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Recent applications of *Cinchona* alkaloids and their derivatives as catalysts in metal-free asymmetric synthesis

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1. Introduction

The *Cinchona* alkaloids are natural products found in the bark of trees of the genus *Cinchona*. The genus comprises about 40 species of trees or shrubs in the family Rubiaceae native to the Andes Mountains of South America.[1] They grow up to 15–20 m in height and produce white, pink or yellow flowers (Fig. 1). Extracts from the powdered bark of *Cinchona* species were used for treatment of malaria dating from the 17th century. Quinine, the main bioactive alkaloid extracted from *Cinchona* bark, was used as the sole cure for malaria until after the Second World War when it was replaced by synthetic analogues such as chloroquine and primaquine. Over the years, extracts of *Cinchona* bark also found applications as anticancer, analgesic, germicide, fungicide, insecticide and antibacterial agents, and as digestion stimulants and bitter flavouring agents for some drinks.[1] Quinidine, another *Cinchona* alkaloid, is employed today in modern medicine in the treatment of abnormal heartbeat and for relieving leg cramps.[1,2] The isolation of quinine was first accomplished in 1820 by Pelletier and Caventou[3] and was the result of intensive research during the early 19th century, fuelled by the increasing demand for malaria cures coupled with the difficulties created by two world wars in obtaining sufficient raw *Cinchona* bark. Although a total of about 30 *Cinchona* alkaloids were eventually isolated from *Cinchona* species, the four best known being quinine, cinchonidine, quinidine and cinchonine, further research focused mainly on quinine[4,5] leading to its molecular structure determination by Rabe (1907),[6] partial total synthesis in 1945 by Woodward and Doering,[7] definite confirmation of its structure by X-ray crystallography (1967),[8] various approaches to its total synthesis[4,9] and, finally, its full synthesis with the correct configuration by Stork in 2001.[10]

Fig. 1. Flowering *Cinchona* tree at the New York botanical garden (RUBIACEAE Cinchona Pubescens.jpg from Wikimedia Commons).

Although the chiral application of the *Cinchona* alkaloids dates back to 1853[11] they have been rediscovered outside their medicinal uses as efficient chiral reagents, chiral auxiliaries and *privileged catalysts* in asymmetric synthesis mainly over the past 30 years.[12]

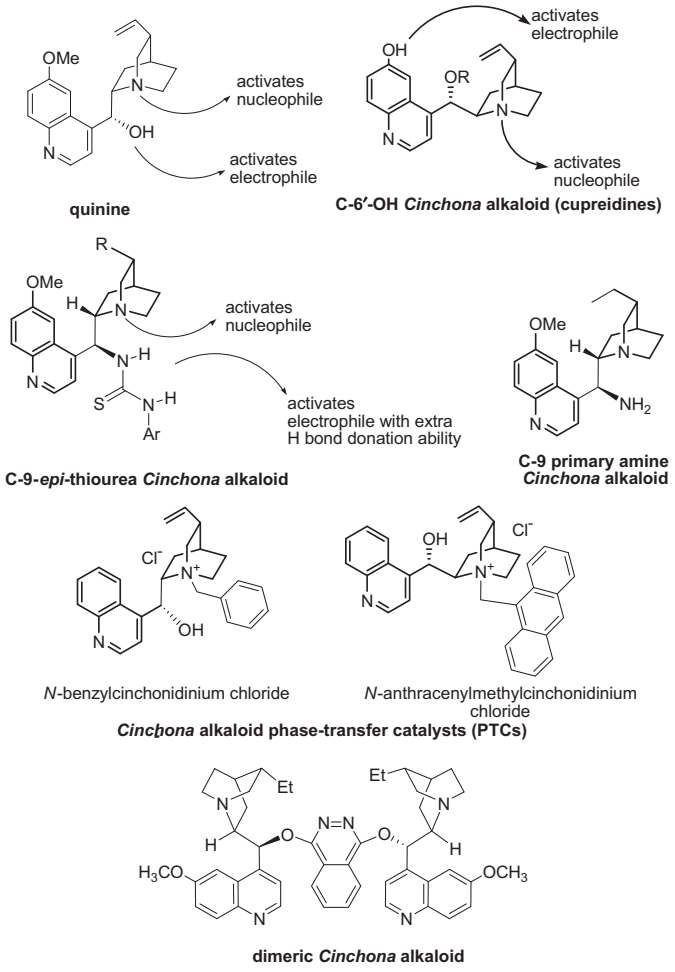


Fig. 2. Representative examples of *Cinchona* alkaloid catalysts.

Various *Cinchona* alkaloids and their derivatives (Fig. 2) have been employed as catalysts in many well-known reactions affording diverse types of enantiopure products (Fig. 3)[13] many of which have been employed as key structural units in the synthesis of other complex natural products. Before the submission of this article, two representative review articles appeared on this topic in 2001 and 2004 (covering research up to 2003).[12d,14]

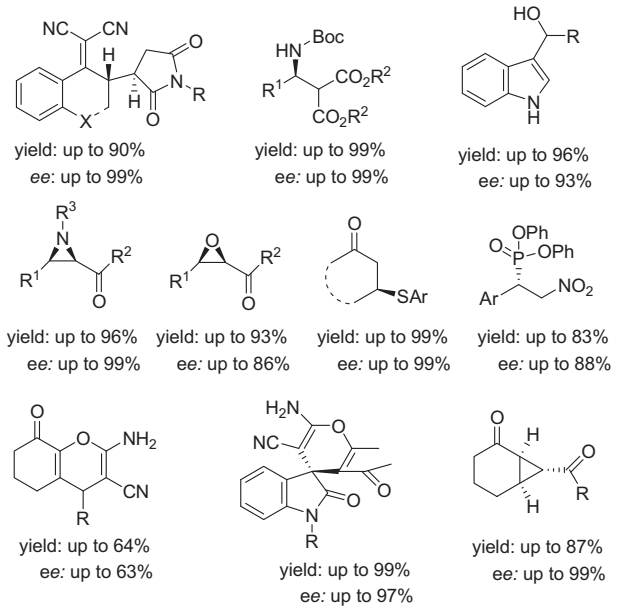
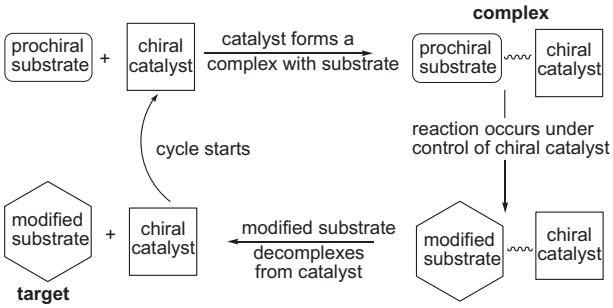


Fig. 3. Representative products from *Cinchona*-catalysed reactions.

The first decade of the 21st century has witnessed an explosion of research in the use of *Cinchona* alkaloids and their derivatives in asymmetric catalysis[15] and this necessitates frequent reviews dealing with different aspects of their chemistry. This review focuses on the application of *Cinchona* alkaloids and their derivatives in asymmetric organocatalysis from 2004 to date. Reactions involving metal catalysts are not covered in this review. The design and efficiency of the catalysts with regard to yield of the product(s) and enantioselectivity are discussed. Only the most efficient catalyst of the trials carried out is mentioned in each case. The reactions are broadly categorised as (i) carbon–carbon bond formation and (ii) carbon–heteroatom (C–N, C–O, C–F, C–S, and C–P) bond-formation reactions. Other reactions such as kinetic resolutions, decarboxylations, desymmetrisation and sulfinyl transfer are also described. Before discussing the applications under these categories, however, it is instructive to briefly describe the mechanism of asymmetric catalysis and the significant structural features of the *Cinchona* alkaloids exploited in asymmetric catalysis.

2. Asymmetric catalysis

Asymmetric catalysis is one of the most important strategies for the synthesis of enantiopure compounds (Fig. 4). Of the three approaches to asymmetric synthesis, i.e., use of the chiral pool, use of chiral auxiliaries and use of chiral catalysts (Scheme 1), the third method has an edge over the others due to its cost effectiveness and environmental friendliness and, hence, it has acquired conspicuous popularity in recent years. In principle, a single molecule of a chiral catalyst can lead to the production of millions of target molecules. The enormous significance attached to chiral catalysts in asymmetric synthesis led to the award of the Nobel Prize for chemistry in 2001 to William S. Knowles and Ryoji Noyori (for their work on chirally catalysed hydrogenation reactions) and to Barry K. Sharpless (for his work on chirally catalysed oxidation reactions).[16] The pioneering work of these three Nobel laureates paved the way for the further development of asymmetric catalysis.



Scheme 1.

2.1. Asymmetric organocatalysts

The use of metal catalysts or metal–ligand catalysts dominated the research scene up to the end of the last century. A change in

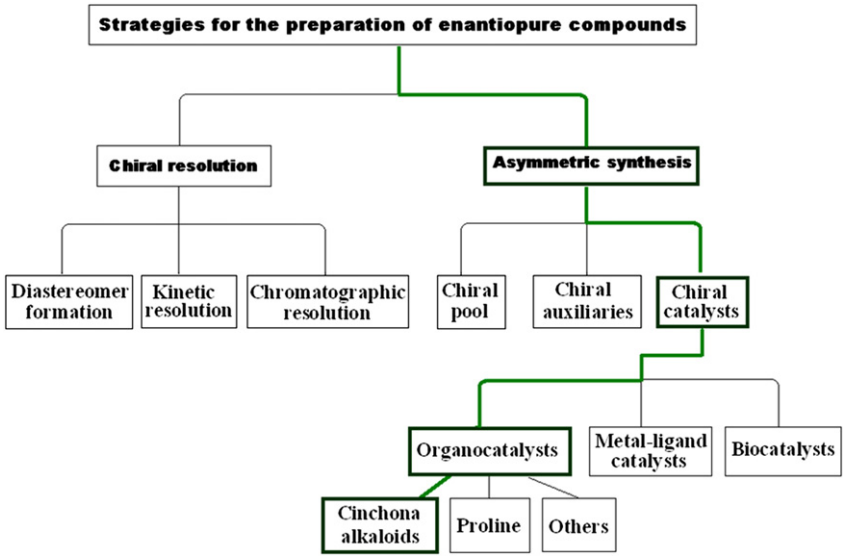


Fig. 4. Strategies for the preparation of enantiopure compounds.

perception in recent years, however, has led to a switch in favour of *organocatalysts* or the utilisation of small chiral organic molecules as metal-free catalysts, especially in the synthesis of pharmaceuticals because of the 'green' advantage of not contaminating the final product with traces of heavy metals.[17] The neologism of *organocatalysis* was created and registered as a trademark by David MacMillan,[18] a key researcher in this rapidly expanding field where considerable effort is being directed towards designing a variety of small organic molecules (organocatalysts) that can match the levels of stereoselectivity observed in enzymatic reactions. The catalytic efficiency of some of the first successful organic molecule candidates turned out to be more than expected, in that, while enzymes are applicable only to specific reactions, the synthesised organocatalysts proved to be effective over a wide range of different reactions and could therefore be described as '*privileged catalysts*'.[12a]

2.2. Mechanistic considerations

There are different types of mechanisms displayed by organocatalysts: (i) some form covalent reactive intermediates, (ii) some stabilise the transition state in a 'chiral pocket' via weak interactions such as hydrogen bonding and (iii) others operate as phase-transfer catalysts (PTCs) by a distinctly different mechanism in which they provide a 'chiral shuttle' for reaction partners located in different phases. In the second type of catalysis, a reacting molecule, that only has a prochiral centre, is temporarily attached to the catalyst and fixed in an asymmetric environment or 'chiral pocket' or 'chiral space' within the catalyst in such a way that favours one trajectory of the reaction more than the other, thus producing an excess of one enantiomer, because a new chiral centre is enantioselectively introduced into the molecule (Fig. 5).[19] The more efficient catalyst would be one that can completely block the other trajectory of reaction. This concept of 'chiral space' has become the basis of rational design and optimisation of organocatalysts as opposed to random searching. Random searching has, however, in the past, led to the discovery of several compounds obtained directly from nature that fit the role of 'privileged catalysts'. Among these, the most versatile are proline (an α-amino acid), and the *Cinchona* alkaloids and their derivatives.

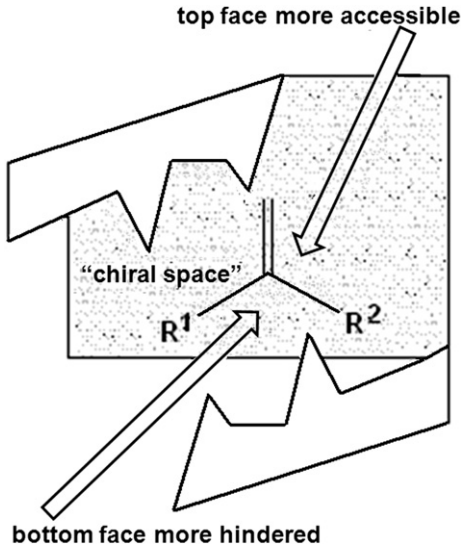


Fig. 5. Model illustrating general asymmetric induction at a prochiral centre.

3. Structural features of *Cinchona* alkaloids

The naturally occurring *Cinchona* alkaloids are an ideal choice as chiral inducers because they are (i) abundantly provided by nature, (ii) commercially available at relatively moderate prices, (iii) bench-top stable and recoverable, (iv) readily modified structurally for diverse catalytic applications and (v) readily obtainable in diastereomeric pairs, allowing access to either enantiomeric product.

The basic structure of the *Cinchona* alkaloids consists of two rigid ring moieties (Fig. 6), namely an aromatic quinoline ring and an aliphatic quinuclidine ring linked by two carbon–carbon single bonds. They contain five stereocentres, C-(3), C-(4), N-(1), C-(8) and C-(9), but they occur in pairs that differ in configuration only at N-(1) and the two connecting single-bond carbons, C-(8) and C-(9). The absolute configuration at C-(3) and C-(4) is identical in both pairs and is the same in all naturally occurring *Cinchona* alkaloids. The eight major *Cinchona* alkaloids **1**–**8** (Fig. 7) are thus related as diastereomeric pairs, but are often referred to as 'pseudoenantiomers'. As an example, the absolute configuration of natural quinine is 1*S*,3*R*,4*S*,8*S*,9*R* and that of quinidine is 1*S*,3*R*,4*S*,8*R*,9*S*. They are diastereomers, yet behave like enantiomers, because, when used as chiral catalysts, quinine yields one enantiomer while quinidine yields the opposite enantiomer with equal selectivity.

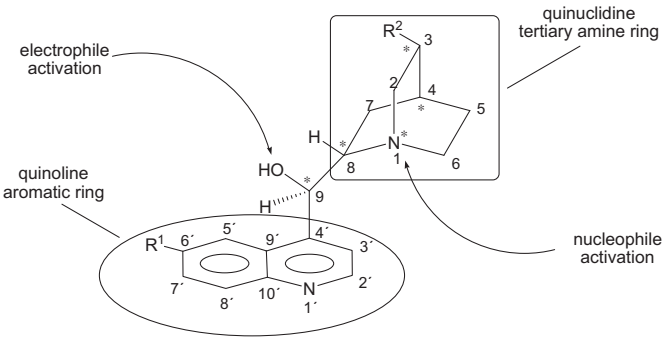


Fig. 6. Important structural features of *Cinchona* alkaloids (numbering initially adopted by Rabe[6]).

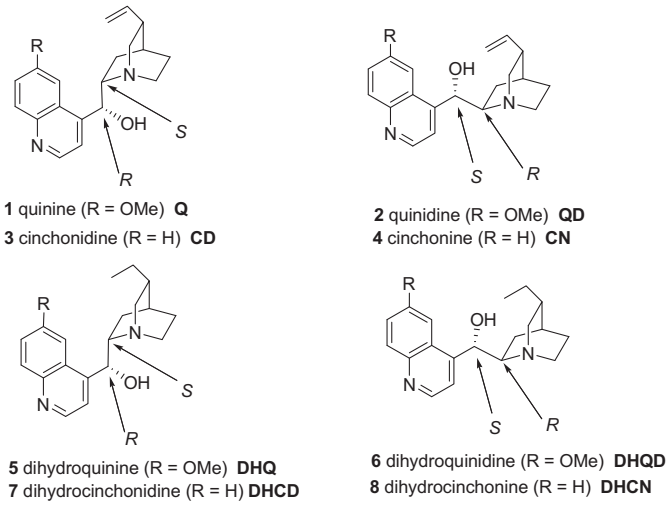


Fig. 7. Structures and configurations of the eight major *Cinchona* alkaloids.

Recent findings from studies on the structural features responsible for the catalytic performance of the *Cinchona* alkaloids are summarised below.[20]

(i) The relative positions adopted by the bulky quinoline and quinuclidine ring systems possibly generate a rigid enzyme-like pocket or 'chiral pocket' around the substrate that forces enantioselective reactions.

(ii) Free rotation around the linker atoms, C8 and C9, creates a dynamic environment that provides many conformations with different stabilities and abilities to impart enantioselectivity in a given catalytic process. In one example, four low-energy conformations of quinidine (Fig. 8) have been identified by Dijkstra and co-workers[21] using NMR studies.

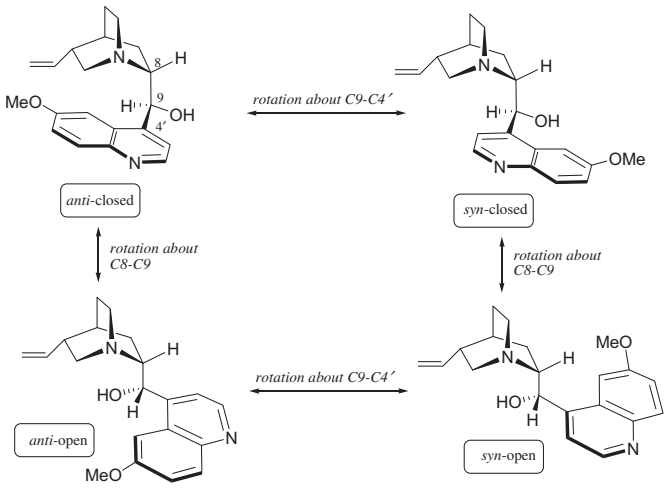


Fig. 8. Low-energy conformations of quinidine.

(iii) The stabilities of different conformers created around the linker carbons may be influenced by the peripheral groups R^1 and R^2 and, hence, the nature of the chiral promotion may ultimately be influenced by these groups. The *Cinchona* alkaloids have been greatly utilised in the rational design of catalysts for asymmetric synthesis because they are tunable by varying R^1 and R^2 in order to increase or decrease bulkiness, thus controlling steric rigidity and, hence, the stereochemical outcome.

(iv) The quinuclidine tertiary amine nitrogen is nucleophilic and is responsible for the basic character of the *Cinchona* alkaloids as its pK_a value in water is about three times higher than that of the quinoline nitrogen. It can act as an effective ligand for a variety of metal-catalysed processes and also as a reactive centre.

(v) The quinoline aromatic ring is a potential secondary binding site and is the site for adsorption onto solid surfaces in heterogeneous catalysis. This flat aromatic ring has electron-donor abilities that could enable the formation of donor–acceptor complexes with electron-deficient molecules.

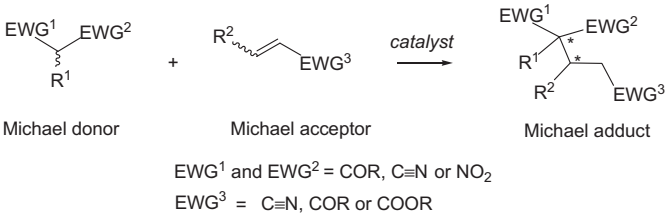
(vi) The C-(9) stereocentre makes both diastereomers available, providing access to both enantiomers of a product with almost identical selectivities.

A study of the mechanism of asymmetric catalysis by *Cinchona* alkaloids using computational methods[22] has shown that these alkaloids generally function as bifunctional catalysts. This mode of catalysis simultaneously utilises the quinuclidine nitrogen to activate the nucleophile via general base catalysis and the hydroxyl group at C-(9) to activate the electrophile via hydrogen bond interactions. In other words, the two functional groups provide specific enzyme-like interactions that pre-organise and orient the reactants in an optimum position for reaction and also stabilise the transition-state structure. The highly structured transition state (stabilised by a network of hydrogen bonds) accounts for the enantioselectivity of the reaction. Cucinotta and co-workers showed that, when the C-(9)–OH was substituted by *O*-benzoyl, the stereoselectivity of the reaction dropped drastically, confirming the role of the OH group in the catalysis process.[22] These findings substantiated earlier studies on the conformational behaviour of the alkaloids that had been carried out by Dijkstra and co-workers,[21] who found that substituents on C-(9) played a key role in determining the conformation of the *Cinchona* alkaloid in solution, e.g., C9 esters are usually present in the anti-closed form, while methyl ethers prefer an anti-open arrangement (Fig. 8).

4. *Cinchona* alkaloids in carbon–carbon bond-forming reactions

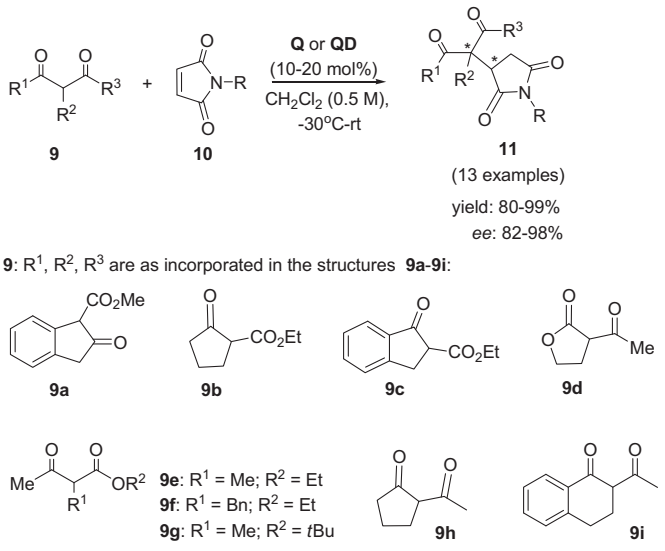
4.1. Michael addition reactions

Michael addition reactions (Scheme 2) are among the most ubiquitous and most exploited for the formation of C–C bonds. As a result of the numerous types of Michael donors and acceptors that can be generated by varying the electron-withdrawing groups (EWGs), Michael reactions cover an expansive spectrum of reactions requiring different types of catalysts. Michael addition reactions, therefore, provide the stage to showcase different classes of *Cinchona* alkaloid catalysts, such as natural *Cinchona* alkaloids, C-6′ hydroxyl *Cinchona* alkaloids, *Cinchona* ureas and thioureas, C-9 primary amine *Cinchona* alkaloids, *Cinchona* alkaloid phase-transfer catalysts, etc.



Scheme 2.

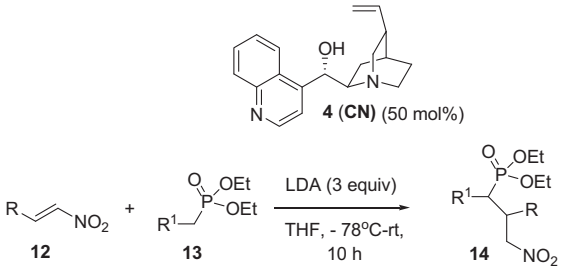
4.1.1. Natural Cinchona alkaloids. Natural *Cinchona* alkaloids quinine **1** (**Q**) and quinidine **2** (**QD**) were employed in the conjugate addition of 1,3-dicarbonyl compounds **9a**–**i** to maleimides **10**. The multifunctional products **11**, obtained in excellent yields with up to 98% ee, featured two adjacent stereogenic carbon atoms with one of them being quaternary (Scheme 3).[23] In the case of *N*-benzylmaleimide **10a**, exceptionally good yields of up to 99% were obtained.



Scheme 3.

The construction of quaternary stereogenic centres is usually highly challenging due to steric factors and yet such centres are important structural motifs in a range of medicinal natural products and pharmaceuticals. It was observed that the unmodified alkaloids were more efficient in comparison to their derivatives for the reaction. The presence of the free C-9 hydroxyl group was essential for high levels of reactivity and selectivity. Asymmetric Michael addition of pentane-2,4-dione to (*E*)-β-nitroolefins in the presence of 10 mol % of quinidine as a catalyst in tetrahydrofuran afforded 52% yield of the adduct, but only in 17% ee.[24]

Namboothiri and co-workers evaluated the catalytic efficiency of (+)-cinchonine (**CN**) together with (*S*)-(−)-binol, (−)-DET, L-proline and (*R*)-diphenylprolinol in the reaction of α-lithiated phosphonates **13a**–**f** with (*E*)-nitrostyrenes **12**. (+)-Cinchonine was found to be the most efficient catalyst, affording yields of **14** ranging from 63 to 99% and enantioselectivities of up to >99% in the reaction of benzyl phosphonate (Scheme 4).[25] The reaction was extended to substituted benzyl phosphonates (Table 1).



12: R = Ar = Ph, 4-Cl-Ph, 4-MeO-Ph

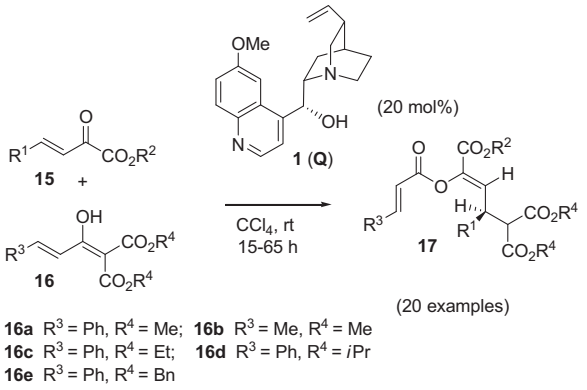
13a-f: R = **a**) H, **b**) Ph, **c**) 4-Cl-Ph, **d**) 4-NO_2-Ph, **e**) 2-naphthyl, **f**) *n*-Pr

Scheme 4.

