attacked the Morita–Baylis–Hillman carbonate to give zwitterionic allylic ylide **W**. Then, the latter attacked the ketimine from the *Re*-face with the possible assistance of a hydrogen bonding interaction between the hydroxy group of the pyrrolidine moiety and the *N*-Boc group, which led to intermediate **X**. Finally, the product was generated after cyclisation and release of the catalyst.



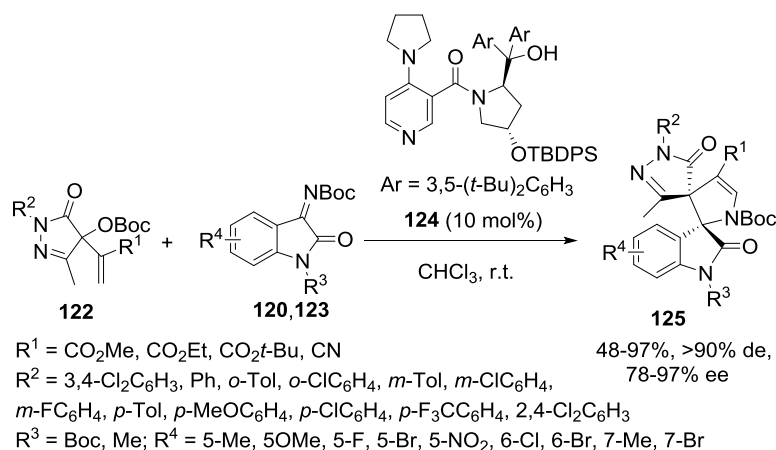
proposed mechanism (with $\text{R}^1 = \text{R}^2 = \text{H}$)



Scheme 34. [3+2] Annulation of isatin-derived Morita–Baylis–Hillman carbonates with isatin-derived *N*-Boc-ketimines.

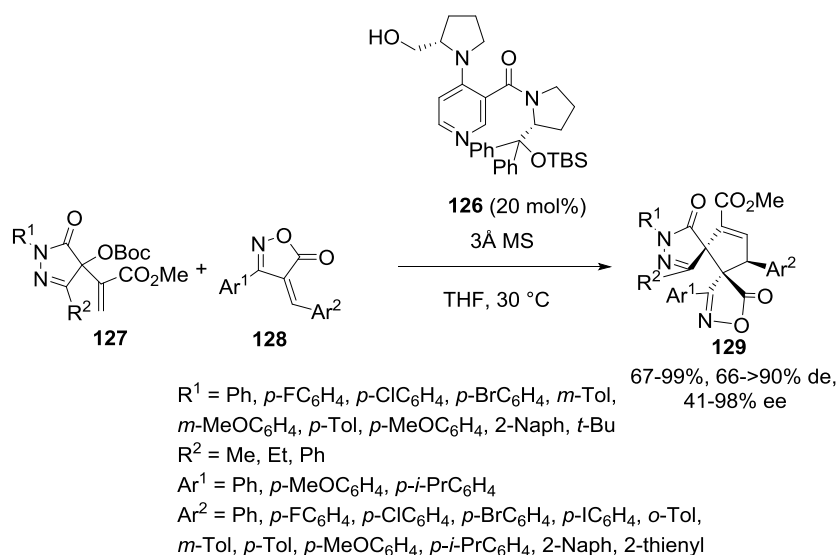
Chiral bispiropyrazolones also constitute challenging molecules for medicinal chemistry. In 2022, Han and Zhan reported a novel route to this type of molecules on the basis of an enantioselective [3+2] cycloaddition between pyrazolone-derived Morita–Baylis–Hillman carbonates **122** and isatin-derived ketimines **120,123** catalysed by a chiral DMAP-derived catalyst (Scheme 35) [77]. Indeed, in the presence of 10 mol% of catalyst **124** in chloroform

as solvent, these substrates reacted at room temperature to produce very complex chiral bispiro[pyrazolone-dihydropyrrole-oxindole] products **125** bearing two contiguous stereocentres with 48-97% yields, and both high diastereo- (>90% de) and enantioselectivities (78-97% ee).

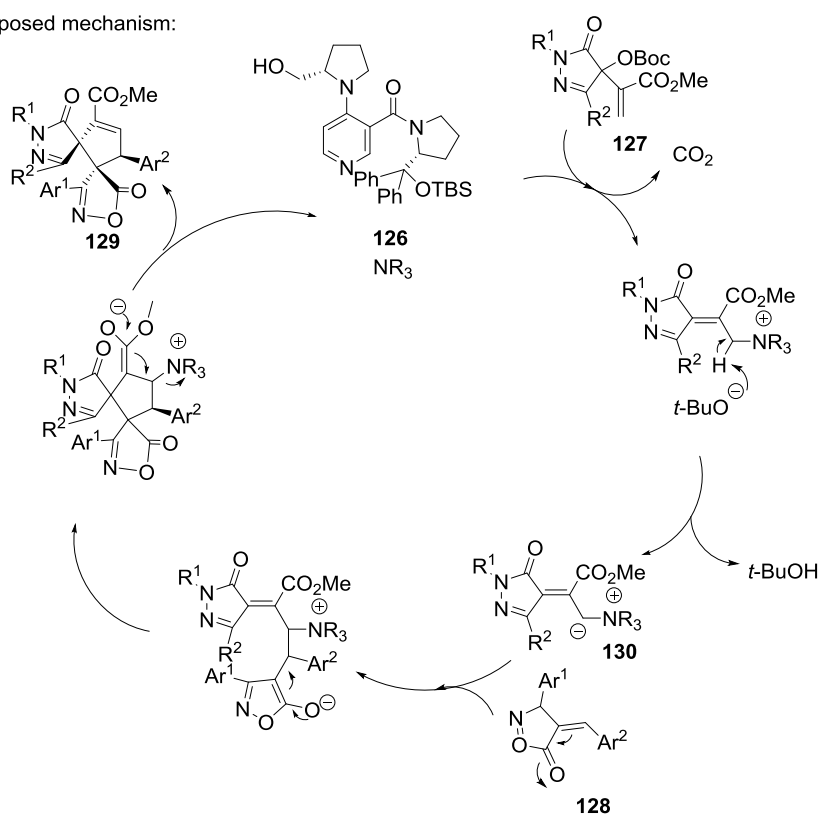


Scheme 35. [3+2] Annulation of pyrazolone-derived Morita–Baylis–Hillman carbonates with isatin-derived ketimines.

In 2024, Wang et al. employed 20 mol% of related chiral DMAP-derived chiral catalyst **126** in THF at 30 °C to promote an asymmetric [3+2] annulation between pyrazolone-based Morita–Baylis–Hillman carbonates **127** with alkylidenyl isoxazolones **128** [78]. The process afforded under mild conditions chiral bispirocyclic pyrazolones **129** bearing vicinal all-carbon quaternary stereocentres within an imbedded cyclopentene ring scaffold in 67-99% yields; 66- >90% de, and 41-98% ee, as shown in Scheme 36. This reaction exhibited a wide substrate range and good functional group tolerance. In almost all cases, the products were obtained as almost single diastereomers (>90% de). The authors proposed the mechanism depicted in Scheme 36, beginning with the nucleophilic addition of the DMAP-derived chiral catalyst onto the Morita–Baylis–Hillman carbonate, which resulted in the formation of allylic nitrogen ylide intermediate **130** with concomitant release of *t*-BuOH and CO₂. Then, the latter underwent two subsequent Michael additions with alkylidenyl isoxazolone to deliver the final cycloadduct along with regenerated catalyst.



proposed mechanism:

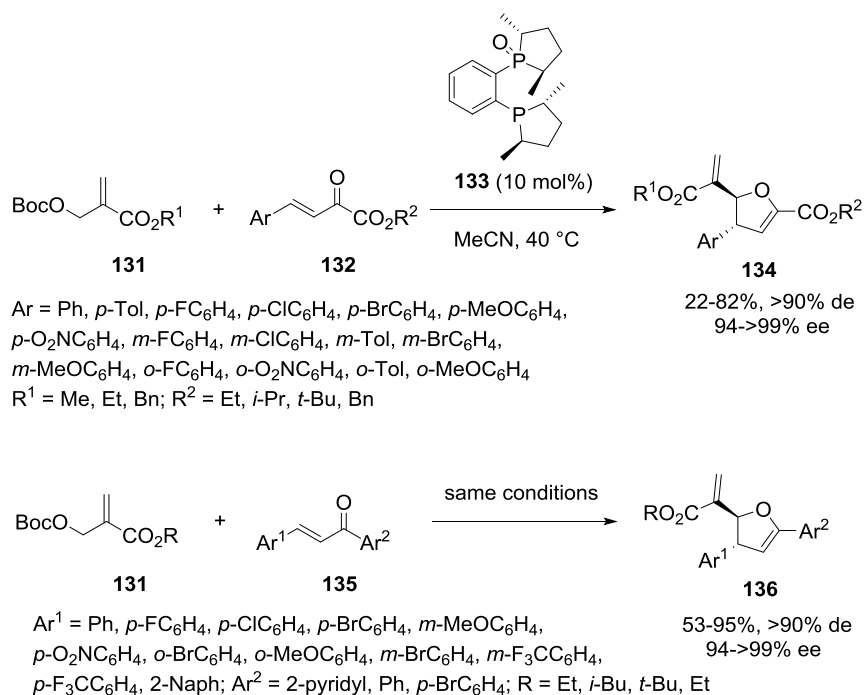


Scheme 36. [3+2] Annulation of pyrazolone-derived Morita–Baylis–Hillman carbonates with alkylidene isoxazolones.

3.1.2. [4+1] Annulations

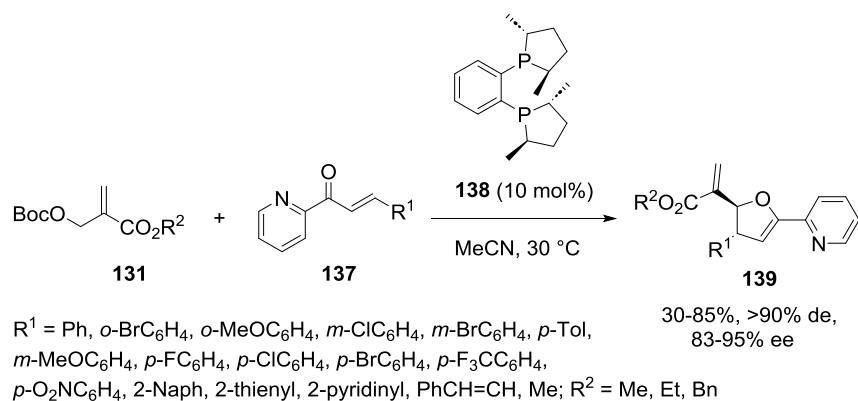
3.1.2.1. With α,β -unsaturated ketones

In contrast to the popularity of the asymmetric [3+2] cycloaddition, asymmetric [4+1] annulations remain less explored [79]. Morita–Baylis–Hillman carbonates can be used as C1 synthons in many asymmetric annulations, such as [4+1] formal cycloadditions, especially for the construction of diversified heterocycles [80]. However, compared with enantioselective [3+2] annulations of Morita–Baylis–Hillman adducts, asymmetric [4+1] annulations of these compounds is much less developed. In 2015, Fu and Kramer described the first example of enantioselective organocatalysed [4+1] annulations of Morita–Baylis–Hillman-allenic-type acetates with sulfonamides, which provided chiral dihydropyrroles with enantioselectivities of up to 93% ee by using a novel chiral spirophosphine catalyst [81]. Later in 2017, Li et al. developed the asymmetric [4+1] annulation of Morita–Baylis–Hillman-type carbonates **131** with β,γ -unsaturated α -keto esters **132** [82]. The reaction was performed at 40 °C in acetonitrile under 1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]-benzene monoxide catalysis. Indeed, in the presence of 10 mol% of chiral phosphine **133**, the annulation afforded a range of chiral 2,3-dihydrofurans **134** as almost single diastereomers (>90% de) with generally high yields (22–82%) and uniformly excellent enantioselectivities (94–>99% ee), as illustrated in Scheme 37. Electron-withdrawing and electron-donating substituents on the phenyl ring of the β,γ -unsaturated α -keto ester were all tolerated, affording the corresponding products in good yields (60–82%), but lower yields (22–33%) were obtained in the reaction of β,γ -unsaturated α -keto esters bearing a nitro group on the phenyl ring. The same conditions could be applied to the asymmetric [4+1] annulation of Morita–Baylis–Hillman-type carbonates **131** with chalcones **135** which afforded the corresponding chiral 2,3-dihydrofurans **136** as single diastereomers (>90% de) in 53–95% yields and 94–>99% ee, as shown in Scheme 37.



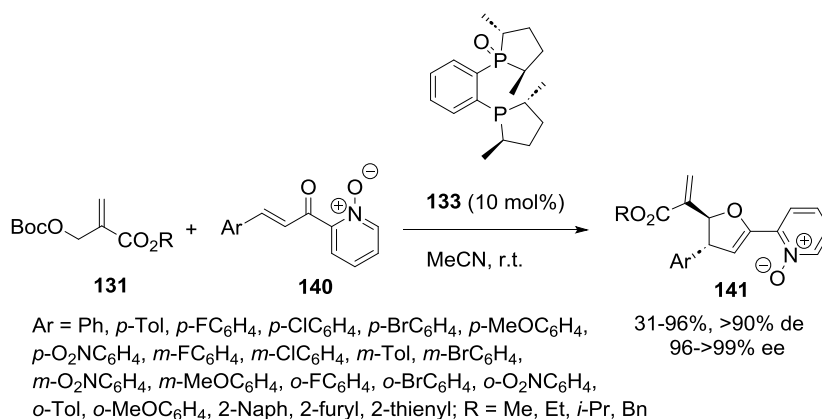
Scheme 37. [4+1] Annulations of Morita–Baylis–Hillman-type carbonates with β,γ -unsaturated α -keto esters and chalcones.

Given the importance of 2-enoylpyridines, in 2018 Li and Li developed an efficient organocatalytic asymmetric [4+1] annulation of Morita–Baylis–Hillman carbonates **131** with 2-enoylpyridines **137** (Scheme 38) [83]. By using at 30 °C 10 mol% of bisphosphine **138** as optimal catalyst in acetonitrile as the solvent, the reaction furnished a series of chiral functionalised 2,3-dihydrofurans **139** featuring pyridine motifs as almost single diastereomers (>90% de) in 30-85% yields and 83-95% ee. It was found that the nature of the ester group (R²) of the Morita–Baylis–Hillman carbonates affected the yield of the reaction without any discernible impact on the enantioselectivity (R² = Me, Et, Bn: 94-95% ee). Indeed, increasing the size of the ester group led to lower yields (R² = Me: 81%, R² = Et: 72%, R² = Bn: 54%). Furthermore, variously substituted 2-enoylpyridines were compatible. Even heteroaromatic substrates (R¹ = 2-thienyl, 2-pyridinyl) were tolerated, leading to the corresponding products with good yields (60-63%) and 94% ee. Interestingly, even aliphatic 2-enoylpyridines (R¹ = PhCH=CH, Me) also reacted smoothly to give the desired chiral 2,3-dihydrofurans with 92% ee and 61-64% yields.



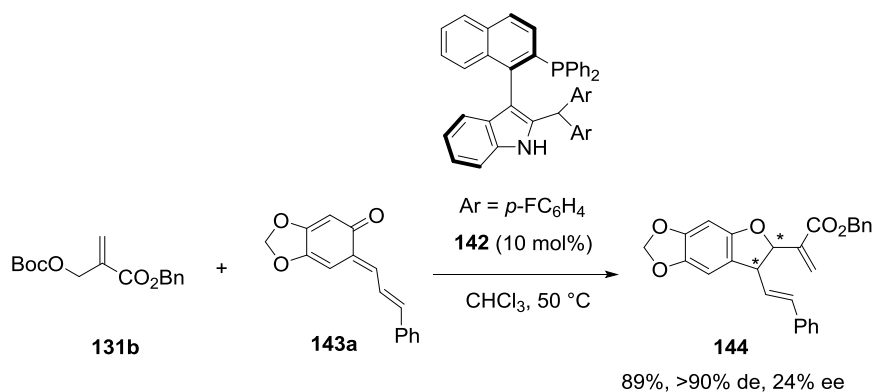
Scheme 38. [4+1] Annulation of Morita–Baylis–Hillman-type carbonates with 2-enoylpyridines.

Later in 2019, chiral phosphine catalyst **133** was applied by the same authors to the development of the first example of phosphine-catalysed enantioselective [4+1] annulations between Morita–Baylis–Hillman-type carbonates and 2-enoylpyridine *N*-oxides (Scheme 39) [84]. In the presence of 10 mol% of **133**, a diversity of Morita–Baylis–Hillman-type carbonates **131** reacted with 2-enoylpyridine *N*-oxides **140** to afford the corresponding almost diastereo- (>90% de) and enantiopure (96->99% ee) 2,3-dihydrofurans **141** in generally high yields (31-96%). It was found that the nature of the ester group (R) of the Morita–Baylis–Hillman-type adduct had no effect on the stereoselectivity of the reaction but the *tert*-butyl carbonate was not compatible. The catalyst system also tolerated the presence of various substituents on the phenyl ring (Ar) of the 2-enoylpyridine *N*-oxide. The position of these substituents was found to have a slight effect on the yields with the reaction of 2-enoylpyridine *N*-oxide bearing a nitro group in *ortho*-position (Ar = *o*-O₂NC₆H₄) providing the lowest yield (31%).



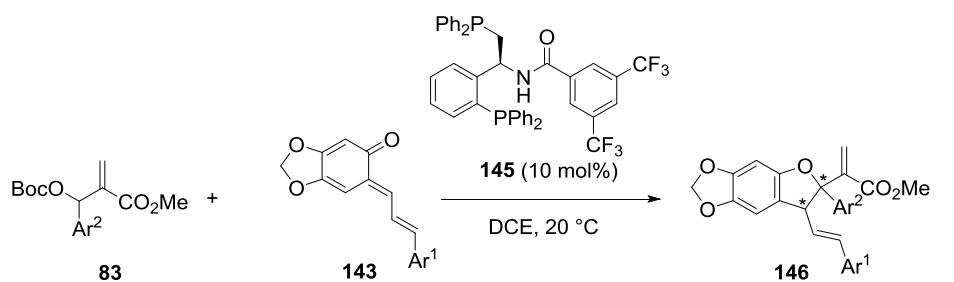
Scheme 39. [4+1] Annulation of Morita–Baylis–Hillman-type carbonates with 2-enoylpyridine *N*-oxides.

While most annulations involving *o*-quinone methides are [4+2] cycloadditions leading to chroman derivatives, examples of [4+1] annulations of these substrates with one-carbon synthons still remain rare. To fill this gap, Shi et al. developed in 2018 the first [4+1] annulation of *o*-quinone methides with Morita–Baylis–Hillman-type carbonates performed in the presence of achiral naphthylindole-derived organocatalysts [85]. The reaction allowed the synthesis of 2,3-dihydrobenzofuran derivatives with high yields (up to 99%) and diastereoselectivities (>90% de). An attempt to develop an asymmetric version of this novel methodology was undertaken by using chiral naphthylindole-derived phosphine catalyst **142** at 10 mol% of catalyst loading in chloroform as the solvent. As presented in Scheme 40, the formal [4+1] cycloaddition between Morita–Baylis–Hillman-type carbonate **131b** and *o*-quinone methide **143a** carried out at 50 °C led to the corresponding enantioenriched 2,3-dihydrobenzofuran **144** with both high yield (89%) and diastereoselectivity (>90% de) albeit with a low ee value (24% ee). In spite of the low level of enantioselectivity achieved, this work constituted the first application of naphthylindole-derived phosphines as organocatalysts in catalytic reactions.



Scheme 40. [4+1] Annulation of a Morita–Baylis–Hillman-type carbonate with an *o*-quinone methide.

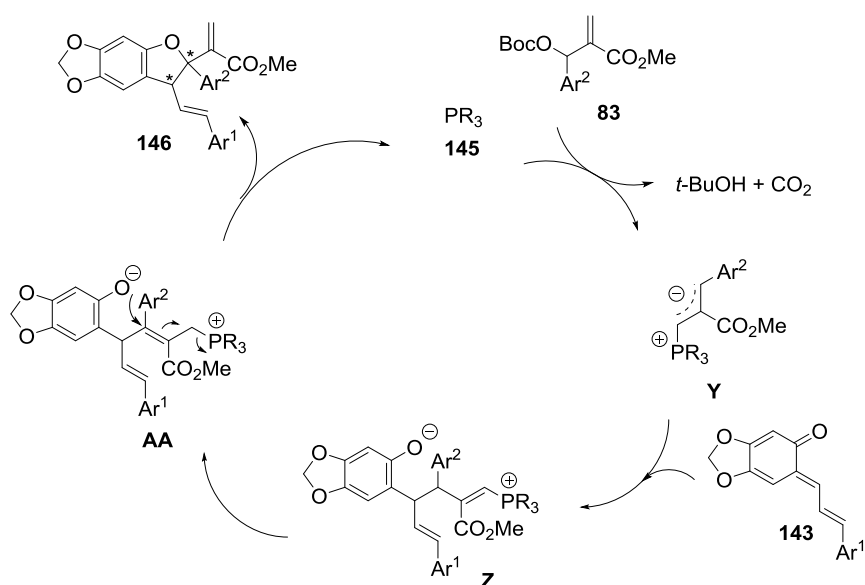
Almost at the same time, Zhang and Liu developed related highly enantioselective formal [4+1] annulation of Morita-Baylis-Hillman carbonates **83** with the same *o*-quinone methides **143** [86]. In this case, another type of organocatalyst was employed as promotor, such as newly designed chiral bisphosphine **145** in DCE as the solvent (Scheme 41). The reaction performed at 20 °C in the presence of 10 mol% of **145** resulted in the formation of chiral polysubstituted dihydrobenzofurans **146** as mixture of two diastereomers with 4-88% de and 58-85% yields. However, both the two diastereomers were obtained in high enantioselectivities (87-99% ee for major diastereomers and 80-90% ee for minor diastereomers). The mechanism of the reaction is assumed to begin with the activation of the carbonate with the catalyst to afford allylic phosphorus ylide **Y**. The latter subsequently attacks the *o*-quinone methide through a γ -regioselective Michael addition to give intermediate **Z**. Then, a 1,3-H shift occurs to generate intermediate **AA**. Finally, its intramolecular cyclisation through addition of the alcoholate to the double bond provides the product and regenerates the catalyst.



