

Asymmetric catalysis with bifunctional cinchona alkaloid-based urea and thiourea organocatalysts

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Cinchona alkaloid derivatives modified to include a (thio)urea component have emerged in the last three years as readily accessible, robust and tunable bifunctional organocatalysts for a range of synthetically useful transformations. The origins of these catalysts and the major developments in their application in enantioselective synthesis are reviewed.

Introduction

The idea of using organic catalysts to promote asymmetric transformations is certainly not a new one,¹ however after considerable time in the wilderness it has rapidly gained widespread currency among organic chemists over the course of the last decade.² While the general advantages associated with the use of organocatalysts have been set down many times² and will not be reiterated here, it is perhaps worth mentioning that one of the most attractive aspects of organocatalysis is that the biomimetic use of multiple, relatively weak catalyst–substrate interactions (as opposed to single, strong Lewis acid–Lewis base attractions, for example) facilitates the design of so-called bifunctional³ catalysts: catalysts which possess (often) complementary functionality capable of activating two components of a chemical reaction simultaneously. Such a strategy – ubiquitous in biocatalytic systems – allows the practitioner to aspire towards unprecedented levels of control over the encounter of reactants in a given transition state, with obvious potential benefits in terms of both reaction rate and (where applicable) stereoselectivity.

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Stephen Connon was born in 1976 and received his PhD from University College Dublin under the supervision of Prof. A. F. Hegarty in 2000. After being awarded an Alexander von Humboldt fellowship he spent two years at the Technische Universität Berlin with Prof. S. Blechert, studying the design of new olefin metathesis catalysis. In 2003 he was appointed to the staff of Trinity College. His research interests include organocatalysis, the discovery and development of novel synthetic methodology and the design of new anti-cancer and anti-bacterial agents.

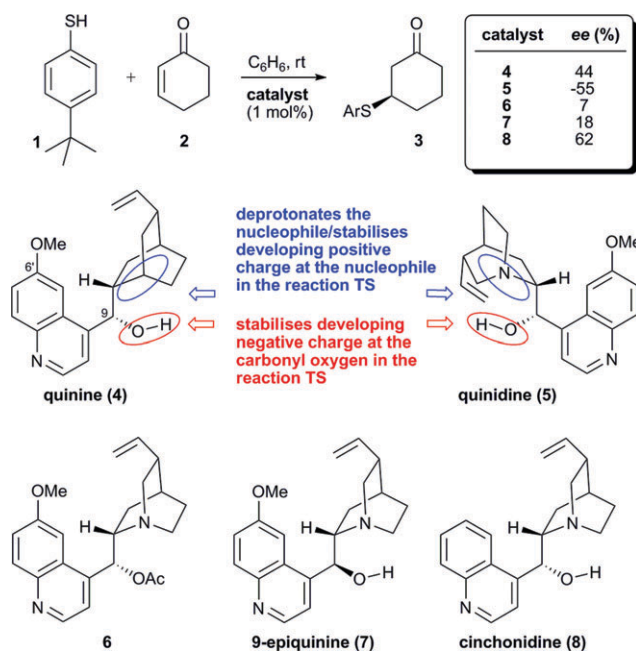
In 1981, Wynberg and Hiemstra^{4,5} published a landmark paper demonstrating that cinchona alkaloids promote the moderately enantioselective addition of thiophenols to cyclic enones (Scheme 1).⁶ Screening a range of both natural and modified alkaloids allowed the authors to recognise that these catalysts operated bifunctionally in this reaction—catalyst activity and selectivity were dependant on the presence of both a basic tertiary amine moiety (capable of deprotonating the thiol pronucleophile) and a hydrogen-bond donating hydroxy group (which activates the enone electrophile) in a stereochemical arrangement conducive to their cooperation in the reaction transition state. As a conclusion to this study Wynberg predicted:

‘The scope of the utility of hydroxy amines can perhaps be extended by constructing a catalyst containing a stronger base or a better hydrogen-bond donor...Perhaps other Michael reactions can then be performed which are not possible with bases like quinine.’

In view of the clear precedent set by Wynberg and the ready availability of cinchona alkaloid derivatives it is somewhat surprising that this field did not undergo immediate rapid growth. At turn of the millenium Hatayekama *et al.* found that the ‘better hydrogen bond donor’ can be obtained from demethylation of the 6'-methoxy moiety in conformationally restricted quinine derivatives,⁷ while Deng and co-workers later demonstrated that readily accessible 6'-demethylated quinine/quinidine (and 9-O-arylated derivatives) could serve as more effective promoters of asymmetric Michael addition processes than their parent alkaloids.⁸ No other modifications to the parent alkaloid structure had been shown to lead to improved bifunctional catalysis.⁹

Early studies: the development of (thio)urea-substituted cinchona alkaloid catalysts

In the early 1990s Curran and Kuo¹⁰ developed the urea catalyst **9** for the promotion of the allylation of cyclic α -sulfinyl radicals with allyltributylstannane^{10a} and Claisen rearrangements.^{10b} The basic concept underpinning the choice of these materials is simple – *N,N'*-diaryl (thio)ureas are robust, tunable and readily preparable catalyst templates



Scheme 1 Bifunctional alkaloid-mediated catalysis by Wynberg.

which were known to be capable of donating two hydrogen bonds to a range of organic and inorganic Lewis-bases,¹¹ therefore it was reasonable to expect that they would be capable of accelerating reactions by forming LUMO-lowering hydrogen bonds to Lewis-basic functionality on an electrophilic reaction component (or, by stabilising developing negative charge at heteroatoms in the transition states of addition reactions).¹² In 1998, Sigman and Jacobsen disclosed that chiral (thio)urea derivatives could efficiently transfer stereochemical information – the chiral α -amino acid-derived catalyst **10** proved capable of promoting highly enantioselective Strecker reactions of *N*-allyl aldimines.¹³ Schreiner and co-workers were the first to show how profoundly catalyst activity can be tuned by simply varying the *N*-aryl substituent and introduced the now almost uniform *N*-trifluoromethylphenyl substituent (*i.e.*, catalyst **11**, Fig. 1) which in all likelihood increases both the solubility and N–H acidity (and hence hydrogen-bond donating ability) of these materials. It has also been postulated that this substituent can increase catalyst rigidity by facilitating an intramolecular hydrogen-

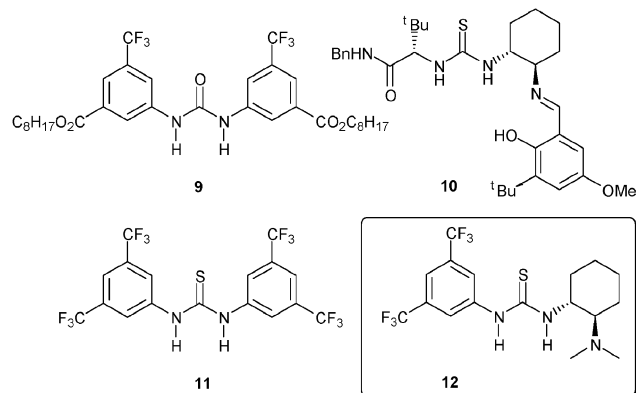


Fig. 1 The first examples of (thio)urea catalysts.

