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Recent developments in the asymmetric organocatalytic Morita–Baylis–Hillman reaction

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A B S T R A C T

The goal of this review is to collect the recent developments in asymmetric organocatalytic (aza)-Morita–Baylis–Hillman reactions reported since the beginning of 2013. It also includes the asymmetric organocatalysed transformations of racemic (aza)-Morita–Baylis–Hillman adducts, illustrating that they constitute synthetically important synthons in organic chemistry. It is divided into four sections, dealing successively with organocatalytic enantioselective Morita–Baylis–Hillman reactions, organocatalytic enantioselective aza-Morita–Baylis–Hillman reactions, asymmetric (aza)-Morita–Baylis–Hillman reactions of chiral substrates and asymmetric organocatalysed applications of Morita–Baylis–Hillman adducts.

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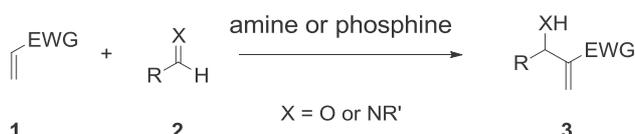
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1. Introduction

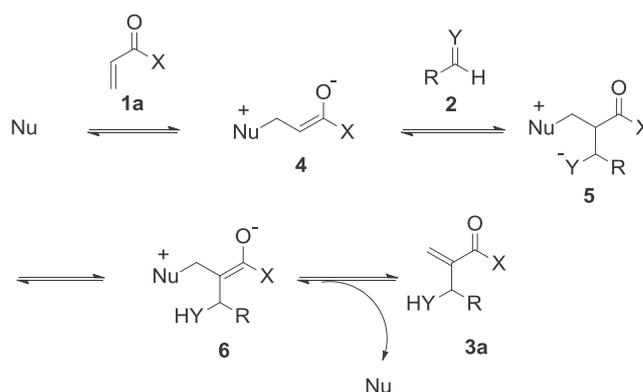
The Morita–Baylis–Hillman reaction involves the carbon–carbon coupling of the α -position of an activated alkene **1** with a carbon electrophile **2** containing an electron-deficient sp^2 carbon atom, such as an aldehyde ($X = O$), catalysed by a tertiary amine or phosphine. This operationally simple and atom-economic process allows the direct preparation of α -methylene- β -hydroxycarbonyl compounds **3** (Scheme 1). Activated imines can also participate instead of aldehydes ($X = NR'$) in this reaction and in this case the process is called aza-Morita–Baylis–Hillman reaction, affording the corresponding α -methylene- β -aminocarbonyl derivatives. Several advantages of the (aza)-Morita–Baylis–Hillman reaction are related to the fact that the starting materials are commercially available, the products are multifunctional, the catalysts employed are most of the time organic and the reaction conditions used often mild. Actually, this reaction is one of the best illustrations of organocatalysis¹ for green chemistry when amines or phosphines are employed as catalysts.

A commonly accepted mechanism for the Morita–Baylis–Hillman reaction, based on experimental and theoretical studies,² involves a sequence of a Michael addition, an aldol reaction, a proton transfer and a β -elimination. As depicted in Scheme 2, the process begins with a reversible conjugate addition of the nucleophilic organocatalyst (Nu) to the activated alkene **1** to generate enolate **4**. The latter intercepts the aldehyde (or imine) through an aldol condensation to afford zwitterionic intermediate **5**. A subsequent proton transfer from the α -carbon atom to the β -alkoxide (amide) followed by a β -elimination then leads to the final (aza)-Morita–Baylis–Hillman adduct **3** along with regenerated organocatalyst. According to kinetic studies reported in the last 1980s by Hill and Isaacs,³ the rate-determining step of the Morita–Baylis–Hillman reaction was suggested to be the aldol step. However, McQuade et al.,^{2b,c} and Aggarwal et al.^{2a} evaluated the Morita–Baylis–Hillman mechanism through kinetic and theoretical studies, focusing on the proton-transfer step and proposed the proton-transfer step as the rate-determining step. In 2015, Singleton and Plata showed the importance of the reaction conditions in the determination of the rate-limiting step of the reaction.^{2j} Indeed, the proton-transfer step was found the primary rate-limiting step at 25 °C, but the aldol step was partially rate-limiting, and became the primary rate-limiting step at low temperatures, thus demonstrating competitive rate-limiting steps.

The origin of the Morita–Baylis–Hillman reaction dates back to 1968 with a pioneering report by Morita who described the reaction of aldehydes with acrylates or acrylonitrile in the presence of tricyclohexylphosphine as a catalyst to provide the corresponding 2-methylene-3-hydroxy alkanones (or alkanenitriles).⁴ Later in 1972, Baylis and Hillman reported in a German patent the corresponding amine-catalysed couplings between various activated alkenes and aldehydes.⁵ In spite of the importance of this promising reaction, it remained ignored by the chemical community for a decade. However, at the beginning of 1980s, this reaction became more popular with the works of Drewes and Emslie,⁶ Hoffmann and Rabe,⁷ Perlmutter and Teo,⁸ and Basavaiah and Gowriswari.⁹ Today, this reaction constitutes one of the most useful and popular carbon–carbon



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



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

bond-forming reactions with an enormous synthetic utility. Its exponential growth and importance are evidenced by the number of reviews published.¹⁰ The Morita–Baylis–Hillman reaction creates a chiral centre, thereby allowing the synthesis of chiral multifunctional molecules by using chiral activated alkenes or chiral electrophiles but even more interestingly chiral organocatalysts of different types, such as chiral phosphines, *Cinchona* alkaloids and thioureas. The goal of the present review is to cover the recent advances in organocatalytic asymmetric (aza)-Morita–Baylis–Hillman reactions reported since the beginning of 2013, since this topic was previously reviewed in 2013 by Shi.^{10t} It must be noted that the special field of enantioselective organocatalysed aza-Morita–Baylis–Hillman reactions is covered only since 2014 since Shi published an account on this field in 2014.^{10u} and concerning the applications of racemic Morita–Baylis–Hillman adducts in asymmetric organocatalysed transformations, they are covered only from the beginning of 2015 since two reviews have been recently published in this area.^{10v-w} For the reader's convenience, this review is divided into four sections, dealing successively with organocatalytic enantioselective Morita–Baylis–Hillman reactions, organocatalytic enantioselective aza-Morita–Baylis–Hillman reactions, asymmetric (aza)-Morita–Baylis–Hillman reactions of chiral substrates and asymmetric organocatalysed applications of Morita–Baylis–Hillman adducts.

2. Organocatalytic enantioselective Morita–Baylis–Hillman reactions

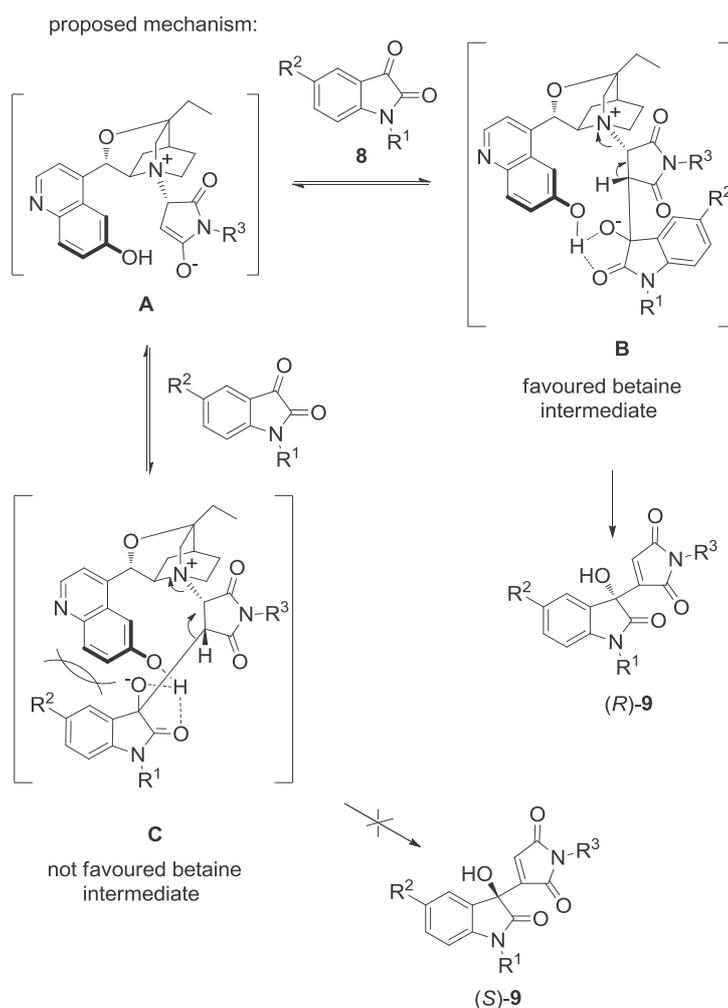
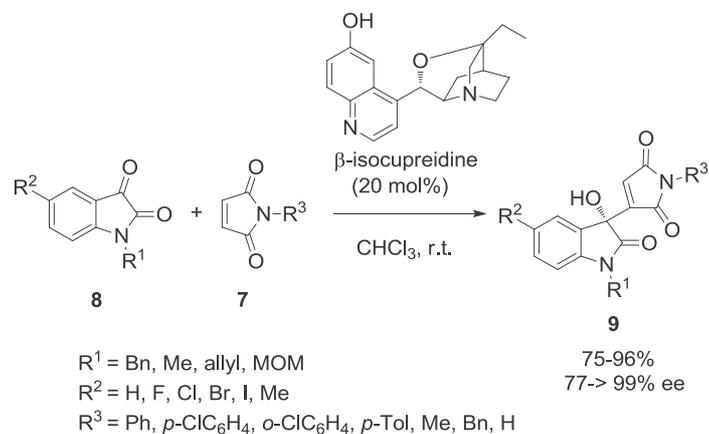
The early works on enantioselective versions of organocatalytic Morita–Baylis–Hillman reactions were reported by Drewes and Roos,^{10a} Isaacs et al.,¹¹ and Marko et al.,¹² focusing on the use of chiral and readily available nitrogen base catalysts, such as brucine, *N*-methylprolinol, *N*-methylephedrine and nicotine, that provided only moderate enantioselectivities ($\leq 20\%$ ee). In 1998, (*S*)-BINAP was also employed by Soai et al. to promote the enantioselective Morita–Baylis–Hillman reaction between acrylates and pyrimidine carboxaldehydes to provide the corresponding adducts in low to moderate enantioselectivities (9–44% ee).¹³ Ever since, very high enantioselectivities have been achieved by involving different types of organocatalysts including chiral bi/multifunctional phosphines and *Cinchona* alkaloids, along with thioureas.¹⁰

2.1. *Cinchona* alkaloid catalysts

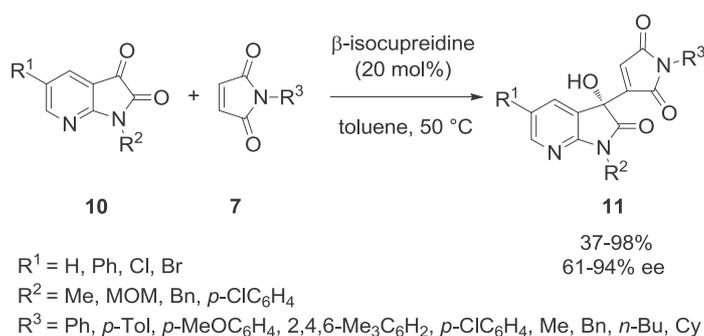
In 1992, Hiram and Oishi prepared a chiral enantiopure DABCO derivative, the C_2 -symmetric 2,3-bis(benzyloxymethyl)-1,4-diazabicyclo[2.2.2]octane, that was further used as catalyst for the first time in the Morita–Baylis–Hillman reaction of methyl vinyl

ketone with aromatic aldehydes.¹⁴ The corresponding Morita–Baylis–Hillman adducts were obtained in moderate to high yields (up to 93%) albeit combined with low to moderate enantioselectivities ($\leq 47\%$ ee). Later in 1999, Hatakeyama et al. reported the first highly enantioselective organocatalysed Morita–Baylis–Hillman reaction (up to 99% ee) between aliphatic aldehydes and the highly reactive Michael acceptor, 1,1,1,3,3,3-

hexafluoroisopropyl acrylate (HFIPA), that was based on the use of modified *Cinchona* alkaloid β -isocupreidine as base-catalyst.¹⁵ This important contribution sparked investigation into catalytic asymmetric Morita–Baylis–Hillman reactions. Ever since, this organocatalyst derived from quinidine has been applied to the enantioselective Morita–Baylis–Hillman reaction and its aza-counterpart of many substrates.^{10f,t} For example in 2013, β -



Scheme 3. β -Isocupreidine-catalysed Morita–Baylis–Hillman reaction of maleimides with isatins.

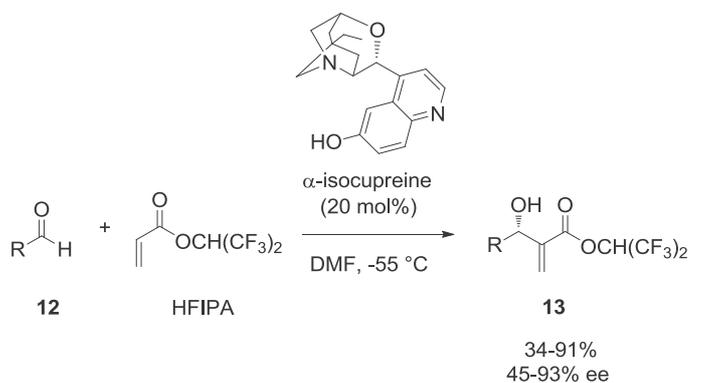


Scheme 4. β -Isocupreidine-catalysed Morita–Baylis–Hillman reaction of maleimides with 7-azaisatins.

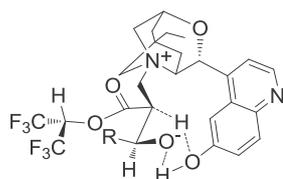
isocupreidine was applied as catalyst by Chimni and Chauhan to the first use of maleimide derivatives **7** as nucleophilic partners in enantioselective Morita–Baylis–Hillman reactions.¹⁶ The latter reacted at room temperature with isatin derivatives **8** in chloroform as solvent to give the corresponding chiral 3-substituted 3-hydroxyindole derivatives **9** in good to high yields (75–96%) and enantioselectivities ranging from 77% to >99% ee (Scheme 3). The substrate scope of the process was found wide since various *N*-protected isatins bearing different *N*-substituents, such as benzyl, methyl, allyl and methoxymethyl ether (MOM), reacted efficiently with *N*-aryl- as well as *N*-alkylmaleimides, leading to the corresponding chiral Morita–Baylis–Hillman adducts **9** in generally both high yields and enantioselectivities of 79–96% and 91–>99% ee, respectively. It must be noted that the lowest enantioselectivity of 77% ee and yield (75%) were obtained in the reaction of an *N*-unprotected maleimide ($\text{R}^3 = \text{H}$). The proposed mechanism for this reaction involved the initial nucleophilic addition of the tertiary amine organocatalyst to the maleimide to give enolate **A** (Scheme 3). This enolate then underwent an aldol-type addition to the *N*-protected isatin to provide betaine intermediates **B** and **C**. The latter were stabilised by intramolecular hydrogen bonding between the

oxyanion and the amide carbonyl group of the isatin with the aromatic hydroxyl group of β -isocupreidine. Actually, the product was generated from betaine intermediate **B** that was free from steric interactions. This novel methodology constituted a novel entry to chiral 3-hydroxy-2-oxindole moieties that occur frequently in natural products and important biologically active compounds.

In comparison with isatins, 7-azaisatins bearing an additional nitrogen atom at the 7-position of the 2-oxindole scaffold can be envisaged as better electrophiles owing to the electron-withdrawing effect of the pyridine motif. Even more importantly, many 7-azaisatins and derivatives are known to exhibit important biological activities. In this context in 2016, Chen et al. employed β -isocupreidine as catalyst to promote the enantioselective Morita–Baylis–Hillman reaction of maleimides **7** with 7-azaisatins **10**.¹⁷ As shown in Scheme 4, the process led to a series of chiral 3-hydroxy-7-aza-2-oxindoles **11** in moderate to quantitative yields (37–98%) and good to high enantioselectivities (61–94% ee) when it was performed in toluene at 50 °C. A variety of *N*-arylated and *N*-alkylated maleimides were compatible but the lowest enantioselectivities of 61–66% ee were obtained in the reaction of *N*-benzyl ($\text{R}^3 = \text{Bn}$) and *N*-butyl ($\text{R}^3 = n\text{-Bu}$) maleimides. Concerning the



proposed intermediate:

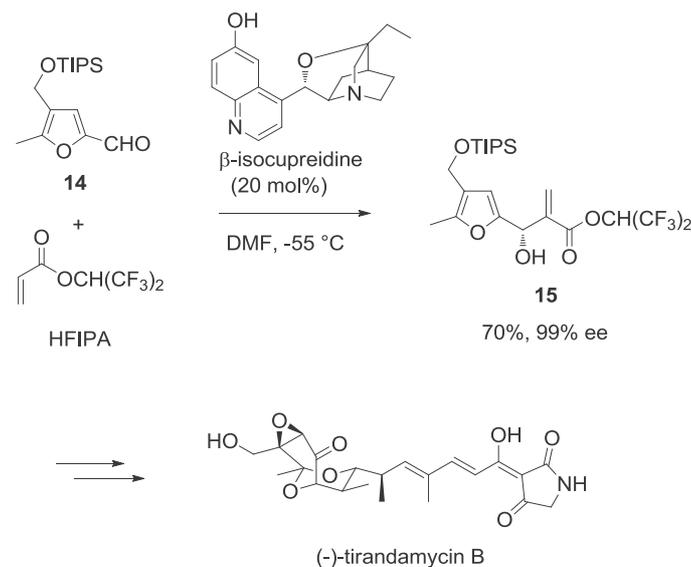


Scheme 5. α -Isocupreine-catalysed Morita–Baylis–Hillman reaction of aldehydes with HFIPA.

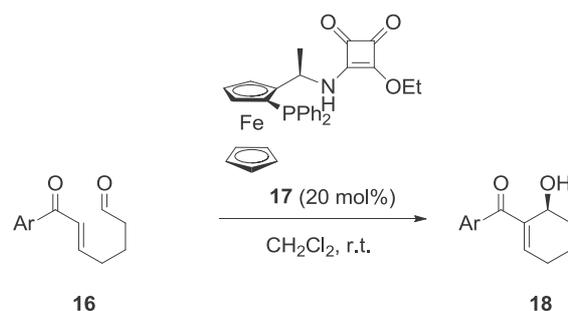
scope of the 7-azaisatins, different N-protecting groups (R^2) were investigated, including methyl, benzyl, methoxymethyl (MOM) and *para*-chlorophenyl groups. The latter three showed a lower reactivity and enantioselectivity than that of the methyl-substituted one ($R^2 = \text{Me}$). Indeed, while the reaction of *N*-arylated malimides with *N*-methyl-substituted 7-azaisatins afforded the corresponding products in 81–98% yields and 85–94% ees, both lower yields (37–92%) and enantioselectivities (71–91% ee) were obtained for products derived from *N*-benzyl, *N*-methoxymethyl and *N*-*para*-chlorophenyl-substituted 7-azaisatins with the lowest (37% yield and 71% ee) in the case of the latter substrate. This study opened a novel and convenient route to access multifunctional chiral 3-hydroxy-7-aza-2-oxindoles having biological potentialities.