58-85%, 4-88% de
87-99% (major), 80-90% ee (minor)

Ar¹ = Ph, 3,4-OMe₂C₆H₃, *p*-Tol, *m*-Tol, 2-thienyl
Ar² = Ph, *p*-Tol, *p*-PrC₆H₄, *p*-*t*-BuC₆H₄, *p*-MeOC₆H₄, *p*-ClC₆H₄, *p*-NCC₆H₄,
p-O₂NC₆H₄, *m*-MeOC₆H₄, *m*-BrC₆H₄, *m*-ClC₆H₄, *m*-FC₆H₄, *o*-BrC₆H₄,
o-FC₆H₄, 3,5-F₃C₂C₆H₃, 2-Naph

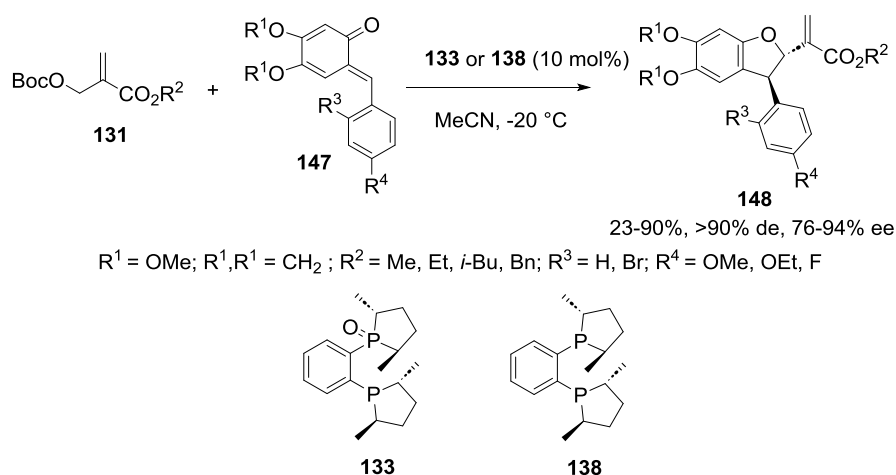
mechanism (with catalyst = PR₃) :



Scheme 41. [4+1] Annulation of Morita–Baylis–Hillman carbonates with *o*-quinone methides.

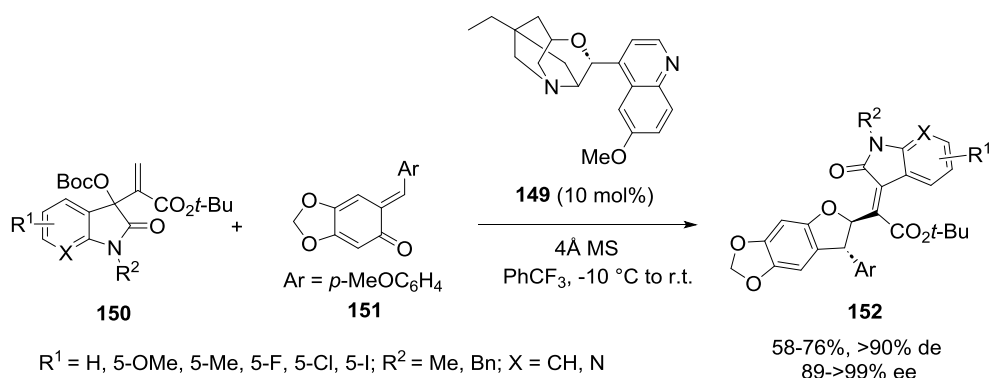
Concomitantly, Li and Li investigated related enantioselective phosphine-catalysed [4+1] annulation of Morita–Baylis–Hillman carbonates **131** with another type of *o*-quinone methides, such as **147** (Scheme 42) [87]. When the reaction was performed in acetonitrile at -20 °C in the presence of 10 mol% of chiral bisphosphine monoxide **135** as catalyst, it afforded chiral 2,3-dihydrobenzofurans **148** as almost single diastereomers (>90% de) in 23-67% yields and 87-94% ee. The nature of the ester group (R²) of the Morita–Baylis–Hillman carbonate was found to have a little effect on the asymmetric induction of the reaction. Moreover, various *o*-quinone methides bearing different substituents were tolerated. Indeed, the presence of either electron-withdrawing or electron-donating substituents on the phenyl

ring had little effect on the yields and stereoselectivity of the annulation. The authors also investigated chiral bisphosphine catalyst **138** as promotor and found a remarkable enhancement of the yield (42-90%) albeit combined with decreased enantioselectivities (76-89% ee).



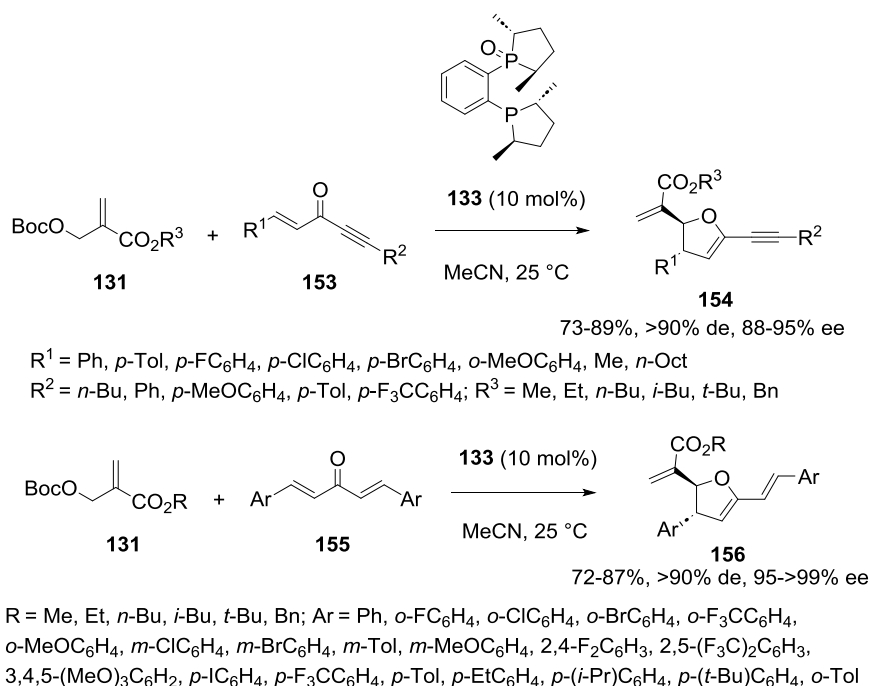
Scheme 42. [4+1] Annulation of Morita–Baylis–Hillman-type carbonates with other *o*-quinone methides.

In 2020, Chen et al. described enantioselective [4+1] annulations of isatin-derived Morita–Baylis–Hillman carbonates with *o*-quinone methides under catalysis with another type of catalysts, such as *Cinchona* alkaloid **149** (Scheme 43) [88]. The reaction of isatin-derived Morita–Baylis–Hillman carbonates **150** derived from *t*-butyl acrylate with *o*-quinone methides **151** in the presence of 10 mol% of *Cinchona* alkaloid catalyst **149** in PhCF_3 as the solvent led to the regioselective formation of complex highly functionalised chiral 2,3-dihydrobenzofurans **152** having a tetrasubstituted alkene moiety. These products were obtained in 58-76% yields and 89->99% ee as almost single diastereomers (>90% de). This result represented the first example of the chiral tertiary amine-catalysed asymmetric α -regioselective [4+1] annulation of isatin-derived Morita–Baylis–Hillman carbonates with *o*-quinone methides



Scheme 43. [4+1] Annulation of isatin-derived Morita–Baylis–Hillman carbonates with *o*-quinone methides.

In 2023, Li and Li investigated enantioselective phosphine-catalysed [1+4] annulations of Morita–Baylis–Hillman carbonates with modified enones [89]. Chiral bisphosphine monoxide **133** was used at 25 °C as promotor at 10 mol% of catalyst loading in acetonitrile as solvent. For the first time, pent-1-en-4-yn-3-ones **153** reacted regioselectively with Morita–Baylis–Hillman carbonates **131** to give the corresponding chiral multifunctionalised 2,3-dihydrofurans **154** as almost single diastereomers (>90% de) with 73-89% yields and 88-95% ee, as presented in Scheme 44. Then, the scope of the methodology was extended to other designed enones, such as penta-1,4-dien-3-ones **155**, which resulted in the synthesis of other 2,3-dihydrofurans **156** with comparable excellent diastereo- (>90% de) and enantioselectivities (95->99% ee) combined with good to high yields (72-87%), as shown in Scheme 44. In both cases of enones, the catalytic system showed an excellent functional group tolerance.

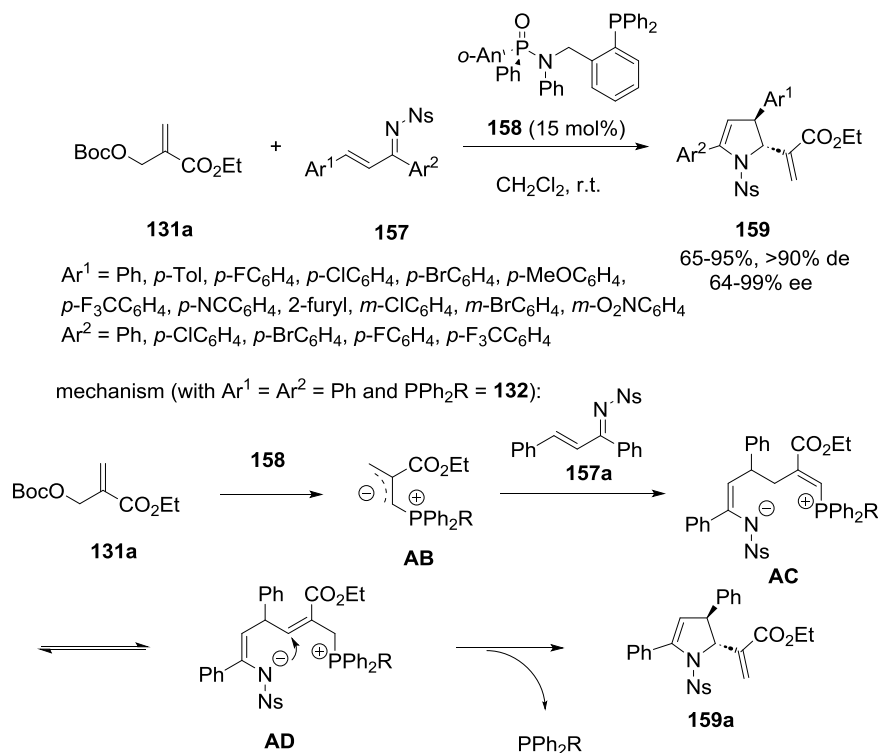


Scheme 44. [4+1] Annulations of Morita–Baylis–Hillman-type carbonates with modified enones.

3.1.2.2. With α,β -unsaturated imines

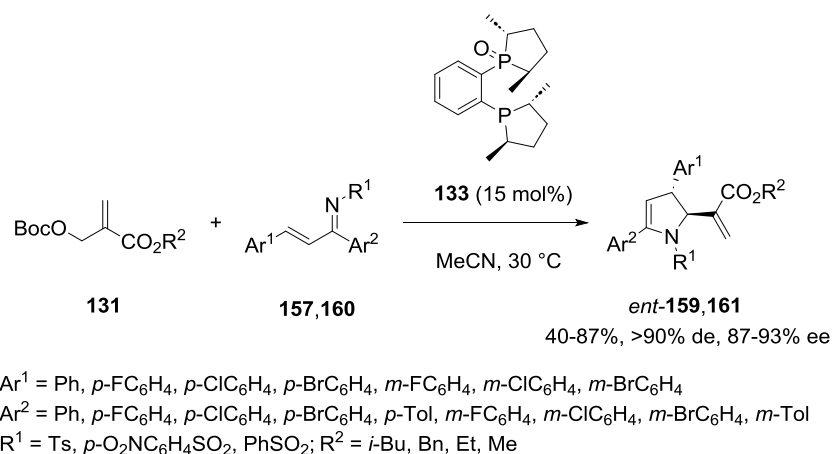
Owing to the significance of chiral pyrrolines in natural products, pharmaceuticals, as well as chiral catalysts, the development of efficient asymmetric synthesis for such cyclic compounds still constitute a challenge. In this context, He et al. designed in 2017 a novel type of P-chiral phosphine oxide–phosphine catalysts to promote enantioselective formal [4+1] cycloaddition of Morita–Baylis–Hillman-type carbonate **131a** with α,β -unsaturated imines **157** (Scheme 45) [90]. The reaction catalysed at room temperature by 15 mol% of optimal bisphosphine catalyst **158** in dichloromethane as the solvent led to chiral polysubstituted 2-pyrrolines **159** as almost single diastereomers (>90% de) in 65-95% yields and 64-99% ee. A diversity of aryl-substituted imines **157** exhibiting either electron-withdrawing or electron-donating groups were compatible, providing generally high levels of enantioselectivity (81-99% ee) except in two cases of imines ($\text{Ar}^1 = p\text{-CF}_3\text{C}_6\text{H}_4$, $\text{Ar}^2 = \text{Ph}$ and $\text{Ar}^1 = p\text{-ClC}_6\text{H}_4$, $\text{Ar}^2 = p\text{-BrC}_6\text{H}_4$.) which reacted with lower enantioselectivities (64-75% ee). A mechanism is depicted in Scheme 45 which begins with the formation of allylic phosphorus ylide **AB** from allylic carbonate **131a** and catalyst **158**. Then, ylide **AB** undergoes a sterically favored γ -carbanion addition to α,β -unsaturated imine **157a** leading to intermediate **AC**, which interconverts with intermediate **AD**. Finally, intermediate **AD** undergoes an intramolecular

Michael addition followed by elimination of the phosphine to afford product **159a** and regenerated catalyst. It must be noted that this work represented a rare example of using *P*-chiral phosphines in asymmetric organocatalysis.



Scheme 45. [4+1] Annulation of a Morita–Baylis–Hillman-type carbonate with α,β -unsaturated imines.

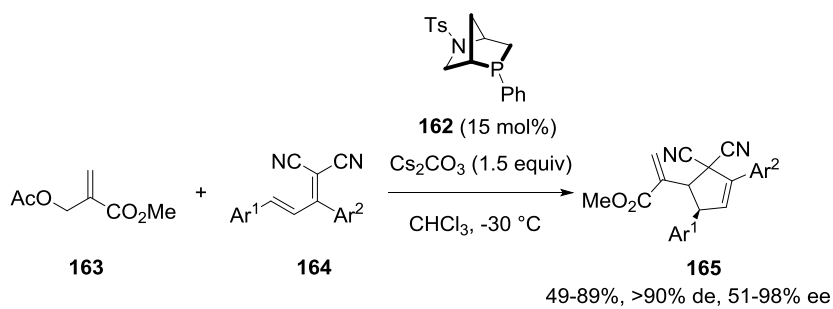
Later in 2019, Li and Li demonstrated that these reactions could also be catalysed by chiral bisphosphine monoxide **133** (Scheme 46) [91]. Indeed, in the presence of 15 mol% of this catalyst in acetonitrile as solvent, Morita–Baylis–Hillman-type carbonates **131** reacted smoothly with α,β -unsaturated imines **157,160** to furnish a series of polysubstituted chiral 2-pyrrolines *ent*-**159,161** in 40-87% yields with both excellent diastereo- (>90% de) and enantioselectivities (87-93% ee). A number of α,β -unsaturated imines bearing different substituents on either the nitrogen atom or the phenyl ring was compatible, offering a facile synthetic approach to the enantiomers of reported enantiopure 2-pyrrolines **159** (Scheme 46). Moreover, the ester group of the Morita–Baylis–Hillman-type carbonates was found to have a slight influence on the yield and enantioselectivity. The effect of the substituent on nitrogen atom of imines was also found negligible.



Scheme 46. [4+1] Annulation of Morita–Baylis–Hillman-type carbonates with α,β -unsaturated imines.

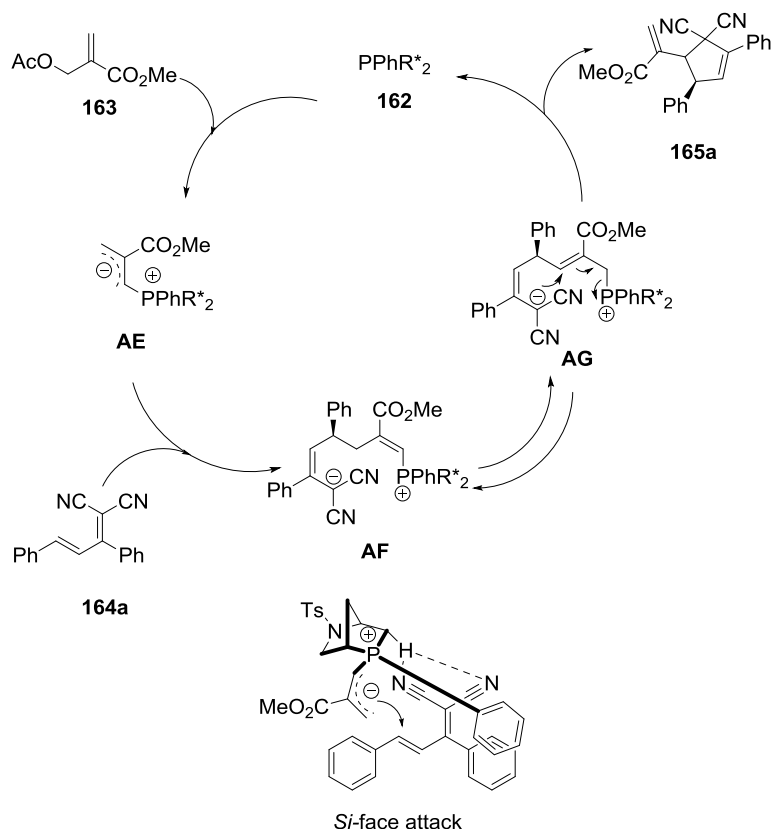
3.1.2.3. With 2-allylidene malononitriles

In 2021, He and Li involved P-chiral bicyclic phosphine **162** as catalyst in asymmetric [4+1] annulation of Morita–Baylis–Hillman-type carbonate **163** with 1,1-dicyano-2,4-diaryl-1,3-dienes **164** (Scheme 47) [92]. The reaction, promoted at $-30\text{ }^\circ\text{C}$ by 15 mol% of this catalyst in chloroform, delivered a series of polysubstituted chiral cyclopentenes **165** as almost single diastereomers (>90% de) with 49–89% yields and 51–98% ee. The mechanism detailed in Scheme 47 began with the formation of chiral 1,3-dipole **AE** from Morita–Baylis–Hillman-type carbonate **163**, followed by the asymmetric conjugate addition to 1,1-dicyano-2,4-diphenyl-1,3-diene **164a** to afford chiral intermediate **AF**. Subsequently, a 1,3-H shift occurred to give intermediate **AG**. Finally, intramolecular $\text{S}_{\text{N}}2'$ reaction of chiral intermediate **AG** yielded chiral product **165a**. The enantioselectivity-determining step was supposed to be the addition of chiral 1,3-dipole **AE** to diene **164a**. As shown in Scheme 47, the hydrogen bond interaction between the cyano groups of diene **164a** and a relatively acidic hydrogen atom on the bicyclic skeleton of ylide **AE** was proposed to facilitate the orientation of diene **164a**. The phenyl group attached to the phosphorus atom in the catalyst was also supposed to facilitate the orientation of the diene through π - π stacking interaction. By such an orientation, the allylic phosphorus ylide **AE** preferentially added to diene **164a** from the *Si*-face, which resulted in the formation of chiral product **165a**.



$\text{Ar}^1 = \text{Ph}, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-Tol}, p\text{-EtC}_6\text{H}_4, p\text{-PhC}_6\text{H}_4,$
 $p\text{-MeOC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, o\text{-BrC}_6\text{H}_4, o\text{-Tol}, 2\text{-Naph}, 2\text{-thienyl}$
 $\text{Ar}^2 = \text{Ph}, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, o\text{-Tol}$

mechanism (with $\text{Ar}^1 = \text{Ar}^2 = \text{Ph}$):



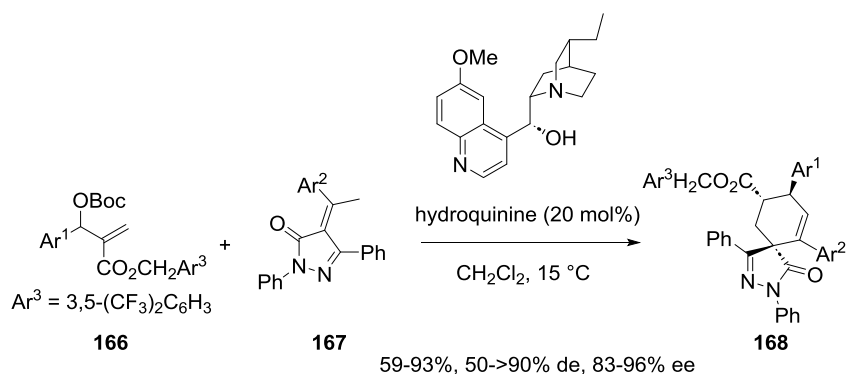
Scheme 47. [4+1] Annulation of a Morita–Baylis–Hillman-type carbonate with 2-allylidene malononitriles.

3.1.3. [3+3] Annulations

3.1.3.1. Morita–Baylis–Hillman carbonates

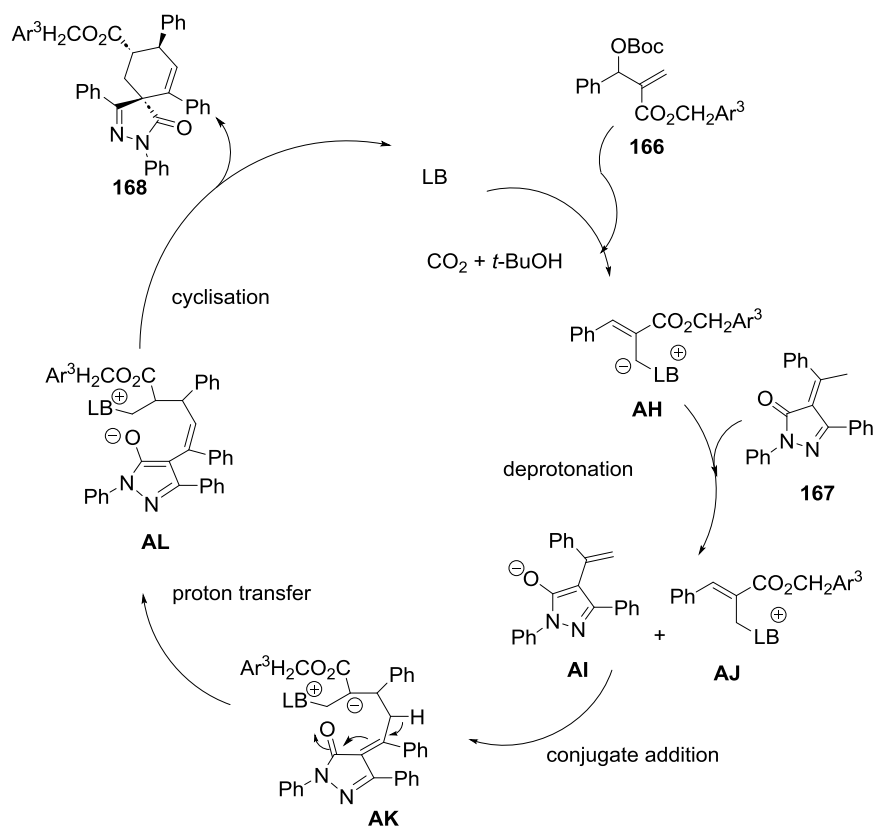
In spite of its significant importance in the synthesis of complex molecules, the formal [3+3] cycloaddition remains unexplored. One of the early examples of enantioselective organocatalytic [3+3] annulations of Morita–Baylis–Hillman adducts was reported in 2015 by Guo et al. [93]. It occurred between a Morita–Baylis–Hillman carbonate and a diazoalkane in

the presence of a chiral phosphine catalyst to provide the corresponding chiral pyridazino[6,1-a]isoquinoline with 98% ee. Later in 2017, the same group developed enantioselective [3+3] annulation of Morita–Baylis–Hillman carbonates **166** with α -arylidene pyrazolinones **167** (Scheme 48) [94]. In this case, the reaction was promoted at 15 °C by 20 mol% of hydroquinine in dichloromethane as solvent, resulting in the formation of chiral pyrazolone-fused spirocyclohexenes **168** bearing an all-carbon quaternary stereocentre. These bicyclic products were in most cases obtained as almost single diastereomers (50->90% de) in 59-93% yields and 83-96% ee. In a possible mechanism depicted below, the reaction begins with the addition of the Lewis base (LB) to the Morita–Baylis–Hillman carbonate to give allylic nitrogen ylide intermediate **AH** and subsequent deprotonation of the α -arylidene pyrazolinone results in simultaneous generation of intermediates **AI** and **AJ**. Then, the conjugate addition of **AI** to **AJ** leads to intermediate **AK** which is further submitted to a proton transfer and enolisation to afford intermediate **AL**. Subsequently, the latter undergoes cyclisation which yields the final product along with regenerated catalyst.



