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Enantioselective protonation

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Enantioselective protonation is a common process in biosynthetic sequences. The decarboxylase and esterase enzymes that effect this valuable transformation are able to control both the steric environment around the proton acceptor (typically an enolate) and the proton donor (typically a thiol). Recently, several chemical methods for achieving enantioselective protonation have been developed by exploiting various means of enantiocontrol in different mechanisms. These laboratory transformations have proved useful for the preparation of a number of valuable organic compounds. Here, we review recent reports of enantioselective protonations, classifying them according to mechanism, and discuss how a deeper understanding of the processes can lead to improved methods for effecting this most fundamental method of obtaining enantiopure compounds.

A fundamental method for generating a tertiary carbon stereocentre is to deliver a proton to a carbanion intermediate. However, enantioselective transfer of a proton presents unusual challenges — specifically, manipulating a very small atom and avoiding product racemization at a particularly labile stereocentre. As a result, the conditions for a successful enantioselective protonation protocol may be very specific to a certain substrate class. Tertiary carbon stereocentres are extremely common in valuable biologically active natural products, and thus the need for synthetically useful enantioselective methods to form these stereocentres is vital[1].

In this review, we discuss several strategic approaches to enantioselective protonation. Emphasis has been placed on recently developed methods and their accompanying mechanisms to update the most recent prior reviews on this topic[2–8]. Each method relies on particular stereochemical control elements based on the mechanism of the protonation transformation. Appreciation of these controlling elements may lead to improved methods for preparing valuable chiral materials for a variety of synthetic applications.

Important factors in achieving enantioselective protonation

Several of the most important practical features of enantioselective protonation were enumerated in Fehr's 1996 review[2]. Principal among these is the fact that enantioselective protonations are necessarily kinetic processes, because under thermodynamic control a racemate would be formed. Accordingly, it is often necessary to match the pK_a of the proton donor and the product to prevent racemization before product isolation. It is unfortunate that the same anion stabilizing groups (for example, ketones) that make protonations relatively easy to achieve also impart a degree of instability in the product. This has led some researchers to explore hydrogen atom transfer reactions in lieu of Brønsted acid-mediated protonations (see 'Enantioselective hydrogen atom transfer' below).

In addition to the obvious challenges of product stability under the reaction conditions, the rapid rate of proton exchange in solution often leads to significant levels of background reaction without the intercession of the chiral control element. As a result, typical proton donors are relatively weak acids that react with the proton acceptor in a slower and more controlled fashion.

As substrates for enantioselective protonation generally involve a prochiral sp^2-hybridized atom, the stereochemistry of the substrate is a concern. In some cases, the ability to generate stereodefined proton acceptors (for example, a pure *E*- or *Z*-enolate) is critical to the success of a protonation method. In other cases, however, the two stereoisomers of enolate may in fact lead to the same enantiomer of product[5]. To obviate this concern many researchers choose to investigate cyclic substrates; in turn, this may lead to a limited substrate scope for a particular system. The method of accessing the reactive proton acceptor is among the most important facets of each protonation system, and many strategies have been explored (for example, conjugate addition, addition to ketenes, and decarboxylation from β-ketoesters).

Finally, the fine mechanistic details of enantioselective protonations are often not well understood. As typical proton acceptors are stabilized anions, there are multiple Lewis basic sites available for protonation. It is likely that these sites protonate at kinetically different rates dependent on the specific reaction conditions. Potentially, enantioselective protonations may be achieved either by direct protonation to generate the desired stereocentre, or by protonation at a different site followed by enantioselective tautomerization. In an important recent report, Fehr[9] demonstrated that isolated enol **1** (Fig. 1) could be transformed enantioselectively into ketone **4** (an immediate precursor to the rose-smelling fragrance compound (*S*)-(α)-damascone) via the proposed aggregate complex **3**, and this mechanistic course seemed to be operative in the analagous protonation of a lithium enolate with the conjugate acid of alkoxide **2**. Based on these findings, perhaps some protonation protocols are more accurately described as enantioselective tautomerization reactions. Although ultimately inconsequential in terms of the products obtained, insights into the specific

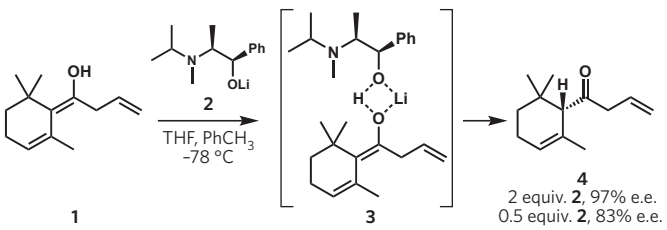

Figure 1 | Enantioselective tautomerization of an isolated enol. Fehr[9] demonstrated that enols in the presence of a chiral Lewis base may be transformed into enantioenriched ketones. This indicates a possible alternative mechanism for enantioselective protonation and suggests that sometimes these transformations may be better described as enantioselective tautomerization rather than protonation.

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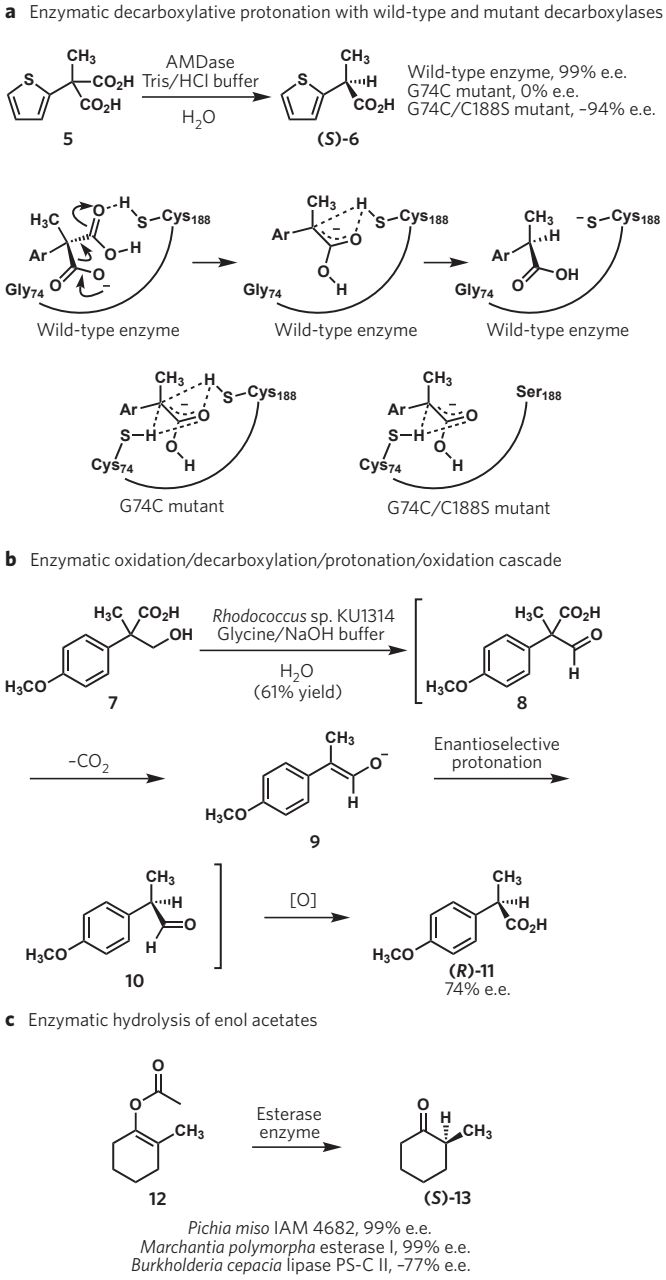

Figure 2 | Enzyme-catalysed enantioselective protonation reactions. a, Ohta and co-workers[10,11] found AMDase transformed arylmalonic acids into enantioenriched arylpropionic acids. Noting the homology of AMDase to racemase enzymes led to the design of mutant enzymes that formed racemic or enantiomeric arylpropionic acids[15,16]. **b**, Ohta and co-workers[18] identified a *Rhodococcus* species capable of initiating an oxidation/decarboxylation/protonation/oxidation cascade to convert tropate derivatives to enantioenriched propionic acids. **c**, Several esterase enzymes have been found to convert enol acetates to enantioenriched ketones[19–21]. Tris, tris(hydroxymethyl)aminomethane.

mechanistic course of the reaction are important to improve these systems. However, only rarely have these levels of mechanistic understanding been realized.