In 2013, Hatakeyama et al. described the use of α -isocupreine derived from quinine as organocatalyst in enantioselective Morita–Baylis–Hillman reactions of aldehydes **12** with HFIPA. ¹⁸ It must be noted that these reactions were previously performed in the presence of β -isocupreidine by the same authors with up to 90% ee. ¹⁵ When the reaction was carried out at -55°C in DMF as solvent in the presence of 20 mol% of α -isocupreine, it afforded the corresponding chiral esters **13** in moderate to high yields (34–91%) and enantioselectivities (45–93% ee), as shown in Scheme 5. Comparable enantioselectivities were obtained with aromatic (82–93% ee) and aliphatic aldehydes (83–93% ee) but the latter generally provided the corresponding Morita–Baylis–Hillman adducts in lower yields than the former (45–72% vs 24–91%). The enantioselectivity of the reaction can be explained by the zwitterionic intermediate depicted in Scheme 5 that was stabilised through hydrogen bonding. From this intermediate, a subsequent intramolecular proton transfer taking place by a six-membered cyclic transition state followed by elimination of the catalyst led to final product **13** exhibiting the (*S*)-configuration. Since the use of β -isocupreidine as catalyst in the early study afforded the corresponding (*R*)-product, ¹⁵ this novel study demonstrated that α -isocupreine was an enantiocomplementary catalyst of β -isocupreidine, providing even higher enantioselectivities (93% ee vs 90% ee).

The synthetic utility of the use of β -isocupreidine as organocatalyst in Morita–Baylis–Hillman reactions of HFIPA with

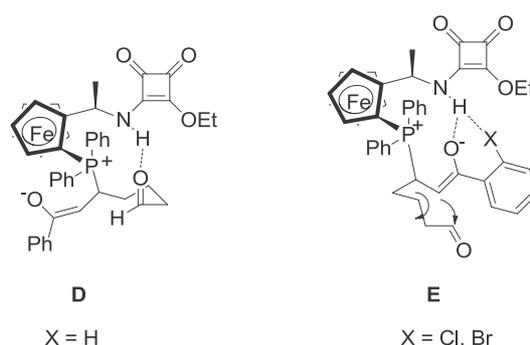


Scheme 6. β -Isocupreidine-catalysed Morita–Baylis–Hillman reaction of a furfural derivative with HFIPA and synthesis of (-)-tirandamycin B.



with Ar = Ph, *p*- $\text{O}_2\text{NC}_6\text{H}_4$, *p*- FC_6H_4 , *p*- BrC_6H_4 , *p*- ClC_6H_4 , *p*- $\text{F}_3\text{CC}_6\text{H}_4$, *m*- BrC_6H_4 , *m*- ClC_6H_4 , *p*-Tol, *p*- MeOC_6H_4 , 2-Naph: 68–85%, 83–96% ee
with Ar = *o*- BrC_6H_4 , *o*- ClC_6H_4 : 73–74%, 10–11% ee

possible transition states:

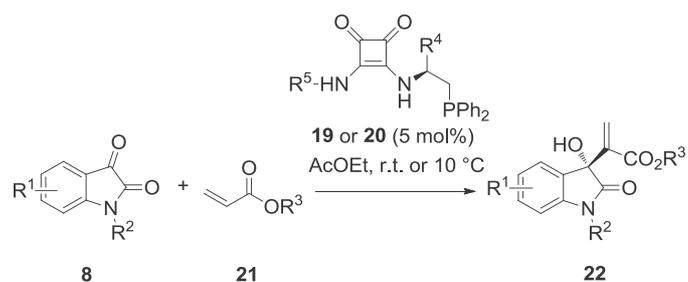


Scheme 7. Squaramide-derived ferrocene-based phosphine-catalysed intramolecular Morita–Baylis–Hillman reaction of 7-aryl-7-oxo-5-heptenals.

aldehydes was demonstrated in its application to the first enantioselective total synthesis of (-)-tirandamycin B, a natural representative member of the dienoyl tetramic acid family of antibiotics. ¹⁹ Indeed, the key step of this unprecedented synthesis was the β -isocupreidine-catalysed Morita–Baylis–Hillman reaction of HFIPA with furfural derivative **14** that provided the corresponding enantiopure multifunctionalised ester **15** in 70% yield (Scheme 6).

2.2. Chiral phosphine catalysts

Chiral phosphines have been intensively employed as efficient organocatalysts in (aza)-Morita–Baylis–Hillman reactions. ²⁰ In particular, excellent results have been obtained with bi/multifunctional phosphine catalysts. ^{10a,21} Indeed, the combination of a hydrogen bonding motif with a highly nucleophilic phosphorus centre within one molecule bearing a chiral framework can synergistically activate the substrates in a stereocontrolled manner, leading to high stereoselectivities. ^{10a} Moreover, the catalytic activities and enantioselectivities of these bi/multifunctional chiral phosphine organocatalysts can be finely tuned by simply varying the chiral scaffold, the phosphorus nucleophilicity and the hydrogen bond donors. In 2014, Chen and Jiang reported the first example of using a ferrocene-based bifunctional phosphine to promote highly enantioselective organocatalysed transformations. ²² Indeed, the enantioselective intramolecular Morita–Baylis–Hillman reaction of 7-aryl-7-oxo-5-heptenals **16** was promoted by novel and easily accessible bifunctional ferrocene-based squaramide-phosphine **17** to give the corresponding chiral



with catalyst **19** ($R^4 = t\text{-Bu}$, $R^5 = 3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3$):

74-93%, 89-95% ee

$R^1 = \text{H, 5-Br, 6-Br, 7-Br, 5-Me, 5-OMe, 5-F, 5-Cl, 7-Cl}$

$R^2 = \text{Me, Et, allyl, Bn, } i\text{-Pr, } n\text{-Pent}$

$R^3 = \text{Me, Et, } n\text{-Bu, } t\text{-Bu}$

with catalyst **20** ($R^4 = i\text{-Pr}$, $R^5 = p\text{-FC}_6\text{H}_4$):

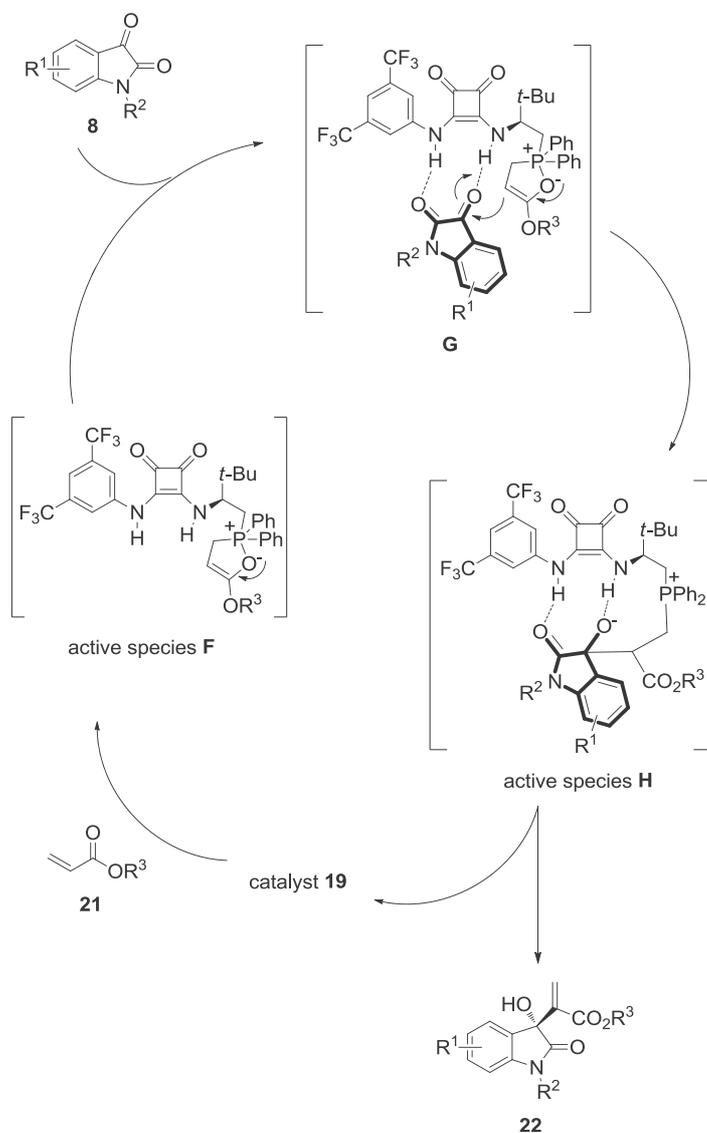
75-88%, 86-90% ee

$R^1 = \text{H, 4-Br}$

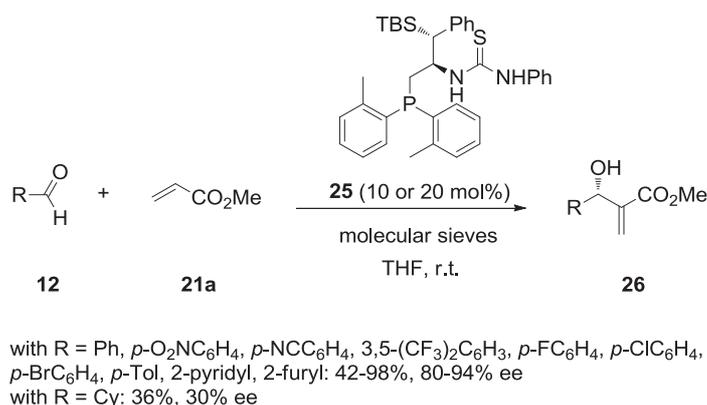
$R^2 = \text{Me, allyl, Bn}$

$R^3 = \text{Me}$

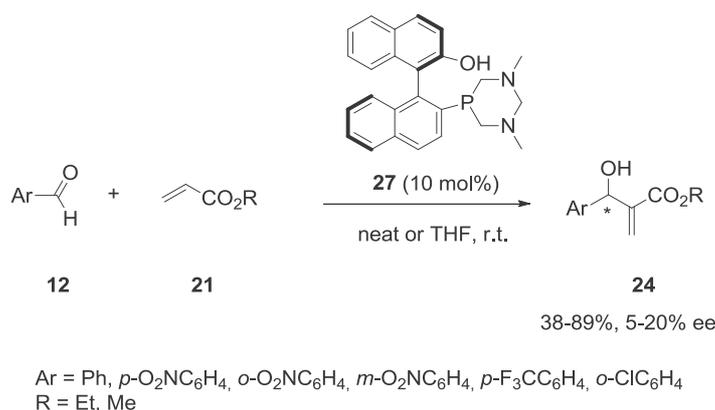
proposed mechanism (with catalyst **19**):



Scheme 8. Squaramide-derived phosphine-catalysed Morita–Baylis–Hillman reaction of *N*-alkyl isatins with acrylates.



Scheme 10. Thiourea-phosphine-catalysed Morita–Baylis–Hillman reaction of aldehydes with methyl acrylate.



Scheme 11. BINOL-derived phosphine-catalysed Morita–Baylis–Hillman reaction of aromatic aldehydes with acrylates.

heteroaromatic aldehydes provided the corresponding allylic alcohols **26** in high yields (83–98%) and enantioselectivities (80–94% ee), except for *para*-methylbenzaldehyde which showed a lower reactivity (42% yield). Moreover, the reaction conditions were compatible to an aliphatic aldehyde (R = Cy) but with much lower yield (36%) and enantioselectivity (30% ee).

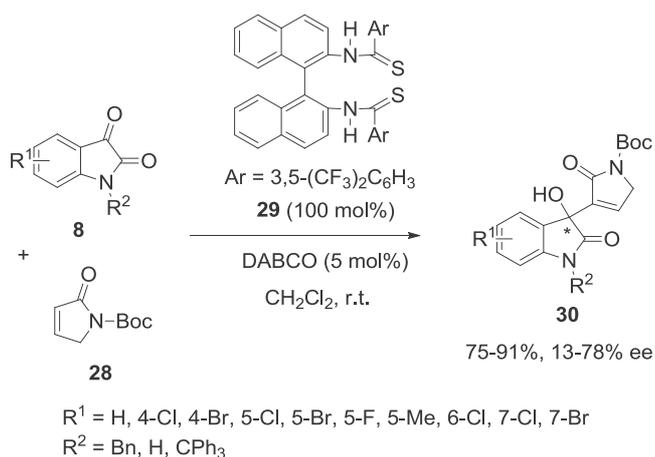
Earlier in 2013, another type of bifunctional tertiary phosphine, such as **27** featuring a cyclic substructure of 1,3,5-diazaphosphinane, was synthesised by He et al. starting from (*R*)-BINOL.²⁷ Investigated as organocatalyst in the Morita–Baylis–Hillman reaction of aromatic aldehydes **12** with acrylates **21**, it led to the corresponding products **24** in moderate to high yields (38–89%) albeit with low enantioselectivities (5–20% ee), as shown in Scheme 11.

2.3. Other organocatalysts

In 2004, Connon and Maher were the first to demonstrate that a simple chiral urea catalyst was capable to activate the DABCO-promoted Morita–Baylis–Hillman reaction between methyl acrylate and aromatic aldehydes.²⁸ Almost at the same time, Nagasawa et al. reported the first highly enantioselective Morita–Baylis–Hillman reaction catalysed by a chiral bis(thiourea) catalyst.²⁹ The process occurred between various aldehydes and cyclohexenone, providing the corresponding Morita–Baylis–Hillman adducts in moderate to high enantioselectivities of up to 90% ee. Ever since, several groups have reported high enantioselectivities of up to 96% ee by applying this type of organocatalysts to related reactions.³⁰ In a recent example, Han and Pan developed the first enantioselective Morita–Baylis–Hillman reaction involving an

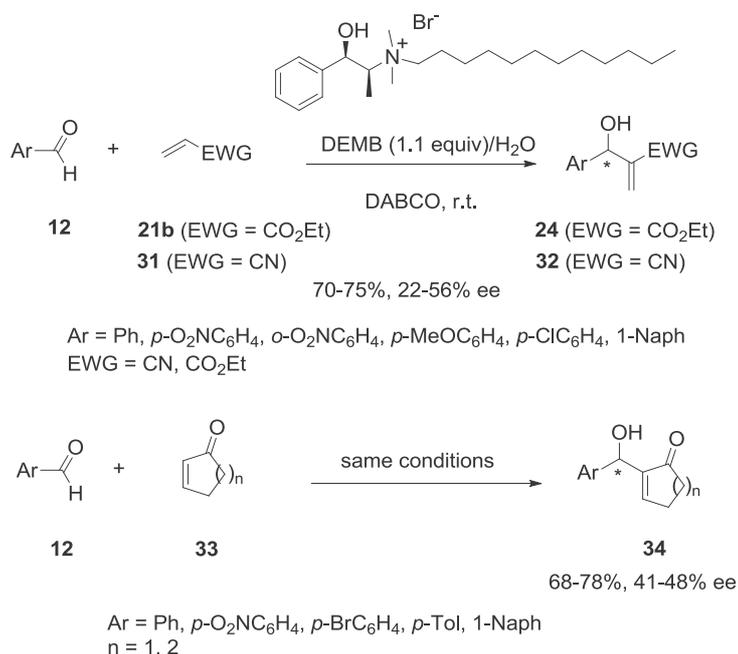
α,β -unsaturated γ -butyrolactam as nucleophile.³¹ As shown in Scheme 12, the reaction occurred between α,β -unsaturated γ -butyrolactam **28** and isatins **8** in the presence of chiral bis(thiourea) **29** and DABCO in dichloromethane at room temperature. It afforded the corresponding chiral 3-hydroxy-2-oxindoles **30** in good to high yields (75–91%) and enantioselectivities of up to 78% ee when the quantity of **29** was increased up to 100 mol% and that of DABCO of 5 mol%. A variety of isatins with different substituents on the benzene ring and various protecting groups at the nitrogen atom were investigated in the reaction. It was found that the nature of the N-substituent of the isatin had an obvious effect on the results with the best enantioselectivity (78% ee) achieved with *N*-benzyl isatin (R² = Bn) as the electrophile. On the other hand, the free isatin (R² = H) provided the corresponding product in dramatically lower enantioselectivity (15% ee). Moreover, employing isatins bearing sterically bulky substituents, such as triphenylmethyl, on the nitrogen atom led to the formation of the product in lower yield and enantioselectivity (75%, 25% ee). In the case of the *N*-Boc protecting group, it must be noted that no enantioselectivity was detected at all. Concerning the substituents on the phenyl moiety of isatins, their electronic properties had almost no influence on both yields and enantioselectivities of the reaction since comparable results were obtained. However, the substituent position on the phenyl ring had an obvious influence on the enantioselectivity of the reaction. For example, the presence of a substituent at the 6-position of the phenyl ring of *N*-benzyl isatins led to higher enantioselectivities than that on other positions.

In 2004, Vo-Thanh et al. were the first to examine chiral ionic liquids as chiral inducers for the asymmetric

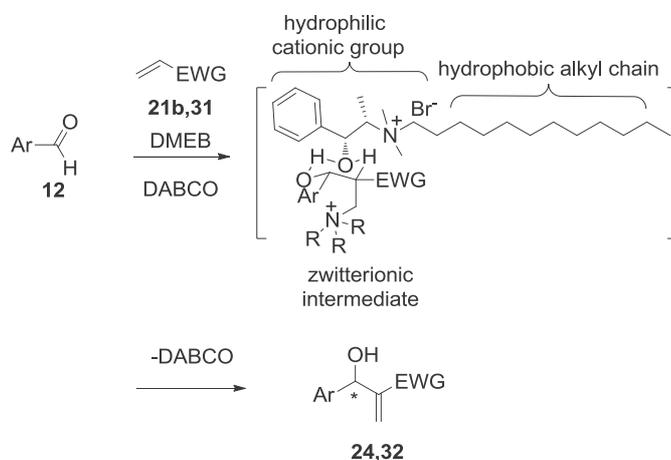


Scheme 12. Bis(thiourea)-catalysed Morita–Baylis–Hillman reaction of isatins with a α,β -unsaturated γ -butyrolactam.