$\text{Ar}^1 = m\text{-FC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, m\text{-F}_3\text{CC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-O}_2\text{NC}_6\text{H}_4,$
 $p\text{-NCC}_6\text{H}_4, m\text{-Tol}, p\text{-Tol}, o\text{-MeOC}_6\text{H}_4, p\text{-EtC}_6\text{H}_4, p\text{-t-BuC}_6\text{H}_4, p\text{-PhC}_6\text{H}_4, 3\text{-Naph}, \text{Ph}$
 $\text{Ar}^2 = \text{Ph}, o\text{-FC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, o\text{-BrC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4,$
 $o\text{-MeOC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, m\text{-Tol}, 2\text{-Naph}, 2\text{-thienyl}$

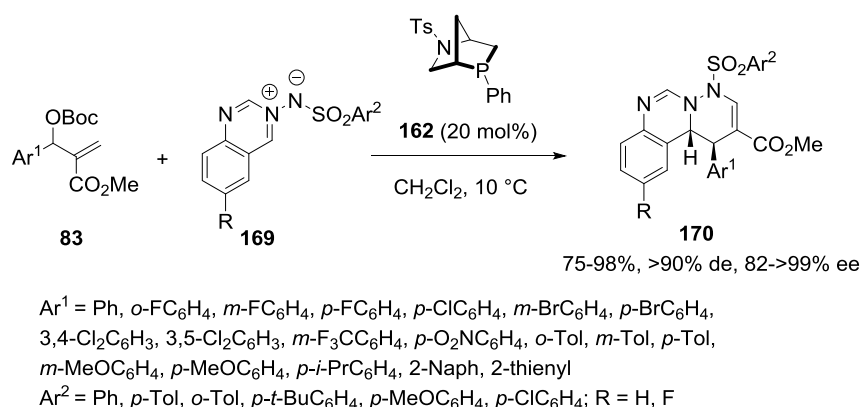
possible mechanism (with $\text{Ar}^1 = \text{Ar}^2 = \text{Ph}$ and catalyst = LB):



Scheme 48. [3+3] Annulation of Morita–Baylis–Hillman carbonates with α -arylidene pyrazolinones.

The synthesis of quinazolines is a challenge due to the abundance of these skeletons in bioactive products. In this context, the same authors also disclosed in 2017 a novel route to these important products on the basis of an enantioselective phosphine-catalysed [3+3] annulation of quinazoline-based 1,3-dipoles **169** with Morita–Baylis–Hillman carbonates **83**

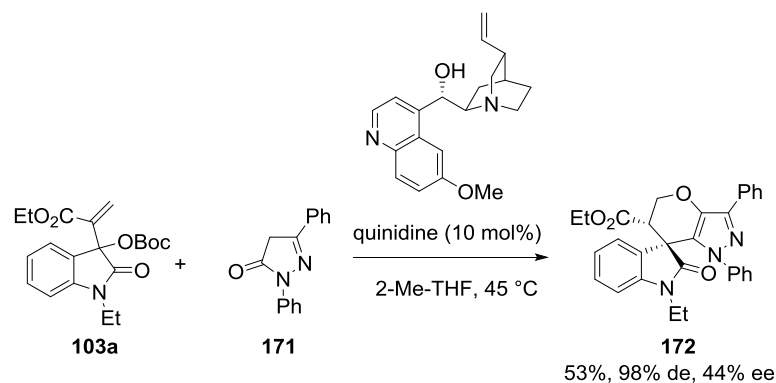
[95]. The catalyst was chiral phosphine **162** employed at 20 mol% of catalyst loading in dichloromethane as the solvent. Under these conditions, a variety of aryl-substituted Morita–Baylis–Hillman carbonates **83** reacted at 10 °C with quinazoline-based 1,3-dipoles **169** to give chiral functionalised quinazoline-fused heterocycles **170** (Scheme 49). The latter were synthesised as single diastereomers (>90% de) with 75-98% yields and 82->99% ee regardless of the position and electronic properties of the substituents exhibited on the phenyl ring of the carbonates (Ar¹). Furthermore, excellent results were also observed in the reaction of fused aromatic (Ar¹ = 2-Naph) and heteroaromatic groups (Ar¹ = 2-furyl, 2-thienyl). The catalyst system also tolerated quinazoline-based dipoles bearing different sulfonyl protecting groups (Ar²).



Scheme 49. [3+3] Annulation of Morita–Baylis–Hillman carbonates with quinazoline-based 1,3-dipoles.

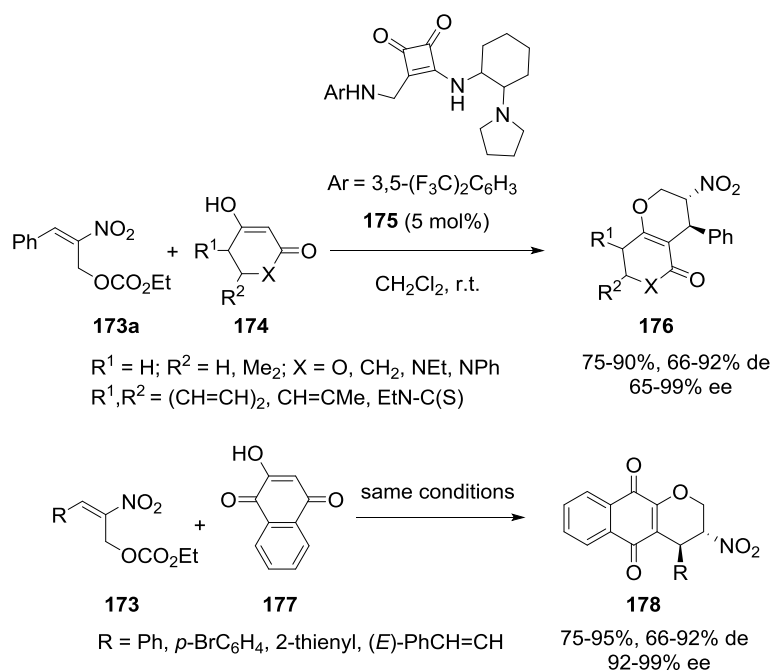
In 2018, Samanta et al. developed [3+3] annulations of isatin-derived Morita–Baylis–Hillman carbonates with several types of pharmacologically attractive enolisable C–H activated cyclic carbonyl compounds, such as pyrazolones, isoxazolones, 4-hydroxyxoumarins, 4-hydroxy-6-methyl- α -pyrone, lawsone and dimedone, catalysed by DABCO [96]. This methodology allowed the synthesis of a series of racemic medicinally promising spirooxindole-fused-dihydropyran scaffolds. An enantioselective version was also developed by using 10 mol% of quinidine (Scheme 50). Carried out at 45 °C in 2-Me-THF as the solvent, it occurred between isatin-derived Morita–Baylis–Hillman carbonate **103a** and 1,3-diphenyl-1H-pyrazol-5(4H)-one **171**, delivering the desired enantioenriched

spirooxindole-fused-dihydropyran **172** as single diastereomer (98% de) albeit with both moderate yield (53%) and enantioselectivity (44% ee).



Scheme 50. [3+3] Annulation of an isatin-derived Morita–Baylis–Hillman carbonate with 1,3-diphenyl-1H-pyrazol-5(4H)-one.

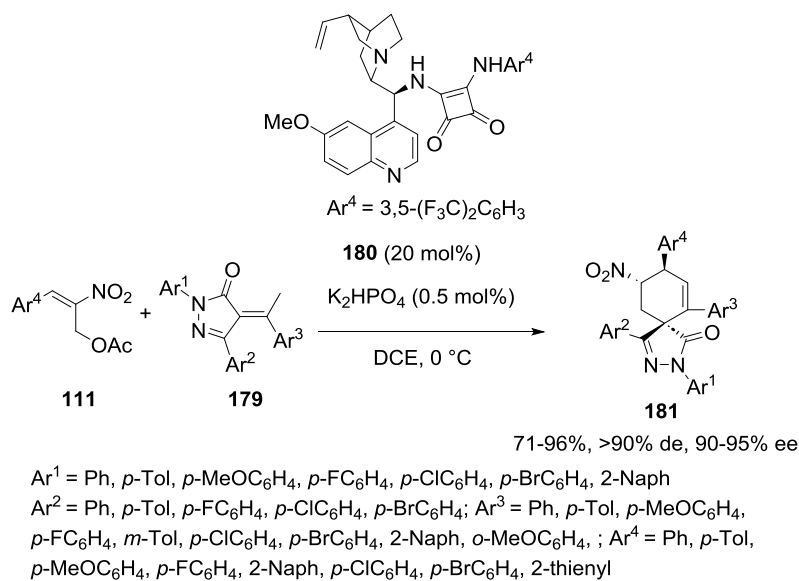
In 2021, Zlotin et al. investigated the reactivity of Morita–Baylis–Hillman-type carbonate **173a** towards cyclic enols **174** in enantioselective [3+3] annulation (Scheme 51) [97]. These reactions employed 5 mol% of tertiary amine-based squaramide catalyst **175** to give in dichloromethane at room temperature the corresponding chiral fused dihydropyranes **176** with good to high yields (75-90%) and moderate to excellent diastereo- (66-92% de) and enantioselectivities (65-99% ee). Furthermore, other chiral products **178** derived from the reaction between other Morita–Baylis–Hillman carbonates **173** and enol **177** were obtained with 92-99% ee, 66-92% de, and 75-95% yields. Interestingly, these fused dihydropyranes can be considered as derivatives of lawsone, the core structure of atovaquone and dihydro- α -caryopterone, which are antimicrobial and anticancer agents. The authors showed that these 2-nitroallylic carbonates exhibited much higher reactivity than the corresponding Morita–Baylis–Hillman acetates.



Scheme 51. [3+3] Annulations of Morita–Baylis–Hillman-type carbonates with cyclic enols.

3.1.3.2. Morita–Baylis–Hillman acetate and naphthoate derivatives

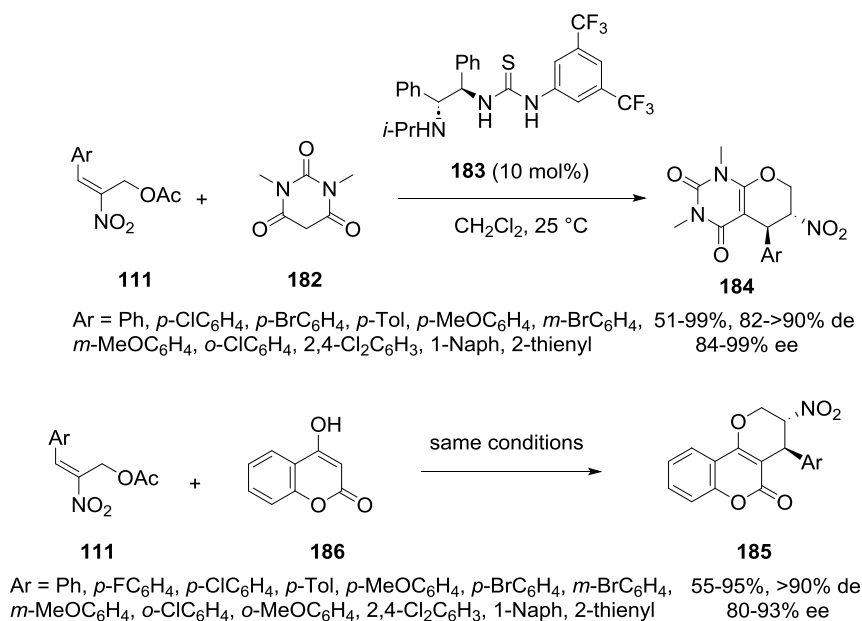
In 2017, Xu et al. reported an asymmetric formal [3+3] cycloaddition between α -arylidene pyrazolinones **179** and Morita–Baylis–Hillman-type acetates **111** catalysed by 20 mol% of chiral quinine-derived squaramide **180** [98]. Performed in DCE at 0 °C in the presence of K₂HPO₄ as an additive, the reaction allowed the synthesis of a range of variously substituted chiral spirocyclohexene pyrazolones **181** as almost single diastereomers (>90% de) with 71–96% yields and 90–95% ee, as shown in Scheme 52. These molecules should be interested in medicinal chemistry. The substrate scope was found to be wide since a variety of pyrazolone derivatives and (*E*)-2-nitroallylic acetates were tolerated, providing the products with remarkable enantioselectivities in all cases. However, a difference in reactivity was observed in the case of electronically different Morita–Baylis–Hillman acetates. Therefore, electron-rich substrates were found more reactive than electron-deficient ones. Moreover, alkyl derivatives failed to undergo the desired reaction.



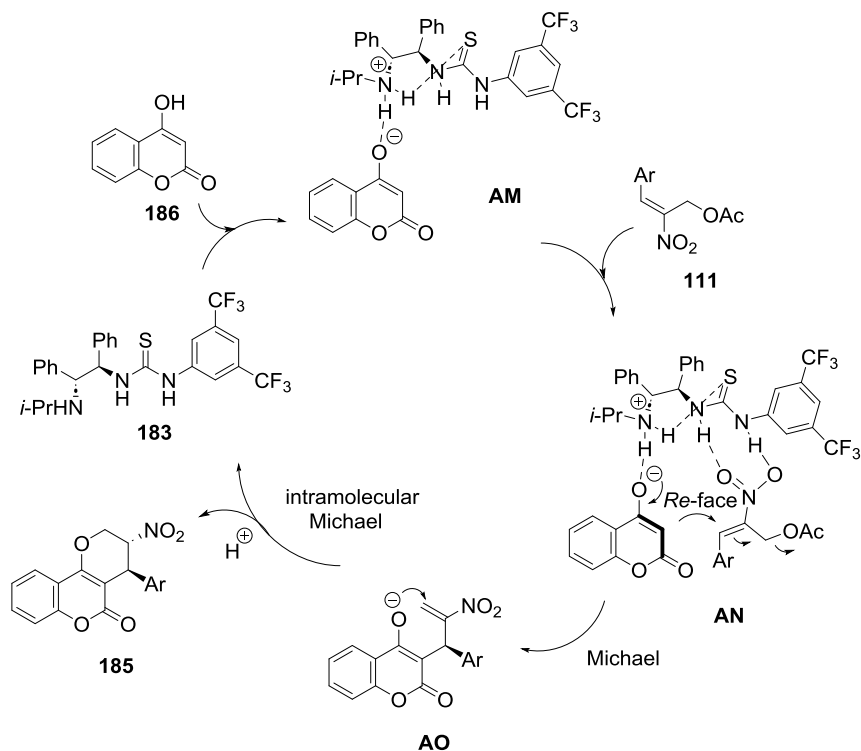
Scheme 52. [3+3] Annulation of Morita–Baylis–Hillman-type acetates with α -arylidene pyrazolinones.

In the same year, Chen and Li developed a novel route to chiral barbiturate-fused tetrahydropyrano derivatives which constitute very important structures in medicinal chemistry, for their antimicrobial, antituberculosis, and antiproliferative activities among many others [99]. The synthesis was based on an enantioselective [3+3] annulation between *N,N'*-dimethylbarbituric acid **182** and Morita–Baylis–Hillman-type acetates **111** promoted at 25 °C by 10 mol% of chiral thiourea **183** in dichloromethane (Scheme 53). Indeed, the annulation of a range of nitroalkenes **111** with *N,N'*-dimethylbarbiturate **182** yielded the corresponding chiral barbiturate-fused tetrahydropyrano scaffolds **184** in 51-99% yields, 82- >90% de, and 84-99% ee. It must be noted that in almost all cases of substrates bearing different types of substituents on the phenyl ring, the products were obtained as single diastereomers (>90% de) with general high ee values while the reaction of a nitroalkene with a more sterically hindered 1-naphthyl group ($\text{Ar} = 1\text{-Naph}$) provided a lower diastereoselectivity (82% de) albeit combined with both high yield (95%) and enantioselectivity (94% ee). The scope of the methodology was extended to the synthesis of other biologically important products that are chiral pyranocoumarins **185** by using 4-hydroxycoumarin **186** as the nucleophile. As shown in Scheme 53, the domino reaction between the latter and Morita–Baylis–Hillman-type acetates **111** afforded the corresponding chiral functionalised tricyclic products **185** as almost single diastereomers (>90% de) with 55-95% yields and 80-93% ee regardless of the nature of the aryl substituent of the nitroalkenes.

A mechanism is proposed in Scheme 53, beginning with the formation of intermediate **AM** through hydrogen bonding interaction between the secondary amino-thiourea catalyst and 4-hydroxycoumarin **186**. Subsequently, the nitroalkene was associated to intermediate **AM** through hydrogen bonding to generate intermediate **AN**. A following intermolecular Michael addition and the removal of the catalyst led to intermediate **AO** which further underwent an intramolecular Michael addition to give the final product.



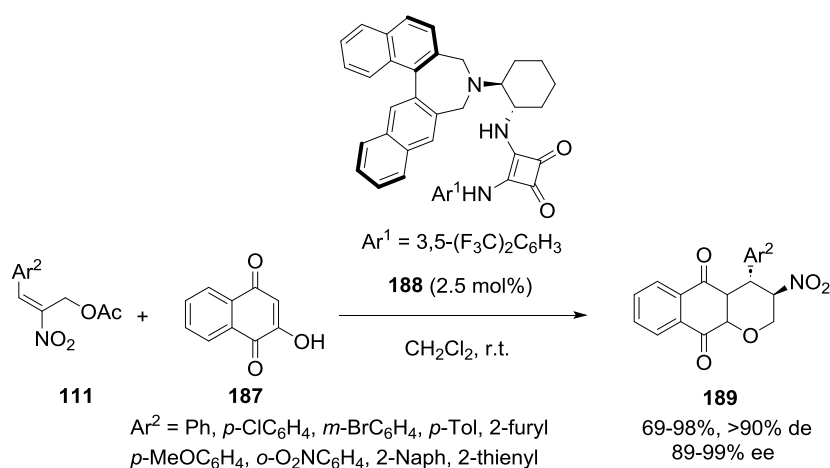
mechanism for the formation of **185**:



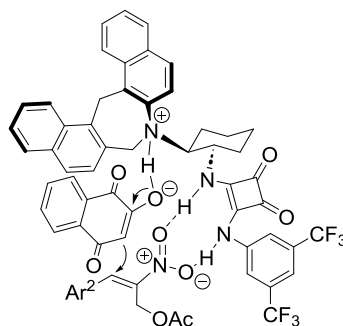
Scheme 53. [3+3] Annulations of Morita–Baylis–Hillman-type acetates with *N,N'*-dimethylbarbiturate/4-hydroxycoumarin.

In 2018, Morita–Baylis–Hillman-type acetates **111** were also involved by Kim et al. in enantioselective [3+3] annulation with 2-hydroxy-1,4-naphthoquinone **187** (Scheme 54)

[100]. In the presence of only 2.5 mol% of binaphthyl-derived tertiary amine-containing squaramide catalyst **188**, these reactions performed in dichloromethane as solvent afforded at room temperature a range of synthetically useful chiral pyranonaphthoquinone derivatives **189** as single diastereomers (>90% de) with 89-99% ee and 69-98% yields. The authors proposed the transition state depicted in Scheme 54 in which the (*E*)-2-nitroallylic acetate substrate was activated by the chiral squaramide catalyst through hydrogen bonding interaction. Then, the enolate of the 2-hydroxy-1,4-naphthoquinone substrate attacked the *Re*-face of the nitroalkene to afford the product.



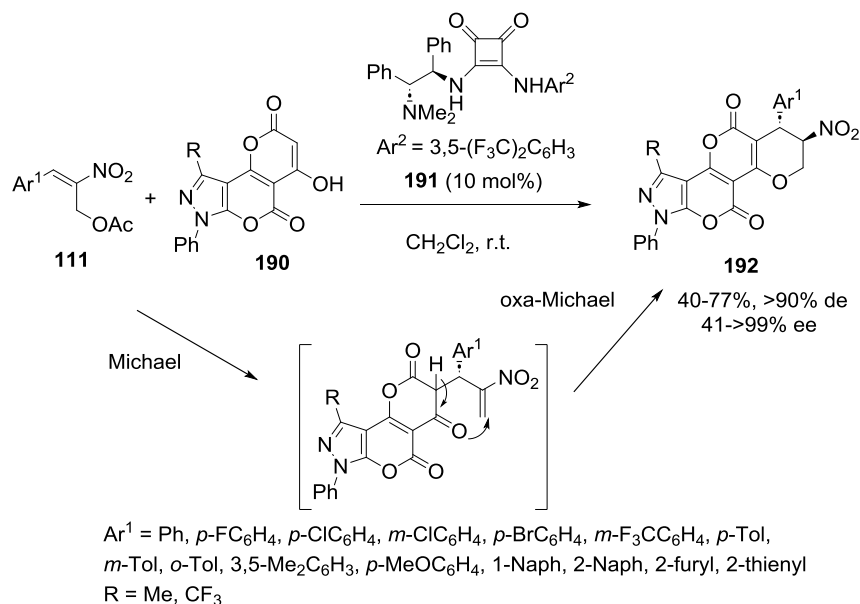
proposed transition state:



Scheme 54. [3+3] Annulation of Morita-Baylis-Hillman-type acetates with 2-hydroxy-1,4-naphthoquinone.