Table 1
Adducts **14** from Cinchonine-catalysed reactions of benzyl phosphonates with (*E*)-nitrostyrenes

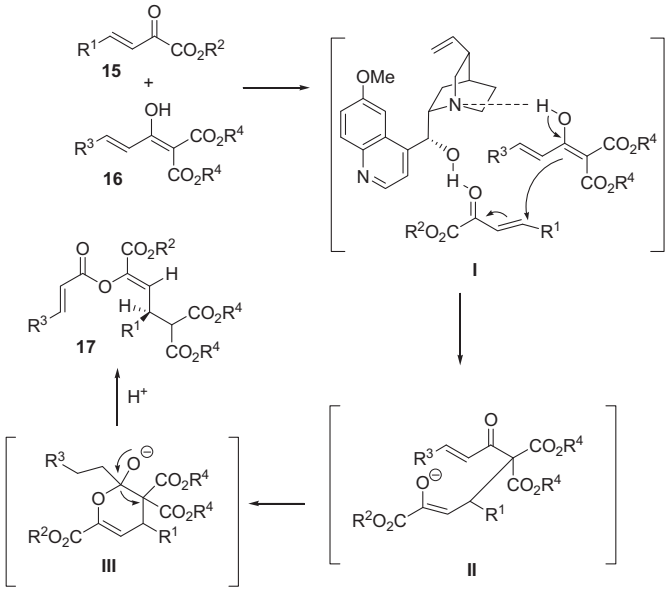
Entry	14		Yields (%)	dr	ee (%)
	R	R^1			
1	4-Cl–Ph	Ph	81	96:4	>99
2	4-Cl–Ph	4-Cl–Ph	69	100:0	>99
3	4-Cl–Ph	4-NO_2–Ph	45	92:08	80
4	4-Cl–Ph	2-Naphthyl	74	100:0	>99
5	4-Cl–Ph	H	61		>99
6	Ph	H	41		68
7	4-MeO–Ph	H	43		82
8	4-Cl–Ph	*n*-Pr	47	72:28	86

The conjugate addition of β,γ-unsaturated α-ketoesters **15** to 2-(1-hydroxy-3-arylallylidene) malonates **16**, resulting in the rearranged products **17** (Scheme 5), has been investigated using quinine, quinidine, cinchonine, cinchonidine, *O*-trimethylsilylquinine, cupreine and *O*-benzylcupreine as catalysts. In addition a modified *Cinchona* alkaloid catalyst, in which the C-9–OH was substituted with a phenyl group, was also tested.[26] Of all the eight catalysts examined, quinine **1** (**Q**) provided the best results in terms of both yield and enantioselectivity. According to the proposed mechanism (Scheme 6), quinine first catalysed the asymmetric Michael addition of **15** and **16** via dual activation of both electrophile and nucleophile (transition-state I) to produce intermediate II, which then underwent an oxanucleophilic attack at the carbonyl group of **15**, generating another intermediate III. This intermediate finally rearranged to form the product **17** after protonation.



16a R^3 = Ph, R^4 = Me; **16b** R^3 = Me, R^4 = Me
16c R^3 = Ph, R^4 = Et; **16d** R^3 = Ph, R^4 = *i*Pr
16e R^3 = Ph, R^4 = Bn

Scheme 5.



Scheme 6.

4.1.2. C-6′-Hydroxyl Cinchona alkaloids. Until the 1990s, bifunctional catalysts based on the *Cinchona* scaffold relied exclusively on the C-9 hydroxyl group as the hydrogen bond donor. Recently, cupreines (CPNs) and cupreidines (CPDs) **18a**–**g** (Fig. 9) have emerged as efficient catalysts that feature a phenolic hydroxyl group at the C-6′ position.[27] Such catalysts utilise the phenolic hydroxyl site, which is more separated from the nucleophile-activating tertiary amine site than in unmodified *Cinchonas*, for electrophile activation. In addition, they have a free site at C-9 that could be additionally functionalised to enhance the enantioselectivity of the reactions by further tuning the rigidity, basicity and conformation.

Deng and co-workers[28,29] have done considerable work using cupreines and cupreidines **18a**–**h** (Fig. 9) as catalysts in a number of different Michael addition reactions. The group investigated the efficiency of catalysts **18a** and **18e** in the addition of malonates **19a** and **19b** to nitroolefins **12** to form adducts **20** (Scheme 7). This group has also investigated the addition of β-ketoester **21** to nitroolefin **12** to form the adduct **23** (Scheme 8).[28] In both cases cupreidine **18a** was found to be the most efficient catalyst producing high yields and enantioselectivity. The reaction of dimethyl malonate with (*E*)-2-nitrostyrene in the presence of cupreidine **18a** has also been reported by Fringuelli and co-workers to yield 92% of the adduct in 74% enantioselectivity.[30]

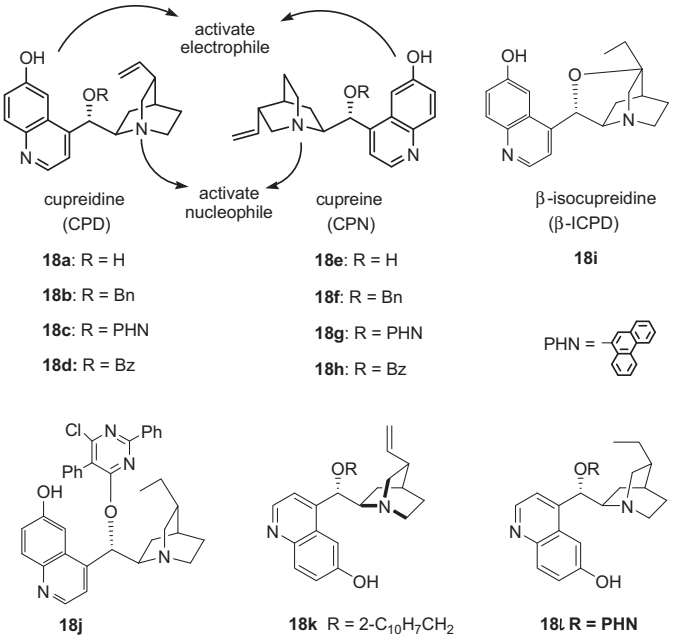
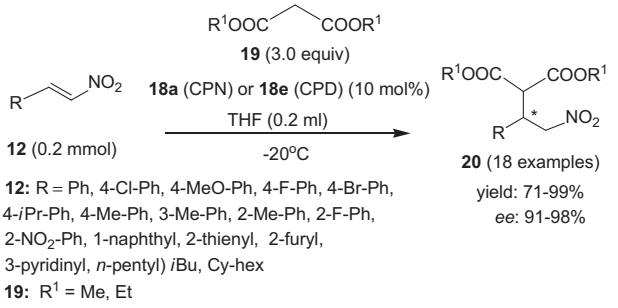
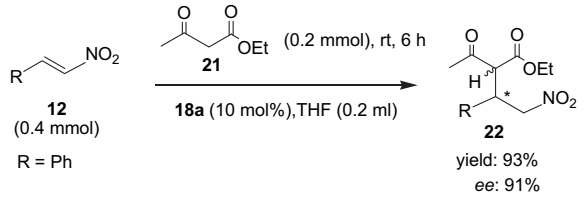


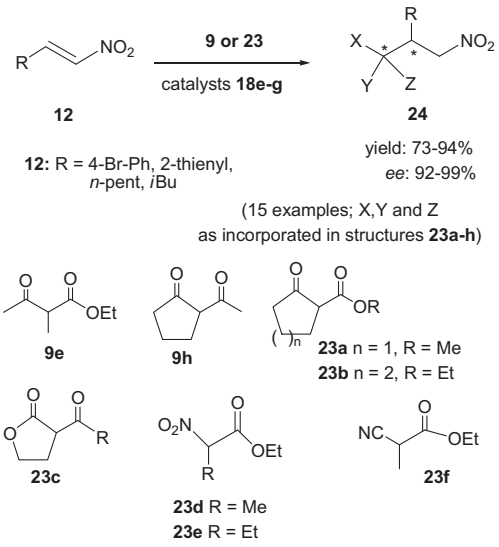
Fig. 9. Cupreines and cupreidines (a new class of *Cinchona* alkaloid catalysts).



Scheme 7.



Scheme 8.



Scheme 9.

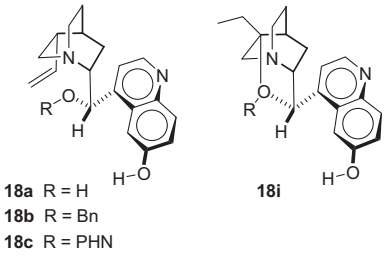


Fig. 10. Active anti-open conformer of catalysts **18a–c** and **18i**.

One focus of interest for the Deng group was the creation of products containing adjacent quaternary and tertiary stereocentre[31] via conjugate addition reactions of trisubstituted Michael donors **9** and **23** to nitroalkenes **12**. The desired products **24** (15 examples) were obtained with excellent enantioselectivities and high yields using cupreines **18e–g** (Scheme 9). The cupreidines **18a–c**, when tested alongside a conformationally rigid analogue **18i**, were also found to have comparable efficiency, thus supporting an anti-open conformer for this group of catalysts in their active state (Fig. 10). A transition-state model **25** was proposed to rationalise the stereochemical outcome, suggesting that the catalyst adopts an anti-open conformer to simultaneously activate and orient the Michael donor and the acceptor by a network of hydrogen-bonding interactions. This is illustrated in Fig. 11 for formation of the product **24a** from **12** and **23b**.

Using **18c** as the most efficient catalyst, the addition of various trisubstituted carbon nucleophiles such as **26** to 2-chloroacrylonitrile **27** led to the development of an asymmetric method for the construction of two noncontiguous stereocentre[32] A tandem Michael addition-asymmetric protonation reaction yielded products **28** with 1,3-tertiary-quaternary stereocentres. Excellent yields (71–96%) and stereoselectivities (78–96% ee, up to 25:1 dr) were achieved. The synthetic utility of **28** was demonstrated by a formal synthesis of (−)-manzacidin A **29** (Scheme 10).

The Deng group's interest in the construction of all-carbon quaternary stereocentres, led to the development of reactions involving conjugate additions of α-substituted β-ketoesters **30a–30h**, to vinyl ketones **31** (Scheme 11) and reactions of **30a** or **30f** with β-substituted vinyl ketones **33a–c** (Scheme 12).[33] The Michael adducts **32** and **34**, respectively, were obtained in high yields and enantioselectivities catalysed by **18c** or **18g** for the former reaction and by **18b** or **18g** for the latter. The products **34** of the latter reaction contained adjacent quaternary–tertiary stereocentres (Scheme 12).

Despite its synthetic importance, conjugate additions to α,β-unsaturated aldehydes have remained elusive.[34] Deng and coworkers carried out research into developing such reactions and by utilising C-6′–OH *Cinchona* alkaloids, the group made significant progress towards this endeavour.[33] They successfully developed enantioselective Michael additions of carbonyl donors such as **30b**, **30e**, **30h** and **30i** to α,β-unsaturated aldehydes **35a–d**.[33] The group identified cupreines **18b**, **18c** or **18g** as being the most efficient catalysts for producing the desired adducts **36** (8 examples) in excellent yields and with high enantioselectivities (Scheme 13). The reaction between the donor **30e** and **35a** (acrolein) afforded the

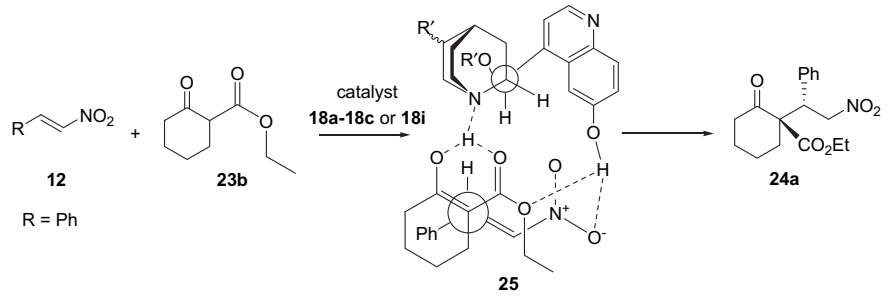
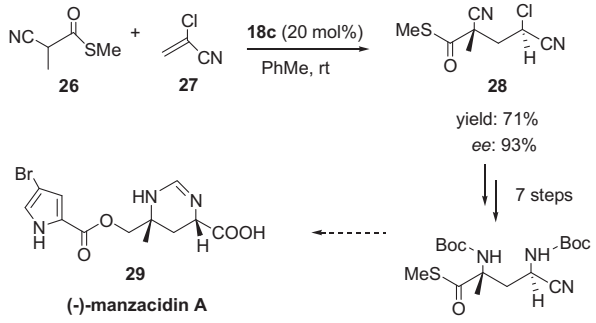
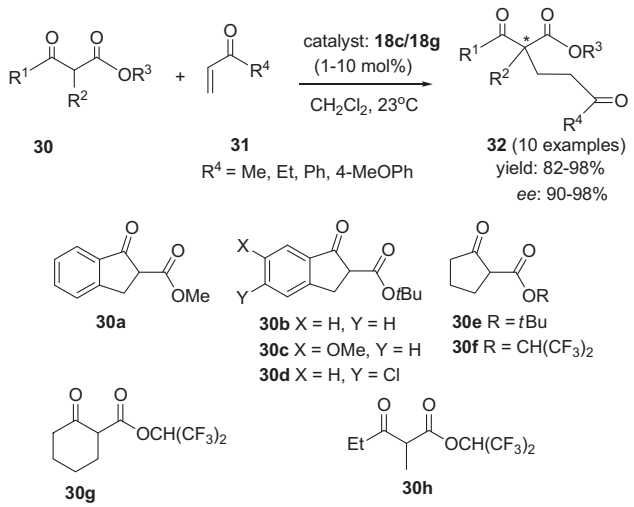


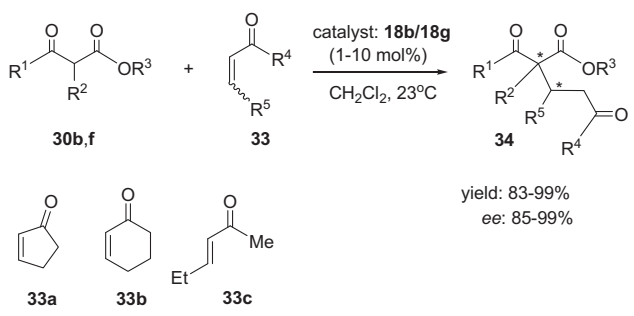
Fig. 11. Proposed model for the transition-state assembly in Michael additions catalysed by **18a**–**c** or **18i**.



Scheme 10.

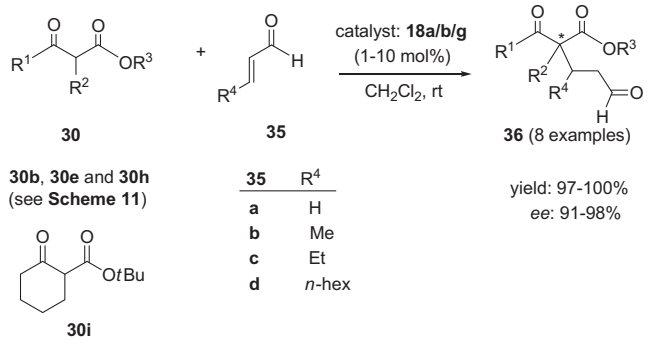


Scheme 11.



Scheme 12.

product **36a** with a high yield of 98% and high enantioselectivity (99% ee). The usefulness of this product was demonstrated by synthesising from it the medicinal compound (+)-tanikolide (Scheme 14). The group also synthesised the structurally novel C-6′–OH *Cinchona* alkaloid catalyst **18j**, which proved highly efficient for the addition of α-aryl α-cyanoacetates **37a**–**e** to **35a** (acrolein), yielding biologically interesting products **38a**–**e** containing all-carbon benzylic quaternary stereocentres (Scheme 15).



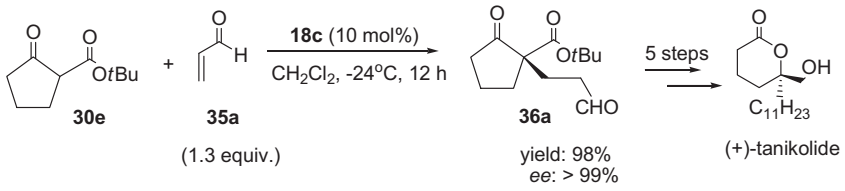
Scheme 13.

A highly efficient asymmetric conjugate addition of anthrone **39** to nitroalkenes **12** using **18h** (*O*-benzoylcupreine, BzCPN) as a catalyst has been reported to afford the adducts **40** (Scheme 16).[35] An enantioselective direct vinylogous Michael addition of α,α-dicyanoolefins **41a**–**e** to maleimides **10a** and **10b** using **18b** or **18k** as catalyst is reported to afford the adducts **42** (Scheme 17).[36]

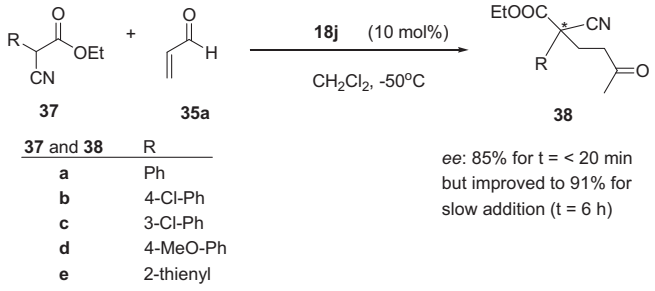
The first enantioselective two- and three-component reactions via a domino Knoevenagel/Michael cyclisation sequence with cupreine **18a** as catalyst have been developed.[37] A reaction of *N*-substituted isatins **43a**–**43j**, malononitrile **44** and 1,3-diketones **45a**–**c** or β-ketoesters **45d**–**e** in the presence of catalyst **18a** led to the synthesis of optically active spiro[4*H*-pyran-3,3′-oxindoles] **46** (16 examples) in excellent yields (up to 99%) with good-to-excellent enantioselectivity (up to 97%) (Scheme 18).

4.1.3. Thiourea and urea derivatives of Cinchona alkaloids. Derivatisation of *Cinchona* alkaloids by substituting the C-9–OH group with a thiourea or urea moiety and their application in asymmetric catalysis has been investigated by several research groups, the rationale being to combine the catalytic and hydrogen bond donating ability of this group with that of the *Cinchona* framework.[38,39] The stereochemistry of such bulky groups at C-9 also directs the rigidity and conformational stability of the transition-state intermediates and, hence, the stereochemical outcome. A number of thiourea and urea derivatives **47** have thus been developed from natural *Cinchona* alkaloids and successfully utilised in asymmetric reactions (Fig. 12).

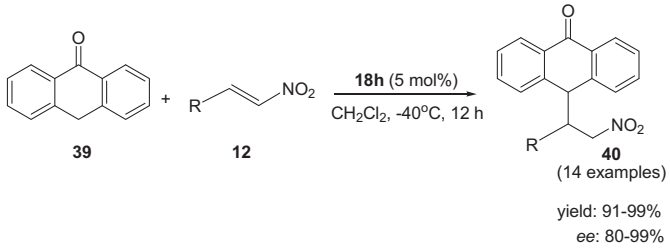
The performance of *Cinchona*-derived urea and thiourea catalysts **47a**, **47c**, **47d** and **47g** in the asymmetric Michael addition of



Scheme 14.

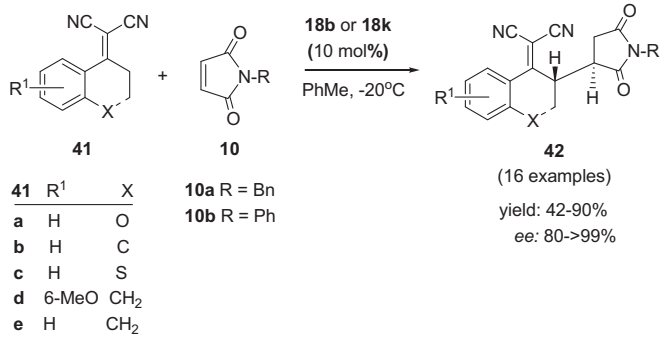


Scheme 15.

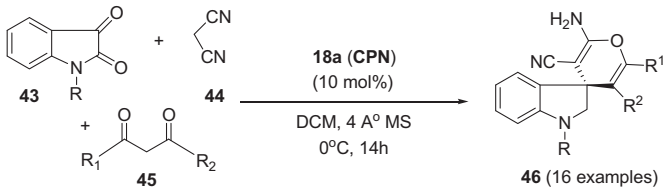


12: R = Ph, 4-Cl-Ph, 4-MeO-Ph, 4-F-Ph, 4-Br-Ph, 1-napthyl, 2-furyl, 3-F-Ph, 2,4-Cl_2-Ph, 2-Cl-Ph, 4-NO_2-Ph, 3-NO_2-Ph, *n*-Pr, (*E*)-PhCH=CH_2

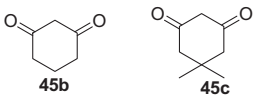
Scheme 16.



Scheme 17.



43a-j: R = **a**) Me, **b**) Bn, **c**) allyl, **d**) MOM, **e**) MOM, 5-Me, **f**) MOM, 5-OMe, **g**) MOM, 5-F, **h**) MOM, 5-Cl, **i**) MOM, 6-Cl, **j**) MOM, 6-Br



Scheme 18.

nitromethane to chalcones **48** has been evaluated.[40] Interestingly, the thiourea derivative with natural stereochemistry at C-9 (i.e., **47a**) was inactive in the addition reaction, as was DHQ itself, while **47c**, **47d** and **47g** with inverted stereochemistry at C-9 displayed high selectivity (86–96% ee) with yields ranging from 59 to 93%. The catalyst **47d** proved to have an edge over the others in forming the desired adducts **49a**–**e** (Scheme 19). These results suggested that the relative stereochemical arrangement of the catalyst functional groups in a manner, that is, conducive for their simultaneous action (nucleophile/electrophile activation) is an important consideration in the catalyst design. The catalyst **47d** was also found to be the most effective in the addition of α-cyanoacetates to chalcones.[41]

The Connon research group investigated the performance of catalysts **47b** and **47d**–**g** in the addition of dimethyl malonate **19** to nitroolefins **12**. The group also identified **47d**–**g** (i.e., the 9-*epi* derivatives with 'unnatural' stereochemistry) as the most efficient catalysts for the conjugate addition reaction (Scheme 20).[38,39] Based on their findings and MM2 calculations, a model for the stable conformation adopted by **47e** in its pre-transition state was proposed to account for the activity and the sense of stereoinduction using the example of addition of malonate **19** to **12** (Scheme 21). The *Cinchona* alkaloid-derived thioureas, however, afforded poor yields and moderate enantioselectivity in the Michael addition of nitroolefins to malononitrile.[42] Asymmetric Michael addition of pentane-2,4-dione to (*E*)-β-nitroolefins in the presence of 10 mol % of thiourea in tetrahydrofuran yielded the adduct in 96% ee, but only in 47% yield.[24]

Marini and co-workers investigated the addition of α-aryl-substituted cyanoacetates to α,β-unsaturated selenones in the presence of various bifunctional urea and thiourea organocatalyts affording adducts in yields ranging from 75 to 97% and ee ranging from 76 to 90%.[43] The *Cinchona* alkaloid derivative 9-*epi*-DHQU **47e** was identified as being an effective catalyst for the creation of adducts containing an all-carbon quaternary stereocentre adjacent to a tertiary stereocentre by conjugate addition of α-phenylcyanoacetate **37a** to the β-substituted vinyl selenone **50**. The desired adduct **51** was formed with moderate diastereo- and good enantioselectivity and, taking advantage of the excellent leaving-group ability of the selenone group, it was smoothly converted to the cyclopropane derivative, *Z*-**52** by treatment with KCN in DMF (Scheme 22).

An interesting Michael addition for the generation of fluorinated quaternary stereogenic centres adjacent to tertiary stereocentres has recently been reported.[44] Fluorine-containing methines **53** were employed as nucleophiles and were added to nitrostyrenes **12** in the presence of a 9-*epi*-quinidine thiourea derivative, 9-*epi*-QDT

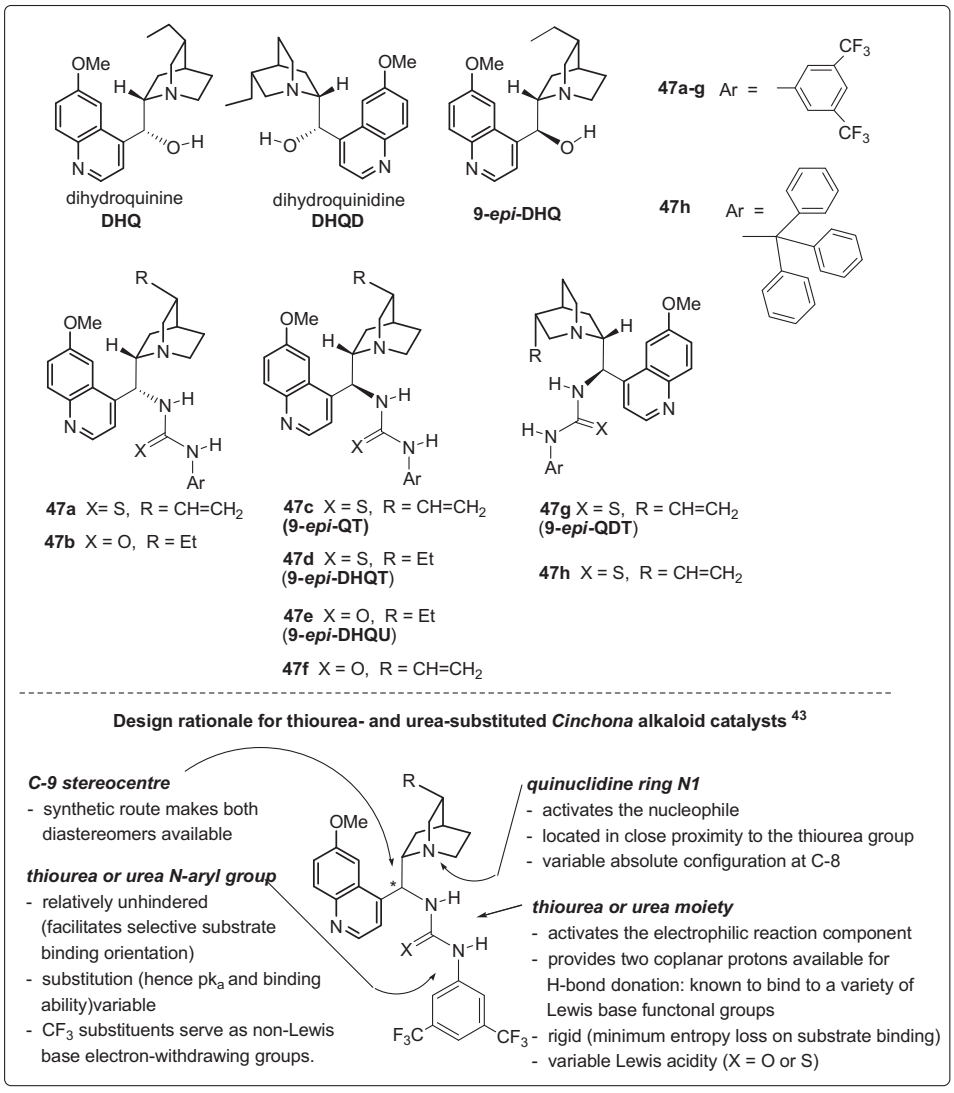
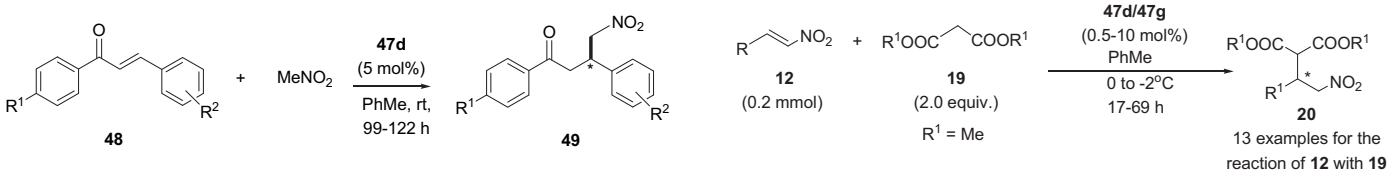


Fig. 12. Thiourea- and urea-substituted *Cinchona* alkaloid derivatives.