Morita–Baylis–Hillman reaction.³² They demonstrated that performing the DABCO-mediated reaction between methyl acrylate and benzaldehyde in the presence of three equivalents of a chiral *N*-octyl-*N*-methylephedrinium trifluoromethanesulfonate salt could provide the corresponding Morita–Baylis–Hillman product in moderate enantioselectivity of 44% ee. More recently, Bhat et al. reported the use of chiral cationic surfactant, *N*-dodecyl-*N*-methylephedrinium bromide (DMEB), in asymmetric DABCO-catalysed Morita–Baylis–Hillman reactions of aromatic aldehydes with various activated alkenes performed in aqueous media.³³ As shown in Scheme 13 (first equation), in the presence of 1.1 equivalents of aqueous DMEB and DABCO, acrylonitrile **31** (EWG = CN) reacted with a range of aromatic aldehydes **12**, having electron-withdrawing as well as electron-donating substituents on the phenyl ring, to give the corresponding chiral allylic alcohols **32** in good yields (70–75%) and moderate enantioselectivities (40–56% ee) while the reaction of ethyl acrylate **21b** led to the corresponding product **24** with a lower enantioselectivity of 22% ee albeit combined with a good yield (73%). The substrate scope was extended to



plausible explanation of the role of DMEB in asymmetric induction in the presence of DABCO (NR_3):



Scheme 13. *N*-Methylephedrinium bromide-mediated Morita–Baylis–Hillman reactions of aromatic aldehydes with activated alkenes.

other activated olefins, such as cyclic enones **33**, that led to the corresponding chiral Morita–Baylis–Hillman products **34** in good yields (68–78%) and moderate enantioselectivities (41–48% ee), as shown in Scheme 13 (second equation). To explain the role of DMEB in the asymmetric induction, the authors proposed the formation of a zwitterionic intermediate (Scheme 13). Indeed, in the presence of DMEB micellar solution, the water insoluble compounds entered into the micellar structure. In this environment, the hydroxyl group of DMEB stabilised the zwitterionic adduct with electrophile through hydrogen bonding interactions. The stabilisation of the zwitterionic intermediate in the micellar phase led to an increase in the rate of both the electrophile addition and proton transfer steps in addition to being guided by the chirality of the ephedrinium head group of the surfactant, thus delivering the chiral product. Even if this last example did not use a true organocatalyst but a micellar catalyst, it was decided to situate it in this section for commodity.

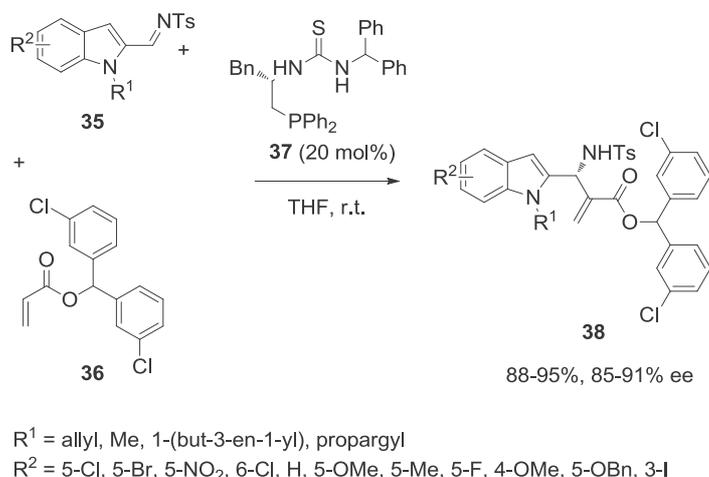
3. Organocatalytic enantioselective aza-Morita–Baylis–Hillman reactions

3.1. Chiral phosphine catalysts

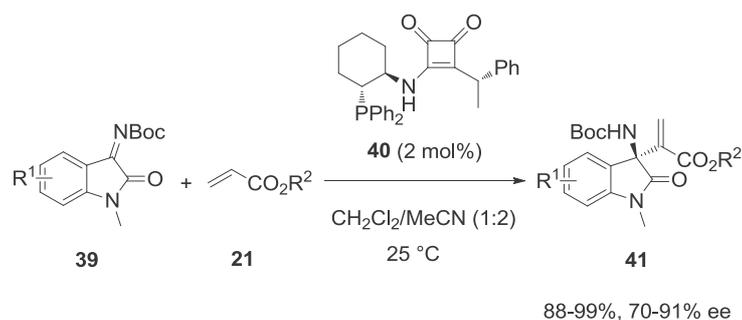
Firstly reported by Perlmutter and Teo in 1984,⁸ the enantioselective aza-Morita–Baylis–Hillman reaction constitutes one of the most important reactions dedicated to the synthesis of chiral α -methylene- β -amino carbonyl compounds.^{10g,j,u} It can be organocatalysed by chiral phosphines or amines. Actually, the first highly enantioselective aza-Morita–Baylis–Hillman reaction was described by Shi and Xu, in 2002.³⁴ It occurred between aromatic aldimines and methyl vinyl ketone in the presence of modified *Cinchona* alkaloid β -isocupreidine as base-catalyst, providing the corresponding chiral aza-Morita–Baylis–Hillman adducts in high yields and excellent enantioselectivities of up to 80% and 99% ee, respectively. Later, these authors extended the scope of this methodology to other activated alkenes, such as ethyl vinyl ketone, acrolein, methyl acrylate, acrylonitrile, or more hindered ones including phenyl acrylate and α -naphthyl acrylate, that provided the corresponding chiral products in moderate to excellent enantioselectivities (40–99% ee).³⁵ Ever since, various bifunctional chiral phosphines, tertiary amines derived from *Cinchona* alkaloids, or thioureas have been successfully applied to catalyse a number of enantioselective aza-Morita–Baylis–Hillman reactions. In particular starting from 2002, Shi et al. widely explored the use of chiral

phosphines in these reactions.³⁶ As a recent example, these authors reported the first enantioselective aza-Morita–Baylis–Hillman reaction of indole-derived tosylimines **35** with bis(3-chlorophenyl) methyl acrylate **36** catalysed by a chiral phosphine, such as multi-functional phosphine **37**.³⁷ Performed at room temperature in THF as solvent, this process led to the corresponding chiral densely functionalised products **38** in both high yields and enantioselectivities of 88–95% and 85–91% ee, respectively (Scheme 14). Remarkably, the results were homogeneously excellent regardless of whether electron-donating or electron-withdrawing substituents (R^2) were introduced at any position of the indole ring of the imines. Only the substrate bearing a phenyl substituent at the 3-position of the phenyl ring gave the corresponding product in only trace, presumably due to steric effect. Concerning the *N*-substitution of indoles (R^1), comparable excellent results were achieved with allyl, propargyl as well as 1-(but-3-en-1-yl) groups while a methyl group provided a lower enantioselectivity (76% ee). The synthetic utility of this novel methodology was demonstrated by the conversion of the formed aza-Morita–Baylis–Hillman adducts into biologically interesting polycyclic indoles, such as dihydropyrido[1,2-*a*]indole and dihydropyrazino[1,2-*a*]indole derivatives.

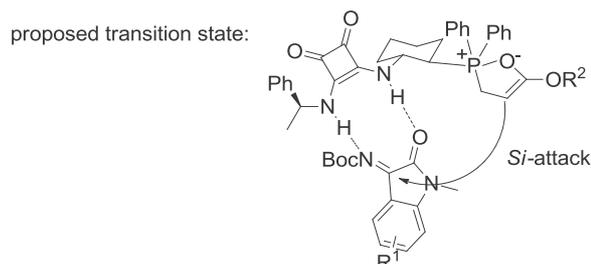
The enantioselective aza-Morita–Baylis–Hillman reaction of isatin-derived ketimines is one of the most efficient and straightforward methods to prepare quaternary 3-amino-2-oxindole chiral motifs which constitute important and ubiquitous structures in many natural products and drugs, however, these reactions have been rarely investigated.³⁸ In 2014, Wu and Sha reported the first example of enantioselective aza-Morita–Baylis–Hillman reaction of acrylates **21** with isatin-derived *N*-Boc ketimines **39**.³⁹ Among several chiral bifunctional phosphines investigated as organocatalysts in these reactions, squaramide-derived phosphine **40** was found optimal to yield the corresponding chiral densely functionalised products **41**. Indeed, in the presence of only 2 mol% of **40**, these products were formed at 25 °C in high to quantitative yields (88–99%) and good enantioselectivities (70–91% ee), as shown in Scheme 15. To achieve these results, a mixed solvent system of dichloromethane with acetonitrile was employed. Various alkyl acrylates were compatible and no obvious change in the enantioselectivity of the reaction was found using unbranched alkyl acrylates ($R^2 = \text{Me, Et, Bn, } n\text{-Bu}$), while *n*-butyl acrylate was less reactive than others (58% yield vs 87–95%). In contrast, due to steric hindrance, *t*-butyl acrylate was inactive under the same reaction conditions. The catalytic system was neither suitable to phenyl



Scheme 14. Phosphine-thiourea-catalysed aza-Morita–Baylis–Hillman reaction of indole-derived tosylimines with bis(3-chlorophenyl)methyl acrylate.



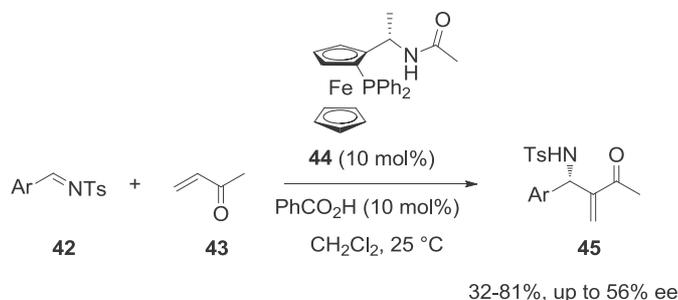
$\text{R}^1 = \text{H}, 5\text{-Cl}, 5\text{-Br}, 5\text{-Me}, 5\text{-OMe}, 6\text{-Cl}, 6\text{-Br}, 7\text{-F}, 7\text{-Cl}, 7\text{-Br}, 7\text{-CF}_3,$
 $7\text{-Me}, 5\text{-Me}, 5\text{-OMe}$
 $\text{R}^2 = \text{Bn}, \text{Me}, \text{Et}, n\text{-Bu}$



Scheme 15. Squaramide-derived phosphine-catalysed aza-Morita–Baylis–Hillman reaction of isatin-derived *N*-Boc ketimines with acrylates.

acrylate since the corresponding product was obtained in only 43% yield and 2% ee. Further exploration of the substrate scope showed that the reaction tolerated a range of *N*-Boc-1-methyl ketimine substrates with either electron-withdrawing or electron-donating groups at 5-, 6-, or 7-positions while the presence of a substituent at the 4-position of the phenyl ring of the isatin rendered the substrate unreactive, probably due to steric hindrance. To explain the results, the authors proposed the transition state depicted in [Scheme 15](#) in which the electrophilic squaramide of the catalyst activated the ketimine through hydrogen-bonding interactions. Then, the chiral cyclohexyl scaffold forced the phosphinoyl associated enolate to attack the activated ketimine from the *Si*-face to form the final product exhibiting the (*S*)-configuration.

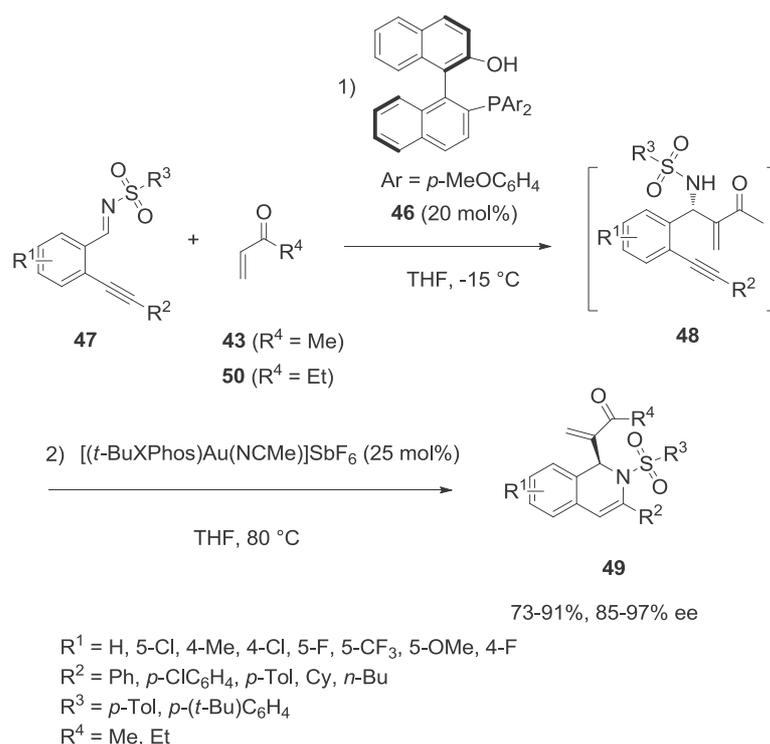
In 2015, Zhong et al. reported the synthesis of novel chiral bifunctional ferrocenylphosphines to be applied as organocatalysts in enantioselective aza-Morita–Baylis–Hillman reactions of aromatic tosylimines **42** with methyl vinyl ketone **43**.⁴⁰ As shown in [Scheme 16](#), using 10 mol% of catalyst **44** at 25 °C in dichloromethane as solvent in the presence of benzoic acid as an additive, the process afforded the corresponding chiral tosylamines **45** in



Scheme 16. Ferrocenyl amidophosphine-catalysed aza-Morita–Baylis–Hillman reaction of tosylimines with methyl vinyl ketone.

moderate to high yields (32–81%) and moderate enantioselectivities of up to 56% ee.

Early in 2003, Shi et al. first demonstrated that BINOL-derived chiral bifunctional biphenylphosphine could be used as an effective catalyst in enantioselective aza-Morita–Baylis–Hillman reaction of *N*-tosylimines with methyl vinyl ketone or phenyl acrylate.^{36b} Ever since, this organocatalyst has been successfully applied to the aza-Morita–Baylis–Hillman reactions of various other substrates.⁴¹ Furthermore in 2010, it was used by Sasai et al. in the first domino reaction based on an enantioselective aza-Morita–Baylis–Hillman reaction which allowed enantioselectivities of up to 93% ee to be achieved.⁴² In 2016, Shi et al. employed a closely related BINOL-derived chiral bifunctional biarylphosphine **46** to promote a tandem reaction the first step of which was the enantioselective aza-Morita–Baylis–Hillman reaction of alkyl vinyl ketones, such as methyl vinyl ketone **43**, with aromatic sulfonated imines **47** tethered with an alkyne moiety.⁴³ As shown in [Scheme 17](#), this reaction was performed with 20 mol% of catalyst **46** in THF at –15 °C to give the intermediate aza-Morita–Baylis–Hillman adducts **48** which subsequently cyclized with the attached electron-deficient alkene intramolecularly under racemic gold catalysis to give the corresponding chiral 1,3-disubstituted dihydroisoquinoline derivatives **49** in good to high yields (73–91%) and good to excellent enantioselectivities (85–97% ee). The study of the substrate scope showed that the benzene ring of the imine could bear electron-rich as well as electron-deficient substituents (R^1) and that different alkyne moieties (R^2) including aliphatic and aromatic ones were compatible, providing comparable very good results. Moreover, in addition to 4-methylphenyl sulfonated imines, a good enantioselectivity of 85% ee was reached in the reaction of 4-*tert*-butylphenyl sulfonated substrate. The reaction conditions were also applicable to ethyl vinyl ketone **50** which gave comparable excellent results (77% yield, 96% ee) than methyl vinyl ketone **43**. To demonstrate the synthetic utility of this novel one-pot methodology, the products were converted into several chiral



Scheme 17. BINOL-derived phosphine-catalysed aza-Morita–Baylis–Hillman reaction of alkyl vinyl ketones with aromatic sulfonated imines tethered with an alkyne moiety as first step of a tandem reaction.

dihydroisoquinoline derivatives bearing two chiral centres, being potentially bioactive molecules.

3.2. Cinchona alkaloid catalysts

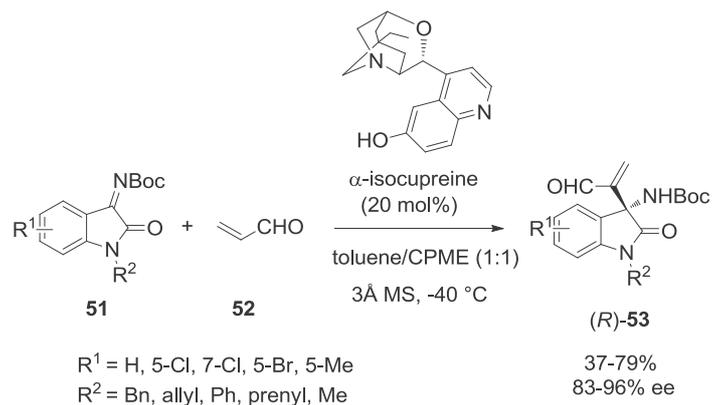
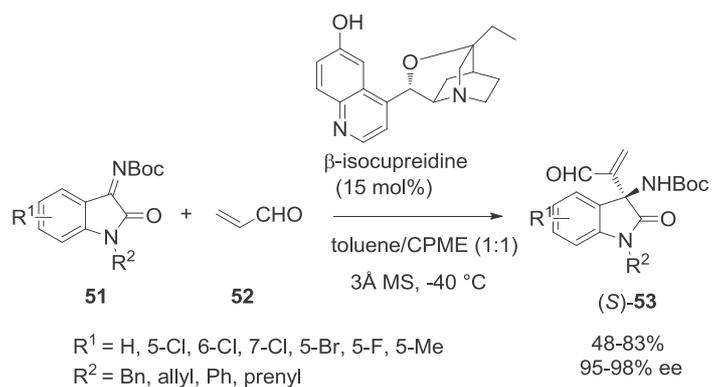
Chiral tertiary amine catalysts based on the quinidine framework, such as β -isocupreidine, for asymmetric aza-Morita–Baylis–Hillman reactions have been intensively investigated⁴¹ since the first highly enantioselective reaction reported by Shi and Xu in 2002, which occurred between aromatic aldimines and methyl vinyl ketone with up to 99% ee (see Section 3.1).³⁴ More recently, remarkable enantioselectivities of 95–98% ee were also reported by Takizawa et al. in enantioselective β -isocupreidine-catalysed aza-Morita–Baylis–Hillman reactions of isatin-derived ketimines **51** with acrolein **52**.⁴⁴ As shown in Scheme 18, a range of chiral 3-amino-2-oxindoles (*S*)-**53** possessing a tetrasubstituted carbon stereogenic centre were obtained almost enantiopure (95–98% ee) in moderate to good yields (48–83%). The excellent enantioselectivities were obtained uniformly irrespective of the electronic nature of the ketimine moiety using 15 mol% of β -isocupreidine as catalyst at $-40\text{ }^\circ\text{C}$ in a 1:1 mixture of toluene and CPME as solvent. While the use of this organocatalyst led to the formation of products exhibiting the (*S*)-configuration, it was demonstrated that using α -isocupreine at 20 mol% instead of 15 mol% of β -isocupreidine under the same reaction conditions allowed the corresponding (*R*)-configured adducts **53** to be obtained in excellent enantioselectivities (83–96% ee) along with moderate to good yields (37–79%), as shown in Scheme 18. To explain these results, a model for the enantioselectivity is proposed in Scheme 18 in which the least steric hindrance between the quinuclidine moiety of the catalyst and the aromatic ring of the substrate resulted in the formation of (*S*)-**53** by using β -isocupreidine or (*R*)-**53** with α -isocupreine.