Enantioselective protonation in enzymatic systems

Nature has evolved several efficient enzymes that catalyse enantioselective protonation reactions on useful organic building blocks. In recent reports, decarboxylases and esterases have proved to be two popular classes of natural enzymes for the construction of α-stereocentres adjacent to ketones. Esterases release latent enolates from prochiral substrates whereas decarboxylases generate enolates *in situ* from malonic acid derivatives (Fig. 2).

Ohta and co-workers[10,11] isolated arylmalonate decarboxylase (AMDase) from the Gram-negative bacterium *Alcaligenes bronchisepticus* and found that it catalyses the decarboxylative enantioselective protonation of α-aryl-α-methyl-malonates through the proposed mechanism in Fig. 2a. Yields and enantiomeric excesses were excellent for substrates with various α-aryl substitutents (up to 99% yield and 99% e.e.). Experiments have shown that the Cys188 residue is essential for activity, and this site is the putative proton donor that stabilizes the enolate intermediate. A Hammett study[12] of the reaction found a value for the reaction constant, ρ, of +1.19, which is consistent with a negatively charged transition state[10]. Recently, preliminary X-ray diffraction experiments and an X-ray crystal structure of AMDase were reported[13,14].

Accessing the opposite enantiomeric series of products required additional investigation[15,16]. Analysis of the enzyme amino acid sequence was carried out to check for homology with known enzymes. The Cys188 residue is conserved in several racemase enzymes from other microorganisms. Glutamate racemase, found in the bacterium *Lactobacillus fermenti,* contains an active site similar to that of AMDase, but with cysteine residues (Cys188 and Cys74) on both sides of the substrate. Presumably, one of the cysteine residues acts as a base and generates an enolate intermediate, which can then be protonated non-selectively from either cysteine residue to give rise to a racemic mixture. When Ohta and co-workers prepared a G74C mutant of AMDase to mimic these racemase enzymes, they found that racemic α-thienylpropionic acid (**6**, Fig. 2a) was formed in 37% yield from the malonic acid substrate (**5**). Further explorations based on this homology hypothesis led to the preparation of a double mutant of AMDase (G74C/C188S) that removed the native cysteine residue while maintaining the mutant residue on the opposite face of the substrate. The opposite enantiomer of product was indeed obtained with this new enzyme in 94% enantiomeric excess, although yields decreased to 60% and the activity of this mutant was several orders of magnitude lower than the wild type. Some activity was rescued by performing random mutagenesis and identifying more active triple mutants[17].

Decarboxylase-type activity was also observed in the conversion of β-hydroxyacid **7** to optically active α-arylpropionic acid (*R*)-**11** by Gram-positive bacteria *Rhodococcus* sp. KU1314 (Fig. 2b)[18]. In the proposed metabolic pathway, enzymes in the microorganism non-selectively oxidize hydroxyacid substrate **7** to aldehyde **8** and then decarboxylate the corresponding acid to form enolate **9**, which undergoes enantioselective protonation to generate aldehyde **10**. Subsequent non-selective oxidation affords enantioenriched α-arylpropionic acid **11**. Mechanistic experiments were consistent with this proposed enantioselective protonation mechanism rather than alternative possibilities such as enantioselective oxidation steps. Enantioselectivity and yield varied considerably depending on the aryl and alkyl groups at the α-position in the substrate, but enantiomeric excesses up to 85% could be achieved. Using an electron-poor aryl group seemed to give poor enantioselectivity due to increased acidity of the proton in the presumed aldehyde intermediate. When the alkyl group was changed from methyl to ethyl, the reaction yield dropped, suggesting that the enzyme is sensitive to sterics.

Several researchers have used esterases to obtain enantioenriched protonation products. In 1990, Ohta and co-workers[19] reported that live *Pichia miso* IAM 4682 yeast cells catalyse the conversion of enol acetates to enantioenriched ketones (for example, **12** → **13**, Fig. 2c). High levels of enantiomeric excess were attained with a variety of enol esters. For larger ring systems, the reaction yield and absolute configuration varied unpredictably with ring size. In an impressive application, this yeast-mediated reaction was used to generate an α-stereocentre in a 12-membered ring with 96% e.e.

Hirata and co-workers[20] reported that liverwort *Marchantia polymorpha* esterase I also catalyses the same reaction on a variety of substrates with differing alkyl side chains, but the facial preference for proton delivery varied for different enolate substitutions. For example, the enzyme delivered (*S*)-2-methylcyclohexanone (**13**) and (*R*)-2-*n*-propylcyclohexanone from their respective enol acetates in 99% conversion and 99% e.e.

Lipase PS-C II, originating from Gram-negative bacteria *Burkholderia cepacia*, may also be used for the hydrolysis of 1-acetoxy-2-methylcyclohexene (**12**). Sakai and co-workers[21] discovered that the enantiomeric excess of the product ((*R*)-**13**) was largely dependent on the temperature and the proton source. The best results were obtained by running the reaction at 0 °C with solid-supported enzyme PS-C II and ethanol as proton source (82% conversion, 77% e.e.).

Among these enzymatic approaches, a general problem appears to be the difficulty of enzyme modification to give the unnatural antipode of product. Another limitation is the need for buffers to help stabilize enzymes or cells. Substrate scope is also limited due to the specificity of substrate recognition. For these reasons, enzymatic reactions do not provide a general solution to the synthesis of enantioenriched protonation products. Laboratory means for enantioselective protonation may enable a more universal protocol due to the ability to tune the structural and electronic features of the catalyst. These natural systems do, however, demonstrate many of the key controlling elements necessary for successful enantioselective protonation.

Approaches for non-enzymatic enantioselective protonation

Using enzymatic systems as a guide to the important factors in achieving enantioselective protonation, two distinct factors have been envisaged as opportunities for asymmetric induction: the use of a chiral Brønsted acid (see 'Enantioselective protonation by a chiral proton donor' below) and generation of a chiral proton-acceptor intermediate (see 'Enantioselective protonation by a chiral Brønsted base' below). Whereas the enzymatic systems exploit both of these control elements, many laboratory methods have sought to use only a single control element, not only to minimize the amount of enantiopure material required for the transformation, but also to eliminate complicating diastereomeric interactions possible in systems with multiple chiral additives. In practice, some of these systems seem to involve protonation through an aggregate complex of both proton acceptor and proton donor, typically in a metal complex (for example, Fehr's tautomerization depicted in Fig. 1).

An additional factor important in improving efficiency of enantioselective protonation systems is achieving catalysis. For example, catalytic generation of a chiral metal–enolate complex *in situ* minimizes the amount of chiral controller required. Alternatively, coupling of a catalytic chiral proton donor to a stoichiometric achiral proton source achieves a similarly efficient use of chiral information. In the latter case, however, a specific order of thermodynamic acidity of the reaction components must be used (necessarily in this order of decreasing Brønsted acidity: stoichiometric proton source, catalytic chiral protonating agent, product). An accompanying balance of kinetic rates of proton transfer between all of these components must also be achieved to allow a reasonable rate of protonation through the catalysed pathway while avoiding undesired background reaction between the prochiral proton acceptor and the stoichiometric achiral proton donor. Vedejs and co-workers have disclosed a study of these factors that is representative of these important issues[22].

Enantioselective protonation by a chiral proton donor

Perhaps the most fundamental means of achieving an enantioselective protonation is to use a chiral proton donor. The acidic proton often comes from an oxygen, nitrogen, or carbon atom in the proton donor. Indeed, the earliest enantioselective protonation protocols used this technique.

Among the most popular substrates for enantioselective protonation are lithium enolates, which are often generated from ketones, enol acetates or silyl enol ethers at low temperatures. This method most closely resembles an esterase approach taken by nature. Kim and co-workers[23] have synthesized a family of hydroxyethers as chiral proton sources (for example, **16**, Fig. 3a) capable of protonating lithium enolates of tetralones and indanones (prepared *in situ* from silyl enol ethers such as **14**) with up to 97% yield and 90% e.e. The acidity of the Brønsted acids had a strong correlation to enantioselectivity and salt-free conditions were important for selectivity. A π–π-stacking interaction between the substrate and rigid proton source was proposed as the chiral controlling interaction during the protonation event. As cyclohexanone-derived enolates lack an aryl group to participate in the stacking interaction, poor enantiomeric excess was observed for these substrates.