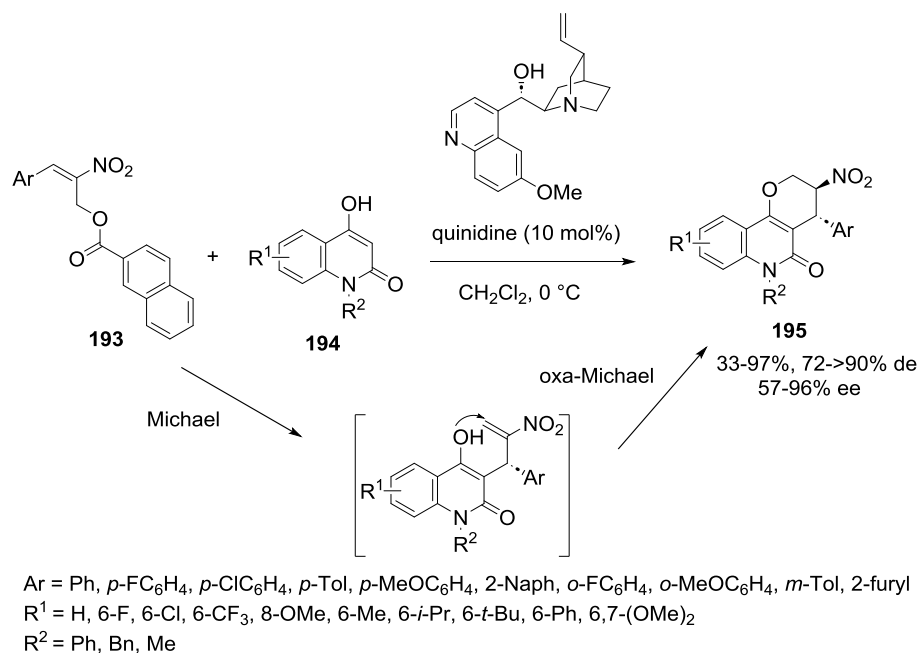
In 2019, an enantioselective [3+3] annulation between Morita-Baylis-Hillman-type acetates **111** and pyrazolones **190** was developed by Zhou et al. (Scheme 55) [101]. It was catalysed at room temperature by 10 mol% of chiral tertiary amine-based squaramide catalyst **191** in dichloromethane as the solvent, thus delivering novel fused chiral polycyclic 3,4-dihydroprano[4,3-b]pyran-5(2H)-one derivatives **192** as single diastereomers (>90% de) with 40-

77% yields and 41->99% ee. The process could evolve through successive Michael and oxa-Michael reactions.



Scheme 55. [3+3] Annulation of Morita–Baylis–Hillman-type acetates with pyrazolones.

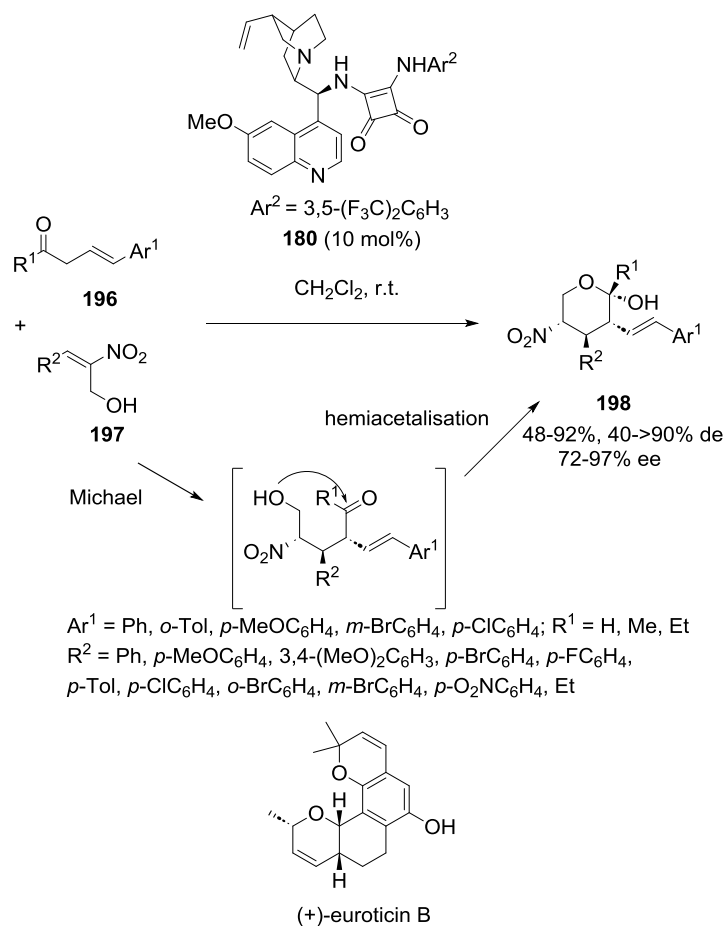
In 2020, Xiong et al. reported the use of Morita–Baylis–Hillman-type 2-naphthoates **193** in enantioselective [3+3] annulations with 4-hydroxyquinoline-2(1H)-ones **194** (Scheme 56) [102]. Naturally occurring quinidine was found to be the optimal catalyst of these processes when employed at 10 mol% of catalyst loading. Carried out at 0 °C in dichloromethane, the reactions afforded a wide variety of chiral densely substituted tetrahydropyran[3,2-c]quinolinones **195** with 33-97% yields, 72->90% de, and 57-96% ee.



Scheme 56. [3+3] Annulation of Morita–Baylis–Hillman-type 2-naphthoates with 4-hydroxyquinoline-2(1H)-ones.

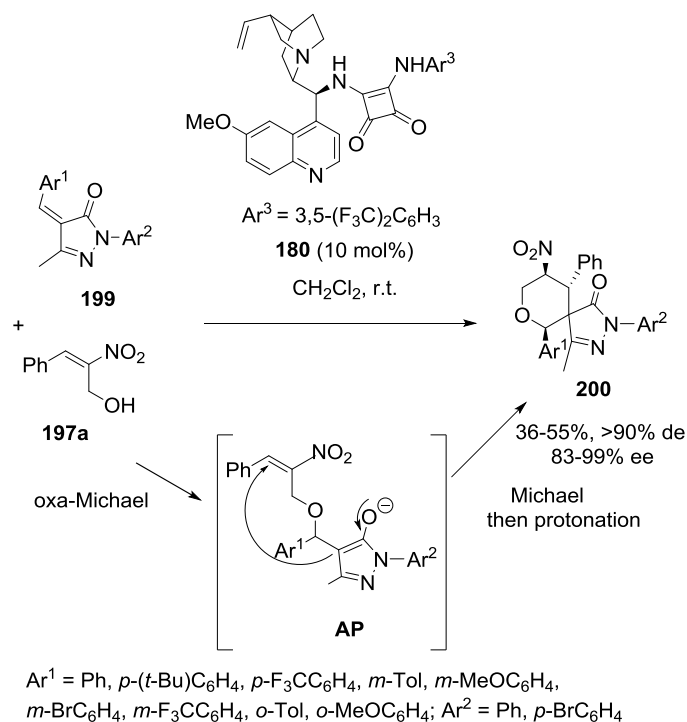
3.1.3.3. Morita–Baylis–Hillman alcohol derivatives

In 2021, Hong et al. employed chiral squaramide **180** to promote an α -alkylation of vinylogous carbonyl compounds **196** with Morita–Baylis–Hillman-type alcohols **197** through Michael addition followed by an intramolecular hemiacetalisation (Scheme 57) [103]. This [3+3] annulation was performed at room temperature in dichloromethane as solvent in the presence of 10 mol% of catalyst **180**, leading to highly substituted pyrans **198** bearing four contiguous stereocentres with 48-92% yields, 72-97% ee, and 40->90% de. The utility of this novel methodology was demonstrated in the synthesis of an analog of the antioxidant natural product euroticin B.



Scheme 57. [3+3] Annulation of Morita–Baylis–Hillman-type alcohols with vinylogous carbonyl compounds.

Later in 2023, Pan et al. developed the first asymmetric synthesis of spiro-tetrahydropyranopyrazolones **200** achieved through enantioselective [3+3] annulation of Morita–Baylis–Hillman-type alcohol **197a** with alkylidene pyrazolones **199** (Scheme 58) [104]. The reaction was promoted at room temperature by 10 mol% of quinine-squaramide catalyst **180** in dichloromethane, resulting in the formation of a range of chiral spiro-tetrahydropyranopyrazolones **200** as single diastereomers (>90% de) in moderate yields (36-55%) and uniformly high enantioselectivities (83-99% ee). The annulation could evolve through an oxa-Michael addition of Morita–Baylis–Hillman alcohol **197** to the benzylic carbon of alkylidene pyrazolone **199** to form intermediate **AP**. Subsequently, an intramolecular Michael addition occurred to give the final spirocyclic compounds.

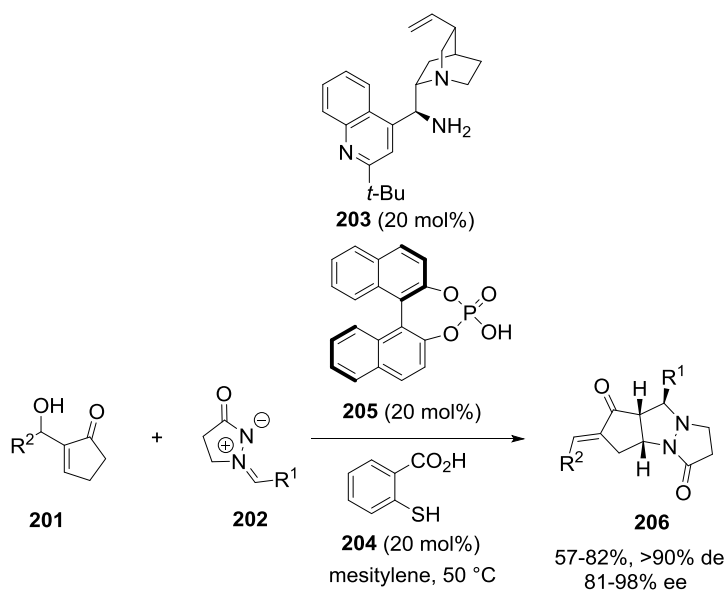


Scheme 58. [3+3] Annulation of a Morita–Baylis–Hillman-type alcohol with alkylidene pyrazolones.

3.1.4. Other annulations

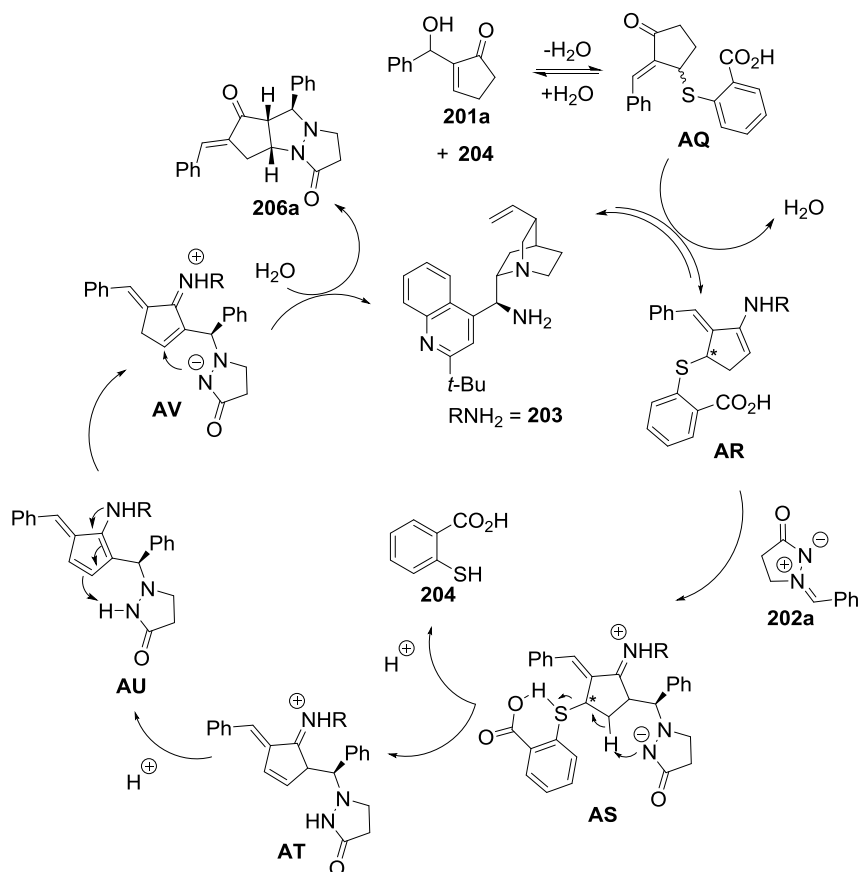
In 2019, Chen and Du reported a novel enantio- and regioselective formal [5+3] annulation of unmodified Morita–Baylis–Hillman alcohols **201** with cyclic azomethine imines **202** [105]. This process involved a multicatalytic system composed of 20 mol% of *Cinchona* alkaloid chiral primary amine **203** and the same quantity of achiral 2-mercaptobenzoic acid **204** in mesitylene as solvent. Performed at 50 °C in the presence of 20 mol% of chiral phosphoric acid **205**, it afforded in mesitylene as the solvent a range of chiral fused tricyclic heterocyclic products **206** as almost single diastereomers (>90% de) with 57-82% yields and 81-98% ee (Scheme 59). A variety of (hetero)aromatic Morita–Baylis–Hillman alcohols were compatible but also substrates bearing either a branched ($\text{R}^2 = \text{Cy}$) or a linear alkyl substitution ($\text{R}^2 = \text{BnCH}_2$) which reacted similarly with high enantioselectivities (84-90% ee). Furthermore, various cyclic azomethine imines exhibiting either electron-withdrawing or electron-donating substituents on the phenyl ring ($\text{R}^1 = (\text{hetero})\text{aromatic}$) were well tolerated as well as a cyclohexyl group-substituted substrate ($\text{R}^1 = \text{Cy}$) which also provided an excellent ee value (89% ee). To explain the results, the authors proposed the mechanism depicted in Scheme 59 evolving through double activation catalysis with chiral amine **203** and achiral thiol **204**. It

began with reversible β -addition of thiol **203** to enone **201a** to give sulfide **AQ** after elimination of H₂O. Then, dienamine intermediate **AR** was generated from **AR** and amine **203**. It subsequently underwent α' -regioselective Mannich-type reaction with azomethine imine **202a** to afford intermediate **AS**. The *ortho*-carboxylic group of thiol **204** could serve as an intramolecular hydrogen bonding donor to generate the partially cationic sulfonium moiety, facilitating the γ -deprotonation and sequential release of **204** to deliver iminium ion **AT**. Then, isomerisation of the latter into intermediate **AU** occurred, and the latter could be β -protonated to give iminium ion **AV**. Finally, intramolecular aza-Michael addition at the γ -position led to final product **206a** and regenerated amine **203** via hydrolysis. It is interesting to note that all proposed intermediates **AQ**, **AR**, **AS**, and **AU** were detected by high-resolution mass spectrometry analysis of the catalytic mixture, further supporting the covalent double activation catalysis.



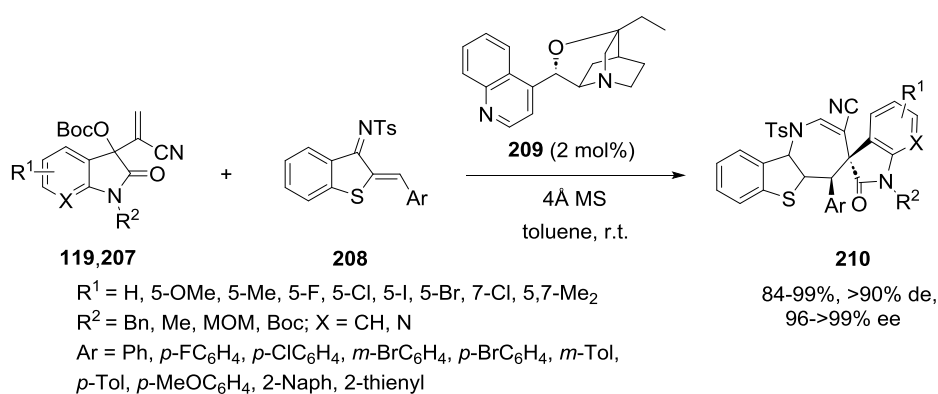
$R^1 = \text{Ph, } o\text{-Tol, } p\text{-ClC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, m\text{-Tol, } o\text{-MeOC}_6\text{H}_4, 1\text{-Naph, 3-furyl, 2-thienyl, Cy}$
 $R^2 = \text{Ph, } o\text{-ClC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, m\text{-Tol, } o\text{-MeOC}_6\text{H}_4, p\text{-Tol, 1-Naph, 2-styryl, 2-thienyl, Cy, BnCH}_2$

proposed mechanism (with $R^1 = R^2 = \text{Ph}$):



Scheme 59. [5+3] Annulation of unmodified Morita–Baylis–Hillman alcohols with cyclic azomethine imines.

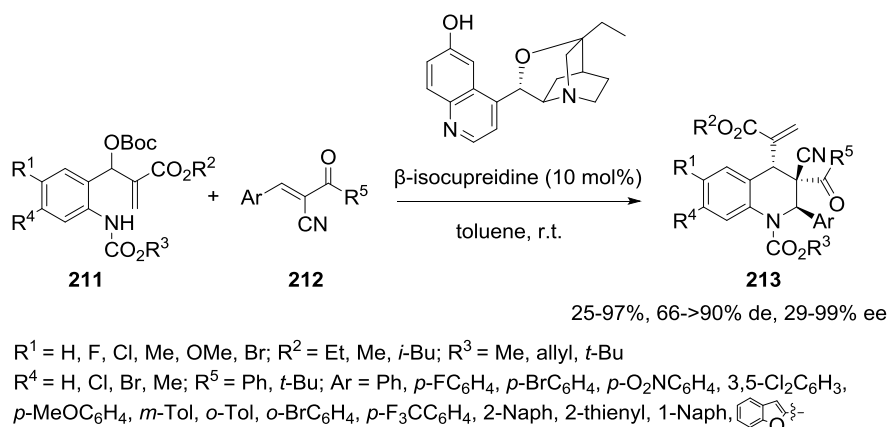
In 2020, Chen et al. developed an enantioselective γ -regioselective [4+3] annulation of isatin-derived Morita–Baylis–Hillman carbonates **119,207** with 1-azadienes **208** catalysed by only 2 mol% of chiral *Cinchona* alkaloid **209** (Scheme 60) [88]. The formal cycloaddition allowed a range of chiral azepane spirooxindoles **210** to be synthesised in both remarkable diastereo- (>90% de) and enantioselectivities (96->99% ee) combined with uniformly high yields (84-99%). Indeed, the catalyst system was compatible with different *N*-substitutions on the Morita–Baylis–Hillman carbonates **119,207** as well as with the presence of electron-donating or electron-withdrawing groups on the phenyl ring. Moreover, excellent results were achieved with a number of benzothiophene-derived 1-azadienes **208** bearing different (hetero)aromatic substituents.



Scheme 60. [4+3] Annulation of isatin-derived Morita–Baylis–Hillman carbonates with 1-azadienes.

Substituted tetrahydroquinolines are privileged structural motifs found in many bioactive molecules and consequently their synthesis is challenging. In 2023, Huang et al. described a novel route to chiral tetrahydroquinolines based on an enantioselective [4+2] annulation between *o*-acylamino-aryl Morita–Baylis–Hillman carbonates **211** and 2-aryl-3-arylacrylonitriles **212** (Scheme 61) [106]. Catalysed at room temperature by 10 mol% β -isocupreidine in toluene, the reaction afforded a wide variety of chiral multifunctionalised tetrahydroquinolines **213** exhibiting three sequential stereogenic centres containing one quaternary stereocentre with both moderate to excellent yields (25-97%) and enantioselectivities (29-99% ee) combined with generally very high diastereoselectivities (66->90% de). Various Morita–Baylis–Hillman carbonates bearing both electron-withdrawing and electron-donating groups on the phenyl ring were compatible, leading to the

corresponding products with good to excellent yields and ee values (61-98% ee). However, it was found that the presence of substituents next to the six-membered ring had a negative influence on both the yields and enantioselectivities ($R^6 = \text{Me, Cl}$: 53-59%, 31-79% ee). The Morita–Baylis–Hillman carbonates could bear different acyl groups (COR^3) but the Boc-substituted substrate ($R^3 = t\text{-Bu}$) reacted with the lowest ee value (29% ee). Furthermore, the catalyst system tolerated a variety of 2-aryl-3-arylacrylonitriles with either electron-donating or electron-withdrawing substituents on the aryl ring. *Ortho*-substituted substrates afforded the corresponding products with decreased enantioselectivities ($\text{Ar} = o\text{-BrC}_6\text{H}_4, o\text{-Tol}$: 43-61% ee).



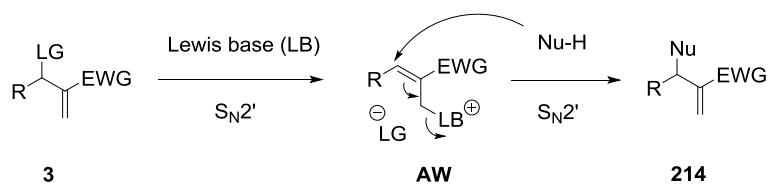
Scheme 61. [4+2] Annulation of *o*-acylamino-aryl Morita–Baylis–Hillman carbonates with 2-aryl-3-arylacrylonitriles.