bonding interaction between the thiourea sulfur atom and a polarised *o*-aryl proton.¹⁴

In 2003, Takemoto and co-workers developed these concepts further with the introduction of the 1,2-*trans*-cyclohexyldiamine-derived thiourea catalyst **12**. This molecule represents a logical extension of Curran's, Jacobsen's and Schreiner's ideas, with the added advantage of including bifunctionality as a design element. The authors convincingly demonstrated that thiourea **12** operates *via* a bifunctional mechanism in the catalysis of highly enantioselective Michael additions of dimethylmalonate to nitroalkenes at room temperature¹⁵ – the Lewis acidic thiourea moiety is proposed by the authors to activate the nitroalkene electrophile by hydrogen bonding while the basic amine deprotonates the pronucleophile.^{16,17} Catalyst analogues devoid of either the thiourea or the amine component gave poor results under the same conditions.

In view of the precedent set by Takemoto's bifunctional catalyst **12**, the development of thiourea-substituted cinchona alkaloid catalysts (general structure in Fig. 2) was the next logical step. Cinchona alkaloids are inexpensive starting materials readily available in both *pseudoenantiomeric* forms. They possess relatively rigid (but not completely locked) structures in which Brønsted basic and hydrogen bond-accepting functionality are located at stereogenic centres in close proximity to one another.¹⁸ Furthermore, the C-9 stereocentre is a secondary alcohol, which can readily be transformed into a (thio)urea derivative *via* the corresponding primary amine. The absolute configuration of the alcohol can be readily inverted if required, which allows the influence of the *relative* stereochemistry at the Lewis basic and Lewis acidic groups on both activity and selectivity to be determined.

Thus four research groups began working independently on the design of readily accessible and tunable (from steric-, stereochemical- and electronic standpoints, Fig. 2) bifunctional catalyst templates based on cinchona alkaloids and reported their results within a half a year of one another. The first report came from Chen and co-workers¹⁹ who found that the thiourea substituted cinchonidine and cinchonine-derived catalysts **13** and **14**, respectively were highly active promoters of the Michael addition of thiophenol to α,β -unsaturated imide **15**, however catalysis proceeded with low enantioselectivity (Scheme 2).

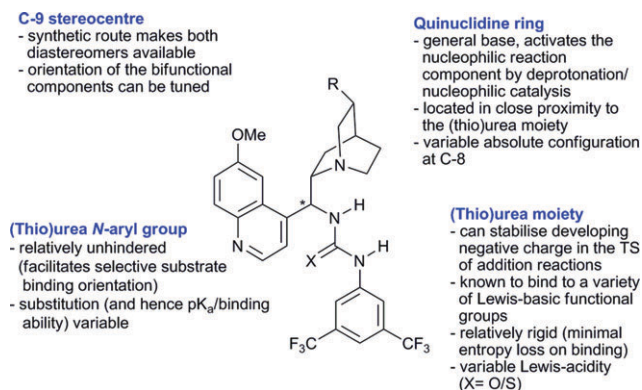
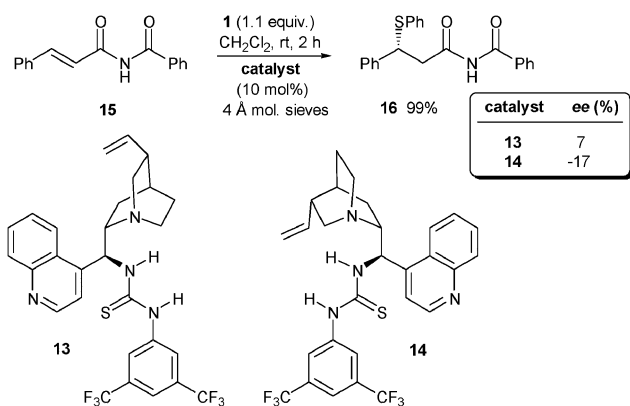


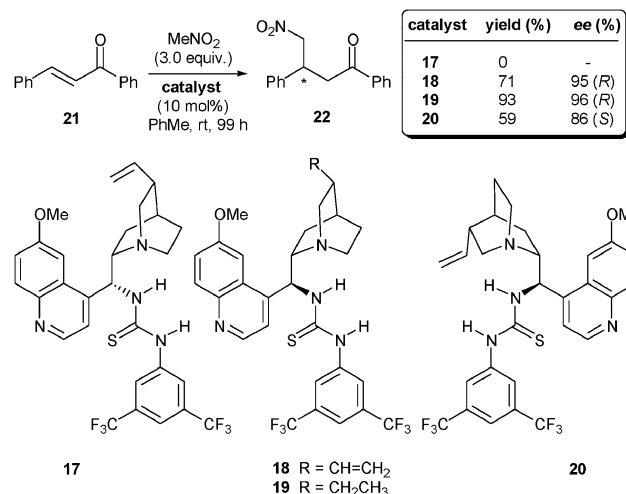
Fig. 2 (Thio)urea-modified cinchona alkaloid catalysts: design elements.



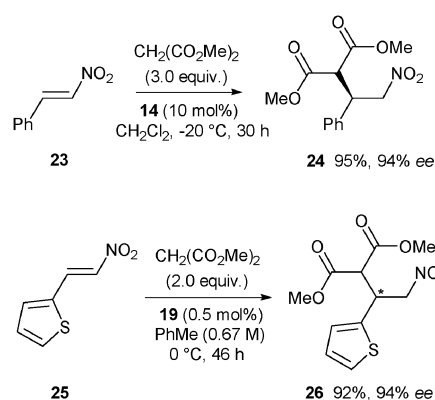
Scheme 2 The first report of thiourea-substituted cinchona alkaloid mediated catalysis by Chen and co-workers

Soós and co-workers²⁰ developed thiourea-substituted quinine/quinidine-derived cinchona alkaloid catalysts **17–20** (Scheme 3) for the enantioselective addition of nitromethane to chalcones. These materials were devised to probe both the potential for bifunctional catalysis and the optimal relative stereochemistry at C-8 and C-9. Somewhat surprisingly (given how useful the ‘privileged’²¹ core cinchona alkaloid structure and stereochemistry have proven as a basis for ligand/catalyst design in the past) the thiourea derivative of ‘natural’ stereochemistry at C-9 (*i.e.* **17**) exhibited no catalytic activity (quinine itself was also inactive) while its C-9 epimers (**18** and **19**) proved both active and highly selective under identical conditions. The relationship between catalyst activity and the relative orientation of the thiourea and quinuclidine moieties strongly indicated that these systems operate *via* a bifunctional mechanism. Long reaction times were required to achieve satisfactory yields at ambient temperature, however heating the reactions to 50–75 °C resulted in more acceptable rates with low catalyst loadings (as low as 1–2 mol%) without an impractical erosion of either product yield or enantioselectivity.