49	R^1	R^2	% yield	% *ee*
a	H	H	93	96
b	4-Cl	H	94	95
c	4-F	H	94	98
d	2-Me	H	93	89
e	H	4-Me	80	96

12: R = Ph, 4-MeO-Ph, 4-Br-Ph, 4-Me-Ph, 2-Me-Ph, 1-naphthyl, 2-thienyl, Cy-hex, 2-NO_2-Ph, *n*-hexyl

Test results for catalyst performance in the reaction of **12** (R = Ph) with **19**

catalyst	mol%	% conv.	% *ee*
DHQ	5	> 98	12 *(S)*
9-*epi*-DHQ	5	46*	18 (R)
47b	5	26	25 *(S)*
47e	2	> 98	88 *(S)*
47d	2	> 98	90 *(S)*
47d	2	> 98**	99 *(S)*

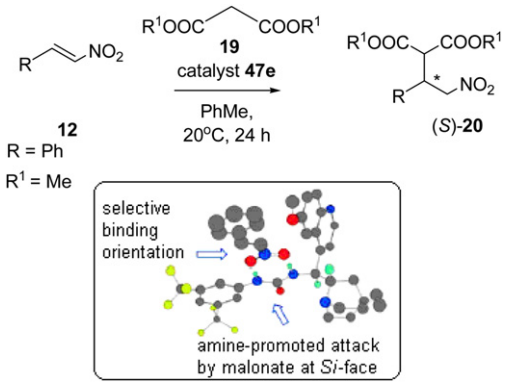
* after 144 h, ** after 30 h at -20 °C

Scheme 19.

Scheme 20.

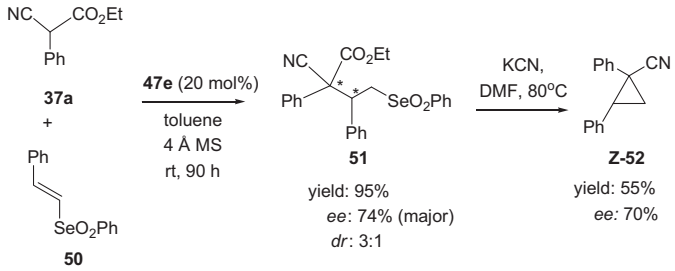
47g (Scheme 23). The Michael adducts **54** containing vicinal fluorinated quaternary and tertiary stereogenic centres were readily convertible into synthetically useful chiral structural scaffolds with three contiguous stereogenic centres, e.g., the adduct **54a** afforded the chiral γ-lactam **55** and the pyrrolidine **56**.

Wennemers and Lubkoll have demonstrated that *Cinchona* alkaloid-derived ureas and thioureas are efficient organocatalysts in organic synthesis reactions that utilise malonic acid half thioesters (MAHTs) as thioester enol equivalents.[45] The urea derivative **47f** was found to efficiently catalyse the decarboxylative Michael addition of the MAHT **57** to nitroolefins **12** producing the adducts **58** in high yields (up to 92%) and enantioselectivity of 55–67% (Scheme 24). Generally, electron-deficient nitroolefins afforded products in yields of greater than 89%, while electron-rich aromatic

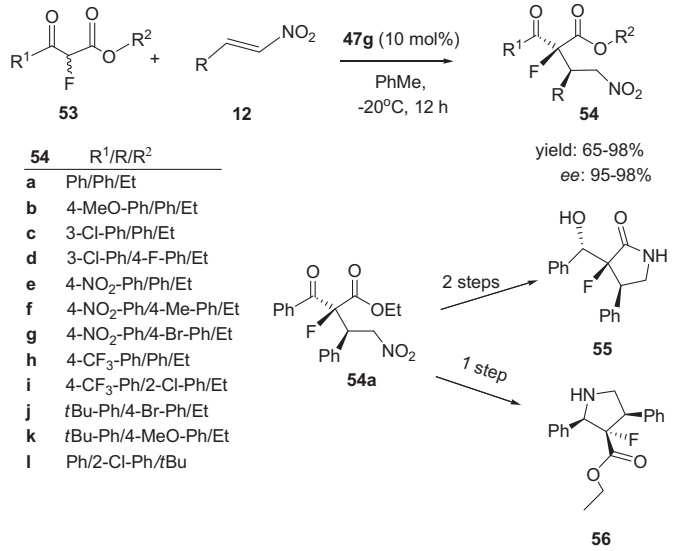


Possible pre -TS assembly for enantioselective addition promoted by catalyst **47e** (9-*epi*-DHQU).

Scheme 21.



Scheme 22.



54	$R^1/R/R^2$
a	Ph/Ph/Et
b	4-MeO-Ph/Ph/Et
c	3-Cl-Ph/Ph/Et
d	3-Cl-Ph/4-F-Ph/Et
e	4-NO_2-Ph/Ph/Et
f	4-NO_2-Ph/4-Me-Ph/Et
g	4-NO_2-Ph/4-Br-Ph/Et
h	4-CF_3-Ph/Ph/Et
i	4-CF_3-Ph/2-Cl-Ph/Et
j	*t*Bu-Ph/4-Br-Ph/Et
k	*t*Bu-Ph/4-MeO-Ph/Et
l	Ph/2-Cl-Ph/*t*Bu

Scheme 23.

nitroolefins gave products in slightly lower yields. The rate of the reaction decreased with increasing equivalents of the ester, which suggested that the coordination of the MAHT to the urea was crucial for catalysis. Simple urea compounds did not mediate the reaction, further demonstrating the significance of bifunctionality for catalysis.

A simple organocatalytic synthesis of pregabalin ((3*S*)-3-(aminomethyl)-5-methylhexanoic acid) **62**, an anticonvulsant drug marketed by Pfizer, has been developed by the Koskinen research group.[46] The key step in the synthetic sequence is the Michael addition of Meldrum's acid **59** to the nitroalkene **60** mediated by the 9-*epi*-quinidine thiourea derivative **47h** (Scheme 25). The Michael adduct **61** was formed with a high yield of 84% with high enantioselectivity (75%). Furthermore, the catalyst **47h** was recovered in good yield (55%) and was reused for a second run of the reaction, which produced **61** in a yield of 82% and the same enantioselectivity of 75%.

The reactions of 2-cyanoindanone and other cyclic α-substituted ketones **63** and of acyclic α-cyanoesters with acrylonitrile **64** have been carried out in the presence of *Cinchona* alkaloid-derived thiourea catalysts (e.g., **47c**), affording high yields of the adducts **65** (Scheme 26).[47] These reactions, when carried out in the presence of natural *Cinchona* alkaloids like quinine and quinidine or cinchonine or cinchinidine afforded poor yields and enantioselectivities.

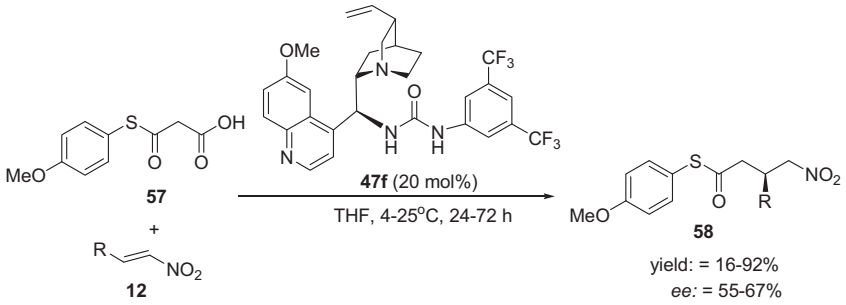
The Michael addition reaction between cyclohexane-1,2-dione **66** and arylidenemalonitriles **67** is followed by cyclisation forming biologically important 2-amino-8-oxo-tetrahydro-4*H*-chromene-3-carbonitriles **68**. The enantiocontrolled version of this reaction has been investigated in the presence of the *Cinchona* alkaloid-derived thioureas, C-9-tosylamino quinidine, cupreine and cupreidine.[48] In this study, the C-9-thiourea-*Cinchona* alkaloid derivatives were observed as the most efficient catalysts as they afforded the highest yields and enantioselectivity. In particular, the C-9-thiourea catalyst **47c** was found to be the most effective catalyst affording a yield of 64% with a moderate ee of 63% in the reaction of **66** with benzylidenemalonitrile **67a** (Scheme 27). More recently, The Michael reaction of cyclohexane-1,2-dione **66** and (*E*)-2-nitroolefin **12** has been reported to form bicyclo[3.2.1]octan-1-ones in the presence of a quinine-derived thiourea as the catalyst. Although four stereogenic centres were created during the reaction, only two diastereomers were obtained in good diastereoselectivity and high enantioselectivity (92–99%).[49]

4.1.4. C-9 Amino Cinchona alkaloids. Primary amine catalysts have been demonstrated to be excellent for asymmetric reactions of carbonyl compounds through enamine or iminium ion catalysis.[50,51] Several such catalysts derived specifically from natural *Cinchona* alkaloids have been developed.[52]

Michael additions of aldehydes and ketones to nitroolefins have been studied using a number of C-9-amino derivatives **69a**–**g** of dihydroquinine (DHQ) and dihydroquinidine (DHQD) (Fig. 13).[53] 9-*epi*-Amino analogues as well as *N*-benzylated analogues were prepared for comparison. The results showed that 9-*epi*-DHQA **69d** and 9-*epi*-DHQDA **69f** were extremely efficient catalysts for the addition of enolisable carbonyl compounds **70** to nitroolefins **12**, which afforded the (*R*) and (*S*) isomers, respectively, of the adducts **71** with good enantioselectivity (Scheme 28). The *N*-benzylated analogues were found to be totally inactive, while DHQA **69c** with 'natural' stereochemistry at C-9 was only mildly active. This reaction had a wide scope as different types of ketones (cyclic/acyclic), aldehydes (straight chain or α,α-disubstituted) and a wide variety of nitroolefins could be used.

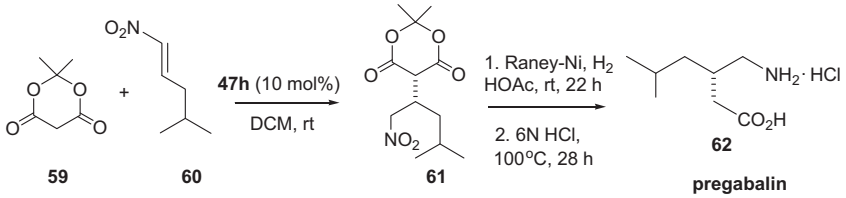
Zhong and co-workers reported a highly enantioselective Michael addition of 1,3-diaryl-1,3-propanediones such as **72** to nitroolefins **12** promoted by 9-*epi*-QA 69b.[54] The multifunctional adducts **73** were obtained in high yields (81–97%) and excellent enantioselectivities (90 to >99% ee) (Scheme 29). The Michael reaction of nitroolefins with dimethyl malonate has been reported to occur with an enantioselectivity of 99% in the presence of a chiral 2-aminobenzimidazole catalyst, prepared by the coupling of 5,7-bis (trifluoromethyl)-2-chlorobenzimidazole with C(9*S*)-aminodihydroquinine or C(9*R*)-aminodihydroquinidine.[55]

A highly enantioselective vinylogous Michael addition of α,α-dicyanoalkenes **74** to α,β-unsaturated ketones **75** promoted by 9-*epi*-QA **69b** has been reported by Xie and co-workers (Scheme 30a).[56] High ee values and excellent diastereoselectivity were observed for the products **76** in all the reactions. An efficient enantioselective



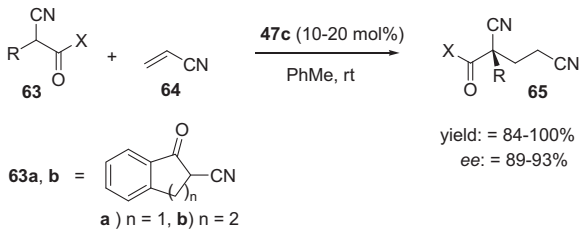
12: R= Ph, 4-Cl-Ph, 4-MeO-Ph, 2-thienyl, 2-NO_2-Ph, *n*-Pentyl, cyclohexyl, 2,4-Cl_2-Ph, 4-NO_2-Ph, 2-CF_3-Ph, 4-OH-Ph

Scheme 24.



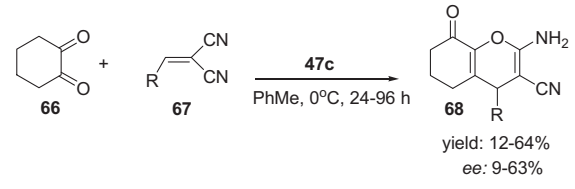
Yield: 84% (1st batch), 82% (2nd batch)
ee: 75% (both batches)

Scheme 25.



63c-f: R = **c**) Ph, **d**) 4-F-Ph, **e**) 4-Br-Ph, f) 4-Cl-Ph

Scheme 26.



67a- i: R = **a**) Ph, **b**) 4-Cl-Ph, **c**) 4-Br-Ph, **d**) 4-CN-Ph, **e**) 4-NO_2-Ph, **f**) 3-Br-Ph, **g**) 4-Me-Ph, **h**) 2-thienyl, **i**) *n*-hexyl

Scheme 27.

Michael addition of cyclic 1,3-dicarbonyls **77** to α,β-unsaturated ketones **75** catalysed by **69b** was also reported by the same research group (Scheme 30b).[57] These versatile Michael addition reactions led directly to the formation of medicinally useful adducts **78** (89–99% ee) including (*S*)-warfarin (96% ee), a chiral anticoagulant drug.

More recently, Kim and Moon have reported the Michael addition of α-nitroacetates such as **79** to aromatic α,β-unsaturated ketones **80** under aqueous-phase reaction conditions at room temperature.[58] The 9-*epi*-amino *Cinchona* alkaloid derivatives, e.g., **69b**, effectively promoted the addition to form the corresponding adducts **81** in high yields and high enantioselectivities (Scheme 31). Benzoic acid (40 mol %) was used as additive in water.

An enantioselective conjugate addition reaction of fluorobis (phenylsulfonyl)methane (FBSM) **82** to α,β-unsaturated ketones **33a**,**b** and **80** catalysed by 9-*epi*-QA **69b** afforded synthetically useful chiral monofluoromethylated ketones **83** with high enantioselectivities and yields under mild reaction conditions (Scheme 32).[59]

A highly enantioselective alkynylation, alkenylation and carbonylation using the conjugate addition of β-keto-heterocyclic sulfones **84** to cyclic α,β-unsaturated ketones **85**, catalysed by the 9-*epi*-amino *Cinchona* alkaloid salt **69g**, has been reported by Jørgensen and co-workers. The reaction yielded the privileged Michael adducts **86**, which could be readily transformed into the corresponding *trans*-3-alkenyl cycloalkanols **87**, β-alkynylketones **88** and 1,5-diketones **89** (Scheme 33).[60]

4.1.5. Cinchona alkaloid phase-transfer catalysts. *Cinchona* alkaloids have been extensively exploited in the development of phase-transfer catalysts (PTCs) as they are relatively inexpensive, easily quaternised and tunable. As a result, *Cinchona* alkaloid-derived PTCs **90a**–**l** are currently in the fourth generation of development (Figs. 14 and 15).[61] A representative mechanism of phase-transfer catalysis by *Cinchona* alkaloid quaternary salts, as suggested by Jew and Park, is shown in Fig. 16.[61] A number of reusable polymer-supported versions of the PTCs **90m**–**o** that are classified by point of attachment to the polymer have also been developed (Fig. 15). It is interesting to note that the first-, second- and third-generation PTCs were developed based on steric factors contributed by the substituents, while the fourth-generation catalysts were developed by screening for the electronic effects of *N*1-substituents with hydrogen-bonding potential such as fluoro, *N*-oxo, and cyano moieties.

A highly enantioselective tandem conjugate addition–elimination synthesis of 4-alkylidenylglutamic acid derivatives **93** using PTC **90e** has been reported (Scheme 34).[62] The reaction of

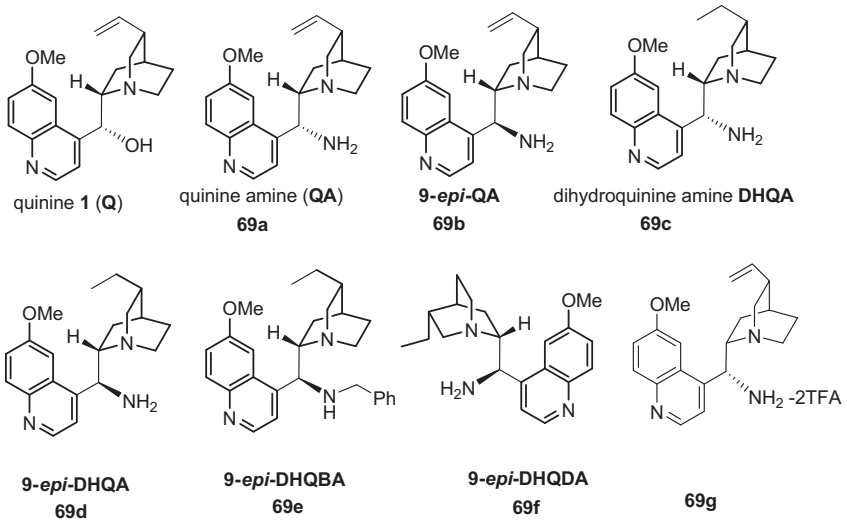
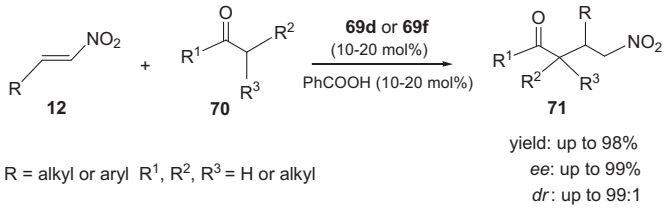
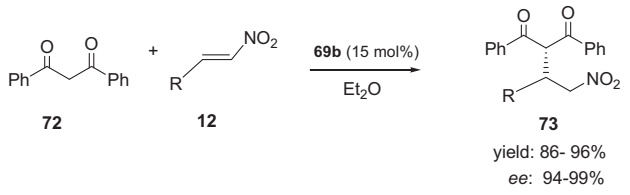


Fig. 13. C-9 Primary amine derivatives of *Cinchona* alkaloids.



Scheme 28.



Scheme 29.

N-(diphenylmethylene)glycine *tert*-butyl ester **91** with the esters **92** afforded the products **93** in yields ranging from 63 to 92% and enantioselectivities ranging from 80 to 92%. It is worth mentioning that glutamic acid is the main excitatory amino acid in the central nervous system.

Nájera and co-workers[63] reported enantioselective Michael addition reactions of the *tert*-butyl ester **91** to electron-poor olefins by utilising dimeric cinchonidinium and cinchoninium-derived ammonium salts such as **90h** as chiral PTCs. The enantioselectivity of the reaction was dependent on the counter-anion present in the quaternary ammonium salt. The best result was obtained for the reaction of **91** with cyclohexenone **33b**, which produced the adduct **94** with a high enantioselectivity of 97% in the presence of the PF_6 salt of **90h** (Scheme 35). The catalyst **90h** and its pseudoenantiomers have also been used in the Michael reaction of cyclic β-ketoesters, such as 2-alkoxycarbonyl-1-indanones and electron-deficient olefins with up to 94% ee.[64] In this case, the dimeric quinine-derived ammonium salt gave a higher enantioselection than its 6′-demethoxylated analogue from cinchonidine, whereas the dimeric quinidine-derived ammonium salt gave a better and opposite enantioselection than its pseudoenantiomer from quinine.

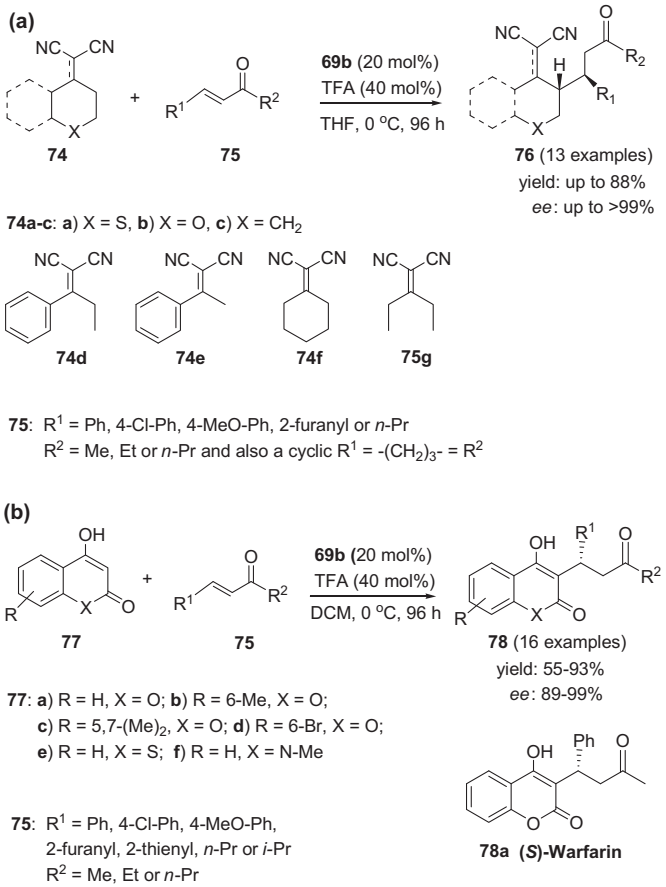
Chinchonine-based PTCs were developed for the addition of electron-deficient alkenes such as methyl acrylate **95** to arylketone glycolates **96**.[65] In the presence of PTC **90f**, the reactions yielded 1,5-dicarbonyl-2-hydroxy-substituted products **97** in good yields and enantioselectivities (Scheme 36).

The use of a co-catalyst could greatly enhance the effectiveness of KOH-mediated asymmetric PTC Michael additions involving glycine imine **91**.[66] Using 2,4,6-trimethylphenol as a co-catalyst together with PTC **90d** in addition reactions of a range of different Michael acceptors such as **64**, **95** and **98** to imine **91**, a very high enantioselectivity was observed in the formation of the products **99** (Scheme 37).

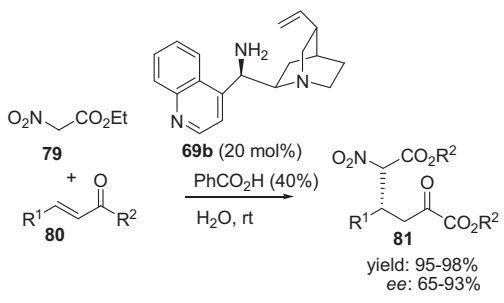
An asymmetric domino Michael addition and lactonisation between various α,β-unsaturated ketones **75** and ketene silyl acetals **100** has been reported.[67] The 3,4-dihydropyran-2-one adducts **102** were formed in good yields and enantioselectivity (Scheme 38) in the presence of quaternary ammonium phenoxides **101**, synthesized from commercially available *Cinchona* alkaloids. Among various chiral quaternary ammonium phenoxides, a cinchonidine-derived catalyst bearing both a sterically hindered *N*1-9-anthracenylmethyl group and a strongly electron-withdrawing 9-*O*-3,5-bis(trifluoromethyl)benzyl group were found to be highly effective.