3.2. Allylic substitution reactions of Morita–Baylis–Hillman carbonates, acetates, carbamates and fluorides

3.2.1. *Cinchona* alkaloid catalysts

The asymmetric allylic alkylation reaction constitutes a powerful methodology to prepare chiral allylic compounds. It was developed by Trost in 1970s [107], setting the basis of the transition-metal-catalysed version evolving through the formation of π -allyl intermediates [108]. It was only in the 2000s that the first reactions catalysed by chiral Lewis base organocatalysts were developed [109]. For example, the first S_N2' reaction of quinidinium salts derived from Morita–Baylis–Hillman bromides to provide the corresponding enantioenriched Morita–Baylis–Hillman propargylic ethers was described by Basavaiah et al.,

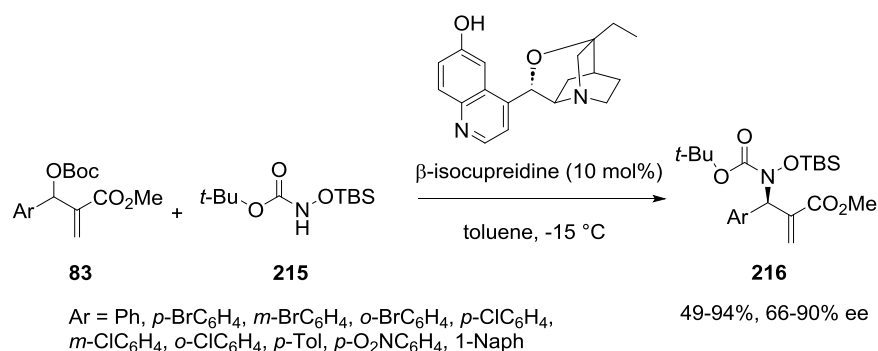
in 2001 ($\leq 40\%$ ee) [110]. Ever since, a number of allylic substitution reactions of Morita–Baylis–Hillman carbonates and acetates with various types of nucleophiles have been promoted by various chiral Lewis bases, such as *Cinchona* alkaloids and chiral phosphines. These γ -allylic substitutions of Morita–Baylis–Hillman adducts catalysed by Lewis bases evolve through a double S_N2' process (Scheme 62). Indeed, an initial S_N2' attack of the Lewis base catalyst (LB) to the Morita–Baylis–Hillman adduct **3** occurs, triggering the elimination of the leaving group (LG). This results in the formation of intermediate **AW** exhibiting an internal alkene activated by an electron-withdrawing group (EWG) as well as a formally positively charged allylic leaving group. In the presence of either a negatively charged or protic nucleophile, a second S_N2' attack occurs, leading to the final allylic alkylation product **214** after regenerating the catalyst. The regioselectivity of the process is secured by the catalyst. In the last decade, many multifunctional chiral organocatalysts, such as phosphine-amides [111], phosphine-thioureas [112], along with modified *Cinchona* alkaloids [113], have been successfully applied to promote these reactions.



Scheme 62. Mechanism for Lewis base-catalysed allylic substitution reaction of Morita–Baylis–Hillman adducts.

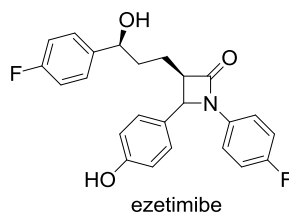
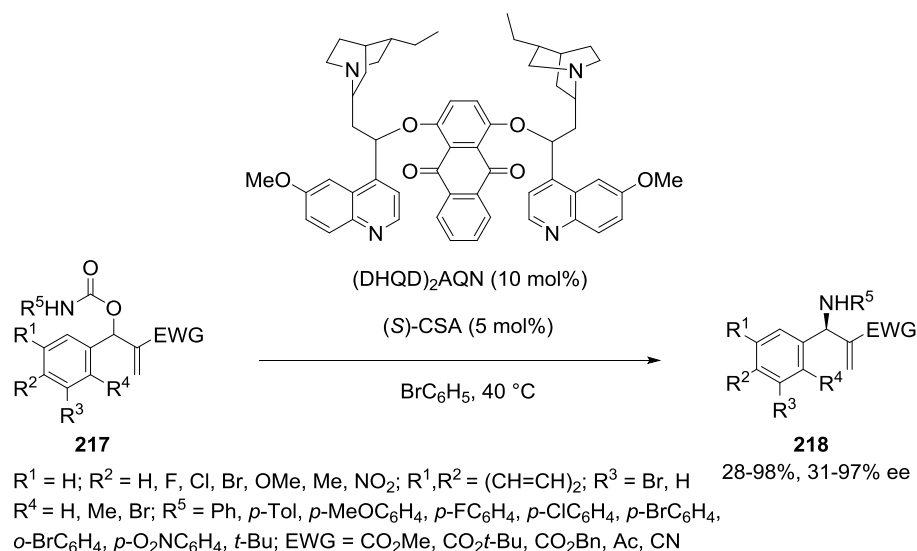
In 2017, Vesely et al. reported enantioselective amination of Morita–Baylis–Hillman carbonates with *O*-silylated *N*-Boc-hydroxylamines catalysed with 10 mol% of β -isocupreidine [114]. Performed at $-15\text{ }^{\circ}\text{C}$ in toluene, the asymmetric allylic amination of differently aryl substituted Morita–Baylis–Hillman carbonates **83** with silylated derivatives of *tert*-butylhydroxycarbamates **215** resulted in the formation of the corresponding allylated chiral products **216** in 49–94% yields and 66–90% ee, as presented in Scheme 63. Carbonates could bear either electron-withdrawing or electron-donating groups in the *para*-position of the phenyl ring. Generally, the reaction of *ortho*- and *meta*-substituted substrates provided lower enantioselectivities than carbonates substituted in the *para*-position. The lowest ee value

(66% ee) was observed in the amination of *ortho*-substituted chlorinated derivative (Ar = *o*-ClC₆H₄). It must be noted that alkyl-substituted carbonates did not undergo amination.



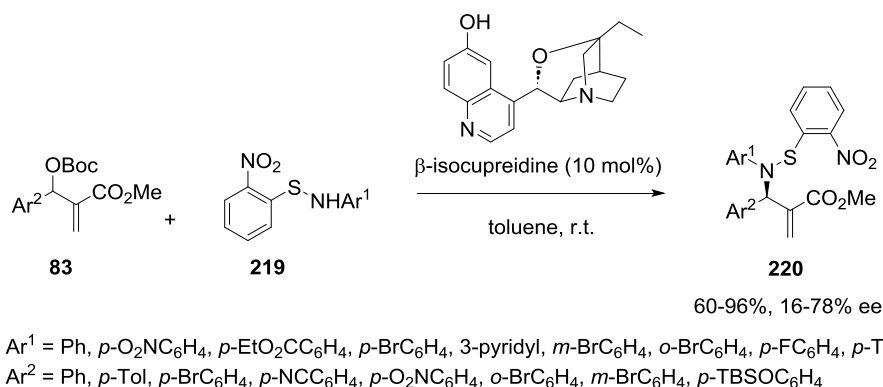
Scheme 63. Allylic amination of Morita–Baylis–Hillman carbonates with *O*-silylated *N*-Boc-hydroxylamines.

Later in 2018, the same authors investigated the asymmetric decarboxylative allylic amination of Morita–Baylis–Hillman carbamates **217** (Scheme 64) [115]. The reaction was efficiently catalysed at 40 °C by 10 mol% of a dimeric *Cinchona* alkaloid-based tertiary amine, such as (DHQD)₂AQN. Performed in BrC₆H₅ as the solvent in the presence of (*S*)-camphor sulfonic acid (CSA) as an additive, it led to chiral allylic amines **218** in 28-98% yields and 31-97% ee. Morita–Baylis–Hillman carbamates bearing substituents at any positions (R¹-R⁴) of the phenyl ring reacted with high yields (74-98%) and uniformly excellent enantioselectivities (90-97% ee). Moreover, the aniline group could be differently substituted at the *para*-position with the lowest ee value (65% ee) obtained in the reaction of *p*-NO₂-aniline (R⁵ = *p*-O₂NC₆H₄). The reaction of an *ortho*-substituted aniline (R⁵ = *o*-BrC₆H₄) resulted in the lowest enantioselectivity (36% ee). Interestingly, a sterically demanding aliphatic amine-derived substrate (R⁵ = *t*-Bu) generated the corresponding product in low yield (28%) but with 86% ee. In addition, carbamates derived from electron-deficient alkenes other than α,β -unsaturated esters showed reduced enantioselectivity (EWG = Ac, CN: 35-70% ee). The synthetic utility of this methodology was demonstrated by its application to develop a formal synthesis of the drug ezetimibe.



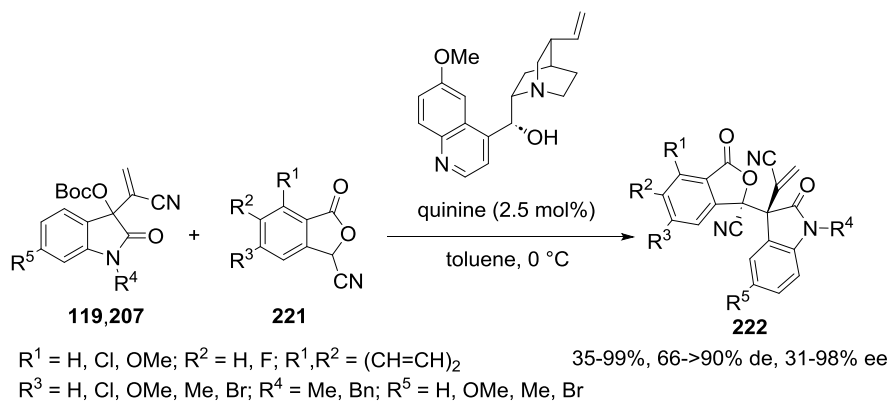
Scheme 64. Decarboxylative allylic amination of Morita–Baylis–Hillman carbamates.

The same authors also developed in 2019 enantioselective allylic amination of Morita–Baylis–Hillman carbonates **83** with 2-nitrophenylsulfenylanilines **219** in the presence of 10 mol% of β -isocupreidine [116]. The reaction led at room temperature in toluene to chiral allylic amines **220** in 60-96% yields and 16-78% ee, as shown in Scheme 65. In particular, allylic amines which derived from Morita–Baylis–Hillman carbonates bearing both electron-withdrawing and electron-donating groups in the *para*-position of the phenyl ring were obtained in 90-96% yields in moderate enantioselectivities (61-78% ee) while lower ee values (16-32% ee) were obtained in the reactions of an aniline substituted in the *ortho*-position ($Ar^1 = o-BrC_6H_4$) and an aniline bearing an electron-donating group ($Ar^1 = p-Tol$).



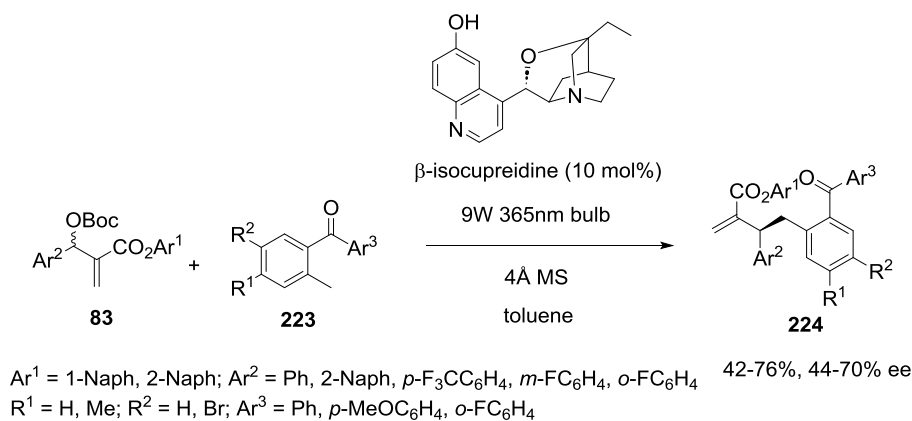
Scheme 65. Allylic amination of Morita–Baylis–Hillman carbonates with 2-nitrophenylsulfenylanilines.

Along with asymmetric allylic aminations of Morita–Baylis–Hillman adducts, a range of enantioselective allylic alkylations have been developed in the last few years. For example in 2018, Liao et al. investigated the first coupling between biologically interesting 3,30-disubstituted oxindoles with valuable pharmacophores, such as phthalides [117]. This was based on the asymmetric allylic alkylation of isatin-derived Morita–Baylis–Hillman carbonates **119,207** with 3-cyanophthalides **221** promoted by only 2.5 mol% of a chiral *Cinchona* alkaloid catalyst. Among several organocatalysts investigated, quinine was found optimal when employed at 0 °C in toluene. As presented in Scheme 66, the enantioselective alkylation afforded a range of chiral phthalide-oxindole hybrids **222** exhibiting two congested adjacent quaternary stereogenic centres in 35-99% yields and both moderate to excellent diastereo- (66->90% de) and enantioselectivities (31-98% ee). The reaction of a series of isatin-derived Morita–Baylis–Hillman carbonates exhibiting electron-donating substituents on the phenyl ring provided excellent enantioselectivities (92-93% ee) while the presence of electron-withdrawing substituents, such as a bromide ($R^5 = \text{Br}$), resulted in a lower ee value (31% ee). Moreover, the catalyst system tolerated variously substituted 3-cyanophthalides but 2-methoxy-phthalide reacted with a lower enantioselectivity (63% ee) than substrates having other electron-deficient groups ($R^1 = \text{Cl}, R^2 = \text{F}, R^3 = \text{Br}, \text{Cl}, \text{Me}$: 80-93% ee). The formed novel complex chiral heterocyclic molecules are of high interest for medicinal chemistry.

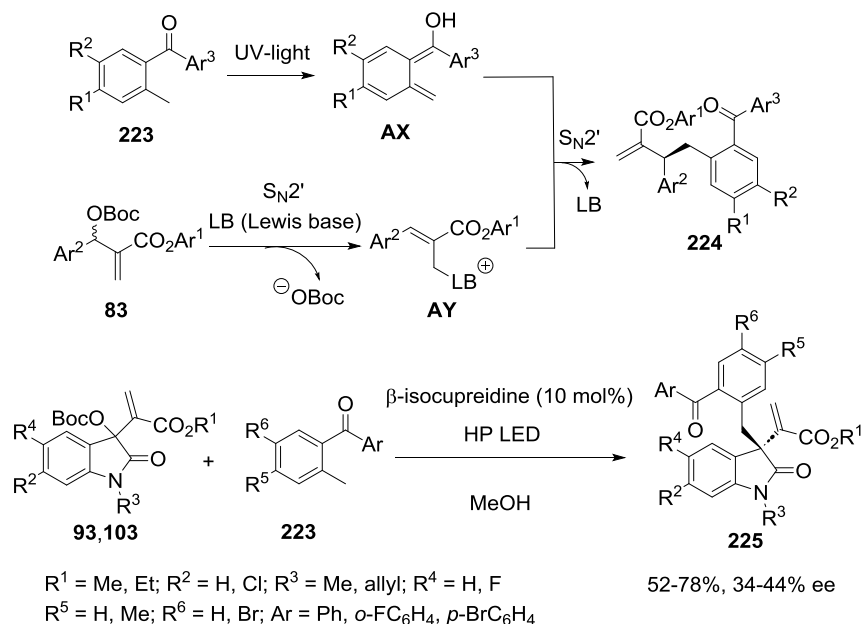


Scheme 66. Allylic alkylation of isatin-derived Morita–Baylis–Hillman carbonates with 3-cyanophthalides.

In 2020, Companyo et al. described asymmetric light-triggered allylic benzylation of Morita–Baylis–Hillman carbonates **83** with 2-methylbenzophenone derivatives **223** as nonstabilised photogenerated C-nucleophiles [118]. Actually, the reaction evolved through a dual activation, involving chiral Lewis-base activation of the electrophile and light activation of the nucleophile. As shown in Scheme 67, the 2-methylbenzophenone derivative generated photoenol intermediate **AX** under UV-light irradiation while chiral Lewis base β -isocupreidine underwent a S_N2' reaction with the Morita–Baylis–Hillman carbonate **83** bearing a naphthyl ester group (Ar = 1-Naph, 2-Naph) to give intermediate **AY**. These two intermediates further underwent a second S_N2' reaction to provide the corresponding chiral benzylated final product **224**. Performed in toluene in the presence of 10 mol% of β -isocupreidine and under irradiation at 365 nm, a range of these products were produced in 42-76% yields and 44-70% ee. The presence of electron-withdrawing substituents on the phenyl ring (R^1) of the Morita–Baylis–Hillman carbonate was tolerated as well as that of either electron-donating or electron-withdrawing groups at the phenyl rings of the 2-methylbenzophenone derivative (R^2, R^3, R^4). In a second time, the catalyst system could be applied to isatin-derived Morita–Baylis–Hillman carbonates **93, 103** which led by reaction with 2-methylbenzophenones **223** to the corresponding chiral 3,3-disubstituted oxindoles **225** bearing an all-carbon quaternary allylic stereocentre. The process was performed in methanol as solvent under high-power 365 nm light-emitting diode. The 3,3-disubstituted benzylated chiral oxindoles were obtained in 52-78% yields with 34-44% ee, as illustrated in Scheme 67.



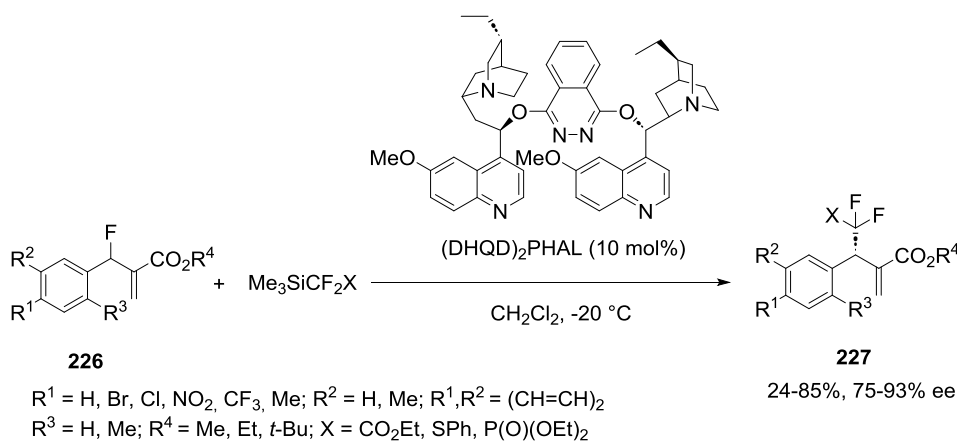
mechanism:



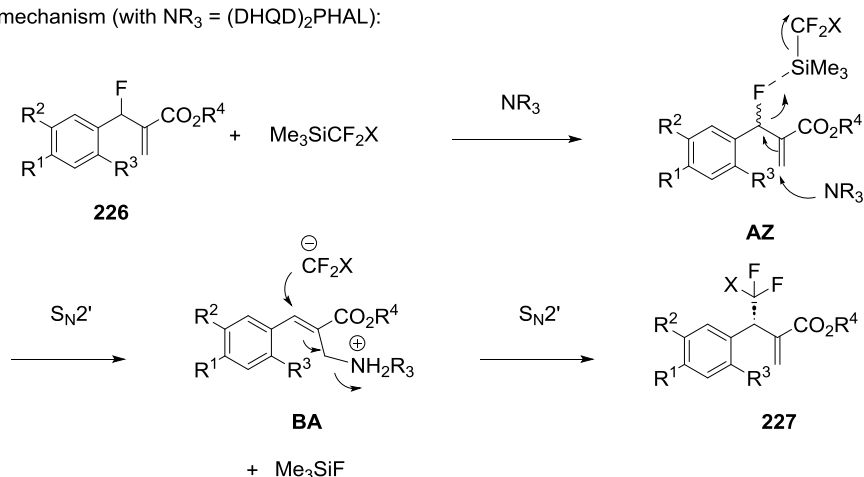
Scheme 67. Allylic benzylations of Morita–Baylis–Hillman carbonates with 2-methylbenzophenones.

Fluorinated products are highly important in pharmaceutical and agrochemical industries. In this context, Shibata et al. reported in 2020 the first enantioselective allylic substitution reaction of Morita–Baylis–Hillman fluorides **226** with ethoxycarbonyl difluoromethyl trimethylsilane ($\text{Me}_3\text{Si-CF}_2\text{CO}_2\text{Et}$) catalysed by a chiral *Cinchona* alkaloid catalyst, such as $(\text{DHQD})_2\text{PHAL}$ [119]. In this process carried out at $-20\text{ }^\circ\text{C}$ and using 10 mol% of this catalyst in dichloromethane as the solvent, a “ $\text{CF}_2\text{CO}_2\text{Et}$ ” group was enantioselectively introduced at the allylic position of a variety of Morita–Baylis–Hillman fluorides **226**, resulting in the formation of chiral ethoxycarbonyl difluoromethylene Morita–Baylis–Hillman products **227** ($\text{X} = \text{CO}_2\text{Et}$) in 24-85% yields and 75-93% ee. This asymmetric ethoxycarbonyldifluoromethylation of Morita–Baylis–Hillman fluorides with $\text{Me}_3\text{Si-}$

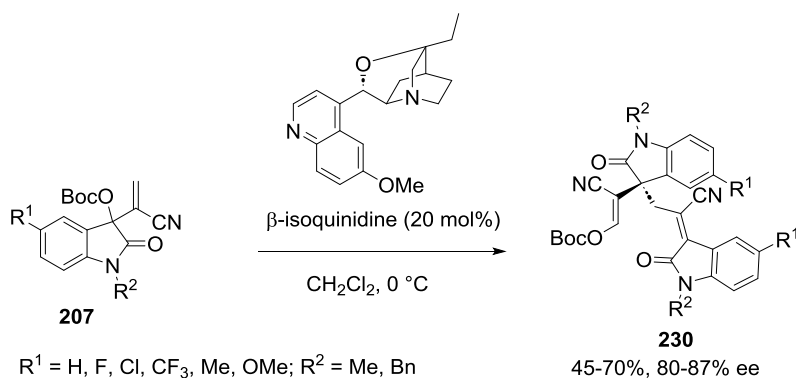
CF₂CO₂Et was supposed to evolve through silicon-assisted C–F bond activation catalysed by (DHQD)₂PHAL. Indeed, its plausible mechanism depicted in Scheme 68 begins with a first S_N2' reaction between (DHQD)₂PHAL and the Morita–Baylis–Hillman fluoride activated by the silicon atom of Me₃Si–CF₂X through the coordination to fluorine in **AZ**. This leads to the formation of chiral ammonium salt intermediate **BA** along with stable trimethylsilyl fluoride Me₃Si–F. Subsequently, a second S_N2' reaction occurs between difluoromethylene anion (–CF₂X) and intermediate **BA** to yield the final product. In addition to ethoxycarbonyl difluoromethyl trimethylsilane (Me₃Si–CF₂CO₂Et), the catalyst system was found compatible with other difluoromethylated nucleophiles, such as Me₃Si–CF₂SPh and Me₃Si–CF₂P(O)(OEt)₂, which provided the corresponding chiral products with both high yields (74–85%) and enantioselectivities (80–84% ee).



mechanism (with NR₃ = (DHQD)₂PHAL):

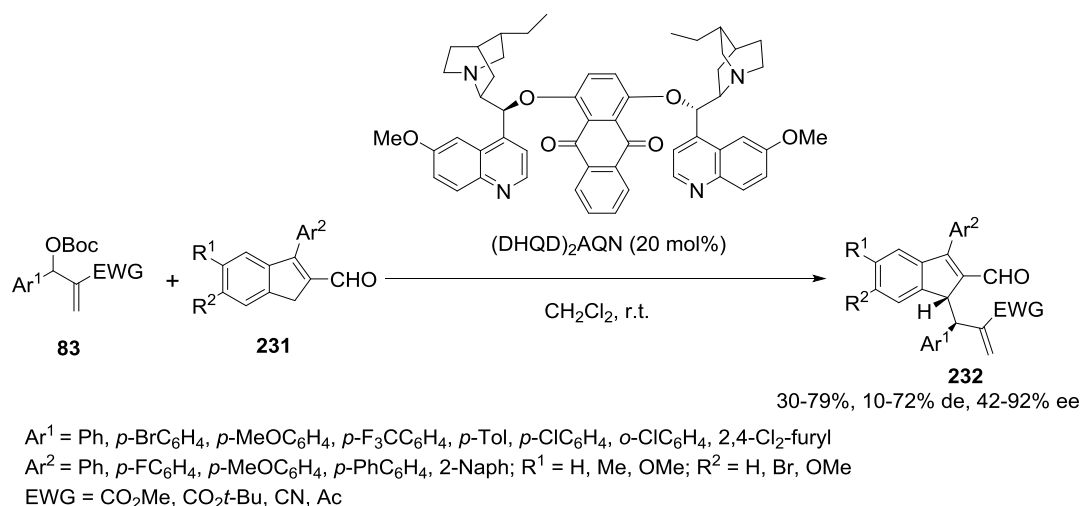


Scheme 68. Allylic alkylation of Morita–Baylis–Hillman fluorides with Me₃Si–CF₂X.