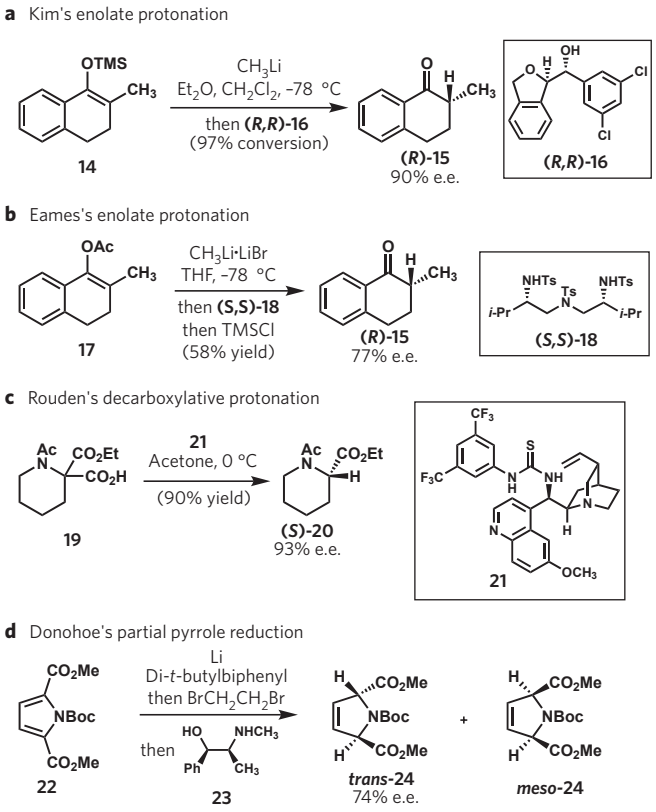

Figure 3 | Enantioselective protonations by means of stoichiometric chiral Brønsted acids. a, Kim and co-workers[23] synthesized several chiral alcohols (for example, **16**) to serve as chiral Brønsted acids. High enantiomeric excess products could be obtained with tetralone-derived enolates, but lower selectivity was found for substrates lacking an aryl group. **b**, Eames and co-workers[24–26] used a series of sulfonamide Brønsted acids (for example, **18**) in enantioselective protonation reactions. In some cases an external quench procedure allowed preparation of the antipode of the ketone product. **c**, Rouden and co-workers[27,28] found that Cinchona alkaloid-derived thioureas (for example, **21**) promoted the decarboxylative protonation of malonate hemiesters. Use of diastereomeric thioureas allowed access to the opposite enantiomer of product with comparable enantiomeric excess. **d**, Donohoe and co-workers[29,30] used amino alcohols (for example, **23**) as proton donors in dissolving metal reductions of pyrroles. In the case of diester **22**, a 1:1 mixture of diastereomeric dihydropyrrole products (**24**) was obtained. TMS, trimethylsilyl; Ac, acetyl; Ts, *para*-toluenesulfonyl; Boc, *t*-butyloxycarbonyl.

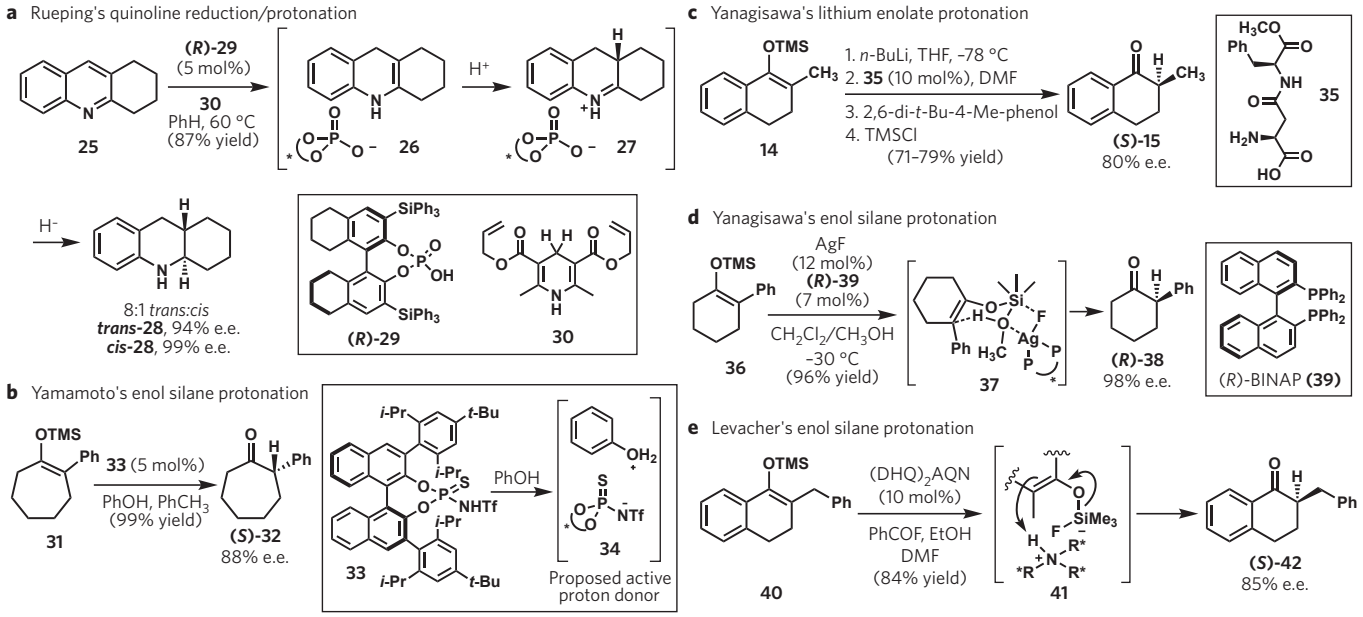

Figure 4 | Enantioselective protonations by means of catalytic chiral Brønsted acids. a, Rueping and co-workers[31] found that chiral phosphoric acid catalysts coupled with Hantzch esters could effect enantioselective enamine protonation in the course of quinoline reductions. **b**, Cheon and Yamamoto[32] recently disclosed the use of *N*-triflyl thiophosphoramide catalyst **33** for the conversion of enol silanes to enantioenriched ketones. Empirical observations suggest that the catalyst forms an oxonium ion pair (**34**) that serves as the active proton donor. **c**, Yanagisawa and co-workers[33] used a catalytic amount of a simple dipeptide **35** to enantioselectively protonate lithium enolates. Small modifications to the dipeptide caused significant decreases in product enantiomeric excess. **d**, A different system developed by Yanagisawa and co-workers[34,35] used a Ag Lewis acid to activate methanol to serve as a proton donor in the conversion of silyl enol ethers to ketones. An aggregate transition state was proposed for the transformation. **e**, Levacher and co-workers[38] reported a protocol for preparing HF *in situ*. The HF then interacts with a *Cinchona*-alkaloid-derived nitrogen base and subsequently activates enol silanes toward protonation by the ammonium species. Tf, trifluoromethanesulfonyl; DMF, *N*,*N*-dimethylformamide; DHQ, dihydroquinine; AQN, anthraquinone 1,4-diyl.

Eames and co-workers[24–26] have developed several strategies for the asymmetric protonation of prochiral tetralone enolates based on structurally different chiral proton sources. In one example[26], tris(sulfonamide) protonating agents with chiral backbones (for example, **18**, Fig. 3b) provided yields of ketone products (for example, **15**) up to 70% and enantiomeric excesses of up to 77%. In these systems, it is believed that the enolates and proton sources can form an organized transition state that is guided by lithium chelation and perhaps more closely resembles a chiral aggregate intermediate than a direct enolate protonation. In some cases it was possible to access the opposite antipode of the product ketone by using an external quench strategy[24].

Enolate intermediates can also be accessed through decarboxylation. Proton donors derived from *Cinchona* alkaloids (for example, **21**, Fig. 3c) have proved to be especially useful reagents for this enantioselective protonation strategy. Rouden and co-workers[27,28] have shown that cyclic and acyclic α-aminomalonate hemiester substrates (for example, **19**) can be protonated with high levels of enantioselectivity. Enantiomeric excesses of product esters (for example, **20**) up to 93% could be achieved in cyclic cases and 89% in acyclic cases. Products in the opposite enantiomeric series could be generated in comparable enantiomeric excess using catalysts prepared from naturally occurring diastereomeric alkaloids. The alkaloid derivatives are believed to serve as dual-purpose reagents: they deprotonate malonate hemiester substrates and promote a decarboxylation event. The intermediate enolate can be protonated by the tertiary ammonium salt to give enantioenriched products. This approach is biomimetic and resembles decarboxylase enzymes in nature.