After its successful application as catalyst in the first use of maleimide derivatives as nucleophilic partners in enantioselective Morita–Baylis–Hillman reactions with isatins reported in 2013 by Chimni and Chauhan,¹⁶ β -isocupreidine was later employed by Chimni et al. to the aza-analogue reactions.⁴⁵ As shown in Scheme 19, the aza-Morita–Baylis–Hillman reaction of a range of 5-substituted isatin-derived ketimines **51** with various maleimides **7** performed in the presence of 20 mol% of β -isocupreidine in chloroform at room temperature afforded the corresponding chiral 3-substituted 3-aminoindolin-2-ones **54** in moderate to good yields (30–79%) and generally excellent enantioselectivities of up to 99% ee. The highest enantioselectivities ranging from 90% to 99% ee were reached with phenyl maleimide ($R^3 = \text{Ph}$) whereas enantioselectivities of 70–76% ee were obtained for the other maleimides used. In contrast, concerning the isatin substrates, the results were independent of the nature of the substituents (R^1 and R^2). In the proposed transition state (Scheme 19), the tertiary amine of the catalyst added to the maleimide which resulted in the formation of an enolate. The latter further attacked the isatin imine to form the final product.

4. Asymmetric (aza)-Morita–Baylis–Hillman reactions of chiral substrates

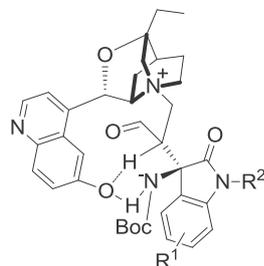
4.1. Chiral electrophiles

A chiral aldehyde, such as (*S*)-*O*-(methoxymethyl)lactaldehyde, was early employed as chiral electrophile in the Morita–Baylis–Hillman reaction by Roos et al., in 1988.⁴⁶ In the presence of methyl vinyl ketone and DABCO, the reaction afforded the corresponding Morita–Baylis–Hillman adduct as a 75:25 mixture of diastereomers. Ever since, many types of chiral electrophiles have been used in these reactions, often allowing excellent

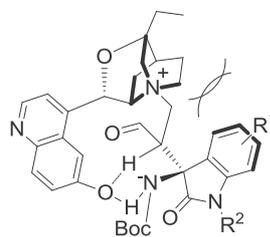


plausible transition states:

with β -isocupreidine:

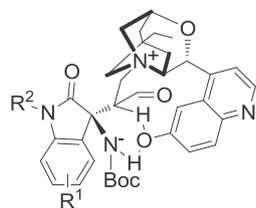


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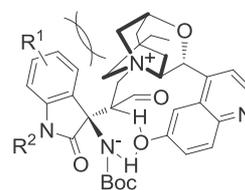


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with α -isocupreine:



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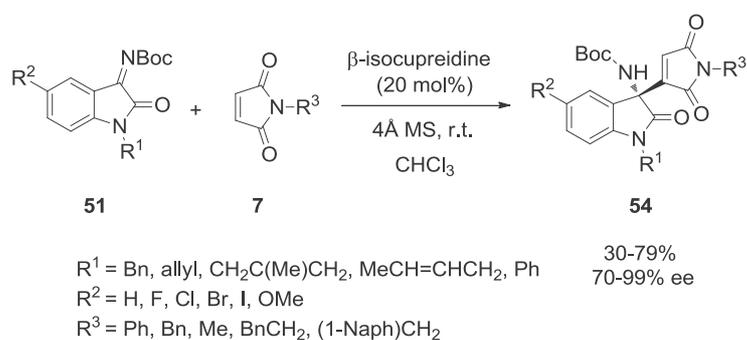


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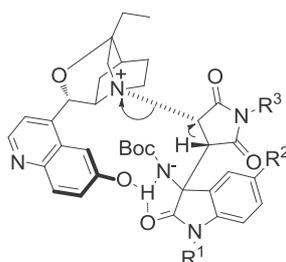
Scheme 18. β -Isocupreidine or α -isocupreine-catalysed aza-Morita–Baylis–Hillman reactions of isatin-derived ketimines with acrolein.

diastereoselectivities to be achieved.^{10a–e,n,t} As a recent example, chiral hydroxylated *cis*-prolinals **55** and **56** were used as chiral

electrophiles in Morita–Baylis–Hillman reactions with methyl acrylate **21a** to give in the presence of DABCO as catalyst the



proposed transition state:



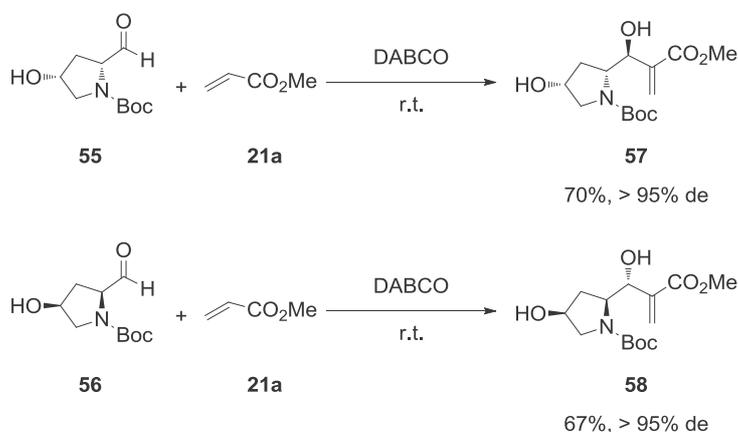
Scheme 19. β -Isocupreidine-catalysed aza-Morita–Baylis–Hillman reaction of isatin-derived ketimines with maleimides.

corresponding chiral allylic alcohols **57** and **58**, respectively.⁴⁷ In each reaction, products **57** and **58** were formed as an almost unique diastereomer (>95% de) in 70% and 67% yields, respectively, as shown in [Scheme 20](#). The synthetic utility of this methodology was shown by the conversion of products **57** and **58** into novel pyrrolizidinones and pyrrolizidines with high potential in total synthesis of natural products.

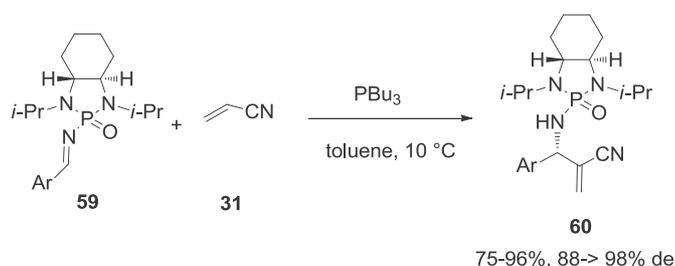
In 2016, Li et al. investigated the use of chiral *N*-phosphonyl imines **59** in aza-Morita–Baylis–Hillman reaction with acrylonitrile **31**.⁴⁸ The process was catalysed by PBu_3 in toluene at 10 °C and afforded the corresponding densely functionalised chiral β -amino nitriles **60** in both high yields (75–96%) and diastereoselectivities (88–>98% de), as shown in [Scheme 21](#). Comparable very good results were achieved for a range of substrates bearing both electron-donating and electron-withdrawing groups at different positions on the aromatic ring (Ar) of the imine in addition to naphthyl- and thienyl-derived *N*-phosphonyl imines. Notably in all cases, the pure aza-Morita–Baylis–Hillman adducts were easily obtained by simply washing the crude products with hexane/ethyl acetate mixture without the use of chromatography and recrystallisation. Moreover,

the chiral auxiliary could be readily removed and recycled. The authors have proposed the catalytic cycle depicted in [Scheme 21](#) the first step of which was the Michael addition of PBu_3 to acrylonitrile to provide zwitterionic intermediate **I**. The latter subsequently added to the *N*-phosphonyl imine to give a second zwitterionic intermediate **J** which underwent a proton transfer to afford intermediate **K**. The subsequent elimination of PBu_3 resulted in the formation of the final product and regeneration of the catalyst.

Soon after, the same authors showed that under related catalytic conditions and using acrylates **21** instead of acrylonitrile **31**, the aza-Morita–Baylis–Hillman reaction of the same *N*-phosphonyl imines **59** enabled the synthesis of the corresponding chiral β -amino acrylates **61**.⁴⁹ As shown in [Scheme 22](#), these products were achieved in good to quantitative yields (70–99%) and generally high diastereoselectivities (86–>98% de) when performing the reaction at room temperature in toluene under catalysis with PPhMe_2 . These conditions were applicable to a range of *N*-phosphonyl imines having various substituents at different positions of the aromatic ring (Ar) attached to the imine unit regardless of

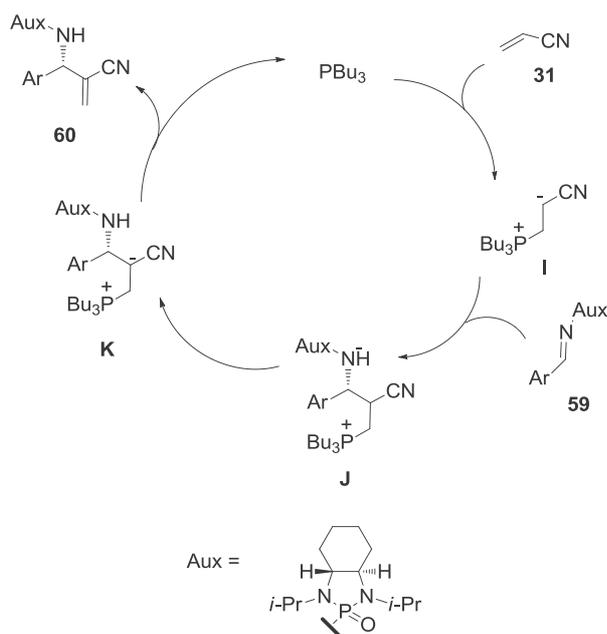


Scheme 20. Morita–Baylis–Hillman reactions of proline-derived aldehydes with methyl acrylate.



Ar = Ph, *o*-Tol, *o*-MeOC₆H₄, *o*-F₃CC₆H₄, *m*-BnOC₆H₄, *m*-FC₆H₄, *p*-Tol, *p*-MeOC₆H₄, *p*-F₃COC₆H₄, *p*-MeSC₆H₄, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-PhC₆H₄, 1-Naph, 2-Naph, 2-thienyl

proposed mechanism:



Scheme 21. Aza-Morita-Baylis-Hillman reaction of chiral *N*-phosfonyl imines with acrylonitrile.

methyl or benzyl acrylate employed. Even sterically demanding 1-naphthyl-, 2-naphthyl- and 6-methoxy-2-naphthyl-substituted *N*-phosfonyl imines gave excellent diastereoselectivities (92->98% de). As for the reaction depicted in [Scheme 21](#), the crude products did not need purification through chromatography or

recrystallisation but only simple washing with hexane/ethyl acetate. Moreover, the chiral diamine auxiliary could be easily removed, recovered with 99% ee and recycled.

4.2. Chiral activated alkenes

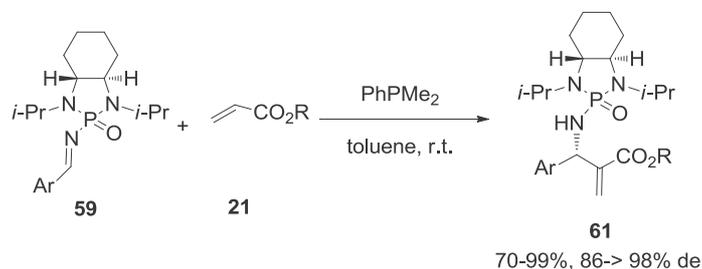
An early example of using a chiral activated alkene in asymmetric Morita-Baylis-Hillman reactions was reported by Brown et al., in 1986.⁵⁰ It involved menthyl acrylate and acetaldehyde as substrates, however, the diastereoselectivity of the reaction was low (16% de). Later, better stereoselectivities were obtained in certain cases with other menthyl acrylates.¹¹ On the other hand, a significant improvement was reported in 1997 by Leahy et al. who used the Oppolzer sultame as chiral auxiliary providing complete diastereoselectivity.⁵¹ Ever since, very high diastereoselectivities have been described by different groups using various chiral activated alkenes mostly acrylates.^{10a-e,n,t} In the last few years, only one example was reported by Kaye et al., dealing with the asymmetric Morita-Baylis-Hillman reaction of camphor-derived acrylates **62** with pyridinecarbaldehydes **63** to give the corresponding allylic alcohols **64**.⁵² When catalysed by DABCO in chloroform, these products were obtained in high to quantitative yields (91->99%) albeit with low diastereoselectivities ($\leq 33\%$ de), as shown in [Scheme 23](#).

5. Asymmetric organocatalysed applications of Morita-Baylis-Hillman adducts

Asymmetric (aza)-Morita-Baylis-Hillman reactions provide efficiently highly functionalised chiral synthons to be used in total synthesis of natural products and biologically relevant compounds.^{10h,n,r,s,v,w} In addition in the last few years, asymmetric organocatalysed transformations of racemic (aza)-Morita-Baylis-Hillman carbonates and acetates have provided straightforward access to a wide variety of optically active acyclic as well as cyclic molecules on the basis of allylic substitution reactions, formal 1,3-dipolar cycloadditions and miscellaneous transformations.

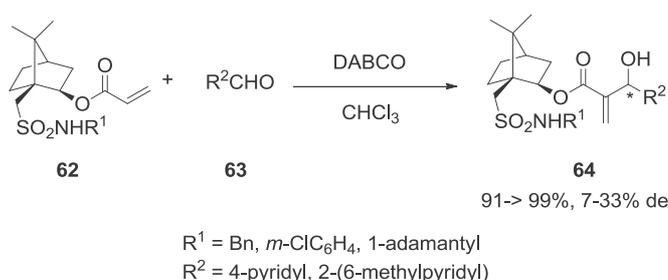
5.1. Allylic substitution reactions of Morita-Baylis-Hillman carbonates and acetates

In 2001, Basavaiah et al. first reported a S_N2' reaction of quinuclidinium salt of Morita-Baylis-Hillman bromides to yield chiral Morita-Baylis-Hillman propargylic ethers with moderate enantioselectivities ($\leq 40\%$ ee).⁵³ More recently, a range of transformations of racemic Morita-Baylis-Hillman carbonates and acetates based on nucleophilic substitution reactions with various nucleophiles have been promoted by chiral Lewis bases, such as



Ar = Ph, *o*-FC₆H₄, *m*-MeOC₆H₄, *m*-BrC₆H₄, *p*-Tol, *p*-MeOC₆H₄, *p*-PhC₆H₄, *p*-F₂HCOC₆H₄, *p*-MeSC₆H₄, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-O₂NC₆H₄, *p*-NCC₆H₄, 1-Naph, 2-Naph, 2-(6-MeONaph), 2-thienyl
R = Bn, Me

Scheme 22. Aza-Morita-Baylis-Hillman reaction of chiral *N*-phosfonyl imines with acrylates.

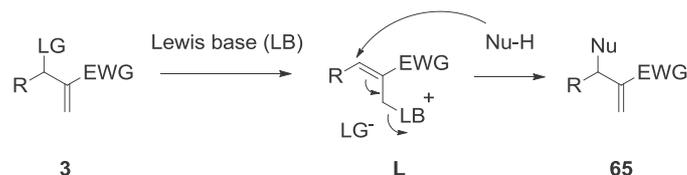


Scheme 23. Morita–Baylis–Hillman reaction of camphor-derived acrylates with pyridinecarbaldehydes.

Cinchona alkaloid catalysts and chiral phosphines, according to the mechanism depicted in Scheme 24. It involves an initial S_N2' attack of the Lewis base catalyst (LB) to the modified Morita–Baylis–Hillman adduct **3** that triggers the elimination of the leaving group (LG). The resulting intermediate **L** bears 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' displacement occurs, producing the final allylic alkylation product **65** after regenerating the Lewis base catalyst. The regioselectivity of the process is secured by the catalyst.

5.1.1. *Cinchona* alkaloid catalysts

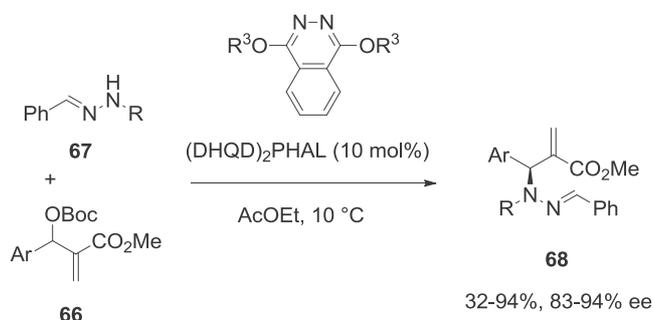
In the last decade, many multifunctional chiral organocatalysts, such as phosphine-amides,⁵⁴ phosphine-thioureas,⁵⁵ along with modified *Cinchona* alkaloids,⁵⁶ have been successfully applied to promote allylic substitution reactions of Morita–Baylis–Hillman carbonates and acetates with various types of nucleophiles. Since the beginning of 2015, several groups reported novel studies in this field. Among these, Wang and Yao developed the first organocatalysed regio- and enantioselective *N*-allylic alkylation of Morita–Baylis–Hillman carbonates **66** with hydrazones **67**.⁵⁷ As shown in Scheme 25, the reaction was performed in ethyl acetate as solvent at 10 °C in the presence of 10 mol% of modified *Cinchona* alkaloid (DHQD)₂PHAL as catalyst. The latter was selected as optimal among a range of *Cinchona* alkaloid-derived catalysts, such as quinine, quinidine, cinchonine, cinchonidine, (DHQD)₂PYR and (DHQD)₂AQN. Under these optimal conditions, a series of carbonates **66** reacted with various *N*-tosylhydrazones hydrazones **67** ($R = \text{Ts}$) to give through exclusive regioselectivity the corresponding chiral *N*-alkylated hydrazones **68** in high yields (76–94%) and uniformly high enantioselectivities (90–94% ee). The results indicated that the electronic properties and position of substituents on the aromatic ring (Ar) of the carbonates had a negligible effect on the catalytic efficiency of the process. On the other hand, the Morita–Baylis–Hillman carbonate bearing a furyl group (Ar = furyl) led to the desired product in only 32% yield with a slightly lower enantioselectivity (87% ee). Concerning the scope of the hydrazone partner, when its electron-withdrawing tosyl group ($R = \text{Ts}$) was switched to a *para*-nitrobenzenesulfonyl or a



Scheme 24. Lewis base-catalysed allylic substitution reaction of modified Morita–Baylis–Hillman adducts.

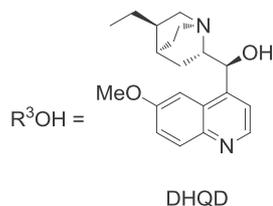
benzenesulfonyl group, the corresponding products were obtained in 61% and 72% yields and 83% and 94% ee, respectively. The results were explained by the transition state depicted in Scheme 25. The Morita–Baylis–Hillman carbonate first underwent a S_N2' reaction at the nitrogen atom of the quinuclidine to yield a cationic intermediate formed as the *E* isomer and stabilised through π - π stacking between the phenyl ring of the carbonate and the quinoline moiety. Then, the *tert*-butoxide anion deprotonated the hydrazone to give the corresponding nucleophile, which attacked the cationic intermediate from the *Si*-face preferentially since its *Re*-face was hindered by the quinoline moiety. Consequently, the formed product exhibited the (*S*)-configuration that was demonstrated through single X-ray crystallographic analysis. To show the utility of this novel methodology, some products were smoothly converted into a series of synthetically useful pyrazolidinones without loss of enantioselectivity.