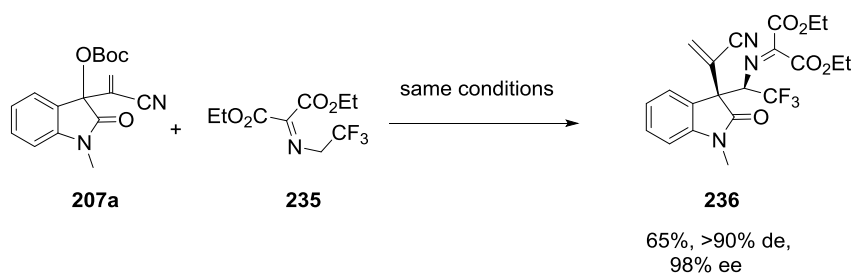
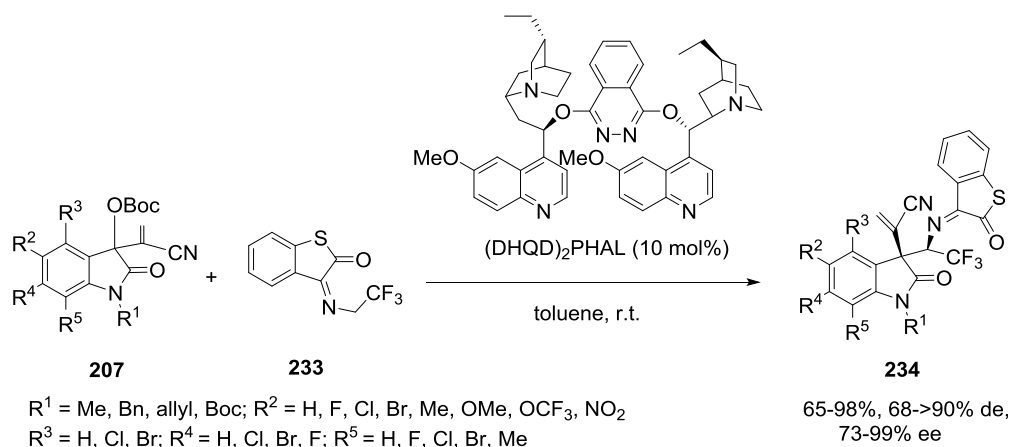
Scheme 70. Intermolecular allylic alkylation of two isatin-derived Morita–Baylis–Hillman carbonates.

In 2023, Albrecht et al. described asymmetric allylic alkylation of Morita–Baylis–Hillman carbonates **83** with indene-2-carbaldehydes **231** (Scheme 71) [122]. Indeed, in the presence of 20 mol% of (DHQD)₂AQN in dichloromethane, indene-2-carbaldehydes **231** generated the corresponding pentaenolate species which underwent asymmetric allylic alkylation of Morita–Baylis–Hillman carbonates **83** at room temperature to produce functionalised chiral indene-2-carbaldehydes **232** with 30-79% yields, 10-72% de, and 42-92% ee.

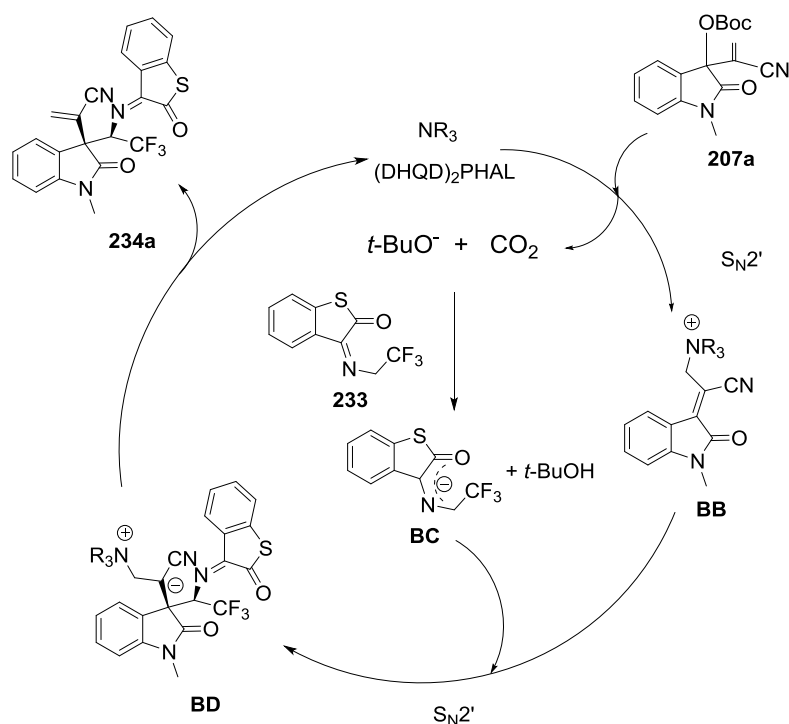


Scheme 71. Allylic alkylation of Morita–Baylis–Hillman carbonates with indene-2-carbaldehydes.

Trifluoromethylamine-containing 3,3'-disubstituted oxindole derivatives constitute highly desirable products for medicinal chemistry. In this context, Huang and Yan developed in 2023 a highly enantioselective γ -regioselective-alkylation of isatin-derived Morita-Baylis-Hillman carbonates **207** with CF₃-containing ketoimines **233** (Scheme 72) [123]. This procedure catalysed at room temperature with 10 mol% of (DHQD)₂PHAL in toluene delivered chiral α -trifluoromethylamine derivatives **234** incorporating an oxindole motif with good to quantitative yields (65-98%) and generally excellent enantioselectivities (73-99% ee). Indeed, the ee values were found uniformly very high (92-99% ee) except in the reaction of an allylated substrate (R¹ = allyl) which provided only 73% ee. Similarly, all the products were isolated as single diastereomers (>90% de) excepted that derived from a Morita-Baylis-Hillman carbonate exhibiting a NO₂ substituent at C5 position (R¹ = Me, R² = NO₂, R³ = R⁴ = R⁵ = H: 68% de). The same conditions were also applied to another type of trifluoromethyl-ketoimines derived from diethyl ketomalonate such as **235**. Pleasingly, the reaction of this substrate with isatin-derived Morita-Baylis-Hillman carbonate **207a** proceeded smoothly to yield the corresponding chiral densely functionalised product **236** with 65% yield as an almost single enantiomer (>90% de, 98% ee). The authors proposed a tandem S_N2'-S_N2' substitution mechanism depicted in Scheme 72. Indeed, the Morita-Baylis-Hillman carbonate underwent a first S_N2' reaction at the nitrogen atom of the quinuclidine to generate a cationic *Z*-configured intermediate **BB**, stabilised by π - π stacking between the phenyl ring of the carbonate and the quinoline moiety. Simultaneously, the *tert*-butoxide anion deprotonated the ketoimine to afford intermediate ylide **BC**, which attacked cationic intermediate **BB** from the *Re*-face to afford intermediate **BD**. Then, the latter delivered the final product through regeneration of the tertiary amine catalyst.



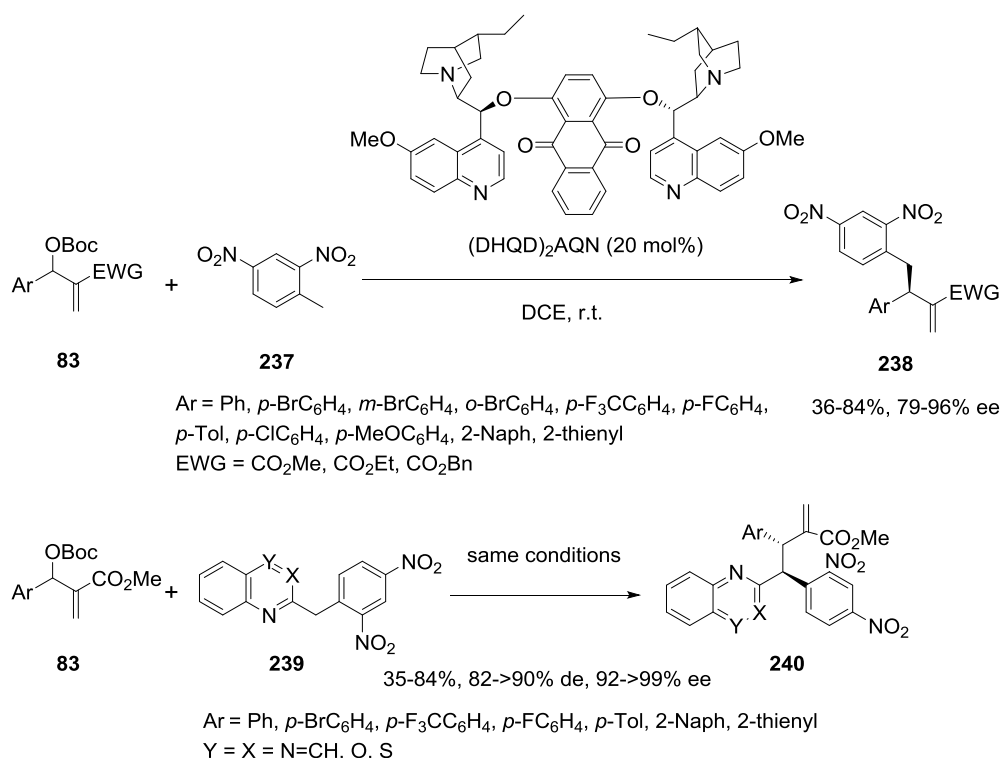
proposed mechanism (with imine **207a** and $\text{R}^1 = \text{Me}, \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{R}^5 = \text{H}$):



Scheme 72. γ -Regioselective alkylations of isatin-derived Morita-Baylis-Hillman carbonates with CF_3 -containing ketoimines.

In 2024, Han et al. described the first asymmetric benzylation reaction of Morita-Baylis-Hillman carbonates **83** with 2,4-dinitrotoluene **237** as the nucleophilic reagents (Scheme 73)

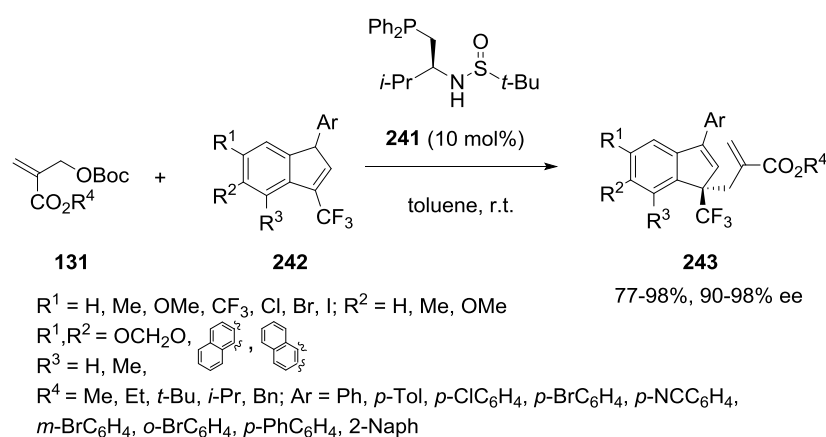
[124]. The process was performed at room temperature in DCE as the solvent in the presence of 20 mol% of (DHQD)₂AQN as catalyst, thus leading to chiral potentially biologically interesting functionalised 2,4-dinitrotoluene derivatives **238** in moderate to high yields (36-84%) and high enantioselectivities (79-96% ee). It must be noted that the ee values were all found $\geq 91\%$ ee excepted for an heteroaromatic substrate (Ar = 2-thienyl) which provided the corresponding product with 79% ee in combination with the lowest yield (36%). The scope of this simple methodology was extended to more complex substrates, such as 2,4-dinitroaryl-substituted azaarenes **239** which led by reaction with Morita-Baylis-Hillman carbonates **83** under the same conditions to the corresponding chiral products **240** bearing azaarene and 2,4-dinitrobenzene moieties with 35-84% yields and generally both excellent diastereo- (82->90% de) and enantioselectivities (92->99% ee), as presented in Scheme 73. These molecules will certainly be important in medicinal chemistry. The lowest yields (35-46%) were obtained in the reaction of Morita-Baylis-Hillman carbonates exhibiting 2-naphthyl and 2-thienyl groups (Ar = 2-Naph, 2-thienyl).



Scheme 73. Allylic benzylation reactions of Morita-Baylis-Hillman carbonates with 2,4-dinitrotoluene derivatives.

3.2.2. Other catalysts

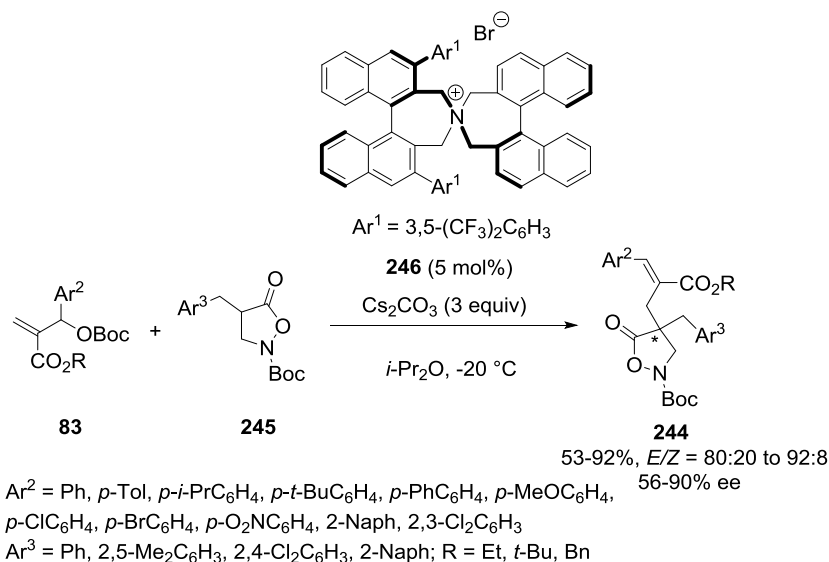
Along with *Cinchona* alkaloid catalysts, a diversity of chiral phosphines have been successfully applied to the catalysis of allylic substitution reactions of Morita–Baylis–Hillman adducts with various nucleophiles [111-112]. In an example described in 2017 by Zhang and Wu, simple chiral sulfinamide phosphine **241** was employed at 10 mol% of catalyst loading in toluene to promote the first enantioselective phosphine-catalysed allylic alkylation of Morita–Baylis–Hillman carbonates **131** with indenenes **242** [125]. This allowed at room temperature the regio- and enantioselective synthesis of biologically interesting chiral 1,1,3-trisubstituted (trifluoromethyl)indene derivatives **243** bearing a quaternary stereogenic centre to be achieved in both uniformly high yields (77-98%) and enantioselectivities (90-98% ee). As shown in Scheme 74, the presence of either electron-donating or electron-withdrawing substituents at different positions of the phenyl ring of the indene was well tolerated. Furthermore, the methyl ester group ($R^4 = \text{Me}$) of the Morita–Baylis–Hillman carbonate could be changed into other alkyl substituents while keeping excellent results.



Scheme 74. Allylic alkylation of Morita–Baylis–Hillman-type carbonates with indenenes.

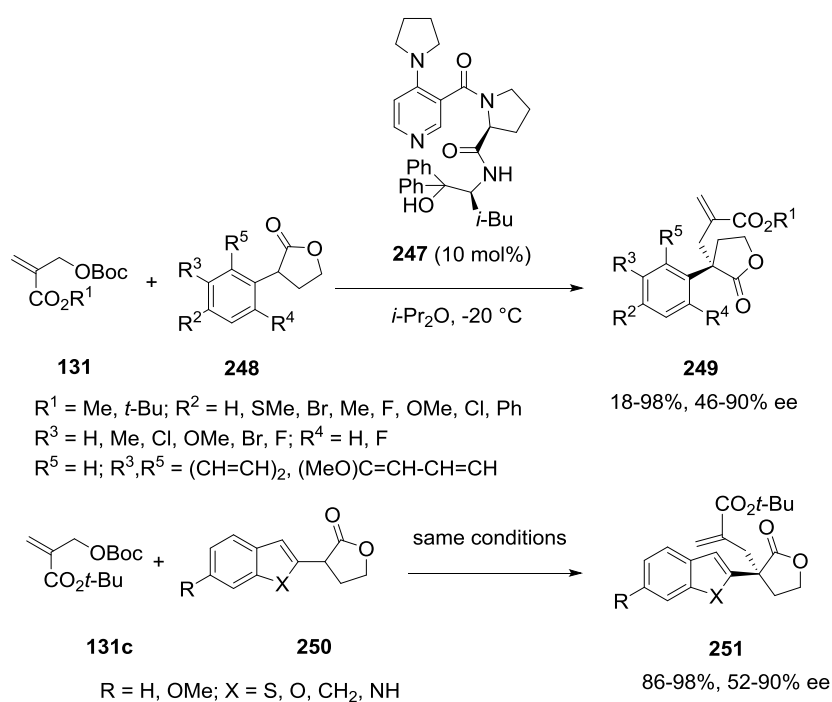
Another type of organocatalysts was employed by Waser et al. in 2018 to promote a novel enantioselective synthesis of α -allylated highly functionalised β -amino acid derivatives **244** through allylic alkylation of Morita–Baylis–Hillman carbonates **83** with isoxazolidin-5-ones **245** [126]. It involved the use of chiral phase-transfer catalyst **246** at only 5 mol% of catalyst loading at $-20\text{ }^\circ\text{C}$ in isopropanol as the solvent (Scheme 75). Performed in the presence of

Cs_2CO_3 as base, the reaction delivered a range of products **244** in moderate to high yields (53-92%), *trans*-diastereoselectivities ($E/Z = 80:20$ to $92:8$) and enantioselectivities (56-90% ee).



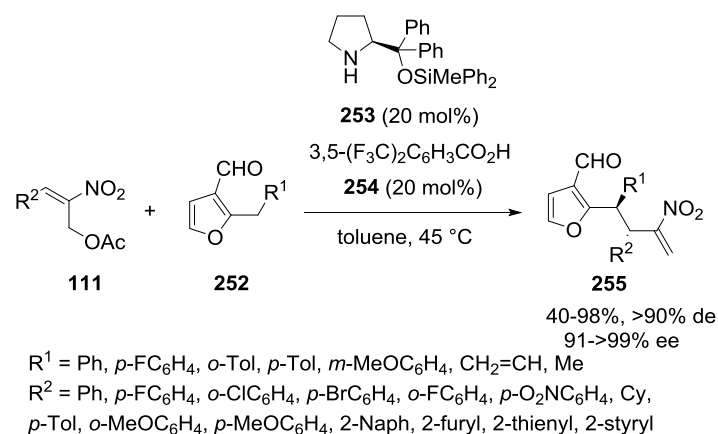
Scheme 75. Allylic alkylation of Morita–Baylis–Hillman carbonates with isoxazolidin-5-ones.

In 2020, Riguet et al. selected chiral DMAP catalyst **247** to promote asymmetric allylic alkylation of Morita–Baylis–Hillman-type carbonates **131** with α -aryl γ -lactones **248** [127]. The reaction carried out at room temperature in chloroform resulted in the formation of a wide range of chiral γ -lactones **249** bearing a quaternary stereocentre in 18-98% yields and 46-90% ee, as illustrated in Scheme 76. The phenyl ring of the α -aryl γ -lactones could be *para*- and *meta*-substituted while the reaction of *ortho*-substituted substrates provided lower ee value (56% ee). The scope of the reaction could be extended to a series of other γ -lactones **250** (Scheme 76). For example, the reaction of α -heteroaryl- γ -lactones **250** ($X = \text{O}, \text{S}, \text{NH}$) with Morita–Baylis–Hillman-type carbonate **131c** led under the same reaction conditions to the corresponding chiral products **251** in 86-98% yields and 52-90% ee. Especially, excellent enantioselectivities (88-90% ee) were obtained for a 3-functionalised benzofuran ($X = \text{O}$) as well as for lactones bearing a benzothiophen ring ($X = \text{S}$). However, a lower ee value (56% ee) was observed in the reaction of lactones exhibiting an unprotected indole ring ($X = \text{NH}$). Actually, the lowest enantioselectivity (52% ee) was obtained in the reaction of a γ -lactone with an indene substituent ($X = \text{CH}_2$).

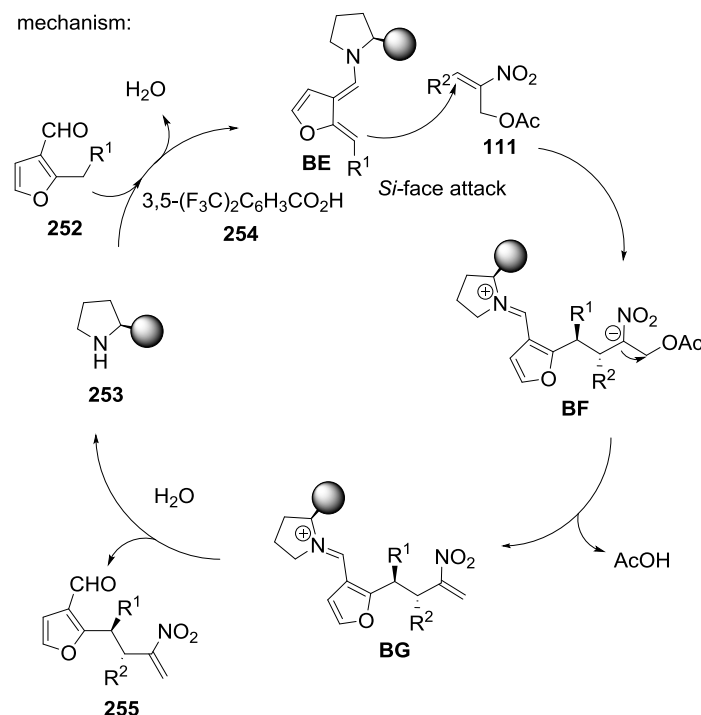


Scheme 76. Allylic alkylations of Morita–Baylis–Hillman-type carbonates with γ -lactones.