Work done by Donohoe and co-workers[29,30] has shown that it is possible to perform dissolving metal reductions of pyrrole esters and quench the resulting enolate intermediates with a chiral proton source. Reduction of 2,5-disubstituted pyrroles (for example, **22**, Fig. 3d) led to a separable 1:1 mixture of *trans*- and *meso*-diastereomers of ester **24**, but the asymmetric induction in the chiral *trans*-product was good when (–)-ephedrine (**23**) was used as the chiral proton source. Based on enantioselectivities of reactions with substituted ephedrine derivatives, it was proposed that the hydroxyl group provides the proton and that the ephedrine molecule needs to interact with the lithium cation in a bidentate fashion for optimal asymmetric induction. Considering this proposal, this transformation may be more accurately described as protonation through a chiral aggregate of Brønsted acid and base. A related transformation of pyrrole mono-esters with oxazolidinone proton donors yielded reduced products in up to 68% e.e. and 58% yield. These partially reduced pyrroles could be elaborated to form uncommon dihydroxylated amino acids found in the marine mussel *Mytilus edulis*[29].

It is often possible to use catalytic amounts of chiral protonating agents, provided that an appropriate stoichiometric proton source can be identified. For this purpose, a number of chiral organic catalysts have been used in various transformations. To achieve a heterocycle reduction/protonation strategy analogous to that used by Donohoe and co-workers (Fig. 3d), Rueping and co-workers[31] were able reduce substituted quinolines enantioselectively (Fig. 4a). Initial hydride reduction of annulated quinoline **25** by a Hantzch dihydropyridine (**30**) to form enamine **26** was followed by enantioselective protonation with a catalytic chiral BINOL-phosphoric acid (**29**). Terminal hydride reduction of iminium ion **27** yielded optically active tetrahydroquinoline **28** as an 8:1 mixture of *trans*- and *cis*-diastereomers with the diastereomers formed in 94% and 99% e.e., respectively. Up to 84% yield and 85% e.e. could be obtained for monosubstituted quinolines using the optimal reaction conditions.

In a mechanistically different approach, Cheon and Yamamoto[32] used a related BINOL *N*-triflyl thiophosphoramide catalyst (**33**) to directly protonate cyclic silyl enol ethers (for example, **31** → **32**, Fig. 4b). Regeneration of the chiral proton source was made possible

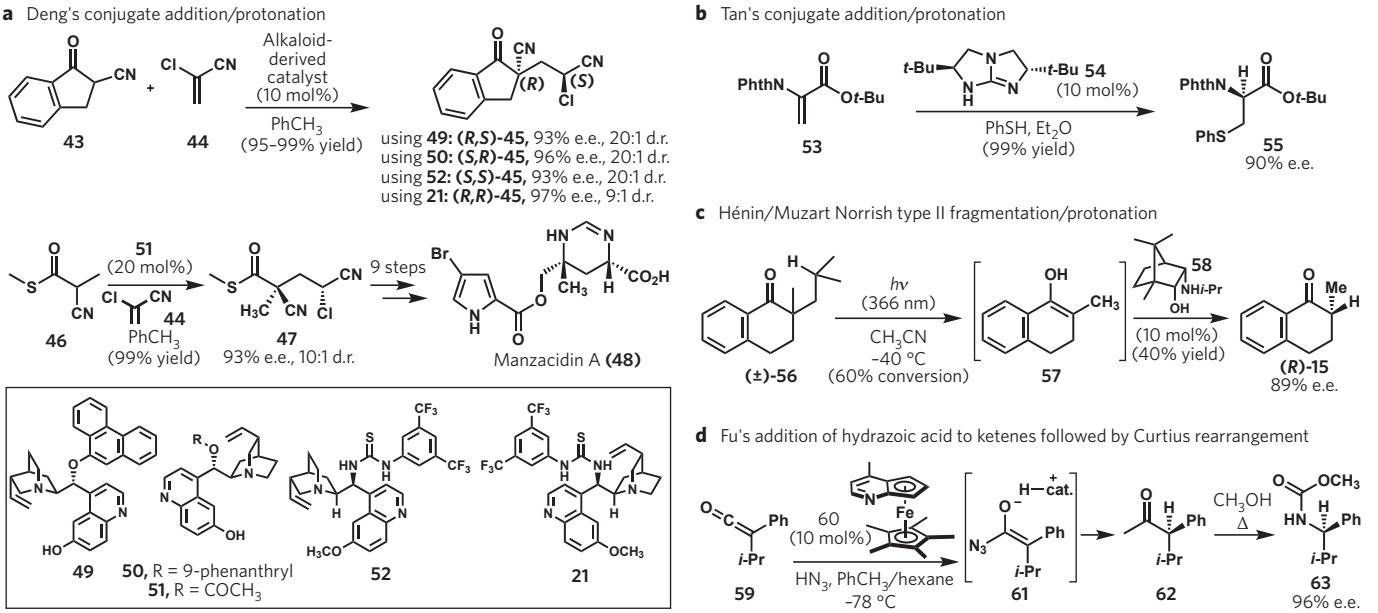

Figure 5 | Enantioselective protonations by means of catalytic chiral Brønsted acids. a, Deng and co-workers[39,40] demonstrated that catalysts derived from quinine and quinidine were capable of catalyzing addition of prochiral nucleophiles to 2-chloroacrylonitrile (**44**). All four stereoisomers of the products (for example, **45**) were accessible in high yield, enantiomeric excess and diastereomeric ratio by using different catalysts. This transformation was used to carry out an enantioselective formal synthesis of the natural product manzacidin A (**48**). **b**, Tan and co-workers[42] developed enantioselective conjugate addition/protonation sequences with heteroatom nucleophiles in the presence of guanidine catalyst **54**. **c**, Hénin, Muzart and co-workers[43,44] found the photochemical fragmentation of racemic α-quaternary ketone **56** generated an enol (**57**) that could undergo enantioselective conversion to (*R*)-2-methyltetralone ((*R*)-**15**) in the presence of amino alcohol catalyst **58**. **d**, Fu and co-workers used planar-chiral heterocycle catalyst **60** to promote addition of hydrazoic acid to ketenes (for example, **59**). Subseqeunt Curtius rearrangement generated chiral carbamate products (for example, **63**) with high enantiomeric excess.

by using phenol as the achiral proton source. With this system, yields up to 99% and enantiomeric excesses up to 90% were achieved. The highest levels of enantioselectivity were obtained with substrates bearing an aryl substituent at the α-position, and 7-membered rings performed somewhat better than 6-membered rings. Comparable selectivity and yield could be obtained with catalyst loadings as low as 0.05 mol%. In control experiments, the protonation reaction did not proceed without an achiral proton source, even with stoichiometric chiral Brønsted acid. This observation led to a proposed mechanism that involves pre-association of the chiral and achiral proton sources to form an oxonium ion pair (**34**) that then protonates the silyl enol ether substrate.

A common approach to enantioselective protonation uses a lithium enolate, catalytic chiral proton source, and stoichiometric achiral proton source. These lithium enolates are often prepared from the corresponding enol silanes. Reports of amino acids as catalytic proton sources have appeared in recent literature. Yanagisawa and co-workers[33] used commercially available dipeptide **35** (Fig. 4c) for the protonation of a lithium enolates of tetralones and cyclohexanones. The catalytic proton source is regenerated through proton transfer from 2,6-di-*t*-butyl-4-methylphenol (BHT). The steric bulk of the phenol is important for suppressing background enolate protonation through a non-selective pathway. The structure of the chiral proton donor is very specific to the success of the reaction because isomeric dipeptide aspartame afforded racemic product. Enolates generated from deprotonation of racemic ketone **15** with lithium diisopropylamide could also be protonated with comparable yield and enantioselectivity using this system.

In separate work from Yanagisawa and co-workers[34,35], enol silanes were found to react in the presence of the complex of AgF and BINAP (**39**, Fig. 4d) and methanol as a proton donor. Excellent enantiomeric excesses were reported for a variety of cyclic ketones. Cyclohexanone-derived enol silanes yielded significantly higher enantiomeric excess products than tetralone-derived enol ethers. The highest levels of enantiomeric excess (up to 99%) were found for α-arylcyclohexanones. Although the fine mechanistic details have not been elucidated, one possibility is that the chiral Lewis acidic Ag·BINAP complex binds methanol to generate a potent chiral Brønsted acid capable of protonating the latent enolate. Taking the fluoride activation component into account, aggregate complex **37** was proposed as a potential intermediate leading to the observed enantiomer of product ketone.