Another organocatalyst derived from *Cinchona* alkaloids, such as (DHQD)₂AQN, was used by Rios et al. to promote the allylic alkylation reaction of various Morita–Baylis–Hillman carbonates with anthrones that constituted important scaffolds in natural products

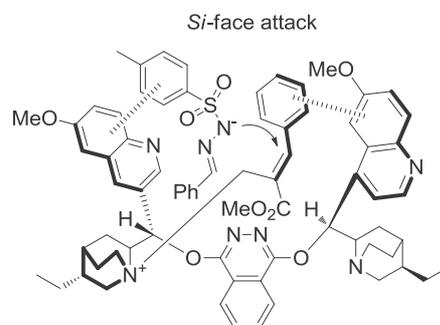


$R = \text{Ts}, \text{Ns}, \text{PhSO}_2$

$\text{Ar} = \text{Ph}, p\text{-BrC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-Tol}, o\text{-MeOC}_6\text{H}_4, 1\text{-Naph}, 2\text{-Naph}, \text{furyl}$



proposed transition state (with $R = \text{Ts}$, $\text{Ar} = \text{Ph}$):

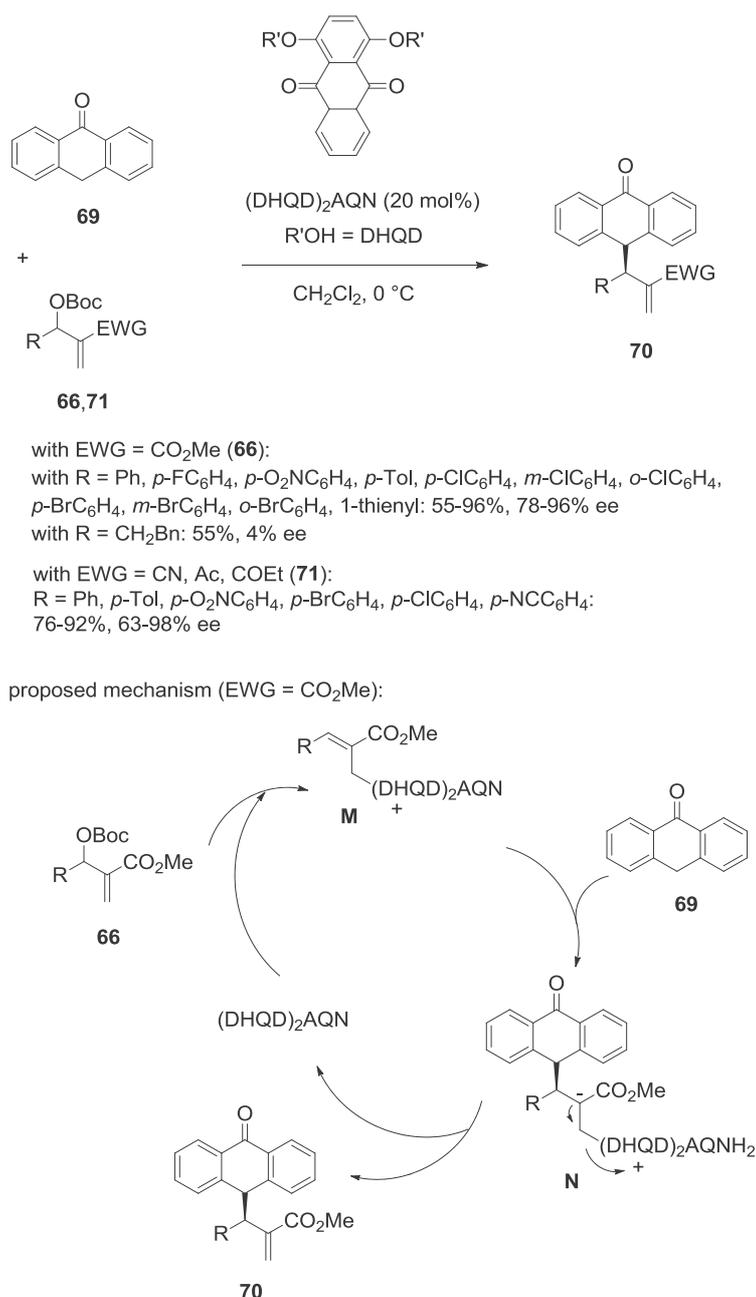


Scheme 25. Allylic alkylation reaction of Morita–Baylis–Hillman carbonates with hydrazones.

and medicinal as well as agrochemical chemistry.⁵⁸ As shown in [Scheme 26](#), this first use of anthrone **69** in reactions with Morita–Baylis–Hillman carbonates **66** (EWG = CO₂Me) performed in dichloromethane at 0 °C in the presence of 20 mol% of (DHQD)₂AQN led to the corresponding highly functionalised chiral anthrone derivatives **70** in moderate to excellent yields (55–96%) along with high enantioselectivities of up to 96% ee. When methyl esters (EWG = CO₂Me) exhibited an aromatic group (R), the enantioselectivities of the reactions were uniformly high (78–96%) while an aliphatic ester (R = CH₂Bn) led to an almost racemic product (4% ee) albeit in good yield (55%). The scope of this methodology was extended to other modified Morita–Baylis–Hillman adducts, such as ketones (EWG = Ac, COEt) and nitriles (EWG = CN) **71**, which also provided the corresponding anthrone derivatives in good to high yields (76–92%) and moderate

to excellent enantioselectivities (63–98% ee). The best results (79–98% ee) were achieved in the case of ketone substrates (EWG = Ac, COEt). Moreover, these reactions tolerated a wide range of substituents, such as halides, electron-withdrawing or electron-donating groups, on the aromatic ring (R) rendering in all cases, the corresponding products in high yields (76–92%). On the other hand, the enantioselectivity of the reaction with nitrile substrates (EWG = CN) was limited to 63% ee. In the proposed mechanism depicted in [Scheme 26](#), the carbonate substrate underwent a conjugate addition with the organocatalyst with elimination of the OBoc group to form the Michael acceptor **M**. Next, the anthrone attacked intermediate **M** to afford novel intermediate **N** which subsequently eliminated the catalyst to give the final product.

In 2016, Liao et al. reported a novel asymmetric catalytic approach for the construction of chiral functionalised 1,2-



Scheme 26. Allylic alkylation reaction of Morita–Baylis–Hillman carbonates with anthrone.

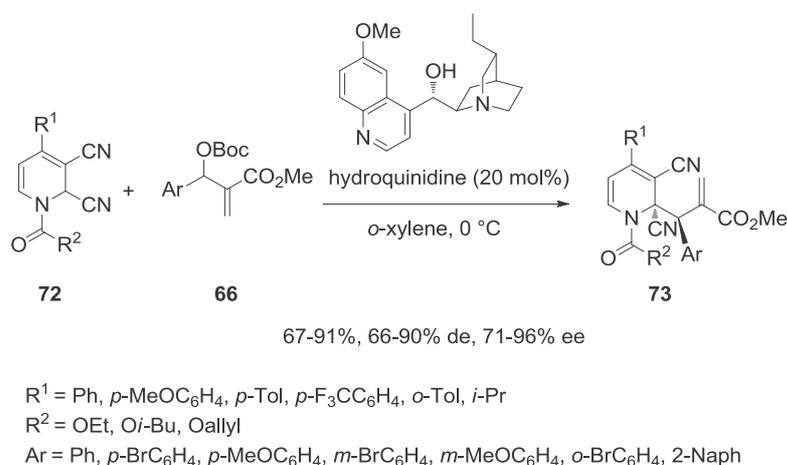
dihydropyridines, constituting biologically highly interesting products.⁵⁹ This was based on the asymmetric allylic alkylation reaction of Morita–Baylis–Hillman carbonates **66** with α -cyano-substituted 1,2-dihydropyridines **72** catalysed by 20 mol% of hydroquinidine in *o*-xylene at 0 °C. As shown in Scheme 27, a range of chiral densely functionalised 1,2-dihydropyridines **73** bearing two adjacent quaternary and tertiary carbon centres were generated in good to high yields (67–91%), diastereoselectivities (66–90% de) and enantioselectivities (71–96% ee). Hydroquinidine was selected as optimal organocatalyst among other *Cinchona* alkaloids, including quinidine, quinine, cinchonidine, cinchonine, (DHQD)₂AQN and (DHQD)₂PHAL, which all provided lower diastereo- and enantioselectivities. Under the optimal reaction conditions, dihydropyridines with different acyl substituents (R² = OEt, Oi-Bu, Oallyl) at the nitrogen were tolerated, providing comparable excellent results. On the other hand, the nature of the substituent (R¹) at the 4-position of the dihydropyridine had distinct effects on the reaction outcome and diastereoselectivity of the reaction. Indeed, substrates bearing aromatic substituents were superior to their alkyl analogues, while the electronic properties of the aromatic substituents of dihydropyridines did not affect the reaction. Concerning the carbonate partner, various aryl moieties (Ar) were well tolerated with the exception of the *ortho*-bromo-substituted dihydropyridine which led to the lowest enantioselectivity (71% ee). On the other hand, the 2-naphthyl-substituted carbonate afforded the corresponding product in high yield (91%) and enantioselectivity (94% ee) albeit combined with decreased diastereoselectivity (84% de) while the reaction conditions were not applicable to alkyl-substituted carbonates.

In 2016, Sun and Wang reported a catalyst-controlled switch of regioselectivity in asymmetric allylic alkylation of Morita–Baylis–Hillman carbonates with oxazolones.⁶⁰ Indeed, according to the nature of the organocatalyst employed to promote the reaction, it was γ - or β -regioselective. For example, when using a quinine-derived catalyst, the process afforded γ -regioselectively the secondary allylic oxazolone derivative (Scheme 28) whereas an addition-elimination reaction occurred when an amino acid-derived bifunctional urea catalyst was employed as organocatalyst, delivering the corresponding β -selective primary product (see Scheme 34). As shown in Scheme 28, in the presence of 20 mol% of quinine-derived organocatalyst **74**, a range of Morita–Baylis–Hillman adducts **75** reacted with oxazolones **76** with almost complete γ -regioselectivity (>95:5) to give the corresponding secondary chiral allylic oxazolones **77** in good to high yields (76–93%), high diastereoselectivities (82–90% de) and

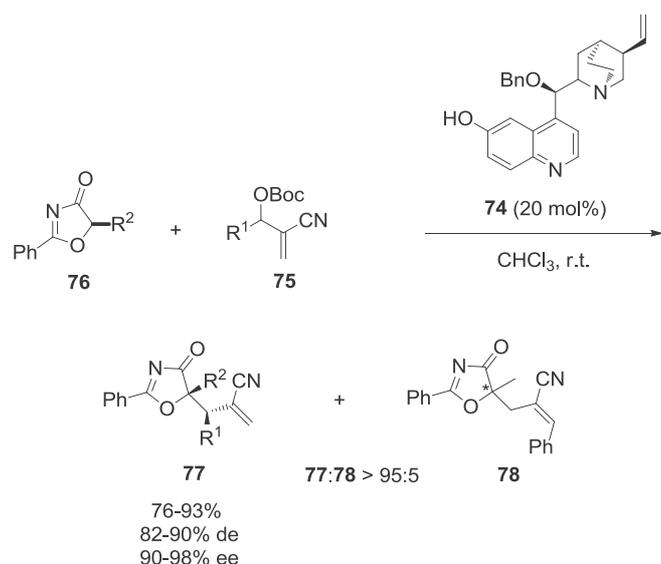
uniformly high enantioselectivities (90–98% ee). The process was applicable to a series of oxazolones bearing an aliphatic substituent (R²) and a wide range of Morita–Baylis–Hillman adducts exhibiting an aromatic group (R¹). It was found that the substitution patterns, regardless of the position, electronic nature or steric hindrance on this aromatic ring, had little effect on the reaction. Even a heteroaryl-substituted substrate (R¹ = 3-furyl) could be involved in the reaction with 76% yield, 82% de and 90% ee.

In 2015, hydroquinine was employed by Liang and Xu to promote the asymmetric vinylogous allylic alkylation reaction of Morita–Baylis–Hillman carbonates **66** with alkylidene azlactones **79** (Scheme 29).⁶¹ Indeed, the reaction of a range of carbonates **66** with various olefinic azlactones **79** in the presence of 20 mol% of hydroquinine in mesitylene at 10 °C afforded the corresponding highly functionalised chiral azlactone derivatives **80** in good to quantitative yields (71–99%), moderate to high *Z/E* diastereoselectivities (86:14 to >95:5) and uniformly very high enantioselectivities (87–97% ee). With respect to the carbonate partner, both electron-donating and electron-withdrawing substituents on the phenyl ring (Ar²) were compatible with the catalytic system. In contrast to the electron-withdrawing substituents, slightly lower reactivity but higher enantioselectivities were observed with the electron-donating ones. The position of the substituents on the phenyl ring of the carbonates was also investigated, showing that the *ortho*-substituted substrates gave lower yields than the corresponding *meta*- and *para*-substituted ones, probably due to steric hindrance. Moreover, naphthyl- and thienyl-substituted carbonates proceeded smoothly (71–76% yield, >95:5 *Z/E*, 91–97% ee). In contrast, the carbonate derived from acetaldehyde only provided a very low yield (6%).

Another recent example of asymmetric vinylogous allylic alkylation reaction of Morita–Baylis–Hillman carbonates **66** and **81** was reported by Li et al., in 2015.⁶² It involved 3-alkylidene oxindoles **82** as nucleophiles, (DHQD)₂AQN as organocatalyst used at 10 mol% and PhCF₃ as solvent at 50 °C. As shown in Scheme 30, the process led to the corresponding chiral γ -substituted alkylidene oxindole derivatives **83** which are commonly found in a variety of natural products as well as pharmaceuticals. These products were obtained in moderate to high yields (40–92%), high *Z/E* diastereoselectivity ratios (90:10 to >95:5) and uniformly high enantioselectivities (87–>99% ee) starting from the corresponding Morita–Baylis–Hillman carbonates **66** and 3-alkylidene oxindoles **82**. It was found that whether electron-withdrawing or electron-donating groups at the *meta*- and *para*-positions of the latter were employed, the reactions proceeded to give the corresponding



Scheme 27. Allylic alkylation reaction of Morita–Baylis–Hillman carbonates with α -cyano-substituted 1,2-dihydropyridines.



$R^1 = \text{Ph, } o\text{-FC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, o\text{-MeOC}_6\text{H}_4, o\text{-O}_2\text{NC}_6\text{H}_4, o\text{-Tol, } m\text{-ClC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, m\text{-O}_2\text{NC}_6\text{H}_4, m\text{-Tol, } m\text{-MeOC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-Tol, } p\text{-MeOC}_6\text{H}_4, 3,4\text{-(MeO)}_2\text{C}_6\text{H}_3, 1\text{-Naph, } 2\text{-Naph, } 3\text{-furyl}$
 $R^2 = \text{Me, Et, } n\text{-Pr, } n\text{-Bu, } i\text{-Pr, } s\text{-Bu, } i\text{-Bu, Bn, } n\text{-C}_6\text{H}_{13}$

Scheme 28. Allylic alkylation reaction of Morita–Baylis–Hillman carbonates with oxazolones.

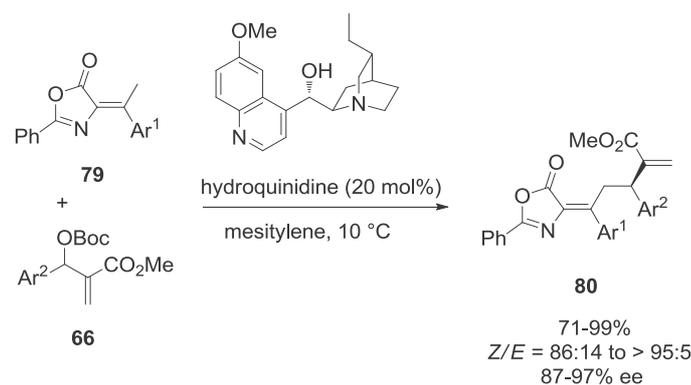
products in moderate yields (42–63%) with excellent enantioselectivities (95–99% ee) and *Z/E* diastereoselectivities (92:8 to 95:5). Studying the substrate scope of the Morita–Baylis–Hillman carbonates, it was shown that varying their substituents led to the corresponding products in moderate to good yields of up to 92%, high enantioselectivities of up to 95% ee and high *Z/E* diastereoselectivities of up to >95:5. The position of the substituents (R^3) linked to the phenyl ring had some effect on the yield, since *ortho*-substituted as well as 2,4- and 3,4-bis-substituted substrates provided higher yields than *para*- and *meta*-substituted substrates. In addition to carbonate **66**, carbonate **81** was compatible to afford the corresponding product in acceptable yield (41%) with high diastereo- and enantioselectivities of >90% de and 94% ee, respectively. In the proposed transition state depicted in Scheme 30, the Morita–Baylis–Hillman carbonate probably underwent the addition at the nitrogen atom of the quinuclidine to give a cationic intermediate. Then, the C=C bond was attacked preferentially through its *Re*-face by the 3-alkylidene oxindole to provide the final product.

In another context, Guo and Xie reported the first use of silanols **84** as the nucleophiles in asymmetric allylic substitutions of Morita–Baylis–Hillman carbonates.⁶³ As shown in Scheme 31, triphenylsilanol **84a** ($R^2 = \text{Ph}$) reacted with a range of carbonates **66** ($R^1 = \text{Me}$) and **81** ($R^1 \neq \text{Me}$) in MTBE as solvent at 90 °C in the presence of *i*-Pr₂NEt as base and chiral Cinchona alkaloid (DHQD)₂PYR as organocatalyst to afford the corresponding silyl ethers **85** in moderate to quantitative yields (50–98%), high enantioselectivities (81–92% ee) and excellent regioselectivities (>95:5). Uniformly high enantioselectivities (89–90% ee) combined with yields ranging from 60% to 79% were obtained for different esters including methyl, ethyl, *tert*-butyl, benzyl, 1-adamantyl and 2-adamantyl ones in reaction with triphenylsilanol **84a**. When electron-withdrawing or electron-donating groups were present at the *ortho*-position of the aromatic ring (Ar) of the Morita–Baylis–Hillman carbonates, the corresponding products were obtained in 90% ee, but lower yields (55–60%) were achieved in the

reaction of Morita–Baylis–Hillman carbonates bearing halogen substituents on the aromatic ring. The presence of methyl or methoxy groups on the *meta*-position of the phenyl ring could afford the corresponding products in higher ee values (91–92%), while electron-withdrawing substitutions led to the corresponding products in 83–86% ees. Slightly lower enantioselectivities (81–84% ee) combined with moderate to high yields (73–95%) were obtained for carbonates bearing *para*-substituents on the aromatic ring. Furthermore, even 2-furyl, 2-thienyl and 3-thienyl-substituted carbonates were compatible, giving the corresponding products in 75–92% yields and 88–92% ees. Concerning the silanol scope, dimethylphenylsilanol **84b** ($R^2 = \text{Me}$) could be used as nucleophile in addition to triphenylsilanol **84a**, providing the corresponding product in only 60% yield and 81% ee. A transition state is proposed in Scheme 31 in which a cationic ammonium intermediate was formed from a Michael-type addition of the nitrogen atom of the organocatalyst to the Morita–Baylis–Hillman adduct. The thus-formed (DHQD)₂PYR–Morita–Baylis–Hillman adduct was preferentially formed as the *E* isomer. The Morita–Baylis–Hillman moiety in the U-shape cleft of the catalyst gave a sandwich-like geometry that was stabilised by the *p*- π stacking between the quinolone moiety and the phenyl ring, which blocked the *Re*-face of the complex. Therefore, the triphenylsilanol anion preferentially attacked from the *Si*-face to give the final product exhibiting the (*R*)-configuration.