A short time later our group²² and then Dixon and co-workers²³ independently reported the design of similar catalyst systems for use in the asymmetric addition reactions of



Scheme 3 Catalysis of the addition of nitromethane to chalcone.



Scheme 4 Catalysis of the addition of dimethylmalonate to nitroolefins.

dimethyl malonate to nitroalkenes. Dixon found that the cinchonine-derived catalyst **14** could efficiently promote the addition of malonate ester derivatives to (*E*)- β -nitrostyrene (**23**) at -20 °C to furnish adduct **24** in excellent yield and enantioselectivity (Scheme 4). In a similar study we prepared a suite of cinchona alkaloid derivatives for use in the same reaction and demonstrated, by analogy with Soós’ results, that while neither epimerisation of the dihydro analogue of the parent alkaloid at C-9 nor substitution of the C-9 hydroxy group with an *N*-aryl(thio)urea moiety without epimerisation improved catalyst activity, a catalyst incorporating both modifications proved both highly efficient and selective (*i.e.* catalyst **19**). The high activity of **19** is underlined by the synthesis of the thienyl nitroalkane **26** in 92% yield and 94% ee using as little as 0.5 mol% of catalyst under mild reaction conditions.

Catalyst application: general

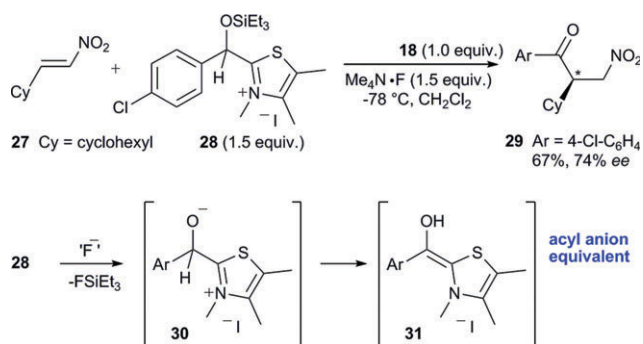
Due largely to their ready accessibility, the synthetic potential of this class of catalyst has been quickly recognised and exploited by several researchers. It is a testament to the wide utility of these systems that writing almost precisely three years after the *submission* of the first report concerning their use, sufficient material has appeared to warrant the organisation of the remainder of this review according to reaction class and electrophile type.

Catalyst application: 1,4-addition reactions

While the field is still very much in its infancy, already it can be stated that (thio)urea-modified cinchona alkaloids have proven particularly adept at the catalysis of asymmetric Michael reactions (*vide supra*). The following section details developments in this area categorised according to the class of Michael acceptor substrate involved.

Nitroalkenes

Nitroalkenes have proven an attractive substrate class to date. Nitro-groups possess two co-planar Lewis-basic oxygen atoms capable of accepting two hydrogen bonds^{11b} from (thio)urea derivatives and the enantioenriched nitroalkane adducts derived from the asymmetric addition of pronucleophiles to

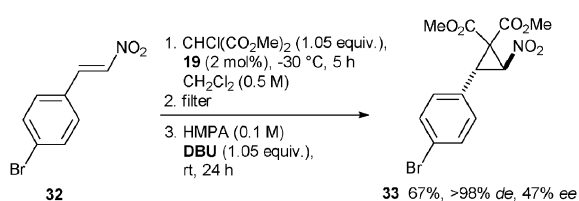


Scheme 5 An *umpolung* Michael reaction promoted by **18**.

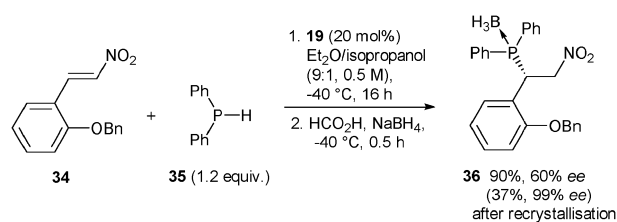
nitroalkenes are highly pliable synthetically.^{24,25} Scheidt and co-workers²⁶ discovered a method for synthesising an adduct formally derived from a Stetter-type addition of an acyl anion equivalent to a nitroolefin. Treatment of a mixture of nitroalkene **27** and thiazolium ion **28** in the presence of a fluoride ion source and stoichiometric amounts of **18** resulted in the formation of β -nitroketone **29** with good levels of enantioselectivity (Scheme 5). It was posited that **28** serves as a precursor to an acyl anion equivalent – on desilylation it forms alkoxide **30** which could form Breslow intermediate **31** (the nucleophilic reaction component) *via* a proton transfer process. While the reaction is not catalytic in thiourea and only a single enantioselective example was reported, this first report of a direct nucleophilic addition of a carbonyl unit to a nitroalkene is nonetheless of some significance and holds considerable synthetic promise.

In a related study to that outlined in Scheme 4, we found that halomalonates could also be added to nitroalkenes in the presence of **19**, which allowed the first asymmetric Michael addition–cyclopropanation reaction sequence involving these substrates.²⁷ 2 Mol% of **19** catalysed the addition of chlorodimethylmalonate to nitroalkene **32**. The Michael adduct could be filtered off and immediately dissolved in HMPA, whereupon addition of the strong amine base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in cyclisation to afford the densely functionalised nitrocyclopropane **33** as a single diastereomer with moderate enantioselectivity (Scheme 6).

The organocatalytic asymmetric addition of secondary phosphines to nitroalkenes has been achieved by Melchiorre and co-workers.²⁸ Catalyst screening studies identified **19** as the optimum promoter of the addition of diphenylphosphine (**35**) to nitroolefins at low temperature. Relatively high catalyst loadings are required to furnish **36** in good yield and moderate ee (after protection with *in situ* formed borane, Scheme 7), however the products can be enantioenriched almost to optical



Scheme 6 An asymmetric Michael addition–cyclopropanation reaction sequence.



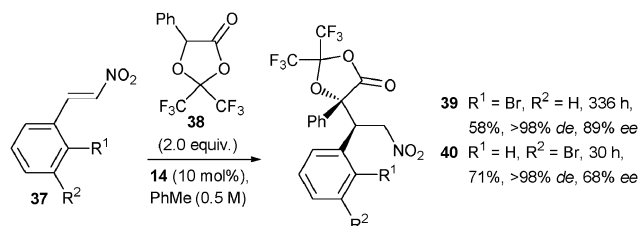
Scheme 7 Asymmetric hydrophosphination.

purity by recrystallisation and are of obvious general interest as ligand candidates in metal-based catalyst systems and are difficult to prepare by other methods.