Levacher and co-workers[36] have reported that catalytic amounts of *Cinchona* alkaloid derivatives can be coupled to latent hydrogen fluoride sources to achieve enantioselective protonation of silyl enol ethers of 1-indanones and 1-tetralones (for example, **40** → **42**, Fig. 4e). The hydrogen fluoride, generated *in situ* from benzoyl fluoride and ethanol, is presumed to interact with the alkaloid-derived catalyst to form a cinchonium fluoride. The fluoride anion of this active catalyst then activates the silyl group to facilitate proton delivery from the ammonium cation (for example, **41**), through a proposed transition state reminiscent of the Ag·BINAP protonation protocol described above. The optimal alkaloid catalyst was $(DHQ)_2(AQN)$, a common ligand for Sharpless's enantioselective dihydroxylation reactions[37]. Yields up to 86% and enantiomeric excesses up to 92% were reported. Protonation of cyclohexanone-derived enol silanes gave moderate enantiomeric excess. Later work revealed that carboxylic acids (for example, citric acid) could be used directly with the alkaloid-derived catalysts to carry out the enol silane protonation[38]. Enantioselectivity for this variant of the reaction was moderately diminished, however (e.e. up to 75%). The use of chiral carboxylic acids revealed a moderate, but measureable, influence of both the proton donor and the catalyst on enantioselection, with the catalyst influence apparently dominating.

In a series of reports by Deng and co-workers[39,40], bifunctional *Cinchona* alkaloid-derivatives (for example, **21**, **49**–**52**, Fig. 5a)

were reported to catalyse tandem asymmetric conjugate addition/protonation reactions of cyclic and acyclic α-cyanoketone nucleophiles (for example, **43** and **46**) to 2-chloroacrylonitrile (**44**). The *Cinchona* alkaloid derivative is proposed to serve two functions: activating the Michael acceptor for addition and serving as the chiral Brønsted acid for the protonation of the nitrile-stabilized carbanion intermediate. The postulated stereochemical model involves a network of hydrogen bonding interactions, and it was found that modification of this network by masking the phenolic hydroxyl group and introducing a thiourea moiety led to preferential formation of the diastereomeric products in excellent enantiomeric excess. By virtue of this discovery, all four stereoisomeric products of **45** could be prepared with high degrees of diastereo- and enantioselectivity. This method was applied to an enantioselective formal synthesis of (–)-manzacidin A (**48**) via the intermediate thioester **47**, prepared in 93% e.e. from α-cyanothioester **46** and 2-chloroacrylonitrile (**44**). A very similar transformation was reported by Wu and co-workers[41] for the conjugate addition of thiophenol to an α-substituted acrylamide with subsequent enantioselective protonation in up to 60% e.e.

Organic catalysts other than *Cinchona* alkaloids have shown promise for catalytic asymmetric protonation as well. Tan and co-workers[42] used thiols and phosphine oxides as nucleophiles for 1,4-addition into various phthalimidoacrylates and itaconimides (for example, **53** → **55**, Fig. 5b). Subsequent protonation of the intermediate enolates by the conjugate acid of chiral bicyclic guanidine catalyst **54** gave up to 99% yield and 94% e.e. Interestingly, the presence of water and relatively acidic thiophenols did not lead to appreciable amounts of non-selective enolate quenching. Kinetic isotope effects were explored with D_2O and a primary kinetic isotope effect of 1.5 was found, consistent with cleavage or formation of a bond containing H or D in the rate-determining step.

An unusual technique to generate an enol *in situ* was reported by Hénin, Muzart and co-workers[43,44]. In this work, a racemic α-quaternary ketone (for example, **56,** Fig. 5c) was exposed to laser photolysis at 366 nm. This irradiation caused a Norrish type II fragmentation (**56** → **57**) to occur with concomitant loss of isobutylene. The enol (**57**) then undergoes enantioselective transformation to the corresponding ketone (**15**) in the presence of amino alcohol **58**. Although high e.e. was realized for this dealkylative protonation in some cases, yields were low largely due to undesired fragmentation reactions initiated by the photochemical irradiation and decomposition of the resulting radical intermediates. This method represents one of the few enantioselective stereoablative transformations[45] involving destruction of a quaternary stereocentre.

A variety of transformations catalysed by planar-chiral heterocycles involve protonation as the enantio-determining step. In one recent example from Fu and co-workers[46], catalyst **60** (Fig. 5d) was found to promote the addition of HN_3 to ketenes (for example, **59**). The resulting acyl azides (for example, **62**) then underwent Curtius rearrangement at elevated temperatures. The carbamate products (for example, **63**) were isolated with up to 97% e.e., presumably from enantioselective protonation of the amide enolate intermediate (**61**). Sterically large ketenes performed best because less encumbered ketenes had the problem of rapid uncatalysed background reaction even at cryogenic temperatures. In control experiments, hydrazoic acid was found to be readily deprotonated by planar-chiral heterocycle catalyst **60**. As the reaction also proceeded with higher selectivity at low substrate concentration, a mechanism involving an ion pair **61** was proposed. This behaviour of the catalyst as a chiral Brønsted acid rather than the more typical role of these catalysts as Lewis bases[47] is somewhat unusual, but also serves as a testament to the privileged nature of these catalysts[48].

Although the particular example in Fig. 5d is thought to occur through a protonated catalyst molecule as the proton donor, other similar transformations may proceed through a different mechanism (see the following section), however in both examples the lack of a nonlinear relationship[49] between catalyst e.e. and product e.e. suggests that only one catalyst molecule is involved in the enantioselective step and therefore a hybrid mechanism is unlikely. Regardless of which of these two mechanistic hypotheses is operative, the transformation remains an enantioselective protonation process. An understanding of the mechanistic details, however, is helpful to understand the stereochemical control elements important to the success of the transformation.

Enantioselective protonation by a chiral Brønsted base

The most common form of chiral Brønsted base used in enantioselective protonations has been chiral metal enolates. To circumvent the challenge of stereoselective generation of acyclic enolates, the majority of methods have focused on cyclic enolate precursors. A variety of techniques for enolate generation have been used including simple deprotonations, pericyclic reactions, decarboxylations and dehalogenations. The synthesis of the specific enolate precursor required for a protonation protocol (for example, enol silane, acrylate or β-ketoester) may determine how useful the method is for the preparation of specific target molecules. Although several successful chiral Brønsted base protonation protocols have been developed, substrate scope remains a significant problem. Especially lacking are general methods capable of protonation of acyclic enolates with high selectivity.

Planar-chiral heterocycle catalysts have also been used in the generation of chiral Brønsted base intermediates for enantioselective protonation. Fu and co-workers[50] used azaferrocene catalyst **65** (Fig. 6a). In the proposed reaction mechanism the heterocycle catalyst reacts with a ketene (for example, **64**) to form a zwitterionic chiral enolate intermediate (**66**). Subsequent protonation of the enolate by methanol or an achiral pyridinium cocatalyst then forms an acylferrocenium ion (for example, **67**) that goes on to form an enantioenriched ester (for example, **68**). Evidence for this distinct reaction mechanism included the fact that catalyst **65** did not appreciably deprotonate methanol in solution[51]. However, in the case above (Fig. 5d) the catalyst **60** does readily deprotonate hydrazoic acid. The remarkable ability of these Lewis base catalysts to achieve enantioselective protonation through two different mechanisms highlights the importance of understanding the details of the reaction pathways. The preliminary mechanistic evidence does not always provide sufficient information to determine the operative mechanism, however[52].

Other organic molecules have been used for the generation of chiral enolates as well. For example, Rovis and co-workers[53] found that treatment of α,α-dichloroaldehydes such as **69** (Fig. 6b) with enantiopure triazolium salt catalyst **70** in the presence of a stoichiometric phenoxide base and phenol led to α-chloroaldehydes with high enantiomeric excess. The proposed path of the reaction involves addition of the carbene conjugate base of catalyst **70** to the aldehyde substrate. Subsequent elimination of HCl then generates a zwitterionic enolate intermediate (**71**) that is subject to protonation to form enantioenriched aldehyde **72**. The precise structure of the putative enolate is a matter of conjecture since a number of different strain elements are likely in competition in this intermediate. Nonetheless, this method represents a very valuable technique for the preparation of useful, but synthetically challenging, chiral synthons.