5.1.2. Chiral phosphine catalysts

A range of chiral phosphines have already been successfully applied to the catalysis of allylic alkylation reactions of modified Morita–Baylis–Hillman adducts with various nucleophiles.^{54,55} A recent example was reported by Wu and Sha with the first phosphine-catalysed enantioselective vinylogous allylic alkylation of Morita–Baylis–Hillman carbonates **66** ($R^3 = \text{OMe}$) and **81** ($R^3 = \text{OEt, } n\text{-Bu, } t\text{-Bu}$) with β,γ -butenolides **86** (Scheme 32).⁶⁴ Indeed, in the presence of 10 mol% of chiral cyclohexane-based squaramide-phosphine **87** as catalyst in chloroform at 25 °C, the corresponding γ,γ -disubstituted butenolides **88** containing adjacent quaternary and tertiary stereogenic centres were obtained in moderate to quantitative yields (52–98%), good to excellent diastereoselectivities (76–98% de) and uniformly excellent enantioselectivities (96–99% ee). The reaction conditions were compatible with Morita–Baylis–Hillman adducts derived from different alkyl

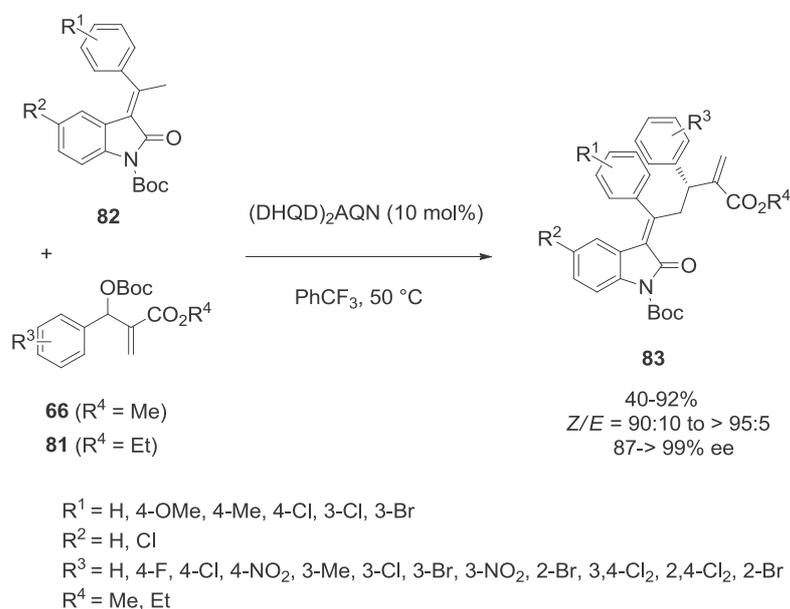


$Ar^1 = \text{Ph, } 2\text{-furyl, } p\text{-F}_3\text{CC}_6\text{H}_4, 2\text{-Naph, } p\text{-BrC}_6\text{H}_4$
 $Ar^2 = \text{Ph, } o\text{-BrC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-O}_2\text{NC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, o\text{-Tol, } m\text{-Tol, } p\text{-Tol, } p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, 3,5\text{-(Br)}_2\text{C}_6\text{H}_3, p\text{-BrC}_6\text{H}_4, 1\text{-Naph, } 2\text{-thienyl}$

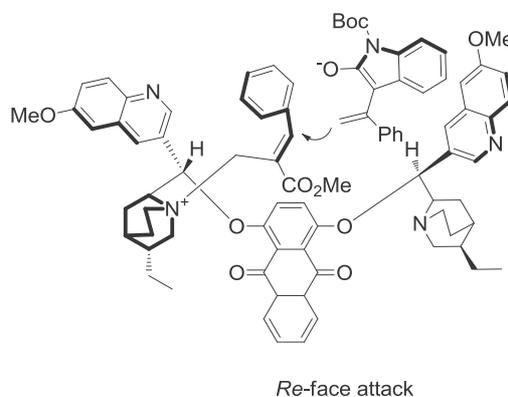
Scheme 29. Vinylogous allylic alkylation reaction of Morita–Baylis–Hillman carbonates with azlactones.

acrylates **66** and **81** and methyl vinyl ketone adduct **89** ($R^3 = \text{Me}$), however, *n*-butyl acrylate and *t*-butyl acrylate reacted with simple γ -methyl-substituted butenolide ($R^1 = \text{Me}$) with lower yields (52–56%) than the other substrates. Carbonates bearing a strong electron-withdrawing group at the 4- or 3-position (R^2) of the aromatic group generally gave better yields than those with a weak electron-withdrawing group or without substituent. On the other hand, carbonates with a substituent at the 2-position of the phenyl ring failed to produce the desired product probably due to an *ortho* effect. Moreover, carbonates bearing an electron-donating group, such as methyl or methoxyl groups, at the phenyl ring were also unreactive substrates. Concerning the β,γ -butenolide substrates, in addition to the γ -methyl-substituted butenolide ($R^1 = \text{Me}$), others bearing different γ -aryl groups ($R^1 = \text{Ar}$) provided good to quantitative yields (78–98%), good to high diastereoselectivities (76–96% de) in combination with remarkable enantioselectivities (98–99% ee) regardless the electronic properties of the substituents on the phenyl ring. This novel methodology allowed a novel route to chiral γ,γ -disubstituted butenolides which represent important motifs in biologically active natural compounds and pharmaceuticals.

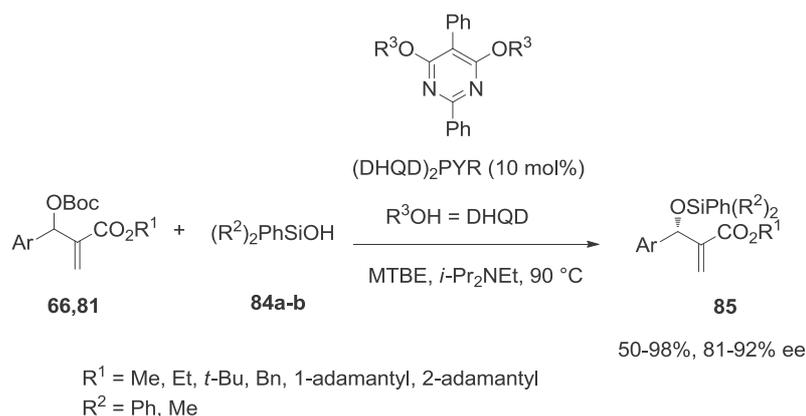
In 2016, Zhong et al. reported the synthesis of novel chiral bifunctional ferrocenylphosphines to be investigated in the enantioselective allylic substitution of Morita–Baylis–Hillman acetates **90** with phthalimide **91** as nucleophile.⁶⁵ As shown in Scheme 33, the reaction was performed in chloroform at room temperature in the presence of 20 mol% of chiral ferrocenylphosphine **92** which was selected as optimal organocatalyst among several other phosphines of this type. Under these mild reaction conditions, the corresponding chiral amines **93** were obtained in moderate to good yields (31–74%) along with moderate to high enantioselectivities (62–96% ee), as shown in Scheme 33. The study of the substrate scope showed that the substrate derived from methyl acrylate ($R = \text{Me}$) delivered a better result (74% yield, 96% ee) than the substrates derived from ethyl and butyl acrylates (60–65% yields, 72–73% ees). It was found that electron-withdrawing aromatic Morita–Baylis–Hillman acetates were more reactive than electron-donating ones. Moreover, high enantioselectivities of 91–94% ee were achieved in the reaction of multisubstituted aromatic compounds ($\text{Ar} = 1\text{-naphthyl}$ or $3,4\text{-Me}_2\text{C}_6\text{H}_3$) albeit with moderate yields (31–36%). In contrast, the authors showed that the catalytic system was not compatible for an aliphatic Morita–Baylis–Hillman



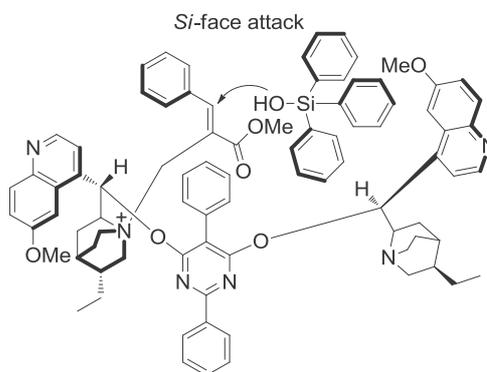
proposed transition state (with $R^1 = R^2 = R^3 = \text{H}, R^4 = \text{Me}$):



Scheme 30. Vinylogous allylic alkylation reaction of Morita–Baylis–Hillman carbonates with 3-alkylidene oxindoles.



proposed transition state (Ar = R² = Ph, R¹ = Me):



Scheme 31. Allylic etherification reaction of Morita–Baylis–Hillman carbonates with silanols.

acetate. A plausible transition state depicted in [Scheme 33](#) proposed that the direct nucleophilic addition of the chiral ferrocenylphosphine catalyst to the Morita–Baylis–Hillman adduct generated an intermediate that the phthalimide further attacked at the γ position of the olefin through its *Re*-face, owing to a steric repulsion between the aromatic group of the catalyst and the phthalimide.

5.1.3. Other catalysts

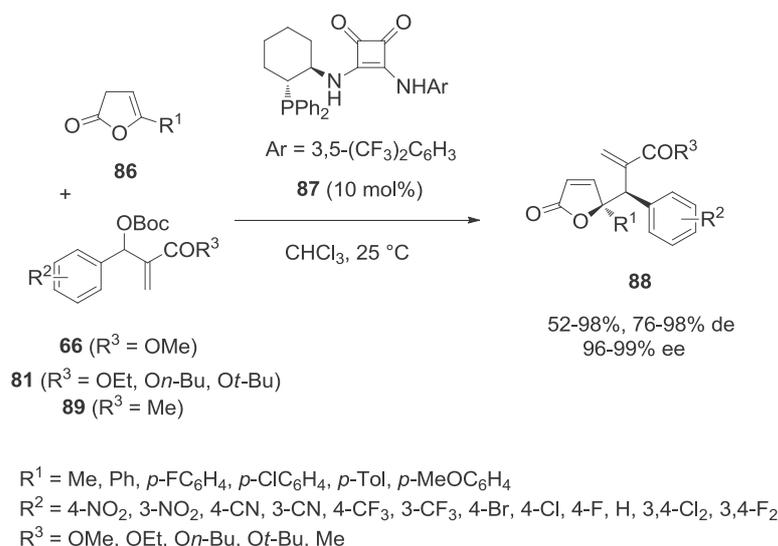
In 2016, Sun and Wang demonstrated a catalyst-controlled switch of regioselectivity in asymmetric allylic alkylations of Morita–Baylis–Hillman carbonates with oxazolones.⁶⁰ Indeed, these authors showed that according to the nature of the organocatalyst employed, the reaction was γ - or β -regioselective. When using quinine-derived catalyst **74**, the process afforded γ -regioselectively the secondary allylic oxazolone derivatives (see [Scheme 28](#)) whereas an addition-elimination reaction occurred when amino acid-derived bifunctional urea catalyst **94** was employed as organocatalyst, delivering the corresponding β -regioselective primary products. As shown in [Scheme 34](#), a wide number of these products were synthesised by reaction of the corresponding Morita–Baylis–Hillman carbonates **66** with oxazolones **76** performed in the presence of 20 mol% of this catalyst in toluene at -20°C . The process occurred with an excellent β -regioselectivity since the corresponding γ -product **95** was obtained only in trace amount along with major β -product **96** (**96:95** > 95:5). The catalytic system was compatible with various oxazolones bearing an aliphatic substituent (R²) and to a range of carbonates exhibiting differently substituted aromatic groups (R¹). In all cases, the products were

achieved in good to high yields (62–95%), excellent *E/Z* ratios (91:9 to >95:5) along with uniformly high enantioselectivities (90–99% ee) regardless of the different substitution patterns including 2-naphthyl and heteroaryl groups (R¹ = 3-furyl, 2-thiophenyl). Even an aliphatic group (R¹ = *i*-Pr) could be tolerated, providing the corresponding product in 65% yield and 99% ee albeit with lower *E/Z* ratio (91:9).

5.2. Formal 1,3-dipolar cycloadditions of Morita–Baylis–Hillman carbonates

5.2.1. Chiral phosphine catalysts

In addition to allylic substitution reactions with nucleophiles, Morita–Baylis–Hillman carbonates can react with electron-deficient olefins through annulation reactions to give multifunctional cyclic compounds. For example, the in situ generated phosphorus ylides from Morita–Baylis–Hillman carbonates in the presence of tertiary phosphines are very reactive 1,3-dipoles in 1,3-dipolar cycloadditions.⁶⁶ This was first demonstrated in 2003 by Lu et al. who developed the first racemic phosphine-catalysed Morita–Baylis–Hillman [3+2] annulation reaction,⁶⁷ while the first asymmetric version was reported by Tang and Zhou, in 2010.⁶⁸ In this study, these authors obtained enantioselectivities of up to 92% ee by using spirobiindane-based chiral phosphines as catalysts in intramolecular [3+2] cycloadditions of modified Morita–Baylis–Hillman adducts. Ever since, a number of chiral phosphines have been applied to promote this type of reactions.⁶⁹ As a recent example, Zhong et al. reported the use of novel chiral bifunctional ferrocenylphosphine **97** to promote the



Scheme 32. Allylic alkylation reaction of Morita–Baylis–Hillman carbonates with butenolides.

enantioselective [3+2] cycloaddition of Morita–Baylis–Hillman carbonates **66** and **81** with maleimides **76**.⁷⁰ The process was performed in toluene at room temperature in the presence of 10 mol% of catalyst **77** and afforded the corresponding chiral bicyclic imides **98** in good to quantitative yields (67–99%), general high diastereoselectivity of >92% de and high to excellent enantioselectivities (84–>99% ee), as shown in Scheme 35. Alkyl- as well as aryl-substituted maleimides reacted smoothly with a range of methyl, ethyl and *n*-butyl esters bearing electron-withdrawing, electron-donating or electron-neutral groups on the aryl ring (Ar). In general, electron-withdrawing aromatic substrates had a slightly better reactivity than electron-donating ones. Very good results were also achieved in the reaction of carbonates bearing heteroaromatic and fused heteroaromatic groups (67–74% yields, 96–99% ees). In contrast, an alkyl Morita–Baylis–Hillman carbonate did not react even at higher temperature (up to 60 °C) or by using a higher catalyst loading. To explain the stereochemical outcome of the reaction, the authors proposed that the organocatalyst attacked the Morita–Baylis–Hillman carbonate to form allylic phosphonium intermediate **O** (Scheme 35). The H-bonding between the catalyst and the maleimide enhanced the reactivity. Then, due to spatial induction of the thiophene ring on the chain, intermediate **O** attacked the maleimide through its *Re*-face to form transition state **P**, which was then transformed into the final product.

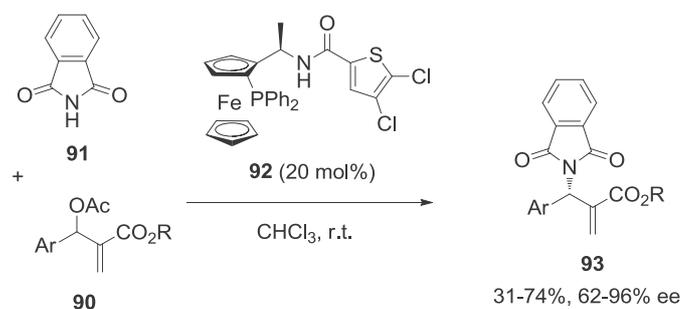
Barbituric acid derivatives constitute important pharmacological products. In this context, Guo et al. recently developed the first asymmetric construction of spirobarbiturate-cyclopentenes.⁷¹ This was based on the enantioselective phosphine-catalysed formal 1,3-dipolar cycloaddition of Morita–Baylis–Hillman carbonates **66** with barbiturate-derived alkenes **99**. As shown in Scheme 36, the process occurred at 80 °C in the presence of 20 mol% of multifunctional chiral phosphine catalyst **100** in trifluorotoluene as solvent, leading to a range of chiral products **101** isolated as almost single diastereomers (>90% de) in moderate to quantitative yields (30–99%) and high to excellent enantioselectivities (81–99% ee). Only aryl-substituted Morita–Baylis–Hillman carbonates were tolerated with electron-donating as well as electron-withdrawing substituents, providing the corresponding products in good to excellent yields (64–99%) and enantioselectivities (85–93% ee). Moreover, the position of the substituents on the phenyl ring seemed to have no remarkable influence on the activities and stereoselectivities of the reaction. In addition, 2-naphthyl and 2-

thienyl-substituted substrates also gave good results (87–90% yields, 90–93% ees). Concerning the barbiturate-derived alkenes, aryl-substituted substrates uniformly provided excellent enantioselectivities (91–99% ee) regardless of the substitution pattern and electronic nature of the substituents combined with moderate to quantitative yields (45–99%) while a cyclohexyl-substituted alkene (R = Cy) displayed a moderate activity (30% yield) albeit combined with a good enantioselectivity (81% ee).

The same authors also applied organocatalyst **100** to promote the enantioselective formal 1,3-dipolar cycloaddition of Morita–Baylis–Hillman carbonates **66** with cyclic 1-azadienes **102**.⁷² As shown in Scheme 37, the reaction evolved in the presence of 20 mol% of this catalyst in dichloromethane at –10 °C, leading to a range of densely functionalised chiral cyclopentenes **103** exhibiting three consecutive tertiary stereocentres as almost single diastereomers (>90% de) in moderate to quantitative yields (45–99%) and uniformly excellent enantioselectivities (91–98% ee) in the case of (hetero)aryl-substituted Morita–Baylis–Hillman carbonates (R = aryl, heteroaryl). In contrast, a low reactivity (15% yield) combined with a moderate enantioselectivity (73% ee) were obtained in the reaction of an alkyl-substituted Morita–Baylis–Hillman carbonate (R = Et). Various aryl-substituted cyclic 1-azadienes were tolerated, providing comparable excellent enantioselectivities (93–99% ee) irrespective of the position and electronic properties of the substituents on the phenyl ring (Ar). Moreover, these products were achieved in excellent yields (97–99%) except the 3,4-(MeO)₂C₆H₃- and 4-F₃C₆H₄-substituted cyclic 1-azadiene substrates which led to the corresponding cyclopentenes in 65% and 45% yields, respectively. The synthetic utility of this novel methodology was shown in the conversion of one of the products into a potential inhibitor of protein phenyltransferases.