4.1.6. Dimeric Cinchona alkaloid catalysts. Many dimeric *Cinchona* alkaloid catalysts **103a**–**c** with different spacers have been designed (Fig. 17) and evaluated for a number of applications. A direct vinylogous Michael addition that utilises electron-deficient malononitriles such as **104** as the nucleophilic Michael donor in addition reactions to nitroolefins **12** displayed exclusive γ-selectivity and high diastereo- and enantioselectivity, giving multifunctional products **105** with two adjacent chiral centres (Scheme 39).[68] Natural quinine and quinidine were tested as catalysts together with three commercially available modified *Cinchona* alkaloid catalysts, $(DHQD)_2AQN$ **103a**, $(DHQD)_2PHAL$ **103b** and $(DHQD)_2PYR$ **103c**, of which **103c** was found to be the most efficient catalyst for the transformation. A similar observation regarding **103c** was reported by Jørgensen and co-workers.[69] These reactions had afforded poor yields and moderate enantioselectivities in the presence of *Cinchona* alkaloid-derived thioureas.[42] The catalyst $(DHQD)_2AQN$ **103a** was observed as the most efficient catalyst in the addition of malononitriles to Morita–Baylis–Hillman carbonates.[70]

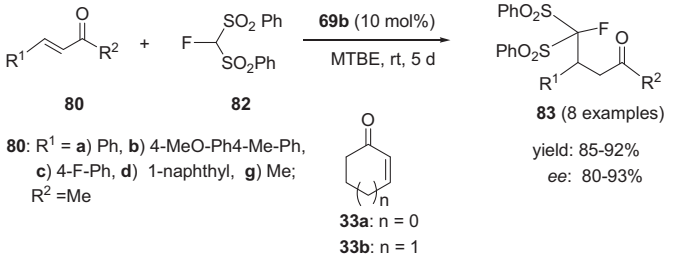
4.1.7. Silyl-substituted Cinchona alkaloids. The deconjugative Michael addition involving an allylic C–C bond-forming addition of



Scheme 30.



Scheme 31.



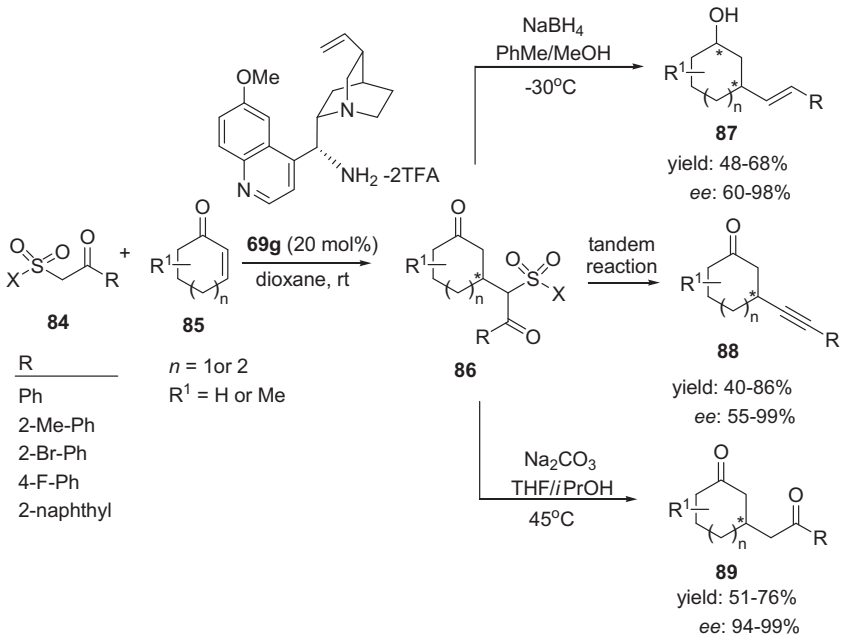
Scheme 32.

activated alkylidenes **106** to acrolein **35a** displayed unusual α-selectivity to form the Michael adducts **110**, which were easily transformed into the desired products **109**–**111**.[71] The most effective catalysts for the reaction were silyl-substituted dihydrocinchonines **107a** or **107b** giving yields of 40–63% with ees of 40–56% (Scheme 40). Although the enantioselectivities of the reactions were only moderate, the products **109**–**111** have proved to be difficult to access by other methods.[71]

An enantioselective synthesis of α,α-disubstituted cyanosulfones has been developed by Ruano and co-workers.[72] The research group synthesised pure cyano *tert*-alkyl sulfones **114** by Michael addition of α-substituted cyanosulfones **112** to vinyl ketones **31** or **113** and to cycloalkenones **33** or **85** using **107b** as catalyst (Scheme 41). The reactions were applicable to a variety of α,β-unsaturated ketones, affording α,α-disubstituted cyanosulfones in excellent yields with ees up to 90%. Sulfones are important structural moieties in medicinal chemistry as they form part of the structure of several internationally recognised drugs.

4.2. Mannich reactions

The Mannich reaction is a fundamentally important carbon–carbon bond-forming reaction in organic synthesis and is highly exploited by synthetic chemists for the construction of pharmaceutically and agriculturally important optically active nitrogen-containing compounds such as amino acids, amino alcohols, amino carbonyls and their derivatives. It involves the reaction between an enolisable substrate and an imine leading to the formation of highly functionalised amine-containing molecules. The prevalence of nitrogen synthons in drugs and natural products has fuelled



Scheme 33.

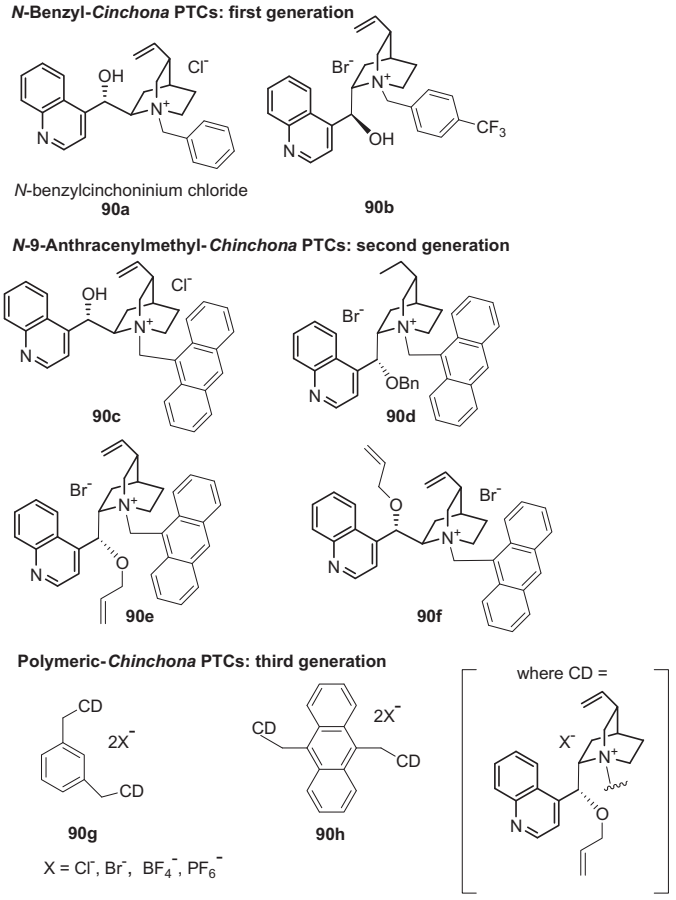


Fig. 14. Representative first-, second- and third-generation *Cinchona* alkaloid-derived PTCs.

extensive research in the development of catalytic asymmetric Mannich reactions in recent years.

An asymmetric direct Mannich addition of β-ketoesters **115** to *N*-acyl aryl imines **116** catalysed by the natural *Cinchona* alkaloids, quinine **Q**, quinidine **QD**, cinchonine **CN** and cinchonidine **CD**, has been studied.[73] Lou and co-workers found the **CN** and **CD** pair to be more efficient in providing the desired product with 80–94% ee as opposed to 45–60% for the quinine pair (Scheme 42). The products **117** were employed to synthesise enantioenriched dihydropyrimidones **118** and β-amino alcohols **119**.

The asymmetric Mannich reaction of malonates **19** with *N*-Boc aryl or alkyl imines **120** catalysed by a thiourea-substituted *Cinchona* alkaloid catalyst **47a** led to almost quantitative yields of the products **121** (Scheme 43).[74] High ee values of up to 99% were also observed. The Mannich products **121** could be readily transformed into *N*-Boc-protected β-amino acids **122**. A similar reaction of dimethyl malonate with methyl arylidenecarbamates, in the presence of a hydroquinine-derived thiourea, is reported to form almost quantitative yields of the products with 86–94% enantioselectivity.[75] Chen and co-workers have reported the highly enantioselective vinylogous Mannich reaction of α,α-dicyanoolefins with *N*-Boc aryl aldimines catalysed by *Cinchona* alkaloid-derived thioureas.[76]

Very recently, an asymmetric aza-Mannich reaction of oxazolones **123** with *N*-tosyl aldimines **124** forming oxazolinone adducts **126** was reported (Scheme 44).[77] A series of 14 adducts (up to 97% ee) were synthesised using a *Cinchona*-derived catalyst **125** with a methoxy group at C-6′ and a trimethylsilyloxy group at C-9. The adducts could be transformed into the corresponding protected chiral α-disubstituted α,β-diamino acids by a one-pot hydrolysis.

4.3. Aldol reactions

Aldol structural units are found in many important naturally occurring molecules. The aldol addition is a powerful tool because it unites two relatively simple molecules into a more complex molecule where complexity arises because two new stereogenic centres (on the α- and β-carbon of the aldol adduct) can be created. These aldol products are immensely valuable in the total synthesis of complex polyoxygenated compounds. As an example, the aldol reaction has been used in the synthesis of the blood cholesterol-lowering drug, Lipitor (atorvastatin) (Fig. 18).[78] Developing efficient catalysts for asymmetric aldol reactions is thus a growing area of research focus.

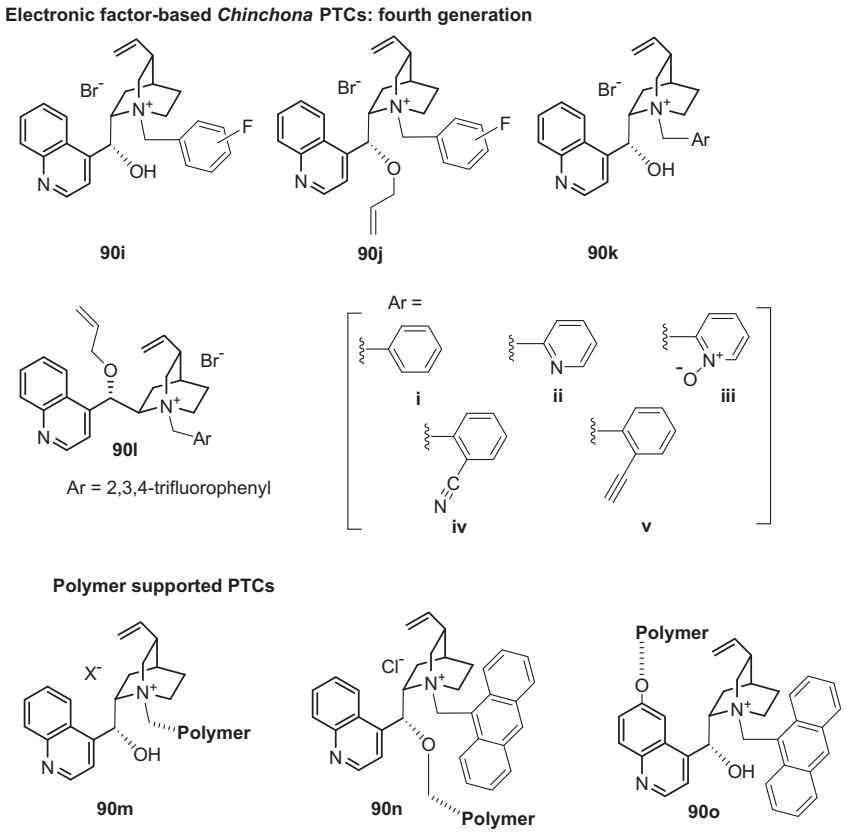
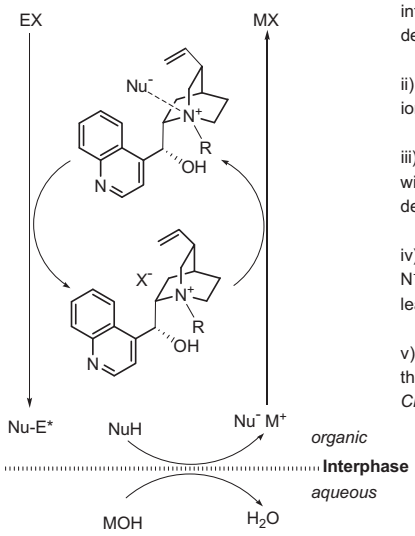


Fig. 15. Representative fourth-generation and polymer-supported *Cinchona* alkaloid-derived PTCs.



i) An anion of the nucleophile such as an active methylene compound, Nu^-, is generated at the interphase of the organic and aqueous phases by deprotonation with an alkali inorganic base.

ii) The quaternary ammonium salt forms a nucleophilic ionic complex, N^+----Nu^-, with Nu^-.

iii) The nucleophilic ionic complex, N^+----Nu^-, then reacts with the electrophile (e.g. an alkyl halide) to form the desired product Nu-E*.

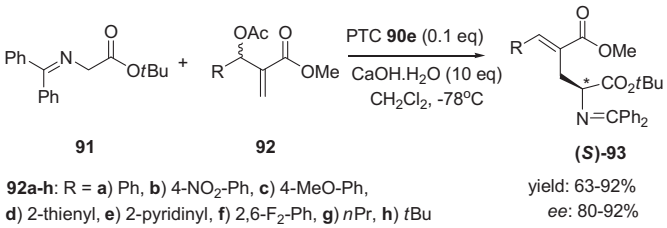
iv) The chiral environment for the reaction is set in the N^+----Nu^- stage where the electrophile approaches the least sterically hindered face.

v) The nature of the chiral space can be tuned by varying the R substituents and or the substitution pattern of the *Cinchona* alkaloid quaternary ammonium salt.

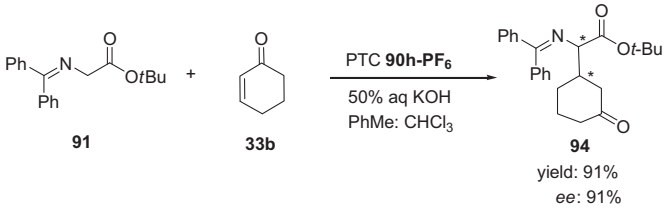
Fig. 16. Interphase mechanism in the presence of a cinchonidine-derived quaternary ammonium salt.[61]

A number of cinchonidine-based phase-transfer catalysts **127** have been designed and their efficiency investigated for the preparation of β-hydroxy α-amino acids through asymmetric aldol reactions (Scheme 45).[79] The designs of the catalysts were based on C-3 modifications to PTC **90l** (Fig. 15; this catalyst was originally designed by Park and Jew in 2002[80]). The Castle research group observed[79] that the performance of catalysts **127a**, **127b** and **127c** showed an improvement on that of the Park–Jew catalyst in terms of yield (**127a**), *syn*/*anti* ratio (**127b**) and ee (**127c**), although no single catalyst worked well in all three areas. The catalysts and reaction investigated are shown in Scheme 45 for the addition of aldehyde **128** to *tert*-butyl 2-(diphenylmethyleneamino)acetate **91**, forming the product **129**. This study, which focused mainly on the performance of the catalysts, could prove to be useful to other researchers interested in modifications of, and improvements in this class of *Cinchona* alkaloid catalysts.

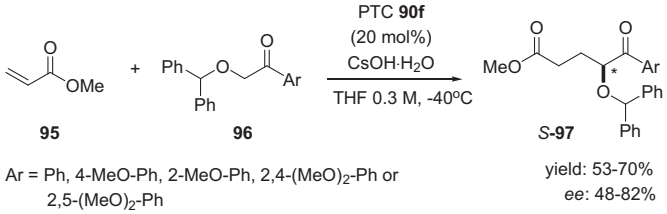
A rational combination of two privileged structures, a *Cinchona* alkaloid and proline, into a single molecule led to the design of



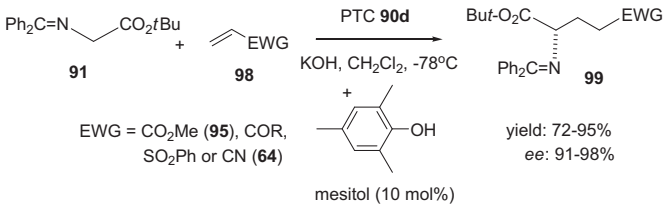
Scheme 34.



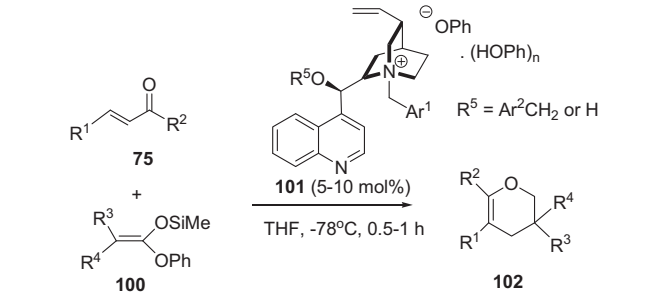
Scheme 35.



Scheme 36.



Scheme 37.



Scheme 38.

a new class of catalysts such as **132a**–**c** (Fig. 19).[81] These catalysts showed excellent enantioselectivities (up to 98% ee) in direct aldol reactions between aldehydes **130** and the ketones **131** (Schemes 46 and 47). The products **133**–**135** were formed with yields of up to 89% and the formation of both enantiomers was achieved through the selection of either **132a** or **132b**, which are pseudoenantiomers.

The reaction of hydroxyacetone **136** with a variety of aromatic and alkyl aldehydes **130**, occurring in the presence of 5–10 mol % of quinine, quinidine, chinchonine and cinchonidine, was studied. Using quinidine as catalyst, the direct aldol products **137** were obtained in reasonable yields with asymmetric induction up to 47% (Scheme 48).[82] The maximum yield of 96% was obtained in the reaction of 2-chlorobenzaldehyde, whereas the minimum yield of 11% was obtained in the reaction of 3-phenylpropanal. The enantioselectivity pattern was opposite; in the case of 3-phenylpropanal it was 40%, but, for 2-chlorobenzaldehyde, it was only 23%. The maximum enantioselectivity of 44% was observed with cinnamaldehyde, affording 22% of the diol.

An asymmetric direct aldol condensation of oxindoles **138** with ethyl 3,3,3-trifluoropyruvate **139**, promoted by the commercially available catalyst **105b** $(DHQD)_2PHAL$ or its pseudoenantiomer $(DHQ)_2PHAL$, led to the formation of oxindoles **140** with two contiguous asymmetric quaternary carbon atoms, including a trifluoromethyl alcohol centre (Scheme 49).[83] Natural products containing oxindole moieties with a quaternary stereogenic centre have shown unique biological activities.[84]

4.4. Henry and aza-Henry reactions

The Henry reaction, also known as the nitroaldol reaction, involves the reaction between an enolisable nitroalkane and a carbonyl compound. It is yet another important synthetic tool for the creation of carbon–carbon bonds and up to two contiguous stereogenic centres. The nitro alcohol products of the reaction can be transformed into a number of nitrogen- and oxygen-containing derivatives such as nitroalkenes, amino alcohols and amino acids. In the past two decades, during which many asymmetric metal catalysts have been developed for the Henry reaction, the number of organocatalysts is considerably less and, hence, there is currently a growing focus of research in this area. Among the organocatalysts that have demonstrated high efficiency in the nitroaldol reaction, some common requirements or features for good performance appear to be the presence of: (i) a basic unit, (ii) a unit capable of binding the nitro (or nitronate) group either through hydrogen bonding or through purely electrostatic interactions, and (iii) a unit capable of forming a hydrogen bond with the acceptor carbonyl.[85]

An amine–thiourea **141**, derived from *Cinchona* alkaloids, has been reported as an efficient catalyst for nitroaldol reactions of a series of aromatic aldehydes **130** with nitromethane providing very high yields and ee values in the range of 85–92% for the products **142** (Scheme 50).[86] The maximum yield of 99% and ee of 92% was obtained in the reaction of 1-naphthaldehyde. 4-Fluorobenazaldehyde also reacted to give 99% of adduct, but the ee was minimum, i.e., 85% in this case. Benzaldehyde afforded the minimum yield of 90% but ee of 92%. The proposed reaction model **143** of the transition state involves hydrogen bonding between the thiourea moiety and the acceptor carbonyl, together with ion pairing between the protonated quinuclidine and the nitronate group (Scheme 50).

A number of cupreidine (CPD) derivatives **18a**–**d** have been prepared and evaluated for their efficiency in nitroaldol reactions between α-ketoesters **144** and nitromethane to form **145**.[87] Outstanding performances were demonstrated for a series of ethyl ketoesters bearing aromatic, aliphatic, or functionalised alkyl side chains (Scheme 51). In the proposed reaction mechanism, the catalyst plays a bifunctional role by utilising the quinuclidine nitrogen and C6′–OH to form hydrogen bonds with the acceptor and the donor, respectively.

The aza-Henry reaction, an extension of the Henry reaction, involves the addition of nitroalkanes to imines (in place of carbonyls), leading to the formation of β-nitroamine derivatives, which can be readily converted into biologically important 1,2-diamines by reduction of the nitro group. A highly enantioselective aza-Henry

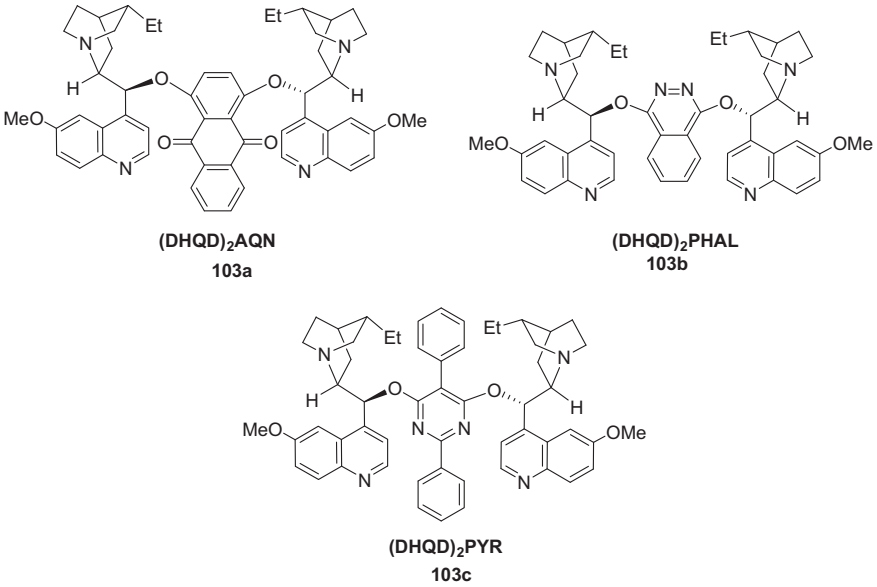
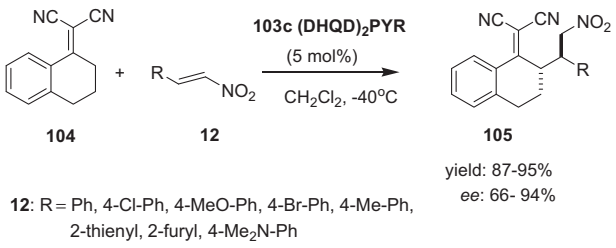


Fig. 17. Dimeric *Cinchona* alkaloid catalysts.

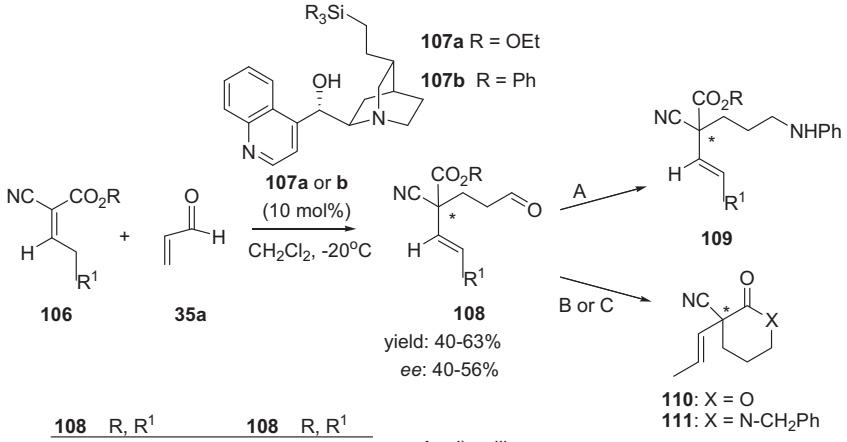


Scheme 39.

reaction using nitromethane and a range of differently protected aryl and heteroaryl imines **146** has been investigated.[88] After a careful screening of a series of natural and modified *Cinchona* alkaloids, the best enantioselectivity (up to 94% ee) was obtained using the thiourea-substituted catalyst **47g**. *N*-Boc- and *N*-Cbz-protected imines gave the highest yields and enantioselectivities of the β-nitroamine products **147** (Scheme 52). A similar reaction of nitromethane and nitroethane with methyl arylidenecarbamates in the presence of a hydroquinine-derived thiourea catalyst is reported to form almost quantitative yields of products with 90–98% enantioselectivity.[75] Only the imine from furan-2-carbaldehyde gave a comparatively lower yield (60% with nitromethane and 73% with nitroethane).

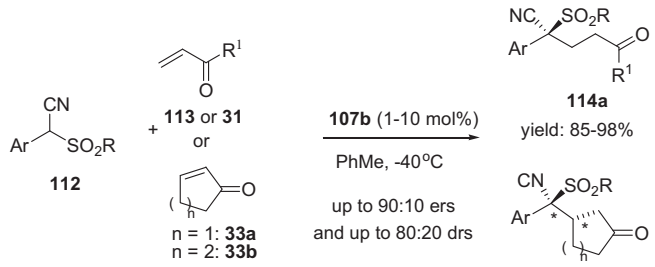
4.5. Fluoromethylation and cyanoformylation of aldehydes

A trifluoromethylation reaction of 2-naphthaldehyde **148** with Me_3SiCF_3 occurring in the presence of commercially available cinchonium bromides, has been investigated.[89] The products were obtained in 34–90% yields, but a maximum ee of 40% was obtained. The catalyst **149** afforded the product **150** in 40% ee, but the yield obtained was only 54% (Scheme 53). Application of cinchonium chloride instead of the bromide afforded the product in 90% yield



108	R, R^1	108	R, R^1
a.	Me, Me	**f**.	Me, *t*-Bu
b.	Me, *n*-Hex	**g**.	Me, Bn
c.	Me, allyl	**h**.	*i*-Pr, Me
d.	Me, $(CH_2)_3OTBS$	**i**.	Bn, Et
e.	Me, *i*-Pr	**j**.	*t*-Bu, Et

Scheme 40.