In a separate application of carbene catalysis, Scheidt and co-workers[54] found that homoenolate equivalents (for example, **75**, Fig. 6c), generated *in situ* from enals such as **73**, could undergo enantioselective protonation when chiral triazolium catalyst **74** was used. Ester products (for example, **76**) were obtained in up to 58% yield and up to 59% e.e,. although competitive formation of over-oxidized enoate byproduct **77** complicated the reaction. Although

the degree of enantioselectivity observed for this transformation was modest, this represents a significant advance in the type of proton acceptor that can be used for enantioselective protonation reactions since the site of protonation is relatively distant from the chiral control element.

Metal-catalysed 1,4-additions of organoboranes or organosilanes to enone systems have proven to be a popular strategy for generating chiral enolates for asymmetric protonation. These reactions can use neutral or cationic rhodium complexes. Arylboron, arylstannane, arylsilicon or arylzinc (and in some cases, vinylboron) reagents can be used for coupling, but yields and enantioselectivities can depend on the type of organometallic reagent chosen. Atropisomeric bis(phosphine) ligands such as BINAP (**39**) and its analogues give excellent enantioselectivities for simple β-unsubstituted enone substrates. Diverse proton sources have been used to enable the formation of α-stereocentres. The optimal proton source varies from system to system, but phenols and other low-pK_a proton sources are common. Recent examples have mainly explored simple β-unsubstituted systems, so issues of diastereoselectivity in the generation of multiple stereocentres have not been fully addressed.

Frost and co-workers[55] explored Rh-catalysed additions of organotrifluoroborate salts to itaconate substrates with water as the stoichiometric proton donor (for example, **78** → **79** → **80**, Fig. 7a). The metal-to-ligand ratio was found to be important in the selectivity of the reaction. Equimolar amounts of metal and ligand gave a racemic product in high yield, but 2.2 equivalents of ligand relative to metal gave product in 82% e.e. and 56% yield. Interestingly, high temperature was found to be an important factor in this reaction; a racemic product was obtained when the reaction was carried out at 60 or 80 °C instead of 110 °C. In related work, Frost showed that organosiloxanes are also viable nucleophilic components for 1,4-addition, but such systems give poor yields and low enantioselectivity[56]. In a separate system involving aryl boronic acid organometallic components in microwave reactors, Frost and co-workers[57] examined whether a chiral proton source affected the stereochemical outcome of the reaction. When (*R*)-, (*S*)- or racemic-BINOL was used with a Rh·BINAP catalyst, the yields and enantioselectivities were comparable in each of the three situations. This suggests that the chirality of the bis(phosphine) ligand is the dominant stereodetermining factor.

Sibi and co-workers[58] also investigated rhodium-catalysed conjugate addition–protonation as a method for accessing β²-amino esters from enoates (for example, **81** → **83**, Fig. 7a). Reaction screening revealed that (*S*)-DifluorPhos ligand (**82**) and phthalimide as the proton donor provided the best enantioselectivity. The best substrate provided 95% yield and 91% e.e. Notably, lower temperatures could be used to increase product e.e.

Hayashi and co-workers[59] reported a related conjugate addition/protonation sequence for an analogous diphenylphosphinylallene (for example, **84**) system with a cationic dimeric rhodium μ_2-hydroxide catalyst (Fig. 7a). Temperature did not seem to have an effect on enantioselectivities, but the choice of tetrahydrofuran (THF) as solvent instead of dioxane improved enantioselectivities by more than 20%. Minimal isomerization of the β,γ-unsaturated products (for example, **85**) was observed under the reaction conditions, and excellent yields (up to 97%) and enantioselectivities (up to 98%) were obtained. In this case, an NMR experiment indicates that the arylboronic acid seems to be acting as the proton source.

Sodeoka and co-workers[60] found that this conjugate addition/protonation sequence is viable with palladium complexes and heteroatom nucleophiles as well (**86** → **87**, Fig. 7b). A bimetallic palladium μ_2-hydroxide complex effected the conjugate addition of aniline derivatives to acrylamides. With BINAP ligand, the enolate intermediate was protonated enantioselectively to give product **87** in 80% yield and 94% e.e. Although this is a promising result, the substrate scope has not been fully investigated.

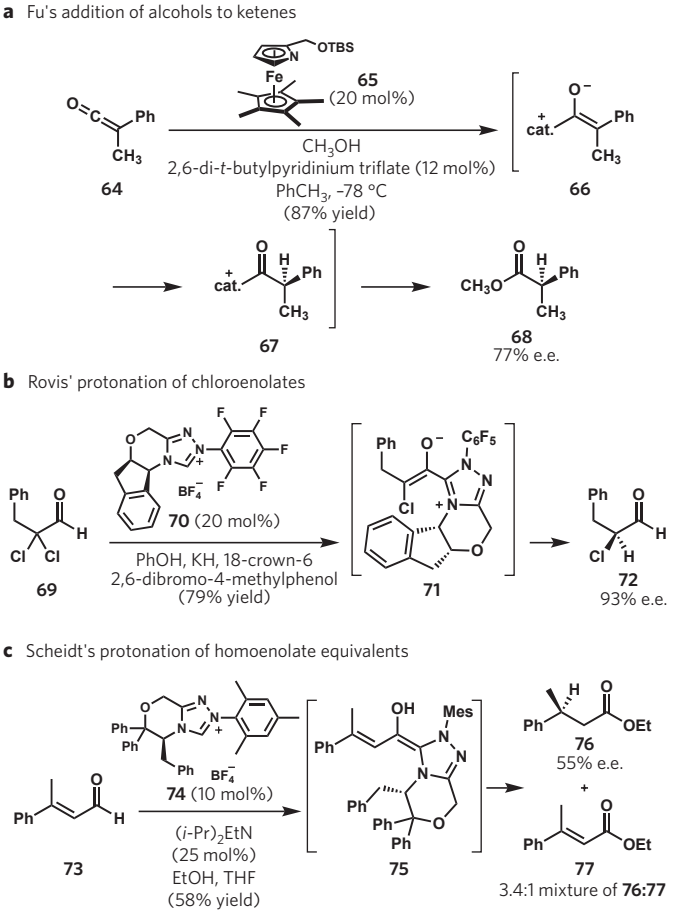

Figure 6 | The use of nucleophilic heterocycle catalysts to generate chiral proton acceptors. a, Fu and co-workers[50] used azaferrocene catalyst **65** to achieve enantioselective addition of alcohols to ketenes. Experimental observations suggest that the mechanism differs from the related reaction in Fig. 5d. **b**, Rovis and co-workers[53] found that triazolium salt **70** catalysed the transformation of α,α-dichloraldehydes (for example, **69**) into synthetically useful enantioenriched mono-chloroaldehydes (for example, **72**). **c**, Scheidt and co-workers[54] achieved enantioselective protonation of homoenolate equivalents with triazolium salt catalyst **74**. This demonstrated that enantioselective protonation could occur at a site distant from the chiral catalyst. TBS, *t*-butyldimethylsilyl.

Genet, Darses and co-workers[61,62] sought to make α-amino esters using a similar conjugate addition/protonation strategy (for example, **88** → **93**, Fig. 7c). In this system, boronic esters, boronic acids and organosilanes did not provide adequate conversion or enantioselectivity. Organostannanes, however, were reactive under these conditions. In the screening of various proton sources, phenol derivatives seemed to provide the best enantioselectivity. Guaiacol (2-methoxyphenol) was determined to be the best proton donor, giving products with up to 91% yield and 88% e.e. Higher temperatures and optimized solvents (such as toluene or dioxane) increased conversion and enantioselectivity. As in Frost's work, the ratio of metal to ligand did have a notable effect on the enantioselectivity of the reaction, with 2.2 equivalents of chiral ligand relative to metal being optimal. Chiral proton sources were also added to see if the chiral ligand or chiral proton source was the dominant selectivity factor. Studies with (*R*)-BINAP and both enantiomers of BINOL provided identical enatiomeric excesses, implying that the chirality of the enolate is dominant, as in the reports by Frost.