Earlier in 2018, Chen et al. reported an enantioselective allylic alkylation of Morita–Baylis–Hillman-type acetates **111** with 2-alkyl-3-furfural derivatives **252** (Scheme 77) [128]. The reaction employed 20 mol% of chiral secondary amine **253** as promotor in the presence of the same quantity of carboxylic acid **254** as an additive in toluene at 45 °C. Under these conditions, it led to a series of chiral densely functionalised 3-furfural derivatives **255** as single diastereomers (>90% de) with 91->99% ee and 40-98% yields. As illustrated in Scheme 77, dienamine-type *ortho*-quinodimethane intermediate **BE** was generated from the reaction between the 3-furfural substrate and the chiral amine catalyst in the presence of carboxylic acid **254**. Then, a Michael addition occurred from the *Si*-face of the 2-nitroallylic acetate to afford intermediate **BF**, which gave iminium ion intermediate **BG** after elimination of acetic acid. Finally, chiral product **255** was delivered after hydrolysis.

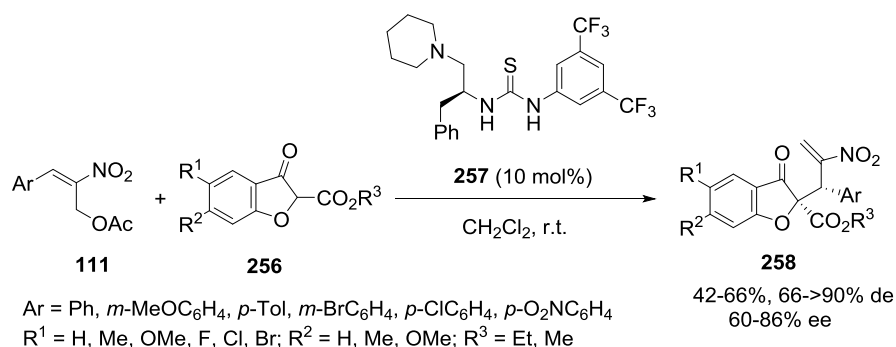


mechanism:



Scheme 77. Allylic alkylation of Morita–Baylis–Hillman-type acetates with 2-alkyl-3-furfural derivatives.

In the same area, Enders et al. disclosed in 2019 related S_N2' allylic substitutions of Morita–Baylis–Hillman-type acetates **111** with benzofuranones **256** as nucleophiles by using 10 mol% of chiral bifunctional thiourea catalyst **257** bearing a tertiary amine moiety (Scheme 78) [129]. Performed at room temperature in dichloromethane, the allylic alkylation of various nitroallylic acetates **111** with differently substituted benzofuranones **258** afforded chiral 2,2-disubstituted benzofuranones **258** with 66->90% de, 60-86% ee, and 42-66% yields. Indeed, the electronic nature of the substituents of the substrates was found to affect the yields, enantiomeric ratios and diastereoselectivities.



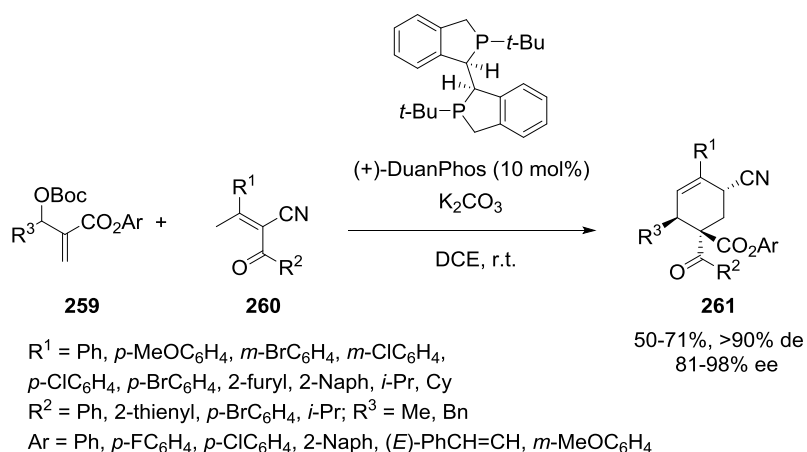
Scheme 78. Allylic alkylation of Morita–Baylis–Hillman-type acetates with benzofuranones.

3.3. Domino/tandem reactions of Morita–Baylis–Hillman carbonates, acetates and alcohols

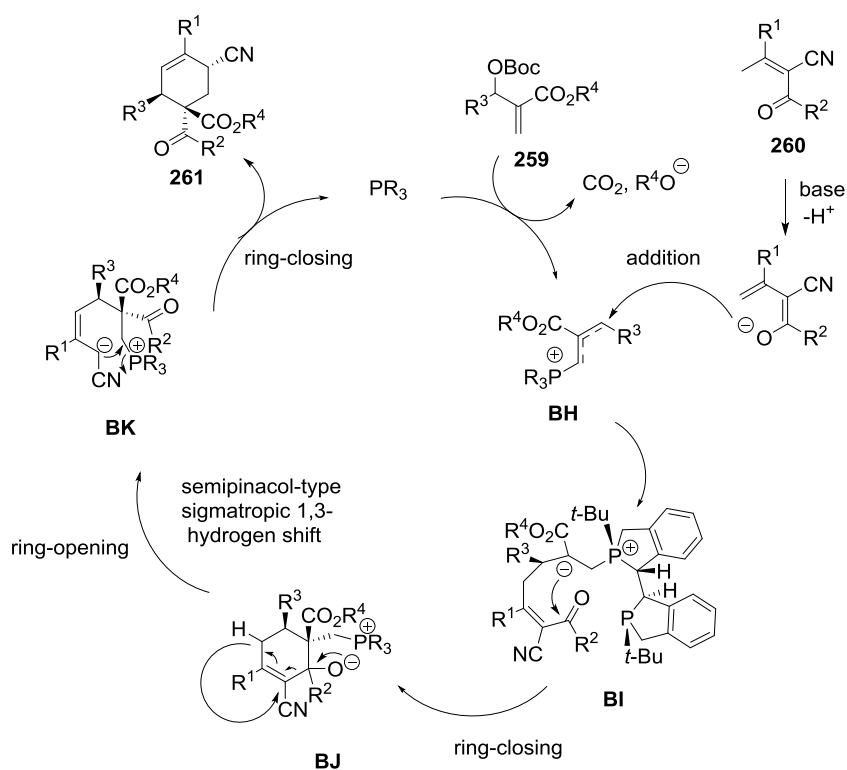
3.3.1. Morita–Baylis–Hillman carbonates

Domino reactions allow very complex molecules to be synthesised through one-pot procedures, avoiding costly isolation and purification of intermediates [130]. In 2018, one of these reactions was described by Jiang et al., involving Morita–Baylis–Hillman carbonates as substrates [131]. As detailed in Scheme 79, it occurred at room temperature between these substrates **259** and 2-(acyl)but-2-enitriles **260** in DCE in the presence of K₂CO₃ as a base. This enantioselective domino [4+2] annulation/semipinacol-type-rearrangement reaction required 10 mol% of chiral bisphosphine catalyst (+)-DuanPhos to yield the corresponding chiral multifunctionalised products **261** as almost single diastereomers (>90% de) in 50-71% yields and 81-98% ee. Actually, enantioselectivities of ≥88% ee were obtained in all cases of Morita–Baylis–Hillman carbonates with the exception of that bearing an olefinic group (R³ = (*E*)-PhCH=CH) which provided the desired product in slightly lower ee value (81% ee). Indeed, a wide range of methyl and benzyl Morita–Baylis–Hillman carbonates bearing either electron-withdrawing or electron-donating substituents on the phenyl ring (R³) but also a naphthyl substituent (R³ = 2-Naph) reacted smoothly with excellent diastereo- and enantioselectivities. Moreover, variously substituted 2-(acyl)but-2-enitriles were compatible, including alkyl-substituted ones (R¹ = *i*-Pr, Cy; R² = *i*-Pr), leading to the corresponding enantiopure products (96-98% ee) with 53-60% yields. A possible mechanism for the domino process is depicted in Scheme 79, beginning with a S_N2' attack of the chiral bisphosphine (PR₃) to the Morita–Baylis–Hillman carbonate, producing phosphonium ylide

intermediate **BH**. Then, the latter was attacked by the enolate arisen from nitrile **260** to give intermediate **BI**. A subsequent stereoselective intramolecular ring-closing afforded intermediate **BJ**. Finally, this intermediate underwent a semipinacol-type sigmatropic 1,3-hydrogen shift which provided ring-opened intermediate **BK**. Finally, a further intramolecular ring-closing with elimination of the regenerated phosphine catalyst furnished the product.

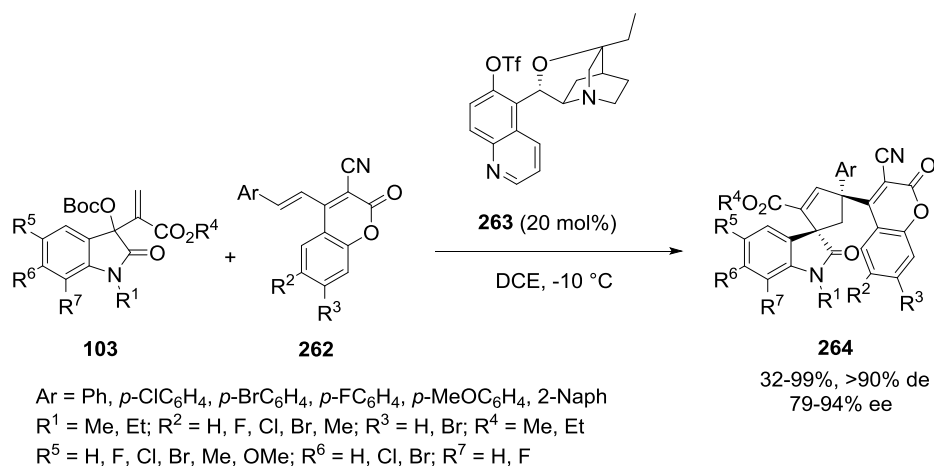


mechanism (with $\text{PR}_3 = (+)\text{-DuanPhos}$):

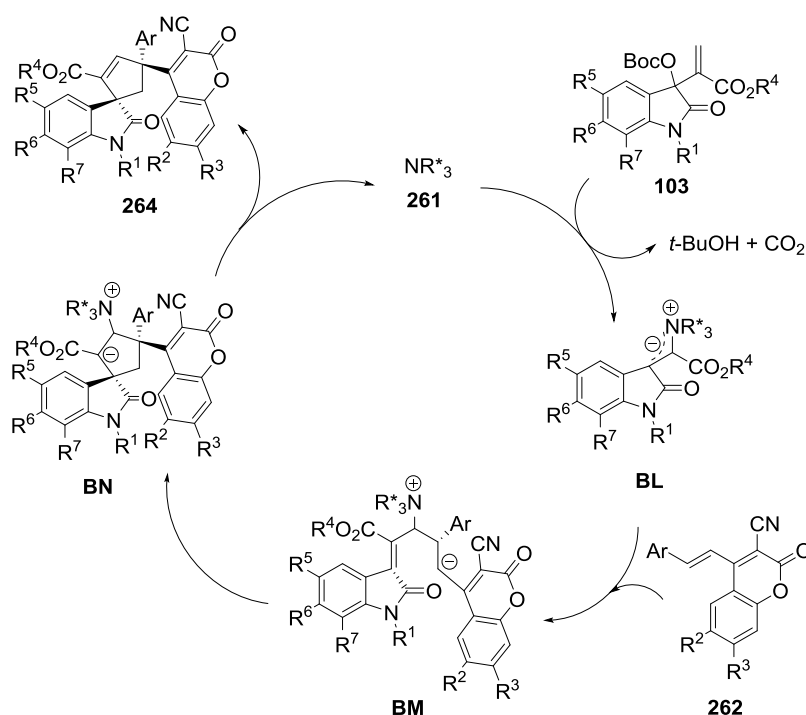


Scheme 79. Domino [4+2] annulation/semipinacol-type-rearrangement reaction of Morita–Baylis–Hillman carbonates with 2-(acyl)but-2-enitriles.

In 2019, Wang and Yuan disclosed an enantioselective α -regioselective domino 1,6-addition/cyclisation reaction between 3-cyano-4-alkenyl-2H-chromen-2-ones **262** and isatin-derived Morita–Baylis–Hillman carbonates **103** which was promoted by 20 mol% of *Cinchona* alkaloid catalyst **263** (Scheme 80) [132]. Carried out in DCE at -10 °C, the reaction produced chiral 3,3'-cyclopentenylspirooxindoles **264** bearing 2H-chromen-2-ones as almost single diastereomers in 32-99% yields with 79-94% ee. A plausible mechanism is depicted in Scheme 80, showing that the tertiary amine unit of **263** attacked the isatin-derived Morita–Baylis–Hillman carbonate to generate ylide intermediate **BL**, which subsequently underwent a nucleophilic α -attack on the 3-cyano-4-alkenyl-2H-chromen-2-one to give intermediate **BM**. Then, the latter led to intermediate **BN** through cyclisation, which afforded the final product along with regenerated catalyst. It must be noted that this reaction constituted the first example of domino reactions using 3-cyano-4-alkenyl-2H-chromen-2-ones as acceptors in 1,6-additions.



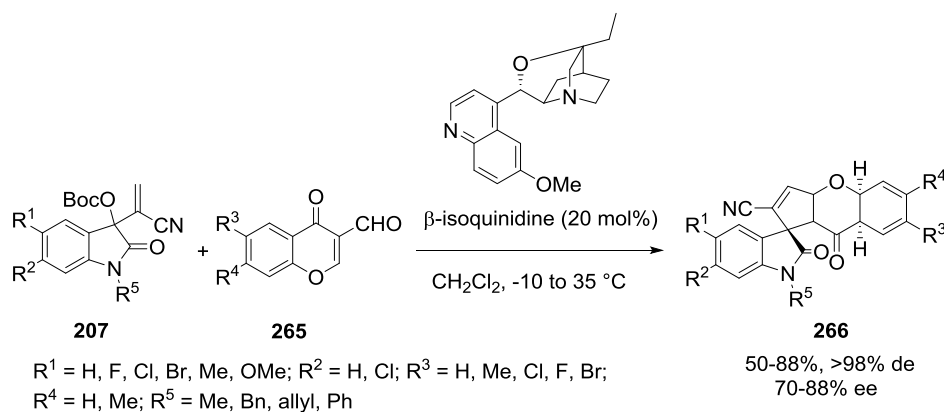
proposed mechanism:



Scheme 80. Domino 1,6-addition/cyclisation reaction of isatin-derived Morita–Baylis–Hillman carbonates with 3-cyano-4-alkenyl-2H-chromen-2-ones.

Later in 2021, Liu and Chen developed an enantioselective domino [3+2] cycloaddition /deformylation reaction, occurring regioselectively between isatin-derived Morita–Baylis–Hillman carbonates **207** and 3-formylchromones **265** [121]. The reaction was performed at -10 to 35 °C in dichloromethane in the presence of 20 mol% of β -isoquinidine (Scheme 81). It resulted in the formation of a range of chiral spirocyclopentene oxindoles **266** as single diastereomers (>98% de) in 50-88% yields and 70-88% ee. The catalyst system was

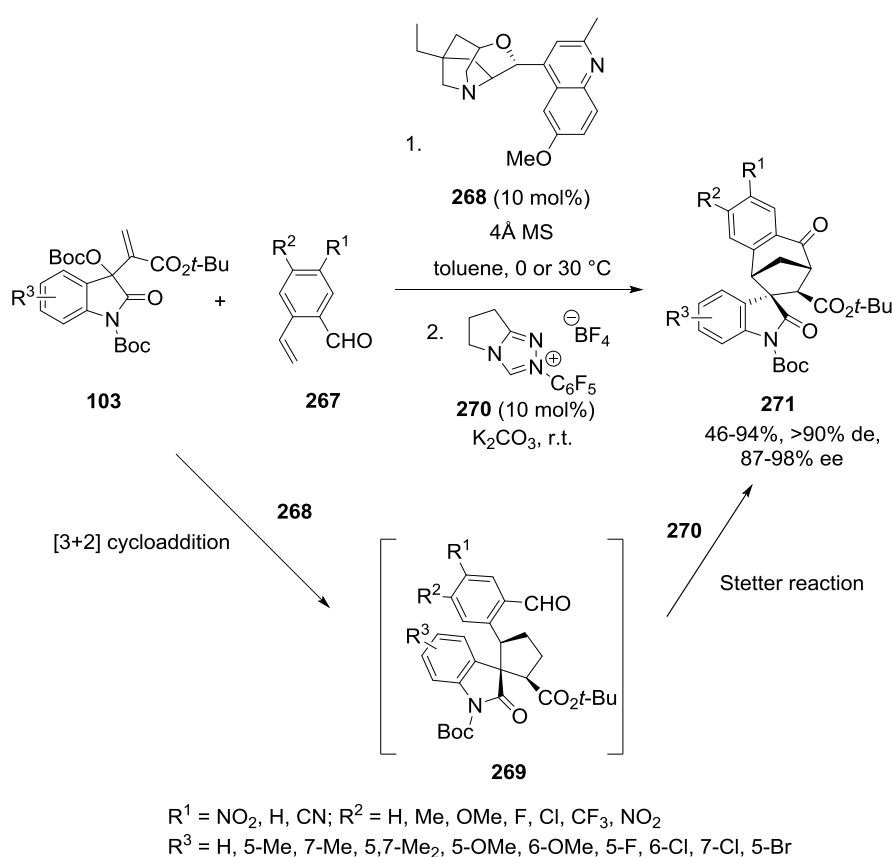
compatible with 3-formylchromones substituted at different position of the phenyl ring by either electron-donating or electron-withdrawing groups. Moreover, isatin-derived Morita–Baylis–Hillman carbonates exhibiting a variety of substituents at the oxindole ring were also tolerated. It was found that the nature of the N-substituent (R^5) had a dramatic influence on the enantioselectivity of the reaction. Indeed, substrates N-substituted with benzyl, allyl and phenyl groups generally gave lower enantioselectivities (70–72% ee) than those containing methyl groups.



Scheme 81. Domino [3+2] cycloaddition/deformylation reaction of isatin-derived Morita–Baylis–Hillman carbonates with 3-formylchromones.

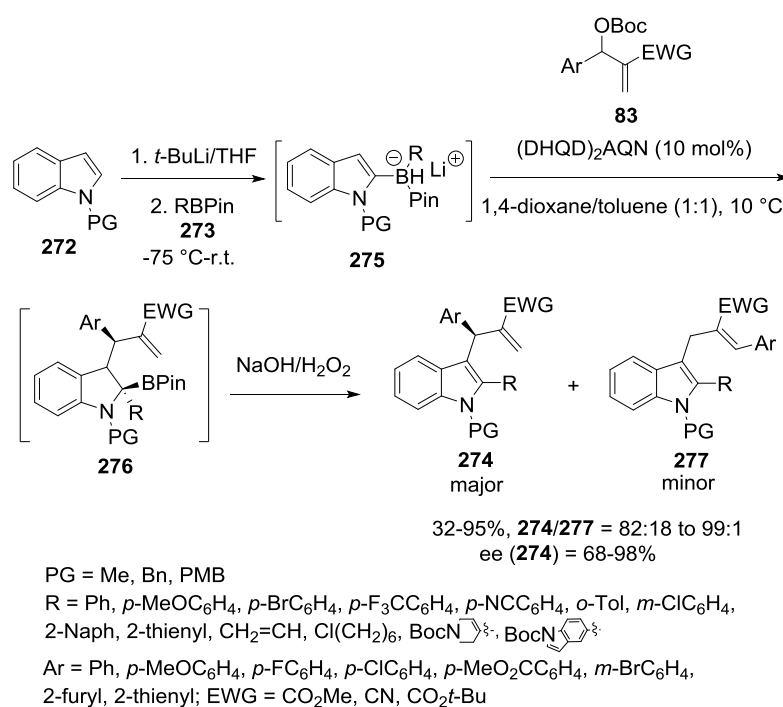
Along with domino reactions, one-pot tandem processes involve a sequence of reactions occurring one after the other with a minimum change in conditions. The only difference between these two types of one-pot reactions lies in the point along the sequence at which one or more catalysts (or reagents) had to be added to effect either the initiation of a sequence (domino reaction) or propagation to the next step (tandem reaction) [133]. In 2019, an example of enantioselective tandem reactions involving isatin-derived Morita–Baylis–Hillman carbonates **103** was reported by Chen and Liang (Scheme 82) [134]. It occurred at 0 or 30 °C in toluene between these substrates and activated *ortho*-vinylbenzaldehydes **267** through an α -regioselective asymmetric [3+2] cycloaddition catalysed by 10 mol% of chiral tertiary amine **268** to give intermediate cycloadducts **269**. After adding 10 mol% of achiral N-heterocyclic carbene catalyst **270**, cycloadducts **271** subsequently underwent an intramolecular Stetter reaction, resulting in the formation of chiral bridged 5,8-methanobenzo[7]annulen-9-one derivatives **271** incorporating a spirooxindole

motif. These functionalised complex products were obtained as single diastereomers (>90% de) with 46-94% yields and 87-98% ee, as illustrated in Scheme 82. Indeed, a range of Morita–Baylis–Hillman carbonates derived from diversely substituted isatins and *tert*-butyl acrylate reacted with 5-nitro-2-vinyl benzaldehyde ($R^1 = \text{NO}_2$, $R^2 = \text{H}$) to give the corresponding chiral products with 87-97% ee. The presence of either an electron-donating or an electron-withdrawing substituent at the 4-position of the 5-nitro-2-vinylbenzaldehyde scaffold ($R^2 = \text{Me}$, OMe, F, Cl: 91-97% ee) had no impact on the enantioselectivity of the reaction excepted in the case of a CF_3 group ($R^2 = \text{CF}_3$: 89% ee). By performing the [3+2] cycloaddition at higher temperature (30 vs 0 °C), 4-nitro-2-vinylbenzaldehyde ($R^1 = \text{H}$, $R^2 = \text{NO}_2$) also reacted with excellent enantioselectivity (98% ee) albeit with a lower yield (46%). Interestingly, an *ortho*-vinylbenzaldehyde bearing CN and F groups ($R^1 = \text{CN}$, $R^2 = \text{F}$) was also tolerated, leading to the desired product with 94% yield and 95% ee.



Scheme 82. Tandem [3+2] cycloaddition/Stetter reaction of isatin-derived Morita–Baylis–Hillman carbonates with activated *ortho*-vinylbenzaldehydes.