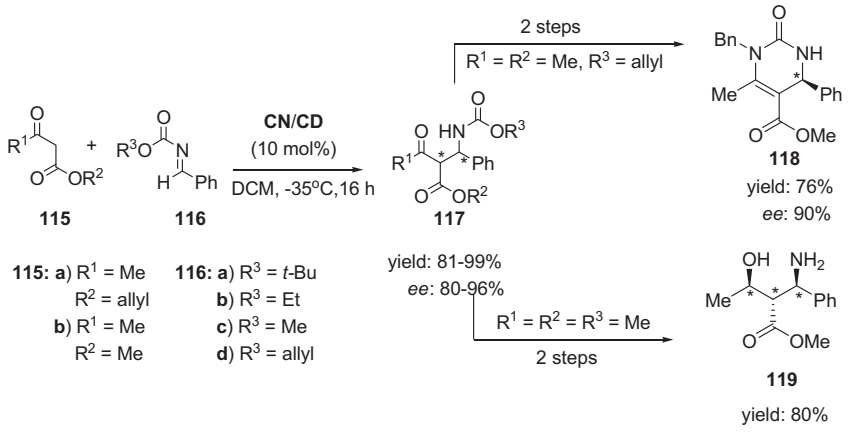


Scheme 41.

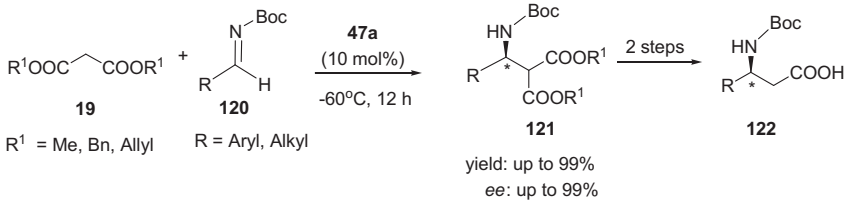
and the ee was almost the same as that for the bromide (36%). The reaction was complete in only 3.5 h.

The first enantioselective difluoromethylation of aromatic aldehydes **130** using $PhSO_2CF_2H$ or $Me_3SiCF_2SO_2Ph$ in the presence of a chiral quaternary ammonium salt **151** as the catalyst and potassium hydroxide as the base was reported to form the products **152** (Scheme 54).[90] The enantioselectivity was substrate dependent and the highest ee of 64% was obtained for 2-chlorobenazaldehyde.

The asymmetric cyanoformylation of various aldehydes **130** with alkyl cyanoformates catalysed by dimeric cinchonidine ammonium salts **154**, has been investigated by Chinchilla and co-workers (Scheme 55).[91] After optimising the reaction with benzaldehyde, methyl cyanoformate **153** was chosen as the best cyanoformylating reagent and the salt **154a** as the most efficient catalyst. In most cases the products **155** were obtained in quantitative yields and up to 88% ee. Only cyclohexanecarbaldehyde and (*E*)-2-octenal gave 86 and 88% yields, respectively. The higher enantioselectivity was observed



Scheme 42.

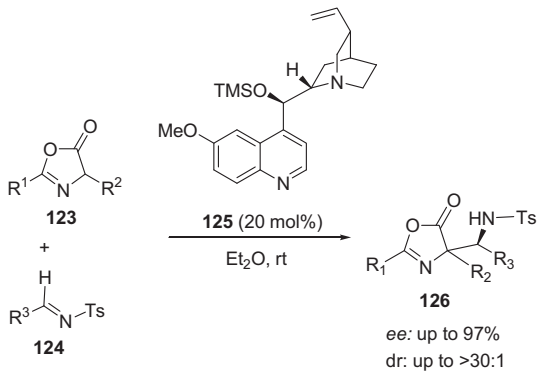


Scheme 43.

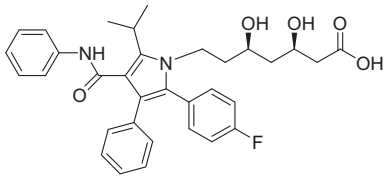
with aldehydes having electron-donating groups, such as methyl and methoxy, in comparison to those with electron-withdrawing groups on the benzene ring. A heteroaromatic aldehyde with basic character, nicotinaldehyde, gave a racemic mixture. The reaction was also extended to diverse types of aromatic, heterocyclic and aliphatic aldehydes. The enantioselectivity was moderate with aliphatic aldehydes (36–60%). However, the sense of stereoinduction observed was always the same.[92]

4.6. Friedel–Craft-type reactions

The frequent appearance of indole structural motifs in biologically and medicinally important natural products has promoted considerable research effort into efficient methods for their asymmetric synthesis. The electron-rich nature of the indole ring makes it a good substrate for Friedel–Craft-type reactions with prochiral electrophiles to generate enantiomerically enriched



Scheme 44.

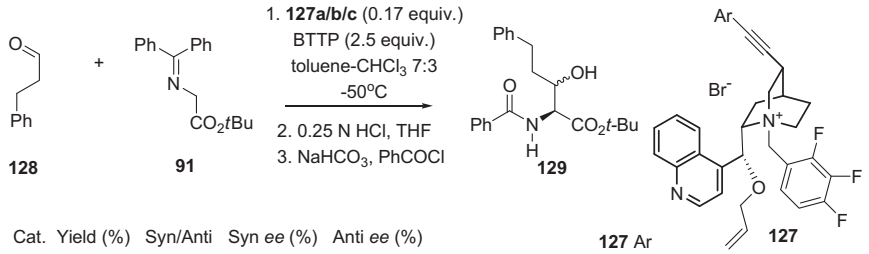


Lipitor (atorvastatin)

Fig. 18. Structure of Lipitor (blood cholesterol-lowering drug) with aldol structural unit.

applicable to a wide variety of indoles and a substantial range of α-ketoesters and aldehydes, producing the corresponding Friedel–Craft adducts **162** and **163** in high yields and enantioselectivities (Scheme 57). The reactions of indoles with non-chelating α,β-unsaturated alkyl ketones, catalysed by 30 mol % C-9 chiral primary amines derived from natural cinchonine, occurred smoothly at 0–20 °C, offering moderate-to-good enantioselectivity (47–89%).[95]

The Friedel–Craft alkylation of simple phenols such as **164** with trifluoropyruvate **165** was accomplished by using *Cinchona* alkaloid



Cat.	Yield (%)	Syn/Anti	Syn *ee* (%)	Anti *ee* (%)
127a	86	1.2:1	82	39
127b	54	2.6:1	82	36
127c	50	1:1.8	91	44

127 Ar
a. 4-F_3CPh
b. 4-FPh
c. 2,4-F_2Ph

Scheme 45.

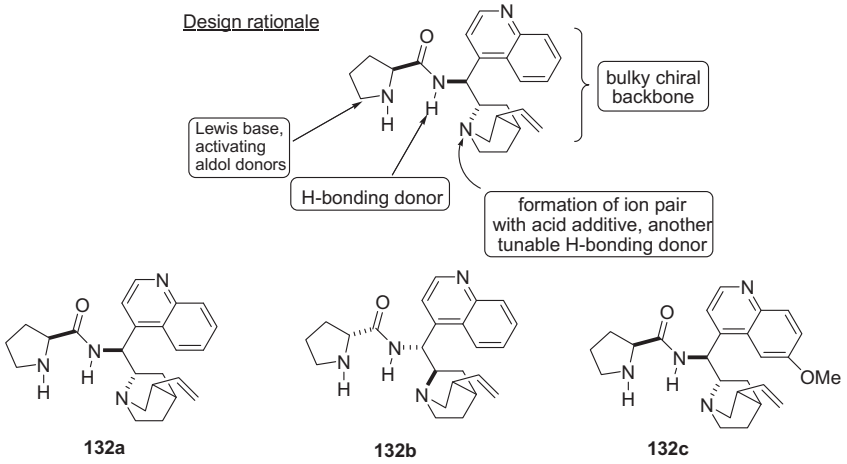
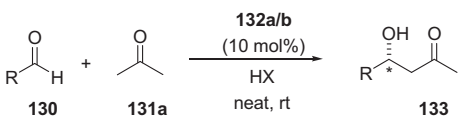
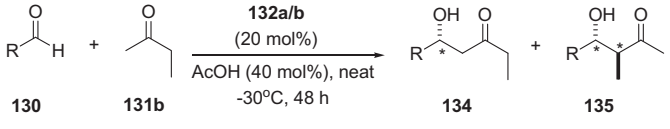


Fig. 19. New catalysts from rational combination of *Cinchona* and proline backbones.



Scheme 46.

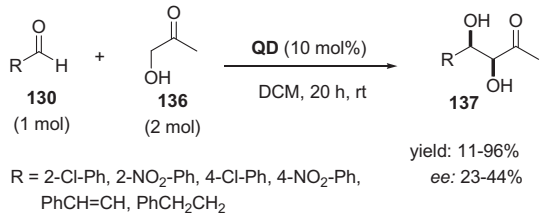


R = 4-NO_2-Ph, Ph, 3-NO_2-Ph, 2-NO_2-Ph, 4-NC-Ph, 4-Br-Ph, 4-Cl-Ph, 2-Cl-Ph, 2,4-Cl_2-Ph, 4-CF_3-Ph, 4-F-Ph, 3,4-F_2-Ph 3-PhO-Ph, 2-furyl, *i*-Pr, 4-NO_2-Ph, 3-NO_2-Ph, 2-NO_2-Ph,

Scheme 47.

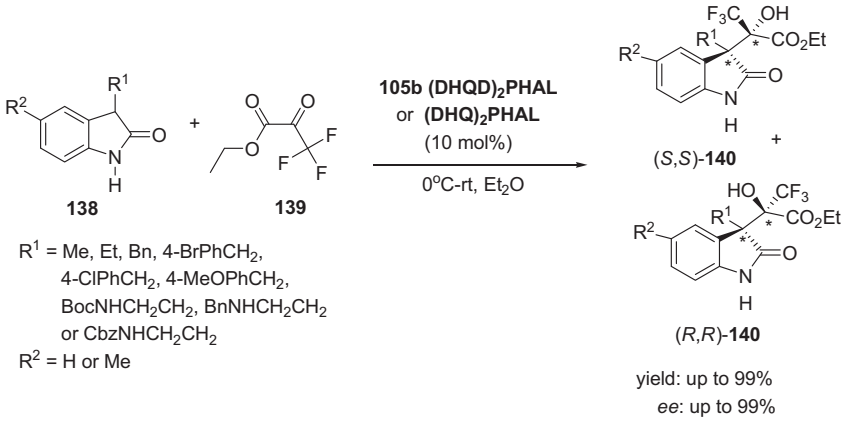
indole derivatives. A highly enantioselective Friedel–Craft reaction of indoles **156** with imines **157** or **158** that was best catalysed by the thiourea-substituted *Cinchona* alkaloids **47a** or **47g**, has been reported recently (Scheme 56).[93] The desired adducts **159** and **160** were formed with high yields (86–98%) and enantioselectivities (86–96%). Subsequently, the Friedel–Craft reaction of indoles **156** with aldehydes **130** or esters **161** was studied.[94] In this case, the thiourea catalysts performed poorly, while C6′–OH *Cinchona* alkaloids were found to be the most efficient. The reaction was

catalysts to yield the products in 71–94% ee.[96] The natural alkaloids such as quinine, quinidine and cinchonidine did not appear very promising, because they offered only moderate enantioselectivity (36–44% ee). If both C-6′–OH and C-9–OH were blocked by methyl and benzyl groups, respectively, a lower catalytic performance was observed. Introduction of thiourea at C-9 was also unsuccessful. With a bulky phenanthrene group at C-9 (as in **166**) the

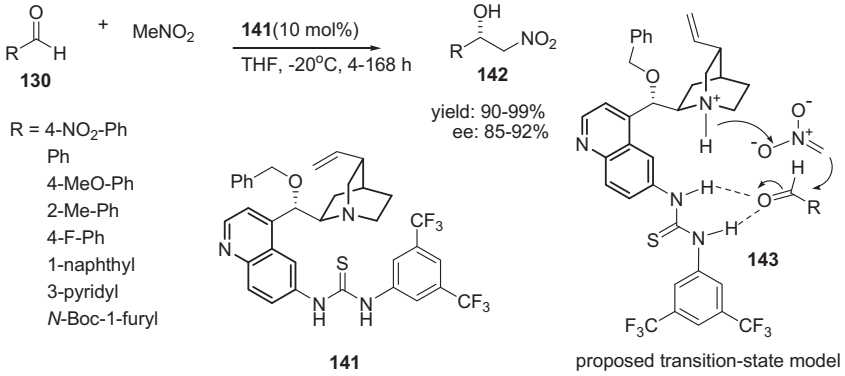


Scheme 48.

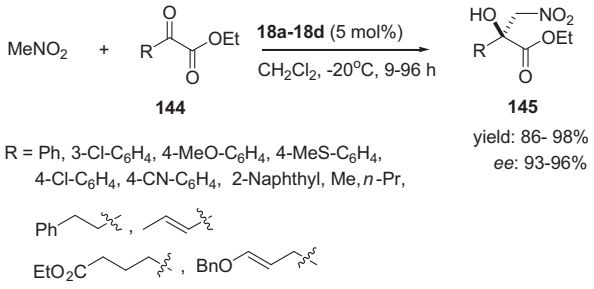
substituents in order to activate the aromatic ring. A variety of different nucleophiles such as carbon, nitrogen and sulphur can be used. The first organocatalytic S_NAr reactions of β-ketoesters such as **9b** with activated aromatic compounds such as **168**, catalysed by a *Cinchona* alkaloid-derived quaternary ammonium salt, have been reported.[97] The formation of *O*-arylated and *C*-arylated products and also the enantioselectivities in the reaction of ethyl 2-oxocyclopentanecarboxylate **9b** with 2,4-dinitrofluorobenzene **168** have been observed to depend on the substituents on the catalyst.[98] At low temperature, the reaction catalysed by the chloride salt **169**



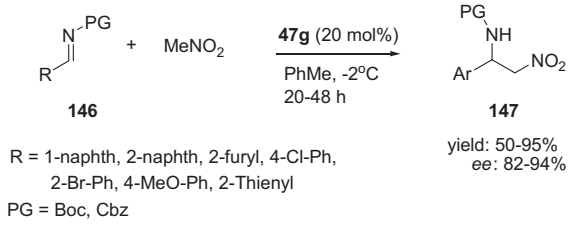
Scheme 49.



Scheme 50.



Scheme 51.



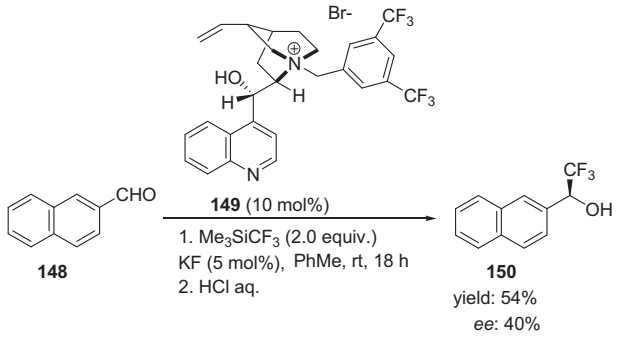
Scheme 52.

enantioselectivity reached 92% in the reaction of 2,6-dimethyl phenol to form **167** (Scheme 58).

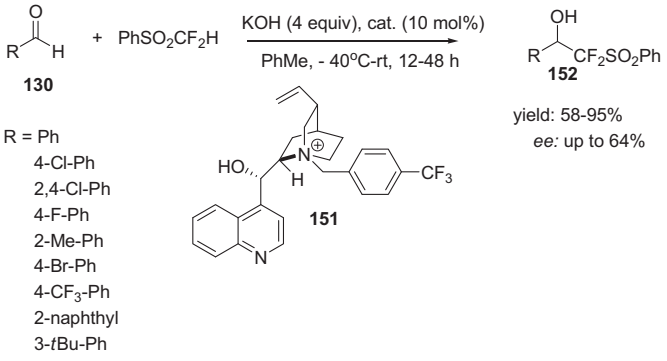
4.7. Nucleophilic aromatic substitution reactions

Nucleophilic aromatic substitution (S_NAr) reactions normally require aromatic compounds having electron-withdrawing

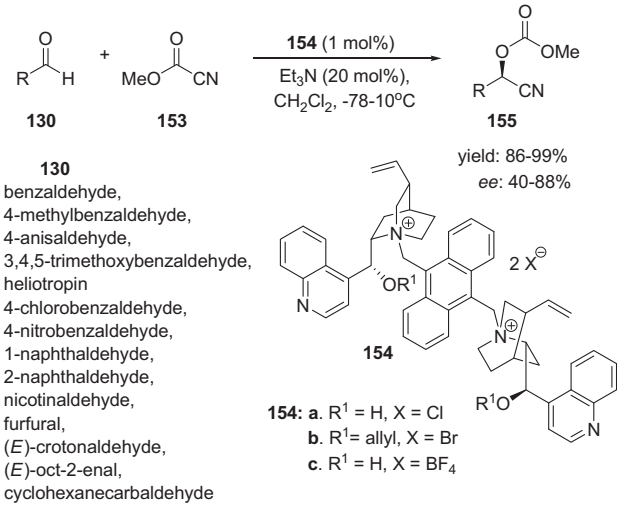
with a benzoyl group on C-9 oxygen and a benzyl group on *N*-1 in toluene yielded the *C*-arylated **171** and *O*-arylated **170** products in a ratio of >50:1 with 87% ee (Scheme 59). In the proposed reaction mechanism, a base removes the acidic proton in the β-ketoester, generating an ambident nucleophile, which interacts with the chiral quaternary ammonium salt, forming a chiral ion pair. Thus,



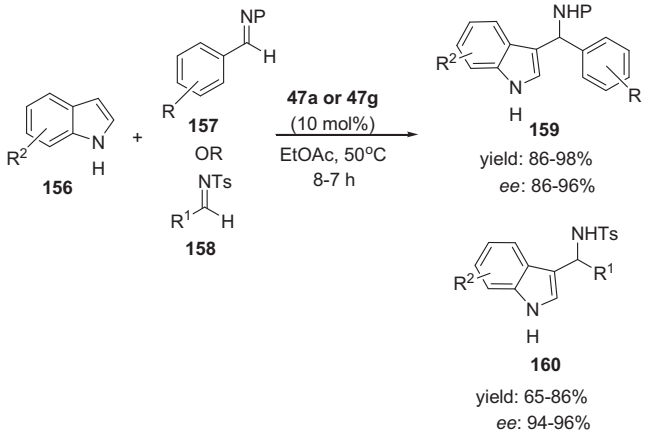
Scheme 53.



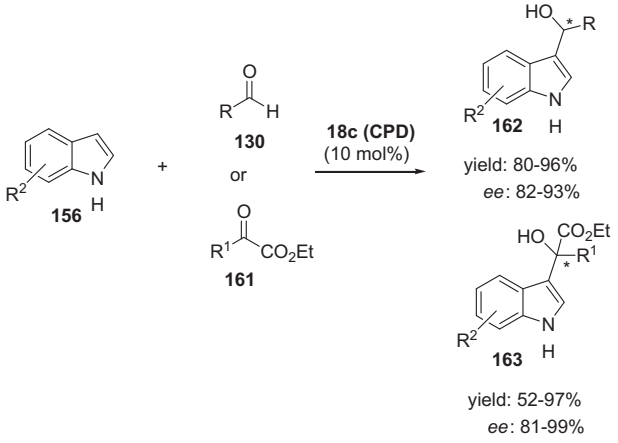
Scheme 54.



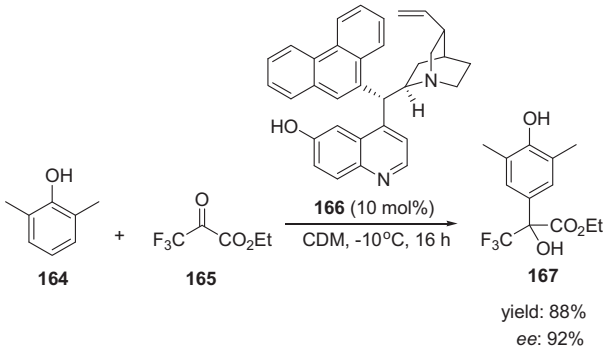
Scheme 55.



Scheme 56.



Scheme 57.

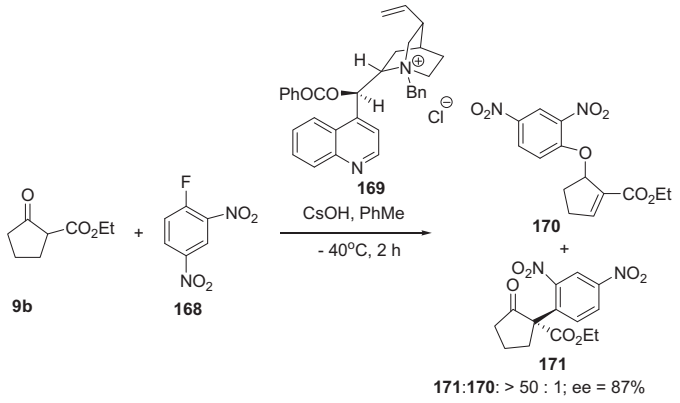


Scheme 58.

the nucleophile is generated in a chiral pocket in which one face is shielded by the chiral *Cinchona* alkaloid salt, leading to an enantioselective nucleophilic approach to the aromatic compound.

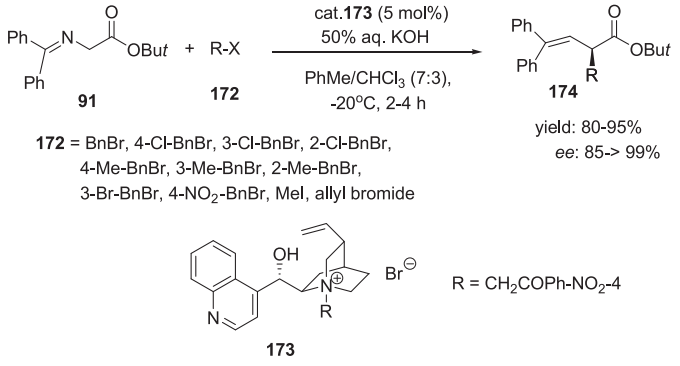
4.8. Alkylation of glycine imine esters

The asymmetric alkylation of benzophenone imines of glycine derivatives, e.g., **91**, with halides **172** has been investigated with the objective of synthesising optically active α-amino acids. Since the first report on the application of chiral phase-transfer catalysts to the asymmetric alkylation of glycine imine esters,[99] many *Cinchona* alkaloid-derived phase-transfer catalysts have been designed and their potential evaluated for this purpose. The enantioselectivity has been observed to depend on the steric bulkiness and electronic factors of the groups at the ammonium ion. A study with acetophenone-based *Cinchona* alkaloid-derived quaternary ammonium salts such as **173** showed that electron-withdrawing groups such as a 4-nitro group on the phenyl ring gave the highest enantioselectivity, whereas electron-donating groups such as 4-methoxy gave the lowest enantioselectivity, in the alkylation of glycine imine *tert*-butyl ester with benzyl bromide.[100] The steric factor had little effect on the enantioselectivity, as the replacement of acetophenone with naphthophenone increased the enantioselectivity only slightly (from 60 to 63%). The temperature also had some effect on



Scheme 59.

the enantioselectivity. In many of the reactions studied, the ee increased from 87 to 90% on decrease of temperature from 0 to −20 °C. Several alkyl bromides were then used to alkylate the imine in the presence of the *Cinchona* alkaloid-derived 4-nitroacetophenone-based phase-transfer catalyst **173** to form the product **174** (Scheme 60). Ramachandran and co-worker have investigated the effect of substituents at the 3- and 4-positions of the *N*-benzyl group in cinchonidium salts on the enantioselectivity of imine alkylation.[101] An enantioselectivity of 94% was achieved with the most efficient catalyst **175** (Scheme 61). A study by Elango and co-workers has shown that optimisation of the bulkiness at the quaternary nitrogen is also important in controlling the enantioselectivity.[102] The *Cinchona* alkaloid PTC may not be a better performer when sterically overcrowded with the quaternising group. Sirit and co-workers used three calixarene-based quaternary ammonium salts of *Cinchona* alkaloids in benzylation of glycine imine ethyl ester to achieve up to 57% enantioselectivity.[103]



Scheme 60.