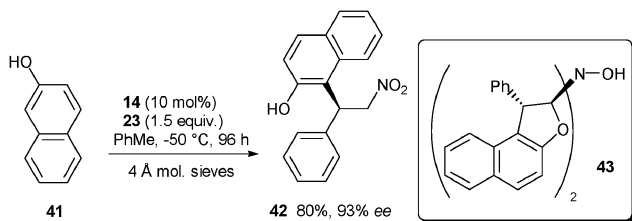
Dixon and co-workers²⁹ added acidic 5-aryl-1,3-dioxolanone heterocycles derived from mandelic acid derivatives and hexafluoroacetone to nitrostyrenes in the presence of the cinchonine-derived catalyst **14**. The products of these reactions are highly versatile and can be easily converted to a range of α -hydroxy acid derivatives. While the diastereoselectivity observed in these processes was close to perfect in most cases, both reaction yield and product enantiomeric excess ranged from *ca.* 60 to *ca.* 90%. Nitroolefin substrates incorporating *ortho*-substitution furnished the products with the higher enantiopurity than less hindered analogues, albeit at the expense of reaction rate (Scheme 8).

The use of naphthols as the nucleophilic reaction component in Friedel–Crafts type reactions has been reported by Chen and co-workers.³⁰ This example is of interest; unlike the cases detailed so far, here the pronucleophile is activated by the amine unit of catalyst **14**, but not at the atom forming a bond to the electrophile. Using the nitroalkene as the limiting reagent good yields and enantioselectivity between 85 and 95% ee could be obtained at low temperatures across a range of aryl- and alkyl-substituted nitroalkene derivatives (Scheme 9). An example of the use of 1-naphthol as the nucleophile was reported to furnish the adduct with lower yield and selectivity (67%, 80% ee). After extended reaction times the authors noticed that the catalyst could promote the dimerisation of the Friedel–Crafts adduct to give **43** (Scheme 9).

Inspired by the mode of action of polyketide synthases, which catalyse decarboxylative acylation reactions of CoA-bound malonic acid half-thioesters in the biosynthesis of fatty acids and polyketides (**A**, Scheme 10), Wennemers and Lubkoll³¹ proposed that a (thio)urea-substituted cinchona alkaloid catalyst could play the oxyanion-stabilising role performed by Asn and His conjugate acid residues in the enzymatic system, while the catalyst's amine unit could deprotonate the substrate, thereby forming an ammonium ion which could, in principle, activate a nitroolefin electrophile (**B**,



Scheme 8 Asymmetric addition of dioxolanones to nitroalkenes.



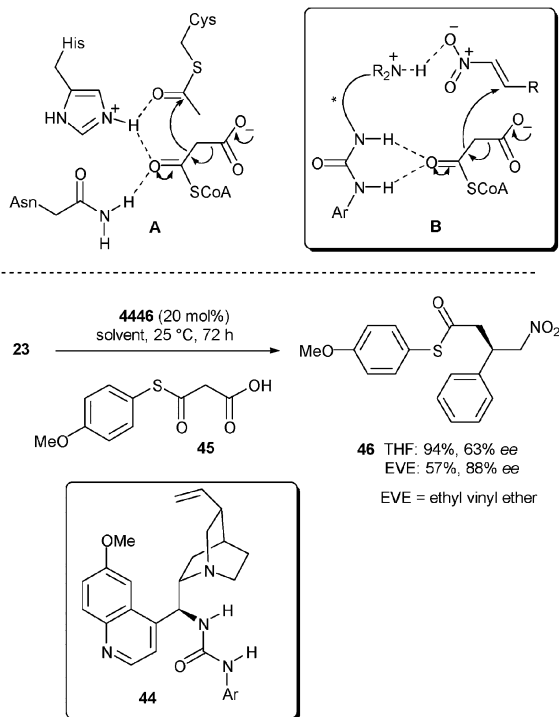
Scheme 9 Catalysis of an asymmetric Friedel-Crafts-type reaction.

Scheme 10). Catalyst screening identified urea **44** as being superior to the corresponding thiourea analogue;³² this catalyst could promote an asymmetric decarboxylation/Michael addition between thioester **45** and **23** to give adduct **46** in good yield and enantioselectivity. The choice of solvent is important in these reactions – the processes are more efficient in THF but more selective in ethyl vinyl ether.

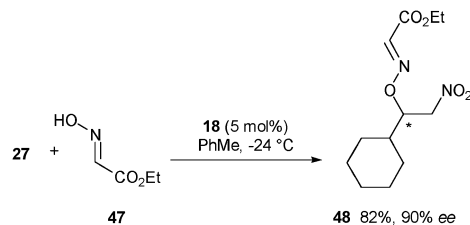
Jørgensen and co-workers³³ demonstrated the enantioselective addition of oximes to nitroolefins catalysed by either **18** or **20** (Scheme 11). For instance the oxy-Michael addition of ethyl glyoxalate oxime **47** to nitroalkene **27** in the presence of **18** (5 mol%) allowed the isolation of adduct **48** in good yield and 90% ee. The method is general for nitroolefin substrates with aliphatic substituents, however nitrostyrenes are not compatible due to a competitive retro-Michael process.

α,β -Unsaturated ketones

Ketones possess a single Lewis-basic heteroatom which has been shown to be capable of accepting two hydrogen bonds from urea derivatives^{11,34} and thus it is perhaps unsurprising that enones have also been shown to be useful substrates



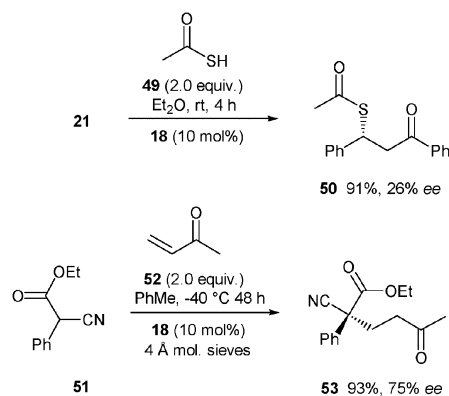
Scheme 10 A biomimetic asymmetric decarboxylative Michael reaction.