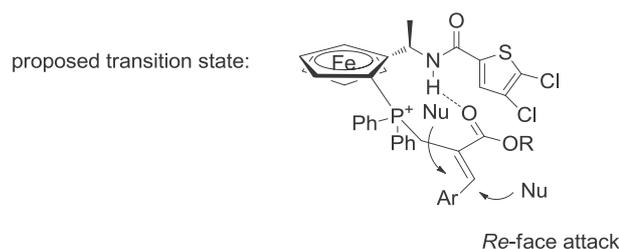
5.2.2. Cinchona alkaloid catalysts

Besides chiral phosphine catalysts, *Cinchona* alkaloids have also been successfully applied to promote various asymmetric 1,3-dipolar cycloadditions of modified Morita–Baylis–Hillman adducts. For example, α -isocupreine was demonstrated by Chen et al. to be an efficient catalyst in the first use of nitroolefins in asymmetric formal 1,3-dipolar cycloadditions of Morita–Baylis–Hillman derivatives.⁷³ Indeed, the reaction of isatin-derived Morita–Baylis–Hillman carbonates **104** with a variety of aromatic

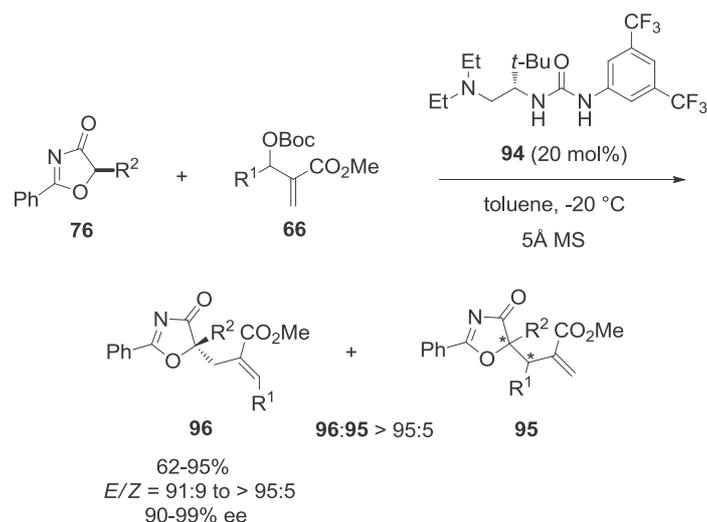


R = Me, Et, *n*-Bu

Ar = Ph, *p*-O₂NC₆H₄, *p*-FC₆H₄, *o*-ClC₆H₄, *m*-ClC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *m*-BrC₆H₄, *p*-Tol, 3,4-Me₂C₆H₃, *p*-MeOC₆H₄, *o*-F₃CC₆H₄, 2,4-Cl₂C₆H₃, 1-Naph



Scheme 33. Allylic alkylation reaction of Morita–Baylis–Hillman acetates with phthalimide.



R¹ = Ph, *o*-FC₆H₄, *o*-ClC₆H₄, *o*-BrC₆H₄, *o*-O₂NC₆H₄, *o*-Tol, *m*-FC₆H₄, *m*-ClC₆H₄, *m*-BrC₆H₄, *m*-Tol, *m*-MeOC₆H₄, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-Tol, *p*-MeOC₆H₄, 2-Naph, 3-furyl, 2-thiophenyl, *i*-Pr
 R² = Me, Et, *n*-Pr, *n*-Bu, *i*-Bu, Bn, *n*-C₆H₁₃, allyl, MeS(CH₂)₂

Scheme 34. Allylic alkylation reaction of Morita–Baylis–Hillman carbonates with oxazolones.

nitroolefins **105** performed in the presence of 10 mol% of α -isocupreine, DIPEA as a base in acetonitrile as solvent at 25 °C led to the corresponding chiral spirocyclic oxindoles **106** incorporating an unusual cyclopentadiene motif. As shown in **Scheme 38**, these multifunctionalised chiral products were achieved in moderate to good yields (40–73%) combined with moderate to excellent enantioselectivities (62–98% ee) after elimination of HNO₂ in the presence of DIPEA. It was found that the electronic properties of the substituents (R) on the aryl ring of the Morita–Baylis–Hillman

carbonates had an influence on the results. For example, the carbonates bearing electron-withdrawing groups exhibited better reactivity than those bearing electron-donating groups. On the other hand, a variety of nitroolefins with diverse β -aryl or heteroaryl groups were compatible. Those with electron-rich aryl rings delivered the corresponding products in moderate yields (58–65%) and excellent enantioselectivities (94–98% ee) while those with electron-deficient groups gave products in higher yields (68–72%) but with moderate to good ee values (62–84% ee). Moreover, 2-

furyl and 2-thienyl groups also showed lower reactivity even at higher temperature (40–46% yields at 35 °C) albeit high enantioselectivities were achieved (87–92% ee). In contrast, nitroolefins exhibiting β -alkyl substituents were unreactive.

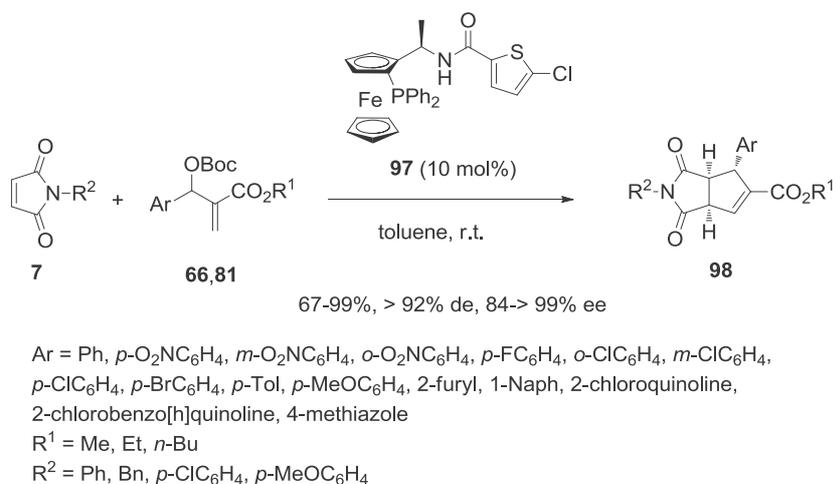
The same authors also reported the highly efficient enantioselective formal 1,3-dipolar cycloaddition of other isatin-derived Morita–Baylis–Hillman carbonates **107** with 2-nitro-1,3-enynes **108**.⁷⁴ Using the same catalyst in chloroform at 0 °C, the reaction regioselectively afforded the corresponding densely functionalised chiral spirooxindoles **109** possessing three contiguous stereogenic carbon centres including adjacent quaternary ones. They were obtained as almost single diastereomers (>90% de) in good to high yields (71–91%) and enantioselectivities (72–95% ee), as shown in Scheme 39. The Morita–Baylis–Hillman carbonates tolerated various substituents (R) as well as the aryl group (Ar) of the 2-nitro-1,3-enynes. The lowest enantioselectivities (72–87% ee) were obtained for the reaction of nitroolefins bearing electron-withdrawing substituents. On the other hand, the 2-naphthyl-substituted nitroolefin delivered the corresponding product with 85% yield and 90% ee. The high synthetic utility of this novel methodology was shown in the transformation of one product into complex chiral polycyclic products.

A range of other densely functionalised chiral spirooxindoles were achieved by these authors on the basis of highly regio-, diastereo- and enantioselective formal 1,3-dipolar cycloadditions of isatin-derived Morita–Baylis–Hillman carbonates **104** (EWG = CO₂Me) and **110** (EWG = CN) with cyclic 1-azadienes (Scheme 40).⁷⁵ Indeed, bulky electron-withdrawing 1,2-benzisothiazole 1,1-dioxide derivatives **111** (X = SO₂) bearing diversely substituted aryl, heteroaryl or styryl groups reacted with

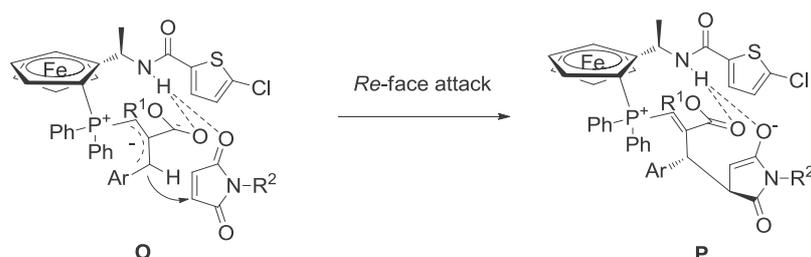
a range of Morita–Baylis–Hillman carbonates **104** exhibiting either electron-donating or electron-withdrawing groups on the aryl ring in the presence of 10 mol% of β -isocupreidine as catalyst. Performed in dichloromethane at room temperature, the reaction remarkably led to the corresponding chiral spirooxindoles **112** as almost single diastereomers (>90% de) in good to quantitative yields (81–98%) and excellent enantioselectivities (87–>99% ee). In addition, a Morita–Baylis–Hillman carbonate derived from isatin and acrylonitrile **110** (EWG = CN) smoothly underwent the reaction to give the corresponding product **113** with excellent yield (93%) and enantioselectivity (94% ee). The scope of the process was extended to other cyclic 1-azadienes, such as 1,2,3-benzoxathiazine 2,2-dioxide derivatives **114** (X = OSO₂), which allowed the corresponding chiral spirooxindoles to be achieved in comparable excellent enantioselectivities (95–99% ee) with slightly lower yields (75–93%).

5.3. Miscellaneous reactions of Morita–Baylis–Hillman carbonates and acetates

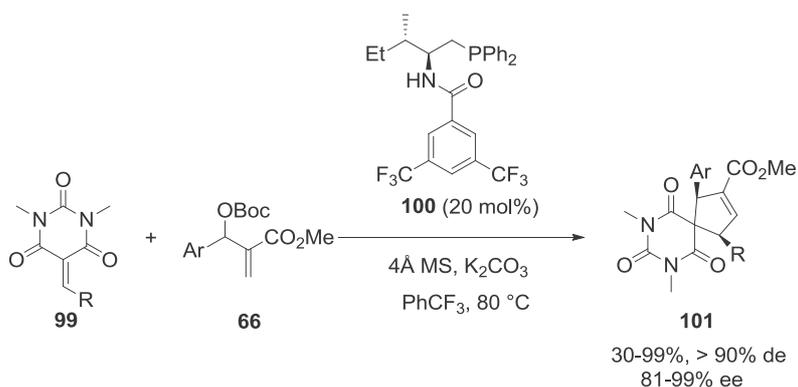
Besides the two typical reactions ascribed to Morita–Baylis–Hillman carbonates and acetates depicted in Sections 5.1 and 5.2, dealing with allylic substitution reactions and [3+2] annulations, these substrates have been recently involved in other types of asymmetric organocatalysed transformations that have greatly enriched their synthetic versatility. For example, the first enantioselective phosphine-catalysed [3+3] annulation of Morita–Baylis–Hillman carbonates **66** (R² = Me) and **81** (R² = Et, Bn) with C,N-cyclic azomethine imines **115** was described by Guo et al. in 2015.⁷⁶ It involved spirocyclic chiral phosphine **116** as catalyst in



proposed transition states:

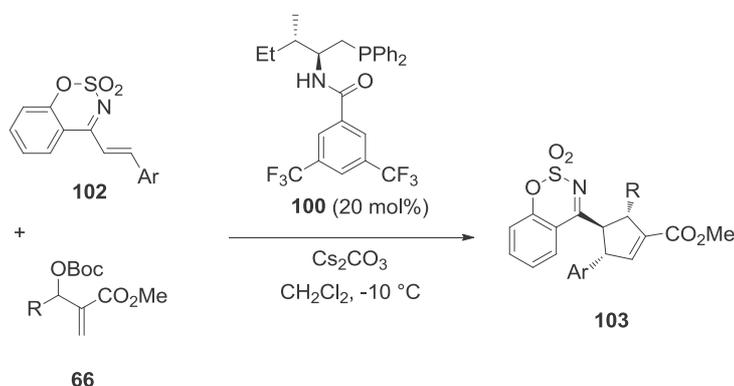


Scheme 35. 1,3-Dipolar cycloaddition of Morita–Baylis–Hillman carbonates with maleimides.



Ar = Ph, *o*-Tol, *m*-Tol, *p*-Tol, *o*-MeOC₆H₄, *p*-MeOC₆H₄, *o*-FC₆H₄, *m*-FC₆H₄, *p*-FC₆H₄, *o*-ClC₆H₄, *m*-ClC₆H₄, *p*-ClC₆H₄, *o*-BrC₆H₄, *m*-BrC₆H₄, 2-Naph, 2-thienyl
R = Ph, *o*-Tol, *m*-Tol, *p*-Tol, *o*-MeOC₆H₄, *p*-MeOC₆H₄, *o*-FC₆H₄, *p*-FC₆H₄, *o*-ClC₆H₄, *p*-ClC₆H₄, *o*-BrC₆H₄, *p*-BrC₆H₄, 2-Naph, 2-thienyl, Cy

Scheme 36. 1,3-Dipolar cycloaddition of Morita–Baylis–Hillman carbonates with barbiturate-derived alkenes.



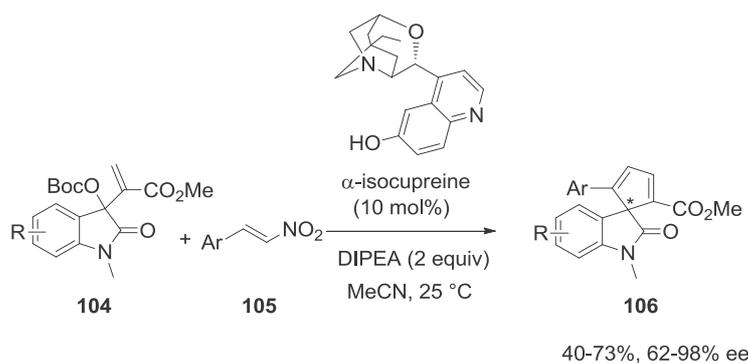
with R = Ph, *o*-Tol, *m*-Tol, *p*-Tol, *o*-MeOC₆H₄, *m*-MeOC₆H₄, *p*-MeOC₆H₄, *p*-*i*-PrC₆H₄, *o*-FC₆H₄, *m*-FC₆H₄, *p*-FC₆H₄, *o*-ClC₆H₄, *m*-ClC₆H₄, *p*-ClC₆H₄, *m*-BrC₆H₄, *p*-BrC₆H₄, *o*-F₃CC₆H₄, 3,4-Cl₂C₆H₃, 3,5-Cl₂C₆H₃, 2-Naph, 2-thienyl
Ar = Ph, *o*-Tol, *m*-Tol, *p*-Tol, *m*-MeOC₆H₄, *p*-MeOC₆H₄, *m*-FC₆H₄, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-F₃CC₆H₄, 3,4-(MeO)₂C₆H₃: 45-99%, 91-98% ee
with R = Et, Ar = Ph: 15%, 73% ee

Scheme 37. 1,3-Dipolar cycloaddition of Morita–Baylis–Hillman carbonates with cyclic 1-azadienes.

dichloromethane at $-10\text{ }^{\circ}\text{C}$. As shown in [Scheme 41](#), the reaction led to a novel class of pharmaceutically interesting 4,6,7,11b-tetrahydro-1*H*-pyridazino[6,1-*a*]isoquinoline derivatives **117** which were obtained in good to excellent yields (61–95%), excellent diastereoselectivity of >90% de in all cases and remarkable enantioselectivities of 98–>99% ee. These uniformly excellent results were achieved with a variety of Morita–Baylis–Hillman carbonates bearing different aromatic groups, regardless of the steric and electronic properties of the substituents on the aromatic ring. 2-Naphthyl- and 2-thienyl-substituted Morita–Baylis–Hillman carbonates also provided an excellent enantioselectivity of >99% ee with satisfactory yields (89% and 61%, respectively). Furthermore, varying the ester moiety (R^2) of the carbonates was tolerated since comparable excellent results were reached. The substrate scope of the azomethine ylide was also wide, since uniformly excellent enantioselectivities were obtained irrespective of the presence of methyl, methoxy and halogen substituents (R^1) on the aromatic ring. Moreover, the steric bulk of the substituents at the *para*-position of the phenyl ring ($Ar^1 = p\text{-}(n\text{-Pr})\text{C}_6\text{H}_4$, $p\text{-}(t\text{-Bu})\text{C}_6\text{H}_4$) of the

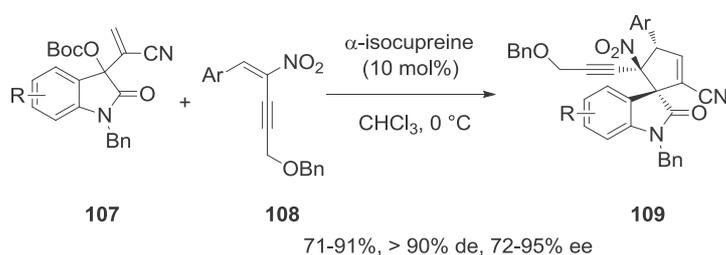
arylsulfonyl protecting group had no significant influence on the stereoselectivity of the reaction, since the corresponding products were also obtained in good yields (67–74%) and excellent diastereo- and enantioselectivities of >90% de and >99% ee, respectively. It must be noted that these novel dinitrogen-fused chiral heterocycles presented the advantage to combine the biologically important tetrahydroisoquinoline core and pyridazine core.

In 2015, Fu and Kramer reported the first enantioselective organocatalytic [4+1] annulation of Morita–Baylis–Hillman-allenic-type acetates **118** with sulfonamides **119** to give the corresponding chiral dihydropyrroles **120**.⁷⁷ These synthetically useful nitrogen chiral heterocycles were produced in the presence of 10 mol% of novel spirophosphine **121** as catalyst, NaOPh as base and 1:1 mixture of CPME/toluene as solvent at $40\text{ }^{\circ}\text{C}$. As shown in [Scheme 42](#), a range of allenic Morita–Baylis–Hillman-type acetates **118** reacted with aromatic sulfonamides **119** to afford the corresponding products **120** in good to high yields (74–95%) and high enantioselectivities (83–93% ee). It was found that the nature of the ester group (R^2) of the Morita–Baylis–Hillman-type adduct had



R = H, 5-F, 5-Cl, 5-Br, 5-I, 7-F, 5-OCF₃, 5-Me, 5-OMe, 5,7-Me₂
 Ar = Ph, *p*-Tol, *m*-Tol, *p*-MeOC₆H₄, *p*-FC₆H₄, *m*-FC₆H₄, *p*-BrC₆H₄,
p-F₃CC₆H₄, 2-furyl, 2-thienyl

Scheme 38. 1,3-Dipolar cycloaddition of isatin-derived Morita–Baylis–Hillman carbonates with nitroolefins.