Nájera and co-workers have used polymer-supported chiral ammonium salts **176** (Fig. 20) derived from cinchonidine and quinine as phase-transfer catalysts in the asymmetric benzylation of glycine imine isopropyl ester **177**.[104] It was observed that the Merrifield-anchored cinchonidine-derived ammonium salt **176a** afforded the product **178** with the highest ee (99%) at 0 °C (Scheme 62), while the use of quinine- or ephedrine-derived ammonium salts gave poor results. In all cases, higher ees were obtained when a hydroxyl group was present in the alkaloid moiety; their *O*-allylated counterparts gave lower enantioselectivities. The effect of several cross-linked polystyrene (PS)- and polyethylene glycol (PEG)-bound *Cinchona* alkaloid ammonium salts on alkylation of glycine imine esters has been investigated by Cahard and co-workers.[105] The polystyrene (1.5 DVB)-bound *O*-9-connected phase-transfer catalysts exhibited high enantioselectivities (up to 96% ee). In fact, both *N*- and *O*-9-connected catalysts appeared much more powerful in

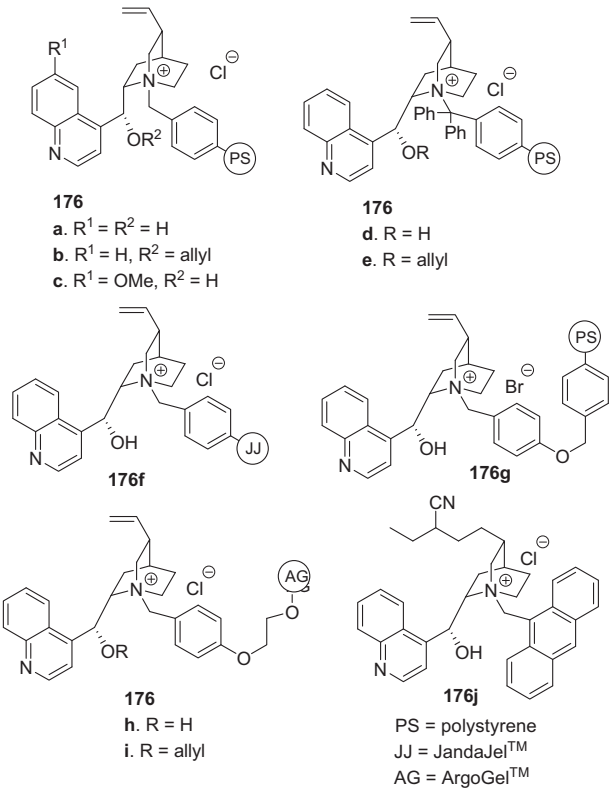
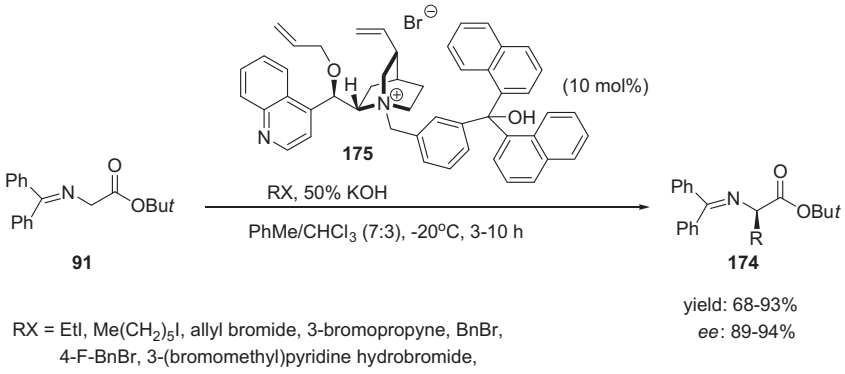
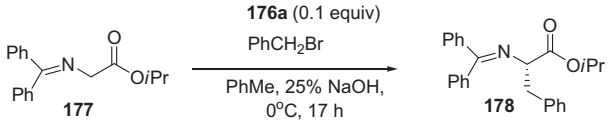


Fig. 20. Some examples of polymer-supported chiral ammonium salts.



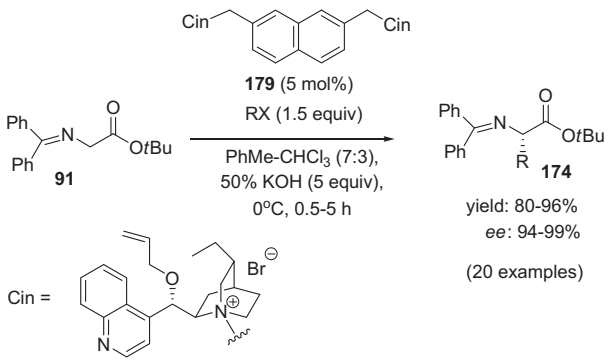
Scheme 61.



Scheme 62.

terms of enantioinduction than their *O*-6′- and *C*-11-connected congeners.

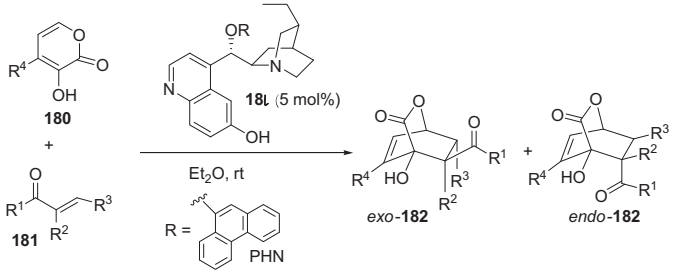
Jeong and co-workers designed a series of dimeric/trimeric chiral quaternary ammonium salts derived from *Cinchona* alkaloids as efficient chiral PTCs for the alkylation of imine esters.[106] From optimisation studies on dimeric salts, they discovered that the 2,7-naphthyl-linked PTCs such as **179** showed excellent catalytic capability on the reactivity and enantioselectivity in the alkylation of glycine imine *tert*-butyl ester **91** to form **174** (Scheme 63).



Scheme 63.

4.9. Diels–Alder reactions

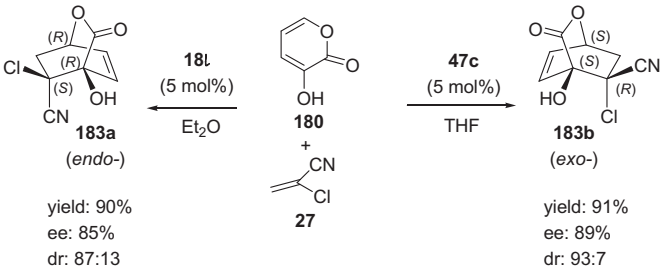
The first reported example of a base-catalysed asymmetric Diels–Alder reaction was the reaction between *N*-methylmaleimide and anthrone in the presence of a catalytic amount of quinidine, carried out by Riant and Kagan in 1989.[107] Recently, Deng and co-workers observed that, in the Diels–Alder reaction of 2-pyrones **180** with α,β-unsaturated carbonyl derivatives **181** (Scheme 64 and Table 2), the C-6′–OH *Cinchona* alkaloid **18l** afforded a much better catalytic efficiency than did natural *Cinchona* alkaloids to form the bicyclic *exo*/*endo* products **182**.[108] The possibility of using bifunctional catalysts to control the *exo*/*endo* selectivity was also investigated by the research group. The Diels–Alder addition between 3-hydroxy-2*H*-pyran-2-one **180** and α-chloroacrylonitrile **27** was carried out in the presence of the quinidine-derived catalysts **18l** or **47c** (Scheme 65).[108] The catalyst **18l** was found to be *endo* selective forming **183a**, whereas the catalyst **47c** afforded preferentially the *exo* adduct **183b**. In addition, by using the quinine-derived pseudoenantiomeric catalysts with the opposite sense of induction, selective pathways to each of



Scheme 64.

Table 2
Diels–Alder cycloadducts **182**

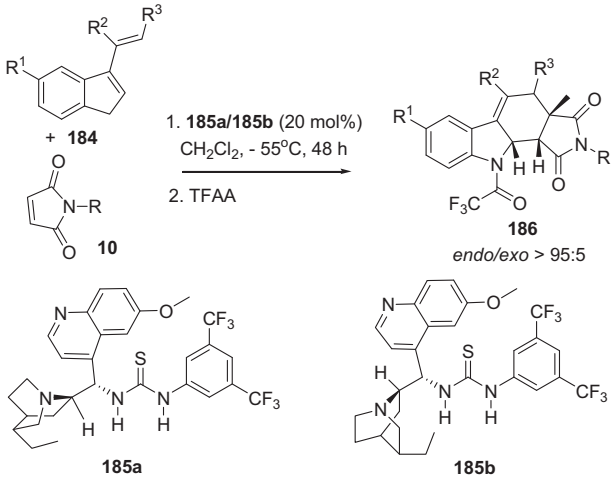
R^1	R^2	R^3	R^4	Yields (%)	*exo*/*endo* Ratio	ee (%)
Ph	H	CO_2Et	H	87	93:7	94
4-Br–Ph	H	CO_2Et	H	91	91:9	91
Ph	H	CO_2Ph	H	100	93:7	90
Me	Me	H	H	65	24:76	91
Ph	H	CO_2Et	Ph	84	95:5	85
Ph	H	CO_2Et	Me	87	88:12	82
Ph	H	CO_2Et	Cl	77	86:14	84
Ph	H	CO_2Et	Br	75	85:15	83



Scheme 65.

the four possible stereoisomers that could be generated from 2-pyrone **180** and α-chloroacrylonitrile **27** were easily accessed. The study was extended to simple α,β-unsaturated methyl ketones with excellent yields and enantioselectivities.[109]

An asymmetric Diels–Alder reaction between 3-vinylindoles **184** and maleimides **10** catalysed by the bifunctional acid–base catalysts such as **185a** or **185b** has been reported as a direct approach to optically active tetrahydrocarbazole derivatives (Scheme 66 and Table 3).[110] The pseudoenantiomeric catalysts **185a** and **185b**, derived from dihydroquinine and dihydroquinidine, respectively, gave access to the enantiomeric pairs of the products **186** with comparable results. The reaction was also investigated with quinines as dienophiles and excellent enantioselectivities (96–99%) were observed. The dual interaction between the basic moiety of the catalyst and the N–H group of the diene, and the thiourea functionality with the dienophile, was suggested as being responsible for the enhancement of the reactivity.



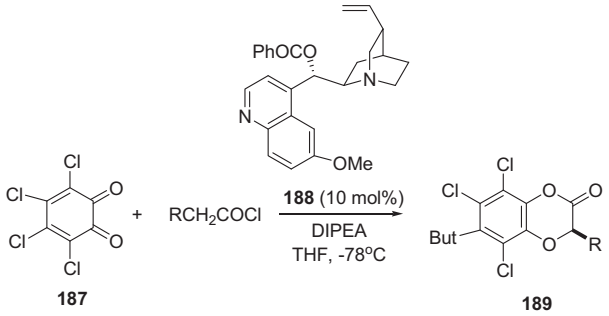
Scheme 66.

The organocatalytic asymmetric Diels–Alder reaction of ketene enolates, generated in situ from the corresponding acyl chlorides and *o*-quinones, has been reported by Lectka and co-worker.[111] Using *o*-chloranil **187** as substrate benzoylquinidine **188** as

Table 3
Yields and ee of Diels–Alder cycloadducts **186**

R^1	R^2	R^3	R	Yield (%)	ee (%)
H	H	H	Ph	91	98
Br	H	H	Ph	86	90
MeO	H	H	Ph	77	96
H	Me	H	Ph	79	96
H	H	Me	Ph	58	92
H	H	H	Me	89	98
H	H	H	Bn	89	96
H	H	H	^{t}Bu	81	88
H	H	H	H	72	52

catalyst, excellent enantioselectivities were achieved for formation of the cycloadducts **189** (Scheme 67 and Table 4). Lower enantioselectivities were achieved with other quinines. The same catalytic system has been applied to the cycloaddition of ketene enolates with *o*-benzoquinone imides[112] and *o*-benzoquinone diimides,[113] affording the corresponding 1,4-benzoxazinones and quinoxalinones, respectively, in excellent enantioselectivities.

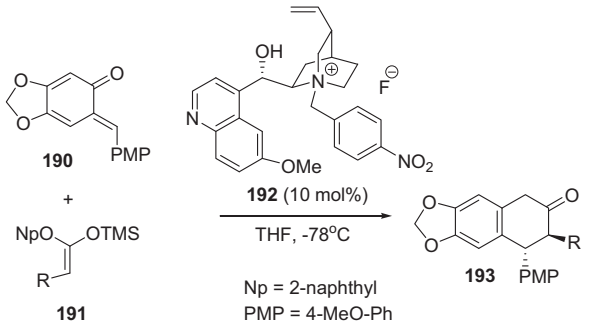


Scheme 67.

Table 4
Yields and ee of Diels–Alder cycloadducts **189**

R	Yields (%)	ee (%)
Et	91	99
i-Pr	75	93
Ph	90	90
Bn	72	99
4-MeO–Ph	58	99
4-Me–Ph	75	93

Leckta and co-workers[114] investigated a formal Diels–Alder reaction between *o*-quinone methides such as **190** and silyl ketene acetals **191** in the presence of a chiral *Cinchona* alkaloid-derived ammonium fluoride precatalyst **192** (Scheme 68 and Table 5). The reaction involved a two-step process, beginning with a Michael-type addition of the ketene acetal (formed in situ by the action of the precatalyst) to the *exo* cyclic double bond. In the next step, an



Scheme 68.

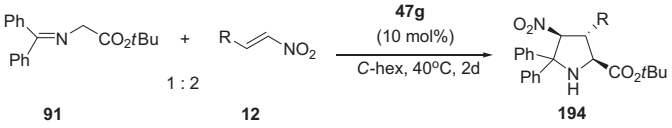
Table 5
Yields, dr and ee of Diels–Alder cycloadducts **193**

R	Yields (%)	dr	ee (%)
Me	85	7.5:1	72
Et	87	15.4:1	80
i-Pr	88	10.2:1	79
i-Bu	91	11.3:1	81
$ClCH_2CH_2$	88	15.2:1	90
$MeSCH_2$	84	9.5:1	85
Bn	86	13.7:1	80

intramolecular nucleophilic attack at the carbonyl forms the final 3,4-dihydrocoumarin derivatives **193**. Thus, the stepwise mechanism resembles that recently demonstrated for polar Diels–Alder reactions.[115]

4.10. 1,3-Dipolar cycloadditions

There are only limited examples of organocatalytic enantioselective 1,3-dipolar cycloadditions.[116] The first 1,3-dipolar cycloaddition reaction of azomethine ylides, generated in situ from the imine **91**, with nitroalkenes **12** has been reported to occur with good enantioselectivity using urea or thiourea catalysts **47** derived from *Cinchona* alkaloids. Generally, the urea derivatives gave better enantioselectivity (50%) but lower yields (57%) of the product. The highly substituted pyrrolidines **194** were obtained with high diastereoselectivities of up to 99:1 but moderate enantioselectivities in the presence of the thiourea derivative **47g** (Scheme 69 and Table 6).[117] The pseudoenantiomeric catalyst gave access to the enantiomeric products. A survey of possible solvents indicated that the use of nonpolar solvents facilitated the reaction proceeding to completion and was beneficial for the stereochemical control.



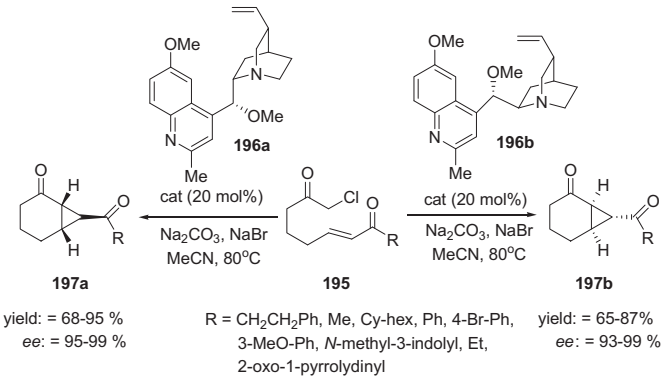
Scheme 69.

Table 6
Yields, dr and ee of pyrrolidines **194**

R	Yields (%)	dr	ee (%)
Ph	77	93:1	63
4-MeO–Ph	63	89:11	65
4-Me–Ph	56	95:5	62
2-Me–Ph	68	88:12	60
4-Br–Ph	65	94:6	49
4-Cl–Ph	63	85:15	46
4-F–Ph	49	87:13	50
2-Thienyl	50	>99:1	59

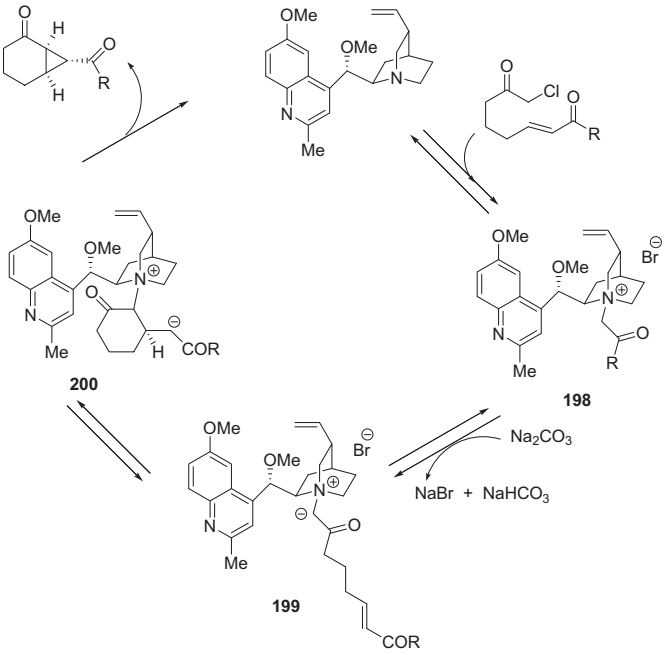
4.11. Cyclisations

A highly enantioselective catalytic intramolecular cyclopropanation reaction of suitably substituted chloroketones **195** that use modified *Cinchona* alkaloids to generate the [4.1.0]-bicycloheptanes **197a** and **197b** in excellent yields (Scheme 70) has been reported by Gaunt and co-workers.[118] The catalysts **196a**/**b** contained a methyl group at the C-2′ position that prevented the quinoline nitrogen atom from interfering in the reaction. In the absence of substituents at C-2′, a very poor yield was obtained because of derailment of the catalyst to alkylation either at one or both nitrogen atoms.



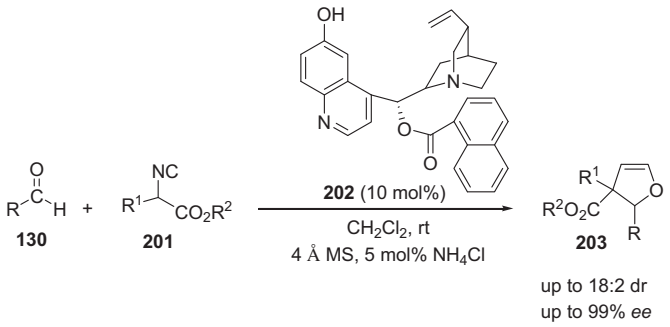
Scheme 70.

The catalytic cycle (Scheme 71) for the reaction initially involves a Finkelstein substitution at the chloroketone unit with sodium bromide. Displacement of the bromide with the catalyst forms the quaternary ammonium salt **198**, which undergoes deprotonation with sodium carbonate to the ylide-type species **199**. Intramolecular conjugate addition forms a new intermediate **200** and, subsequently, the cyclopropane, thus expelling the catalyst to restart the cycle.



Scheme 71.

The reaction of α-aryl isocyanoesters **201** with aldehydes **130** resulted in cyclisation leading to an symmetric synthesis of chiral oxazolines **203**. The reaction was catalysed by a C-9 *O*-naphthoyl-substituted *Cinchona* alkaloid derivative **202** to yield the products in up to 90% ee (Scheme 72).[119]



Scheme 72.

5. *Cinchona* alkaloids in C–X bond-forming reactions

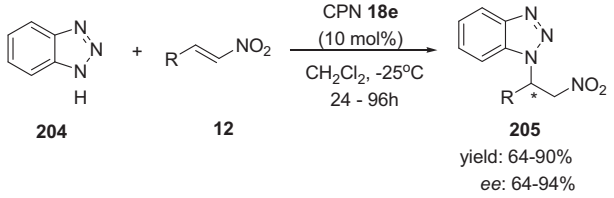
The formation of C–X bonds is an important synthetic endeavour because such bonds involving nitrogen, oxygen, sulphur, phosphorus or fluorine occur in many drugs and biologically important molecules. The important methodologies for the formation of C–X bonds include aza-Michael reactions, α-amination reactions, aziridinations, epoxidations, hydroxylation reactions and fluorinations, etc. Asymmetric organocatalysis using various natural and synthetic catalysts has been employed for the formation of C–X bonds. Some important examples of such reactions utilising *Cinchona* alkaloids and their derivatives as catalysts are discussed in the following sub-sections.

5.1. Carbon–nitrogen bond formation

Nitrogen is the most frequently occurring heteroatom in organic and bioorganic compounds and, hence, the development of methodologies for the formation of C–N bonds is of utmost importance. Since, in most compounds, both enantiomers do not possess the same biological and chemical properties, the significance of asymmetric versions of the methodologies already in existence has greatly increased. Among the organocatalysts, *Cinchona* alkaloids have acquired conspicuous popularity in recent years for the synthesis of chiral compounds containing nitrogen atoms such as amino acids, lactams, aziridines and amines, etc.

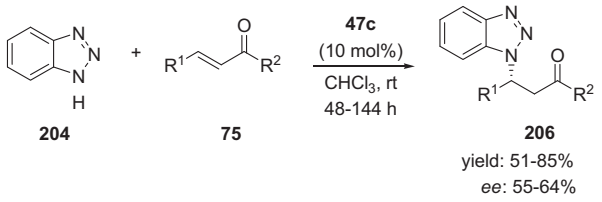
5.1.1. Aza-Michael additions. The aza-Michael addition, an extension of the Michael addition, involves the conjugate addition of nitrogen nucleophiles resulting in the synthesis of β-amino carbonyl compounds and is the most common reaction type for the formation of C–N bonds. Organocatalytic asymmetric aza-Michael addition reactions have been reviewed by Enders and co-workers.[120]

The first enantioselective aza-Michael addition of benzotriazole **204** to nitroolefins **12** catalysed by the *Cinchona* alkaloid derivative CPN **18e** was reported by Wang and co-workers in 2006.[121] Benzotriazole **204** formed bonds using *N*-1, affording the products **205** with yields of up to 90% and enantiomeric excesses up to 94% (Scheme 73). The reaction was then extended to a variety of α,β-unsaturated ketones **75**, forming the products **206** in good yields (up to 85%) but only moderate ees of up to 64%. In this case, the *Cinchona* thiourea catalyst **47c** was found to be the most efficient (Scheme 74).[122] This catalyst was also found to be the most efficient for the aza-Michael addition of *O*-benzylhydroxylamine **207** to chalcones **208** (Scheme 75).[123] An unmodified *Cinchona* alkaloid like quinine resulted in poor transformation, while application of

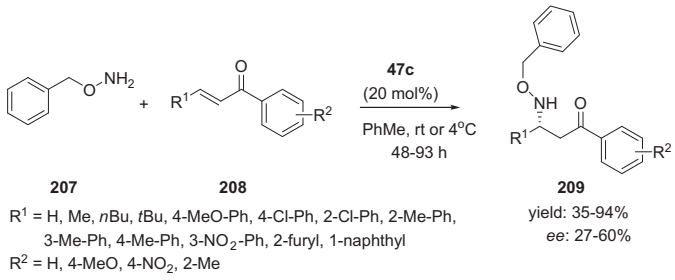


R = 4-Me-Ph, 4-Cl-Ph, 4-BnO-Ph, 2-BnO-Ph, 2,3-$(MeO)_2$-Ph, 2-Ph-Ph, 2-$(NO_2$-$PhCO_2)$-Ph, *n*-pent, *n*-hex, *i*Bu, $PhCH_2CH_2$, 4-*N*-trityl-1*H*-imidazole, 2-(*n*-Cbz)pyrrole, 2-thiophene, 2-naphthyl, 2-(4-ClPhS)Ph, 2-$(PhCO_2)$Ph

Scheme 73.



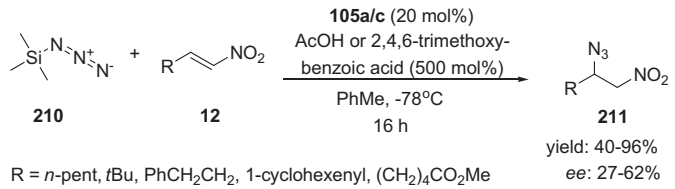
Scheme 74.



Scheme 75.

20 mol % of the catalyst **47c** yielded the desired adducts **209** in moderate-to-very-good yields, although the enantioselectivites were moderate (27–60% ee).

An organocatalysed addition of trimethylsilyl azide **210** to nitroalkenes **12** was developed by Jørgensen and co-workers.[124] The dimeric quinidines $(DHQD)_2AQN$ **105a** or $(DHQD)_2PYR$ **105c** were found to be the most efficient catalysts giving the addition products **211** in 40–96% yield and up to 62% ee (Scheme 76).

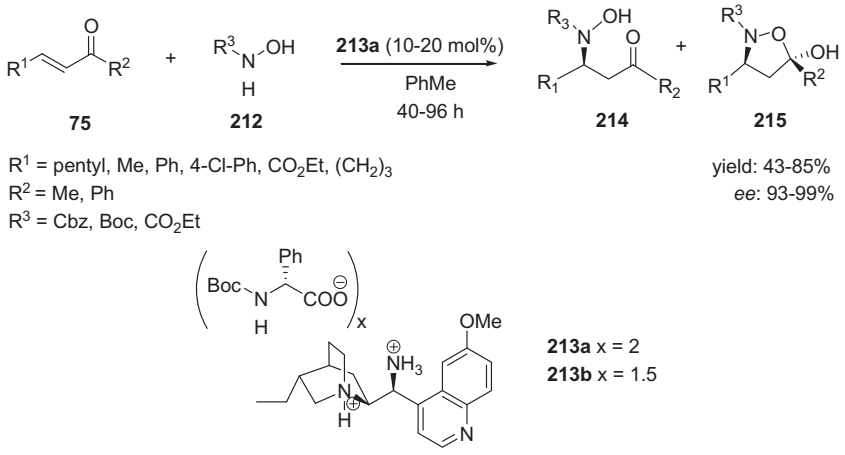


Scheme 76.