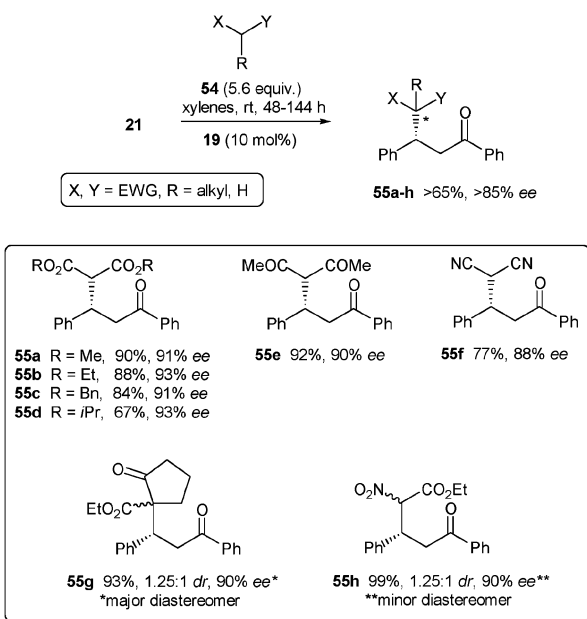
Scheme 11 Oxime-addition to nitroolefins.

for use in conjunction with thiourea modified cinchona alkaloids. After Soos' seminal work in this area, bifunctional thiourea-catalysed additions of thioacetic acid and α -substituted cyanoacetates to chalcone and methyl vinyl ketone, respectively were reported by the groups led by Wang³⁵ and Chen³⁶ (Scheme 12). The latter case is of interest as stereoselectivity comes not from the formation of an sp^3 -stereogenic centre on the addition of a nucleophile to an internal activated olefin, but rather from the attack of the Michael acceptor at a single enolate face of the conjugate base of the pronucleophile. In both reactions however Takemoto's catalyst **12** offered superior levels of product enantioselectivity and thus the cinchona alkaloid catalysts were not investigated further.

Wang *et al.*³⁷ investigated the asymmetric addition of carbon acids to chalcones catalysed by **19** at 10 mol% levels. These reactions were of exceptionally broad scope – the Michael reaction between a range of acidic pronucleophiles of general type **54** and **21** to give adducts **55a–h** could be carried out with excellent efficiency and enantioselectivity at ambient temperature (Scheme 13). It is noteworthy that in these reactions **19** was found to be a superior catalyst to both **18** and **12**. Use of a β -ketoester substrate resulted in the formation of a product with a quaternary stereocentre with high enantio- but poor diastereoselectivity. Further studies determined that the methodology was also robust with respect to the chalcone reaction component: the addition of diethyl malonate to chalcones of variable steric and electronic characteristics occurs with uniformly high product yields and excellent ee. Chen and co-workers later studied the addition of α -cyanoacetate to chalcones.³⁸ Again catalyst **19** proved optimal and the reactions proceeded with high enantioselectivity but low diastereoselectivity (*ca.* 2 : 1 *syn* : *anti* in most cases).

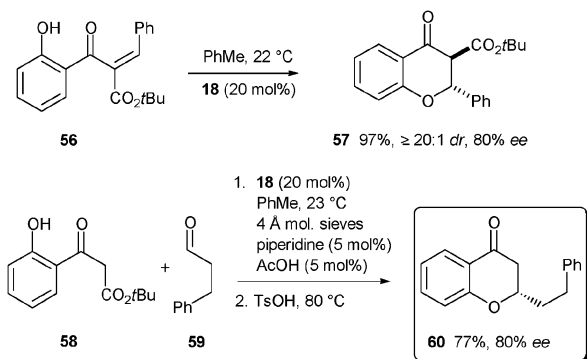


Scheme 12 Addition of thioacetic acid and cyanoacetates to enones.

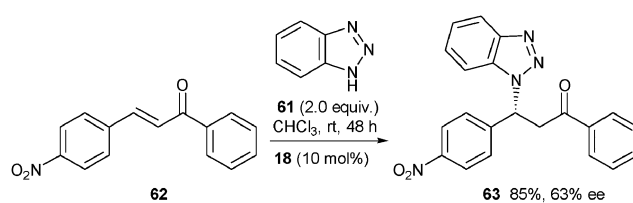


Scheme 13 Addition of a range of acidic pronucleophiles to **21**.

Scheidt *et al.*³⁹ have developed a thiourea-catalysed enantio- and diastereoselective 6-*endo*-trig cyclisation reaction of *o*-acyl phenol **56** to give **57** with excellent levels of stereocontrol (Scheme 14) using catalyst **18** at 20 mol% loading.⁴⁰ A subsequent acid catalysed *tert*-butyl ester deprotection/decarboxylation sequence could also be carried out in one pot to give derivatives of the medicinally relevant flavanone family if desired. The authors extended this concept further to the one pot synthesis of a chromanone natural product – treatment of a solution of β -ketoester **58** and aldehyde **59** under Knoevenagel conditions in the presence of **18** led to the condensation of the two carbonyl compounds to form the Michael acceptor substrate capable of being cyclised to form an analogue of **57** which could be deprotected and decarboxylated in the presence of acid at 80 °C to yield flindersiachromanone (**60**) in good yield and ee. It was suggested that the catalyst operates *via* both hydrogen bonding between the thiourea component and the β -ketoester moiety and deprotonation of the phenol nucleophile by the quinuclidine ring. This proposal was supported by the observation that the monofunctional catalyst *N,N*-bis-trifluoromethylphenyl thiourea failed to promote the



Scheme 14 Asymmetric synthesis of flavanones and chromanones.



Scheme 15 Asymmetric addition of benzotriazole to chalcones.

reaction, while neither quinine nor a combination of quinine and the aforementioned thiourea catalysed the reaction with high ee.

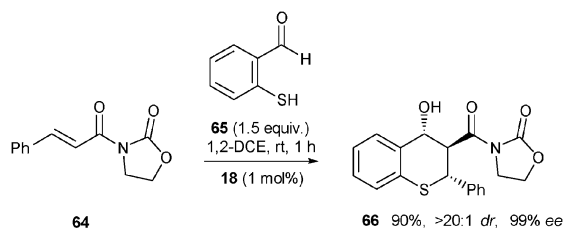
The addition of a heterocyclic pronucleophile to chalcones has also been reported.⁴¹ These reactions are not as enantioselective as those involving carbon-based nucleophiles detailed in Scheme 12. Under optimum conditions 1*H*-benzotriazole (**61**) could be added to chalcone **62** in the presence of **18** to furnish the heterocyclic adduct **63** in good yield and moderate enantiomeric excess (Scheme 15).

α,β -Unsaturated amides⁴²

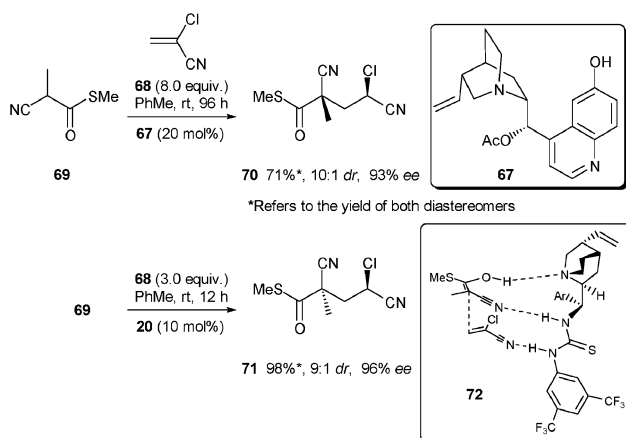
In an extension of the methodology from Chen's group¹⁹ which marked the introduction of thiourea-modified cinchona alkaloid catalysts, Wang and co-workers⁴³ have discovered a highly efficient organocatalysed stereoselective tandem Michael–aldol reaction sequence (Scheme 16). Exposure of oxazolidinone **64** to a 1.5-fold excess of thiophenol **65** in the presence of just 1 mol% of catalyst **18** in 1,2-dichloroethane gives the cyclised product **66** with excellent yield and outstanding levels of control over the formation of three new contiguous stereocentres. Subsequent studies revealed that the steric and electronic characteristics of both the oxazolidinone aryl substituent and the thiophenol pronucleophile exerted minimal influence over either reactivity or selectivity (reported yields >75%, selectivity >90% ee, >20 : 1 dr in all cases).