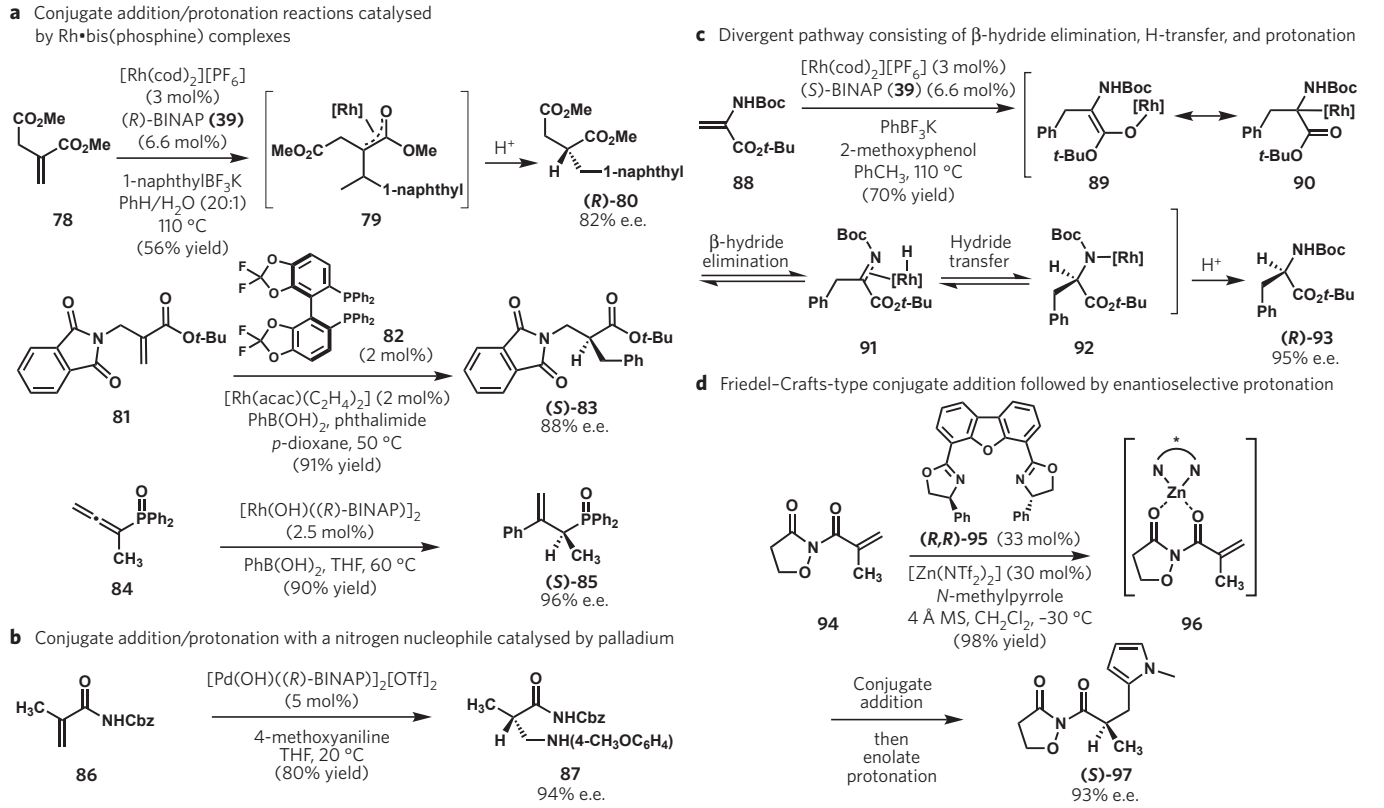

Figure 7 | Conjugate addition/protonation sequences catalysed by chiral metal complexes. a, Several research groups[55,57–59] have explored Rh-catalysed conjugate addition/protonation sequences with various activated electrophiles and carbon-based nucleophiles. **b**, Sodeoka and co-workers[60] found that nitrogen nucleophiles could undergo enantioselective conjugate addition/protonation in the presence of a cationic Pd catalyst. **c**, Darses, Genet and co-workers[61,62] successfully synthesized α-amino acid derivatives through a conjugate addition/protonation sequence, although later mechanistic evidence suggested a different reaction mechanism than they originally postulated. **d**, Sibi and co-workers[63] achieved enantioselective protonation of Zn-enolate generated by Friedel–Crafts-type addition of a pyrrole to an acrylimide. cod, *cis*,*cis*-cycloocta-1,5-diene; acac, acetylacetone; Cbz, benzyloxycarbonyl; 4 Å MS, 4 Å molecular sieves.

Mechanistic studies showed that the hydrogen on the enamide was essential for reactivity. Deuterium labelling studies showed that the reaction did not proceed via a direct protonation of the rhodium enolate (**89**); in a substrate with a labelled carbamate proton, deuterium incorporation at the α-carbon was high (41%). Based on this observation, a mechanism involving sequential conjugate addition, β-hydride elimination from the carbamate (**90** → **91**), and intramolecular hydride transfer to the α-carbon (**91** → **92**) was proposed. This proposed reaction pathway was supported by DFT calculations with the B3LYP/BII level of theory[62]. In light of these mechanistic insights, a more electron-poor bis(phophine) ligand was chosen to facilitate the postulated β-hydride elimination step, and DifluorPhos (**82**) was shown experimentally to give higher enantiomeric excesses.

A related conjugate addition/enantioselective protonation strategy consisted of a Friedel–Crafts-type addition of pyrroles to α-substituted acrylates (for example, **94** → **97**, Fig. 7d)[63]. Sibi and co-workers used $Zn(NTf_2)_2$ complexed with chiral Ph-DBFOX ligand **95** as a Lewis acid catalyst to achieve up to 98% yield and up to 98% e.e. The enolate intermediate (**96**) generated from the Friedel–Crafts reaction can be quenched by a proton from the pyrrole fragment to give a chiral product. The isoxazolidinone auxiliary is thought to be critical for improving reactivity and providing greater enolate control during the course of the reaction.

A distinct method of accessing a chiral metal enolate is the use of a pericyclic reaction. In the case of the Nazarov cyclization[64–67], the enantioselective reaction would not only generate a new stereocentre, but also a new five-membered ring. However, until recently enantioselective variants of this classical reaction were unknown[68–73]. In studies directed towards the development of a general enantioselective Nazarov cyclization, Trauner and co-workers[68,70] discovered that high e.e. cyclopentenone products could be synthesized from electronically activated substrates such as dienone **98** in the presence of Sc·PYBOX complex **99** (Fig. 8a). Interestingly, this enantioselective protonation protocol requires no external proton source. Unfortunately, in cases where a second stereocentre would be generated at the β-carbon (that is, **103** where R ≠ H), low diastereoselectivity was observed. This was interpreted as a result of low stereoselectivity in the electrocyclization step (**100** → **101**) followed by high selectivity in the protonation step (**102** → **103**). In recent work, Rueping and co-workers have achieved a very similar electrocyclization/enantioselective protonation sequence using a chiral Brønsted acid catalyst[74].

A different strategy for accessing chiral metal enolates is decarboxylation of β-ketoesters. The nature of the ester is typically important to enable enolate formation. In the case of palladium-catalysed protonation reactions, benzyl and allyl esters have been the most common enolate precursors. The first examples of these reactions, developed extensively by Hénin, Muzart and co-workers[75], used an initiation step such as Pd-mediated hydrogenolysis to generate an achiral enol (or enolate)[76–78] intermediate that was subsequently protonated with a chiral Brønsted acid (typically an amino alcohol). The results of these studies showed a strong dependence on the specific reaction conditions (for example, temperature and source of palladium on carbon). More recently, this strategy has been refined to instead generate a chiral Pd-enolate intermediate from allyl β-ketoester substrates (for example, **104** and **107**, Fig. 8b) in the hopes that chirality at

the metal might impart improved stereocontrol in the protonation step and obviate the need for heterogeneous Pd catalysts. Stoltz and co-workers[79] found that the catalyst derived from $Pd(OAc)_2$ and phosphinooxazoline (PHOX) ligand **105** was capable of achieving enantioselective protonation in the presence of formic acid and molecular sieves (MS). High enantiomeric excesses were obtained for a range of cyclic ketone products including tetralone- and cyclohexanone-derived ketones (for example, **106** and **109**). Attempts to track the source of the proton incorporated in the product with isomeric mono-deuterated formic acids (DCO_2H and HCO_2D) led to inconclusive results: with DCO_2H the formyl deuteron was not incorporated into the product, but with HCO_2D only 35% D incorporation was observed in the product, suggesting that another unidentified proton donor is also participating in the reaction. The heterogeneous additive (MS) in the reaction is important to the selectivity for protonation in preference to the competitive allylation reaction also catalysed by the Pd·PHOX complex[80–83], and the specific amount required varied somewhat depending on the substrate. To address this issue, a related homogeneous protonation system was developed by Stoltz and co-workers[84] using Meldrum's acid (**108**) as the achiral proton donor and a Pd·PHOX catalyst. Similar substrate scope and enantioselectivity was observed with this system, but without the need to optimize the amounts of additives to achieve optimal results. Initial mechanistic studies found zero-order kinetic dependence in substrate, which suggests a fast initial reaction between catalyst and substrate and a slow subsequent step, presumably either decarboxylation or protonation of the putative enolate intermediate common to both the protonation and allylic alkylation reactions with this catalyst system[85]. However, in the protonation reaction opposite enolate facial preference was observed for tetralone- and cyclohexanone-derived enolates, whereas in the alkylation reaction consistent enantiofacial selectivity was observed[80–82]. This unexpected result suggests a substantial difference in the bond-forming portion of the mechanism.