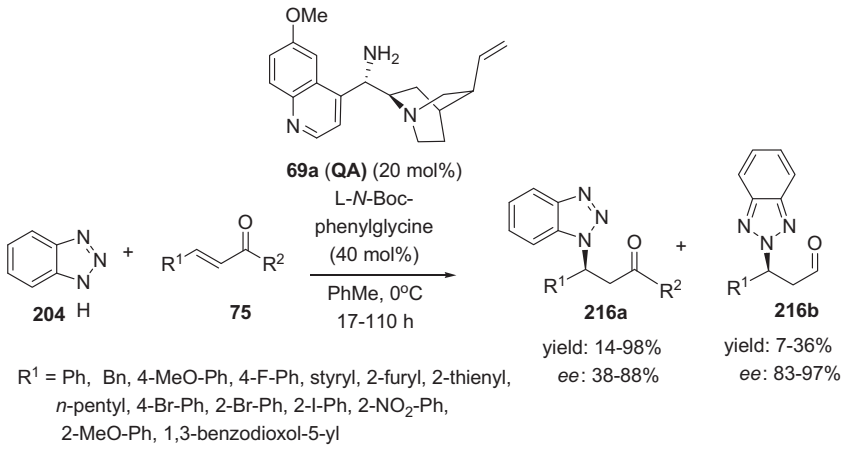
A highly enantioselective aza-Michael addition reaction between protected hydroxylamine derivatives **212** and α,β-unsaturated ketones **75** was reported by Melchiorre and co-worker.[125] Depending on the substrates used, the acyclic products **214** or the cyclised 5-hydroxyisoxazolidines **215** were obtained as the main products (Scheme 77). The primary amine salts **213a** and **213b** derived from *Cinchona* alkaloids were employed as catalysts. Wang and co-worker have used the quinine-derived amine **69a** (20 mol %) with L-*N*-Boc-phenylglycine as an additive for the aza-Michael addition of benzotriazole **204** to α,β-unsaturated ketones **75** to form the *N*-1 addition products **216a** as well as the isomeric *N*-2 addition products **216b**, although the latter were isolated in lower yields (up to 36%) (Scheme 78).[126]

An asymmetric aza-Michael addition of hydrazones such as **217** to cyclic enones **218** has been achieved in good yields and enantioselection of **219** using cheap and commercially available *Cinchona* alkaloids as catalysts (Scheme 79).[127] A systematic study of the influence of the structure of the enones was carried out. The enantioselectivity was observed to depend on the ring size of the enone and the substitution pattern of the ring. 2-Cyclooctenone afforded the optically active product with up to 77% ee, while, in the case of 2-cyclopentenone, the reaction proceeded well with a yield of 87%, but only with 31% ee. For 2-cyclohexenones, the reactivity was very low when two methyl groups were placed on C-4, due to steric factors. Placing the methyl groups on C-5, however, re-established the reactivity and the enantioselectivity was 76%. Increasing the ring size to seven- and eight-membered rings led to an improvement in the enantioselectivity of up to 77%. The catalyst, dihydroquinine (**DHQ**) **5**, afforded the highest enantioselectivity.

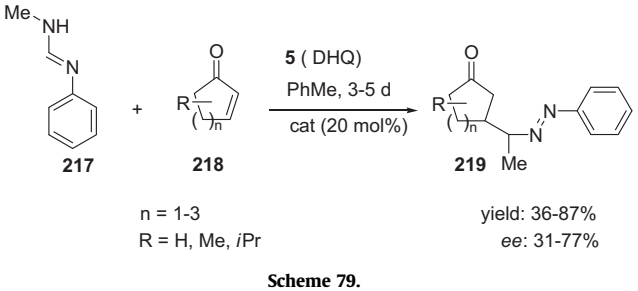
5.1.2. Asymmetric aziridinations. The smallest possible saturated azaheterocycles, aziridines, have attracted chemists, due to their reactivity associated with the highly strained three-membered ring.[128] There are some reports in the literature on the application of *Cinchona* alkaloid derivatives in the asymmetric synthesis of aziridines. 2-(Phenylsulfanyl)-2-cycloalkenones **220a–d** were reacted with ethyl nosyloxycarbamate ($NsONHCO_2Et$) under two different heterogeneous conditions, using an aqueous sodium bicarbonate solution as base or calcium oxide. A second-generation *Cinchona* alkaloid phase-transfer catalyst **90c** and a first-generation phase-transfer catalyst **90b** were used under both conditions. An aza-Michael-initiated ring closure led to the synthesis of 2-(phenylsulfanyl)aziridines **221a–d** (Scheme 80).[129] The catalyst **90b** was found to be more effective than the catalyst **90c**. Higher yields were obtained under liquid–liquid heterogeneous conditions (use of $NaHCO_3$), while a high enantioselectivity was observed under solid–liquid heterogeneous conditions (use of CaO). The salts that were used usually behave as pseudoenantiomeric catalysts in many stereocontrolled reactions. Surprisingly, both catalysts in this case



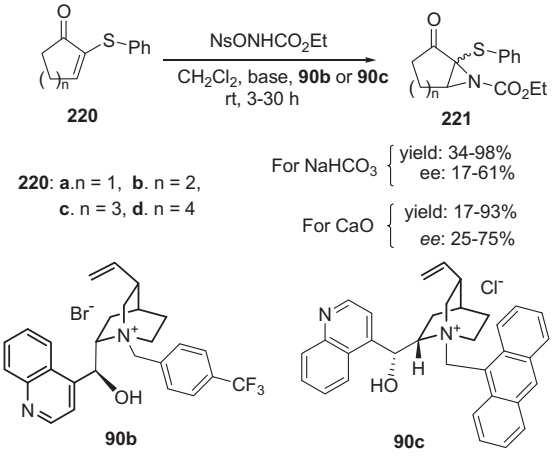
Scheme 77.



Scheme 78.



Scheme 79.

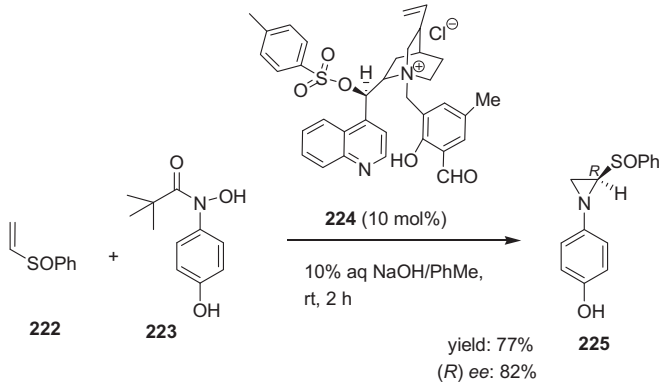


Scheme 80.

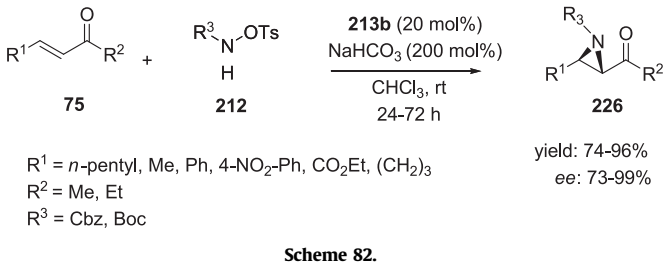
led to the same major enantiomer, probably due to steric hindrance on the catalysts.

The formation of (*R*)-4-((2-phenylsulfinyl)aziridine-1-yl)phenol **225** has been reported in 77% isolated yield and 82% ee by the reaction of vinylsulfinylbenzene **222** with *N*-hydroxy-*N*-(4-hydroxy) phenylpivalamide **223** in the presence of a new chiral phase-transfer catalyst **224** derived from a *Cinchona* alkaloid (Scheme 81).[130]

Recently, an organocatalytic aziridination has been reported using the *Cinchona* alkaloid-derived primary amine salts **213a** and **b** in the reaction of *N*-alkyl/aryl-*O*-tosyloxyhydroxylamines **212** with α,β-unsaturated ketones **75**, leading to highly enantiroenriched acylaziridines **226** in almost diastereomerically pure form and good yields (Scheme 82).[125]

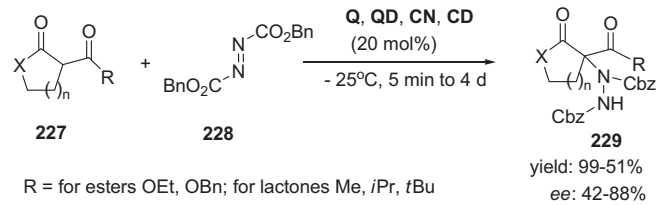


Scheme 81.



Scheme 82.

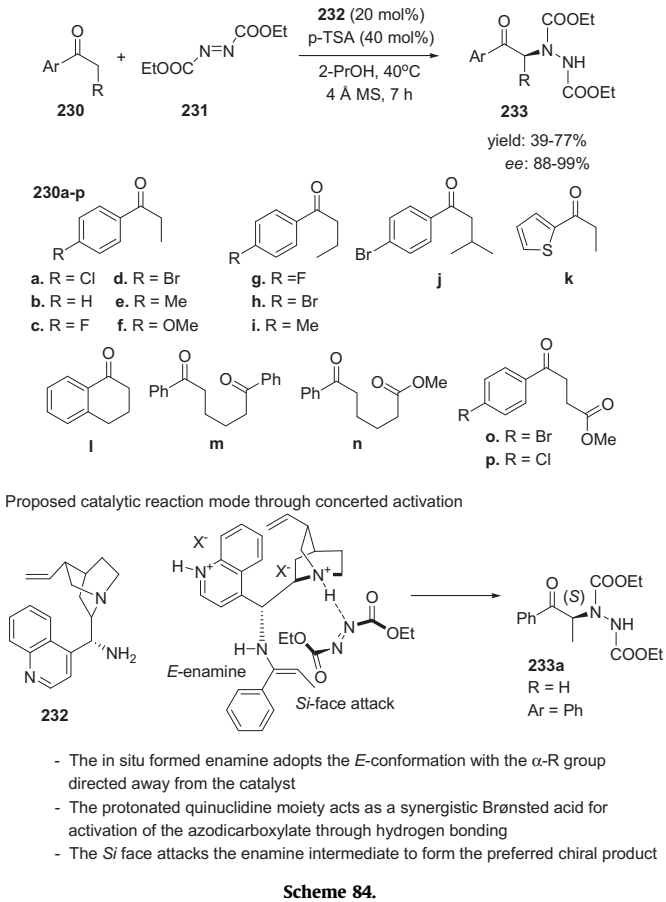
5.1.3. Direct α-aminations. The asymmetric direct α-amination reactions of β-ketoesters or β-keto lactones **227** by azodicarboxylates **228** catalysed by *Cinchona* alkaloids, have been investigated. α-Amination reactions of β-ketoesters and of β-keto lactones with dibenzyl azodicarboxylate are catalysed by *Cinchona* alkaloids, affording the products **229** in up to 99% yield and 90% ee (Scheme 83).[131] The five-membered ring compounds reacted most



Scheme 83.

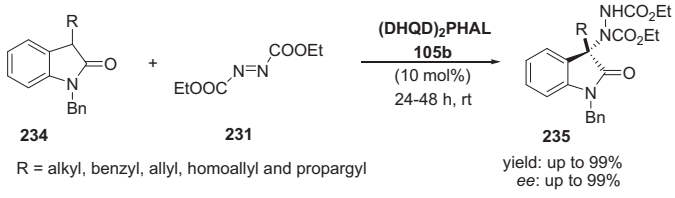
efficiently (in 2–40 min) and this has been attributed to the higher reactivity of the resulting enolates. The *tert*-butyl-substituted enolate however, suffered 1,3-allylic strain[132] and reacted much more slowly (4 days). Slightly better enantioselectivities were observed with cinchonine, compared to cinchonidine, while quinine and quinidine offered poor enantioselectivity.

The first highly enantioselective direct α-amination of aryl alkyl ketones **230a**–**p** with electrophilic diethyl azodicarboxylate **231** to form **233a**–**p** was reported by Chen and co-workers using 9-amino-9-deoxyepicinchonine **232** as the most efficient catalyst (Scheme 84).[133] The presence of 4 Å molecular sieves was of great assistance for the high conversions and enantiocontrol. A plausible catalytic mode for the amination reaction was proposed.



Scheme 84.

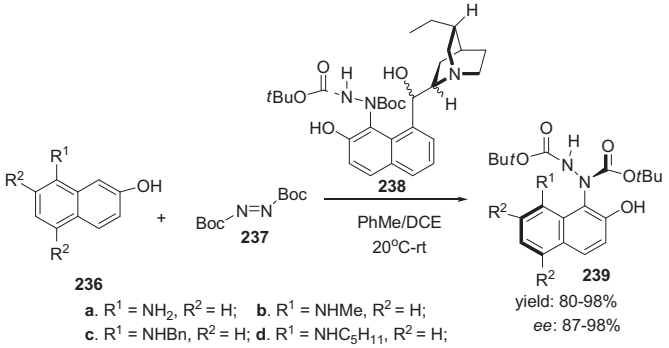
A general organocatalytic method has been developed for the construction of a C–N bond at the C-3 position of oxindoles, which at the same time creates a nitrogen-containing quaternary carbon chiral centre at that position.[134] This was achieved through a highly enantioselective α-amination of oxindoles **234** with diethyl azodicarboxylate **231**. The reactions were generally best catalysed by the commercially available dimeric quinidine derivative, $(DHQD)_2PHAL$ **105b**, affording the desired products **235** in excellent yields and good-to-excellent enantioselectivity (Scheme 85). Oxindoles are important structural motifs found in a wide array of natural and



Scheme 85.

biologically active molecules. Those that bear an oxygen or a nitrogen atom at the C-3 position are of particular interest as potential drug candidates.[135,136] The synthesis of oxindoles has therefore become an attractive target for many synthetic chemists.

Asymmetric Friedel–Craft amination of 2-hydroxy-8-aminonaphthols **236a**–**e** by di-*tert*-butyl azodicarboxylate **237** in the presence of *Cinchona* alkaloid-derived catalysts has been investigated by Jørgensen and co-workers.[137] Of the various catalysts explored, catalyst **238**, derived from either dihydroquinine or dihydroquinidine, afforded 1-aminated naphthols **239a**–**e** in excellent yields and enantioselectivity (Scheme 86).



Scheme 86.

5.2. Carbon–oxygen bond formation

5.2.1. Epoxidation reactions. Epoxides are among the most versatile intermediates in organic synthesis and, as a result, their synthesis by simple and easily scalable methods represents a major challenge that has promoted the development of numerous procedures since Sharpless and Katsuki reported the asymmetric epoxidation of allylic alcohols in 1980.[138] As an example, Wang and co-workers have developed a catalytic asymmetric epoxidation of chalcones **75** catalysed by PEG-supported *Cinchona* alkaloid PTCs **240a**–**c** (Fig. 21).[139] The most suitable oxidant for the reaction was found to be ^{t}BuOOH and the highest ee for the products **241** was 86%, obtained with the cinchonidine-derived catalyst **240c** in the formation of product bearing two phenyl groups (Scheme 87 and Table 7). All other chalcones afforded lower enantioselectivities.

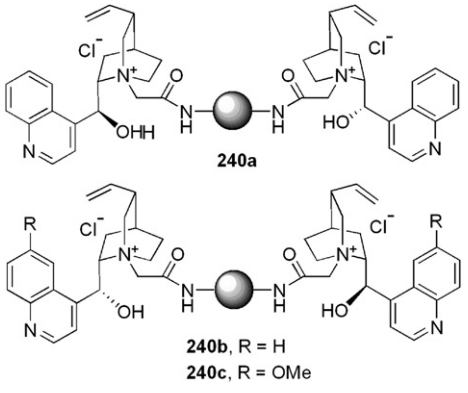
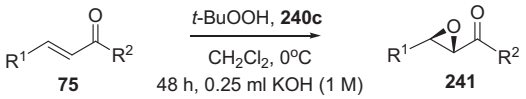


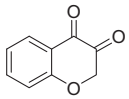
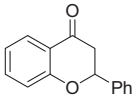
Fig. 21. *Cinchona* alkaloid-derived PEG resin-supported PTCs.

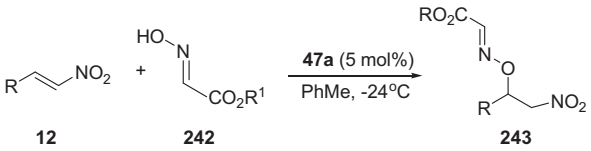
5.2.2. Hydroxylation reactions. The first enantioselective organocatalytic β-hydroxylation of nitroalkenes **12** was developed by Jørgensen and co-workers[140] using oximes **242a**–**j** as easily accessible oxygen sources, and bifunctional thiourea-*Cinchona* alkaloids **47** as catalysts (Scheme 88 and Table 8). The products **243a**–**j**



Scheme 87.

Table 7
Yields and ee of epoxides **241a**

Entry	R^1	R^2	Product	Yields (%)	ee (%)
1	Ph	Ph	**241a**	90	86
2	3-NO_2–Ph	Ph	**241b**	72	57
3	4-NO_2–Ph	Ph	**241c**	55	57
4	4-Me–Ph	Ph	**241d**	86	49
5	4-MeO–Ph	Ph	**241e**	Trace	—
6	4-Cl–Ph	Ph	**241f**	93	33
7	Ph	4-MeO–Ph	**241g**	77	35
8			**241h**	Trace	—
9			**241i**	Trace	—
10	*i*-Pr	Ph	**241j**	85	19



Scheme 88.

Table 8
Yields and ee of nitroalkenes hydroxylation products **243**

Entry	R/Nitroalkene	R^1	Product	Yields (%)	ee (%)
1	Pentyl	Et	**243a**	79	91
2	Pentyl	^{t}Bu	**243b**	83	90
3	Me	Et	**243c**	63	90
4	^{t}Bu	Et	**243d**	69	90
5	Cy-hex	Et	**243e**	82	90
6	$Ph(CH_2)_2$	Et	**243f**	68	89
7	Hex-3-enyl	Et	**243g**	79	93
8	$MeOCO(CH_2)_4$	Et	**243h**	68	89
9	$MeS(CH_2)_2$	Et	**243i**	82	89
10	1-Nitrocyclohexene	Et	**243j**	73	48

were readily converted into optically active nitro- and amino alcohols. Thiourea catalysts prepared from cinchonine, cinchonidine, quinidine and quinine were all tested and the quinine derivative **47a** surfaced as the most effective for forming the products **243** with good yields (63–83%) and high enantioselectivities (89–93%). These products were readily convertible to both optically active nitro- and amino alcohols.

5.2.3. Intramolecular oxa-Michael addition. Using intramolecular conjugate addition of a phenolic nucleophile on an α,β-unsaturated ester **244** or **245** catalysed by *Cinchona* alkaloids, a new asymmetric synthesis of 2-substituted chiral chromanes **247** has been devised (Scheme 89).[141] Functionalised chromanes possess potentially useful biological properties.[142] High enantioselectivities were observed with cinchonine and its derivatives **246a–d**. Steric hindrance and hydrogenation of the vinyl side chain of the catalyst generally had a positive effect, whereas electron-withdrawing groups led to low conversions. Cyclisation of the *E*-isomer was always faster, but less enantioselective, compared to the *Z*-isomer. Of the catalysts used, that with a 2-phenethyl group on C-3 gave the highest enantioselectivities for both *Z* (80% ee) and *E* (52% ee). These observations have been rationalized by ab initio quantum chemistry calculations of transition-state structures.

5.3. Carbon–sulphur bond formation

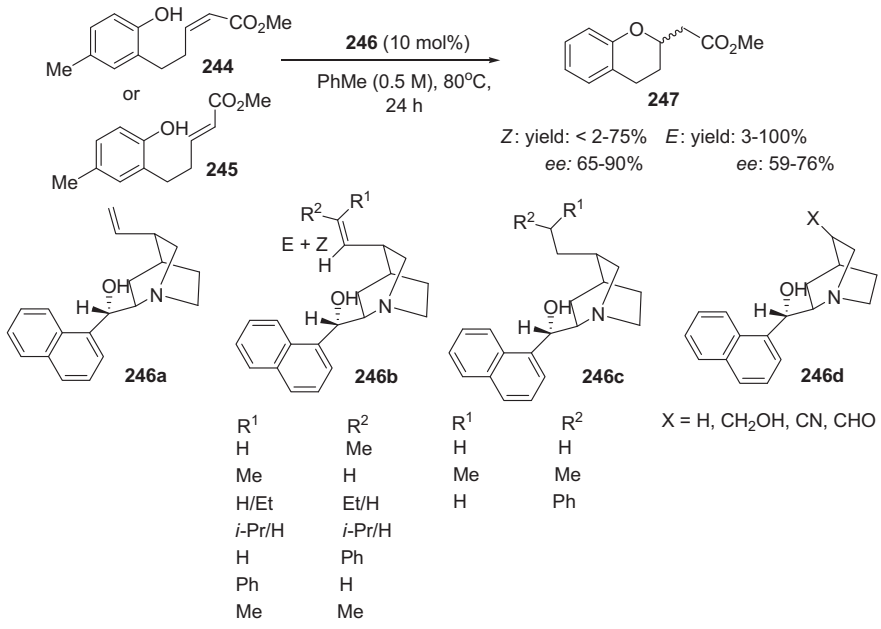
Optically active sulfides are versatile precursors for the synthesis of biologically interesting compounds.[143] The formation of C–S bonds has been investigated by Michael reactions using thiols. Quinidine and quinine were used to promote the asymmetric Michael addition reactions of thiols in the early 1980s.[144] Later, modified forms of these *Cinchona* alkaloids were used for conjugate reactions of thiols to cyclic enones with significantly improved enantioselectivities.[145] Recently, Deng and co-workers have reported the enantioselective conjugate addition of simple alkyl thiols **248** to α,β-unsaturated *N*-acylated oxazolidin-2-ones **249** catalysed by 6′-thiourea-*Cinchona* alkaloids (Scheme 90).[146] The catalyst screening and tuning studies led to the discovery of a new *Cinchona* alkaloid derivative **250** as the most efficient catalyst for the reaction. In the reaction of the α,β-unsaturated ketone having R as methyl and the thiol having R^1 as 4-methoxybenzyl, this catalyst afforded the adduct **251** in 99% yield and 96% ee. A minimum yield of 84% was obtained when R was 4-chlorophenyl in the Michael acceptor and allylthiol was the donor, whereas the minimum ee of 87% was observed when R was phenyl in the Michael acceptor and R^1 was 4-MeO–Bn in the donor. The application of this reaction was further demonstrated by the conversion of an adduct into a β-mercaptoester.

More recently, the asymmetric Michael addition of a number of thiophenols **252** to 2-cyclohexenone **33b** has been investigated in the presence of some urea and thiourea derivatives of *Cinchona* alkaloids (Scheme 91).[147] The *Cinchona* alkaloid urea **47e** was identified as the most efficient catalyst, affording almost quantitative yields of the adducts **253** and >99% ee in some cases. According to the proposed transition-state model **254** (Fig. 22) of the reaction, the enone is activated by the urea moiety through double hydrogen bonding, while the thiol (activated by the basic quinuclidine nitrogen atom) approaches the *Si* face of the enone leading to the formation of the major stereoisomer. This catalyst was also applied in the reactions of some other cycloalkenones and alkenones with thiophenols, affording the sulfa-adducts in excellent yields and enantioselectivity.

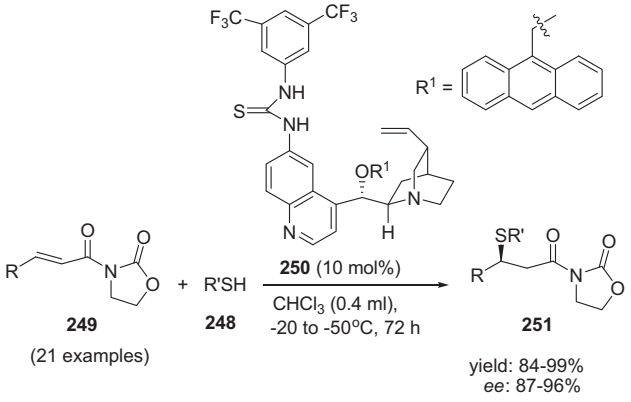
The use of quinidine and quinine in the reaction of nitroolefin **12** with thioacetic acid **255** has been reported recently to decrease the reaction time from 24 h to a couple of minutes (Scheme 92 and Table 9).[148] The yields of the product **256** were also increased from 71% in an uncatalysed reaction to >90% in the catalysed reactions. The maximum enantioselectivity observed, however, was 34%. A benzyl group was introduced at C-9 with the objective of enhancing the rigidity of the catalyst and the possibility of increasing the enantioselectivity, but this was unsuccessful.

5.4. Carbon–phosphorus bond formation

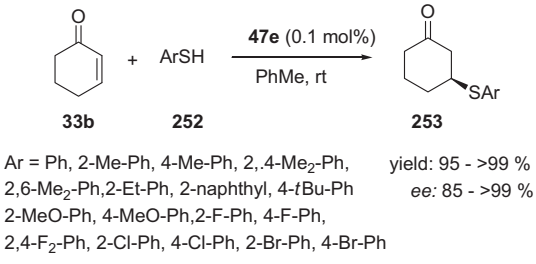
The enantioselective synthesis of α- and β-aminophosphonic acids has received considerable attention in recent years, because of their increasing application in peptide and medicinal chemistry.[149,150] They serve as surrogates of α- and β-amino acids in peptides and peptidomimetics with significantly improved bioactivities. β-Aminophosphonate derivatives have been used for the synthesis of enzyme inhibitors, agrochemicals and pharmaceuticals.[150] While considerable research has been carried out on the



Scheme 89.



Scheme 90.



Scheme 91.

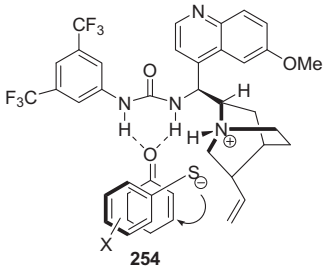
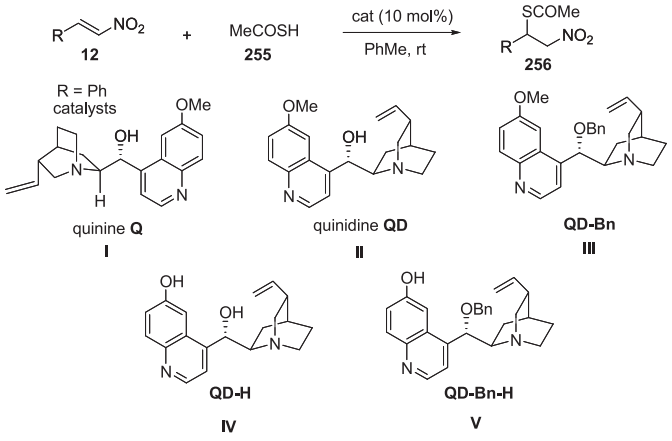


Fig. 22. Proposed transition-state model for the asymmetric Michael addition of thiophenols to 2-cyclohexenone.