α,β -Unsaturated nitriles

Deng's group have been interested in the design of catalytic reactions which generate products with two non-contiguous stereocentres. While reactions which generate contiguous stereocentres with good stereocontrol are not uncommon (*e.g. vide supra*), the analogous stereoselective processes where the chiral centres are not adjacent are comparatively rare. Previously they had reported that the 6'-demethylated cinchona alkaloid catalyst **67** promotes the Michael addition between α -chloroacrylonitrile (**68**) and the α -cyanothioester **69** (for example) to give the adduct **70** with good diastereo- and enantioselectivity (Scheme 17).^{8g} Later the same group explored the same chemistry with the thiourea catalyst **18** and its



Scheme 16 A highly stereoselective tandem Michael-aldol process.



Scheme 17 Formation and control over non-adjacent stereocentres.

quinidine-derived analogue **20** and found that not only do these materials promote smooth reactions at lower loadings with approximately the same levels of stereocontrol, the adduct formed is the complementary diastereomer (*i.e.* **71**) to that formed using **67**.⁴⁴ Thus by using both the quinine and quinidine-derived analogues of both catalyst systems any one of the four diastereomers of **70** (and a wide range of related analogues derived from variants of **69**) can be synthesised with in high enantiopurity under mild conditions. A stereochemical model (model using catalyst **18** shown) was proposed involving the activation of the pronucleophile by the thiourea unit and the quinuclidine moiety while the Michael acceptor also accepts a hydrogen bond from the thiourea catalyst component – allowing both the Michael addition and subsequent proton transfer reaction to occur in a controlled chiral environment.

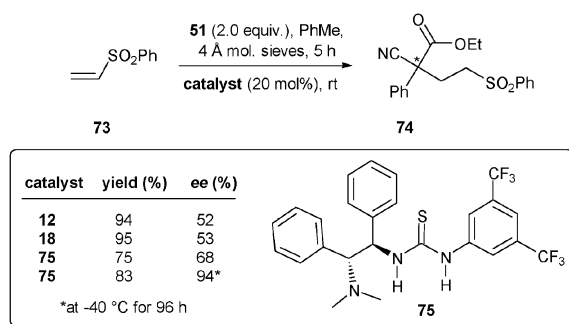
Vinyl sulfones

The potential of vinyl sulfones to serve as synthetically versatile (hydrogen-bond accepting) substrates in catalytic asymmetric Michael addition reactions has begun to be realised recently.^{45,46} Chen and co-workers⁴⁷ screened a range of bifunctional thiourea-based organocatalysts as promoters of the addition of α -substituted cyanoacetates to vinyl sulfone (**73**). While both Takemoto's thiourea and modified cinchona alkaloids bring about efficient catalysis at room temperature, product enantiomeric excess was moderate. Somewhat surprisingly, use of the more flexible catalyst **75** resulted in more selective addition and under optimum conditions **74** could be prepared in good yield and 94% ee (Scheme 18). Further investigation of the substrate scope determined that a variety of different α -aryl cyanoacetates are compatible with the methodology and that α -alkyl cyanoacetates can be added to 1,1-bis(vinyl)sulfones, albeit generally with lower enantioselectivity.

Catalyst application: 1,2-addition reactions

Imines

Asymmetric addition reactions to imines and their derivatives were the first transformations to succumb to catalysis by chiral



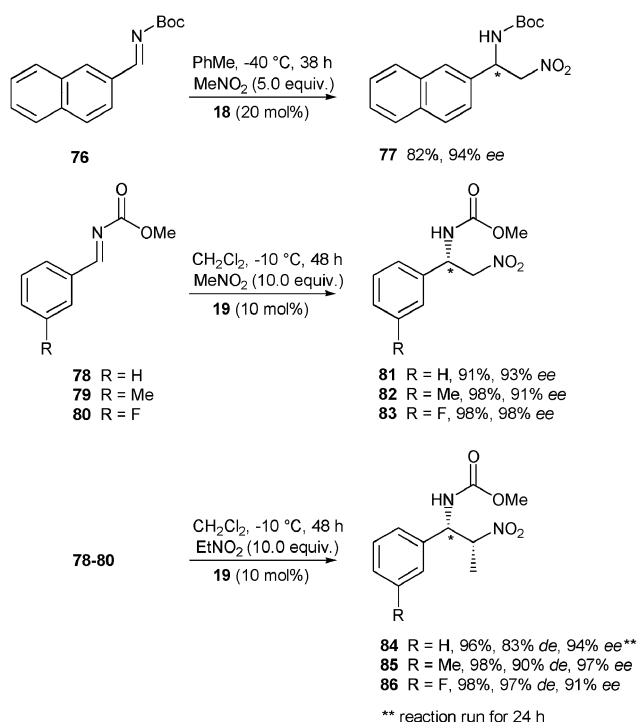
Scheme 18 Addition of α -aryl cyanoacetates to vinyl sulfone.

(thio)urea derivatives.⁴⁸ This precedent, together with the general importance of the development of new routes to enantioenriched amines prompted the rapid application of thiourea-substituted cinchona alkaloids to the catalysis of addition reactions to imines.

The first such report detailed the asymmetric addition of nitromethane to a variety of *N*-protected aromatic aldimines. Ricci *et al.*⁴⁹ demonstrated that of eight quinine-derived compounds of variable substitution and absolute configuration at C-9 tested (including the parent alkaloid itself) **18** proved the most active and enantioselective as a catalyst for the aza-Henry reaction⁵⁰ between nitromethane and the *N*-Boc imine derived from benzaldehyde. Other carbamate protecting groups gave similar results, however, use of phosphinoyl-, tosyl, aryl and simple amide protecting groups resulted in diminished product enantioselectivity. Subsequent optimisation of the reaction conditions resulted in a highly enantioselective addition of nitromethane to optimal substrate **76** catalysed by 20 mol% of **18** to give the β -nitro amine product **77** with excellent enantiopurity (Scheme 19).