Kanai, Shibasaki and co-workers[86] recently reported the use of a chiral gadolinium complex for the enantioselective protonation of Gd-enolates generated *in situ* (Fig. 8c). The Gd-enolates were accessed by two means: transmetallation from enol silane (for example, **14**) or conjugate addition of cyanide to *N*-acryloyl pyrroles (for example, **111**). Based on optimization studies, a polymetallic enolate intermediate was proposed. The optimal ligand-to-metal ratio is consistent with a 5:6 complex. The lack of reactivity in the absence of ligand **110** was also interpreted as the necessity of polynuclear Gd complexes for the success of the reaction. Kinetic studies also suggested that the reaction proceeds via transmetallation from Si to Gd, and that this step is rate-limiting. 2,6-dimethylphenol was the preferred proton source, providing indanone and tetralone products in up to 99% yield and up to 88% e.e. The same Gd·**110** complex was also effective for the conjugate addition/protonation of cyanide to *N*-acryloyl pyrroles (for example, **111** → **112**). In this case, hydrogen cyanide was the preferred proton source. This transformation was capable of producing *N*-acyl pyrroles in up to 99% yield and up to 91% e.e. In the case of product **112**, recrystallization could be carried out to provide a 74% yield of material with >99% e.e. The versatility of this polynuclear Gd catalyst for effecting protonation of considerably different enolate intermediates is important to the prospect of a general system for enolate protonation.

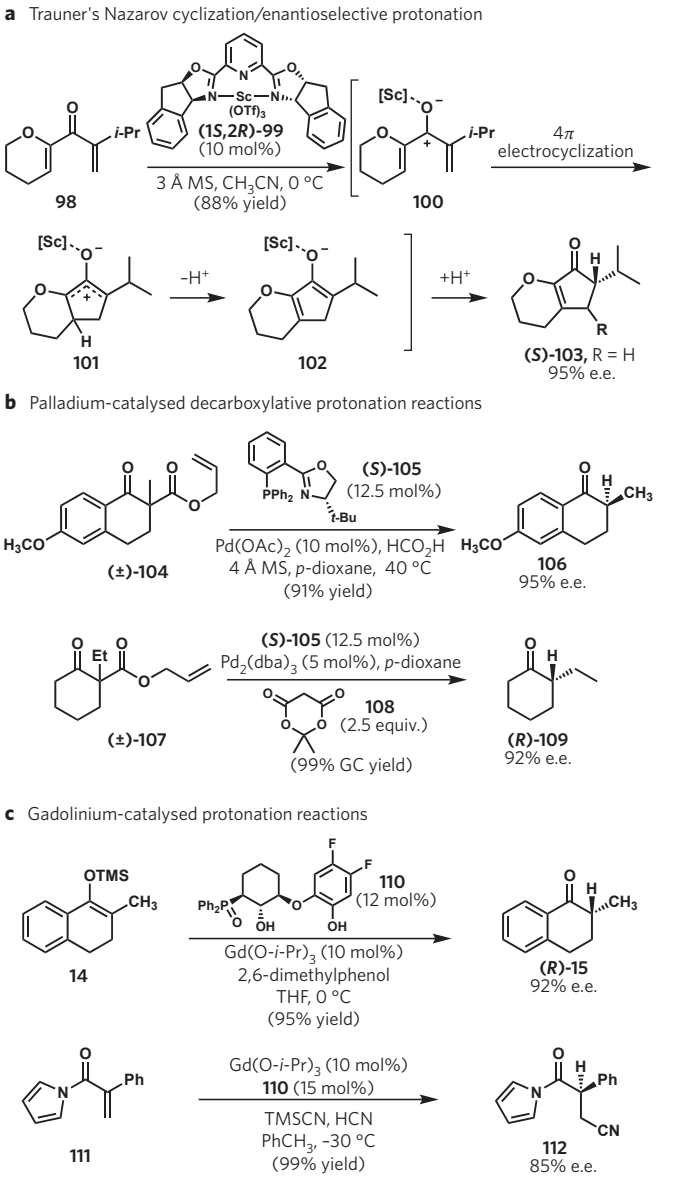

Figure 8 | Transition metal-catalysed enantioselective protonation reactions by means of chiral metal enolates. a, Trauner and co-workers[70] developed a scandium-catalysed cascade Nazarov cyclization/enolate protonation sequence to access cyclopentenones. **b**, Stoltz and co-workers[79,84] used a chiral palladium complex to effect decarboxylative protonation reactions from allyl β-ketoester substrates (for example, **104** and **107**). Two different proton sources were effective in this transformation: formic acid in the presence of molecular sieves, and Meldrum's acid (**108**). **c**, Kanai, Shibasaki and co-workers[86] found that a chiral gadolinium complex was useful for enantioselective protonation of enolates generated from either enol silanes or conjugate addition of cyanide to *N*-acryloyl pyrroles. dba, dibenzylideneacetone.

Enantioselective hydrogen atom transfer

An analogous strategy for arriving at protonation products is to exploit radical chemistry with a terminal H-atom abstraction step. Although not explicitly an enantioselective protonation reaction, many of the same challenges apply when manipulating a hydrogen atom. A recent example of this tactic by Sibi and co-workers[87,88] has led to new methods for synthesizing β-amino acid derivatives (Fig. 9). By using a Lewis acid complex formed from MgI_2 and bis(oxazoline) ligand **113**, tributyltin hydride, and triethylborane/O_2, alkyl radicals (from alkyl halides) can undergo radical conjugate addition followed by enantioselective hydrogen atom transfer to afford optically active products (for example, **114**) in up to 95% yield and up to 98% e.e. The reaction is believed to proceed through a bidentate chelate of the substrate to the chiral magnesium complex. The process can be made catalytic in a Lewis acid without a significant effect on yield, but product e.e. suffered

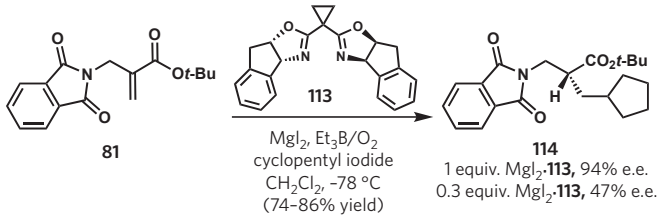

Figure 9 | Radical conjugate addition followed by enantioselective H-atom transfer. Sibi and co-workers[87,88] demonstrated that Mg·bis(oxazoline) complexes effectively promoted radical conjugate addition to enoates followed by enantioselective quenching of the radical intermediate by H-atom transfer. High enantiomeric excess was observed with stoichiometric amounts of Lewis acid, but in some cases substoichiometric amounts of Lewis acid led to significantly lower product enantiomeric excess.

greatly in some cases due to a rapid uncatalysed background reaction. These reactions have the benefit of being essentially neutral as opposed to the acidic or basic conditions required for the transformations described above.

Conclusion

From the enantioselective enzymatic protonation reactions of nature to the variety of techniques for achieving enantioselective protonation in laboratories, a great deal of energy has been dedicated to understanding this deceptively simple transformation. Despite the many systems reported to date, the search for a highly efficient system with a broad scope continues. Moreover, although many of the key parameters needed to create a successful system have been enumerated here and elsewhere, the current level of mechanistic understanding in nearly all of the enantioselective protonation reactions reported to date remains relatively immature. Nonetheless, these useful transformations allow the synthesis of valuable chiral materials including natural products such as α- and β-amino acids. Given these preliminary successes and improved understanding of the underlying mechanisms, enantioselective protonation reactions should continue to rise to prominence as an important tool for synthetic organic chemistry.

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