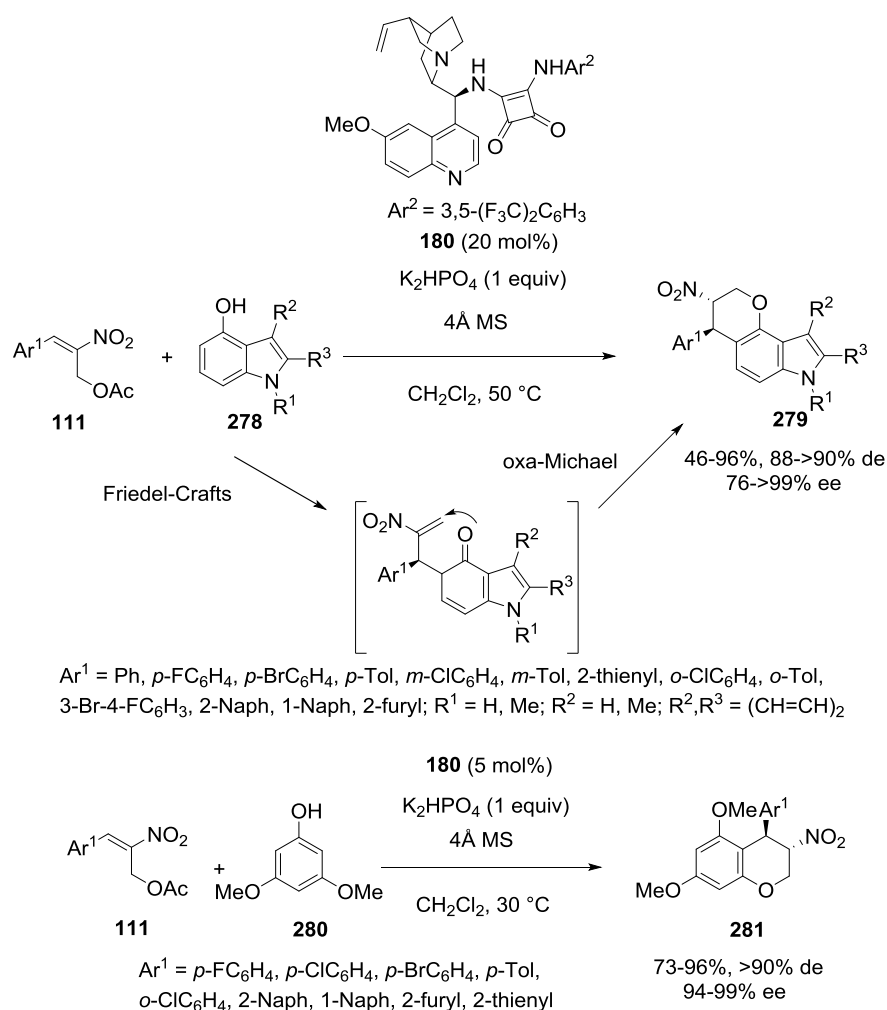
In 2024, Aggarwal et al. disclosed an organocatalytic asymmetric three-component of 1,2-boronate rearrangement, involving Morita–Baylis–Hillman carbonates **83**, indoles **272**, and boronic esters **273**, allowing the synthesis of chiral highly substituted indole derivatives **274** (Scheme 83) [135]. Actually, the tandem process consisted in the organocatalysed reaction of Morita–Baylis–Hillman carbonate **83** with intermediate indole boronate **275**, derived from the interaction between *N*-protected-indole **272** and boronic ester **273**. The process employed 10 mol% of (DHQD)₂AQN as catalyst in a 1:1 mixture of 1,4-dioxane and toluene as solvent. Performed at 10 °C, it resulted in the formation of boronic ester product **276**. The latter was further oxidised to regioselectively provide highly substituted chiral indole **274** as major product along with minor linear regioisomer **277**. The indoles were obtained in moderate to excellent yields (32-95%) with high regioselectivity (**274/277** = 82:18 to 99:1) and moderate to excellent enantioselectivities (68-98% ee for **274**).



Scheme 83. Tandem boronate formation/allylic substitution/oxidation reaction of Morita–Baylis–Hillman carbonates, indoles, and boronic esters.

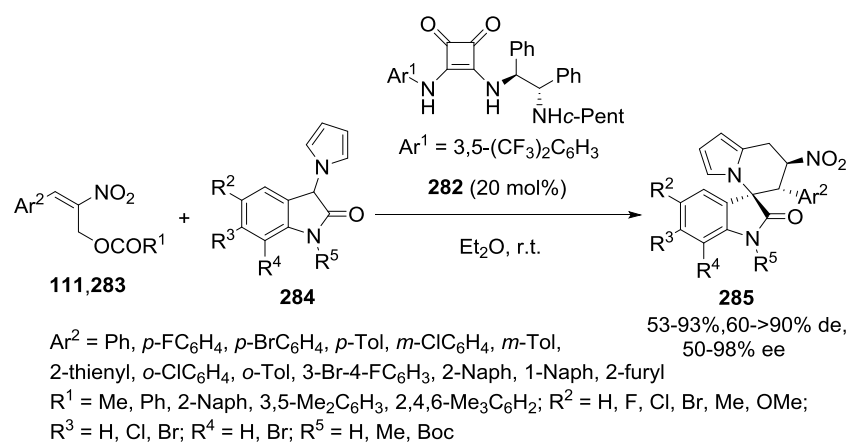
3.3.2. Morita–Baylis–Hillman acetate derivatives

In 2018, Morita–Baylis–Hillman-type acetates **111** were found by Xu et al. to smoothly react with 4-hydroxyindoles **278** (Scheme 84) [136]. Promoted at 50 °C in dichloromethane by 20 mol% of chiral quinine-squaramide bifunctional catalyst **180**, the enantioselective domino Friedel–Crafts/oxa-Michael reaction allowed the synthesis of a range of chiral tetrahydropyranoindoles **279** bearing two contiguous stereocentres to be prepared with 46-96% yields, 88->90% de, and 76->99% ee. The use of K₂HPO₄ as stoichiometric additive was required to neutralise acetic acid generated in the reaction mixture which allowed the improvement of the yields. The scope of the methodology could be extended to an electron-rich phenol, such as 3,5-dimethoxyphenol **280**, which was found to react with different Morita–Baylis–Hillman-type acetates **111** to produce the corresponding chiral tetrahydropyranoindoles **281** as single diastereomers (>90% de) in 73-96% yields and 94-99% ee, as illustrated in Scheme 82. In this case, the reaction was performed at lower temperature (30 vs 50 °C) and required only 5 mol% of catalyst loading.



Scheme 84. Domino Friedel–Crafts/oxa-Michael reactions of Morita–Baylis–Hillman-type acetates with 4-hydroxyindoles/3,5-dimethoxyphenol.

In 2024, Li et al. designed novel bifunctional amine-squaramide catalyst **282** to promote at 20 mol% of catalyst loading the enantioselective domino Michael/Friedel–Crafts reaction between Morita–Baylis–Hillman-type acetates **111,283** and 3-pyrrolyloxindoles **284** (Scheme 85) [137]. Carried out in diethyl ether at room temperature, the reaction afforded the corresponding chiral spirooxindole-containing tetrahydroindolizines **285** bearing three contiguous stereocentres, including an all-carbon quaternary one. These functionalised tetracyclic products were obtained with 53-93% yields, 60->90% de, and 50-98% ee. Notably, uniformly high enantioselectivities of 78-98% ee were achieved in all cases of substrates except for heteroaromatic ones ($\text{Ar}^2 = 2\text{-furyl}, 2\text{-thienyl}$) which afforded the desired products with only 50-51% ee, while as only single diastereoisomers (>90% de).

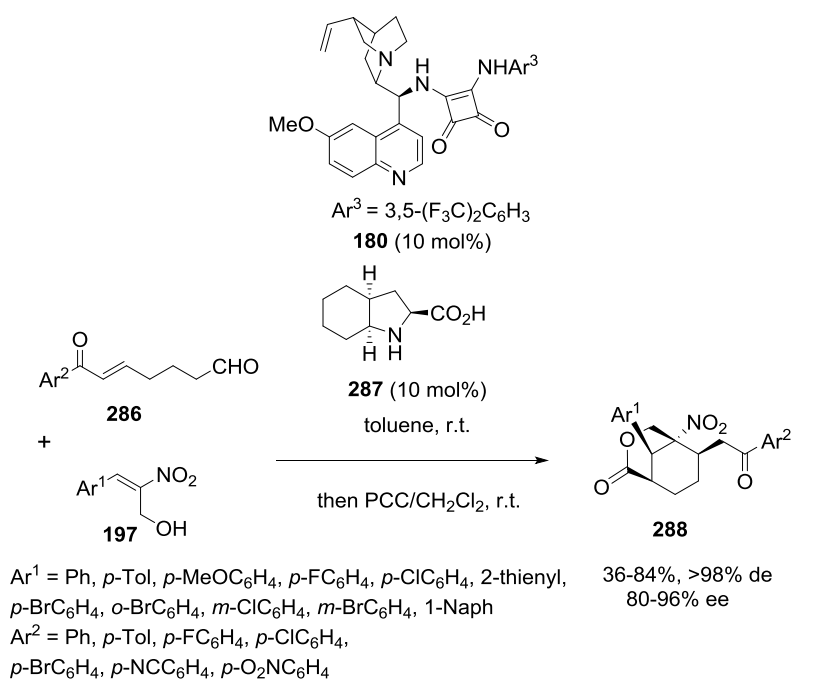


Scheme 85. Domino Michael/Friedel–Crafts reaction of Morita–Baylis–Hillman-type acetates with 3-pyrrolyloxindoles.

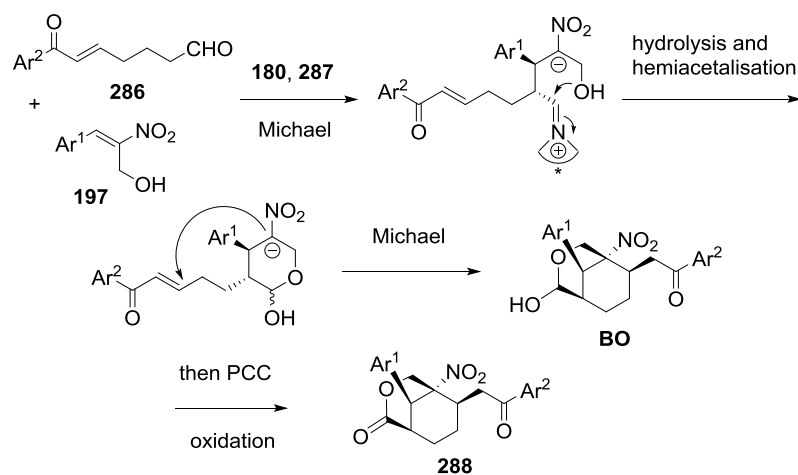
3.3.3. Morita–Baylis–Hillman alcohol derivatives

In 2019, Zhao et al. reported an enantioselective domino Michael/hemiacetalisation/Michael reaction of Morita–Baylis–Hillman-type alcohols **197** derived from nitroalkenes with (*E*)-7-aryl-7-oxohept-5-enals **286** [138]. The process evolved at room temperature in toluene in the presence of 10 mol% of a combination of two chiral

organocatalysts, such as chiral amino acid **287** and quinine-derived squaramide **180** (Scheme 86). The authors demonstrated that the reaction did not occur in the presence of *Cinchona* catalyst **180** or amino acid catalyst **287** alone, thus indicating the need for a modularly designed catalytic system for the reaction to occur. The bicyclic hemiacetal products **BO** were subsequently submitted to oxidation in the presence of PCC to give the corresponding chiral 3-oxabicyclo[3.3.1]nonan-2-ones **288** exhibiting four contiguous stereocentres as single diastereomers (>98% de) with excellent regiocontrol, moderate to high yields (36-84%), and uniformly high ee values (80-96% ee).



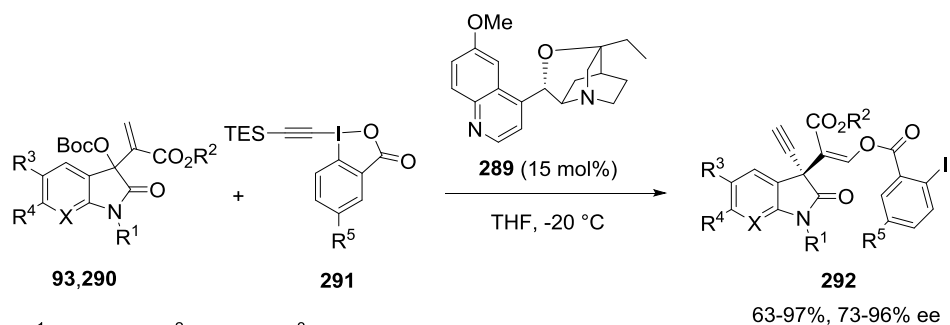
mechanism:



Scheme 86. Domino Michael/hemiacetalisation/Michael reaction of Morita–Baylis–Hillman-type alcohols with (*E*)-7-aryl-7-oxohept-5-enals followed by oxidation.

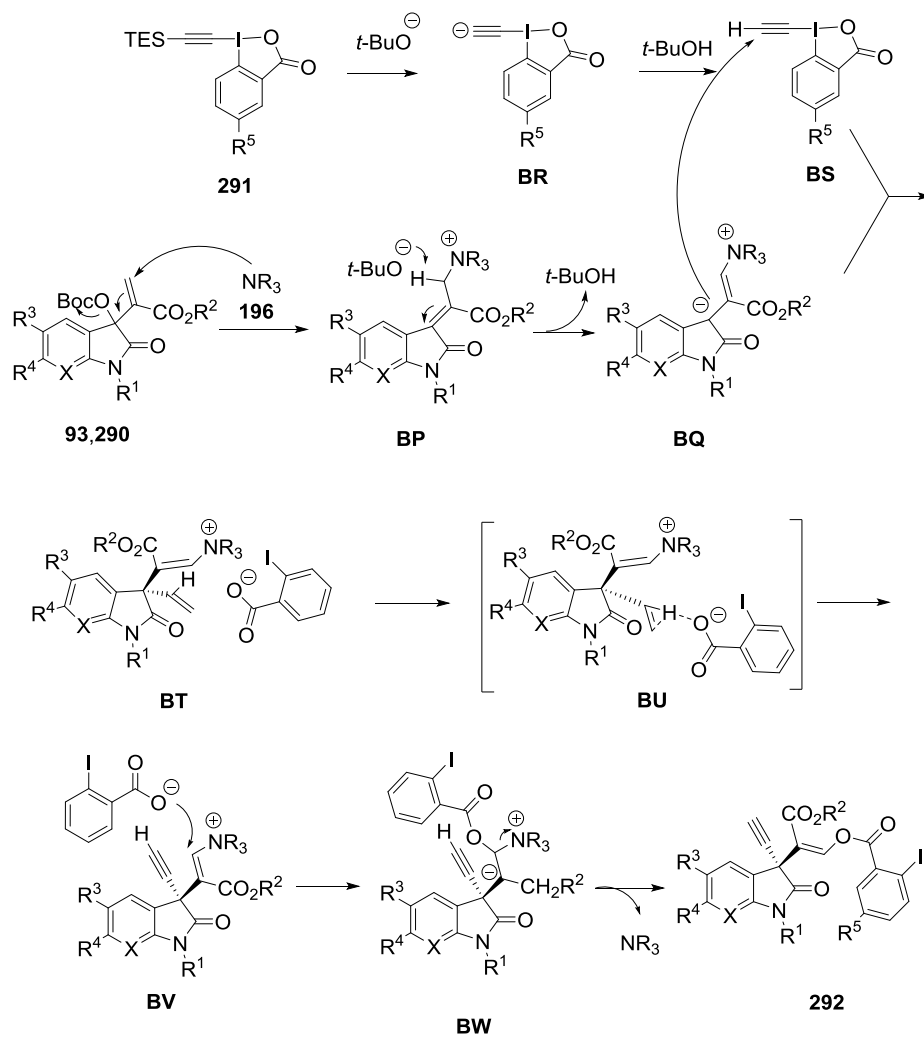
3.4. Miscellaneous reactions of Morita–Baylis–Hillman carbonates

In 2018, chiral *Cinchona* alkaloid catalyst **289** was used at 15 mol% of catalyst loading in THF by Chen and Liang to promote asymmetric 1,3-oxo-ethynylation reaction of isatin-derived Morita–Baylis–Hillman carbonates **93,290** with silyl ethynyl-1,2-benziodoxol-3(1H)-ones **291** (Scheme 87) [139]. The reaction led at -20 °C in THF to densely functionalised chiral products **292** bearing a quaternary stereocentre with 63-97% yields and 73-96% ee. Ethynylbenziodoxol(on)e reagents exhibiting either electron-donating or electron-withdrawing substituents on the phenyl ring uniformly reacted with high enantioselectivity as well as isatin-derived Morita–Baylis–Hillman carbonates bearing electron-donating groups on the aryl ring (90-93% ee) while reduced ee values were obtained in the reaction of Morita–Baylis–Hillman carbonates possessing electron-withdrawing substituents (80-87% ee). It was found that Morita–Baylis–Hillman carbonates derived from 7-azaisatins (X = N) were also tolerated, yielding the corresponding chiral products with high yields (85-87%) and lower enantioselectivities (73-78% ee). Indeed, generally both higher yields (63-97%) and ee values (77-96% ee) were obtained in the reaction of isatin-derived substrates (X = CH, C(Me), C(Cl)). To explain the results, the authors proposed the mechanism depicted in Scheme 87, beginning with the *in situ* generation of ammonium salt **BP** and *t*-butoxide by reaction of the Morita–Baylis–Hillman carbonate with the catalyst (NR₃). Then, zwitterionic *N*-allylic ylide **BQ** and *t*-butanol were formed through deprotonation. In the same time, silylated ethynylbenziodoxol(on)e reagent **291** underwent desilylation to afford alkyne anion **BR** in the presence of *t*-butoxide. A subsequent protonation afforded ethynyl-1,2-benziodoxol-3(1H)-one intermediate **BS**. Then, the condensation of **BQ** to intermediate **BS** resulted in the formation of complex **BT** with elimination of 2-iodobenzoate. A subsequent 1,2-hydride-shift occurred through transition state **BU** assisted by carboxylate group. The Michael addition of 2-iodobenzoate to **BV** further provided intermediate **BW**, which finally led to the thermally more stable *Z*-configured product along with regenerated catalyst.



$R^1 = \text{Me, allyl}; R^2 = \text{Me, Et}; R^3 = \text{H, Me, OMe, F, COCF}_3, \text{I, Br};$
 $R^4 = \text{H, Me, Br}; R^5 = \text{H, Me, } t\text{-Bu, F}; X = \text{CH, C(Me), C(Cl), N}$

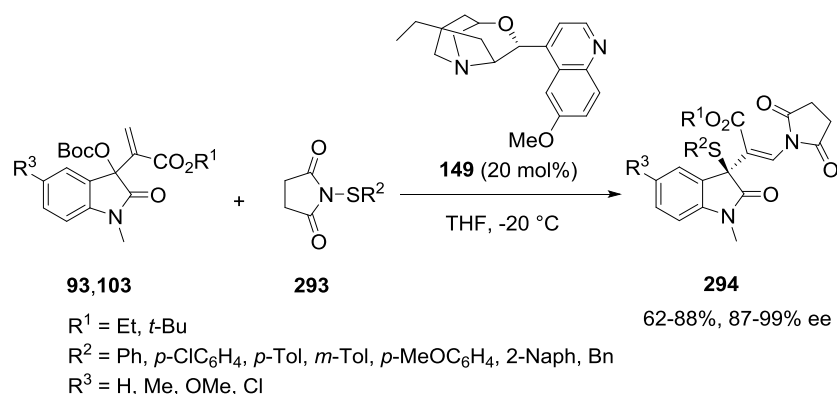
mechanism:



Scheme 87. 1,3-Oxo-ethynylation reaction of isatin-derived Morita–Baylis–Hillman carbonates with silyl ethynyl-1,2-benziodoxol-3(1H)-ones.

A comparable strategy could be applied to another types of electrophiles, such as *N*-(aryl/alkylthio)succinimides **293** [139]. In the presence of 20 mol% of related *Cinchona*

alkaloid catalyst **149** in THF, these substrates reacted at $-20\text{ }^{\circ}\text{C}$ with isatin-derived Morita–Baylis–Hillman carbonates **93,103** through enantioselective 1,3-aminosulfenylation reaction to give the corresponding chiral densely functionalised products **294** with 62–88% yields and 87–99% ee, as shown in Scheme 88. Both these two asymmetric 1,3-difunctionalisations (Schemes 87–88) allowed the synthesis of highly functionalised chiral molecules potentially valuable in medicinal chemistry.



Scheme 88. 1,3-Aminosulfenylation reaction of isatin-derived Morita–Baylis–Hillman carbonates with *N*-(aryl/alkylthio)succinimides.

4. Conclusions

Among enantioselective carbon–carbon bond forming reactions, the simple (aza)-Morita–Baylis–Hillman reaction has become one of the most popular and synthetically useful. In the last seven years, the discovery of novel organocatalysts, including chiral phosphines, *Cinchona* alkaloids, diols, and proline derivatives based on the concept of bi/multifunctionality, to promote these environmentally friendly reactions has significantly extended their scope.

Exhibiting three functional groups in close-proximity, the readily accessible Morita–Baylis–Hillman adducts constitute versatile sources for discovering new catalytic asymmetric transformations. This review shows that among these transformations, a wide range of novel organocatalysed enantioselective annulations of different types, including [3+2], [4+1], [3+3] among others, has allowed the synthesis of many types of chiral complex cyclic products with enantioselectivities of up to >99% ee. The second most developed field

of asymmetric transformations of Morita–Baylis–Hillman adducts is that of enantioselective organocatalysed allylic substitutions of Morita–Baylis–Hillman carbonates, carbamates and fluorides with different types of carbon and nitrogen nucleophiles achieved with up to 98% ee. Along with these two types of transformations, are also sophisticated enantioselective organocatalysed domino and tandem reactions achieved with remarkable enantioselectivities. Among them, are enantioselective domino double Michael reactions of Morita–Baylis–Hillman-type acetates with *N,N'*-dimethylbarbiturate or 4-hydroxycoumarin catalysed by a bifunctional thiourea with 99% ee; domino [4+2] annulation/semipinacol-type-rearrangement reactions of Morita–Baylis–Hillman carbonates with 2-(acyl)but-2-enitriles promoted by a chiral bisphosphine to give the corresponding products with 98% ee; and tandem [3+2] cycloaddition/Stetter reactions of isatin-derived Morita–Baylis–Hillman carbonates with activated *ortho*-vinylbenzaldehydes using a chiral *Cinchona* alkaloid catalyst providing 99% ee. In another context, miscellaneous enantioselective transformations also provided excellent results, such as 1,3-oxo-ethynylation reaction of isatin-derived Morita–Baylis–Hillman carbonates with silyl ethynyl-1,2-benziodoxol-3(1H)-ones (96% ee), and 1,3-aminosulfonylation reaction of isatin-derived Morita–Baylis–Hillman carbonates with *N*-(aryl/alkylthio)succinimides (99% ee).

Based on the powerful concept of organocatalysis, the simple asymmetric Morita–Baylis–Hillman reaction will undoubtedly continue to attract a great attention, by allowing a direct and simple access to a wide diversity of multifunctionalised chiral products. In the near future, efforts will also certainly be applied to the synthesis of more bioactive and/or natural products, considering the importance of biological activities of many Morita–Baylis–Hillman adducts and derivatives [140]. Moreover, the synthetic usefulness of the Morita–Baylis–Hillman adducts will allow the discovery of novel asymmetric reactions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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