In a similar study Schaus and co-workers⁵¹ utilised **19** to promote the same reaction class involving methylcarbamate derivatives and a relatively large excess of nitromethane in dichloromethane solvent at -10 °C. Under these conditions the aromatic Mannich adducts **81–83** could be isolated with >90% ee (Scheme 19). When nitroethane was used as the pronucleophile under otherwise identical conditions excellent *syn*-diastereoselectivity results without a significant erosion of enantioselectivity (Scheme 19). Based on molecular modeling studies the authors proposed a rationale to explain the stereoselectivity observed which hinges on the binding of the pronucleophile conjugate base (and not the electrophile) to both the thiourea moiety and the protonated quinuclidine catalyst component.^{51,52}

Dixon and co-workers⁵³ extended the scope of this reaction to include dicarbonyl pronucleophiles. Acetyl acetone, malonate esters and β -ketoesters could all participate in an asymmetric Mannich reaction⁵⁴ with *N*-carbamoyl protected imines with good to excellent product enantiomeric excess (particularly in the case of the latter two pronucleophile classes) in the presence of **14** at low temperature. For example, the Cbz-protected aldimine **87** underwent a clean Mannich reaction with dimethylmalonate, which allowed the isolation of adduct **88** in essentially quantitative yield and 97% ee. The hydrolysis and decarboxylation of representative adducts to reveal orthogonally protected β -amino acid derivatives without racemisation in a one-pot



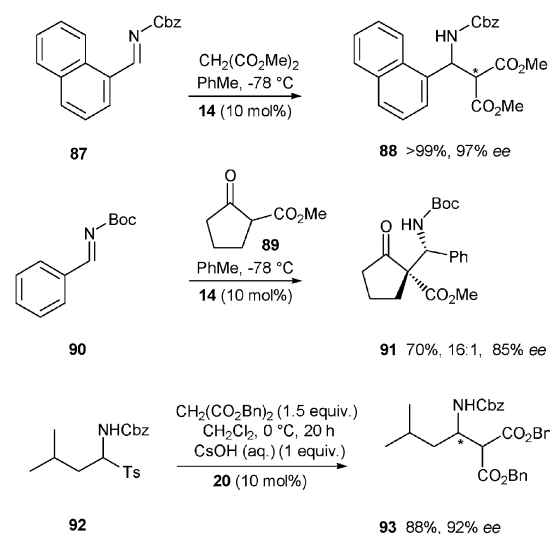
Scheme 19 Modified cinchona alkaloid catalysed aza-Henry reactions.

procedure was also demonstrated. β -Ketoesters such as methylcyclopentanone-2-carboxylate (**89**) reacted with similar efficiency and good diastereoselectivity but enantioselectivity was inferior to that observed using malonates (Scheme 20). Shortly afterwards first Deng and co-workers⁵⁵ and then Schaus and co-workers⁵¹ obtained similar findings using quinine and quinidine-derived catalyst analogues. Interestingly, Schaus found that smooth and selective (>90% ee) addition to the methyl carbamate **78** in CH_2Cl_2 catalysed by **18** at higher reaction temperatures of -35°C .

One of the drawbacks associated with these methodologies is their incompatibility with alkyl-substituted aldimines, which tautomerise to the corresponding enamine derivatives under the reaction conditions. In a separate report, Deng's group⁵⁶ circumvented this problem by generating the substrate *in situ* from the base-mediated elimination of HSO_2Ar from α -amido sulfones. Under these conditions both Boc- and Cbz-protected aliphatic aldimines could be generated and trapped by dibenzylmalonate catalysed by either **18** or **20** at 0°C . The Cbz-protecting group is superior to a Boc-carbamate in these reactions as the *in situ*-synthesised imines from the latter substrate class underwent tautomerisation under the reaction conditions. Of the eight α -amido sulfone substrates evaluated **92** proved optimal (Scheme 20).

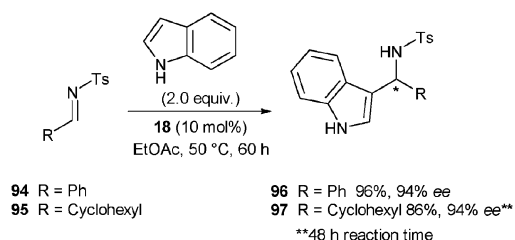
Chen and co-workers found that **18** catalyses asymmetric vinylogous Mannich reactions between **90** and α,α -dicyanoolefins.

While the enantiomeric excess of the product from this reaction was appreciable (61% ee), a modified analogue of Takemoto's catalyst was shown to be superior in this reaction and no further experimentation with the cinchona alkaloid-based system was reported.⁵⁷



Scheme 20 Asymmetric modified cinchona-alkaloid catalysed Mannich reactions.

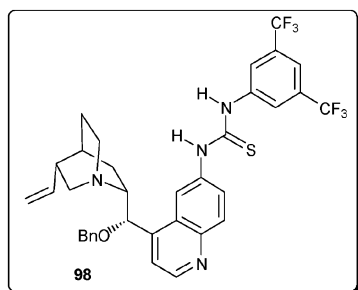
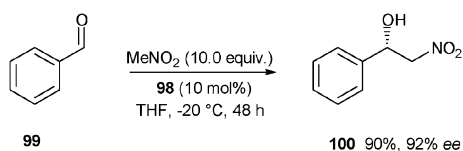
The 3-indolyl methanamine subunit is a constituent of a number of indole-alkaloid natural products.⁵⁸ Recognising a gap in the literature concerning the catalytic asymmetric synthesis of these compounds from indoles and imines *via* a robust methodology applicable to both aromatic and alkyl-substituted aldimine derivatives, Deng and co-workers⁵⁹ developed the first asymmetric organocatalytic route to this important class of compound using catalysts **18** and **20**. A range of substituted indoles could be added to *N*-sulfonyl protected imines with high levels of enantiomeric excess at 50°C in concentrated solution. This method offers several advantages over the previous literature benchmark for this reaction,⁶⁰ not least of which is the uniformly high enantioselectivity observed regardless of the electronic characteristics of either reaction component. This study also reported the first examples the participation of alkyl imines in this enantioselective Friedel-Crafts-type⁶¹ process (Scheme 21).



Scheme 21 Asymmetric Friedel-Crafts-type reactions with imine substrates.

Aldehydes

In 2005 Hiemstra and co-workers⁶² submitted a report demonstrating that C-9 is not the sole position on the cinchona alkaloid backbone where thiourea functionality can be installed with advantage. Substitution of the 6'-OMe group with a thiourea moiety and benzylation of the C-9 hydroxy substituent without disturbing the stereochemical configuration of



Scheme 22 Asymmetric Henry reaction catalysed by a C-6' substituted catalyst.

the natural alkaloid resulted in a powerful catalyst for the asymmetric Henry reaction.

The quinuclidine-derived catalyst **98** was capable of promoting the highly enantioselective Henry reaction between nitromethane and aromatic aldehydes (electron rich, electron deficient and hindered variants) in THF at $-20\text{ }^{\circ}\text{C}$ (Scheme 22). The corresponding quinine-derived catalyst proved just as useful and the authors proposed a mode of action involving activation of the aldehyde by the thiourea unit and deprotonation of the nitromethane acid by the catalyst's quinuclidine ring.