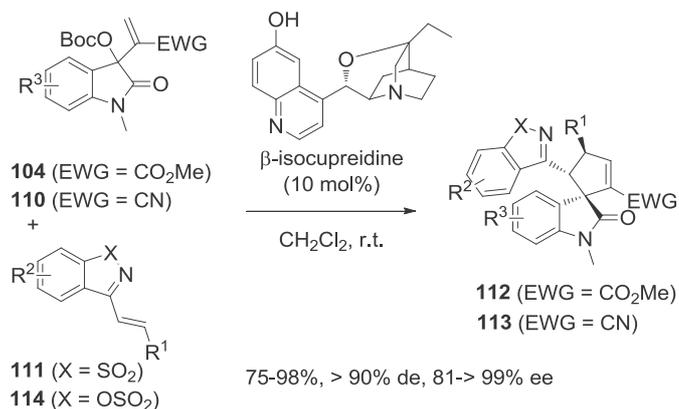


R = H, 5-Me, 5-OMe, 5-F, 5-Cl, 6-Br, 7-Cl
 Ar = Ph, *p*-Tol, *o*-MeOC₆H₄, *p*-MeOC₆H₄, *p*-FC₆H₄, *m*-ClC₆H₄, *p*-ClC₆H₄,
m-F₃CC₆H₄, 2-Naph

Scheme 39. 1,3-Dipolar cycloaddition of isatin-derived Morita–Baylis–Hillman carbonates with 2-nitro-1,3-enynes.

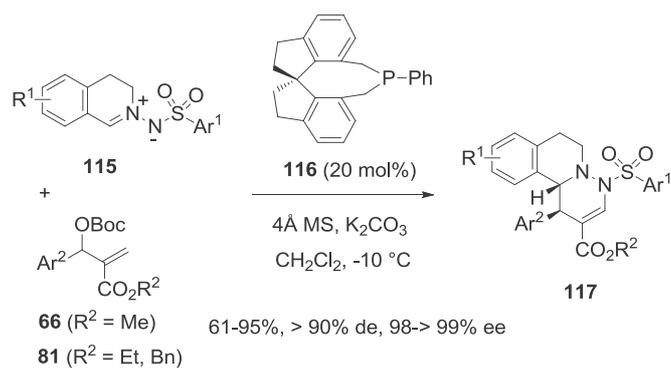
almost no impact on both the yield and enantioselectivity of the reaction. In addition to simple alkanes, the allene could exhibit as R¹ substituent an alkyne, a silyl ether, a dialkyl ether, an imide and a thiophene, providing comparable results. Different aromatic

sulfonamides were also compatible with the best results achieved when the aryl groups exhibited electron-withdrawing substituents, such as nitro, cyano or trifluoromethyl groups in *para* or *ortho* positions, while lower yields and enantioselectivities were observed if



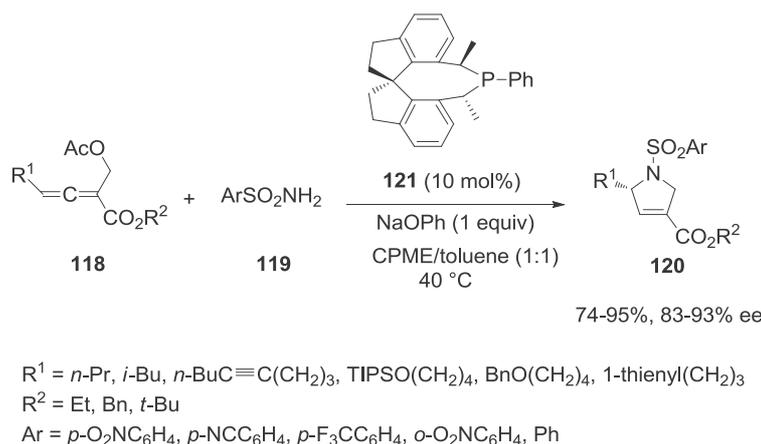
R¹ = Ph, *m*-Tol, *p*-Tol, *o*-MeOC₆H₄, *p*-MeOC₆H₄, *p*-FC₆H₄, *o*-ClC₆H₄,
p-F₃CC₆H₄, 3,4-Cl₂C₆H₃, 1-Naph, 2-Naph, 2-furyl, 2-styryl, 2-thienyl
 R² = H, 6-Br, 5,7-Me₂, 7-F
 R³ = H, 5-Me, 5-OMe, 5,7-Me₂, 5-F, 5-Cl, 5-Br, 5-I, 5-OCF₃, 7-F
 EWG = CO₂Me, CN
 X = SO₂, OSO₂

Scheme 40. 1,3-Dipolar cycloaddition of isatin-derived Morita–Baylis–Hillman carbonates with cyclic 1-azadienes.

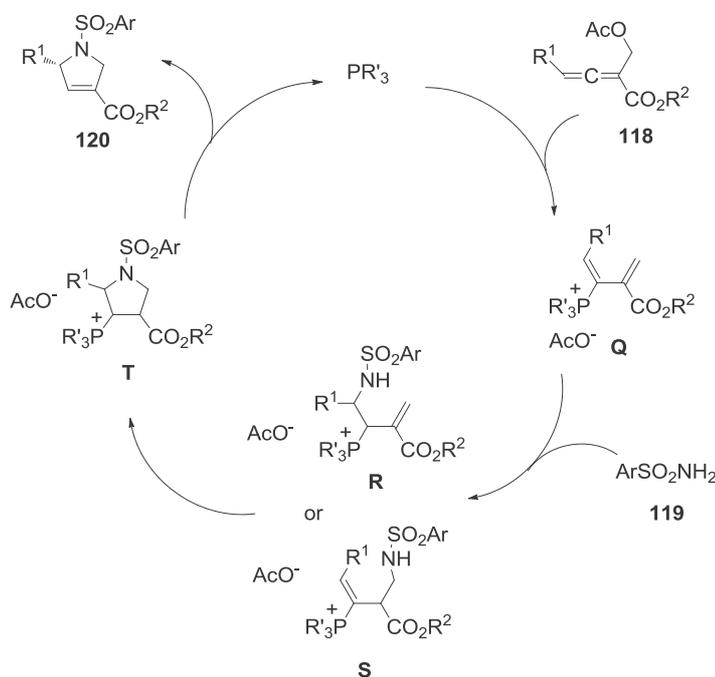


R¹ = H, 5-Me, 7-Me, 7-OMe, 7-Cl, 5-Br, 6-Br, 7-Br
 Ar¹ = *p*-Tol, Ph, *p*-(*n*-Pr)₂C₆H₄, *p*-(*t*-Bu)₂C₆H₄
 R² = Me, Et, Bn
 Ar² = Ph, *o*-FC₆H₄, *m*-FC₆H₄, *p*-FC₆H₄, *o*-ClC₆H₄, *m*-ClC₆H₄, *p*-ClC₆H₄,
m-BrC₆H₄, *p*-BrC₆H₄, *m*-O₂NC₆H₄, *p*-O₂NC₆H₄, *m*-F₃CC₆H₄, *m*-NCC₆H₄,
 3,4-Cl₂C₆H₃, 3,5-Cl₂C₆H₃, 3,4,5-Cl₃C₆H₂, *m*-Tol, *p*-Tol, *m*-MeOC₆H₄,
p-MeOC₆H₄, *p*-(*i*-Pr)₂C₆H₄, 2-Naph, 2-thienyl

Scheme 41. [3+3] Annulation of Morita–Baylis–Hillman carbonates with C,N-cyclic azomethine imines.



proposed mechanism:

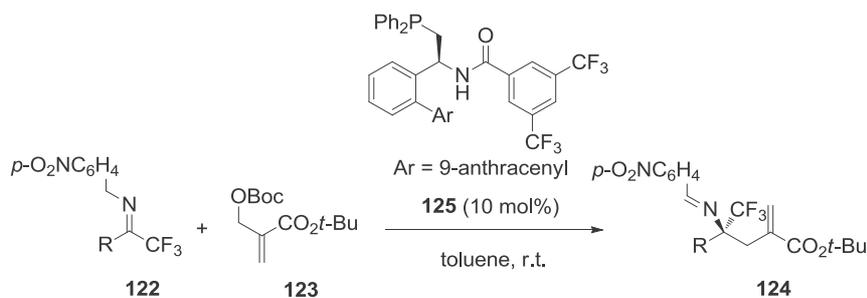


Scheme 42. [4+1] Annulation of Morita–Baylis–Hillman-type acetates with sulfonamides.

the aromatic group was not electron-poor ($\text{Ar} = \text{Ph}$). A possible mechanism for this novel process is depicted in **Scheme 42**, beginning with the nucleophilic β -addition of the phosphine catalyst to the allene, leading to intermediate **Q**. Next, the sulfonamide added to either olefin, providing intermediates **R** and/or **S**. Finally, the intramolecular addition of the sulfonamide to the other olefin afforded intermediate **T**, which then underwent elimination to give the final product and the regenerated phosphine catalyst.

In another area, Zhang et al. recently developed the highly enantioselective phosphine-catalysed umpolung addition of trifluoromethyl ketimines **122** to Morita–Baylis–Hillman carbonate **123**, allowing a novel route to chiral trifluoromethyl amines **124**.⁷⁸ As shown in **Scheme 43**, the process was promoted by 10 mol% of novel phosphine catalyst **125** in toluene at room temperature and led to a range of products **124** in good to high yields (70–91%) and uniformly excellent enantioselectivities (90–99% ee). It was

compatible to various aryl trifluoromethyl ketimines ($\text{R} = \text{aryl}$) bearing diverse functional groups, such as halogens, electron-donating- as well as electron-withdrawing groups at the *para* position of the phenyl ring, providing the corresponding products with 93–99% ee and good yields (70–91%). Slightly lower enantioselectivities (94–95% ee) were achieved in the reaction of *meta*-substituted phenyl substrates. Other aryl groups, such as 2-naphthyl and 1-thienyl were also tolerated, giving the corresponding amines in comparable enantioselectivities (94–96% ee). The scope of the process was also extended to alkyl trifluoromethyl ketimines ($\text{R} = \text{alkyl}$), which could be linear or α,β -branched ones and bear diverse functional groups, yielding the corresponding products in high yields (73–90%) and enantioselectivities (90–99% ee). To illustrate the synthetic utility of this novel methodology, the authors converted some products into chiral α -methylene γ -lactams which constitute valuable synthetic building blocks and,



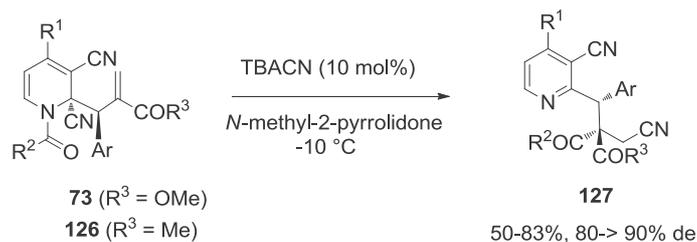
with R = Ph, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-(*t*-Bu)C₆H₄, *p*-Tol, *p*-F₃CC₆H₄,
p-MeOC₆H₄, *m*-Tol, *m*-MeOC₆H₄, 2-Naph, 1-thienyl: 70-91%, 93-99% ee
 with R = Me, Et, *n*-Hex, *c*-Pent, Cy, CyCH₂, *c*-Pent(CH₂)₂, Bn, (*E*)-PhCH=CH,
 CH₂=CH(CH₂)₈, Cl(CH₂)₄: 73-90%, 90-99% ee

Scheme 43. Umpolung addition of trifluoromethyl ketimines to a Morita–Baylis–Hillman carbonate.

moreover, are often found in many anticancer drugs.

Chiral functionalised 1,2-dihydropyridines **73** (R³ = OMe) and **126** (R³ = Me), synthesised by Liao et al. through enantioselective hydroquinine-catalysed allylic alkylation reaction of modified Morita–Baylis–Hillman adducts with α -cyano-substituted 1,2-dihydropyridines (Scheme 27), were further submitted by treatment with tetrabutylammonium cyanide (TBACN) to a stereospecific intramolecular acylcyanation.⁵⁹ As shown in Scheme 44, the

reaction performed in *N*-methyl-2-pyrrolidone as solvent at –10 °C stereospecifically gave rise to the corresponding chiral functionalised pyridines **127** in moderate to good yields (50–83%), high diastereoselectivities (80->90% de) and almost complete enantioselectivity ($\geq 99\%$). Allyl-substituted dihydropyridines including aromatic as well as aliphatic substituents (R¹) provided comparable results with diastereoselectivities ranging from 84% to >90% de. The lowest diastereoselectivity of 80% de was obtained for the reaction



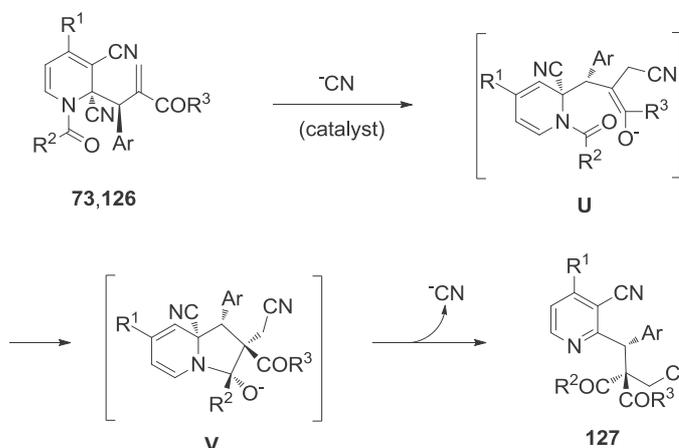
R¹ = Ph, *p*-MeOC₆H₄, *p*-Tol, *p*-F₃CC₆H₄, *o*-Tol, *i*-Pr

R² = OEt, *Oi*-Bu, Oallyl

R³ = OMe, Me

Ar = Ph, *p*-BrC₆H₄, *p*-MeOC₆H₄, *m*-BrC₆H₄, *m*-MeOC₆H₄, *o*-BrC₆H₄, 2-Naph

proposed mechanism:



Scheme 44. Intramolecular acylcyanation of Morita–Baylis–Hillman carbonates and acetates.

of dihydropyridine **126** bearing a ketone moiety ($R^3 = \text{Me}$) instead of an ester one. The mechanism of this process promoted by an achiral organocatalyst is shown in [Scheme 44](#). It begins with the formation of enolate **U** arisen from the Michael addition of the cyanide anion to the activated C=C bond of the enantioenriched 1,2-dihydropyridine. Because of the facial selectivity of this enolate, an intramolecular condensation between the latter (*Si*-face) with the amide group subsequently occurred stereospecifically, providing intermediate **V**, which then afforded the final product and the regenerated cyanide ion.

6. Conclusions

Based on two important concepts, such as organocatalysis and atom economy, the powerful, simple and synthetically useful asymmetric Morita–Baylis–Hillman reaction has stimulated a remarkable and increasing interest among asymmetric carbon–carbon bond forming reactions, providing access to a wide variety of chiral densely functionalised products. In the last few years, the discovery of novel organocatalysts, such as chiral phosphines, amines and (thio)ureas based on the concept of bi/multifunctionality, to promote these environmentally friendly reactions has significantly extended their scope. Besides commonly used electrophiles, such as simple aldehydes and imines, other electrophilic substrates have been recently successfully applied to these reactions. For example, enantioselectivities ranging from 91% to >99% ee have been achieved by using (7-aza)isatins, indole-derived imines, isatin-derived ketimines or sulfonated imines among others. Furthermore, novel activated alkenes such as maleimides or α,β -unsaturated γ -butyrolactams along with various more simple acrylates, acrylonitriles, acrolein and enones have provided excellent enantioselectivities of up to >99% ee. In spite of these excellent results, it must be noted that one universal catalyst suitable for a family of substrates is, however, still lacking and consequently, efforts will have to be made in the near future to develop effective catalysts applicable to even more types of activated alkenes and electrophiles.

In the area of the asymmetric organocatalysed applications of Morita–Baylis–Hillman adducts, it must be noted that these readily accessible racemic reagents, exhibiting at least three functional groups in close-proximity, are recognised as an excellent source for discovering new catalytic asymmetric transformations. In particular, enantioselective organocatalysed allylic substitutions of racemic Morita–Baylis–Hillman carbonates and acetates with many types of nucleophiles have been widely developed. In the last two years, remarkable enantioselectivities ranging from 94% to >99% ee have been reported by several groups using nucleophiles as diverse as hydrazones, anthrone, α -cyano-substituted 1,2-dihydropyridines, oxazolones, azlactones, 3-alkylidene oxindoles, butenolides, phthalimide, oxazolones and silanols. On the other hand, the organocatalytic generation of allylic ylides from Morita–Baylis–Hillman carbonates and acetates has been applied to develop many enantioselective formal 1,3-dipolar cycloadditions with activated alkenes. Newly designed phosphine- and/or amine-based chiral organocatalysts have been proven effective in the stereocontrol of these annulations. For example, excellent enantioselectivities ranging from 93% to >99% ee have been recently achieved by using maleimides, barbiturate-derived alkenes, cyclic 1-azadienes and nitroolefins as activated alkenes in formal [3+2] cycloadditions of racemic Morita–Baylis–Hillman carbonates. Other novel interesting enantioselective organocatalysed transformations of these modified adducts have encountered success, such as [3+3] annulations with C,N-cyclic azomethine ylides achieved with >99% ee, [4+1] annulations with sulfonamides performed in 93% ee, or umpolung additions of trifluoromethyl

ketimines providing 99% ee. In spite of these recent excellent developments, the reactivity of Morita–Baylis–Hillman derivatives has not been fully exploited by organic chemists so far and there is much more to understand and design more appropriate strategies for proper tuning of their three functional groups to discover novel asymmetric reaction pathways and further apply them in the synthesis of natural products as well as biologically relevant molecules.

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Abbreviations

- Ar: aryl
 AQN: anthraquinone
 BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
 BINOL: 1,1'-bi-2-naphthol
 Bn: benzyl
 Boc: tert-butoxycarbonyl
 CPME: cyclopentylmethyl ether
 Cy: cyclohexyl
 DABCO: 1,4-diazabicyclo[2.2.2]octane
 de: diastereomeric excess
 DHQD: dihydroquinidine
 DIPEA: diisopropylethylamine
 DMEB: N-dodecyl-N-methylephedrinium bromide
 DMF: dimethylformamide
 ee: enantiomeric excess
 EWG: electron-withdrawing
 HFIPA: 1,1,1,3,3,3-hexafluoroisopropyl acrylate
 LG: leaving group
 MOM: methoxymethyl
 MS: molecular sieves
 MTBE: methyl t-butyl ether
 Naph: naphthyl
 Nu: nucleophile
 Pent: pentyl
 PHAL: 1,4-phthalazinediyl
 r.t.: room temperature
 TBACN: tetrabutylammonium cyanide
 THF: tetrahydrofuran
 TIPS: triisopropylsilyl
 TMS: trimethylsilyl
 Tol: tolyl
 Ts: 4-toluenesulfonyl (tosyl)