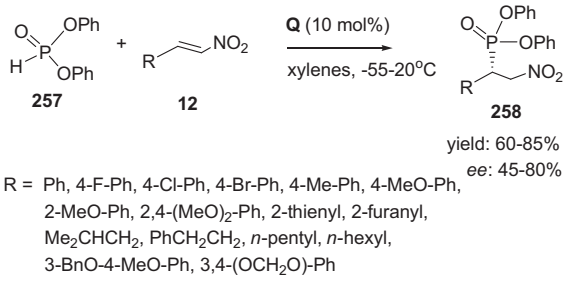


Scheme 92.

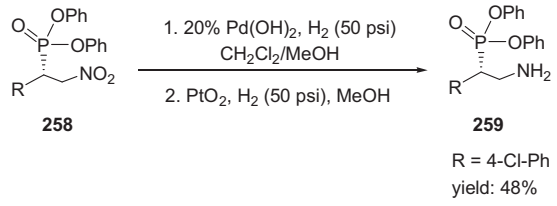
enantioselective synthesis of α-aminophosphonic acids,[151] there are only a few reports on the synthesis of β-aminophosphonic acids. Wang and co-workers have recently synthesised β-nitrophosphonates **258** in good yields and good enantioselectivity by the Michael addition of diphenyl phosphite **257** to *trans*-β-nitroalkenes **12** in the presence of quinine **Q** as catalyst (Scheme 93).[152] The aromatic nitroalkenes gave better yields (67–88%) than their alkyl counterparts (60–77%). The highest yield of 85% was obtained with the 4-fluoro-substituted nitrostyrene, whereas the highest enantioselectivity of 88% was achieved with the 2-thienyl-substituted nitrostyrene. The Michael adducts **258** could be conveniently transformed into chiral aminophosphonic acids **259** (Scheme 94). The proposed reaction mechanism for the enantioselective Michael addition invokes H bonding between both substrates and the catalyst (Fig. 23). In the proposed transition-state model, the *trans*-β-nitrostyrene is activated by the hydroxyl group of the catalyst. The amino moiety activates and directs the phosphite group, via the second H bonding interaction, for *Si* face attack of the *trans*-β-nitrostyrene, which affords the observed (*S*) product.

Table 9
Reaction of nitroolefin **12** and thioacetic acid **255** in the presence of *Cinchona* catalysts

Entry	Catalyst	Time	Yields (%)	ee (%)
1	None	24 h	71	0
2	I	15 min	94	17
3	II	15 min	95	23
4	III	1.5 h	94	0
5	IV	5 min	95	19
6	V	15 min	93	31



Scheme 93.



Scheme 94.

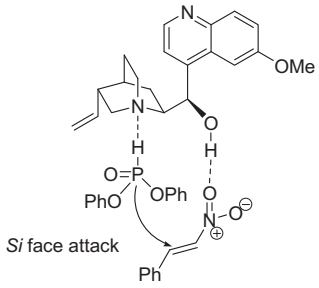


Fig. 23. Proposed transition-state model for the quinine-catalysed enantioselective Michael addition of diphenyl phosphite to *trans*-β-nitrostyrene.

5.5. Carbon–fluorine bond formation

Fluorinated organic molecules have exploded into the medicinal scene in the past 20 years and hundreds of fluorinated drugs are currently on the market including the pharmaceutical blockbusters fluoxetine (Prozac®), paroxetine (Paxil®) and ciprofloxacin (Cipro®) (Fig. 24).[153] It has been observed, in many cases, that the incorporation of fluorine into a compound improves its pharmacological profile.[154] Over the years, an extensive range of techniques for synthesising biologically active fluorinated compounds has thus been developed and a number of fluorinating reagents have been utilised.

In recent years, Selectfluor®, a quaternary *N*-fluoroammonium salt of 1,4-diazabicyclo[2.2.2]octane (DABCO), has been widely used for electrophilic fluorination. A chiral version of Selectfluor® was developed by Toru and co-workers.[155] Its structural features were analogous to *Cinchona* alkaloids and, thus, by a rational combination of the two reagents, a transfer fluorination takes place from Selectfluor® to produce a *Cinchona* alkaloid chiral fluorinating agent (Scheme 95). Relief from the dicationic state of Selectfluor® to generate two monocationic ammonium salts provides the thermodynamic driving force for the transfer.

Scheme 95.

The protocol for enantioselective fluorination mediated by Selectfluor®/*Cinchona* alkaloid combinations was developed by Toru and co-workers in 2006.[155,156] A catalytic amount of dihydroquinine benzoate (DHQB) **261** or bis-dihyroquinine anthraquinone $(DHQ)_2AQN$ **262** was used in combination with Selectfluor® to fluorinate enol ethers **260a**–**e** in the presence of sodium acetate in dichloromethane to produce α-fluoroketones **263a**–**e** in good yields and up to 54% ee (Scheme 96). Although the enantioselectivity was only moderate, the results represented the highest values for the production of fluorinated ketones at the time.

The scope of enantioselective fluorinations was extended by the Toru research group and an effective catalytic system utilising *Cinchona* alkaloid ammonium salt/TMAF (tetramethylammonium fluoride) combinations **265** was devised for the enantioselective trifluoromethylation of acyclic aryl ketones **264**. Using the Ruppert–Prakash fluorinating reagent [(trifluoromethyl)trimethylsilane, Me_3SiCF_3], trifluoromethylated alcohols **266** with a quaternary carbon atom were obtained in high yields and with very good enantioselectivities (Scheme 97).[157] Tetrasubstituted α-trifluoromethyl aryl alcohols are important building blocks in the design of many drug candidates.[158]

A catalytic enantioselective fluorination of allyl silanes and silyl enol ethers **267** with *N*-fluorobenzenesulfonimide (NFSI) as fluorinating agent together with a catalytic amount of a *bis*-*Cinchona* alkaloid such as $(DHQ)_2PYR$ or $(DHQ)_2PHAL$ **268a**/**b** has been developed.[159] The reaction was carried out in the presence of excess base to produce the desired fluorinated compounds **269** that feature a fluorine-substituted quaternary carbon centre. The fluorodesilylation proceeded efficiently with good yields (58–95%) and up to 95% ee. The methodology was also extended to the catalytic

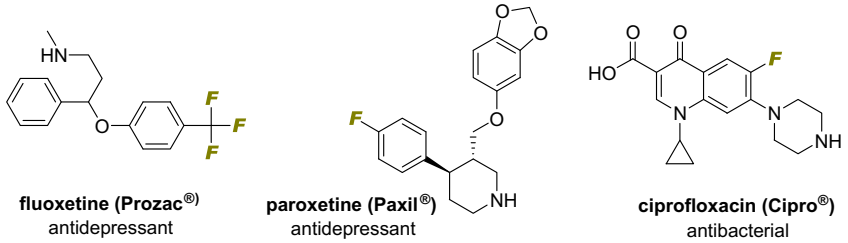
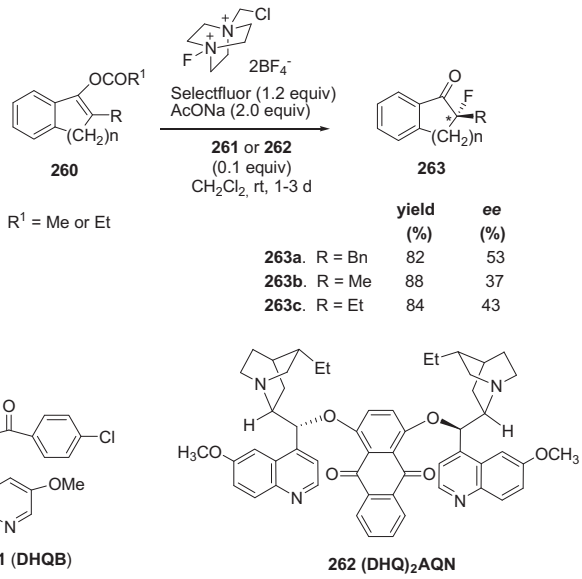
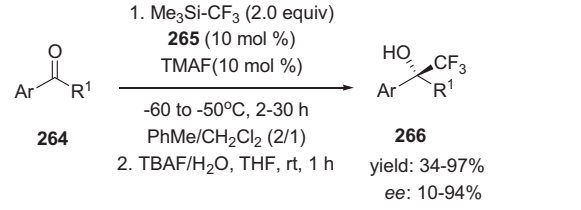


Fig. 24. Structures of some important fluorine-containing drugs.



Scheme 96.



Scheme 97.

enantioselective fluorination of oxindoles **270**, affording the corresponding fluorinated oxindoles **271** with up to 87% ee (Scheme 98).

6. Kinetic resolutions

Various *O*-alkylated quinidine and quinine derivatives have been screened as catalysts for the kinetic resolution of urethane-protected α-amino acid *N*-carboxyanhydrides (UNCAs) **272a** to **272b** with alcohol (Scheme 99).[160] The readily prepared, *O*-propargylquinidine **273a** and *O*-propargylquinine **273b**, were discovered to be highly enantioselective and practical catalysts for the synthesis of chiral α-amino esters **274** and α-amino acids **275** from UNCAs. Deng and co-worker[161] have also recently used the commercially available catalyst **105a** $(DHQD)_2AQN$, (10 mol %) for the kinetic resolution of UNCAs **272a** using ethanol (1.5 equiv) in diethyl ether over 4 Å molecular sieves (Table 10).

7. Decarboxylation reactions

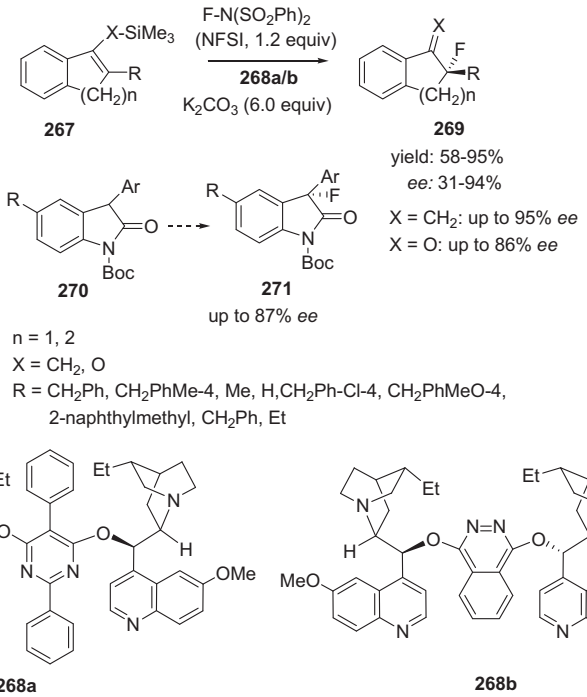
The first example of an enantioselective decarboxylation was reported in 1904. For more than 70 years this reaction received little attention. From the 1970s onward, however, many metal-mediated asymmetric decarboxylations have been reported. Rouden and co-workers have recently reported an organocatalytic, *Cinchona* alkaloid-catalysed decarboxylation of *N*-protected piperidinohemimalonates **276** at room temperature, leading to the formation of enantioenriched pipecolic esters **278** in good yields (Scheme 100).[162] The reactions were performed under very simple metal-free conditions catalysed by quinine or cinchonine-derived analogues. The temperature of the reaction was shown to influence only the rate of reaction and not the enantioselection. In general, the cinchonine analogues performed better as catalysts than did their quinine counterparts. It was also observed that the '*epi*' configuration at C-9 afforded better enantioselectivities than the natural configuration. Thus 9-*epi*-cinchonine **277** was observed to be the best catalyst for the enantioselective decarboxylation reaction. The same research group later reported the use of *Cinchona* alkaloid-derived thiourea **47c** as a catalyst in the asymmetric decarboxylative protonation of cyclic, acyclic, or bicyclic α-aminomalonate hemiesters such as **279** to afford enantioenriched amino esters such as **280** in high yields and enantioselectivities of up to 93% (Scheme 101).[163] The group synthesised both enantiomers of the amino esters with equal selectivity using the pseudoenantiomeric catalysts.

8. Sulfinyl transfer

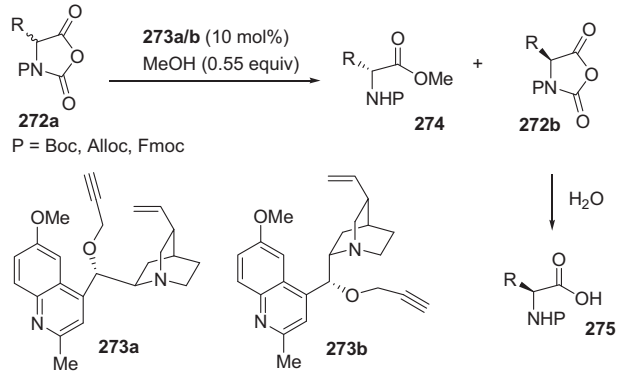
The commercially available *Cinchona* alkaloid, quinidine **QD**, has been used as a catalyst for the sulfinyl-transfer reaction of *tert*-butanesulfinyl chloride **281** and a variety of benzyl alcohols **282**, leading to the synthesis of chiral sulfinate esters **283** (Scheme 102).[164] *ortho*-Substituted benzyl alcohols afforded higher yields and enantioselectivity. Sulfinyl transfer with 2,4,6-trichlorobenzyl alcohol and 10 mol % of the catalyst provided the sulfinate ester product in 92% yield and with 90% ee. The yields and enantioselectivities were compared in tetrahydrofuran and toluene. The former solvent gave the better yields in most cases while the latter offered the better enantioselectivities. It is worth mentioning that chiral sulfinate esters are versatile intermediates for the synthesis of diverse chiral sulphur compounds, including sulfoxides and sulfonamides.[165]

9. Interrupted Feist–Bénary reaction

The Feist–Bénary reaction involves the base-promoted condensation of β-dicarbonyl compounds with α-haloketones, providing an easy access to furan derivatives via the initial hydroxydihydrofuran product.[166] If the reaction is checked at the hydroxydihydrofuran stage, it is referred to as an 'interrupted' Feist–Bénary or IFB reaction.[167] Different *Cinchona* alkaloid derivatives have been evaluated as catalysts in the asymmetric IFB reaction of bromoketoesters such as ethyl bromopyruvate **284** and β-phenyl-substituted ethyl bromopyruvate with cyclohexane-1,3-dione **45b**. The corresponding chiral hydroxyl dihydrofurans such as **286** have been obtained in excellent yields and with up to 94% ee (Scheme 103).[168] Quinidine- and dihydroquinidine-derived ester derivatives **285** afforded better yields and enantioselectivities in comparison to cinchonine and cinchonidine derivatives. A study of the effect of phthaloyl bridging groups showed that the ee increased with *para*-bis esters. All the reactions were performed in tetrahydrofuran at −78 °C, and completed in 10 min with high yields.



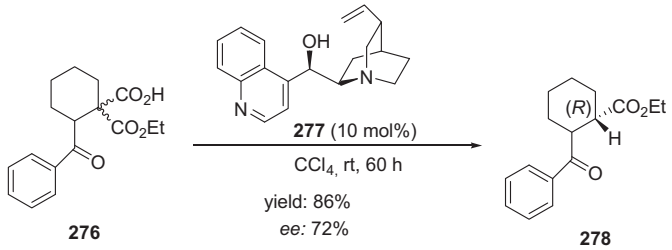
Scheme 98.



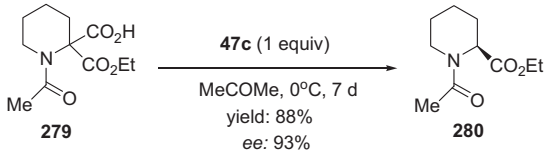
Scheme 99.

Table 10
Kinetic resolution of UNCA **272a** via modified *Cinchona* alkaloid-catalysed alcoholysis

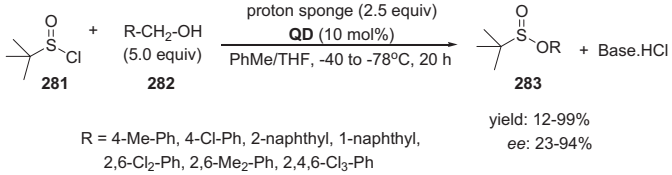
R	Temp (°C)	Time (h)	Conv (%)	ee (Yields) (%)	
				(*S*)-**275**	(*R*)-**274**
	−78	14	51	95 (42)	93 (49)
	−40	7.5	57	96 (42)	75 (55)
	−52	19	52	99 (44)	93 (50)
	−52	18	52	95 (44)	85 (50)
	−40	13	57	96 (38)	74 (57)
	−73	42	49	91 (40)	95 (48)



Scheme 100.



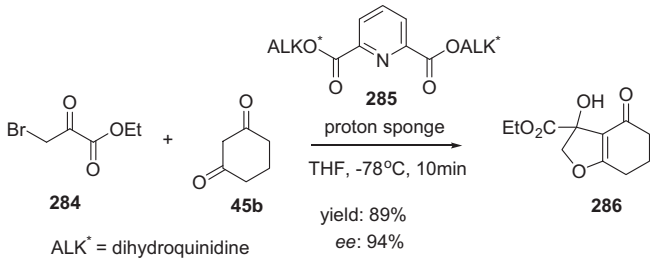
Scheme 101.



Scheme 102.

10. Asymmetric desymmetrisations

Asymmetric desymmetrisation of *meso* compounds, where multiple stereocentres can be created in a single step, is a powerful tool to synthesise enantiomerically enriched products. Deng and co-workers had reported earlier a general and highly enantioselective catalytic desymmetrisation of prochiral *meso*-cyclic anhydrides using mono- and bis-*Cinchona* alkaloid derivatives as catalysts,[169] among which, 1,4-bis(dihydroquinidinyl)anthraquinone $(DHQD)_2AQN$ **105a**, in general afforded high enantioselectivities (up to 98% ee) with a catalyst loading of 8 mol %. The anchoring of a homogeneous analogue of $(DHQD)_2AQN$ onto a polymer support has been reported.[170] Han and co-workers, in 2004, reported a one-pot conversion of *meso*-cyclic anhydrides **287**



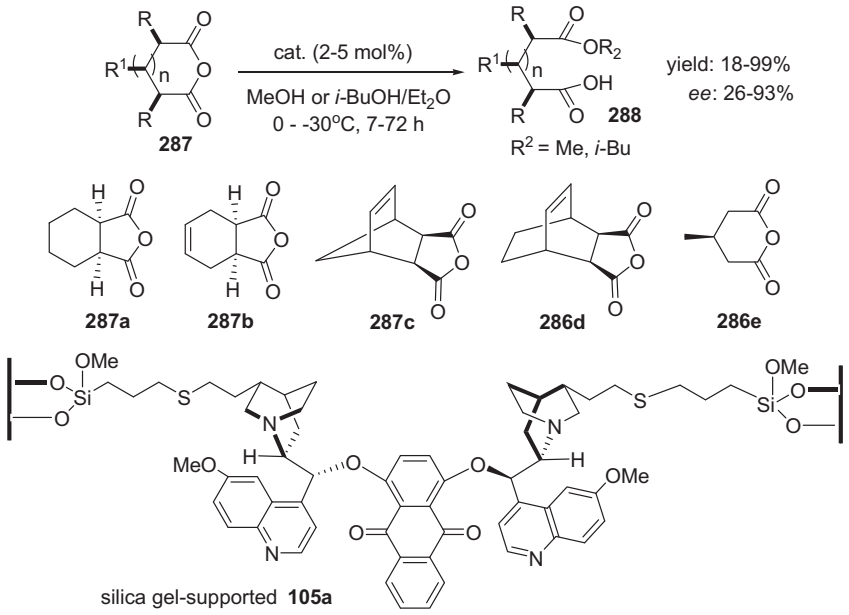
Scheme 103.

into the corresponding desymmetrised mono-ester acids **288**, with alcoholysis in diethyl ether using a silica gel-supported $(DHQD)_2AQN$ **105a** as a chiral catalyst (Scheme 104).[171] In order to optimise the yield and enantioselectivity, the effect of temperature and solvent was studied. An increase in temperature increased the yield, but decreased the enantioselectivity.

as catalyst, showed a high enantioselectivity but too slow a reaction speed at low temperature.[173]

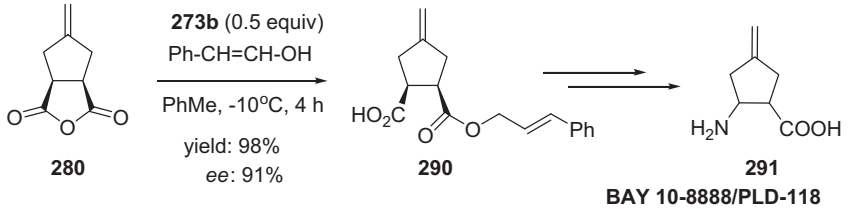
11. Concluding remarks

The *Cinchona* alkaloids and their derivatives during the current decade have undoubtedly emerged as privileged organocatalysts for asymmetric synthesis, that is, evident from their application in diverse types of chemical reactions. Many of them are commercially available, inexpensive, easily tunable and recyclable catalysts used to transform achiral, *meso*, and *racemic* substrates into valuable chiral building blocks. Natural *Cinchona* alkaloids such as quinine, quinidine and cinchonine have been used successfully in the Michael addition of α-lithiated phosphonates to nitroolefins affording 99% ee. In several reactions, however, urea and thiourea derivatives, and ammonium salts have been found to be more effective than the natural alkaloids. In their use as dimeric catalysts, the choice of spacer and polymer compatibility with the reaction



Scheme 104.

Furukawa and co-worker[160] have reported the desymmetrization of 5-methylenetetrahydrocyclopenta[c]furan-1,3-dione **289** with cinnamyl alcohol using 0.5 equiv of *O*-propargylquinine **273b** to obtain the (+)-half-ester **290**, a key intermediate in the synthesis of the β-amino acid **291**, which is a novel antifungal agent coded as BAY 10-8888/PLD-118 (Scheme 105). An efficient large-scale production of **291** had previously been reported by Mittendorf and co-workers using quinine or $(DHQD)_2AQN$ as catalyst.[172] Furukawa and co-workers in their attempts to improve on the Mittendorf procedure observed a slightly better catalytic performance and efficiency for large-scale production of the drug by using the *O*-propargylquinine/quinidine catalysts. Another example of desymmetrization of a cyclic *meso*-anhydride with $(DHQD)_2AQN$ conditions is important. *Cinchona* alkaloid derivatives have been applied in several important reactions such as Mannich reactions, aldol reactions, Diels–Alder cycloadditions, dynamic kinetic resolution and desymmetrisation of anhydrides, in many cases creating one or more quaternary carbon stereocentres. In most of the cases reviewed, a thorough screening of a range of catalysts, in terms of steric, electronic and other factors, was required in order to develop the optimised catalyst specifically tailored for each reaction. In many cases, the yield and enantioselectivity were observed to depend on the reaction temperature. Generally, high temperatures favoured high yields and low temperatures favoured high enantioselectivity and so an optimum temperature was required to strike a balance between the yield and enantioselectivity.



Scheme 105.

Hopefully, these catalysts will replace metals in many more powerful reactions, leading to the formation of complex bioactive molecules through carbon–carbon and carbon–heteroatom bond-forming reactions.

Acknowledgements

We are grateful to the Chemistry Department, University of Botswana, Gaborone, Botswana, for providing the facilities.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.12.050.

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Biographical sketch

Elizabeth M.O. Yeboah trained as a chemistry teacher in the University of Cape Coast, Ghana where she obtained a B.Sc. (General) Education degree in 1976 followed by a B.Sc. Hons Chemistry degree in 1977 and an M.Sc. degree in inorganic chemistry in 1981. While accompanying her husband, Samuel Yeboah, on his travels and raising three children, she worked as a tutor/demonstrator and taught undergraduate chemistry at the Ondo State University in Nigeria (1983–1987), and was appointed as a lecturer in chemistry in the Basic Science Department of the University of Botswana (1987–1989), followed by an eight-year spell as chemistry lecturer in the Botswana College of Agriculture (1992–2000). She returned to the University of Botswana in 2001 as a demonstrator in the chemistry department and worked up to 2007. During this period, she developed a keen interest in the ongoing research on natural products chemistry and joined the Ph.D. program of the department under the supervision of Prof. R.R.T. Majinda. She is currently working on isolation and characterisation of compounds from an indigenous medicinal plant. Recently, she has been fascinated by the history of the *Cinchona* alkaloids especially by their role for decades as medicine for malaria and currently by their use as organocatalysts in the asymmetric synthesis of other medicinally useful compounds.

Samuel O. Yeboah obtained his Ph.D. degree in organic chemistry from Queen Mary College, University of London, in 1974, after which he returned to his home country to teach in the University of Cape Coast, Ghana, for seven years. This was followed by a five-year lectureship tour at the then Ondo State University, Nigeria. Dr. Yeboah was a Fulbright Research Fellow at Brandeis University, Waltham, Massachusetts, USA, (July–October1977), where he worked with Professor J.B. Hendrickson in organic synthesis. In 1981–1982 Dr. Yeboah worked with Professor Leslie Crombie on the synthesis of Chalaurenol at the University of Nottingham, UK, as a research fellow of the Commonwealth Scholarship Commission. Since 1987 Dr. Yeboah has taught general organic chemistry, physical organic chemistry and lipid chemistry at the University of Botswana. Dr. Yeboah's current research is in natural products chemistry, especially in characterization, structural and compositional studies of the lipid classes in non-conventional seed oils from Africa south of the Sahara and has several publications to his credit in his area of research interest.

Girija S. Singh was born in Sasaram (Bihar), India. He received his B.Sc. and M.Sc. degrees from the U.P. College, Varanasi, India, in 1977 and 1979, respectively. He received his Ph.D. degree from the Banaras Hindu University (BHU), India, completing his doctoral thesis on the reactions of diazoalkanes and diazoketones with imines, amines and hydrazones in October, 1984. Since then he has occupied teaching and research positions in various universities such as Osaka University, Japan (PDF), BHU (JRF, SRF, PDF, RA, Pool-Officer and Reader), University of Zambia (Lecturer), and University of Botswana (Lecturer, Senior Lecturer and Associate Professor). He has authored 65 publications in books and in peer-