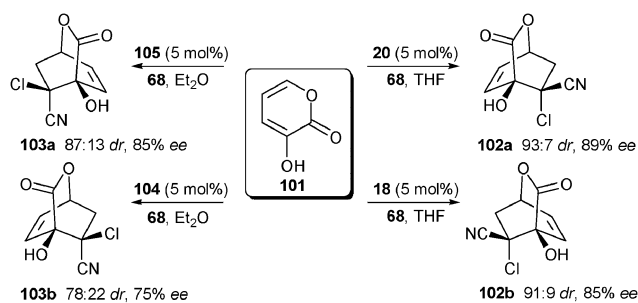
Catalyst application: other reactions

Diels–Alder reactions

Deng and co-workers⁶³ have applied both thiourea-substituted and C-6' demethylated cinchona alkaloid derivatives to the catalysis of the Diels–Alder reaction between 2-pyrones and α,β -unsaturated electrophiles. For example, based on the known ability of **18** and **20** to promote asymmetric additions to acrylonitriles,⁴⁴ Deng reasoned that these catalysts could bring about a HOMO-elevating interaction between the quinuclidine nitrogen atom and the hydroxy group of diene **101**, and a LUMO-lowering hydrogen-bonding interaction between the thiourea and the nitrile lone pair of dienophile **68**. At 5 mol% loading **18** and **20** could catalyse the formation of **102a,b** with good *exo*-selectivity and excellent enantioselectivity (Scheme 23). Most usefully (as was the case with the study detailed earlier – see Scheme 17), C-6' demethylated cinchona alkaloid derivatives **104** and **105** promote the formation of the corresponding *endo*-diastereomers **103a,b** with high enantiomeric excess and reduced (but synthetically acceptable) diastereoselectivity. Thus all four diastereomeric products can be obtained with high levels of enantiopurity.

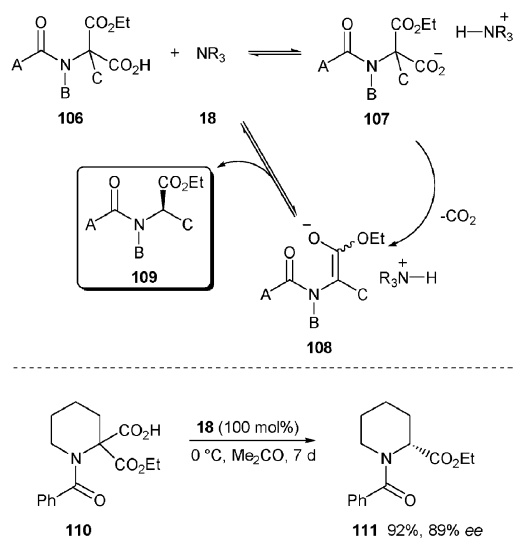
Decarboxylative protonation

Rouden and co-workers⁶⁴ utilised **18** and **20** as chiral bases in the decarboxylative protonation of α -aminomalonnate hemi-

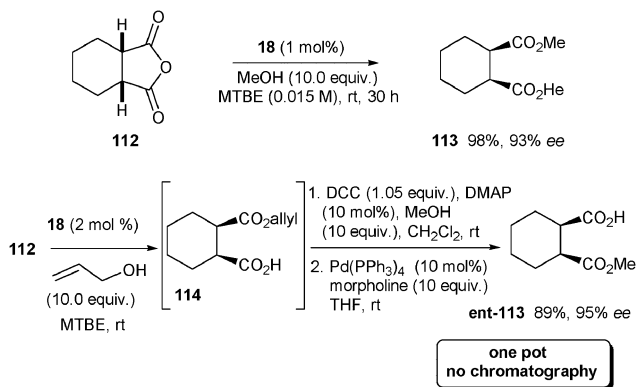


Scheme 23 Asymmetric Diels–Alder reactions.

esters. The idea is that treatment of carboxylic acid **106** with the chiral base **18** would lead to ion pair **107** – the decarboxylation of which leads to ammonium enolate **108**. Subsequent proton transfer in a face-selective manner gives the protected α -amino acid derivative **109** with regeneration of **18** (Scheme 24). It was found that this methodology could be successfully applied to a range of protected α -aminomalonnates. High yields and enantioselectivities (the highest reported for any organic base) were possible at $0\text{ }^{\circ}\text{C}$ in polar aprotic solvents. While (as the proposed mechanism suggests) **18** can be utilised in catalytic amounts, its activity is not sufficient under these conditions for application at substoichiometric loadings: even at 100 mol% levels the reaction requires 7 days to run to completion. A compensating factor is that the catalyst can be readily recycled and reused after reaction.



Scheme 24 Enantioselective decarboxylative protonation.



Scheme 25 Desymmetrisation of *meso* anhydrides.

Desymmetrisation of *meso* anhydrides

The catalytic asymmetric desymmetrisation of *meso* anhydrides *via* alcoholysis is a powerful methodology for the preparation of synthetically useful hemiesters with the generation of either single or multiple stereocentres with high levels of enantiocontrol. The benchmark catalyst systems for this reaction developed independently by the groups of Bolm^{65,66} and Deng^{67,68} both involve the use of cinchona alkaloid derivatives as general-base catalysts for the addition reaction. While these methodologies are very useful, they are not entirely amenable to use on process scale – excellent yields and enantioselectivities are possible with catalyst loadings of 110 mol% or between 5–30 mol% and temperatures of –55 °C or between –20 and –40 °C, respectively. We proposed that catalysts capable of also activating the anhydride moiety *via* hydrogen bonding should offer potential advantages in terms of both rate and selectivity.⁶⁹ Screening studies allowed the identification of conditions under which 1 mol% of catalyst **18** promoted the desymmetrisation of **112** (for example) at ambient temperature to give hemiemester **113** in excellent yield and enantiomeric excess in 30 h (Scheme 25). We also found that allyl alcohol could be used as the nucleophile in these reactions – this allows the synthesis of both antipodes of **113** using a single catalyst system *via* the manipulation of allyl hemiemester **114** without chromatography (**113** is isolated pure after a simple acid/base wash/extraction sequence).

Conclusions

It is now almost exactly three years since the submission of the first report detailing the use of thiourea-substituted cinchona alkaloid-based catalysts. In this short time these compounds have proven themselves to be extraordinarily useful catalysts for (*inter alia*) the 1,4- or 1,2-asymmetric addition of acidic pronucleophiles to a wide range of substrates. The key to their success is their ability to interact with both the ‘nucleophilic’ and ‘electrophilic’ reaction components simultaneously and to control their encounter in a well-defined chiral environment. The catalysts are easily synthesised from the readily available alkaloids and have been shown to catalyse enantioselective reactions at temperatures ranging from –78 to 75 °C. Much has already been demonstrated, however the scope and utility of these materials has not yet been fully explored and while it is

already certain that their place alongside other modified cinchona alkaloid derivatives in the organocatalysis toolbox is assured, for the time being their contribution to this burgeoning field looks set to continue apace.

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